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Surgical Method, Postoperative Complications, and Gastrointestinal Motility of Thoraco-Laparoscopy 3-Field Esophagectomy in Treatment of Esophageal Cancer

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Background: The aim of this study was to investigate the surgical method, postoperative complications, and gastrointestinal motility of thoraco-laparoscopic esophagectomy in the treatment of esophageal cancer.

Material/Methods: Using random sampling method, we selected 132 esophageal cancer patients who were treated in our hospital from January 2012 to December 2014; these patients were regarded as the study group and underwent thoraco-laparoscopy 3-field surgery treatment. Another 108 esophageal cancer patients admitted to our hospital over the same period were regarded as the control group and underwent traditional open McKeown esophagectomy.

Results: The amount of blood loss and postoperative drainage of pleural fluid in the study group were significantly lower ($P < 0.05$) and the time to removal of the chest tube and hospital stay were significantly shorter ($P < 0.05$). The incidence of anastomotic fistula, vocal cord paralysis, chylothorax, and arrhythmia were significantly lower in the study group than in the control group ($P < 0.05$). However, no significant differences in the incidence of pneumonia, atelectasis, or acute respiratory distress were detected ($P > 0.05$). For postoperative gastrointestinal motility, first flatus time, first defecation time, and bowel tone recovery time after the operation, as well as the total amount of gastric juice draining, were reduced in the thoraco-laparoscopic esophagectomy group ($P < 0.05$). The postoperative MTL and NO levels were higher but VIP level was lower in the thoraco-laparoscopic group ($P < 0.05$).

Conclusions: Thoraco-laparoscopic esophagectomy was technically feasible and safe; it was associated with lower incidence of certain postoperative complications and had less effect on postoperative gastrointestinal motility. Skilled technique and cooperation could further shorten the operation time and might lead to better patient outcomes.

MeSH Keywords: **Cycloleucine • Esophagectomy • Pulmonary Atelectasis**

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Background

According to the National Cancer Institute (National Institutes of Health, USA), an estimated 16 640 individuals were diagnosed with esophageal cancer in 2010, and 14 500 died from the disease [1]. In China, the incidence and mortality of esophageal cancer are much higher in males vs. females and in rural areas vs. urban areas. The incidence rates were: 22.14/100 000 (30.44/100 000 for males and 13.64/100 000 for females, 14.21/100 000 in urban and 38.44/100 000 in rural areas). The mortality rates were: 16.77/100 000 (23.29/100 000 for males and 10.11/100 000 for females, and 10.59/100 000 in urban and 29.47/100 000 in rural areas) [2]. Surgery, often in combination with chemotherapy and radiation, is the primary curative therapy for patients with resectable esophageal cancer. Different techniques of esophagectomy are available for intervention [3]. A study has shown that esophagectomy has a greater than 37% survival rate in treatment of esophageal cancer [4]. The criteria for wide acceptance of minimally invasive esophagectomy include manageable safety profile, adherence to basic oncologic principles, and comparable long-term outcomes with previous standard open approaches [5]. The 3-phase thoraco-abdominal McKeown resection via a right thoracotomy using the stomach for esophageal substitution, especially for middle and upper esophageal cancer, is also widely used. It entails cervical anastomosis and gastric tube production. Compared with intrathoracic anastomosis, cervical anastomosis significantly reduces the risk of anastomotic fistula. Gastric tube reconstruction in esophagogastrostomy during esophagectomy is better physiologically, and ensures better long-term life quality [6]. Based on the theory of McKeown resection, we introduced the thoraco-laparoscopic esophagectomy, including laparoscopic mobilization of the stomach, thoracoscopic esophageal mobilization, and creation of a cervical anastomosis. A previous clinical study has found that thoraco-laparoscopic esophagectomy was technically feasible and safe, and was associated with shorter hospital stay [7]. However, no report is available comparing routine open McKeown esophagectomy with thoraco-laparoscopic esophagectomy to reduce the incidence of postoperative surgical and respiratory complications, especially the effect of thoraco-laparoscopic surgery on gastrointestinal motility. Low gastrointestinal motility is a common complication of esophagectomy and directly contributes to the incidence of anastomotic fistula [1]. In this retrospective study, we compared the effect of thoraco-laparoscopic esophagectomy on gastric motility with the routine McKeown operation and investigated the advantages of minimally invasive thoraco-laparoscopy in terms of postoperative recovery.

Material and Methods

Ethics Statement

This study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval number AF/SC-08/02.0).

General information

Between January 2012 and December 2014, 132 patients (male: 80, female: 52; median age, 64 years: range 41–77) with esophageal cancer underwent minimally invasive McKeown esophagectomy with thoraco-laparoscopic technique, and 108 patients (male: 72 female: 36; median age was 61 years: range 39–70) with esophageal cancer underwent routine open McKeown esophagectomy. All the surgeries were carried out by a single surgical group with advanced training in minimally invasive esophageal procedures. The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Individual consent was also obtained from all the patients. Preoperative staging was based on upper gastrointestinal endoscopy with biopsy, computed tomography of the chest and abdomen, and endoscopic ultrasonography. All patients were diagnosed with esophageal cancer located in the middle upper part of the esophagus, without evidence of invasion or distant metastasis to other organs. The stomach was the organ used for esophageal reconstruction, which was placed and fixed in a plastic bag before it was pulled into the neck. Neoadjuvant chemotherapy and radiotherapy were not acceptable to all the patients. Patient demographics are displayed in Table 1. A wide esophagogastric end-to-end anastomosis was performed in a single layer by using a gastrointestinal anastomosis stapler (Figure 1B). Ileoanal anastomosis (J-pouch) surgery was performed as a total surgical procedure.

Surgical technique

Thoraco-laparoscopic esophagectomy

The first step in thoraco-laparoscopic esophagectomy entails thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy. All patients were intubated with a double-lumen endotracheal tube. After intubation, patients were moved into semi-prone position with beanbags under the chest and pelvis, leaving the abdomen free for respiratory movements. Four thoracoscopic ports were established (Figure 2A). Before the mobilization of the esophagus from esophageal hiatus to cervical esophagus, the azygous vein was completely divided using an electrocautery hook dissector and was doubly ligated with one 12-mm and one 10-mm Hem-o-Lok clip (Figure 2B). A conventional mediastinal lymph node dissection was performed (Figure 3A–3F).

Table 1. General comparison.

General data	Thoracolaparoscopic group (132 cases)	Routine open McKeown group (108 cases)	Significance
Sex			P > 0.05
Male	80	72	
Female	52	36	
Age (y)	65.13±12.31	59.56±10.17	P>0.05
Weight (kg)	64.89±17.73	69.45±19.65	P>0.05
Tumor location (cases)			P>0.05
Upper part	15	12	
Middle part	79	65	
Preoperative staging			P>0.05
0	4	1	
I A	9	7	
I B	14	10	
II A	40	39	
II B	45	34	
III A	10	17	
Histological type			P>0.05
Small cell carcinoma	131	105	
Squamous cell carcinoma	1	3	

In the second step, laparoscopic mobilization of the stomach and gastric tube formation was carried out. The patient was placed in a 30° head-up tilt and tilt back to supine position. A pneumoperitoneum (12–14 cmH₂O) was established by CO₂ injection through an umbilical port. A 30-degree laparoscope was introduced via a 10-mm umbilical port. The other 4 ports were placed in the upper abdomen under direct laparoscopic visualization (Figure 4A). Stomach mobilization was initiated with the division of the greater curvature by ultrasound knife, and suspicious lesser curvature lymph nodes were dissected (Figure 4B). The left gastric vessel was divided at its origin from the celiac trunk and ligated by use of a Hem-o-Lok clip (Figure 4C). After the mobilization of the stomach was completed, the gastric tube was created with a linear cutting stapler (Figure 4D) and completed with a width of 3 cm (Figure 1A). We then re-established pneumoperitoneum under laparoscopic guidance, and the gastric tube was pulled through the posterior mediastinum and brought to the neck incision by careful traction. Neck, thoracic, and abdominal wounds were closed in layers after placing the tube-drain.

Traditional McKeown esophagectomy

After general anesthesia, intubation with a double-lumen endotracheal tube for single-lung ventilation, and left lateral decubitus, were completed. The mobilization of the thoracic esophagus was carried out under trans-right-thoracic posterolateral incision. The mobilization of the cervical esophagus was conducted in supine position and amputated. Trans-abdominal mobilization of stomach and gastric tube formation were routinely conducted. Cervical esophagogastric anastomosis was accomplished after subtotal resection of the esophagus.

The paraesophageal, subcarinal, postmediastinal, left gastric artery, cardiac, and recurrent laryngeal nerve lymph nodes were synchronously cleared, regardless of the surgical technique.

Detection indexes

Operative parameters

In all 132 patients who underwent thoraco-laparoscopic esophagectomy, non-emergent conversion occurred. No patients

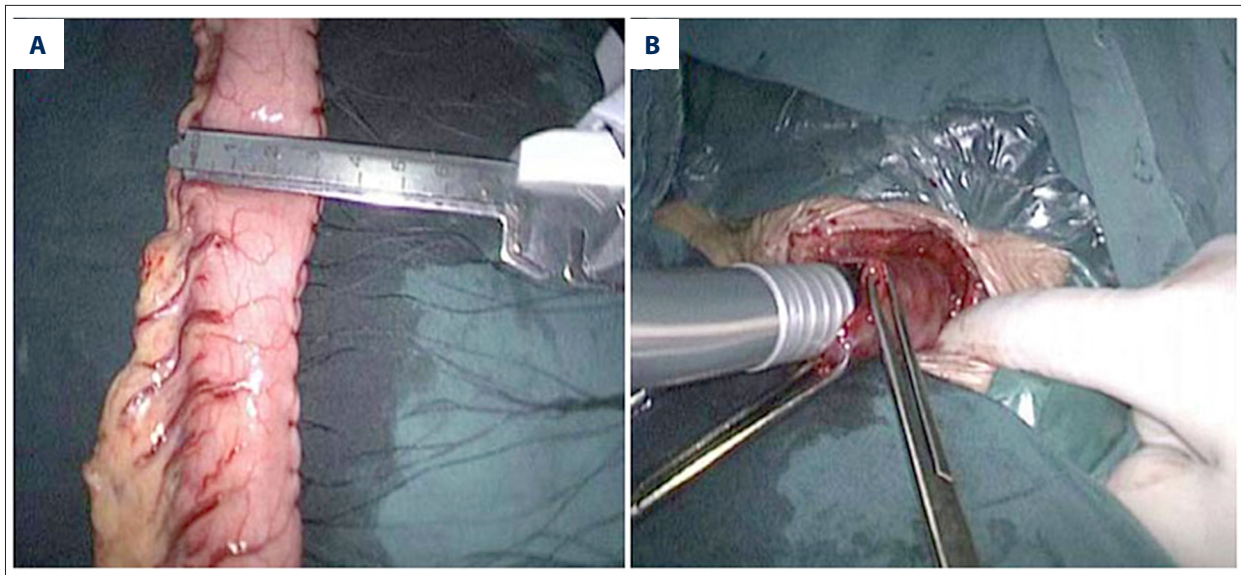


Figure 1. Thoracoscopic mobilization of esophagus. **(A)** Four thoracoscopic ports were marked. Thoracoscopic observation was performed through a 12-mm camera port in the sixth intercostal space at the right posterior axillary line. The first operation hole (5 mm in diameter) was placed at the right posterior axillary line in the third intercostal space to enable surgical manipulation with ultrasound knife and electric coagulation hook. The second operation hole (5 mm in diameter) and auxiliary operating hole (12 mm in diameter) were placed at the right scapular line in the fifth and ninth intercostal spaces, respectively, to assist with tissue exposure and endoscopic grasping devices. **(B)** The mediastinal pleura are opened, and the arch of the azygos vein is mobilized and transected.

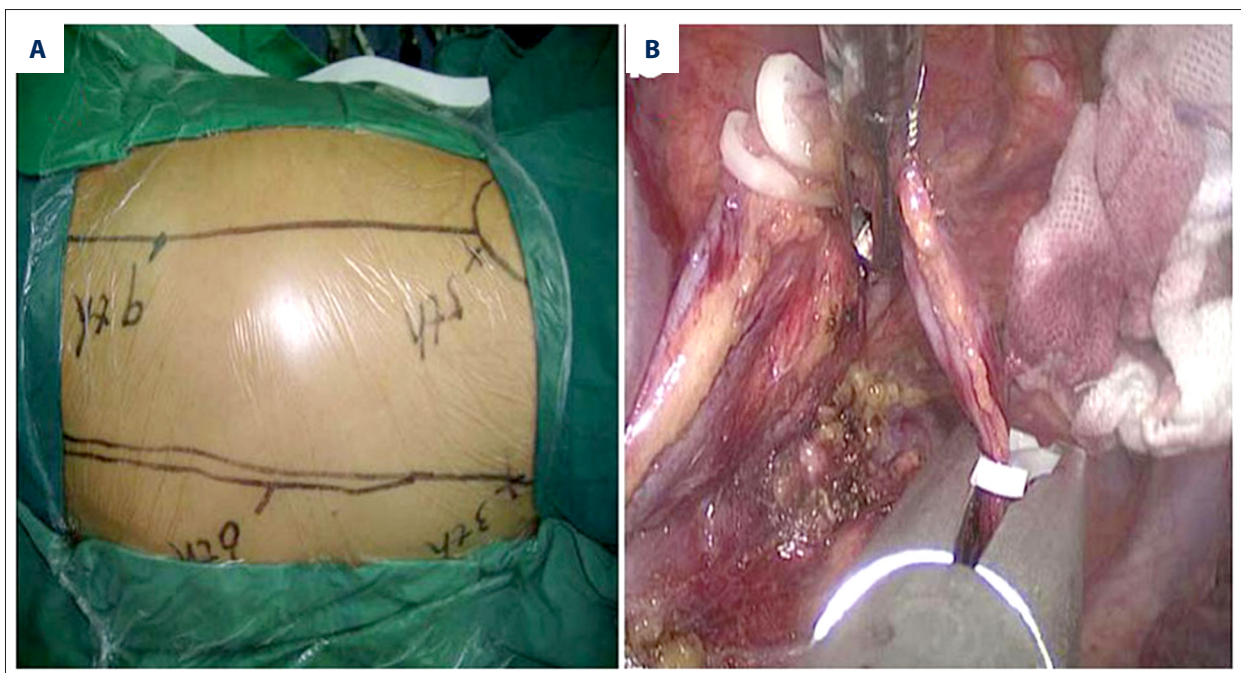


Figure 2. Conventional mediastinal lymph node dissection. **(A)** Mobilization of the esophagus close to the tracheal carina and dissection of subcarinal lymph node. **(B)** Lymph node of azygos arch was dissected. **(C)** Pretracheal retrocaval lymph node was cleared, space between the right bronchus and superior vena cava is dissected, and soft tissues are cleared. **(D)** The left recurrent laryngeal nerve lymph node was dissected. **(E)** The right recurrent laryngeal nerve lymph node was dissected. **(F)** Mobilization of the esophagus was completed and mediastinal lymph nodes were completely cleared.

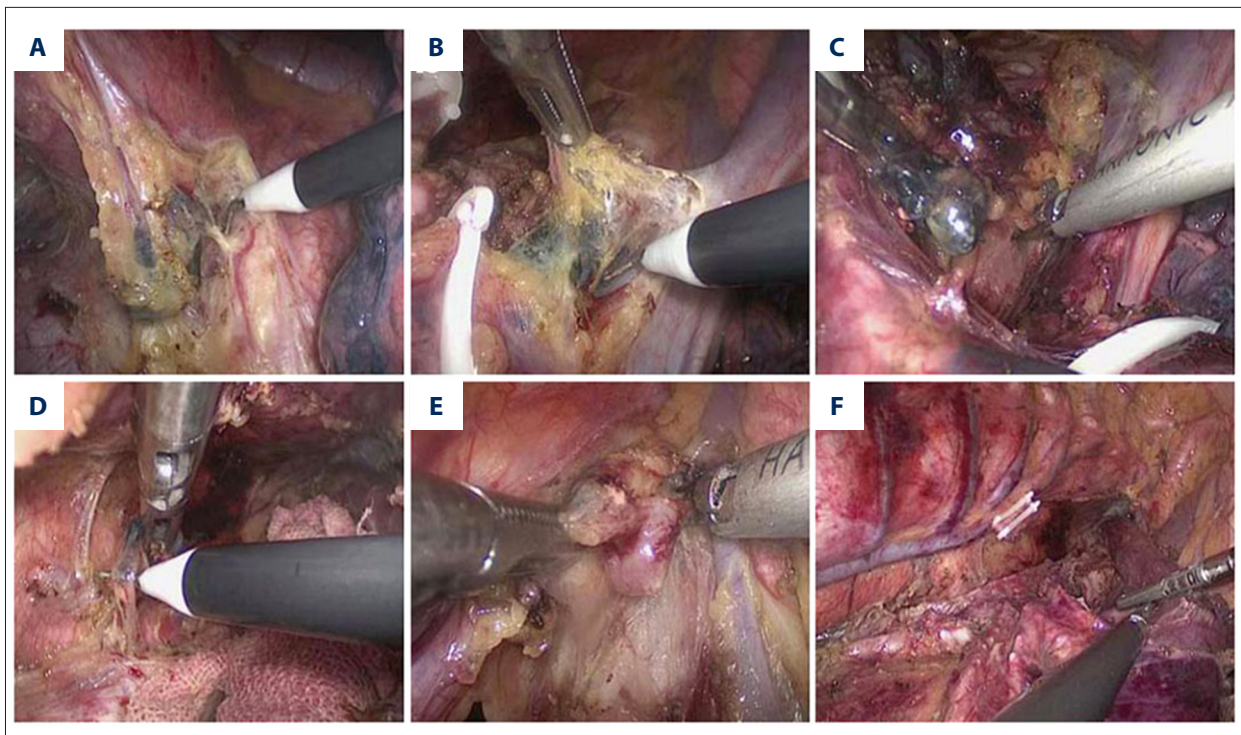


Figure 3. Laparoscopic mobilization of the stomach and gastric tube formation. (A) A total of 4 abdominal ports (two 5 mm and two 12 mm) were used. A 30-degree laparoscope was introduced via the 12-mm infraumbilical port. The other 4 ports were placed in the upper abdomen under direct laparoscopic visualization. We applied liver suspension by round ligament plication. (B) During the mobilization of the stomach, suspicious lesser curvature lymph nodes were dissected. (C) Left gastric vessel was divided and ligated by Hem-o-Lok. (D) Gastric tube formation was accomplished by linear cutting stapler.

required blood transfusion during or after surgery. All patients were extubated in the operating room and none were transferred to the ICU. Intraoperative parameters (mean operative time, mean intraoperative estimated blood loss, and the number of lymph node dissection) and postoperative parameters (thoracic drainage, the time of extracting drainage tube and postoperative hospital stay) were collected and analyzed.

Postoperative management of complications

All patients in the 2 groups were subjected to similar postoperative treatment: patients were anesthetized and extubated tracheally. After return to their wards, they were administered enteral nutrition and nasal feeding. Patients were provided only liquid diet for 7–8 days after surgery. Gastrointestinal decompression was instituted until 5–6 days after surgery. Patients were discharged after routine blood test results were normal. Postoperative surgical complications were associated with postoperative anastomotic fistula, vocal cord paralysis, and chylothorax. Respiratory complications included pneumonia, atelectasis, and acute respiratory distress.

Postoperative gastric motility

Some parameters of postoperative gastric motility were detected. Detection indices of gastrointestinal motility included first flatus time, first defecation time, bowel tone recovery time after the operation, and total amount of gastric juice draining between the first day and the third day after the operation of all patients, and these were recorded.

Detection of plasma MTL, VIP, and NO

After informed consent, plasma motilin (MTL), vasoactive intestinal peptide (VIP), and nitric oxide (NO) contents were detected before the operation and on the seventh day after surgery. This stage was important for anastomotic growth and recovery of gastrointestinal motility. Blood (5 ml) was drawn from each patient into a tube containing 40 μ L aprotinin and 30 μ L EDTA. The tube was centrifuged at 3000 rpm for 10 min at 4°C. The supernatant was transferred to an Eppendorf tube and preserved at –80°C as reserve. The contents of MTL, VIP, and NO in plasma were measured using the enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's protocol. Samples were detected by use of a SN-695 intelligent RIA gamma survey meter.

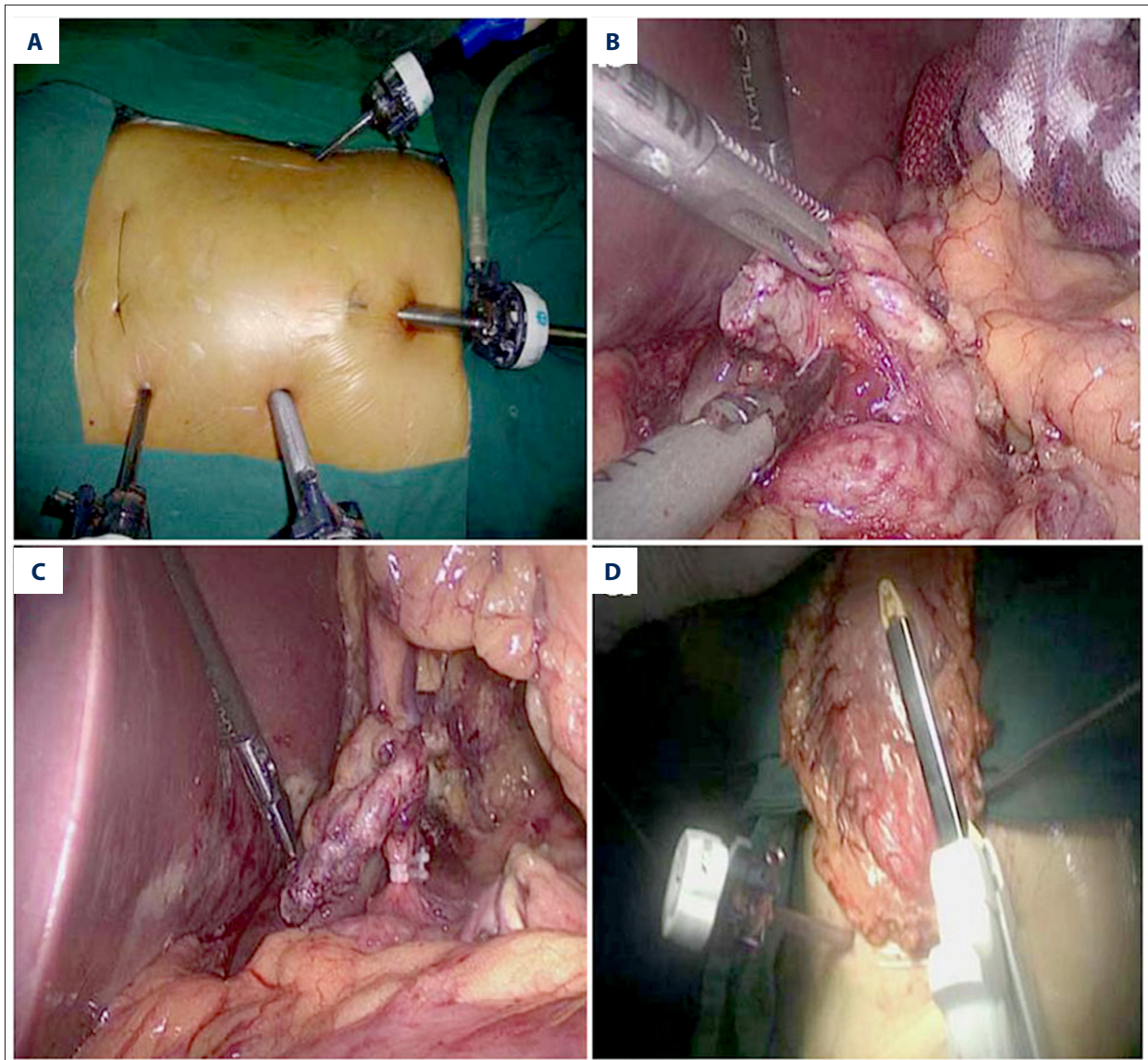


Figure 4. Gastric tube formation and cervical anastomosis. (A) Gastric tube was completed with a width of 3 cm. (B) End-to-end esophagogastric anastomosis was performed in a single layer by using a gastrointestinal anastomosis stapler.

Statistical analysis

Data were analyzed with the SPSS program for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Continuous data were described as $\bar{x} \pm s$. The 2-sample *t* test was used for comparison between groups. Categorical variables were described as rate and compared by chi square test. P-values <0.05 were considered significant.

Results

Comparison of operative and postoperative parameters

In all 132 patients who underwent thoraco-laparoscopic esophagectomy, the mean intraoperative estimated blood loss and postoperative thoracic drainage were significantly lower than in the routine McKeown group ($P < 0.01$, $P < 0.05$). The time to removal of the chest tube and hospital stay were also significantly shorter than in the routine McKeown group ($P < 0.05$). No significant differences were seen in the mean operative time or the number of lymph node dissections between the thoraco-laparoscopic group and the routine McKeown group ($p > 0.05$) (Table 2).

Table 2. Comparison of operative and postoperative parameters.

Group	Thoracoscopic group (132 cases)	Routine open McKeown group (108 cases)	P value
Operative parameter			
Mean operative time (min)	253.5±50.5	276.5±45.7	0.71 (p>0.05)
Intraoperative estimated blood loss (ml)	180.8±37.5	330.8±47.5	0.000 (p<0.01)
The number of lymph node dissection	21.6±2.5	20.5±1.9	0.57 (p>0.05)
Postoperative parameter			
Thoracic drainage (ml)	540±30.5	1 120±40.2	0.027 (p<0.05)
Pull out the chest tube (d)	4.5±1.3	8.4±1.9	0.046 (p<0.05)
Hospital stay (d)	11.7±2.5	18.7±2.3	0.038 (p<0.05)

Table 3. Comparison of postoperative complications.

Complications	Thoracoscopic group (132 cases)	Routine open McKeown group (108 cases)	χ ²	sig
Operation complications				
Anastomotic fistula*	5 (4.5%)	11 (10.2%)	3.907	0.048
Arrhythmia*	2 (1.5%)	9 (8.3%)	6.314	0.012
Vocal cord paralysis*	4 (3.0%)	12 (11.1%)	6.234	0.013
Chylothorax*	1 (0.7%)	7 (6.4%)	6.040	0.014
Respiratory complications				
Pneumonia**	10 (7.6%)	15 (13.9%)	2.573	0.11
Atelectasis**	4 (3.0%)	6 (5.6%)	0.949	0.33
Acute respiratory distress**	1 (0.7%)	5 (4.6%)	3.654	0.056
Perioperative mortality**	0 (0.0%)	2 (1.9%)	0.116	2.465

P value: thoracoscopic group vs. routine open McKeown group (* P<0.05, ** P>0.05).

Comparison of complications in thoraco-laparoscopic group and routine McKeown group

Statistically significant differences were seen between the thoraco-laparoscopic esophagectomy and routine McKeown esophagectomy groups in postoperative arrhythmia, vocal cord paralysis, and chylothorax (P<0.05). The incidence of anastomotic fistula was also lower in the thoraco-laparoscopic group (P>0.05). However, no significant differences were seen in the incidence of pneumonia, atelectasis, or acute respiratory distress (p>0.05) (Table 3). Besides these, 2 patients in the thoraco-laparoscopic group and 3 patients in the routine McKeown group died from postoperative acute respiratory distress caused by pulmonary infection.

Comparison of clinical indices and hormones in gastrointestinal motility

The first flatus time, first defecation time, bowel tone recovery time after the operation, and total amount of the gastric juice draining were significantly less in the thoraco-laparoscopic esophagectomy group compared with the routine McKeown operation group (Table 4) (P<0.05, P<0.01). MTL and VIP affected the gastrointestinal motility and blood flow. NO dilated the gastric vessels and increased the gastric blood flow. Plasma levels of MTL, VIP, and NO reflected the gastric motility and blood flow. Our original data indicate that all 60 patients had lower postoperative MTL, VIP, and NO levels irrespective of the type of surgical intervention (thoraco-laparoscopy vs. routine McKeown operation). However, as shown

Table 4. Comparison of clinical indices of gastrointestinal motility (x±s).

Group	Cases	The first flatus time (h)	The first defecation time (h)	The bowel tone recovery time (h)	Total amount of the gastric juice draining (ml)
Routine open McKeown group	108	34.1±6.36	29.00±5.90	151.60±14.90	456.90±60.20
Thoracolaparoscopic group	132	27.2±4.39	23.5±3.4	89.30±7.80	247.60±38.40
P value		0.031	0.025	0.008	0.044

P value: thoracolaparoscopic group vs. routine open McKeown group (P<0.01, P<0.05).

Table 5. Comparison of plasma MLT, VIP and NO content.

Group	Cases	Stage	MTL (ng/L)	VIP (ng/L)	NO (μmol/L)
Routine open McKeown group	30	Preoperative	370.45±45.51	182.37±44.78	58.60±9.71
		Postoperative	323.26±62.84	149.83±40.27	37.00±5.80
		Difference Value	47.18±18.28	32.55±12.04	21.6±9.68
Thoracolaparoscopic group	30	Preoperative	413.67±63.46	151.19±31.44	58.96±10.52
		Postoperative	388.19±44.86*	85.45±20.76**	47.69±8.75***
		Difference Value	25.48±10.59#	65.74±20.78##	11.27±4.84###

* P=0.019 postoperative MTL content of thoracolaparoscopic group vs. routine open McKeown group; ** P=0.015 postoperative VIP content of thoracolaparoscopic group vs. routine open McKeown group; *** P=0.048 postoperative NO content of thoracolaparoscopic group vs. routine open McKeown group; # P=0.004 pre-and post-operative difference value of MTL content in thoracolaparoscopic group vs. routine open McKeown group; ## P=0.024 pre-and post-operative difference value of VIP content in thoracolaparoscopic group vs. routine open McKeown group; ### P=0.000 pre-and post-operative difference value of NO content in thoracolaparoscopic group vs. routine open McKeown group.

In Table 5, the postoperative MTL and NO levels were higher and VIP level was lower in the thoraco-laparoscopic group than in the routine McKeown operation group (P<0.05). Compared with the preoperative levels, postoperative MTL, VIP, and NO levels in the thoraco-laparoscopic group showed significantly less reduction (P<0.05).

Discussion

Significant experience (e.g., in laparoscopic antireflux procedures) had been gained with a minimally invasive approach to the lower esophagus and stomach, virtually eliminating use of an open approach for a variety of benign conditions. This growing experience has made minimal invasive esophagectomy one of the more challenging procedures in the field of general thoracic surgery [8]. At present there is no clear clinical consensus for the surgical indications of thoraco-laparoscopic esophagectomy. Combining our clinical experiences and reports in the literature, we thought that thoraco-laparoscopic esophagectomy could be used in esophageal cancer following the stage T₃N₁M₀. However, classification of surgical indications

also needs to be supported by accumulation of clinical cases and evidence-based medicine. Thoraco-laparoscopic esophagectomy could avoid some deficiencies of traditional thoracotomy, such as rib-spreading, large incision, and destroying the integrity of thoracic and abdominal wall, and also could theoretically reduce surgical trauma and incidence of complications.

Compared with routine open esophagectomy, thoraco-laparoscopic esophagectomy is associated with reduced incidence of complications, due to minimal surgical trauma [1]. Results from our clinical study indicated minimal blood loss, as well as reduced hospital stay and pleural effusion, in patients undergoing thoraco-laparoscopic esophagectomy, due to surgical efficiency and distinguishing anatomical structures. The incidence of postoperative anastomotic fistula, vocal cord paralysis, and chylothorax was also lower. Our surgical team has performed more than 200 thoraco-laparoscopic esophagectomies. In addition to close cooperation between the surgeon and assistants, the team is skilled in endoscopic suturing technique. Although the mean overall operative time was not shortened compared to routine McKeown operations, the high-definition endoscopic view enabled easy identification of the vascular

branches, thoracic duct, and recurrent laryngeal nerve. As a result, the thoraco-laparoscopic esophagectomy prevented excessive bleeding, chylothorax, and vocal cord paralysis caused by injury to these tissues. No significant differences were seen in the incidence of pneumonia, atelectasis, or acute respiratory distress between routine open esophagectomy and thoraco-laparoscopic esophagectomy; however, most patients who underwent thoraco-laparoscopic esophagectomy had favorable voluntary cough due to the lower level of pain associated with the minimally invasive incision. We suspect that the obligatory requirement for one-lung ventilation (OLV) and long-term OLV were the main causes. Improving the surgical condition and reducing the incidence of respiratory complications will be our primary goal in the future.

In addition to respiratory complications, decreased gastrointestinal motility is also one of the most common complications of esophagectomy. Delayed gastric emptying and duodeno-gastro-esophageal reflux manifest clinically as celiodynia, ventrosity, nausea, emesis, anepithymia, decreased bowel sounds, lack of voluntary evacuation, and defecation. Postoperative gastric motility disorder also increases the incidence of esophagus-stomach anastomotic fistula. Serious symptoms include gastrointestinal paralysis and intestinal obstruction resulting in death [9]. Gastrointestinal function plays an important role in the physiological recovery, such as postoperative anastomotic healing, and affects the prognosis of esophagectomy. Recovery of gastrointestinal motility after esophagectomy is always a clinical challenge. Pyloroplasty following esophagectomy appeared to reduce the incidence of gastric outlet obstruction and to accelerate gastric emptying, as well as improving gastrointestinal motility [1]. However, Nguyen et al. [10] reported that routine pyloroplasty during minimally invasive esophagectomy can be safely omitted, with a reduction in operative time and minimal adverse effects associated with postoperative gastric function. In the present study we compared the postoperative gastrointestinal motility of thoraco-laparoscopic esophagectomy with routine open 3-field esophagectomy in terms of clinical symptoms (e.g., first flatus time, first defecation time, and bowel tone recovery time) and functional index (e.g., total amount of gastric juice draining). Our results showed there were fewer of these indexes in the thoraco-laparoscopic esophagectomy group compared with the routine McKeown operation group, indicating that the gastrointestinal motility of patients in the thoraco-laparoscopic group recovered faster than those in the routine open group. Combined

with clinical symptoms, we further quantitatively demonstrated the effect of thoraco-laparoscopic conditions on postoperative gastrointestinal motility by determining relative serological indices. Here, we compared the 2 kinds of gastrointestinal hormones: MLT and VIP. MLT receptors stimulate the stage III migrating motor complex to prompt gastrointestinal motility and the secretion of pepsin [11]. In addition, MLT has a potent gastric vasodilator effect and appears to regulate gastric arterial blood flow [1]. In contrast, VIP relaxes the gastrointestinal smooth muscle, inhibits the secretion of gastric acid and pepsin, and inhibits gastrointestinal motility. Shen et al. found that increased levels of VIP inhibited gastric motility of stressed rats by modulating the effect of electroacupuncture [12]. In addition, NO has the function of promoting gastric motility and dilating gastric vessels. Postoperative MTL and NO levels were higher but VIP levels were lower in the thoraco-laparoscopic group than in the routine open group. Postoperative MTL, VIP, and NO levels showed less reduction in the thoraco-laparoscopic group. We conclude that the thoraco-laparoscopic operation had less effect on gastrointestinal hormone secretion. Determining how to increase the gastric blood supply and improve gastric motility will be our research focus in the future.

Clinically, thoraco-laparoscopic esophagectomy has been associated with outcomes as good as or better than most open series. Our study focused on changes in gastric tube activity under 2 different surgical modes, along with the underlying mechanisms. In the future, we will not only improve the surgical technique of thoraco-laparoscopic esophagectomy, but also investigate the molecular mechanisms relating to the postoperative complications.

Conclusions

Thoraco-laparoscopic esophagectomy is technically feasible and is associated with lower incidence of postoperative complications, but it had no significant effect on respiratory complications. Clinical data and serological analysis suggest that the thoraco-laparoscopic operation had less effect on the postoperative gastrointestinal motility and gastric blood flow.

Conflict of interests

All authors declare that they have no conflict of interests.

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