Adjuvant Esophagectomy versus Definitive Chemoradiotherapy for Patients with Clinical Stage N0 and Pathological Stage T1b Esophageal Squamous Cell Carcinoma After Endoscopic Submucosal Dissection: Study Protocol for A Multicenter Randomized Controlled Trial (Ad-ESD Trial)

CURRENT STATUS: UNDER REVIEW

Yang Yang
Shanghai Jiao Tong University Affiliated Chest Hospital

Yuchen Su
Shanghai Jiao Tong University Affiliated Chest Hospital

Xiaobin Zhang
Shanghai Jiao Tong University Affiliated Chest Hospital

Jun Liu
Shanghai Jiao Tong University Affiliated Chest Hospital

Hong Zhang
Shanghai Jiao Tong University Affiliated Chest Hospital

Bin Li
Shanghai Jiao Tong University Affiliated Chest Hospital

Rong Hua
Shanghai Jiao Tong University Affiliated Chest Hospital

Lijie Tan
Zhongshan Hospital Fudan University

Hezhong Chen
Changhai Hospital

Zhigang Li
Shanghai chest hospital
Abstract
Background: Esophagectomy is still the prior additional treatment for pathological T1b (pT1b) esophageal squamous cell carcinoma (ESCC) after endoscopic resection (ER). ER followed with definitive chemoradiotherapy (dCRT) has showed increased quality of life as well as comparable oncological outcomes to esophagectomy. However, there is no well-designed, phase III trial to compare the two treatment for patients with pT1b ESCC.

Methods: One hundred seventy-six patients with clinical stage N0 (cN0) and pT1b ESCC will be recruited at three centers and randomized to the esophagectomy group or the dCRT group. The clinical lymph node status will be measured by image examination including computer tomography and positron emission tomography-computed tomography. The pathological tumor status will be diagnosed after endoscopic submucosal dissection (ESD). All patients will be followed up for 60 months after randomization. The primary endpoint is the 5-year overall survival. The secondary endpoints are quality of life, related adverse events, 3-year overall survival and relapse-free survival rates.

Discussion: To the best of our knowledge, this is the first phase III randomized controlled trial to compare the esophagectomy and dCRT for patients with cN0-pT1b ESCC after ESD. Based on the results of this study, we will show whether dCRT will benefit patients more than esophagectomy, which will contribute more high-quality evidence to the primary salvage treatment for these patients.

Trial registration : ClinicalTrials.gov, NCT04135664. Registered on 10 August 2019.

Administrative Information
Adjuvant Esophagectomy versus Definitive Chemoradiotherapy for Patients with Clinical Stage N0 and Pathological Stage T1b Esophageal Squamous Cell Carcinoma After Endoscopic Submucosal Dissection: Study Protocol for A Multicenter Randomized Controlled Trial (Ad-ESD Trial)

ClinicalTrials.gov, NCT04135664. Registered on 10 August 2019.

This study is funded by the Gaofeng Clinical Medicine Grant Support of Shanghai Municipal Education Commission.

Yang Yang, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: yangyang321879@163.com
Yuchen Su, Department of Endoscopy, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: inalcohol@126.com
Xiaobin Zhang, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: zxb5212@163.com
Jun Liu, Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: drjunliu@qq.com
Hong Zhang, Department of Endoscopy, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: 79757393@qq.com
Bin Li, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: drbinlee@126.com
Rong Hua, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: askyou999@126.com
Lijie Tan, Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China. E-mail: tan.lijie@zs-hospital.sh.cn
Hezhong Chen, Department of Thoracic Surgery, Shanghai Chest Hospital, Naval Military Medical University, Shanghai, China. E-mail: rchenhz@126.com
Zhigang Li, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China. E-mail: zhigang_li_sch@163.com
Y. Y., Y. S and X. Z contributed equally to this study protocol.

Zhigang Li, MD, PhD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, No. 241, West Huaihai Rd, Shanghai, 200030, China. Tel: +86 21 22200000-2601. Email: zhigang_li_sch@163.com

ZL carried out the trial design and financial supervision.

Introduction

Background and rationale {6a}

Esophageal cancer is the seventh common malignant tumor and ranks sixth in tumor-related mortality worldwide [1]. In terms of the histological subtypes, adenocarcinoma is frequently observed in Europe and the United States, while squamous cell carcinoma is the predominant form in China [2].
Tumor invasion of the submucosa (T1b) is a watershed in the treatment of esophageal cancer from endoscopy to esophagectomy. Esophagectomy with extended lymph node dissection is recommended as the primary treatment for pT1b ESCC due to the high incidence of lymph node metastasis [3, 4]. Previous studies showed that patients with pT1b ESCC after esophagectomy have a favorable 5-year survival rate which was about 70~73.6% [5, 6]. Although 30~50% of these patients have a risk of lymph node metastasis, however, more than half of them are presented with local superficial lesions [7]. In addition, esophagectomy is associated with a higher morbidity and mortality rate as well as decreased quality of life [8]. Therefore, esophagus-preserving has always been the ultimate goal of treatment for low-risk submucosal esophageal cancer.

Previous studies have demonstrated that dCRT can achieve a comparable survival rate as esophagectomy for submucosal esophageal cancer [9]. However, local failure without distant metastasis after dCRT remains a major challenge to achieve long-term survival [10]. ER has been demonstrated with satisfied control for submucosal esophageal cancer without lymph node metastasis [11]. Therefore, the combination of ER and dCRT conforms to the aim of non-surgical treatment of submucosal esophageal cancer, which can maximize the removal of primary lesions and additional disposition of residual lesions or potential lymph nodes metastasis [12-14]. The Japan Clinical Oncology Group (JCOG) phase II trial (JCOG0508) was the only prospective clinical study conducted to evaluate the efficiency and safety of combined treatment of ER and CRT for clinical stage I ESCC [15]. The results showed that for patients with pT1b with R0 and pT1a with LVI (+) after ER, the 3-year OS was 90.7% (90% CI, 84.0%-94.7%) after prophylactic CRT. They concluded that the combination of ER and selective CRT should be considered as a minimally invasive treatment option for clinical stage I ESCC [16].

Based on the encouraging results of JCOG0508 and other previous studies, we hypothesized that concurrent dCRT may achieve comparable survival results and better quality of life to esophagectomy for submucosal esophageal cancer. Therefore, we designed this randomized controlled trial (RCT) to compare the two salvage treatments for pT1b ESCC after ER.

Objectives {7}
The aim of this trial is to compare esophagectomy versus definitive chemoradiotherapy for patients with clinical stage N0 and pathological stage T1b esophageal squamous cell carcinoma after endoscopic submucosal dissection.

**Trial design {8}**

This study is a multicentre, randomized, open-label, phase III trial. All participants will be allocated to the two intervention groups at 1:1 ratio. The flow-chart is illustrated in Fig. 1.

**Methods: Participants, Interventions And Outcomes**

**Study setting {9}**

Patients with cN0-pT1b ESCC after ESD will receive two concurrent salvage treatments. The intervention randomized with either esophagectomy or dCRT will start at approximately 3 weeks after ESD, followed by a 60-months follow-up period. To achieve the primary endpoint, 176 patients will be recruited from three high-volume centres (>100 cases of esophagectomies) in China (Shanghai Chest Hospital, Zhongshan Hospital and Changhai Hospital).

**Eligibility criteria {10}**

**Inclusion criteria**

1. Biopsy proven with ESCC.

2. Clinical N0 stage diagnosed by imaging examinations.

3. Pathological T1b stage confirmed by endoscopic submucosal resection.

4. Age ranges from 18 to 75 years.

5. Primary tumors are located at the intrathoracic esophagus.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

7. Written informed consent.

**Exclusion criteria**

1. Prior treatment before endoscopic submucosal resection.

2. Inability to accept any treatment component.

3. Prior intervention (surgery, chemoradiation, et al.) for other primary tumor disease.
4. Positive vertical resection margin.
5. Distant metastasis.
6. Inability to understand the informed consent.

**Who will take informed consent? {26a}**

Informed consent document will be collected from each participant prior to enrolment.

**Additional consent provisions for collection and use of participant data and biological specimens {26b}**

No additional consent provisions are needed in this trial.

**Interventions**

**Explanation for the choice of comparators {6b}**

SPIRIT guidance: Explanation for choice of comparators.

**Intervention description {11a}**

The treatment will be performed by thoracic surgeons or radiologists. Patients who are eligible to the inclusion criteria will be recruited and randomized into two treatment groups.

**Esophagectomy**

Patients will undergo an open, hybrid or minimally invasive esophagectomy (McKeown or Ivor Lewis) with at least two-field lymphadenectomy. Selection of surgical technique will depend on patient and tumor characteristics as well as local expertise and preference [17-19]. According to the National Comprehensive Cancer Network (NCCN) guideline [20], the number of dissected lymph nodes should be at least 15 including the lymph nodes at the station of upper para-esophagus, right recurrent laryngeal nerve, middle para-esophagus, lower para-esophagus, left recurrent laryngeal nerve, subcarinal station, left main trachea, right main trachea, para-cardiac, left gastric artery, lesser curve.

**Chemoradiotherapy**

**Radiotherapy** Radiotherapy will be delivered with photons (6 -10MV) in daily fractions on 5 days per week. Intensity modulated radiotherapy (IMRT) based on CT simulation planning system with 5-mm-thick scan slice throughout the entire neck and thorax and upper abdomen is required.
Target volumes need to be carefully defined.

Gross tumor volume (GTV): The GTV should include the positive margin according to the pathology after ESD.

Clinical target volume (CTV): The CTV is defined as tumor bed and elective lymph-node regions. For proximal third of the esophagus: consider treatment of para-esophageal lymph nodes, bilateral supraclavicular lymph nodes and mediastinum lymph nodes. For middle third of the esophagus: consider treatment of para-esophageal lymph nodes. For distal third of the esophagus: consider para-esophageal, lesser curvature, splenic nodes, and celiac axis nodal regions.

Planning target volume (PTV): The PTV includes PTV-G and PTV-C. Due to set-up deviation and organ movement, PTV-G is defined as a further 6-10mm expansion to the GTV in all directions, PTV-C is defined as a further 6-10mm expansion to the CTV.

The prescribed dose of PTV-G is 6020cGy (215cGy/d), PTV-C is 5040cGy (180cGy/d), both in 28 fractions.

Chemotherapy The following chemotherapeutic agents were used: Cisplatin was administered at a dose of 70 mg/m$^2$ by a slow drip infusion on days 1 and 29. 5-fluorouracil (5-FU) was administered at a dose of 700 mg/m$^2$/d by a continuous infusion for 24 h on days 1-4 and 29-32.

Criteria for discontinuing or modifying allocated interventions {11b}

Allocated interventions will not be modified as a rule, except for participants who cannot finish chemoradiation due to severe adverse events.

Strategies to improve adherence to interventions {11c}

Not applicable.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable.

Provisions for post-trial care {30}

All participants will be followed-up until death or over a period of at least 60 months.

Outcomes {12}
**Primary endpoint**

The 5-year OS in all randomized patients. OS is defined as the time from the date of randomization to the day of death or to the last follow-up.

**Secondary endpoints**

Quality of life (QoL): QoL is assessed among patients by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) and EORTC QLQ-OES18 [21, 22]. Patients will be invited to finish the two questionnaires at the day of recruitment, 1st, 3rd, 6th, 12th and 24th month after randomization.

Oncological outcomes: The 3-year OS and 3, 5-year RFS. RFS is defined as the time from the date of randomization to the day of tumor recurrence, tumor progression or patients’ death assessed up to 60 months.

**Participant timeline {13}**

Time schedule of enrolment, interventions, assessments and visits for participants is presented in the following schematic diagram.
According to previous studies, the 5-year OS of patients with pT1b ESCC who underwent esophagectomy was 70~80% [23], whereas the rate was about 90% in patients who received ER plus chemoradiation [16]. We assumed that the 5-year OS was 75% in the esophagectomy group and 90% in the dCRT group. The proportion dropping out of the study is considered to be 5%. Therefore, a sample size of 88 patients in each group is required at a significance level of 5% and a power of 80%.

Recruitment {15}
A total of 176 patients with cN0-pT1b ESCC after ESD will be considered as eligible for this trial. The cN0 stage will be measured by imaging examinations at the pre-treatment period, and the pT1b stage will be confirmed by the pathology after ESD treatment.

Assignment of interventions: allocation
Sequence generation \{16a\}
The allocation sequence is according to the computer-generated random numbers.

Concealment mechanism \{16b\}
Sealed envelope will be used in implementing the allocation sequence.

Implementation \{16c\}
CRC of the Ad-ESD trial will generate the allocation sequence. Clinical physician will be in charge of the enrolment of participants and assign participants to each intervention.

Assignment of interventions: Not Blinding

Who will be blinded \{17a\}
This trial is not double-blinded due to the different interventions.

Procedure for unblinding if needed \{17b\}
No.

Data collection and management

Plans for assessment and collection of outcomes \{18a\}
After completion of allocated treatments, patients will be followed-up until death or over a period of at least 60 months. All patients will be required to send back the QoL questionnaires at 1\textsuperscript{st}, 3\textsuperscript{rd}, 6\textsuperscript{th}, 12\textsuperscript{th} and 24\textsuperscript{th} month after randomization. The CT scan of chest and abdominal and ultrasound of the neck will be performed at six-month intervals for the first three years and every year for the next two years after treatment. PET-CT will be used selectively.

Plans to promote participant retention and complete follow-up \{18b\}
A regular telephone follow-up (per 3 months) is performed in the participating centres.

Data management \{19\}
Data will be entered into online encrypted database and a separate excel form from the CRC staff. Researchers must have an authorized account to access the database.

Confidentiality \{27\}
All personal information about potential and enrolled participants will be safely maintained in order to
protect confidentiality before, during, and after the trial.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}**

No biological specimens were collected as part of this trial.

**Statistical methods**

**Statistical methods for primary and secondary outcomes {20a}**

Statistical analyses are performed using SPSS version 20.0 software (SPSS Inc. Chicago, Illinois, USA).

The statistical analysis will be performed in accordance with both the intention to treat (ITT) and the per-protocol (PP) principles. Survival will be estimated by Kaplan-Meier methods and analysed using log-rank test. Continuous variables will be compared using a Student’s t-test or Wilcoxon rank-sum test as appropriate and represented as the mean ± standard deviation or median and range.

Categorical variables will be compared using Fisher’s exact test or Wilcoxon rank-sum test as appropriate and represented as number of patients and percentage. For the quality of life, changes QLQ-C30 and QLQ-OES18 from pretreatment to 12 months, parametric or nonparametric statistical methods will be used, depending on the data distribution.

**Interim analyses {21b}**

An interim analysis will be performed after 80 patients have been included. This analysis will be performed similarly to the primary data analysis. Primary investigators from all participating centres will have access to these interim results.

**Methods for additional analyses (e.g. subgroup analyses) {20b}**

This analysis will be performed similarly to the primary data analysis.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}**

Not applicable.

**Plans to give access to the full protocol, participant level-data and statistical code {31c}**

All participating centers have access to the full protocol, participant-level dataset, and statistical code.
Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}
SPIRIT guidance: Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee).

Composition of the data monitoring committee, its role and reporting structure {21a}
A data monitoring committee (DMC) will be established that will test the modifying rules repeatedly and report the relevant results to researches. It is independent from the sponsor and competing interests.

Adverse event reporting and harms {22}
Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the treatment procedures. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded during the period of study.

Frequency and plans for auditing trial conduct {23}
The process will be independent from investigators and the sponsor.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}
If the protocol needs to be modified, all primary investigators will discuss it through the meeting and make a final decision.

Dissemination plans {31a}
Authorship eligibility guidelines will follow International Committee of Medical Journal Editors (ICMJE) guidelines. The final trial dataset will be available to the investigative team and on reasonable request.

Discussion
Increasing number of patients with superficial lesions are primary treated with ER after receiving lymph node and distant metastases evaluation. However, the treatment choice will face a dilemma
between esophagectomy and dCRT when the pathology of ER specimen reveals submucosal invasion, which is an increasingly common clinical problem [24]. In the past, the selection is based on the preferences of patient and doctor. Although previous retrospective studies have confirmed that adjuvant chemotherapy or surgery can achieve comparable long-term survival outcomes, however, small sample size and low proportion of pT1b patients reduced the credibility of evidence [14, 16]. The present study is the first prospective randomized controlled clinical trial to compare the salvage esophagectomy and dCRT for patients with cN0-pT1b ESCC after ESD. Our results will provide high-level evidence to establish an appropriate treatment strategy for these patients.

Superficial esophageal cancer is defined as tumor invaded into mucosal and submucosal lesion. In the retrospective studies, tumor invaded into muscular mucosal (M3) and submucosal (SM) layers are usually treated in the same way, due to the high rate of lymph node metastasis [25]. However, we selected T1b as the study subject and excluded M3 patients in this trial, which is mainly based on the following considerations. Firstly, it is difficult to be recruited because majority of patients with mucosal myometrium after R0 resection in China will choose surveillance. Second, we set a very strict clinical evaluation criteria for lymph node status in this trial which greatly reduced the probability of occurrence of high-risk M3, so there is no need to adjuvant therapy. Therefore, the T1b patients after ESD were selected as the study subjects.

In this trial design, we did not exclude patients who were with positive lateral resection margin. Because previous studies have confirmed that the tumor invasion within the submucosa can be well controlled by radiotherapy. Then, for the residual lesions in the lateral resection margin after ESD, subsequent adjuvant chemoradiotherapy or surgery are sufficient to obtain local radical treatment [26]. Therefore, those patients don't need to be excluded, which was also consistent with the JCOG0508 study [16]. However, patients with positive vertical resection margin will not be recruited due to the tumor has invaded into the muscular layer (T2).

For superficial lesions, the lymph node metastasis is balanced upward and downward. In our retrospective study, it can be found that the metastasis rates of the upper mediastinum and the left gastric artery are basically equivalent in the final pathology (data not shown). However, in the long-
term follow-up, high rate of recurrence was found in the upper mediastinum, whereas rarely in the lower mediastinum and abdominal cavity. The results indicate that lymph node recurrence may occur in both upstream and downstream after ESD in early stage patients. Therefore, the design of radiation target of should cover the longer longitudinal and abdominal cavity, not just the lesion. However, there are two main limitations of this trial. First, the study is not double-blinded due to the different interventions. And the recruitment may be challenging causing of the different interventions and cost of treatments. Second, the sample size calculation was based on our clinical observation and the previous report.

**Trial status**

The trial began recruitment in November 2019. Anticipated time of study completion will be December 2027, if necessary. The protocol version 2.0 was discussed on October 25 2019 by principle investigators from all participating centres.

**Abbreviations**

dCRT: definitive chemoradiotherapy; ESD: endoscopic submucosal dissection; ER: endoscopic resection; ESCC: esophageal squamous cell carcinoma; CT: Computed tomography; JCOG: Japan Clinical Oncology Group; NCCN: National Comprehensive Cancer Network; ECOG: Eastern Cooperative Oncology Group; RCT: randomized controlled trial; EGD: esophagogastroduodenoscopy; EUS: endoscopic ultrasonography; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume; 5-FU: 5-fluorouracil; ITT: intention to treat; PP: per-protocol; ICMJE: International Committee of Medical Journal Editors; IMRT: Intensity-modulated radiation therapy; OS: overall survival; RFS: relapse-free survival; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life-Oesophageal Module 18 Questionnaire; QoL: Quality of life.

**Declarations**

**Acknowledgements**

None.

**Authors’ contributions {31b}**
YY and YS were responsible for patient recruitment in all participating centres as well as designing the trial and drafting the manuscript. XZ carried out the pilot study and sample size estimation. BL and RH performed the statistical analysis. JL and YS participated in the study design and coordination. LT was responsible for patient management in one local centre. HC was responsible for patient management in another local centre. ZL carried out the trial design and financial supervision. All authors read and approved the final manuscript.

**Funding {4}**

This study is funded by the Gaofeng Clinical Medicine Grant Support of Shanghai Municipal Education Commission. The funding body has no role in the design of the study, data collection and analysis, data interpretation and in writing the manuscript.

**Availability of data and materials {29}**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, and in ClinicalTrials.gov, NCT04135664.

**Ethics approval and consent to participate {24}**

This study was approved by Shanghai Chest Hospital Independent Ethics Committee. The approval number is KS1917, and the ethics approval applies to the other two participating centres. Written informed consent will be collected from each study participant prior to enrolment.

**Consent for publication {32}**

Not applicable.

**Competing interests {28}**

The authors declare that they have no competing interests.

**Author details**

1 Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China.
2 Department of Endoscopy, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China.
3 Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China.
4 Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai,
References

1. Ferlay, J., et al., Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer, 2019. 144(8): p. 1941-1953.

2. Chen, W., et al., Cancer statistics in China, 2015. CA Cancer J Clin, 2016. 66(2): p. 115-32.

3. Rice, T.W., D.T. Patil, and E.H. Blackstone, 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg, 2017. 6(2): p. 119-130.

4. Kato, H., et al., Cervical, mediastinal, and abdominal lymph node dissection (three-field dissection) for superficial carcinoma of the thoracic esophagus. Cancer, 1993. 72(10): p. 2879-82.

5. Gertler, R., et al., Long-term outcome of 2920 patients with cancers of the esophagus and esophagogastric junction: evaluation of the New Union Internationale Contre le Cancer/American Joint Cancer Committee staging system. Ann Surg, 2011. 253(4): p. 689-98.

6. Akutsu, Y., et al., The overall prevalence of metastasis in T1 esophageal squamous cell carcinoma: a retrospective analysis of 295 patients. Ann Surg, 2013. 257(6): p. 1032-8.

7. Endo, M., et al., Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus, 2000. 13(2): p. 125-9.

8. Dubecz, A., et al., Predictors of Lymph Node Metastasis in Surgically Resected T1 Esophageal Cancer. Ann Thorac Surg, 2015. 99(6): p. 1879-85; discussion 1886.
9. Nemoto, K., et al., Results of radiation therapy for superficial esophageal cancer using the standard radiotherapy method recommended by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. Anticancer Res, 2006. 26(2B): p. 1507-12.

10. Motoori, M., et al., Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. Ann Surg Oncol, 2012. 19(7): p. 2135-41.

11. Wang, J., et al., Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma and precancerous lesions. World J Gastroenterol, 2018. 24(26): p. 2878-2885.

12. Suzuki, G., et al., Endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer: choice of new approach. Radiat Oncol, 2018. 13(1): p. 246.

13. Kawaguchi, G., et al., The effectiveness of endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer. Radiat Oncol, 2015. 10: p. 31.

14. Ikeda, A., et al., Endoscopic Submucosal Dissection (ESD) with Additional Therapy for Superficial Esophageal Cancer with Submucosal Invasion. Intern Med, 2015. 54(22): p. 2803-13.

15. Kurokawa, Y., et al., A phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma: Japan Clinical Oncology Group Study JCOG0508. Jpn J Clin Oncol, 2009. 39(10): p. 686-9.

16. Minashi, K., et al., Efficacy of Endoscopic Resection and Selective Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma. Gastroenterology, 2019. 157(2): p. 382-390 e3.
17. Wang, H., et al., Outcomes, quality of life, and survival after esophagectomy for squamous cell carcinoma: A propensity score-matched comparison of operative approaches. J Thorac Cardiovasc Surg, 2015. 149(4): p. 1006-14; discussion 1014-5 e4.

18. van der Sluis, P.C., et al., Oncologic Long-Term Results of Robot-Assisted Minimally Invasive Thoraco-Laparoscopic Esophagectomy with Two-Field Lymphadenectomy for Esophageal Cancer. Ann Surg Oncol, 2015. 22 Suppl 3: p. S1350-6.

19. Biere, S.S., et al., Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet, 2012. 379(9829): p. 1887-92.

20. Ajani, J.A., et al., Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 2019. 17(7): p. 855-883.

21. Aaronson, N.K., et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 1993. 85(5): p. 365-76.

22. Blazeby, J.M., et al., Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer, 2003. 39(10): p. 1384-94.

23. Tachimori, Y., et al., Comprehensive Registry of Esophageal Cancer in Japan, 2011. Esophagus, 2018. 15(3): p. 127-152.

24. Qin, J., et al., Comparative study of esophagectomy, endoscopic therapy, and radiotherapy for cT1N0M0 esophageal cancer in elderly patients: A SEER database analysis. Thorac Cancer, 2019. 10(7): p. 1511-1520.

25. Hisano, O., et al., Additional radiotherapy following endoscopic submucosal
dissection for T1a-MM/T1b-SM esophageal squamous cell carcinoma improves locoregional control. Radiat Oncol, 2018. 13(1): p. 14.

26. Goense, L., et al., Role of adjuvant chemoradiotherapy after endoscopic treatment of early-stage esophageal cancer: a systematic review. Minerva Chir, 2018. 73(4): p. 428-436.

Figures

![Flow chart of the trial.](image)

Figure 1

Flow chart of the trial.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

SPIRIT Checklist.doc