



ORIGINAL ARTICLE

Postoperative short-term outcomes of minimally invasive versus open esophagectomy for patients with esophageal cancer: An updated systematic review and meta-analysis

Naeem M. Akhtar^{1†}, Donglai Chen^{2†} , Yuhuan Zhao^{1†}, David Dane¹, Yuhang Xue¹, Wenjia Wang¹, Jiaheng Zhang¹, Yonghua Sang^{1‡}, Chang Chen^{2‡} & Yongbing Chen^{1‡} 

1 Department of Thoracic Surgery, School of Medicine, The Second Affiliated Hospital of Soochow University, Suzhou, China

2 Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China

Keywords

Esophageal cancer; esophagectomy; minimally-invasive surgery.

Correspondence

Yongbing Chen, Department of Thoracic Surgery, The Second Affiliated Hospital of Soochow University, School of Medicine, 1055 Sanxiang Road, Gusu District, Suzhou 215004, China.

Tel: +86 13914018774

Email: chentongt@sina.com

[†]Drs. Akhtar N.M., Chen D. and Zhao Y. equally contributed to the work.

[‡]These authors are listed as co-senior authors.

Received: 14 January 2020;

Accepted: 14 March 2020.

doi: 10.1111/1759-7714.13413

Thoracic Cancer **11** (2020) 1465–1475

Abstract

Background: We performed a systematic review and meta-analysis to synthesize the available evidence regarding short-term outcomes between minimally invasive esophagectomy (MIE) and open esophagectomy (OE).

Methods: Studies were identified by searching databases including PubMed, EMBASE, Web of Science and Cochrane Library up to March 2019 without language restrictions. Results of these searches were filtered according to a set of eligibility criteria and analyzed in line with PRISMA guidelines.

Results: There were 33 studies included with a total of 13 269 patients in our review, out of which 4948 cases were of MIE and 8321 cases were of OE. The pooled results suggested that MIE had a better outcome regarding all-cause respiratory complications (RCs) (OR = 0.56, 95% CI = 0.41–0.78, $P = <0.001$), in-hospital duration (SMD = -0.51 ; 95% CI = -0.78 – 0.24 ; $P = <0.001$), and blood loss (SMD = -1.44 ; 95% CI = -1.95 – 0.93 ; $P = <0.001$). OE was associated with shorter duration of operation time, while no statistically significant differences were observed regarding other outcomes. Additionally, subgroup analyses were performed for a number of different postoperative events.

Conclusions: Our study indicated that MIE had more favorable outcomes than OE from the perspective of short-term outcomes. Further large-scale, multicenter randomized control trials are needed to explore the long-term survival outcomes after MIE versus OE.

Introduction

Esophageal cancer is the seventh most common cause of cancer-related death globally.¹ The overall five-year survival is below 20%.^{2,3} The main course of treatment is surgical resection, which is usually combined with chemotherapy or chemoradiotherapy for locally advanced tumors.⁴ Conventional surgical treatment involves open esophagectomy (OE) using trans-thoracic or transhiatal approaches which are associated with high morbidity and mortality. Respiratory complications (RCs) are common with OE and can increase the risk of death up to 20%.^{5–7} In recent decades, minimally invasive esophagectomy (MIE) has become an alternative to OE. MIE encompasses a number of techniques including total MIE (tMIE), hybrid minimally invasive esophagectomy (hMIE) and robotic surgery.⁸

Given the technical complexity of MIE, a number of concerns exist regarding the benefits of MIE compared with OE in terms of postoperative complications and short-term mortality. On one hand, even though a number of previously performed studies have established MIE as a relatively safe procedure in terms of post-operative outcomes,^{9–13} on the other, studies performed by Seesing *et al.* and Mariette *et al.* state the opposite.^{14,15}

With a number of emerging studies regarding MIE and OE in recent years, there has been a lack of a systematic study to investigate the short-term outcomes after MIE versus OE. Furthermore, a detailed and updated meta-analysis concerning the two approaches might help surgeons with their surgical decisions. Ergo, the purpose of this systematic review and meta-analysis was not only to

use the latest and largest population-based data to extensively compare and summarize the postoperative complications after MIE versus OE for esophageal cancer, but also to clarify whether MIE could improve the post-operative outcomes and overall survival of patients with esophageal cancer.

Methods

Literature search strategy

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Literature was identified by searching databases including PubMed, EMBASE, Web of Science and Cochrane Library up to June 2019 without language restrictions. The search terms used for literature identifications include “esophageal carcinoma, esophageal cancer, esophagectomy, minimally invasive esophagectomy, open esophagectomy and thoracoscopic laproscopic esophagectomy”.

Eligibility criteria for literature selection

Literature included in the study had to meet the following criteria: (i) studies comparing MIE with OE; (ii) studies published in English only; (iii) studies including at least 20 or more patients; (iv) studies with assigned NOS (Newcastle-Ottawa quality assessment scale) score of seven or higher; (iv) prospective, randomized controlled trials or retrospective studies only; and (v) studies where full text was available.

Data extraction and quality assessment

Literature included in the study was independently assessed for methodological quality purposes (N.A and D.D). First, the titles and abstracts were screened to assess the eligibility of included literature, and then the full text was reviewed. Any discrepancies were resolved in discussion with a third author (C.D). The information recorded for each study is given in Table 1.

Definition of study endpoints

In total, we discussed 11 endpoints in our study: one primary and 10 secondary endpoints. All-cause respiratory complications (RCs) were chosen to be discussed as the primary endpoint. These RCs included atelectasis, pneumonia, acute respiratory distress syndrome (ARDS), pleural effusion, pneumothorax and respiratory insufficiency. The details of 10 secondary endpoints are given below. All-cause cardiac complications (CCs) which included

cardiac arrest, myocardial infarction, atrial & ventricular dysrhythmia, congestive heart failure and pericarditis; all-cause anastomotic leakage (AL) defined as full thickness GI defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification; total length of in-hospital stay; total operation time; total blood loss; R0 resection; 30-day mortality; 90-day mortality; all-cause in-hospital mortality; and reoperation rate.

Statistical analysis

SPSS software was used for general data analysis. Data was extracted and entered into review manager. Continuous variables were expressed as median and interquartile ratio or range, and the mean and SD were estimated from the available data. The Mantel-Haenszel method for dichotomous data was used. Fixed or random-effects models were used in this study. Forest plots were provided to illustrate pooled odds ratios (ORs), and corresponding 95% confidence intervals (CIs). Cochran's *Q* test and Higgins *I*² were used to test the heterogeneity of different studies. A *P*-value of less than 0.1 was considered significant. Heterogeneity was interpreted according to the thresholds outlined in the Cochrane Handbook. With significant heterogeneity, a pooled effect was calculated with a random-effects model; otherwise, a fixed-effects model was applied. The reasons for interstudy heterogeneity were explored by using subgroup analysis. We also conducted sensitivity analysis by omission of each single study to evaluate stability of the results. Publication bias was assessed by using funnel plots.

Results

Selection of eligible studies

The PRISMA flowchart diagram is shown in Figure 1. In summary, our literature search strategy initially identified 150 articles. Finally, 33 articles qualified to be included in our meta-analysis study.

Characteristics of included literature

A total of 13 269 patients were included in this meta-analysis study, out of which 4948 cases were of MIE and 8321 cases were of OE. Table 1 provides detailed characteristics of the articles included. In summary, six studies had a RCT study design, 12 had a prospective study design and the remaining 15 had a retrospective study design.

Table 1 Detailed characteristics of included studies

No.	Authors (year)	Country or Region	Study design	Intervention	No. of cases	Sex ratio (M:F)	Median age, years (IQ range) mean ± SD	ASA classification					TNM staging					Pathology (adeno/squam/ others)	Neoadjuvant therapy (chemo-radio /chemo)	NOS score
								1	2	3	4	0	1	2	3	4				
1	Mariette et al. (2019) ¹⁵	France	RCT	hMIE	103	88/15	59 (23–75)	25	61	17	0	NA	18	30	50	NA§	57/46/0	36/41	9	
2	Stratman et al. (2017) ¹⁶	The Netherlands	RCT	MIE	104	87/17	62 (41–78)	34	58	12	0	NA	19	33	48	NA§	66/38/0	30/45	9	
3	Kinjo et al. (2011) ¹⁷	Japan	Retrospective	TE	56	46/10	62.3 ± 8.4	15	32	08	01	1	4	22	4	NA	35/24/0	52/4	8	
4	Sarkaria et al. (2018) ¹⁸	USA	Prospective	hMIE	72	58/14	62.7 ± 7.4	35	3	0	NA	NA	21	26	16	9	07/1/1	NA	8	
5	Safranek et al. (2010) ¹⁹	UK	Prospective	hMIE	34	29/5	64.2 ± 8.8	15	19	0	NA	NA	11	7	9	7	3/3/1/0	NA	8	
6	Paireder et al. (2018) ²⁰	Austria	RCT	MIE	79	70/9	63.3 ± 8.6	36	41	02	NA	NA	18	27	20	14	37/1/5	NA	9	
7	Sihag et al. (2016) ²¹	USA	Retrospective	MIE	64	53/11	61 (45–82)	NA	09	51	04	13	22	15	14	NA	59/4/0	47/1	8	
8	Schoppmann et al. (2010) ²²	Austria	Prospective	MIE	106	91/15	63 (28–83)	NA	15	84	07	20	25	33	27	NA	98/7/1	85/2	8	
9	Kleibro et al. (2018) ²³	Sweden	Prospective	MIE	41	25/16	64 (44–76)	NA	NA	NA	NA	2	2	14	16	NA	23/17/1	0/34	8	
10	Pery et al. (2009) ²⁴	USA	Retrospective	LE	34	28/6	63 ± 10.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	29/3/2	0/27	8	
11	Seeing et al. (2017) ¹⁴	The Netherlands	Retrospective	MIE	46	38/8	60 (44–77)	NA	NA	NA	NA	0	6	11	29	NA	43/3/0	0/34	8	
12	Mass et al. (2013) ²⁵	The Netherlands	RCT	MIE	14	10/4	64.5 (40–75)	NA	NA	NA	NA	1	4	2	6	1§	10/4/0	0/9	8	
13	Glatz et al. (2017) ²⁶	Germany	Retrospective	hMIE	12	10/2	62.5 (49–77)	NA	NA	NA	NA	2	4	2	3	1§	11/1/0	0/7	7	
14	Tang et al. (2018) ²⁷	China	Retrospective	MIE (nCRT)	814	658/156	63.3 ± 10.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	
15	Lee et al. (2011) ²⁸	Taiwan	Prospective	hMIE	2966	2492/474	63.2 ± 10.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8	
16	Bonavina et al. (2016) ²⁹	Italy	Retrospective	TE	31	25/6	61.5 (35.7–74.8)	14	13	04	NA	NA	10	4	14	1	17/14/0	NA	8	
17	Hamouda et al. (2009) ³⁰	UK	Prospective	LE	31	21/10	58.6 (33.7–76.8)	15	11	05	NA	NA	4	9	15	2	12/19/0	NA	7	
18	Kauppi et al. (2014) ³¹	Finland	Prospective	MIE	201	162/39	67 (33–83)	NA	NA	NA	NA	NA	19	13	119	32	153/41/7	125/20	8	
19				OE	165	132/33	65 (36–82)	NA	NA	NA	NA	NA	28	34	93	5	120/42/3	55/59	7	
20				OE	21	18/3	69 ± 8	(1–2 = 13)†	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	
21				OE	21	17/4	61 ± 9	(1–2 = 13)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	
22				OE	433	335/58	64 ± 9.0	80	271	82	NA	NA	26	86	310	11§	305/128/0	375/21	9	
23				OE	433	335/58	64 ± 8.7	65	287	81	NA	NA	24	82	311	17§	311/122/0	376/21	9	
24				OE	14	10/4	65 (56–75)	NA	NA	NA	NA	NA	NA	NA	NA	NA	13/1/0	NA	8	
25				OE	13	12/1	62 (52–74)	NA	NA	NA	NA	NA	NA	NA	NA	NA	11/2/0	NA	8	
26				hMIE	60	49/11	61 (42–92)	(1–2 = 36)†	NA	NA	NA	NA	9	14	14	1	46/14/0	12/35	9	
27				OE	60	52/8	61 (44–84)	(1–2 = 33)	NA	NA	NA	NA	14	14	14	5	47/13/0	12/38	9	
28				MIE (nCRT)	76	64/12	61 (44–79)	24	48	04	0	NA	NA	NA	47	29§	NA	NA	7	
29				OE (nCT)	42	33/9	61 (46–73)	13	27	02	0	NA	NA	NA	28	14§	NA	NA	7	
30				hMIE	57	51/6	60 (41–73)	19	36	02	0	NA	NA	NA	37	20§	NA	NA	7	
31				hMIE	30	30/0	59.7 ± 10.32	NA	NA	NA	NA	2	3	11	12	2	1/29/0	NA	7	
32				hMIE	44	43/1	59.7 ± 11.17	NA	NA	NA	NA	12	13	14	5	1	1/43/0	NA	7	
33				OE	64	61/3	56.5 ± 11.60	NA	NA	NA	NA	7	17	25	14	1	5/69/0	NA	8	
34				TE	80	46/34	61.5 (53–70)	15	56	09	0	NA	25	25	23	7	9/68/3	31/1	8	
35				OE	80	71/9	63.5 (55–68)	21	47	12	0	NA	15	22	31	12	63/15/2	17/1	8	
36				LE	26	25/1	62	NA	NA	NA	NA	1	0	4	19	2§	21/4/1	NA	7	
37				OE	24	23/1	60	NA	NA	NA	NA	0	1	1	18	3§	21/3/0	NA	7	
38				MIE	74	59/15	66 (51–85)	NA	NA	NA	NA	NA	NA	28	44	0	NA	3/55	7	
39				OE	79	68/11	63 (39–82)	NA	NA	NA	NA	NA	NA	25	54	0	NA	12/59	7	

Table 1 Continued

No.	Authors (year)	Country or Region	Study design	Intervention	No. of cases	Sex ratio (M/F)	Median age, years (IQ range) mean ± SD	ASA classification							TNM staging							Pathology (adeno/squam/ others)	Neoadjuvant therapy (chemo-radio /chemo)	NOS score
								1	2	3	4	0	1	2	3	4	0	1	2	3	4			
19	Guo et al. (2013) ³²	China	RCT	TE	111	68/43	57.3 ± 11.8	NA	NA	NA	NA	NA	NA	NA	24	80	7	NA§	NA	NA	7	NA	7	
20	Sihvo et al. ²³	Finland	Retrospective	MIE	150	119/31	63.9 (9.2)	NA	NA	NA	NA	NA	NA	NA	31	74	5	NA§	NA	NA	5	NA	8	
21	Pham et al. (2010) ³⁴	USA	Retrospective	TLE	44	41/3	63 ± 8.6	(1-2 = 12)†	NA	NA	NA	NA	NA	NA	6	14	18	2	34/8/0	NA	2	34/8/0	NA	8
22	Scarpa et al. (2015) ³⁵	Italy	Retrospective	hMIE	46	33/13	61 ± 10.7	(1-2 = 17)	0	0	(3-4 = 29)	0	7	13	18	18	1	34/6/2	NA	1	34/6/2	NA	8	
23	Biere et al. (2013) ³⁶	The Netherlands	RCT	MIE	34	62/5	62 (52-70)	5	22	07	NA (0-1-2 = 29)	NA	NA	NA	NA	NA	NA	24/10/0	NA	24/10/0	22	NA	9	
24	Parameswaran et al. (2013) ³⁷	UK	Prospective	LE	59	43/16	62 (34-75)	10	34	14	01	NA	NA	NA	NA	NA	NA	24/35/0	NA	24/35/0	54/5	NA	9	
25	Noble et al. (2012) ³⁸	UK	Prospective	MIE	56	46/10	62 (42-75)	15	32	08	01	NA	NA	NA	NA	NA	NA	36/19/1	NA	36/19/1	52/4	NA	8	
26	Burdall et al. (2014) ³⁹	UK	Retrospective	LE	36	24/12	64 (45-84)	NA	NA	NA	NA	6	6	13	10	10	0	22/8/5	NA	22/8/5	23	NA	8	
27	Dolan et al. (2013) ⁴⁰	USA	Retrospective	MIE	31	13/8	67 (48-79)	NA	NA	NA	NA	1	5	12	13	13	0	27/3/0	NA	27/3/0	27	NA	9	
28	Hsu et al. (2013) ⁴¹	Taiwan	Retrospective	TE	19	15/4	64 (51-77)	NA	NA	NA	NA	0	0	8	11	11	0	16/3/0	NA	16/3/0	17	NA	8	
29	Kanekiyo et al. (2017) ⁴²	Japan	Retrospective	TE	53	43/10	66 (45-85)	4	44	05	NA	2	0	9	42	42	0	47/4/1	NA	47/4/1	1/12	NA	8	
30	Rinieri et al. (2016) ⁴³	France	Prospective	MIE	53	45/8	64 (36-81)	10	32	11	NA	0	1	15	33	33	4	48/3/0	NA	48/3/0	2/9	NA	8	
31	Thomson et al. (2010) ⁴⁴	Australia	Prospective	TE	184	151/33	64.8 (39-79)	NA	NA	NA	NA	6	32	25	119	119	2	167/14/3	NA	167/14/3	0/158	NA	8	
32	Yerokun et al. (2016) ⁴⁵	USA	Retrospective	MIE	67	48/19	65.4 (36-79)	NA	NA	NA	NA	3	37	9	18	18	0	53/7/0	NA	53/7/0	0/23	NA	8	
33	Zingg et al. (2009) ⁴⁶	Australia	Prospective	OE	83	67/16	63.9 (43-77)	NA	NA	NA	NA	1	12	10	60	60	0	74/8/1	NA	74/8/1	0/76	NA	8	
			Retrospective	MIE	82	65/17	67 (60-76)	1	28	47	03	NA	NA	31	48	48	0	NA	NA	NA	74	NA	8	
			Retrospective	OE	64	55/9	69 (63-75)	0	16	35	04	NA	NA	23	33	33	NA	NA	NA	NA	39	NA	7	
			Retrospective	OE	66	61/5	58.8 ± 10.4	NA	NA	NA	NA	NA	24	14	25	25	3	NA	NA	NA	0/10	NA	8	
			Retrospective	TE	63	58/5	60 ± 11.3	NA	NA	NA	NA	NA	15	12	33	33	3	NA	NA	NA	0/14	NA	8	
			Retrospective	OE	65	56/9	66 (62-70)	16	45	04	0	(0-1 = 24)	NA	NA	NA	NA	NA	NA	NA	NA	0/37	NA	8	
			Prospective	OE	65	58/7	66 (61-70)	14	47	04	0	(0-1 = 24)	NA	NA	NA	NA	NA	NA	NA	NA	0/35	NA	8	
			Prospective	MIE	70	59/11	61.1 ± 9	9	48	13	0	15	22	15	17	17	1	50/20/0	NA	50/20/0	NA	NA	8	
			Prospective	OE	70	54/16	61 ± 9	14	40	16	0	15	23	11	20	20	1	55/15/0	NA	55/15/0	NA	NA	8	
			Prospective	TE	165	134/31	68 (36-84)	(1-2 = 120)†	NA	NA	(3-4 = 45)†	NA	51	46	68	68	NA	128/37/0	NA	128/37/0	NA	NA	8	
			Retrospective	OE	56	45/11	65 (42-82)	(1-2 = 30)	NA	NA	(3-4 = 26)	NA	5	16	35	35	NA	48/8/0	NA	48/8/0	NA	NA	8	
			Retrospective	MIE	1077	905/172	57 (64-70)	NA	NA	NA	NA	194	350	149	291	291	6	861/216/0	NA	861/216/0	643/0	NA	8	
			Retrospective	rMIE	231	195/36	57 (64-70)	NA	NA	NA	NA	52	72	31	63	63	1	186/45/0	NA	186/45/0	157/0	NA	8	
			Retrospective	OE	2958	2474/484	57 (64-70)	NA	NA	NA	NA	494	812	443	852	852	12	2305/653/0	NA	2305/653/0	800/0	NA	8	
			Prospective	OE	56	45/11	66.3 (1.3)	NA	NA	NA	NA	15	9	21	11	11	NA	46/10/0	NA	46/10/0	40	NA	8	
			Prospective	OE	98	71/27	67.8 (1.1)	NA	NA	NA	NA	14	15	33	27	27	NA	65/29/4	NA	65/29/4	48	NA	8	

adeno; adenocarcinoma; ASA, American Society of Anesthesiologists; chemo, chemotherapy; chemo-radio, chemo-radiotherapy; hMIE, Hybrid minimally invasive esophagectomy; IQ, interquartile; LE, laparoscopic-assisted esophagectomy; M/F, Male/Female; NA, not available; nCRT, neoadjuvant chemo-radiotherapy; nCT, neoadjuvant chemotherapy; NOS, Newcastle-Ottawa quality assessment scale; OE, open esophagectomy; RCT, randomized controlled trial; rMIE, robotic-assisted minimally invasive esophagectomy; SD, standard deviation; squam; squamous cell carcinoma; TE, thoracoscopic esophagectomy; TLE, thoracoscopic laparoscopic esophagectomy; tMIE, total minimally invasive esophagectomy. †The ASA classification data for multiple stages is provided together. ‡The TNM staging data for multiple stages is provided together. §Mention of size or direct extension of primary tumor only. ¶Not specified whether the neoadjuvant therapy was chemo-radiotherapy or chemotherapy.

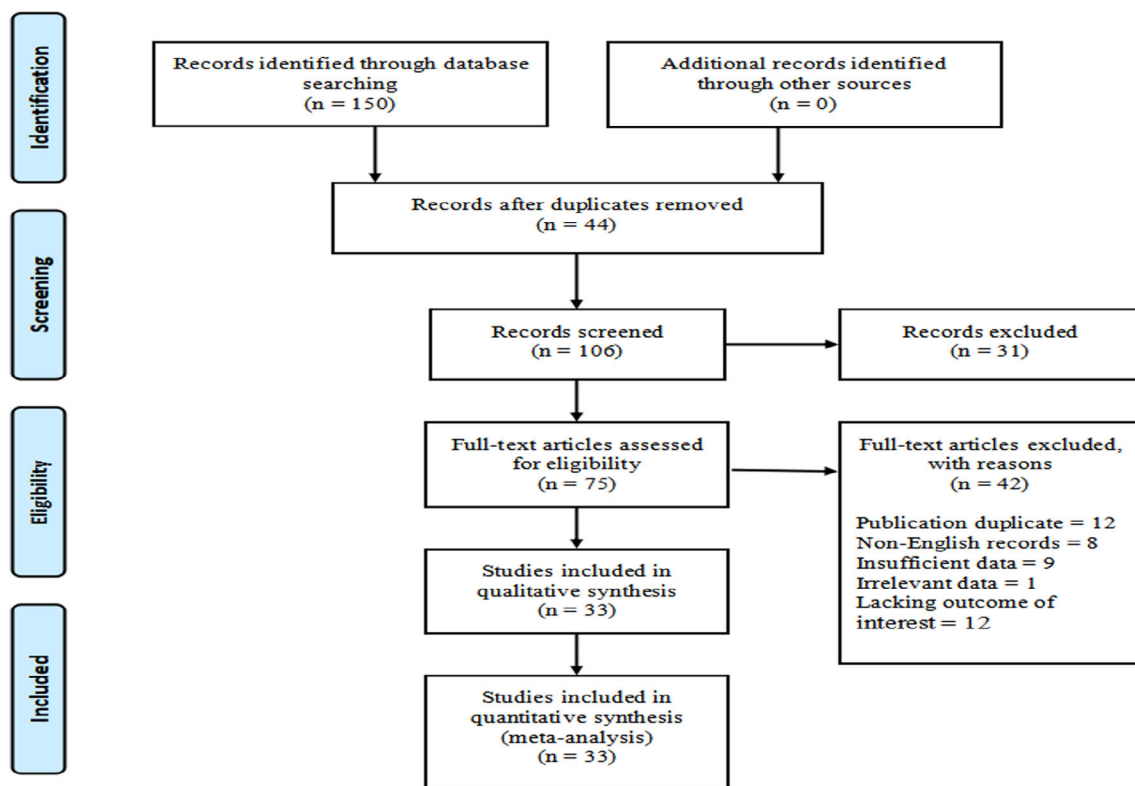


Figure 1 PRISMA flowchart of literature search strategy.

Primary outcome: All-cause RCs

A total of 24 studies^{14–22,24–30,32,34–38,42} with 7117 patients were involved in the analysis of all-cause RCs. Figure 2a shows that the patients who underwent MIE experienced less postoperative RCs as compared to those who underwent OE (OR = 0.56; 95% CI = 0.41, 0.78; $P < 0.001$). Test of heterogeneity showed considerable heterogeneity ($I^2 = 77%$ and $P < 0.001$). Subgroup analyses were conducted to explore potential sources of that heterogeneity (Table 2). The pooled ORs of most subgroups were not markedly changed by the study characteristics. However, the subgroup analysis by intervention type showed considerable significance for tMIE/OE ($P < 0.001$; $I^2 = 91%$) as compare to hMIE/OE ($P = 0.07$; $I^2 = 35%$) which was less significant. We also noted the changes in statistical heterogeneity in the subgroup analysis of different institutes and facilities (single center, $I^2 = 64%$; multicenter, $I^2 = 83%$), initial inclusion period (< 2008 , $I^2 = 68%$; ≥ 2008 , $I^2 = 88%$), study design (RCT, $I^2 = 74%$; prospective, $I^2 = 79%$; retrospective, $I^2 = 54%$), and NOS score (7, $I^2 = 56%$; 8, $I^2 = 74%$; 9, $I^2 = 87%$). Sensitivity analysis was conducted by omission of each single study to evaluate the stability of results indicating an unaffected pooled OR. The funnel plots displaying the publication bias of all cause RCs is shown in Figure S2b.

Secondary endpoints

A total of 22 studies^{14–22,24–30,32,34–36,38,42} with 6925 patients were included in the analysis of all-cause AL, which showed low level of heterogeneity ($P = 0.08$, $I^2 = 32%$) and no statistical difference between MIE versus OE (OR = 1.08; 95% CI = 0.92, 1.26; $P = 0.35$) (Figs 2b, S2c). Data for all-cause CCs was reported in 13 studies^{13,14,18,24,26,27,29–31,35,38,42} with 2302 patients and showed neither heterogeneity ($P = 0.99$, $I^2 = 0%$), nor statistically significant difference between MIE or OE (OR = 0.97; 95% CI = 0.74, 1.26; $P = 0.81$) (Figs 3a, S2d).

Evaluation of data for total length of in-hospital stay from 21 studies^{14,15,17,18,20,22,24–29,32,34–36,38,40,42,46} with 3265 patients showed that patients who underwent MIE got to experience less in-hospital duration compared with those who underwent OE (SMD = -0.51 ; 95% CI = -0.78 , -0.24 ; $P < 0.001$) (Fig. 3b). Substantial heterogeneity ($P < 0.001$, $I^2 = 92%$) was found and subgroup analyses were performed to explore the potential source of heterogeneity as shown in Table S1. A total of 23 studies^{15–18,20,22,24–29,31,32,34–36,38,40–42,46} with 2796 patients included in analyzing the data for total operation time showed that the patients who underwent MIE experienced longer operation time compared to those who underwent OE (SMD = 0.52; 95% CI = 0.16, 0.89; $P = 0.005$) (Fig. 4a and Table S2).

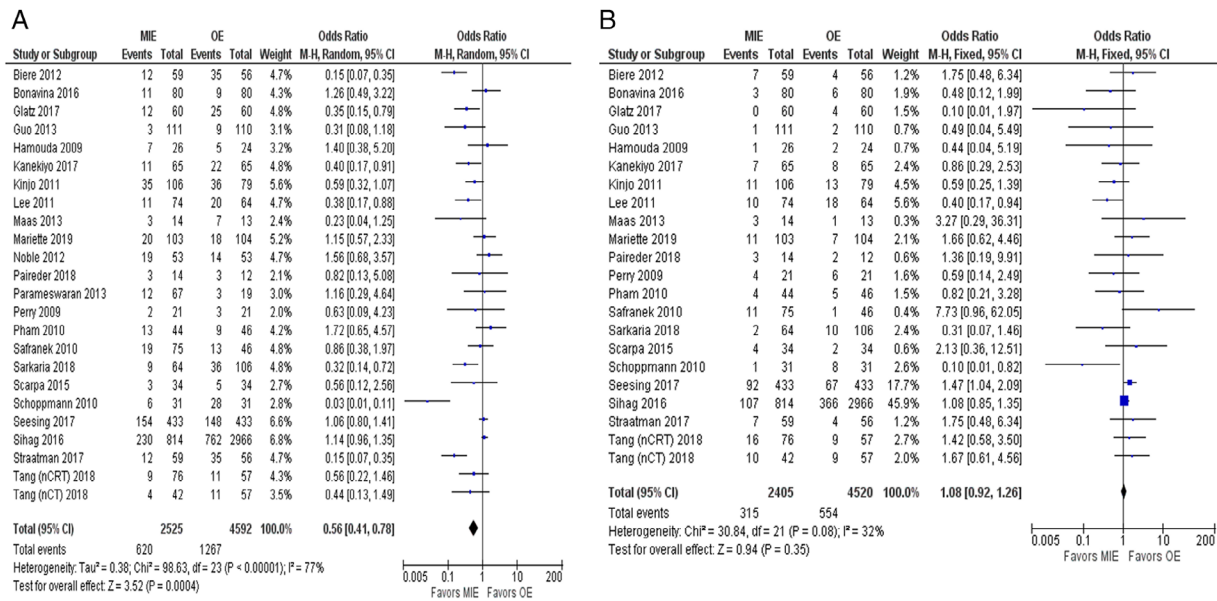


Figure 2 (a) Forest plot of all-cause RCs. (b) Forest plot of all-cause AL.

Data for total blood loss gathered from 17 studies^{16–18,24,25,27–29,32,34,36,38,40–42,46} with 2160 patients revealed that MIE resulted in less blood loss in comparison with OE (SMD = -1.44; 95% CI = -1.95, -0.93; P = <0.001) (Fig. 4b). The outcome also indicated the presence of substantial heterogeneity (P = <0.001, I² = 96%) which led us to perform subgroup analyses to analyze the source of heterogeneity (Table S3). Other outcomes such as R0 resection (OR = 1.47; 95% CI = 1.13, 1.92; P = 0.004), 30-day mortality (OR = 0.92; 95% CI = 0.69, 1.22; P = 0.56), 90-day mortality (OR = 0.52; 95% CI = 0.29, 0.91; P = 0.02), in-hospital mortality (OR = 0.73; 95% CI = 0.38, 1.41; P = 0.35), and the rate of reoperation (OR = 1.30; 95% CI = 0.85, 1.98; P = 0.22) showed no significant statistical differences between MIE and OE as shown in Figs S1a–S1d, S2a.

Discussion

This study compared the outcomes of OE with both tMIE and hMIE. Due to the complexity of esophagectomy, different types of surgical approaches might lead to different kinds of surgical complications, but the main morbidities remain the same which include RCs, CCs, AL and the aforementioned.

Most of the meta-analysis studies comparing the outcomes of MIE and OE previously performed were either based on retrospective studies only, or had a small sample size.^{11,47–49} Although, Lv *et al.* had a relatively larger sample size of 6025

patients from 20 studies, their study only included literature up to 2016.¹² Since then, a considerable number of updated studies have been published, showing new findings and discrepancies in their results.^{9,13–16,18,20,23,26,27,33,42} In contrast, we included 33 studies in total involving 13 269 patients in our meta-analysis to provide the latest and more robust outcomes comparing MIE and OE.

Postoperative RCs are of great importance and could impact the prognosis of patients, which are also the most frequent morbidity events after esophagectomy. Some previous studies have shown contradictory results regarding the advantages of MIE over OE with respect to postoperative RCs. Two retrospective studies showed no significant differences regarding RCs between two groups.^{13,50} On the other hand, two RCTs showed a significantly lower incidence of respiratory complications after MIE than OE.^{36,51} Pooled data from our study also showed that patients who underwent MIE experienced fewer postoperative RCs compared to those who underwent OE (Fig. 2a). The association of MIE with fewer postoperative RCs could be explained by the elegance of the MIE operation procedure which decreases surgical trauma to the chest wall and does less harm to pulmonary tissues.

The results from our study showed that MIE was associated with a longer operative time as compared to OE. These results were consistent with other recently published studies and could be attributed to the technical difficulty in MIE and a limited operating space for surgeons to

Table 2 Subgroup analyses of all-cause RCs of MIE and OE

Variable	Studies	Test of association			Test of heterogeneity	
		OR	95% CI	P-value	I ² (%)	P-value
Total	24	0.56	0.41–0.78	<0.001	77	<0.001
Publication year						
<2016	13	0.51	0.29–0.90	<0.001	72	0.02
≥2016	11	0.61	0.42–0.90	<0.001	77	0.01
No. of cases						
<100	9	0.52	0.22–1.24	0.001	69	0.014
>100	15	0.57	0.40–0.81	<0.001	80	0.002
Research region						
The Netherlands	4	0.29	0.08–1.07	<0.001	92	0.06
The UK	4	1.19	0.72–1.96	0.79	0.00	0.49
The USA	4	0.84	0.40–1.74	0.02	71	0.63
China (Mainland)	3	0.45	0.24–0.88	0.78	0.00	0.02
Italy	2	1.1	0.45–2.24	0.38	0.00	0.99
Japan	2	0.51	0.32–0.84	0.45	0.00	0.007
Austria	2	0.14	0.00–4.13	0.004	88	0.25
Miscellaneous regions (Germany, France, Taiwan)	3	0.55	0.25–1.21	0.05	67	0.14
Institutes/facilities						
Single center	14	0.56	0.36–0.88	0.01	64	<0.001
Multicenter	10	0.57	0.36–0.90	0.02	83	<0.001
Initial inclusion period						
<2008	12	0.64	0.38–1.08	<0.001	68	0.09
≥2008	12	0.50	0.32–0.77	<0.001	82	0.002
Study design						
RCT	6	0.33	0.14–0.79	0.001	74	0.01
Prospective	7	0.52	0.23–1.20	<0.001	79	0.13
Retrospective	11	0.79	0.59–1.05	0.02	54	0.11
Intervention						
tMIE/OE	7	0.33	0.16–0.68	<0.001	91	0.002
hMIE/OE	17	0.68	0.51–0.90	0.07	35	0.008
Neoadjuvant therapy						
With	13	0.59	0.37–0.92	<0.001	76	0.02
Without	11	0.52	0.30–0.90	<0.001	77	0.02
NOS score						
7	7	0.66	0.39–1.11	0.03	56	0.12
8	10	0.64	0.39–1.06	<0.001	74	0.08
9	7	0.48	0.24–0.97	<0.001	87	0.04

CI, confidence interval; hMIE, hybrid minimally invasive esophagectomy; NOS, Newcastle-Ottawa quality assessment scale; OR, odds ratio; RCT, randomized controlled trial; tMIE, total minimally invasive esophagectomy.

perform the delicate procedure.^{16,18,42} Data analyses also demonstrated that patients who underwent MIE experienced shorter postoperative in-hospital stay and had less in-operative blood loss, as compared to those who underwent OE. Both these results were in accordance with previous studies and can be associated with the less intrusive nature of MIE.^{23,26,36}

Notably, pooled results and subgroup analyses from our study showed no significant correlation between neoadjuvant therapy and improvement of postoperative outcomes, either after MIE or OE.

Principle findings and limitations

Our meta-analysis provides strong evidence for the association of MIE with overall better short-term outcomes (Table 3). When stratified by publication year, initial inclusion period, number of cases, types of surgical intervention, and NOS quality score, the results remained mostly constant. Meanwhile, the heterogeneity in subgroup analyses was shown to be not considerable in general. In addition, with the application of some advanced statistical methods, the results have demonstrated that the outcomes tend to be

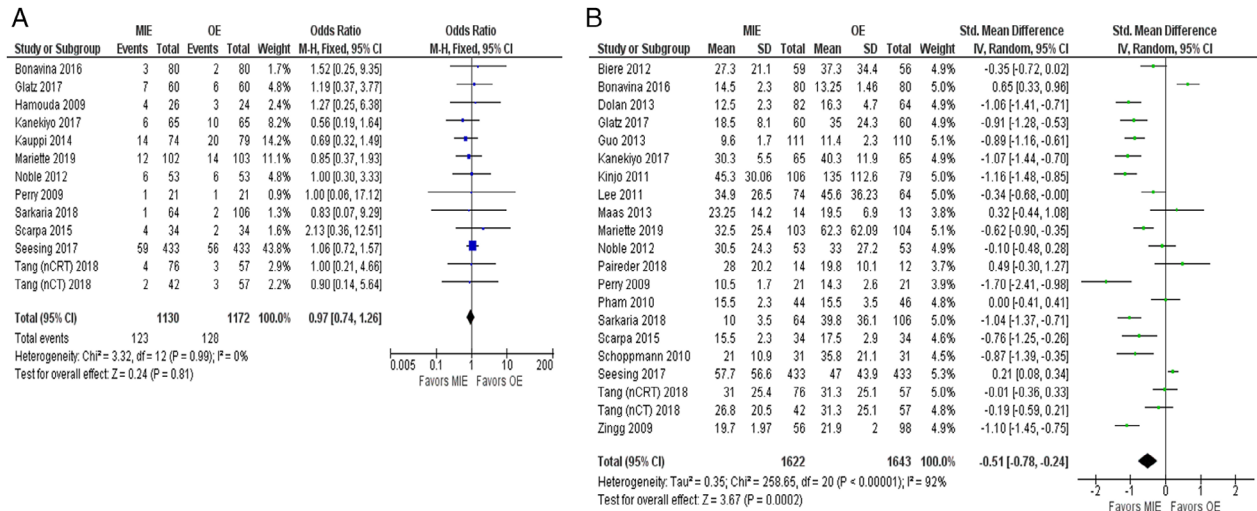


Figure 3 (a) Forest plot of all-cause CCs. (b) Forest plot of in-hospital stay.

much more stable with the increasing number of studies over time.

There are several limitations to our study that should also be acknowledged. First, as shown in Table 1, the pathological TNM staging and ASA classification is missing from several included studies, which resulted in undeniable differences in their quality and strength. Second, patients of different ethnical groups were placed together into MIE or OE groups, which would also have effects on the results of this study. Third, different MIE methods (tMIE or hMIE) were used in different included studies, which makes it difficult to more specifically point out if there was any particular MIE technique that was the most beneficial

for better outcomes. Fourth, there is also a possibility that patients with beneficial prognostic variables, for example, younger age and less comorbidity, were more readily selected for MIE rather than OE. Finally, even though our study included several RCTs, the lack of larger number of multi-institutional RCTs might reduce the effectiveness of the research. Consequently, the work definitely needs to be improved when there are more RCTs. Although advanced statistical methods were applied, publication bias was inevitable as shown in Fig. S2.

In conclusion, while OE was associated with shorter operation time and a slightly better surgical clearance of the tumor (R0 resection rates) compared with MIE, MIE

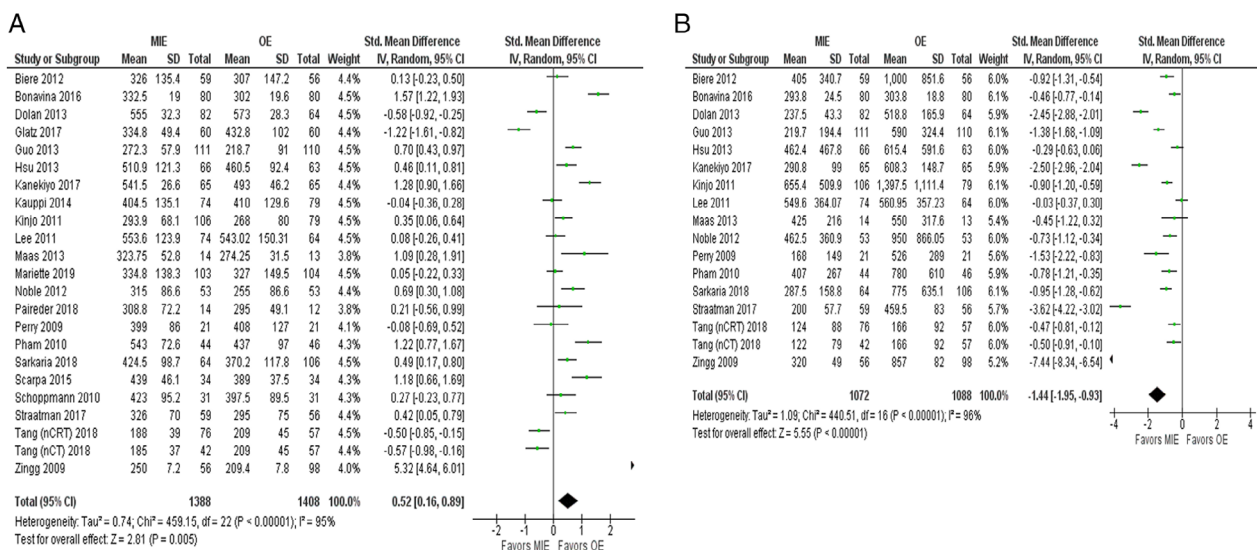


Figure 4 (a) Forest plot of total operation time. (b) Forest plot of blood loss.

Table 3 Summary of the final results of all primary and secondary endpoints

Endpoints	Studies	Cases	OR/SMD	95%CI	P-value	I ²	P-value	Favors
All-cause RCs	24	7117	0.56	0.41, 0.78	<0.001	77%	<0.001	MIE
All-cause AL	22	6925	1.08	0.92, 1.26	0.35	32%	0.08	None
All-cause CCs	13	2302	0.97	0.74, 1.26	0.81	0%	0.99	None
In-hospital stay	21	3265	-0.51	-0.78, -0.24	<0.001	96%	<0.001	MIE
Total operation time	23	2796	0.52	0.16, 0.89	0.005	95%	<0.001	OE
Blood loss	17	2160	-1.44	-1.95, -0.93	<0.001	96%	<0.001	MIE
R0 resection	13	2938	1.47	1.13, 1.92	0.004	0%	0.56	None
30-day mortality	12	7976	0.92	0.69, 1.22	0.56	0%	0.95	None
90-day mortality	6	1095	0.52	0.29, 0.91	0.02	0%	0.91	None
In-hospital mortality	8	846	0.73	0.38, 1.41	0.35	0%	0.71	None
Reoperation	10	4767	1.30	0.85, 1.98	0.22	33%	0.14	None

AL, anastomotic leakage; CCs, cardiac complications; CI, confidence interval; MIE, minimally invasive esophagectomy; OE, open esophagectomy; OR, odds ratio; RCs, respiratory complications; SMD, standardized mean difference.

was associated with fewer RCs, lesser blood loss, shorter postoperative in-hospital stay and better overall postoperative outcomes. Further large-scale, multicenter RCTs are needed to continue to explore further long-term survival outcomes of patients with MIE and OE.

Acknowledgments

This study was supported by the projects from Shanghai Hospital Development Center (SHDC12015116), the National Natural Science Foundation of China (81802256), Science and Technology Commission of Shanghai Municipality (15 411 968 400 and 14 411 962 600), Suzhou Key Laboratory of Thoracic Oncology (SZS201907), Suzhou Key Discipline for Medicine (SZXK201803), the Science and Technology Research Foundation of Suzhou Municipality (SYS2018063, SYS2018064) and Municipal Program of People's Livelihood Science and Technology in Suzhou (SS2019061).

Disclosure

The authors report that there are no conflicts of interest.

References

- Fitzmaurice C, Akinyemiju TF, Al Lami FH *et al.* Global burden of disease cancer collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study. *JAMA Oncol* 2018; **4**: 1553–68.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7–30.
- Anderson LA, Tavilla A, Brenner H *et al.* Survival for oesophageal, stomach and small intestine cancers in Europe 1999–2007: Results from EURO-CARE-5. *Eur J Cancer* 2015; **51**: 2144–57.
- Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. *Lancet* 2017; **390**: 2383–96.
- Reichert M, Schistek M, Uhle F *et al.* Ivor Lewis esophagectomy patients are particularly vulnerable to respiratory impairment - a comparison to major lung resection. *Sci Rep* 2019; **9**: 1.
- Ohi M, Toiyama Y, Omura Y *et al.* Risk factors and measures of pulmonary complications after thoracoscopic esophagectomy for esophageal cancer. *Surg Today* 2018; **49**: 176–86.
- Hayami M, Watanabe M, Ishizuka N *et al.* Prognostic impact of postoperative pulmonary complications following salvage esophagectomy after definitive chemoradiotherapy. *J Surg Oncol* 2017; **117**: 1251–9.
- Decker G, Coosemans W, De Leyn P *et al.* Minimally invasive esophagectomy for cancer. *Eur J Cardiothorac Surg* 2009; **35**: 13–21.
- Sakamoto T, Fujiogi M, Matsui H, Fushimi K, Yasunaga H. Comparing perioperative mortality and morbidity of minimally invasive esophagectomy versus open esophagectomy for esophageal cancer. *Ann Surg* 2019; **1**: <https://doi.org/10.1097/SLA.0000000000003500>.
- Luketich J, Pennathur A, Awais O *et al.* Outcomes after minimally invasive esophagectomy. *Ann Surg* 2012; **256**: 95–103.
- Xiong W, Li R, Lei H, Jiang Z. Comparison of outcomes between minimally invasive oesophagectomy and open oesophagectomy for oesophageal cancer. *ANZ J Surg* 2015; **87**: 165–70.
- Lv L, Hu W, Ren Y, Wei X. Minimally invasive esophagectomy versus open esophagectomy for esophageal cancer: A meta-analysis. *Onco Targets Ther* 2016; **9**: 6751–62.
- Gottlieb-Vedi E, Kauppila J, Malietzis G, Nilsson M, Markar S, Lagergren J. Long-term survival in esophageal cancer after minimally invasive compared to open esophagectomy. *Ann Surg* 2019; **270**: 1005–17.

- 14 Seesing M, Gisbertz S, Goense L *et al.* A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in The Netherlands. *Ann Surg* 2017; **266**: 839–46.
- 15 Mariette C, Markar S, Dabakuyo-Yonli T *et al.* Hybrid minimally invasive esophagectomy for esophageal cancer. *N Engl J Med* 2019; **380**: 152–62.
- 16 Straatman J, van der Wielen N, Cuesta M *et al.* Minimally invasive versus open esophageal resection. *Ann Surg* 2017; **266**: 232–6.
- 17 Kinjo Y, Kurita N, Nakamura F *et al.* Effectiveness of combined thoracoscopic–laparoscopic esophagectomy: Comparison of postoperative complications and midterm oncological outcomes in patients with esophageal cancer. *Surg Endosc* 2011; **26**: 381–90.
- 18 Sarkaria I, Rizk N, Goldman D *et al.* Early quality of life outcomes after robotic-assisted minimally invasive and open esophagectomy. *Ann Thorac Surg* 2019; **108**: 920–8.
- 19 Safranek P, Cubitt J, Booth M, Dehn T. Review of open and minimal access approaches to oesophagectomy for cancer. *Br J Surg* 2010; **97**: 1845–53.
- 20 Paireder M, Asari R, Kristo I *et al.* Morbidity in open versus minimally invasive hybrid esophagectomy (MIOMIE). *Eur Surg* 2018; **50**: 249–55.
- 21 Sihag S, Kosinski AS, Gaissert HA, Wright CD, Schipper PH. 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**: 1281–9.
- 22 Schoppmann S, Prager G, Langer F *et al.* Open versus minimally invasive esophagectomy: A single-center case controlled study. *Surg Endosc* 2010; **24**: 3044–53.
- 23 Klevebro F, Scandavini C, Kamiya S, Nilsson M, Lundell L, Rouvelas I. Single center consecutive series cohort study of minimally invasive versus open resection for cancer in the esophagus or gastroesophageal junction. *Dis Esophagus* 2018; **31**: 10.
- 24 Perry K, Enestvedt CK, Pham T *et al.* Comparison of laparoscopic inversion esophagectomy and open transhiatal esophagectomy for high-grade dysplasia and stage I esophageal adenocarcinoma. *Arch Surg* 2009; **144**: 679–84.
- 25 Maas K, Biere S, van Hoogstraten I, van der Peet D, Cuesta M. Immunological changes after minimally invasive or conventional esophageal resection for cancer: A randomized trial. *World J Surg* 2013; **38**: 131–7.
- 26 Glatz T, Marjanovic G, Kulemann B, Sick O, Hopt U, Hoepfner J. Hybrid minimally invasive esophagectomy vs. open esophagectomy: A matched case analysis in 120 patients. *Langenbeck's Arch Surg* 2017; **402**: 323–31.
- 27 Tang H, Zheng H, Tan L *et al.* Neoadjuvant chemoradiotherapy followed by minimally invasive esophagectomy: Is it a superior approach for locally advanced resectable esophageal squamous cell carcinoma? *J Thorac Dis* 2018; **10**: 963–72.
- 28 Lee J, Cheng J, Lin M, Huang P, Chen J, Lee Y. Is there any benefit to incorporating a laparoscopic procedure into minimally invasive esophagectomy? The impact on perioperative results in patients with esophageal cancer. *World J Surg* 2011; **35**: 790–7.
- 29 Bonavina L, Scolari F, Aiolfi A *et al.* Early outcome of thoracoscopic and hybrid esophagectomy: Propensity-matched comparative analysis. *Surgery* 2016; **159**: 1073–81.
- 30 Hamouda A, Forshaw M, Tsigris K *et al.* Perioperative outcomes after transition from conventional to minimally invasive Ivor-Lewis esophagectomy in a specialized center. *Surg Endosc* 2009; **24**: 865–9.
- 31 Kauppi J, Räsänen J, Sihvo E, Huuhtanen R, Nelskylä K, Salo J. Open versus minimally invasive esophagectomy: Clinical outcomes for locally advanced esophageal adenocarcinoma. *Surg Endosc* 2014; **29**: 2614–9.
- 32 Guo M, Xie B, Sun X, Hu M, Yang Q, Lei Y. A comparative study of the therapeutic effect in two protocols: Video-assisted thoracic surgery combined with laparoscopy versus right open transthoracic esophagectomy for esophageal cancer management. *Chin-German J Clin Oncol* 2013; **12**: 68–71.
- 33 Sihvo E, Helminen O, Gunn J, Sipilä J, Rautava P, Kytö V. Long-term outcomes following minimally invasive and open esophagectomy in Finland: A population-based study. *Eur J Surg Oncol* 2019; **45**: 1099–104.
- 34 Pham T, Perry K, Dolan J *et al.* Comparison of perioperative outcomes after combined thoracoscopic-laparoscopic esophagectomy and open Ivor-Lewis esophagectomy. *Am J Surg* 2010; **199**: 594–8.
- 35 Scarpa M, Cavallin F, Saadeh L *et al.* Hybrid minimally invasive esophagectomy for cancer: Impact on postoperative inflammatory and nutritional status. *Dis Esophagus* 2015; **29**: 1064–70.
- 36 Biere S, van Berge HM, Maas K *et al.* Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicentre, open-label, randomised controlled trial. *Lancet* 2012; **379**: 1887–92.
- 37 Parameswaran R, Titcomb D, Blencowe N *et al.* Assessment and comparison of recovery after open and minimally invasive esophagectomy for cancer: An exploratory study in two centers. *Ann Surg Oncol* 2013; **20**: 1970–7.
- 38 Noble F, Kelly J, Bailey I, Byrne J, Underwood T. A prospective comparison of totally minimally invasive versus open Ivor Lewis esophagectomy. *Dis Esophagus* 2012; **26**: 263–71.
- 39 Burdall O, Boddy A, Fullick J *et al.* A comparative study of survival after minimally invasive and open oesophagectomy. *Surg Endosc* 2014; **29**: 431–7.
- 40 Dolan J, Kaur T, Diggs B *et al.* Impact of comorbidity on outcomes and overall survival after open and minimally invasive esophagectomy for locally advanced esophageal cancer. *Surg Endosc* 2013; **27**: 4094–103.

- 41 Hsu P, Huang C, Wu Y, Chou T, Hsu W. Open versus thoroscopic esophagectomy in patients with esophageal squamous cell carcinoma. *World J Surg* 2013; **38**: 402–9.
- 42 Kanekiyo S, Takeda S, Tsutsui M *et al.* Low invasiveness of thoroscopic esophagectomy in the prone position for esophageal cancer: A propensity score-matched comparison of operative approaches between thoroscopic and open esophagectomy. *Surg Endosc* 2017; **32**: 1945–53.
- 43 Rinieri P, Ouattara M, Brioude G *et al.* Long-term outcome of open versus hybrid minimally invasive Ivor Lewis oesophagectomy: A propensity score matched study. *Eur J Cardiothorac Surg* 2016; **273**: 1–7.
- 44 Thomson I, Smithers B, Gotley D *et al.* Thorascopic-assisted esophagectomy for esophageal cancer. *Ann Surg* 2010; **252**: 281–91.
- 45 Yerokun BA, Sun Z, Yang C-FJ *et al.* Minimally invasive versus open esophagectomy for esophageal cancer: A population-based analysis. *Ann Thorac Surg* 2016; **102**: 416–23.
- 46 Zingg U, McQuinn A, DiValentino D *et al.* Minimally invasive versus open esophagectomy for patients with esophageal cancer. *Ann Thorac Surg* 2009; **87**: 911–9.
- 47 Nagpal K, Ahmed K, Vats A *et al.* Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. *Surg Endosc* 2010; **24**: 1621–9.
- 48 Dantoc M, Cox MR, Eslick GD. Evidence to support the use of minimally invasive esophagectomy for esophageal cancer: A meta-analysis. *Arch Surg* 2012; **147**: 768–76.
- 49 Sgourakis G, Gockel I, Radtke A *et al.* Minimally invasive versus open esophagectomy: Meta-analysis of outcomes. *Dig Dis Sci* 2010; **55**: 3031–40.
- 50 Takeuchi H, Miyata H, Gotoh M *et al.* A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. *Ann Surg* 2014; **260**: 259–66.
- 51 Nozaki I, Mizusawa J, Kato K *et al.* Impact of laparoscopy on the prevention of pulmonary complications after thorascopic esophagectomy using data from JCOG0502: A prospective multicenter study. *Surg Endosc* 2017; **32**: 651–9.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. (a) Forest plot of R0 resection; (b) forest plot of 30-day mortality; (c) forest plot of 90-day mortality; and (d) forest plot of in-hospital mortality.

Figure S2. (a) Forest plot of reoperation; (b) funnel plot of all-cause RCs; (c) funnel plot of all-cause AL; and (d) funnel plot of all-cause CCs.

Table S1. Subgroup analysis of in-hospital stay between MIE and OE.

Table S2. Subgroup analysis of total operation time between MIE and OE.

Table S3. Subgroup analysis of blood loss between MIE and OE.