

The effect of postoperative complications on survival of patients after minimally invasive esophagectomy for esophageal cancer

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Received: 29 February 2016 / Accepted: 21 November 2016 / Published online: 6 December 2016
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Abstract

Background Minimally invasive esophagectomy (MIE) has been shown to be a feasible technique for the treatment of esophageal cancer; however, its postoperative morbidity remains high. This retrospective study aimed to evaluate the effect of postoperative complications on long-term outcomes in patients who have undergone MIE for esophageal squamous cell carcinoma (ESCC).

Methods This retrospective study enrolled patients who had undergone MIE for ESCC between September 2009 and November 2014; all procedures were performed by a single surgical team. Relevant patient characteristics and postoperative variables were collected and evaluated. The disease-free survival (DFS) and disease-specific survival (DSS) were determined by the Kaplan–Meier method, and compared by log-rank tests. Possible predictors of survival were subjected to univariate analysis and multivariate Cox proportional hazard regression analysis.

Results In all, data on 214 patients with ESCC were analyzed, including 170 men and 44 women. All study subjects had undergone thoracoscopic or thoracoscopic–laparoscopic esophagectomy and cervical esophago-gastric anastomosis. One hundred and thirty patients (60.7%) had postoperative complications (Grades 1–4). The overall DFS and DSS rates were 80.0 and 88.9% at 1 year, 48.6 and 54.2% at 3 years, and 43.2 and 43.5% at 5 years, respectively. Univariate analysis and multivariate Cox

proportional hazard regression analysis showed that *T* stage, *N* stage, and tumor grade were independent prognostic factors for long-term survival; however, postoperative complications had no significant effect on the DFS or DSS of this patient cohort (log-rank test, $p = 0.354$ and 0.160, respectively).

Conclusions Postoperative complications have no significant effect on long-term survival in patients who have undergone MIE for ESCC.

Keywords Minimally invasive esophagectomy · Esophageal cancer · Complication · Clavien classification · Survival

Esophageal cancer (EC) is one of the deadliest and most aggressive cancers. It is the sixth most common cause of cancer deaths in men and the ninth most common in women globally [1]. In China, EC mainly occurs in the form of esophageal squamous cell carcinoma (ESCC), which accounts for ~90% of all cases of EC [2]. Surgical resection is the mainstay of treatment aimed at prolonging survival and achieving definitive cure [3].

The two most common minimally invasive esophagectomy (MIE) procedures, combined thoracoscopic and laparoscopic esophagectomy and combined thoracoscopic and laparotomy esophagectomy, were developed to reduce the trauma resulting from surgical treatment of esophageal cancer. The established benefits of MIE over open esophagectomy include less estimated blood loss, more lymph nodes resected, and shorter length of hospital stay [4–6]. This procedure is also associated with superior overall survival and perioperative mortality and fewer severe postoperative complications [7]. However, MIE remains a complex procedure with some risk of postoperative morbidity and mortality.

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The effect of postoperative complications on long-term survival of EC patients who have undergone esophagectomy is currently controversial. Several studies have reported that major perioperative morbidity does not affect long-term survival of patients undergoing esophagectomy for cancer of the esophagus or gastroesophageal junction [8, 9], whereas Lerut et al. [10] reported a strong correlation between severity of complications and time to tumor recurrence. In a recent study, Luc et al. [11] found a significant association between occurrence of complications and shorter time interval until death owing to recurrence. However, most of these studies included both patients with ESCC and esophageal adenocarcinoma (EAC); additionally, the surgical procedures varied. Therefore, evaluation of the impact of postoperative complications on long-term survival has been difficult. The aim of this study was to explore the impact of postoperative complications on the long-term survival of patients who had undergone MIE for ESCC in a single institution.

Patients and methods

Patients

From September 2009 to November 2014, 249 thoracoscopic esophagectomies for ESCC of the thoracic esophagus were performed in the Department of Thoracic Surgery, Daping Hospital, Third Military Medical University (Chongqing, China). Exclusion criteria were as follows: loss to follow-up, non-curative (R1 or R2) resection (tumor-free margin <1 mm), postoperative death, and death from causes unrelated to esophageal cancer. All surgeries were performed by the same surgeon (W.G.). Data were collected retrospectively by chart review and relevant patient characteristics and intraoperative and postoperative variables analyzed. Preoperative staging was performed by endoscopic ultrasound and thoracoabdominal computed tomography scanning. Postoperative TNM stage was classified in accordance with the 7th edition of the American Joint Committee on Cancer staging protocol [12]. Postoperative death was defined as death within 30 days after surgery or before discharge from hospital. The study patients had given written consent to the operative procedures, and the study was approved by the Ethics Committee of Daping Hospital.

Operative procedures

All operations were performed by three-stage combined thoracoscopic and laparoscopic esophagectomy or combined thoracoscopic and laparotomy esophagectomy; 228 cases were placed in the left lateral position and 21 cases in the prone position, all operations were performed under

general anesthesia and double-lumen intubation. These procedures have been described previously [13–15]. Briefly, the mediastinal pleura overlying the anterior aspect of the esophagus was cauterized and the esophagus mobilized away from the hilum and pericardium. Mobilization extended to the level of the azygos vein, which was skeletonized and ligated with 10-mm ligaclips. Using electrocautery, the parietal pleura posterior to the esophagus was opened from the level of the azygos vein to the crus. After dissecting the esophagus and mediastinal lymph nodes, the thoracic duct was routinely mass ligated immediately above the diaphragmatic hiatus [12]. For the second stage, the patient was placed in a supine position and laparotomy or laparoscopy performed. Following dissection of the pericardiac and celiac nodes, the stomach was prepared for reconstruction by dividing it at the cardia with a stapler. In the third stage, the cervical esophagus was dissected through a left oblique incision and the stomach pulled up through the posterior mediastinum. The procedure was completed with a cervical esophagogastric anastomosis.

Postoperative complications and classification of patient groups

Postoperative surgical and medical complications were graded according to a modification of the Clavien–Dindo classification [16] as follows: Grade 0, no complications; Grade 1, deviation from normal postoperative course without need for medical intervention; Grade 2, complications requiring pharmacological treatment; Grade 3, complications requiring invasive or radiological intervention; Grade 3a, does not require general anesthesia; Grade 3b, requires general anesthesia; Grade 4, life-threatening complications requiring intensive care unit management; and Grade 5, death. Patients who developed two or more than grades of postoperative complications were classified as having the more serious grade. The patients were divided into the following three groups: Group 1 (Grade 0 complications), Group 2 (Grades 1–3a), and Group 3 (Grades 3b–4b).

Follow-up

After surgery, all patients were followed up regularly in the outpatient clinic every 3 months during the first year, every 6 months until the fifth year, and then annually. All included subjects had complete follow-up information until death or November 2014. The duration of follow-up ranged between 2.7 and 63.9 months (mean 26.3 ± 15.0 months). At follow-up visits, specific examinations such as barium swallow, magnetic resonance imaging, biopsy, and positron emission tomography were performed as indicated.

Recurrence was diagnosed based on pathologic or radiologic findings and classified as locoregional recurrence, distant metastasis, or death from ESCC. Disease-specific survival (DSS) was defined as survival from operation to death from ESCC.

Statistical analysis

Numerical data are expressed as the mean \pm standard deviation. Continuous variables were compared by using χ^2 test and quantitative variables by one-way analysis of variance. Life table analysis was used to calculate the 1-, 2-, 3-, 4-, and 5-year survival rates. Patient survival curves were constructed by the Kaplan–Meier method. The log-rank test was used to compare survival difference between groups for each variable, and multivariate Cox proportional hazard regression analysis were used to identify potential prognostic factors. All statistical calculations were performed using SPSS statistical software, version 19.0 (IBM SPSS, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

During the study period, 249 video-assisted thoracoscopic esophagectomies for squamous cell carcinoma of the thoracic esophagus were performed by the same surgeon (W.G.). Twenty-four of these cases were lost to follow-up (24/249, 9.64%), two suicided postoperatively, three had undergone R1 or R2 resection, one died from oropharyngeal cancer, and one died from asphyxia for an unknown reason in the 51st day after operation. Furthermore, four patients who died within the first 30 postoperative days were also excluded because our aim was to analyze the effect of complications on long-term outcomes. Exclusion of the above-listed patients left 214 consecutive patients in this study. The overall 30-day mortality after surgery was 1.6% (4/249).

Among the 214 study patients, 170 were men, the sex ratio being 3.86 men to 1 woman (Table 1). The average age was 60.2 ± 8.1 years (range, 37–79 years). One hundred and fifty patients (70.1%) had a smoking history and 64 (29.9%) were never-smokers. The average operative time was 281.0 ± 64.6 min, and the mean postoperative hospital stay was 21.3 ± 12.2 days. There were significant differences in average operative time and mean postoperation hospital stay among the different groups ($p = 0.049$ and 0.000 , respectively). Patient characteristics (TNM classification, lung function, intraoperative blood loss) did not differ significantly between the groups.

The complications encountered are shown in detail in Table 2. Eighty-four patients (39.3%) had an unremarkable postoperative course (Grade 0, Group 1). The majority of

patients (130/214, 60.7%) did have postoperative complications (Grades 1–4). As described in the Materials and Methods section, these patients were subdivided into two groups: Group 2 (Grade 1–3a, $n = 110$) and Group 3 (Grade 3b–4b, $n = 20$). The most common complications were anastomotic leakage (9.3%, 20/214), pneumothorax (8.9%, 19/214), pleural infusion (8.9%, 19/214), pneumonia (7.9%, 17/214), adult respiratory distress syndrome (5.6%, 12/214), and chylothorax (3.7%, 8/214).

Seventy-two of the 214 study patients (33.6%) had died from ESCC, whereas 142 (66.4%) remained alive at the end of the study period. Ten of the 142 survivors had locoregional recurrence or distant metastasis at the end of the follow-up period. In this study, the disease-free survival (DFS) and disease-specific survival (DSS) were 80.0 and 88.9% at 1 year, 56.1 and 67.7% at 2 years, 48.6 and 54.2% at 3 years, 43.2 and 51.1% at 4 years, and 43.2 and 43.5% at 5 years after surgery, respectively (Fig. 1). The mean DFS and DSS times were 37.6 ± 2.0 and 41.7 ± 1.9 months, respectively.

Univariate analysis indicated that sex ($p = 0.254$), smoking history ($p = 0.618$), tumor location ($p = 0.254$), and grade of complication ($p = 0.160$) did not significantly influence survival, whereas tumor grade ($p = 0.007$), T stage ($p = 0.002$), and N stage ($p = 0.025$) were significantly associated with survival. According to multivariate Cox proportional hazard regression analysis, T stage ($p = 0.002$), N stage ($p = 0.014$), tumor grade ($p = 0.021$), and location ($p = 0.033$) were all significantly correlated with patient survival (Table 3). There were no significant differences in DFS and DSS among Groups 1–3 ($p = 0.354$ and 0.160 , respectively) (Fig. 2).

Discussion

Previous studies have demonstrated that thoracoscopic esophagectomy is technically feasible, surgically safe, and oncologically adequate, with potentially faster postoperative recovery, reduced trauma, and shorter operative time than open surgery [5–7]. In a recent, multicenter randomized controlled trial, Biere et al. [17] provided evidence for the short-term benefits of MIE in patients with resectable esophageal cancer. Another study in which Ninomiya et al. [18] reviewed their 10-year experience also reported favorable oncologic outcomes of thoracoscopic esophagectomy with extended lymph node dissection in the left lateral position. However, the incidence of postoperative complications after MIE remains high, reportedly ranging from 10 to 57.8% [5–7, 9, 11, 17–20].

In our study, the overall 30-day mortality after surgery was 1.6% (4/249). The postoperative complication rate was 60.7% (130/214), the majority being minor complications (Group 2, 51.4%, 110/214) such as fever, hoarseness, and

Table 1 Patient characteristics of our study

Factor	Total	Group 1 (<i>n</i> = 84)	Group 2 (<i>n</i> = 110)	Group 3 (<i>n</i> = 20)	<i>p</i> value ^a
Gender					0.185
Males	170	62	90	18	
Females	44	22	20	2	
Age (years)	60.2 ± 8.1	59.3 ± 7.2	60.3 ± 8.8	63.7 ± 6.4	0.086 ^b
Smoking history					0.485
No smoking	64	29	30	5	
Smoking	150	55	80	15	
Tumor location					0.500
Upper thoracic	41	15	23	3	
Middle thoracic	152	64	73	15	
Lower thoracic	21	5	14	2	
<i>T</i> stage					0.035
<i>T</i> 1	29	17	10	2	
<i>T</i> 2	54	24	26	4	
<i>T</i> 3	107	37	56	14	
<i>T</i> 4	24	6	18	0	
<i>N</i> stage					0.690
<i>N</i> 0	112	46	57	9	
<i>N</i> 1	64	24	31	9	
<i>N</i> 2	30	10	18	2	
<i>N</i> 3	8	4	4	0	
Distant metastasis (<i>M</i>)					>0.999
<i>M</i> 0	214	84	110	20	
<i>M</i> 1	0	0	0	0	
Grade					0.576
Well differentiated (<i>G</i> 1)	69	30	35	4	
Moderately differentiated (<i>G</i> 2)	107	38	58	11	
Poorly differentiated (<i>G</i> 3)	38	16	17	5	
FVC (%)	92.7 ± 17.0	91.7 ± 14.3	92.3 ± 18.4	99.8 ± 19.3	0.193 ^b
FEV1 (%)	91.4 ± 17.8	90.9 ± 18.7	91.2 ± 17.0	95.1 ± 18.9	0.672 ^b
MVV (%)	90.6 ± 19.8	90.6 ± 18.7	89.9 ± 20.1	94.4 ± 23.5	0.688 ^b
Operative time (min)	281.0 ± 64.6	268.8 ± 65.3	291.1 ± 64.3	276.8 ± 55.4	0.049 ^b
Intraoperative blood loss (ml)	267.2 ± 184.5	236.4 ± 97.7	285.2 ± 226.6	297.5 ± 196.3	0.205 ^b
Postoperative hospital stay (days)	21.3 ± 12.2	13.4 ± 3.1	25.0 ± 11.7	34.5 ± 17.5	0.000 ^b

T tumor stage (depth of invasion), *N* lymphatic dissemination stage (according to the 7th edition of the American Joint Committee on Cancer (AJCC) [13]: *N*0 no positive lymph nodes, *N*1 1 ~ 2 positive lymph nodes, *N*2 3 ~ 6 positive lymph nodes, *N*3 > 6 positive lymph nodes), *FVC* forced vital capacity, *FEV1* percentage of 1-s forced expiratory volume, *MVV* maximal vital volume

^a χ^2 test unless indicated otherwise

^b One-way analysis of variance (ANOVA) test

gastric motor disorders. The incidence of severe complications was 9.3% (20/214), which is clearly lower than that reported by others (15–30%) [9, 11]. Possible explanations for these apparent discrepancies include differences in surgical procedures and pathological types of cancer. Furthermore, we modified the Clavien classification [21] of postoperative complications according to the therapy needed to address the complication. For example, the main complication of anastomotic leakage was classified as

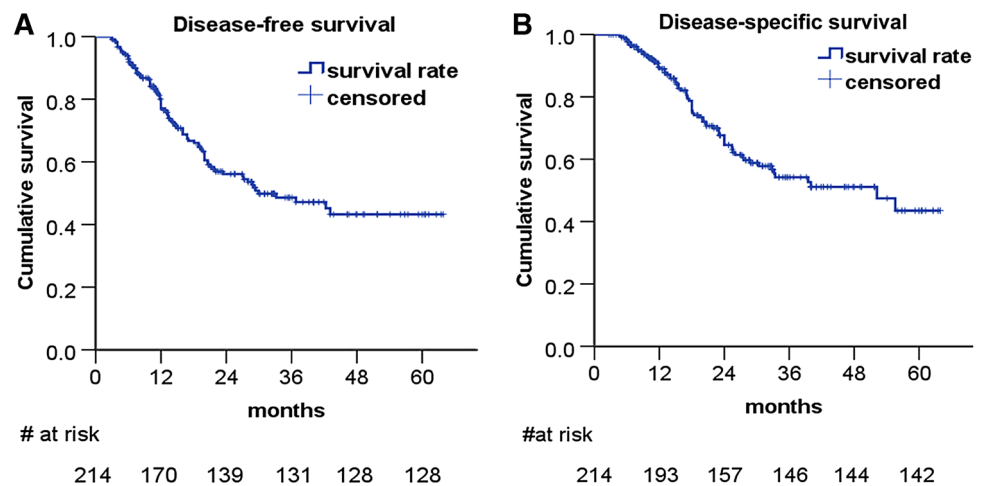
Grade 1, whereas fistulas with local infection requiring antibiotics were classified as Grade 2. Empyema caused by anastomotic leakage requiring treatment by closed thoracic drainage was classified as Grade 3a. Thus, the same complication could be allotted different grades according to the therapy required.

In our study, the 5-year DFS and DSS rates were 43.2 and 43.5%, respectively. Until now, only a few case–control studies have reported long-term survival of patients

Table 2 Overall complications in our study

Clavien–Dindo classification	Complications	No. of patients	Percentage (%)
Grade 0	No complications	84	39.3
Grade 1	Fever, small mount pleural infusion, hoarse, anastomotic leakage, fat liquefaction of incision, gastric motor disorders	39	18.2
Grade 2	Pneumonia, liver function damage, gastric motor disorders, anastomotic leakage, atrial fibrillation, chylothorax, wound infection, atelectasis, delirium	33	15.4
Grade 3a	Pleural infusion, pneumothorax, empyema that need pleural puncture or closed thoracic drainage	38	17.8
Grade 3b	Reoperation like chylothorax, hemothorax	4	1.9
Grade 4a	ARDS, renal insufficiency, heart failure	15	7.0
Grade 4b	ARDS in combination with renal insufficiency	1	0.5

Clavien–Dindo classification: Grade 0, no complications; Grade 1, deviation from normal postoperative course without need for medical intervention; Grade 2, complications requiring pharmacological treatment; Grade 3, complications requiring invasive or radiological intervention; Grade 3a, does not require general anesthesia; Grade 3b, requires general anesthesia; Grade 4, life-threatening complications requiring intensive care unit management; Grade 4a, single-organ dysfunction; Grade 4b, multi-organ dysfunction

Fig. 1 Kaplan–Meier survival curves for DFS (A) and DSS (B) of 214 patients

who have undergone MIE. However, several studies reporting stage-specific survival following MIE have concluded that this procedure also achieves excellent long-term outcomes. For example, Smithers et al. [22] reported the following 5-year stage-specific survival rates after MIE: 85% for Stage I, 33% for Stage IIA, 37% for Stage IIB, and 16% for Stage III (TNM classification, 6th edition). In their non-randomized study, Burdall et al. [23] found significantly better survival following minimally invasive procedures than after open esophagectomy. Ninomiya et al. [18] also reported favorable oncologic outcomes of thoracoscopic esophagectomy with extended lymph node dissection. In their study, the overall 5-year survival rates for Stage I, II, and III disease after curative video-assisted thoracoscopic esophagectomy were 79.1, 77.9, and 56.7%, respectively. In the current study, the follow-up protocol included re-examination of all patients every 3 months; 249 patients attended for these regular

follow-ups, whereas 24 were lost to follow-up. During the study period, 72 patients died. No port-site recurrences were observed. The DSS rates were 88.9% at 1 year, 54.2% at 3 years, and 43.5% at 5 years, whereas the DFS rates were 80.0% at 1 year, 48.6% at 3 years, and 43.2% at 5 years, indicating that MIE can achieve excellent long-term outcomes in patients with ESCC. Moreover, considering the proportion of T3 and T4a lesions in our series (131/214, 61.2%), we believe that MIE achieves satisfactory long-term results in patients with locally advanced esophageal cancer.

Univariate and multivariate Cox proportional hazard regression analyses identified T stage, N stage, and tumor grade as independent prognostic factors for long-term survival, which is in accordance with a previous study [13]. Notably, although patients in Group 1 (no complications) and Group 2 (minor complications) had shorter operative times and postoperative hospital stays than patients in

Table 3 Survival differences after multivariate Cox proportional hazard regression analysis for 214 patients submitted to follow-up

Characteristic	No. of patients	Univariate log-rank <i>p</i> value	Multivariate regression <i>p</i> value	Hazard ratio	95% confidence interval
Gender		0.254	0.242	0.613	0.270–1.391
Male	170				
Female	44				
Smoking history		0.618	0.708	0.873	0.430–1.775
No smoking	64				
Smoking	150				
<i>T</i> stage		0.002	0.002	1.656	1.203–2.279
<i>T</i> 1	29				
<i>T</i> 2	54				
<i>T</i> 3	107				
<i>T</i> 4a	24				
<i>N</i> stage		0.025	0.014	1.391	1.069–1.810
<i>N</i> 0	112				
<i>N</i> 1	64				
<i>N</i> 2	30				
<i>N</i> 3	8				
Tumor grade		0.007	0.021	0.639	0.437–0.934
<i>G</i> 1	69				
<i>G</i> 2	107				
<i>G</i> 3	38				
Location		0.375	0.033	0.593	0.367–0.957
Upper thoracic	41				
Middle thoracic	152				
Lower thoracic	21				
Grade of complication		0.160	0.211	0.773	0.516–1.157
No complication (Grade 0)	84				
Minor complication (Grades 1–3a)	110				
Major complication (Grades 3b–4b)	20				

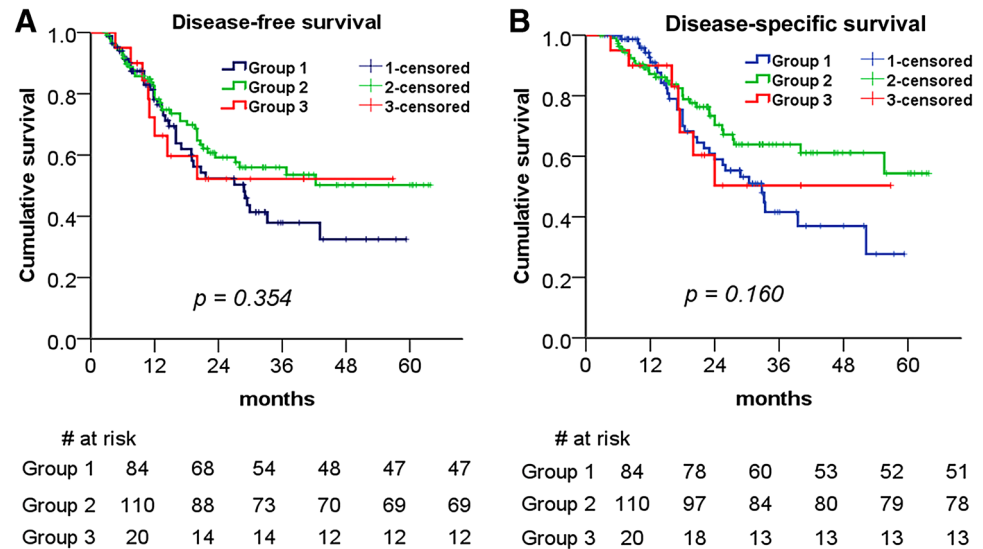
Group 3 (severe complications), postoperative complications had no significant effect on the DFS and DSS of our patients (log-rank test, $p = 0.354$ and 0.160 , respectively). Moreover, multivariate Cox proportional hazard regression analysis also showed that the grade of complications was not an independent prognostic factor in these patients ($p = 0.211$), confirming that postoperative complications did not affect the long-term survival.

There were several studies have investigated the possible effect of postoperative complications on survival of patients underwent esophagectomy [8–11]. The results from Lindner [8] and Xia [9] demonstrated that major perioperative morbidity had no obvious effect on long-term survival, whereas Lerut [10] and Luc [11] found that there was significant correlation between complications and time to tumor recurrence. Notably, these studies enrolled

patients with ESCC and EAC, and the surgical procedures applied in these studies also varied. Therefore, evaluating the actual impact of postoperative complications on long-term survival was difficult, and the conclusions of these studies might lack conviction. In our series, we enrolled patients with ESCC and the surgical procedure applied was uniform, thus making the results and conclusion persuasive. Up to date, there was still few study mentioned the effect of postoperative complications on the long-term survival after MIE, so we believed that our study was helpful to understand the potential effect of complications on survival of patients underwent MIE.

As for the reason why major postoperative complications could not have clinical impact on the long-term outcomes, we speculated that major postoperative complications may have impact on short-time outcome by

Fig. 2 Kaplan–Meier survival curves for DFS (A) and DSS (B) of different groups. Data were compared by using the log-rank test



different paths like systemic inflammatory response and stress. According to previous study, inflammatory onco-taxis, the cytokines in response to stress, with the resulting inflammation, were associated with infection causing a hormonal milieu more conducive to the regrowth of cancer cells [24]. However, the effect of MIE on palliating the systemic inflammatory and catabolic response after surgical trauma has been demonstrated [25]. Therefore, we speculated that major postoperative complications may have impact on short-time outcome by different paths such as systemic inflammatory response and stress, while after the short-time effect was extinguished, the long-term survival was not affected. In fact, the effect and potential paths of different postoperative complications on short-time and long-term outcome after MIE were the focus of our further research.

Although our sample was from a single institution and was relatively small compared with the worldwide collaborative esophageal cancer database, the database in our department and patients' follow-up system were well established, and the surgical procedures, pathologic examinations, and patient follow-up were highly uniform throughout the entire study period. Additionally, all patients enrolled in this study had ESCC, and the operations were performed by a single surgeon using a uniform surgical approach. Therefore, we believe that our results are robust and valid. Of course, further studies with larger cohorts and longer follow-up are needed to validate our results.

In conclusion, MIE is a complex procedure with potential postoperative morbidities. Postoperative complications in patients who have undergone MIE for ESCC may have an impact on short-time survival and quality of life, but do not significantly affect long-term survival.

Compliance with ethical standards

Disclosures Kun-Kun Li, Yin-Jian Wang, Xue-Hai Liu, Qun-You Tan, Yao-Guang Jiang, and Wei Guo have no conflict of interest or financial ties to disclose.

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