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RESEARCH ARTICLE

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A single blinded randomized controlled trial comparing semi-mechanical with hand-sewn cervical anastomosis after esophagectomy for cancer (SHARE-study)

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Abstract

Objective: The aim was to compare leak rate between hand-sewn end-to-end anastomosis (ETE) and semi-mechanical anastomosis (SMA) after esophagectomy with gastric tube reconstruction.

Background Data: The optimal surgical technique for creation of an anastomosis in the neck after esophagectomy is unclear.

Methods: Patients with esophageal cancer undergoing esophagectomy with gastric tube reconstruction and cervical anastomosis were eligible for participation after written informed consent. Patients were randomized in 1:1 ratio. Primary endpoint was anastomotic leak rate defined as external drainage of saliva from the site of the anastomosis or intra-thoracic manifestation of leak. Secondary endpoints included anastomotic stricture rate at one year follow up, number of endoscopic dilatations, dysphagia-score, hospital stay, morbidity, and mortality. Patients were blinded for intervention.

Results: Between August 2011 and July 2014, 174 patients with esophageal cancer underwent esophagectomy. Ninety-three patients were randomized to ETE ($n = 44$) or SMA ($n = 49$). Anastomotic leak occurred in 9 of 44 patients (20%) in the ETE group and 12 of 49 patients (24%) in the SMA group (absolute difference 4%, 95% CI −13% to +21%; $p = .804$). There was no significant difference in dysphagia at 1 year postoperatively (ETE 25% vs. SMA 20%; $p = .628$), in stricture rate (ETE 25% vs. 19% in SMA, $p = .46$), nor in median hospital stay (17 days in the ETE group, 13 days in the SMA group), morbidity (82% vs. 73%, $p = .460$) or mortality (0% vs. 4%, $p = .175$) between the groups.

KEYWORDS

anastomosis, end-to-end, esophageal cancer, esophagectomy, gastric tube, hand-sewn, randomized controlled trial, semi-mechanical

1 | INTRODUCTION

Neoadjuvant chemotherapy or chemoradiation followed by esophagectomy is the treatment of choice for locally advanced esophageal cancer. Following esophagectomy, the continuity of the gastrointestinal tract is preferably restored with a gastric tube. Failure of the anastomosis[1–4] between the remnant esophagus and the gastric tube occurs in 5%–30% of patients. Anastomotic leakage delays oral intake, prolongs hospital stay, is associated with a deterioration of health-related quality of life[5,6] and results in increased heath care costs.[7,8] Anastomotic leakage is a risk factor for stenosis of the anastomosis[3,9] and up to 40% of patients need endoscopically guided dilatations.[10,11] Anastomotic leakage is also a risk factor for in-hospital mortality (3%–6%).[1,4,12]

The optimal technique for creating a cervical anastomosis between the esophagus and gastric conduit is largely unknown due to a lack of randomized trials. As patients live longer, perioperative morbidity and late complications of surgery tend to become more important. A previous randomized controlled trial compared a cervical hand-sewn end-to-end anastomosis (ETE) to a cervical hand-sewn end-to-side (ETS) anastomosis. This study reported that an ETE anastomosis was associated with a lower leak rate, but a higher rate of stenosis compared to an end-to-side anastomosis.[13] However, the reported leak rates were still high: 22% in the ETE group and 41% in the ETS group.

In 1998 Collard et al.[14] published a new technique for the cervical esophagogastrostomy. Retrospective studies have suggested that this semi-mechanical side-to-side anastomosis (SMA) is associated with a low anastomotic leak rates and stricture rate. The aim of this study was to assess the leak and stricture rate of the SMA technique. We hypothesized that the SMA reduces the anastomotic leak and stricture rate as compared to our standard hand-sewn ETE anastomosis.

2 | PATIENTS AND METHODS

2.1 | Trial design

This was a single center, single blinded, parallel group with balanced randomization (1:1), clinical trial. The trial was registered at the Dutch trial registry (NTR3029). The study took place at the Department of Surgery, Erasmus MC, Rotterdam, the Netherlands. The Erasmus MC is an academic hospital and serves as a tertiary referral center for esophageal diseases. Ethical approval was obtained from the ethics committee of the Erasmus MC (trial number NL35746.078.11). After approval of the protocol on 11 August 2011, there were no changes or amendments made. The trial is reported according to the CONSORT 2010 guidelines.[15] The trial was in compliance with the Helsinki Declaration.

2.2 | Patients

Eligible participants were patients aged ≥18 years with esophageal or junctional cancer and who were scheduled for a transhiatal or transthoracic esophagectomy with gastric tube reconstruction and a cervical anastomosis. Only patients who underwent surgery with curative intent (stage cT1-4aN0-2M0) were eligible. Neoadjuvant treatment (chemotherapy or chemoradiation) was allowed.

Exclusion criteria were a planned intra-thoracic anastomosis, patient not available for follow up (up to 1 year postoperatively), cervical esophageal cancer (tumor extending from upper esophageal sphincter to the sternal notch), American Society of Anesthesiologists (ASA) score of ≥4.

Patients were informed about the study in the outpatient clinic by one of the consultant surgeons 4–8 weeks before the operation. An information leaflet was handed out. The day before the operation, the patient was admitted to the hospital and the patient was asked to participate in the study. After written informed consent the patients were registered as trial participant.

2.3 | Interventions

Three experienced esophageal surgeons (HWT, JJBvL, BPLW), proficient in both anastomotic techniques, participated in the study and performed the resection and reconstruction or supervised the fellow.

An open three stage transthoracic esophagectomy (McKeown) or transhiatal esophagectomy (Orringer) was performed depending on the patient's condition and location of the tumor.[16] A nasojejunal feeding tube or percutaneous jejunostomy was placed.

2.4 | Surgical techniques

2.4.1 | End-to-end anastomosis

After esophagectomy, a 3–4 cm wide gastric tube was created and brought up to the neck via the prevertebral route. A hand-sewn, single layer running end-to-end esophagogastrostomy (ETE) was constructed with PDS 3/0 (Johnson & Johnson) as described before 3–4 cm below the upper esophageal sphincter.[13] The anastomosis was performed as distal as possible on the gastric tube (towards the pylorus) and any redundant gastric tissue was resected. However, great care was taken to prevent any tension on the anastomosis.

2.4.2 | Semi-mechanical anastomosis

The semi-mechanical anastomosis (SMA) was performed according to Collard et al.[14] with some modifications. After complete mobilization of the esophagus, the cervical esophagus was transected with a linear stapler (Covidien) 8–10 cm below the upper esophageal sphincter via the neck incision. Once a 3–4 cm width gastric tube was created and brought up to the neck, five stay sutures with Ti-Cron 3/0 (Medtronic) kept the esophageal remnant and gastric tube in a

parallel position to each other. A small incision was made in gastric tube and the cervical esophagus. Another two stay sutures were placed between the esophagus and gastric tube via the enterotomy. The jaws of an Endostapler (Ethicon) were placed across the two opposing walls with the anvil in the gastric lumen and the cartridge of staples in the esophageal lumen. The stapler was fired to allow forward displacement of the knife and the delivery of three rows of staples on each side. The stapler was removed and thus a V-shaped join was created. The anterior wall of the anastomosis was closed using a double-layer running suture technique.

2.5 | Outcomes

The primary endpoint was anastomotic leakage within 30 days after the operation. This was defined as opening of the neck wound with subsequent drainage of saliva and/or ingested fluids through the wound site or intrathoracic manifestations of anastomotic leakage including mediastinitis or abscess/empyema formation detected with radiologic imaging (CT scan with oral contrast) or endoscopy.

Secondary endpoints included anastomotic stricture within 1 year, defined as dysphagia (scored according to the Sugahara score)[17] and with stenosis seen on endoscopy, number of dilatations within 1 year. Other endpoints were hospital stay, stay in the ICU, overall morbidity and mortality (within 1 year, and also in-hospital mortality).

2.6 | Sample size

The previously reported leak rate for ETE in our center was 22%.[13] A SMA has a leak rate of 5%.[14] Hence, a 17% reduction in the leak rate in favor of SMA was anticipated. A sample size was calculated using an α of 0.05 (two-sided) and a power of 85%. Seventy-six patients had to be included per study arm. To correct for mortality within 1 year, the study arms were enlarged to 100 patients each. No formal interim analysis was planned.

2.7 | Randomization

The Department of Biostatistics supervised the randomization process (by preparing the envelopes). A computer based hidden block size of 10 was used by the Department of Biostatistics. After the tumor was resected and the gastric tube was brought up to the neck, the lead surgeon decided if the patient could be randomized. Randomization took place in the operating room using sealed opaque envelopes prepared by the Department of Biostatistics. Reasons for not randomizing patients were inability to construct ETE or SMA (when the esophageal remnant or gastric tube was too short), distant metastasis found during the operation, reconstruction with colon or a retrosternal or presternal route of the conduit. Stratification was performed for surgical approach (ie, transhiatal or transthoracic approach).

2.8 | Independent data monitoring and safety committee

An independent Data Safety and Monitoring Board (DSMB), consisting of two surgeons and a biostatistician, reviewed unblinded data for patients' safety. No interim analysis for efficacy or futility was planned. The DSMB monitored the (cumulative) incidence of serious adverse events every 3 months. Serious adverse events (SAEs) included anastomotic leakage requiring surgical re-intervention, any complication requiring prolonged hospital stay, any complication that results in death, re-admittance to the hospital, recurrence of disease, or death. The DSMB could advise on the termination of the study. All SAEs were reported through the web portal ToetsingOnline to the accredited Medical Ethics Committee that approved the protocol, within 15 days after the sponsor was informed about a serious adverse event.

2.9 | Postoperative care

After the operation patients were transferred to the ICU and were extubated in the operating room or within the following hour, if possible. ICU staff was unaware of the anastomotic technique. Patients were transferred to the surgical ward the day after surgery if they were not on inotropic agents and were hemodynamically and respiratory stable. At the ward a standardized care pathway was followed and a checklist with postoperative instructions was used by the attending surgeon, the nurse specialist or registrar. Patients were kept nil by mouth, but ice chips were allowed according to the study protocol. Radiological examination of the anastomotic integrity was not performed routinely. Oral intake was commenced on postoperative Day 7. On postoperative Day 8, thickened fluids were allowed (yoghurt/custard) and on Day 9 semi-solids and soft foods were introduced until discharge. Enteral feeds were given by the nasojejunal feeding tube or the jejunostomy starting postoperative Day 1. A dietician was involved in the assessment of caloric intake by the patients in the hospital and after discharge. Preferably, patients were discharged without a need for additional enteral feeding via the feeding tube.

2.10 | Follow up

Patients were seen in the outpatient clinic 3 weeks after discharge and every three months in the first year after surgery. The second year, patients were seen every 6 months and from year three onwards once a year. For the first year, the surgeon filled out a questionnaire and case record forms regarding dysphagia and complications after interviewing the patient.

2.11 | Statistical analysis

Analysis of data was according to intention to treat. Values are shown as means and standard deviation (SD) or medians with their range. Groups were compared using non-parametrical Mann-Whitney U test or student's T test, if normally distributed. For cross tabulations, Pearson's Chi Square test with continuity correction was used, or Fisher's exact test when cells had an expected count less than 5. All statistical analyses were performed on the statistical package SPSS 24.0 (SPSS Inc). A *p*-value <.05 was considered statistically significant (two-sided). No futility analysis was performed because the study was ended prematurely due to slow accrual.

3 | RESULTS

3.1 | Patients

From August 2011 to July 2014, 174 patients with esophageal cancer underwent esophagectomy with gastric tube reconstruction for esophageal cancer. The CONSORT flow diagram is shown in Figure 1.

Due to slow accrual and the publication of a similar trial,[18] the DSMB recommended to stop the trial and report the outcomes. In total, 93 patients had been randomized at that moment. The ETE group consisted of 44 patients and the SMA group of 49 patients.

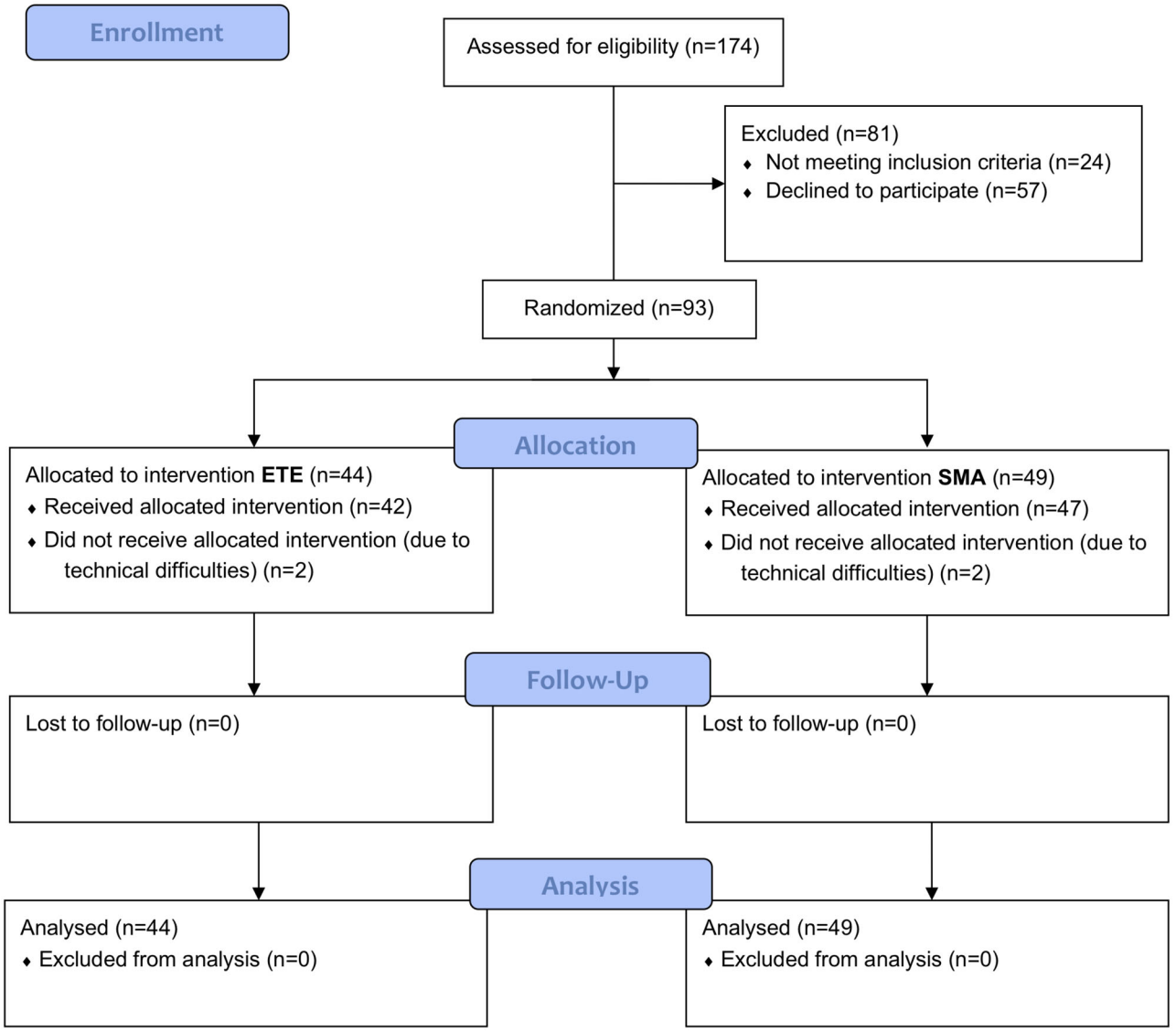

FIGURE 1 Consort flow diagram of the study. Reasons for exclusion: no signed informed consent (*n* = 57), intra-thoracic anastomosis, no availability for follow up at 1 year (*n* = 2), upper thoracic/cervical esophageal cancer, American Society of Anesthesiologists score larger or equal to 4. Reasons not to randomize patients in the operating room were: technically not possible to perform SMA (*n* = 8), metastasis found during the operation (*n* = 5), no gastric tube created (*n* = 2), retrosternal route of the conduit (*n* = 1), reconstruction after previous esophageal resection (*n* = 6). All four patients who were randomized but did not receive the allocated anastomosis received either an ETE or ETS anastomosis. ETE, end-to-end; ETS, end-to-side; SMA, semi-mechanical anastomosis [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patient characteristics

	ETE ($n = 44$)	SMA ($n = 49$)	p-value
Age (yr) median (range)	65 [41–83]	64 [44–83]	.971
Sex (M:F)	40:4	36:13	.035
Body mass index	26.9 [19–39]	24.8 [17–40]	.309
Histology			.069
Squamous cell carcinoma	7 (16%)	18 (37%)	
Adenocarcinoma	36 (82%)	31 (63%)	
Undifferentiated	1 (3%)	0 (0%)	
Tumor site			.138
Esophagus	34 (77%)	38 (78%)	
Gastroesophageal junction	10 (23%)	11 (22%)	
Neo-adjuvant treatment			.501
None	5 (11%)	3 (6%)	
Chemotherapy	6 (14%)	4 (8%)	
Chemoradiation	33 (75%)	42 (86%)	
Comorbidity			
Cardiovascular	26 (59%)	26 (53%)	.531
Respiratory	3 (7%)	6 (12%)	.494
Diabetes Mellitus	10 (23%)	8 (16%)	.440
ASA			.945
1	4 (9%)	5 (10%)	
2	32 (73%)	34 (69%)	
3	8 (18%)	10 (21%)	
4	0 (0%)	0 (0%)	
5	0 (0%)	0 (0%)	

Abbreviations: ETE, end-to-end anastomosis; SMA, semi-mechanical anastomosis.

Patient characteristics are listed in Table 1. The median (range) age was 65 (41–83) years in the ETE group, and 64 (44–83) years in the SMA group. Neoadjuvant treatment (chemotherapy or chemoradiation) was given to 39 (89%) of patients in the ETE group and 46 (94%) patients in the SMA group. Operative characteristics and pathology data are shown in Table 2.

3.2 | Primary outcome

Anastomotic leakage occurred in 9 of 44 (20%) patients in the ETE group and in 12 of 49 (24%) patients in the SMA group (absolute difference 4%, 95% CI −13% to +21%; $p = .804$) (Table 3). In one patient from the SMA group a reoperation was required because of a massive leak resulting in pneumohydrothorax. The gastric tube was

TABLE 2 Operative characteristics and pathology

	ETE ($n = 44$)	SMA ($n = 49$)	p-value
Mean operating time (SD)	398.9 (16.8)	389.9 (14.0)	.681
Surgical approach			.994
Transhiatal esophagectomy	18 (41%)	20 (41%)	
Transthoracic esophagectomy	26 (59%)	29 (59%)	
Pathology			
Radicality of the operation			.273
RO	41 (93%)	42 (86%)	
R1	3 (7%)	7 (14%)	
R2	0 (0%)	0 (0%)	
Histology			.034
Squamous cell carcinoma	3 (7%)	11 (22%)	
Adenocarcinoma	29 (66%)	28 (57%)	
No malignancy left after neoadjuvant treatment	11 (25%)	10 (20%)	
Lymphoepithelioma	1 (3%)	0 (0%)	
Median (range) number of lymph nodes resected	19 (2–43)	18 (8–41)	.624
pT-category			.236
T0	11 (25%)	13 (27%)	
T1	8 (18%)	8 (16%)	
T2	11 (25%)	5 (10%)	
T3	14 (32%)	21 (43%)	
T4	0 (0%)	2 (4%)	
pN-category			.572
N0	26 (53%)	25 (51%)	
N1	13 (27%)	13 (27%)	
N2	4 (8%)	8 (16%)	
N3	1 (2%)	3 (6%)	
pM-stage			.330
M0	42 (95%)	49 (100%)	
M1	2 (5%)	0 (0%)	
Disease stage			.891
0	10 (23%)	9 (18%)	
Ia	8 (18%)	7 (14%)	
Ib	5 (11%)	4 (8%)	
IIa	3 (7%)	6 (12%)	
IIb	6 (14%)	5 (10%)	
IIIa	8 (18%)	8 (16%)	
IIIb	3 (7%)	5 (10%)	
IIIc	1 (2%)	3 (6%)	
IV	0 (0%)	2 (4%)	

Abbreviations: ETE, end-to-end; SMA, semi-mechanical anastomosis.

TABLE 3 Postoperative complications

	ETE (*n* = 44)	SMA (*n* = 49)	*p*-value
Any complication	36 (82%)	36 (73%)	.460
Anastomosis related complications			
Anastomotic leakage[a]	9 (20%)	12 (24%)	.804
Reoperation required for leakage	0 (0%)	1 (2%)	1.000
Dysphagia	11 (25%)	10 (20%)	.628
Stenosis of the anastomosis on endoscopy	11 (25%)	9 (18%)	.460
Median (range) number of dilatations (1 year)	6 [1–11]	3 [1–9]	.276
Other complications			
Postoperative bleeding[b]	3 (7%)	0 (0%)	.249
Chylothorax[c]	4 (9%)	3 (6%)	.704
Vocal cord paralysis	3 (7%)	5 (16%)	.561
Wound dehiscence (abdominal)	2 (5%)	1 (2%)	.601
Pneumonia[d]	14 (32%)	17 (35%)	.828
Mediastinitis	4 (9%)	5 (10%)	1.000
Cardiac complication (other than AF)[e]	8 (18%)	8 (16%)	1.000
Atrial fibrillation	6 (14%)	10 (20%)	.423
Sepsis	1 (2%)	2 (4%)	1.000
Delirium	5 (11%)	1 (2%)	.097
Thrombosis[f]	1 (2%)	1 (2%)	1.000
Readmission to ICU	3 (7%)	7 (14%)	.324
Readmission to hospital[g]	6 (14%)	13 (27%)	.186
In-hospital mortality	0 (0%)	2 (4%)	.175

Note: Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Abbreviations: AF, atrial fibrillation; ETE, end-to-end; ICU, intensive care unit; SMA, semi-mechanical anastomosis.

[a]Anastomotic leakage was defined as: opening of the neck wound with subsequent drainage of saliva and/or ingested fluids through the wound site or intrathoracic manifestations of anastomotic leak including mediastinitis or abscess formation detected with radiological imaging (CT scan with oral contrast) or endoscopy.

[b]Postoperative bleeding was defined as blood loss with the need of transfusion or operative intervention.

[c]Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid (>1 mmol per liter [89 mg per deciliter]) were found in combination with high fluid production of the drain.

[d]Pneumonia was defined as: isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph.

[e]Cardiac complications included arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (two or three of the following: previous myocardial infarction, electrocardiographic changes suggesting myocardial infarction, or enzyme changes suggesting myocardial infarction), cardiac decompensation and left ventricular failure (marked pulmonary edema on a chest radiograph).

[f]Thrombosis was defined as the physical presentation of an acute deep venous thrombosis, confirmed by radiological exam or a pulmonary embolism, confirmed by spiral computed tomography.

[g]Reasons for readmission: unable to maintain oral intake, pneumonia, wound infection.

resected and an esophagostomy in the neck was created together with a feeding jejunostomy. In all other patients, leakage was managed conservatively by opening of the neck wound, antibiotics or percutaneous drainage of a mediastinal or pleural abscess/empyema.

3.3 | Secondary outcomes

Dysphagia within 1 year postoperatively was reported by 11 patients (25%) in the ETE group and 10 patients (20%) in the SMA group ($p = .628$). Most of these patients required dilatation for a benign anastomotic stricture as diagnosed on endoscopy. The median (range) number of dilatations within 1 year after surgery was 6 (1–11) in the ETE group and 3 (1–9) in the SMA group ($p = .628$).

Median (range) stay at the Intensive Care Unit was 3 (1–20) days for patients in the ETE group compared to 3 days (1–11 days) for patients in the SMA group. Median (range) hospital stay was 17 (10–95) days for patients in the ETE group compared to 15 days (5–78 days) for patients in the SMA group ($p = .261$). In-hospital mortality for the ETE group was 0% versus 4% in the SMA group ($p = .175$). One patient from the SMA group died within 30 days after the operation due to postoperative complications (2%). Ninety-day mortality was 0% in the ETE group versus 8% in the SMA group ($p = .118$). The incidence of other postoperative complications was not significantly different between the groups (Table 3).

4 | DISCUSSION

This study shows no statistically significant difference in anastomotic leak rate between a cervical ETE and SMA after esophagectomy with gastric tube reconstruction. The leak rate in this study of 20%–24% is high, but comparable to a previous study from our group.[19] The present study could not confirm the hypothesis that SMA reduces the leak rate as reported by other.[14,20] Before start of the study the experience of the surgical team with SMA was limited. A senior surgeon from another surgical unit (Leuven, Belgium) who had a vast experience in SMA technique taught the study coordinator (BPLW) the details of the procedure. During the study period, all anastomoses were created or supervised by a staff surgeon. Despite this, the learning curve for SMA may not have been passed yet and minor but crucial details in the construction of SMA may have been missed. However, the leak rate did not change during the study period. One could argue though, that a longer pretrial learning period should have been introduced to optimize the surgical technique before the start of the trial. As a recently published retrospective multicenter study shows that incidence of leakage went from 18.8% to 4.5% ($p < .001$) after 119 cases, a plateau level needs to be reached.[21]

Other studies using the SMA technique show lower leak rates (between 4% and 16%).[22–25] The difference with the present study could be explained by the diligent way we scored the postoperative complications and the prospective study design. Also, the term "semi-mechanical anastomosis" includes many different techniques that

have similarities (usually side to side) but also differ in details (single vs. double layer of sutures) between the studies that describe this technique. Hence, a comparison of the leak rate in our study with other studies is difficult. The leak rate of 20% in the ETE group is within the range reported in the literature.

This is not the first trial comparing a hand-sewn anastomosis with a (semi-)mechanical anastomosis. Again, the interpretation and clinical applicability of these studies and meta-analyses is difficult due to the different techniques used, varying definitions of leaks and strictures and different periods of follow-up. Previous studies have compared a hand-sewn end-to-side anastomosis with a circular stapled[26,27] or linear stapled anastomosis.[14,20,22–25,28,29] In 2005, Ercan et al.[23] published a retrospective cohort study of 274 patients and showed a benefit in postoperative morbidity for the SMA (modified Collard technique) anastomosis compared to the hand-sewn technique. Other studies reported a low leak rate of a V-shaped SMA (modified Collard, Collard, Orringer, linear stapled) (5%), and described it as a major refinement of the surgical technique.[14,20,22,25] Meta-analyses,[26,28,29] however, showed no statistically significant difference in anastomotic leakage or 3-month mortality between several techniques (circular stapled, linear stapled or hand-sewn). A systematic review, published in 2010 showed a lower stricture rate in the hand-sewn group, but also concluded that there is insufficient evidence to recommend one anastomotic technique over the other.[24] Another review showed an increased rate of postoperative anastomotic stricture, but shorter operating time for the stapled technique.[30]

Dysphagia, often defined as a need for dilatation, is reported between 4% and 63% for patients using the SMA technique and 16%–88% in patients with a hand-sewn anastomosis at 1 year.[24,31–33] The lower limit of the published percentages corresponds to studies with a short follow-up (2–3 months postoperatively). The upper margin of patients with dysphagia is derived from studies with follow-up until 12 months postoperatively and therefore is comparable to the present study. The theoretical concept of SMA is to create a wide, triangular V-shaped connection between the gastric tube and the esophagus and this might translate in reduced stricture of the anastomosis. The difference between the groups was not statistically significant however, which may be due to the premature termination of the study and thus the smaller sample size than anticipated. However, the number of dilatations needed was less in the SMA group.

The major limitation of the present study is that it was decided to stop it prematurely because of slow accrual. Hence, the anticipated number of patients to be enrolled was not met and the study is underpowered to show a statistically significant difference (if any) in leak rate. The reasons for the slow accrual were changes in regional organization and as a result referral of esophageal cancer patients. This resulted in a shift towards more complex patients that were not eligible for participation in the study. In 2013, Wang et al published a randomized controlled trial in which the SMA technique was compared to a hand-sewn and circular stapled anastomosis. In this trial, the primary endpoint was stenosis, but leakage was also not significantly different in the compared groups (0% vs 5.8% vs 2.1%).[18] Hence, the Data Safety Monitoring Board advised the steering committee of the study to end the study prematurely.

Although there was no significant difference in postoperative morbidity or mortality between the groups, the present study reports high complication rates after esophagectomy with gastric tube reconstruction. The prospective design of the study warrants detailed and timely reporting of all adverse events according to good clinical practice guidelines. Hence, the data reflect real practice and are in line with our nationwide prospective Dutch Upper GI Cancer Audit (DUCA)[34] and ECCG data.[35]

With an absolute difference of 4% and a 95% confidence interval of −13% to 21% for anastomotic leakage, absolute differences larger than 21% in favor of the SMA and of 13% in favor of ETE are unlikely. This study was underpowered to show significantly smaller differences in leak rates and it should be concluded that superiority or inferiority of any technique cannot be proven. A futility analysis can be done to calculate the chance for the trial to be successful if one would proceed with the study based on the numbers from an interim analysis. However, given the fact that the decision was taken to stop the trial due to slow accrual, a futility analysis is not useful for better interpretation of the data.

It is unlikely that a larger study will be initiated. At least in the Netherlands, most centers are moving towards an intrathoracic anastomosis (Ivor Lewis esophagectomy) instead of the three stage McKeown with cervical anastomosis. A recently started Dutch RCT will answer the question whether leak rate, stenosis and quality of life are better in patients with an intrathoracic anastomosis compared to those with a cervical anastomosis (ICAN study, trial register NTR4333).

In conclusion, statistically, we could not show a difference in anastomotic leak rate between a hand-sewn end-to-end and a semi-mechanical cervical esophagogastrostomy, nor could we rule out differences that are clinically relevant due to premature ending of the study.

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DATA AVAILABILITY STATEMENT

Data available on request.

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