Current surgical treatment of esophagogastric junction adenocarcinoma

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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.
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[1-3]. 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[4].

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[5]. 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[6] (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 (8th) 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[7,8]. Cancer genetics will be included in the next (9th) edition staging of EGJ cancers.

Japanese gastric cancer treatment guidelines define EGJ cancer as a tumor (≤ 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[9]. 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 (≤ 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.[10]

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[11]. 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[12]. 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[11]. More recent studies from Japan yielded similar results. LNs, including nos. 1, 2, 3a, and 7, had a frequent incidence of metastasis[13], 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[11].

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., 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. 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%.

Several retrospective studies of abdominal LN metastasis in type II cancer were performed in Japan. Fujitani et al., Yoshikawa et al., and Yamashita et al. 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%), and that in the celiac axis around the splenic artery and the splenic hilum was less than 10%. 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%. 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. Among the perigastric LNs, nos. 4a, 4sb, 4d, 8a, 9, and 11p show a high risk of metastasis, whereas LN nos. 1, 2, 3, and 7 do not. 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. It is recommended that the splenectomy be performed only to obtain R0 resection. 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, with an incidence of ≥ 60% in T2 and ≥ 85% in T3-4 patients. It was also reported that tumor size is a predictor of LN metastasis, especially in large tumors (> 4 cm).

**LYMPHADENECTOMY AND PROGNOSIS**

LN metastasis is also an indicator of prognosis. The highest risk factor is the number
of metastatic LNs ≥ 7%. Locoregional LN involvement is associated with improved survival compared with para-aortal or other distant LNs. In a systematic review including 2252 type II cancer patients, ≥ 7 metastatic LNs (N3) indicated much worse survival (2.0%-17.4%) compared to no LN metastasis (up to 82.7%). 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. 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. 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. 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. A study from the United Kingdom (n = 606) and another recent retrospective cohort study from Denmark (n = 510) 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 RESSECTION MARGIN

The definition of R0 resection for EGJ is important. Feith et al. 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 esophageal resection required for the prevention of recurrence and longer survival remains controversial. Ito et al. advocated the proximal gross margin length of at least 6 cm in patients with Siewert type II/III EGJ cancers, while Mariette et al. 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. 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 (≥ T2 and ≤ 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. 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). Feng et al. 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. A similar result was reported from the United States Gastric Cancer Collaborative. 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 transthoracic 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 esophagogastrectomy 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 esophagogastrectomy 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. 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 esophago-jejunostomy with a Roux-en-Y reconstruction. 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. 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, and TH can be used to treat esophageal cancer, with similar OS and even less morbidity. 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. 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. 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. 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. 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. 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 ≤ 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. Yan et al. 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 |
|          | Mckeown            | Right thoracotomy | Increased risk for recurrent laryngeal nerve injury |
|          |                    | Midline laparotomy | 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 | No middle or upper thoracic lymphadenectomy |
|          |                    | Transdiaphragmatic thoracotomy | No middle or upper thoracic lymphadenectomy |
| TH       | -                  | 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\(^{53}\). Omloo et al\(^{37}\) 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 ≤ 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\(^{54}\) in 1993, and after one year, Kitano et al\(^{55}\) 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\(^{56}\) 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\(^{56}\). 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)\(^{57}\) and side-to-side
anastomosis with a linear stapler (with or without barbed sutures)\textsuperscript{[83]}. The minimally invasive McKeown procedure commences with a right thoracoscopic 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\textsuperscript{[89]}. van Workum et al\textsuperscript{[65]} conducted a systematic review (\(n = 1681\)) to compare the totally minimally invasive McKeown and Ivor Lewis techniques 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\textsuperscript{[83]}. 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\textsuperscript{[91]}. 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\textsuperscript{[89]}. 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 LN are resected, and then the vagal nerves and esophagus above the cancer are transected. Because of the limited size of the hiatus, the OrVil\textsuperscript{®} (Medtronic, Inc., Minneapolis, MN, United States) is usually used to perform the end-side esophageojunostomy anastomosis\textsuperscript{[93]}. 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\textsuperscript{[66]-\textsuperscript{68]}. 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\textsuperscript{[64,65]}. 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 µm without the abovementioned risk factors may also be suitable for ER\textsuperscript{[87]}. 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\textsuperscript{[89]}. 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\textsuperscript{[89]}. 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 ≤ 500 µm without LVI, without a poorly differentiated component, and measuring ≤ 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[6]. 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.

**REFERENCES**

1. **Imamura Y, Watanabe M, Tohida T, Takamatsu M, Kawachi H, Haraguchi I, Ogata Y, Yoshida N, Saeki H, Oki E, Taguchi K, Yamamoto M, Morita M, Mine S, Hiki N, Baba H, Sano T. Recent Incidence Trend of Surgically Resected Esophagogastric Junction Adenocarcinoma and Microsatellite Instability Status in Japanese Patients.** Digestion 2019; 99: 6-13 [PMID: 30554205 DOI: 10.1159/000494406]

2. **Steevens J, Botterweck AA, Dirx MJ, van den Brandt PA, Schouten LJ. Trends in incidence of oesophageal and stomach cancer subtypes in Europe.** Eur J Gastroenterol Hepatol 2010; 22: 669-678 [PMID: 19474750 DOI: 10.1097/MEG.0b013e32832ca091]

3. **Bolischweiler E, Wöllgarten E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males.** Cancer 2001; 92: 549-555 [PMID: 11503399 DOI: 10.1002/1097-0142(20010801)92:15<549::AID-CNCR1354>3.0.CO;2-1]

4. **Kauppila JH, Lagergren J. The surgical management of esophago-gastric junctional cancer.** Surg Oncol 2016; 25: 394-400 [PMID: 27916171 DOI: 10.1016/j.suronc.2016.09.004]

5. **Riddell RH. The genesis of Barrett esophagus: has a histologic transition from gastroesophageal reflux disease-damaged epithelium to columnar metaplasia ever been seen in humans? Arch Pathol Lab Med 2005; 129: 164-169 [PMID: 15679412]

6. **Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction.** Br J Surg 1998; 85: 1457-1459 [PMID: 9823902 DOI: 10.1046/j.1365-2168.1998.00940.x]

7. **Hayakawa Y, Sethi N, Sepulveda AR, Bass AJ, Wang TC. Oesophageal adenocarcinoma and gastric cancer: should we mind the gap?** Nat Rev Cancer 2016; 16: 305-318 [PMID: 27112208 DOI: 10.1038/nrc.2016.24]

8. **Cancer Genome Atlas Research Network.** Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

9. **Japanese Gastric Cancer Association.** Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017; 20: 1-19 [PMID: 27324899 DOI: 10.1007/s10120-016-0022-4]

10. **Parry K, Haverkamp E, Bruijnen RC, Siessena PD, Offerhaus GJ, Ruurda JP, van Hillegersberg R. Staging of adenocarcinoma of the gastroesophageal junction.** Eur J Surg Oncol 2016; 42: 400-406 [PMID: 26777127 DOI: 10.1016/j.ejso.2015.11.014]

11. **Feith M, Stein HJ, Siewert JR. Adenocarcinoma of the esophagogastric junction: surgical therapy based on 1602 consecutive resected patients.** Surg Oncol Clin N Am 2006; 15: 751-764 [PMID: 17030271 DOI: 10.1016/j.soc.2006.07.015]

12. **Goto H, Tokunaga M, Miki Y, Makuchi R, Sugisawa N, Tanizawa Y, Bando E, Kawamura T, Niihara M, Tsushima Y, Terashima M. The optimal extent of lymph node dissection for adenocarcinoma of the esophagogastric junction differs between Siewert type II and Siewert type III patients.** Gastric Cancer 2014 [PMID: 24658651 DOI: 10.1007/s10120-014-0564-0]
Yoshikawa T, Takeuchi H, Hasegawa S, Nozaki I, Kishi K, Ito S, Ohi M, Mine S, Haraji M, Satsuda T, Hiki N, Kurokawa Y. Theoretical therapeutic impact of lymph node dissection on adenocarcinoma and squamous cell carcinoma of the esophagogastric junction. *Gastric Cancer* 2016; 19: 143-149 [PMID: 25414051 DOI: 10.1007/s10120-014-0439-z]

Kurokawa Y, Hiki N, Yoshikawa T, Kishi K, Ito Y, Ohi M, Wada N, Takiguchi S, Mine S, Hasegawa S, Satsuda T, Takeuchi H. Medial lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction. *Surgery* 2015; 157: 551-555 [PMID: 25532434 DOI: 10.1016/j.surg.2014.08.099]

Oksenh C, Svendsen LB, Achiam MP. Status and prognosis of lymph node metastasis in patients with cardiac cancer - a systematic review. *Surg Oncol* 2014; 23: 140-146 [PMID: 24953457 DOI: 10.1016/j.suronc.2014.06.001]

Fujitani K, Miyashiro I, Mikata S, Tamura S, Inamurra H, Hara J, Kurokawa Y, Fujita J, Nishikawa K, Kimura Y, Takiguchi S, Mori M, Doki Y. Pattern of abdominal nodal spread and optimal abdominal lymphadenectomy for advanced Stewert type II adenocarcinoma of the esophagus: results of a multicenter study. *Gastric Cancer* 2013; 16: 301-308 [PMID: 22895616 DOI: 10.1007/s10120-012-0183-0]

Yamashita H, Kati H, Morita S, Saka M, Taniguchi H, Fukagawa T. Optimal extent of lymph node dissection for Stewert type II esophagogastric junction carcinoma. *Ann Surg* 2011; 254: 274-280 [PMID: 21772128 DOI: 10.1097/SLA.0b013e3182263911]

Mine S, Sano T, Hiki N, Yamada K, Kosuga T, Nuneo S, Yamaguchi T. Proximal margin length with transhiatal gastrectomy for Stewert type II and III adenocarcinomas of the esophagogastric junction. *Br J Surg* 2013; 100: 1050-1054 [PMID: 23754647 DOI: 10.1002/bjs.9170]

Mine S, Kurokawa Y, Takeuchi H, Kishi K, Ito Y, Ohi M, Matsuda T, Harakawa S, Hasegawa S, Yoshikawa T, Hiki N. Distribution of involved abdominal lymph nodes is correlated with the distance from the esophagogastric junction to the distal end of the tumor in Stewert type II tumors. *Eur J Surg Oncol* 2015; 41: 1348-1353 [PMID: 26087995 DOI: 10.1016/j.ejso.2015.05.004]

Pedrazzani c, de Manzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, Rampone B, Rovelli F. Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. *J Thorac Cardiovasc Surg* 2007; 134: 378-385 [PMID: 17602770 DOI: 10.1016/j.jtcvs.2006.11.046]

Meier I, Merkel S, Papadopoulos T, Sauer R, Hohenberger W, Brunner TB. Adenocarcinoma of the esophagogastric junction: the pattern of metastatic lymph node dissemination as a rationale for elective lymphatic target volume definition. *Int J Radiat Oncol Biol Phys* 2008; 70: 1408-1417 [PMID: 18374226 DOI: 10.1016/j.ijrobp.2007.08.052]

Mönig SP, Baldus SE, Zirbes TK, Collet PH, Schröder W, Schneider PM, Dienes HP, Höslicher AH. Topographical distribution of lymph node metastasis in adenocarcinoma of the gastroesophageal junction. *Hepatogastroenterology* 2002; 49: 419-422 [PMID: 11995464]

Kakeji Y, Yamamoto M, Ito S, Sugiyama M, Egashira A, Saecki H, Morita M, Sakaguchi Y, Toh Y, Machida Y. Lymph node metastasis from cancer of the esophagogastric junction, and determination of the appropriate nodal dissection. *Surg Today* 2012; 42: 351-358 [PMID: 22245924 DOI: 10.1007/s00595-011-0114-4]

Hosokawa Y, Kinoshita T, Komishi M, Takahashi S, Gotohda N, Kato Y, Daiko H, Nishimura M, Katsumata K, Sugiyama Y, Kinoshita T. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Stewert classification: experiences at a single institution. *Ann Surg Oncol* 2011; 19: 677-683 [PMID: 21822549 DOI: 10.1245/s10434-011-1983-x]

Hasegawa S, Yoshikawa T, Rino Y, Oshima T, Aoyama T, Hayashi T, Sato T, Yukawa N, Kameda Y, Sasaki T, Omo H, Tsuda K, Cho H, Kunisaki C, Masuda M, Tsuburaya A. Priority of lymph node dissection for Stewert type II/III adenocarcinoma of the esophagogastric junction. *Ann Surg Oncol* 2013; 20: 4525-4529 [PMID: 23943020 DOI: 10.1245/s10434-013-0306-0]

Nuneo S, Ohyama S, Sonoo H, Hiki N, Fukunaga T, Seta T, Yamaguchi T. Benefit of mediastinal and para-aortic lymph-node dissection for advanced gastric cancer with esophageal invasion. *J Surg Oncol* 2008; 97: 392-395 [PMID: 18236414 DOI: 10.1002/jso.20987]

Mariette C, Piessens G, Briez N, Grommier C, Triboulet JP. Oesophagogastric junction adenocarcinoma: which therapeutic approach? *Lancet Oncol* 2011; 12: 296-305 [PMID: 21109491 DOI: 10.1016/S1470-2045(10)70125-X]

Lutz MP, Zalcberg JR, DeManzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, Rampone B, Rovelli F. Lymph node involvement in advanced gastroesophaegau Junction adenocarcinoma. *Eur J Surg Oncol* 2012; 28: 2941-2953 [PMID: 22921116 DOI: 10.1016/j.ejso.2012.07.029]

Ielpo B, Pernaute AS, Elia S, Buonomo OC, Valladares LD, Aguirre EP, Petrella G, Garcia AT. Impact of lymph node dissection on survival of adenocarcinoma of the esophagogastric junction. *Interact Cardiovasc Thorac Surg* 2010; 10: 704-708 [PMID: 20154347 DOI: 10.1161/icvts.109.222772]

Shimada H, Suzuki T, Nakajima K, Hori S, Hayashita H, Takeda A, Arima M, Gunji Y, Koide Y, Ochiai T. Lymph node metastasis with adenocarcinoma of the gastric cardia: clinicopathological analysis and indication for D1 dissection. *Int J Cancer* 1999; 84: 13-17 [PMID: 10421011]

Okholm C, Fjederholt KT, Mortensen FV, Svendsen LB, Achiam MP. The optimal lymph node dissection in patients with adenocarcinoma of the esophagogastric junction. *Surg Oncol* 2018; 27: 36-43 [PMID: 29549002 DOI: 10.1016/j.suronc.2017.11.004]

Davies AR, Sandhu H, Pillai A, Sinha P, Mattsson F, Forskow MJ, Gossage JA, Lagergren J, Allum WH, Mason RC. Surgical resection strategy and the influence of radicality on outcomes in esophageal cancer. *Br J Surg* 2014; 101: 511-517 [PMID: 24615656 DOI: 10.1002/bjs.9456]

Hulscher JB, Van Sandick JW, Offerhaus GJ, Tilanus HJ, Obertop H, Van Lanschot J. Prospctive analysis of the diagnostic yield of extended nodal resection for adenocarcinoma of the oesophagus or gastric cardia. *Br J Surg* 2001; 88: 715-719 [PMID: 11354487 DOI: 10.1046/j.1365-2125.2001.01746.x]

Yamashita H, Seto Y, Sano T, Makucushi H, Aoyama T, Sasaki M, Japanese Gastric Cancer Association and the Japan Esophagogastric Preservation. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. *Gastric Cancer* 2017; 20: 69-83 [PMID: 27796514 DOI: 10.1007/s10120-016-0663-3]

Puyere CG, Hagen JA, DeMeester SR, Altoriki NK, Ancona E, Griffin SM, Höslicher A, Lerut T, Law S,
Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. 2003; Langenbecks Arch Surg 402: 162-169 [PMID: 27858584 DOI: 10.1089/lap.2016.0430]

Luketich JD. Extended transhiatal resection compared with limited transthoracic resection for adenocarcinoma of the mid/distal esophagus: I. 5-year survival of a randomized clinical trial. J Surg Oncol 2007; 96: 992-1000; discussion 1000-1 [PMID: 18043101 DOI: 10.1002/jso.20437]

Lagergren J, Mattisson F, Zylstra J, Chang F, Gossage J, Mason R, Lagergren P, Davies A. Extent of Lymphadenectomy and Prognosis After Esophageal Cancer Surgery. JAMA Surg 2016; 151: 32-39 [PMID: 26331431 DOI: 10.1001/jamasurg.2015.2661]

Mariette C, Castel B, Balon JM, Van Seuningen I, Triboulet JP. Extent of esophageal resection for adenocarcinoma of the esophagogastric junction. Eur J Surg Oncol 2003; 29: 588-593 [PMID: 12943624 DOI: 10.1054/ejso.2003.0185]

Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW, Colt DG, Brennan MF. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg 2007; 246: 1-8 [PMID: 17592282 DOI: 10.1097/01.sla.0000255653.65157.d2]

Mine S, Sano T. Authors’ reply: Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the gastroesophageal junction (Br J Surg 2013; 100: 1055-1054). Br J Surg 2014; 101: 735-736 [PMID: 24723024 DOI: 10.1002/bjs.9504]

Feng F, Tian Y, Xu G, Liu S, Liu Z, Zheng G, Guo M, Lian X, Fan D, Zhang H. The length of proximal margin does not influence the prognosis of Siewert type I/III adenocarcinoma of esophagogastric junction after transthiatal curative gastrectomy. Springerplus 2016; 5: 588 [PMID: 27247855 DOI: 10.1186/s40064-016-2240-2]

Ito H, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ, Ashley SW, Zinner MJ, Whang EE. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg 2004; 199: 880-886 [PMID: 15559791 DOI: 10.1016/j.jamcollsurg.2004.08.015]

Postlewait LM, Squires MH, Kooby DA, Poulsides GA, Weber SM, Bloomston M, Fields RC, Pawlik TM, Votanopoulos KI, Schmid CR, Ejaz A, Acher AW, Worhunsky DJ, Saunders N, Swords D, Jin LX, Cho CS, Winslow ER, Cardona K, Staley CA, Maithel SK. The importance of clinical resection margin distance for proximal gastric adenocarcinoma: A multi-institutional study of the US Gastric Cancer Collaborative. J Surg Oncol 2015; 112: 203-207 [PMID: 26272801 DOI: 10.1002/jso.23971]

Brown AM, Giugliano DN, Berger AC, Pucci MJ, Palazzo F. Surgical approaches to adenocarcinoma of the gastroesophageal junction: the Siewert II conundrum. Langenbecks Arch Surg 2017; 402: 1153-1158 [PMID: 28803334 DOI: 10.1007/s00423-017-1479-5]

Di Leo A, Zanoni A. Siewert III adenocarcinoma: treatment update. Updates Surg 2017; 69: 319-325 [PMID: 2830319 DOI: 10.1007/s13304-017-0429-9]

Giacopuzzi S, Bencivenga M, Weindelmayer J, Verlato G, de Manzoni G. Western strategy for EGJ carcinoma. Gastric Cancer 2017; 20: 60-68 [PMID: 28039533 DOI: 10.1007/s11786-016-1151-2]

Chang AC, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. Br J Surg 2015; 102: 424-429 [PMID: 18222237 DOI: 10.1016/j.bjsurg.2007.10.007]

Boshier PB, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophageogastric cancer: a meta-analysis. Ann Surg 2011; 254: 894-906 [PMID: 21785341 DOI: 10.1097/SLA.0b013e3182263781]

Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662-1669 [PMID: 12448180 DOI: 10.1056/NEJMoa022348]

Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M, Japan Clinical Oncology Group (JCOG9502). Left thoracoabdominal approach versus transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol 2006; 7: 644-651 [PMID: 16877481 DOI: 10.1016/S1470-2045(06)70760-4]

Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasa Y, Nashimoto A, Ito S, Kurita A, Mizusawa J, Nakamura K, Japan Clinical Oncology Group (JCOG9502). Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the gastroesophageal junction or gastric cardia. Br J Surg 2015; 102: 341-348 [PMID: 25603628 DOI: 10.1002/bjs.9764]

Yan R, Ding C. Meta-analysis of Transhiatal Esophagectomy in carcinoma of esophageal carcinoma, does it have an advantage? Int J Surg 2017; 42: 183-190 [PMID: 28343629 DOI: 10.1016/j.ijsu.2017.03.052]

Buschier A. Endoscopic subtotal esophagectomy for cancer using the right thoracoscopic approach. Surg Oncol 1993; 2 Suppl 1: 3-11 [PMID: 8252219 DOI: 10.3109/09691749309089717]

Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1994; 4: 146-148 [PMID: 8180768]

Zhou C, Zhang L, Wang H, Ma X, Shi B, Chen W, He J, Wang K, Liu P, Ren Y. Superiority of Minimally Invasive Oesophagectomy in Reducing In-Hospital Mortality of Patients with Resectable Oesophageal Cancer: A Meta-Analysis. PLoS One 2015; 10: e0132889 [PMID: 26190135 DOI: 10.1371/journal.pone.0132889]

Wiesel O, Whang B, Cohen D, Fischella PM. Minimally Invasive Esophagectomy for Adenocarcinomas of the Gastroesophageal Junction and Distal Esophagus: Notes on Technique. J Laparoendosc Adv Surg Tech A 2017; 27: 162-169 [PMID: 27858384 DOI: 10.1089/lap.2016.0430]

Irimo T, Tsai JA, Ericson J, Nilsson M, Lundell L, Rouvelas I. Thoracic side-to-side esophagogastrostomy by use of linear stapler-a simplified technique facilitating a minimally invasive Ivor-Lewis operation. Langenbecks Arch Surg 2016; 401: 315-322 [PMID: 26960591 DOI: 10.1007/s00423-016-1396-1]

Leuketic JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCallaghan JS, Little VR, Schauer PR, Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;
van Workum F, Berkelmans GH, Klarenbeek BR, Nieuwenhuijzen GAP, Luyer MDP, Rosman C. McKeown or Ivor Lewis totally minimally invasive esophagectomy for cancer of the esophagus and gastroesophageal junction: systematic review and meta-analysis. *J Thorac Dis* 2017; 9: S826-S833 [PMID: 28815080 DOI: 10.21037/jtd.2017.03.173]

van Workum F, Bouwense SA, Luyer MD, Nieuwenhuijzen GA, van der Peet DL, Daams F, Kouwenhoven EA, van Dei MJ, van den Wildenberg FJ, Polat F, Gisbertz SS, Henegouwen ML, Heisterkamp J, Langenhoff BS, Martijnse IS, Grutters JP, Klarenbeek BR, Rovers MM, Rosman C. Intrathoracic versus Cervical A Anastomosis after minimally invasive esophagectomy for esophageal cancer: study protocol of the ICAN randomized controlled trial. *Trials* 2016; 17: 505 [PMID: 27756415 DOI: 10.1186/s13063-016-1636-2]

Parry K, Haverkamp L, Bruijnen RC, Siersema PD, Ruurda JP, van Hillegersberg R. Surgical treatment of adenocarcinomas of the gastro-esophageal junction. *Ann Surg Oncol* 2015; 22: 597-603 [PMID: 25190126 DOI: 10.1245/s10434-014-4047-1]

Ai B, Zhang Z, Liao Y. Laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis for middle or lower esophageal carcinoma. *J Thorac Dis* 2014; 6: 1354-1357 [PMID: 25276383 DOI: 10.3978/j.issn.2072-1439.2014.07.38]

Singh T, Sanaka MR, Thota PN. Endoscopic therapy for Barrett’s esophagus and early esophageal cancer: Where do we go from here? *World J Gastrointest Endosc* 2018; 10: 165-174 [PMID: 30283599 DOI: 10.4253/wjge.v10.i9.165]

Singh T, Sanaka MR, Thota PN. Endoscopic therapy for Barrett’s esophagus and early esophageal cancer: Where do we go from here? *World J Gastrointest Endosc* 2018; 10: 165-174 [PMID: 30283599 DOI: 10.4253/wjge.v10.i9.165]
