Efficacy and safety of esophagectomy via left thoracic approach versus via right thoracic approach for middle and lower thoracic esophageal cancer: a multicenter randomized clinical trial (NST1501)

You-Sheng Mao[1#], Shu-Geng Gao[1#], Yin Li[1,2#], An-Lin Hao[3], Jun-Feng Liu[4], Xiao-Fei Li[5], Tie-Hua Rong[6], Jian-Hua Fu[6], Jian-Qun Ma[7], Mei-Qing Xu[8], Ren-Quan Zhang[9], Gao-Ming Xiao[10], Xiang-Ning Fu[11], Ke-Neng Chen[12], Wei-Min Mao[13], Yong-Yu Liu[14], Hong-Xu Liu[14], Zhi-Rong Zhang[1], Yan Fang[3], Dong-Hong Fu[3], Xu-Dong Wei[3], Li-Gong Yuan[1], Shan Muhammad[1], Wen-Qiang Wei[15], Philip Wai-Yan Chiu[16], Shane Lloyd[17], Francisco Schlottmann[18,19], Kenneth Meredith[20], Jose M. Pimiento[21], Yi-Bo Gao[1], Jie He[1]

[1]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Thoracic Surgery, Henan Cancer Hospital, Zhengzhou, China; [3]Department of Thoracic Surgery, Anyang Cancer Hospital, Anyang, China; [4]Department of Thoracic Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [5]Department of Thoracic Surgery, The Fourth Military University Hospital, Xi'an, China; [6]Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; [7]Department of Thoracic Surgery, Heilongjiang Cancer Hospital, Harbin, China; [8]Department of Thoracic Surgery, Anhui Provincial Hospital, Hefei, China; [9]Department of Thoracic Surgery, First Affiliated Hospital, Anhui Medical University, Hefei, China; [10]Department of Thoracic Surgery, Hunan Cancer Hospital, Changsha, China; [11]Department of Thoracic Surgery, Tongji Hospital, Tongji University, Wuhan, China; [12]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing University, Beijing, China; [13]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, China; [14]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang, China; [15]Department of Epidemiology, National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [16]Division of Upper Gastrointestinal and Metabolic Surgery, Department of Surgery, Prince of Wales Hospital, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; [17]Department of Radiation Oncology, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA; [18]Department of Surgery, Hospital Alemán of Buenos Aires, Buenos Aires, Argentina; [19]Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA; [20]Gastrointestinal Oncology, Sarasota Memorial Institute for Cancer Care, Sarasota, FL, USA; [21]Department of Gastrointestinal Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Contributions: (I) Conception and design: J He, YS Mao, WQ Wei; (II) Administrative support: YS Mao, YB Gao; (III) Provision of study materials or patients: SG Gao, Y Li, AL Hao, JF Liu, XF Li, TH Rong, JH Fu, JQ Ma, MQ Xu, RQ Zhang, GM Xiao, XN Fu, KN Chen, WM Mao, YY Liu, HX Liu; (IV) Collection and assembly of data: ZR Zhang, Y Fang, DH Fu, XD Wei; (V) Data analysis and interpretation: LG Yuan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jie He. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan South Lane, Chaoyang District, Beijing 100021, China. Email: prof.jiehe@gmail.com.

Background: Left thoracic approach (LTA) has been a favorable selection in surgical treatment for esophageal cancer (EC) patients in China before minimally invasive esophagectomy (MIE) is popular. This study aimed to demonstrate whether right thoracic approach (RTA) is superior to LTA in the surgical treatment of middle and lower thoracic esophageal squamous cell carcinoma (TESCC).

Methods: Superiority clinical trial design was used for this multicenter randomized controlled two-parallel group study. Between April 2015 and December 2018, cT1b-3N0-1M0 TESCC patients from 14 centers were recruited and randomized by a central stratified block randomization program into LTA or RTA groups. All enrolled patients were followed up every three months after surgery. The software SPSS 20.0 and R 3.6.2. were used for statistical analysis. Efficacy and safety outcomes, 3-year overall survival (OS) and disease-free survival (DFS) were calculated and compared using the Kaplan-Meier method and the log-rank test.

Results: A total of 861 patients without suspected upper mediastinal lymph nodes (umLN) were finally enrolled in the study after 95 ineligible patients were excluded. 833 cases (98.7%) were successfully followed up until June 1, 2020. Esophagectomies were performed via LTA in 453 cases, and via RTA in 408 cases. Compared with the LTA group, the RTA group required longer operating time (274.48±78.92 *vs.* 205.34±51.47 min, P<0.001); had more complications (33.8% *vs.* 26.3% P=0.016); harvested more lymph nodes (LNs) (23.61±10.09 *vs.* 21.92±10.26, P=0.015); achieved a significantly improved OS in stage IIIa patients (67.8% *vs.* 51.8%, P=0.022). The 3-year OS and DFS were 68.7% and 64.3% in LTA arm versus 71.3% and 63.7% in RTA arm (P=0.20; P=0.96).

Conclusions: Esophagectomies via both LTA and RTA can achieve similar outcomes in middle or lower TESCC patients without suspected umLN. RTA is superior to LTA and recommended for the surgical treatment of more advanced stage TESCC due to more complete lymphadenectomy.

Trial Registration: ClinicalTrials.gov NCT02448979.

Keywords: Esophageal cancer (EC); esophagectomy; outcomes; left thoracic approach (LTA); right thoracic approach (RTA)

Submitted Jan 05, 2022. Accepted for publication Aug 17, 2022.
doi: 10.21037/atm-22-3810
View this article at: https://dx.doi.org/10.21037/atm-22-3810

Introduction

Esophageal cancer (EC) is one of the most prevalent malignancies with high incidence and death rate in China. According to the report from the China National Cancer Registry Office in 2022, there were an estimated 252,500 newly diagnosed EC cases, and 193,900 cases died of EC. The incidence and mortality of EC ranked sixth and fifth, respectively, among all malignancies in China (1). Surgical treatment or surgery-based multidisciplinary treatment is still the mainstream. Historically, most of the esophagectomies for middle and lower thoracic EC in China have been performed via left thoracotomy and the diaphragmatic incision (Sweet procedure) (2-5). About 90% of EC patients continued to undergo esophagectomies through the left thoracic approach (LTA) until 2010 (3-5). The 5-year overall survival (OS) rate via LTA was reported to be between 30% and 40%, which has not been improved for several decades due to the high incidence of recurrence in the lower neck and the upper mediastinum in several large Chinese surgical series (3-7). It has been speculated that the long-term prognosis of EC patients treated surgically through LTA may be compromised by the limited upper mediastinal lymphadenectomy due to sheltering of these nodes by the aortic arch and its branches (6,7). Since 2000, several retrospective studies have reported that the 5-year OS rate in patients receiving esophagectomies through the right thoracotomy approach (RTA) such as Ivor-Lewis or McKeown procedures was much more favorable than that through LTA (8-10). However, no significant difference has been observed for survival and recurrence between LTA and RTA, even after propensity score matching (PSM) (11-13). Since then, it has been a controversial topic in China whether esophagectomy for middle or lower thoracic EC should be performed through LTA or RTA, and whether the efficacy, safety and survival of RTA is comparable to that of LTA. Based on the results from the recently published studies (8-10), the current consensus considered that RTA is an optimal approach for EC patients with suspected lymph node (LN) metastasis in the upper mediastinum. However, for those without suspected LN metastasis in the upper mediastinum, it has remained unclear which approach is optimal. In order to clarify whether LTA (Sweet) still has a role in the surgical treatment for such patients, a prospective multicenter randomized controlled study was designed to compare the efficacy, safety and survival between LTA and RTA for middle and lower thoracic ECs without suspected upper mediastinal lymph node (umLN) metastasis. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3810/rc).

Methods

Study design and patient enrollment

This study was designed as a prospective multicenter randomized controlled two-parallel group clinical trial (RCT) with an allocation ratio of 1:1 to compare LTA with RTA. The primary outcomes were the difference in OS and disease-free survival (DFS) between LTA and RTA. The secondary outcomes were efficacy and safety difference including the degree of LN dissection, postoperative complications and perioperative parameters, recurrence rate between the two approaches. Based on previously published studies, we calculated the 5-year survival rates of patients treated via left and right thoracotomies to be about 30–40% and 45–55%, respectively (4,5,9,10). It was assumed that the 5-year survival achieved via RTA was about 15% more than that of via LTA. The sample size was estimated by calculation formula of superiority clinical trial design. If the level of significance test of "α" was set as 0.05 (one-sided), and the power was set to 80% (β=0.2), the participants of the 2 arms would be enrolled at an equal frequency. The whole clinical trial lasted for 5 years. The lost to follow-up rate was estimated as 5%, the estimated sample size was 358 cases in each arm, and at least a total of 716 cases would be included in this study. All hospitalized patients with middle or lower thoracic ECs who met the following inclusion criteria at 14 authorized centers, were recruited into this study.

Inclusion criteria: (I) pathologically diagnosed squamous cell EC by preoperative fiberoptic esophagoscopic biopsy; (II) no previous history of malignant tumors; (III) no previous anti-tumor therapy including neoadjuvant chemotherapy or radiotherapy or chemoradiation; (IV) preoperative clinical tumor-node-metastasis (TNM) stage within cT1b-3N0-1M0 by neck-chest-abdomen computed tomography (CT), brain magnetic resonance imaging (MRI)/CT, bone scintigraphy or positron emission tomography (PET)-CT, fiberoptic esophagoscopy (FOE), endoscopic ultrasonography (EUS); (V) age of 18–75 years with an Eastern Cooperative Oncology Group (ECOG) performance status (0–1) indicating the ability to tolerate esophagectomy; (VI) no suspicious umLN metastasis detected by thoracic and abdominal CT and/or EUS (short diameter of LN <0.8 cm and/or shortest diameter/longest diameter <0.65) (14); (VII) the border of lesions was between the gastroesophageal junction and inferior edge of the aortic arch by CT and/or FOE; and (VIII) willing to participate in the clinical trial and provide written informed consent.

Exclusion criteria: (I) non-squamous cell EC by postoperative pathological examination; (II) receiving neoadjuvant preoperative or postoperative adjuvant anti-tumor therapies; (III) refusal to sign the informed consent or follow the treatment plan of the trial protocol; (IV) undergo a palliative resection or exploration alone.

Standards and quality control of the esophagectomies for the study centers

(I) The esophagectomies needed to be performed by experienced senior surgeons (≥50 cases each year) in the high-volume centers (≥200 esophagectomies/each year), using the approach stipulated by randomization; (II) all the selected centers were subjected to review before enrolling patients and reassessed on site by a principal investigator every 6 months after patient enrollment, and the centers which did not meet the study standards would be expelled from this trial; (III) persistent esophagectomy quality control by on-site watching, live demonstration and displaying unedited recording video on website.

Patient enrollment and randomization

Through an authorized computer in each center, the hospitalized eligible patients after precise assessment based on the above inclusion criteria across the following 14 authorized centers were randomized into either an LTA arm or RTA arm by a central automatic randomizing program (stratified block randomization) from a platform run by a third party. Each random sequence was designed to contain 20 patients, who had equal chances of being randomized into either LTA or RTA, which could not be predicted before randomization. All data of these randomized patients including assessment of preoperative surgical risks and cTNM stage, surgery, complications, pathological results, and follow-up information were entered in the National Clinical Trial (NCT) database through the authorized computers connected through a network in each center. In this study, all patients and outcome assessors were blinded to the interventions of the two groups after invention assignment.

The 14 authorized centers in this study were: (I) Institute & Hospital, Chinese Academy of Medical Sciences (principal investigation center); (II) Beijing Cancer Hospital, Beijing University; (III) Henan Cancer Hospital, Zhengzhou; (IV) The Fourth Hospital of Hebei Medical University, Shijiazhuang; (V) Heilongjiang Cancer Hospital, Harbin;

(VI) Liaoning Cancer Hospital, Shenyang; (VII) Hunan Cancer Hospital, Changsha; (VIII) Sun Yat-sen University Cancer Center; Guangzhou; (IX) Zhejiang Cancer Hospital, Hangzhou; (X) Tongji Hospital, Tongji University, Wuhan; (XI) Anyang Cancer Hospital, Anyang; (XII) The Fourth Military University Hospital, Xian; (XIII) Anhui Provincial Hospital, Hefei; (XIV) First Affiliated Hospital, Anhui Medical University, Hefei.

Study modification and reason

To accelerate enrollment, another 4 qualified collaborating centers in addition to the 10 primary centers were added to this study in October 2015. The original protocol was designed to compare the outcomes of open esophagectomy (OE) via left thoracotomy with via right thoracotomy. However, minimally invasive esophagectomy (MIE) by video-assisted thoracoscopy/laparoscopy had been gaining popularity in China since 2010, and patients frequently demanded MIE instead of OE, which compelled us to modify our protocol accordingly. Therefore, we added MIE via right chest with an anastomosis in the chest or neck as an alternative procedure for the RTA arm from October 2015. However, there was no MIE via left chest for equivalent modification in the LTA arm. Therefore, the esophagectomy with anastomosis in the neck via left thoracotomy and left neck incision, which was routinely performed in Henan Cancer Hospital, was added as an alternative procedure for LTA arm to balance the procedures and leakage rate between the 2 arms.

Surgical intervention

The eligible patients were randomized into either the LTA arm or RTA arm and underwent esophagectomies performed by experienced senior surgeons familiar with both approaches.

LTA arm

Sweet esophagectomy with standard 2-field lymphadenectomy was performed via left thoracotomy with an anastomosis in the apex (left posterolateral thoracic incision + diaphragmatic incision) or left thoracotomy plus left neck incision with an anastomosis in the neck (left posterolateral thoracic incision + diaphragmatic incision + left neck incision). Through a diaphragmatic incision, the stomach was completely mobilized with preservation of the right gastroepiploic arteries, and all LNs around the gastric cardia, lesser gastric curvature and the left gastric artery were dissected. The esophagus in the chest was then completely mobilized. All LNs, including LNs in the subcarinal area and around the thoracic esophagus in the lower mediastinum, were dissected. For the LN in the upper mediastinum, limited lymphadenectomy by palpation along the tracheoesophageal groove was usually performed. A gastric conduit was made and then pulled into the apex of the left chest along the left surface of the aorta or to the neck through the esophageal bed, then an end-to-side esophagogastric anastomosis was performed using a circular stapler or hand suturing.

RTA arm

Ivor-Lewis or McKeown esophagectomy with extended 2-field lymphadenectomy was performed by open or minimally invasive procedures. The OEs were performed via the conventional two incisions (right posterolateral thoracic incision + midline abdominal incision) or conventional 3 incisions (right posterolateral thoracic incision + midline abdominal incision + left neck incision). The MIEs were performed via thoracoscopic/laparoscopic port incisions on the chest and abdominal wall. The esophagus in the chest was completely mobilized. All LNs around the thoracic esophagus, in the subcarinal area, and along the bilateral recurrent nerves in the upper mediastinum were dissected. The stomach was then completely mobilized with preservation of the right gastroepiploic arteries. All LNs around the gastric cardia, lesser gastric curvature, left gastric artery, splenic artery, and the common hepatic artery were dissected. A gastric conduit was made and pulled into the apex of the right chest or the neck through esophageal bed, and an end-to-side esophagogastric anastomosis was performed using a circular stapler or hand suturing.

A small chest tube (20 F) for drainage was placed along the gastric conduit to the apex of the left chest in LTA or the right chest in RTA and was usually retained until oral intake of semi-liquid food was safe and without risk of leakage.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval (No. 15-032/959) for this study was issued on April 23, 2015 by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences. The rest 13 centers had signed a study cooperation agreement with principal instigation center before authorization and recruiting patient. Written informed consent was provided by all participants and collected before randomization. In order to protect patient privacy, participant names and their personal identification data were replaced by computer-assigned code numbers after inputting into the NCT database.

The staging system of the American Joint Committee on Cancer (AJCC) 7th edition for EC was used for cTNM and pTNM staging. Postoperative complications were classified according to the Clavien-Dindo scoring system (15). Total postoperative complications and all major surgical complications beyond Clavien-Dindo grade II associated with surgical manipulation such as bleeding, chylothorax, anastomotic leakage, empyema, recurrent laryngeal nerve paralysis, and incision infection were recorded and compared between the two approaches. Non-surgery related complications such as arrhythmia, myocardial infarction, pulmonary embolism, and so on, were also recorded. .

Statistical analysis

The outcomes of LTA and RTA were analyzed and compared by using software SPSS 20.0 (SPSS Inc., Chicago, IL, USA). All baseline characteristics, perioperative parameters, complications, and LN dissection as well as recurrence rate between LTA and RTA were compared using Pearson's chi-squared test for categorical data and Student's *t*-test for measurement data. The 3-year OS and DFS were calculated using the Kaplan-Meier method by R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistically significant differences in OS and DFS between LTA and RTA were assessed using the log-rank test. Because MIE may have influenced the postoperative parameters, complications, and survival. Therefore, the outcomes of the RTA and LTA subgroups treated only by open procedures were also compared. A P value of <0.05 (2-sided) was considered statistically significant. Patients who were excluded from the trial due to non-squamous cell carcinomas/unwillingness to adhere to the surgical protocol by randomization/surgical exploration alone or lost to follow-up, were not included in the final survival analysis (*Figure 1*).

After removing all ineligible patients, the final effective size for efficacy, safety and survival comparison analysis should be more than 358 cases in each group and 716 cases in total at least based on study protocol.

Follow-up

All participants were followed up once every 3 months by a fixed team through telephone calls. All participants were asked to see their surgeons for follow-ups and undergo examinations at their local hospitals where they underwent their esophagectomies. The follow-up data were obtained by telephone interview with the participants or their family members. The oncologic follow-up examinations usually consisted of high-resolution CT scan for the chest and abdomen, ultrasonography for the cervical LN, and upper gastrointestinal barium swallowing esophagogram or esophagogastroscopy, at least every 3 months in the first 2 years and 6 months in the remaining post-surgical 3 years. Other examinations including brain MRI and bone scans were performed to detect recurrence and/or metastasis, when necessary.

In order to minimize the confounding effect of adjuvant therapy on the prognosis which may lead to biased results, postoperative adjuvant chemotherapy/radiotherapy was not recommended for the participants with radical resection unless they had confirmed recurrence. Locoregional recurrence was defined as recurrence in the operation field such as anastomotic or tumor bed area or LNs in the chest and abdomen. Distant metastases were defined as metastases in the distant organs and LNs beyond surgical fields. All recurrences were confirmed based on radiological evidence or biopsy, if possible.

Results

Patient inclusion and exclusion

A total of 956 hospitalized patients were primarily recruited to this trial between April 2015 and December 2018, including 489 (51.2%) in the LTA and 467 (48.8%) in the RTA arm after randomization. In Total, 95 patients (9.9%) were excluded from the study, including 36 patients (3.8%) in the LTA arm due to non-squamous cell carcinomas (12 cases), unwillingness to adhere to the protocol (21 cases), or surgical exploration without resection (3 cases); and 59 (6.1%) in the RTA arm because of non-squamous cell carcinoma (18 cases), unwillingness to adhere to the protocol (39 cases), and surgical exploration without resection (2 cases) (*Figure 1*).

Baseline demographic characteristics of LTA and RTA

Finally, 861 eligible patients were recruited to this study, including 710 males (82.5%) and 151 females (17.5%). The mean age was 60.5 years (range, 36 to 74 years). There were no significant differences in all baseline demographic

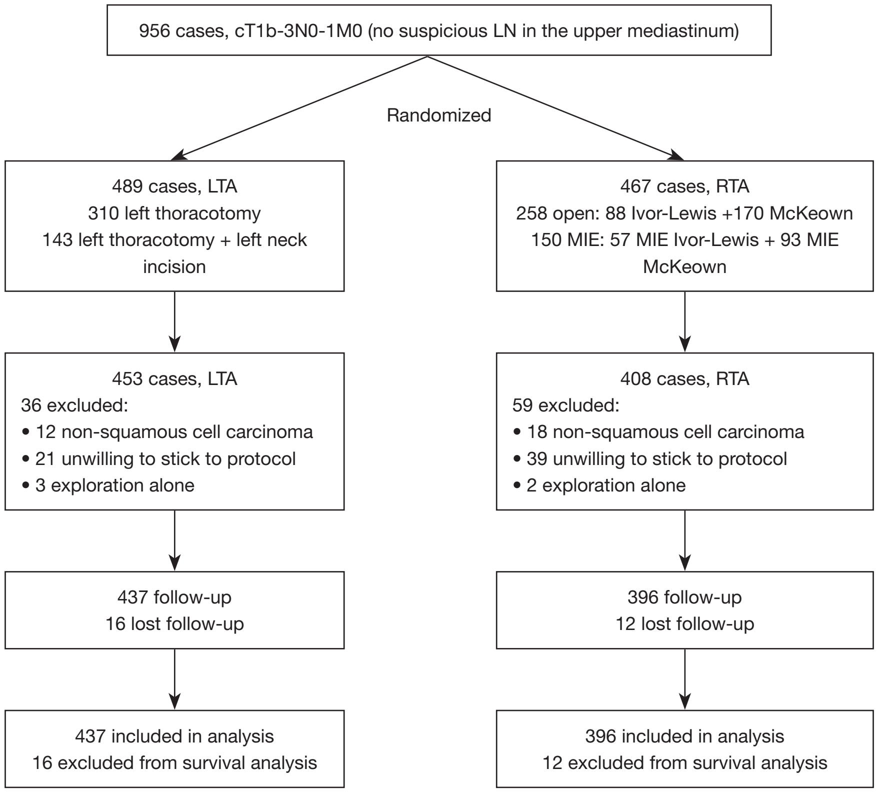


Figure 1 CONSORT flow diagram of patient enrollment and randomization. LN, lymph node; LTA, left thoracic approach; RTA, right thoracic approach; MIE, minimally invasive esophagectomy.

characteristics including age, gender, cTNM, pTNM, tumor location, and differentiation between LTA and RTA arms (*Table 1*).

Surgical intervention by RTA and LTA

A total of 453 patients received esophagectomy through LTA (Sweet approach)—310 participants (68.4%) underwent left thoracotomy alone followed by an anastomosis in the thoracic cavity, and the remaining 143 participants (31.6%) received left thoracotomy plus left cervical incision with an anastomosis in the left neck.

Esophagectomy through RTA was performed on 408 patients, among whom 258 patients (63.2%) received open right thoracotomy, including 88 (21.5%) by Ivor-Lewis and 170 (41.7%) by McKeown, and 150 cases (36.7%) by MIE, with a thoracic anastomosis in 57 cases (13.9%, minimally invasive Ivor-Lewis) and cervical anastomosis in 93 cases (22.8%, minimally invasive McKeown).

Perioperative parameters of RTA and LTA

The perioperative parameters of LTA arm versus RTA arm are summarized in the *Table 2*. Except for the operating time, which was significantly shorter for the LTA arm as compared with the RTA arm (P<0.001), there were no statistically significant differences noted in all the perioperative outcomes including intraoperative blood loss, postoperative length of hospital-stay, chest tube indwelling time, and total drainage volume.

Lymphadenectomy through RTA and LTA

The comparison of total number of dissected LNs and LN stations in the thoracic and abdominal cavities between the LTA arm and RTA arm was summarized in *Table 2*. There was a significant difference in the total number of dissected LNs and in the LN stations (P<0.05) between RTA and LTA, especially in the upper mediastinum (P<0.001). The LN metastasis rate in the upper mediastinum was 15.9%

Table 1 Basic demographic characteristics of LTA versus RTA

Characteristics	LTA (N=453)	RTA (N=408)	P value
Age (years), mean ± SD	61.1±6.9	60.6±7.5	0.328
Gender, n (%)			0.414
Male	369 (81.5)	341 (83.6)	
Female	84 (18.5)	67 (16.4)	
cTNM, n (%)			0.866
I	68 (15.0)	56 (13.7)	
II	284 (62.7)	260 (63.7)	
III	101 (22.3)	92 (22.5)	
pT stage, n (%)			0.422
T1	105 (23.2)	86 (21.1)	
T2	80 (17.7)	82 (20.1)	
T3	254 (56.1)	233 (57.1	
T4	14 (3.1)	7 (1.7)	
pN stage, n (%)			0.687
N0	283 (62.5)	245 (60.0)	
N1	99 (21.9)	103 (25.2)	
N2	56 (12.4)	46 (11.3)	
N3	15 (3.3)	14 (3.4)	
M classification, n (%)			
M0	453 (100.0)	408 (100.0)	
Location, n (%)			0.143
Upper	13 (2.9)	20 (4.9)	
Middle	284 (62.7)	266 (65.2)	
Lower	156 (34.4)	122 (29.9)	
Tumor differentiation, n (%)			0.691
Well	82 (18.1)	78 (19.1)	
Moderate	264 (58.3)	226 (55.4)	
Poor	107 (23.6)	104 (25.5)	
pTNM stage, n (%)			0.875
IA	17 (3.8)	16 (3.9)	
IB	81 (17.9)	62 (15.2)	
IIA	77 (17.0)	74 (18.1)	
IIB	138 (30.5)	124 (30.4)	
IIIA	72 (15.9)	76 (18.6)	
IIIB	46 (10.2)	36 (8.8)	
IIIC	22 (4.9)	20 (4.9)	

LTA, left thoracic approach; RTA, right thoracic approach.

(65/408) in the RTA arm versus 10.2% (46/453) in the LTA arm. There was a significant difference between the two approaches [hazard ratio (HR) 1.569, 95% confidence interval (CI): 1.102 to 2.233, P=0.014].

Complications of RTA and LTA

The comparison of surgery-related major complications and other postoperative complications between the LTA arm and RTA arm was summarized in the *Table 3*. A significantly higher rate of postoperative complications was found in the RTA participants (138 cases, 33.8%) than that in LTA participants (119 cases, 26.3%), with a statistically significant difference between the two approaches [odds ratio (OR) 0.697; 95% CI: 0.52 to 0.934; P=0.02]. The incidence of total postoperative respiratory complications (OR 0.715, 95% CI: 0.518 to 0.986; P<0.04) and anastomotic leakage (OR 0.536, 95% CI: 0.313 to 0.919; P<0.02) were significantly higher in the RTA arm than those in the LTA arm. However, when the anastomotic leakage rates were calculated based on the anastomosis locations in the neck and chest, they were 10.3% (27/263) and 6.9% (10/145) in RTA arm versus 6.3% (9/143) and 4.5% (14/310) in the LTA arm. There was no significant difference between the two approaches (P=0.179, P=0.29).

Survival of RTA and LTA

Of 861 recruited cases, 833 cases (98.7%) consisting of 396 cases in RTA and 437 cases in LTA, were successfully followed up until the last follow-up on 1 June 2020. A total of 28 cases (3.3%), with 12 cases (1.4%) in the RTA arm and 16 cases (1.9%) in the LTA arm, were lost to follow up and subsequently excluded from the final survival analysis. The mean follow-up time was 44 months (range, 18 to 62 months). Of 833 patients, 265 (31.8%) died during this study period, including 116 in the RTA arm (29.3%) and 149 in the LTA arm (34.1%). Of these, 235 patients (88.7%) died of EC recurrences, 22 patients (8.3%) of surgery-related complications, 1 (0.4%) of a second primary cancer (pancreatic carcinoma), and 2 died of car accidents.

The 3-year OS was 68.7% in the LTA arm versus 71.3% in the RTA arm (*Figure 2A*). There was no significant difference in the OS between the two approaches (HR 0.85, 95% CI: 0.65 to 1.13; P=0.20). The 3-year DFS was 64.3% in the LTA arm and 63.7% in RTA arm (*Figure 2B*). There was also no significant difference in DFS between the two approaches (HR 0.98, 95% CI: 0.76 to 1.27; P=0.96). When

Table 2 Perioperative parameters and LN dissection of LTA versus RTA

Characteristics	Left thoracic approach	Right thoracic approach	P value
Perioperative parameters			
Operation time (min), mean ± SD	205.34±51.47	274.48±78.92	<0.001
Hospital-stay time (d), mean ± SD	23.13±11.20	24.40±10.76	0.175
Chest tube indwelling time (d), mean ± SD	9.46±7.94	10.12±6.72	0.148
Intraoperative bleeding loss (mL), mean ± SD	167.86±190.25	197.16±272.83	0.364
Drainage volume (mL), mean ± SD	1,877.66±1,818.31	1,909.69±2,518.01	0.263
LN dissection			
Total No. of dissected LNs, mean ± SD	21.92±10.26	23.61±10.09	0.015
Total No. of dissected LN stations, mean ± SD	4.34±1.23	5.29±1.72	<0.001
No. of dissected thoracic LNs, mean ± SD	11.93±6.84	13.75±6.99	<0.001
No. of dissected upper mediastinal LNs, mean ± SD	7.06±5.36	10.05±5.91	<0.001

LN, lymph node; LTA, left thoracic approach; RTA, right thoracic approach.

Table 3 Postoperative complications of LTA versus RTA

Characteristics	LTA, n (%)	RTA, n (%)	P value	OR (R/L)	95% CI
Surgery-related complications					
Postoperative bleeding	5 (1.1)	3 (0.7)	0.574	0.664	(0.158–2.795)
Anastomotic leakage	23 (5.1)	37 (9.1)	0.022	1.865	(1.088–3.195)
Respiratory complications	89 (19.6)	104 (25.5)	0.040	1.399	(1.015–1.930)
Wound infection	18 (4.0)	20 (4.9)	0.508	1.246	(0.649–2.389)
Unplanned second surgery	11 (2.4)	9 (2.2)	0.829	0.906	(0.372–2.21)
Recurrent laryngeal nerve paralysis	5 (1.1)	10 (2.5)	0.131	2.250	(0.763–6.642)
Chylothorax	5 (1.1)	4 (1.0)	0.859	0.887	(0.237–3.326)
Other complications					
Arrhythmia	3 (0.7)	3 (0.7)	0.898	1.110	(0.223–5.536)
Cardiac infarction	2 (0.4)	1 (0.2)	0.625	0.554	(0.05–6.133)
Pulmonary artery embolism	0	1 (0.2)	0.292	NA	NA
Total complications	119 (26.3)	138 (33.8)	0.016	1.435	(1.07–1.92)

LTA, left thoracic approach; RTA, right thoracic approach; (R/L), right/left; OR, odds ratio; CI, confidence interval; NA, not available.

the 3-year OS of subgroups was compared based on the stages, there was no significant difference in the OS and DFS across all stages between the two approaches except for stage IIIA (*Table 4*). The RTA arm had significantly better OS (67.8% *vs.* 51.8%, HR 0.551, 95% CI: 0.329 to 0.925, P=0.022) and much better DFS (58.1% *vs.* 46.9%, HR 0.726, 95% CI: 0.456 to 1.155, P=0.17) than did the LTA arm in stage IIIA.

Comparison between RTA and LTA subgroups by OE

In the RTA arm, MIE may have influenced the postoperative parameters, complications, and survival. Therefore, participants treated only by open procedures were compared between

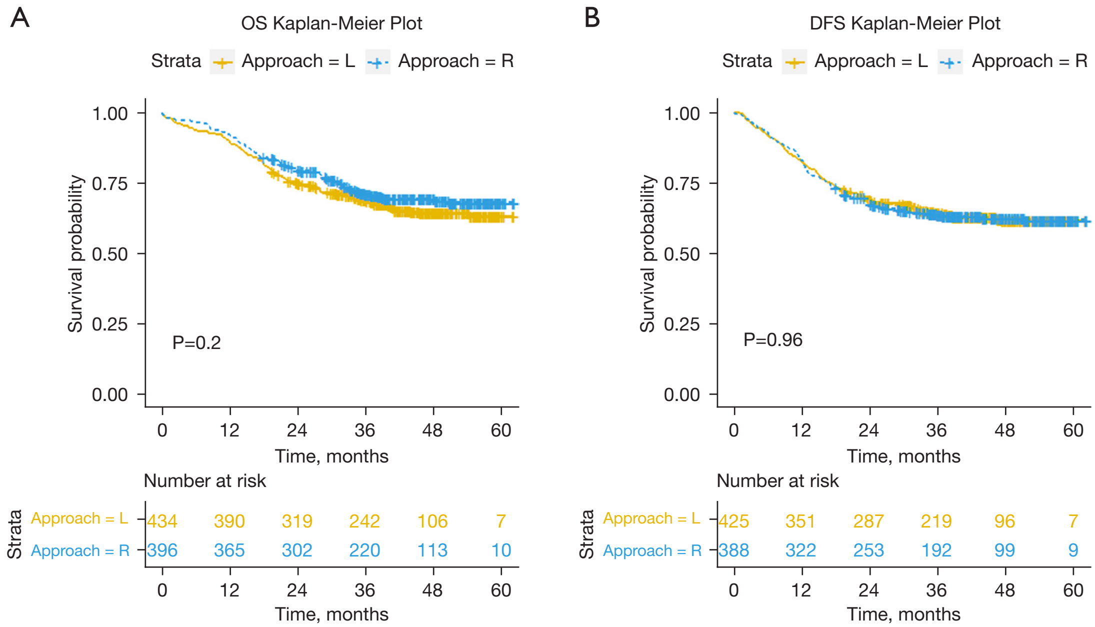


Figure 2 OS (A) and DFS (B) of LTA versus RTA. OS, overall survival; DFS, disease-free survival; LTA (L), left thoracic approach; RTA (R), right thoracic approach.

Table 4 Comparison of OS and DFS between RTA and LTA among different stages

pTNM	Surgical approach	No. of cases	OS		DFS	
			3-year (%)	P value	3-year (%)	P value
IA	LTA	16	93.8	0.982	93.8	0.55
	RTA	16	93.8		87.5	
IB	LTA	76	83.8	0.401	82.3	0.26
	RTA	62	85.5		70.7	
IIA	LTA	76	76.0	0.119	73.0	0.6
	RTA	72	83.3		75.2	
IIB	LTA	130	74.2	0.886	70.2	0.8
	RTA	119	74.6		70.9	
IIIA	LTA	71	51.8	0.022	46.9	0.17
	RTA	75	67.8		58.1	
IIIB	LTA	43	40.4	0.419	31.2	0.51
	RTA	35	41.8		22.2	
IIIC	LTA	22	26.5	0.61	22.7	0.81
	RTA	17	26.5		23.5	

OS, overall survival; DFS, disease-free survival; LTA, left thoracic approach; RTA, right thoracic approach.

the RTA and LTA. Compared with the LTA arm (453 cases), the RTA arm (258 cases) still had longer operation time (262.60±70.54 *vs.* 205.34±51.47, P<0.001), much more respiratory complications (31.8% *vs.* 19.6%, P<0.001) and total complications (38.8% *vs.* 26.3%, P=0.001), and similar 3-year OS (70.9% *vs.* 69.0%; HR 1.169, 95% CI: 0.885 to 1.544, P=0.27) and 3-year DFS (64.6% *vs.* 63.9%; HR 1.02, 95% CI: 0.787 to 1.321, P=0.88). No significant impact of MIE on the overall postoperative parameters, complications, and survival was observed in the RTA arm (*Figure 3A,3B*). When the 3-year survival of subgroups was compared based on the stages, there was also no significant difference in all stages except IIIA stage between the two approaches (*Table 5*). The RTA arm had significantly better OS (69.2% *vs.* 52.5%, HR 0.492, 95% CI: 0.269 to 0.902, P=0.019) and much better DFS (57.5% *vs.* 46.9%, HR 0.702, 95% CI: 0.416 to 1.185, P=0.18) than did LTA in the stage IIIA patients with open surgery.

Postoperative 30-day mortality

The postoperative 30-day mortality rate was 1.7% (15 cases), consisting of 8 participants (1.8%) in the LTA arm and 7 participants (1.8%) in the RTA arm, and there was no significant difference between the two approaches (P=0.946). In addition, the postoperative 90-day mortality rate was 3.0% (26 cases), including 16 participants (3.7%) in the LTA arm and 10 participants (2.5%) in the RTA arm (P=0.346), and no significant difference was observed between the 2 approaches. All patient deaths were due to postoperative complications and there were no operative deaths in this study.

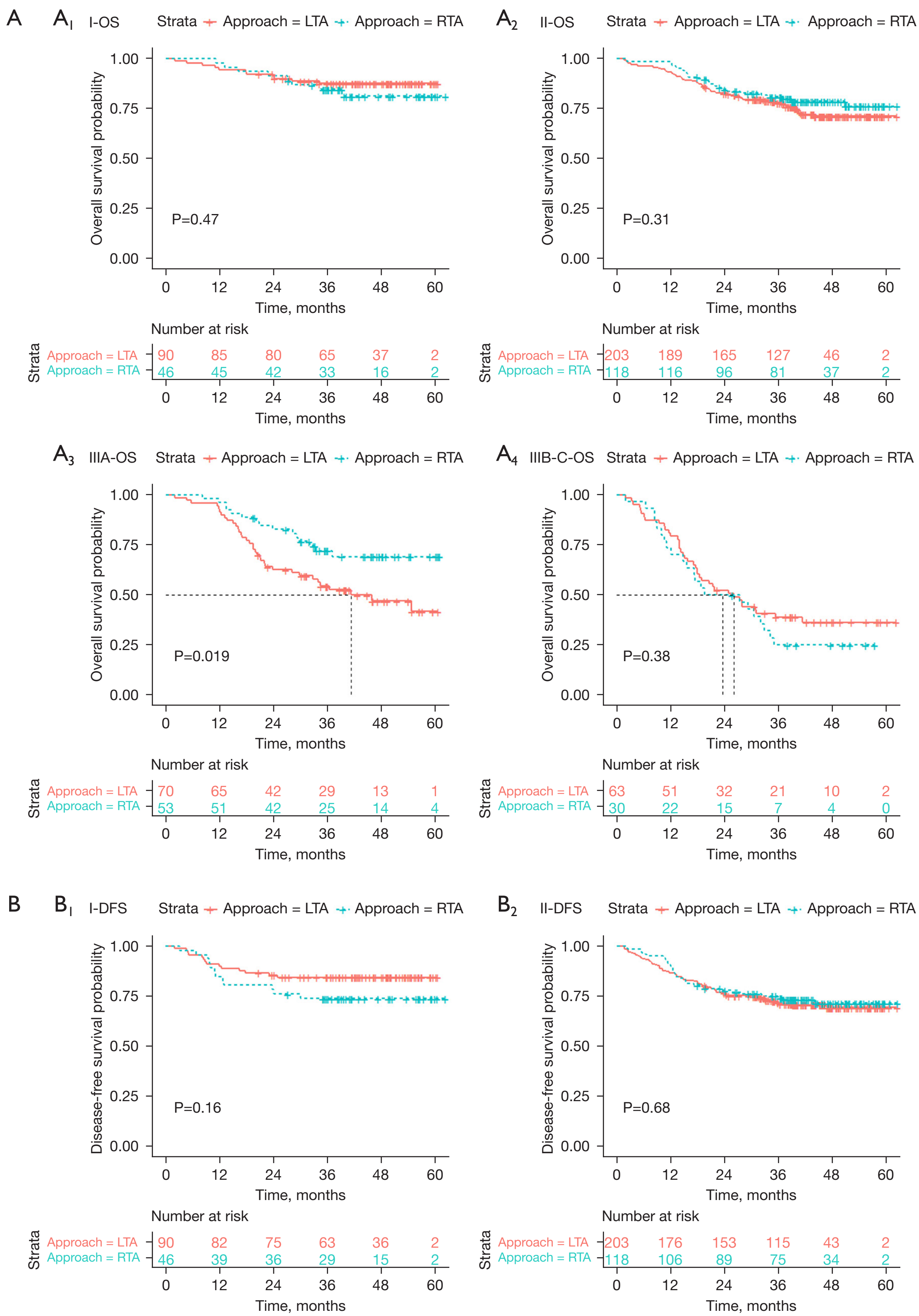
Recurrence rate of RTA and LTA

A total of 716 cases had full 3-year follow-up until the last follow-up on 1 June 2020, including 382 cases in the LTA arm and 334 cases in the RTA arm. The recurrence rate of the LTA arm was 35.6% (135/382) versus 37.7% (126/334) in the RTA arm, and there was no statistically significant difference between the two approaches (OR 0.91, 95% CI: 0.67 to 1.24, P=0.59).

Discussion

The commonest surgical approaches for resection of thoracic EC include the left and the right transthoracic approaches as well as the transhiatal approach. However, Sweet esophagectomies via left thoracotomy remained the most common surgical approach in China for the resection of the middle and lower EC in the past decades (16,17). According to the National Registration Database of surgically treated EC patients in hospitals with high volume of esophagectomies, the LTA accounted for 72% of esophagectomies before 2014 (18). The reason for the popularity of left thoracotomy (Sweet) in China is historical: the first esophagectomy in China on a patient with lower thoracic EC was successfully performed through left thoracotomy (Sweet), in 1940 (2). Since then, almost all senior thoracic surgeons in China have been trained to perform esophagectomy through left thoracotomy for middle and lower thoracic EC during the past decades because it is relatively technically simple and time-saving compared to open Ivor-Lewis or McKeown esophagectomy in open surgery era (16,17).

It was reported that the most frequent metastasis stations in the thorax are the LNs along bilateral recurrent laryngeal nerves, especially in the nodes beside the right recurrent laryngeal nerve (19,20), which are difficult to dissect through the LTA due to the sheltering of aorta and its branches, and frequently lead to postoperative recurrence (7). As reported in recently published literature, the number of metastatic LNs is negatively correlated with survival, and the number of harvested LNs and the extent of lymphadenectomy also have a great impact on survival (21-23). Therefore, selection of an optimal surgical approach based on the stages of EC and the ability to perform a standardized and complete LN dissection are critically important for decreasing the risk of post-operative recurrence and improving survival rate in patients with thoracic EC (7,21-25). It has been widely reported that more LNs could be harvested through RTA than LTA and may improve survival of thoracic EC patients. The results of this study also verified this trend. Therefore, the current consensus in China is that for patients with suspected LN metastasis in the upper mediastinum, the RTA should be applied as the optimal approach in order to achieve complete LN dissection and better survival (26,27). However, for patients without suspected LN metastasis in the upper mediastinum, the optimal approach remains unknown. In recent years, although application of MIE via right chest with a esophagogastric anastomosis in the left neck or right chest apex has gradually increased in large hospitals across China, many surgeons still stick to performing Sweet esophagectomy due to time saving, technically easier maneuverability, and much lower incidence of fatal postoperative complications such as


A
A1 I-OS
Strata + Approach = LTA + Approach = RTA
Overall survival probability
1.00
0.75
0.50
0.25
0.00
P=0.47
0 12 24 36 48 60
Time, months
Number at risk
Strata
Approach = LTA 90 85 80 65 37 2
Approach = RTA 46 45 42 33 16 2
0 12 24 36 48 60
Time, months
A2 II-OS
Strata + Approach = LTA + Approach = RTA
Overall survival probability
P=0.31
Time, months
Number at risk
Approach = LTA 203 189 165 127 46 2
Approach = RTA 118 116 96 81 37 2
Time, months
A3 IIIA-OS
Strata + Approach = LTA + Approach = RTA
Overall survival probability
P=0.019
Time, months
Number at risk
Approach = LTA 70 65 42 29 13 1
Approach = RTA 53 51 42 25 14 4
Time, months
A4 IIIB-C-OS
Strata + Approach = LTA + Approach = RTA
Overall survival probability
P=0.38
Time, months
Number at risk
Approach = LTA 63 51 32 21 10 2
Approach = RTA 30 22 15 7 4 0
Time, months
B
B1 I-DFS
Strata + Approach = LTA + Approach = RTA
Disease-free survival probability
P=0.16
Time, months
Number at risk
Approach = LTA 90 82 75 63 36 2
Approach = RTA 46 39 36 29 15 2
Time, months
B2 II-DFS
Strata + Approach = LTA + Approach = RTA
Disease-free survival probability
P=0.68
Time, months
Number at risk
Approach = LTA 203 176 153 115 43 2
Approach = RTA 118 106 89 75 34 2
Time, months

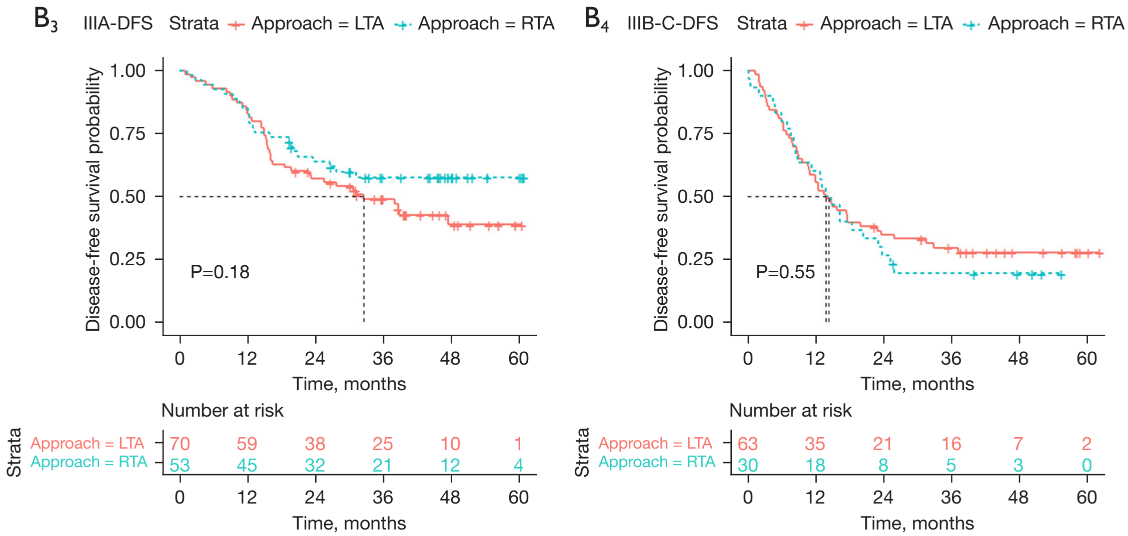


Figure 3 OS and DFS of patients with open esophagectomy between LTA and RTA. (A): (A_1) OS of stage I; (A_2) OS of stage II; (A_3) OS of stage IIIA; (A_4) OS of stage IIIB-C. (B): (B_1) DFS of stage I; (B_2) DFS of stage II; (B_3) DFS of stage IIIA; (B_4) DFS of stage IIIB-C. LTA, left thoracic approach; RTA, right thoracic approach; OS, overall survival; DFS, disease-free survival.

Table 5 Comparison of OS and DFS in the patients with open surgery between RTA and LTA among different stages

pTNM	Surgical approach	No of cases	OS		DFS	
			3-year (%)	P value	3-year (%)	P value
IA	LTA	16	93.8	0.43	93.8	0.76
	RTA	10	100.0		90.0	
IB	LTA	74	86.1	0.3	82.3	0.14
	RTA	36	80.3		69.3	
IIA	LTA	75	77.0	0.18	73.0	0.37
	RTA	47	83.9		77.8	
IIB	LTA	128	77.5	0.83	70.2	0.83
	RTA	71	75.3		70.0	
IIIA	LTA	70	52.5	0.019	46.9	0.18
	RTA	53	69.2		57.5	
IIIB	LTA	41	46.0	0.3	31.2	0.37
	RTA	20	30.0		20.0	
IIIC	LTA	22	26.5	0.97	22.7	0.92
	RTA	10	12.5		20.0	

OS, overall survival; DFS, disease-free survival; LTA, left thoracic approach; RTA, right thoracic approach.

recurrent laryngeal nerve paralysis and tracheoesophageal fistula compared with MIE (11-13,28,29). Therefore, there has been a disagreement regarding whether the LTA is still feasible and has its role in the treatment for EC since the year 2000. Several retrospective studies have reported that for patients without suspected metastatic LNs in the upper mediastinum, esophagectomy via LTA can achieve similar outcomes when compared with patients treated via RTA (11-13,30). However, until now, only a single-center prospective RCT on the outcome of esophagectomies for middle and lower thoracic esophageal squamous cell carcinoma (TESCC) via LTA versus via RTA has been reported (31). The results of this trial showed that the 3-year OS and DFS were significantly better in the RTA group than the LTA group, especially for patients with positive nodes operated on via RTA. However, our multicenter RCT demonstrated no statistically significant differences in 3-year OS, DFS, and tumor recurrence among patients with non-suspected metastatic LNs in the upper mediastinum who were treated via LTA and RTA, but subgroup analysis showed that the IIIA stage patients (T1-2N2/T3N1) treated via RTA had a significantly better 3-year OS and much better DFS than those treated via LTA. Therefore, for the node-positive patients, both studies demonstrated that RTA is superior to LTA in achieving significantly better survival due to complete lymphadenectomy. Since there were more advanced cases enrolled in the single center trial (45.1% N+, 35.7% R1/R2) than in our multicenter trial (38.6% N+, 0% R1/R2), and some patients with positive LN received postoperative chemotherapy/radiotherapy, these two cohorts of patients are not comparable.

It has been reported that better survival and lower postoperative complications were observed in EC patients when esophagectomies were performed by experienced surgeons in high-volume centers (32,33). In this study, compared with LTA, RTA had more postoperative complications due to high incidence of recurrent laryngeal nerve palsy and secondary respiratory complications in the patients who undergo more extensive lymphadenectomy along the bilateral recurrent laryngeal nerve in the upper mediastinum during open or MIE Ivor-Lewis/McKeown procedures via right thoracic approach (RTA), while during the open Sweet procedures via LTA, lymphadenectomy was more limited and done around the upper third thoracic esophagus due to sheltering of the aortic arch and its branches. Therefore, the incidence of recurrent laryngeal nerve palsy and secondary respiratory complications were relatively low. Other reasons was because most of participating surgeons who had more experience in the LTA than in RTA and were still in their learning curve of MIE during the trial. Therefore, more patients in RTA had a leakage than those in LTA. However, the single center study demonstrated that much more postoperative complications occurred in the LTA arm than in the RTA arm (31). This is also not consistent with the results of our multicenter trial. The possible reasons are that the single center trial was completed only in a single center where the surgeons had seldom performed Sweet esophagectomies in the recent years, and had limited experience in the esophagectomy via LTA. Furthermore, the sample size after exclusion in each approach in that particular single center trial might be relatively small for the comparative analysis. Therefore, our multicenter prospective RCT may better reflect the reality in high volume institution.

There are several limitations of the current study. Firstly, PET-CT was not employed as a routine preoperative staging procedure because most of the patients cannot afford due to high cost. Secondly, regarding the confounding effect of these additional adjuvant therapies on survival, certain patients who may have required neoadjuvant therapy or postoperative therapy were not included in this study. Thirdly, while the esophagectomies in the LTA group were all performed through open left thoracotomy, some patients of the RTA group underwent MIE, which should theoretically improve the perioperative recovery. However, this should not have effect on OS and DFS according to numerous retrospective studies (34-36). Fourthly, most of the surgeons were still in their learning curve stage of MIE procedure when this trial started in 2015, so there might be a variation in technical proficiency among surgeons and centers, which might have some impact on the incidence of postoperative complications.

Our study demonstrated that LTA may still have its role in the surgical treatment of patients with relatively early-stage middle and lower thoracic EC or tumors of gastroesophageal junction who have no suspected metastatic LNs in the upper mediastinum, However, LTA should not be recommended for patients with advanced stage disease (cIIIA) especially for those with high risk of LN metastasis in the upper mediastinum.

In conclusion, although esophagectomies via both LTA and RTA can achieve similar outcomes in the patients with a relatively early-stage middle or lower thoracic EC who have no suspected upper mediastinal metastatic LNs after precise preoperative evaluation, RTA is superior to LTA in the surgical treatment for more advanced stage EC due to its capacity for complete lymphadenectomy.

Acknowledgments

The authors extend their thanks to all participants of NST1501 trial including the patients, doctors, assistants for follow-up, who contributed to this clinical trial and data processing. The authors appreciate the academic support from the AME Thoracic Surgery Collaborative Group, and also appreciate the great support from Dr. Magnus Nilsson (Karolinska University Hospital, Sweden) in improving the quality of this paper.

Funding: This work was supported by the grants from National Science and Technology Support Program (Study ID Number: NKTRDP-2015BAI12B08-01, You-Sheng Mao).

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3810/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3810/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3810/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3810/coif). YSM, SGG, YL, ALH, JFL, XFL, THR, JHF, JQM, MQX, RQZ, GMX, XNF, KNC, WMM, YYL, HXL, ZRZ, YF, DHF, XDW, LGY, SM, WQW, YBG, JH report that this work was supported by the grants from National Science and Technology Support Program (Study ID Number: NKTRDP-2015BAI12B08-01, YSM). The other 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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval (No. 15-032/959) for this study was issued on April 23, 2015 by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences. The rest 13 centers had signed a study cooperation agreement with principal instigation center before authorization and recruiting patient. Written informed consent was provided by all participants and collected before randomization.

References

1. Zheng R, Zhang S, Zeng H, et al. Cancer incidence and mortality in China, 2016. Journal of the National Cancer Center 2022;2:1-9.
2. Wu YK, Loucks HH. Surgical treatment of carcinoma of the esophagus. Chin Med J, 1941, 60:1-33.
3. Huang GJ, Wang LJ, Liu JS, et al. Surgery of esophageal carcinoma. Semin Surg Oncol 1985;1:74-83.
4. Shao LF, Chen YH, Cao ZR, et al. Surgical treatment of carcinoma of esophagus and gastric cardia-A 34-year investigation. The Chinese-German Journal of Clinical Oncology 2002;1:61-4.
5. Zhang DW, Cheng GY, Huang GJ, et al. Operable squamous esophageal cancer: current results from the East. World J Surg 1994;18:347-54.
6. Sun K, Zhang R, Zhang D, et al. Prognostic significance of lymph node metastasis in surgical resection of esophageal cancer. Chin Med J (Engl) 1996;109:89-92.
7. Xiao ZF, Yang ZY, Miao YJ, et al. Influence of number of metastatic lymph nodes on survival of curative resected thoracic esophageal cancer patients and value of radiotherapy: report of 549 cases. Int J Radiat Oncol Biol Phys 2005;62:82-90.
8. Peng L, Cheng LH, Li Q, et al. Prognosis of sub-total esophagectomy and two-field lymph node dissection by Ivor-Lewis for esophageal cancer. China Oncology 2003;13:574-6.
9. Lv YY, Chen JH, Meng L, et al. Surgical treatment by modified Ivor-Lewis for 576 cases with esophageal cancer. Chin J Clin Thorac Cardiovasc Surg (Chinese) 2006;13:204-5.
10. Wu CR, Xue HC, Zhu ZH, et al. Analysis of the

therapeutic effect of esophagectomy with extended 2-field lymph node dissection for esophageal carcinoma. Zhonghua Zhong Liu Za Zhi 2009;31:630-3.
11. Luo KJ, Fu JH, Hu Y, et al. Efficacy of surgical resection of left and right transthoracic approaches for middle thoracic esophageal squamous cell carcinoma. Ai Zheng 2009;28:1260-4.
12. Ma J, Zhan C, Wang L, et al. The sweet approach is still worthwhile in modern esophagectomy. Ann Thorac Surg 2014;97:1728-33.
13. Yang D, Mao YS, He J, et al. Long-term survival of the middle and lower thoracic esophageal cancer patients after surgical treatment through left or right thoracic approach. J Thorac Dis 2018;10:2648-55.
14. Liu JF, Shao HF, Qu D, et al. The criteria for preoperative diagnosis of metastatic lymph nodes by multi-slice spiral CT in esophageal cancer. Oncol Prog 2016;14:56-8.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
16. Mao YS, He J, Cheng GY. Current status and controversy of staging and treatment for esophageal cancer. China Oncology 2011;21:511-7.
17. Mao Y, He J, Gao S, et al. Controversies in the surgical treatment for esophageal carcinoma and future investigation. Zhonghua Wei Chang Wai Ke Za Zhi 2015;18:851-4.
18. Mao YS, Gao SG, Wang Q, et al. Analysis of a registry database for esophageal cancer from high-volume centers in China. Dis Esophagus 2020;33:doz091.
19. Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol 2008;15:3278-88.
20. Fujita H, Kakegawa T, Yamana H, et al. Lymph node metastasis and recurrence in patients with a carcinoma of the thoracic esophagus who underwent three-field dissection. World J Surg 1994;18:266-72.
21. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248:549-56.
22. Chen YM, Li JQ, Zhu KS, et al. The relationship between number of metastatic lymph node and prognosis of thoracic-esophageal cancer patients treated with radical resection. Chin J Thorac Cardiovasc Surg 2014;30:76-8.
23. Liu SY, Zhu KS, Zheng QF, et al. Comparison of survival between three-field and two-field lymph node dissections for thoracic esophageal squamous carcinoma. Chin J Thorac Cardiovasc Surg 2014;30:645-8.
24. Shimada H, Okazumi S, Matsubara H, et al. Impact of the number and extent of positive lymph nodes in 200 patients with thoracic esophageal squamous cell carcinoma after three-field lymph node dissection. World J Surg 2006;30:1441-9.
25. Natsugoe S, Matsumoto M, Okumura H, et al. Clinical course and outcome after esophagectomy with three-field lymphadenectomy in esophageal cancer. Langenbecks Arch Surg 2010;395:341-6.
26. Kayani B, Zacharakis E, Ahmed K, et al. Lymph node metastases and prognosis in oesophageal carcinoma--a systematic review. Eur J Surg Oncol 2011;37:747-53.
27. Mao Y, Yu Z, You B, et al. Society for Translational Medicine Expert consensus on the selection of surgical approaches in the management of thoracic esophageal carcinoma. J Thorac Dis 2019;11:319-28.
28. Wang Q, Wu Z, Zhan T, et al. Comparison of minimally invasive Ivor Lewis esophagectomy and left transthoracic esophagectomy in esophageal squamous cell carcinoma patients: a propensity score-matched analysis. BMC Cancer 2019;19:500.
29. Scholtemeijer MG, Seesing MFJ, Brenkman HJF, et al. Recurrent laryngeal nerve injury after esophagectomy for esophageal cancer: incidence, management, and impact on short- and long-term outcomes. J Thorac Dis 2017;9:S868-78.
30. Ma Q, Liu W, Long H, et al. Right versus left transthoracic approach for lymph node-negative esophageal squamous cell carcinoma. J Cardiothorac Surg 2015;10:123.
31. Li B, Hu H, Zhang Y, et al. Extended Right Thoracic Approach Compared With Limited Left Thoracic Approach for Patients With Middle and Lower Esophageal Squamous Cell Carcinoma: Three-year Survival of a Prospective, Randomized, Open-label Trial. Ann Surg 2018;267:826-32.
32. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-37.
33. Rodgers M, Jobe BA, O'Rourke RW, et al. Case volume as a predictor of inpatient mortality after esophagectomy. Arch Surg 2007;142:829-39.
34. Straatman J, van der Wielen N, Cuesta MA, et al. Minimally Invasive Versus Open Esophageal Resection: Three-year Follow-up of the Previously Reported Randomized Controlled Trial: the TIME Trial. Ann Surg 2017;266:232-6.

35. Hsu PK, Huang CS, Wu YC, et al. Open versus thoracoscopic esophagectomy in patients with esophageal squamous cell carcinoma. World J Surg 2014;38:402-9.
36. Wang H, Shen Y, Feng M, 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;149:1006-14; discussion 1014-5.e4.

Cite this article as: Mao YS, Gao SG, Li Y, Hao AL, Liu JF, Li XF, Rong TH, Fu JH, Ma JQ, Xu MQ, Zhang RQ, Xiao GM, Fu XN, Chen KN, Mao WM, Liu YY, Liu HX, Zhang ZR, Fang Y, Fu DH, Wei XD, Yuan LG, Muhammad S, Wei WQ, Chiu PW, Lloyd S, Schlottmann F, Meredith K, Pimiento JM, Gao YB, He J. Efficacy and safety of esophagectomy via left thoracic approach versus via right thoracic approach for middle and lower thoracic esophageal cancer: a multicenter randomized clinical trial (NST1501). Ann Transl Med 2022;10(16):904. doi: 10.21037/atm-22-3810

