

University of Groningen

Worldwide Techniques and Outcomes in Robot-assisted Minimally Invasive Esophagectomy (RAMIE)

UGIRA Study Group; Kingma, B. Feike; Grimminger, Peter P.; van der Sluis, Pieter C.; van Det, Marc J.; Kouwenhoven, Ewout A.; Chao, Yin Kai; Tsai, Chun Yi; Fuchs, Hans F.; Bruns, Christiane J.

Published in:
Annals of Surgery

DOI:
[10.1097/SLA.0000000000004550](https://doi.org/10.1097/SLA.0000000000004550)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

UGIRA Study Group, Kingma, B. F., Grimminger, P. P., van der Sluis, P. C., van Det, M. J., Kouwenhoven, E. A., Chao, Y. K., Tsai, C. Y., Fuchs, H. F., Bruns, C. J., Sarkaria, I. S., Luketich, J. D., Haveman, J. W., Etten, B. V., Chiu, P. W., Chan, S. M., Rouanet, P., Mourregot, A., Hölzen, J. P., ... van Hillegersberg, R. (2022). Worldwide Techniques and Outcomes in Robot-assisted Minimally Invasive Esophagectomy (RAMIE): Results From the Multicenter International Registry. *Annals of Surgery*, 276(5), e386-e392. <https://doi.org/10.1097/SLA.0000000000004550>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Worldwide Techniques and Outcomes in Robot-assisted Minimally Invasive Esophagectomy (RAMIE)

Results From the Multicenter International Registry

B. Feike Kingma, MD, Peter P. Grimminger, MD,†
Pieter C. van der Sluis, MD, PhD,*† Marc J. van Det, MD, PhD,‡
Ewout A. Kouwenhoven, MD, PhD,‡ Yin-Kai Chao, MD, PhD,§ Chun-Yi Tsai, MD,§
Hans F. Fuchs, MD, PhD,|| Christiane J. Bruns, MD, PhD,||
Inderpal S. Sarkaria, MD,¶ James D. Luketich, MD,¶ Jan W. Haveman, MD, PhD,#
Boudewijn van Etten, MD, PhD,# Philip W. Chiu, MD, PhD,**
Shannon M. Chan, MD,** Philippe Rouanet, MD, PhD,†† Anne Mourregot, MD,††
Jens-Peter Hölzen, MD,‡‡ Rubens A. Sallum, MD, PhD,§§
Ivan Ceconello, MD, PhD,§§ Jan-Hendrik Egberts, MD,|||
Frank Benedix, MD, PhD,¶¶ Mark I. van Berge Henegouwen, MD, PhD,##
Suzanne S. Gisbertz, MD, PhD,## Daniel Perez, MD,*** Kristina Jansen, MD,***
Michal Hubka, MD,††† Donald E. Low, MD,††† Matthias Biebl, MD, PhD,‡‡‡
Johann Pratschke, MD, PhD,‡‡‡ Paul Turner, MD, PhD,§§§ Kish Pursnani, MD,§§§
Asif Chaudry, MD,|||| Myles Smith, MD, PhD,|||| Elena Mazza, MD,¶¶¶
Paolo Strignano, MD,¶¶¶ Jelle P. Ruurda, MD, PhD,* and
Richard van Hillegersberg, MD, PhD,*✉ UGIRA Study Group*

Objective: This international multicenter study by the Upper GI International Robotic Association aimed to gain insight in current techniques and outcomes of RAMIE worldwide.

Background: Current evidence for RAMIE originates from single-center studies, which may not be generalizable to the international multicenter experience.

Methods: Twenty centers from Europe, Asia, North-America, and South-America participated from 2016 to 2019. Main endpoints included the surgical techniques, clinical outcomes, and early oncological results of ramie.

Results: A total of 856 patients undergoing transthoracic RAMIE were included. Robotic surgery was applied for both the thoracic and abdominal phase (45%), only the thoracic phase (49%), or only the abdominal phase (6%). In most cases, the mediastinal

lymphadenectomy included the low paraesophageal nodes (n = 815, 95%), subcarinal nodes (n = 774, 90%), and paratracheal nodes (n = 537, 63%). When paratracheal lymphadenectomy was performed during an Ivor Lewis or a McKeown RAMIE procedure, recurrent laryngeal nerve injury occurred in 3% and 11% of patients, respectively. Circular stapled (52%), hand-sewn (30%), and linear stapled (18%) anastomotic techniques were used. In Ivor Lewis RAMIE, robot-assisted hand-sewing showed the highest anastomotic leakage rate (33%), while lower rates were observed with circular stapling (17%) and linear stapling (15%). In McKeown RAMIE, a hand-sewn anastomotic technique showed the highest leakage rate (27%), followed by linear stapling (18%) and circular stapling (6%).

Conclusion: This study is the first to provide an overview of the current techniques and outcomes of transthoracic RAMIE worldwide. Although

From the *University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands; †University Medical Center of the Johannes Gutenberg University, Mainz, Germany; ‡ZGTAlmelo, Almelo, The Netherlands; §Chang Gung Memorial Hospital-Linko, Chang Gung University, Taoyuan, Taiwan; ||University of Cologne, Cologne, Germany; ¶University Pittsburgh Medical Center, Pittsburgh, PA; #University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; **The Chinese University of Hong Kong, Division of Upper GI and Metabolic Surgery, Department of Surgery, Faculty of Medicine, Hong Kong; ††Montpellier Cancer Institute, Montpellier, France; ‡‡Universitätsklinikum Münster, Münster, Germany; §§University of São Paulo, São Paulo, Brazil; |||Universitätsklinikum Kiel, Kiel, Germany; ¶¶University Hospital Magdeburg, Magdeburg, Germany; ##Amsterdam UMC Cancer Center Amsterdam, University of Amsterdam, Amsterdam, The Netherlands; ***University Hospital Eppendorf, Hamburg, Germany; †††Virginia Mason Hospital, Seattle, WA; ‡‡‡Charite University Medicine Berlin, Berlin, Germany; §§§Lancashire Teaching Hospitals, Preston, UK; ||||The Royal Marsden, London, UK; and ¶¶¶Città della Salute e della Scienza, Università

degli Studi di Torino, Turin, Italy.

✉R.vanHillegersberg@umcutrecht.nl.

The principal investigator of this study was R.v.H. The coordinating investigator was F.K., who was also responsible for the analyses of this study. By means of repeated face-to-face Upper GI International Robotic Association meetings and continuous digital interaction, all other authors contributed this work by: 1) substantial contributions, the acquisition and interpretation of data; 2) participation in drafting the article and revising it critically for important intellectual content; and 3) final approval of the version to be published.

An Intuitive Clinical Research Grant was received in 2018 to support this research. Intuitive Surgical Inc (Sunnyvale, CA) had no role in the collection, analyses, or interpretation of data. R.v.H., J.R., P.G., J.H., M.v.D., and E.K. are proctors for surgeons who are implementing RAMIE, which is coordinated through Intuitive Surgical Inc.

The authors report no conflicts of interest.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0003-4932/22/27605-e386

DOI: 10.1097/SLA.0000000000004550

these results indicate high quality of the procedure, the optimal approach should be further defined.

Keywords: esophagectomy, minimally invasive surgery, RAMIE, robotics

(*Ann Surg* 2022;276:e386–e392)

Curative treatment for esophageal cancer by means of esophagectomy achieves a 5-year survival rate of approximately 40% to 50% when it is preceded by neoadjuvant therapy.^{1,2} Esophagectomy is traditionally performed by an open approach that includes both a thoracotomy and a laparotomy.³ Aiming to reduce surgical trauma and decrease morbidity, minimally invasive esophagectomy (MIE) was adopted by many centers worldwide.⁴

The TIME trial showed that MIE offers advantages over open esophagectomy in terms of blood loss, postoperative pain, postoperative pulmonary complications, and postoperative quality of life.^{5,6} However, conventional MIE is a complex procedure, as is demonstrated by an estimated learning curve of 20 to 175 procedures, mainly depending on the surgeon's experience and chosen parameters of proficiency.⁷ Results from nation-wide audits raised concerns regarding the safety, with a higher number of reinterventions being reported following MIE when compared with open esophagectomy.^{8–11} Some of the technical challenges of MIE, such as 2-dimensional vision and restricted dexterity, can be overcome by using robotic assistance.^{12–14} Robot-assisted MIE (RAMIE) was introduced in 2003 and has repeatedly been shown to be feasible and safe.^{15–17} Moreover, the ROBOT trial showed that RAMIE was superior to open esophagectomy regarding blood loss, postoperative pain, pulmonary and cardiac complications, and functional recovery.¹⁸ Although the results of randomized controlled trials comparing RAMIE to MIE are still awaited,^{19,20} available evidence indicates that RAMIE is an excellent option to be used for esophageal cancer patients undergoing curative treatment.^{13,21,22} Nonetheless, esophageal resection remains a highly invasive procedure with substantial morbidity, even after RAMIE.

While RAMIE is gaining popularity, current literature mainly consists of single-center studies with considerable variation regarding the exact surgical techniques. For example, while a hybrid RAMIE technique was initially reported by the pioneering center (robotic thoracic phase combined with a laparoscopic abdominal phase), there is an increasing adoption of a fully robotic approach.^{16,23,24} To gain insight in worldwide practice and ultimately identify the optimal RAMIE technique, an international multicenter collaboration was established by the Upper GI International Robotic Association (UGIRA). The current study aimed to gain insight in the current techniques and outcomes of RAMIE in these robotic centers worldwide.

METHODS

Patient Population

The UGIRA was founded in 2017 by a multicontinental group of robotic surgeons, striving to facilitate the worldwide implementation and advancement of robotic esophagogastric surgery. To gain insight in outcomes and perform quality control, UGIRA established a comprehensive international registry for RAMIE in that same year. This registry has now been used for the first time to analyze the outcomes of patients who underwent transthoracic RAMIE for cancer between 2016 and

2019. Centers that were known to perform RAMIE were contacted to establish a consortium that represents worldwide practice. The following 20 centers participated in this study: University Medical Center Utrecht (The Netherlands), University Medical Center of the Johannes Gutenberg University (Germany), ZGT Hospitals Almelo (the Netherlands), Chang Gung Memorial Hospital-Linko Chang Gung University (Taiwan), University of Cologne (Germany), University Pittsburgh Medical Center (USA), University Medical Center Groningen (The Netherlands), The Chinese University of Hong Kong (Hong Kong), Montpellier Cancer Institute (France), Universitätsklinikum Münster (Germany), University of São Paulo (Brazil), Universitätsklinikum Kiel (Germany), University Hospital Magdeburg (Germany), Amsterdam UMC (The Netherlands), University Hospital Eppendorf (Germany), Virginia Mason Hospital (USA), Charite University Medicine Berlin (Germany), Lancashire Teaching Hospitals (United Kingdom), The Royal Marsden (United Kingdom), and Città della Salute e della Scienza Università degli Studi di Torino (Italy). A minimum of 10 RAMIE cases had to be performed to be eligible for participation. Central institutional review board approval was obtained in the UMC Utrecht (17/837) and the local ethical approval was obtained in each center.

Outcomes and Data Collection

UGIRA Study Group consensus was reached regarding the essential registry items during an initial face-to-face meeting, which was followed by construction of a user-friendly online electronic case report form (eCRF) that captures the selected outcomes. The eCRF is accessible through the UGIRA website (<https://www.ugira.org>) and hosted by the Epidemiology Department of the UMC Utrecht. Data collection was partly retrospective (2016) and partly prospective (2017–2019). No personal details were collected to guarantee fully anonymous data collection, protecting patient privacy. Although this means that registered data could not be checked and revised at patient level, the quality of data was ensured by built-in validation checks. These checks were designed to prevent accidental skips and errors in completing the questionnaire by forcing the investigator to register all items or account for incomplete data before submitting a case. All data is encrypted and managed according to internationally accepted guidelines for an indeterminate time period. Data are accessible for the data managers and the coordinating investigator.

Centers were instructed to consecutively register their RAMIE cases. Collected demographic data include age, sex, body mass index, comorbidities, ASA score, tumor histology, clinical TNM stage, and type of neoadjuvant treatment. Surgical details of the RAMIE procedures, which were the primary outcomes of the current study, include the type of robotic system used, surgical approach, application of robotic surgery during distinct parts of the procedure (ie, the thoracic and/or abdominal phases), patient positioning, type of reconstruction, anastomotic technique, extent of mediastinal lymphadenectomy, blood loss, operating time, intraoperative complications, and conversions to an open procedure. The occurrence of complications and severity of overall morbidity (Clavien-Dindo score) were collected in line with the Esophagectomy Complications Consensus Group agreements.²⁵ The specific grade of anastomotic leakage was not collected, since this outcome is partly determined by the type of initial treatment and the timing of resuming oral intake, which widely varied amongst the UGIRA centers depending on the individual postoperative care pathways. The UGIRA Study Group agreed to the following other key outcomes: length of

stay on the intensive care unit and in the hospital, short-term mortality (ie, during postoperative hospitalization or within 30 days after surgery), lymph node yield, and completeness of resection as defined by the College of American Pathologists (ie, no tumor cells within the resection margins).²⁶

Statistical Analysis

All analyses were performed by using SPSS 25.0 (IBM Corp, Armonk, NY). Analyses were performed separately for 2-stage Ivor Lewis and 3-stage McKeown procedures. These groups were further divided into totally robotic (robotic thoracic and robotic abdominal phase) and hybrid robotic (robotic thoracic and laparoscopic abdominal phase) approaches. For each subgroup, the main endpoints were reported and the number of patients with textbook outcome was calculated. Textbook outcome was defined as: complete resection (R0), no intraoperative complications, a lymph node yield ≥ 15 , no complications of Clavien-Dindo 3 or higher, no reinterventions, no readmission to the intensive care unit, no length of hospital stay > 21 days, no hospital readmission < 30 days, no mortality < 30 days, and no in hospital mortality.²⁷ Continuous data were depicted as medians with ranges or means with standard deviations (SD), depending on data distribution. Categorical data were shown as frequencies with percentages (%) and their 95% confidence intervals (95%CI).

RESULTS

Patient Demographics

During the inclusion period, a total of 874 patients who underwent RAMIE were registered by the 20 participating centers.

After excluding 8 patients who underwent surgery because of benign disease and 10 robotic transhiatal esophagectomies, 856 transthoracic RAMIE procedures were included (682 from Europe, 95 from Asia, 56 from North-America, and 23 from South-America). The mean age was 63.5 years (SD ± 10.5) and the mean body mass index was 26.0 kg/m² (range 15.2–46.3 kg/m², SD ± 4.8). The majority of patients were male (n = 711, 83%), and nearly all patients had an ASA score ≥ 2 (n = 793, 93%). Cardiovascular comorbidity was most common (n = 393, 46%), followed by pulmonary comorbidity (n = 144, 17%). Adenocarcinoma (n = 581, 68%) and squamous cell carcinoma (n = 253, 30%) were the most prevalent histological subtypes. Neoadjuvant therapy mostly involved chemoradiotherapy (n = 556, 65%) or chemotherapy (n = 164, 19%).

Surgical Techniques and Intraoperative Results

RAMIE was conducted by a 2-stage Ivor Lewis (n = 622, 73%) or a 3-stage McKeown approach (n = 234, 27%) and Table 1 shows the full details for each approach separately. Overall, robotic surgery was applied for both the thoracic and abdominal phase (n = 386, 45%), only the thoracic phase (n = 415, 49%), or only the abdominal phase (n = 55, 6%). Conversion to an open procedure was required during the thoracic phase in 22 patients (3%) and during the abdominal procedure in 15 patients (2%). In most cases, mediastinal lymphadenectomy involved a dissection of the subcarinal nodes (n = 774, 90%) and low para-esophageal nodes (n = 815, 95%). High mediastinal dissection along the recurrent laryngeal nerves was performed in over half of cases (n = 537, 63%).

Postoperative Outcomes

In the total of 856 RAMIE procedures, postoperative complications occurred in 512 cases (60%), a complete resection (R0) was achieved in 801 cases (94%), the median lymph node yield was 28 nodes [0–89], and short-term mortality was reported in 26 cases (3%). The perioperative details are shown separately for totally robotic (robotic thoracic phase combined with a robotic abdominal phase) and hybrid robotic (robotic thoracic phase combined with conventional laparoscopy) Ivor Lewis and McKeown procedures in Table 2. The overall rate of textbook outcome was 41% with a range of 40% to 43% amongst the specific subgroups. In patients undergoing Ivor Lewis esophagectomy with the use of the robot during at least the thoracic phase (n = 568), recurrent laryngeal nerve (RLN) injury occurred in 9 out of 307 patients who underwent paratracheal lymphadenectomy (2%) while no RLN injury was reported in the 261 patients who did not undergo paratracheal lymphadenectomy (0%). In patients undergoing McKeown esophagectomy with the use of the robot during at least the thoracic phase, RLN injury occurred in 23 out of 206 patients who underwent paratracheal lymphadenectomy (11%) and in 2 out of 27 patients who did not undergo this dissection (7%). The leakage rate of each anastomotic technique is presented in Table 3.

DISCUSSION

This is the first study to report clinical and short-term oncological results of RAME in a large, worldwide, multicenter setting. Variations were mainly found regarding the application of robotic surgery during the thoracic and abdominal phase, the anastomotic technique, and the extent of mediastinal lymphadenectomy. The overall postoperative complication rate was 60% and mortality occurred in 3% (in-hospital or within 30 days after surgery). Furthermore, a median lymph node yield of 28 nodes was found and a complete resection was achieved in 94% of cases. Textbook outcome was attained in 41% of patients undergoing RAMIE and the outcomes of totally robotic and hybrid robotic procedures seemed to be similar.

RAMIE Versus Conventional MIE

The current study shows that RAMIE is associated with good overall perioperative results and an overall textbook outcome rate of 41%, which is higher than the average of 30% that was reported by a previous study that mostly included open and conventional minimally invasive esophagectomies from the Dutch national database between 2011 and 2014.²⁷ With regard to the individual clinical and oncological outcomes such as complications and completeness of resection rate, the current results are in line with recently published international benchmarking studies on esophagectomy.^{28,29} Although RAMIE is a relatively novel technique, this registry shows that the outcomes are already similar to those of the ECCG consortium, which consists of expert esophageal cancer treatment centers.²⁸ This is an important observation, as it confirms the high quality of data and feasibility of using the ECCG definitions to collect and report multicenter outcomes for esophagectomy in a standardized and reproducible way.

The current outcomes of RAMIE in terms of postoperative complications and lymph node yield seem to be comparable to previous benchmarks that were established for conventional MIE.²⁸ This is particularly interesting when realizing that this previous study only included esophageal cancer patients that were classified as being “low risk,” while the current study reported real-world outcomes for the overall patient population

TABLE 1. Characteristics of the Transthoracic RAMIE Procedures (n = 856)

	Ivor Lewis (n = 622)		McKeown (n = 234)	
	n	(%)	n	(%)
Continent				
Europe	569	(91)	113	(48)
North-America	53	(9)	3	(1)
Asia	0	(0)	95	(41)
South-America	0	(0)	23	(10)
Clinical T stage				
cTx/unknown	18	(3)	1	(0)
cT1	42	(7)	20	(9)
cT2	112	(18)	53	(23)
cT3	426	(69)	145	(62)
cT4	24	(4)	15	(6)
Clinical n stage				
cNx/unknown	16	(3)	1	(0)
cN0	195	(31)	69	(30)
cN1	326	(52)	81	(35)
cN2	75	(12)	68	(29)
cN3	10	(2)	15	(6)
Robotic system				
Da Vinci Xi	458	(74)	154	(66)
Da Vinci Si	153	(24)	80	(34)
Da Vinci X	11	(2)	0	(0)
Use of robot				
Robot thorax + robot abdomen	331	(54)	55	(24)
Robot thorax + laparoscopy	207	(33)	152	(65)
Robot thorax + laparotomy	30	(5)	26	(11)
Robot abdomen + thoracoscopy	27	(4)	1	(0)
Robot abdomen + thoracotomy	27	(4)	0	(0)
Patient positioning during thoracic phase				
Semiprone	445	(72)	220	(94)
Left lateral decubitus	154	(25)	12	(5)
Prone	22	(3)	2	(1)
Other	1	(0)	0	(0)
Mediastinal lymphadenectomy				
High—paratracheal nodes	330	(53)	207	(89)
Mid—subcarinal nodes	541	(87)	233	(100)
Low—para-esophageal nodes	588	(95)	227	(97)
Reconstruction technique				
Gastric conduit	621	(100)	230	(98)
Colon interposition	1	(0)	2	(1)
None	0	(0)	2	(1)
Anastomotic type				
End-to-side	484	(78)	151	(64)
End-to-end	58	(13)	16	(7)
Side-to-side	80	(9)	65	(28)
NA (no primary reconstruction)	0	(0)	2	(1)
Anastomotic technique				
Circular stapled	379	(61)	64	(27)
Hand-sewn	151	(24)	102	(44)
Linear stapled	92	(15)	66	(28)
NA (no primary reconstruction)	0	(0)	2	(1)

undergoing RAMIE. While these positive findings for RAMIE are promising, it should be noted that the prior benchmarking study included an older cohort (years 2011-2016) than the current study (years 2016-2019), hampering a head-to-head comparison. Enhanced recovery after surgery (ERAS) protocols for esophagectomy have been increasingly implemented over the last years, as they were shown to be effective in accelerating recovery.³⁰⁻³² However, the median length of intensive care unit and hospital stay were still 2 and 13 days in this study, respectively. As ERAS principles were not uniformly applied amongst the UGIRA centers, the current outcomes seem to highlight the importance of ERAS in optimizing the outcomes of RAMIE.

Considering that the currently presented data were partly collected from centers that were still in their learning curve, the outcomes of RAMIE are expected to improve. To avoid the initial problems of conventional MIE that were reported in terms of reintervention rates, effective training and an adequate case volume are crucial.⁸⁻¹¹ In this context, UGIRA has established a structured training pathway for RAMIE, which has been found to be safe and effective for centers that are wanting to implement this technique.³³ This training pathway is now recommended by UGIRA and will be further optimized based on other surgeons' experiences. In addition to improving training, multicenter comparisons of RAMIE to other techniques will be needed in the near future. At present, surgeons generally switch to RAMIE because of their personal belief that

TABLE 2. Perioperative Clinical and Pathological Outcomes in Totally Robotic (Robot Thorax + Robot Abdomen) or Hybrid Robotic (Robot Thorax + Laparoscopy) RAMIE (n = 745)

	Ivor Lewis (n = 538)		McKeown (n = 207)	
	Totally Robotic (n = 331)	Hybrid Robotic (n = 207)	Totally Robotic (n = 55)	Hybrid Robotic (n = 152)
Textbook outcome*	141 (43%)	85 (41%)	22 (40%)	60 (40%)
Operative time, median minutes [range]	400 [264–790]	433 [134–1017]	421 [323–682]	435 [193–783]
Blood loss, median mL [range]	100 [10–800]	200 [20–1600]	100 [50–1000]	100 [5–900]
Postoperative complications				
Any	174 (53%)	139 (67%)	41 (75%)	97 (64%)
Pulmonary (including pneumonia)	77 (23%)	67 (32%)	21 (38%)	51 (34%)
Anastomotic leakage	65 (20%)	53 (26%)	12 (22%)	27 (18%)
Cardiac (including atrial fibrillation)	50 (15%)	20 (10%)	7 (13%)	14 (9%)
Recurrent laryngeal nerve injury	3 (1%)	6 (3%)	5 (9%)	17 (11%)
Chyle leakage	16 (5%)	12 (6%)	2 (4%)	8 (5%)
Wound infection	4 (1%)	1 (1%)	0 (0%)	5 (3%)
Clavien-Dindo of most severe complication				
0 (No complication)	157 (47%)	68 (33%)	14 (26%)	55 (36%)
1	10 (3%)	15 (7%)	13 (24%)	18 (12%)
2	65 (20%)	31 (15%)	12 (22%)	28 (18%)
3a	39 (12%)	51 (25%)	3 (6%)	18 (12%)
3b	26 (8%)	21 (10%)	2 (4%)	16 (11%)
4	26 (8%)	17 (8%)	9 (16%)	16 (11%)
5	8 (2%)	4 (2%)	2 (4%)	1 (1%)
Length of stay				
ICU/MCU stay, median days [range]	2 [0–112]	3 [0–112]	4 [1–84]	1 [1–106]
Hospital stay, median days [range]	12 [6–118]	15 [5–168]	13 [8–92]	13 [5–124]
Postoperative mortality†	10 (3%)	6 (3%)	3 (6%)	3 (2%)
Lymph node yield				
Total, median number [range]	28 [3–81]	29 [8–70]	27 [11–71]	28 [4–89]
Tumor-positive, median number [range]	0 [0–33]	0 [0–34]	0 [0–33]	0 [0–13]
R0 resection‡	313 (95%)	195 (94%)	51 (93%)	141 (93%)

*Definition: complete resection (R0), no intraoperative complications, a lymph node yield ≥ 15 nodes, no complications of Clavien-Dindo 3 or higher, no re-interventions, no readmission to the ICU, no length of hospital stay > 21 days, no hospital readmission < 30 days, no mortality < 30 days, and no in hospital mortality.

†Refers to mortality that occurred due to any cause during postoperative hospitalization or within 30 days after esophagectomy.

‡Refers to R0 as defined by the College of American Pathologists (ie, absence of malignant cells within the resection margins).95% CI indicates 95% confidence interval; ICU, intensive care unit; MCU, medium care unit; NA, not applicable.

robotic surgery improves their procedure and ergonomics. However, the currently presented data indicate that the clinical benefits of RAMIE over MIE remain to be elucidated. Several studies showed that the learning curve of RAMIE is about 24 cases when a structured training pathway is followed by surgeons who are experienced in MIE, which is relatively short.^{33,34} The technical advantages of robotic surgery (ie, 3-dimensional vision, tremor filtration, increased dexterity) most probably contribute to a short learning curve. For experienced robotic surgeons, particular benefits are exhibited in the most challenging cases, such as salvage esophagectomy or the resection of tumors and lymph nodes metastases located near the upper thoracic inlet.³⁵ Furthermore,

lymphadenectomy along the recurrent laryngeal nerves may be facilitated, although RLN injury rates of 3% and 11% were still found after upper mediastinal dissection during RAMIE by an Ivor Lewis and McKeown approach, respectively. While this difference might be explained by the cervi-cotomy that is part of a McKeown procedure, it could also be possible that paratracheal lymphadenectomy was performed more extensively in patients who underwent McKeown esophagectomy in this cohort. To elevate the overall outcomes of RAMIE over MIE, technological developments such as augmented reality may be crucial, as this technology will increasingly be brought to robotic systems to facilitate training or even allow surgical navigation.^{36,37}

TABLE 3. Anastomotic Techniques and Associated Leakage RBates in RAMIE (n = 856)

	Anastomotic Leakage	
	n	(%)
Ivor Lewis (n = 622)		
Circular stapled intrathoracic anastomosis	(n = 315)	64 (17)
Linear stapled intrathoracic anastomosis	(n = 92)	14 (15)
Hand-sewn intrathoracic anastomosis	(n = 151)	49 (33)
McKeown (n = 234)	(n = 64)	4 (6)
Circular stapled cervical anastomosis		
Linear stapled cervical anastomosis	(n = 66)	12 (18)
Hand-sewn cervical anastomosis	(n = 102)	27 (27)

Anastomotic Technique

Although the outcomes of RAMIE were generally good in this study, the anastomotic leakage rate was relatively high in relation to previous findings in the literature. This seems to be mainly explained by an aggregate leakage rate of 33% in a large subgroup of patients who underwent RAMIE with a hand-sewn intrathoracic anastomosis, suggesting that a stapled anastomosis achieves better outcomes within the current dataset. However, several centers switched directly from a cervical to a robotic hand-sewn intrathoracic anastomosis during this study and most subsequently changed to a stapled technique due to unsatisfying initial outcomes of hand-sewing. Hence, the current results should be interpreted in the context of a developing technique and learning curve.

Irrespective of the exact technique, the overall learning curve of RAMIE has been reported to plateau after 80 cases and a previous study found that 119 cases may be required to reach anastomotic proficiency when adopting an intrathoracic anastomosis.^{34,38–41} Only 5 centers included more than 80 RAMIE procedures at the end of the inclusion phase, of which only 1 had completed their learning curve before starting inclusion. Moreover, none of the participating centers had performed this number of robotic hand-sewn anastomoses at the time of analyses. As most centers are still in their learning curve for RAMIE, we are still in an early stage of global adaptation. It is too early to differentiate between a learning curve effect and a true difference in technique-related outcomes. The lack of tactile feedback in robotic surgery can be challenging during the learning curve, as the gastric conduit is easily harmed by manipulation during construction of the anastomosis. This is one of the reasons why experienced robotic surgeons avoid grasping the tissue, and rather bluntly lift or retract. Further research should clarify whether a robotic hand-sewn technique can achieve similar leakage rates as stapling. This might be aided by intraoperative near-infrared imaging by means of Firefly technology to assess conduit perfusion technology, which could not be evaluated in this study. In addition, future studies need to clarify whether the duration of the required learning curve for this anastomotic technique is acceptable.

Previous meta-analyses comparing hand-sewn versus stapling techniques never found convincing evidence to support the possible idea that a stapled technique is associated with lower leakage rates after esophagectomy.^{14,42,43} Although a manual anastomosis offers the surgeon maximal control over the reconstruction procedure, suturing is challenging during conventional thoracoscopy, leading many surgeons to perform a mechanical anastomosis during conventional MIE. Robotic instruments provide greater dexterity, facilitating manual suturing. While a hand-sewn anastomosis requires the most extensive manual suturing, it should be noted that some suturing is also needed when constructing a mechanical anastomosis (ie, a purse-string suture for a circular stapled anastomosis and a running suture to close part of the circumference for a linear stapled anastomosis). In this light, robotic assistance may aid the construction of all types of anastomoses.

Strengths and Limitations

This study derives particular strength from its international multicenter design. The participating centers were selected from all parts of the world. Although not all known RAMIE centers contributed their data, this study established a representative overview of current real-world practice in RAMIE. The data collection was performed through a specifically developed online eCRF, which included perioperative variables that were meticulously chosen based on UGIRA Study Group consensus and ECCG agreements.²⁵ These essential steps ensured the standardized high-quality data collection, which is a prerequisite for multicenter studies of this kind. However, this study also has limitations. For the sake of feasibility, the RAMIE registry collects data with a limited level of detail and length of follow-up. Therefore, no analyses could be performed for the severity of each separate complication, lymph node yield per station, or survival.

CONCLUSIONS

Totally robotic and hybrid RAMIE are associated with good clinical and short-term oncological results. Variations in technique were mainly found regarding the use of robotic surgery during the

thoracic and abdominal phase, anastomotic technique, and extent of lymphadenectomy. A relatively high leakage rate was observed with a robotic hand-sewn intrathoracic anastomosis. Although these results are encouraging, the optimal technique needs to be further defined based on the current findings.

REFERENCES

- van der Sluis PC, Ruurda JP, Verhage RJ, et al. Oncologic long-term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer. *Ann Surg Oncol*. 2015;22(suppl 3):S1350–S1356.
- Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemo-radiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16:1090–1098.
- Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med*. 2002;347:1662–1669.
- Haverkamp L, Seesing MF, Ruurda JP, et al. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. *Dis Esophagus*. 2017;30:1–7.
- Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multi-centre, open-label, randomised controlled trial. *Lancet*. 2012;379:1887–1892.
- Straatman J, van der Wielen N, Cuesta MA, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial. *Ann Surg*. 2017;266:232–236.
- Claassen L, van Workum F, Rosman C. Learning curve and post-operative outcomes of minimally invasive esophagectomy. *J Thorac Dis*. 2019;11(suppl 5):S777–S785.
- Seesing MFJ, Gisbertz SS, Goense L, et al. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. *Ann Surg*. 2017;266:839–846.
- Sihag S, Kosinski AS, Gaissert HA, et al. Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from the society of thoracic surgeons national database. *Ann Thorac Surg*. 2016;101:1281–1288.
- Takeuchi H, Miyata H, Ozawa S, et al. Comparison of short-term outcomes between open and minimally invasive esophagectomy for esophageal cancer using a nationwide database in Japan. *Ann Surg Oncol*. 2017;24:1821–1827.
- Mamidanna R, Bottle A, Aylin P, et al. Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: a population-based national study. *Ann Surg*. 2012;255:197–203.
- Kingma BF, de Maat MFG, van der Horst S, et al. Robot-assisted minimally invasive esophagectomy (RAMIE) improves perioperative outcomes: a review. *J Thorac Dis*. 2019;11(suppl 5):S735–S742.
- Kingma BF, Ruurda JP. Comment on: “early outcomes of robot-assisted versus thoracoscopic-assisted ivor lewis esophagectomy for esophageal cancer: a propensity score-matched study”. *Ann Surg*. 2019;26:1178–1178.
- Borggreve AS, Kingma BF, Domrachev SA, et al. Surgical treatment of esophageal cancer in the era of multimodality management. *Ann NY Acad Sci*. 2018;1434:192–209.
- Ruurda JP, van der Sluis PC, van der Horst S, et al. Robot-assisted minimally invasive esophagectomy for esophageal cancer: a systematic review. *J Surg Oncol*. 2015;112:257–265.
- van Hillegersberg R, Boone J, Draaisma WA, et al. First experience with robot-assisted thoracoscopic esophagolymphadenectomy for esophageal cancer. *Surg Endosc*. 2006;20:1435–1439.
- Sarkaria IS, Rizk NP, Goldman DA, et al. Early quality of life outcomes after robotic-assisted minimally invasive and open esophagectomy. *Ann Thorac Surg*. 2019;108:920–928.
- van der Sluis PC, van der Horst S, May AM, et al. Robot-assisted minimally invasive thoracoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. *Ann Surg*. 2019;269:621–630.
- Chao YK, Li ZG, Wen YW, et al. Robotic-assisted Esophagectomy vs Video-Assisted Thoracoscopic Esophagectomy (REVATE): study protocol for a randomized controlled trial. *Trials*. 2019;20:346–419.
- Yang Y, Zhang X, Li B, et al. Robot-assisted esophagectomy (RAE) versus conventional minimally invasive esophagectomy (MIE) for

- resectable esophageal squamous cell carcinoma: protocol for a multicenter prospective randomized controlled trial (RAMIE trial, robot-assisted minimally invasive Esophagectomy). *BMC Cancer*. 2019;19:608–619.
21. Zhang Y, Han Y, Gan Q, et al. Early outcomes of robot-assisted versus thoracoscopic-assisted Ivor Lewis esophagectomy for esophageal cancer: a propensity score-matched study. *Ann Surg Oncol*. 2019;26:1284–1291.
 22. Tagkalos E, Goense L, Hoppe-Lotichius M, et al. Robot-assisted minimally invasive esophagectomy (RAMIE) compared to conventional minimally invasive esophagectomy (MIE) for esophageal cancer: a propensity-matched analysis. *Dis Esophagus*. 2020;33:doz060.
 23. Grimminger PP, Hadzijusufovic E, Ruurda JP, et al. The da Vinci Xi robotic four-arm approach for robotic-assisted minimally invasive Esophagectomy. *Thorac Cardiovasc Surg*. 2018;66:407–409.
 24. Egberts JH, Stein H, Aselmann H, et al. Fully robotic da Vinci Ivor-Lewis esophagectomy in four-arm technique-problems and solutions. *Dis Esophagus*. 2017;30:1–9.
 25. Low DE, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg*. 2015;262:286–294.
 26. Verhage RJ, Zandvoort HJ, ten Kate FJ, et al. How to define a positive circumferential resection margin in T3 adenocarcinoma of the esophagus. *Am J Surg Pathol*. 2011;35:919–926.
 27. Busweiler LAD, Schouwenburg MG, Van Berge Henegouwen MI, et al. Textbook outcome as a composite measure in esophagogastric cancer surgery. *Br J Surg*. 2017;104:742–750.
 28. Schmidt HM, Gisbertz SS, Moons J, et al. Defining benchmarks for transthoracic esophagectomy: a multicenter analysis of total minimally invasive esophagectomy in low risk patients. *Ann Surg*. 2017;266:814–821.
 29. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. *Ann Surg*. 2019;269:291–298.
 30. Markar SR, Karthikesalingam A, Low DE. Enhanced recovery pathways lead to an improvement in postoperative outcomes following esophagectomy: systematic review and pooled analysis. *Dis Esophagus*. 2015;28:468–475.
 31. Markar SR, Schmidt H, Kunz S, et al. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. *J Gastrointest Surg*. 2014;18:1238–1246.
 32. Low DE, Allum W, De Manzoni G, et al. Guidelines for perioperative care in esophagectomy: enhanced recovery after surgery (ERAS(R)) society recommendations. *World J Surg*. 2019;43:299–330.
 33. Kingma BF, Hadzijusufovic E, van der Sluis, et al. A structured training pathway to implement robot-assisted minimally invasive esophagectomy (RAMIE): the learning curve results from a high volume center. *Dis Esophagus*, in press.
 34. van der Sluis PC, Ruurda JP, van der Horst S, et al. Learning curve for robot-assisted minimally invasive thoracoscopic esophagectomy: results from 312 cases. *Ann Thorac Surg*. 2018;106:264–271.
 35. van der Horst S, Weijs TJ, Ruurda JP, et al. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer in the upper mediastinum. *J Thorac Dis*. 2017;9(suppl 8):S834–S842.
 36. Hung AJ, Chen J, Gill IS. Automated performance metrics and machine learning algorithms to measure surgeon performance and anticipate clinical outcomes in robotic surgery. *JAMA Surg*. 2018;153:770–771.
 37. Hashimoto DA, Rosman G, Rus D, et al. Artificial intelligence in surgery: promises and perils. *Ann Surg*. 2018;268:70–76.
 38. Park S, Hyun K, Lee HJ, et al. A study of the learning curve for robotic oesophagectomy for oesophageal cancer. *Eur J Cardiothorac Surg*. 2018;53:862–870.
 39. Zhang H, Chen L, Wang Z, et al. The learning curve for robotic McKeown esophagectomy in patients with esophageal cancer. *Ann Thorac Surg*. 2018;105:1024–1030.
 40. Sarkaria IS, Rizk NP, Grosser R, et al. Attaining proficiency in robotic-assisted minimally invasive esophagectomy while maximizing safety during procedure development. *Innovations (Phila)*. 2016;11:268–273.
 41. van Workum F, Stenstra MHBC, Berkelmans GHK, et al. Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study. *Ann Surg*. 2019;269:88–94.
 42. Liu QX, Min JX, Deng XF, et al. Is hand sewing comparable with stapling for anastomotic leakage after esophagectomy? A meta-analysis. *World J Gastro-enterol*. 2014;20:17218–17226.
 43. Markar SR, Karthikesalingam A, Vyas S, et al. Hand-sewn versus stapled oesophago-gastric anastomosis: systematic review and meta-analysis. *J Gastrointest Surg*. 2011;15:876–884.