Overview on Gastric Cancer

Chapter 1

Surgical Management of Esophagogastric Junction Tumours

Fernández MC, MD[1]*; Barrios ME, MD[1]; López F, MD, PhD[2]; Martí R, MD, PhD[3]; Ortega J, MD, PhD[4]

[1]Staff surgeon. Upper GI and peritoneal oncology surgery unit.

[2]Chief of Upper GI and peritoneal oncology surgery unit.

[3]Staff surgeon. Upper GI and peritoneal oncology surgery unit.

[4]Chief of Department of General Surgery.

**Correspondence to: Fernández MC, MD, Staff surgeon. Upper GI and peritoneal oncology surgery unit.*

Email: ferlomo@gmail.com

Abstract

Management of tumours located at the esophagogastric junction remains a challenge for surgeons. These tumours can be managed as esophageal or gastric tumours and the available classifications are changing the therapeutic approach. The extent of surgery may vary depending on the stage of the tumour. There is a wide range of possibilities, from endoscopic resection to extended gastric and esophageal resection. Furthermore, the extent of lymphadenectomy is also controversial and different protocols are used in the East and West. Best neoadjuvant and adjuvant therapies remain unclear and are still being tested in an attempt to clarify which of them is the best option to improve the outcome of these patients. We discuss in this chapter the most recent published evidence and propose a management algorithm to treat this condition.

Keywords: Esophagogastric junction; Esophageal tumours; Gastric tumours; Siewert classification; esophagogastric junction tumours

Abbreviations: EGJ: esophagogastric junction; SCC: Squamous Cell Carcinoma; AC: Adenocarcinoma; EP: Epithelium; LN: Lymph Node; LVI: lymphovascular involvement; PG: Proximal gastrectomy; CRM: Circumferential Resection Margin.

Citation: Fernández MC, MD, (2020) Overview on Gastric Cancer, Vol. 4, Chapter 1, pp. 1-22.

1. Introduction

Tumour location is essential when determining the treatment strategy for esophagogastric junction (EGJ) cancer. Although an appropriate classification may help to choose the surgical approach and produce comparable results from different institutions, the different classifications and options of treatment make it difficult to standardize a surgical protocol for EGJ tumours.. We discuss in this chapter the most relevant classifications, available surgical techniques and current evidence in lymphadenectomy extension for EGJ cancer.

2. Definition

Considering an EGJ tumour as gastric or esophageal cancer for management remains controversial [1]. Squamous cell carcinoma developed in EGJ region is unanimously treated as esophageal cancer. For EGJ adenocarcinoma, Siewert classification has been widely used [2]:

- Type I (adenocarcinoma of the distal esophagus), tumours with an epicenter located more than 1 cm above the EGJ

- Type II (true cardia cancer), tumours with an epicenter located within 1 cm oral and 2 cm aboral from the EGJ

- Type III (subcardial cancer), tumours with an epicenter located below 2 cm from the EGJ

In the Japanese Classification of Gastric Carcinoma, junctional cancer has been defined as cancer (adenocarcinoma or squamous cell carcinoma) with its center located 2 cm within the esophagogastric junction [3]. This definition is based on Nishi´s classification which defines five types of EGJ cancer with 40 mm or less in dimension and an epicenter within 2 cm proximal or distal to the EGJ, irrespective of the histological type. The “E-G” terms of “E,” “EG,” “E=G,” “GE” and “G” were used to describe the subtype according to the epicenter location at the rostral and caudal portions of the EGJ [4] (**Table 1**).

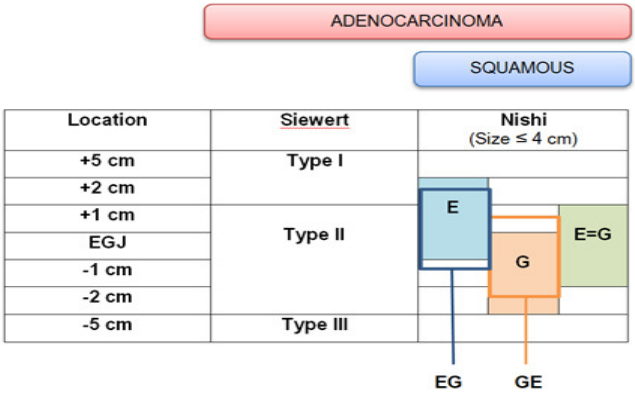

Table 1: Comparison between Siewert and Nishi´s classifications.

Among clinical implications of Siewert classification is the management of Siewert type I and III tumours like esophageal and gastric cancers, respectively. However, in 7th AJCC TNM classification, both Siewert type II and III tumours were classified as esophageal cancer [5]. Currently, in 8th version, type III was changed to gastric cancer classification, while type II still remains in the esophageal classification: Cancers involving the EGJ whose epicenter is within the proximal 2 cm of the cardia (Siewert types I/II) have to be staged as esophageal. Cancers whose epicenter is more than 2 cm distal from the EGJ will be staged using the stomach cancer TNM and stage even if the EGJ is involved [6].

3. Multimodal Treatments

Multimodal treatments have been recommended against locally advanced EGJ cancer since recurrence, especially systemic recurrence, is commonly observed even when curative surgery is performed[7]. Several multimodality strategies such as preoperative chemotherapy or chemoradiotherapy, perioperative chemotherapy, postoperative chemoradiotherapy and adjuvant chemotherapy have been investigated, but the lack of studies focused on EGJ cancer exclusively and the different results between countries make controversial the current therapies for EGJ tumours [8].

The role of neoadjuvant chemoradiation therapy has been the subject of debate for numerous decades. In some randomized trials, no survival benefit could be shown, and some meta-analyses suggest a survival benefit of neoadjuvant chemoradiotherapy, occasionally at the cost of increased postoperative morbidity and mortality [9].

503 patients were randomized in the MAGIC trial (26% of them were EGJ tumours) to receive 3 cycles of epirubicin, cisplatin, and 5-fluorouracil (ECF) before and after surgery or surgery alone. This trial demonstrated a survival benefit with the use of perioperative chemotherapy, with an improvement of 13% in the 5-year survival rate and an estimated 25% reduction in the risk of death [10].Therefore, perioperative chemotherapy became a standard choice for patients with EGJ cancer.

Later, a phase II trial (n=300) between FLOT (docetaxel, oxaliplatin, leucovorin, 5FU) versus MAGIC regimen determined that the pathological remission was significantly better and the rate of curative resections was higher with FLOT regimen [11]. Also, superior outcomes with FLOT compared to epirubicin, cisplatin, and fluorouracil/capecitabine (ECF/ECX) were noted in the 3-year overall survival (OS) (57% versus 48%) in the FLOT4 trial [12]. However, FLOT could result a toxic regimen and is not recommended for every patient.

The CROSS trial (carboplatin and paclitaxel plus 41.4 Gy of radiation followed by surgery versus surgery alone) showed a significantly higher OS in the chemoradiotherapy and surgery arm than in the surgery alone group (49.4 versus 24.0 months; $p = 0.003$) for

patients with adenocarcinoma or squamous cell carcinoma of the esophagus and EGJ tumours. Furthermore, patients treated with neoadjuvant chemoradiotherapy followed by surgery had a 34% lower risk of death during follow-up [9]. Shapiro et al further confirmed the survival benefits of chemoradiotherapy including 366 patients (75% with EGJ adenocarcinoma) and in their subgroup analysis demonstrated greater benefit for patients with squamous cell carcinoma [13].

Given the different results between studies, we could not conclude which is the best treatment approach in relation to chemotherapy or chemoradiotherapy [14]. Although, an attempt to determine which is the best perioperative treatment strategy is being made with a multicenter fase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286) [15]. This is an ongoing investigation and the results are still pending.

Ronellenfitsch et al analysed 14 trials (2,422 patients) evaluating surgery versus preoperative chemotherapy or chemoradiotherapy and showed a significant survival benefit for preoperative treatment over surgery alone and a 5-year absolute overall survival gain of 9% [16]. Recent meta-analyses award superior survival to neoadjuvant chemoradiotherapy followed by surgery as treatment of resectable esophageal cancer and EGJ cancer, although it comes with significantly increased perioperative mortality [17,18]. In addition, the role of chemotherapy solely in a neoadjuvant setting is described as questionable and it should be consolidated with adjuvant chemotherapy after definitive surgery [17].

In addition to different chemotherapy agents, targeted drugs are being studied to determine if they can help treat patients with gastric and EGJ cancer.The only standard targeted drug for EGJ cancer is the HER2 antibody: Trastuzumab. The FLOT study group confirmed the benefits of trastuzumab when added to the FLOT protocol in the HER-FLOT trial [19]. Several ongoing trials, such as the European Organisation for Research and Treatment of Cancer (EORTC) INNOVATION study are evaluating the effects of administering pertuzumab in addition to trastuzumab in HER2-positive patients in the curative and perioperative context [20].

Previous studies have shown positive results of ramucirumab (binds to VEGF-R2 receptor and inhibits further ligand binding) as a second-line treatment in patients with EGJ cancer [21,22]. Also, ramucirumab is being investigated as a second-line treatment agent in addition to perioperative FLOT in patients with gastric and EGJ cancers [14].

Currently, in most of Europe and the USA, preoperative chemoradiation is the standard practice for Siewert types I and II tumours. Siewert type III tumours are treated either with perioperative MAGIC/FLOT type chemotherapy or postoperative chemo-radiation [23]. There is little agreement on the optimal multimodality therapy, and practices vary across the world. Several ongoing studies will help to answer how to choose multimodality therapy for EGJ carcinoma (**Table 2**).

Table 2: Ongoing randomized controlled trials on multimodal treatments for resectable EGJ cancer.

Trial	n	Arms	Hypothesis	Target	Endpoint
ESOPEC	n=438	FLOT vs CROSS	Perioperative chemotherapy improves OS compared to neoadjuvant chemoradiation	EGJ AC	OS
TOPGEAR	n=620	Perioperative ECF/ ECX/EOX/FLOT vs neoadjuvant ECF/ ECX/EOX/FLOT+45 Gy	Adding preoperative chemoradiation to perioperative chemotherapy will improve OS	Gastric and EGJ AC	OS/Safety and feasibility of RT
PREACT	n=682	SOX (S-1 + oxaliplatin) plus 45 Gy vs perioperative SOX	Preoperative chemoradiation could improve survival compared to preoperative chemotherapy	Locally advanced gastric cancer or EGJ AC	3-year DFS
INNOVATION	n=220 (3arms)	Perioperative ECF/ECX vs XP/ CF+trastuzumab vs XP/CF+trastuzumab+ pertuzumab	Increase in major pathological response rate with both trastuzumab and pertuzumab	Gastric and EGJ AC (overexpressing HER2)	Major pathological response rate/ R0, locoregional and distant failure
PETRARCA	n=100 (2arms)	Perioperative FLOT vs perioperative FLOT/trastuzumab/ pertuzumab	Efficacy and safety of Herceptin and pertuzumab in combination with FLOT in the perioperative treatment	Locally advanced EG AC (overexpressing HER2)	Pathological response rates
RAMSES/ FLOT7	n=150 (2arms)	Perioperative ramucirumab+FLOT vs perioperative FLOT	Efficacy and safety of ramucirumab in combination with FLOT in the perioperative treatment of resectable adenocarcinoma of the stomach or EGJ.	Locally advanced resectable adenocarcinoma of stomach or EGJ	Pathological response rates/ OS
RAINFALL	n=675	XP+ramucirumab vs XP	Efficacy of ramucirumab, in combination with capecitabine and cisplatin compared to capecitabine and cisplatin alone	Metastatic gastric or EG AC	PFS

EGJ: Esophagogastric Junction; AC: Adenocarcinoma; OS: Overall Survival; DFS: Disease-Free Survival; EG: Esophagogastric; PFS: Progression-Free Survival

4. Surgical Options

The main goal for curative-intent surgery is to choose the best approach, which allow removing en bloc the primary tumour and the lymph nodes involved. Resection with negative margin is the main prognostic factor (R0 resection) and should dictate the choice of surgical approach.

4.1. Early carcinoma

Early or superficial lesions, whose invasion is limited to the mucosa or the submucosa, are categorized as in-situ cancer (Tis: M1 or EP, intraepithelial cancer) and T1 tumour. Furthermore, T1 cancers divided into T1a and T1b subcategories, depending on the depth of invasion. T1a cancers are further subclassified into M2 or LPM, cancer with invasion into the lamina propria mucosae; and M3 or MM, cancer reaching the muscularis mucosae. T1b tumors are divided into three categories: SM1, cancer with invasion into the superficial one third of the submucosa; SM2, cancer with invasion into the middle third of the submucosa; and SM3, cancer with invasion into the lower third of submucosa (**Figure 2**). For lesions involving muscularis mucosa only, the rate of lymph node metastasis is about 9.3%, but when the depth of invasion reaches the submucosal layer, the rate of metastasis can be higher [24].

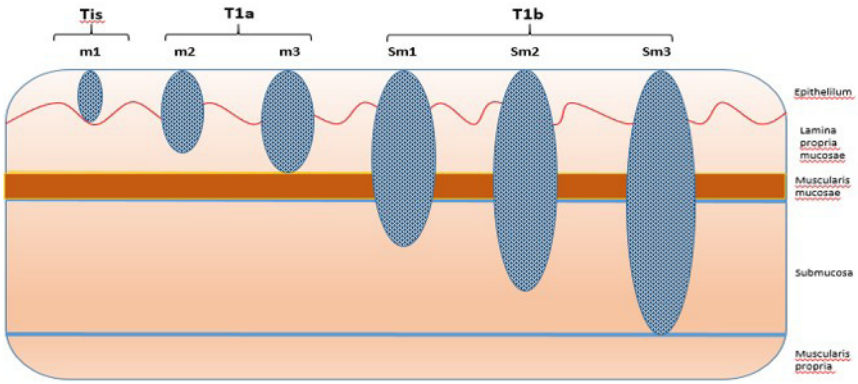

Figure 1: Classification of early tumours according to the depth of invasion

4.1.1. Endoscopic treatment

-Squamous cell carcinoma (SCC)

Frequency of LN metastasis in ESCC differs from EAC. Endoscopic therapy is recommended for M1 and M2 lesions with no lymphovascular invasion, while SM2 and SM3 tumours should not be resected endoscopically. For well-differentiated M3 and SM1 (up to 200 μm) cancers without lymphovascular invasion, endoscopic therapy can be employed but it is generally investigational and should be selected with care [25].

-Adenocarcinoma (AC)

Tumour size >3 cm, poor differentiation, and the presence of lymphovascular involvement (LVI) are risk factors for lymph node metastases. The European Society of Gastrointestinal Endoscopy recommends endoscopic resection for patients with T1a or low risk SM1 (less than 500 μm invasion, well or moderate differentiation, and no LVI) [26]. NCCN guideline recommends endoscopic resection for T1a or superficial pT1b tumour with no LVI and no poor differentiation [27].

4.1.2. Limited resections

For preoperative patients with T1 tumours and with no evidence of lymph node metastasis, a limited resection of the proximal stomach, cardia, and distal esophagus permits a complete EGJ (SCC or AC) tumour resection, adequate lymphadenectomy, and excellent functional results. In early EGJ tumours, limited resections will be an option when endoscopic treatment is not indicated or when after endoscopic treatment the final pathologic evaluation requires surgery as a next step [28].

In selected cases of T2 AC tumours without lymph node metastasis or other risk factors as: grading G3, G4, diffuse type of Lauren subtype or poorly cohesive carcinoma a limited resection can be considered [29].

For patients with proximal esophagogastric cancer with tumours unfit for endoscopic resection, total gastrectomy was the most commonly chosen surgical procedure for radical treatment. Since total gastrectomy has many adverse consequences, especially in hematological and nutritional status [30] some research groups and surgeons have suggested the proximal gastrectomy (PG) as an alternative to total gastrectomy for proximal esophagogastric cancer [31].

PG has demonstrated its oncological safety for early EGJ tumours and long-term OS is similar when comparing PG and total gastrectomy [32-34]. In fact, lymph node metastasis along the lower part of the stomach is not observed in proximal gastric cancer confined to the muscularis propria and it usually metastasizes to LN stations 2, 3, and 7 [35,36]. Meanwhile, PG has been associated with severe reflux esophagitis and anastomotic stenosis as the most common factors that limit the application of this surgical technique.

To resolve this issue different types of reconstruction were devised (**Figure 1**):

– Direct esophagogastrostomy or esophagogastrostomy but with anti-refux anastomosis such as the double-fap technique.

– Merendino procedure with jejunal interposition between esophagus and stomach

– Double tract reconstruction with Roux-en-Y esophagojejunostomy, gastro-jejunostomy and jejunojejunostomy

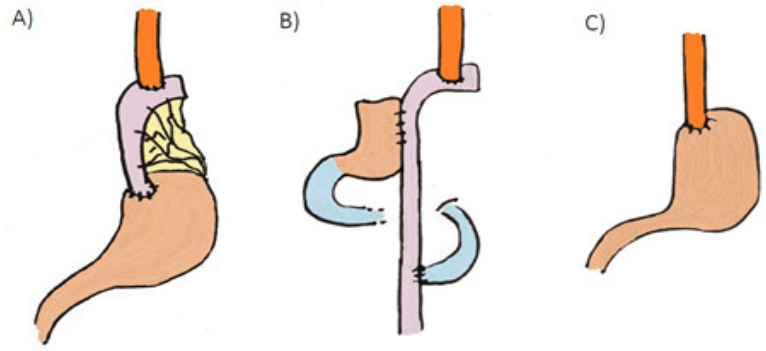

Figure 1: Types of reconstructions after limited resection of EGJ tumours: A) Merendino B) double tract C) esophago-gastrostomy.

Direct esophagogastrostomy presents high rates of serious gastroesophageal reflux. Modified procedures have been reported to solve this problem, including reverse double stapling, lower esophageal sphincter preserving, gastric tube, gastropexy, fundoplication and acute angle esophagogastrostomy among others. A novel procedure is the laparoscopic esophagogastrostomy "open-door" technique in which after esophagogastrostomy a double seromuscular flap is created to cover the anastomosis.Only one anastomosis is needed and the preliminary data suggest a very low incidence of reflux esophagitis [37].

According to Xiao et al, double-tract reconstruction approach is recommended over traditional Roux-en-Y esophagojejunostomy for Siewert types II and III tumours. Although both seem to show similar rates of tumour recurrence, metastasis and long-term survival, double-tract approach considerably improves the near-term quality of life, especially in terms of early recovery and decreased reflux esophagitis [38].

In a metanalysis conducted by Li et al, 592 patients with early gastric cancer subject either to proximal gastrectomy with double-tract reconstruction or total gastrectomy were compared. This study showed that proximal gastrectomy was a both safe and feasible procedure, and did not increase the incidences of reflux esophagitis and anastomotic stenosis, compared to total gastrectomy. Additionally, none of the included studies showed worse hematological and nutritional status for double-tract reconstruction compared with total gastrectomy, while maintaining similar oncological outcomes [39].

Nomura et al comparing laparoscopic jejunal interposition and laparoscopic double-tract against laparoscopic total gastrectomy, similarly found that laparoscopic jejunal interposition and laparoscopic double-tract almost completely maintain the preoperative gradual intestinal absorption and achieve a better postoperative quality of life as function-preserving procedures than laparoscopic total gastrectomy [40].

Moreover, 4 anti-reflux methods for proximal gastrectomy (jejunal interposition,

jejunal pouch interposition, double tract jejunal interposition, and tube-like stomach esophagogastrostomy) were the object of a systematic rewiew [41]. All demonstrated to be excellent in preventing reflux, which is the major cause of decrease in quality of life for patients after proximal gastrectomy. On the other hand, the anti-reflux methods were found to have increased incidence of stenosis and residual food.

4.2. Advanced carcinoma

Advanced tumours include those whose invasion extends into or beyond the muscularis propia irrespective of the presence of regional lymph node metastases (T2–T4 tumours).

4.2.1. Prognostic factors related to surgery

R0 resection is one of the most important factors associated with long-term survival. Incomplete resection (R1 or R2) has showed a decreased 5-year survival [42]. Good quality surgical resection for EGJ carcinoma should aim to provide optimal longitudinal resection margins (proximal and distal), circumferential resection margin and removal of all lymph node stations at risk of metastasis.

4.2.1.1. Longitudinal resection margins

For squamous cell carcinoma was reported that the anastomotic recurrence rate was 20%, 8% and 0% when the resection margin was less than 5 cm, between 5 and 10 cm and more than 10 cm, respectively [43]. For EGJ adenocarcinoma there are several recommendations for oral margin from 5 to 12 cm [44-46] but in general the oral safety margin at the esophagus should be at least 2 cm on the extended fresh specimen, otherwise the prognosis is significantly inferior [47]. The distal resection margin for EGJ tumours of 4–6 cm is reported as safe for all Siewert types by several authors [48,49].

4.2.1.2. Circumferential resection margin (CRM)

CRM is associated with a poor prognosis (50,51). The College of American Pathologists defines the CRM as positive if tumour cells are present at the resection margin, whereas the Royal College of Pathologists label CRM as positive if the tumour cells reach to within 1 mm of the CRM (52). A meta-analysis showed that patients are better stratified for RCP definition (53). The significance of CRM has been questioned over other more potent prognostic factors such as nodal status, especially after neoadjuvant therapy (54-56).

4.2.1.3. Node spread

Lymph node metastasis is recognized as a major prognostic factor in EGJ tumours and is predictive of loco-regional or distant recurrence and survival then it involve an important issue in the surgical approach of these patients. The lymphatic drainage of these tumours will

be discussed below. The recommendations for the minimum number of nodes to be resected are different depending on the guidelines, but in general at least 15 nodes need to be resected [27]. Several authors defend a more extended lymphadenectomy with an increased number of resected nodes until 30 [57] to improve prognosis. The reason why increasing the number of resected nodes reflects on survival is not fully understood. However, a possible explanation is the elimination of micrometastases. A meta-analysis on esophageal and EGJ cancer showed that occult lymph node metastasis is a prognostic factor in these patients [58]. Hence, the probability to eliminate micrometastases could explain the survival advantage with extended lymphadenectomy.

4.2.2. Surgical approach based on Siewert type

4.2.2.1. Siewert I

These tumours should be treated as esophageal and then esophagectomy with en bloc removal of esophagus and adjacent lymph nodes are essential to a radical resection. Different surgical approaches including minimally invasive options are summarized in **Figure 1**.

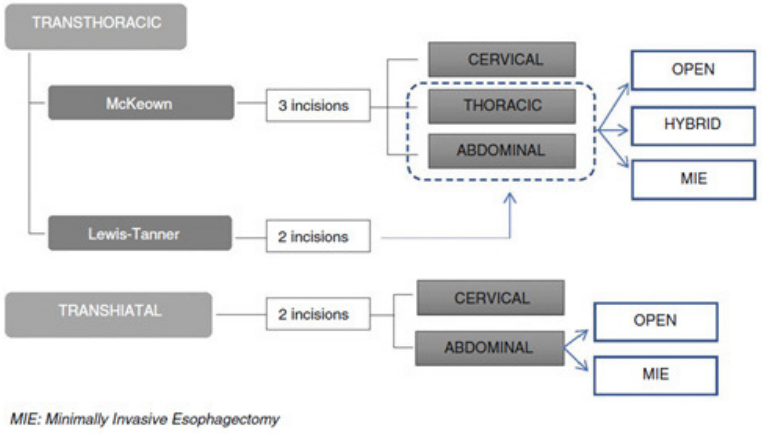

Figure 2: Surgical approaches for esophagectomy

The transhiatal approach is associated with a reduced postoperative morbidity with minor pulmonary complications rates [59,60]. However, other studies reported differences between these two approaches in morbidity and mortality but they were not statistically significant [61]. In respect to survival, Dutch HIVEX-trial which compared transhiatal vs transthoracic esophagectomy found differences in survival rates between these two approaches for Siewert I tumours, being the survival rates after transthoracic esophagectomy higher (51% versus 37%; $p = 0.33$) [62]. Recently, a large cohort study described that no differences in overall and disease-free survival were found between transhiatal and transthoracic approach for Siewert I tumours [63].

Regardless of the approach for esophagectomy, minimally invasive esophagectomy avoiding thoracotomy and/or laparotomy has showed to reduce postoperative complications and without compromising oncological outcomes [64,65]. The TIME multicentre trial compared

open and minimally invasive esophagectomy and pulmonary complications rate was lower in the minimally invasive group (34% versus 12%; p = 0.005) [66]. After 1-year follow-up, quality of life was assessed in the same cohort of patients, and a better quality of life was related to minimally invasive esophagectomy [67].

For distal esophageal tumours as Siewert I type, Lewis-Tanner and McKeown procedures are widely used. A prospective multi-centered trial showed that Ivor Lewis esophagectomies were associated with decreased perioperative complications and 90-day mortality [68]. However, a recent meta-analysis showed that Ivor Lewis technique was associated with improved outcomes in terms of anastomotic leak or stricture, vocal cord injury, pulmonary complications, blood loss and duration of hospital stay, but both procedures had similar rates of 30-day and 90-day mortality, severe anastomotic leak and oncologic outcomes [69].

4.2.2.2. Siewert II

The treatment of these tumours remains controversial. The literature concerning surgical results of Siewert II is not very conclusive on the ideal type of surgery. The different options in this type of tumours are a subtotal esophageal and proximal gastric resection with gastric pull-up or a distal esophageal resection with total gastrectomy and esophagojejunostomy. A recent web-based worldwide questionnaire showed that most of surgeons prefer an extended gastrectomy for Siewert II tumours [70].

Siewert II cancers often show significant esophageal invasion and 5 cm clear proximal margins are requested for these tumours. Transthoracic or transhiatal esophagectomy can obtain long longitudinal margins but achieving this length with gastrectomy can be more limited. Furthermore, esophagectomy for Siewert II tumours has shown a reduced risk of circumferential resection margin involvement (11% versus 29%; p = 0.025) and more complete mediastinal nodal dissection [71]. The incidence of R1 resection has been described higher with extended gastrectomy than with esophagectomy (38% versus 7%, p = 0.04) [49]. In fact, NCCN has also recommended similar surgical procedures for Siewert type 1 and 2 adenocarcinoma [27].

However, several publications have compared the short- and long-term outcomes between the esophagectomy and gastrectomy for these tumours; no significant differences in postoperative morbidity and mortality were observed and both procedures presented similar rates of radical resection margins, number of lymph nodes removed and 5-year mortality [72-74]. Siewert group recommends ‘an extended total gastrectomy including wide splitting of the diaphragmatic hiatus, transhiatal resection of the distal esophagus, and en bloc lymphadenectomy of the lower posterior mediastinum, in addition to a formal abdominal D2 lymphadenectomy’ for the treatment of the Siewert II tumours (75).

A Japanese randomized trial of left thoracoabdominal esophagectomy versus a

transhiatally extended total gastrectomy for Siewert type 2 and 3 tumours with less than 3 cm esophageal involvement aimed to compared these two approaches and the trial was closed prematurely because the probability of the left thoracoabdominal approach having a significantly better overall survival than the transabdominal approach was very low and with an increased morbidity [76]. There were no differences in the 10-year overall survival rate (24% versus 37%, p = 0.06) in the two operation groups, respectively, and subgroup analysis showed that survival was also similar in the two Siewert types of tumours (II and III) (77). Japanese Gastric Cancer Association recommends to treat Siewert type II tumours with up to 3 cm esophageal involvement, with a transhiatally extended total gastrectomy and reserve the transthoracic approach for tumours with a more extensive involvement of the esophagus (3).

Then, several factors must be considered to select the best approach in these tumours: extent of esophageal involvement (less or more than 3 cm), presence of mediastinal nodes, patient fitness to undergo a transthoracic procedure, and the experience of the surgical team to carry out adequate mediastinal lymphadenectomy through the transhiatal route.

Recently, Hölscher and Law insisted on the individualized treatment of Siewert type II adenocarcinoma of the EGJ considering the different types of surgical resection and possibilities of reconstruction and they expose the factors in favour of every surgical approach (**Table 3**) (78):

Table 3: Criteria which are important for decision making about the best surgical procedure for Siewert II tumours treatment.

ABDOMINO-TRANSHIATAL APPROACH AND EXTENDED TOTAL GASTRECTOMY	TRANSTHORACIC APPROACH AND ESOPHAGECTOMY
Small superficial tumour cT1 (cT2) but diffuse type of Lauren, Grading G3, G4, L1, V1 or poorly cohesive carcinoma	Large tumour with substantial esophageal infltration
Normal esophagus	Edematous and unhealthy esophagus
Good exposure at the esophageal hiatus	Bad exposure at the esophageal hiatus
No suspicion of mediastinal lymph node metastasis	Suspicion of mediastinal lymph node metastasis
Good circumstances for reconstruction by jejunal Roux en-Y loop	Normal stomach with good prerequisites for reconstruction
Elderly patients with increased risk	

4.2.2.3. Siewert III

The typical surgical approach consists of total gastrectomy and distal esophagectomy. Based on previous studies of Siewert's classification there has been wide consensus on the surgical treatment for type III tumours with transhiatal approach especially when there is an esophageal invasion of 3 cm or less [79,80]. The JCOG9502 study reported no benefit for lower mediastinal lymph node dissection through a left thoracoabdominal approach in patients with ≤ 3 cm esophageal invasion. Thus, lower-mediastinal lymph node dissection through a right or left thoracic approach would be unnecessary for these patients [76].

In Japan the present surgical strategy for tumours involving the EGJ is a transhiatal extended proximal gastrectomy (with lower mediastinum lymphadenectomy) for esophageal invasion of 3 cm or less and distal invasion not exceeding the upper third of the stomach. Extended transhiatal total gastrectomy (with lower mediastinal lymphadenectomy) is preferred when distal invasion exceeds the upper third of the stomach [81].

Zhao et al found in their study that transhiatal proximal gastrectomy with extended periproximal lymphadenectomy showed an advantage in terms of survival compared with total gastrectomy with complete perigastric lymphadenectomy for patients with EGJ tumours ≤ 30 mm in diameter and in Stage IA-IIIA. However, for more advanced and larger esophagogastric junction cancers (Stage IIIB), no survival benefit was demonstrated [82].

No standard surgical approach has been defined for tumours with esophageal invasion of > 3 cm, but in order to achieve adequate margins, transthoracic approach could become necessary.

Reconstruction of the digestive tract can be achieved with a Roux-en-Y esophagojejunal anastomosis, which can be performed via an unique abdominal approach if esophageal invasion is inferior to 2 cm or otherwise with a transthoracic approach [83].

4.2.3. Lymphadenectomy

Lymph node metastasis is a prognostic factor and the main goal of lymph node dissection is to optimize tumour staging, to reduce recurrence and improve survival. Lymphographic studies showed that the main lymphatic pathways originating from the lower esophagus (type I tumours) advance both up into the mediastinum and down to the celiac axis. Lymphatics from the gastric cardia and subcardial region (type II and III tumours) preferentially spread to the celiac axis [84]. These anatomical features should be considered for the extent of the lymphadenectomy and it will be discussed in detail for the different tumour types.

4.2.3.1. Siewert I

Type I tumours do predominantly metastasize into the paraesophageal nodes in the lower mediastinum and into the upper abdominal lymph nodes. Mediastinal nodes are frequently affected accounting for around 45 % (17–77 %) of cases [85]. The presence of cervical affected nodes has also been described with inclusive 26%-37% of positive cervicothoracic nodes [86]. However, a three-field lymphadenectomy is associated with a higher morbidity and is not related to an improved prognosis [87]. Recommendations for surgical treatment of Siewert I tumours expose that an extended two-field lymphadenectomy should be done [88]. The fields to dissect are those with frequent involvement: abdominal paracardial nodes (stations 1 and 2), together with lesser curvature (station 3) left gastric artery nodes (station 7) and coeliac trunk

nodes (stations 9). Hence, a D1+ abdominal dissection is indicated.

Mid-and-lower mediastinal nodes are frequently involved; therefore, a standard mediastinal dissection is indicated. However, the impact of extended lymphadenectomy on survival has not been proven [62].

4.2.3.2. Siewert II

Studies describe 22% of patients with positive mediastinal lymph nodes in Siewert II tumours and consequently with lower survival ($p = 0.009$) than those without mediastinal lymph nodes affected [89]. A comparative study in 2015 between esophagectomy and gastrectomy in patients with Siewert II tumours did not show differences in OS at 5 years ($p = 0.606$) and DFS ($p = 0.251$) but it described 11% of positive lymph nodes in the upper mediastinum [90]. An increased incidence of mediastinal positive nodes when invasion of the esophagus is more than 1 cm has been reported [91]. Furthermore, upper and middle mediastinal nodes are significantly more probably affected when esophageal invasion is >3 cm, and inferior mediastinal nodes are significantly more probably affected when esophageal invasion is >2 cm [92].

Recommendations for surgical treatment of Siewert II tumours are: in the event of a transhiatal approach, two-field lymphadenectomy should be done via the hiatus with a lower mediastinectomy. For a transthoracic approach, extended two-field lymphadenectomy should be done.

The risk of nodal metastases in Siewert type II is similar to type I. Abdominal paracardial nodes (stations 1 and 2), together with lesser curvature (station 3), left gastric artery nodes (station 7), coeliac trunk (station 9), and splenic artery nodes (station 11) should always be included in the field of dissection. Hence, a D2 abdominal dissection is recommended. Mid-and-lower mediastinal nodes (stations 108 and 110, respectively) are frequently involved; therefore, a standard mediastinal dissection is indicated although with the transhiatal approach, lymphadenectomy is more limited.

Although Japanese guidelines include in D2 lymphadenectomy the para-aortic nodes in tumours invading the esophagus, it remains a subject of active research. Two trials conducted in Japan have not found any survival advantage in routinely adding para-aortic node dissection to a D2 lymphadenectomy [93,94].

Splenectomy is not necessary to perform a D2 dissection but it is necessary to obtain an R0 in case of infiltration.

Special aspects of lymphadenectomy in early-stages:

Abdominal nodes will be removed entirely by D2 lymphadenectomy except in cases

with limited gastric resection when a D1-D1+ lymphadenectomy can be an option. The rate of lymph node metastasis in the omentum is very low and therefore total omentectomy is avoided especially in the T1 or T2 category [3].

In 2012–2013, the Japanese Gastric Cancer Association and Japan Esophageal Society conducted a nationwide surveillance of junctional cancer of ≤4 cm diameter, and retrospective data of 3,177 patients operated on between 2001 and 2010 were collected from 273 institutions [3]. Among the conclusions of this study we find:

- Nodes along the distal portion of the stomach (4, 5, 6) were much less often metastatic in any stages, though those were dissected in most cases. Survival analysis failed to show the benefit of those dissections.

- Lower mediastinal LN dissection might contribute to improve survival for the EGJ cancer with esophagus-predominance or esophageal invasion.

An algorithm for the extent of lymphadenectomy based on the tumour location, histology and T-categories was constructed and we summarized it in the next tables:

cT1 (size < 4 cm)		
E, EG, E=G 2 cm ← EGJ → 1 cm		GE, G 0.5 cm ← EGJ → 2 cm
SCC	AC	AC
1, 2, 3, 7	1, 2, 3, 7, 9	1, 2, 3, 7
19, 20	19, 20	19, 20
Lower + middle mediastinal	Lower mediastinal	

≥cT2 (size < 4 cm)		
E, EG, E=G 2 cm ← EGJ → 1 cm		GE, G 0.5 cm ← EGJ → 2 cm
SCC	AC	AC
1, 2, 3, 7, 8a, 9, 11p	1, 2, 3, 7, 8a, 9, 11p, 11d	1, 2, 3, 7, 8a, 9, 11p, 11d
19, 20	19, 20	19, 20
Lower + middle + upper mediastinal	Lower mediastinal	

4.2.3.3. Siewert III

The nodal spread of Siewert type III tumours is mostly confined to the abdomen. In terms of lymphadenectomy, as for gastric cancers, D2 dissection without distal splenopancreatectomy is recommended.

Paracardial (stations 1 and 2), lesser curvature (station 3), left gastric artery nodes (station 7), coeliac trunk, common hepatic artery, splenic artery, and infrapyloric nodes (stations 9,

8a, 11, and 6) are frequently involved. Para-aortic nodes are reported in around 20–30 % of advanced patients. Like for type II, a D3 lymphadenectomy might be proposed for advanced cases [94].

Like in Siewert II, splenic hilar nodes might be involved, but no survival advantage has been demonstrated by adding splenectomy when performing D2 lymphadenectomy. However, after reviewing their series retrospectively, Hosoda et al recommend that these patients undergo dissection of the lower mediastinal lymph nodes, and those with invasion of the greater curvature should undergo dissection of the splenic hilar lymph nodes [95].

5. Conclusions and Future Perspectives

There are many controversial aspects in EGJ tumours management. The optimal type of lymphadenectomy is difficult to standardize because of the lack of evidence. The ongoing TIGER trial will help to determine the distribution of lymph node metastases in patients with resectable EGJ carcinoma in whom a transthoracic esophagectomy with a 2- or 3-field lymphadenectomy is performed. Best surgical approach is mainly based on tumour location and esophageal invasion but many other clinical and intraoperative factors influence the final decision. A current Japanese nationwide prospective trial for EGJ cancer is expected to lead to the standardization of surgical approaches for these tumours in the future. The question of best perioperative approach remains unanswered; results of ongoing studies addressing this question and new targeted therapies are awaited. Meanwhile, multidisciplinary approach is essential to optimize patient outcomes.

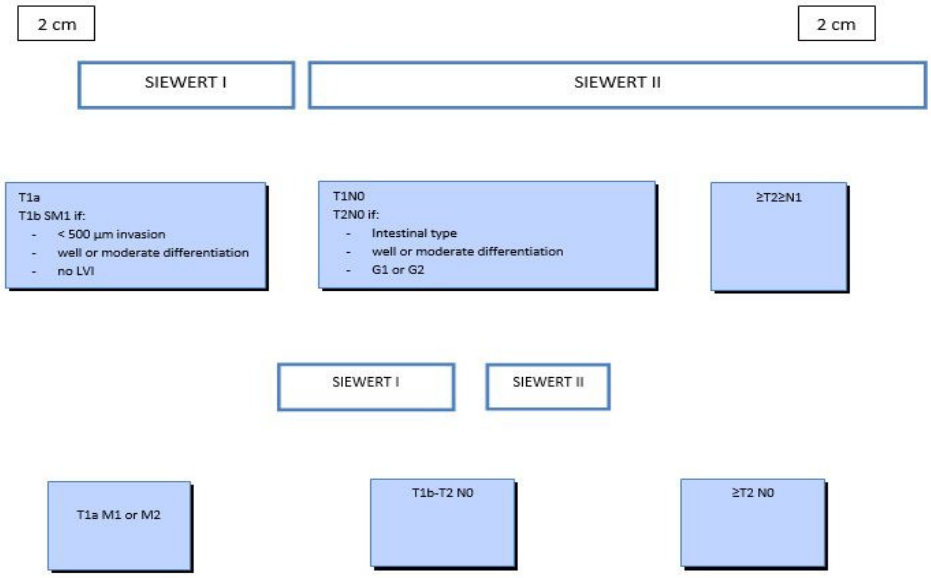

Figure 3: Clinical practice algorithm with the current definition of EGJ tumours of the 8th TNM classification in our institution.

6. References

1. Nobel T, Molena D. Surgical principles for optimal treatment of esophagogastric junction adenocarcinoma. Ann Gastroenterol Surg. 2019;3(4):390–395.

2. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg (1998) 85:1457–1459

3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (ver.5). Gastric Cancer. 2020.

4. Berlth F, Hoelscher AH. History of Esophagogastric Junction Cancer Treatment and Current Surgical Management in Western Countries. J Gastric Cancer. 2019;19:139-147.

5. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. Ann Surg Oncol. 2010;17:1721–4.

6. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Ann Cardiothorac Surg. 2017;6:119-130.

7. Gee DW, Rattner DW. Management of gastroesophageal tumours. Oncologist 2007;12:175–185.

8. Cheng J, Cai M, Shuai X, Gao J, Wang G, Tao K. Multimodal treatments for resectable esophagogastric junction cancer: a systematic review and network meta-analysis. Ther Adv Med Oncol. 2019;11:1758835919838963.

9. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.

10. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.

11. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-1708.

12. Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB, Meiler J et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO). J Clin Oncol 2017;35:4004.

13. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-1098

14. Goetze TO, Al-Batran S-E, Berlth F, Hoelscher AH. Multimodal Treatment Strategies in Esophagogastric Junction Cancer: a Western Perspective. J Gastric Cancer. 2019;19:148-156.

15. Hoeppner J, Lordick F, Brunner T, Glatz T, Bronsert P, Röthling N, Schmoor C, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer. 2016;16:503.

16. Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, Burmeister B, et al. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. Eur J Cancer. 2013; 49:3149-3158.

17. Kumar T, Pai E, Singh R, Neville JF, Pandey M. Neoadjuvant strategies in resectable carcinoma esophagus: a meta-analysis of randomized trials. World J Surg Oncol. 2020;18:59.

18. Zhao X, Ren Y, Hu Y, Cui N, Wang X, Cui Y. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or the gastroesophagealjunction: A meta-analysis based on clinical trials. PLoS One. 2018;13:e0202185.

19. Hofheinz R, zur Hausen G, Borchert K, Kretzschmar A, Ebert EP, Ettrich TJ, Koenigsmann M et al. Perioperative trastuzumab and pertuzumab in combination with FLOT versus FLOT alone for HER2 positive resectable esophagogastric adenocarcinoma: Petrarca—A phase II trial of the German AIO. J Clin Oncol 2017;35:TPS4133.

20. Lordick F. Integration of trastuzumab, with or without pertuzumab, into perioperative chemotherapy of HER2-positive stomach cancer: the INNOVATION Trial (EORTC-1203-GITCG). Oncol Res Treat 2016;39:153-154.

21. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39.

22. Kim TY, Yen CJ, Al-Batran SE, Ferry D, Gao L, Hsu Y, Cheng R et al. Exposure-response relationship of ramucirumab in East Asian patients from RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. Gastric Cancer 2018;21:276-284.

23. Aggelis V, Cunningham D, Lordick F, Smyth EC. Peri-operative Therapy for Operable Gastroesophageal Adenocarcinoma: Past, Present and Future. Ann Oncol. 2018;29:1377-1385.

24. Newton AD, et al. Surgical management of early-stage esophageal adenocarcinoma based on lymph node metastasis risk. Ann Surg Oncol. 2018;25:318–25.

25. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, Kawamura O, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 1. Esophagus. 2019;16:1–24.

26. Park CH, Yang DH, Kim JW, Kim JH, Kim JH, Min YW, et al. Clinical Practice Guideline for Endoscopic Resection of Early Gastrointestinal Cancer. Clin Endosc. 2020;53(2):142-166. doi:10.5946/ce.2020.032

27. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:855-883.

28. Stein HJ, Feith M, Mueller J, Werner M, Siewert JR. Limited resection for early adenocarcinoma in Barrett's esophagus. Ann Surg. 2000;232:733-742.

29. Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G, et al. Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer. 2019;22:1-9.

30. Masuzawa T, Takiguchi S, Hirao M, Imamura H, Kimura Y, Fujita J, Miyashiro I, et al. Comparison of perioperative and long-term outcomes of total and proximal gastrectomy for early gastric cancer: a multi-institutional retrospective study. World J Surg. 2014;38(5):1100-6.

31. Yoo CH, Sohn BH, Han WK, Pae WK. Long-term results of proximal and total gastrectomy for adenocarcinoma of the upper third of the stomach. Cancer Res Treat. 2004;36:50–5.

32. Ichikawa D, Komatsu S, Kubota T, Okamoto K, Shiozaki A, Fujiwara H, Otsuji E. Long-term outcomes of patients who underwent limited proximal gastrectomy. Gastric Cancer. 2014;17(1):141-5.

33. Nozaki I, Hato S, Kobatake T, Ohta K, Kubo Y, Kurita A. Long-term outcome after proximal gastrectomy with jejunal interposition for gastric cancer compared with total gastrectomy. World J Surg. 2013;37(3):558-64.

34. Zhao P, Xiao SM, Tang LC, Ding Z, Zhou X, Chen XD. Proximal gastrectomy with jejunal interposition and TGRY anastomosis for proximal gastric cancer. World J Gastroenterol. 2014; 20(25):8268-8273.

35. Kong SH, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. Reverse double-stapling end-to-end esophagogastrostomy in proximal gastrectomy. Dig Surg. 2010; 27(3):170-4.

36. Kitamura K, Yamaguchi T, Nishida S, Yamamoto K, Ichikawa D, Okamoto K, Taniguchi H, et al. The operative indications for proximal gastrectomy in patients with gastric cancer in the upper third of the stomach. Surg Today. 1997;27(11):993-8.

37. Hosoda K, Yamashita K, Moriya H, Mieno H, Ema A, Washio M, Watanabe M. Laparoscopically Assisted Proximal Gastrectomy with Esophagogastrostomy Using a Novel "Open-Door" Technique : LAPG with Novel Reconstruction. J Gastrointest Surg. 2017;21(7):1174-1180.

38. Xiao JW, Liu ZL, Ye PC, Luo YJ, Fu ZM, Zou Q, Wei SJ. Clinical comparison of antrum-preserving double tract reconstruction vs roux-en-Y reconstruction after gastrectomy for Siewert types IIand III adenocarcinoma of the esophagogastric junction. World J Gastroenterol 2015; 21(34):9999-10007.

39. Li S, Gu L, Shen Z, Mao D, Parikshit AK, Su H. A meta-analysis of comparison of proximal gastrectomy with double-tract reconstruction and total gastrectomy for proximal early gastric cancer. BMC Surgery. 2019;19:117.

40. Nomura E, Kayano H, Lee S W, Kawai M, Machida T, Yamamoto S, Nabeshima K, et al. Functional evaluations comparing the double-tract methodand the jejunal interposition method following laparoscopic proximal gastrectomy for gastric cancer: an investigation including laparoscopic total gastrectomy. Surg Today. 2019;49:38–48.

41. Wang S, Lin S, Wang H, Yang J, Yu P, Zhao Q, Li M. Reconstruction methods after radical proximal gastrectomy a systematic review. Medicine. 2018;97:11(e0121).

42. 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;15:751–64.

43. Tam PC, Siu KF, Cheung HC, Ma L, Wong J. Local recurrences after subtotal esophagectomy for squamous cell carcinoma. Ann Surg. 1987;205:189–94.

44. Migliore M, Rassl D, Criscione A. Longitudinal and circumferential resection margin in adenocarcinoma of distal esophagus and cardia. Future Oncol. 2014;10:891–901

45. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rsuch VW, Coit DG et al. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg. 2007;246:1–8.

46. Mariette C, Castel B, Balon JM, Van Seuningen I, Triboulet JP. Extent of oesophageal resection for adenocarcinoma of the oesophagogastric junction. Eur J Surg Oncol. 2003;29:588–93.

47. Mine S, Sano T, Hiki N, Yamada K, Kosuga T, Nunobe S, Yamaguchi T. Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. Br J Surg. 2013;100:1050–4.

48. DiMusto PD, Orringer MB. Transhiatal esophagectomy for distal and cardia cancers: implications of a positive gastric margin. Ann Thorac Surg. 2007;83(6):1993–1999.

49. Ito H, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ, Ashley SW et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg. 2004;199(6):880–886.

50. Wu J, Chen QX, Teng LS, Krasna MJ. Prognostic significance of positive circumferential resection margin in esophageal cancer: a systematic review and meta-analysis. Ann Thorac Surg. 2014;97:446–53.

51. Sagar PM, Johnston D, McMahon MJ, Dixon MF, Quirke P. Significance of circumferential resection margin

involvement after oesophagectomy for cancer. Br J Surg. 1993;80:1386–8.

52. Knight WRC, Zylstra J, Wulaningsih W, et al. Impact of incremental circumferential resection margin distance on overall survival and recurrence in oesophageal adenocarcinoma. BJS Open. 2018;2(4):229-237.

53. Chan DS, Reid TD, Howell I, Lewis WG. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. Br J Surg 2013; 100: 456–464

54. Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM. The prognostic value of circumferential resection margin involvement in oesophageal malignancy. Eur J Surg Oncol. 2006;32:413–9.

55. Mirnezami R, et al. Multivariate analysis of clinicopathological factors influencing survival following esophagectomy for cancer. Int J Surg. 2010;8:58–63.

56.Hulshoff JB, et al. Prognostic value of the circumferential resection margin in esophageal cancer patients after neoadjuvant chemoradiotherapy. Ann Surg Oncol. 2015;22:1301–9.

57. Rizk NP, Ishwaran H, Rice TW, Chen L, Schipper PH, Kesler A, Law S et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251(1):46–50.

58. McGuill MJ, Byrne P, Ravi N, Reynolds J. The prognostic impact of occult lymph node metastasis in cancer of the esophagus or esophago-gastric junction: systematic review and meta-analysis. Dis Esophagus. 2008;21(3):236–240.

59. Ott K, Bader FG, Lordick F, et al. Surgical factors influence the outcome after Ivor-Lewis esophagectomy with intrathoracic anastomosis for adenocarcinoma of the esophagogastric junction: a consecutive series of 240 patients at an exper ienced center. Ann Surg Oncol. 2009;16:1017–25.

60. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended Transthoracic Resection Compared With Limited Transhiatal Resection for Adenocarcinoma of the Esophagus. N Engl J Med 2002;347:1662-9

61. Rentz J, Bull D, Harpole D, Bailey S, Neumayer L, Pappas T, Krasnicka B, Henderson W, Daley J, Khuri S.Transthoracic versus transhiatal esophagectomy: a prospective study of 945 patients. J Thorac Cardiovasc Surg. 2003 May; 125(5):1114-20.

62. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 2007;246:992-1000.

63. Davies AR, Sandhu H, Pillai A, Sinha P, Mattsson F, Forshaw MJ, et al. Surgical resection strategy and the influence of radicality on outcomes inoesophageal cancer. Br J Surg. 2014;101:511–7.

64. Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol. 2016;14(1):304.

65. Wang Q, Wu Z, Zhan T, et al. Comparison of minimally invasive Ivor Lewis esophagectomy and left transthoracic esophagectomy in esophageal squamous cell carcinoma patients: a propensity score-matched analysis. BMC Cancer. 2019;19(1):500.

66. Biere SS, Maas KW, Bonavina L, et al. Traditional invasive vs. minimally invasive esophagectomy: a multi-center, randomized trial (TIME-trial). BMC Surg. 2011;11:2.

67. Maas KW, et al. Quality of life and late complications after minimally invasive compared to open esophagectomy: results of a randomized trial. World J Surg. 2015;39:1986–93.

68. Brown AM, Pucci MJ, Berger AC, Tatarian T, Evans NR, Rosato EL, et al. A standardized comparison of peri-operative complications after minimally invasive esophagectomy: Ivor Lewis versus McKeown. Surg Endosc. 2018;32(1):204–11

69. Deng J, Su Q, Ren Z, Wen J, Xue Z, Zhang L, et al. Comparison of short-term outcomes between minimally invasive McKeown and Ivor Lewis esophagectomy for esophageal or junctional cancer: a systematic review and meta-analysis. OncoTargets Ther. 2018;11:6057–69

70. Haverkamp L, Seesing MF, Ruurda JP, Boone J, V Hillegersberg R. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. Dis Esophagus. 2017;30(1):1–7.

71. Parry K, Haverkamp L, Bruijnen RCG et al (2014) Surgical treatment of adenocarcinomas of the gastro-esophageal junction. Ann Surg Oncol 22(2):597–603

72. Johansson J, Djerf P, Oberg S, et al. Two different surgical approaches in the treatment of adenocarcinoma at the gastroesophageal junction. World J Surg. 2008;32(6):1013–20.

73. Mariette C, Castel B, Toursel H, Fabre S, Balon JM, Triboulet JP. Surgical management of and long-term survival after adenocarcinoma of the cardia. Br J Surg. 2002;89(9):1156–63

74. Kauppila JH, Wahlin K, Lagergren J. Gastrectomy compared to oesophagectomy for Siewert II and III gastro-oesophageal junctional cancer in relation to resection margins, lymphadenectomy and survival. Sci Rep. 2017;7(1):17783.

75. Siewert JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg. 2000;232(3):353-361.

76. Sasako M, et al. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol. 2006;7:644–51

77. Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. Br J Surg. 2015;102(4):341–8.

78. Hölscher AH, Law S. Esophagogastric junction adenocarcinomas: individualization of resection with special considerations for Siewert type II, and Nishi types EG, E=G and GE cancers. Gastric Cancer. 2019;23:3-9.

79. Wei MT, Zhang YC, Deng XB et al. Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. World J Gastroenterol. 2014;20(29):10183–10192

80. Hosokawa Y, Kinoshita T, Konishi M et al. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. Ann Surg Oncol. 2012;19(2):677–683.

81. Kumamoto T, Kurahashi Y, Niwa H, Nakanishi Y, Okumura K, Ozawa R, Ishida Y, et al. True esophagogastric junction adenocarcinoma: background of its definition and current surgical trends. Surg Today 2019

82. Zhao B, Zhang Z, Mo D, Lu Y, Hu Y, Yu J, Liu H et al. Optimal Extent of Transhiatal Gastrectomy and Lymphadenectomy for the Stomach-Predominant Adenocarcinoma of Esophagogastric Junction: Retrospective Single-Institution Study in China. Front Oncol. 2018;8:639.

83. Yajima K, Kanda T, Kosugi S, et al. Intrathoracic esophagojejunostomy using OrVil™ for gastric adenocarcinoma involving the esophagus. World J Gastrointest Surg. 2014;6(12):235-240.

84. Aikou T, Shimazu H. Difference in main lymphatic pathways from the lower esophagus and gastric cardia. Jpn J Surg. 1989;19:290-295.

85. Pedrazzani C, de Manzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, Rampone B, Roviello F. Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. J Thorac Cardiovasc Surg. 2007;134:378–385.

86. Lerut T, Nafteux P, Moons J et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962–972.

87. Shang QX, Chen LQ, Hu WP, Deng HY, Yuan Y, Cai J. Three-field lymph node dissection in treating the esophageal cancer. J Thorac Dis. 2016;8(10):E1136-E1149.

88. Peyre CG, Hagen JA, DeMeester SR et al (2008a) The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 248(4):549–556

89. Lagarde SM, et al. Prospective analysis of patients with adenocarcinoma of the gastric cardia and lymph node metastasis in the proximal field of the chest. Br J Surg. 2005;92:1404–8.

90. Parry K, et al. Surgical treatment of adenocarcinomas of the gastro-esophageal junction. Ann Surg Oncol. 2015;22:597–603

91. Kakeji Y, Yamamoto M, Ito S et al (2012) Lymph node metastasis from cancer of the esophagogastric junction, and determination of the appropriate nodal dissection. Surg Today 42(4):351–358

92. Kurokawa Y, Hiki N, Yoshikawa T et al (2015) Mediastinal lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction. Surgery 157(3):551–555

93. Yonemura Y, et al. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. Int J Clin Oncol. 2008;13:132–7.

94. Sasako M, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359:453–62.

95. Hosoda K, Yamashita K, Moriya H, Mieno H, Watanabe M. Optimal treatment for Siewert type II and III adenocarcinoma of the esophagogastric junction: A retrospective cohort study with long-term follow-up. World J Gastroenterol 2017;23(15): 2723-2730.