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)

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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...
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 (≥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, Xi’an; (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 thoroscopic/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, 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 or 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
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%
(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, 26.3%) 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 during this period, including 116 in the RTA arm (29.3%) and 149 in the LTA arm (34.1%). Of these, 235 patients (88.7%) 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 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 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 during this study period, including 116 in the RTA arm (29.3%) and 149 in the LTA arm (34.1%).
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

### 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.
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 tranhiatal 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**

| Strata | Approach = LTA | Approach = RTA |
|--------|---------------|---------------|
| I-OS   |               |               |
| II-OS  |               |               |
| IIIA-OS|               |               |
| IIIB-C-OS |             |               |

**B**

| Strata | Approach = LTA | Approach = RTA |
|--------|---------------|---------------|
| I-DFS  |               |               |
| II-DFS |               |               |

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**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 | 0.76 |       |        |
| IB   | LTA              | 74          | 86.1 | 0.3  | 82.3 | 0.14   |
|      | RTA              | 36          | 80.3 | 0.55 |       |        |
| IIA  | LTA              | 75          | 77.0 | 0.18 | 73.0 | 0.37   |
|      | RTA              | 47          | 83.9 | 0.07 |       |        |
| IIB  | LTA              | 128         | 77.5 | 0.83 | 70.2 | 0.83   |
|      | RTA              | 71          | 75.3 | 0.06 |       |        |
| IIIA | LTA              | 70          | 52.5 | 0.019 | 46.9 | 0.18   |
|      | RTA              | 53          | 69.2 | 0.019 | 57.5 | 0.57   |
| IIIB | LTA              | 41          | 46.0 | 0.3  | 31.2 | 0.37   |
|      | RTA              | 20          | 30.0 | 0.07 |       |        |
| IIIIC| LTA              | 22          | 26.5 | 0.97 | 22.7 | 0.92   |
|      | RTA              | 10          | 12.5 | 0.07 |       |        |

OS, overall survival; DFS, disease-free survival; LTA, left thoracic approach; RTA, right thoracic approach.
were relatively low. Other reasons was because most of nerve palsy and secondary respiratory complications branches. Therefore, the incidence of recurrent laryngeal esophagus due to sheltering of the aortic arch and its was more limited and done around the upper third thoracic procedures via right thoracic approach (RTA), while during mediastinum during open or MIE Ivor-Lewis/McKeown along the bilateral recurrent laryngeal nerve in the upper medicastinum.

patients who undergo more extensive lymphadenectomy 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.

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Footnote

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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

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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.

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