

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2015-008328
Article Type:	Protocol
Date Submitted by the Author:	27-Mar-2015
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Primary Subject Heading:	Oncology

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Secondary Subject Heading:	Surgery
Keywords:	Gastrointestinal tumours < ONCOLOGY, Cardiothoracic surgery < SURGERY, Clinical trials < THERAPEUTICS

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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 per 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

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3 including blood loss, operative time, the number and location of lymph nodes
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5 dissected, and mortality in hospital, the length of hospital stay, total expenses in
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7 hospital, mortality within 30 days, survival rate after two years, postoperative pain,
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9 and HRQoL. 324 patients in each group will be needed and a total of 648 patients will
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11 finally be enrolled into the study.
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15 **Key words:** esophageal cancer, surgery, minimally invasive surgery, esophagectomy,
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17 randomized controlled trials
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20 21 **Strengths and limitations of this study**

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23 First large multicenter randomized controlled trial comparing open three-stage
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25 transthoracic esophagectomy vs minimally invasive thoraco-laparoscopic
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27 esophagectomy for esophageal cancer in China.
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31 The results of this study may add new evidence to support the use of minimally
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33 invasive esophagectomy in surgical treatment of esophageal cancer.
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Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide¹. 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 per 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China². 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 rate⁷. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction⁸. 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 approach⁹⁻¹³.

Apart from observational studies⁹⁻¹³, one randomized controlled trial conducted in Dutch brought promising results for MIE¹⁴. 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 be generalized to other approaches such as three-stage esophagectomy or

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4 enbloc esophagectomy.

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6 There are some small randomized trials regarding minimally invasive versus open
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8 esophagectomy, with enroll 56 to 200 subjects[15-19]. The main endpoints were
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10 5-year survival or quality of time and 30-day mortality. Of these trials, three studies
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12 concern tri-incision MIE versus open esophagectomy^{17,19,20}. Others mainly care for
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14 two-stage esophagectomy by MIE or open[15-16,18]. In the Netherlands study, the
15
16 complication rate was surprisingly high than these previous reports⁹⁻¹⁴. And the
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18 number in other two studied were relatively small^{19,20}.

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20 Here we aims to conduct a multicenter prospective randomized, open controlled trial,
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22 in order to evaluate the effectiveness of MIE versus open esophagectomy through a
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24 three-stage approach for the surgical treatment of resectable esophageal cancer.
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33 34 **Methods and analysis**

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36 This is a three year multicenter prospective randomized, open and parallel controlled
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38 trial, which aims to compare the effectiveness of minimally invasive
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40 thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy
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42 for resectable esophageal cancer.
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46 Patients with resectable thoracic esophageal carcinoma in T1b-4aN0-2M0 are eligible
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48 for inclusion²¹. Cervical esophageal cancer and adenocarcinoma of the esophagogastric
49
50 junction are excluded. Group A patients receive minimally invasive esophagectomy
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52 which involve thoracoscopic esophagectomy and laparoscopic gastric mobilization.
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56 Group B patients receive the open three-stage transthoracic esophagectomy involves a
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4 right thoracotomy and laparotomy with cervical anastomosis. The flow chart for the
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6 trial is showed in Figure 1.
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10 11 **1 Objectives**

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14 The primary endpoints include respiratory complications within 30 days after
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16 operation. These respiratory complications involve respiratory distress or failure after
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18 operation with continuation of mechanical ventilation, pulmonary atelectasis
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20 required sputum suction by bronchocopy, pneumonia required specific antibiotics
21
22 confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and
23
24 acute respiratory distress syndrome (ARDS).
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29 The secondary endpoints include other postoperative complications not involved in
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31 the primary endpoints, change of pulmonary function which is evaluated by vital
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33 capacity (VC%), forced expiratory volume in 1 second (FEV1), FEV1%, diffusing
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35 capacity of the lung for carbon monoxide (DLCO%) preoperatively and within the
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37 first three months postoperatively, intraoperative variables involve blood loss,
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39 operative time, the number and location of lymph nodes dissected, postoperative pain
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41 evaluated by pain-score and quality of life questionnaires (EORTC QLQ-C30 and
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43 QLQ-0ES18). The type and number of analgesics needed after operation will be
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45 recorded. Furthermore, mortality within in-hospital period and within the first 30 days
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47 postoperatively, the length of hospital stay, total expenses in hospital, two-year
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49 survival rate will also be recorded and analyzed.
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56 Besides, the laboratory data include C-reactive protein, interleukin-6 from blood
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4 samples of esophageal carcinoma patients will be tested in third and seventh day
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6 postoperatively.
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10 11 **2 Participating surgeons and hospitals** 12

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14 All operations in the study are to be performed by surgeons with sufficient experience
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16 and skill in both open three-stage transthoracic esophagectomy and minimally
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18 invasive thoraco-laparoscopic esophagectomy. In order to prevent institution bias,
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20 only hospital with high volume (more than 30 cases per year) will participate in the
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22 trial.
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26 Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer
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28 Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan
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30 Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology,
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32 Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University;
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34 Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan,
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36 China; The First Affiliated Hospital of Chongqing Medical University, Chongqing,
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38 China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of
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40 Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer
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42 Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's
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44 Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning,
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56 **3 Inclusion criteria** 57 58 59 60

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4 Subjects may enter the trial with all of the following : (1) esophageal carcinoma
5 confirmed by pathology ; (2) resectable thoracic esophageal carcinoma in
6 T1b-4aN0-2M0 ; (3) esophageal carcinoma can be resected initially by
7 multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy;
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9 (4) $18 \leq \text{age} \leq 75$; (5) ECOG PS score ≤ 2 ; (6) with a life expectancy ≥ 12 months; (7) tolerate
10 tracheal intubation and general anesthesia ; (8) laboratory findings in 14 days before
11 operation meet the criteria; (9) informed consents must be signed before the beginning
12 of any procedures in the study.
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27 **4 Exclusion criteria**

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29 Subjects may not enter the trial with one of the following : (1) cervical esophageal
30 cancer and adenocarcinoma of the oesophagogastric junction; (2) history of thoracic or
31 abdominal operations which may affect the study; (3) can't tolerate tracheal intubation
32 and general anesthesia; (4) severe comorbidities such as any unstable systemic
33 disease, including active infection, uncontrolled hypertension, angina happening in
34 three months, congestive heart failure, myocardial infarction happened in six months
35 before adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.; (5)
36 poor compliance of follow-up; (6) pregnant or lactating women; (7) ECOG PS scores $>$
37 2; (8) other patients considered to be unqualified.
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55 **5 Ethics**

56 The trial is conducted in accordance with the principles of the Declaration of Helsinki
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4 and ICH-GCP, local laws and regulations. The study protocol has been approved by
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6 the Institutional Ethics Committees of all participating institutions. During the study,
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8 all modifications, extensions and updates of trial procedures should be reviewed and
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10 approved by the medical ethics committee in every participating center.
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13 14 15 16 **6 Randomization**

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18 When the eligible patients are confirmed and informed consent is obtained, the
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20 researchers login through the trial randomization system and input the number of
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22 patient and other patients' related informations. Then the patient will be randomized
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24 to open three-stage transthoracic esophagectomy group or minimally invasive
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26 thoraco-laparoscopic esophagectomy group through a group number produced by
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28 SPSS software.
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33 34 **7 Trial intervention (Surgical technique)**

35 36 *Minimally invasive thoraco-laparoscopic esophagectomy*

37 38 *Thoracoscopic phase*

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40 Minimally invasive thoraco-laparoscopic esophagectomy was described previously
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42 [1]. The patient's posture is placed in the left lateral decubitus position. The position
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44 of the double-lumen tube was verified, and single-lung ventilation was used. Four
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46 thoracoscopic ports were established. A 10 mm port was placed at the seventh
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48 intercostals space, just along the anterior axillary line, for the camera. Another 10mm
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50 port was placed at the eighth or ninth intercostals space, posterior to the axillary line,
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52 for the dissection instrument (ultrasonic coagulating shears) and passage of the
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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, along 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

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4 were then divided after retraction of the stomach anteriorly. The left gastric vessel was
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6 divided at its origin from the celiac trunk with an endoscopic gastrointestinal
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8 anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were
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10 included in the resection. Subsequently, the right crus was visualized and dissected,
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12 followed by dissecting and defining the left crura of the diaphragm. The abdominal
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14 esophagus was dissected as far as possible toward the distal end. Pyloroplasty was not
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16 routinely performed. The abdomen is inspected to make sure that hemostasis is
17
18 adequate and the incisions are closed.
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23 ***Cervical anastomosis***

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

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48 As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure
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50 is followed in the open group. The first stage is started with a right posterolateral
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52 thoracotomy. The mediastinal pleura overlying the esophagus are divided with
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54 electrotome. The thoracic esophagus, alone with the periesophageal tissue and
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4 mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the
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6 level of inlet of thorax. The second stage is the mobilization of the stomach which is
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8 started with the division of the greater curvature using ultrasonic coagulating shears.
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11 The short gastric vessels were divided with ultrasonic coagulating shears as well. The
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13 gastrocolic omentum was then divided, with care taken to preserve the right
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15 gastroepiploic artery. The posterior attachments of the stomach were then divided
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17 after retraction of the stomach anteriorly. The left gastric vessel was divided at its
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19 origin from the celiac trunk with sutures. Lymphatic tissues around vessels were
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21 included in the resection. Subsequently, the abdominal esophagus was dissected as far
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23 as possible toward the distal end. Pyloroplasty was not routinely performed. The
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25 abdomen is inspected to make sure that hemostasis is adequate and the incisions are
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27 closed. For the last stage, the cervical incision is made and then anastomosis is to be
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29 performed like minimally invasive esophagectomy.
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36 **8 Sample size calculation**

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38 According to the literatures, the incidence of respiratory complications after
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40 esophagectomy for esophageal carcinoma was 27%-31%^{2,3}. Therefore, we plan to
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42 decrease incidence rate of respiratory complications from 30% to 20% in minimally
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44 invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral
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46 significance level of $\alpha=0.025$ and a power of $\beta=0.8$. after adding 10% loss of the
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48 sample, thus 324 patients in each group will be needed and a total of 648 patients will
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50 finally be enrolled into the study.
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56 **9 Statistical analysis**

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4 Statistical analyses were carried out using SPSS software for Windows, version 16.0
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6 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm
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8 standard deviation and compared using Student's t-test or ANOVA test. Categorical
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10 variables were reported as absolute numbers (frequency percentages) and analyzed
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12 using χ^2 test. The survival was estimated by means of Kaplan-Meier curves, and
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14 survival was compared using log-rank test. A two-tailed P value < 0.05 was
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16 considered statistically significant.
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20 21 22 23 24 **Discussion**

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26 This is the largest multi-center prospective randomized controlled trial designed to
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28 compare open three-stage transthoracic esophagectomy and minimally invasive
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30 thoraco-laparoscopic esophagectomy for esophageal cancer in China. We hope the
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32 results of this study add new evidence to support the use of MIE in surgical treatment
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34 of esophageal cancer.
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38 39 **List of abbreviations**

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41 MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome;
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43 VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing
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45 capacity of the lung for carbon monoxide; EORTC: European Organization for
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47 Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT:
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49 multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS:
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51 performance status.
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55 56 **Acknowledgements**

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4 The authors thank the funding of Capital health technology development priorities
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6 research project (No.2014-1-4021).
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8 9 **Authors' contributions**

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11 MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation,
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13 supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY,
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15 DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and
16
17 inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is
18
19 responsible for the present paper; All authors read and approved the final manuscript.
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23 24 **Competing interests**

25
26 The authors declare that they have no competing interests.
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29 **Ethics and dissemination** The trial is registered at ClinicalTrials.gov on 26 January
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31 2015 (NCT number 02355249). The findings of this trial will be disseminated to
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33 patients and through peer-reviewed publications and international presentations.
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37 **Funding:** This work was supported by Capital health technology development
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39 priorities research project, grant number: No.2014-1-4021.
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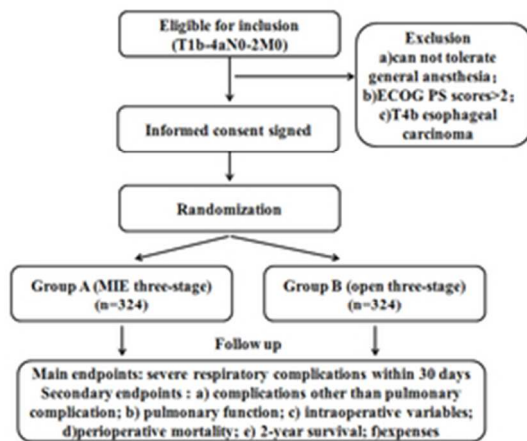
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Figure legend

Figure 1 Flow chart of the study.

For peer review only



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

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-008328.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2015
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Primary Subject Heading:	Oncology

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Secondary Subject Heading:	Surgery
Keywords:	Thoracic surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Adult oncology < ONCOLOGY

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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 per 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

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3 including blood loss, operative time, the number and location of lymph nodes
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5 dissected, and mortality in hospital, the length of hospital stay, total expenses in
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7 hospital, mortality within 30 days, survival rate after two years, postoperative pain,
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9 and HRQoL. Three hundred and twenty four patients in each group will be needed
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11 and a total of 648 patients will finally be enrolled into the study.
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19 **Ethics and dissemination** The study protocol has been approved by the Institutional
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21 Ethics Committees of all participating institutions. The findings of this trial will be
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23 disseminated to patients and through peer-reviewed publications and international
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25 presentations.
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28 **Study registration number** The trial is registered at ClinicalTrials.gov on 26
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30 January 2015 (NCT number 02355249).
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Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide¹. 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 per 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China². 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 rate⁷. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction⁸. 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 approach⁹⁻¹³.

Apart from observational studies⁹⁻¹³, two finished randomized controlled trials Netherlands brought promising results for MIE^{14,15}. In the Netherlands study¹⁴, 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.

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4 Moreover the technically complications in this trial were the same in the two groups,
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6 after neoadjuvant therapy. However, multiple surgical procedures were used in the
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8 study, and the complication rate was higher than those in previous reports⁹⁻¹⁴ In the
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10 French study¹⁵, Mariette et al found that the rate of pulmonary complication was
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12 significant lower in MIE group than in open esophagectomy group. The procedure
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14 used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using
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16 Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy.
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18 There are several ongoing randomized trials regarding the comparison of minimally
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20 invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects¹⁶⁻¹⁹.
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22 The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE
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24 vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and
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26 laparotomy)¹⁶. The procedures used in ROMIO study include open or MIE Ivor-Lewis
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28 procedure. Other three ongoing RCTs used Mckeown MIE procedure¹⁷⁻¹⁹.The
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30 ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE
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32 versus open Mckeown esophagectomy for resectable esophageal cancer¹⁷.
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34 Robot-assisted MIE received popularity in developing and developed countries in
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36 recent years^{20,21}. However, it has not been widely used as thoraco-laparoscopic MIE.
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38 NCT02017002 is a trial which aims to compare the outcomes of Ivor Lewis and
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40 tri-incision approaches for patients with esophageal cancer in Taiwan¹⁸.
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42 NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy
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44 followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou
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46 China¹⁹. The proctol used in study NCT02188615 was Mckeown MIE with or
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4 without neo-adjuvant chemoradiotherapy. Although guidelines are supportive of
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6 neo-adjuvant chemoradiotherapy plus surgery over surgery alone²², the reported
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8 studies lacked well-designed series, almost all mixing stages and types of tumor²³.
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10 Therefore, surgeons and oncologists might have different opinions about which
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12 modality to recommend, especially in clinical stage II or III. Although TIME and
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14 MIRO trial reported advantages of MIE over open esophagectomy, currently the
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16 majority of esophageal surgery is done by means of open approach worldwide²³.
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18 Therefore, more studies are needed to clarify the role of MIE in the surgical treatment
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20 of esophageal cancer. Here we aims to conduct a multicenter prospective randomized,
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22 open controlled trial, in order to evaluate the effectiveness of MIE versus open
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24 esophagectomy through a McKeown procedure for the surgical treatment of
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26 resectable esophageal cancer. We hope the results of our study will provide high level
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28 clinical evidence to support the routine use of MIE.
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39 **Methods and analysis**

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41 This is a three year multicenter prospective randomized, open and parallel controlled
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43 trial, which aims to compare the effectiveness of minimally invasive
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45 thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy
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47 for resectable esophageal cancer.
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51 Patients with resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 are
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53 eligible for inclusion using Chest CT preoperatively²⁴. Cervical esophageal cancer
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55 and adenocarcinoma of the esophagogastric junction (GEJ) are excluded. In China,
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4 cancer of cervical esophagus are treated mainly with radiotherapy, and cancer of GEJ
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6 is resected via single left thoracic approach. Patients are divided into two groups:
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9 group A and group B. Group A patients receive McKeown MIE which involve
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11 thoracoscopic esophagectomy and laparoscopic gastric mobilization with cervical
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13 anastomosis. Group B patients receive open McKeown esophagectomy involves a
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15 right thoracotomy and laparotomy with cervical anastomosis. All patients received
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17 two field lymphedectomy which involve resection of lymph nodes in the thorax and
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19 abdomen. The flow chart for the trial is showed in Figure 1. Neo-adjuvant
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21 chemotherapy will be performed for patients according to local guidelines of
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23 participating cancer.
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31 **1 Objectives**

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34 The primary endpoints were major respiratory complications within 30 days after
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36 operation. These respiratory complications involve respiratory distress or failure after
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38 operation with continuation of mechanical ventilation, pulmonary atelectasis
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40 required sputum suction by bronchocopy, pneumonia required specific antibiotics
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42 confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and
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44 acute respiratory distress syndrome (ARDS).
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49 The secondary endpoints include other postoperative complications not involved in
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51 the primary endpoints according to systematic classification of morbidity and
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53 mortality after thoracic surgery²⁵. Other secondary endpoints include change of
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55 pulmonary function preoperatively and three months postoperatively, intraoperative
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3 variables involve volume of blood loss, duration of operation, the number and
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5 location of lymph nodes dissected, postoperative pain scale evaluated by pain-score
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7 and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital
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9 mortality and thirty days mortality rate, the length of hospital stay, total expenses in
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11 hospital, two-year survival rate and 5 year survival. Besides, the laboratory data
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13 include C-reactive protein, interleukin-6 from blood samples will be tested in the third
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15 and seventh day postoperatively in order to analyze the influences of MIE on
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17 surgery-related inflammatory reaction of the patients postoperatively.
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26 **2 Participating surgeons and hospitals**

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28 All operations in the study are to be performed by surgeons with sufficient experience
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30 and skill in both open three-stage transthoracic esophagectomy and minimally
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32 invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases
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34 of MIE annually was determined to be sufficient experience and skill in our study. In
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36 order to prevent institution bias, only hospital with high volume (more than 30 cases
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38 of MIE annually) participate the study.
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44 Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer
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46 Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan
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48 Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology,
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50 Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University;
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52 Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan,
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54 China; The First Affiliated Hospital of Chongqing Medical University, Chongqing,
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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) $18 \leq \text{age} \leq 75$; (5) ECOG PS score ≤ 2 ; (6) with a life expectancy ≥ 12 months; (7) tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preoperatively; (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 oesophagogastric junction; (2) history of thoracic or abdominal operations which may affect the study; (3) can't tolerate tracheal intubation

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4 and general anesthesia as determined by anesthesiologist preoperatively; (4)severe
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6 comorbidities such as any unstable systemic disease, including active infection,
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8 uncontrolled hypertension, angina happening in three months, congestive heart failure,
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10 myocardial infarction happened in six months before adoption, severe arrhythmias,
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12 and liver, kidney or other metabolic diseases.; (5)poor compliance of follow-up;(6)
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14 pregnant or lactating women; (7)ECOG PS scores > 2; (8)other patients considered to
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16 be unqualified such as patients who do not agree to participate the trial.
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24 **5 Ethics**

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26 The trial is conducted in accordance with the principles of the Declaration of Helsinki
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28 and ICH-GCP, local laws and regulations. The study protocol has been approved by
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30 the Institutional Ethics Committees of all participating institutions. During the study,
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32 all modifications, extensions and updates of trial procedures should be reviewed and
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34 approved by the medical ethics committee in every participating center.
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41 **6 Randomization**

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43 When the eligible patients are confirmed and informed consent is obtained, the
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45 researchers login through the trial randomization system and input the number of
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47 patient and other patients' related informations. Then the patient will be randomized
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49 to open three-stage transthoracic esophagectomy group or minimally invasive
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51 thoraco-laparoscopic esophagectomy group through a group number produced by
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53 SPSS software.
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7 Trial intervention (Surgical technique)

Minimally invasive thoraco-laparoscopic esophagectomy

Thoracoscopic phase

Minimally invasive thoraco-laparoscopic esophagectomy was described previously¹³

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, along 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

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4 and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal
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6 lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube
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8 was routinely placed.
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10 11 *Laparoscopic phase* 12

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14 The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH₂O)
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16 was established by CO₂ injection through an umbilical port. A total of five abdominal
17
18 ports (three 5 mm and two 10mm) were used. After placement of the ports, the first
19
20 step of the laparoscopic phase is an exploration of the abdomen to rule out advanced
21
22 disease. The mobilization of the stomach was started with the division of the greater
23
24 curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short
25
26 gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic
27
28 omentum was then divided, with care taken to preserve the right gastroepiploic artery.
29
30 The posterior attachments of the stomach were then divided after retraction of the
31
32 stomach anteriorly. The left gastric vessel was divided at its origin from the celiac
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34 trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock.
35
36 Lymphatic tissues around vessels were included in the resection. Subsequently, the
37
38 right crus was visualized and dissected, followed by dissecting and defining the left
39
40 crura of the diaphragm. The abdominal /distal esophagus was dissected as far as
41
42 possible toward the distal end. The gastric conduit was made extracorporeally.
43
44 Pyloroplasty or gastric drainage procedure not routinely performed in our study. And
45
46 a feeding jejunostomy tube created was not created. Instead, we insert duodenal
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48 nutrition tube before anastomosis in the operation. The abdomen is inspected to make
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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 electro-tome. The thoracic esophagus, along 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

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4 origin from the celiac trunk with sutures. Lymphatic tissues around vessels were
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6 included in the resection. Subsequently, the abdominal esophagus was dissected as far
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8 as possible toward the distal end. Pyloroplasty was not routinely performed. The
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10 abdomen is inspected to make sure that hemostasis is adequate and the incisions are
11
12 closed. For the last stage, the cervical incision is made and then anastomosis is to be
13
14 performed like minimally invasive esophagectomy.
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19 **8 Postoperative care**

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21 The patients will be placed in intensive care unit or discharged to ward directly from
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23 operation room according to the guidelines of participating center. Assessment of
24
25 recurrent laryngeal nerve injury was done in the 1st day postoperatively. Postoperative
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27 Respiratory tract management included chest physiotherapy and early ambulation.
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29 And patient-controlled analgesia was given to every patient to control postoperative
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31 pain.
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36 **9 Sample size calculation**

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38 According to the literatures, the incidence of respiratory complications after
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40 esophagectomy for esophageal carcinoma was 27%-31%^{2,3}. Therefore, we plan to
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42 decrease incidence rate of respiratory complications from 30% to 20% in minimally
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44 invasive thoraco-laparoscopic esophagectomy. This is based on a unilateral
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46 significance level of $\alpha=0.025$ and a power of $\beta=0.8$. After adding 10% loss of the
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48 sample, thus 324 patients in each group will be needed and a total of 648 patients will
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50 finally be enrolled into the study.
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56 **10 Statistical analysis**

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4 Statistical analyses were carried out using SPSS software for Windows, version 16.0
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6 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm
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8 standard deviation and compared using Student's t-test or ANOVA test. Categorical
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10 variables were reported as absolute numbers (frequency percentages) and analyzed
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12 using χ^2 test. The survival was estimated by means of Kaplan-Meier curves, and
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14 survival was compared using log-rank test. A two-tailed P value < 0.05 was
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16 considered statistically significant.
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20 21 22 23 24 **Discussion**

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26 Although adenocarcinoma of the esophagus has become the main type of esophageal
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28 cancer in Western countries, esophageal squamous cell carcinoma is still the
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30 predominant histologic type in China. Therefore, both Ivor Lewis and McKeown
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32 esophagectomy are important in the surgical treatment of esophageal squamous cell
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34 carcinoma. Experiences from the TIME and MIRO trial were important, which
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36 concluded that MIE is not only feasible, but perhaps superior to open esophagectomy.
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38 However, there are no RCTs designed to compare the outcome of MIE McKeown
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40 procedure and open McKeown procedure for esophageal squamous cell carcinoma,
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42 except one study which aims to compare the outcomes of McKeown MIE with or
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44 without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell
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46 esophageal cancer. Therefore, we conducted this study, which aims to investigate
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48 the difference between MIE McKeown procedure and open McKeown procedure for
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50 esophageal squamous cell carcinoma.
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4 Mass et al found that less surgical trauma could lead to better preserved acute-phase
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6 and stress responses and fewer clinical manifestations of respiratory infections in
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8 patients who underwent MIE compared to patients who underwent open
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10 esophagectomy⁸. Our previous study showed that overall morbidity rate was significant
11
12 decreased in MIE McKeown group compared with open MIE McKeown group, and
13
14 no significant differences were found on the number of harvested lymph nodes¹³. For
15
16 these reasons, We hypothesize that MIE Mckeown procedure may provide a
17
18 significant decrease of major respiratory complications compared with open
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20 Mckeown procedure for esophageal squamous cell carcinoma, without comprising the
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22 oncologic clearance.
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29 This is the largest multi-center prospective randomized controlled trial designed to
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31 compare open McKeown esophagectomy and MIE McKeown esophagectomy for
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33 esophageal cancer in China. We hope the results of this study add new evidence to
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35 support the use of MIE in surgical treatment of esophageal cancer.
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39 **List of abbreviations**

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41 MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome;
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43 VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing
44
45 capacity of the lung for carbon monoxide; EORTC: European Organization for
46
47 Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT:
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49 multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS:
50
51 performance status.
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55 **Acknowledgements**

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4 The authors thank the funding of Capital health technology development priorities
5
6 research project (No.2014-1-4021).
7

8 9 **Authors' contributions**

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11 MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation,
12
13 supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY,
14
15 DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and
16
17 inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is
18
19 responsible for the present paper; All authors read and approved the final manuscript.
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23 24 **Competing interests**

25
26 The authors declare that they have no competing interests.
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Figure legend

Figure 1 Flow chart of the study.

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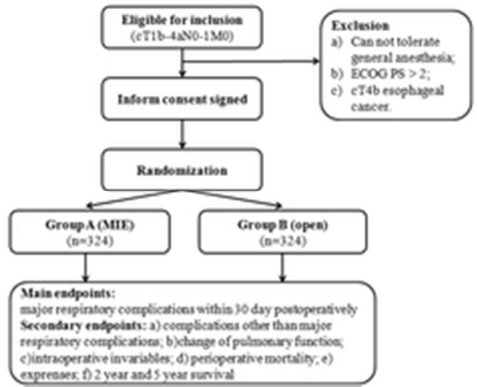


Figure 1 Flow chart of the study.
20x16mm (300 x 300 DPI)

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-008328.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Aug-2015
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Primary Subject Heading:	Oncology

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Secondary Subject Heading:	Surgery
Keywords:	Thoracic surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Adult oncology < ONCOLOGY

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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 MIE with 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

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4 on the pulmonary function, blood loss during operation, operative time, the number
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6 and location of lymph nodes dissected, and mortality in hospital, the length of hospital
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8 stay, total expenses in hospital, mortality within 30 days, survival rate after five years,
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10 postoperative pain, and health related quality of life (HRQOL). Three hundred and
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12 twenty four (324) patients in each group was considered to be necessary and a total of
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16 648 patients were enrolled into this study.
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21 **Ethics and dissemination:** This study protocol was approved by the Institutional
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23 Ethics Committees of all participating institutions. The findings of this clinical trial
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25 will be disseminated to patients and through peer-reviewed publications and
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27 international presentations.
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31 **Study registration number** This clinical trial is registered at ClinicalTrials.gov on
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33 26 January 2015 (NCT number 02355249).
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Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide¹. 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 per 100,000 person-years, according to an epidemiological statistics of incidence and death of esophageal cancer in 2009 in China². 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 rate⁷. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction⁸. 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 approach⁹⁻¹³.

Apart from observational studies⁹⁻¹³, two completed randomized controlled trials the Netherlands demonstrated promising results for MIE^{14,15}. In the Netherlands study¹⁴, 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.

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4 Moreover the technically complications in this trial were the same in the two groups,
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6 after neoadjuvant therapy. However, multiple surgical procedures were used in the
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8 study, and the complication rate was higher than those in previous reports⁹⁻¹⁴ In the
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10 French study¹⁵, Mariette et al found that the rate of pulmonary complication was
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12 significant lower in MIE group than in open esophagectomy group. The procedure
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14 used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using
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16 Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy.
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18 There are several ongoing randomized trials regarding the comparison of minimally
19
20 invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects¹⁶⁻¹⁹.
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22 The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE
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24 vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and
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26 laparotomy)¹⁶. The procedures used in ROMIO study include open or MIE Ivor-Lewis
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28 procedure. Other three ongoing RCTs used Mckeown MIE procedure¹⁷⁻¹⁹.The
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30 ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE
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32 versus open Mckeown esophagectomy for resectable esophageal cancer¹⁷.
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34 Robot-assisted MIE received popularity in developing and developed countries in
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36 recent years^{20,21}. However, it has not been widely used as thoraco-laparoscopic MIE.
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38 NCT02017002 is a trial which aims to compare the outcomes of Ivor Lewis and
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40 tri-incision approaches for patients with esophageal cancer in Taiwan¹⁸.
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42 NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy
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44 followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou
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46 China¹⁹. The proctol used in study NCT02188615 was Mckeown MIE with or
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4 without neo-adjuvant chemoradiotherapy. Although guidelines are supportive of
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6 neo-adjuvant chemoradiotherapy plus surgery over surgery alone²², the reported
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8 studies lacked well-designed series, almost all mixing stages and types of tumor²³.
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10 Therefore, surgeons and oncologists might have different opinions about which
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12 modality to recommend, especially in clinical stage II or III. Although TIME and
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14 MIRO trial reported advantages of MIE over open esophagectomy, currently the
15
16 majority of esophageal surgery is done by means of open approach worldwide²³.
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18 Therefore, more studies are needed to clarify the role of MIE in the surgical treatment
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20 of esophageal cancer. Here we aims to conduct a multicenter prospective randomized,
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22 open controlled trial, in order to evaluate the effectiveness of MIE versus open
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24 esophagectomy through a McKeown procedure for the surgical treatment of
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26 resectable esophageal cancer. The results of our study may provide high level clinical
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28 evidence to support the routine use of MIE.
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39 **Methods and analysis**

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41 This is a three year multicenter prospective randomized, open and parallel controlled
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43 trial, which aims to compare the effectiveness of minimally invasive
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45 thoraco-laparoscopic esophagectomy to open three-stage transthoracic esophagectomy
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47 for resectable esophageal cancer.
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51 Patients with resectable thoracic esophageal carcinoma in cT1b-4aN0-2M0 are
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53 eligible for inclusion using chest CT preoperatively²⁴. Ultrasonography of the upper
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55 abdomen are routinely done to rule out liver metastasis. Head CT and bone scan are
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4 indicated when patients had symptoms of central nervous system such as headache
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6 and nausea, and bone pains. Cervical esophageal cancer (definition according to
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8 AJCC cancer staging manual that the length of cervical esophagus is from the incisors
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10 are from 15 to <20 cm via endoscopic measurement) and adenocarcinoma of the
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12 esophagogastric junction (GEJ) are excluded. In China, cancer of cervical esophagus
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14 are treated mainly with radiotherapy, and cancer of GEJ is resected via single left
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16 thoracic approach. Patients are divided into two groups: group A and group B. Group
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18 A patients received McKeown MIE which involve thoracoscopic esophagectomy and
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20 laparoscopic gastric mobilization with cervical anastomosis. Group B patients
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22 received open McKeown esophagectomy which involves a right thoracotomy and
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24 laparotomy with cervical anastomosis. All patients received two field lymphedectomy
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26 which involve resection of lymph nodes in the thorax and abdomen. The flow chart
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28 for the trial is showed in Figure 1. Neo-adjuvant chemotherapy will be performed for
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30 patients according to local guidelines of participating cancer.
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41 **1 Objectives**

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43 The primary endpoint was to assess the major respiratory complications within 30
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45 days after operation. These respiratory complications involve respiratory distress or
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47 failure after operation with continuation of mechanical ventilation, pulmonary
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49 atelectasis required sputum suction by bronchocopy, pneumonia required specific
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51 antibiotics confirmed by thorax X-ray or CT scan of thorax and a positive sputum
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53 culture, and acute respiratory distress syndrome (ARDS).
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4 The secondary endpoints include other postoperative complications not involved in
5
6 the primary endpoints according to systematic classification of morbidity and
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8 mortality after thoracic surgery²⁵. Other secondary endpoints include change of
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10 pulmonary function preoperatively and three months postoperatively, intraoperative
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12 variables involve volume of blood loss, duration of operation, the number and
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14 location of lymph nodes dissected, postoperative pain scale evaluated by pain-score
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16 and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital
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18 mortality and thirty days mortality rate, the length of hospital stay, total expenses in
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20 hospital, two-year survival rate and 5 year survival rate. Besides, the laboratory data
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22 included blood C-reactive protein and interleukin-6 were measured in the third and
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24 seventh day postoperatively in order to analyze the influences of MIE on
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26 surgery-related inflammatory reaction of the patients postoperatively.
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36 **2 Participating surgeons and hospitals**

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38 All operations in the study are to be performed by surgeons with sufficient experience
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40 and skill in both open three-stage transthoracic esophagectomy and minimally
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42 invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases
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44 of MIE annually was determined to be sufficient experience and skill in our study. In
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46 order to prevent institution bias, only hospital with high volume (more than 30 cases
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48 of MIE annually) participate the study.
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54 Thirteen Chinese academic centers or hospitals participated in the trial: Cancer
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56 Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan
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4 Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology,
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6 Peking University, Beijing, China; Chaoyang Hospital, Capital Medical of University;
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8 Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan,
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10 China; The First Affiliated Hospital of Chongqing Medical University, Chongqing,
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12 China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of
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14 Guangxi Autonomous Region, Guangxi Autonomous Region, China; Hunan Cancer
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16 Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's
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18 Hospital, Jiangxi, China; The First Hospital of China Medical University, Liaoning,
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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 metastasis preoperatively ; (3) esophageal carcinoma can be resected initially by multidisciplinary treatment (MDT), or ones can be resected after neoadjuvant therapy; (4) $18 \leq \text{age} \leq 75$; (5) ECOG PS score ≤ 2 ; (6) with a life expectancy ≥ 12 months; (7) tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preoperatively; (8) laboratory findings including liver and kidney function, and electrolyte findings in 14 days before operation meet the criteria, laboratory findings

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4 including abnormal liver and renal function which exclude a patient from immediate
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6 surgery, and patients then received medical therapies to recover liver and renal
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8 function; (9) informed consents must be signed before the beginning of any
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10 procedures in the study.
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13 14 15 16 **4 Exclusion criteria** 17

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19 Subjects may not enter the trial when they met the following criteria: (1)cervical
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21 esophageal cancer and adenocarcinoma of the oesophagogastric junction; (2)history of
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23 thoracic or abdominal operations which may affect the study; (3) can't tolerate
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25 tracheal intubation and general anesthesia as determined by anesthesiologist
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27 preoperatively; (4)severe comorbidities such as any unstable systemic disease,
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29 including active infection, uncontrolled hypertension, angina happening in three
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31 months, congestive heart failure, myocardial infarction happened in six months before
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33 adoption, severe arrhythmias, and liver, kidney or other metabolic diseases.; (5)poor
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35 compliance of follow-up;(6)pregnant or lactating women; (7)ECOG PS scores > 2; (8)
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37 other patients considered to be unqualified such as patients who do not agree to
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39 participate the trial.
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49 50 **5 Ethics** 51

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53 The trial is conducted in accordance with the principles of the Declaration of Helsinki
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55 and ICH-GCP, local laws and regulations. The study protocol has been approved by
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57 the Institutional Ethics Committees of all participating institutions. During the study,
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4 all modifications, extensions and updates of trial procedures should be reviewed and
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6 approved by the medical ethics committee in every participating center.
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10 11 **6 Randomization**

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14 When the eligibility of the patients was confirmed and informed consent was
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16 obtained, the researchers login through the trial randomization system and input the
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18 number of patient and other patients' related information. Then the patient will be
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20 randomized to open three-stage transthoracic esophagectomy group or minimally
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22 invasive thoraco-laparoscopic esophagectomy group through a group number
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24 produced by SPSS software.
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28 29 **7 Trial intervention (Surgical technique)**

30 31 *Minimally invasive thoraco-laparoscopic esophagectomy*

32 33 *Thoracoscopic phase*

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35 Minimally invasive thoraco-laparoscopic esophagectomy was described previously¹³
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38 The patient's posture is placed in the left lateral decubitus position. The position of
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40 the double-lumen tube was verified, and single-lung ventilation was used. Four
41
42 thoracoscopic ports were established. A 10 mm port was placed at the seventh
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44 intercostals space, just along the anterior axillary line, for the camera. Another 10mm
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46 port was placed at the eighth or ninth intercostals space, posterior to the axillary line,
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48 for the dissection instrument (ultrasonic coagulating shears) and passage of the
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50 end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port
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52 was placed in the anterior axillary line, at the third or fourth intercostals space, and
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4 this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow
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6 exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to
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8 place the instruments for retraction and counter traction. The inferior pulmonary
9
10 ligament was divided. The mediastinal pleura overlying the esophagus was divided
11
12 and opened to the level of the azygous vein to expose the thoracic esophagus. The
13
14 azygous vein was then dissected and divided with an endoscopic vascular stapler or
15
16 Hem-lock. The thoracic esophagus, along with the periesophageal tissue and
17
18 mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the
19
20 level of inlet of the thorax. Mediastinal lymphadenectomy is done for every patient
21
22 including region of left recurrent and right subclavian, paratracheal, subcarinal, left
23
24 and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal
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26 lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube
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28 was routinely placed. But we do not place anastomotic drains routinely.
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36 ***Laparoscopic phase***

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38 The patient was placed in a supine position. A pneumoperitoneum (12-14 cmH₂O)
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40 was established by CO₂ injection through an umbilical port. A total of five abdominal
41
42 ports (three 5 mm and two 10mm) were used. After placement of the ports, the first
43
44 step of the laparoscopic phase is an exploration of the abdomen to rule out advanced
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46 disease. The mobilization of the stomach was started with the division of the greater
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48 curvature using a Harmonic scalpel (Ethicon Endo-Surgery, OH, USA). The short
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50 gastric vessels were divided with ultrasonic coagulating shears. The gastrocolic
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52 omentum was then divided, with care taken to preserve the right gastroepiploic artery.
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4 The posterior attachments of the stomach were then divided after retraction of the
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6 stomach anteriorly. The left gastric vessel was divided at its origin from the celiac
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8 trunk with an endoscopic gastrointestinal anastomosis (GIA) stapler or Hem-lock.
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10 Lymphatic tissues around vessels were included in the resection. Subsequently, the
11
12 right crus was visualized and dissected, followed by dissecting and defining the left
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14 crura of the diaphragm. The abdominal /distal esophagus was dissected as far as
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16 possible toward the distal end. The gastric conduit was made extracorporeally. As the
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18 length of port was 4 cm in our study which made the extracorporeal gastric conduit
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20 creation easily. Pyloroplasty or gastric drainage procedure not routinely performed in
21
22 our study. And a feeding jejunostomy tube created was not created. Instead, we insert
23
24 duodenal nutrition tube before anastomosis in the operation. After
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26 esophagogastronomy was completed, nasogastric tube was inserted and was bound
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28 with duodenal feeding tube together, Then duodenal feeding tube was pulled out with
29
30 nasogastric tube. The surgeon adjusted the location of duodenal feeding tube through
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32 the abdominal port (4 cm) and made sure that the duodenal feeding tube was placed in
33
34 the duodenum. The abdomen is inspected to make sure that hemostasis is adequate
35
36 and the incisions are closed.

37 38 39 40 41 42 43 44 45 46 ***Cervical anastomosis***

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

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4 abdomen is inspected to make sure that hemostasis is adequate and the incisions are
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6 closed. For the last stage, the cervical incision is made and then anastomosis is to be
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8 performed like minimally invasive esophagectomy.
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10 11 **8 Postoperative care**

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14 The patients will be placed in intensive care unit or discharged to ward directly from
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16 operation room according to the guidelines of participating center. As the injury of
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18 recurrent laryngeal nerve may lead to hoarseness. We made regular round in the 1st
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20 day postoperatively or when the patient can speak after liberation from mechanical
21
22 ventilation because of respiratory insufficiency, to make sure that whether the patient
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24 had hoarseness. Then we will make indirect laryngoscope to confirm the diagnosis of
25
26 recurrent laryngeal nerve injury. Postoperative respiratory tract management included
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28 chest physiotherapy and early ambulation. And patient-controlled analgesia was given
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30 to every patient to control postoperative pain.
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36 37 **9 Sample size calculation**

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39 According to the literatures, the incidence of respiratory complications after
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41 esophagectomy for esophageal carcinoma was 27%-31%^{2,3}. Therefore, we plan to
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43 decrease incidence rate of respiratory complications from 30% to 20% in the patient
44
45 group who received minimally invasive thoraco-laparoscopic esophagectomy. This is
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47 based on a unilateral significance level of $\alpha=0.025$ and a power of $\beta=0.8$. After adding
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49 10% loss of the sample, thus 324 patients in each group will be needed and a total of
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51 648 patients will finally be enrolled into the study.
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56 57 **10 Statistical analysis**

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4 Statistical analyses were carried out using SPSS software for Windows, version 16.0
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6 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm
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8 standard deviation and compared using Student's t-test or ANOVA test. Categorical
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10 variables were reported as absolute numbers (frequency percentages) and analyzed
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12 using χ^2 test. The survival was estimated by means of Kaplan-Meier curves, and
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14 survival was compared using log-rank test. A two-tailed P value < 0.05 was
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16 considered statistically significant.
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20 21 22 23 24 **Discussion**

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26 Although adenocarcinoma of the esophagus has become the main type of esophageal
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28 cancer in Western countries, esophageal squamous cell carcinoma is still the
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30 predominant histologic type in China. Therefore, both Ivor Lewis and McKeown
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32 esophagectomy are important in the surgical treatment of esophageal squamous cell
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34 carcinoma. Experiences from the TIME and MIRO trial were important, which
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36 concluded that MIE is not only feasible, but perhaps superior to open esophagectomy.
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38 However, there are no RCTs designed to compare the outcome of MIE McKeown
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40 procedure and open McKeown procedure for esophageal squamous cell carcinoma,
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42 except one study which aims to compare the outcomes of McKeown MIE with or
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44 without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell
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46 esophageal cancer. Therefore, we conducted this study, which aims to investigate
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48 the difference between MIE McKeown procedure and open McKeown procedure for
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50 esophageal squamous cell carcinoma.
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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 esophagectomy⁸. 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 nodes¹³. 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 squamous cell carcinoma, without comprising the oncologic clearance.

To our knowledge, this is the largest multi-center prospective randomized controlled trial designed to compare open McKeown esophagectomy and MIE McKeown 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.

Acknowledgements

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4 The authors thank the funding of Capital health technology development priorities
5
6 research project (No.2014-1-4021).
7

8 9 **Authors' contributions**

10
11 MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation,
12
13 supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY,
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15 DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and
16
17 inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is
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19 responsible for the present paper; All authors read and approved the final manuscript.
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23 24 **Competing interests**

25
26 The authors declare that they have no competing interests.
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Figure legend

Figure 1 Flow chart of the study.

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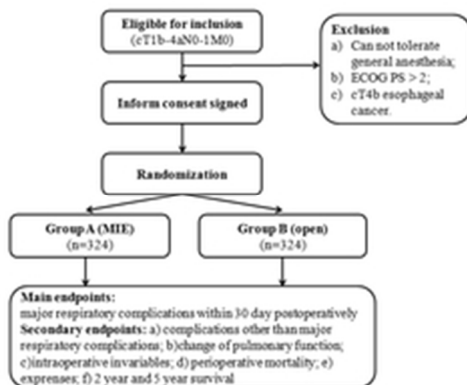


Figure 1 Flow chart of the study.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2015-008328.R3
Article Type:	Protocol
Date Submitted by the Author:	25-Sep-2015
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Primary Subject Heading:	Oncology

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Secondary Subject Heading:	Surgery
Keywords:	Thoracic surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Adult oncology < ONCOLOGY

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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 per 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

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

Esophageal cancer is the eighth most common cause of cancer worldwide¹. 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 per 100 000 person-years, according to a statistics of incidence and death of esophageal cancer in 2009 in China². 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 rate⁷. The mechanisms of MIE may lie in minimization of surgery injury reaction and inflammatory reaction⁸. 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 approach⁹⁻¹³.

Apart from observational studies⁹⁻¹³, two finished randomized controlled trials Netherlands brought promising results for MIE^{14,15}. In the Netherlands study¹⁴, 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

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4 the patients were operated by 3 stage procedure, being adenocarcinoma and SCC.
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6 Moreover the technically complications in this trial were the same in the two groups,
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8 after neoadjuvant therapy. However, multiple surgical procedures were used in the
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10 study, and the complication rate was higher than those in previous reports⁹⁻¹⁴ In the
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12 French study¹⁵, Mariette et al found that the rate of pulmonary complication was
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14 significant lower in MIE group than in open esophagectomy group. The procedure
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16 used in the MIRO trial was Ivor-Lewis procedure. However, a beneficial using
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18 Ivor-Lewis MIE in that study may not be generalized to Mckeown esophagectomy.
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21 There are several ongoing randomized trials regarding the comparison of minimally
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23 invasive versus open esophagectomy, with enrollment of over 100 to 850 subjects¹⁶⁻¹⁹.
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26 The ROMIO trial was a 3 arms trial which aims to compare the outcomes of total MIE
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28 vs hybrid MIE vs conventional open esophagectomy (open thoracotomy and
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30 laparotomy)¹⁶. The procedures used in ROMIO study include open or MIE Ivor-Lewis
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32 procedure. Other three ongoing RCTs used Mckeown MIE procedure¹⁷⁻¹⁹.The
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ROBOT trial was designee to compare the outcomes of robot-assisted Mckeown MIE
versus open Mckeown esophagectomy for resectable esophageal cancer¹⁷.
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 Taiwan¹⁸.
NCT02188615 is trial that investigate outcomes of neo-adjuvant chemoradiotherapy
followed by MIE for squamous cell esophageal cancer (NACRFMIE) in Taizhou

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China¹⁹. The protocol 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 alone²², the reported studies lacked well-designed series, almost all mixing stages and types of tumor²³. 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 worldwide²³. Therefore, more studies are needed to clarify the role of MIE in the surgical treatment of esophageal cancer. Here we aim 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

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4 bone scan²⁴. We do not include a PET/CT as a preoperative workup because medical
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6 insurance does not cover the expense of a PET/CT. Cervical esophageal cancer and
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8 adenocarcinoma of the esophagogastric junction (GEJ) are excluded. In China, cancer
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10 of cervical esophagus are treated mainly with radiotherapy, and cancer of GEJ is
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12 resected via single left thoracic approach. Patients are divided into two groups: group
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14 A and group B. Group A patients receive McKeown MIE which involve thoracoscopic
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16 esophagectomy and laparoscopic gastric mobilization with cervical anastomosis.
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18 Group B patients receive open McKeown esophagectomy involves a right
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20 thoracotomy and laparotomy with cervical anastomosis. All patients received two
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22 field lymphedectomy which involve resection of lymph nodes in the thorax and
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24 abdomen. The flow chart for the trial is showed in Figure 1. Neo-adjuvant
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26 chemotherapy will be performed for patients according to local guidelines of
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28 participating cancer.
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39 **1 Objectives**

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41 The primary endpoints were major respiratory complications within 30 days after
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43 operation. These respiratory complications involve respiratory distress or failure after
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45 operation with continuation of mechanical ventilation, pulmonary atelectasis
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47 required sputum suction by bronchocopy, pneumonia required specific antibiotics
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49 confirmed by thorax X-ray or CT scan of thorax and a positive sputum culture, and
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51 acute respiratory distress syndrome (ARDS).
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56 The secondary endpoints include other postoperative complications not involved in
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4 the primary endpoints according to systematic classification of morbidity and
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6 mortality after thoracic surgery²⁵. Other secondary endpoints include change of
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8 pulmonary function preoperatively and three months postoperatively, intraoperative
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10 variables involve volume of blood loss, duration of operation, the number and
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12 location of lymph nodes dissected, postoperative pain scale evaluated by pain-score
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14 and quality of life questionnaires (EORTC QLQ-C30 and QLQ-0ES18) , in-hospital
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16 mortality and thirty days mortality rate, the length of hospital stay, total expenses in
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18 hospital, two-year survival rate and 5 year survival. Besides, the laboratory data
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20 include C-reactive protein, interleukin-6 from blood samples will be tested in the third
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22 and seventh day postoperatively in order to analyze the influences of MIE on
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24 surgery-related inflammatory reaction of the patients postoperatively.
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33 **2 Participating surgeons and hospitals**

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35 All operations in the study are to be performed by surgeons with sufficient experience
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37 and skill in both open three-stage transthoracic esophagectomy and minimally
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39 invasive thoraco-laparoscopic esophagectomy. A surgeon who accomplished 30 cases
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41 of MIE annually was determined to be sufficient experience and skill in our study. In
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43 order to prevent institution bias, only hospital with high volume (more than 30 cases
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45 of MIE annually) participate the study.
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51 Thirteen Chinese academic centers or hospitals will participate in the trial: Cancer
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53 Hospital of Chinese Academy of Medical Sciences, Beijing, China; Sino-Japan
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55 Friendship Hospital, Beijing, China; Beijing Cancer Hospital & School of Oncology,
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6 Peking University Third Hospital, Beijing, China; Sichuan Cancer Hospital, Sichuan,
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8 China; The First Affiliated Hospital of Chongqing Medical University, Chongqing,
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10 China; The First Hospital of Quanzhou City, Fujian, China; The People's Hospital of
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14 Hospital, Hunan, China; Nantong Tumor Hospital, Jiangsu, China; Jiangxi People's
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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) $18 \leq \text{age} \leq 75$; (5) ECOG PS score ≤ 2 ; (6) with a life expectancy ≥ 12 months; (7) tolerate tracheal intubation and general anesthesia as determined by anesthesiologist preoperatively; (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

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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 as determined by anesthesiologist preoperatively; (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

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4 to open three-stage transthoracic esophagectomy group or minimally invasive
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6 thoraco-laparoscopic esophagectomy group through a group number produced by
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8 SPSS software.
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10 11 **7 Trial intervention (Surgical technique)**

12 13 *Minimally invasive thoraco-laparoscopic esophagectomy*

14 15 *Thoracoscopic phase*

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17 Minimally invasive thoraco-laparoscopic esophagectomy was described previously¹³

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19 The patient's posture is placed in the left lateral decubitus position. The position of
20
21 the double-lumen tube was verified, and single-lung ventilation was used. Four
22
23 thoracoscopic ports were established. A 10 mm port was placed at the seventh
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25 intercostals space, just along the anterior axillary line, for the camera. Another 10mm
26
27 port was placed at the eighth or ninth intercostals space, posterior to the axillary line,
28
29 for the dissection instrument (ultrasonic coagulating shears) and passage of the
30
31 end-to-end circular stapler (EEA; Covidien or Johnson) or Hem-lock. A 5 mm port
32
33 was placed in the anterior axillary line, at the third or fourth intercostals space, and
34
35 this was used to pass a fan-shaped retractor to retract the lung anteriorly and allow
36
37 exposure of the esophagus. A 5 mm port was placed just below the subscapular tip to
38
39 place the instruments for retraction and counter traction. The inferior pulmonary
40
41 ligament was divided. The mediastinal pleura overlying the esophagus was divided
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43 and opened to the level of the azygous vein to expose the thoracic esophagus. The
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45 azygous vein was then dissected and divided with an endoscopic vascular stapler or
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47 Hem-lock. The thoracic esophagus, alone with the periesophageal tissue and
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4 mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the
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6 level of inlet of the thorax. Mediastinal lymphadenectomy is done for every patient
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8 including region of left recurrent and right subclavian, paratracheal, subcarinal, left
9
10 and right bronchial, lower posterior mediastinum, para-aortic, para-oesophageal
11
12 lymph nodes. The chest is inspected closely, and hemostasis is verified. Chest tube
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14 was routinely placed.
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18 **Laparoscopic phase** The patient was placed in a supine position. A
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20 pneumoperitoneum (12-14 cmH₂O) was established by CO₂ injection through an
21
22 umbilical port. A total of five abdominal ports (three 5 mm and two 40mm) were used.
23
24 After placement of the ports, the first step of the laparoscopic phase is an exploration
25
26 of the abdomen to rule out advanced disease. The mobilization of the stomach was
27
28 started with the division of the greater curvature using a Harmonic scalpel (Ethicon
29
30 Endo-Surgery, OH, USA). The short gastric vessels were divided with ultrasonic
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32 coagulating shears. The gastrocolic omentum was then divided, with care taken to
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34 preserve the right gastroepiploic artery. The posterior attachments of the stomach
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36 were then divided after retraction of the stomach anteriorly. The left gastric vessel was
37
38 divided at its origin from the celiac trunk with an endoscopic gastrointestinal
39
40 anastomosis (GIA) stapler or Hem-lock. Lymphatic tissues around vessels were
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42 included in the resection. Subsequently, the right crus was visualized and dissected,
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44 followed by dissecting and defining the left crura of the diaphragm. The abdominal
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46 /distal esophagus was dissected as far as possible toward the distal end. The gastric
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48 conduit was made extracorporeally. Pyloroplasty or gastric drainage procedure not
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4 routinely performed in our study. And a feeding jejunostomy tube created was not
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6 created. Instead, we insert duodenal nutrition tube before anastomosis in the operation.
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8 We insert duodenal feeding tube as following steps. First, prior the esophagogastric
9
10 anastomosis, we enclose a candy ball using sterile gloves peel and fix it to the front
11
12 end of the feeding tube through the small laparotomy incision. Push the feeding tube
13
14 until the front end and the candy ball lies in the duodenum, and put the rest of the
15
16 feeding tube into the gastral cavity and bound it with nasogastric tube. Then, pull
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18 nasogastric tube out from the nose and fixed. Then reinserted the nasogastric tube into
19
20 the gastric cavity. The abdomen is inspected to make sure that hemostasis is adequate
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22 and the incisions are closed.
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28 ***Cervical anastomosis***

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30 After laparoscopic phase and thoracoscopic phase, next, a 4- to 6-cm horizontal neck
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32 incision is made. The cervical esophagus is exposed. Careful dissection is performed
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34 down until the thoracic dissection plane is encountered, generally quite easily since
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36 the VATS dissection is continued well into the thoracic inlet. The esophagogastric
37
38 specimen is pulled out of the neck incision and the cervical esophagus divided high.
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40 The specimen is removed from the field. An anastomosis is performed between the
41
42 cervical esophagus and gastric tube using standard techniques (mechanical stapled or
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44 handsewn anastomosis in an end-to-side fashion).
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50 ***Open three-stage transthoracic esophagectomy***

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52 As minimally invasive thoraco-laparoscopic esophagectomy, a three-stage procedure
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54 is followed in the open group. The first stage is started with a right posterolateral
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4 thoracotomy. The mediastinal pleura overlying the esophagus are divided with
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6 electrotome. The thoracic esophagus, along with the periesophageal tissue and
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8 mediastinal lymph nodes, was circumferentially mobilized from the diaphragm to the
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10 level of inlet of thorax. The second stage is the mobilization of the stomach which is
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12 started with the division of the greater curvature using ultrasonic coagulating shears.
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14 The short gastric vessels were divided with ultrasonic coagulating shears as well. The
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16 gastrocolic omentum was then divided, with care taken to preserve the right
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18 gastroepiploic artery. The posterior attachments of the stomach were then divided
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20 after retraction of the stomach anteriorly. The left gastric vessel was divided at its
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22 origin from the celiac trunk with sutures. Lymphatic tissues around vessels were
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24 included in the resection. Subsequently, the abdominal esophagus was dissected as far
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26 as possible toward the distal end. Pyloroplasty was not routinely performed. The
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28 abdomen is inspected to make sure that hemostasis is adequate and the incisions are
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30 closed. For the last stage, the cervical incision is made and then anastomosis is to be
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32 performed like minimally invasive esophagectomy.
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41 **8 Postoperative care**

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43 The patients will be placed in intensive care unit or discharged to ward directly from
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45 operation room according to the guidelines of participating center. Assessment of
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47 recurrent laryngeal nerve injury was done in the 1st day postoperatively. Postoperative
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49 Respiratory tract management included chest physiotherapy and early ambulation.
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51 And patient-controlled analgesia was given to every patient to control postoperative
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53 pain.
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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 $\alpha=0.025$ and a power of $\beta=0.8$. 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 \pm standard deviation and compared using Student's t-test or ANOVA test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using χ^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 squamous cell carcinoma is still the predominant histologic type in China. Therefore, both Ivor Lewis and McKeown esophagectomy are important in the surgical treatment of esophageal squamous cell

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4 carcinoma. Experiences from the TIME and MIRO trial were important, which
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6 concluded that MIE is not only feasible, but perhaps superior to open esophagectomy.
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9 However, there are no RCTs designed to compare the outcome of MIE Mckeown
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11 procedure and open Mckeown procedure for esophageal squamous cell carcinoma,
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13 except one study which aims to compare the outcomes of Mckeown MIE with or
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15 without neo-adjuvant chemoradiotherapy (NCT02188615) for squamous cell
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17 esophageal cancer. Therefore, we conducted this study, which aims to investigate
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19 the difference between MIE Mckeown procedure and open Mckeown procedure for
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21 esophageal squamous cell carcinoma.
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26 Mass et al found that less surgical trauma could lead to better preserved acute-phase
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28 and stress responses and fewer clinical manifestations of respiratory infections in
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30 patients who underwent MIE compared to patients who underwent open
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32 esophagectomy⁸. Our previous study showed that overall morbidity rate was significant
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34 decreased in MIE McKeown group compared with open MIE McKeown group, and
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36 no significant differences were found on the number of harvested lymph nodes¹³. For
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38 these reasons, We hypothesize that MIE Mckeown procedure may provide a
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40 significant decrease of major respiratory complications compared with open
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42 Mckeown procedure for esophageal squamous cell carcinoma, without comprising the
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44 oncologic clearance.
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51 This is the largest multi-center prospective randomized controlled trial designed to
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53 compare open McKeown esophagectomy and MIE McKeown esophagectomy for
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55 esophageal cancer in China. We hope the results of this study add new evidence to
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4 support the use of MIE in surgical treatment of esophageal cancer.

5 6 **List of abbreviations**

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8 MIE: minimally invasive esophagectomy; ARDS: acute respiratory distress syndrome;
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10 VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing
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12 capacity of the lung for carbon monoxide; EORTC: European Organization for
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14 Research on Treatment of Cancer; QLQ: quality of life questionnaire; MDT:
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16 multidisciplinary treatment; ECOG: Eastern Cooperative Oncology Group; PS:
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18 performance status.
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23 24 **Acknowledgements**

25
26 The authors thank the funding of Capital health technology development priorities
27
28 research project (No.2014-1-4021).
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31 32 **Authors' contributions**

33
34 MJ wrote the manuscript; HJ, MJ were involved in the study design, implementation,
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36 supervision and drafting; MJ, GS, MY, XQ, YZ, LN, SK, YK, LD, CK, LH, YT, HY,
37
38 DM, XR, WZ, WW, SM, XQ, XS, and HJ were involved in the study design and
39
40 inclusion of patients in the trial; HJ is the study coordinator, obtained the grant and is
41
42 responsible for the present paper; All authors read and approved the final manuscript.
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46 47 **Competing interests**

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49 The authors declare that they have no competing interests.
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52 **Ethics and dissemination** The study protocol has been approved by the Institutional
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54 Ethics Committees of all participating institutions. The findings of this trial will be
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56 disseminated to patients and through peer-reviewed publications and international
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4 presentations.

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6 **Study registration number** The trial is registered at ClinicalTrials.gov on 26
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9 January 2015 (NCT number 02355249).

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Figure legend

Figure 1 Flow chart of the study.

For peer review only

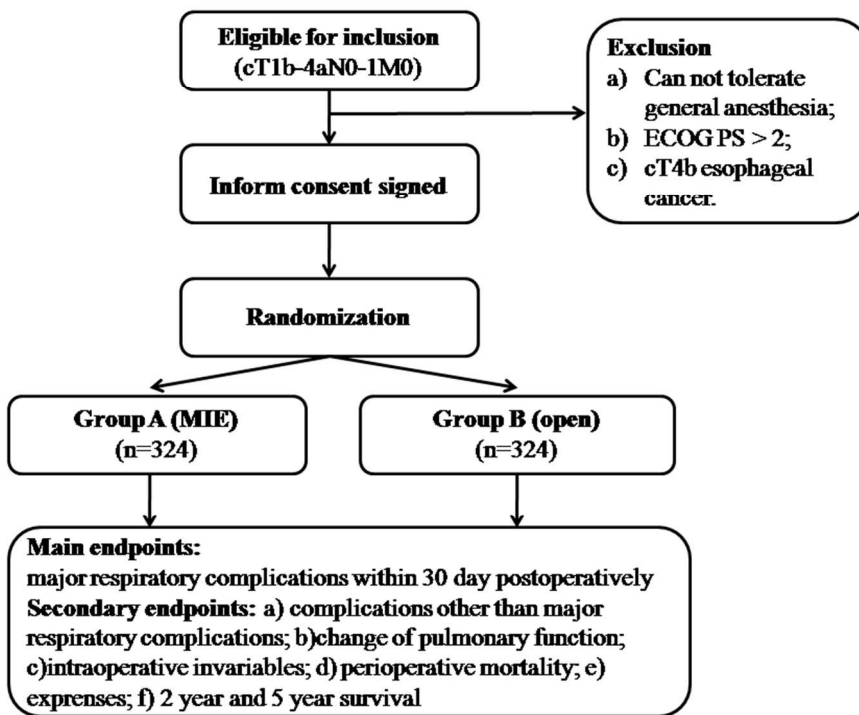


Figure 1 Flow chart of the study.
254x190mm (96 x 96 DPI)

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