Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer

A Randomized Controlled Trial

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Background: The standard curative treatment for patients with esophageal cancer is perioperative chemotherapy or preoperative chemoradiotherapy followed by open transthoracic esophagectomy (OTE). Robot-assisted minimally invasive thoracolaparoscopic esophagectomy (RAMIE) may reduce complications.

Methods: A single-center randomized controlled trial was conducted, assigning 112 patients with resectable intrathoracic esophageal cancer to either RAMIE or OTE. The primary endpoint was the occurrence of overall surgery-related postoperative complications (modified Clavien-Dindo classification grade 2–5).

Results: Overall surgery-related postoperative complications occurred less frequently after RAMIE (59%) compared to OTE (80%) [risk ratio with RAMIE (RR) 0.74; 95% confidence interval (CI), 0.57–0.96; $P = 0.02$]. RAMIE resulted in less median blood loss (400 vs 568 mL, $P < 0.001$), a lower percentage of pulmonary complications (RR 0.54; 95% CI, 0.34–0.85; $P = 0.005$) and cardiac complications (RR 0.47; 95% CI, 0.27–0.83; $P = 0.006$) and lower mean postoperative pain (visual analog scale, 1.86 vs 2.62; $P < 0.001$) compared to OTE. Functional recovery at postoperative day 14 was better in the RAMIE group [RR 1.48 (95% CI, 1.03–2.13; $P = 0.038$)] with better quality of life score at discharge [mean difference quality of life score 13.4 (2.0–24.7, p = 0.02)] and 6 weeks postdischarge [mean difference 11.1 quality of life score (1.0–21.1; $P = 0.03$)]. Short- and long-term oncological outcomes were comparable at a medium follow-up of 40 months.

Conclusions: RAMIE resulted in a lower percentage of overall surgery-related and cardiopulmonary complications with lower postoperative pain, better short-term quality of life, and a better short-term postoperative functional recovery compared to OTE. Oncological outcomes were comparable and in concordance with the highest standards nowadays.

Keywords: esophageal cancer, esophageal carcinoma, minimally invasive, minimally invasive esophagectomy, robot assisted, robot-assisted minimally invasive thoracolaparoscopic esophagectomy

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Worldwide, the standard treatment for locally advanced esophageal cancer with curative intent is perioperative chemotherapy or preoperative chemoradiotherapy followed by open transthoracic esophagectomy (OTE) with gastric conduit reconstruction.[1–3]

Minimally invasive esophagectomy (MIE) was developed to improve the postoperative outcome by reducing the surgical trauma, with comparable short-term oncologic results.[4–6] MIE is, however, a highly complex procedure associated with a long learning curve.[2,6]

In 2003, robot-assisted minimally invasive thoracolaparoscopic esophagectomy (RAMIE) was developed to overcome the technical limitations of MIE.[6] Robotic surgery benefits from a stable 3-dimensional, magnified view and articulated instruments enabling precise dissection with 7 degrees of freedom of movement.[7,8]

Results from several cohort studies show that RAMIE is feasible and safe combining the benefits of the minimally invasive approach with good oncological outcome.[7–9] No randomized comparison between RAMIE and OTE has, however, been performed yet.[10,11]

In this randomized controlled trial, RAMIE was compared to OTE in a center that passed the learning curve with 10 years of RAMIE experience. The primary objective of this randomized controlled trial was to investigate differences between the 2 surgical approaches on postoperative complications. Secondary outcomes were functional recovery, postoperative pain, (short-term) quality of life (QoL), and oncologic outcomes.

METHODS

Study Design

This single-center randomized controlled trial was an investigator-initiated and investigator-driven randomized superiority controlled parallel-group, comparing RAMIE (Da Vinci robotic system Intuitive Surgical Inc, Sunnyvale, CA) with OTE.[11] This trial followed the Consolidated Standards of Reporting of Trials guidelines

and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.[12,14,15] The medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all participating patients.

Randomization and Quality Control

Patients were screened and informed at the outpatient department for inclusion in the ROBOT trial. Patients had at least 1 week time to consider informed consent for inclusion in the trial. After obtaining written informed consent, patients were randomized by the study coordinators distant and separate from the surgeons who informed the patients for inclusion in the trial. Allocation of concealment was performed using computer generated random numbers in sealed opaque envelopes corresponding to either RAMIE or OTE. Operator blinding for the procedure was not possible. All surgical procedures were performed by the same experienced surgeons in the UMC Utrecht (J.R. and R.H.) who performed at least 50 RAMIE and 50 OTE procedures each. All outcomes were recorded daily and prospectively by the trail coordinators (P.S. and S.H.). Outcomes were discussed in a weekly multidisciplinary meeting, where the participants were unaware of treatment allocation.

Patients

The inclusion and exclusion criteria diagnostic workup, neoadjuvant treatment, pathologic examination, and postoperative management were described previously and are shown in supplementary methods S1, http://links.lww.com/SLA/B505.[7–11,13–20]

For the open 3-stage transthoracic esophagectomy, the patient is placed in a left lateral decubitus position and the procedure commences with a right posterolateral thoracotomy. After incision and desufflation of the right lung the pulmonary ligament is incised followed by identification of the azygos vein. The azygos vein is clipped and ligated at the level of the azygos arch. The thoracic duct is identified, clipped, and ligated. The esophagus is resected en bloc with the surrounding mediastinal lymph nodes. The resected specimen will contain right-sided paratracheal (lymph node station 2R), tracheobronchial (lymph node station 4), aortopulmonary window (station 5), carinal (station 7), and periesophageal (station 8) lymph nodes.[18] The patient is turned to a supine position for the abdominal phase via supraumbilical laparotomy. The stomach is mobilized with special care for the gastroepiploic and short gastric vessels. The left gastric artery is identified, clipped, and ligated. Lymph node dissection is performed around the celiac trunk and the lesser omentum. A linear stapler (GIATM 80, 3×8 mm; Covidien, Mansfield, MA) is used to create a gastric conduit 4 cm wide, which is routinely oversewn. The gastric conduit is pulled up through the mediastinum along the original anatomic tract of the esophagus with the aid of a plastic tube (laparoscopic camera bag). A cervical handsewn end-to-side anastomosis is created between the gastric tube and the cervical esophagus using a 3/0 polydioxanone single-layer running suture. A feeding jejunostomy is placed in the second loop after the ligament of Treitz for postoperative feeding. The abdomen is closed in layers with polydioxanone (PDS) loop for the fascia and skin intracutaneously with monocryl. Patients are transferred to the intensive care unit (ICU) after the surgical procedure.

For the thoracic phase of RAMIE, the patient is positioned in the left lateral decubitus position, tilted 45° toward the prone position. The robotic system (daVinci Si system, Intuitive Surgical Inc, Sunnyvale, CA) is brought into the field at the dorsocranial side of the patient. Three ports are placed for the robotic system as well as 2 thoracoscopic ports for the assisting surgeon (Fig. 1A). After incision and installation of the operation robot and selective desufflation of the right lung, the pulmonary ligament is divided. Hereafter, the parietal pleura is dissected at the anterior side of the esophagus from the diaphragm up to the azygos arch. The azygos vein is ligated with Hem-o-lok (Teleflex Medical, Weck Drive, NC) and divided.[22] Dissection of the parietal pleura is continued above the azygos arch to establish dissection of the right paratracheal lymph nodes. At the posterior side of the esophagus, the parietal pleura is dissected cranially to caudally along the azygos vein, including the thoracic duct. The thoracic duct is clipped with a 10-mm endoscopic clipping device (EndoclipTM II; Covidien) to prevent chylous leakage. To facilitate esophageal mobilization a Penrose drain is placed around the esophagus to manipulate the esophagus for further mobilization. The esophagus is resected en bloc with the surrounding mediastinal lymph nodes. The resection specimen will contain the same lymph nodes as described for the open procedure.

For the abdominal phase, the patient is placed in supine position. Figure 1B shows the position of the laparoscopic trocars. The lesser omentum is opened and transected closely to the liver, until the left crus of the diaphragm is reached. Hereafter, the greater gastric curvature is dissected using a harmonic ace. An abdominal lymphadenectomy is performed including lymph nodes surrounding the celiac trunk, along the left gastric and splenic artery and the lesser omental lymph nodes. The left gastric artery and vein are ligated with Hem-o-lok (Teleflex Medical) and transected at their origin.

A nasogastric tube and bilateral chest tubes were routinely placed.[7–11] No postoperative swallow tests were performed.[22] In the absence of clinical signs of anastomotic dehiscence, patients started with sips of water at day 5 and the oral intake was gradually increased to solid food. Enhanced recovery after surgery (ERAS) guidelines were not used in the postoperative protocol.

End Points and Follow-up

The primary endpoint of this study was the percentage of overall surgery-related postoperative complications modified Clavien-Dindo classification (MCDC) surgical complications grade $\geq$2.[11,23]

Secondary endpoints (MCDC grade $\geq$2) included pulmonary complications (pneumonia, pneumothorax, pulmonary embolus, acute respiratory distress syndrome), cardiac complications (atrial fibrillation, cardiac asthma, myocardial infarction), and postoperative bleeding.[11,23] Anastomotic leakage, mediastinitis, gastric conduit necrosis, chylothorax, and recurrent laryngeal nerve injury were graded according to definitions stated by the Esophagectomy Complications Consensus Group (ECCG).[24] In-hospital mortality and mortality within 30 and 60 days, length of ICU, and hospital stay (days) were recorded.

The operation time was defined as time from incision until closure (minutes) for both the thoracic phase and the abdominal phase of the procedure. Intraoperative complications and blood loss during operation (milliliters per phase) were recorded. In case of conversion, the reason for conversion was explained.

Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. Disease-free survival (DFS) was calculated from the date of surgery to recurrence or death related to disease and/or treatment or last date of follow-up.

Postoperative functional recovery was defined as: removal of thoracic tubes, no requirement of intravenous fluid resuscitation, tolerance for solid oral intake, the ability to mobilize independently, and adequate pain control with oral analgesics. A visual analog scale (1–10 scale) for pain was noted at the following times preoperatively and were measured each morning after clinical examination every day during the first 14 days after surgery.

Preoperatively, at discharge, and during postoperative outpatient department visits, QoL questionnaires (Short Form-36, EORTC Quality-of-life Questionnaire Core 30, EORTC OES18, and EQ-5D)

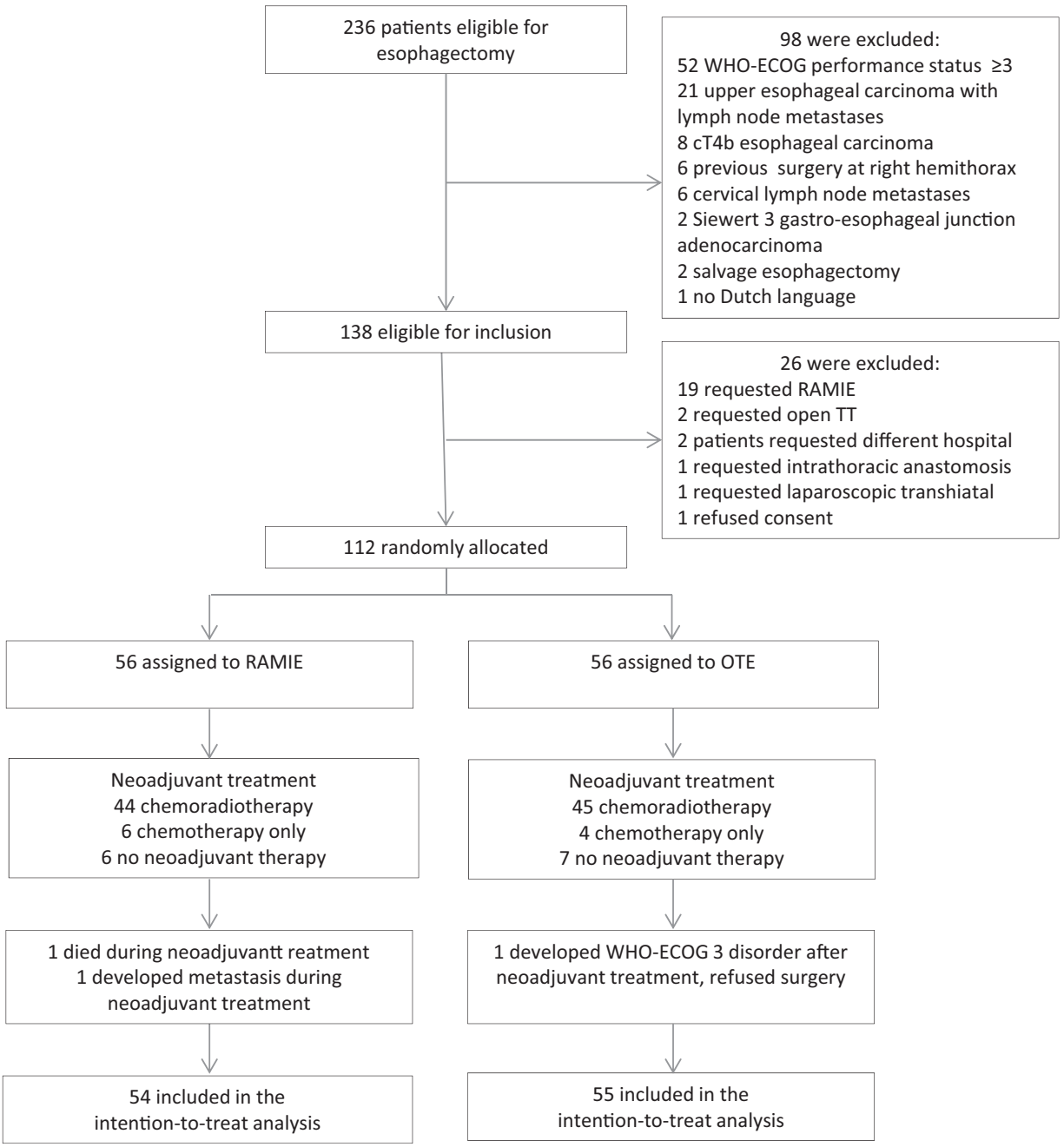


FIGURE 1. Trial Enrollment, Randomization and Follow-up.

were completed until 5 years after surgery. The results of Quality-of-life Questionnaire Core 30 at discharge and 6 weeks postdischarge are presented in this article.[25] A difference of 10 points or higher between groups has been shown to be clinically relevant.[26] All other QoL scores will be reported when the long-term follow-up has been completed.

The response rate for preoperative and immediate postoperative QoL was in the beginning of the trial 33%. To improve this rate, the logistics of collecting the patient data were changed after 36 patients, which improved response rate to 71%.

Sample Size and Statistical Analysis

In a prospective analysis of our own series, it was calculated that 102 patients (51 in each arm) with resectable esophageal cancer would be required to detect a 22% reduction in the absolute risk of overall surgery-related complications based on a 2-sided significance level (alpha) of 0.05 and a power of 0.80.[11] An estimated compensation of 10% for drop out was included in the total number of patients, resulting in a total of 112 patients, 56 in each arm.[11]

All analyses were performed according to the intention-to-treat (ITT) principle. Results are presented as risk ratios (RRs) with

corresponding 95% confidence intervals (CIs). To evaluate significance of differences between groups, the χ^2 test was used as appropriate for categorical variables and the Student *T* test and nonparametric Mann-Whitney *U* test for continuous variables.

Differences over time in QoL and pain scores between and within treatment groups were assessed using linear mixed-effects models adjusted for the baseline value. Overall and progression-free survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. All reported *P* values were 2 sided. Significance level was set at 0.05.

RESULTS

Patients

Between January 2012 and August 2016, 236 patients with resectable intrathoracic esophageal cancer were screened of whom 138 patients were considered eligible for inclusion in the ROBOT trial (Fig. 1). Finally, 112 patients (allocation ratio 81%) were randomized to undergo either RAMIE or OTE. In the RAMIE group, 1 patient died and 1 patient developed metastases during neoadjuvant treatment. In the OTE group, 1 patient physically deteriorated to WHO-eastern cooperative oncology group (ECOG) 3 after neoadjuvant treatment and refused surgery. These patients were not included in the ITT analysis. In the RAMIE group, 1 patient had an esophageal perforation during neoadjuvant treatment and underwent emergency laparoscopic transhiatal esophagectomy. One crossover occurred: 1 patient assigned to the OTE group underwent RAMIE due to a WHO-ECOG score of 3 after neoadjuvant treatment. In the RAMIE group, 2 patients were found to have irresectable disease intraoperatively. In 1 patient tumor ingrowth to the aorta was found and in 1 patient liver metastases were discovered intraoperatively. All these patients were included in the ITT analysis. In total, 54 and 55 patients were analyzed in the RAMIE and OTE group (Fig. 1). Demographic and clinical characteristics were similar at baseline (Table 1 and Table S2, http://links.lww.com/SLA/B505).

TABLE 1. Baseline Characteristics (n = 109)

	RAMIE (n = 54)	OTE (n = 55)
Age, yr*	64 (±8.9)	65 (±8.2)
Sex [n (%)]		
M	46 (85)	42 (76)
F	8 (15)	13 (24)
BMI, kg/m²*,†	26.1 (±4.4)	25.5 (±4.7)
ASA score [n (%)]		
1	13 (24)	11 (20)
2	37 (69)	34 (62)
3	6 (11)	10 (18)
WHO-ECOG [n (%)]		
0	17 (32)	16 (29)
1	34 (63)	32 (59)
2	3 (6)	7 (13)
Type of carcinoma [n (%)]		
Adenocarcinoma	41 (76)	43 (78)
Squamous cell carcinoma	13 (24)	12 (23)
Location of tumor [n (%)]		
Upper third	1 (2)	0 (0)
Middle third	5 (9)	8 (15)
Lower third	26 (48)	29 (53)
Gastroesophageal junction	22 (41)	18 (33)
Neoadjuvant treatment [n (%)]		
Chemoradiotherapy	42 (79)	44 (80)
Chemotherapy	6 (11)	4 (7)
None	6 (11)	7 (13)
Tumor length, cm, range*	5.0 (±2.1)	4.4 (±1.8)
Comorbidity [n (%)]		
Yes	43 (80)	41 (75)
No	11 (20)	14 (26)
Clinical stadium [n (%)]		
cT1N0	4 (7)	4 (7)
cT1N1	1 (2)	2 (4)
cT2N0	5 (9)	3 (6)
cT2N1	4 (7)	4 (7)
cT2N2	1 (2)	0 (0)
cT2N3	1 (2)	0 (0)
cT3N0	6 (11)	12 (22)
cT3N1	12 (22)	21 (38)
cT3N2	13 (24)	6 (11)
cT3N3	6 (11)	2 (4)
cT4aN2	1 (2)	0 (0)
cT4aN3	0 (0)	1 (2)
Clinical stage [n (%)]		
IA	4 (7)	4 (7)
IIA	5 (9)	3 (6)
IIB	11 (20)	18 (33)
IIIA	13 (24)	21 (38)
IIIB	13 (24)	6 (11)
IIIC	8 (15)	3 (6)

*Plus-minus values are means ± SD.
†ASA indicates American Society of Anesthesiologists; BMI, body mass index.

Clinical End Points

The primary endpoint of the occurrence of overall surgery-related postoperative complications (MCDC grade ≥2) occurred in 32 of 54 patients after RAMIE (59%) and in 44 of 55 patients after OTE (80%) {RAMIE RR 0.74 [95% CI with RAMIE (CI), 0.57–0.96; $P = 0.02$]} (Table 2). Overall postoperative complications (MCDC grade ≥2) occurred in 34 of 54 (63%) patients after RAMIE and in 44 of 55 (80%) patients after OTE (RR, 0.79; 95% CI 0.62–1.00; $P = 0.049$).

Pulmonary complications occurred in 17 of 54 patients in the RAMIE group (32%) and in 32 of 55 patients in the OTE group (58%) [RR 0.54 (95% CI, 0.34–0.85; $P = 0.005$]. Cardiac complications were observed in 17 of 45 patients in the RAMIE group (22%) and in 26 of 55 patients in the OTE group (47%) [RR 0.47 (95% CI 0.27–0.83; $P = 0.006$)]. There were no statistically significant differences in all other complications and mortality. In the RAMIE group 2 patients died from mediastinitis after anastomotic leakage and in the OTE group 1 patient died in hospital due to a tracheoesophageal fistula. Median ICU stay was 1 day in both groups ($P = 0.45$) and median hospital stay was 14 days in the RAMIE group and 16 days in the OTE group ($P = 0.33$; Table 2).

Functional Recovery, Pain, and Short-term Quality of Life

Functional recovery at postoperative day 14 was significantly better in the RAMIE group (38/54 patients, 70%) compared to the OTE group (28/55 patients, 51%) [RR 1.48 (95% CI 1.03–2.13; $P = 0.04$)]. There were only 2 patients, 1 in each arm, who did never recover on the item tolerance for solid oral intake. The median day of functional recovery was 10 days in the RAMIE group and 13 days in the OTE group ($P = 0.14$).

Mean postoperative pain (visual analog scale) during the first 14 days was significantly lower after RAMIE compared to OTE (1.86 vs 2.62, $P < 0.001$, Fig. 2). Both at discharge and 6 weeks postdischarge, short-term QoL was higher after RAMIE compared to OTE [mean difference 13.4 (2.0–24.7, $P = 0.02$) and 11.1 (1.0–21.1; $P = 0.03$)]. Also physical functioning was higher

TABLE 2. Postoperative Statistics (n = 109)

	RAMIE (n = 54)	OTE (n = 55)	*P*
Primary endpoint [n (%)]			
Related complications (MCDC 2, 3, 4, and 5)*	32 (59)	44 (80)	0.02
No related complications (MCDC 0,1)	22 (41)	11 (20)	
Secondary endpoints [n (%)]			
Pulmonary complications	17 (32)	32 (58)	0.005
Pneumonia	15 (28)	30 (55)	0.005
Pneumothorax	0 (0)	3 (6)	0.24¶
Pulmonary embolism	3 (6)	1 (2)	0.36¶
ARDS	0 (0)	1 (0)	1.00¶
Cardiac complications	12 (22)	26 (47)	0.006
Atrial fibrillation	12 (22)	25 (46)	0.01
Cardiac asthma	1 (2)	1 (2)	1.00¶
Wound infections	2 (4)	8 (14)	0.09¶
Cervical	2 (4)	1 (2)	0.61¶
Thoracic	0 (0)	5 (9)	0.06¶
Abdominal	0 (0)	2 (4)	0.50¶
Anastomotic leakage†			0.57
Type I (conservative)	0 (0)	0 (0)	
Type II (nonsurgical intervention)	1 (2)	0 (0)	
Type III (surgical intervention)	12 (22)	11 (20)	
Mediastinitis	12 (22)	11 (20)	0.42
Thoracic empyema	2 (4)	3 (6)	1.00¶
Gastric conduit necrosis†			1.00¶
Type III (conduit necrosis extensive, treated with resection and diversion)	1 (2)	2 (4)	
Chylothorax†			0.69
Type I (dietary, low-fat elemental formula gavage)	9 (17)	6 (11)	
Type II (total parenteral nutrition)	6 (11)	5 (9)	
Type III (operative)	2 (4)	1 (2)	
Recurrent laryngeal nerve injury†			0.78
Type I (no therapy)	5 (9)	6 (11)	
Postoperative bleeding	2 (4)	2 (4)	1.00¶
Dehiscence of abdominal fascia	0 (0)	1 (2)	1.00¶
Readmission intensive care unit	10 (19)	7 (13)	0.41
Reoperations	13 (24)	18 (33)	0.32
In-hospital mortality	2 (4)	1 (2)	0.62¶
30-Day mortality	1 (2)	0 (0)	0.50¶
60-Day mortality	3 (6)	1 (2)	0.36¶
90-Day mortality	5 (9)	1 (2)	0.11¶
Hospital stay (days—IQ range)	14 (11–25)	16 (11–27)	0.33
Intensive care unit stay (days—IQ range)	1 (1–2)	1 (1–3)	0.45
Postoperative anastomotic dilatation	28 (52)	26 (47)	0.50
Functional recovery and quality of life			
Functional recovery within first 2 weeks [n (%)]	38 (70)	28 (51)	0.04
Day functional recovery (median—IQ range)	10 (9–13)	13 (9–34)	0.14
Hospital readmission within 30 days [n (%)]	6 (12)	4 (7)	0.52¶
Epidural insufficiency (first 4 days, additional PCA)	24 (44)	22 (41)	0.70
Additional PCA after removal of epidural [n (%)]	1 (2)	5 (9)	0.11¶
Quality of life (QLQ-C30)‡ [30,31]			
Health-related quality of life (discharge)§	57.9 (49.9–66.1)	44.6 (36.7–52.5)	0.02
Health-related quality of life (6 wk)§	68.7 (61.5–75.9)	57.6 (50.6–64.6)	0.03
Physical functioning (discharge)§	54.5 (45.8–63.3)	41.0 (32.4–49.6)	0.03
Physical functioning (6 wk)§	69.3 (61.6–76.9)	58.6 (51.1–66.0)	0.049

*Related complications are MCDC grade 2 complications and higher, consisting of pulmonary complications, cardiac complications, wound infections, mediastinitis, thoracic empyema, postoperative bleeding, and dehiscention of abdominal fascia[20] or type II and higher complications according to the international consensus on standardization of data collection for complications associated with esophagectomy for anastomotic leakage, chylothorax, recurrent laryngeal nerve injury.[21]

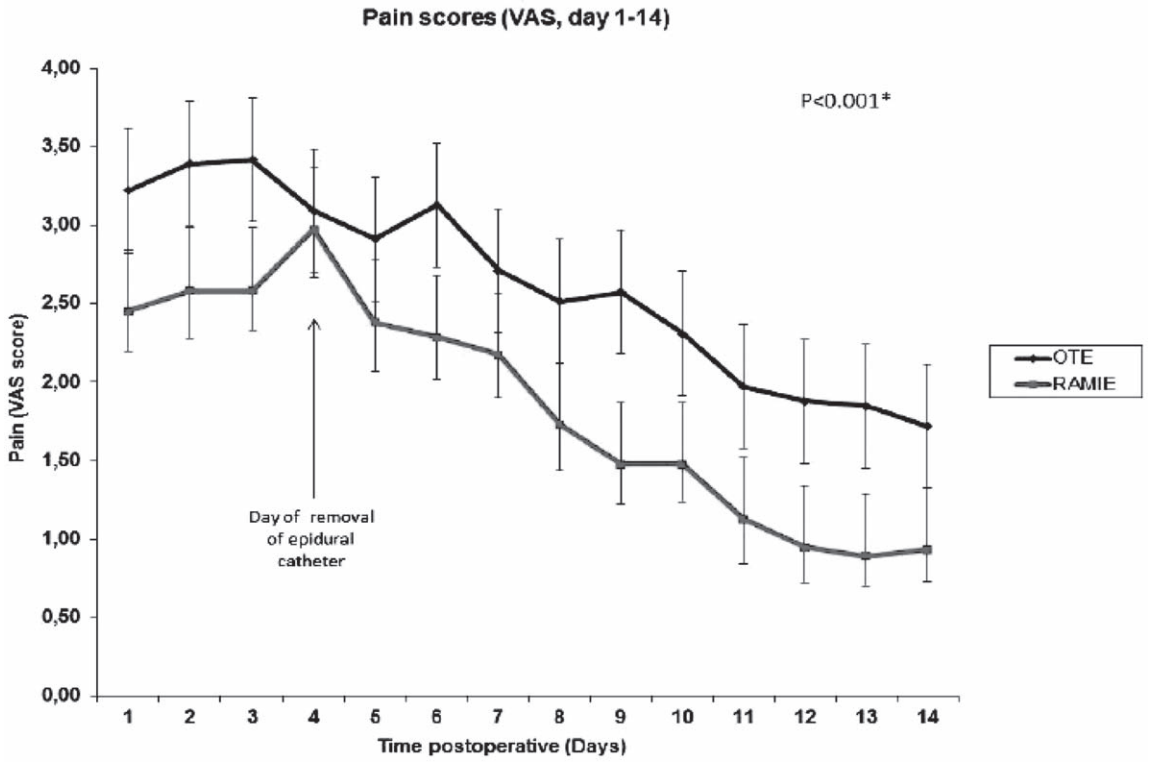
†Complications graded according to Low et al.[24]

‡In total, 64 patients (59%) were included in the quality-of-life analysis, 31 in the RAMIE group, and 33 in the OTE group.

§95% CI.

¶Fisher exact test.

IQ range indicates interquartile range; PCA, patient-controlled analgesia.



	VAS Day 1	VAS Day 2	VAS Day 3	VAS Day 4	VAS Day 5	VAS Day 6	VAS Day 7	VAS Day 8	VAS Day 9	VAS Day 10	VAS Day 11	VAS Day 12	VAS Day 13	VAS Day 14	Overall
RAMIE (n=54)	2.45	2.58	2.58	2.97	2.38	2.29	2.18	1.73	1.48	1.48	1.13	0.95	0.89	0.93	1.86
OTE (n=55)	3.22	3.39	3.41	3.09	2.91	3.13	2.71	2.51	2.58	2.31	1.97	1.88	1.85	1.72	2.62
SE#	0.40	0.40	0.40	0.40	0.40	0.40	0.39	0.39	0.39	0.39	0.39	0.40	0.40	0.40	0.13
P-value	0.05	0.04	0.04	0.76	0.18	0.03	0.15	0.05	0.01	0.03	0.03	0.02	0.02	0.05	<0.001

* During the first 14 days, overall postoperative pain (VAS) was significantly lower for RAMIE compared to OTE using a mixed effects linear model adjusted for baseline pain scores.

SE denotes standard error of the mean

FIGURE 2. Mean pains scores on a visual analoque scale (VAS) in the first 14 days postoperatively, corrected for preoperative pain scores. On the 4th day postoperatively, the epidural catheter was removed.

in the RAMIE group as compared OTE [13.5 (1.2–25.7, $P = 0.03$) and 10.7 (0.04–21.4; $P = 0.049$) at discharge and 6-week post-discharge].

Intraoperative Outcomes

For RAMIE the mean thoracic operating time was 170 versus 134 minutes for OTE ($P < 0.001$), and total operating time for RAMIE was 349 versus 296 minutes in the OTE group ($P < 0.001$; Table 3). For RAMIE the median thoracic blood loss was 120 versus 200 mL for OTE ($P < 0.001$) and total median blood loss was 400 mL after RAMIE compared to 569 mL after ($P < 0.001$). Conversions of RAMIE were observed in 3 of 54 patients (5%). In 1 RAMIE procedure, the thoracic phase was converted to a laparoscopic transhiatal esophagectomy due to pleural adhesions. In 2 patients the laparoscopic abdominal phase was converted to a laparotomy, due to intra-abdominal bleeding. All other intraoperative outcomes were comparable (Table 3).

Oncologic Outcomes

A radical resection (R0) was achieved in 50 of 54 patients after RAMIE (93%) and in 53 of 55 patients after OTE (96%, $P = 0.35$). The number of retrieved lymph nodes and all pathologic outcomes were comparable in both groups (Table 3 and Table S4, http://links.lww.com/SLA/B505).

All patients were included in the OS analysis. There were no statistically significant differences in OS (log rank test, $P = 0.427$) (Fig. 3A) at a median follow-up of 40 months. Median OS was not yet reached.

TABLE 3. Intraoperative and Pathological Statistics (n = 109)

	RAMIE (n = 54)	OTE (n = 55)	*P*
Operating time*			
Thoracic operating time, min	170 (±34.6)	135 (±23.3)	<0.001
Abdominal and cervical operating time, min	186 (±38.7)	161 (±30.1)	<0.001
Total operating time, min	349 (±56.9)	296 (±33.9)	<0.001
Blood loss			
Thoracic blood loss, mL—IQ range	120 (78–200)	200 (195–313)	<0.001
Total blood loss, mL—IQ range	400 (258–581)	568 (428–800)	<0.001
Conversion [n (%)]	3 (5)	NA	
Conversion thorax	1 (2)	NA	
Conversion abdomen	2 (4)	NA	
Intraoperative complications [n (%)]	7 (13)	9 (16)	0.62
Resection (n (%))			
Esophagectomy	52 (96)	55 (100)	0.24†
Irresectable disease	2 (4)	0 (0)	
Liver metastases	1 (2)	0 (0)	
Aortic ingrowth	1 (2)	0 (0)	
Type of reconstruction [n (%)]			0.22
Gastric conduit (Cervical, hand sewn, end-to-side)	52 (96)	54 (98)	
Colonic interposition (Cervical, hand sewn, end-to- end)	0 (0)	1 (2)	
Irresectable	2 (4)	0 (0)	
Additional resections [n (%)]‡	5 (9)	10 (18)	0.18
Radicality of surgery [n (%)]			0.35
R0	50 (93)	53 (96)	
R1	2 (4)	2 (4)	
Irresectable disease	2 (4)	0 (0)	
Lymph nodes number (number—IQ range)	27 (17–33)	25 (17–31)	0.41
Type of carcinoma [n (%)]			
Adenocarcinoma	41 (76)	43 (78)	0.78
Squamous cell carcinoma	13 (24)	12 (22)	
Pathological stadium [n (%)]			0.62
pT0N0	10 (19)	10 (18)	
pT0N1	6 (11)	3 (6)	
pT1aN0	1 (2)	0 (0)	
pT1aN1	1 (2)	1 (2)	
pT1bN0	1 (2)	2 (4)	
pT1bN1	3 (6)	1 (2)	
pT1bN2	0 (0)	1 (2)	
pT2N0	6 (11)	8 (15)	
pT2N1	4 (7)	2 (4)	
pT2N2	0 (0)	1 (2)	
pT2N3	1 (2)	0 (0)	
pT3N0	6 (11)	12 (22)	
pT3N1	6 (11)	7 (13)	
pT3N2	4 (7)	2 (4)	
pT3N3	2 (4)	4 (7)	
pT4aN1	0 (0)	1 (2)	
pT4aN3	1 (2)	0 (0)	
Irresectable disease	2 (4)	0 (0)	
Tumor regression (Mandard) [n (%)]§			0.35
1	15 (28)	10 (18)	
2	10 (19)	7 (13)	
3	8 (15)	18 (33)	
4	11 (20)	11 (20)	
5	3 (6)	2 (4)	

*Plus-minus values are means ± SD.
†Fisher exact test.
‡Additional resections are described in Table S3, http://links.lww.com/SLA/B505.
§According to Mandard et al.[19]
IQ range indicates interquartile range.

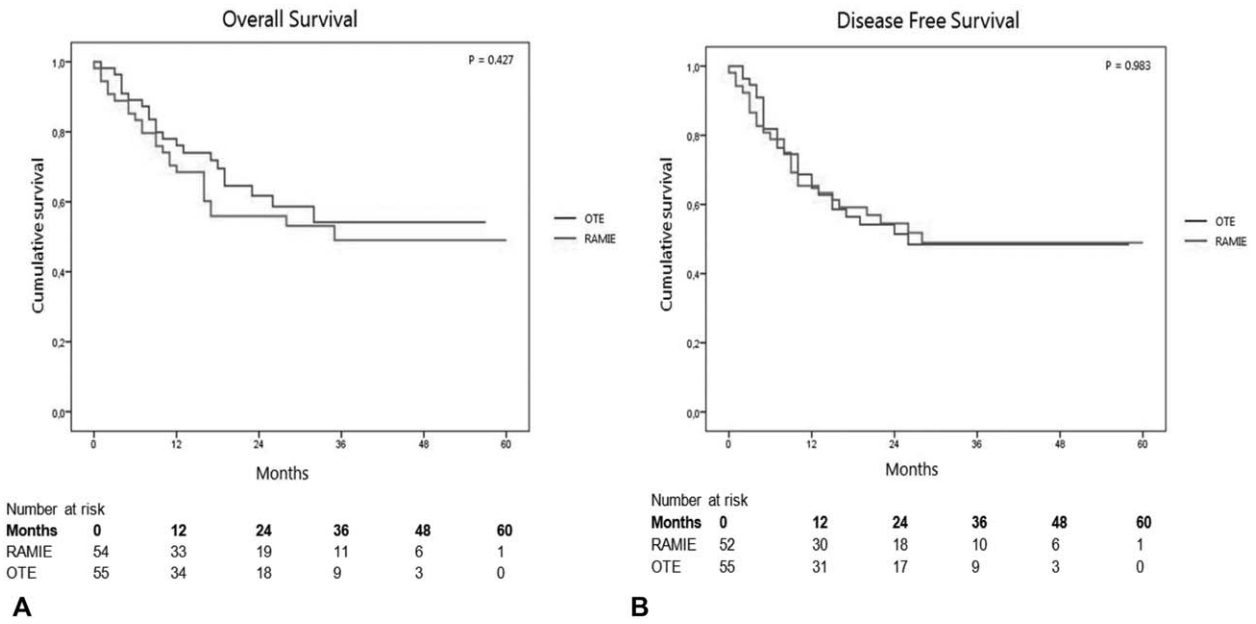


FIGURE 3. Kaplan–Meier Plots of overall and disease free survival.

Out of 109 patients, 107 were included in the DFS and recurrence analyses (2 irresectable patients in the RAMIE group were excluded). In the OTE group there were 2 deaths without recurrence and in the RAMIE group there were 3 deaths without recurrence. These were all related to a complicated postoperative course after surgery and were therefore included in the DFS analysis.

There were no statistically significant differences in median DFS between groups (26 mo for RAMIE and 28 mo for OTE, log rank test, $P = 0.983$; Fig. 3B) and recurrence patterns were comparable (Table S5, http://links.lww.com/SLA/B505).

DISCUSSION

This is the first randomized controlled trial worldwide, comparing RAMIE to OTE in patients with esophageal cancer. RAMIE was associated with a significant lower percentage of overall surgery-related postoperative complications, less blood loss, a lower percentage of pulmonary complications, and cardiac complications compared to OTE. Postoperative pain during the first 14 days was lower after RAMIE compared to OTE. RAMIE resulted in a higher proportion of patients who were functionally recovered within 14 days. Short-term Quality of life after RAMIE was better, both at discharge and 6 weeks after discharge. There were no significant differences in oncologic outcome parameters.

RAMIE was compared to OTE, which is considered to be the criterion standard for resectable esophageal cancer worldwide.[2] Before any comparison of a novel surgical technique to the criterion standard can be performed, the learning curve has to be completed. In 2012, when the trial was initiated, our center was the only center worldwide that had clearly passed the learning phase with a joint experience of >170 RAMIE procedures.[27] Hence, it was decided to perform a single-center randomized controlled trial.[11,27]

The single-center design could be considered a limitation of this study and might hamper generalizability of these results to other centers. Currently, several centers have been proctored for RAMIE and the results from this trial should be reproducible in these centers.[28] Strengths of this study are the randomized design, the fact the surgeons passed the learning curve and the use of the IDEAL recommendations for the assessment of surgical innovation.[29]

The primary endpoint of this study was the percentage of overall surgery-related postoperative complications according to the MCDC of surgical complications grade $\geq$2.[23] For esophagectomy-specific complications, the definitions stated by the ECCG were used.[24] The registration of complications in this trial was performed prospectively in a weekly multidisciplinary meeting, where all complications were noted meticulously and uniformly. This explains a relatively high rate of overall complications recorded in this trial.

Pulmonary complications were most common and mainly consisted of pneumonia (Table 2). The incidence of pneumonia is highly dependent on definition.[30] In this study, the decision to start antibiotics to treat pneumonia was used (MCDC $\geq$2).[23] This resulted in a pneumonia rate of 28% in the RAMIE group and a 55% pneumonia rate in the OTE group. In the previously published CROSS study, a different definition was used for pneumonia, namely the isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph, resulting in a 44% pulmonary complication rate.[17] Applying the same definition for pneumonia as used in the CROSS trial in our study would decrease the rate of pneumonia to 7% in the RAMIE group and 32% in the OTE group ($P = 0.004$, RR 0.488, 95% CI 0.328–726). Sputum culture results are, however, not independently associated with pneumonia treatment.[30] We therefore used the decision to start antibiotics to treat pneumonia (MCDC $\geq$2) in this study.[23]

Cardiac complications were frequently observed and consisted mainly of atrial fibrillation (Table 2).

The incidence of cardiac complications is directly related to the presence of cardiovascular comorbidity.[31] A history of cardiac disease was present in 29% of patients, which represent the population of patients with esophageal cancer in a Western world. With similar baseline characteristics in both the RAMIE group and the OTE group, differences in postoperative cardiac complications were related to the surgical approach in favor of RAMIE.

A cervical esophagogastric anastomosis was used to restore gastrointestinal continuity. Recent studies show that a cervical anastomosis is associated with a higher incidence of anastomotic leakage compared to an intrathoracic anastomosis.[32,33] In this trial all clinical or nonclinical signs of anastomotic leak were scored prospectively, which probably resulted in relatively higher leak rates in both trial arms. Anastomotic leakage with any sign of mediastinal involvement (mediastinitis) was treated with antibiotic treatment and surgical drainage of the mediastinum through the cervical incision. These interventions were scored as type III anastomotic leakage (reoperation) according to the ECCG definitions, explaining the percentage of reinterventions in both arms.[24]

The incidence of chylothorax was relatively high, reflecting a radical en-bloc esophagolymphadenectomy including a thoracic duct resection. The vast majority of patients only required treatment with dietary modification (type 1).

Because of a radical upper mediastinal lymph node dissection combined with a cervical anastomosis, a recurrent laryngeal nerve complication rate of approximately 10% was observed. All observed recurrent laryngeal nerve injuries were type I and temporary. This percentage is comparable to other studies in which routine paratracheal lymph node dissections were performed in combination with a cervical anastomosis.[32,33]

As the previously published studies on postoperative complications after esophagectomy use various definitions for complications, the outcomes are difficult to compare.[17,24] Comparisons between studies can only be performed if the same definitions for complications are used and comorbidities are reported in detail. For all surgical studies for esophageal cancer in the future, it is highly recommended to use ECCG definitions to facilitate comparison between studies.[24]

The question arises whether RAMIE is superior to conventional MIE, which has shown comparable benefits compared to OTE in a randomized trial (TIME trial).[5] Outcomes of a randomized trial comparing the hybrid esophagectomy versus OTE are awaited (MIRO trial).[34] To show the benefits of RAMIE over conventional MIE in a multicenter randomized trial would require a large number of patients and might not be feasible. Future initiatives such as the ESODATA prospective international registry, using the uniform ECCG scoring system would allow for comparisons between RAMIE and MIE.[24]

Postoperative pain, recovery, and QoL were better in favor of RAMIE compared to OTE. Although functional recovery was achieved in a median of 10 days for RAMIE, logistics keep the patient regularly longer in the hospital. A nonsignificant decrease from 16 to 14 days in hospital stay in favor of RAMIE was observed without the use of an ERAS program in both arms, which is comparable to trials comparing open versus laparoscopic colectomy.[35]

At the time of initiation of this trial in 2012, there was no ERAS program after esophagectomy. Recent studies have shown a substantial improvement of postoperative results using the ERAS program following esophageal resection.[36]

In this single-center randomized controlled trial, RAMIE resulted in a lower percentage of overall surgery-related and cardiopulmonary complications with lower postoperative pain, better short-term QoL, and a better postoperative functional recovery compared to OTE. Oncological outcomes were equal and in concordance with the highest standards nowadays. This randomized controlled trial provides evidence for the use of RAMIE to improve short-term postoperative outcomes in patients with resectable esophageal cancer.

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