



Society for Translational Medicine Expert consensus on the selection of surgical approaches in the management of thoracic esophageal carcinoma

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Introduction

Esophageal cancer (EC) is a highly prevalent malignancy in China. According to the data released by National Cancer Registry Center of China in 2015, the prevalence of EC was 21.17/100,000 in China in 2012, ranking fifth among all malignancies; the mortality rate was 15.58/100,000, ranking fourth. It is expected that there will be 477,900 new EC cases nationwide in 2015, whereas 375,000 people will die from EC (1,2). Worldwide, EC is the 8th most common malignancy, with 416,000 new cases in 2012 (3). At present, EC treatment is based on multidisciplinary treatment, but surgery remains the most effective therapy in optimizing long-term prognosis in patients without metastatic disease. The ideal surgical approach is a matter of debate.

Transthoracic vs. transhiatal

In the United States and in much of Europe, the transhiatal approach for esophagectomy is still common. This is typically performed through an upper laparotomy with blunt dissection of the esophagus within the mediastinum, creation of a gastric tube and celiac trunk lymphadenectomy followed by a cervical anastomosis. By avoiding a thoracic incision, the transhiatal approach has the advantage of less pulmonary complications compared to a transthoracic approach. Disadvantages are the lack of complete thoracic lymphadenectomy and the blind mediastinal dissection. Although several studies have found that a more extensive mediastinal lymphadenectomy is associated with improved survival after esophagectomy (4,5), a Dutch prospective randomized trial comparing the transhiatal versus transthoracic esophagectomy for very distal esophageal adenocarcinomas did not show a

statistically significant survival advantage to one method over the other, but long term survival for Siewert type I tumors might be better with the transthoracic approach. There was not difference in survival for Siewert type II tumors between the two approaches (6). A Japanese trial (JCOG 9502) comparing left thoracoabdominal *vs.* transhiatal esophagogastrectomy for Siewert type II and III tumors also failed to demonstrate improved survival for a more extended lymphadenectomy (7). Minimally invasive transhiatal approach may overcome some of the limitations of the standard transhiatal esophagectomy by allowing a more extensive mediastinal lymphadenectomy, while also decreasing pulmonary complications, but an adequate mediastinal lymphadenectomy by minimally invasive transhiatal approach remains difficult. Due to its shortcomings in lymph node dissection and the risks of a blind dissection such as bleeding and tracheal injuries, the transhiatal procedure is not commonly used in China.

Impact of the left and right thoracotomy approaches for esophageal carcinoma on lymph node dissection and prognosis

The most common surgical approaches for esophageal resection include left and right thoracotomy as well as transhiatal approach. The left thoracotomy approach includes: a single left posterolateral thoracotomy; or, two incisions (a left posterolateral thoracotomy incision and a left cervical incision). The right thoracotomy approaches include two approaches (midline laparotomy and right posterolateral thoracotomy, Ivor Lewis; or midline laparotomy and right posterior muscle-sparing thoracotomy), or three incisions (left neck incision + right

posterolateral thoracotomy incision + midline abdominal incision, McKeown). Both right sided approaches can be performed by minimally invasive techniques. In recent years, along with advances in endoscopic technologies, the thoracoscopic/laparoscopic esophagectomy + left cervical anastomosis has gradually been popularized in China and has become a mainstream procedure in large hospitals.

There is a dense lymphatic network in the esophageal wall. Once EC involves the submucosal layer, lymph node metastasis occurs in over 20% of patients (8). The risk of lymph node metastasis is associated with depth of tumor invasion (T stage). The number of metastatic lymph nodes negatively correlates with survival. Studies have shown that the number of harvested lymph nodes may impact survival (4,5). Liu *et al.* (9) and Chen *et al.* (10) from Fujian Tumor Hospital reported that the number of involved lymph nodes after three-field lymph node dissection in thoracic esophageal carcinoma was an important independent prognostic factor; according to the 7th Edition of the AJCC Cancer Staging Manual, the 5-year survival in EC with N₀, N₁, N₂, or N₃ metastasis was 77.5%, 41.2%, 22.2%, and 7.0%, respectively (P<0.0001). Therefore, selecting the corresponding surgical approach according to the specific characteristics of EC and its stage and carrying out standardized and complete lymph node dissection are critically important for improving survival in patients with EC and lowering the risk of post-operative recurrence (9-15).

In China, the left thoracotomy approach was the first approach used for treatment of EC, and it is still widely applied in northern China. During the treatment of EC via the left thoracotomy approach, the presence of the aortic arch and the left subclavian artery and the narrow triangle area above the arch limits the ability to dissect the superior mediastinum lymph nodes, especially those near the left and right tracheoesophageal areas and recurrent laryngeal nerves. Resection of lymph nodes in the celiac axis may also be limited. Complete thoraco-abdominal lymph node dissection therefore cannot be achieved completely via a left side approach. Besides, the use of multimodality therapy (neoadjuvant chemo/radiation therapy followed by surgery) was not common in China prior to 2000. As a result, the effectiveness of surgical treatment for EC had not been improved before 2000 and the patients' 5-year survival remained around 30% (12,16-18).

In the last 10 years, many hospitals in China, especially those in southern China, have adopted procedures such as the Ivor Lewis esophagectomy (a midline laparotomy plus right posterolateral thoracotomy or right posterior muscle-

sparing thoracotomy), during which the lymph nodes in the thoracic and abdominal fields (especially those near the left and right tracheoesophageal areas and recurrent laryngeal nerve) were completely removed; owing to this reason partly, the patients' 5-year survival was remarkably improved (19-21). In addition, some hospitals in China also have used radical *en bloc* resection of esophagus, including three field lymph node dissection (cervical, thoracic, and abdominal fields); *en bloc* three field esophagectomy allows for a thorough removal of lymph nodes in superior mediastinum and neck and may improve survival (22,23). These results of three-field lymph node dissection were consistent with the findings by Japanese investigators and others who are more experienced in three-field lymph node dissection for EC (12,14,24). Unfortunately, postoperative complications are significantly increased with the *en bloc* approach (12,14,24,25). Currently, the 5-years overall survival range 38.7–57.6% following surgical treatment of esophageal carcinoma via the right thoracotomy approach, showing superiority to the left thoracotomy approach (19,21,26-28). Mao *et al.* (21) from Chinese Academy of Medical Sciences reported that they had performed surgical treatment in 559 patients with thoracic EC and the average number of lymph nodes dissected via the left and right thoracotomy approaches was 23.4 and 24.6, respectively (P<0.001) and the postoperative 5-year survival was 38.2% and 42.1%, and the differences were not statistically significant ($\chi^2=0.246$, P=0.620). In a retrospective controlled study comparing two approaches: the left thoracotomy approach and right thoracotomy approach, Luo *et al.* (27) from Sun Yat-sen University Cancer Center found that the average number of lymph node dissected was 11.8±6.6 in left thoracotomy approach group and 16.3±8.0 in right thoracotomy approach group (P<0.001). The 1- and 3-year survivals were 78.9% and 48.2% in the left thoracotomy approach group and 82.6% and 57.6% in the right thoracotomy approach group respectively. The median survival in the left and right thoracotomy groups was (25.63±0.63) months and (27.42±1.01) months, respectively, showing no significant difference (P=0.080); the incidence of complications in the left and right groups was 35.4% and 57.6% (P<0.001). The recurrence rate in the left and right groups was 50.0% (175/350) and 42.4% (56/132) (P=0.138). It was concluded that although the left thoracotomy approach was easy to perform, reducing postoperative complications, while right thoracotomy approach had an increased number of lymph nodes dissected. In a clinical randomized controlled study performed by Li *et al.* (29) from Fudan University Shanghai

Table 1 Lymph node dissection via different surgical approaches in patients with esophageal cancer and the post-operative survival rates in some studies

| Authors | Year of publication | Number of lymph node dissected via an approach | Statistical difference | 5-yr survival | Statistical difference |
|----------------|---------------------|--|------------------------|---|------------------------|
| Altorki N (24) | 2002 | Three-field lymph node dissection: 47 | None | 51% | None |
| Kang CH (30) | 2007 | Ivor Lewis group: 21.0 ±12.5 Three-field lymph node dissection: 33.1±15.7 | P<0.01 | Ivor Lewis group: 36.3% Three-field lymph node dissection group: 53.7% | P=0.019 |
| Luo KJ (27) | 2009 | Left-sided: 11.8±6.6 Right-sided: 16.3±8.0 | P<0.001 | 3-yr survival Left-sided: 48.2%; right-sided: 57.6%. | P=0.080 |
| Mao YS (21) | 2012 | Left-sided: 23.4 Right-sided: 24.6 | P<0.001 | Left-sided: 38.2%; right-sided: 42.1% | P=0.620 |
| Sihag S (31) | 2012 | Minimally invasive Ivor Lewis: 19 Open Ivor Lewis: 21 | P=0.740 | No statistics | None |
| Ma J (26) | 2014 | Left-sided: 17.45 ±8.591 Right-sided: 18.89±10.085 | P= 0.087 | Left-sided: 46.56% Right-sided: 48.35% | P=0.388. |
| Xu T (28) | 2015 | Left-sided: 12.9±8.4 Right-sided: 16.3±7.9 | P<0.05 | Left-sided: 34.7% Right-sided: 38.7% | P>0.05 |
| Li B (29) | 2015 | Left-sided: 18 Right-sided: 22 | P <0.001 | No statistics | No statistics |
| Yang JX (32) | 2014 | Left-sided: 12.3 Right-sided: 21.8 | P<0.05 | No statistics | None |
| Wang CQ (33) | 2015 | Left-sided: 11.44±3.22 Right-sided: 15.92±5.41 | P<0.05 | No statistics | None |
| Liu DT (34) | 2015 | Left-sided: 20±7 Right-sided: 40±13 | P<0.01 | No statistics | None |
| Lin J (35) | 2014 | Ivor Lewis group: 25.5±9.6 McKeown group: 27.3±9.8 | P=0.394 | No statistics | None |

Cancer Center, the average number of lymph node dissected via the left and right thoracotomy approach was 18 and 22 (P<0.001) and the incidence of postoperative complications was 41.3% and 30% (P=0.04) respectively; they concluded that the procedure via the right thoracotomy approach not only could remove more lymph nodes (compared with left thoracotomy approach) but also could lower the incidences of postoperative complications; however, the authors did not describe data on long-term survival. Peng *et al.* (19) from Sichuan provincial Cancer Hospital performed Ivor Lewis esophagectomy with two-field (thoraco-abdominal) lymph node dissection via median laparotomy and right posterolateral thoracotomy approach, and obtained a postoperative 5-year survival of 55.49%. Nasser Altorki *et al.* (24) from U.S.A. reported an average yield of 47

lymph nodes obtained by a 3-field lymphadenectomy via the right thoracotomy with a postoperative 5-year survival of 51%. Shimada *et al.*, (12) from Japan reported a postoperative 5-year survival of 52.0% after radical treatment for EC via the right thoracotomy approach. A summary of recent studies on the results of lymph node dissection and prognosis following surgical treatment of EC after dissection of two or three-field lymphadenectomy via left thoracotomy approach is depicted in *Table 1*. The currently available findings both in China and abroad have shown that the right thoracotomy approach obtains a more extensive lymphadenectomy (in thorax and abdomen) than the left thoracotomy approach and the right thoracotomy approach enables a 3-field lymph node dissection (not possible via left thoracotomy) and in this may improve

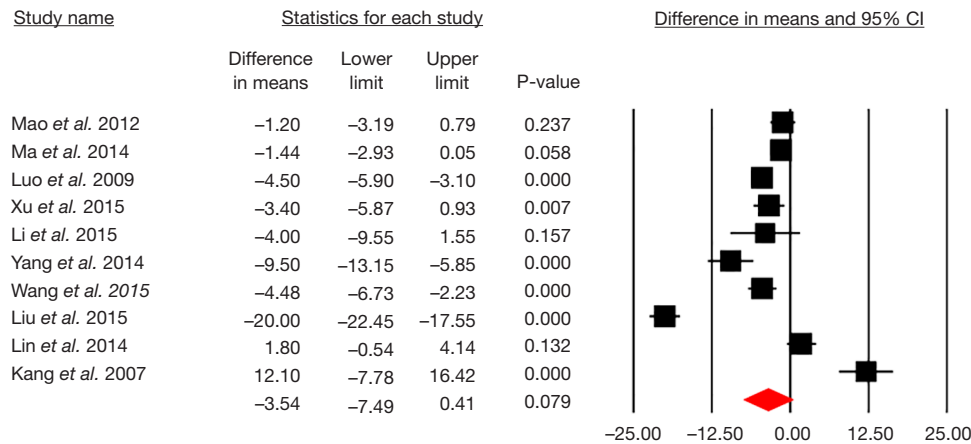


Figure 1 Mean difference in the number of lymph nodes retrieved between left and right-sided approaches.

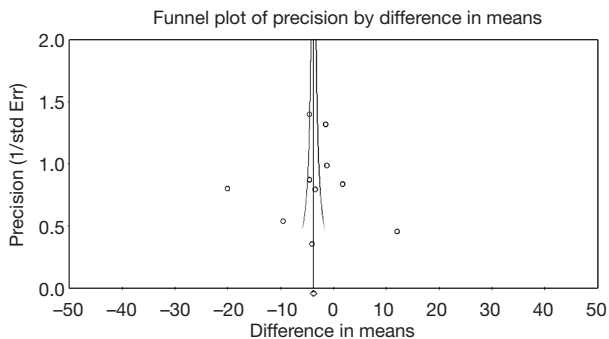


Figure 2 Funnel plot shows no evidence of publication bias.

prognosis in selected patients (30); However, most of the studies were retrospective, and there are few prospective randomized studies with large sample size. Therefore, large-scale prospective randomized controlled studies are still warranted to confirm the impact of surgical approach on survival in patients with EC.

A meta-analysis by Guy Eslick of these studies which includes 3,539 patients (2,080 esophagectomy through left thoracotomy); and 1,459 patients resected via the right thoracotomy) and compared the number of lymph nodes retrieved. Survival analysis was possible in only 1,019 left-sided esophagectomy and 920 right-sided esophagectomy patients. The pooled analysis suggests that the left-sided approach retrieves 3.54 less lymph nodes than the right-sided approach (*Figure 1*) (36).

There was a high level of heterogeneity between the studies ($I^2=96.65$, $P<0.001$), but there was no evidence of publication bias ($P=0.99$) (*Figure 2*).

Moreover, the right-sided approach offers superior survival compared to the left-sided approach (*Figure 3*).

These studies had low heterogeneity that was not statistically significant and again there was no evidence of publication bias (*Figure 4*).

Minimally invasive approaches

Minimally invasive esophagectomy (MIE) may include different approaches such as total MIE (laparoscopy, and thoracoscopy in different positions (in lateral position, in prone position or in semiprone position), the RAMIE (robot assisted MIE), the MIE transhiatal approach and hybrid approaches (type 1 combines laparoscopy and right thoracotomy and type 2 include the laparotomy and thoracoscopy). MIE means less operative trauma and as consequence of this has potential advantages such as less blood loss, less postoperative respiratory infections, less pain, shorten intensive care and hospital stay, and better postoperative quality of life (36). Uncertainty includes questions about increased operative time, and the long-term oncologic safety and outcomes. Multiple studies, long series, meta-analysis and two randomized control trials, have demonstrated the short and long-term oncological safety (at three years follow up) of MIE compared to open esophagectomy (36-39) The TIME trial, a small, prospective trial (115 patients in two arms) found significantly decreased pulmonary infections in patients undergoing MIE compared to open esophagectomy (36). In addition, quality of life at one-year follow-up was better in the MIE group. Although it was a small study, no difference

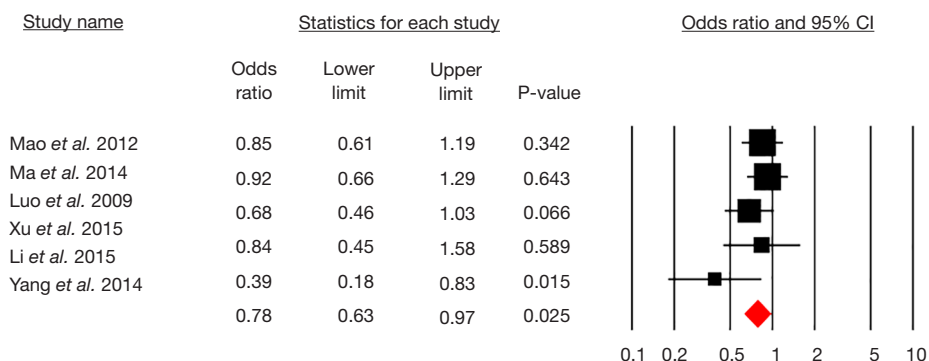


Figure 3 Comparing survival between esophagectomy approaches.

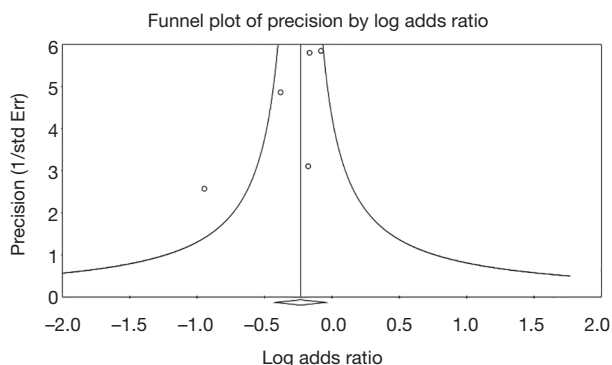


Figure 4 Funnel plot showing no evidence of publication bias.

in survival at one and three years was seen (40,41). Many centers in China have had large experiences with MIE with acceptable short-term outcomes. Meta-analysis of Yibulayin *et al.* (42) included 57 studies with 15,790 patients. They concluded that MIE is superior to OE in terms of perioperative complications (also anastomotic leaks) and in hospital mortality. Mu *et al.* (43), performed a controlled randomized study comparing the short-term outcomes and 3-year survival between total MIE 3 stage McKeown and the so called dual-incision esophagectomy through an open left thoracotomy (DIE = Sweet procedure). They concluded that MIE and DIE yielded comparable short-term outcomes, however MIE was associated with better three year overall and disease-free survival (43). Moreover, Sun *et al.* (44) performed an important control randomized study comparing two groups of patients operated by MIE 3 stage McKeown esophagectomy. One group was treated by early oral feeding and the other by traditional late oral feeding. They concluded that between the two forms of oral feeding (early versus

late oral feeding after MIE McKeown) there were no differences in major complication rates and importantly there was an increase in Quality of Life if early feeding was given. Likewise, Wang *et al.* from Fudan University Shanghai Cancer Center performed a propensity-score matched analysis of 735 MIE patients compared to 652 open esophagectomy patients and found improved quality of life among the MIE patients. The MIE group also had lower rates of complication. No difference in survival was found (45). Using the National Cancer Database, Weksler did not find a significant difference in survival among patients undergoing open, minimally invasive, or robotic esophagectomy (46).

How to select approaches of individualized surgical treatment for EC at different sites and stages

Based on currently available guidelines and expert consensus in China, we suggest a few recommendations for patient selection. For resectable middle and lower thoracic esophageal carcinoma with if preoperative EUS, and CT scan of the chest and abdomen, and whole body PET-CT reveals a clinical stage of T₂N₀₋₁M₀, neoadjuvant concurrent chemo radiation followed by resection of esophageal carcinoma with thoracic or cervical anastomosis via the conventional two incisions (abdomen and chest) or three incisions (chest, abdomen, and neck), minimally invasive or open with complete two-field (thorax and abdomen) or three-field (neck, thorax, and abdomen) lymphadenectomy is recommended. Patients with clinical stage of T_{1b}-N₀ can forgo preoperative therapy. For resectable upper thoracic EC, Akiyama *et al.* (47) found that the upper thoracic EC

might have a high probability of metastasis in the upper mediastinum and in the cervical areas and therefore the three-field lymphadenectomy should be considered. The rates of cervical lymph node metastasis of the upper, middle, and lower EC were 46.3%, 29.2%, and 27.2%, respectively. According to Liu *et al.* (9), the three-field lymphadenectomy (compared with two-field lymphadenectomy) can significantly prolong the postoperative 5-year survival in patients with upper thoracic EC (53.2% *vs.* 34.1%, $P=0.002$). Therefore, for resectable upper thoracic EC, esophageal resection and left cervical esophagogastrostomy via 3 incision procedure, MIE, total or hybrid, or open, with total two-field (thorax and abdomen) or three-field (neck, thorax, and abdomen) lymphadenectomy is recommended. For these patients, whether a left or right thoracotomy approach should be selected for surgical treatment remains controversial (21,26-28). According to Ma Ma *et al.* (26) from Shanghai Zhongshan Hospital, for patients without suspected lymph node metastasis in the superior mediastinum, the 5-year survival rate following left thoracotomy and right thoracotomy was not different, 46.56% and 48.35%, respectively ($P=0.388$), and the median survival was 52 months and 48 months; the incidence of postoperative complications in the left and right thoracotomy groups was 12.3% and 20.4% ($P=0.002$), the local relapse rate was 14.8% and 13.3% ($P=0.695$), and the distant relapse rate 30.4% and 24.8% ($P=0.274$) respectively. In our opinion, for patients without suspected lymph node metastasis in the superior mediastinum, there are until now no clear evidence of statistical difference in terms of local relapse and long-term survival between left and right thoracotomy approach. However, for middle and lower thoracic EC, if the preoperative EUS + thoraco-abdominal CT/PET-CT reveals the presence of suspected lymph node involvement and metastasis in the superior mediastinum, the current recommended treatment is: resection of EC and complete two-field/three-field lymph node dissection via the conventional two or three stage, MIE, total or hybrid, or open through the right thoracic approach including a two or three-field lymphadenectomy (18-20,40).

Role of neoadjuvant therapy

Important point in the treatment of EC is the current implementation of neoadjuvant therapy in the form of chemoradiotherapy or chemotherapy (48,49). Remarkable are the long-term results of the CROSS study, in which

patients with clinically resectable esophageal or junctional cancer (cT1-1N1M0 or cT2-3N0-1M0) were randomly assigned to receive weekly administration of Carboplatin and Paclitaxel for 5 weeks with concurrent radiotherapy (41.4 Gy given in 23 fractions, 5 days per week), followed by surgery, or surgery alone. Radical resection (R0) was accomplished in 92% of patients in the group of nCRT plus surgery group and 69% in the surgery alone group. Because the decrease in size of the tumors after nCRT, resection was considered easier to perform. Moreover, a pathological complete response was achieved in 49% of the squamous cell cancer patients. Five-year overall survival rate was 47% in the nCRT plus surgery group and 33% in the surgery alone group, respectively (in the Squamous cell cancer it was, 61% versus 30% respectively).

Moreover, the neoadjuvant chemotherapy studies, such as the MAGIC trial have showed a 5 years improvement of 13% compare to surgery alone (48). Important is to remark, that the highest benefit of the CROSS neoadjuvant chemoradiotherapy is observed in the squamous cell cancer which is radiosensitive and the most frequent EC in China.

Levels of evidence

According to the above systematic review, the levels of evidence were at level III, the quality of the evidence was average, and the strength of recommendation is medium. Thus, according to the findings of retrospective studies and a few prospective studies, performed in China and abroad, the right transthoracic approach is superior to left thoracotomy approach for performing the two-field lymphadenectomy for thoracic EC. This approach can reduce the incidence of postoperative local relapse in the upper mediastinum and thus increase the survival benefit. Therefore, for resectable upper thoracic EC, EC resection plus two-field (thorax and abdomen) or three-field (neck, thorax, and abdomen) lymphadenectomy dissection is strongly recommended through the right thoracotomy approach. However, due to the low evidence levels, large-scale prospective randomized controlled studies are still warranted.

Future research directions

More research is needed to better definitively evaluate if a left thoracotomy approach yields equivalent outcomes to a right thoracotomy approach for middle and lower thoracic EC without suspected lymph node involvement.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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