OFFICIAL TITLE
A Phase III Study of Left Side Thoracotomy Approach (Sweet Procedure) Versus Right Side Thoracotomy Plus Midline Laparotomy Approach (Ivor-Lewis Procedure) Esophagectomy in Middle or Lower Third Intrathoracic Esophageal Cancer

SETTING
Fudan University Shanghai Cancer Center

RESPONSIBLE PARTY
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This study was discussed in the Multidisciplinary Treatment Team for Thoracic cancer, approved by the Institutional Review Board of Fudan University Shanghai Cancer Center, and registered in Clinicaltrial.gov under number NCT01047111.

1. Background:
Esophageal carcinoma is an aggressive disease with a poor prognosis. Surgical resection remains the primary option for this malignancy. Although different approaches have been described for the surgical resection of esophageal cancer, there is no statistical evidence based on large scale prospective randomized trials with regard to the issue that which one is the optimal surgical approach for esophageal cancer. In China, Sweet esophagectomy (left thoracic approach), with the benefit of a single patient position and incision, is widely performed as majority of patients with the squamous cell carcinoma located in the middle and lower esophagus, although this procedure is criticized for inadequate lymphadenectomy due to frequently involved lymph nodes in the upper mediastinum. While the Ivor Lewis procedure, which may offer better visualization of thoracic esophagus and facilitate extended lymph node dissection in the abdomen and mediastinum through laparotomy and right thoracotomy, is performed limitedly in China as it seems to be more invasive than Sweet procedure.

2. Purpose:
The purpose of this study is to test two different approach of transthoracic esophagectomy (Right Side Thoracotomy plus Midline Laparotomy Approach [Ivor-Lewis Procedure] and Left Side Thoracotomy Approach [Sweet Procedure]) for middle or lower third intrathoracic esophageal cancer. This research is being done to see whether one approach is superior over the other approach with acceptable postoperative short-term outcome.

3. **Trial:**
   1) Allocation: Randomized (sealed envelope method).
   2) Endpoint Classification: Efficacy Study.
   3) Intervention Model: Parallel Assignment.
   4) Masking: Open Label.
   5) Primary Purpose: Treatment.
   6) Single-institutional.

4. **Measures:**

4.1 **Primary Outcome Measures:**

   Postoperative morbidity [Jan 2010-Jan 2012]:
   a) Anastomotic leak: Identified clinically or radio-graphically,
   b) Respiratory complications: Clinical manifestation of pneumonia or bronchopneumonia confirmed by CT scan
   c) Cardiovascular complications: Persistent arrhythmia requiring medical treatment
   d) Chylothorax: Appearance of milky fluid from the thoracic drains after onset of enteral nutrition
   e) Wound infections: Wound opened and daily bedside dressing is needed.
   f) Delayed gastric emptying: Delayed oral food intake and confirmed by contrast swallow.
   g) Pleural effusion: A thoracentesis was need.
   h) Recurrent nerve injury: Hard to define, and recorded according to the change compared with the voice before surgery identified by patient and surgeon in charge.

4.2 **Secondary Outcome Measures:**
1. **Postoperative mortality [Jan 2010-Jan 2012]**

   Hospital death defined as any death during hospital stay.

2. **Oncological efficacy [Jan 2010-Jan 2012]**

   Numbers of the lymph nodes resected and positive nodes in the mediastinum and upper abdomen.

4.3 **Estimated outcomes:**

   Ivor-Lewis esophagectomy is associated with more postoperative complications, but more lymph nodes retrieve.

5. **Study protocol:**

5.1 **Estimated Enrollment:** 300.

   PASS (power analysis and sample size software) were used for sample size calculation. Previous data indicated a 15% difference in 3-year survival between Sweet procedure (35%) and Ivor Lewis procedure (50%). With an estimation of 10% loss of follow-up, 140 patients per study arm were necessary, using 80% statistic power. To reduce to proportion of loss of follow-up, we plan to include 150 patients for each group.

5.2 **Randomization:**

   Randomization, by the sealed envelope method, took place on the morning of the day of the planned resection. Sealed envelopes were prepared and provided by the Department of Biostatistics, Fudan University.

5.3 **Study Start Date:** May 2010; **Estimated Study Completion Date:** July 2012 (for short-term outcomes)

5.4 **Surgery and postoperative treatment.**

   Surgery was performed by consultant thoracic surgeons who had performed at least 50 esophagectomies each year. Esophageal resection specimens were histopathologically assessed by experienced pathologists using a standardized protocol in which site and size of the primary cancer, sample margins and tumor
differentiation were recorded in addition to presence of lymphovascular invasion. All lymph nodes resected were labeled for pathologic examination according to the anatomical sites.

Arm A:

Ivor-Lewis Procedure: Esophagectomy was conducted through right side thoracotomy plus midline laparotomy approach.

Patient is placed supine initially. Through an upper midline abdominal incision, gastric tubulization about 4 cm in width is completed and a feeding jejunostomy was also performed. Then the patient was positioned in left lateral decubitus, a right thoracotomy with a muscle-sparing incision was made in the fourth intercostal space. After ligating and dissecting the azygos vein, the esophagus was resected. Then the gastric tube was delivered into the thorax and a circular stapled end-to-side esophagogastric anastomosis is fashioned in the upper mediastinum. Thoracic duct ligation was routinely conducted in the Ivor Lewis procedure, however, not in the Sweet procedure. A nasogastric tube was also positioned in the gastric tube to prevent vomiting and acute gastric tube distension. During Ivor Lewis procedure, total lymphadenectomy was performed, including lymph nodes along the bilateral recurrent nerves and those resected during standard lymphadenectomy.

Arm B:

Sweet Procedure: Esophagectomy was conducted through left side thoracotomy or thoracoabdominal incision.

Patients were placed in a right lateral decubitus position at an angle of 80°. A thoracic incision was performed through the sixth or seventh intercostal space. The diaphragm was incised to access and expose the abdominal cavity. The esophagus was mobilized, and the gastric tube, about 4 cm in width, was completed along the greater curvature. The tumor is resected with at least 5 cm proximal clearance, and a frozen-section histological analysis of the proximal margin was routinely performed. Finally, an end to side esophagogastric anastomosis was fashioned with a circular staple at sub-aortic or supra-aortic level. Anastomosis with manual suture in the left neck was performed in selected cases. A feeding tube was inserted in the jejunum and a nasogastric tube was positioned in the gastric tube. During the Sweet procedure, standard lymphadenectomy was performed removing all lymph nodes in the middle
and lower periesophageal portion, subcarinal region, lower posterior mediastinum, perigastric region and those along the left gastric artery and splenic artery.

**Postoperative treatment:**

Patients in both groups received similar postoperative treatment. Patients were extubated at the end of the procedure if physiologically stable, and were then admitted to the intensive care unit and discharged the next day to a thoracic surgery ward. In the first 3 days after surgery, patient-controlled epidural analgesia was the main postoperative pain control system. On postoperative day (POD) 1, patients were encouraged to move out of bed, and enteral nutrition was commenced via the feeding tube. Contrast swallow, not routinely but optionally, was performed on POD 5 or 6. Patients were started on sips of clear liquids on POD 6 and soft solid foods on POD 7, and discharged routinely on POD 8 or 9.

**5.5 Patients.**

**Ages Eligible for Study:** 18 Years to 75 Years

**Genders Eligible for Study:** Both.

**Healthy Volunteers:** No.

**Preoperative evaluation:**

Oncological evaluation included upper GI endoscopy with histologic examination, upper GI barium swallow, computerized tomography of the chest and upper abdomen, and ultrasound of the cervical region. Pulmonary and cardiac functions were also performed to assess the medical operability.

**Criteria**

**Inclusion Criteria:**

1. Patients with histologically proven squamous cell esophageal cancer

2. Patients with cT1-T3/N0-N1 mid or distal third (inferior to carina and 3 cm superior to cardia) operable esophageal lesion. Staging investigations including esophagogastroduodenoscopy, chest and abdominal CT scan, barium swallow and selective endoscopic ultrasonography showing no evidence of invading adjacent structure such as spine, bronchus, pericardium, descending aorta and without enlargement cervical and celiac nodes (diameter of short axis greater than 1.5 cm) measured at CT scans.

3. Karnofsky performance status greater than or equal to 80%
4. Pulmonary and cardiac function must be acceptable for surgery according to institutional standards.

5. Acceptable hepatic, renal and bone marrow function

**Exclusion Criteria:**

1. Patients with low performance status (Karnofsky score <80%)
2. Past history of malignancy
3. Stage investigations indicating unresectable advanced disease (T4 or M1a, M1b)
4. Patients with any other serious underlying medical condition that would impair the ability of the patient to receive or comply with protocol treatment
5. Patients medically unfit for surgical resection.
6. Lymph nodes in the upper mediastinum larger than 5mm (diameter of longaxis)

5.6 Data collection

All collected data will be entered into a statistical software package for subsequent analysis.

6. Long-term outcomes and follow-up

6.1 Primary Outcome Measures:

1. **Disease free survival [Jan 2010-Jan 2016]:** Time from surgery to the first recurrence (locoregional, hematogenous, and others)
2. **Overall survival [Jan 2010-Jan 2016]:** Time from surgery to the death due to cancer.

6.2 Secondary Outcome Measures:

Locoregional recurrence and recurrence pattern [Jan 2010-Jan 2016]: Recurrence were classified as locoregional (at the site of the primary tumor, the anastomotic site, or the lymph node), hematogenous, and other.

6.3 Postoperative adjuvant treatment:

Postoperative adjuvant treatment was given according to the postoperative pathological findings:

a) Radio-therapy was performed for patients with T3/4 tumors, or positive resection margins.
b) Chemo-therapy was performed for patients with positive lymph nodes.

6.4 Long-term follow-up

Patients will be followed up three monthly for the first two years and six monthly for the third to fifth years and annually thereafter. A detailed history and clinical examination and CT scan, barium swallow and ultrasound will be done routinely on every follow up. Patients were seen either at our outpatient’s clinic or by telephone interview.