

**REVIEW ARTICLE**

# Surgical principles for optimal treatment of esophagogastric junction adenocarcinoma

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**Abstract**

The incidence of esophagogastric junction (EGJ) adenocarcinoma is increasing worldwide. Management of these tumors remains controversial given their unique location between the esophagus and the stomach. Debate surrounding the optimal therapy for EGJ adenocarcinoma has often centered around the tumor origin as defined by the Siewert classification system. However, the optimal surgical management should focus on adhering to important surgical principles that will allow for the best outcomes and prognosis regardless of tumor location including resection with appropriate and negative histological margins, adequate lymphadenectomy, minimization of morbidity and mortality, and preservation of quality-of-life. In this article, we provide a discussion of the controversy surrounding EGJ adenocarcinoma within the framework of these concepts.

**KEYWORDS**

esophageal adenocarcinoma, esophageal cancer, esophagectomy, esophagogastric junction adenocarcinoma, Siewert classification

## 1 | INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has increased both in the West and in Asia.<sup>1,2</sup> It has been estimated that the rate of esophageal adenocarcinoma increased sixfold between 1975 and 2000 in both Europe and the USA.<sup>3,4</sup> Improved medical and surgical treatments over the past 40 years have increased survival from 5% to 19%.<sup>5</sup> Surgical resection remains the cornerstone of curative therapy, with the addition of neoadjuvant chemotherapy and radiation showing improved survival among patients with locoregional disease.<sup>6</sup>

Management of esophagogastric junction (EGJ) adenocarcinoma presents a unique challenge given its location in the distal esophagus and proximal stomach, and there is a lack of consensus as to whether this disease represents gastric or esophageal cancer. The main risk factors for EGJ adenocarcinoma include factors specific to either esophageal or gastric cancer such as obesity, reflux, smoking

and *Helicobacter pylori*.<sup>7,8</sup> Additionally, it is often difficult to discern the exact anatomical location of the origin of EGJ adenocarcinoma.<sup>7</sup>

The origin of EGJ adenocarcinoma has traditionally had important management implications for several reasons. First, management of locoregional disease differs between esophageal and gastric cancer, with the standard approach being neoadjuvant chemoradiation therapy for the former whereas the latter receive chemotherapy alone. Given that one-third of new esophageal cancers are locoregional at diagnosis, this concern remains important for most patients.<sup>9</sup> Second, the type of lymphadenectomy carried out differs in the surgical management of these two cancers. Finally, and most importantly, the optimal surgical approach, including esophagectomy or gastrectomy, is very controversial. It is often institution specific with limited consensus.

In this article, we discuss several principles to guide decision-making for optimal surgical treatment of EGJ adenocarcinoma.

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## 2 | CLASSIFICATION

The Siewert classification system, proposed in 1996, has become the widely accepted method for anatomical definition of EGJ tumors.<sup>10</sup> Tumors are defined by the topographic location of the tumor center in relation to the EGJ, which includes the area ranging from 5 cm proximal and distal to the cardia, identified by the proximal end of the gastric folds on endoscopy. Tumors with epicenter 1-5 cm above the EGJ are classified as type I, with type II including tumors with epicenter within 1 cm above and 2 cm below the cardia, and type III as those 2-5 cm below the EGJ.

Given that type I disease typically arises within Barrett's esophagus as compared to only 6% and <1% prevalence observed in types II and III disease, it has traditionally been considered a disease of the esophagus.<sup>11,12</sup> In contrast, type III cancers have been treated as gastric whereas the status of type II disease continues to be an area of debate.<sup>13</sup> The 7th edition of the AJCC Cancer Staging Manual considered type I/II to be esophageal whereas type III (cardiac tumors within 5 cm of the EGJ) tumors without EG junction involvement were gastric.<sup>14</sup> In response to increasing criticism of the Siewert classification system, the 8th edition of the AJCC Cancer Staging Manual has further modified this definition to include only cancers with epicenters no more than 2 cm into the cardia.<sup>15</sup>

Given difficulties identifying true EGJ, relying on the Siewert classification system for treatment selection may not be the optimal approach. The squamocolumnar junction (Z line) may be shifted in Barrett's esophagus, and the location may be better defined by the proximal margin of the gastric folds.<sup>7,16</sup> However, visualization of the gastric folds may be difficult in the setting of hiatal hernias, which have up to 50% incidence in Western populations.<sup>17</sup> Consequently, in practice, patients are often arbitrarily classified into a system that may not fit their disease and may receive treatment that does not match their disease.

## 3 | SURGICAL TREATMENT OF EGJ CANCER

Most review articles on the subject of surgical management of EGJ adenocarcinoma classify their discussion of surgical treatment by

Siewert classification.<sup>7,12,13,18</sup> In this discussion of surgical management of EGJ, we will take an alternative approach by instead providing an overview of important surgical principles to consider in order to provide the best outcomes and prognosis regardless of Siewert class.

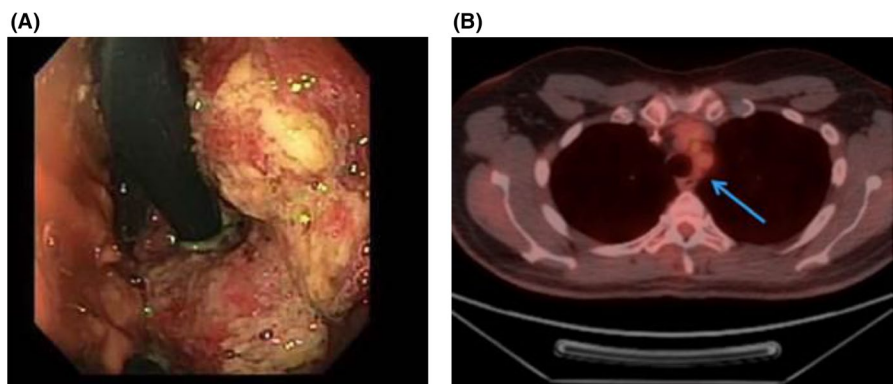
### 3.1 | Principle 1: Achieve negative margins

First, the most important principle is to achieve resection with appropriate margins. Residual primary disease has been shown to be the most important predictor of prognosis. It has been well documented that positive margins (R1/R2) after resection of EGJ adenocarcinoma are associated with poor survival regardless of operative approach or tumor location.<sup>19-22</sup> Studies have shown that median overall survival was 8-25 months longer after R0 resection as compared to those with positive margins.<sup>20,22</sup> In the 2000 study by Siewert et al. of 1002 patients with EGJ adenocarcinoma, neither Siewert type nor operative approach (esophagectomy vs gastrectomy) predicted overall survival; however, survival was related to the ability to completely resect the tumor and achieve R0 resection.<sup>23</sup>

Consequently, this has raised the question of whether surgical treatment should be selected based on achievable margin length. In a series of patients with EGJ adenocarcinoma from our institution, gastrectomy had worse survival as compared to extended esophagectomy (22 months vs 37 months).<sup>24</sup> However, after adjusting for resection margin, margins >3.8 cm were associated with improved survival whereas operation type was not. Similar findings were subsequently replicated in a series of 140 patients that underwent gastrectomy.<sup>25</sup> Achievement of a >5 cm margin has subsequently been adopted as the preferred goal. Therefore, the decision of which surgery to carry out must ultimately, irrespective of other factors, be that which enables an R0 resection.

### 3.2 | Principle 2: Ensure adequate lymphadenectomy

To improve patient prognosis, it is important to ensure that all regional nodal metastasis has also been properly resected. Previous data have suggested that Siewert type I cancers most commonly spread to the upper abdominal and lower posterior mediastinal



**FIGURE 1** A 43-year-old man with lesser curvature esophagogastric adenocarcinoma seen on endoscopy (A) with obvious mediastinal nodal involvement on chest imaging (B). The arrow indicates a high left paratracheal lymph node which was positive for metastatic involvement

nodes whereas type II and III tumors predominantly drain along the celiac axis and greater curvature.<sup>7,18,23</sup> However, in practice, this is not always the case and reliance on Siewert classification alone may result in missed nodal disease. For example, Figure 1 shows the images of a 43-year old man with extensive disease of the lesser curvature with positive nodes up to the thoracic inlet seen on endoscopic ultrasound. This case highlights the inherent challenges of management of cancer of the EGJ. In this case, because we knew the patient had positive nodes preoperatively, a bilateral paratracheal dissection was carried out. However, for distal EGJ tumors this is not done routinely unless there are clinical signs of nodal disease.

Siewert showed that patients with type II/III disease had only a 15% incidence of positive paraesophageal nodes, suggesting limited need for extensive mediastinal dissection.<sup>23</sup> As such, the current standard is often to carry out lymphadenectomy limited to the lower mediastinum and D2 abdominal nodes for type II/III disease. However, it is important to note that Siewert included only patients with transhiatal dissection, so higher mediastinal nodes were never assessed pathologically. Similarly, other studies showing a low rate of mediastinal lymphadenopathy in type II/III disease included very few patients that had undergone mediastinal lymphadenectomy, so the true incidence is largely undefined.<sup>11,26</sup> Given that patients with type II disease may have nodal spread in either direction, it is our practice to carry out a two-field lymphadenectomy as it is not possible at this time to accurately to predict which nodes are involved. The extent of lymphatic resection is also debated among patients with type I disease with lack of consensus as to whether a two- or three-field lymphadenectomy is indicated.<sup>27,28</sup> The reported incidence of upper mediastinal/cervical nodal disease in type I disease has ranged from 5% to 18%.<sup>18,27</sup>

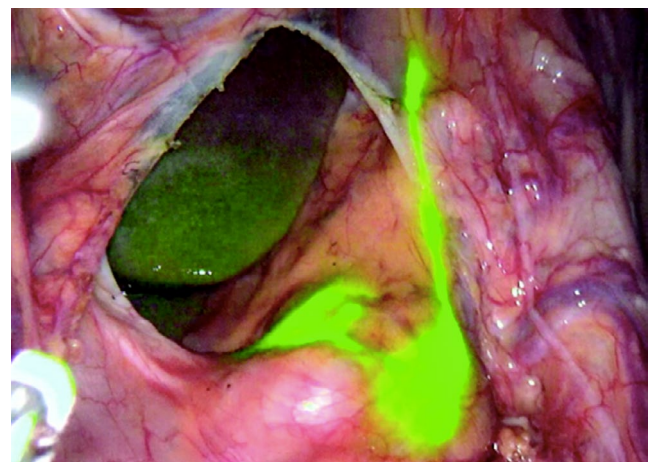
Results of recent studies call into question the role of the Siewert classification system in the selection of appropriate lymphadenectomy. A 2009 study which compared nodal distribution among 144 patients with distal esophageal and EGJ adenocarcinoma showed a similar prevalence of mediastinal nodal disease between groups (47% and 41%).<sup>29</sup> Furthermore, 8% of patients in both groups had positive mediastinal nodes in the absence of abdominal disease. Unpublished data from our own institution comparing 184 patients with positron-emission tomography (PET)-positive nodal disease (71 type I, 99 type II and 14 type III) showed that across all Siewert groups nearly half of patients had evidence of supradiaphragmatic nodal disease, either in combination with PET-positive abdominal nodes ( $n = 29$ , 16%) or without evidence of abdominal nodal disease ( $n = 53$ , 29%). Unfortunately, given that only 22% (181/828) of patients that underwent resection of EGJ cancer had PET-positive disease, relying on preoperative imaging alone is not sufficient for carrying out a limited lymphadenectomy.

Highlighting the importance of removing all regional disease, it has previously been shown that survival is improved with increased nodal resection. Evaluation of over 4600 patients in the Worldwide Esophageal Cancer Collaboration showed that increasing the extent of lymphadenectomy improved 5-year overall survival, especially in patients with T3/T4 disease (30-50 nodes).<sup>30</sup> Extensive

lymphadenectomy appeared less important among patients with limited stage disease and plateaued at approximately 15 nodes for T2 tumors with N0 or N1/2 disease. Results of a clinical trial that randomized patients with types I and II disease to transhiatal esophagectomy or transthoracic esophagectomy with en bloc lymphadenectomy showed similar survival between groups.<sup>31</sup> However, stratification by number of positive nodes ( $\leq 8$  or  $>8$ ) showed that patients with  $\leq 8$  positive nodes had significantly improved survival with the transthoracic approach (64% vs 23%), whereas no difference was seen in patients with  $>8$  positive nodes. Given that extensive nodal disease likely reflects cancer that is already subclinical systemic metastatic disease, it is not surprising that patients with  $>8$  positive nodes did not experience a survival benefit with more extensive lymphadenectomy.<sup>32,33</sup> However, patients with more limited regional disease appear to benefit from the transthoracic approach.

Most patients diagnosed with locoregional disease consequently undergo neoadjuvant therapy with chemoradiation or chemotherapy alone. The relationship between the number of nodes harvested and diseased nodes is difficult to assess, given that downstaging occurs after chemoradiation. Preoperative radiation therapy may be associated with a reduced number of nodes harvested.<sup>34</sup> Although retrospective analysis of CROSS study data has suggested that lower nodal harvest after chemoradiation may not matter, it is certainly possible that inadequate lymphadenectomy may lead to positive nodes being missed.<sup>34</sup>

The above discussion suggests that prediction of nodal drainage in EGJ adenocarcinoma is challenging, and that using Siewert classification alone is not sufficient to achieve proper lymphatic resection. As such, given the potential for extensive spread, should extensive lymphadenectomy be considered to achieve maximal patient outcomes in all patients? Our preferred approach for EGJ adenocarcinoma is to carry out an extensive two-field lymphadenectomy. The abdominal resection involves complete removal of the hepatic and left gastric nodes at the base of the celiac trunk, in addition to the splenic artery nodes. In the mediastinum, extensive lymphadenectomy is carried out but we do not routinely go above the carina.



**FIGURE 2** Use of indocyanine green for intraoperative assessment of nodal drainage during resection of esophagogastric junction adenocarcinoma

The concept of sentinel node mapping, as in breast cancer and melanoma, has recently been considered as a method to better identify patients that may be eligible for more limited lymphadenectomy. In a pilot study of nine EGJ adenocarcinoma patients using near-infrared fluorescent imaging, the first nodal station identified by indocyanine green (ICG) drainage was along the left gastric nodes in most patients with only one having drainage above the diaphragm<sup>35</sup> (Figure 2). Of three patients with positive nodal disease, all of them had positive nodes in the first station identified with ICG. Other small series have similarly demonstrated the feasibility of this concept and it is possible that, in the future, this approach may become standard as a guide to lymphadenectomy as further data are accrued.<sup>36,37</sup>

### 3.3 | Principle 3: Minimize postoperative morbidity and mortality

Given that esophagectomy is an inherently complex procedure, the common perception is that this approach is associated with worse postoperative outcomes. However, several studies have suggested similar postoperative morbidity and mortality among patients undergoing esophagectomy as compared to gastrectomy.<sup>38,39</sup> In a large population-based study, the authors showed that morbidity and 30-day mortality rates were similar among patients undergoing gastrectomy and esophagectomy despite higher use of preoperative radiation in the esophagectomy group.<sup>39</sup> Furthermore, a systematic review demonstrated similar morbidity (33%-39% vs 11%-54%) and 30-day mortality (1%-2.3% vs 1.8%-2.7%) between esophagectomy and gastrectomy, respectively.<sup>40</sup> It has been well demonstrated that hospital volume and surgeon experience remain important factors associated with postoperative complications after esophagectomy

and, therefore, among experienced surgeons, this should not be an important part of determining the optimal surgery to carry out for a given patient.

One factor that has been associated with improved postoperative outcomes is increased use of the minimally invasive approach to esophagectomy (MIE). As compared to the traditional open esophagectomy (OE), MIE has been demonstrated to be less traumatic with earlier postoperative recovery, less pain, fewer wound and cardiopulmonary complications, and better visualization.<sup>5</sup> In a large meta-analysis comparing open versus minimally invasive esophagectomy, both morbidity (41% vs 48%) and mortality (3.8% vs 4.5%) were shown to be lower in MIE as compared to OE.<sup>41</sup> Additionally, the oncological safety of MIE has also been shown, suggesting that a MIE approach should be considered as an initial approach for most patients.<sup>42</sup>

Anastomotic leak is the Achilles' heel of esophagectomy given the morbidity and mortality associated with this complication. There are several adjuncts that we are currently using to further improve postoperative results. In order to ensure that the conduit is well perfused, especially following radiation, fluorescence imaging is also being used to assess perfusion and length after transposition into the chest.<sup>43</sup> If the tip is found to be ischemic, it is divided. We then buttress the anastomosis with pleura and omentum as this may prevent a patient with a small contained leak from becoming septic. This is especially important in patients that underwent preoperative radiation given impaired healing. Another technique we use is coverage of the trachea with omentum to minimize the risk of tracheoesophageal fistula in patients that do develop a leak.

Finally, another area of debate is that of pyloric drainage. We recently demonstrated that MIE patients without any pyloric

## Minimally invasive esophagectomy pathway

Surgery date: \_\_\_\_\_ Expected discharge date: \_\_\_\_\_

These are goals for your recovery. Your experience may not follow this pathway exactly. Your doctor or nurse will tell you what to expect.

	Before surgery	Day of surgery	Day 1 after surgery
What should I do?	<ul style="list-style-type: none"> <li>Buy a wedge pillow.</li> <li>From now until surgery, exercise 30 minutes (such as walking 1 mile) every day.</li> <li>Brush your teeth after you eat.</li> <li>Stop smoking 2 or more weeks before surgery.</li> <li>Plan your ride home after surgery.</li> </ul> <p><b>The night before surgery:</b></p> <ul style="list-style-type: none"> <li>Wash with Hibiclens®</li> </ul>	<ul style="list-style-type: none"> <li>Wash with Hibiclens in the morning.</li> <li>Brush your teeth.</li> </ul>	<ul style="list-style-type: none"> <li>Raise the head of your bed to 30 degrees.</li> <li>Use your incentive spirometer 10 times each hour you're awake.</li> <li>Do coughing &amp; deep breathing exercises.</li> <li>Sit up in your chair.</li> <li>Walk 5 laps around the nursing unit.</li> <li>Brush your teeth and use mouth rinses 3 or more times a day.</li> <li>Learn about caring for your incisions and feeding tube.</li> </ul>
What tests, procedures, and medical devices should I expect?	<p><b>Presurgical testing appointment:</b></p> <ul style="list-style-type: none"> <li>Bring a list of all medications you take.</li> <li>Your nurse practitioner may order more tests or appointments.</li> </ul>	<p><b>Placed before surgery:</b></p> <ul style="list-style-type: none"> <li>Intravenous (IV) line</li> <li>Compression boots</li> </ul> <p><b>Placed during surgery:</b></p> <ul style="list-style-type: none"> <li>Chest tubes</li> <li>Feeding tube</li> <li>Urinary (Foley®) catheter</li> <li>Nasogastric (NG) tube</li> </ul>	<ul style="list-style-type: none"> <li>Chest tubes</li> <li>NG tube</li> <li>Fluids in your IV line</li> <li>Chest x-ray</li> <li>Blood tests</li> <li>Weight measurement</li> <li>Urinary catheter may be removed</li> </ul>

**FIGURE 3** Example of patient information given as part of enhanced recovery program after minimally invasive esophagectomy. NG, nasogastric

intervention did better than those with either surgical drainage or botulinum injection, suggesting that pyloric drainage may be omitted without increased adverse events postoperatively.<sup>44</sup>

Morbidity and mortality are not simply a reflection of what occurs in the operating room. It is important to have a multidisciplinary team of providers to take care of patients postoperatively. We have recently adopted an Enhanced Recovery after Surgery (ERAS) program to ensure that postoperative care is standardized (Figure 3).

### 3.4 | Principle 4: Preserve quality of life

The final argument that has been used in treatment selection is that quality of life (QOL) differs by operative approach. As survival improves after treatment of esophageal cancer, recent data have suggested that patients want more information on postoperative QOL and, therefore, it is important to consider this factor in treatment selection.<sup>45</sup> Increased patient comorbidities, postoperative complications and open surgery have been associated with worse QOL.<sup>38</sup> In the setting of similar oncological outcomes between procedures, it is important to consider whether there is different impairment in quality of life between procedures.

Although data are limited, recent data have suggested that QOL is comparable between esophagectomy and gastrectomy.<sup>38,46</sup> In a recent series of 176 patients comparing 6-month outcomes between esophagectomy and total gastrectomy, no differences in QOL, physical function, pain or reflux were demonstrated.<sup>38</sup> In a comparison of 123 patients with disease-free survival greater than 24 months, only dyspnea, physical function and reflux were significantly higher among esophagectomy patients as compared to extended gastrectomy.<sup>46</sup> However, it is important to note that only 36% of 357 eligible patients participated in this study and a low threshold for clinical significance was used, suggesting that these results may have a high risk for selection bias and overestimation of associated symptoms.<sup>38</sup> Use of previously reported surveying cutoffs has suggested that only dyspnea would have been significantly higher among patients with EGJ adenocarcinoma.

Proximal gastrectomy is another surgical technique that may be used as an alternative to total gastrectomy for patients that allows for preservation of the physiological functions of the gastric remnant without compromising oncological safety. However, this has fallen out of favor at our own institution over the last 10 years because of QOL-related problems. Previous studies have shown increased reflux esophagitis and anastomotic stenosis among proximal gastrectomy patients as compared to total gastrectomy.<sup>47,48</sup>

Based on the current available data, the choice of surgery should be based on oncological assessment rather than QOL for patients with EGJ adenocarcinoma. However, given that more severe long-term reflux symptoms have been demonstrated with proximal gastrectomy and that this approach is without any oncological benefit over total gastrectomy, we prefer not to use this approach.

## 4 | SUMMARY

The incidence of EGJ adenocarcinoma is rising. Given the poor prognosis associated with this disease, appropriate treatment selection is very important. EGJ adenocarcinoma is a complex disease, and it is vital to understand the locoregional extension of the tumor prior to planning the optimal surgical approach. The type of resection carried out should be tailored to the extent of disease rather than personal experience or classification. The principles of surgical resection, including complete resection of the primary tumor and lymphatic disease, must be respected independently of the selected operative procedure. Ultimately, it is the residual disease rather than selected surgical technique that will define outcomes after resection.

### DISCLOSURE

Authors declare no conflicts of interest for this article.

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