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EVIDENCE REVIEW

Evidence-based approach to the treatment of esophagogastric junction tumors

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Abstract

The incidence of esophagogastric junction (EGJ) adenocarcinoma is increasing in developed nations due to the rising prevalence of obesity and gastroesophageal reflux disease. Due to the peculiar location in a histological transition zone between the esophagus and the stomach, the management of EGJ tumors is controversial. Two main surgical approaches exist: total gastrectomy with distal esophagectomy or esophagectomy by either transhiatal or transthoracic approach. These operations differ significantly in the extent of lymphadenectomy. In addition, patients with locally advanced disease can receive either preoperative chemoradiation or perioperative chemotherapy. This evidence-based review analyzes current evidence regarding the management of EGJ tumors in order to help defining the best surgical and systemic treatment of these patients.

Key Words: Esophagogastric junction tumors; Esophagectomy; Gastrectomy; Esophageal adenocarcinoma; Chemotherapy; Chemoradiation

Core Tip: Management of patients with esophagogastric junction tumors is challenging. Several surgical approaches and systemic therapies are currently available to treat these patients. This evidence-based review will help determining the optimal treatment for this complex disease.

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INTRODUCTION

Adenocarcinoma of the esophagogastric junction (EGJ) remains a major global health problem associated with poor prognosis[1]. The majority of patients are diagnosed at an advanced stage, and only half of the patients undergo curative treatment[2]. EGJ tumors arise in the histological transition area between the esophagus and the stomach. This zone is vulnerable to gastric acid reflux and consequently has an increased risk of malignant transformation[3]. The incidence of EGJ tumors vary among countries, but it has been increasing in the past years due to the rising prevalence of obesity and gastroesophageal reflux disease in developed nations[4,5].

Siewert described three types of EGJ tumors based on the relationship of the epicenter of the tumor and the endoscopic location of the Z line (*i.e.*, squamocolumnar junction): type I (distal esophageal tumors) when the epicenter is 1-5 cm above Z line, type II (true EGJ tumors) from 1 over to 2 cm below the Z line, and type III (subcardial tumors) when the epicenter is 2-5 cm distal to the Z line[6]. The Nishi classification is also based on where the center of the tumor is located; there are 5 types depending on the relative extent of the esophageal or gastric involvement (E, EG, E=G, GE, and G) and true EGJ tumors are represented by EG, E=G or GE[7].

Both Siewert and Nishi classifications describe the location of the center of the lesion, but do not consider the proximal or distal extent of the tumor, which is more relevant to guide the extent of surgical resection. In addition, the lymphatic drainage of EGJ cancers is variable. Specifically, type II tumors can metastasize to either paraoesophageal nodes in the lower mediastinum or upper abdominal lymph nodes[8].

Two main surgical approaches for EGJ tumors exist: total gastrectomy with distal esophagectomy and esophagectomy by either transhiatal or transthoracic approach[9,10].

Both operations allow for adequate dissection of para-celiac and para-aortic lymph nodes. However, better mediastinal lymph node dissection and larger proximal resection margins can be achieved with an esophagectomy[11,12].

Some oncological and surgical principles that are well-established for esophageal and gastric tumors cannot be simply applied to junctional cancers due to their specific location and pathological features. The aim of this study was to review the available evidence in an attempt to determine the optimal treatment for patients with EGJ tumors.

SURGICAL TREATMENT OF EGJ TUMORS

Esophagectomy remains the cornerstone of curative treatment of esophageal cancer. The goals of the operation are to achieve a resection with clear margins, with an adequate lymphadenectomy, and with acceptable morbidity and mortality rates in order to offer better long-term survival.

Surgical approach

R0 resection remains one of the most important prognostic factors for survival irrespectively of the tumor type or surgical approach. Consequently, technical considerations regarding proximal margin should influence surgical strategy. Most experts base their surgical approach on Siewert classification, recommending an esophagogastrectomy for type I tumors and a total gastrectomy for type III tumors. However, the main debate arises for type II lesions: esophagectomy or gastrectomy?

Different approaches are proposed for true cardia tumors. Some authors support esophagectomy because it allows an extensive mediastinal lymph node resection along with a longer proximal resection margin that may decrease the likelihood of microscopically positive margins. On the other hand, a total gastrectomy with distal esophagectomy may be preferred because it avoids entering the chest, and an adequate abdominal lymph node dissection can be achieved (potentially the most important nodes in these patients).

Esophagectomy and gastrectomy are significantly different in terms of invasiveness, type of reconstruction, and, more importantly, extent of gastric and esophageal resection. After analyzing 1002 consecutive patients undergoing surgery for EGJ cancers, Siewert *et al*[13] concluded that in patients with type II EGJ tumors an esophagectomy offers no advantage over an extended gastrectomy if a complete tumor resection can be achieved. No differences were observed in R0 resection rates or number of lymph nodes removed. In addition, esophagectomy was associated with higher 30-d mortality when compared with total gastrectomy[13].

Barbour *et al*[11] evaluated whether the length of esophageal resection or the operative approach influences the outcomes in patients with EGJ tumors. They analyzed 153 patients undergoing gastrectomy and 352 esophagectomy. No differences were found regarding lymph nodes harvested, R0 resection rates, or mortality between groups. Gastrectomy was indeed associated with shorter proximal margins than those undergoing esophagectomy for each Siewert type. Improved outcomes were seen with an esophageal margin > 3.8 cm. The authors concluded that if an adequate proximal margin is achieved, the operative approach might not modify overall survival[11]. Another study, which included 266 patients with surgically resected type II EGJ tumors, found that gastrectomy was more frequently associated with a positive circumferential resection margin than esophagectomy (29% *vs* 11%; $P = 0.025$) [14]. Considering how critical is to achieve adequate proximal margins in these patients, we strongly believe that a gastrectomy should only be considered if a large proximal margin is feasible.

Another matter of debate are the morbidity and mortality rates associated with the different surgical approaches proposed for EGJ tumors. A previous study compared patients undergoing thoracoabdominal esophagectomy ($n = 56$) with transhiatal extended gastrectomy ($n = 186$); this study did not find significant differences regarding perioperative morbidity, anastomotic leak rates, pulmonary complications, or mortality[15]. Another study analyzed two large databases, including 4996 patients with type II EGJ tumors, which found similar major postoperative morbidity (34% *vs* 33%; $P = 0.84$) and 30-d mortality (1.9% *vs* 3.4%; $P = 0.24$) with the esophageal and gastric approach. In addition, the surgical approach was not an independent predictor of overall survival[16]. These findings were supported by other authors[17-19]. Nevertheless, postoperative morbidity after an esophagectomy remains high[20]. In an effort to decrease morbidity, minimally invasive esophagectomy (MIE) has been widely adopted in the last decades[21]. For instance, the TIME trial was the first randomized trial comparing patients undergoing MIE or open esophagectomy and showed that postoperative pulmonary infections rates significantly decrease after MIE. Also, shorter length of stay and better quality of life were achieved in the MIE group[22].

Lymphadenectomy

Lymph node metastasis is another critical prognostic factor in patients with esophageal adenocarcinoma. Therefore, another major goal of the operation is to perform an adequate lymphadenectomy. As an increased number of metastatic lymph nodes is predictive of poor survival, an extensive lymphadenectomy is recommended by the American Joint Committee on Cancer in order to achieve accurate N staging[23]. However, whether extensive lymphadenectomy can improve overall survival because of better control of locoregional disease or better staging remains unclear. In addition, an extensive lymphadenectomy may potentially increase surgical morbidity.

Many studies have tried to determine how many nodes should be removed in patients with EGJ tumors for achieving optimal oncological outcomes[24-27]. For instance, Samson *et al*[26] found that sampling 15 or more lymph nodes was independently associated with lower overall mortality. Moreover, overall survival was improved when more than 20-25 lymph nodes were sampled even in patients with negative nodes, probably due to an increased staging accuracy[26]. This finding was also supported by other authors[25,28]. Greenstein *et al*[29] found that in patients with T2/T3 tumors, better survival rates were observed when more than 10 lymph nodes retrieved, and for T1 tumors, more than 18 lymph nodes were needed for superior survival rates. A recent study recommends the removal of at least 15 lymph nodes in both primary surgery and after induction therapy[24]. Sihag *et al*[28] analyzed 778 patients with locally advanced esophageal adenocarcinoma and found that overall and disease-free survival improved when harvesting up to 20-25 lymph nodes. A lower number of lymph node resection was independently associated with worse overall and disease-free survival[28].

Overall nodal metastasis rate in EGJ tumors varies among the literature between 40% and 80%[30-32]. The EGJ has two main lymphatic drainage pathways: abdominal and mediastinal. Mediastinal lymph nodes involvement varies between 15%-45% in the literature[31,32]. Siewert *et al*[13] evaluated the pattern of lymphatic spread specifically in type II EGJ cancers and showed that almost 70% of the tumors spread towards paracardial, lesser curvature, and left gastric artery nodes while only 15% towards lymphatic nodes in lower posterior mediastinum. However, as all patients underwent a gastrectomy, upper mediastinal nodes were not evaluated in these patients.

Leers *et al*[30] analyzed patients with distal esophageal and EGJ tumors undergoing an esophagectomy with systematic mediastinal and upper abdominal lymphadenectomy. The authors found that 26% of the distal esophageal tumors and 25% of the EGJ tumors had positive mediastinal nodes. Moreover, in 9% and 8% of the patients, respectively, this location was the only site of nodal involvement, concluding that mediastinal node dissection was essential in the surgical therapy for EGJ tumors[30].

Yamashita *et al*[33] recently showed that nodal metastasis in EGJ tumors more frequently involve abdominal nodes, especially those at the right and left cardia, lesser curvature, and along the left gastric artery.

A recent study showed higher incidence of metastasis or recurrence in the upper and middle mediastinal zones when the esophageal invasion length was more than 25 mm[34]. These findings were supported by a Japanese prospective study that included 363 patients undergoing either gastrectomy by a transhiatal approach or distal esophagectomy by a right transthoracic approach. The authors

concluded that upper and lower mediastinal station dissections should be performed in cases of more than 4 cm or 2 cm of esophageal involvement, respectively[35]. Conversely, routine dissection of lymph nodes at the lesser curvature and along the left gastric artery for any EGJ tumor was recommended.

A randomized trial was conducted to compare extended transthoracic resection with limited transhiatal resection for Siewert type I and II. Although a higher number of lymph nodes were harvested through the transthoracic approach (31 *vs* 16), the 5-year survival was similar between groups (34% *vs* 36%). A subgroup analysis was also performed for type I tumors, and a survival benefit of 14% was achieved with the transthoracic approach (51% *vs* 37%). The authors concluded that in type I tumors the transthoracic approach might have survival advantages, especially in those with 1 to 8 positive nodes in the resection specimen[36]. Parry *et al*[14] also showed that a better mediastinal lymph node resection was achieved with an esophagectomy, and these results were supported by other authors [11,37,38].

Advanced techniques to optimize intraoperative lymphadenectomy have been developed in the last decades. For instance, the indocyanine green (ICG) fluorescence imaging for the evaluation of lymph node involvement has increasingly been used, and it might help guiding lymphadenectomy. The goal of this technology is to sample specific tumor-associated lymph nodes and increase pathological evaluation of more likely affected nodes. A targeted lymphadenectomy might provide more accurate and relevant prognostic information and may potentially decrease operative time and reduce postoperative complications. For instance, a previous study evaluated the lymphatic drainage pattern in patients with distal esophageal or EGJ cancer and found that in 89% of the cases, the first nodal station was along the left gastric artery. Interestingly, all patients with nodal involvement had positive nodes in the first nodal station identified with ICG[39]. Therefore, histopathological examination of the first nodal station might avoid unnecessary extensive lymphadenectomy. Further studies are needed to determine how fluorescence imaging can guide lymphadenectomy during an esophagectomy.

Expert commentary

Current evidence shows that surgical resection of an EGJ tumor can be achieved by either an esophagectomy or gastrectomy.

Type I tumors should probably be resected with an esophagectomy due to the higher risk of mediastinal lymph nodes involvement and the impossibility to achieve adequate margins with a gastrectomy. Type III tumors are adequately treated with a gastrectomy and abdominal lymphadenectomy.

Conflicting data exist regarding the optimal approach and the extent of lymphadenectomy for type II tumors. Although both approaches have shown similar oncological and clinical outcomes in these patients, we prefer an esophagectomy in order to obtain safe proximal margins and achieve adequate mediastinal lymphadenectomy.

Overall, tumor extension, lymph node involvement in preoperative imaging, patient's comorbidities and frailty, and experience of the surgical team should all be considered when deciding the surgical approach.

Table 1 describes potential advantages and disadvantages of the "esophageal" and "gastric" approach for the treatment of EGJ tumors.

NEOADJUVANT THERAPY

The optimal systemic therapy for EGJ tumor is also a debatable topic. It is clear that neoadjuvant therapy is required for locally advanced EGJ tumors to increase overall survival[40]. For this purpose, neoadjuvant chemoradiation and perioperative chemotherapy are both valid treatment modalities. However, which is the best approach for patients with EGJ tumors remains controversial.

Neoadjuvant chemoradiation

In 2012, the benefits of neoadjuvant therapy in patients with esophageal cancer were revealed by the results of the CROSS trial. This study randomized patients with esophageal or esophagogastric junction tumors to surgery alone (n = 188) or preoperative chemoradiotherapy (carboplatin and paclitaxel + concurrent radiotherapy) followed by surgery (n = 178). Patients receiving preoperative chemoradiotherapy had higher rates of R0 resections (92% *vs* 69%; $P < 0.001$) and better overall survival (49.4 mo *vs* 24 mo). In addition, 29% of the patients with chemoradiotherapy had complete pathological response [40]. The long-term results of the trial confirmed the benefits of neoadjuvant chemoradiotherapy. It is worth to mention, however, that patients with squamous cell carcinoma (ESCC) (23% of the included patients in the trial) had greater overall survival benefit than patients with adenocarcinoma[41].

Perioperative chemotherapy

In 2006, the MAGIC trial evaluated the role of perioperative chemotherapy for patients with gastric and EGJ tumors, comparing those receiving 3 cycles of Epirubicin – Cisplatin - Fluorouracil (ECF) before and after the operation against those undergoing surgery alone. The study showed significantly improved

Table 1 Potential advantages (+) and disadvantages (-) of total gastrectomy and esophagectomy for the treatment of esophagogastric junction tumors

Gastrectomy	Esophagectomy
+ Only abdominal approach, avoiding thoracotomy/thoracoscopic associated morbidity	+ Better proximal and circumferential resection margins
+ Adequate abdominal lymph node dissection	+ Extensive mediastinal lymph node dissection
+ No GERD/No PPI	+ Preservation of ¾ of stomach
- Inadequate mediastinal lymph node dissection	- Abdominal and thoracic approach
- Shorter proximal margins	- Hiatal herniation risk
- Vitamin B12 malabsorption	- Gastroesophageal reflux (necessity of PPI)
- Dumping	- Pylorospasm

GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor.

overall and progression-free survival in patients receiving chemotherapy[42]. Two things, however, should be highlighted: only 11% of the patients had EGJ adenocarcinoma, and only 42% were able to complete the full six-cycle regimen.

In 2011, the ACCORD-07 trial compared patients receiving 2 or 3 cycles of cisplatin and fluorouracil before and after surgery with patients undergoing surgery alone. In this study, 64% of the patients had EGJ tumors. The trial showed better overall survival (38% *vs* 24%), 5-year disease-free survival (34% *vs* 19%), and higher rates of R0 resections in patients receiving perioperative chemotherapy[43].

In 2019, the FLOT trial (fluorouracil, leucovorin, oxaliplatin, and docetaxel) compared the use of perioperative FLOT (n = 356) or ECF (n = 360) plus surgery in patients with locally advanced gastric and EGJ tumors. The study demonstrated an overall survival benefit with the use of FLOT (50 *vs* 35 mo). Remarkably, only 50% of the patients completed the entire perioperative FLOT treatment[44]. These results have motivated the adoption of FLOT as the standard perioperative chemotherapy for patients with EGJ tumors.

CROSS vs FLOT

Few studies have compared the efficacy of both approaches. A propensity score-matched analysis of patients with esophageal and EGJ adenocarcinoma compared the outcomes of CROSS (n = 40) against FLOT (n = 40). Patient receiving CROSS had higher rates of complete pathological response (97% *vs* 85%; P = 0.049) and higher rates of negative lymph node metastases (68% *vs* 40%; P = 0.014). However, overall survival was similar in both groups[45]. A recent study using the National Cancer database investigated whether preoperative chemoradiation offers an advantage over chemotherapy alone in patients with lower esophageal or gastric cardia adenocarcinoma. The authors found that although patients undergoing chemoradiation had higher rates of complete pathological response (2.7 times), overall survival was similar with both treatment modalities[46]. Similar survival outcomes with CROSS and FLOT were also seen in other studies[47-49].

Expert commentary

Current evidence is weak and scarce but shows that patients with locally advanced EGJ tumors have similar survival with either preoperative chemoradiation or perioperative chemotherapy. We believe that both location and burden of disease (*i.e.* ability to obtain R0 resection) are key determinants.

For patients with Siewert type III tumors, perioperative chemotherapy is undoubtedly more reasonable due to the multiple trials supporting this approach (*i.e.* MAGIC, ACCORD, and FLOT). FLOT has shown to be the most effective regimen, and thereby should be chosen whenever possible.

Although for patients with Siewert type I and II the debate is still open, we think that avoiding the morbidity of radiation (whenever possible) is a better strategy. Patients with squamous cell carcinoma of the distal esophagus might still benefit from neoadjuvant chemoradiation. EGJ adenocarcinomas are probably better treated with perioperative chemotherapy.

Future directions: Immunotherapy

Overall survival of patients with locally advanced EGJ tumors remains low. Moreover, recurrence rates after neoadjuvant chemoradiotherapy plus surgery are high, especially among patients who do not have a pathological complete response[50-52]. Therefore, there is special interest in developing novel treatment modalities to improve outcomes. Multiples targeted therapies and immunotherapies are currently being investigated. Immunotherapy utilizes monoclonal antibodies directed against immune checkpoints proteins (*e.g.*, PD-1, PD-L1, CTLA-4). Multiples trials have shown clinical benefits with the use of immunotherapy in patients with metastatic or recurrent esophageal cancer[53-56]. The

KEYNOTE-590 study showed that adding pembrolizumab to cisplatin-fluoropyrimidine chemotherapy improved overall survival in patients with ESCC[53]. The ATTRACTION-3 trial, which included patients who had a previously treated advanced gastroesophageal cancer, showed a 2.5-mo difference in median overall survival in favor of nivolumab in comparison with chemotherapy[54]. The ATTRACTION-4 trial, on the other hand, did not show overall survival benefit, despite improvements in progression-free survival[55]. Recently, the Checkmate-577 phase III trial was conducted to compare postoperative nivolumab monotherapy against placebo in patients with locally advanced tumors who underwent resection and did not achieve complete pathologic response. Nivolumab monotherapy improved significantly disease-free survival in compared with placebo (median disease-free survival: 22.4 mo *vs* 11.0 mo; $P = 0.0003$). Interestingly, in the subgroup analysis according to histopathological type, the median disease-free survival period of patients with ESCC treated with nivolumab was better than for EAC patients. Despite this encouraging data, the trial was discontinued because of adverse events[56]. The trials PALACE-1 and PERFECT have also investigated the use of neoadjuvant chemoradiotherapy combined with immunotherapy in an effort to achieve higher rates of complete pathologic response[57,58]. However, phase 3 trials evaluating immunotherapy as neoadjuvant therapy are still warranted.

Overall, although immunotherapy has shown promising results, additional studies are needed to define safety and efficacy of this novel treatment modality.

CONCLUSION

Management of patients with EGJ tumors is challenging. Several surgical approaches and systemic therapies are currently available to treat these patients. Appropriate surgical margins and adequate lymphadenectomy should be the main goals of surgical treatment. Patients with locally advanced disease should also receive preoperative chemoradiation or perioperative chemotherapy. Tumor size and extension, nodal involvement in preoperative imaging and patient's comorbidities should all be considered for choosing the optimal treatment in these patients.

FOOTNOTES

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