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Intrathoracic vs Cervical Anastomosis After Totally or Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer
A Randomized Clinical Trial

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BACKGROUND Transthoracic minimally invasive esophagectomy (MIE) is increasingly performed as part of curative multimodality treatment. There appears to be no robust evidence on the preferred location of the anastomosis after transthoracic MIE.

OBJECTIVE To compare an intrathoracic with a cervical anastomosis in a randomized clinical trial.

DESIGN, SETTING, AND PARTICIPANTS This open, multicenter randomized clinical superiority trial was performed at 9 Dutch high-volume hospitals. Patients with midesophageal to distal esophageal or gastroesophageal junction cancer planned for curative resection were included. Data collection occurred from April 2016 through February 2020.

INTERVENTION Patients were randomly assigned (1:1) to transthoracic MIE with intrathoracic or cervical anastomosis.

MAIN OUTCOMES AND MEASURES The primary end point was anastomotic leakage requiring endoscopic, radiologic, or surgical intervention. Secondary outcomes were overall anastomotic leak rate, other postoperative complications, length of stay, mortality, and quality of life.

RESULTS Two hundred sixty-two patients were randomized, and 245 were eligible for analysis. Anastomotic leakage necessitating reintervention occurred in 15 of 122 patients with intrathoracic anastomosis (12.3%) and in 39 of 123 patients with cervical anastomosis (31.7%; risk difference, −19.4% [95% CI, −29.5% to −9.3%]). Overall anastomotic leak rate was 12.3% in the intrathoracic anastomosis group and 34.1% in the cervical anastomosis group (risk difference, −21.9% [95% CI, −32.1% to −11.6%]). Intensive care unit length of stay, mortality rates, and overall quality of life were comparable between groups, but intrathoracic anastomosis was associated with fewer severe complications (risk difference, −11.3% [−20.4% to −2.2%]), lower incidence of recurrent laryngeal nerve palsy (risk difference, −7.3% [95% CI, −12.1% to −2.5%]), and better quality of life in 3 subdomains (mean differences: dysphagia, −12.2 [95% CI, −19.6 to −4.7]; problems of choking when swallowing, −10.3 [95% CI, −16.4 to 4.2]; trouble with talking, −15.3 [95% CI, −22.9 to −7.7]).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, intrathoracic anastomosis resulted in better outcome for patients treated with transthoracic MIE for midesophageal to distal esophageal or gastroesophageal junction cancer.

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In the Western world, the incidence of esophageal cancer is increasing; it is the sixth cause of cancer-associated death.[1] Transthoracic esophagectomy is considered the cornerstone of curative treatment by many surgeons because it allows for adequate thoracic lymph node dissection. Transthoracic esophagectomy is most often performed in combination with neoadjuvant chemoradiotherapy or perioperative chemotherapy.[2,3] Transthoracic esophagectomy can be performed with either intrathoracic[4] or cervical[5] anastomosis. In open esophagectomy, intrathoracic anastomosis is associated with a clinically relevant lower anastomotic leak rate, although the evidence is of limited quality.[6] However, this difference in anastomotic leak rate may be important, because anastomotic leakage is a severe complication associated with considerable morbidity, decreased quality of life, a mortality rate of 2% to 12%, and decreased long-term survival.[6-9]

In the last decade, minimally invasive esophagectomy (MIE) has been shown to be superior compared with open esophagectomy regarding postoperative outcomes, without compromising oncologic safety.[10-12] Although not all surgeons are convinced of the benefits of MIE (eg, MIE has also been associated with increased complication rates in registries), it has led to many surgeons implementing transthoracic MIE with cervical anastomosis, because minimally invasive creation of an intrathoracic anastomosis is considered more challenging.[13,14] To our knowledge, no randomized clinical trial has compared the outcome of intrathoracic anastomosis vs cervical anastomosis after transthoracic MIE. Although some nonrandomized studies have shown lower anastomotic leak rates after intrathoracic anastomosis, other studies failed to show a difference.[15-18] However, these studies were of limited quality and likely to be flawed by confounding by indication. As a consequence, transthoracic MIE with intrathoracic anastomosis and cervical anastomosis are equally favored. The aim of this study was to compare transthoracic MIE with intrathoracic anastomosis with transthoracic MIE with cervical anastomosis, in terms of anastomotic leakage necessitating reintervention and other postoperative morbidity and mortality outcomes in patients with potentially curable esophageal or gastroesophageal junction cancer.

Key Points

Question Is an intrathoracic or cervical anastomosis the preferable location of the anastomosis after a transthoracic, minimally invasive esophagectomy, in terms of anastomotic leakage requiring reintervention?

Findings In this randomized clinical trial of 245 patients, anastomotic leakage necessitating reintervention occurred in 15 of 122 patients (12.3%) with intrathoracic anastomosis and 39 of 123 patients (31.7%) with cervical anastomosis.

Meaning In this study, intrathoracic anastomosis resulted in better outcome for patients treated with transthoracic minimally invasive esophagectomy for midesophageal to distal esophageal or gastroesophageal junction cancer.

Methods

Trial Design

This open randomized clinical superiority trial was performed in 9 high-volume hospitals in the Netherlands, including 5 university medical centers and 4 teaching hospitals. Dutch centers that had performed more than 50 total cases of transthoracic MIE with intrathoracic anastomosis, more than 50 total cases of transthoracic MIE with cervical anastomosis, and more than 30 cases of transthoracic MIE per year were invited to participate. Prior to participation, operative videos and outcomes of the centers from the last 2 years were reviewed in a study group meeting, in which expert consensus was achieved on whether centers were suitable for participation. The study protocol was approved by the institutional review board of the Radboud University Medical Center and all participating centers. All patients provided written informed consent. The ICAN trial is registered in the Dutch trial register (NL4183 [NTR4333]), and the protocol has been published previously.[19]

Participants

Adult patients with histologically proven primary esophageal adenocarcinoma or squamous cell carcinoma were screened for eligibility. Patients were eligible for participation in the study if the tumor was resectable (cT1b-4a, N0-3, and M0) and located in the midesophagus (from the level of the carina to the distal esophagus) or distal esophagus or at the level of the gastroesophageal junction (ie, Siewert levels I to II).[20] Patients with a second, prognosis-determining malignant condition and patients who had undergone previous major gastric or major thoracic surgery were excluded. All patients were screened for malnutrition by dieticians and received preoperative supplemental enteral nutrition, if necessary, according to local protocols.

Interventions

According to national guidelines, patients received neoadjuvant chemoradiotherapy[3] or perioperative chemotherapy,[2] unless this was contraindicated. All patients were subsequently scheduled to undergo either a transthoracic MIE with intrathoracic anastomosis or a transthoracic MIE with cervical anastomosis, by either a hybrid minimally invasive approach (ie, laparoscopy and thoracotomy) or totally minimally invasive approach (ie, laparoscopy and thoracoscopy). Originally, this trial was designed to compare intrathoracic anastomosis with cervical anastomosis for thoracolaparoscopic MIE. Since the results of the French MIRO trial[11] were presented during the trial, the trial steering committee recognized the interest to additionally include patients undergoing transthoracic hybrid MIE, because this might increase generalizability of the study. Therefore, we allowed 1 high-volume hospital that only performed transthoracic hybrid MIE resections to include patients, on the conditions that (1) patients undergoing transthoracic hybrid MIE would not be counted in the sample size calculation and (2) results of patients with transthoracic hybrid MIE and transthoracic total MIE were also reported separately, in addition to a pooled analysis. Transthoracic total MIE

consisted of a laparoscopic and thoracoscopic approach, and transthoracic hybrid MIE consisted of a laparoscopic and open thoracic approach. A 2-field lymph node dissection was performed in all included patients, irrespective of the location of the anastomosis. Anastomotic techniques were chosen as preferred by the operating surgeon to ensure that surgeons used their most-used technique and had extensive experience with the performed type of anastomosis. In all patients, an omental wrap around the anastomosis was performed. In the case of a cervical anastomosis, a neck drain was routinely left in 6 of 9 hospitals. To evaluate surgical quality of the trial, the operation videos of 1 in 5 randomized patients per center were assessed (eMethods 1 in the Supplement). Pyloric drainage procedures were not routinely performed, and feeding jejunostomy tubes were routinely placed in 7 of 9 participating hospitals.

Sample Size

The sample size calculation was based on an incidence of anastomotic leakage requiring endoscopic, radiologic, or surgical reintervention of 10% after transthoracic total MIE with intrathoracic anastomosis and 25% after transthoracic total MIE with cervical anastomosis (based on literature[6,21,22]). A sample size of 200 (100 per group) was needed to achieve 80% power to detect a clinically relevant difference of 15% between the intrathoracic anastomosis and cervical anastomosis groups at 5% (2-sided) significance level.

Randomization

Patients were enrolled by their treating surgeons or research staff and randomly assigned at the outpatient clinic 1 to 6 weeks before surgery, in a 1:1 ratio either to transthoracic MIE with intrathoracic anastomosis or transthoracic MIE with cervical anastomosis. Patients were randomized by an online randomization service (http://www.castoredc.com), which was used by the coordinating investigators and/or principal investigator (F.v.W., M.H.P.V., and C.R.) to assign the patients. This online system ensured allocation concealment and stratified patients by treatment site using random, permuted blocks of 2, 4, 6, or 8.[23] Allocation and block size were concealed to all investigators.

Outcomes

The primary end point was anastomotic leakage within 30 days after esophagectomy for which endoscopic, radiologic, or surgical reintervention was needed. This corresponds to the definition of the Esophagectomy Complications Consensus Group of anastomotic leakage types 2 and 3.[24] Anastomotic leakage was defined as clinical suspicion confirmed (1) by a computed tomography scan with intravenous and oral contrast, (2) by an endoscopy, (3) by drainage of ingested materials or saliva into the chest tube or at the cervical wound, (4) during reintervention, or (5) at autopsy. Diagnostic investigations were performed on indication. Predefined secondary end points included the incidence of postoperative complications, recurrent laryngeal nerve palsy (defined as vocal cord palsy on laryngoscopy), tumor-free resection margin rate, number of examined lymph nodes, hospital and intensive care unit length of stay, intensive care unit readmission rate, and mortality (in-hospital, 30-day, and 90-day). This predefined set of outcome parameters and their definitions corresponds to the internationally defined standardized template for data collection after esophagectomy.[24] Quality of life was measured using the cancer-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire[25] (EORTC QLQ) C30 and the esophagogastric cancer-specific EORTC QLQ-OG25 at baseline (1 to 4 weeks prior to esophagectomy) and 6 weeks postoperatively via mail, email, or telephone. Predetermined end points were overall quality-of-life scores and the specific subdomains.[26,27] In keeping with previously published literature, a difference in mean scores of more than 10 points was considered clinically relevant.[28-30]

Data Collection, Storage, Validation, and Sharing

Data collection occurred from April 2016 through February 2020. Data were recorded on a daily basis in a secure electronic case report form with online logbook functionalities.[23] Data validation was performed by checking the case report forms with the medical records of all patients in the trial on the primary outcome and main secondary outcome parameters by the study coordinator (M.H.P.V.). Discrepancies were discussed by the data verification committee, including the coordinating investigator (M.H.P.V.), principal investigator (C.R.), and lead investigators (D.L.v.d.P., J.H., E.A.K., G.A.P.N., S.S.G., J.W.H., and J.J.B.v.L.). In addition, the data verification committee checked all records on the primary outcome parameter and associated grading (ie, Esophagectomy Complications Consensus Group grading and Clavien-Dindo classification) and reinterventions.

Statistical Analysis and Reporting

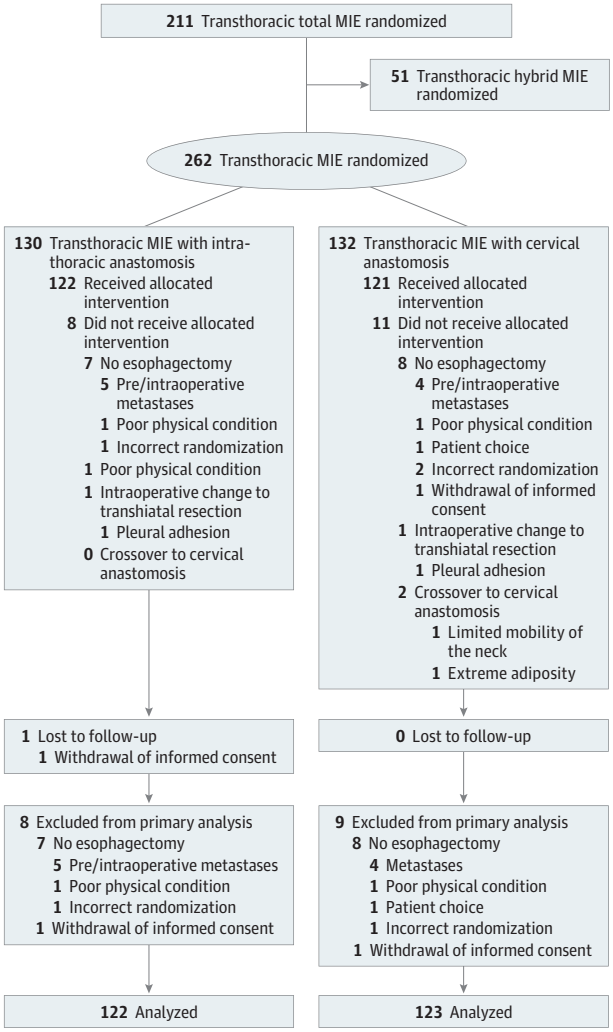
Statistical analysis was in line with the previously published trial protocol,[19] and an overview of the analysis and the syntax that was used are shown in eMethods 2 in the Supplement. Trial data was reported according to the CONSORT statement. Data analysis was completed with SPSS version 25 (IBM) and RStudio version 3.6.2 (RStudio).

Results

Patients and Surgical Procedures

Between April 2016 and October 2019, a total of 262 patients (median [interquartile range] age: those with intrathoracic anastomosis, 67 [5.1] years vs those with cervical anastomosis, 68 [9.2] years; male patients: those with intrathoracic anastomosis, 98 of 122 [80.3%] vs those with cervical anastomosis, 92 of 123 [74.8%]) were randomly assigned to transthoracic MIE with intrathoracic anastomosis (n = 130) or transthoracic MIE with cervical anastomosis (n = 132). Seventeen patients were excluded from analysis, mainly because they were found to have metastatic disease just before or during surgery, and 4 patients received a different procedure than allocated (**Figure**). The baseline characteristics of the participants are presented in **Table 1**. Using a structured analysis of the videos, no relevant differences in surgical quality were

Figure. CONSORT Flow Diagram



MIE indicates minimally invasive esophagectomy.

demonstrated between the groups (eResults in the Supplement).

Primary Outcome

Anastomotic leakage for which endoscopic, radiologic, or surgical reintervention was performed, occurred in 15 patients in the intrathoracic anastomosis group (12.3%) and 39 patients in the cervical anastomosis group (31.7%; risk difference, −19.4% [95% CI, −29.5% to −9.3%]) (**Table 2**), and details of reinterventions are shown in eTable 1 in the Supplement. Post hoc correction for center did not substantially change this result (estimated difference, −18.4% [95% CI, −28.6% to −8.2%]). Additional per-protocol analyses did not alter the results regarding the primary outcome (eTable 2 in the Supplement). The predefined subgroup analysis for anastomosis configuration showed no significant differences in the primary end point. Analysis of both total MIEs and hybrid MIEs showed comparable results regarding the primary outcome (eTables 3 and 4 in the Supplement).

Table 1. Baseline Characteristics

Characteristics	Transthoracic minimally invasive esophagectomy, No. (%)	
	With intrathoracic anastomosis (n = 122)	With cervical anastomosis (n = 123)
Age, median (interquartile range), y	67 (5.1)	68 (9.2)
Male	98 (80.3)	92 (74.8)
Female	24 (19.7)	31 (25.2)
American Society of Anesthesiologists classification		
1	12 (10.2)	14 (11.7)
2	80 (67.8)	83 (69.2)
3	25 (21.2)	23 (19.2)
4	1 (0.8)	0 (0.0)
Charlson Comorbidity Index score		
0	81 (66.4)	80 (65.0)
1	22 (18.0)	21 (17.1)
2	9 (7.4)	10 (8.1)
3	7 (5.7)	7 (5.7)
4	2 (1.6)	2 (1.6)
5	0	2 (1.6)
6	1 (0.8)	1 (0.8)
7	0	0
Tumor type		
Adenocarcinoma	105 (86.1)	114 (92.3)
Squamous cell carcinoma	12 (9.8)	7 (5.7)
Other	5 (4.1)	2 (1.6)
Tumor location		
Intrathoracic midesophagus	6 (4.9)	3 (2.4)
Intrathoracic distal esophagus	105 (86.1)	106 (86.2)
Gastroesophageal junction	11 (9.0)	14 (11.4)
cT stage		
T1	2 (1.6)	4 (3.2)
T2	23 (18.9)	19 (15.4)
T3	68 (55.7)	65 (52.8)
T4	1 (0.8)	2 (1.6)
Tx	28 (23.0)	33 (26.8)
cN stage		
N0	53 (43.4)	60 (48.8)
N1	45 (36.9)	39 (31.7)
N2	16 (13.1)	19 (15.4)
N3	3 (2.5)	1 (0.8)
N+	3 (2.5)	3 (2.4)
Nx	2 (1.6)	1 (0.8)
Neoadjuvant treatment		
Yes		
Chemoradiotherapy	118 (96.7)	117 (95.1)
Chemotherapy	2 (1.6)	3 (2.4)
None	2 (1.6)	3 (2.4)
Operation type		
Total minimally invasive esophagectomy	97 (79.5)	100 (81.3)
Hybrid minimally invasive esophagectomy	25 (20.5)	23 (18.7)
Configuration of anastomosis		
End to end	3 (2.5)	46 (37.4)
End to side	42 (34.4)	2 (1.6)
Side to side	77 (63.1)	75 (61.0)
Anastomosis technique		
Handsewn	4 (3.3)	108 (87.8)
Stapled	118 (96.7)	15 (12.2)

Secondary Outcome Parameters

Secondary outcome parameters for all patients are presented in Table 2. Overall anastomotic leak rate (ie, ECCG grades 1, 2, and 3) was 12.3% after transthoracic MIE with intrathoracic

Table 2. Primary and Secondary Outcome Parameters

Characteristic	Transthoracic minimally invasive esophagectomy, No. (%)		Difference in pooled mean scores (95% CI)	*P* value
	With intrathoracic anastomosis (n = 122)	With cervical anastomosis (n = 123)		
Anastomotic leakage				
Requiring reintervention	15 (12.3)	39 (31.7)	−19.4 (−29.5 to −9.3)	<.001
Total	15 (12.3)	42 (34.1)	−21.9 (−32.1 to −)	<.001
Gastric conduit				
Leakage	1 (0.8)	0	0.8 (−1.4 to 3.1)	.47
Necrosis	1 (0.8)	2 (1.6)	−0.8 (−3.6 to 1.9)	.57
Pulmonary complications				
Pneumonia	14 (11.5)	23 (18.4)	−7.2 (−16.1 to 1.7)	.11
Pneumothorax requiring drainage	3 (2.5)	7 (5.7)	−3.2 (−8.2 to 1.7)	.20
Pleural effusion requiring drainage	12 (9.8)	26 (21.1)	−11.3 (−20.2 to −2.4)	.01
Empyema requiring drainage	4 (3.3)	6 (4.9)	−1.6 (−6.5 to 3.3)	.53
Tracheobronchial defect	0	1 (0.8)	−0.8 (−3.0 to 1.4)	.47
Respiratory failure requiring reintubation	10 (8.2)	13 (10.6)	−2.4 (−9.7 to 4.9)	.52
Mediastinal fluid collection	1 (0.8)	6 (4.9)	−4.1 (−8.2 to 0.1)	.05
Cardiac complications				
Supraventricular arrhythmia	16 (13.1)	26 (21.1)	−8.0 (−17.4 to 1.4)	.09
Ventricular arrythmia	2 (1.6)	1 (0.8)	0.8 (−1.9 to 3.6)	.57
Cardiac decompensation	1 (0.8)	2 (1.6)	−0.8 (−3.6 to 1.9)	.57
Myocardial infarction	0	0	0.0 (−1.6 to 1.6)	1.0
Chyle leakage	9 (7.4)	11 (8.9)	−1.6 (−0.8 to 0.1)	.65
Recurrent laryngeal nerve palsy	0	9 (7.3)	−7.3 (−12.1 to −2.5)	.003
Severe complication with Clavien-Dindo level ≥3b	13 (10.7)	27 (22.0)	−11.3 (−20.4 to −2.2)	.02
Comprehensive complication index, mean (SD)	22.9 (21.6)	19.2 (23.0)	−3.8 (−9.4 to 1.8)	.19
Length of stay, median (IQR), d				
Hospital	10.0 (7)	11.5 (9)	0.19[a]	.003
Intensive care unit	2 (1)	2 (2)	0.10[a]	.12
Intensive care unit readmission	11 (9.0)	22 (17.9)	−8.9 (−17.3 to −0.4)	.04
Mortality				
In-hospital	3 (2.5)	1 (0.8)	1.6 (−1.5 to 4.8)	.31
30-d	3 (2.5)	1 (0.8)	1.6 (−2.2 to 5.5)	.31
90-d	4 (3.3)	2 (1.6)	1.7 (−2.2 to 5.5)	.40
Conversion				
To laparotomy	0	7 (5.7)	−5.7 (−10.0 to −1.3)	.01
To thoracotomy	3 (2.5)	2 (1.6)	0.8 (−2.7 to 4.4)	.64
Operating time, median (IQR), min	267 (100)	272 (90)	0.12[a]	.06
Blood loss, median (IQR), mL	100 (200)	100 (198)	0.07[a]	.31
Lymph nodes, median (IQR)				
Retrieved	22 (11)	22 (11)	0.04[a]	.55
Positive	0 (1.5)	0 (1)	0.03[a]	.62
R0 resection	121 (99.2)	121 (98.4)	0.8 (−1.9 to 3.6)	.57

Abbreviations: IQR, interquartile range; R0, radical.

[a] Effect size is given here as $r = Z/\sqrt{N}$, without 95% CIs.

anastomosis and 34.1% after transthoracic MIE with cervical anastomosis (risk difference, −21.9% [95% CI, −32.1% to −11.6%]). The incidence of recurrent laryngeal nerve palsy (risk difference, −7.3% [95% CI, −12.1% to −2.5%]) and severe complications (risk difference, −11.3% [−20.4% to −2.2%]) was lower and median hospital length of stay (median [interquartile range], 10.0 [7] days vs 11.5 [9] days; *P* = .003) was shorter in the intrathoracic group. Mortality rates were comparable between the groups.

In the subgroup of patients with anastomotic leakage, the severity of cervical vs intrathoracic anastomotic leakage was similar (**Table 3**). In addition to the predefined set of outcome parameters, 3 patients underwent a reoperation. Indications for reoperations were deviation of the trachea because of a bulky omentum (in a patient in the cervical group), herniation of lung through the ribs (in a patient in the intrathoracic group), and iatrogenic damage to the anastomosis by a nasogastric tube (in a patient randomized for cervical anastomosis who crossed over to intrathoracic anastomosis). Separate outcomes for hybrid MIE and total MIE are presented in eTables 3 and 4 in the Supplement.

Table 3. Detailed Outcomes of Patients With Anastomotic Leakage

Characteristic	Anastomotic leakage, No. (%)	
	After intrathoracic anastomosis (n = 15)	After cervical anastomosis (n = 42)
Anastomotic leakage by Esophagectomy Complications Consensus Group classification, grade		
I	0	3 (7.1)
II	11 (73.3)	35 (83.3)
III	4 (26.7)	4 (9.5)
Anastomotic leakage by Clavien-Dindo classification, grade		
I	0	5 (11.9)
II	0	8 (19.0)
IIIa	9 (60)	15 (35.7)
IIIb	0	4 (9.5)
IVa	4 (26.7)	10 (23.8)
IVb	1 (6.7)	0
V	1 (6.7)	0
Total number of reinterventions, No.		
Radiologic	8	6
Endoscopic	16	41
Reoperation	4	7
Hospital admission		
Hospital length of stay, median (IQR), d	30.5 (19.8)	19.0 (20.0)
Hospital readmission	3 (20.0)	11 (26.2)
Intensive care unit admission		
Length of stay, median (IQR), d	1.0 (5.0)	2.0 (4.8)
Readmission	4 (26.7)	15 (35.7)
Mortality		
In-hospital	1 (6.7)	1 (2.4)
30-d	1 (6.7)	1 (2.4)
90-d	1 (6.7)	2 (4.8)

Abbreviation: IQR, interquartile range.

Quality of Life

Six weeks after transthoracic MIE, patients with intrathoracic anastomosis reported fewer problems of dysphagia compared with patients with cervical anastomosis (mean difference, −12.2 [95% CI, −19.6 to −4.7]). In addition, patients with intrathoracic anastomosis experienced fewer problems of choking when swallowing (mean difference, −10.3 [95% CI, −16.4 to 4.2]) and trouble with talking (mean difference, −15.3 [95% CI, −22.9 to −7.7]). An overview of all quality-of-life domains is shown in **Table 4**.

Discussion

This randomized clinical trial showed that transthoracic MIE with intrathoracic anastomosis resulted in a lower anastomotic leak rate compared with transthoracic MIE with cervical anastomosis. In addition, an intrathoracic anastomosis was associated with a lower recurrent laryngeal nerve palsy rate, a lower rate of severe complications, shorter hospital length of stay, and a better quality of life at 6 weeks postoperatively regarding dysphagia, choking when swallowing, and trouble with talking. No differences were observed in intensive care unit length of stay and mortality rates.

Strengths

The major strength of our study is that it is a high-quality randomized clinical trial giving insight in the important question whether transthoracic MIE with intrathoracic or cervical anastomosis should be preferred. Stringent trial participation criteria and video and outcome assessment ensured that only surgical teams that were proficient in both techniques participated in this study. The use of a standardized outcome set for reporting complications,[24] real-time data collection, and an extensive data validation process contributed to ensuring reproducibility and robustness of data.

Limitations

Some limitations should also be discussed. First, patients and outcome assessors were not blinded, since this was considered not to be feasible at the time of design of the trial. Given the results of a more recent study, blinding of patients and outcome assessors might have been possible.[31] However, our primary outcome parameter definition enabled objective assessment, and this was verified in all patients by the data verification committee, making it less likely that blinding would have led to different results. Second, data on the number of patients screened were not reliably retrieved during the study, and so unknown selection bias cannot be ruled out. Third, although patients were randomized and stratification by treatment site was performed, we did not correct for confounders and correction for within-site correlation was performed only post hoc. Fourth, it may be argued that differences in intervention, such as various techniques to create intrathoracic or cervical anastomoses (eg, configuration, handsewn or stapled), influenced trial outcome. However, we did not find any substantial differences between different anastomotic techniques in a predefined subgroup analysis. The pragmatic trial design was chosen to ensure the trial would reflect nationwide practice, and therefore some heterogeneity of interventions was allowed. Fifth, although nearly all videos were retrieved for structured quality analysis, some video material was not available. However, we do believe surgical quality was adequate, since assessment showed good scores in both groups. In addition, the comparably good anastomotic scores make it less likely that bias has occurred, because surgeons were not using their preferred technique. Moreover, we applied strict qualitative and quantitative entry rules for centers that participated in the study. In fact, these strict rules for participation may have resulted in less generalizability of the trial results, because not all surgeons may have the same level of experience as the surgeons in this trial. We aim to investigate this in a future study. Finally, even though strict trial participation rules were used, we cannot rule out that the outcomes were affected by a learning curve. This may particularly be important for the intrathoracic group, since this was the newer intervention in the study, and it has been described that learning curve effects are important for this procedure.[32]

Table 4. Quality-of-Life Outcomes After Multiple Imputation at 6 Weeks After Esophagectomy[a]

Characteristic	Transthoracic minimally invasive esophagectomy, mean (SD)		Difference in pooled mean scores (95% CI)
	With intrathoracic anastomosis (n = 122)	With cervical anastomosis (n = 123)	
QLQ-C30			
Global health status	65.6 (18.6)	62.0 (20.6)	3.7 (−1.5 to 8.2)
Functional scales			
Physical	70.7 (20.3)	64.5 (23.7)	6.3 (0.4 to 12.2)
Role	55.6 (30.3)	51.1 (29.2)	4.5 (−3.4 to 12.4)
Emotional	82.5 (19.3)	81.2 (20.0)	1.3 (−3.8 to 6.4)
Cognitive	86.3 (18.8)	84.0 (22.0)	2.4 (−3.2 to 7.8)
Social	72.4 (26.6)	67.4 (28.0)	5.0 (−2.2 to 12.1)
Symptom scales			
Fatigue	43.9 (24.2)	47.6 (24.4)	−3.6 (−10.1 to 2.8)
Nausea and vomiting	21.4 (25.2)	21.8 (26.9)	−0.4 (−7.4 to 6.7)
Pain	22.6 (22.1)	23.4 (26.5)	−0.79 (−7.4 to 5.8)
Dyspnea	32.0 (27.9)	33.0 (30.0)	−1.03 (−8.7 to 6.7)
Insomnia	32.2 (28.7)	33.7 (30.4)	−1.5 (−9.4 to 6.5)
Appetite loss	42.4 (35.0)	41.0 (33.5)	−1.4 (−7.67 to 10.4)
Constipation	10.8 (20.5)	9.9 (20.5)	0.97 (−4.4 to 6.4)
Diarrhea	22.3 (27.1)	23.7 (29.5)	−1.4 (−9.3 to 6.4)
Financial difficulties	5.4 (15.3)	7.5 (15.8)	−2.1 (−6.2 to 1.9)
QLQ-C30 summary score	72.7 (14.8)	71.6 (15.8)	1.1 (−2.9 to 5.1)
QLQ-OG25			
Symptom scale			
Dysphagia	22.9 (24.5)	35.0 (30.9)	−12.2 (−19.6 to −4.7)
Eating	42.9 (28.4)	49.6 (29.2)	−6.7 (−14.5 to 1.0)
Reflux	13.8 (21.5)	14.4 (25.0)	−0.5 (−6.8 to 5.7)
Odynophagia	14.8 (19.9)	20.5 (25.3)	−5.8 (−12.2 to 0.7)
Pain and discomfort	13.1 (16.9)	16.2 (23.1)	−3.1 (−8.5 to 2.4)
Anxiety	31.0 (23.7)	36.1 (27.8)	−5.1 (−11.9 to 1.6)
Eating with others	14.8 (26.2)	20.1 (30.9)	−5.3 (−13.3 to 2.6)
Dry mouth	27.0 (30.0)	33.4 (33.6)	−6.3 (−14.7 to 2.0)
Trouble with taste	28.6 (34.2)	28.3 (33.6)	0.4 (−8.7 to 9.5)
Body image	14.5 (23.3)	23.0 (30.4)	−8.5 (−15.8 to −1.2)
Trouble swallowing saliva	10.9 (21.7)	19.1 (30.4)	−8.2 (−15.4 to −1.0)
Choking when swallowing	10.1 (17.7)	20.4 (25.1)	−10.3 (−16.4 to −4.2)
Trouble with coughing	48.7 (28.9)	58.0 (28.1)	−9.3 (−17.0 to −1.6)
Trouble with talking	14.1 (23.1)	29.4 (33.1)	−15.3 (−22.9 to −7.7)
Weight loss	28.7 (28.7)	24.1 (27.4)	4.6 (−2.8 to 12.0)
Hair loss	14.1 (23.0)	12.3 (20.9)	1.7 (−4.6 to 8.1)

Abbreviations: QLQ-C30, Quality of Life Questionnaire C30 (cancer-specific questionnaire); QLQ-OG25, Quality of Life Questionnaire OG25 (esophagogastric cancer–specific questionnaire).

[a] Outcomes are displayed as pooled mean scores with SD in parentheses.

However, even if a learning curve influenced the results of this trial, it would have resulted in an even larger difference in our primary outcome parameter. We are therefore confident that our findings are robust.[33-39]

Although the anastomotic leak rates in both groups are higher than reported in other studies,[10,40,41] we believe that the comparison between both techniques is valid, since similar rates have been reported in other randomized clinical trials and in the Dutch national registry.[3,17,18,42] We did not find any evidence to support hypotheses that the high leak rates could be explained by surgical technique (eResults in the Supplement) or case mix. The inclusive definition and careful data registration may have contributed to a comprehensive and complete reporting of anastomotic leak rate.

The lower anastomotic leak rate, shorter hospital length of stay, and lower incidence of recurrent laryngeal nerve palsy after intrathoracic anastomosis is in agreement with other nonrandomized studies.[17,18,22] For the hybrid MIE subgroup, we were unable to formally establish whether anastomotic leakage is lower after intrathoracic anastomosis, because we did not power for this analysis. In our opinion, however, it is likely that intrathoracic anastomosis has a similar beneficial effect, given the found effect size in this study and similar effects in other trials comparing intrathoracic vs cervical anastomosis in open esophagectomy.[6] The lower anastomotic leak rate in the intrathoracic group may be explained by relatively less ischemia at the tip of the shorter gastric tube in esophagectomy with intrathoracic anastomosis. In addition to the incidence of anastomotic leakage, it is also important to appreciate the severity of anastomotic leakage. Many surgeons believe that intrathoracic anastomotic leakage is more severe than cervical anastomotic leakage, although the evidence is scarce.

Following this train of thought, a higher incidence of anastomotic leakage after cervical anastomosis may not outweigh more severe sequelae of intrathoracic anastomotic leakage, although severe intrathoracic consequences of anastomotic leakage may develop in cervical anastomotic leakage, too.[43] In the subgroup of patients that experienced anastomotic leakage, no important differences were observed in patients with intrathoracic vs cervical anastomotic leakage in terms of reoperation rate, intensive care unit length of stay, and mortality rates, but hospital length of stay was longer for patients with an intrathoracic leak. Overall, however, patients had a significantly shorter length of stay after intrathoracic anastomosis, and it must be kept in mind that the present study was not powered to assess differences in outcome in the subgroup of patients with leakages.

The results of this trial support implementation of intrathoracic anastomosis in patients undergoing minimally invasive esophagectomy, although the choice for anastomotic location should be individualized for each patient and each surgeon. The technical challenge of creating a minimally invasive intrathoracic anastomosis, which is specific to transthoracic total MIE (as opposed to transthoracic hybrid MIE, in which the creation of the anastomosis is performed by means of open surgery), could hamper broad implementation. This is supported by a previous study from our group, which showed a significant learning curve and learning associated morbidity of transthoracic total MIE with intrathoracic anastomosis, even for surgeons who were experienced in MIE with cervical anastomosis.[39] These findings underline the importance of safe implementation, which may be facilitated by structured training programs, proctorship, feedback with validated competency assessment tools, and learning the procedure in a high-volume center.[44]

Conclusions

In conclusion, intrathoracic, as opposed to cervical, anastomosis resulted in better outcome for patients treated with transthoracic MIE for midesophageal to distal esophageal or gastroesophageal junction cancer. Future research will be needed to evaluate to what extent broad implementation of transthoracic MIE with intrathoracic anastomosis will lead to improved patient outcomes and assess long-term functional and oncological outcome between patients with intrathoracic and cervical anastomosis after transthoracic MIE.

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Invited Commentary

Does the Location Matter for the Anastomosis for Minimally Invasive Esophagectomy?

Robert E. Merritt, MD

The morbidity and mortality associated with anastomotic leakage after esophagectomy remain high, despite improvements in surgical techniques and patient selection.[1] The great debate regarding the optimal location (cervical vs intrathoracic) for the esophagogastric anastomosis for esophagectomy has persisted for decades. In 1989, a small prospective randomized clinical trial by Chasseray et al[2] demonstrated that cervical anastomosis had a higher anastomotic leak rate (26% vs 4%) than intrathoracic anastomosis after open esophagectomy. In addition, there was no evidence of increased mortality in the intrathoracic anastomosis group who experienced an anastomotic leak, which debunked the myth that intrathoracic anastomotic leaks resulted in a higher mortality rate.[2] In another small randomized clinical trial, Ribet et al[3] also demonstrated a higher anastomotic leak rate for the cervical anastomosis after esophagectomy. Despite the body of evidence demonstrating a higher anastomotic leak rate for cervical anastomosis, the technique has been used with almost equal frequency with intrathoracic anastomosis with minimally invasive esophagectomy (MIE).[4] Until recently, to my knowledge, there was no multicenter, randomized clinical trial to compare the outcomes of intrathoracic and cervical anastomoses after MIE.

Related article page 601

In this issue of *JAMA Surgery*, van Workum et al[5] reported a multicenter randomized clinical trial comparing intrathoracic and cervical anastomoses after totally or hybrid minimally invasive esophagectomy for esophageal cancer. A total of 262 patients were randomized to a cervical or an intrathoracic anastomosis. Anastomotic leak requiring intervention occurred in 12.3% of the patients with an intrathoracic anastomosis and 31.7% of patients with a cervical anastomosis. The overall anastomotic leak rate was 12.3% in the intrathoracic anastomosis group and 34.1% in the cervical anastomosis group.[5] The intensive care unit length of stay, mortality rates, and overall quality of life were similar between the groups. These results make a compelling argument for the exclusive use of the intrathoracic anastomosis for MIE.

There are some important considerations regarding the generalizability of the results of this well-designed randomized clinical trial.[5] Only high-volume hospitals performing greater than 50 cases of transthoracic MIE with either intrathoracic anastomosis or cervical anastomosis were allowed to enroll patients into the clinical trial. In addition, operative videos and esophagectomy outcomes from participating hospitals were reviewed, and an expert consensus group decided whether medical centers could participate. This rigorous process essentially ensured that only experienced esophageal surgeons from high-volume esophagectomy centers could enroll patients, which has been associated with improved surgical outcomes.[6] The technical difficulty of performing the intrathoracic anastomosis with MIE may be a barrier to the widespread conversion to the technique. The authors[5] plan to evaluate structured training programs and proctorships at high-volume esophagectomy centers for safe implementation of the transthoracic anastomosis with MIE, which could potentially mitigate the learning curve at lower-volume centers.

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