



# The surgical management of esophago-gastric junctional cancer



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## ABSTRACT

The best available surgical strategy in the treatment of resectable esophago-gastric junctional (EGJ) cancer is a controversial topic. In this review we evaluate the current literature and scientific evidence examining the surgical treatment of locally advanced EGJ cancer by comparing esophagectomy with gastrectomy, transhiatal with transthoracic esophagectomy, minimally invasive with open esophagectomy, and less extensive with more extensive lymphadenectomy. We also assess endoscopic procedures increasingly used for early EGJ cancer.

The current evidence does not favor any of the techniques over the others in terms of oncological outcomes. Health-related quality of life may be better following gastrectomy compared to esophagectomy. Minimally invasive procedures might be less prone to surgical complications. Endoscopic techniques are safe and effective alternatives for early-stage EGJ cancer in the short term, but surgical treatment is the mainstay in fit patients due to the risk of lymph node metastasis. Any benefit of lymphadenectomy extending beyond local or regional nodes is uncertain.

This review demonstrates the great need for well-designed clinical studies to improve the knowledge in how to optimize and standardize the surgical treatment of EGJ cancer.

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## 1. Introduction

Esophageal cancer is the 8th most common cancer and the 6th most common cause of cancer death worldwide, while gastric cancer is the 5th most common type of cancer and 2nd most common cause of cancer death [1]. A cancer located in the distal esophagus or proximal stomach is typically referred to as an esophago-gastric junctional (EGJ) cancer [2]. The main risk factors for adenocarcinoma of the EGJ are partly shared with those of esophageal adenocarcinoma, i.e. gastroesophageal reflux disease, obesity, and tobacco smoking [3–7], and partly shared with those of gastric adenocarcinoma, i.e. *Helicobacter pylori* infection and dietary factors [8,9]. The incidence of EGJ cancer has increased along with esophageal adenocarcinoma in Europe [10]. For gastric cancer, *Helicobacter pylori*-infection is the main risk factor and it seems to increase the risk in a subgroup of EGJ cancer [8,11], while

weaker risk factors include tobacco smoking and dietary factors, i.e. salty, smoked, or poorly preserved foods [12,13]. Both esophageal and gastric cancers are associated with a diet low in fruit and vegetables and low socioeconomic status [4,6,12,13]. Assessment of prevalent risk factors for either esophageal or gastric cancer can help in distinguishing between the origin of EGJ cancer [8,9].

Surgery, often after completion of neoadjuvant therapy, is the cornerstone of curatively intended treatment of EGJ cancer. The 5-year survival following surgery for EGJ cancer is in the range of 25–40% [14,15]. Even among patients with a localized (resectable) tumor who are fit and therefore eligible for surgery, the majority of operated patients die from recurrence of the EGJ cancer [16,17]. The postoperative prognosis is closely related to tumor stage at the time of surgery, i.e. after neoadjuvant therapy, particularly with lymph nodal status [18,19]. The addition of neoadjuvant chemotherapy or chemoradiotherapy, centralization of surgical treatment, improvements in perioperative care, as well as more accurate patient selection following developments in imaging techniques and involvement of a multi-disciplinary team, have all had positive effects on the EGJ cancer prognosis following surgery [20,21]. Yet, the optimal surgical strategy for these tumors remains controversial.

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The lack of consensus regarding the definition of EGJ cancer and the difficulties in assessing the exact origin of these tumors contribute to this controversy [22]. In this review, we evaluate the existing evidence and rationale for various surgical strategies in the surgical treatment of adenocarcinoma of the EGJ.

## 2. Tumor classification

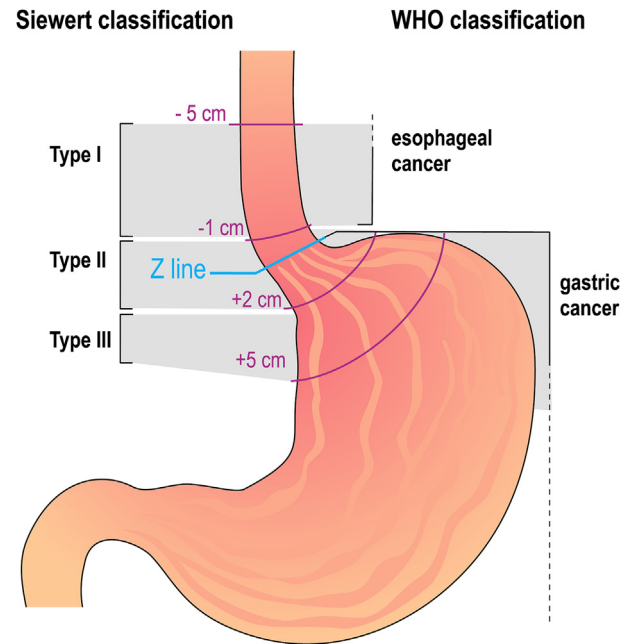
There are several challenges to the classification of cancers in the EGJ. The EGJ itself is often difficult to define. The squamocolumnar junction, also called the Z-line, is one potential anatomical basis for the definition [23], but in the presence of a columnar-lined esophagus (Barrett's esophagus), the Z-line shifts proximally, which is misleading [24]. Therefore, the location of the junction is better defined by the proximal margin of the gastric folds, where the tubular esophagus shifts to the sac-shaped stomach, although gastric folds can be obscured by hiatal hernias. Gastric inflation during endoscopy, however, can cause normal gastric folds to temporarily disappear, making this landmark less clear [25]. Large tumors are often difficult to evaluate in relation to any adjacent anatomical landmarks. There is no way to macroscopically assess the distal border of the gastric cardia, as the parietal cells cannot be visualized endoscopically [26]. Examination of biopsy specimens can also be problematic, because cardiac mucosa can also be found in the distal esophagus and are not necessarily found more than 3 mm below the squamocolumnar junction in the anatomical gastric cardia [27]. If the mucosa below the tumor is sampled, the biopsy specimen showing healthy gastric mucosa suggests esophageal etiology of the tumor, while an inflamed mucosa indicates a gastric origin [28–30].

The adenocarcinomas of the EGJ are often classified according to the Siewert classification, which is based on the macroscopic location of the epicenter of the tumor in relation to the EGJ [2]. Cancers occurring 1–5 cm above the EGJ represent Siewert type I, cancers within 1 cm above and 2 cm below the EGJ are type II, and cancers 2–5 cm below the EGJ are type III cancers. Cancers more proximal than 5 cm above the EGJ are classified as esophageal cancers and those more distal than 5 cm below the EGJ are labelled distal (or non-cardia) gastric cancers [2]. In the current (7th) edition of the tumor staging manual (TNM), EGJ cancers are staged as esophageal cancer when the tumor extends to the esophagus and as gastric cancer when no esophageal extension is visible. Thus, EGJ cancers of Siewert type I and II are staged using the TNM system for esophageal cancer, while Siewert type III cancers are staged together with gastric cancer (Fig. 1) [31]. However, the optimal surgical treatment of each of the Siewert type I, II and III cancers remains controversial, and the differentiation between these types is often difficult and arbitrary in clinical practice.

The distribution of the premalignant metaplasia Barrett's esophagus indicates differences in the etiology of Siewert type I-III tumors and when detected it can facilitate the Siewert categorization. Barrett's esophagus is typically present in Siewert type I tumors, while this prevalence is only 5.6% in type II and <1% in type III tumors [7]. The male predominance is also higher (10.7:1) in type I tumors compared to type II (4.9:1) and type III tumors (2.2:1) [7]. These data indicate that type I tumors are esophageal adenocarcinomas, type III tumors are gastric adenocarcinomas, while type II tumors represent a mixture of these. If this is the case, the EGJ does not constitute a separate anatomic entity.

## 3. Surgical approaches for esophago-gastric junctional tumors

Regardless of the surgical approach, complete removal of the primary tumor is of highest prognostic relevance, regardless of the



**Fig. 1.** The Siewert classification of esophago-gastric junctional (EGJ) cancers. In the WHO classification cancers extending into the esophagus or EGJ are staged as esophageal cancer and the rest as gastric cancer. The EGJ itself can be defined by the location of the Z-line or better by the proximal margin of the gastric folds.

tumor stage [23]. Moreover, better results in both the short- and long term are achieved in high-volume centers in general, and by high-volume surgeons in particular [32–36]. Another potentially important, but controversial factor is the surgical approach, which is discussed in more detail below. Five questions addressing key aspects of the surgical approach for EGJ cancer are evaluated in turn.

### 3.1. Esophagectomy or gastrectomy?

Esophagectomy for EGJ cancer is usually performed using a transthoracic (more common) or a transhiatal approach, and includes resection of the proximal stomach (Fig. 2A). Transthoracic esophagectomy is done using laparotomy and thoracotomy, and sometimes cervical incision, allowing exposure to the entire mediastinum. Gastrointestinal continuity is preserved by an intrathoracic anastomosis (Ivor Lewis approach) or cervical anastomosis (McKeown modification includes cervical incision) [23,37,20,38]. Transhiatal esophagectomy is performed through laparotomy and cervical incision, without thoracotomy. The diaphragmatic hiatus is opened anteriorly, allowing access to the lower posterior mediastinum. A narrow gastric tube following the great curvature or colon or jejunal interposition is used to replace the resected esophagus and proximal stomach for both approaches [7,39,40].

Gastrectomy for EGJ cancer includes removal of the entire stomach and the distal part of the esophagus via a laparotomy, where the diaphragm is opened (Fig. 2B). The anastomosis is usually placed in the distal part of the chest. The reconstruction is typically an esophago-jejunostomy with a Roux-en-Y reconstruction [23].

Most EGJ cancers of Siewert type I and II are surgically managed by esophagectomy, while total gastrectomy is often applied when the tumor is confined to the stomach (type III) [22]. However, in clinical practice, the exact origin of EGJ tumors can sometimes be hard to define, which complicates the choice between gastrectomy and esophagectomy [28].

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