Original protocol (January, 2015)

Comparison of surgical outcomes through left thoracic approach versus through right thoracic approach for middle and lower thoracic esophageal cancer without suspected upper mediastinal lymph node metastasis: A phase III multicenter prospective randomized controlled study（NST1501）

ClinicalTrials.gov Identifier: NCT02448979

Sponsor: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College,

Principle investigator: Jie He, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College,

Executive principle investigator: You-sheng Mao, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College,

Collaborators:

Ke-neng, Chen, *Beijing cancer hospital, Beijing University, Beijing, China;*

Yin Li, *Henan Cancer Hospital, Zhengzhou, China;*

Jun-feng Liu, *The Fourth Hospital, Shijiazhuan,China;*

Jian-qun Ma, *Heilongjiang Cancer Hospital, Harbin, China;*

Yong-yu Liu, *Liaoning Cancer Hospital, Shenyang, China;*

Gao-ming Xiao, *Hunan Cancer Hospital, Changsha, China;*

Jian-hua Fu, *Sun Yat-sen University Cancer Center; Guangzhou, China;*

Wei-min Mao, *Zhejiang Cancer Hospital, Hangzhou, China;*

Xiang-ning Fu, *Tongji Hospital, Tongji University, Wuhan, China;*

- Purpose

Esophageal carcinoma is an aggressive malignant disease with poor prognosis. Surgical resection remains the most effective method for this malignancy. As to the middle and lower thoracic esophageal cancer patients without upper mediastinal lymph node metastasis, the rational transthoracic approach either through right or left chest has not been clarified to date due to lack of large scale multicenter randomized trials. Although some single-center

randomized trials were conducted recently, however, not enough convincing evidences were achieved to adapt right thoracic approach to treat all lower and middle thoracic esophageal cancer patients surgically. Due to inability to dissect the upper mediastinal lymph nodes, left thoracic approach(Sweet procedure) is considered less beneficial for patients with upper mediastinal lymph node metastasis. However, through right thoracic approach, the upper mediastinal lymph node can be dissected completely and which may bring a better long-term survival rate in such patients. Therefore, this study is designed to enroll patients with the middle or lower thoracic esophageal cancer who have no preoperative suspected upper mediastinal lymph node metastasis after preoperative precise evaluation by CT+EUS / PET-CT/EUS. Ten qualified hospitals with ≥200 esophagectomies each year will participate in this study. The purpose of this study is to compare the long-term outcomes of esophagectomy and postoperative recurrence rate through left and right transthoracic approaches in the middle and lower thoracic esophageal cancer patients without preoperative suspected upper mediastinal lymph node metastasis.

- Study Type: Interventional
- Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Efficacy Study

➢ Primary Outcomes:

- ✓ 3- and 5- year overall survival and disease free survival

➢ Secondary Outcomes:

- ✓ Degree of lymph node dissection
- ✓ Postoperative complications and perioperative parameters
- ✓ 3- and 5- year recurrence

➢ Estimated Enrollment: 800

➢ Study Start Date: January 2015

➢ Estimated Primary Completion Date: December 2017

➢ Estimated Study Completion Date: December 2019

Arms	Assigned Interventions
Active Comparator: Left thoracotomy Esophagectomy through left side transthoracic approach, with esophagogastric anastomosis above aortic arch and two-field lymphadenectomy (thoracic and abdominal lymph node)	Procedure/Surgery: Left thoracotomy Transthoracic approach is the surgical procedure including the open and minimally invasive thoracotomy.

Active Comparator: Right thoracotomy Esophagectomy through right side transthoracic approach, with esophagogastric anastomosis above azygos vain arch or on the top of chest cavity and two-field lymphadenectomy (thoracic and abdominal lymph node)	Procedure/Surgery: Right thoracotomy Transthoracic approach is the surgical procedure including the open and minimally invasive thoracotomy.

- Study design description

Hospitalized patients with resectable middle or lower thoracic squamous cell esophageal carcinoma who has no suspected enlarged upper mediastinal lymph nodes and within cT1b-3N0-1M0 after preoperative precise evaluation by CT/EUS or PET-CT/EUS, bone scan and brain MRI examination and other preoperative examinations (blood tests, cardiopulmonary function test, etc.) will be randomly assigned into two arms (Fig.1. CONSORT diagram):

Arm A: Esophagectomy through left transthoracic approach with esophagogastric anastomosis above aortic arch and two -field lymphadenectomy (thoracic and abdominal lymph nodes).

Arm B: Esophagectomy through right transthoracic approach with esophagogastric anastomosis above azygos vain arch or on the apex of right chest cavity and two -field lymphadenectomy (thoracic and abdominal lymph nodes),

Sample size:

According to the reported results of literatures in China, the 5-year survival rates of middle and lower thoracic esophageal cancer patients treated by esophagectomy through left and right transthoracic approach was about 30-40% and 40-50%, respectively. According to the sample size calculation formula of superiority-inferiority clinical trial design, if the level of significance test of 'α' is set at 0.05(one-side), the power is set to 80%(β=0.2), the subjects of the two groups should be enrolled at an equal frequency, the whole experiment is supposed to last for 5 years, the lost to follow-up rate is estimated as 5%, the estimated sample size is supposed to be 358 cases in each group, a total of 716 cases are required.

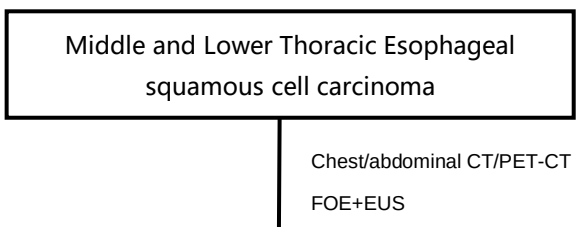

Fig. 1. CONSORT diagram of randomization and estimated enrollment

- Inclusion criteria
  - ⑴ Patients with histologically proved squamous cell esophageal cancer by fibrogastroscopic biopsies
  - ⑵ The preoperative clinical TNM stage by preoperative chest and abdominal CT, brain MRI and bone scan or PET-CT within cT1b-3N0-1M0; no history of other malignancy or simultaneous malignancy.

(3) Adequate function of heart, lungs, liver, brain and kidneys with normal WHO performance status (grade 0) to tolerate esophagectomy either through left or right thoracotomy;

(4) Age of 18~75 years;

(5) Without any preoperative anti-tumor therapy;

(6) No evidence showing suspicious upper mediastinal lymph node metastasis (short diameter of LN <0.8cm or shortest diameter / longest diameter <0.65) confirmed by the thoracic and abdominal CT and endoscopic ultrasonography (EUS).

(7) Willing to participate the clinical trial and signing the informed consent before enrolling into the clinical trail.

- Exclusion criteria

(1) Non-squamous cell esophageal carcinoma by fibrogastroscopic biopsies or postoperative pathological examination;

(2) The preoperative clinical TNM stage: N2-3 or M1;

(3) Inadequate cardiopulmonary, liver, brain and kidneys function with WHO performance status (>grade 0) for tolerating the esophagectomy;

(4) With any previous anti-cancer therapies prior to the surgery;

(5) Previous history of other or simultaneous malignancies;

(6) Suspicious upper mediastinal lymph node metastasis (LN short diameter≥ 0.8cm or shortest diameter / longest diameter≥ 0.65) confirmed by thoracic and abdominal CT and endoscopic ultrasonography(EUS).

(7) Unwilling to participate the clinical trial or refusing to sign the informed consent or receiving the treatment not consistent with the treatment plan of the trial protocol (palliative resection or exploration alone).

- Statistical analysis plan

The primary goal of this study was to compare 3- and 5- year OS and DFS in the middle and lower thoracic esophageal cancer patients who has no suspected upper mediastinal lymph node metastasis and were surgically treated through RTA versus through LTA. The secondary

goal was to compare the perioperative parameters, lymph node dissection and complications as well as 3- and 5- year recurrence between the two different approaches.

SPSS 20.0 (SPSS Inc, Chicago, IL, USA) is used for statistical analysis. All baseline characteristics, perioperative parameters, complications and lymph node dissection as well as recurrence rate between LTA and RTA are compared using the Pearson's chi-squared test for categorical data and student *t* test for measurement data. 3-year overall survival (OS) and disease-free survival (DFS) are estimated using the Kaplan-Meier method by SPSS or R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistically significant differences in OS and DFS between LTA and RTA are assessed using Log-rank test. A P-value of <0.05 was considered statistically significant.

- Contacts and Locations
  - Locations

Cancer hospital, Chinese Academy of Medical Sciences, Beijing, China, 100021

- Contact:

Yousheng Mao (Executive PI), MD, 86-10-87787138, maoysherx@126.com

Principal Investigator: Jie He, MD,PhD, 86-10-87788207, hejie@cicams.ac.cn

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Protocol modification (October 2015)

- Supplementary Collaborators:

An-lin Hao, *Anyang Cancer Hospital, Anyang, China;*

Xiao-fei Li, *The Fourth Military University Hospital, Xian, China;*

Mei-xin Xu, *Anhui Provincial Hospital, Hefei, China;*

Ren-quan Zhang, *First Affiliated Hospital, Anhui Medical University, Hefei, China;*

Reason for modification:

Prof. Yong-yu Liu who used to work at Liaoning Cancer Hospital, Shenyang moved to another hospital in October 2015. Since then, the enrollment at Liaoning Cancer Hospital, Shenyang was halted. Another reason was that the recruitment of patients at several primary collaborating hospitals was too slow to complete this trial in time. To compensate this, another four qualified collaborating hospitals were added to this study.

- Modification for surgical procedures:

Reason for modification:

The original protocol was designed to compare the outcomes of open esophagectomy via left thoracotomy with via right thoracotomy. However, VATS esophagectomy was getting more and more popular in China since 2010, patients frequently demanded VATS esophagectomy instead of open esophagectomy before singing the informed consent, which made us to modify our protocol accordingly. Therefore, we added VATS esophagectomy via right chest with an anastomosis in the chest or neck as an alternative procedure for right thoracic approach arm. However, there was no VATS esophagectomy via left chest for equivalent modification in the left thoracic approach arm, we could only add the esophagectomy with an anastomosis in the neck via left thoracotomy as an alternative procedure for left thoracic approach arm. Even though VATS esophagectomy is a minimally invasive procedure, it may have some confound effects, mainly the postoperative respiratory complications, which would not affect our primary outcomes, and we would still be able to do the subgroup analysis to compare the two different approaches in patients who undergo open esophagectomies.

Arms	Assigned Interventions
Active Comparator: Left thoracotomy Esophagectomy through left transthoracic approach, with	Procedure/Surgery: Left thoracotomy Transthoracic approach is the surgical procedure including the open and minimally

esophagogastric anastomosis above aortic arch or in the left neck and two-field lymphadenectomy (thoracic and abdominal lymph node)	invasive thoracotomy.
Active Comparator: Right thoracotomy Esophagectomy through right transthoracic approach, with esophagogastric anastomosis above azygos vain arch or in the apex of right chest cavity or in the left neck and two-field lymphadenectomy (thoracic and abdominal lymph node)	Procedure/Surgery: Right thoracotomy Transthoracic approach is the surgical procedure including the open and minimally invasive thoracotomy and VATS.

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