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Original Article

Oncological and surgical outcomes of minimally invasive versus open esophagectomy for esophageal squamous cell carcinoma: a matched-pair comparative study

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Abstract: Only a few series have demonstrated the safety and efficacy of minimally invasive esophagectomy (MIE) for esophageal squamous cell carcinoma and the benefits of this approach. This report describes the results of a pair-matched comparative study between minimally invasive and open esophagectomy (OE) for esophageal squamous cell carcinoma. Patients were retrospectively matched in pairs for the following criteria: age, sex, American Society of Anesthesiology (ASA) score, clinical TNM stage, tumor location, and type of resection. A total of 97 patients undergoing MIE were compared with patients undergoing OE during the same period. Operative, postoperative, and oncologic outcomes were compared. Significantly less bleeding was observed in the MIE group ($P = 0.001$). Transfusion was required for three patients in the MIE group and ten patients in the OE group ($P = 0.044$). Overall morbidity was similar in the two groups. The hospital stay was significantly shorter for the patients undergoing MIE ($P = 0.027$). The surgical margin and tumor stage were not affected by MIE. The overall survival rates in the MIE group were 54% at 5 years and 46% in the OE group ($P = 0.631$). The disease-free survival rates in the MIE group were 45% at 5 years, 41% in the OE group ($P = 0.704$). In summary, MIE for esophageal squamous cell carcinoma for selected patients gave a better postoperative outcome without oncologic consequences.

Keywords: Esophageal squamous cell carcinoma, esophagectomy, minimally invasive surgery, prognosis

Introduction

Technical refinements and improvements in postoperative intensive care management have increased the safety of radical esophagectomy as a curative treatment for esophageal squamous cell carcinoma [1-5]. Screening for esophageal squamous cell carcinoma among patients with upper gastrointestinal tract disease facilitates the early detection of early stage tumors, increasing the number of curative therapeutic options available [6-8]. Recent studies have suggested that minimally invasive esophagectomy (MIE) reduces postoperative inflammatory reaction. The safety and feasibility of the MIE approach and its short-term benefits for esophageal carcinoma have been demonstrated by only a few series to date [9-11]. In addition, the oncologic results of MIE for esophageal squamous cell carcinoma remain a matter of debate. We report the short- and long-term results of a pair-matched comparative study between OE and MIE for esophageal squamous cell carcinoma.

Patients and methods

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

Between March 2007 and December 2014, 97 of 489 esophagectomy with radical intent for esophageal squamous cell carcinoma at our institution were performed by MIE and were included in this study. Each patients undergoing

MIE for resectable esophageal squamous cell carcinoma was matched retrospectively with a patient undergoing open esophagectomy (OE) carried out during the same period. The selection criteria for MIE were clinical T1-3N0M0 esophageal squamous cell carcinoma, tumors in the thoracic esophagus, without neoadjuvant therapy, with no evidence of metastasis, without extended resection for complete resection. The patients in the OE and MIE groups were matched for the following criteria: age, sex, American Society of Anesthesiology (ASA) score, clinical TNM stage, tumor location, and type of resection. All procedures were performed according to the same surgical and oncologic principles, and the patients in the MIE and OE groups received similar preoperative assessment and postoperative management [12].

The preoperative workup included upper gastrointestinal endoscopy, biopsy, magnetic resonance imaging scan or computed tomographic scan of brain, computed tomographic scan chest, and ultrasonography of neck and abdominal. In selected cases, positron emission tomography-computerized tomography (PET-CT), mediastinoscopy and bone scanning were performed when tumor metastasis was suspected. The clinical stage of esophageal squamous cell carcinoma was based on the 7th edition of the TNM classification of esophageal squamous cell carcinoma which was proposed by American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) [13]. For those of the patients treated before 2010, their staging was recalculated to match the 7th TNM classification by AJCC and UICC.

The resection was performed with curative intention in all patients. MIE was defined as combined thoracoscopic-laparoscopic esophagectomy. The technique for MIE has beendescribed elsewhere [12].

The surgical variables evaluated were duration of intervention, blood loss, and transfusion rate. The pathologic variables were resection margin, tumor stage, vascular invasion, and tumor differentiation. Four clinical variables were evaluated to assess postoperative outcome: morbidity, mortality, and length of postoperative hospital stay. Morbidity was defined as postoperative complications occurring within 30 postoperative days. Mortality was defined as death of any cause occurring within 30 postoperative days. Postoperative complication severity was stratified according to the modified Clavien classification. The definition of Clavien-Dindo system was as follows [14]: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2.

All the patients were followed with a standard oncologic protocol of surveillance that included abdominal and chest computed tomography scan and ultrasonography of neck every 6 months after esophagectomy. Upper gastrointestinal endoscopy is suggested every once a year after esophagectomy. The last follow up was February 2015. Tumor recurrence was diagnosed by history, physical examination, endoscopic evaluation, radiologic investigations, or pathology when available. Recurrence was classified as locoregional recurrence, distant metastasis and mixed. Locoregional disease was defined as recurrence within the esophagus bed, the regional lymph nodes, or the anastomosis [15-17]. Distant disease included metastasis at distant organ sites (brain, lung, liver, bone, distant lymph nodes or other organs). 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.

Data were presented as mean and 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 semi-quantitative 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. SPSS (Solutions Statistical Package for the Social Sciences)

Table 1. Demographic data and tumor characteristics in the two groups

	MIE (*n* = 97)	OE (*n* = 97)	*P* value
Age (years)	63 (38-78)	61 (40-72)	0.540
Sex			0.653
Male	64	61	
Female	33	36	
ASA score			0.380
I	71	76	
II	21	18	
III	5	3	
Primary tumor location			0.650
Upper thoracic esophagus	16	19	
Middle thoracic esophagus	42	45	
Lower thoracic esophagus	39	33	
Clinical TNM stage (7th AJCC-UICC)			0.881
IB	19	17	
IIA	67	70	
IIB	11	10	
Type of resection			0.756
Cervical-right thoracic-abdominal esophagectomy	29	31	
Right thoracic-abdominal esophagectomy	68	66	

Table 2. Surgical and pathological data in the two groups

	MIE (*n* = 97)	OE (*n* = 97)	*P* value
Operative time (min)	260 (180-340)	210 (160-310)	0.010
Blood loss (ml)	230 (180-600)	390 (240-590)	0.001
Blood transfusion (patients)	3	10	0.044
Retrieved lymph nodes	17 (14-32)	18 (13-34)	0.741
Pathological TNM stage			0.547
IB	10	11	
IIA	38	39	
IIB	21	23	
IIIA	12	14	
IIIB	11	6	
IIIC	5	4	
Resection margin			0.734
R0	92	93	
R1	5	4	
R2	0	0	

15.0 for Windows version (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

As defined by the study protocol, all the patients were matched for age, sex, ASA score, clinical TNM stage, tumor location, and type of resection (**Table 1**).

In the MIE group, the combined thoracoscopic-laparoscopic procedure was successfully completed for all patients without conversion to open resection. Significantly less bleeding was observed in the MIE group than in the OE group ($P = 0.001$). Transfusion was required for three patients in the MIE group and ten patients in the OE group ($P = 0.044$). The median duration of surgery was longer in the MIE group ($P = 0.010$). The two groups did not differ significantly in terms of pathological characteristics, namely, surgical margin, pathological TNM stage and lymph nodes harvested (**Table 2**).

We then compared mortality and morbidity data between the two groups (**Table 3**). One death occurred in each group. The cause of death was ARDS (adult respiratory distress syndrome) for the patient in the MIE group and STEMI (ST segment elevation myocardial infarction) for the patient in the OE group. Overall morbidity was similar after MIE and OE. The severity of complications, according to the

Table 3. Postoperative data in the two groups

	MIE (*n* = 97)	OE (*n* = 97)	*P* value
Mortality	1 (due to ARDS)	1 (due to STEMI)	1.000
Overall complications *n* (%)	19 (19.6)	26 (26.8)	0.234
Pulmonary embolism	2	3	
Anastomosis leakage	7	8	
Recurrent laryngeal nerve injury	1	3	
Pneumonia	3	6	
Urinary tract infection	1	1	
Atelectasis	2	2	
Heart failure	3	3	
Major complications *n* (%)	3 (3.1)	7 (7.2)	0.194
Minor complications *n* (%)	16 (16.5)	19 (19.6)	0.575
Postoperative stay (d)	10 (8-18)	15 (12-35)	0.027

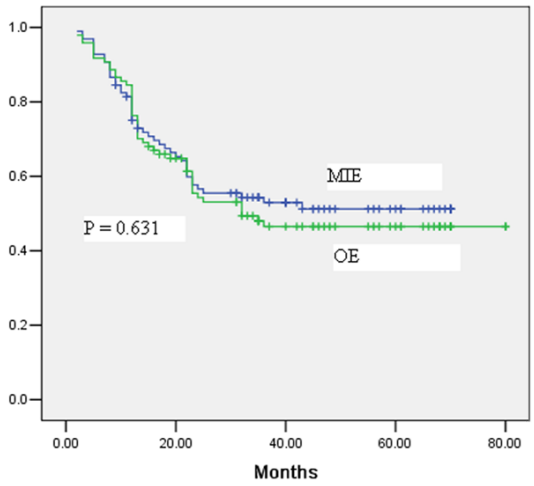

Figure 1. Overall survival in the two groups (*P* = 0.631). MIE: minimally invasive esophagectomy. OE: open esophagectomy.

Clavien classification, was similar in the two groups. The mean hospital stay after surgery was significantly shorter for the patients who underwent MIE than for the patients who underwent OE (*P* = 0.027).

The median follow-up period was 40 month in the whole cohort. Five patients in the MIE group and seven patients in the OE group died without evidence of cancer recurrence during follow-up period. The 5-year overall survival rate was 54% in the MIE group. In the OE group, the 5-year overall survival rate was 46%. Comparison by Kaplan-Meier methodology is shown in **Figure 1**, with no significant difference identified between the MIE and OE group with respect to overall survival (*P* = 0.631, log-rank test).

Cancer recurrence developed for 45 patients in the MIE group and 46 patients in the OE group. A component of locoregional recurrence was seen in 24 patients of the MIE group and 22 patients of the OE group. Distant disease was present in 16 patients of the MIE group and 16 patients of the OE group. Mixed recurrence was seen in 5 patients of the MIE group and 8 patients of the OE group (**Table 4**). None of the differences were statistically significant. The 5-year disease-free survival was 45% for the MIE group and 41% for the OE group. Comparison of disease-free survival between the two groups using Kaplan-Meier methodology is shown in **Figure 2** (*P* = 0.704, log-rank test). No trocar-site deposits were observed in the laparoscopic group.

Our oncological data were similar to other studies reported in English literatures (**Table 5**).

Discussion

Radical esophagectomy for esophageal carcinoma have improved considerably over the past last decade, with fewer complications and better survival having achieved, mostly due to early diagnosis and improvements in perioperative care [27]. Minimally invasive resection is more frequently proposed as a curative treatment for esophageal carcinoma. Our series confirms the feasibility, safety, and efficacy of minimally invasive surgery for selected patients undergoing radcial esophagectomy.

Transfusion rates have been identified as an independent prognostic factor for disease-free survival and overall survival in esophageal carcinoma, and blood loss during radical esophagectomy was shown to be associated with recurrence and survival rates after resection of esophageal carcinoma [27]. In the current comparative study, the patients lost significantly less blood during minimally invasive resections.

In our series, minimally invasive surgery required more time than open resection. This may

Table 4. Recurrence data in the two groups

	MIE (*n* = 97)	OE (*n* = 97)	*P* value
Overall recurrence *n* (%)	45 (46.4)	46 (47.4)	0.886
Locoregional *n* (%)	24 (24.7)	22 (22.7)	0.736
Distant *n* (%)	16 (16.5)	16 (16.5)	1.000
Mixed *n* (%)	5 (5.2)	8 (8.2)	0.389
Recurrence-free interval from esophagectomy (median)	19 months	16 months	0.091

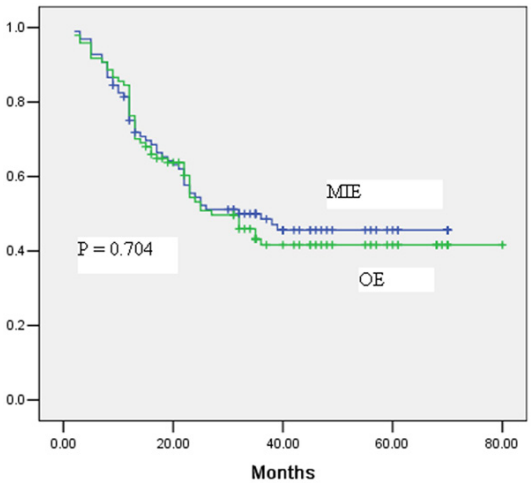

Figure 2. Disease-free survival in the two groups (*P* = 0.704). MIE: minimally invasive esophagectomy. OE: open esophagectomy.

reflect the inclusion in these series of early cases, with patients undergoing surgery at a time when surgeons were still developing each technical step.

No significant difference in the frequency of overall postoperative 30-day complications was observed between the two groups. Fewer major complications were observed in the MIE group, although this difference was not statistically significant due to small sample size. Finally, hospital stay was significantly shorter after MIE than after open resection.

The surgical margin affects prognosis after resection of esophageal carcinoma [4, 5]. It was initially feared that MIE would decrease the surgical margin due to the lack of palpation [4, 5, 27]. However, palpation probably is less important when a wide resection is planned. In the current study, the surgical margin was similar in the MIE and OE groups. The rate of local recurrence was acceptable and did not differ between the two groups. We observed no significant difference in disease-free or overall survival between the MIE and OE groups to radical esophagectomy for esophageal carcinoma.

Minimally invasive surgery also was feared to increase the risk of trocar-site metastasis [28]. Cases reported during early experiences with minimally invasive surgery probably were related to inappropriate manipulation of the tumor. In the current series, we observed no trocar-site deposit in the follow-up period.

An important concern in MIE for esophageal carcinoma is whether the adoption of the combined thoracoscopic-laparoscopic approach will increase recurrence and compromise prognosis. To avoid the difference in biological behavior of different malignant tumors, we limited our study to esophageal squamous cell carcinoma only [29]. Only a few series in the literature reported the long-term result of MIE for esophageal carcinoma. The reported 5-year overall survival after MIE for esophageal carcinoma ranged from 33%-56%, and the 5-year disease-free survival ranged from 36%-55%. The 5-year overall and disease-free survival in the minimally invasive surgery in our series were 54% and 45%, respectively, which compares favorably with the previous series [30]. To adjust for the difference in disease stage and magnitude of operation, we compared our MIE group with a matched OE group for long-term result. Our data showed that the incidences of overall recurrence were similar between the two groups. There also was no difference in the 5-year overall and disease-free survival rates between the two groups.

The results of our study are limited by the non-randomized design, small number of cases, and the selection bias related to the choice of approach based merely on tumor characteristics. Although the potential bias was reduced by the study design, resulting in an open resection group that was well matched with a mini-

Table 5. Literature review of oncological data of esophagectomy by minimally invasive surgery versus open approach for esophageal carcinoma

Study	No. of cases	Number of retrieved lymph nodes	R0 resection rate	Survival
Noble F (2013, UK) [18]	MIE (53) OE (53)	19 (7-50) 18 (7-52)	38 (72%) 43 (81%)	1-year OS: 82% (MIE) 80% (OE) 1-year DFS: 68% (MIE) 67% (OE)
Dolan JP (2013, USA) [19]	MIE (82) OE (64)	18.0 (14.0-23.8) 9.5 (5.0-15.2)	78 (95 %) 54 (84 %)	5-year OS: 41% (MIE) 33% (OE) DFS: NR
Kinjo Y (2012, Japan) [20]	MIE (72) OE (79)	28 (2-50) 18 (1-56)	66 (92%) 68 (86%)	OS: NR 2-year DFS: 71.6% (MIE) 58.3% (OE)
Sundaram A (2012, USA) [21]	MIE (47) OE (26)	20 (14-27) 19 (14.75-24.75)	93.61% 92.3%	5-year OS: 38% (MIE) 36% (OE) 5-year DFS: 55% (MIE) 53% (OE)
Lee JM (2011, China) [22]	MIE (30) OE (64)	13.97 ± 7.70 18.41 ± 9.06	NR	5-year OS: 56% (MIE) 48% (OE) 5-year DFS: 38% (MIE) 36% (OE)
Singh RK (2011, India) [23]	MIE (33) OE (31)	14 (6-16) 8 (3-14)	NR	2-year OS: 55% (MIE) 32% (OE) 2-year DFS: 55% (MIE) 26% (OE)
Schoppmann SF (2010, Austria) [24]	MIE (31) OE (31)	17.9 ± 7.74 20.52 ± 12.6	29 (93.5%) 30 (96.8%)	3-year OS: 65% (MIE) 46% (OE) 3-year DFS: 59% (MIE) 50% (OE)
Parameswaran R (2009, UK) [25]	MIE (50) OE (30)	23 (7-49) 10 (2-23)	NR	2-year OS: 74% (MIE) 58% (OE) 2-year DFS: NR
Zingg U (2009, Australia) [26]	MIE (56) OE (98)	NR	NR	5-year OS: 40% (MIE) 40% (OE) 5-year DFS: NR

NR: not reported. MIE: minimally invasive esophagectomy. OE: open esophagectomy. OS: overall survival. DFS: disease-free survival.

mally invasive resection group for age, sex, ASA score, clinical TNM stage, tumor location, and type of resection, our follow-up period was not longer enough to detect later cancer recurrence. Thus, a larger group of patients and further examinations are necessary to analyze the role of combined thoracoscopic-laparoscopic esophagectomy.

In conclusion, this study demonstrates significantly less blood loss and a shorter hospital stay after MIE than after open resection for operable esophageal carcinoma. Minimal invasiveness and the magnification of images provided by thoracoscopy and laparoscopy were considered to be the main factors responsible for this improvement in results. Furthermore, the long-term oncologic results were similar for the two types of radical resection. However, this study involved retrospective comparison. Furthermore, the MIE patients were highly selected and underwent surgery in the hands of expert surgeons. A prospective comparative study should be designed to confirm the advantages of MIE for the management of esophageal carcinoma.

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Disclosure of conflict of interest

None.

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