Study Protocol

Transcervical versus transthoracic minimally invasive esophagectomy: a randomized and controlled trial protocol

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Background: Anatomically, the esophagus is located within the mediastinum, and thus it potentially a transcervical approach for esophagectomy, which avoids thoracic manipulation, could be an alternative to transthoracic esophagectomy for the surgical resection of esophageal cancer. A modified transcervical minimally invasive esophagectomy (MIE), laparo-gastroscopic esophagectomy (LGE), was recently introduced using an integrated gastroscope to mobilize the esophagus. As such, a randomized controlled trial (RCT) is necessary to validate its value compared to transthoracic MIE, which carries a high risk of morbidity due to thoracic manipulation.

Methods: This prospective study plans to enroll patients with resectable esophageal cancer with a pathological diagnosis of squamous cell carcinoma or adenocarcinoma patients over a 2-year period. Patients will be randomly assigned to one of 2 groups in a 1:1 ratio: patients in Group A will radical LGE and patients in Group B will receive radical laparo-thoracoscopic esophagectomy (LTE). Perioperative and long-term outcomes of all patients will be collected and analyzed. The primary end point will be perioperative morbidity, and the secondary end points will include 5-year overall survival (OS) and disease-free survival (DFS) and quality of life (QOL) score. Other data that will be collected and compared between the groups include the number of harvested lymph nodes, surgical Apgar score, and duration of operation.

Discussion: Transthoracic MIE is the most widely accepted approach for treating esophageal cancer. In this RCT, transthoracic MIE and transcervical LGE will be compared with respect to oncological and surgical outcomes (oncological none-inferiority and surgical superiority).

Trial Registration: This study is registered in Chinese Clinical Trial Registry (ChiCTR2200055312) with the name of 'Transcervical versus Transthoracic Minimally Invasive Esophagectomy: A Randomized and Controlled Trial' on January 6, 2022. Details can be found on http://www.chictr.org.cn/showproj.aspx?proj=133224.

Keywords: Esophageal cancer; transcervical esophagectomy; transthoracic esophagectomy; laparo-gastroscopic esophagectomy (LGE); laparo-thoracoscopic esophagectomy (LTE)

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Introduction

The transthoracic approach is the classical method for the surgical resection of esophageal cancer (1). However, pulmonary morbidity is increased with transthoracic manipulations (2), and the difficulty of the operation is increased when pleural adhesions are present. To overcome these problems, the transcervical approach was introduced as it avoids thoracotomy; however, the procedure is not often performed because of difficulties maintaining the mediastinal space.

To overcome the difficulties associated with transcervical esophagectomy, technical modifications have been consecutively introduced since the initial report by Orringer *et al.* (3). The procedure was modified from blind and blunt dissection to visible and sharp dissection by Fujiwara *et al.* (4). In another modification, an artificial pneumomediastinum was produced which allowed subtotal esophagectomy and extensive mediastinal lymphadenectomy (5). However, even when the mediastinum was expanded with CO_2, instrument collisions remained common resulting in iatrogenic injuries to nearby structures. In addition, an artificial pneumomediastinum can potentially lead to hemodynamic instability and contribute to postoperative morbidity (6).

Recently our team reported a further modification of transcervical minimally invasive esophagectomy (MIE) in which extraluminal gastroscopic esophageal mobilization is performed instead of mediastinoscopic esophagectomy (7). The safety and efficacy have also been proven by our serial successful cases. Thus, herein we present a protocol for a randomized controlled trial (RCT) to compare transthoracic and transcervical MIE. We present the following article in accordance with the SPIRIT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1180/rc).

Methods and design

Study design

The study is a prospective RCT performed at Zhongshan Hospital, Fudan University, China. Its objective is to compare the perioperative and long-term outcomes between transcervical and transthoracic MIE. Patient enrollment will begin June 2022. Patients with esophageal cancer who meet the inclusion criteria will be randomly assigned to receive either transcervical or transthoracic MIE. The study was approved by IRB of Zhongshan hospital (No. B2021-634), Fudan university (Shanghai, China). The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent will be taken from all individual participants.

Patient inclusion and exclusion

Consecutive patients with a diagnosis of esophageal cancer seen at Zhongshan Hospital, Fudan University, will be evaluated by our multi-disciplinary team (MDT). Lesions will be clinically staged by endoscopy, tissue biopsy, thoraco-abdominal computed tomography (CT), and positron emission tomography (PET)-CT. Inclusion criteria for the study are:

(I) Age from 18 to 70 years;
(II) Eastern Cooperative Oncology Group (ECOG) score 0 or 1;
(III) Tumor located in the thoracic esophagus;
(IV) Squamous cell carcinoma or adenocarcinoma;
(V) Clinical stage $cT_{1-3}N_0M_0$;
(VI) Patient provided written informed consent for surgical procedures and participation in the study.

Exclusion criteria are:

(I) History of another malignancy;
(II) Rare pathological type of esophageal cancer;
(III) Severe preoperative comorbidities: forced expiratory volume (FEV)1 <50% predicted, or ejection fraction (EF) <50%, or major organ failure;
(IV) Received preoperative corticosteroid treatment;
(V) Presence of a cognitive disorder.

Study interventions

Patients assigned to arm A will receive radical laparo-gastroscopic esophagectomy (LGE), and patients assigned to arm B will receive radical laparo-thoracoscopic esophagectomy (LTE). Details of LGE and LTE have been reported previously (7,8). The procedural steps of LTE and LGE are shown in *Figure 1* and *Figure 2*, respectively. Esophagectomy and lymph node dissection will be required in both arms, and the number and stations of harvested lymph nodes will be recorded. All patients will receive a preoperative MDT evaluation, and be required to comply with routine postoperative follow-up examinations.

Outcome measures

Primary end point

A comparison of postoperative morbidity between the 2

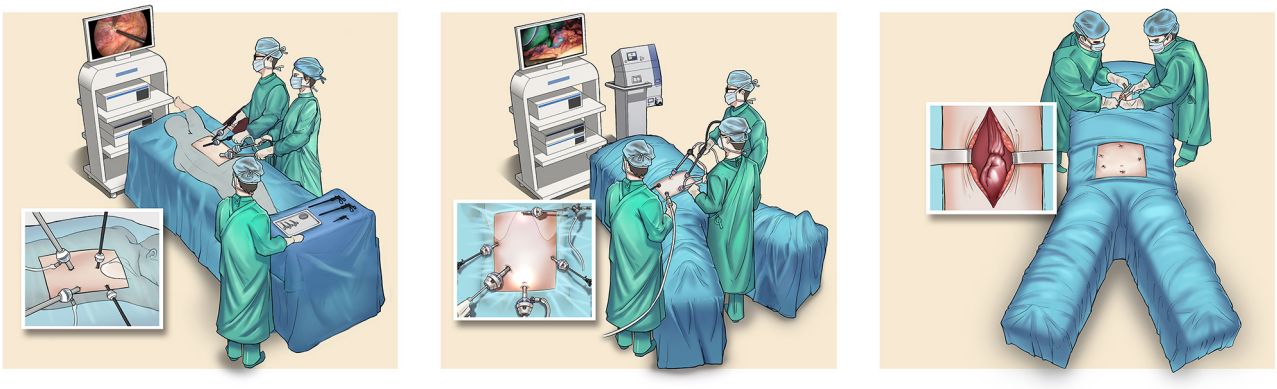

Figure 1 Transthoracic laparo-thoracoscopic minimally invasive esophagectomy.

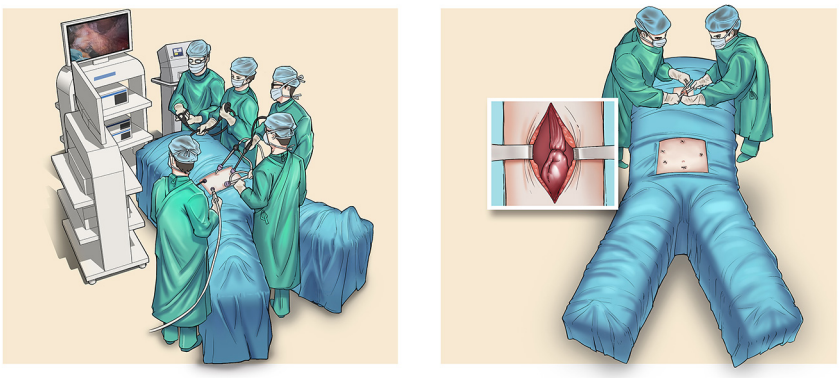

Figure 2 Transcervical laparo-gastroscopic minimally invasive esophagectomy.

groups is the primary endpoint of the study. Morbidities are classified based on the standard list proposed by the Esophageal Complications Consensus Group (9). Chest X-ray and routine blood testing are conducted to identify possible pulmonary complications after surgery. Cardiac complications are recorded as cardiac arrest requiring cardiopulmonary resuscitation, or dysrhythmia requiring additional medical treatment. Gastrointestinal complications are anastomotic leakage confirmed by radiographic evidence.

Secondary end points

The secondary outcomes of the study include the number of harvested lymph nodes, 5-year overall survival (OS) and 5-year disease-free survival (DFS), quality of life (QOL) score, surgical Apgar score (10), and duration of the operation. QOL is scored at randomization, 1-month after surgery, and then every 3 months up to 36 months using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) and EORTC QLQ-OES18.

Assessments, data collection, and follow-up

Pre-therapeutic assessments

All patients will receive standard preoperative laboratory tests, a physical examination, and recording of medical history and demographic data. Evaluation for tumor staging includes gastroscopy and biopsy, CT scan, ultrasound, and PET-CT, as necessary. All patients will receive pulmonary function testing, cardiac ultrasound, and electrocardiogram before surgery.

Assessments during the treatment phase

Perioperative data collected includes details of the operation, perioperative morbidities and mortality, vital signs, body temperature, and the results of laboratory tests and other related examinations.

Table 1 The schedule of enrolment, interventions, and assessments

	Study period							
	Enrolment			Allocation				Close-out
Timepoint	$-t_1$	0	t_1	t_2	t_3	t_4	etc.	t_x
Enrolment								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Interventions								
Esophagectomy			X					
Assessments								
Demographics	X							
Postoperative morbidity				X				
5-year OS and 5-year DFS, QOL score, surgical Apgar score					X	X	X	X

OS, overall survival; DFS, disease-free survival; QOL, quality of life.

Follow-up

The first follow-up will be 1 month after surgery. Then, patients will be seen every 3 months for the first 2 years, and then every 6 months. All patients will be required to have a minimum follow-up of 5 years.

Assessments during follow-up include chest CT scan, ultrasound examinations of the neck and abdomen, EORTC QLQ-C30 and EORTC QLQ-OES18 questionnaires to assess QOL, and blood test including complete blood count (CBC) tests of renal and liver function, and tumor biomarkers.

Participant timeline

The time schedule of the study is presented in *Table 1*. The time point of patient allocation is set as time '0'. The time point before patient allocation is recorded as $-t_1$, $-t_2$, etc. And the time point after patient allocation is recorded as t_1, t_2, etc. 'X' means the end of study.

Sample size

The sample size calculation was based on the primary end point. The estimated rate of perioperative morbidity is 25% in arm A and 45% in arm B based on the results of other RCTs and our studies (8,11). With a sample size of 96 patients per arm, there will be 80% power to detect a difference of overall morbidity between the 2 arms with a 2-side type I error of 5%, and assuming a 10% drop out rate.

Statistical analysis

Data will be summarized as the mean and standard deviation, or median and interquartile range (IQR), as appropriate, for continuous variables, and count and percentage for categorical variables. Continuous variables will be compared by Student's *t*-test or Mann-Whitney U test, as appropriate, and categorical variables will be compared by chi-square test or Fisher's exact test, as appropriate. A value of $P<0.05$ will be considered to indicate statistical significance. Statistical analysis will be performed using GraphPad Prism version 6.0 software (GraphPad Software, CA, USA).

Discussion

Based on the surgical innovation of LGE, the purpose of the proposed study is to compare the outcomes of transcervical and transthoracic MIE (*Figure 3*). The evidence collected from this RCT will assist surgeons is choosing the most appropriate surgical route to resect esophageal cancer.

The choice of surgical route for the resection of esophageal cancer depends on its capability of realizing R_0 resection with acceptable morbidity and mortality

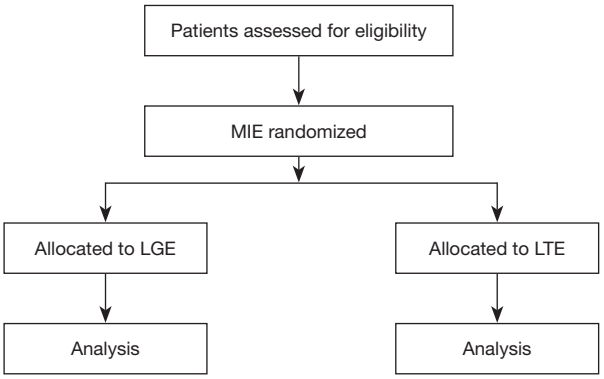

Figure 3 Flow chart of patient inclusion, allocation, and analysis. MIE, minimally invasive esophagectomy; LGE, laparo-gastroscopic esophagectomy; LTE, laparo-thoracoscopic esophagectomy.

rates (12). Yet, the reasons for not choosing a certain route may be multifactorial (13). Currently, transcervical esophagectomy, also known as transhiatal esophagectomy, serves as an alternative surgical method for patients who are compromised by morbidities (14). Hulscher *et al*. suggested that transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy (15).

However, the procedure is not as popular as transthoracic MIE, and it is associated with 2 major concerns.

First, due to anatomic structures transcervical esophageal mobilization is technically demanding and requires the use of multiple surgical instruments within the confined mediastinal space. Instrumental collision using a single cervical port is a common problem and is associated with major complications following surgery (16). Iatrogenic injury of structures such as the trachea and recurrent laryngeal nerves can be catastrophic for the patient (17). Second, extensive lymphadenectomy is compromised with transcervical esophagectomy as compared to transthoracic surgery. Although extensive lymph node dissection with transcervical approach was achieved in some previous reports (4,5), its wider application on larger population was not reported till recently (17). These issues have led to transcervical MIE being an unattractive alternative to transthoracic MIE.

However, modifications to transcervical MIE have expanded its role for esophageal cancer. Previously, our team introduced transcervical mediastinoscopic esophagectomy and observed comparable survival results in select patient groups (18). Parker *et al*. pioneered transcervical esophageal mobilization under artificial pneumomediastinum in a small group of patients (19). Fujiwara *et al*. applied the technique in larger population with good results (20). The procedure was further refined to allow adequate lymph node dissection (5). Based on the previous modifications, we developed extraluminal gastroscopic esophageal mobilization through a cervical incision, in which a single gastroscope is used instead of multiple thoracoscopic instruments within the mediastinum, and without artificial pneumomediastinum (7). The results of our primary study have led to the question if transcervical LGE has comparable efficacy to conventional transthoracic MIE.

The proposed study will compare the results of transcervical and transthoracic MIE in patients with clinical stage $cT_{1-3}N_0M_0$ disease. Patients with more advanced disease will be excluded as neoadjuvant therapy is recommended for this group (21). During gastroscopic mobilization, approaching manipulation is performed in the space of esophageal tunica adventitia, leaving potential risks of R_1 or R_2 resection with more advanced lesions. Yet, an expansion study will be proposed following this primary RCT to validate the efficacy of LGE in more advanced cases.

Checkpoint inhibitors have revolutionized neoadjuvant therapy (22), and this protocol includes translation study with residual tumor analysis and the association with patient prognosis. Based on the primary findings of residual tumor distribution (23), the translational analysis will be based on radiomics/pathomics study using artificial intelligence. This additional study that is focused on radiological and pathological data is separate from the primary RCT, and patients will be required to provide a separate written informed consent for participation.

The current study protocol is based on the initial technical study, and the following safety and efficacy analysis retrospective study. There is a relatively steep learning curve for the new innovation of the surgical procedure. Due to its single center design, the results of this study may not be applicable to procedures performed at other centers and will require further multicenter validation. In the near future, our next multicenter study will be open for other qualified medical centers, and enroll patients within the inclusion criteria.

Conclusions

The advances and modifications of the transcervical approach make it a potential choice for radical esophagectomy. The current study was designed to compare the safety and efficacy between LGE and LTE.

Select patients with esophageal cancer will be enrolled and assigned to receive either LGE or LTE. It is hypothesized that LGE will have comparable perioperative outcomes as LTE without the need for thoracic incisions.

Trial status

The protocol (version 1.0, January 6, 2022) began recruitment from June 1, 2022 and the approximate date of completion will be May 31, 2024.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1180/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1180/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by IRB of Zhongshan hospital (No. B2021-634), Fudan university (Shanghai, China). The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent will be taken from all individual participants.

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