

## Original Article

# Comparison of long-term outcomes of minimally invasive esophagectomy and open esophagectomy for esophageal squamous cell carcinoma

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Received June 13, 2016; Accepted June 18, 2016; Epub July 15, 2016; Published July 30, 2016

**Abstract:** Objective: To compare surgical outcomes and oncologic efficacy between minimally invasive esophagectomy (MIE) and open esophagectomy (OE) for operable esophageal squamous cell carcinoma. Methods: 81 consecutive esophageal squamous cell carcinoma patients who underwent MIE and another 81 patients who underwent open resection between January 2007 and December 2013 were enrolled in this study. Results: There were no significant differences in the demographic characteristics and pathological features between the two groups of patients. Regarding short-term outcomes, blood loss, post-operative analgesia and postoperative stay were significantly shorter in the MIE group than in the open group, while operation time was significantly longer in the MIE group than in the open group. Overall morbidity was similar in the two groups. There were no significant differences in the 5-year overall and disease-free survival rate between the two groups. In multivariate analysis, surgical approach was not found to be a significant predictor for overall survival and disease-free survival. Conclusion: This case-control study presented that MIE may be a safe and acceptable procedure in terms of long-term results for operable esophageal squamous cell carcinoma.

**Keywords:** Esophageal carcinoma, esophagectomy, minimally invasive surgery, survival

## Introduction

With recent developments in instrument design and surgical techniques [1-6], minimally invasive esophagectomy (MIE) [combined thoracoscopic-laparoscopic esophagectomy] has become an excellent surgical option for the treatment of operable esophageal carcinoma [7]. However, MIE is performed only at a limited number of hospitals; the most important reason for its low degree of popularity is that MIE is more technically difficult with uncertain long-term outcomes. In recent years, there have been several reports on the safety and feasibility of MIE, and the short-term outcomes have also been reviewed [8-11]. However, these studies are mostly with a small number (less than 30 cases), lacking relatively large sample sizes (more than 50 cases) and long-term follow up data [12-21]. In China, esophageal squamous cell carcinoma is one of the most common malignancies and one of the most frequent

causes of cancer-related death [22]. In the present study, we reviewed our experience with MIE in the treatment of esophageal squamous cell carcinoma and evaluated the long-term outcome of this approach through a case-control study

## Material and methods

### *Patient evaluation*

This study complied with the Declaration of Helsinki and approved by local ethics committees. The need for informed consent from patients was waived because of retrospective study, not prospective research.

This study was a retrospective case-control study, including 81 patients who underwent MIE and 81 patients who underwent open esophagectomy (OE) for esophageal squamous cell carcinoma in our institution from January 2007 to December 2013. The criteria for inclu-

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**Table 1.** Patient characteristic of the two groups

	MIE (n=81)	OE (n=81)	P value
Age (years)	60 (46-77)	60 (42-75)	0.879
Sex			0.608
Male	55	58	
Female	26	23	
ASA score			0.720
I	52	54	
II	23	22	
III	6	5	
Comorbidity			0.530
Liver cirrhosis	1	1	
Hypertension	5	3	
Diabetes Mellitus	1	3	
COPD	1	2	
Arrhythmia	1	1	
Clinical TNM stage (7th AJCC-UICC)			0.817
IB	28	27	
IIA	43	43	
IIB	10	11	

COPD: chronic obstructive pulmonary disease. MIE: minimally invasive esophagectomy. OE: open esophagectomy.

sion were the patients who underwent MIE or OE for clinical T1-3N0M0 esophageal squamous cell carcinoma, tumors in the middle and lower thoracic esophagus, without neoadjuvant therapy or evidence of metastasis or extended resection. Patients in both groups were matched for age, sex, American Society of Anesthesiology risk class (ASA) and clinical TNM stage. Clinical and pathological data were obtained from operative and pathological reports from our institution. In this study, both the procedures (MIE and OE) were suitable for all patients who met our inclusion criteria. After a sufficient explanation of the surgical and oncologic risks for both procedures, the surgical procedure (MIE or OE) was chosen by patients and their families when a written informed consent was signed preoperatively.

The routine preoperative evaluation included upper gastrointestinal endoscopy, endoscopic ultrasonography, computed tomographic scans of brain, chest, and upper abdomen and ultrasonography of neck. Positron emission tomography-computerized tomography (PET-CT), mediastinoscopy and bone scanning were performed in selected cases. The clinical stage of esophageal squamous cell carcinoma was based on the 7th edition of the TNM classification

of gastric cancer which was proposed by Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) [23]. For those of the patients operated before 2010, their staging was recalculated to match the 7th TNM classification by UICC and AJCC.

### *Short-term outcome and postoperative complications*

All patients were managed according to the same standardized pre- and postoperative esophagectomy protocol. Data regarding short-term outcome were obtained from in-hospital database. Postoperative complications and morbidity occurrence within 30 postoperative days or hospital stay were classified using Clavien-Dindo classification, which simplified the definition of postoperative complications and graded the

severity of these events [24]. Major complications were defined as grades 3b, 4a, 4b and 5. Minor complications were classified as 1, 2 and 3a. The detail of Clavien-Dindo classification has been reported.

### *Follow up*

Data regarding follow-up were obtained from our institutional follow up database. Patients were scheduled to perform abdominopelvic and chest computed tomography scan and ultrasonography of neck every 6 months after esophagectomy for the follow-up. Endoscopy was suggested for once a year after surgery. The overall survival was assessed from the date of surgery until the last follow up or death of any cause. The disease-free survival was calculated from the date of surgery until the date of cancer recurrence or death from any cause. Disease recurrence was defined as locoregional or distant metastasis proven by radiology or pathology when available. The last follow up was October 2014.

### *Surgical technique*

All the surgeries were performed by two experienced surgeons (Xiuqu Fei and Jie Liao) with

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**Table 2.** Pathological data of the two groups

	MIE (n=81)	OE (n=81)	P value
Retrieved lymph nodes	20 (16-23)	20 (15-28)	0.406
Pathological TNM stage (7th AJCC-UICC)			0.528
IB	19	20	
IIA	23	26	
IIB	25	24	
IIIA	8	7	
IIIB	4	3	
IIIC	2	1	
Residual tumor (R0/R1/R2)	81/0/0	81/0/0	1.000

MIE: minimally invasive esophagectomy. OE: open esophagectomy.

**Table 3.** Surgical data of the two groups

	MIE (n=81)	OE (n=81)	P value
Operative time (min)	270 (200-300)	210 (180-270)	0.000
Blood loss (ml)	175 (160-320)	400 (230-600)	0.000
Number of analgesic injections	5 (3-6)	6 (4-9)	0.000
Postoperative stay (d)	10 (8-15)	16 (8-25)	0.000
Overall complications n (%)	20 (24.7)	26 (32.1)	0.296
Major complications n (%)	5 (6.2)	10 (12.3)	0.175
Pulmonary embolism	1	3	
Anastomosis leakage	2	2	
Recurrent laryngeal nerve injury	1	2	
Heart failure	1	3	
Minor complications n (%)	15 (18.5)	15 (18.5)	0.844
Recurrent laryngeal nerve injury	3	3	
Pneumonia	8	12	
Urinary tract infection	2	1	
Atelectasis	2	1	

MIE: minimally invasive esophagectomy. OE: open esophagectomy.

proven expertise in esophageal carcinoma. The resection was performed with curative intention in all patients. The procedures of the MIE were as follows: thoracoscopic esophageal mobilization and mediastinal lymphadenectomy, laparoscopic gastric mobilization, gastric tube formation, abdominal lymphadenectomy and cervical anastomosis. The regional lymph nodes removal were as follows: mediastinal lymph nodes (thoracic paratracheal lymph nodes, upper paraesophageal lymph nodes, subcarinal lymph nodes, middle paraesophageal lymph nodes, hilar lymph nodes, lower paraesophageal lymph nodes, diaphragmatic lymph nodes and posterior mediastinal lymph nodes); abdominal lymph nodes (right cardiac lymph nodes, left cardiac lymph nodes, lesser

curvature lymph nodes, left gastric artery lymph nodes, common hepatic artery lymph nodes, coeliac artery lymph nodes and splenic hilum lymph nodes). A detailed procedure of MIE and OE has been described elsewhere [15].

### Statistical analysis

SPSS 17.0 for Microsoft windows version (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean  $\pm$  standard deviations for variables following normal distribution and were analyzed by *t* test. For data following non-normal distribution, results were expressed as median and range and were compared by nonparametric test. Differences of semiquantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. Survival rates were analyzed using the Kaplan-Meier method; differences between the two groups were analyzed with the log-rank test. Univariate

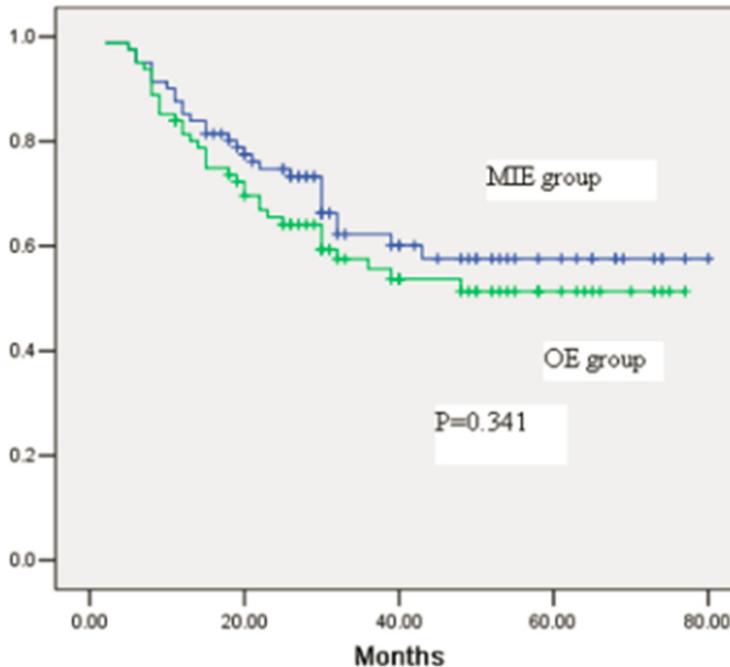
analyses were performed to identify prognostic data related to overall survival and disease-free survival. Univariate variables with probability values less than 0.05 were selected for inclusion in the multivariate Cox regression model.  $P < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

Patient characteristics, such as age, sex, ASA score, comorbidities and clinical stage were similar between the two groups (**Table 1**). PET-CT was used for staging in 15% of patients in the MIE group and 16% in the OE group.

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**Figure 1.** Kaplan-Meier overall survival curves of the MIE group and the OE group. No significant difference was observed ( $P=0.341$ ). MIE: minimally invasive esophagectomy; OE: open esophagectomy.

median blood loss in MIE group (175 ml; ranged from 160 ml to 320 ml) was less than that in OE group (400 ml; ranged from 230 ml to 600 ml), which presented the advantage of minimally invasive surgery. The use of analgesic drugs was significantly less in MIE group, and the length of postoperative stay in the 2 groups was 10 days (ranged from 8 days to 15 days) and 16 days (ranged from 8 days to 25 days), respectively. The rate of postoperative complications was similar in both groups ( $P=0.296$ ). More complications were classified as major in OE group according to the Clavien-Dindo classification ( $P=0.175$ ), albeit no statistically difference (**Table 3**).

### Overall survival

The last follow up was October 2014. After a median follow-up period of 45 months, the 5-year cumulative overall survival rate in the MIE group was 58%, compared to 51% in the OE group. The overall survival analysis indicated no significant difference in the overall survival rate between the 2 groups (**Figure 1**,  $P=0.341$ ). In regard to prognostic factors for overall survival, age, operation time, tumor size, pathological T state and pathological N stage were prognostic factors in univariate analysis. In multivariate analysis, pathological T state and pathological N stage were independent prognostic factors (**Table 4**).

### Disease-free survival

The disease-free 5-year survival rate was 41% in the MIE group and 33% in the OE group, respectively, with no significant differences between the 2 groups (**Figure 2**,  $P=0.122$ ). The location of the recurrence and recurrence-free interval were not significantly different between the two groups (**Table 5**). There was no port-site recurrence in patients underwent MIE. In regard to prognostic factors for disease-free survival, tumor size, pathological T state and pathological N stage were prognostic factors in univariate

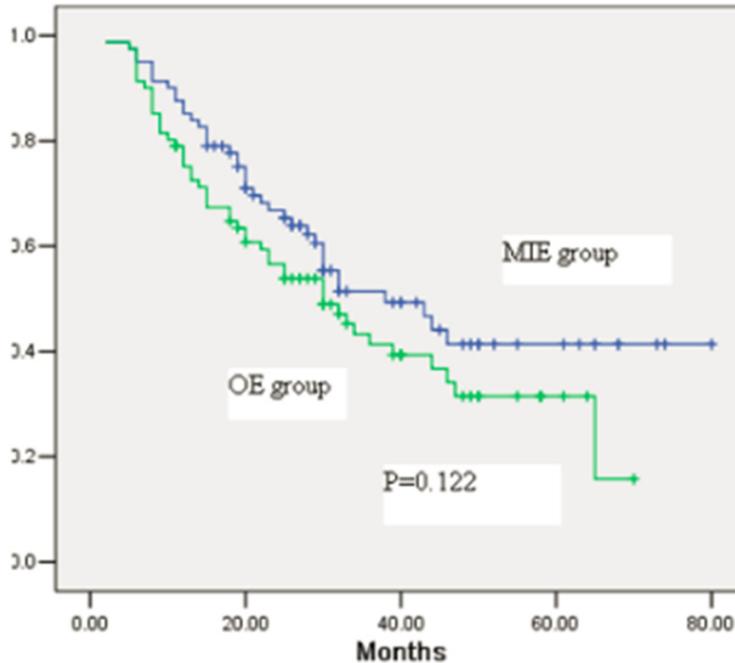
**Table 4.** Prognostic factors for overall survival after esophagectomy

Factors	Univariate <i>P</i> value	Multivariate <i>P</i> value
Age	0.032	
Sex	0.103	
Comorbidity	0.193	
Operation time	0.032	
Morbidity	0.681	
Tumor size	0.016	
Tumor location	0.602	
Pathological T state	0.001	0.006
Pathological N stage	0.010	0.008
Adjuvant therapy	0.613	

### Short-term outcomes

There were no significant differences in pathological TNM stage ( $P=0.528$ ) and resection margin ( $P=1.000$ ). The number of harvested lymph nodes was similar in the two groups ( $P=0.207$ ) (**Table 2**). There were no in-hospital or 30-day mortality occurred. The median operative time for MIE was 270 min (ranged from 200 min to 300 min) compared with 210 min (ranged from 180 min to 270 min) for OE. The

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**Figure 2.** Comparison of disease-free survival rate between the MIE group and the OE group. There was no significant difference between the 2 groups ( $P=0.122$ ). MIE: minimally invasive esophagectomy; OE: open esophagectomy.

**Table 5.** Recurrences after esophagectomy

	MIE (n=81)	OE (n=81)	P value
Overall recurrence n (%)	19 (23.5)	23 (28.4)	0.473
Locoregional n (%)	12 (14.8)	10 (12.3)	0.581
Cervical lymph node	3	1	
Anastomosis	4	5	
Mediastinal lymph nodes	5	4	
Distant n (%)	7 (8.6)	13 (16.0)	0.966
Brain	3	5	
Liver	2	3	
Lung	1	2	
Bone	1	3	
Recurrence-free interval (median)	21 months	18 months	0.390

MIE: minimally invasive esophagectomy. OE: open esophagectomy.

ate analysis. In multivariate analysis, pathological T state and pathological N stage were also independent prognostic factors (Table 6).

Our long-term data were similar to other studies (Table 7).

### Discussion

This study was designed to compare clinical outcomes of MIE and OE for esophageal squa-

mous cell carcinoma with particular attention paid to long-term outcomes. To the best of our knowledge, this is a relatively large matched cohort study of this technique. In the present study, MIE was associated with significantly faster recovery and less trauma, but longer operative time, compared with OE. Consequently, we observed that MIE offers similar oncological outcomes compared to that of OE.

MIE for esophageal squamous cell carcinoma has been used more widely in many medical centers since Cushi-eri et al. first performed esophagectomy by mobilizing the esophagus via thoracoscopy for esophageal carcinoma in 1992. The MIE approach attracts an increasing number of patients and surgeons because of its expected low invasiveness and good cosmesis despite its association with some unresolved oncologic problems.

Several publications [8-11, 25] have already described the short-term results of MIE as equivalent to those of OE, and we similarly have observed less intraoperative blood loss and a longer operative time. The data in our study are comparable with other published data including intraoperative blood loss and operative time. Careful manipulation enabled by the magnified vision of the laparoscope and the thoracoscope contributes to lower blood loss.

Our study revealed no differences in the postoperative complications between the 2 groups, also consistent with previous reports [8-11, 25]. The overall postoperative complication rate of combined thoracoscopic-laparoscopic esophagectomy has been reported to be around 20%-40% [8-11, 25]. Some investiga-

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**Table 6.** Prognostic factors for disease-free survival after esophagectomy

Factors	Univariate P value	Multivariate P value
Age	0.350	
Sex	0.520	
Comorbidity	0.323	
Operation time	0.320	
Morbidity	0.103	
Tumor size	0.030	
Tumor location	0.713	
Pathological T state	0.011	0.001
Pathological N stage	0.020	0.000
Adjuvant therapy	0.402	

tors have reported a lower incidence of overall postoperative complications with minimally invasive surgery than that with open surgery; however, the number of patients in these studies was small and the difference in patient backgrounds could have biased the results [25-27]. Additionally, the 30-day mortality rate of combined thoracoscopic-laparoscopic esophagectomy was consistent between our current study and previous studies (0-3%) [25-29]. These reports indicate that surgical stress still occurs despite thorough lymphadenectomy with MIE.

Some publications have reported the number of retrieved lymph nodes in MIE as similar to that in OE [8-11, 25]. The number of lymph nodes in our analysis also showed that MIE could produce satisfactory lymph node dissection, suggesting that oncologically appropriate lymph node dissection could be carried out with MIE.

As described above, because MIE and OE achieved similar pathological outcomes including lymph node dissection, it is expected that the long-term outcomes will be comparable as well. In this study, we found similar 5-year disease-free survival and 5-year overall survival for MIE and OE, in agreement with other reports [12-21]. Although recurrence patterns did not differ statistically between the two groups, more recurrence in OE was hematogenous. Because the number of recurrence is small, it seems to be difficult to compare recurrence pattern at the same stage and to find out the reasons of difference in hematogenous recur-

rence between the two groups. In addition, we did not have any experience of port site metastasis after MIE. In our study, the significant prognostic factor for tumor recurrence was pathologic T stage and metastatic lymph node status. These data suggest that MIE is an oncologically safe procedure for esophageal squamous cell carcinoma.

Although the difference in overall survival and disease-free survival did not reach statistical significance, overall survival and disease-free survival rates tended to be higher in the MIE group, indicating that oncologic efficacy was not compromised by the application of combined thoracoscopic-laparoscopic techniques in esophagectomy. Our data were similar with other reports [12-21]. A possible explanation of this phenomenon is the magnified vision afforded by thoracoscopy and laparoscopy, which facilitates more delicate lymph node dissection and better tumor clearance. Therefore, despite similar pathological TNM stage, R0 resection, and lymph nodes harvested, the combined thoracoscopic-laparoscopic techniques could remove more unrecognized tumor cells, or tissue harboring micrometastasis, and in turn improve patient long-term outcomes. Another possible explanation for better long-term outcomes in MIE group may be that because combined thoracoscopic-laparoscopic techniques provides earlier and faster recovery than open resection, patients resume to normal activity in a shorter period and are more likely to be physically capable to receive further adjuvant therapy after surgery or additional treatment for cancer recurrence. Similar observation has been reported in lung cancer patients that application of endoscopic techniques may improve the delivery of additional treatments [30].

Nevertheless, this study had several limitations. The main limitation of this study remains its retrospective nature. Imbalance between patient characteristics that were not recorded could bias the results. This limitation should be taken into account when interpreting the results. In addition, the postoperative follow-up period was shorter in the MIE group, so recurrence or death in this group may not have been observed during the time of analysis.

In conclusion, our analysis demonstrated that MIE for esophageal squamous cell carcinoma

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**Table 7.** Literature review of follow-up data of esophagectomy by minimally invasive surgery versus open approach for esophageal carcinoma

Study	Approach	<i>n</i>	Overall survival	Disease-free survival
Noble F (2013, UK) [21]	MIE	53	1-year: 82%	1-year: 68%
	OE	53	1-year: 80%	1-year: 67%
Dolan JP (2013, USA) [19]	MIE	82	5-year: 41%	NR
	OE	64	5-year: 33%	
Kinjo Y (2012, Japan) [14]	MIE	72	NR	2-year: 71.6%
	OE	79		2-year: 58.3%
Sundaram A (2012, USA) [16]	MIE	47	5-year: 38%	5-year: 55%
	OE	26	5-year: 36%	5-year: 53%
Lee JM (2011, China) [17]	MIE	30	5-year: 56%	5-year: 38%
	OE	64	5-year: 48%	5-year: 36%
Singh RK (2011, India) [15]	MIE	33	2-year: 55%	2-year: 55%
	OE	31	2-year: 32%	2-year: 26%
Schoppmann SF (2010, Austria) [13]	MIE	31	3-year: 65%	3-year: 59%
	OE	31	3-year: 46%	3-year: 50%
Parameswaran R (2009, UK) [20]	MIE	50	2-year: 74%	NR
	OE	30	2-year: 58%	
Zingg U (2009, Australia) [18]	MIE	56	5-year: 40%	NR
	OE	98	5-year: 40%	

NR: not reported. MIE: minimally invasive esophagectomy. OE: open esophagectomy.

provided an acceptable prognosis. This result indicates that MIE performed by a medical team skilled in minimally invasive surgery could be applicable for the treatment of esophageal squamous cell carcinoma. However, randomized controlled trials comparing MIE and OE are required to elucidate the actual influence of MIE on the long-term results.

### Acknowledgements

We sincerely thank the patients, their families and our hospital colleagues who participated in this research.

### Disclosure of conflict of interest

None.

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