

## Surgical approach for Siewert type II adenocarcinoma of the esophagogastric junction: transthoracic or transabdominal? A retrospective analysis in a single center

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### Abstract

**Background:** Adenocarcinoma of the esophagogastric junction (AEG) is a special type of challenging carcinoma between esophageal and gastric cancer with controversy in the diagnosis, treatment and prognosis. The Siewert classification is widely accepted by the majority of scholars at home and abroad, in which, type I and type III AEG are usually treated based on the guidelines for esophageal cancer and gastric cancer, respectively. However, the surgical approach to patients with type II AEG still remains controversial. In this study, we intended to realize the different surgical approach for Siewert type II AEG treatment by analyzing the data retrospectively.

**Methods:** Patients with Siewert type II AEG were collected in Guangdong General Hospital from 2004 to 2014. We compared the clinicopathological outcome and prognosis in transthoracic (TT) and transabdominal (TA) approach.

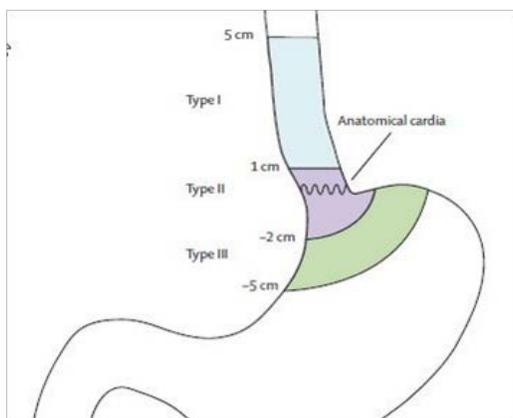
**Results:** A total of 158 patients with Siewert type II AEG were enrolled. Overall median survival was 52 months and the 5-year survival rate was 39.1%. The 5-year survival rate was comparable between TT and TA group (35.1% vs 43.2%,  $p > 0.05$ ), while more lymph nodes were dissected in TA group ( $23.7 \pm 0.2$  vs  $18.1 \pm 0.3$ ,  $p < 0.05$ ), with less postoperative complications (14.3% vs 28.4%,  $p < 0.05$ ) and shorten hospital stay ( $12 \pm 4$  d vs  $15 \pm 7$  d,  $p < 0.05$ ).

**Conclusion:** For Siewert type II AEG patients, there is no significant difference in survival outcome as treated with TT or TA approach. However, fewer lymph nodes dissection number was conducted in transthoracic group, with a higher incidence of postoperative complication. Therefore, we consider that transabdominal approach is more suitable for patients with Siewert type II AEG to achieve an optimal extent of lymph node dissection, and reduce the incidence of complication, shorten hospital stay and promote the recovery. But our study is only a single-center, retrospective, small sample clinical study that represents our previous clinical treatment experience and we need more multi-center, prospective, and a large sample of clinical studies to be validated.

**Keywords:** Adenocarcinoma of the esophagogastric junction, Siewert type II, Surgical approach

### Introduction

During the recent years, the incidence of adenocarcinoma of the esophagogastric junction (AEG) shows the increasing trend progressively [1]. The classification of AEG proposed by Siewert and Stein is popularly applied at the present time. The basis of this classification is on the central distance of carcinoma within 5cm up and down of dentate line [2] (Figure 1).



**Figure 1.** Siewert classification of adenocarcinoma of esophagogastric junction.

Union for International Cancer Control (UICC) has suggested that AEG can be categorized with the standards of gastric cancer or esophageal cancer [1]. However, a variety of differences exist in aspects of epidemiology, diagnosis, treatment and prognosis between gastric cancer and esophageal cancer [2,3]. According to Japanese gastric cancer treatment guideline, the transabdominal approach is recommended if lower esophageal invasion segment  $< 3$ cm. The lymphadenectomy should be performed till be to a certain extent, which indicates the treatment of Siewert type II/III AEG needs referring to gastric cancer model [4]. In the latest National Comprehensive Cancer Network (NCCN) guideline, Siewert type I/II AEG and type III AEG were respectively included in the content of esophageal cancer guideline and gastric cancer guideline [5]. Therefore, it has been agreed that Siewert type I and type III AEGs should be operated transthoracically as like an esophageal cancer and transabdominally as like a gastric cancer. However, there is still controversy on the surgery for Siewert type II AEG. In this study, the different surgical approach for Siewert type II AEG was investigated by analyzing the clinical data retrospectively.

## Materials and methods

We have received ethical approval for this case series from the hospital's ethical board/committee, and consent for publication from the patients.

### Patients

Patients with Siewert type II AEG were enrolled from 2004-2014 in Guangdong General Hospital. Informed consent was signed by each patient before operation.

The inclusion criteria were:

- Siewert type II AEG;
- purely TT or TA approaches with total or proximal gastrectomy;
- no distal metastasis;
- No neoadjuvant chemoradiotherapy before operation;
- complete medical records available.

The exclusion criteria were:

- remnant stomach cancer and non-epithelial malignant tumors;
- other malignant diseases.

The staging was completed according to TNM staging of gastric cancer described in the American Joint Committee on Cancer (AJCC) (Version 7).

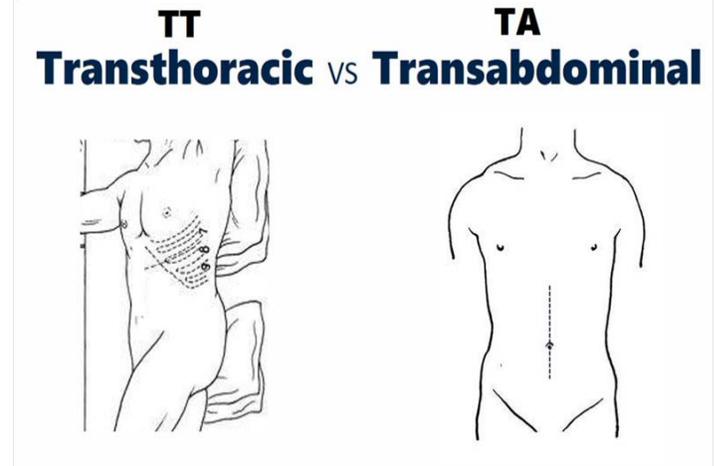
### Surgical procedure

The transthoracic surgery was performed by thoracic surgeons. Lateral incision was made at the left-side chest intercostals space between 7<sup>th</sup> and 8<sup>th</sup> ribs for total or proximal gastrectomy. The transabdominal surgery was performed by gastrointestinal surgeon. The abdominal midline incision was made was performed (Figure 2). According to Japanese gastric cancer treatment guidelines (ver.4) [4], when performing total gastrectomy, all the cases did a D2 lymphadenectomy, if tumors invading the esophagus, the range of lymphadenectomy mainly covered posterior mediastinal lymph nodes (group 110 and 111), inferior phrenic lymph nodes (group 19), diaphragmatic lymph nodes (group 20) and perigastric lymph node (Figure 3). When performing proximal gastrectomy, all the cases should did a D1+ lymphadenectomy, for tumors invading the esophagus, D1+ should include NO.110 (Figure 3). Proximal gastrectomy did esophagogastric anastomosis and total gastrectomy did esophagus-jejunum Roux-en-Y anastomosis (Figure 4).

### Parameters for postoperative observation and follow-up

Based on relevant literature published at home and abroad, the clinical information, surgical and pathological outcomes and survival including age, gender, BMI, TNM stage, tumor diameter, histological differentiation, combination, postoperative adjuvant chemotherapy, operation time, blood loss, number of lymph node dissection, proximal margin, incidences of cardiopulmonary complications, pancreatic fistula, anastomotic leakage and hospital stay etc. Patients were followed up via phone calls, hospital visits or letters to track the patients's survival status, survival time, living quality after surgery and postoperative therapy. The survival time

was defined as the period from the surgical day till tumor-related death, or the last day of follow up on a monthly basis. The last follow up day was October 1st, 2017.



**Figure 2.** Different incisions based on transthoracic and transabdominal approach.

### Statistical analysis

Statistical analysis was performed using SPSS 19.0. Categorical data were compared by X<sup>2</sup> tests or Fisher exact test. Survival curves were derived from Kaplan–Meier estimates and the curves were compared by log-rank test. Prognostic factors were identified by univariate analysis and further tested by multivariate analysis. P-value <0.05 was considered statistically significant.

## Results

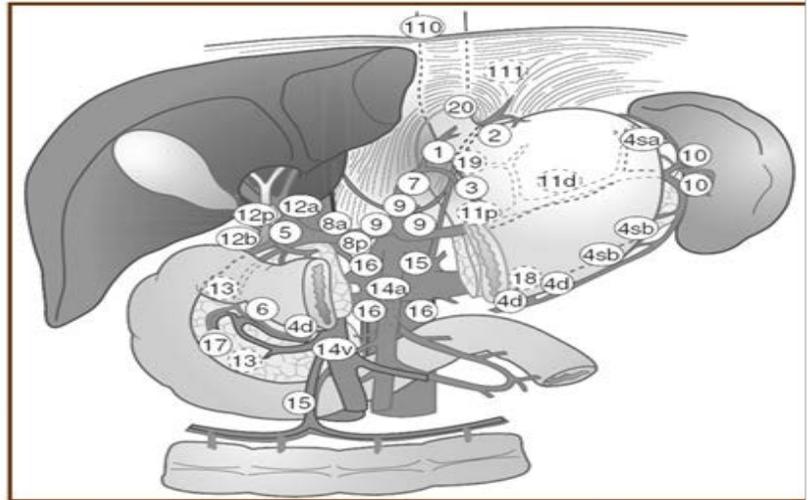
### Patient characteristics

A total of 158 cases with Siewert type II AEG were enrolled in accordance with the inclusion criteria (4 cases with combined thoraco-abdominal surgery were excluded). In which, 81 and 77 cases were treated with transthoracic and transabdominal surgery. Clinicopathological characteristics including age, gender, BMI, TNM stage, tumor diameter, histological differentiation, Borrmann type, vascular tumor emboli, combination, postoperative adjuvant chemotherapy. There were no significant differences between the TT group and TA group in all the clinical and pathological characteristics (P>0.05) (Table 1).

### Surgical outcome

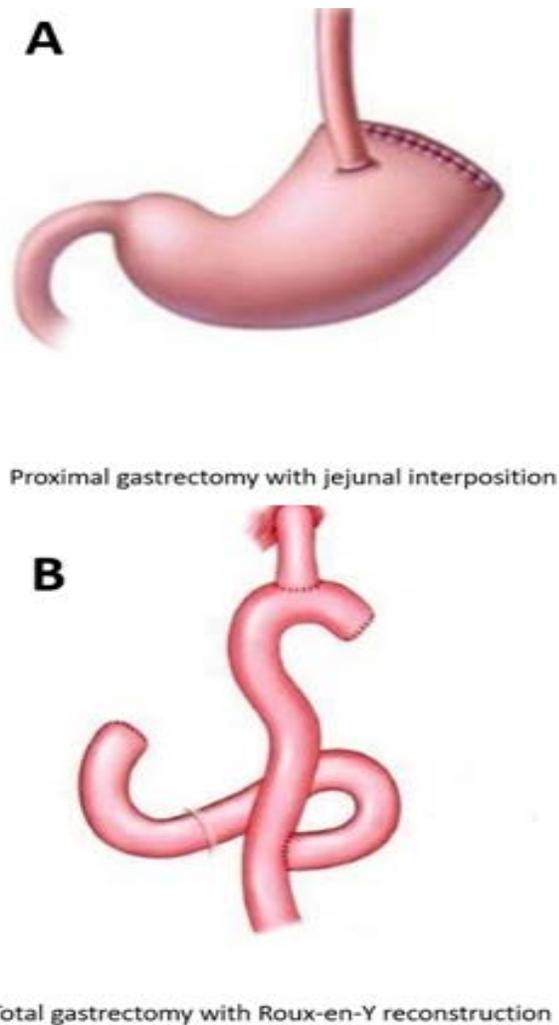
The surgical outcomes are listed in Table 2. The operative time in TT group was significantly longer than that in TA group (215±39 vs. 168±26 min, P<0.05). For surgical resection way, TT group had more proximal gastrectomy cases while TA group had more total gastrectomy cases, there was a significant difference between the two groups (p<0.05). The number of lymph nodes dissection in total was 18.1±0.3 in TT group and 23.7±0.2 in TA group (P<0.05). But there was no difference in the number of positive lymph node between the two groups, 4.1±2.1 in TT group and 4.7±2.9 in TA group (P<0.05). There was no difference in proximal margin between the two groups, and the curative resection rate (R0) was 95.1% in TT group and 93.5% in TA group (P=0.324).

- No. 1 Right paracardial LN
- No. 2 Left paracardial LN
- No. 3 LN along the lesser curvature
- No. 4sa LN along the short gastric vessels
- No. 4sb LN along the left gastroepiploic vessels
- No. 4d LN along the right gastroepiploic vessels
- No. 5 Suprapyloric LN
- No. 6 Infrapyloric LN
- No. 7 LN along the left gastric artery
- No. 8a LN along the common hepatic artery
- No. 9 LN around the celiac artery
- No. 10 LN at the splenic hilum
- No. 11p LN along the proximal splenic artery
- No. 11d LN along the distal splenic artery
- No. 12a LN in the hepatoduodenal ligament
- No. 19 Infradiaphragmatic LN
- No. 20 LN in the esophageal hiatus of the diaphragm
- No. 110 Paraesophageal LN in the lower thorax
- No. 111 Supradiaphragmatic LN
- No. 112 Posterior mediastinal LN

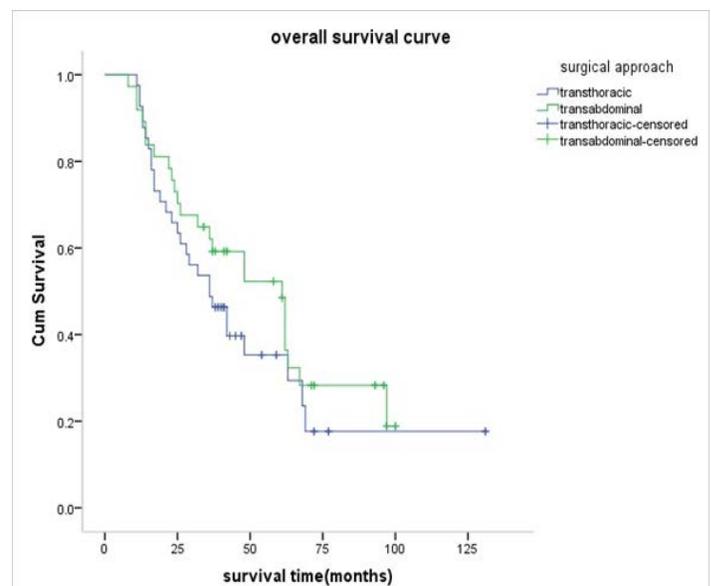


LN, lymph node

**Figure 3.** Lymph node dissection for Siewert type II AEG (adenocarcinoma of the esophagogastric junction).



**Figure 4.** Digestive reconstruction after proximal/total gastrectomy.



**Figure 5.** Kaplan-Meier survival curves of Siewert type II AEG patients. There was no significant difference in survival rate between two groups. The 5-year overall survival (OS) rate was 35.1% in TT group and 43.2% in TA group ( $P=0.278$ ).

### Morbidity and mortality

Two patients in the Tt group and one case died during the first 30 d after surgery and there was no significant difference in postoperative mortality ( $p>0.05$ ). The length of postoperative hospital stay showed significant difference between in TT group and TA group ( $15\pm 7d$  vs.  $12\pm 4d$ ,  $P<0.05$ ). Postoperative morbidity of these two groups were comparable (Table 3). There was a significant difference of postoperative morbidity between the two groups, in which, 23 patients in TT group (mainly of pneumonia, 11 cases), whereas only 11 patients in TA group ( $P<0.05$ ).

		TT group N=81	TA group N=77	P-value
Age (years)		64±12	62±10	0.727
Gender	Male	60	55	0.126
	Female	21	22	
BMI (kg/m <sup>2</sup> )		24.5±5.7	23.8±6.1	0.487
T stage	T1	5	4	0.921
	T2	16	15	
	T3	42	41	
	T4	18	17	
N stage	N0	23	21	0.728
	N1	20	17	
	N2	12	14	
	N3	26	25	
TNM stage	I	12	13	0.963
	II	34	31	
	III	35	33	
Tumor diameter (cm)		4.2±1.7	4.7±1.5	0.853
Histological differentiation	Poor	41	37	0.685
	Mid	37	36	
	High	3	4	
Borrmann type	0-2	38	35	0.426
	4-Mar	43	42	
Vascular tumor embolism	Yes	62	57	0.285
	No	19	20	
(hypertension, DM, CHD, malnutrition)	13		12	0.348
Postoperative adjuvant chemotherapy	23		23	0.81

**Table 1.** Clinical and pathological characteristics of 158 Siewert type II AEG patients.

		TT group N=81	TA group N=77	P-value
Operating time (min)		215 ± 39	168 ± 26	<0.05
Intraoperative blood loss (ml)		198 ± 85	202 ± 79	0.725
Surgical resection way	PG	73	27	<0.05
	TG	8	50	
Other organ resection	Splenectomy	7	8	0.417
	Pancreatic tail resection	1	3	
No. Of lymph node dissection		18.1 ± 0.3	23.7 ± 0.2	<0.05
No. Of positive lymph node		4.1 ± 2.1	4.7 ± 2.9	0.549
Proximal margin	Negative	77	72	0.324
	Positive	4	5	
Hospital stay (days)		15 ± 7	12 ± 4	<0.05

AEG: Adenocarcinomas of the Esophagogastric Junction; TT: Transthoracic; TA: Transabdominal; PG: Proximal Gastrectomy; TG: Total Gastrectomy; No: Number.

**Table 2.** Surgical outcome of 158 Siewert type II AEG patients.

	TT group N=81	TA group N=77	P-value
Postoperative complications (≥grade II)*	23(28.4%)	11(14.3%)	<0.05
Pneumonia	11	4	
Pleural effusion	5	2	
Abdominal infection	1	1	
Postoperative Hemorrhage	3	1	
Anastomotic leak	2	2	
Pancreatic fistula	1	1	
Postoperative mortality	2	1	0.324

AEG: Adenocarcinomas of the Esophagogastric Junction;TT: Transthoracic; TA:Transabdominal.\*according to the Clavien–Dindo grading system.

**Table 3.** Postoperative morbidity and mortality of 158 Siewert type II AEG patients.

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.127 (0.561-2.26)	0.037	1.210 (0.761-1.942)	0.543
Gender	0.733 (0.361-1.48)	0.897		
Other organ resection	0.678 (0.456-1.289)	0.887		
Surgical approach	0.771 (0.391-1.519)	0.278		
Surgical resection way	0.728 (0.364-1.455)	0.181		
Blood loss	1.271 (0.644-2.507)	0.608		
T stage	6.897 (3.190-14.911)	0		
N stage	3.061 (2.078-4.510)	0	2.247 (1.820-2.775)	0
TNM stage	5.027 (2.925-8.638)	0		
No. of lymphadenectomy	1.860 (0.903-3.830)	0.027		
Tumor size	1.107 (0.491-2.495)	0.005	1.311 (0.814-2.112)	0.345
Histological differentiation	1.349 (0.575-2.082)	0.024	0.836 (0.584-1.195)	0.273
Vascular tumor emboli	1.094 (0.575-2.082)	0.022	1.661 (1.021-2.732)	0.175
Hospitalization days	0.902 (0.470-1.730)	0.099		
Chemotherapy	0.796 (0.402-1.576)	0.012	0.752 (0.482-1.171)	0.327

AEG: Adenocarcinomas of the Esophagogastric Junction;HR(95% CI): 95% confidence interval of the risk ratio.

**Table 4.** Univariate and multivariate analyses of 158 Siewert type II AEG patients for overall survival

## Survival and prognostic factors

The cut-off date of this study was October 1st, 2017. The median overall survival time was 42 months. Medium survival of TA group and TT group were 51 and 36 months, respectively. There were no significant differences between the two groups with regards to survival time. The 5-year OS rates were 35.1% in the group TT and 43.2% in group TA (Figure 5). For Siewert type II AEG, Univariate analyses showed that age, T stage, N stage, TNM stage, histological differentiation, vascular tumor emboli, tumor size, number of lymphadenectomy, adjuvant chemotherapy are the factors that affects the prognosis ( $p < 0.05$ ). Multivariate analyses showed that the N stage was the independent factor affecting prognosis (Table 4)

## Conclusion

Adenocarcinoma of the esophagogastric junction (AEG) is a type of malignant tumor across esophageal and gastric cancer with great challenging and poor prognosis [1]. Previous studies demonstrated that the biological behavior and pathological features of adenocarcinoma at this portion were completely different from those of gastric and esophageal cancer. Thus, no treatment consensus was concluded so far on the classification, diagnosis, treatment and prognosis for this kind of disease [6,7]. Currently, the Siewert classification is accepted by the experts at home and abroad [2], which is based on the central distance of carcinoma within 5cm up and down from dentate line (Figure 1). Siewert type I AEG is more common in European countries, while type II and III are more common in Asia [1,2]. Siewert classification is of great significance in guidance of clinical diagnosis, treatment and prognosis of AEG. According to NCCN guideline, Siewert type I/II AEG has been classified into the therapeutic range of esophageal carcinoma, and the transthoracic approach is recommended for surgical procedure [5]. However, a number of Asian Studies and Japanese gastric cancer treatment guidelines considered [4,7], that the biological behavior and pathological features of Siewert type II and III AEG in Asian patients are more similar to those in gastric cancer. Therefore, the therapeutic regime should be referred to the guideline for gastric cancer and the transabdominal approach is preferentially adopted. From the current study situation [3], the clinical consensus has been formed that Siewert type I AEG is a lower esophageal cancer and should be treated according to guidelines for esophageal cancer by transthoracic surgery with additional mediastinal lymph node dissection. Siewert type III AEG is an upper gastric cancer and should be treated with total gastrectomy plus D2 lymph node dissection according to Japanese treatment guidelines for gastric cancer [4]. Nevertheless, treatment of Siewert type II AEG still remains controversy including the selection of surgical approach and the coverage of lymph node dissection. It is worthy for the surgeon to do further exploration.

Previous literatures disclosed [3-6], transthoracic and transabdominal approach are the most common surgical approaches for Siewert type II AEG. Also, the advantages of thoraco-abdominal approach were compared with transabdominal approach. The results showed that thoraco-abdominal approach failed to improve the long-term survival, but increased the perioperative complications and mortality. Thus, it should be handled cautiously [8]. In this study, long-term survival of Siewert

type II AEG patients treated with transthoracic and transabdominal surgical approach was analyzed and compared. The typical Dutch study in Netherlands revealed that Siewert type II AEG patients treated with transthoracic approach had significantly lower 5-year survival rate than those with transabdominal surgical approach [9]. In JCOG9052 Phase III trial conducted by Japanese investigator Sasako, 167 AEG patients including 95 Siewert type II patients were enrolled. The subgroup analysis indicated there was no significant difference in survival rate between TT group and TA group [10]. In the current study, medium overall survival was 42 months, in which, medium survival for TT group and TA group were 51 and 36 months, respectively. Although the survival is lack of statistically significance between 2 groups ( $p = 0.278$ ), the survival curve demonstrated a survival advantage and tendency in TA group, which was similar with the results of Zhang' [11] and Zheng' [12] study.

The extent of lymph node dissection is the important factor to affect the prognosis. Currently, the extent of lymph node dissection for patients with Siewert type I and III AEG has been recognized by the majority of experts. However, the metastasis of lymph node may be towards to the chest and abdomen for Siewert type II AEG. Thus, many controversies and difficulties are present in surgical treatment [13,14]. Numerous studies [15-17], indicated that lymph nodes metastasis in Siewert type II AEG patient can transfer to the chest and abdomen, mainly involving abdominal lymph nodes (especially to lymph nodes groups 1, 2, 3 and 7). Theoretically, the thoraco-abdominal approach would provide more complete dissection of lymph nodes. However, it was not recommended in clinical practice due to lower metastasis rate of thoracic lymph node and increased rate of complication [18,19]. Meanwhile, many investigators believed that transabdominal approach was more favorable to do the abdominal lymph node dissection than thoracic approach, which would result in a more satisfactory survival outcome. Thus, lymph node dissection via transabdominal approach was recommended [20-22]. In our study, we found that the number of lymph nodes dissection in transabdominal approach was significantly higher than transthoracic approach ( $23.7 \pm 0.2$  vs  $18.1 \pm 0.3$ ,  $P < 0.05$ ). The result was consistent with previous reports [11,12], which may explain the survival advantage of transabdominal approach. But in our study, there was no difference in positive lymph nodes. This may be the reason why TT or TA approach could get the similar survival rate. That means these two approaches can meet the radical standard of lymph node dissection. In the study of Goto H [19], AEG lymph nodes metastasis was mainly abdominal metastasis and concentrated on No.1,2,3,7,9 and 19 group of lymph nodes around proximal stomach, among which, metastasis rates of No. 1 and No. 3 lymph nodes groups were higher (37.0%-52.5%), while, metastasis rates of distal No.4,5,6 lymph nodes were low. So, the lymph node dissection extent in TT or TA group (No. 1, 2, 3a, 4sa, 4sb, 7, 8a, 9, 11p) for proximal or total gastrectomy could meet the radical requirements in oncology.

The incidence of complication is an important factor for surgeon taking into account in selecting surgical approach, which will affect the recovery, hospital stay, cost of hospitalization and beginning time of adjuvant chemotherapy, etc. The Dutch study

and JCOG9502 clinical trial demonstrated that for Siewert type II AEG patients, the incidence of postoperative complications such as cardiac dysfunction, anastomotic leakage and chylous leakage and prolonged hospitalization were significantly increased in TT group than those in TA group [9,10]. Meanwhile, a meta analysis including 16 studies indicated that significantly higher incidence of cardiovascular and respiratory complications, and longer length of hospital stay were observed in TT group than in TA group [12]. In our study, the incidence of postoperative complications, mainly of pulmonary dysfunction in TT group was significantly higher than that in TA group, which was in consistency with previous studies.

## Conclusion

Transthoracic or transabdominal approach did not affect the survival of Siewert type II AEG patients. However, our results showed that the less lymph node dissection was followed by a higher incidence of postoperative complications and a longer length of hospitalization in TT group. Therefore, we recommend to select the transabdominal approach to treat Siewert type II AEG in order to achieve optimal extent of lymphadenectomy, decrease the postoperative complications, shorten the hospitalization. Nonetheless, limitation is obvious in our study. This study is only a single-center, a small-samples retrospective analysis. The multi-center, prospective randomized controlled trials are required for further verifying our results.

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Received: Apr. 12, 2018; Accepted: Apr. 20, 2018; Published: Apr. 27, 2018

Cancer Ther. 2018;1(1):1  
DOI: [gsl.cancer.2018.00002](https://doi.org/10.1002/gsl.cancer.2018.00002)

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