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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Completely Minimally Invasive Esophagectomy Versus Hybrid Esophagectomy for Esophageal and Gastroesophageal Junctional Cancer: Clinical and Short-Term Oncological Outcomes

Krashna Patel, FRCS, Omar Abbassi, MRCS, Cheuk Bong Tang, FRCS, MD, Bruno Lorenzi, PhD, Alexandros Charalabopoulos, FRCS, PhD, Sritharan Kadirkamanathan, FRCS, PhD, and Naga Venkatesh Jayanthi, FRCS, MD

Essex Upper GI, Regional Centre for Oesophagogastric Surgery, Broomfield Hospital, Chelmsford, UK

ABSTRACT

Background. Minimally invasive surgery for resectable esophageal and gastroesophageal junctional (GEJ) cancer significantly reduces morbidity when compared with open surgery, as is evident from published landmark trials. Comparison of outcomes between hybrid esophagectomy (HE) and completely minimally invasive esophagectomy (CMIE) remains unclear.

Objective. We aimed to ascertain whether CMIE is associated with less postoperative complications compared with HE without oncological compromise.

Methods. All consecutive two-stage HEs and CMIEs performed between 2016 and 2018 were included. All procedures were performed with an intrathoracic anastomosis. Primary clinical outcomes were pulmonary infective and overall complications within 30 days of surgery, while primary oncological outcomes included overall survival (OS) and disease-free survival (DFS) at both 6 months and to date. Secondary outcomes included intraoperative variables and postoperative clinical parameters.

Results. Overall, 98 patients had CMIEs and 49 patients had HEs. There were no baseline differences between the two groups. Thirty-day postoperative pulmonary infection rates were lower in the CMIE group compared with the HE group (12.2% vs. 28.6%; $p = 0.014$), and 30-day overall postoperative complication rates were also lower following CMIE (35.7% vs. 59.2%; $p = 0.007$). OS and DFS were similar between the two groups at 6 months ($p = 0.201$ and $p = 0.109$, respectively).

Conclusions. CMIE is associated with less pulmonary infective and overall postoperative complications compared with HE for resectable esophageal and GEJ cancer. No intergroup difference was observed regarding short-term survival and cancer recurrence in patients undergoing CMIE and HE. A randomized controlled trial comparing the two operative approaches is required to validate these findings.

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K. Patel, FRCS
e-mail: krashna@doctors.org.uk

Esophageal cancer is the eighth most frequently diagnosed malignancy worldwide and sixth most common cause of cancer-associated death.[1–3] Esophagectomy remains the cornerstone of curative treatment for esophageal and gastroesophageal junction (GEJ) tumors in the Western world and is usually combined with neoadjuvant chemotherapy or chemoradiation therapy. Primary surgical objectives include achieving an R0 resection by en bloc tumor resection with lymphadenectomy.

Open esophagectomy (OE) has historically been associated with high morbidity and mortality, however this has significantly reduced within the last few decades due to increased surgical experience, superior preoperative staging, centralization of oncological surgery to high-volume centers, and the introduction of Enhanced Care After Surgery (ERAS) pathways.[4–6] The emergence of minimally invasive techniques has increased the surgical armamentarium available to surgeons worldwide in the surgical management of esophageal and GEJ malignancies. The TIME trial randomized to either OE or completely minimally invasive esophagectomy (CMIE), replacing thoracotomy and laparotomy with thoracoscopic and laparoscopic operative phases.[7] It reported fewer pulmonary infective complications, quicker postoperative recovery, and shorter length of stay following CMIE compared with OE.[7] CMIE has also been shown to achieve non-inferior long-term survival rates when compared with OE.[8] The recently published randomized controlled MIRO trial reported reduced major complications, particularly pulmonary-specific, with hybrid esophagectomy (HE) involving a right thoracotomy with laparoscopic gastric mobilization compared with OE without compromise to overall survival (OS) and disease-free survival (DFS) at 3 years.[9] This robust trial provided evidence of oncological equivalence with superior clinical outcomes following HE over OE. Only a few retrospective, single-center studies exist in the literature comparing clinical and oncological outcomes between HE and CMIE, of which most included a cervical esophagogastric anastomosis.[10–15] Superiority from either operative approach is yet to be established with heterogeneity of findings observed within these studies.

Within this study, we compared clinical and short-term oncological outcomes between CMIE and HE in the management of esophageal and GEJ cancers. We hypothesized CMIE with an intrathoracic anastomosis results in lower postoperative overall and pulmonary infective complications compared with HE with an intrathoracic anastomosis without compromise to short-term OS and DFS.

METHODS

Study Design

Data analysis of a prospectively maintained institutional database was performed on all patients undergoing a CMIE (two-stage [laparoscopic and thoracoscopic] with intrathoracic anastomosis) or HE (two-stage [laparoscopic and right thoracotomy] with intrathoracic anastomosis) for esophageal or GEJ cancers between January 2016 and September 2018 at a single high-volume tertiary referral institution in UK compromising of four esophagogastric cancer surgeons performing a minimum of 20 resections each per annum. Three-stage esophagectomies were excluded from this study. Allocation to surgical approach was based on non-selective surgeon assignment at the time of patient referral to our tertiary referral unit. Each surgeon within our institution had a preferential operative approach: surgeon 1 (NVJ) performed only CMIEs, surgeon 2 (CBT) performed only HEs, and surgeons 3 and 4 (BL and AC) were mentored and transitioned from HE to CMIE from August 2016 onwards. Operative preference from one surgical approach to the other was independent of tumor characteristics, anticipated complexity of surgery, or neoadjuvant treatment administered. All four surgeons had more than 5 years' operative experience performing esophageal resections regardless of approach.

All patients over 18 years of age who had histological-proven, resectable (T1-3, N0-2, M0) esophageal or GEJ malignancies were included. Patients who underwent an esophagectomy for radiologically suspicious tumors with no definitive histology were also included. Esophagectomies performed for palliative or non-malignant indications were excluded. Preoperative staging and administration of multimodality oncological treatment was guided by a regional esophagogastric cancer multidisciplinary team (MDT) process. Cardiopulmonary exercise testing (CPET) was performed during the preoperative work-up of all patients to stratify operative risk and identify those not physiologically fit for surgery. Medical optimization and prehabilitation was guided by anesthesiologists with a special interest in preoperative assessment and esophagogastric surgery. Post neoneoadjuvant CPET was performed in all patients to ensure suitability to proceed to operative resection.

Surgical Approach and Technique

All patients included in this study had a two-stage esophagectomy with a standard two-field lymphadenectomy. Those requiring a three-stage esophagectomy due to tumor site were excluded. Intraoperative one-lung ventilation was used in all patients from both operative groups, facilitated by either double-lumen endotracheal intubation or use of a bronchial blocker, dependent on anesthesiologist preference. All those having HE were positioned in the left lateral position during the thoracic phase, while prone positioning was preferred for CMIE. Thoracic epidural analgesia was used in all patients from both groups.

The HE approach consisted of an open right thoracotomy with laparoscopic gastric mobilization and conduit formation. A standard 5-port technique was adopted using a combination of 5 and 12 mm ports. Either a bipolar or ultrasonic dissection energy device was implemented for tissue dissection, dependent on the operating surgeon. An electronic linear stapler device was used to create the gastric conduit. A right thoracotomy was performed for the open thoracic phase of the operation. The patient was repositioned in the left lateral position with a mid-chest table break. A posterolateral thoracotomy resecting the fifth rib was used for thoracic access. The intrathoracic esophagogastric anastomosis was performed using a circular stapler via an anterior gastrotomy on the gastric conduit.

A CMIE had combined laparoscopic and thoracoscopic phases. The operative steps of the laparoscopic phase were similar to those detailed for HE. Operative positioning for the thoracoscopic phase was a prone swimmer's position with a mid-thoracic operating table break. A three-port technique was implemented with subsequent esophageal mobilization and lymphadenectomy, as detailed previously in literature from our institution.[11] Esophagogastric anastomosis within the thorax was performed using either a one- or two-layer continuous hand-sewn technique, dependent on the operating surgeon. The operative specimen was extracted via an extension of the eighth intercostal port incision.

All anastomoses were tested intraoperatively under vision, with delivery of methylene blue dye via a nasogastric tube. Chest drains were inserted into the right pleural cavity under vision prior to wound closure. Left-sided chest drains were only inserted when the left parietal pleura was breached intraoperatively. Pyloric drainage procedures or feeding jejunostomies were not routinely performed unless clinically indicated or at the discretion of the operating surgeon. All patients were managed in the intensive care unit (ICU) following surgery and transferred to the surgical ward at the discretion of the operating surgeon and intensivists. No formal ERAS pathway exists within our institution, however ERAS principles were generally followed during postoperative care uniformly, for both HE and CMIE patients. All patients were reviewed in an outpatient clinic setting 6 weeks following surgery and thereafter on a 3-monthly basis during the study time period.

Study Outcomes

Primary clinical outcomes for this study were postoperative pulmonary infective complications and postoperative overall complications of any type within 30 days of surgery. Postoperative pulmonary infective complications were defined by clinical manifestations suggesting infection confirmed radiologically by lung infiltrates, consolidation, or lung cavitation present on a chest radiograph or computed tomography (CT). Clinical manifestations include crackles on chest auscultation associated with at least one of the following: new-onset fever (> 38.0 °C), purulent sputum production, drop in oxygen saturations, leucocytosis (white cell count $> 12 \times 10^9$/L), or positive organism isolate on sputum or transtracheal culture. Within this study, acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin criteria.[16] These study definitions are in accordance with those implemented in the Esophagectomy Complications Consensus Group (ECCG) recommendations for data collection on esophagectomy-associated complications.[17] The Clavien–Dindo classification was used to grade the severity of complications as a result of surgery. Primary oncological short-term outcomes included OS and DFS at both 6 months following surgery and to date.

Secondary outcomes were intraoperative (operative blood loss, duration of surgery, total number of lymph nodes retrieved, resection margin positivity, R0 resection rates) and postoperative (length of hospital stay, length of ICU stay, 30-day mortality, 30-day complication-specific rates for anastomotic leak, chyle leak and cardiac complications, postoperative anastomotic stricture rates) parameters. Resection margin positivity was defined as tumor cells within 1 mm from the resection margin as per the Royal College of Pathologists' standards for histopathological examination of esophageal cancer specimens.[18]

Statistical Analysis

For descriptive analysis, categorical data were expressed with whole numbers and percentages, while continuous numerical data were expressed by mean values with standard deviations or median values with ranges for parametric and non-parametric data, respectively. The Student *t* test or Mann–Whitney *U* test were used for comparison of continuous data, and the Pearson Chi square or Fisher's exact tests, depending on group size, were used for categorical data. Relative risk (RR) with 95% confidence intervals (CIs) was used to statistically describe the comparison between clinical outcomes following CMIE and HE.

Kaplan–Meier survival curves were used for comparison of OS and DFS between the CMIE and HE cohorts. The log-rank test compared survival between the two operative groups. Univariate regression analysis was used to determine which variables predicted postoperative 30-day infective pulmonary complications. Variables demonstrating significance were further evaluated with binary logistic regression in multivariate analyses to identify independent predictors of postoperative 30-day infective pulmonary complications. The Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corporation, Armonk, NY, USA) was implemented for descriptive and comparative data analysis, as well as for creation of Kaplan–Meier curves. Percentages were rounded to one decimal place and *p* values were rounded to three decimal places. A *p* value < 0.05 was considered statistically significant within this study.

This study obtained ethical approval, prior to initiation, from a national Research Ethics Committee (REC) within the National Health Service (NHS) Health Research Authority (HRA).

RESULTS

Patient Demographics

Overall, 147 consecutive patients were identified from our institutional database within the study period; 98 (66.7%) underwent a CMIE and 49 (33.3%) underwent an HE. All included procedures were two-stage en bloc esophagectomies with two-field lymph node dissection. Baseline patient demographics are displayed in Table 1. There were no significant differences between the two operative groups in respect of sex, age, body mass index, American Society of Anesthesiologists (ASA) physical status classification score, World Health Organization performance status, or smoking status. There was a higher proportion of male patients in both operative groups, and there were no intergroup differences in dominant presenting symptom at initial diagnosis, tumor location, tumor stage, or histology, as detailed in Table 2.

TABLE 1 Baseline patient demographics

	HE (n = 49)	CMIE (n = 98)	p value
Age at diagnosis, years	66 (31–81)	68 (47–83)	0.242
Sex			0.214
Male	38 (77.6)	84 (85.7)	
Female	11 (22.4)	14 (14.3)	
BMI, kg/m^2	27 (21–41)	27 (19–49)	0.772
ASA physical status classification			0.661
1	2 (4.1)	7 (7.1)	
2	35 (71.4)	61 (62.2)	
3	12 (24.5)	30 (30.6)	
4	0 (0)	0 (0)	
WHO performance status			0.407
0	19 (38.8)	33 (33.7)	
1	27 (55.1)	52 (53.1)	
2	3 (6.1)	13 (13.3)	
3	0 (0)	0 (0)	
Smoking status			0.890
Current smoker	4 (7.8)	9 (9.2)	
Ex-smoker	24 (49.0)	51 (52.0)	
Never smoked	21 (42.9)	38 (38.8	

Data are expressed as whole numbers (%) or median (range)

P values from Fisher's exact test or Chi square test for categorical data and Mann–Whitney *U* test for continuous data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *WHO* World Health Organization

Primary Clinical Outcomes

Primary clinical outcomes from this study are detailed in Table 3. Pulmonary infective complication rates within 30 days of surgery were significantly lower in the CMIE group than in the HE group (12.2% vs. 28.6%; RR 0.43, 95% CI 0.21–0.86; p = 0.014). Five (10.2%) patients in the HE group and two (2.0%) in the CMIE group required chest drain insertion to manage their postoperative pulmonary infections. Re-intubation and return to ICU was required for severe respiratory compromise secondary to pulmonary infection in a single patient from the HE cohort and two patients from the CMIE cohort. A single patient in each group developed ARDS secondary to infection within the thorax. Pulmonary infections directly related to acute anastomotic leaks or postoperative fistulas were not included in the reported 30-day pulmonary infective complication rates.

There were also fewer overall complications within 30 days of surgery in the CMIE group versus the HE group (35.7% vs. 59.2%; RR 0.60, 95% CI 0.42–0.86; p = 0.007). In regard to postoperative complication severity as per the Clavien–Dindo classification, both groups were similar. Thirty-day mortality rates were lower following HE, however this difference was not significant (2.0% vs. 3.1%; p = 0.720). Overall, three patients from the CMIE group died (one as a result of multiorgan failure secondary to anastomotic leak, one developed gastric conduit necrosis following a myocardial infarction postoperatively, and one as a result of respiratory failure exacerbated by a large pleural effusion) and one patient from the HE group (gastric conduit necrosis).

Primary Oncological Outcomes

OS and DFS are tabulated in Table 4. There were no significant differences in OS at either 6 months or to date, with a median follow up of 23.5 months following HE and 14.8 months following CMIE ($p < 0.01$). Figure 1a displays a Kaplan–Meier curve for OS between the two groups, with no significant difference using the log rank test (p = 0.254). Similarly, DFS yielded no significant intergroup difference at either 6 months or to date (Fig. 1b; log-rank test: p = 0.272). The most common locations for organ cancer recurrence included the liver, lung, and peritoneum. There were no overall differences between the two groups in regard to location of cancer recurrence (p = 0.590).

Secondary Intraoperative Outcomes

Table 5 shows comparative analyses performed between the two operative groups for intraoperative variables.

TABLE 2 Baseline clinical and tumor characteristics

	HE (n = 49)	CMIE (n = 98)	p value
Dominant presenting symptom			0.634
Dysphagia	34 (69.4)	79 (80.6)	
Bleeding	3 (6.1)	4 (4.1)	
Reflux	4 (8.2)	6 (6.1)	
Barrett's surveillance	5 (10.2)	5 (5.1)	
Anemia	1 (2.0)	0 (0)	
Weight loss	1 (2.0)	2 (2.0)	
Other	1 (2.0)	2 (2.0)	
Tumor location			0.186
Middle esophagus	3 (6.1)	1 (1.0)	
Distal esophagus	22 (44.9)	56 (57.1)	
GEJ Siewert 1	13 (26.5)	19 (19.4)	
GEJ Siewert 2	11 (22.4)	22 (22.4)	
Clinical preoperative T stage			0.531
1A	0 (0)	0 (0)	
1B	1 (2.0)	5 (5.1)	
2	10 (20.4)	15 (15.3)	
3	38 (77.6)	78 (79.6)	
4	0 (0)	0 (0)	
Clinical preoperative N stage			0.565
0	21 (42.9)	47 (48.0)	
1	26 (53.1)	44 (44.9)	
2	2 (4.1)	7 (7.1)	
3	0 (0)	0 (0)	
Tumor histological type			0.374
Adenocarcinoma	44 (89.8)	92 (93.9)	
SCC	1 (2.0)	3 (3.1)	
Mixed (adenosquamous)	3 (6.1)	1 (1.0)	
Adenocarcinoma with NET features	0 (0)	2 (2.0)	
HGD	1 (2.0)	0 (0)	

Data are expressed as whole numbers (%)

P values from Fisher's exact test or Chi square test for categorical data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy, *GEJ* gastroesophageal junction, *SCC* squamous cell carcinoma, *NET* neuroendocrine tumor, *HGD* high-grade dysplasia

Duration of surgery was significantly longer with CMIE compared with HE (418 min vs. 390 min; $p = 0.014$). Median total number of lymph nodes retrieved intraoperatively was fewer following HE compared with CMIE (22 vs. 27; $p = 0.040$). Operative blood loss was less during CMIE compared with HE, however this difference was not statistically significant (349 mL vs. 436 mL; $p = 0.194$). Other variables, including tumor size, R0 resection rates, specimen margin positivity, and conversion to open rates, demonstrated no significant intergroup differences. There were also no significant differences in T or N staging on final histopathological examination of operative specimens from surgery.

Secondary Postoperative Clinical Outcomes

Data regarding length of ICU and in-hospital stay, as well as postoperative complication subtype intergroup analysis, are tabulated in Table 6. Overall length of stay in hospital was 12 days following HE and 10 days following CMIE ($p = 0.080$). Similarly, length of stay in the ICU was longer following HE (5 days vs. 4 days; $p = 0.490$); however, again, this was a non-significant difference. There was a significant increase in overall pulmonary complications following HE when compared with CMIE (36.7% vs. 17.3%; $p = 0.009$). There were no intergroup differences for rates of cardiac complications, atrial fibrillation, anastomotic leak, gastric conduit necrosis, chyle leak, and postoperative anastomotic stricture.

TABLE 3 Primary clinical outcomes

	HE (n = 49)	CMIE (n = 98)	p value
30-day pulmonary infective complication	14/49 (28.6)	12/98 (12.2%)	**0.014**
ARDS related to pneumonia	1 (2.0)	1 (1.0%)	
Re-intubation related to pneumonia	1 (2.0)	2 (2.0%)	
30-day overall complications	29/49 (59.2)	35/98 (35.7%)	**0.007**
Clavien–Dindo classification	(n = 29)	(n = 35)	0.406d
I	2 (6.9)	0 (0)	
II	11 (37.9)	21 (60.0)	
IIIa	5 (17.2)	4 (11.4)	
IIIb	4 (13.8)	4 (11.4)	
IVa	4 (13.8)	3 (8.6)	
IVb	2 (6.9)	1 (2.9)	
V	1 (3.4)	2 (5.7)	
30-day mortality	1/49 (2.0)	3/98 (3.1)	0.720

Bold values indicate statistical significance ($p < 0.05$)

Data are expressed as whole numbers (%)

P-values from Fisher's exact test or Chi square test for categorical data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy, *ARDS* acute respiratory distress syndrome

TABLE 4 Primary oncological outcomes

	HE (n = 49)	CMIE (n = 98)	p value
OS			
Inpatient OS	47 (95.9)	94 (95.9)	1.000
30-day OS	48 (98.0)	95 (96.9)	0.720
6-month OS	47 (95.9)	88 (89.8)	0.201
OS to date	34 (69.4)	66 (67.3)	0.803
DFS			
6-month DFS	46 (93.9)	83 (84.7)	0.109
DFS to date	33 (67.3)	66 (67.3)	1.000
Cancer recurrence location			
Liver	2	10	
Lung	3	2	
Local recurrence	4	2	
Metastatic lymph node	2	8	
Peritoneal	2	6	
Other	5	15	

Data are expressed as whole numbers (%)

P values from Fisher's exact test or Chi square test for categorical data and Mann–Whitney U test for continuous data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy, *OS* overall survival, *DFS* disease-free survival

Multivariate Analysis for Predictors of Postoperative 30-Day Pulmonary Infective Complications

Surgical approach with HE and presence of anastomotic leak were associated with pulmonary infections within 30 days of surgery on univariate analysis. No significant associations were otherwise found on univariate analysis of patient demographics, tumor characteristics, and preoperative and intraoperative variables. Multivariate analysis revealed only surgical approach with HE was identified as an independent predictor of 30-day pulmonary infective complications (Table 7).

DISCUSSION

We report a significantly lower risk of pulmonary infective and overall complications associated with CMIE compared with HE. There was no difference in short-term OS or DFS following surgery between the two operative groups. These findings correlate with our initial primary outcome study hypotheses.

We found a 57% reduction in the risk of pulmonary infective complications associated with CMIE and replacing a right thoracotomy with a minimally invasive thoracoscopic approach. The TIME trial reported a similar reduction in pulmonary infection within 2 weeks of surgery, from 29 to 9% when comparing OE with CMIE.[7] From the previous literature comparing CMIE and HE approaches, three European studies have reported lower pulmonary infection rates following CMIE comparable with our findings.[10,13,15] Multivariate analysis in this study found that adopting HE as a surgical approach was the only independent predictor for 30-day pulmonary infective complications, similar to the findings reported by Souche et al.[15] Adopting a thoracoscopic approach over thoracotomy has a multitude of benefits from a respiratory point of

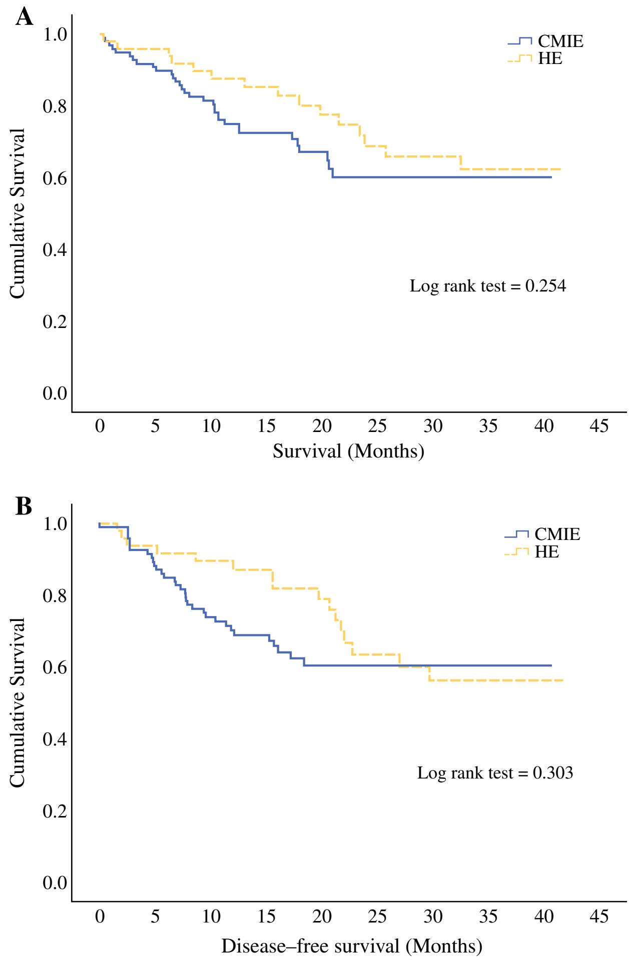

FIG. 1 **a** Overall survival and **b** disease-free survival in patients undergoing CMIE versus HE. *CMIE* completely minimally invasive esophagectomy *HE* hybrid esophagectomy

view, including reduced chest wall surgical trauma and associated incision-related pain. CMIE has previously been identified as an independent factor for long-term lung function, with a significantly lower decline in forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) 1 year after surgery when compared with OE, likely due to less intrathoracic adhesion formation.[19] Post-thoracotomy pain can affect up to half of those undergoing open surgery, with patients reporting more pain at 1-year postoperatively compared with those undergoing CMIE.[20] Prone intraoperative positioning during the thoracoscopic phase during esophagectomies can also significantly improve postoperative recovery and reduce pulmonary infective complications.[21]

Regarding overall complications, our HE group reported a 59.2% 30-day complication rate. This was higher than the 36% reported within the MIRO trial and other comparative studies involving patients undergoing HE.[9,10] This discrepancy may be explained by the large number of pleural effusions within our HE group (20.4%) and the addition of Clavien–Dindo type I complications, which were not included in similar previously published studies. We postulate the difference in pleural effusion rates may be attributed to the larger incision and rib resection involved with an open thoracotomy compared with the thoracoscopic approach, resulting in more insult to the parietal pleura. Our overall complication rate in the CMIE group was 35.7%, which is comparable with other mentioned similar studies and below a previously reported benchmark for 30-day complications following CMIE.[7,10,22,23] Anastomotic leak and 30-day mortality rates within this study were comparable with previous randomized controlled trials (RCTs) and the UK National Oesophago-Gastric Cancer Audit (NOGCA) data.[7,10,24] Anastomotic leak was observed more frequently in the HE cohort, however this was not significantly different to the CMIE group. Previous studies have reported higher anastomotic leak rates associated with CMIE.[15,25–27] Our outcomes did not reflect this, which is possibly explained by operative experience and established operative technique with CMIE within our practice.

No significant differences in OS or DFS were found at 6 months from either operative group. To date, these survival parameters were also comparable, however median follow-up differed between the two groups. Short-term survival findings after HE and CMIE were similar to that from previous studies.[10,11] Survival after HE was comparable with the MIRO trial outcomes.[9]

In parallel with findings from previous studies, operative time was longer in CMIE compared with HE.[11–13,15] The duration of surgery in CMIE within our study is prolonged as a result of performing a hand-sewn intrathoracic anastomosis, as opposed to using a circular stapler in HE. Two surgeons in our unit adopted a two-layer hand-sewn technique, while another surgeon implemented a single-layer technique. This largely explains the discrepancy in operative time between CMIE and HE. Interestingly, we observed a higher lymph node yield within the CMIE group. Plausible reasons for these findings could be intersurgeon variability in regard to the radicality of lymphadenectomy and also the enhanced magnified views during thoracoscopy compared with an open approach, therefore potentially facilitating a more extensive thoracic field lymphadenectomy. Our study demonstrates at least non-inferiority of CMIE when compared with HE in regard to quality of oncological en bloc resection and extent of lymphadenectomy. Although the length of stay in hospital was shorter by 2 days following CMIE, this was not significant on statistical analysis. Again, these parameters were similar to the NOGCA national averages.[24]

TABLE 5 Intraoperative parameters

	HE (n = 49)	CMIE (n = 98)	p value
Operative blood loss, mls	436 (49–1505)	349 (32–940)	0.194
Duration of surgery, min	390 (243–549)	418 (270–693)	**0.014**
Conversion to open	3/49 (6.1)	1/97 (1.0)	0.073
Total number of lymph nodes retrieved	22 (7–61)	27 (11–56)	**0.040**
Total number of malignant lymph nodes	1 (0–9)	1 (0–39)	0.077
Tumor size, mm	30 (0–150)	35 (0–140)	0.059
R0 resection	35/49 (71.4)	61/98 (62.2)	0.270
Histological T stage			0.358
No cancer	4 (8.2)	2 (2.0)	
Low-grade dysplasia	0 (0)	1 (1.0)	
High-grade dysplasia	2 (4.1)	2 (2.0)	
1A	1 (2.0)	6 (6.1)	
1B	5 (10.2)	8 (8.2)	
2	8 (16.3)	11 (11.2)	
3	29 (59.2)	68 (69.4)	
4	0 (0)	0 (0)	
Histological N stage			0.628
0	22 (44.9)	36 (36.7)	
1	12 (24.5)	22 (22.4)	
2	9 (18.4)	21 (21.4)	
3	6 (12.2)	19 (19.4)	
Operative specimen margins and invasion			
Negative proximal margin	47/49 (95.9)	96/98 (98.0)	0.473
Negative distal margin	47/49 (95.9)	96/98 (98.0)	0.473
Negative circumferential resection margin	35/49 (71.4)	61/98 (62.2)	0.270
Absence of lymphovascular invasion	26/49 (53.1)	48/98 (49.0)	0.218
Absence of perineural invasion	32/49 (65.3)	51/98 (52.0)	0.126

Bold values indicate statistical significance ($p < 0.05$)

Data are expressed as whole numbers (%) or median (range)

P values from Fisher's exact test or Chi square test for categorical data and Mann–Whitney *U* test for continuous data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy

Several limitations of this study must be considered. This was a non-controlled observational study using data from a single-center, prospectively maintained database. Surgeons within our unit have different levels of experience and use varying operative techniques, which can lead to performance and procedure bias. These sources of bias and confounding factors could have a consequential influence on study results, particularly with postoperative complications and intraoperative parameters. Our operative group sample sizes were different and were not propensity matched. Our HE group in particular may be too small in size to detect significant differences in outcomes measured with this study, possibly representing type II error. However, our study numbers were similar to those within the TIME trial and no intergroup significant differences were observed in baseline patient demographics or tumor characteristics. Only short-term oncological survival was examined. Longer follow-up would be required to evaluate the influence of operative approach on long-term survival parameters. All included patients were randomly allocated to their operating surgeon at the time of referral. No patients within this study changed their operating surgeon from the time of allocation. Previous studies have been prone to selection bias by opting for CMIE in early-stage or less complex malignancies, unlike in this study.

Notwithstanding the above shortcomings, the patients included in this study were non-selected, consecutive patients operated in our center. While there was no formal randomization, patients had either CMIE or HE at random, as is evident in the lack of differences in the patient demographics and tumor characteristics (Tables 1 and 2).

TABLE 6 Postoperative clinical parameters

	HE (n = 49)	CMIE (n = 98)	p value
Overall length of hospital stay, days	12 (6–97)	10 (6–105)	0.080
Overall length of ICU stay, days	5 (2–41)	4 (2–38)	0.490
ICU readmission	1/49 (2.0)	2/98 (2.0)	1.000
Cardiac complication	6/49 (12.2)	12/98 (12.2)	1.000
Atrial fibrillation	4 (8.2)	9 (11.2)	
Non-atrial fibrillation arrhythmia	1 (2.0)	1 (1.0)	
Myocardial infarction	1 (2.0)	2 (2.0)	
Pulmonary complication	18/49 (36.7)	17/98 (17.3)	**0.009**
Pneumonia/empyema	14 (28.6)	12 (12.2)	
Pleural effusion	10 (20.4)	5 (5.1)	
Pneumothorax	1 (2.0)	0 (0.0)	
Other	1 (2.0)	2 (2.0)	
Anastomotic leak	6/49 (12.2)	6/98 (5.5)	0.201
Gastric conduit necrosis	1/49 (2.0)	2/98 (2.0)	1.000
Chyle leak	4/49 (8.2)	5/98 (5.1)	0.466
Anastomotic stricture	6/49 (12.2)	18/98 (18.4)	0.344

Bold value indicates statistical significance ($p < 0.05$)

Data are expressed as whole numbers (%) or median (range)

P values from Fisher's exact test or Chi square test for categorical data and Mann–Whitney *U* test for continuous data

HE hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy, *ICU* intensive care unit

TABLE 7 Multivariate logistic regression analyses for 30-day pulmonary infective complications

	OR	95% CI	p value
Surgical approach (HE vs. CMIE)	2.687	1.114–6.479	**0.028**
Anastomotic leak (yes vs. no)	3.421	0.956–12.237	0.059

Bold value indicates statistical significance ($p < 0.05$)

OR odds ratio, *CI* confidence intervals, *HE* hybrid esophagectomy, *CMIE* completely minimally invasive esophagectomy

This is the largest study to date in the literature comparing HE with CMIE with two-stage procedures adopting an intrathoracic anastomosis. Intrathoracic anastomoses performed thoracoscopically is technically challenging and has been previously associated with higher rates of anastomotic leakage. However, our series reports favorable clinical outcomes and at least non-inferiority in short-term oncological outcomes from CMIE with an intrathoracic anastomosis over HE. These findings augment the existing limited literature in support of CMIE over other surgical approaches for the management of esophageal cancer and GEJ cancer.

Following publication of the MIRO trial, many advocate HE over OE as becoming the gold standard operative approach for esophageal and GEJ cancers.[28,29] Future trials and national surgical dataset studies should examine CMIE outcomes compared with HE. There is a need for an adequately powered robust RCT to validate the findings of this study. This should ideally examine short- and long-term clinical and oncological outcomes as well as quality of life parameters to ascertain potential superiority of CMIE over HE. The currently recruiting ROMIO trial aims to compare OE, HE, and CMIE in terms of postoperative quality of life (primary outcome), and clinical and survival outcomes in a Western population.[30] Although this trial will provide an invaluable comparison between these operative techniques, it will not be adequately powered to directly compare HE and CMIE for clinical and survival primary outcomes.

CONCLUSIONS

Our study shows CMIE results in fewer postoperative complications, particularly pulmonary complications, when compared with HE for resectable esophageal and GEJ cancer. Longitudinal findings suggest non-inferiority in short-term OS and DFS in patients undergoing CMIE compared with those undergoing HE. A robust RCT comparing these two operative approaches is required to validate these findings.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2019;69(1):7–34
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet.* 2013;381(9864):400–12
3. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893–917
4. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg*. 2002;183(6): 630–41
5. Munitiz V, Martinez-de-Haro LF, Ortiz A, et al. Effectiveness of a written clinical pathway for enhanced recovery after transthoracic (Ivor Lewis) oesophagectomy. *Br J Surg*. 2010;97(5):714–8
6. Markar SR, Naik R, Malietzis G, et al. Component analysis of enhanced recovery pathways for esophagectomy. *Dis Esophagus.* 2017;30(10):1–10
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
8. Guo W, Ma X, Yang S et al. Combined thoracoscopic-laparoscopic esophagectomy versus open esophagectomy: a meta-analysis of outcomes. *Surg Endosc.* 2016;30:3873–3881
9. Mariette C, Markar SR, Dabakuyo-Yonli TS, et al. Hybrid minimally invasive esophagectomy for esophageal cancer. *N Engl J Med*. 2019;380:152–62
10. Berlth F, Plum PS, Chon SH, et al. Total minimally invasive esophagectomy for esophageal adenocarcinoma reduces postoperative pain and pneumonia compared to hybrid esophagectomy. *Surg Endosc.* 2018;32:4957–4965
11. Bonavina L, Scolari F, Aiolfi A, et al. Early outcome of thoracoscopic and hybrid esophagectomy: propensity-matched comparative analysis. *Surgery* 2016;159:1073–81
12. Elshaer M, Gravante G, Tang CB, et al. Totally minimally invasive two-stage esophagectomy with intrathoracic hand-sewn anastomosis: short-term clinical and oncological outcomes. *Dis Esophagus.* 2017;31(3). https://doi.org/10.1093/dote/dox150
13. Grimminger PP, Tagkalos E, Hadzijusufovic E, et al. Change from hybrid to fully minimally invasive and robotic esophagectomy is possible without compromises. *Thorac Cardiovasc Surg.* 2019;67(7):589–596. https://doi.org/10.1055/s-0038-1670664
14. Nozaki I, Mizusawa J, Kato K et al. Impact of laparoscopy on the prevention of pulmonary complications after thoracoscopic esophagectomy using data from JCOG0502: a prospective multicentre study. *Surg Endosc.* 2018;32(2):651–9
15. Souche R, Nayeri M, Chati R et al. Thoracoscopy in prone position with two-lung ventilation compared to conventional thoracotomy during Ivor Lewis procedure: a multicentre case-control study. *Surg Endosc.* 2020;34:142–152
16. Ranieri VM, Rubenfeld GD, Thompson BT et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–33
17. Low DE, Alderson D, Cecconello I et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286–94
18. Grabsch HI, Mapstone NP, Novelli M. Dataset for histopathological reporting of oesophageal and gastric carcinoma. 3rd ed. London: Royal College of Pathologists; 2019.
19. Kosumi K, Yoshida N, Okadome K, et al. Minimally invasive esophagectomy may contribute to long-term respiratory function after esophagectomy for esophageal cancer. *Dis Esophagus.* 2018; 31(6). https://doi.org/10.1093/dote/dox153
20. Maas KW, Cuesta MA, van Berge Henegouwen MI, et al. Quality of life and late complications after minimally invasive compared to open esophagectomy: results of a randomised trial. *World J Surg*. 2015;39:1986–93
21. Otsubo D, Nakamura T, Yamamoto M et al. Prone position in thoracoscopic esophagectomy improves postoperative oxygenation and reduces pulmonary complications. *Surg Endosc.* 2017;31:1136–1141
22. Schmidt HM, Gisbertz SS, Moons J, et al. Defining benchmarks for transthoracic esophagectomy: a multicentre analysis of total minimally invasive esophagectomy in low risk patients. *Ann Surg*. 2017;266(5):814–821
23. Merritt RE, Kneuertz PJ, D'Souza DM et al. Total laparoscopic and thoracoscopic Ivor Lewis esophagectomy after neoadjuvant chemoradiation with minimal overall and anastomotic complications. *J Cardiothorac Surg.* 2019;14(1):123
24. NOGCA Project Team. National Oesophago-gastric Cancer Audit 2018: Annual Report. Leeds: Healthcare Quality Improvement Partnership. Available at: https://www.nogca.org.uk/reports/2018-annual-report/. Accessed 27 Jun 2019.
25. 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(4):1281–8
26. 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(5):839–846
27. 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(2):197–203
28. Voron T, Lintis A, Piessen G. Hybrid oesophagectomy. *J Thorac Dis.* 2019;11(Suppl 5):S723–S727
29. Romero D. Hybrid minimally invasive surgery overtakes open surgery. *Nat Rev Clin Oncol.* 2019;16(3):144
30. Metcalfe C, Avery K, Berrisford R et al. Comparing open and minimally invasive surgical procedures for oesophagectomy in the treatment of cancer: the ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open feasibility study and pilot trial). *Health Technol Assess.* 2016;20(48):1–68

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