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Is There Any Benefit to Incorporating a Laparoscopic Procedure into Minimally Invasive Esophagectomy? The Impact on Perioperative Results in Patients with Esophageal Cancer

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Abstract
Background The benefit of using the laparoscopic approach in minimally invasive esophagectomy (MIE) has not been established. We therefore compared the outcome of esophagectomy for patients with esophageal cancer performed with open surgery, video-assisted thoracic surgery (VATS)/laparotomy (hybrid MIE), and VATS/laparoscopy (total MIE).
Methods Patients with esophageal cancer undergoing tri-incisional esophagectomy with three different approaches between 2005 and 2009 were analyzed from a prospective database.
Results Three groups of patients underwent esophagectomy by open surgery ($n = 64$), hybrid MIE ($n = 44$), and total MIE ($n = 30$). The total MIE group had significantly longer operative times but had shorter postoperative ventilator usage times postoperative hospital stay, and they began jejunostomy feeding sooner ($P < 0.05$, compared with the other groups). There was a significant trend toward a decrease in postoperative pulmonary complications and anastomotic leakage in parallel to the proportion of minimally invasive procedures for esophagectomy ($P < 0.05$ for the trend test), with a significant difference between the open surgery and total MIE groups (30% vs. 6.7%, and 28% vs. 6.7%, respectively; $P < 0.05$).
Conclusions Use of a laparoscopic procedure in MIE for patients with esophageal cancer might provide benefit by facilitating postoperative recovery and reducing the rates of post-esophagectomy pulmonary complications and anastomotic leakage.

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Introduction

Esophagectomy for esophageal cancer is a technically complex procedure that is associated with high perioperative mortality, even in high-volume centers [1]. To facilitate the postoperative recovery of esophagectomized patients by reducing surgical trauma, an increasing number of surgeons have attempted minimally invasive esophagectomy (MIE) to treat patients with esophageal cancer [2–10]. However, there is no consensus regarding the optimal method for performing an esophagectomy within the rubric of a minimally invasive surgical technique. In addition, the benefit of this approach has not been clearly confirmed, because of the limited number of retrospective comparative studies available at the present time [3, 11, 12], although its potential for improving perioperative outcome has been demonstrated by meta-analyses [13]. It is especially unclear whether adding laparoscopic procedures in MIE can further help the patients [3]. In the present study we sought to clarify the value of incorporating a laparoscopic procedure in MIE by analyzing the perioperative results of esophagectomy in patients with esophageal cancer via three different approaches: i.e., open surgery, video-assisted thoracic surgery (VATS)/laparotomy (hybrid MIE), and VATS/laparoscopy (total MIE).

Patients and methods

This study enrolled the esophageal cancer patients who underwent esophagectomy at the National Taiwan University Hospital from January 2005 to March 2009 and compared the surgical results of total MIE with those of a completely open surgical approach and those of VATS esophagectomy with esophageal reconstruction under laparotomy (hybrid MIE). In our institute, total MIE was adopted beginning in January 2008 with VATS esophagectomy and laparoscopic-assisted esophageal reconstruction in a gasless setting, a procedure that is described in the following sections. Most of the operations have been performed by the surgeons on our esophageal team, including Y. C. Lee, J. M. Lee, and P. M. Hung. The team has been performing more than 40 cases of open esophagectomy annually since well before the start of this study. To exclude possible confounders, only patients undergoing tri-incisional esophagectomy were enrolled in this study. Patients undergoing esophagectomy via the Ivor-Lewis or left thoracoabdominal approaches were excluded. Informed consent was obtained from each patient before surgery. Clinical profiles were collected from our prospective data base for these patients. Anastomotic leakage was defined as spillage of saliva or gastric contents through the anastomotic site or contrast extravasations by image study. Pulmonary complications were defined by the presence of pneumonia, acute lung injury, or acute respiratory distress that developed within 30 days after surgery, according to the criteria proposed by the Centers for Disease Control and Prevention [14] and the American and European Consensus Conference [15].

Anesthesia and perioperative care

Epidural analgesia was administered to the patients before surgery. The patients were intubated and ventilated with a double-lumen endotracheal tube during the operation. After surgery, temporary ventilator support was administered to all patients in the intensive care unit (ICU), and each patient was weaned based on established weaning parameters and the patient's general condition. Because many patients had undergone chemoradiation before surgery, we attempted postoperative extubation of the endotracheal tube only when the patient's coughing ability resumed and there was no evidence of infection. Jejunostomy feeding was begun after stool or flatus passage. Oral intake began after an esophagogram examination demonstrated that there was no anastomotic leakage, usually 7–10 days after surgery (10–14 days for the patients receiving neoadjuvant chemoradiation therapy).

Surgical techniques

Open esophagectomy and esophageal reconstruction

For esophagectomy with an open approach, a posterolateral thoracotomy via the 4th to 5th intercostal space was made. The paraesophageal, subcarinal, subaortic, and bilateral paratracheal lymph nodes were dissected (Stations 105 and 106 of the right recurrent laryngeal nerve and pretracheal regions 107, 108, 110, 111, and 112 according to the classification proposed by the Japanese Society for esophageal disease [16]), whereas the pulmonary branch of both the vagus nerve and the right bronchial artery were preserved. We did not routinely divide the thoracic duct unless there was evidence of invasion by tumor or metastatic lymph nodes. In the second stage of the operation, the stomach was mobilized with an upper midline laparotomy. A gastric tube 3–5 cm in width was made after completion of proximal gastrectomy. The gastric conduit was lifted up to the neck via the retrosternal route, and esophagogastrostomy was performed in the left neck with hand-sewn interrupted sutures or liner staplers (EndoGIA 45 $\times$ 3.0 mm, Covidien-Valleylab, Boulder, CO). Jejunostomy was performed for all patients. Pyloroplasty or pyloromyoplasty was performed except for patients with a thin and loosening pyloric ring.

VATS esophagectomy

For the video-assisted procedure, the patient was placed in the left lateral decubitus position with the operating surgeon standing at the back of the patient. A 10 mm camera port was created along the 7th or 8th intercostal space (ICS) about 2 cm anterior to the midaxillary line. Another three working ports were created on the posterior axillary line along the 8th or 9th ICS, the 5th ICS (10 mm), and on an anterior axillary line along the 4th ICS (3 cm). The mediastinal lymph nodes were dissected in the same way as in the open surgical approach. The tissue dissection was performed with ultrasonic coagulating shears (Ethicon Endosurgery, Cincinnati, OH). After completion of dissection, the esophagus was divided by endoscopic staplers (EndoGIA 60 $\times$ 3.5 mm; Covidien-Valleylab) at the proximal and distal ends and removed to avoid tumor contamination during retrieval of the specimen from the neck. For the patients with laparoscopic gastric mobilization during the second stage of surgery, a ribbon was fixed on the distal and proximal esophagus as a guide to the neck during esophageal reconstruction.

Laparoscopic-assisted esophageal reconstruction in a gasless setting

The laparoscopic procedure we used was based on a previously reported method by one of the authors in

gastrectomy for gastric cancer [17], and it involved lifting the abdominal wall with self-retaining retractors instead of establishing CO_2 pneumoperitoneum during the operation (Fig. 1). This approach allowed the whole procedure to be performed under normal pressure, which we thought more closely resembled the usual pulmonary procedures done in VATS and thus established an operative field that was more easily accessed by a thoracic surgeon. This setting would also ensure a stable surgical endoscopic field even if bleeding was encountered and the diaphragmatic hiatus had to be opened to lift the gastric conduit. It was with these considerations in mind that we adopted this approach instead of utilizing CO_2 pneumoperitoneum for the laparoscopic procedure.

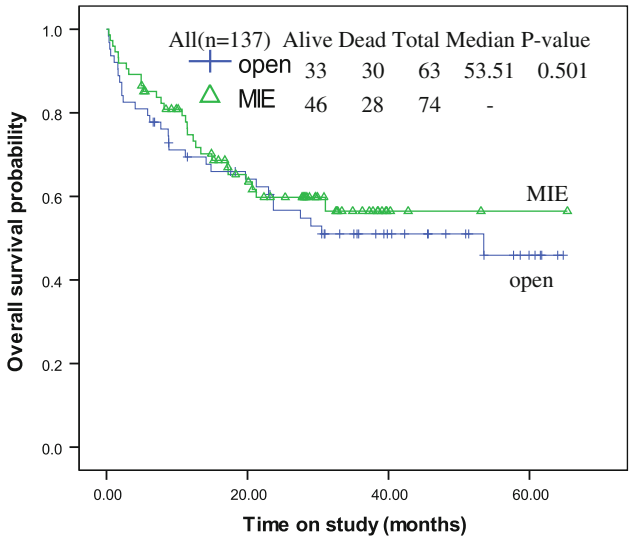

Fig. 1 The overall survival curve comparing the patients between the open (*plus sign*) (mean survival: 37.93 months) and minimally invasive esophagectomy (MIE; hybrid and total MIE) (*open triangle*) (mean survival: 41.85 months) groups ($P = 0.501$; $n = 137$)

At the start of the procedure the patient was placed in the supine position and a four-finger breadth mini-laparotomy incision was made in the upper abdominal midline. The abdominal wound was then lifted from the mini-laparotomy wound by four self-retaining retractors (Fig. 2a), creating an opening through which the surgical instrument was introduced into the abdominal cavity. A camera port (12 mm) was created in the periumbilical region by pulling the gastric tube up, another two working ports were created bilaterally in the subcostal regions (12 mm), and finally a 5 mm port was created on the right flank for insertion of a liver retractor. The operating surgeon stood to the right of the patient with his right hand working through the right subcostal port and his left hand working through the mini-laparotomy wound. The assistant stood at the left of the patient, working through the left subcostal port. Dissection and mobilization of the stomach was performed with a LigaSure (Covidien-Valleylab). The lymph nodes along the left gastric and celiac trifurcation were dissected during mobilization of the stomach. The short gastric artery and left gastric artery were divided with the LigaSure. If exposure of the short

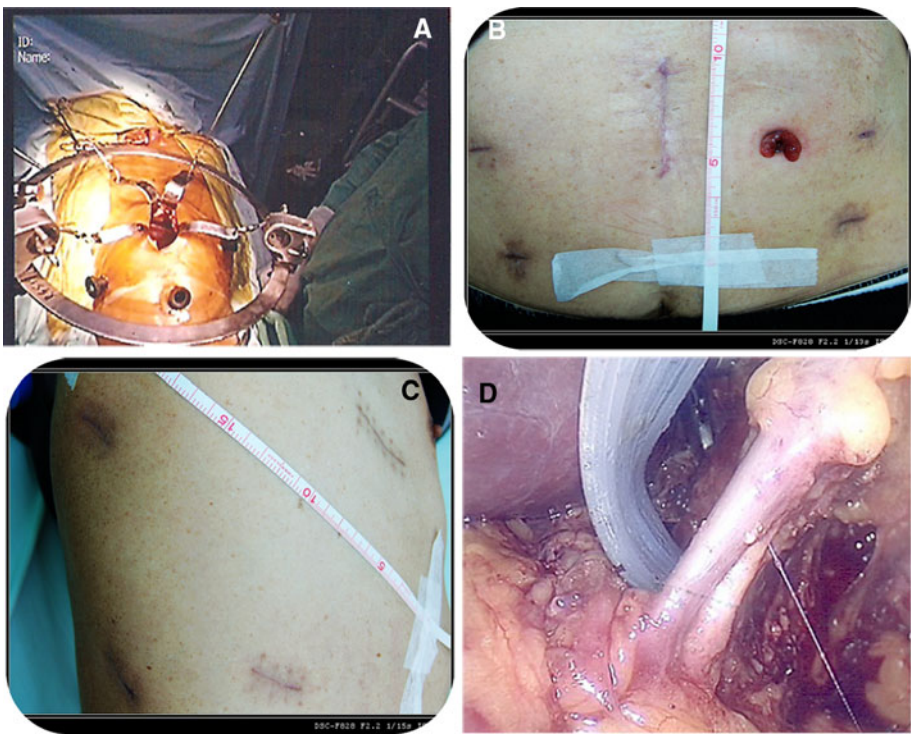

Fig. 2 The mini-laparotomy wound lifted by self-retaining retractors during the gasless laparoscopy-assisted esophageal reconstruction surgery (**a**). The abdominal and thoracic wounds after surgery (**b** and **c**, respectively). The view in laparoscopy from the abdominal cavity into mediastinum and the exposed left gastric vessels after removal of adjacent lymphatic tissue (**d**)

gastric artery was hindered by peritoneal fat, several traction stitches were placed from the gastric fundus downward to the right lower port. Figure 2d demonstrates the exposed left gastric vessels after removal of the adjacent lymphatic tissue during the laparoscopic procedure. A gastric tube 3–5 cm in width was made by proximal gastrectomy with a linear stapler (EndoGIA 60 × 3.5 mm, Covidien Valleylab) and a pyloromyotomy was performed after complete mobilization of the stomach. The fascia around the duodenum was released to provide further lengthening of the gastric tube. To facilitate the laparoscopic procedure, the gastric tube was introduced up to the neck through a posterior mediastinal tunnel, guided by the ribbons fixed onto the proximal esophagus made during the VATS phase of the operation. A cervical esophagogastrostomy was performed in the same manner as for open surgery, with a hand-sewn end-to-side or stapled side-to-side cervical esophagogastrostomy and a feeding jejunostomy created before conclusion of the procedure.

Statistical analysis

All continuous values were presented as mean ± standard deviation (SD). The demographic and clinical data were compared between the three surgical groups with the χ^2 test or Fisher's exact test, as appropriate. A trend analysis was used to examine the linear regression of the surgical results among the three groups of patients according to the proportion of minimally invasive procedures in esophagectomy. The duration of overall survival was analyzed with the Kaplan-Meier method.

Results

The three groups included 64, 44, and 30 patients with esophageal cancer who underwent esophagectomy with an open surgical approach, the hybrid approach, and the total MIE approach, respectively. The patient clinical profiles are presented in Table 1. There were no significant differences in patient age, gender, pathological staging, tumor location, preoperative lung function, serum albumin, and hemoglobin level between groups. There was a significantly lower rate of preoperative chemoradiation in the patients undergoing hybrid MIE compared to that of the open surgical group ($P < 0.05$). The perioperative results are presented in Table 2. The duration of surgery was significantly longer in the total MIE group than in the open and hybrid groups ($P < 0.05$). The mean number of retrieved lymph nodes was significantly lower in the hybrid and total MIE groups than in the open group. There was no significant difference in blood loss among the three groups of patients. The length of ICU stay was significantly shorter for the total MIE group than for the hybrid MIE group. In addition, the total MIE group had a shorter duration of ventilator usage and an earlier starting time for jejunostomy feeding than the other groups ($P < 0.05$). There was a significant trend toward a decrease in postoperative hospital stay, pulmonary complications, and anastomotic leakage as the proportion of minimally invasive procedures increased in esophagectomy ($P < 0.05$ for the trend test), with a significant difference between the total MIE group and the other two groups ($P < 0.05$). The mean overall survival (OS) and tumor progression-free survival (PFS) of patients in the MIE group (OS: 41.85; PFS: 33.01 months) and the open group (OS: 37.93; PFS: 32.18 months (was not significantly different; Figs. 1 and 3, respectively). Similar results were obtained both when the comparison was confined to patients with early stage disease (stages I and IIa) ($P = 0.52$ and 0.94 for overall and tumor progression-free survival duration) and when it was confined to late stage disease (stage IIa or greater: $P = 0.13$ and 0.28 for overall and tumor progression-free survival duration, respectively). In the total MIE group, one patient died of sepsis, and culture revealed the growth of *Mycobacterium tuberculosis* 2 weeks after his death. Eight patients (13 %) in the open surgery group died in the immediate postoperative period, 1 of acute renal failure, 1 of gastrointestinal bleeding, and 6 of sepsis. Three patients (7%) in the hybrid MIE group died immediately postoperatively, 1 from acute respiratory distress syndrome and 2 from sepsis. No statistical difference was noted among these three groups of patients ($P = 0.124$ for the trend test).

Discussion

Our data confirm previous reports that a minimally invasive approach for esophagectomy can provide an acceptable surgical option in the treatment of esophageal cancer. The mid-term survival duration was not compromised by this approach. The addition of laparoscopy-assisted esophageal reconstruction to VATS esophagectomy can lead to significantly earlier enteral feeding, shortening of postoperative ventilator support duration, lessening of the hospital stay, and a decrease in the incidence of pulmonary complications.

To date there is no consensus regarding the ideal laparoscopic setting for esophageal reconstruction. Luketich et al. retrieved the esophageal stump from the neck [2], whereas another author removed the tumor specimen through a 5 cm mini-laparotomy incision after the laparoscopic procedure [3, 4]. In our patients, the mini-laparotomy incision was created at the outset and was lifted with four self-retaining retractors to facilitate the laparoscopy-assisted procedure. It is unknown whether this

Table 1 Clinical profiles of the three groups of patients with esophageal cancer

Variables	Open surgery ($n = 64$)	Hybrid MIE ($n = 44$)	Total MIE ($n = 30$)
Sex			
Male	61 (95.31%)	43 (97.73%)	30 (100%)
Female	3 (4.69%)	1 (2.27%)	0 (0%)
Age, years			
Mean ± SD	56.58 ± 11.60	59.70 ± 11.17	59.73 ± 10.32
Range	30–90	44–78	37–80
Pathology			
Adenocarcinoma	5 (7.81%)	1 (2.27%)	1 (3.33%)
Sq C C	59 (92.19%)	43 (97.73%)	29 (96.67%)
Tumor site			
Upper third	9 (14.06%)	8 (18.18%)	6 (20%)
Middle-lower third	55 (85.94%)	36 (81.82%)	24 (80%)
Stage[a]			
0	7	12	2
I	17	13	3
II	25	14	11
III	14	5	12
IV	1	1	2
CCRT rate (%)	81	57*	73
Preoperative condition			
FVC (%)	106.28 ± 16.13	104.67 ± 14.45	102.10 ± 15.86
FEV1 (%)	100.66 ± 21.63	99.95 ± 15.10	97.28 ± 17.84
Hemoglobin (g/dl)	12.33 ± 1.84	12.58 ± 2.19	12.16 ± 1.63
Albumin (g/dl)	4.16 ± 0.54	4.31 ± 0.50	4.35 ± 0.49

Open surgery: esophagectomy and esophageal reconstruction with thoracotomy and laparotomy; hybrid minimally invasive esophagectomy (MIE): video-assisted thoracic surgery (VATS) esophagectomy and esophageal reconstruction via laparotomy; total MIE: VATS esophagectomy and gasless laparoscopy-assisted esophageal reconstruction

MIE minimally invasive esophagectomym, *Sq C C* squamous cell carcinoma, *CCRT* neoadjuvant concurrent chemoradiation, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s

* $P < 0.05$ as compared to open group

[a] Staging was accomplished according to the proposed classification of the Japanese Committee for Registration of Esophageal Carcinoma [16]

mini-incision might increase wound pain and hinder postoperative recovery [3] beyond levels observed after a laparoscopic procedure performed under CO_2 pneumoperitoneum without a mini-incision [2]. Any shortcomings of this approach can be balanced to some degree by the advantages derived from maintaining a normal pressure environment for the duration of the abdominal procedure in a gasless setting.

In a laparoscopic procedure done with CO_2 pneumoperitoneum, an average of 15 mmHg of pressure must be maintained to provide an adequate surgical space and a clear endoscopic field, and this has been shown to compromise gastric submucosal tissue perfusion in laparoscopic cholecystectomy [18, 19]. In addition to the abdominal cavity, the intrathoracic organs can also be affected by CO_2 insufflation [20]. This decrease in tissue perfusion may have a significant impact on the perioperative results of esophageal reconstruction in MIE after longer exposure to a high-pressure environment, thus diluting the benefits of MIE for postoperative recovery. A prospective randomized clinical trial comparing the laparoscopic procedure using gasless versus CO_2-pneumoperitoneum approaches in MIE is required in the future.

Pulmonary complication remains a major co-morbidity and cause of death after esophagectomy, with an average rate of 15–35% after the procedure [21, 22], compatible with that of our open surgical group. The immediate surgical outcomes are recognized to be closely related to the inherent learning curve of this complicated surgical procedure [23]. In our hospital, more than 40 cases of open esophagectomy have been performed annually for many years, with a history of consistent surgical results prior to the initiation of this study [24]. Braghetto et al. compared the results of total MIE and open surgical esophagectomy

Table 2 Perioperative results of the three groups of patients with esophageal cancer

	Open surgery	Hybrid MIE	Total MIE	*P* value[a]
Procedure-related variables				
Operative time (min)	543.02 ± 150.31	507.16 ± 126.51*	621.67 ± 83.11*,**	0.036
Blood loss (l)	560.95 ± 357.23	549.55 ± 364.07	465.38 ± 289.49	0.284
Lymph nodes harvested	18.41 ± 9.06	14.64 ± 8.80*	13.97 ± 7.70*	0.011
Postoperative course				
ICU stay (days)	9.64 ± 12.03	10.73 ± 11.67	5.84 ± 3.79**	0.144
Ventilator use (days)	6.78 ± 8.31	8.86 ± 11.19	3.63 ± 3.08*,**	0.193
Starting jejunostomy feeding, days	7.35 ± 3.99	6.84 ± 3.44	3.14 ± 1.66*,**	<0.001
Postoperative hospital stay (days)	43.58 ± 36.23	42.75 ± 30.19	23.45 ± 13.58*,**	0.010
Postoperative complications				
Leakage	18 (28%)	8 (18%)	2 (6.7%)*	0.015
Pulmonary complications	20 (30%)	9 (20%)	2 (6.7%)*	0.012
Others	8 (13%)	12 (27%)	6 (20%)	0.224
Mortality	8 (13%)	3 (7%)	1 (3%)	0.124

ICU intensive care unit

* $P < 0.05$ as compared to open group; ** $P < 0.05$ as compared to hybrid MIE group

[a] Trend analysis was used to examine the linear regression of the surgical results among the three groups of patients according to the proportion of minimally invasive procedures in esophagectomy

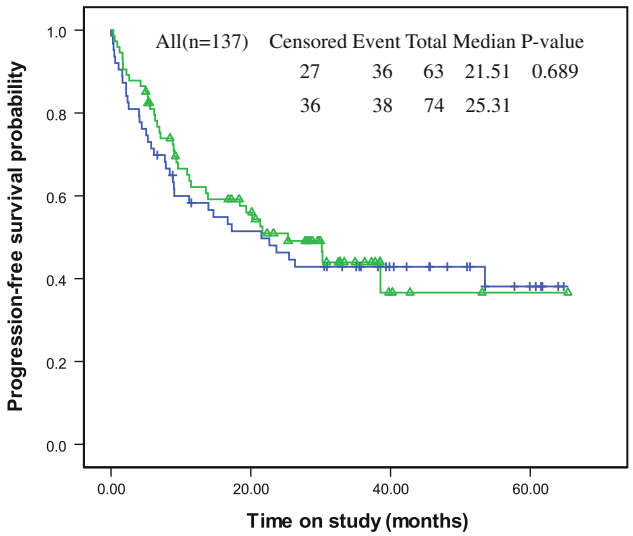

Fig. 3 The progression-free survival curve comparing the patients between the open (*plus sign*) (mean: 32.18 months) and MIE (hybrid and total MIE) (*open triangle*)(mean: 33.01 months) groups ($P = 0689$; $n = 137$)

and found a significant reduction of pulmonary and overall complications offered by total MIE [25], but this result was not observed by other authors [3, 26, 27]. We further found that an approximately 30% reduction in pulmonary complications was achieved by adding VATS and laparoscopy in esophagectomy. A similar improvement was observed with regard to the length of postoperative hospital stay. Our findings therefore suggest an additional benefit from incorporating laparoscopic procedures with VATS for esophagectomy.

The explanation for the difference in the rate of anastomotic leakage between the total MIE group and either the hybrid MIE group or the open group is unclear. The cervical anastomosis of the MIE group was done in a manner similar to that used in open surgery. However, in the patients with open laparotomy and hybrid MIE gastric conduits were reconstructed through the retrosternal route, whereas those of the total MIE group were reconstructed via the posteromediastinal route. This might be a significant factor influencing the anastomotic leakage rate, although the two routes have been demonstrated to be associated with comparable anastomotic leakage rates [28]. Additionally, a reduced surgical trauma in the minimally invasive procedure may confer additional benefit by maintaining an adequate blood supply and allowing earlier enteral feeding, providing a better tissue healing capacity of the partially devascularized gastric conduit after reconstruction [29, 30].

Compatible with earlier studies [3], we found no survival difference in patients treated either with open surgery or the MIE approach, although the number of retrieved lymph nodes was significantly lower in the MIE group than the open group. The number of harvested lymph nodes of our patients might be influenced by learning curves of each procedure, as well as by the frequent use of neoadjuvant chemoradiation (CCRT) of our patients. It has been found that lymph node numbers among patients who have undergone CCRT prior to surgery are significantly smaller

than among those who have gone directly to surgery [31]. The effectiveness of lymph node dissection between the VATS and open surgical procedures can therefore be more objectively compared in the patients who did not receive neoadjuvant CCRT.

The limitation of this study mainly comes from its retrospective nature and from the non-randomized cohorts of patients. We tried to avoid confounding caused by the surgical procedures by excluding patients undergoing esophagectomy with intrathoracic esophagogastrostomy. However, because of the considerable heterogeneity of the study cohort and its relatively small size, we suggest cautious interpretation of the results presented here.

Conclusions

Mid-term survival is not compromised with the use of a minimally invasive procedure for esophagectomy in esophageal cancer patients. Use of laparoscopic technique for the preparation of the esophageal substitute following VATS esophagectomy, has the potential to further shorten postoperative recovery time and to reduce the incidence of major postoperative complications. Therefore in the implementation of minimally invasive surgical technique for esophagectomy, the laparoscopic procedure is suggested as worthwhile to pursue once VATS esophagectomy has been mastered.

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Conflict of interest There is no conflict of interest for any of the authors in regard to publication of this manuscript.

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