Outcomes, quality of life, and survival after esophagectomy for squamous cell carcinoma: A propensity score–matched comparison of operative approaches

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Background: Minimally invasive esophagectomy (MIE) theoretically offers advantages compared with open esophagectomy (OE). However, the long-term outcomes have not been well studied, especially for esophageal squamous cell carcinoma. We retrospectively compared postoperative outcomes, quality of life (QOL), and survival in a matched population of patients undergoing MIE, with a control (OE) group.

Methods: From May 2004 to August 2013, MIE was performed for a group of 735 patients, which was compared with a group of 652 cases of OE. Eventually, 444 paired cases, matched using propensity-score matching, were selected for further statistical analysis.

Results: Compared with the OE group, the MIE group had shorter operation duration (191 ± 47 minutes vs 211 ± 44 minutes, $P < .001$); less blood loss (135 ± 74 ml vs 163 ± 84 ml, $P < .001$); similar lymph node harvest (24.1 ± 6.2 vs 24.3 ± 6.0 , $P = .607$); shorter postoperative hospital stay (11 days [range: 7-90 days] vs 12 days [range: 8-112 days], $P < .001$); fewer major complications (30.4% vs 36.9%, $P = .039$); a lower readmission rate to the intensive-care unit (5.6% vs 9.7%, $P = .023$); and similar perioperative mortality (1.1% vs 2.0%, $P = .281$). At a median follow-up of 27 months, the 2-year overall survival rates in the MIE and OE group were: (1) stage 0 and I: 92% versus 90% ($P = .864$); (2) stage II: 83% versus 82% ($P = .725$); (3) stage III: 59% versus 55% ($P = .592$); (4) stage IV: 43% versus 43% ($P = .802$). The generalized estimating equation analysis showed that MIE had an independently positive impact on patients' postoperative QOL.

Conclusions: In our experience, MIE is a safe and effective procedure for the treatment of esophageal squamous cell carcinoma. It may offer better perioperative outcomes, better postoperative QOL, and equal oncologic survival, compared with OE. (J Thorac Cardiovasc Surg 2015;149:1006-15)

See related commentary on pages 1016-7.

Supplemental material is available online.

Although traditional open esophagectomy (OE) offers a potential cure for esophageal cancer, it is associated with high perioperative morbidity and mortality. Recently, minimally invasive esophagectomy (MIE) has become the

recommended approach, popularized in centers with experienced surgeons.¹ Theoretically, MIE offers advantages, compared with conventional OE, and has been preliminarily shown to provide benefits in perioperative outcomes. Nevertheless, the long-term efficacy of MIE compared with OE has not been well studied, especially for esophageal squamous cell carcinoma (ESCC), which is quite different from esophageal adenocarcinoma in terms of area of prevalence, tumor location, biological behavior, and prognosis.

We started our practice of MIE in 2004 and have performed more than 700 such procedures, most of which were for ESCC. Thus, we retrospectively studied postoperative outcomes, quality of life (QOL), and cancer survival in a matched population of patients undergoing MIE, with a control (OE) group.

MATERIALS AND METHODS

Patients

From May 2004 to August 2013, patients with ESCC were enrolled in this study. All patients underwent esophagogastroduodenoscopy and were given a diagnosis of pathologic disease. Imaging examinations, including thoracoabdominal, enhanced computed tomography, cervical ultrasonography, and endoscopic ultrasonography (as well as positron

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Abbreviations and Acronyms

cTis	= Clinical Trials Information System
cTNM	= clinical tumor-node-metastasis
ESCC	= esophageal squamous cell carcinoma
MIE	= minimally invasive esophagectomy
OE	= open esophagectomy
pTNM	= pathologic tumor-node-metastasis
QOL	= quality of life

emission tomography, if possible), were used to determine the clinical stage.

For patients with cTis 3 N1 M0 or more-advanced disease, neoadjuvant therapy was performed. The treatment was determined by a multidisciplinary team. For patients with a cTis 3 N0 M0 classification (including cases that were down-staged after neoadjuvant therapy), surgery was performed after risk assessment. Patients chose which procedure (MIE or OE) to undergo, during the preoperative interview. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram is shown in Figure 1. The institutional review board of Zhongshan Hospital, Fudan University approved the use of a prospectively maintained database of patients with esophageal carcinoma for this retrospective study (No. 2013154).

Surgical Procedures

Anesthesia and ventilation. All patients received a combination of epidural (0.1875% bupivacaine and morphine) and general anesthesia (inhaled sevoflurane) during the operation. For the OE group, patients were intubated with a left-side double-lumen endotracheal tube and single-lung ventilation. The intraoperative, mechanical ventilation parameters were set to a tidal volume of 8 ml/kg. For the MIE group, intubation and ventilation were the same as in the OE group, early on²; later, however, we adopted a single-lumen endotracheal tube and double-lung ventilation with a tidal volume of 6 to 8 ml/kg, which was assisted by an artificial CO₂ pneumothorax at 8 mm Hg.

Surgical position. For the MIE group, initially, patients were placed in the left lateral decubitus position. The surgeon and 2 assistants stood on either side of the patient, and 4 thoracoscopic ports of approximately 0.5 to 1.2 cm were placed on the thoracic cavity. Details are described in our previous publication.³ Afterward, we adopted the prone position for patients, and then the semiprone position, for better surgical exposure and operative ergonomics. The surgeon and 1 assistant stood on the ventral side of the patient, and 4 ports were used.² For the OE group, patients were placed in the left lateral decubitus position.

Operation procedures. In the MIE group, for the majority of cases (in which the tumor was located in the thoracic esophagus), the procedures consisted of the following 3 stages: (1) mobilization of the intrathoracic esophagus and dissection of the intrathoracic lymph node by thoracoscopy; (2) mobilization of the stomach, with dissection of the celiac lymph node via laparotomy (mainly in the early period) or laparoscopy; and (3) resection of the tumor, pulling up of the gastric conduit, and gastroesophageal reconstruction with cervical anastomosis. For the tumors located in the upper esophagus, cervical lymphadenectomy was performed. For the other cases (in which the tumor was located in the abdominal esophagus), the procedures comprised the following 2 stages: (1) mobilization of the stomach, with dissection of the celiac lymph node via laparoscopy; and (2) mobilization of the intrathoracic esophagus and dissection of the intrathoracic lymph node via thoracoscopy, pulling up of the gastric conduit, resection of the tumor,

and gastroesophageal reconstruction with intrathoracic anastomosis. Details of the techniques are described elsewhere.^{2,4} In the OE group, the procedure involved open Ivor-Lewis esophagectomy and open Ivor-Lewis McKeown esophagectomy.

Mediastinal lymphadenectomy. In the early period (before June 2009), conventional lymphadenectomy was performed for the dissection of the subcarinal and paraesophageal lymph nodes. Later, we added the extensive lymphadenectomy along the bilateral recurrent laryngeal nerves, which had been our regular procedure. Details of the techniques are described elsewhere.⁵

Perioperative management. Milk was administered to patients orally, 6 hours before surgery, which facilitated visualization of the thoracic duct, thereby minimizing the risk of it sustaining iatrogenic injury during MIE.⁶ Postoperatively, epidural analgesia was used until the thoracic drainage was removed (within approximately 3–5 days). A feeding jejunostomy was established in all cases, and enteral nutrition was started on postoperative day 1. An examination of the patient's water-soluble swallow was performed on postoperative day 7, before oral feeding was started.

Follow-up

Patients were evaluated at regular intervals: every 3 months in the first year, and every 6 months beginning in the second year. Follow-up investigations included clinical examinations, evaluation of the biochemistry of tumor-marker (carcino-embryonic antigen, squamous cell carcinoma-related antigen, etc) levels, CT scanning of the thorax and abdomen, and gastroendoscopy whenever indicated.

Health-Related Quality-of-Life Assessment

The assessment of health-related QOL was based on a previously validated questionnaire, QLQ-C30 (version 3.0; quality-of-life questionnaire), combined with an esophageal cancer-specific module, QLQ-OES18, which were developed by the European Organization for Research and Treatment of Cancer.⁷ That organization's questionnaire includes: 1 global QOL scale; 5 functional scales (physical, role, emotional, cognitive, and social); and 19 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties, dysphagia, eating, reflux, esophageal pain, swallowing saliva, choking when swallowing, dry mouth, taste problem, coughing and speech problem). After obtaining informed consent from the patients, we asked them to complete the questionnaires, before the operation and at multiple follow-up intervals (1, 3, 6, 12, 18, and 24 months postoperatively), via mail, in-person visit, or outpatient consultation.

Data Collection and Statistical Analysis

Clinical data for all cases were collected from the prospectively maintained database at our institution. The pathologic classification was made according to the Union for International Cancer Control esophageal cancer TNM (tumor-node- metastasis) staging system (6th edition). All collected data were tabulated using Microsoft Excel (Microsoft, Redmond, Wash) for further analysis.

Statistical analyses were performed according to the intent-to-treat principle. To control for potential differences in the characteristics of patients between the 2 groups, the method of propensity-score matching was used. By using a logistic regression model, which included variables such as age, gender, body mass index, Charlson Comorbidity Index, ASA (American Society of Anesthesiologists) grade, tumor location, cTNM (clinical) stage, neoadjuvant therapy, pTNM (pathologic) stage, and historical period of surgery, propensity scores were computed as the conditional probability of receiving cases, via either MIE or OE. Using the nearest neighbor-matching algorithm, we created propensity score-matched pairs without replacement (a 1:1 match). The caliper

FIGURE 1. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram. *ESCC*, Esophageal squamous cell carcinoma; *MDT*, multidisciplinary team; *MIE*, minimally invasive esophagectomy; *OE*, open esophagectomy; *ESD*, endoscopic submucosal dissection.

definition was set at 0.02. Eventually, 444 paired cases were matched from the cohort, and the 2 groups were comparable in patient characteristics (Table 1 and Table E1).

Statistical analysis was undertaken using SPSS 22.0 (SPSS Inc, Chicago, Ill). Variables were compared using the Mann-Whitney *U* test, the Student *t* test, χ^2 analysis, and the Fisher exact test. Survival curves based on the TNM classification were estimated using the Kaplan-Meier method, and the significance of between-group differences was assessed with the log-rank test. Scores from the QOL assessment, which were derived from the questionnaires, were linearly transformed into a 0-to-100 scale according to the European Organization for Research and Treatment of Cancer Scoring Manual. Higher scores for the categories of global QOL and physical function represent a higher QOL status, whereas higher scores for the fatigue, pain, and dyspnea categories indicate a lower QOL status. We used a generalized estimating equation to do the longitudinal data analysis, to determine the effective impact of correlative factors on postoperative QOL, including age, gender, body mass index, Charlson Comorbidity Index, ASA grade, tumor location, neoadjuvant therapy, cTNM stage, pTNM stage, historical period of surgery, surgical approach, and length of postoperative time period. The analysis was done using R 3.0.1.

RESULTS

Operative Features

In 735 cases, MIE was performed, with conversion to thoracotomy in 8 patients (in 2 because of bleeding, in 5 because of technical difficulty, and in 1 because of tracheal injury). The operative features of the patients are described in Table 2. Compared with the OE group, the MIE group had shorter operation duration, less blood loss, and a shorter postoperative length of hospital stay; the 2 groups had similar lymph node harvest.

Morbidity and Mortality

The rate of total complications (based on the Common Terminology Criteria for Adverse Events) was similar in the 2 groups (Table 2). However, the MIE group had fewer major complications (30.4% vs 36.9%, $P = .039$), especially respiratory complications (8.6% vs 13.3%,

TABLE 1. Patient demographics

Variable	Before matching		<i>P</i> value	After matching		<i>P</i> value
	MIE (n = 735)	OE (n = 652)		MIE (n = 444)	OE (n = 444)	
Age, median (y [IQR])	56 (32-83)	57 (34-77)	.872	56 (32-77)	56 (38-76)	.531
Sex (male/female)	603/132	529/123	.664	362/82	358/86	.732
BMI, mean ± SD	22.3 ± 2.4	22.1 ± 2.9	.359	22.2 ± 2.4	22.1 ± 2.9	.519
CCI			.511			.220
0	3	2		1	1	
1	43	33		23	27	
2	233	235		181	158	
3	274	246		156	191	
4	157	121		70	52	
5	22	13		11	13	
6	3	2		2	2	
ASA grade			.873			.812
I	492	443		321	328	
II	215	187		107	99	
III	28	22		16	17	
Tumor location			.995			.657
Upper	106	95		63	68	
Middle	412	364		244	251	
Lower	217	193		137	125	
Neoadjuvant therapy			.335			.878
Chemoradiotherapy	84	90		58	53	
Chemotherapy	36	36		22	22	
None	615	526		364	369	
cTNM stage			.342			.898
Tis N0 M0	25	19		15	15	
T1 N0 M0	99	70		49	56	
T2 N0 M0	448	402		271	269	
T3 N0 M0	163	161		109	104	
pTNM stage			.272			.710
0 & I	121	85		62	69	
II	427	384		254	255	
III	149	142		100	99	
IV	38	41		28	21	

P values were computed using χ^2 analysis, except for the following: age, Mann-Whitney *U* test; gender (in addition to χ^2 analysis) and body mass index, Student *t* test; CCI (after matching), Fisher exact test. Values for cTNM stage include cases of down-staging after neoadjuvant therapy. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *IQR*, interquartile; *BMI*, body mass index; *CCI*, Charlson Comorbidity Index; *ASA*, American Society of Anesthesiologists; *cTNM*, clinical tumor-node-metastasis; *pTNM*, pathologic tumor-node-metastasis; *SD*, standard deviation.

P = .024) (Table 3). To treat the major complications, reoperation was needed for 3 (0.7%) cases in the MIE group and 8 (1.8%) cases in the OE group. In addition, readmission to the intensive-care unit occurred less in the MIE than in the OE group (5.6% vs 9.7%, *P* = .023). As a result, the perioperative mortality was similar in the 2 groups after matching (1.1% vs 2.0%, *P* = .281) (Table 4).

Survival

At a median follow-up of 27 months, the 2-year overall survival rates based on pathologic stage in the MIE and OE group, respectively, were: (1) stage 0 and I: 92% versus 90% (*P* = .864); (2) stage II: 83% versus 82% (*P* = .725);

(3) stage III: 59% versus 55% (*P* = .592); (4) stage IV: 43% versus 43% (*P* = .802). No statistical difference was found on the survival curves for each pathologic stage between the 2 groups (Figures 2-5).

Health-Related Quality of Life

At the baseline level before operation, the scores on all scales were similar in the 2 groups, with no statistically significant difference. Postoperatively, the patients in the MIE group had higher scores for the physical function category, but lower scores for the fatigue, pain, and dyspnea categories, compared with the OE group. Consistent with this result, the scores on global QOL were higher in the MIE group than in the OE group, especially in the first

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TABLE 2. Comparison of operative features (after matching)

Variable	MIE (n = 444)	OE (n = 444)	P value
Operation duration (min)	191 ± 47	211 ± 44	<.001
Blood loss (ml)	135 ± 74	163 ± 84	<.001
Number of lymph nodes harvested (n)	24.1 ± 6.2	24.3 ± 6.0	.607
Length of ICU stay (d)	1 (0-30)	1 (0-39)	.407
Length of postoperative hospital stay (d)	11 (7-90)	12 (8-112)	<.001
Total no. complications (%)	230 (51.8)	254 (57.2)	.106
Grade 1-2	95	90	
Grade 3	112	123	
Grade 4	23	41	

P values were computed by Student *t* test, except for: both length-of-stay categories (Mann-Whitney *U* test); and complications. Complications (Chi-square tests) were graded according to the Common Terminology Criteria for Adverse Events. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *ICU*, intensive-care unit.

year of survival. Furthermore, the result of the generalized estimating equation analysis showed that the surgical approach (MIE vs OE) and the length of the postoperative time period independently had a positive impact on patients' postoperative QOL (global QOL, physical function, fatigue symptoms, pain symptoms, and dyspnea symptoms), whereas age and neoadjuvant chemotherapy independently had a negative impact on global QOL (Table 5 and Tables E2 and E3).

TABLE 3. Comparison of major complications (after matching)

Variable	MIE (n = 444)	OE (n = 444)	P value
Respiratory complications	38 (8.6)	59 (13.3)	.024
Pneumonia	29 (6.5)	44 (9.9)	
ARDS	9 (2.0)	15 (3.4)	
Circulatory complications	7 (1.6)	15 (3.4)	.084
Heart failure	3 (0.7)	7 (1.6)	
Myocardial infarction	1 (0.2)	3 (0.7)	
Pulmonary embolism	1 (0.2)	2 (0.5)	
Severe arrhythmia	1 (0.2)	1 (0.2)	
Cerebrovascular accident	1 (0.2)	2 (0.5)	
Digestive complications	60 (13.5)	50 (11.3)	.308
Cervical anastomotic leak	52 (11.7)	29 (6.5)	
Intrathoracic gastric conduit necrosis or intrathoracic anastomotic leak	4 (0.9)	15 (3.4)	
Delayed gastric emptying	4 (0.9)	6 (1.4)	
Operation-related complications	30 (6.3)	40 (8.8)	.213
Postoperative bleeding	1 (0.2)	2 (0.5)	
Chylothorax	2 (0.5)	3 (0.7)	
Hoarseness	26 (5.9)	28 (6.3)	
Tracheal injury	1 (0.2)	1 (0.2)	
Wound infection	0	6 (1.4)	
Total major complications	135 (30.4)	164 (36.9)	.039

Values are n (%). P values were computed using χ^2 analysis. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *ARDS*, acute respiratory distress syndrome.

TABLE 4. Intervention for major complications and mortality

Variable	MIE (n = 444)	OE (n = 444)	P value
Reoperation (total)	3 (0.7)	8 (1.8)	.129
Surgical hemostasis	1	2	
Ligation of thoracic duct	1	2	
Tracheal repair	1	1	
Debridement and suturing	0	3	
Readmission to ICU	25 (5.6)	43 (9.7)	.023
Perioperative mortality	5 (1.1)	9 (2.0)	.281

Values are n (%). P values were computed using χ^2 analysis. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *ICU*, intensive-care unit.

DISCUSSION

This retrospective study involved a comprehensive comparison of MIE versus OE in a matched population of ESCC patients, which showed that the MIE group had better perioperative features, better postoperative QOL, and equal oncologic survival. An increasing number of institutions are using MIE in clinical practice. Luketich and colleagues¹ published the largest volume of MIE procedures (ESCC: 11%; adenocarcinoma: 76%). Conversion to open surgery was required for 4.5% of the patients. The median number of lymph nodes resected was 21; the length of stay was 8 days (range: 6-14 days), and the intensive-care unit stay was 2 days (range: 1-3 days). The major morbidity was 26.4%, and the 30-day mortality was 1.7%.

The feasibility of MIE has been confirmed in several other large case reports.⁸⁻¹⁰ However, the pathologic type in these cases is mainly adenocarcinoma in the distal esophagus or gastroesophageal junction. Nevertheless, our study showed that MIE is equally suitable for treating ESCC that is located mainly in the middle region of the esophagus.

Growing evidence suggests that MIE could provide equal-quality or better operative features compared with open surgery.¹¹⁻¹⁶ Biere and colleagues¹⁷ conducted a multicenter randomized controlled trial, lending weight to their findings comparing MIE (n = 59) with OE (n = 56) in the treatment of esophageal cancer (ESCC: 37.4%; adenocarcinoma: 61.7%). The results showed that MIE, versus OE, resulted in a longer operation duration (329 minutes [range: 90-559 minutes] vs 299 minutes [range: 66-570 minutes], *P* = .002); less blood loss (200 ml [range: 20-1200 ml] vs 475 ml [range: 50-3000 ml], *P* < .001); a shorter hospital stay (11 days [range: 7-80 days] vs 14 days [range: 1-120 days], *P* = .044); less pulmonary infection in the first 2 weeks (9% vs 29%, *P* = .005) and in-hospital (12% vs 34%, *P* = .005). No statistically significant difference was found for other morbidities, or for mortality (3% [MIE] vs 2% [OE], *P* = .590). These findings are similar to those in our series on ESCC cases, confirming the advantage of MIE in regard to perioperative outcomes.

TABLE 5. Analysis of QOL (generalized estimating equation)

	Global QOL		Physical function		Fatigue symptoms		Pain symptoms		Dyspnea symptoms	
	Estimation	P value	Estimation	P value	Estimation	P value	Estimation	P value	Estimation	P value
Intercept	−20.946	<.001	−32.937	<.001	24.927	<.001	38.952	<.001	13.736	<.001
Age	−0.205	.015	−0.079	.186	0.076	.314	−0.012	.820	0.025	.483
Sex	−0.234	.712	−0.232	.639	−0.306	.627	−0.618	.160	−0.467	.099
BMI	−0.117	.226	−0.054	.474	0.016	.841	−0.027	.654	0.056	.166
CCI	0.572	.205	−0.035	.924	−0.068	.871	0.136	.647	−0.444	.028
ASA grade	−0.817	.266	−0.519	.383	0.383	.583	0.181	.706	1.170	<.001
Tumor location (U)	0.086	.909	0.391	.501	−0.028	.965	0.148	.783	0.622	.076
Tumor location (M)	0.620	.260	0.306	.486	0.066	.900	−0.437	.237	−0.004	.989
Neoadjuvant chemotherapy	−2.858	.016	−1.119	.292	1.850	.070	1.436	.064	−0.112	.839
Neoadjuvant chemoradiotherapy	0.302	.750	0.571	.417	−0.690	.489	−0.538	.370	0.137	.730
cTNM stage	0.918	.180	0.675	.194	0.664	.315	0.087	.858	0.515	.142
pTNM stage	−0.712	.279	−0.321	.484	−0.299	.603	0.413	.335	−0.255	.430
Historical period of surgery	−0.349	.537	−0.228	.590	0.227	.682	0.511	.194	−0.133	.634
Surgical approach	19.506	<.001	21.742	<.001	−10.599	<.001	−21.537	<.001	−6.677	<.001
Length of postoperative time	1.656	<.001	1.624	<.001	−1.292	<.001	−1.567	<.001	−0.221	<.001

Bold indicates statistical significance ($P < .05$). QOL, Quality of life; BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; U, upper; M, middle; cTNM, clinical tumor-node-metastasis; pTNM, pathologic tumor-node-metastasis.

Survival is the critical measure for evaluation of treatment of malignant diseases. However, very few studies have reported on the survival of patients after MIE, especially on the basis of pathologic stage and in comparison with OE. In the 1011 cases of MIE (ESCC: 11%; adenocarcinoma: 76%) reported by Luketich and colleagues,¹ the

overall survival rates at 1 year, stratified by pathologic stage, were 86% (stage 0); 89% (stage I); 80% (stage IIa); 76% (stage IIb); 63% (stage III); and 44% (stage IV), as measured at the median follow-up of 20 months.

Nafteux and colleagues¹⁸ reported a comparative analysis of MIE (n = 65) versus OE (n = 101) for early

FIGURE 2. The survival curve of pathologic stage 0 & I of the 2 groups, after matching. MIE, Minimally invasive esophagectomy; OE, open esophagectomy; cum, cumulative.

Patients at risk (after matching)

Time (months)	0	12	24	36	48	60	72	84	96
MIE	254	224	171	101	68	41	22	11	4
OE	255	229	172	97	68	45	22	10	4

	2-year survival	5-year survival	Median (m)	95% confidence intervals (m)	P value
MIE	83%	50%	59.0	38.7-79.3	0.725
OE	82%	48%	51.0	32.5-69.5	

FIGURE 3. The survival curve of pathologic stage II of the 2 groups. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *cum*, cumulative.

esophageal and gastroesophageal-junction carcinoma (adenocarcinoma was predominant in these cases, at 75%); the 5-year cancer-specific and the recurrence-free

survival, stratified to the pathologic T-stage, were similar. Lazzarino and colleagues¹⁹ reported the outcomes following MIE (n = 699) versus OE (n = 17,974) in

Patients at risk (after matching)

Time (months)	0	12	24	36	48	60	72
MIE	100	85	52	31	14	9	0
OE	99	82	49	25	12	6	1

	2-year survival	5-year survival	Median (m)	95% confidence intervals (m)	P value
MIE	59%	33%	38.0	27.4-48.6	0.592
OE	55%	34%	30.0	20.4-39.6	

FIGURE 4. The survival curve of pathologic stage III of the 2 groups. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *cum*, cumulative.

FIGURE 5. The survival curve of pathologic stage IV of the 2 groups. *MIE*, Minimally invasive esophagectomy; *OE*, open esophagectomy; *cum*, cumulative.

England from 1996 to 2008 and found that the 1-year survival with MIE was similar to that with OE (odds ratio = 0.68, 95% confidence interval = 0.46-1.01, $P = .058$). However, these reports were mainly from western countries with predominantly a histological type of adenocarcinoma. Further, in our series of ESCC, no statistically significant difference was found between the 2 groups, with stage-by-stage analysis.

Moreover, for malignant disease, such as esophageal cancer, which has high morbidity and a poor prognosis, survival alone may not adequately reflect the efficacy of treatment. Health-related QOL refers to patients' self-reported perception of their ability to live a useful and fulfilling life,^{20,21} which has been advocated by the U.S. Food and Drug Administration as the second-most relevant outcome measure to assess cancer therapy. However, very few studies have compared the impact of these 2 procedures on patients' postoperative QOL, especially for ESCC.

In the comparative analysis of MIE versus OE for early esophageal and gastroesophageal-junction cancer, conducted by Nafteux and colleagues,¹⁸ a statistically significant difference was found, favoring MIE, in the categories of role functioning and gastrointestinal pain in postoperative months 1 to 3. In our series, much greater benefit of MIE was found for patients during the follow-up (especially within the first year of survival), confirmed by the multivariable regression model analysis

mentioned earlier. However, the QOL, after 1 year and longer time intervals, found at these 2 centers was similar, including in a more recent and larger study from Nafteux and colleagues.²² Therefore, MIE seems to provide better QOL for patients with esophageal carcinoma, despite the diversity in histological type, tumor location, and race.

However, our study has limitations. It is retrospective and from only a single center. The selection of patients for MIE and OE was not a randomized procedure. Both of these study design features can lead to bias. Therefore, new prospective randomized controlled trials in multiple centers are needed to validate these findings.

CONCLUSIONS

In our experience, MIE is a safe and effective procedure for the treatment of ESCC. It may offer better perioperative outcomes, better postoperative QOL, as well as equal oncologic survival for patients, thereby providing an advantage in benefit to patients, compared with OE.

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2014/files/Monday/20140428_300PM_320PM_Hao_Wang.mp4.

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Discussion

Dr A. Lerut (Leuven, Belgium). Thank you, Mr Chairman. I have no disclosures.

I congratulate Dr Wang and his group for a fine presentation, and excellent results. I also thank the authors for sending the article well in advance. I have a couple of comments and 3 questions. In this presentation, the authors compare a large series of minimally invasive esophagectomies with open esophagectomies, both performed in the same period of time. As a preliminary remark, I want to say that during my recent 2-month stay in Shanghai, at the Fudan Cancer Center, I was privileged to visit Dr Tan's group at Zhongshan Hospital, among other institutions, and I must say that I was impressed by these highly skilled surgeons working in a state-of-the-art operating theater complex, clearly explaining these outstanding, remarkable results. However, I also want to indicate some differences in the demographics of their patient population as compared with most centers in the Western Hemisphere, and in particular, our own minimally invasive esophagectomy series. Besides the fact that it deals only with squamous cell carcinoma, the average age of patients in this series is markedly younger, 56 years, as compared with 63 years, from our experience. The mean BMI was 22 in your series, versus 27 in ours, with 20% who had a BMI of >30 in our series. As to the comorbidities, the pulmonary comorbidity was 8% versus 13%; cardiac was 6% versus 17%; and ASA III score, was 4% versus the 19% from our experience. In your series, as described in the article, you excluded all previous abdominal and thoracic surgery, which today, in our experience, is nearly 20%. Here are my 3 questions, and I will ask each one separately so you can answer after each question. You mentioned perioperative mortality, but I would like to know what your definition is of perioperative mortality, in the sense that, today, there is a growing tendency to provide 90-day mortality as the real figure, rather than 30-day mortality. Did you look at 90-day mortality? Was your figure 30-day mortality? Can you comment on this?

Dr Wang. Thank you. We defined the perioperative mortality in this study as 30-day mortality. The reason we used this parameter is that we wanted to compare it with other previously published results in the literatures. Maybe 90-day mortality is a better parameter, and we will use it in our future papers.

Dr Lerut. Thank you. I encourage everybody in the audience to use 90-day mortality in the future because it is just simply doubling as compared with 30-day mortality, and that is important in your discussions with patients. My second question relates to the anastomotic leaks. You have in the minimally invasive esophagectomy group an anastomotic leak rate of 12.2%, which is more than double the 5.8% leak rate in the open group. Do you have an explanation for this quite high incidence of leaks in the MIE group as compared with the open group? Did you use a different technique for the conduit construction and the anastomotic construction? Could you comment on this, please?

Dr Wang. I think that there are 2 reasons. In the MIE group, cervical anastomosis was performed in 720 patients, and

intrathoracic anastomosis was performed in only 7 patients. In the open group, cervical anastomosis was performed in nearly half of the patients, and intrathoracic anastomosis was performed in the other half. As we know, the leak rate in cervical anastomosis is usually higher than it is in intrathoracic anastomosis. Maybe that is 1 of the reasons. Another reason may be the learning curve. As we do laparoscopy in the early stage, immature skills often lead to the injury of the stomach and decrease the blood supply for the anastomosis. In that time, the cervical anastomosis leak rate was about 20%; as skills improved, the stomach was better protected, and the leak rate at present has decreased to approximately 5%.

Dr Lerut. Thank you. From your article, I noticed that in the series with MIE, you had 63 patients who underwent what I would call a hybrid intervention, in that they received a formal laparotomy instead of a laparoscopy. In this subset, what were the scores for quality of life over time for physical functioning, fatigue, pain, dyspnea, and global quality? Were they more like the results you had in open surgery for these parameters, or were they the same as in the other patients who had a formal laparoscopy?

Dr Wang. In this series, my impression is that the hybrid patients had almost the same quality of life as the MIE patients. As I know from the literature, the benefit of laparoscopy for esophagectomy is controversial, and in my opinion, the thoracoscopy may contribute much more to the benefit of MIE.

Dr Lerut. Along that line, to finish, I noticed in your article that 118 patients had neoadjuvant upfront induction therapy, and again, my question is whether you have looked at the same quality-of-life scores for this subset for over time? Were there any differences in this group versus the group who had minimally invasive esophagectomies without induction therapy?

Dr Wang. Do you mean the patients who received neoadjuvant therapy?

Dr Lerut. Yes.

Dr Wang. Yes. In our experience, the patients who received neoadjuvant therapy usually had a lower quality of life. However, the patients whose status was too low would not have been included in the surgery, so in my opinion, the decrease in quality of life was not severe in this series. On the other hand, the rates of neoadjuvant therapy in the 2 groups were similar, so the 2 groups had similar quality of life at baseline.

Dr Lerut. Thank you. I also thank the association for the privilege of discussing this paper.

Dr Wang. Thank you very much.

Dr B. Meyers (St. Louis, Mo). Congratulations on an excellent presentation. I particularly commend you on giving your results for the entire series, including the very early patients. It would have been tempting, and we would have totally understood, if you had just shown the last 500 patients and maybe omitted the early patients that were on your learning curve. Your outcomes would have looked better, but we would not have learned as much as we did by your showing the graded approach you took with the airway management, and the improvement of your results over time.

You had a very low rate of chylothorax, and I was interested and impressed by the fact that you gave the patients milk 6 hours before the operation. Maybe you could comment about that? Did you do that for all of the patients, or did you start part way through this series of 790 patients to give the milk before surgery, to help identify and fix the chylothorax during the primary procedure?

Dr Wang. Oral intake of whole milk is used to facilitate the exposure of the thoracic duct in the operation. We have used this method for approximately 5 years. Thank you.

Readers who found these articles interesting may also like to read the following papers found in recent and future issues of our sister publications, *Seminars in Thoracic and Cardiovascular Surgery* and *Operative Techniques in Thoracic and Cardiovascular Surgery*!

Otis Rickman. Electromagnetic Navigation Assisted Bronchoscopy. *Oper Tech Thorac Cardiovasc Surg.* Summer 2014;19(2):199-218.

Eric Grogan. Localization techniques for small lung nodules. *Oper Tech Thorac Cardiovasc Surg.* Summer 2014;19(2):179-198.

Donald Nuss. The Minimally Invasive Repair of Pectus Excavatum. *Oper Tech Thorac Cardiovasc Surg.* Summer 2014; 9(2):199-218.

John Kucharczuk. Total Pectus Excavatum Repair: Open Approach. *Oper Tech Thorac Cardiovasc Surg.* Expected publication February 2015.

TABLE E1. The logistic regression analysis for propensity-score matching

Parameters	Estimation	SD	χ^2	P value	OR (95% CI)
Intercept	11.58	1.23	87.94	<.0001	—
Age	−0.23	0.02	122.72	<.0001	0.80 (0.77, 0.83)
BMI	0.04	0.02	2.60	.11	1.04 (0.99, 1.08)
Historical period of surgery = 1 (of 3)	−1.09	0.14	63.28	<.0001	0.10 (0.06, 0.18)
Historical period of surgery = 2 (of 3)	−0.10	0.09	1.39	.24	0.27 (0.18, 0.42)
Sex = 1 (of 2)	0.01	0.07	0.01	.91	1.02 (0.76, 1.36)
CCI = 0 (of 6)	−3.24	0.91	12.78	.00	0.01 (<0.001, 0.20)
CCI = 1 (of 6)	−1.33	0.40	11.22	.00	0.06 (0.01, 0.71)
CCI = 2 (of 6)	0.03	0.34	0.01	.93	0.22 (0.02, 2.61)
CCI = 3 (of 6)	0.37	0.33	1.23	.27	0.32 (0.03, 3.61)
CCI = 4 (of 6)	1.46	0.36	16.08	<.0001	0.94 (0.08, 10.36)
CCI = 5 (of 6)	1.19	0.69	2.99	.08	0.72 (0.10, 5.08)
ASA grade = 1 (of 3)	−0.02	0.32	0.00	.95	1.03 (0.19, 5.47)
ASA grade = 2 (of 3)	0.07	0.28	0.06	.81	1.12 (0.23, 5.50)
Tumor location = 1 (of 3)	−0.02	0.11	0.04	.85	0.98 (0.68, 1.41)
Tumor location = 2 (of 3)	0.02	0.08	0.09	.77	1.03 (0.80, 1.33)
Neoadjuvant therapy = 0 (of 2)	0.20	0.19	1.07	.30	1.29 (0.73, 2.28)
Neoadjuvant therapy = 1 (of 2)	−0.14	0.20	0.48	.49	0.93 (0.51, 1.68)
cTNM = 1 (of 4)	−0.66	0.48	1.95	.16	0.27 (0.04, 1.64)
cTNM = 2 (of 4)	−0.52	0.40	1.74	.19	0.31 (0.06, 1.62)
cTNM = 3 (of 4)	0.53	0.40	1.80	.18	0.89 (0.41, 1.92)
pTNM = 1 (of 4)	0.97	0.60	2.63	.10	3.93 (0.74, 20.88)
pTNM = 2 (of 4)	−0.30	0.25	1.44	.23	1.11 (0.53, 2.31)
pTNM = 3 (of 4)	−0.26	0.27	0.94	.33	1.15 (0.68, 1.95)

The C-statistic of our model is 0.70. OR, Odds ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; cTNM, clinical tumor-node-metastasis; pTNM, pathologic tumor-node-metastasis; SD, standard deviation.

TABLE E2. Assessment of QOL (after matching)

Variable	MIE (n = 444)	OE (n = 444)	P value
Global QOL			
Baseline	72.8 ± 10.6	73.0 ± 10.9	.860
1 mo	55.7 ± 12.4	40.1 ± 9.2	<.001
3 mo	66.2 ± 13.0	42.6 ± 14.1	<.001
6 mo	68.5 ± 11.6	54.0 ± 15.0	<.001
12 mo	70.5 ± 13.3	64.7 ± 10.4	<.001
18 mo	72.1 ± 13.0	71.2 ± 12.7	.116
24 mo	72.5 ± 13.9	71.2 ± 13.4	.341
Physical function			
Baseline	84.8 ± 10.6	84.7 ± 9.0	.960
1 mo	66.8 ± 9.2	47.4 ± 8.1	<.001
3 mo	72.0 ± 11.1	49.3 ± 9.7	<.001
6 mo	77.1 ± 12.1	49.3 ± 9.7	<.001
12 mo	78.8 ± 12.3	71.6 ± 13.3	<.001
18 mo	80.4 ± 9.0	78.4 ± 10.4	.028
24 mo	80.8 ± 6.1	80.3 ± 7.5	.492
Fatigue symptoms			
Baseline	21.8 ± 12.5	21.6 ± 11.2	.566
1 mo	44.2 ± 14.2	56.8 ± 16.7	<.001
3 mo	40.3 ± 14.3	54.9 ± 15.0	<.001
6 mo	33.3 ± 14.0	46.1 ± 15.5	<.001
12 mo	26.9 ± 13.0	31.2 ± 10.8	<.001
18 mo	26.7 ± 7.9	27.2 ± 7.7	.424
24 mo	26.4 ± 7.4	26.8 ± 7.1	.501
Pain symptoms			
Baseline	15.2 ± 8.0	15.6 ± 8.0	.476
1 mo	34.8 ± 13.8	62.7 ± 13.9	<.001
3 mo	30.8 ± 10.7	50.7 ± 12.5	<.001
6 mo	28.5 ± 11.6	36.6 ± 9.7	<.001
12 mo	25.4 ± 11.7	26.1 ± 8.0	.019
18 mo	24.7 ± 10.8	25.1 ± 12.3	.411
24 mo	24.3 ± 11.1	24.3 ± 9.1	.792
Dyspnea symptoms			
Baseline	10.7 ± 7.1	10.5 ± 6.8	.738
1 mo	23.3 ± 7.3	34.5 ± 9.9	<.001
3 mo	20.9 ± 7.5	25.7 ± 8.5	<.001
6 mo	18.9 ± 6.9	21.5 ± 8.6	<.001
12 mo	17.4 ± 6.7	18.0 ± 6.4	.181
18 mo	16.8 ± 7.6	17.3 ± 6.6	.604
24 mo	16.9 ± 6.2	17.1 ± 5.7	.820

P values were determined by Mann-Whitney *U* test. A higher score on global QOL and physical function represents better QOL status, whereas a higher score on fatigue, pain, and dyspnea symptoms indicates worse QOL status. *QOL*, Quality of life; *MIE*, minimally invasive esophagectomy; *OE*, open esophagectomy.

TABLE E3. Analysis of QOL (generalized estimating equation) in detail

	Estimate	Standard error	Wald statistics	P value
(1) Global QOL				
Intercept	−20.946	4.093	26.190	<.001
Age	−0.205	0.084	5.976	.015
Sex	−0.234	0.636	0.136	.712
BMI	−0.117	0.097	1.467	.226
CCI	0.572	0.451	1.610	.205
ASA grade	−0.817	0.734	1.240	.266
Tumor location (U)	0.086	0.757	0.013	.909
Tumor location (M)	0.620	0.551	1.268	.260
Neoadjuvant chemotherapy	−2.858	1.181	5.851	.016
Neoadjuvant chemoradiotherapy	0.302	0.948	0.101	.750
cTNM stage	0.918	0.685	1.796	.180
pTNM stage	−0.712	0.657	1.174	.279
Historical period of surgery	−0.349	0.566	0.381	.537
Surgical approach	19.506	0.616	1003.639	<.001
Length of postoperative time	1.656	0.064	672.271	<.001
(2) Physical function				
Intercept	−32.937	2.970	122.967	<.001
Age	−0.079	0.060	1.748	.186
Sex	−0.232	0.494	0.221	.639
BMI	−0.054	0.075	0.512	.474
CCI	−0.035	0.367	0.009	.924
ASA grade	−0.519	0.595	0.760	.383
Tumor location (U)	0.391	0.580	0.453	.501
Tumor location (M)	0.306	0.440	0.485	.486
Neoadjuvant chemotherapy	−1.119	1.061	1.112	.292
Neoadjuvant chemoradiotherapy	0.571	0.703	0.660	.417
cTNM stage	0.675	0.519	1.686	.194
pTNM stage	−0.321	0.459	0.489	.484
Historical period of surgery	−0.228	0.423	0.291	.590
Surgical approach	21.742	0.524	1721.569	<.001
Length of postoperative time	1.624	0.020	6722.664	<.001
(3) Fatigue symptoms				
Intercept	24.927	3.477	51.386	<.001
Age	0.076	0.076	1.014	.314
Sex	−0.306	0.631	0.235	.627
BMI	0.016	0.082	0.040	.841
CCI	−0.068	0.421	0.026	.871
ASA grade	0.383	0.699	0.301	.583
Tumor location (U)	−0.028	0.636	0.002	.965
Tumor location (M)	0.066	0.521	0.016	.900
Neoadjuvant chemotherapy	1.850	1.021	3.282	.070
Neoadjuvant chemoradiotherapy	−0.690	0.997	0.479	.489
cTNM stage	0.664	0.661	1.010	.315
pTNM stage	−0.299	0.575	0.270	.603
Historical period of surgery	0.227	0.552	0.168	.682
Surgical approach	−10.599	0.850	155.531	<.001
Length of postoperative time	−1.292	0.034	1432.795	<.001
(4) Pain symptoms				
Intercept	38.952	2.586	226.926	<.001
Age	−0.012	0.054	0.052	.820
Sex	−0.618	0.440	1.973	.160
BMI	−0.027	0.060	0.200	.654
CCI	0.136	0.298	0.210	.647
ASA grade	0.181	0.479	0.143	.706

(Continued)

TABLE E3. Continued

	Estimate	Standard error	Wald statistics	P value
Tumor location (U)	0.148	0.538	0.076	.783
Tumor location (M)	−0.437	0.370	1.397	.237
Neoadjuvant chemotherapy	1.436	0.776	3.424	.064
Neoadjuvant chemoradiotherapy	−0.538	0.601	0.803	.370
cTNM stage	0.087	0.487	0.032	.858
pTNM stage	0.413	0.428	0.930	.335
Historical period of surgery	0.511	0.393	1.690	.194
Surgical approach	−21.537	0.414	2708.927	<.001
Length of postoperative time	−1.567	0.030	2745.508	<.001
(5) Dyspnea symptoms				
Intercept	13.736	1.749	61.691	<.001
Age	0.025	0.036	0.493	.483
Sex	−0.467	0.283	2.719	.099
BMI	0.056	0.041	1.916	.166
CCI	−0.444	0.202	4.858	.028
ASA grade	1.170	0.334	12.278	<.001
Tumor location (U)	0.622	0.351	3.139	.076
Tumor location (M)	−0.004	0.252	0.000	.989
Neoadjuvant chemotherapy	−0.112	0.548	0.041	.839
Neoadjuvant chemoradiotherapy	0.137	0.398	0.119	.730
cTNM stage	0.515	0.351	2.153	.142
pTNM stage	−0.255	0.323	0.622	.430
Historical period of surgery	−0.133	0.279	0.226	.634
Surgical approach	−6.677	0.479	194.276	<.001
Length of postoperative time	−0.221	0.041	28.450	<.001

Bold indicates statistical significance ($P < .05$). *QOL*, Quality of life; *BMI*, body mass index; *CCI*, Charlson Comorbidity Index; *ASA*, American Society of Anesthesiologists; *U*, upper; *M*, middle; *cTNM*, clinical tumor-node-metastasis; *pTNM*, pathologic tumor-node-metastasis.

GTS