Original Investigation

Comparison of Ivor-Lewis vs Sweet Esophagectomy for Esophageal Squamous Cell Carcinoma
A Randomized Clinical Trial

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IMPORTANCE Sweet esophagectomy is performed widely in China, while the Ivor-Lewis procedure, with potential benefit of an extended lymphadenectomy, is limitedly conducted owing to concern for a higher risk for morbidity. Thus, the role of the Ivor-Lewis procedure for thoracic esophageal cancer needs further investigation.

OBJECTIVE To determine whether Ivor-Lewis esophagectomy is associated with increased postoperative complications compared with the Sweet procedure.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial was conducted from May 2010 to July 2012 at Fudan University Shanghai Cancer Center, Shanghai, China, of 300 patients with resectable squamous cell carcinoma in the middle and lower third of the thoracic esophagus. Intent-to-treat analysis was performed.

INTERVENTIONS Patients were randomly assigned to receive either the Ivor-Lewis (n = 150) or Sweet (n = 150) esophagectomy.

MAIN OUTCOMES AND MEASURES The primary outcome of this clinical trial was operative morbidity (any surgical or nonsurgical complications). Secondary outcomes included oncologic efficacy (number of lymph nodes resected and positive lymph nodes), postoperative mortality (30-day and in-hospital mortality), and patient discharge.

RESULTS Resection without macroscopical residual (R0/R1) was achieved in 149 of 150 patients in each group. Although there was no significant difference between the 2 groups regarding the incidence of each single complication, a significantly higher morbidity rate was found in the Sweet group (62 of 150 [41.3%]) than in the Ivor-Lewis group (45 of 150 [30%]) (P = .04). More patients in the Sweet group (8 of 150 [5.3%]) received reoperations than in the Ivor-Lewis group (1 of 150 [0.7%]) (P = .04). The median hospital stay was 18 days in the Sweet group vs 16 days in the Ivor-Lewis group (P = .002). Postoperative mortality rates in the Ivor-Lewis (1 of 150) and Sweet (3 of 150) groups were 0.7% and 2.0%, respectively (P = .25). More lymph nodes were removed during Ivor-Lewis esophagectomy than during the Sweet procedure (22 vs 18, P < .001).

CONCLUSIONS AND RELEVANCE Early results of this study demonstrate that the Ivor-Lewis procedure can be performed with lower rates of postoperative complications and more lymph node retrieval. Ivor-Lewis and Sweet esophagectomies are both safe procedures with low operative mortalities.

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Esophageal cancer is one of the most common lethal malignant diseases worldwide.[1] Surgery offers the best curative option; however, the optimal surgical technique is still under debate with regard to the surgical approaches and extent of lymphadenectomy. Controversy in the West exists between an extended transthoracic approach and a limited transhiatal esophagectomy.[2,3] In China, Sweet esophagectomy is widely performed through a single left-sided thoracic incision,[4-6] although it is criticized for inadequate lymphadenectomy in the upper mediastinum. However, the right-sided Ivor-Lewis procedure, while offering better visualization of the thoracic esophagus and thus facilitating an extended lymph node dissection, is performed less often because it is considered to be associated with more postoperative complications.[5]

To our knowledge, only a few retrospective studies to date have compared left- and right-sided thoracic esophagectomies and with controversial clinical outcomes regarding short-term complications and long-term survival.[7-11] In an attempt to answer this question, we undertook a randomized clinical trial to compare Ivor-Lewis esophagectomy with Sweet esophagectomy in patients with esophageal squamous cell carcinoma in the middle and lower third of the thoracic esophagus, assessing short-term outcomes of perioperative morbidity, mortality, and oncologic efficacy.

Methods

Study Design

This study was a randomized single-center trial sponsored by the Key Construction Program of the National 985 Project (grant 985III-YFX0102). The study protocol was approved by the institutional review board of Fudan University Shanghai Cancer Center, China (Supplement). Outcomes were assessed on the day of patient discharge. All patients enrolled provided written informed consent.

Participants

Oncological evaluation included upper gastrointestinal endoscopy with histologic examination, upper gastrointestinal barium swallow, computerized tomography of the chest and upper abdomen, and ultrasonography of the cervical region. Eligible patients included those with resectable disease (cT1-T3, N0-N1, and M0), no evidence of distant metastases (including the absence of histologically confirmed tumor-positive cervical or positive celiac lymph nodes), and histologically confirmed squamous cell carcinoma or high-grade dysplasia in the middle and lower thirds of the thoracic esophagus (inferior to carina and 3 cm superior to cardia). Exclusion criteria included age older than 75 years, presence of enlarged lymph nodes in the upper mediastinum (>5 mm), history of other malignant disease, previous gastric or esophageal surgery, neoadjuvant chemotherapy or radiotherapy, severe major organ dysfunction, and Karnofsky Index score less than 80.

Randomization

Eligible patients were randomly assigned to undergo either the Ivor-Lewis or Sweet procedures. Randomization, by the sealed envelope method, took place on the morning of the planned resection. Sealed envelopes were prepared and provided by the Department of Biostatistics, Fudan University. Masking was not done. Patients, surgeons, and trial management staff who collected the data were aware of the assigned treatment (**Figure**).

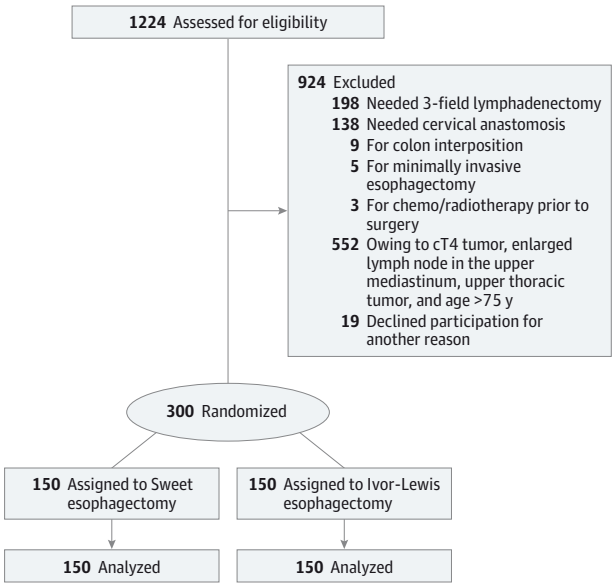
Surgery

Surgery was performed by consultant thoracic surgeons who had performed at least 400 esophagectomies. The surgical technique of both procedures has been described elsewhere.[12,13]

Briefly, in the Sweet procedure, 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 a gastric tube, about 4 cm in width, was placed along the greater curvature. The tumor was then resected with at least 5 cm of proximal clearance, and a frozen-section histological analysis of the proximal margin performed. Finally, an end-to-side esophagogastric anastomosis was fashioned with a circular staple at the sub- or supra-aortic level. Anastomosis with manual suture on the left side of the neck was performed in selected cases. A feeding tube was inserted in the jejunum and nasogastric tube positioned in the gastric tube.

In the Ivor-Lewis procedure, the patient was placed initially supine. Through an upper midline abdominal incision, gastric tubulization was completed and feeding jejunostomy performed. Then, the patient was positioned in the left lateral decubitus, and 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

Figure. Trial Profile of Perioperative Data



Patients underwent esophagectomy for cancer between May 2010 and July 2012.

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and a circular stapled end-to-side esophagogastric anastomosis was fashioned in the upper mediastinum. A nasogastric tube was also positioned in the gastric tube to prevent vomiting and acute gastric tube distension. It should be noted that thoracic duct ligation was routinely conducted in the Ivor-Lewis procedure but not in the Sweet procedure.

Lymphadenectomy

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 and splenic arteries. However, common hepatic and celiac nodes were not routinely removed owing to limited exposure through the left thoracic incision and rare metastases according to the map of lymph nodes metastases in our previous study for esophageal squamous cell carcinoma.[14] During the Ivor-Lewis procedure, total lymphadenectomy was performed including lymph nodes along the bilateral recurrent nerves and those resected during standard lymphadenectomy. All lymph nodes resected were labeled for pathologic examination according to anatomical sites.

Postoperative Treatment

Patients in both groups received similar postoperative care. Patients were extubated at the end of the procedure if physiologically stable, then admitted to the intensive care unit, and finally discharged the next day to a general surgical 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 feeding tube. Contrast swallow, not routinely but optionally, was performed on POD 5 or 6. Patients were given sips of clear liquids on POD 6, soft solid foods on POD 7, and discharged routinely on POD 8 or 9.

Data of postoperative complications were collected prospectively, and data regarding tumor size, histologic type, tumor penetration, lymph node metastases, and TNM stage were obtained from the pathologic records.

Outcomes

The primary outcome of this study was operative morbidity. Secondary outcomes included oncologic efficacy and postoperative mortality.

Postoperative complications included anastomotic leak (identified clinically or radiographically); respiratory complications (defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by computed tomographic scan); cardiovascular complications (defined as persistent arrhythmia requiring medical treatment); chylothorax (defined as the appearance of milky fluid from thoracic drains after onset of enteral nutrition); wound infections; and other complications (delayed gastric emptying, pleural effusion, recurrent nerve injury). Postoperative mortality was defined as death from any cause.

Statistical Analysis

We used power analysis and sample-size software for sample-size calculation. Previous data indicated a 15% difference in 3-year survival between the Sweet (35%) and Ivor-Lewis (50%) procedures.[11,15-17] With an estimation of 10% loss of follow-up, 140 patients per study arm were necessary, using 80% statistical power. To reduce the proportion of loss of follow-up, we included 150 patients for each group. The χ^2 or Fisher exact tests were used to compare categorical data and the *t* test or Mann-Whitney *U* test for continuous data. All analyses were performed with the statistical package SPSS (SPSS 16.0). $P < .05$ was considered statistically significant.

Results

Characteristics of the Patients

From May 2010 to July 2012, 300 eligible patients were randomly assigned to receive either the Ivor-Lewis (n = 150) or Sweet (n = 150) esophagectomy in Fudan University Shanghai Cancer Center (Figure). Baseline demographics and clinicopathologic characteristics, including age, sex, body mass index, comorbidities (hypertension, diabetes mellitus, and heart disease), and tumor site, of the 2 groups were comparable (**Table 1**). Final pathologic reports also showed similar TNM stage distribution between the 2 groups (**Table 2**).

Morbidity and Mortality

Postoperative mortality did not differ significantly between the 2 cohorts (3 of 150 [2.0%] in the Sweet vs 1 of 150 [0.7%] in the Ivor-Lewis groups; $P = .25$) (**Table 3**). In the Sweet group, 2 patients died of respiratory failure secondary to pulmonary infections and 1 patient died of acute gastrointestinal bleeding. In the Ivor-Lewis group, only 1 patient died of cerebrovascular accident.

Although operating time was significantly longer in the Ivor-Lewis than in the Sweet groups (mean [SD], 202 [38] minutes vs 174 [35] minutes, respectively; $P < .001$), the hospital stay was significantly shorter for patients who underwent the Ivor-Lewis esophagectomy (median, 18 days in the Sweet group vs 16 days in the Ivor-Lewis group; $P = .002$). The incidences of anastomotic leakage, chylothorax, and pulmonary infections were numerically, but not significantly, higher in the Sweet group. There was no significant difference with regard to other postoperative complications. However, a significantly higher morbidity rate was found in patients who underwent Sweet esophagectomy (62 of 150 [41.3%]) than those who underwent Ivor-Lewis esophagectomy (45 of 150 [30%]) ($P = .04$).

Of the 10 patients with chylothorax in the Sweet group, 3 patients were reoperated on for thoracic duct ligation by thoracotomy. In 1 patient, the ligation was not successful, and the patient died of respiratory failure. Significantly more patients in the Sweet group underwent reoperations (8 of 150 [5.3%] in the Sweet group vs 1 of 150 [0.7%] in the Ivor-Lewis group; $P = .04$). In the Sweet group, 8 patients (5.3%) underwent reoperation: 3 for control of chylothorax, 3 because of anastomotic leakage, 1 for intrathoracic hemorrhage, and 1 for jejunostomy. However, in the Ivor-Lewis group, only 1 patient (0.7%) had reoperation, which was for control of chylothorax.

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Table 1. Basic Patient Characteristics and Clinical Data

Characteristic	Groups, No. (%) Sweet (n = 150)	Ivor-Lewis (n = 150)	*P* Value
Age, median (range), y	60 (39-74)	60 (38-74)	.56
Sex			
Male	124 (82.7)	118 (78.7)	.38
Female	26 (17.3)	32 (21.3)	
BMI			
<25	104 (69.3)	113 (75.3)	.25
≥25	46 (30.7)	37 (24.7)	
Comorbidities, No. (%)			
Hypertension	28 (18.7)	26 (17.3)	.76
Diabetes mellitus	10 (6.7)	7 (4.7)	.45
Heart disease	5 (3.3)	2 (1.3)	.45
Total	37 (24.7)	32 (21.3)	.49
Tumor site			
Middle	82 (54.7)	95 (63.3)	.13
Lower	68 (45.3)	55 (36.7)	
Histology			
High-grade dysplasia	6 (4.0)	2 (1.3)	.30
Squamous cell carcinoma	140 (93.3)	146 (97.3)	
Small cell carcinoma	3 (2.0)	1 (0.7)	
Other	1 (0.7)	1 (0.7)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 2. Histological Parameters

Parameter	Groups, No. (%) Sweet (n = 150)	Ivor-Lewis (n = 150)	*P* Value
Tumor length, median (range)	3.0 (0.5-7.5)	2.5 (0.5-8.0)	.24
Tumor stage			
Tis	6 (4.0)	2 (1.3)	.40
T1a	7 (4.7)	8 (5.3)	
T1b	25 (16.7)	23 (15.3)	
T2	31 (20.7)	46 (30.7)	
T3	73 (48.7)	66 (44.0)	
T4a	7 (4.7)	4 (2.7)	
T4b	1 (0.7)	1 (0.7)	
Nodal status			
N0	81 (54.0)	84 (56.0)	.93
N1 (1-6)	64 (42.7)	60 (40.0)	
N2 (6-9)	4 (2.7)	5 (3.3)	
N3 (≥9)	1 (0.7)	1 (0.7)	
TNM stage			
0	6 (4.0)	2 (1.3)	.64
I	23 (15.3)	28 (18.7)	
IIA	53 (35.3)	55 (36.7)	
IIB	19 (12.7)	24 (16.0)	
IIIA	43 (28.7)	34 (22.7)	
IIIB	4 (2.7)	5 (3.3)	
IV	2 (1.3)	2 (1.3)	

Lymphadenectomy

Because we lacked the data on circumferential involvement, the percentage of R0 resection was unavailable. Resection without macroscopical residual (R0/R1) was achieved in 149 of 150 patients (99.3%). A significantly higher number of lymph nodes was retrieved in the Ivor-Lewis group (median, 22; range, 8-56) compared with the Sweet group (median, 18; range, 3-51; $P < .001$). We further classified lymph node groups according

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Table 3. Postoperative Outcomes

Outcome	Groups, No. (%)		P Value
	Sweet (n = 150)	Ivor-Lewis (n = 150)	
Intraoperative data			
Operative time, mean (SD), min	174 (35)	202 (38)	<.001
Blood transfusion	1 (0.7)	2 (1.3)	>.99
ICU stay, median (range), d	1 (0-12)	1 (0-12)	.28
Hospital stay, median (range), d	18 (10-90)	16 (10-60)	.002
Postoperative complications			
Anastomotic leakage	8 (5.3)	2 (1.3)	.10
Pulmonary infection	16 (10.7)	13 (8.7)	.56
Cardiac complication	21 (14.0)	17 (11.3)	.49
Chylothorax	11 (7.3)	5 (3.3)	.20
Delayed gastric emptying	4 (2.7)	7 (4.7)	.54
Pleural effusion	9 (6.0)	7 (4.7)	.71
Vocal cord paralysis	4 (2.7)	3 (2.0)	>.99
Wound infection	1 (0.7)	2 (1.3)	>.99
Total	62 (41.3)	45 (30.0)	.04
Reoperations	8 (5.3)	1 (0.7)	.04
In-hospital mortality	3 (2.0)	1 (0.7)	.25

Abbreviation: ICU, intensive care unit.

Table 4. Number of Lymph Nodes Resected

Region	Groups, Median (Range)		P Value
	Sweet (n = 150)	Ivor-Lewis (n = 150)	
Mediastinum			
Upper	0 (0-10)	3 (0-27)	<.001
Middle	7 (0-36)	8 (0-27)	.02
Lower	2 (0-15)	1 (0-21)	<.001
Middle/lower	10 (0-36)	9 (0-27)	.96
Perigastric	7 (0-25)	7 (0-27)	.35
Celiac	0 (0-10)	1 (0-14)	<.001
Total	18 (3-51)	22 (8-56)	<.001

to dissection area. The Ivor-Lewis procedure showed superiority in the dissection of lymph nodes both in the upper mediastinum and areas around the common hepatic and celiac arteries, whereas the number of lymph nodes retrieved in the middle/lower esophagus and perigastric regions was similar between the 2 groups (**Table 4**). Consequently, more patients in the upper mediastinum had positive lymph nodes following the Ivor-Lewis procedure (18 of 150 [12.0%]) than the Sweet procedure (5 of 150 [3.3%]) (P = .005). Three cases in the Ivor-Lewis group had positive celiac nodes, although there was no significant difference in this area (**Table 5**).

Discussion

Esophagectomy is among the surgical procedures with the highest incidence of complications. Although Ivor-Lewis esophagectomy is advocated by the Chinese Anti-Cancer Association,[18] a left posterolateral approach with limited lymphadenectomy remains a priority in China given the debate on the extent of lymphadenectomy necessary and, more importantly, concern about the Ivor-Lewis esophagectomy being associated with higher postopera-tive complications. However, our study has demonstrated that patients in the Ivor-Lewis group experienced a lower incidence of in-hospital morbidity and shorter hospital stay compared with those in the Sweet group, although operative time was somewhat longer. Importantly, our trial showed significantly better lymph node resection in the Ivor-Lewis procedure than in the Sweet esophagectomy.

The overall incidence of patients having at least 1 postoperative complication was 35% in our trial. Although the incidence of each complication did not differ significantly between the 2 groups, more patients in the Sweet group did experience postoperative complications than in the Ivor-Lewis group. This higher incidence of morbidity in the Sweet group was associated with a higher rate of reoperations and longer hospital stay.

As previously reported,[19,20] pulmonary events constituted most of the complications in this trial. A variety of factors, including advanced age, preexisting poor pulmonary function,

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Table 5. Regions of Lymph Nodes Metastases

Region	Groups, No. (%)		*P* Value
	Sweet (n = 150)	Ivor-Lewis (n = 150)	
Mediastinum			
Upper	5 (3.3)	18 (12.0)	.005
Middle	18 (12.0)	26 (17.3)	.19
Lower	25 (17.3)	17 (11.3)	.14
Abdominal	46 (30.7)	33 (22.0)	.09
Perigastric	46 (30.7)	31 (20.7)	.047
Celiac	0 (0)	3 (2.0)	.25

poor performance status, smoking status, and, notably, surgical approach, were believed to be related to respiratory problems.[21] In our trial, no patient in the Sweet group underwent surgery through the combined thoracoabdominal approach, in consideration of potentially increased postoperative pain with costal cartilage incision. This may explain our lower incidence of pulmonary complications than that in published reports.[22] Although the incidence was comparable between the 2 groups in our trial, we prefer the Ivor-Lewis procedure because of more lymph nodes being resected. During the Sweet procedure, division of the diaphragm and 1-lung anesthesia throughout the operation may also contribute to pulmonary problems. Of note, no Ivor-Lewis group patient died of pulmonary complication, whereas death was due to pulmonary complication in 2 of 3 patients following Sweet esophagectomy.

Anastomotic leakage is an important issue in the management of surgical complications because it can be fatal. The rate of leakage in our series was lower than that in many other series using a similar intrathoracic stapling technique.[17,22,23] High surgeon volume may be an important factor for this lower incidence.[24] Although there was no significant difference, more patients in the Sweet group experienced anastomotic leakage. We note that the Ivor-Lewis procedure was our preferred approach and more widely performed during the period of this study. The Sweet approach was our major surgical approach prior to 2006, during which time our chief surgeons performed at least 50 Sweet esophagectomies. Hence, the comparison is valid. Importantly, no death in this trial was related to anastomotic leakage. Early identification, clear thoracic and mediastinal drainage, and sometimes reoperation for drainage seem to be of most importance in the avoidance of additional severe complications.

Chylothorax was another major postoperative complication, and it was the main reason for reoperation in this trial. In our center, thoracic duct ligation was routinely performed in the Ivor-Lewis procedure, while not in the Sweet procedure owing to access during the left-sided approach, and thus, postoperative chylothorax occurred more frequently in the Sweet than in the Ivor-Lewis procedures, although there was no statistical significance. Our study supported the preventive effect of thoracic duct ligation on chylothorax demonstrated in another trial.[25] Therefore, the Ivor-Lewis procedure would seem to be the optimal approach for reducing chylothorax.

Cardiovascular events and other minor complications, including wound infection, pleural effusion, and delayed gastric emptying, were also comparable between the 2 groups. Although the incidence of persistent recurrent nerve injuries can be biased because none received laryngoscopy in the postoperative period, strict criteria of patient selection contributed to this low incidence. Only patients without enlarged lymph nodes in the upper mediastinum (>5 mm in diameter) were enrolled so that the possibility of recurrent nerve injury was reduced during upper mediastinal lymphadenectomy.

Compared with other esophageal cancer centers where more left-sided thoracic approaches were performed, the number of lymph nodes examined in our center was larger.[4,5,14,26] In this trial, we confirmed the superiority of lymph node retrieval using the Ivor-Lewis approach. Although the distribution of TNM stages was similar between the 2 groups, stage migration may still be a consideration owing to inadequate lymphadenectomy during the Sweet procedure. Lymph nodes in 2 regions were always omitted during Sweet esophagectomy: those along bilateral recurrent nerves in the upper mediastinum due to anatomical limitation by the aortic arch and lymph nodes along the common hepatic and celiac arteries in the upper abdomen because we chose a single left-sided thoracic approach for the Sweet procedure, which resulted in poor exposure in these regions. Although abdominal lymphatic involvement was rare, involvement in the upper mediastinum was common.[14] In this study, 18 of 150 (12.0%) patients in the Ivor-Lewis group showed positive lymph nodes along bilateral recurrent nerves. This implies that the more extensive lymph node resection of the former procedure was needed to remove more potential positive lymph nodes, thus offering better tumor staging. With regard to the current question on the extent of lymphadenectomy, future follow-up of this trial may clarify the long-term benefits of the extended lymphadenectomy using the Ivor-Lewis procedure.

One limitation of this study was that we did not evaluate postoperative functional status and therefore cannot comment in detail on quality of life following surgery. Moreover, pulmonary complications may be reduced if a left thoracoabdominal approach is performed with the diaphragm incised at its periphery, thus preserving its innervation.[27] Likewise, the thoracic duct is easily ligated when using a left thoracoabdominal approach with its better exposure, thus reducing the incidence of chylothorax. However, because of what is widely done in China and considering potentially increased wound complication and postoperative pain, we chose the left-sided thoracic approach with the diaphragm incised vertically in this study.

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Conclusions

Our data provide evidence for the superiority of the Ivor-Lewis esophagectomy over the Sweet procedure with regard to short-term outcomes such as lymph node retrieval and overall morbidity for patients with squamous cell cancer in the middle and lower third of the thoracic esophagus. Further follow-up may elucidate whether the Ivor-Lewis procedure also has an advantage in disease control and long-term survival.

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