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Open three-stage transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer: a multicenter prospective, open and parallel, randomized controlled trial

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Abstract

Introduction Esophageal cancer is the eighth most common cause of cancer worldwide. In 2009 in China, the incidence and death rate of esophageal cancer is 22.14 per 100 000 person-years and 16.77 pre 100 000 person-years respectively, being the first one in the world. Minimally invasive esophagectomy (MIE) was introduced into clinical practice which aims to reduce the morbidity rate. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction. There are some small randomized trials regarding minimally invasive versus open esophagectomy, with only enroll 56 to 200 subjects. For now, no large randomized controlled trial comparing minimally invasive versus open esophagectomy was reported in China where squamous cell carcinoma predominated over adenocarcinoma of esophagus.

Methods and analysis This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer. Group A patients receive minimally invasive esophagectomy which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients receive the open three-stage transthoracic esophagectomy involves a right thoracotomy and laparotomy with cervical anastomosis. Primary endpoints include respiratory complications within 30 days after operation. The secondary endpoints include other postoperative complications, influences on pulmonary function, intraoperative data

including blood loss, operative time, the number and location of lymph nodes dissected, and mortality in hospital, the length of hospital stay, total expenses in hospital, mortality within 30 days, survival rate after two years, postoperative pain, and HRQoL. 324 patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

Key words: esophageal cancer, surgery, minimally invasive surgery, esophagectomy, randomized controlled trials

Strengths and limitations of this study

First large multicenter randomized controlled trial comparing open three-stage transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer in China.

The results of this study may add new evidence to support the use of minimally invasive esophagectomy in surgical treatment of esophageal cancer.

Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide[1].It is reported that the incidence and death rate of esophageal cancer in China to be top one in the world, with an incidence of 22.14 per 100 000 person-years and a death rate of 16.77 pre 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China[2]. Surgery is still the gold standard for the treatment of resectable esophageal cancer.

However, esophagectomy for esophageal cancer is a complex procedure which carries high risk of morbidity rate of 23% to 50% and a mortality rate of 2% to 8% respectively in western countries[3,4], and a morbidity rate from 9% to 29% and mortality rate from 2% to 4% respectively in China[5,6].

Minimally invasive esophagectomy (MIE) was introduced into clinical practice in 1992 for the first time which aims to reduce the morbidity rate [7]. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction[8]. Reduced morbidity rate of 11% to 25% and reduced mortality rate of 1% to 3% have been reported by many surgeons, which is lower than these of previous numbers in traditional open approach[9-13].

Apart from observational studies[9-13], one randomized controlled trial conducted in Dutch brought promising results for MIE[14]. In that study, the numbers of lymph node harvest were comparable in two groups which manifest good oncologic effect in MIE group, but a reduction of pulmonary infection rate was noted in the MIE group compared with open group. However, a two-stage approach in that study may not generalized to other approaches such as three-stage esophagectomy or

enbloc esophagectomy.

There are some small randomized trials regarding minimally invasive versus open esophagectomy, with enroll 56 to 200 subjects[15-19]. The main endpoints were 5-year survival or quality of time and 30-day mortality. Of these trials, three studies concern tri-incision MIE versus open esophagectomy[17,19,20]. Others mainly care for two-stage esophagectomy by MIE or open[15-16,18]. In the Netherlands study, the complication rate was surprisingly high than these previous reports[9-14].And the number in other two studied were relatively small [19,20].

Here we aims to conduct a multicenter prospective randomized, open controlled trial, in order to evaluate the effectiveness of MIE versus open esophagectomy through a three-stage approach for the surgical treatment of resectable esophageal cancer.

Methods and analysis

This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer.

Patients with resectable thoracic esophageal carcinoma in T1b-4aN0-2M0 are eligible for inclusion[21]. Cervical esophageal cancer and adenocarcinoma of the esophagogastric junction are excluded. Group A patients receive minimally invasive esophagectomy which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization. Group B patients receive the open three-stage transthoracic esophagectomy involves a

right thoracotomy and laparotomy with cervical anastomosis. The flow chart for the trial is showed in Figure 1.

1 Objectives

The primary endpoints include respiratory complications within 30 days after operation. These respiratory complications involve respiratory distress or failure after operation with continuation of menchanical ventilation, pulmonary atelectasis required sputum suction by bronchocopy, pneumonia required specific antibiotics confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and acute respiratory distress syndrome (ARDS).

The secondary endpoints include other postoperative complications not involved in the primary endpoints, change of pulmonary function which is evaluated by vital capacity (VC%)，forced expiratory volume in 1 second (FEV1)，FEV1%，diffusing capacity of the lung for carbon monoxide (DLCO%) preoperatively and within the first three months postoperatively, intraoperative variables involve blood loss, operative time, the number and location of lymph nodes dissected, postoperative pain evaluated by pain-score and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18). The type and number of analgesics needed after operation will be recorded. Furthermore, mortality within in-hospital period and within the first 30 days postoperatively, the length of hospital stay, total expenses in hospital, two-year survival rate will also be recorded and analyzed.

Besides, the laboratory data include C-reactive protein, interleukin-6 from blood

samples of esophageal carcinoma patients will be tested in third and seventh day postoperatively.

2 Participating surgeons and hospitals

All operations in the study are to be performed by surgeons with sufficient experience and skill in both open three-stage transthoracic esophagectomy and minimally invasive thoraco-laparoscopic esophagectomy. In order to prevent institution bias, only hospital with high volume (more than 30 cases per year) will participate in the trial.

Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology, Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University; Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning, China.

3 Inclusion criteria

Subjects may enter the trial with all of the following :(1)esophageal carcinoma confirmed by pathology ; (2) resectable thoracic esophageal carcinoma in T1b-4aN0-2M0 ; (3) esophageal carcinoma can be resected initially by multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy; (4)18≤age≤75;(5)ECOG PS score≤2;(6)with a life expectancy ≥ 12 months;(7)tolerate tracheal intubation and general anesthesia ; (8)laboratory findings in 14 days before operation meet the criteria; (9)informed consents must be signed before the beginning of any procedures in the study.

4 Exclusion criteria

Subjects may not enter the trial with one of the following : (1)cervical esophageal cancer and adenocarcinoma of the oesophagogastric junction; (2)history of thoracic or abdominal operations which may affect the study; (3)can't tolerate tracheal intubation and general anesthesia; (4)severe comorbidities such as any unstable systemic disease, including active infection, uncontrolled hypertension, angina happening in three months, congestive heart failure, myocardial infarction happened in six months before adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.; (5) poor compliance of follow-up;(6)pregnant or lactating women; (7)ECOG PS scores > 2; (8)other patients considered to be unqualified.

5 Ethics

The trial is conducted in accordance with the principles of the Declaration of Helsinki

and ICH-GCP, local laws and regulations. The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. During the study, all modifications, extensions and updates of trial procedures should be reviewed and approved by the medical ethics committee in every participating center.

6 Randomization

When the eligible patients are confirmed and informed consent is obtained, the researchers login through the trial randomization system and input the number of patient and other patients' related informations. Then the patient will be randomized to open three-stage transthoracic esophagectomy group or minimally invasive thoraco-laparoscopic esophagectomy group through a group number produced by SPSS software.

7 Trial intenvention (Surgical technique)

Minimally invasive thoraco-laparoscopic esophagectomy

Thoracoscopic phase

Minimally invasive thoraco-laparoscopic esophagectomy was described previously [1]. The patient's posture is placed in the left lateral decubitus position. The position of the double-lumen tube was verified, and single-lung ventilation was used. Four thoracoscopic ports were established. A 10 mm port was placed at the seventh intercostals space, just along the anterior axillary line, for the camera. Another 10mm port was placed at the eighth or ninth intercostals space, posterior to the axillary line, for the dissection instrument (ultrasonic coagulating shears) and passage of the

end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port was placed in the anterior axillary line, at the third or fourth intercostals space, and this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to place the instruments for retraction and counter traction. The inferior pulmonary ligament was divided. The mediastinal pleura overlying the esophagus was divided and opened to the level of the azygous vein to expose the thoracic esophagus. The azygous vein was then dissected and divided with an endoscopic vascular stapler or Hem-lock. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of the thorax. The chest is inspected closely, and hemostasis is verified.

Laparoscopic phase

We start the operation with the laparoscopic exploration in patients in whom an Ivor-Lewis anastomosis is planned. The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH2O) was established by CO2 injection through an umbilical port. A total of five abdominal ports (three 5 mm and two 10mm) were used. After placement of the ports, the first step of the laparoscopic phase is an exploration of the abdomen to rule out advanced disease. The mobilization of the stomach was started with the division of the greater curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach

were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were included in the resection. Subsequently, the right crus was visualized and dissected, followed by dissecting and defining the left crura of the diaphragm. The abdominal esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not routinely performed. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed.

Cervical anastomosis

After laparoscopic phase and thoracoscopic phase, next, a 4- to 6-cm horizontal neck incision is made. The cervical esophagus is exposed. Careful dissection is performed down until the thoracic dissection plane is encountered, generally quite easily since the VATS dissection is continued well into the thoracic inlet. The esophagogastric specimen is pulled out of the neck incision and the cervical esophagus divided high. The specimen is removed from the field. An anastomosis is performed between the cervical esophagus and gastric tube using standard techniques (mechanical stapled or handsewn anastomosis).

Open three-stage transthoracic esophagectomy

As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure is followed in the open group. The first stage is started with a right posterolateral thoracotomy. The mediastinal pleura overlying the esophagus are divided with electrotome. The thoracic esophagus, alone with the periesophageal tissue and

mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of thorax. The second stage is the mobilization of the stomach which is started with the division of the greater curvature using ultrasonic coagulating shears. The short gastric vessels were divided with ultrasonic coagulating shears as well. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with sutures. Lymphatic tissues around vessels were included in the resection. Subsequently, the abdominal esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not routinely performed. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed. For the last stage, the cervical incision is made and then anastomosis is to be performed like minimally invasive esophagectomy.

8 Sample size calculation

According to the literatures, the incidence of respiratory complications after esophagectomy for esophageal carcinoma was 27%-31%[2,3]. Therefore, we plan to decrease incidence rate of respiratory complications from 30% to 20%in minimally invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral significance level of α=0.025 and a power of β=0.8. after adding 10% loss of the sample, thus 324 patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

9 Statistical analysis

Statistical analyses were carried out using SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and compared using Student's t-test or ANOVA test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using $\chi 2$ test. The survival was estimated by means of Kaplan-Meier curves, and survival was compared using log-rank test. A two-tailed P value < 0.05 was considered statistically significant.

Discussion

This is the largest multi-center prospective randomized controlled trial designed to compare open three-stage transthoracic esophagectomy and minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer in China. We hope the results of this study add new evidence to support the use of MIE in surgical treatment of esophageal cancer.

List of abbreviations

MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome; VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; EORTC: European Organization for Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT: multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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Authors' contributions

MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation, supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY, DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is responsible for the present paper; All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics and dissemination The trial is registered at ClinicalTrials.gov on 26 January 2015 (NCT number 02355249). The findings of this trial will be disseminated to patients and through peer-reviewed publications and international presentations.

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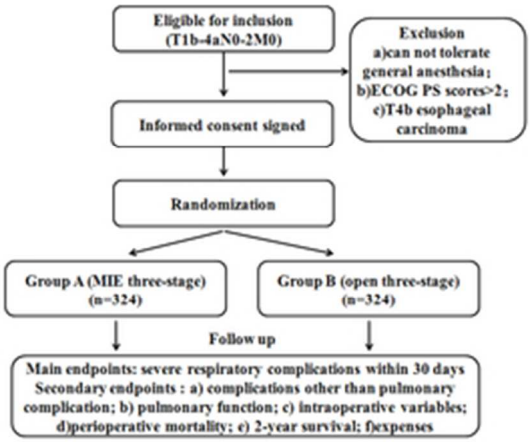
Figure legend

Figure 1 Flow chart of the study.



Flow chart of the study.
23x19mm (300 x 300 DPI)

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Abstract

Introduction Esophageal cancer is the eighth most common cause of cancer worldwide. In 2009 in China, the incidence and death rate of esophageal cancer is 22.14 per 100 000 person-years and 16.77 pre 100 000 person-years respectively, being the first one in the world. Minimally invasive esophagectomy (MIE) was introduced into clinical practice which aims to reduce the morbidity rate. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction. There are some small randomized trials regarding minimally invasive versus open esophagectomy, with enroll 100 to 850 subjects. For now, no large randomized controlled trial comparing minimally invasive versus open esophagectomy was reported in China where squamous cell carcinoma predominated over adenocarcinoma of esophagus.

Methods and analysis This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer. Group A patients receive minimally invasive esophagectomy which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients receive the open three-stage transthoracic esophagectomy involves a right thoracotomy and laparotomy with cervical anastomosis. Primary endpoints include respiratory complications within 30 days after operation. The secondary endpoints include other postoperative complications, influences on pulmonary function, intraoperative data

including blood loss, operative time, the number and location of lymph nodes dissected, and mortality in hospital, the length of hospital stay, total expenses in hospital, mortality within 30 days, survival rate after two years, postoperative pain, and HRQoL. Three hundred and twenty four patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

Ethics and dissemination The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. The findings of this trial will be disseminated to patients and through peer-reviewed publications and international presentations.

Study registeration number The trial is registered at ClinicalTrials.gov on 26 January 2015 (NCT number 02355249).

Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide[1].It is reported that the incidence and death rate of esophageal cancer in China to be top one in the world, with an incidence of 22.14 per 100 000 person-years and a death rate of 16.77 pre 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China[2]. Surgery is still the gold standard for the treatment of resectable esophageal cancer.

However, esophagectomy for esophageal cancer is a complex procedure which carries high risk of morbidity rate of 23% to 50% and a mortality rate of 2% to 8% respectively in western countries[3,4], and a morbidity rate from 9% to 29% and mortality rate from 2% to 4% respectively in China[5,6].

Minimally invasive esophagectomy (MIE) was introduced into clinical practice in 1992 for the first time which aims to reduce the morbidity rate [7]. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction[8]. Reduced morbidity rate of 11% to 25% and reduced mortality rate of 1% to 3% have been reported by many surgeons, which is lower than these of previous numbers in traditional open approach[9-13].

Apart from observational studies[9-13], two finished randomized controlled trials Netherlandsbrought promising results for MIE[14,15]. In the Netherlands study[14], a reduction of pulmonary infection rate was noted in the MIE group compared with open group, and the numbers of lymph node harvest were comparable in two groups which manifest good oncologic effect in MIE group.. In the TIME trial, the majority of the patients were operated by 3 stage procedure, being adenocarcinoma and SCC.

Moreover the technically complications in this trial were the same in the two groups, after neoadjuvant therapy. However, multiple surgical procedures were used in the study, and the complication rate was higher than those in previous reports[9-14] In the French study[15], Mariette et al found that the rate of pulmonary complication was significant lower in MIE group than in open esophagectomy group. The procedure used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy. There are several ongoing randomized trials regarding the comparison of minimally invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects[16-19]. The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and laparotomy)[16]. The procedures used in ROMIO study include open or MIE Ivor-Lewis procedure. Other three ongoing RCTs used Mckeown MIE procedure[17-19].The ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE versus open Mckeown esophagectomy for resectable esophageal cancer[17]. Robot-assisted MIE received popularity in developing and developed countries in recent years[20,21]. However, it has not been widely used as thoraco-laparoscopic MIE. NCT02017002 is a trial which aims to compare the outcomes of Ivor Lewis and tri-incision approaches for patients with esophageal cancer in Taiwan[18]. NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou China[19]. The procotol used in study NCT02188615 was Mckeown MIE with or

without neo-adjuvant chemoradiotherapy. Although guidelines are supportive of neo-adjuvant chemoradiotherapy plus surgery over surgery alone[22], the reported studies lacked well-designed series, almost all mixing stages and types of tumor[23]. Therefore, surgeons and oncologists might have different opinions about which modality to recommend, especially in clinical stage II or III.Although TIME and MIRO trial reported advantages of MIE over open esophagectomy, currently the majority of esophageal surgery is done by means of open approach worldwide[23]. Therefore, more studies are needed to clarify the role of MIE in the surgical treatment of esophageal cancer. Here we aims to conduct a multicenter prospective randomized, open controlled trial, in order to evaluate the effectiveness of MIE versus open esophagectomy through a McKeown procedure for the surgical treatment of resectable esophageal cancer. We hope the results of our study will provide high level clinical evidence to support the routine use of MIE.

Methods and analysis

This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer.

Patients with resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 are eligible for inclusion using Chest CT preoperatively[24]. Cervical esophageal cancer and adenocarcinoma of the esophagogastric junction (GEJ) are excluded. In China,

cancer of cervical esophagus are treated mainly with radiotherapy, and cancer of GEJ is resected via single left thoracic approach. Patients are divided into two groups: group A and group B. Group A patients receive McKeown MIE which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients receive open McKeown esophagectomy involves a right thoracotomy and laparotomy with cervical anastomosis. All patients received two field lymphedectomy which involve resection of lymph nodes in the thorax and abdomen. The flow chart for the trial is showed in Figure 1. Neo-adjuvant chemotherapy will be performed for patients according to local guidelines of participating cancer.

1 Objectives

The primary endpoints were major respiratory complications within 30 days after operation. These respiratory complications involve respiratory distress or failure after operation with continuation of menchanical ventilation, pulmonary atelectasis required sputum suction by bronchocopy, pneumonia required specific antibiotics confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and acute respiratory distress syndrome (ARDS).

The secondary endpoints include other postoperative complications not involved in the primary endpointsaccording to systematic classification of morbidity and mortality after thoracic surgery[25]. Other secondary endpoints include change of pulmonary function preoperatively and three months postoperatively, intraoperative

variables involve volume of blood loss, duration of operation, the number and location of lymph nodes dissected, postoperative pain scale evaluated by pain-score and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital mortality and thirty days mortality rate, the length of hospital stay, total expenses in hospital, two-year survival rate and 5 year survival. Besides, the laboratory data include C-reactive protein, interleukin-6 from blood samples will be tested in the third and seventh day postoperatively in order to analyze the influences of MIE on surgery-related inflammatory reaction of the patients postoperatively.

2 Participating surgeons and hospitals

All operations in the study are to be performed by surgeons with sufficient experience and skill in both open three-stage transthoracic esophagectomy and minimally invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases of MIE annually was determined to be sufficient experience and skill in our study. In order to prevent institution bias, only hospital with high volume (more than 30 cases of MIE annually) participate the study.

Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology, Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University; Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing,

China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning, China.

3 Inclusion criteria

Subjects may enter the trial with all of the following :(1)esophageal carcinoma confirmed by pathology ; (2) resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 using Chest CT preoperatively; (3)esophageal carcinoma can be resected initially by multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy;(4)18≤age≤75; (5)ECOG PS score≤2; (6)with a life expectancy ≥ 12 months; (7)tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preopeartively; (8)laboratory findings including liver and kidney function, and electrolyte findings in 14 days before operation meet the criteria; (9) informed consents must be signed before the beginning of any procedures in the study.

4 Exclusion criteria

Subjects may not enter the trial with one of the following : (1)cervical esophageal cancer and adenocarcinoma of the oesophagogastic junction; (2)history of thoracic or abdominal operations which may affect the study; (3)can't tolerate tracheal intubation

and general anesthesia as determined by anesthesiologist preopeartively；(4)severe comorbidities such as any unstable systemic disease, including active infection, uncontrolled hypertension, angina happening in three months, congestive heart failure, myocardial infarction happened in six months before adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.；(5)poor compliance of follow-up;(6) pregnant or lactating women；(7)ECOG PS scores > 2；(8)other patients considered to be unqualified such as patients who do not agree to participate the trial.

5 Ethics

The trial is conducted in accordance with the principles of the Declaration of Helsinki and ICH-GCP, local laws and regulations. The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. During the study, all modifications, extensions and updates of trial procedures should be reviewed and approved by the medical ethics committee in every participating center.

6 Randomization

When the eligible patients are confirmed and informed consent is obtained, the researchers login through the trial randomization system and input the number of patient and other patients' related informations. Then the patient will be randomized to open three-stage transthoracic esophagectomy group or minimally invasive thoraco-laparoscopic esophagectomy group through a group number produced by SPSS software.

7 Trial intenvention (Surgical technique)

Minimally invasive thoraco-laparoscopic esophagectomy

Thoracoscopic phase

Minimally invasive thoraco-laparoscopic esophagectomy was described previously[13] The patient's posture is placed in the left lateral decubitus position. The position of the double-lumen tube was verified, and single-lung ventilation was used. Four thoracoscopic ports were established. A 10 mm port was placed at the seventh intercostals space, just along the anterior axillary line, for the camera. Another 10mm port was placed at the eighth or ninth intercostals space, posterior to the axillary line, for the dissection instrument (ultrasonic coagulating shears) and passage of the end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port was placed in the anterior axillary line, at the third or fourth intercostals space, and this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to place the instruments for retraction and counter traction. The inferior pulmonary ligament was divided. The mediastinal pleura overlying the esophagus was divided and opened to the level of the azygous vein to expose the thoracic esophagus. The azygous vein was then dissected and divided with an endoscopic vascular stapler or Hem-lock. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of the thorax. Mediastinal lymphadenectomy is done for every patient including region of left recurrent and right subclavian,paratracheal, subcarinal, left

and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube was routinely placed.

Laparoscopic phase

The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH2O) was established by CO2 injection through an umbilical port. A total of five abdominal ports (three 5 mm and two 10mm) were used. After placement of the ports, the first step of the laparoscopic phase is an exploration of the abdomen to rule out advanced disease. The mobilization of the stomach was started with the division of the greater curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were included in the resection. Subsequently, the right crus was visualized and dissected, followed by dissecting and defining the left crura of the diaphragm. The abdominal /distal esophagus was dissected as far as possible toward the distal end. The gastric conduit was made extracorporeally. Pyloroplasty or gastric drainage procedure not routinely performed in our study. And a feeding jejunostomy tube created was not created. Instead, we insert duodenal nutrition tube before anastomosis in the operation. The abdomen is inspected to make

sure that hemostasis is adequate and the incisions are closed.

Cervical anastomosis

After laparoscopic phase and thoracoscopic phase, next, a 4- to 6-cm horizontal neck incision is made. The cervical esophagus is exposed. Careful dissection is performed down until the thoracic dissection plane is encountered, generally quite easily since the VATS dissection is continued well into the thoracic inlet. The esophagogastric specimen is pulled out of the neck incision and the cervical esophagus divided high. The specimen is removed from the field. An anastomosis is performed between the cervical esophagus and gastric tube using standard techniques (mechanical stapled or handsewn anastomosis in an end-to-side fashion).

Open three-stage transthoracic esophagectomy

As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure is followed in the open group. The first stage is started with a right posterolateral thoracotomy. The mediastinal pleura overlying the esophagus are divided with electrotome. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of thorax. The second stage is the mobilization of the stomach which is started with the division of the greater curvature using ultrasonic coagulating shears. The short gastric vessels were divided with ultrasonic coagulating shears as well. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its

origin from the celiac trunk with sutures. Lymphatic tissues around vessels were included in the resection. Subsequently, the abdominal esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not routinely performed. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed. For the last stage, the cervical incision is made and then anastomosis is to be performed like minimally invasive esophagectomy.

8 Postoperative care

The patients will be placed in intensive care unit or discharded to ward directly frome operation room according to the guidelines of participating center. Assessment of recurrent laryngeal nerve injury was done in the 1st day postoperatively. Postoperative Respiratory tract management included chest physiotherapy and early ambulation. And patient-controlled analgesia was given to every patient to control postoperative pain.

9 Sample size calculation

According to the literatures, the incidence of respiratory complications after esophagectomy for esophageal carcinoma was 27%-31%[2,3]. Therefore, we plan to decrease incidence rate of respiratory complications from 30% to 20%in minimally invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral significance level of α=0.025 and a power of β=0.8. After adding 10% loss of the sample, thus 324 patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

10 Statistical analysis

Statistical analyses were carried out using SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and compared using Student's t-test or ANOVA test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using $\chi 2$ test. The survival was estimated by means of Kaplan-Meier curves, and survival was compared using log-rank test. A two-tailed P value < 0.05 was considered statistically significant.

Discussion

Although adenocarcinoma of the esophagus has become the main type of esophageal cancer in Western countries, esophageal suqamous cell carcinoma is still the predominant histholgic type in China. Therefore, both Ivor lewis and Mckeown esophagectomy are important in the surgical treatment of esophageal suqamous cell carcinoma. Experiences from the TIME and MIRO trial were important, which concluded that MIE is not only feasible, but perhaps superior to open esophagectomy. However, there are no RCTs designed to compare the outcome of MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma, except one study which aims to compare the outcomes of Mckeown MIE with or without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell esophageal cancer. Therefore, we conducted this study, which aims to investigate the difference between MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma.

Mass et al found that less surgical trauma could lead to better preserved acute-phase and stress responses and fewer clinical manifestations of respiratory infections in patients who underwent MIE compared to patients who underwent open esophagectmy[8]. Our previous study showed that overall morbidity rate was significant decreased in MIE McKeown group compared with open MIE McKeown group, and no significant differences were found on the number of harvested lymph nodes[13]. For these reasons, We hypothesize that MIE Mckeown procedure may provide a significant decrease of major respiratory complications compared with open Mckeown procedure for esophageal suqamous cell carcinoma, without comprising the oncologic cleareance.

This is the largest multi-center prospective randomized controlled trial designed to compare open MeKeown esophagectomy and MIE MeKeown esophagectomy for esophageal cancer in China. We hope the results of this study add new evidence to support the use of MIE in surgical treatment of esophageal cancer.

List of abbreviations

MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome; VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; EORTC: European Organization for Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT: multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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Authors' contributions

MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation, supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY, DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is responsible for the present paper; All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure legend

Figure 1 Flow chart of the study.

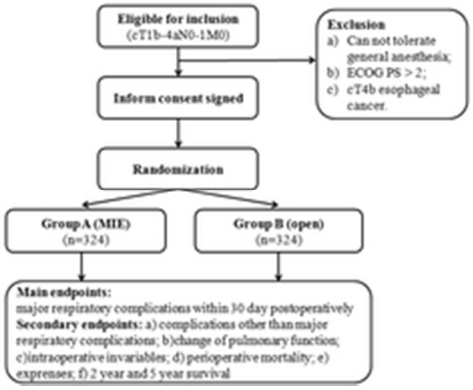

Figure 1 Flow chart of the study.
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Open three-stage transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer: a multicenter prospective, open and parallel, randomized controlled trial

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Open three-stage transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer: a multicenter prospective, open and parallel, randomized controlled trial

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Abstract

Introduction Esophageal cancer is the eighth most common cause of cancer worldwide. In 2009, the incidence and death rate of esophageal cancer is 22 per 100,000 person-years in China versus 17 per 100,000 person-years world wide respectively, being the first one in the world. Minimally invasive esophagectomy (MIE) was introduced into clinical practice which aims to reduce the morbidity rate. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction. There are some randomized trials regarding MIE versus open esophagectomy, which enrolled 100 to 850 patients. So far, no large scale, randomized, controlled clinical trial which compares the MIEwith open esophagectomy has been reported in China, where squamous cell carcinoma predominated over adenocarcinoma of esophagus.

Methods and analysis This is a three-year, multicenter, prospective randomized, open and parallel controlled clinical trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer. Patients in group A received minimally invasive esophagectomy which involved thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Patients in group B received the open three-stage transthoracic esophagectomy which included a right thoracotomy and laparotomy with cervical anastomosis. The primary endpoint was to assess the respiratory complications within 30 days after operation. The secondary endpoints included other postoperative complications, such as effects

on the pulmonary function, blood loss during operation, operative time, the number and location of lymph nodes dissected, and mortality in hospital, the length of hospital stay, total expenses in hospital, mortality within 30 days, survival rate after five years, postoperative pain, and health related quality of life (HRQOL). Three hundred and twenty four (324) patients in each group was considered to be necessary and a total of 648 patients were enrolled into this study.

Ethics and dissemination: This study protocol was approved by the Institutional Ethics Committees of all participating institutions. The findings of this clinical trial will be disseminated to patients and through peer-reviewed publications and international presentations.

Study registeration number This clinical trial is registered at ClinicalTrials.gov on 26 January 2015 (NCT number 02355249).

Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide[1]. It is reported that the incidence and death rate of esophageal cancer in China is the number one in the world, with an incidence of 22 per 100,000 person-years and a death rate of 17 pre 100,000 person-years, according to an epidemiological statistics of incidence and death of esophageal cancer in 2009 in China[2]. Surgery is still the gold standard for the treatment of resectable esophageal cancer.

However, esophagectomy for esophageal cancer is a complex procedure which carries high risk of morbidity rate of 23% to 50% and a mortality rate of 2% to 8% respectively in western countries[3,4], and a morbidity rate from 9% to 29% and mortality rate from 2% to 4% respectively in China[5,6].

Minimally invasive esophagectomy (MIE) was introduced into clinical practice in 1992 for the first time which aims to reduce the morbidity rate [7]. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction[8]. Reduced morbidity rate of 11% to 25% and reduced mortality rate of 1% to 3% have been reported by many surgeons, which is lower than these of previous numbers in traditional open approach[9-13].

Apart from observational studies[9-13], two completed randomized controlled trials the Netherlandsdemonstrated promising results for MIE[14,15]. In the Netherlands study[14], a reduction of pulmonary infection rate was noted in the MIE group compared with open group, and the numbers of lymph node harvest were comparable in two groups which manifest good oncologic effect in MIE group.. In the TIME trial, the majority of the patients were operated by 3 stage procedure, being adenocarcinoma and SCC.

Moreover the technically complications in this trial were the same in the two groups, after neoadjuvant therapy. However, multiple surgical procedures were used in the study, and the complication rate was higher than those in previous reports[9-14] In the French study[15], Mariette et al found that the rate of pulmonary complication was significant lower in MIE group than in open esophagectomy group. The procedure used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy. There are several ongoing randomized trials regarding the comparison of minimally invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects[16-19]. The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and laparotomy)[16]. The procedures used in ROMIO study include open or MIE Ivor-Lewis procedure. Other three ongoing RCTs used Mckeown MIE procedure[17-19].The ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE versus open Mckeown esophagectomy for resectable esophageal cancer[17]. Robot-assisted MIE received popularity in developing and developed countries in recent years[20,21]. However, it has not been widely used as thoraco-laparoscopic MIE. NCT02017002 is a trial which aims to compare the outcomes of Ivor Lewis and tri-incision approaches for patients with esophageal cancer in Taiwan[18]. NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou China[19]. The procotol used in study NCT02188615 was Mckeown MIE with or

without neo-adjuvant chemoradiotherapy. Although guidelines are supportive of neo-adjuvant chemoradiotherapy plus surgery over surgery alone[22], the reported studies lacked well-designed series, almost all mixing stages and types of tumor[23]. Therefore, surgeons and oncologists might have different opinions about which modality to recommend, especially in clinical stage II or III.Although TIME and MIRO trial reported advantages of MIE over open esophagectomy, currently the majority of esophageal surgery is done by means of open approach worldwide[23]. Therefore, more studies are needed to clarify the role of MIE in the surgical treatment of esophageal cancer. Here we aims to conduct a multicenter prospective randomized, open controlled trial, in order to evaluate the effectiveness of MIE versus open esophagectomy through a McKeown procedure for the surgical treatment of resectable esophageal cancer. The results of our study may provide high level clinical evidence to support the routine use of MIE.

Methods and analysis

This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer.

Patients with resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 are eligible for inclusion using chest CT preoperatively[24]. Ultrasonography of the upper abdomen are routinely done to rule out liver metastasis. Head CT and bone scan are

indicated when patients had symptoms of central nervous system such as headache and nausea, and bone pains. Cervical esophageal cancer (definition according to AJCC cancer staging manual that the length of cervical esophagus is from the incisors are from 15 to <20 cm via endoscopic measurement) and adenocarcinoma of the esophagogastic junction (GEJ) are excluded. In China, cancer of cervical esophagus are treated mainly with radiotherapy, and cancer of GEJ is resected via single left thoracic approach. Patients are divided into two groups: group A and group B. Group A patients received McKeown MIE which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients received open McKeown esophagectomy which involves a right thoracotomy and laparotomy with cervical anastomosis. All patients received two field lymphedectomy which involve resection of lymph nodes in the thorax and abdomen. The flow chart for the trial is showed in Figure 1. Neo-adjuvant chemotherapy will be performed for patients according to local guidelines of participating cancer.

1 Objectives

The primary endpoint wwas to assess the major respiratory complications within 30 days after operation. These respiratory complications involve respiratory distress or failure after operation with continuation of menchanical ventilation, pulmonary atelectasis required sputum suction by bronchocopy, pneumonia required specific antibiotics confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and acute respiratory distress syndrome (ARDS).

The secondary endpoints include other postoperative complications not involved in the primary endpointsaccording to systematic classification of morbidity and mortality after thoracic surgery[25]. Other secondary endpoints include change of pulmonary function preoperatively and three months postoperatively, intraoperative variables involve volume of blood loss, duration of operation, the number and location of lymph nodes dissected, postoperative pain scale evaluated by pain-score and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital mortality and thirty days mortality rate, the length of hospital stay, total expenses in hospital, two-year survival rate and 5 year survival rate. Besides, the laboratory data included blood C-reactive protein and interleukin-6 were measured in the third and seventh day postoperatively in order to analyze the influences of MIE on surgery-related inflammatory reaction of the patients postoperatively.

2 Participating surgeons and hospitals

All operations in the study are to be performed by surgeons with sufficient experience and skill in both open three-stage transthoracic esophagectomy and minimally invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases of MIE annually was determined to be sufficient experience and skill in our study. In order to prevent institution bias, only hospital with high volume (more than 30 cases of MIE annually) participate the study.

Thirteen Chinese academic centers or hospitals participated in the trial: Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan

Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology, Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University; Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning, China.

3 Inclusion criteria

Subjects may enter the trial based on the following criteria :(1)esophageal carcinoma confirmed by pathology ; (2) resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 using chest CT and ultrasonography of the upper abdomen, head CT and bone scan are indicated when patients had symptoms of central nervous system such as headache and nausea, and bone pains to confirm or exclude distant metastasispreoperatively ; (3) esophageal carcinoma can be resected initially by multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy; (4)18≤age≤75; (5) ECOG PS score≤2; (6)with a life expectancy ≥ 12 months; (7) tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preopeartively; (8) laboratory findings including liver and kidney function, and electrolyte findings in 14 days before operation meet the criteria, laboratory findings

including abnormal liver and renal function which exclude a patient from immediate surgery, and patients then received medical therapies to recover liver and renal function；(9) informed consents must be signed before the beginning of any procedures in the study.

4 Exclusion criteria

Subjects may not enter the trial when they met the following criteria: (1)cervical esophageal cancer and adenocarcinoma of the oesophagogastic junction；(2)history of thoracic or abdominal operations which may affect the study；(3) can't tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preopeartively；(4)severe comorbidities such as any unstable systemic disease, including active infection, uncontrolled hypertension, angina happening in three months, congestive heart failure, myocardial infarction happened in six months before adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.；(5)poor compliance of follow-up;(6)pregnant or lactating women；(7)ECOG PS scores > 2；(8) other patients considered to be unqualified such as patients who do not agree to participate the trial.

5 Ethics

The trial is conducted in accordance with the principles of the Declaration of Helsinki and ICH-GCP, local laws and regulations. The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. During the study,

all modifications, extensions and updates of trial procedures should be reviewed and approved by the medical ethics committee in every participating center.

6 Randomization

When the eligiblility of the patients was confirmed and informed consent was obtained, the researchers login through the trial randomization system and input the number of patient and other patients' related information. Then the patient will be randomized to open three-stage transthoracic esophagectomy group or minimally invasive thoraco-laparoscopic esophagectomy group through a group number produced by SPSS software.

7 Trial intenvention (Surgical technique)

Minimally invasive thoraco-laparoscopic esophagectomy

Thoracoscopic phase

Minimally invasive thoraco-laparoscopic esophagectomy was described previously[13] The patient's posture is placed in the left lateral decubitus position. The position of the double-lumen tube was verified, and single-lung ventilation was used. Four thoracoscopic ports were established. A 10 mm port was placed at the seventh intercostals space, just along the anterior axillary line, for the camera. Another 10mm port was placed at the eighth or ninth intercostals space, posterior to the axillary line, for the dissection instrument (ultrasonic coagulating shears) and passage of the end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port was placed in the anterior axillary line, at the third or fourth intercostals space, and

this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to place the instruments for retraction and counter traction. The inferior pulmonary ligament was divided. The mediastinal pleura overlying the esophagus was divided and opened to the level of the azygous vein to expose the thoracic esophagus. The azygous vein was then dissected and divided with an endoscopic vascular stapler or Hem-lock. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of the thorax. Mediastinal lymphadenectomy is done for every patient including region of left recurrent and right subclavian,paratracheal, subcarinal, left and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube was routinely placed. But we do not place anastomotic drains routinely.

Laparoscopic phase

The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH2O) was established by CO2 injection through an umbilical port. A total of five abdominal ports (three 5 mm and two 10mm) were used. After placement of the ports, the first step of the laparoscopic phase is an exploration of the abdomen to rule out advanced disease. The mobilization of the stomach was started with the division of the greater curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery.

The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were included in the resection. Subsequently, the right crus was visualized and dissected, followed by dissecting and defining the left crura of the diaphragm. The abdominal /distal esophagus was dissected as far as possible toward the distal end. The gastric conduit was made extracorporeally. As the length of port was 4 cm in our study which made the extracorporeal gastric conduit creation easily.Pyloroplasty or gastric drainage procedure not routinely performed in our study. And a feeding jejunostomy tube created was not created. Instead, we insert duodenal nutrition tube before anastomosis in the operation. After esophagogastrostomy was completed, nasogastric tube was inserted and was bound with duodenal feeding tube together, Then duodenal feeding tube was pulled out with nasogastric tube. The surgeon adjusted the location of duodenal feeding tube through the abdominal port (4 cm) and made sure that the duodenal feeding tube was placed in the duodenum. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed.

Cervical anastomosis

After laparoscopic phase and thoracoscopic phase, next, a 4- to 6-cm horizontal neck incision is made. The cervical esophagus is exposed. Careful dissection is performed down until the thoracic dissection plane is encountered, generally quite easily since the VATS dissection is continued well into the thoracic inlet. The esophagogastric

specimen is pulled out of the neck incision and the cervical esophagus divided high. The specimen is removed from the field. An anastomosis is performed between the cervical esophagus and gastric tube using standard techniques (mechanical stapled or handsewn anastomosis in an end-to-side fashion, All patients received cervical stapled anastomosis in an end-to-side manner routinely. Under the following circumstances hand-sewn anastomosis was made: first, the length of gastric tube was short, and second, the length of residual esophagus was relatively short).

Open three-stage transthoracic esophagectomy

As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure is followed in the open group. The first stage is started with a right posterolateral thoracotomy. The mediastinal pleura overlying the esophagus are divided with electrotome. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of thorax. The second stage is the mobilization of the stomach which is started with the division of the greater curvature using ultrasonic coagulating shears. The short gastric vessels were divided with ultrasonic coagulating shears as well. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with sutures. Lymphatic tissues around vessels were included in the resection. Subsequently, the abdominal esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not routinely performed. The

abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed. For the last stage, the cervical incision is made and then anastomosis is to be performed like minimally invasive esophagectomy.

8 Postoperative care

The patients will be placed in intensive care unit or discharged to ward directly from operation room according to the guidelines of participating center. As the injury of recurrent laryngeal nerve may lead to hoarseness. We made regular round in the 1st day postoperatively or when the patient can speak after liberation from mechanical ventilation because of respiratory insufficiency, to make sure that whether the patient had hoarseness. Then we will make indirect laryngoscope to confirm the diagnosis of recurrent laryngeal nerve injury. Postoperative respiratory tract management included chest physiotherapy and early ambulation. And patient-controlled analgesia was given to every patient to control postoperative pain.

9 Sample size calculation

According to the literatures, the incidence of respiratory complications after esophagectomy for esophageal carcinoma was 27%-31%[2,3]. Therefore, we plan to decrease incidence rate of respiratory complications from 30% to 20% in the patient group who received minimally invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral significance level of α=0.025 and a power of β=0.8. After adding 10% loss of the sample, thus 324 patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

10 Statistical analysis

Statistical analyses were carried out using SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and compared using Student's t-test or ANOVA test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using $\chi 2$ test. The survival was estimated by means of Kaplan-Meier curves, and survival was compared using log-rank test. A two-tailed P value < 0.05 was considered statistically significant.

Discussion

Although adenocarcinoma of the esophagus has become the main type of esophageal cancer in Western countries, esophageal suqamous cell carcinoma is still the predominant histholgic type in China. Therefore, both Ivor lewis and Mckeown esophagectomy are important in the surgical treatment of esophageal suqamous cell carcinoma. Experiences from the TIME and MIRO trial were important, which concluded that MIE is not only feasible, but perhaps superior to open esophagectomy. However, there are no RCTs designed to compare the outcome of MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma, except one study which aims to compare the outcomes of Mckeown MIE with or without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell esophageal cancer. Therefore, we conducted this study, which aims to investigate the difference between MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma.

Mass et al found that less surgical trauma could lead to better preserved acute-phase and stress responses and fewer clinical manifestations of respiratory infections in patients who underwent MIE compared to patients who underwent open esophagectmy[8]. Our previous study showed that overall morbidity rate was significant decreased in MIE McKeown group compared with open MIE McKeown group, and no significant differences were found on the number of harvested lymph nodes[13]. For these reasons, We hypothesize that MIE Mckeown procedure may provide a significant decrease of major respiratory complications compared with open Mckeown procedure for esophageal suqamous cell carcinoma, without comprising the oncologic cleareance.

To our knowledge, this is the largest multi-center prospective randomized controlled trial designed to compare open MeKeown esophagectomy and MIE MeKeown esophagectomy for esophageal cancer in China. The results of this study may add new evidence to support the use of MIE in surgical treatment of esophageal cancer.

List of abbreviations

MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome; VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; EORTC: European Organization for Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT: multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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Authors' contributions

MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation, supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY, DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is responsible for the present paper; All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure legend

Figure 1 Flow chart of the study.

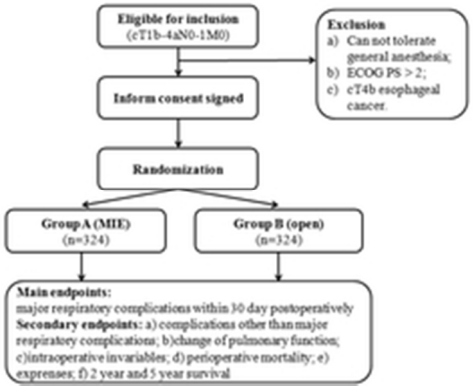

Figure 1 Flow chart of the study.
20x16mm (300 x 300 DPI)

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Open three-stage transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer: protocol for a multicenter prospective, open and parallel, randomized controlled trial

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Abstract

Introduction Esophageal cancer is the eighth most common cause of cancer worldwide. In 2009 in China, the incidence and death rate of esophageal cancer is 22.14 per 100 000 person-years and 16.77 pre 100 000 person-years respectively, being the first one in the world. Minimally invasive esophagectomy (MIE) was introduced into clinical practice which aims to reduce the morbidity rate. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction. There are some small randomized trials regarding minimally invasive versus open esophagectomy, with enroll 100 to 850 subjects. For now, no large randomized controlled trial comparing minimally invasive versus open esophagectomy was reported in China where squamous cell carcinoma predominated over adenocarcinoma of esophagus.

Methods and analysis This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer. Group A patients receive minimally invasive esophagectomy which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients receive the open three-stage transthoracic esophagectomy involves a right thoracotomy and laparotomy with cervical anastomosis. Primary endpoints include respiratory complications within 30 days after operation. The secondary endpoints include other postoperative complications, influences on pulmonary function, intraoperative data

including blood loss, operative time, the number and location of lymph nodes dissected, and mortality in hospital, the length of hospital stay, total expenses in hospital, mortality within 30 days, survival rate after two years, postoperative pain, and HRQoL. Three hundred and twenty four patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide[1].It is reported that the incidence and death rate of esophageal cancer in China to be top one in the world, with an incidence of 22.14 per 100 000 person-years and a death rate of 16.77 pre 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China[2]. Surgery is still the gold standard for the treatment of resectable esophageal cancer.

However, esophagectomy for esophageal cancer is a complex procedure which carries high risk of morbidity rate of 23% to 50% and a mortality rate of 2% to 8% respectively in western countries[3,4], and a morbidity rate from 9% to 29% and mortality rate from 2% to 4% respectively in China[5,6].

Minimally invasive esophagectomy (MIE) was introduced into clinical practice in 1992 for the first time which aims to reduce the morbidity rate [7]. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction[8]. Reduced morbidity rate of 11% to 25% and reduced mortality rate of 1% to 3% have been reported by many surgeons, which is lower than these of previous numbers in traditional open approach[9-13].

Apart from observational studies[9-13], two finished randomized controlled trials Netherlands brought promising results for MIE[14,15]. In the Netherlands study[14], a reduction of pulmonary infection rate was noted in the MIE group compared with open group, and the numbers of lymph node harvest were comparable in two groups which manifest good oncologic effect in MIE group. In the TIME trial, the majority of

the patients were operated by 3 stage procedure, being adenocarcinoma and SCC. Moreover the technically complications in this trial were the same in the two groups, after neoadjuvant therapy. However, multiple surgical procedures were used in the study, and the complication rate was higher than those in previous reports[9-14] In the French study[15], Mariette et al found that the rate of pulmonary complication was significant lower in MIE group than in open esophagectomy group. The procedure used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy.

There are several ongoing randomized trials regarding the comparison of minimally invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects[16-19]. The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and laparotomy)[16]. The procedures used in ROMIO study include open or MIE Ivor-Lewis procedure. Other three ongoing RCTs used Mckeown MIE procedure[17-19].The ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE versus open Mckeown esophagectomy for resectable esophageal cancer[17]. Robot-assisted MIE received popularity in developing and developed countries in recent years[20,21]. However, it has not been widely used as thoraco-laparoscopic MIE. NCT02017002 is a trial which aims to compare the outcomes of Ivor Lewis and tri-incision approaches for patients with esophageal cancer in Taiwan[18]. NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou

China[19]. The procotol used in study NCT02188615 was Mckeown MIE with or without neo-adjuvant chemoradiotherapy. Although guidelines are supportive of neo-adjuvant chemoradiotherapy plus surgery over surgery alone[22], the reported studies lacked well-designed series, almost all mixing stages and types of tumor[23]. Therefore, surgeons and oncologists might have different opinions about which modality to recommend, especially in clinical stage II or III.

Although TIME and MIRO trial reported advantages of MIE over open esophagectomy, currently the majority of esophageal surgery is done by means of open approach worldwide[23]. Therefore, more studies are needed to clarify the role of MIE in the surgical treatment of esophageal cancer. Here we aims to conduct a multicenter prospective randomized, open controlled trial, in order to evaluate the effectiveness of MIE versus open esophagectomy through a McKeown procedure for the surgical treatment of resectable esophageal cancer. We hope the results of our study will provide high level clinical evidence to support the routine use of MIE.

Methods and analysis

This is a three year multicenter prospective randomized, open and parallel controlled trial, which aims to compare the effectiveness of minimally invasive thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy for resectable esophageal cancer.

Patients with resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 are eligible for inclusion using chest CT, ultrasonography of the abdomen, head CT and

bone scan [24]. We do not include a PET/CT as a preoperative workup because medical insurance does not cover the expense of a PET/CT. Cervical esophageal cancer and adenocarcinoma of the esophagogastic junction (GEJ) are excluded. In China, cancer of cervical esophagus are treated mainly with radiotherapy, and cancer of GEJ is resected via single left thoracic approach. Patients are divided into two groups: group A and group B. Group A patients receive McKeown MIE which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical anastomosis. Group B patients receive open McKeown esophagectomy involves a right thoracotomy and laparotomy with cervical anastomosis. All patients received two field lymphedectomy which involve resection of lymph nodes in the thorax and abdomen. The flow chart for the trial is showed in Figure 1. Neo-adjuvant chemotherapy will be performed for patients according to local guidelines of participating cancer.

1 Objectives

The primary endpoints were major respiratory complications within 30 days after operation. These respiratory complications involve respiratory distress or failure after operation with continuation of menchanical ventilation, pulmonary atelectasis required sputum suction by bronchocopy, pneumonia required specific antibiotics confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and acute respiratory distress syndrome (ARDS).

The secondary endpoints include other postoperative complications not involved in

the primary endpoints according to systematic classification of morbidity and mortality after thoracic surgery[25]. Other secondary endpoints include change of pulmonary function preoperatively and three months postoperatively, intraoperative variables involve volume of blood loss, duration of operation, the number and location of lymph nodes dissected, postoperative pain scale evaluated by pain-score and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital mortality and thirty days mortality rate, the length of hospital stay, total expenses in hospital, two-year survival rate and 5 year survival. Besides, the laboratory data include C-reactive protein, interleukin-6 from blood samples will be tested in the third and seventh day postoperatively in order to analyze the influences of MIE on surgery-related inflammatory reaction of the patients postoperatively.

2 Participating surgeons and hospitals

All operations in the study are to be performed by surgeons with sufficient experience and skill in both open three-stage transthoracic esophagectomy and minimally invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases of MIE annually was determined to be sufficient experience and skill in our study. In order to prevent institution bias, only hospital with high volume (more than 30 cases of MIE annually) participate the study.

Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology,

Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University; Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning, China.

3 Inclusion criteria

Subjects may enter the trial with all of the following :(1)esophageal carcinoma confirmed by pathology ; (2) resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 using chest CT preoperatively, ultrasonography of the abdomen, head CT and bone scan; (3)esophageal carcinoma can be resected initially by multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy; (4)18≤age≤75; (5)ECOG PS score≤2; (6)with a life expectancy ≥ 12 months; (7)tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preopeartively; (8)laboratory findings including liver and kidney function, and electrolyte findings in 14 days before operation meet the criteria; (9)informed consents must be signed before the beginning of any procedures in the study.

4 Exclusion criteria

Subjects may not enter the trial with one of the following : (1)cervical esophageal cancer and adenocarcinoma of the oesophagogastic junction；(2)history of thoracic or abdominal operations which may affect the study；(3)can't tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preopeartively；(4)severe comorbidities such as any unstable systemic disease, including active infection, uncontrolled hypertension, angina happening in three months, congestive heart failure, myocardial infarction happened in six months before adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.；(5)poor compliance of follow-up;(6) pregnant or lactating women；(7)ECOG PS scores > 2；(8)other patients considered to be unqualified such as patients who do not agree to participate the trial.

5 Ethics

The trial is conducted in accordance with the principles of the Declaration of Helsinki and ICH-GCP, local laws and regulations. The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. During the study, all modifications, extensions and updates of trial procedures should be reviewed and approved by the medical ethics committee in every participating center.

6 Randomization

When the eligible patients are confirmed and informed consent is obtained, the researchers login through the trial randomization system and input the number of patient and other patients' related informations. Then the patient will be randomized

to open three-stage transthoracic esophagectomy group or minimally invasive thoraco-laparoscopic esophagectomy group through a group number produced by SPSS software.

7 Trial intenvention (Surgical technique)

Minimally invasive thoraco-laparoscopic esophagectomy

Thoracoscopic phase

Minimally invasive thoraco-laparoscopic esophagectomy was described previously[13] The patient's posture is placed in the left lateral decubitus position. The position of the double-lumen tube was verified, and single-lung ventilation was used. Four thoracoscopic ports were established. A 10 mm port was placed at the seventh intercostals space, just along the anterior axillary line, for the camera. Another 10mm port was placed at the eighth or ninth intercostals space, posterior to the axillary line, for the dissection instrument (ultrasonic coagulating shears) and passage of the end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port was placed in the anterior axillary line, at the third or fourth intercostals space, and this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to place the instruments for retraction and counter traction. The inferior pulmonary ligament was divided. The mediastinal pleura overlying the esophagus was divided and opened to the level of the azygous vein to expose the thoracic esophagus. The azygous vein was then dissected and divided with an endoscopic vascular stapler or Hem-lock. The thoracic esophagus, alone with the periesophageal tissue and

mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of the thorax. Mediastinal lymphadenectomy is done for every patient including region of left recurrent and right subclavian,paratracheal, subcarinal, left and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube was routinely placed.

Laparoscopic phase The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH2O) was established by CO2 injection through an umbilical port. A total of five abdominal ports (three 5 mm and two 40mm) were used. After placement of the ports, the first step of the laparoscopic phase is an exploration of the abdomen to rule out advanced disease. The mobilization of the stomach was started with the division of the greater curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were included in the resection. Subsequently, the right crus was visualized and dissected, followed by dissecting and defining the left crura of the diaphragm. The abdominal /distal esophagus was dissected as far as possible toward the distal end. The gastric conduit was made extracorporeally. Pyloroplasty or gastric drainage procedure not

routinely performed in our study. And a feeding jejunostomy tube created was not created. Instead, we insert duodenal nutrition tube before anastomosis in the operation. We insert duodenal feeding tube as following steps. First, prior the esophagogastric anastomosis, we enclose a candy ball using sterile gloves peel and fix it to the front end of the feeding tube through the small laparotomy incision. Push the feeding tube until the front end and the candy ball lies in the duodenum, and put the rest of the feeding tube into the gastral cavity and bound it with nasogastric tube. Then, pull nasogastric tube out from the nose and fixed. Then reinserted the nasogastric tube into the gastric cavity. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed.

Cervical anastomosis

After laparoscopic phase and thoracoscopic phase, next, a 4- to 6-cm horizontal neck incision is made. The cervical esophagus is exposed. Careful dissection is performed down until the thoracic dissection plane is encountered, generally quite easily since the VATS dissection is continued well into the thoracic inlet. The esophagogastric specimen is pulled out of the neck incision and the cervical esophagus divided high. The specimen is removed from the field. An anastomosis is performed between the cervical esophagus and gastric tube using standard techniques (mechanical stapled or handsewn anastomosis in an end-to-side fashion).

Open three-stage transthoracic esophagectomy

As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure is followed in the open group. The first stage is started with a right posterolateral

thoracotomy. The mediastinal pleura overlying the esophagus are divided with electrotome. The thoracic esophagus, alone with the periesophageal tissue and mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the level of inlet of thorax. The second stage is the mobilization of the stomach which is started with the division of the greater curvature using ultrasonic coagulating shears. The short gastric vessels were divided with ultrasonic coagulating shears as well. The gastrocolic omentum was then divided, with care taken to preserve the right gastroepiploic artery. The posterior attachments of the stomach were then divided after retraction of the stomach anteriorly. The left gastric vessel was divided at its origin from the celiac trunk with sutures. Lymphatic tissues around vessels were included in the resection. Subsequently, the abdominal esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not routinely performed. The abdomen is inspected to make sure that hemostasis is adequate and the incisions are closed. For the last stage, the cervical incision is made and then anastomosis is to be performed like minimally invasive esophagectomy.

8 Postoperative care

The patients will be placed in intensive care unit or discharded to ward directly frome operation room according to the guidelines of participating center. Assessment of recurrent laryngeal nerve injury was done in the 1st day postoperatively. Postoperative Respiratory tract management included chest physiotherapy and early ambulation. And patient-controlled analgesia was given to every patient to control postoperative pain.

9 Sample size calculation

According to the literatures, the incidence of respiratory complications after esophagectomy for esophageal carcinoma was 27%-31%[2,3]. Therefore, we plan to decrease incidence rate of respiratory complications from 30% to 20%in minimally invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral significance level of α=0.025 and a power of β=0.8. After adding 10% loss of the sample, thus 324 patients in each group will be needed and a total of 648 patients will finally be enrolled into the study.

10 Statistical analysis

Statistical analyses were carried out using SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and compared using Student's t-test or ANOVA test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using $\chi 2$ test. The survival was estimated by means of Kaplan-Meier curves, and survival was compared using log-rank test. A two-tailed P value < 0.05 was considered statistically significant.

Discussion

Although adenocarcinoma of the esophagus has become the main type of esophageal cancer in Western countries, esophageal suqamous cell carcinoma is still the predominant histholgic type in China. Therefore, both Ivor lewis and Mckeown esophagectomy are important in the surgical treatment of esophageal suqamous cell

carcinoma. Experiences from the TIME and MIRO trial were important, which concluded that MIE is not only feasible, but perhaps superior to open esophagectomy. However, there are no RCTs designed to compare the outcome of MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma, except one study which aims to compare the outcomes of Mckeown MIE with or without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell esophageal cancer. Therefore, we conducted this study, which aims to investigate the difference between MIE Mckeown procedure and open Mckeown procedure for esophageal suqamous cell carcinoma.

Mass et al found that less surgical trauma could lead to better preserved acute-phase and stress responses and fewer clinical manifestations of respiratory infections in patients who underwent MIE compared to patients who underwent open esophagectmy[8]. Our previous study showed that overall morbidity rate was significant decreased in MIE McKeown group compared with open MIE McKeown group, and no significant differences were found on the number of harvested lymph nodes[13]. For these reasons, We hypothesize that MIE Mckeown procedure may provide a significant decrease of major respiratory complications compared with open Mckeown procedure for esophageal suqamous cell carcinoma, without comprising the oncologic cleareance.

This is the largest multi-center prospective randomized controlled trial designed to compare open MeKeown esophagectomy and MIE MeKeown esophagectomy for esophageal cancer in China. We hope the results of this study add new evidence to

support the use of MIE in surgical treatment of esophageal cancer.

List of abbreviations

MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome; VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; EORTC: European Organization for Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT: multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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Authors' contributions

MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation, supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY, DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is responsible for the present paper; All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics and dissemination The study protocol has been approved by the Institutional Ethics Committees of all participating institutions. The findings of this trial will be disseminated to patients and through peer-reviewed publications and international

presentations.

Study registeration number The trial is registered at ClinicalTrials.gov on 26 January 2015 (NCT number 02355249).

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Figure legend

Figure 1 Flow chart of the study.

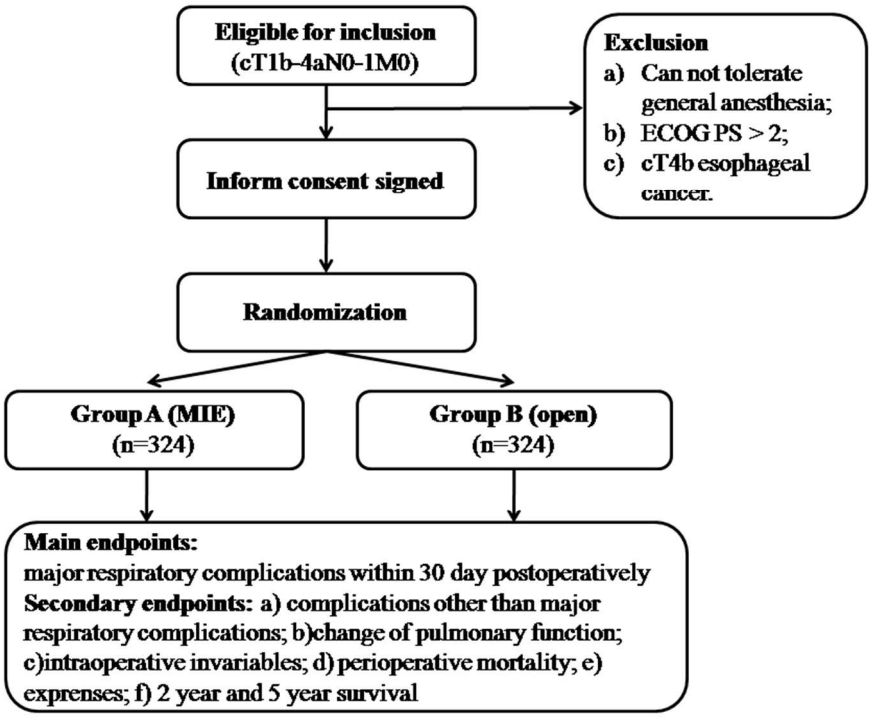

Figure 1 Flow chart of the study.
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