

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2019 August 15; 11(8): 567-651



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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Florin Burada, MD, PhD, Associate Professor, Department of Medical Genetics and Human Genomics Laboratory, Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy of Craiova, Craiova 200349, Romania

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*World Journal of Gastrointestinal Oncology* (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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## RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Yun-Xiaojuan Wu

Proofing Production Department Director: Xiang Li

### NAME OF JOURNAL

*World Journal of Gastrointestinal Oncology*

### ISSN

ISSN 1948-5204 (online)

### LAUNCH DATE

February 15, 2009

### FREQUENCY

Monthly

### EDITORS-IN-CHIEF

Monjur Ahmed, Rosa M Jimenez Rodriguez, Pashtoon Murtaza Kasi

### EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

### EDITORIAL OFFICE

Jin-Lei Wang, Director

### PUBLICATION DATE

August 15, 2019

### COPYRIGHT

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### PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

### ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

### STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

### ONLINE SUBMISSION

<https://www.f6publishing.com>



## Current surgical treatment of esophagogastric junction adenocarcinoma

Shun Zhang, Hajime Orita, Tetsu Fukunaga

**ORCID number:** Shun Zhang (0000-0002-3493-1247); Hajime Orita (0000-0002-8263-7069); Tetsu Fukunaga (0000-0003-4802-8945).

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

**Supported by** Japan China Sasakawa Medical Fellowship.

**Conflict-of-interest statement:** No potential conflicts of interest.

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**Manuscript source:** Invited manuscript

**Received:** February 26, 2019

**Peer-review started:** February 27, 2019

**First decision:** June 4, 2019

**Revised:** June 26, 2019

**Accepted:** July 16, 2019

**Shun Zhang,** Department of Gastroenterology Surgery, Shanghai East Hospital (East Hospital Affiliated to Tongji University), Shanghai 200120, China

**Shun Zhang, Hajime Orita, Tetsu Fukunaga,** Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, Tokyo 113-8431, Japan

**Corresponding author:** Tetsu Fukunaga, MD, PhD, Professor, Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan. [t2fukunaga@juntendo.ac.jp](mailto:t2fukunaga@juntendo.ac.jp)

**Telephone:** +81-0358021556

**Fax:** +81-0358021557

### Abstract

The incidence of esophagogastric junction (EGJ) adenocarcinoma has shown an upward trend over the past several decades worldwide. In this article, we review previous studies and aimed to provide an update on the factors related to the surgical treatment of EGJ adenocarcinoma. The Siewert classification has implications for lymph node spread and is the most commonly used classification. Different types of EGJ cancer have different incidences of mediastinal and abdominal lymph node metastases, and different surgical approaches have unique advantages and disadvantages. Minimally invasive surgeries have been increasingly applied in clinical practice and show comparable oncologic outcomes. Endoscopic resection may be a good therapy for early EGJ cancer. Additionally, there is still a great need for well-designed, large RCTs to forward our knowledge on the surgical treatment of EGJ cancer.

**Key words:** Esophagogastric junction cancer; Surgery; Lymph nodes; Siewert classification

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**Core tip:** This is a review article on the current strategies for the surgical management of esophagogastric junction (EGJ) cancer. This article covers the different aspects related with the surgical treatment of EGJ cancer and provides comparison between different modalities discussed.

**Citation:** Zhang S, Orita H, Fukunaga T. Current surgical treatment of esophagogastric

**Article in press:** July 16, 2019  
**Published online:** August 15, 2019

**P-Reviewer:** Ouaisi M, Bintintan VV, Karamouzis MV  
**S-Editor:** Dou Y  
**L-Editor:** A  
**E-Editor:** Qi LL



junction adenocarcinoma. *World J Gastrointest Oncol* 2019; 11(8): 567-578  
**URL:** <https://www.wjgnet.com/1948-5204/full/v11/i8/567.htm>  
**DOI:** <https://dx.doi.org/10.4251/wjgo.v11.i8.567>

## INTRODUCTION

Gastrointestinal (GI) cancers are aggressive diseases, accounting for more than one-fourth of the newly diagnosed cancers worldwide (more than 4 million new cases per year). Among the GI cancers, the esophagogastric junction, or esophagogastric junction (EGJ), is a special anatomical site with a remarkably high risk of adenocarcinoma. The incidence of EGJ adenocarcinoma has shown an upward trend over the past several decades both in the West and East<sup>[1-3]</sup>. Due to its location between the esophagus and stomach, some investigators regard EGJ cancer as an entity separate from esophageal and gastric cancers. There has been much debate as to the pathogeny, diagnosis, classification, and optimal therapy for EGJ cancer, and the debate continues<sup>[4]</sup>.

The definition of the location of the EGJ by endoscopy or upper GI radiography and its appearance on histopathology are different. The EGJ or Z-line is theoretically defined as the histological transition from the squamocolumnar junction between the esophagus and stomach. Actually, this transition does not occur exactly in the anatomical transition between the esophagus and stomach<sup>[5]</sup>. In clinical practice, the EGJ is defined by the proximal margin of the longitudinal folds of the stomach transformed by the tubular esophagus.

In this article, we review previous studies and aimed to provide an update on the different aspects related to the surgical treatment of EGJ cancer.

## EGJ CANCER CLASSIFICATION

To improve the diagnosis and to allow the comparison of treatment results, Siewert and coworkers developed a system that separated EGJ tumors into three subtypes based purely on the macroscopic location of the tumor epicenter<sup>[6]</sup> (Table 1). Type I tumors are with an epicenter 1-5 cm above the EGJ; type II: Those within 1 cm above and 2 cm below the EGJ; and type III: Those 2-5 cm below the EGJ. The Siewert classification has practical implications for lymph node spread and is the most commonly used classification. The aim of the Siewert classification is not only for prognosis but also for therapeutic decision-making.

In the current (8<sup>th</sup>) edition of the TNM classification of malignant tumors, EGJ adenocarcinoma was redefined. Tumor epicenters within 2 cm proximal or distal to the EGJ are staged as esophageal adenocarcinomas, and those whose epicenters are more than 2 cm distal from the EGJ are staged as gastric cancer. The TNM classification also indicated that using the genetic signature of EGJ cancers may identify the cell of origin for cancer staging more accurately than the gross location of the tumor<sup>[7,8]</sup>. Cancer genetics will be included in the next (9<sup>th</sup>) edition staging of EGJ cancers.

Japanese gastric cancer treatment guidelines define EGJ cancer as a tumor ( $\leq 4$  cm diameter) with an epicenter located within 2 cm of the EGJ, whether adenocarcinoma or squamous cell carcinoma. The Japanese classification was based on retrospective data from 3177 patients operated on between 2001 and 2010 from 273 institutions<sup>[9]</sup>. Siewert type III and part of Siewert type I tumors are not covered by the Japanese classification.

## THE IMPORTANCE OF THE PRECISE LOCALIZATION OF TUMORS

EGJ cancers have unique characteristics that make the risk of lymph node (LN) metastasis high, and both the mediastinal and abdominal fields are the main lymphatic drainage areas. The surgical approach and type of lymphadenectomy have a close relationship with LN metastasis. The pattern of LN spread is also closely related to the location of the EGJ tumor. To develop the optimal treatment for EGJ cancers, it is important to identify the exact tumor location and estimate the exact length and depth of esophageal and gastric invasion preoperatively.



**Table 1** Different classification of esophagogastric junction cancer

System	Classification	Description
Siewert classification	Type I	1-5 cm above the EGJ
	Type II	Within 1 cm above and 2 cm below the EGJ
	Type III	2-5 cm below the EGJ
AJCC/UICC TNM	Esophageal adenocarcinomas	Within 2 cm proximal or distal to the EGJ
	Gastric cancer	More than 2 cm distal from the EGJ
Japanese classification	-	A tumor ( $\leq 4$ cm diameter) with an epicenter locating within 2 cm of the EGJ, whether adenocarcinoma or squamous cell carcinoma

EGJ: Esophagogastric junction; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

The precise localization of tumors can be frequently difficult to assess through endoscopic ultrasound (EUS) and computed tomography (CT), which are thought to be the best techniques currently available. This is particularly problematic for Siewert II type cancer. EUS precisely localizes tumors only 66% of the time, and CT precisely localizes tumors 57% of the time, compared to final operative pathology<sup>[10]</sup>.

## LYMPH NODE METASTASES ACCORDING TO THE SIEWERT CLASSIFICATION

EGJ cancers have unique characteristics, and lymphatic drainage occurs in both the mediastinal and abdominal areas. Adequate LN lymphadenectomy is an important key to oncologically successful surgical resection. The incidence of LN metastases increases with the depth of tumor infiltration, but LN location depends on the tumor location. Siewert's group reported the incidence of lymph node metastasis based on 1602 consecutive surgical patients<sup>[11]</sup>. Type II and type III cancers showed a higher risk of LN metastases. The incidence of metastasis was 51.9%, 65.2%, and 77.8% for type I, type II, and type III, respectively. Studies from Japan report that the incidence of metastasis was 64.1% and 75% for type II and III, respectively<sup>[12]</sup>. The data were based on 126 patients who underwent curative resection.

## LN METASTASES IN TYPE I EGJ CANCER

Type I EGJ cancers metastasize to lower mediastinal LNs, and 15% metastasize to upper mediastinal LNs. Paracardial regions and lower posterior mediastinal LNs are the most frequently observed locations in type I cancers<sup>[11]</sup>. More recent studies from Japan yielded similar results. LNs, including nos. 1, 2, 3a, and 7, had a frequent incidence of metastasis<sup>[13]</sup>, while other LNs were rarely involved. Therefore, total gastrectomy for type I cancer is not routine due to the extremely rare risk of LN metastases in the lower perigastric LNs. A surgical approach allowing both upper perigastric and mediastinal lymphadenectomy would be suitable for type I cancer.

## LN METASTASES IN TYPE II EGJ CANCER

Most studies focus on Siewert type II cancer, since it is considered the true EGJ tumor, and the characteristics of metastases to mediastinal LNs remain debatable. The extent of lymph node dissection determines the surgical field and the type of surgery. In particular, it has an important influence on the topic of the transabdominal approach due to the potential risk of leaving positive nodes in the mediastinal region. Twelve percent of LN metastases involve lower mediastinal regions among surgical patients reported by Siewert's group. They also indicated that as the location of the tumor approaches the gastric side, the incidence of mediastinal LN metastases gradually decreases, while the incidence of abdominal LN metastases increases<sup>[11]</sup>.

Many other studies have indicated that the location of mediastinal LN metastases is closely related to the distance from the EGJ to the tumor. A Japanese multicenter study retrospectively analyzed 315 pT2-4 Siewert II patients who received R0 or R1 resection. The results showed that the incidence of metastasis or recurrence was 4%,

7%, and 11% in the upper, middle, and lower mediastinal LNs, respectively. Among 315 patients in the study by Kurokawa *et al*<sup>[14]</sup>, 176 underwent LN dissection in the lower mediastinal region, and the metastasis rate in the lower mediastinal nodes was 17.6%. In 139 other patients who did not undergo dissection, the researchers described a long follow-up period. The recurrence rate among these 139 patients was 3.6%. Therefore, the researchers combined metastasis with recurrence to determine the final overall rate of metastasis or recurrence, which was 11.4%. We should recognize that recurrence does not always reflect metastasis at the time of surgery. This point was the limitation of their study. It also revealed that the length of esophageal invasion correlated with the number and location of mediastinal LN metastases. The incidence of metastasis was much higher when the length of esophageal invasion was > 3 cm for the upper or middle mediastinal nodes and > 2 cm for the lower mediastinal nodes<sup>[14]</sup>. The authors indicated that based on this result, if esophageal invasion of > 3 cm is noted, the upper and middle mediastinal LNs should be harvested. A systematic review reported that the frequency of LN metastasis in the lower mediastinal stations ranged from 7.5 to 23.8%, whereas patients with upper mediastinal node involvement had a frequency of LN metastasis below 4%<sup>[15]</sup>.

Several retrospective studies of abdominal LN metastasis in type II cancer were performed in Japan<sup>[12,13,16-19]</sup>. Fujitani *et al*<sup>[16]</sup>, Yoshikawa *et al*<sup>[13]</sup> and Yamashita *et al*<sup>[17]</sup> all reported that the incidence of metastasis was especially low in the lower perigastric LNs (nos. 4d-6), whereas it was higher in the upper half of perigastric LNs (nos. 1, 2, and 3) and the second-tier LNs (nos. 7, 9, and 11). LN nos. 1 and 3 had the highest metastasis incidence (up to 39.1%)<sup>[12]</sup>, and that in the celiac axis around the splenic artery and the splenic hilum was less than 10%<sup>[12,18]</sup>. However, if the distance from the EGJ to the distal end of the tumor was more than 5 cm, the LN metastasis incidence at the greater curvature (nos. 4sa, 4sb, 4d, and 6) or antrum was as high as 20%<sup>[19]</sup>. These results may indicate that harvesting the perigastric nodes of the lower half of the stomach is not beneficial if the distance from the EGJ to the anal edge of the tumor is greater than 5 cm.

Taken together, these results show that type II cancers mainly metastasize to the abdominal LNs around the stomach. The lower mediastinal compartment is the most common site of mediastinal LN metastases. Esophagectomy with proximal gastrectomy might be enough in type II cancer; however, it is better that the lower mediastinal compartment be routinely sampled during the operation. An accurate preoperative evaluation of the length of esophageal invasion is therefore essential, as it can be used as a reference point for mediastinal LN metastases.

## LN METASTASES IN TYPE III EGJ CANCER

Regarding type III cancer, perigastric LNs are the most common metastasis areas, with approximately 2% to 18% of them having simultaneous positive mediastinal nodes<sup>[20-23]</sup>. Among the perigastric LNs, nos. 4sa, 4sb, 4d, 8a, 9, and 11p show a high risk of metastasis, whereas LN nos. 1, 2, 3, and 7 do not<sup>[20,24]</sup>. Although the incidence of LN no. 10 metastasis ranges from 10%-20%, there is no survival benefit associated with adding a splenectomy to a D2 lymphadenectomy<sup>[25,26]</sup>. It is recommended that the splenectomy be performed only to obtain R0 resection<sup>[27,28]</sup>. Notably, a splenic hilar lymphadenectomy is technically difficult and quite sophisticated due to the deeply located operative field, limited space, and tortuous and variant vessels at this site. With the accumulation of experience, new technological emergences and new surgical energy instruments, this procedure has gradually become possible.

Taken together, these results indicate that total gastrectomy should be conducted for type III cancers to obtain enough LNs, but splenectomy is not routine only to obtain R0 resection.

## TUMOR SIZE AND INVASION WITH LN METASTASIS

The depth of tumor invasion is another factor that is significantly correlated with the presence of distal positive nodes<sup>[29]</sup>, with an incidence of ≥ 60% in T2 and ≥ 85% in T3-4 patients<sup>[20,21]</sup>. It was also reported that tumor size is a predictor of LN metastasis, especially in large tumors (> 4 cm)<sup>[30]</sup>.

## LYMPHADENECTOMY AND PROGNOSIS

LN metastasis is also an indicator of prognosis. The highest risk factor is the number

of metastatic LNs  $\geq 7$ <sup>[15,31]</sup>. Locoregional LN involvement is associated with improved survival compared with para-aortal or other distant LNs<sup>[15]</sup>. In a systematic review including 2252 type II cancer patients,  $\geq 7$  metastatic LNs (N3) indicated much worse survival (2.0%-17.4%) compared to no LN metastasis (up to 82.7%)<sup>[15]</sup>. Whether a more extensive lymphadenectomy in EGJ cancer is correlated with survival benefits has not been determined. Extended dissection might improve the prognosis, but the morbidity and mortality rates might also increase. In particular, some studies from the West have shown no superior survival rates compared with the East when using a more extended lymphadenectomy<sup>[31-34]</sup>. A multicenter retrospective study from the United States indicated that the number of LNs harvested was an independent predictor for survival after surgery. The authors concluded that a minimum of 23 regional LNs harvested can offer a survival benefit<sup>[35]</sup>. A cohort study of 262 pN0 type II patients from China also confirmed this conclusion. The researchers indicated that more than 15 LNs were recommended for patients undergoing curative resection<sup>[36]</sup>. Whether a more extensive lymphadenectomy in EGJ cancer can provide more survival benefit was recently challenged. A Dutch study found no benefit from an extended lymphadenectomy for type II disease<sup>[37]</sup>. A study from the United Kingdom ( $n = 606$ )<sup>[38]</sup> and another recent retrospective cohort study from Denmark ( $n = 510$ )<sup>[31]</sup> also showed no significant difference in survival between the extended and the less extended lymphadenectomy.

Therefore, although LN metastasis puts a patient at high risk and is considered an indicator of a poor prognosis, existing evidence does not support the benefits of an extensive lymphadenectomy. Moderately extensive lymph node removal may be enough to maximize the outcomes after EGJ cancer surgery.

## PROXIMAL RESECTION MARGIN

The definition of R0 resection for EGJ is important. Feith *et al*<sup>[11]</sup> retrospectively analyzed 1602 patients and found that the 5-year survival rate was 43.2% for a negative margin versus 11% for a positive margin. However, the optimal extent of esophagus resection required for the prevention of recurrence and longer survival remains controversial<sup>[18,39-42]</sup>. Ito *et al*<sup>[43]</sup> advocated the proximal gross margin length of at least 6 cm in patients with Siewert type II/III EGJ cancers, while Mariette *et al*<sup>[39]</sup> advocated that 8 cm is necessary to prevent local recurrence.

A longer proximal margin length can ensure a negative margin, but it can also increase the operation difficulty. An increasing number of studies have indicated that a shorter proximal resection length may prove to be an adequate oncologic margin. Barbour *et al*<sup>[40]</sup> reported that 5 cm of a grossly normal *in vivo* (approximately 3.8 cm *ex vivo*) proximal esophagus was associated with improved survival for patients ( $\geq T2$  and  $\leq 6$  positive lymph nodes) with Siewert types I/II/III. There were 58 patients with more than 6 positive LNs. However, both univariate and multivariable analyses showed that the proximal margin carried no prognostic significance for these patients. Mine *et al*<sup>[18]</sup> reported another study of an even shorter proximal margin in Siewert type II and III patients who received a transhiatal (TH) total gastrectomy. They indicated improved survival with a proximal resection margin of 3.0 cm *in vivo* (approximately 2.0 cm *ex vivo*)<sup>[18]</sup>. Feng *et al*<sup>[42]</sup> found that the proximal margin length had no relationship with the survival of patients with Siewert type II/III EGJ cancers. They concluded that a negative proximal margin may be sufficient during the surgical resection of Siewert type II/III tumors<sup>[42]</sup>. A similar result was reported from the United States Gastric Cancer Collaborative<sup>[44]</sup>. The authors found that the proximal margin length was not associated with local recurrence or overall survival. They suggested that achieving a specific proximal margin distance should be abandoned.

In conclusion, there is a trend that a shorter proximal resection margin is being adopted in clinical practice due to similar oncology outcomes. Surgery is much easier if the distal esophagus can be dissected through a transabdominal approach rather than a transthoracic approach in an attempt to pursue a longer proximal margin.

## SURGERY CHOICE ACCORDING TO THE SIEWERT CLASSIFICATION

The key factors to a successful oncologic surgery are as follows: curative R0 resection, adequate LN dissection, and the minimization of surgical morbidity. An esophago-gastrectomy with a moderate, adequate lymphadenectomy is still considered the standard surgical strategy for EGJ cancer, although there are some differences according to Siewert types.



Because type I cancers arise from the distal esophagus, most experts and guidelines recommend that they be treated surgically as esophageal cancer, with an esophagogastrectomy plus both mediastinal and upper perigastric LN resection. For type II cancers, some individuals recommend an esophagectomy with a proximal gastrectomy, which allows the dissection of both the abdominal and mediastinal LNs. Others advocate for a total gastrectomy and extended lymph node dissection with a TH approach into the posterior mediastinum<sup>[45]</sup>. For type III cancers, an esophagogastrectomy includes a total gastrectomy plus a distal esophagectomy via laparotomy, by which the diaphragm is opened. The final anastomosis site is in the distal part of the thoracic cavity. GI anastomosis is commonly an esophagojejunostomy with a Roux-en-Y reconstruction<sup>[46]</sup>. However, there is still no consensus as to which surgical approach is suitable for an esophagogastrectomy. To summarize, there are three main approaches for EGJ cancer resection - all are based on the Siewert classification (Table 2): (1) The right transthoracic (RT) approach (the 2-step Ivor-Lewis approach or the 3-step McKeown approach); (2) The left transthoracic (LT) approach; and (3) The TH approach. Every approach has potential advantages and disadvantages.

The transthoracic approach is usually performed with a laparotomy plus a thoracotomy and sometimes with a cervical incision, allowing exploration of the entire mediastinum. The final anastomosis is performed in the intrathoracic area (Ivor Lewis approach) or the cervical area (McKeown approach). The potential advantages of the RT approach are as follows: (1) There is a sufficient distance of the proximal resection margin even in advanced EGJ cancers with extensive esophageal invasion; and (2) It allows the exposure to the entire mediastinum to harvest even the upper mediastinal LN. This procedure may especially benefit advanced-stage patients with long esophageal invasion. Due to the low rate of invaded upper mediastinal LNs, the Ivor Lewis approach without upper mediastinal LN dissection is usually performed in Western countries<sup>[47]</sup>. The LT consisting of the left thoracoabdominal (LTA) approach and left thoracophrenolaparotomy is not commonly used, although it has the following advantages: (1) A sufficient proximal margin can be ensured; (2) Body position change is not needed during the operation; and (3) The surgical procedure around the esophageal hiatus is easy to perform under direct visualization. TH esophagectomy is usually performed through a laparotomy with a cervical incision, without a thoracotomy. Surgical stress, particularly respiratory damage, is the main disadvantage of a thoracotomy. The TH approach consisting of the TH surgical operation from the abdomen to the lower mediastinum minimizes such disadvantages due to the avoidance of a thoracotomy. Changes in body position are also not needed during the TH operation.

TH is inappropriate for esophageal cancer due to limited periesophageal LN harvesting. However, many studies on esophageal cancer have demonstrated no significant survival advantage for more radical surgery<sup>[48]</sup>, and TH can be used to treat esophageal cancer, with similar OS and even less morbidity<sup>[49]</sup>. Regarding EGJ cancers, few studies comparing TH and the transthoracic approach have been reported.

Two randomized controlled trials comparing transthoracic with TH esophagectomy were performed in the West and East<sup>[50,51]</sup>. The Dutch phase III clinical trial ( $n = 205$ ) compared RT with TH in patients with type I or type II EGJ cancer. The RT group did not achieve a survival benefit but instead exhibited higher postoperative morbidity<sup>[50]</sup>. In a subgroup analysis, the 5-year OS rate was similar between RT and TH for patients with type II cancer but higher following RT than TH for patients with type I cancer<sup>[37]</sup>. The authors concluded that RT may be recommended only for patients with type I tumors and not type II tumors. The Japanese phase III trial ( $n = 67$ ) compared oncologic outcomes between LTA and TH in patients with type II or type III EGJ cancer. However, due to limited efficacious resection, the trial was stopped at the first interim analysis<sup>[51]</sup>. After 10 years of follow-up, the LTA achieved no benefits in OS or DFS and did not reduce the cancer recurrence rate in LNs. However, the LTA was associated with higher morbidity and mortality<sup>[52]</sup>. Based on these results, the researchers suggested that the LTA be avoided as a surgical therapy for adenocarcinoma of the EGJ or the gastric cardia. In Japan, the consensus is that Siewert type II and type III cancers should be treated by an abdominal, TH approach with en bloc lower mediastinal dissection with a length of esophageal invasion  $\leq 3$  cm.

A United Kingdom cohort study ( $n = 664$ ) found no differences between TH and transthoracic approaches regarding survival or tumor recurrence in patients with esophageal or EGJ cancer<sup>[32]</sup>. Yan *et al*<sup>[53]</sup> conducted a systematic review of 2202 patients to compare the clinical outcomes between TH and open thoracic esophagectomy in EGJ cancer. The TH group showed decreased hospitalization, operation time, and blood loss, with less LN dissection. The complication and survival rates were not different between these approaches. A subtype analysis showed no

**Table 2** Different approach for esophagogastric junction cancer

Approach	Surgical technique	Procedure	Disadvantage
RT	Ivor Lewis	Midline laparotomy	Limited proximal margin Requirement of body position change Surgical stress is significant
		Right thoracotomy	Increased risk for recurrent laryngeal nerve injury
	McKeown	Midline laparotomy Left cervical	Surgical stress is significant
LT	LTA	Left thoracotomy extended to upper midline laparotomy	No middle or upper thoracic lymphadenectomy Surgical stress is significant
	Left thoracophrenolaparotomy	Transdiaphragmatic thoracotomy	No middle or upper thoracic lymphadenectomy
TH	-	Midline laparotomy	Surgical stress is significant
		Midline laparotomy	Limited proximal margin
		Left cervical	Surgical view of the lower mediastinum is poor No middle or upper thoracic lymphadenectomy
TG	-	Midline laparotomy	Limited proximal margin
			No thoracic lymphadenectomy

RT: Right Transthoracic; LT: Left Transthoracic; TH: transhiatal; TG: Total Gastrectomy.

significant differences according to the Siewert type<sup>[53]</sup>. Omloo *et al*<sup>[37]</sup> compared the transthoracic and TH approaches for esophagectomy and found that the TH approach was associated with a lower morbidity; however, better medium-term survival with transthoracic esophagectomy was observed in two subgroups: patients with type I AEG and those with  $\leq 8$  metastatic nodes.

Taken together, existing evidence does not support one technique over the other regarding oncological outcomes. Future large RCTs are still needed to examine these techniques and their effects on long-term OS.

## MINIMALLY INVASIVE SURGERIES FOR EGJ CANCER

Minimally invasive surgeries are the gold standard in many fields of surgery. The first minimally invasive esophagectomy was described by Cuschieri *et al*<sup>[54]</sup> in 1993, and after one year, Kitano *et al*<sup>[55]</sup> reported the first minimally invasive gastrectomy. Since then, the techniques for gastric cancer have evolved from laparoscopic assisted to total laparoscopic surgery, and the techniques for esophagectomy have also evolved from hybrid approaches to an entirely minimally invasive manner. Both minimally invasive surgeries show similar surgical and oncological outcomes compared with open surgeries, especially in early-stage patients. Zhou *et al*<sup>[56]</sup> conducted a systematic review of minimally invasive esophagectomy approaches for esophageal or EGJ cancer. The review that included 1 RCT and 47 observational studies indicated that minimally invasive procedures ( $n = 4509$ ) have lower pulmonary complications compared with open surgery ( $n = 6347$ ). There were no differences in anastomotic leak or gastric tip necrosis between the two groups<sup>[56]</sup>. However, in the minimally invasive procedures group, the authors included not only total minimally invasive procedures but also thoracoscopy-assisted or hybrid procedures.

For type I and II cancers, there are different minimally invasive techniques according to transthoracic or TH approaches compared to open surgery. Usually, the minimally invasive Ivor-Lewis technique is the main choice, although intrathoracic anastomosis is sometimes difficult. The operation starts with a laparoscopy with a proximal gastrectomy plus a lymphadenectomy. Then, the operation is followed by a right thoracoscopy, including esophagus mobilization and a mediastinal lymphadenectomy between the area from the carina to the azygos vein. The gastric tube is pulled into the thorax through the hiatus to create an intrathoracic anastomosis. The anastomosis methods include end-to-side anastomosis with a manual or circular stapler (with or without an OrVil device)<sup>[57]</sup> and side-to-side

anastomosis with a linear stapler (with or without barbed sutures)<sup>[58]</sup>.

The minimally invasive McKeown procedure commences with a right thoracoscopy followed by esophagus dissection and a mediastinal lymphadenectomy, which are similar to the previous description of the Ivor Lewis technique. Subsequently, the patient's position is changed to a supine position, and then a laparoscopic gastrectomy with a lymphadenectomy is performed. The formation of the gastric tube is also similar to that described in the Ivor Lewis technique. After the laparoscopy, a left cervical incision is made, and the divided esophagus is anastomosed with a gastric tube manually using end-to-end anastomosis<sup>[59]</sup>. van Workum *et al.*<sup>[60]</sup> conducted a systematic review ( $n = 1681$ ) to compare the totally minimally invasive McKeown and Ivor Lewis technique used for esophageal and EGJ cancers. The Ivor Lewis group showed decreased RLN trauma, hospitalization, and blood loss compared to the McKeown group, while the anastomotic leakage rate was not different<sup>[60]</sup>. It is noteworthy that the evidence is limited, and all included studies were cohort studies with a moderate risk of bias. It is still uncertain which minimally invasive technique is suitable. The Netherlands is now performing the first randomized controlled trial containing 200 patients between minimally invasive McKeown and Ivor Lewis approaches. This clinical trial is powered for finding differences in morbidity, the severity of complications and quality of life<sup>[61]</sup>. The minimally invasive TH procedure consists of a laparoscopy and a left cervical incision followed by a gastrectomy plus a lymphadenectomy and TH dissection of the distal esophagus through a laparoscopy. The gastric tube is created extracorporeally and then pulled into the cervical area where the anastomosis is made<sup>[62]</sup>.

For type III cancers, a laparoscopic gastrectomy is the main choice. A total D2 gastrectomy is performed, and the duodenum is divided using a linear stapler. The diaphragm is opened, and the distal esophagus is mobilized. Only the distal periesophageal LNs are resected, and then the vagal nerves and esophagus above the cancer are transected. Because of the limited size of the hiatus, the OrVil® (Medtronic, Inc., Minneapolis, MN, United States) is usually used to perform the end-side esophagojejunostomy anastomosis<sup>[63]</sup>.

In conclusion, there is still no agreement about the ideal type of minimally invasive surgery, and existing evidence does not support that one technique is much better than the other. Many anastomotic methods can be adopted, such as manual, circular stapler, linear stapler, and even robot-assisted anastomoses. Large randomized controlled trials are still needed to test which minimally invasive technique is most suitable for EGJ cancer.

## ENDOSCOPIC RESECTION FOR EARLY EGJ CANCER

Endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is used to remove superficial neoplasms from the GI tract<sup>[64,65]</sup>. However, the curative resection criteria, particularly for type II cancers, differ between esophageal cancer and gastric cancer, since the rate of LN metastasis is different<sup>[66]</sup>.

The indications for ER in early EGJ adenocarcinoma are also under study. A Japanese multicenter study retrospectively analyzed 458 esophageal or EGJ adenocarcinoma patients who received surgical or ER treatment. Lymphovascular involvement, a poorly differentiated tumor, and lesion size  $> 30$  mm were independent risk factors for metastasis. Mucosal and submucosal cancers with invasion of less than 500  $\mu\text{m}$  without the abovementioned risk factors may also be suitable for ER<sup>[67]</sup>.

Favorable oncological results were also reported in several studies. A systematic review analyzed 359 early EGJ adenocarcinoma patients who received ESD treatment. More than 20% of tumors were reported to have deep submucosal invasion ( $> 500$  mm from the muscularis mucosa). The en bloc resection and complete resection rates were 98.6% and 87%, respectively. Patients with curative resection showed no local recurrence or distant metastases<sup>[68]</sup>. A Korean retrospective study demonstrated similar 5-year OS rates between ESD and surgery (93.9% *vs* 97.3%, respectively,  $P = 0.37$ ). Local recurrence and cancer-related deaths were not observed<sup>[69]</sup>. Recently, a retrospective study from 13 centers in Japan reported the long-term outcomes of ER for EGJ adenocarcinoma. The 5-year cumulative incidences of local recurrence were 13% for EMR and 0.5% for ESD. In this study, patients were classified into 2 groups based on the risk of metastasis according to the histologic features. Patients at a low risk for metastasis were defined as those with mucosal cancer without LVI and a poorly differentiated component or those with a cancer with an SM depth  $\leq 500$   $\mu\text{m}$  without LVI, without a poorly differentiated component, and measuring  $\leq 30$  mm.

High-risk patients were defined as those with mucosal and SM EGJ (except for low-risk criteria). According to the abovementioned risk factors for LN metastasis, there were 277 patients in the low-risk group and 95 patients in the high-risk group. The 5-year OS rates of the low-risk group, the high-risk group with additional treatment, and the high-risk group without additional treatment were 93.9%, 77.7%, and 81.6%, respectively. The authors concluded that patients with a low risk for LN metastasis may obtain favorable long-term outcomes after ER treatment<sup>[70]</sup>.

Therefore, ER may be a good therapy for early-stage (intramucosal) EGJ cancer. Not all patients with early EGJ cancer can be treated with ER. The incidence of metastasis should be understood, and a confirmation of the indication would maximize the benefits of ER for early EGJ cancer. However, RCTs are needed to inform the benefits and harms of ER therapy for early EGJ cancer.

## CONCLUSION

The incidence of EGJ cancer is increasing. Tumor location is an important factor in determining the optimal surgical therapy for EGJ. The Siewert classification has implications for lymph node spread and is the most commonly used classification. Different types of EGJ cancer have different incidences of mediastinal and abdominal LN metastases, and different surgical approaches have unique advantages and disadvantages. The length of the tumor and the depth of tumor invasion should also be considered when deciding the proper surgical technique. An extensive lymphadenectomy may not provide additional benefits. Minimally invasive surgeries are increasingly applied in clinical practice and show comparable oncologic outcomes. ER may be a good therapy for early EGJ cancer. Additionally, there is still a great need for well-designed large RCTs to forward our knowledge in the surgical treatment of EGJ cancer.

## ACKNOWLEDGEMENTS

The authors thank Prof. Mike Gibson (Vanderbilt University School of Medicine, United States) for his critical correction of the English language in the manuscript.

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