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Esophago-Gastric Junction Carcinoma: State of the Art and Ongoing Trials in a Multimodal Approach

Short Communication

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Abstract

Clinical management of Esophago-Gastric Junction (EGJ) carcinoma represents a challenge for gastrointestinal multidisciplinary tumor boards because of the opportunity of multimodal and combined treatments. The evolution of the guidelines, also in view of the classifications that have progressively helped to discriminate the various disease subsets and considering the evidence from clinical trials, can be very complex. The aim of this study is to report the main evidence on which the current guidelines are based, with a special focus on the grey areas that still exist and on ongoing studies that may provide further useful elements for the clinical management of this type of patient.

Keywords: Esophago-gastric junction carcinoma; Multimodal approach; Tailored treatment; Mini-invasive approach; Preoperative chemo-radiotherapy

Background

Esophago-Gastric Junction (EGJ) carcinoma represents an anatomical site of neoplasia that, increasingly and progressively, is being considered autonomously from other neighboring sites (cranially esophageal neoplasms, caudally gastric) in terms of perspectives of treatment and clinical management [1]. From an anatomical and histopathological point of view, this site represents the boundary between esophagus and stomach i.e., the site where the esophageal squamous epithelium transitions from the esophageal squamous epithelium to a columnar epithelium of the cardia and stomach [2]. Siewert et colleagues provided a classification to define the individual subsets of this pathology [3] according to the position of the lesion at the endoscopy relative to the z-line. Siewert I tumors refers to the lesions of the distal esophagus (often associated with Barrett's esophagus) with epicenter located 1 to 5cm above the Z line. Siewert II tumors are limited to the cardial region proper, located within 1cm above and 2cm below the Z line. Siewert III tumors are sub-cardial presentations with epicenter located between 2 and 5cm below the Z line. Regarding staging, the 8th edition of the American Joint Committee on Cancer (AJCC) includes Sievert I and II tumors as afferent forms of the esophageal neoplasm classification while Sievert III tumors are staged following the stomach neoplasm classification [4]. In Western countries, adenocarcinoma histotype appears to be progressively increasing, while in Eastern Europe and Asia squamous forms remain the most common esophageal and junctional neoplasia [5].

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Clinical Management of EGJ: Main Guidelines and Evidence

Early Stage EGJ (cT1 cN0 cM0) and surgical management

Surgery represents the milestone of treatment of EGJ cancers. According to Siewert's classifications the principles of surgical treatment of EGJ tumors change. In Siewert type I and II cancers, the treatment is analogous to the surgical treatment of esophageal cancer; at the contrary, in Siewert type III tumors, the treatment is analogous to that of gastric cancers. Fundamental principle for an adequate surgical treatment is an adequate anesthesiologic evaluation of the patient and an accurate clinical-radiological staging of the neoplasm [6]. If pre-operative clinical staging is not sufficient, a laparoscopy should be performed to identify occult metastases (frequent in Siewert's type I and II cancers) or to perform a peritoneal cytology that, if positive, in absence of macroscopic peritoneal carcinomatosis, represents a poor prognostic factor in EGJ cancers [7]. In the context of the surgical management of EGJ cancers, an adequate lymphadenectomy is to be considered mandatory to guarantee an adequate anatomical-pathological staging of the neoplasm. The number of harvested lymph nodes has been shown to be an independent predictor of survival after esophagectomy and several analyses on large databases (SEER database [8], WECC database [9]) demonstrated that a greater extent of lymphadenectomy was associated with increased survival for all patients with node-positive cancers. According to these evidence, NCCN guidelines recommended the resection of at least 15 lymph nodes for patients with esophageal cancer also after preoperative therapy [10].

The intra-operative pathological examination of resection margins is mandatory and should be ever performed [10].

There are several types of surgery available in the case of a tumor of the EGJ and the choice of the better approach should consider the initial clinical stage and on cancer location. In case of Tis or T1a EGJ cancers an endoscopic approach (endoscopic mucosal resection, EMR, or endoscopic submucosal dissection, ESD) could be adopted. ESD seems to be better than EMR in terms of en-bloc resection rate and rate of local recurrences [11,12]. After endoscopic treatment, deep margin invasion, lympho-vascular invasion, low differentiation grade, ulceration and large tumor size are considered risk factors for lymph node metastases which represents an indication for resective surgery with adequate lymphadenectomy [5]. For T1b-T4a EGJ cancers, which require a surgical R0 resection with an adequate lymphadenectomy, several options exist and can be choice according to tumor site and to the local extensions of the neoplasm. Siewert's type I EGJ cancers should be treated as esophageal cancer; so, the surgical options are the same of esophageal cancers:

1) The Ivor-Lewis transthoracic esophagectomy (right thoracotomy and laparotomy) is the most frequently used procedure for transthoracic esophagectomy, with an intrathoracic esophagogastric anastomosis at the level of the azygos vein, after stomach mobilization, using laparotomy and right thoracotomy [13]. The Ivor-Lewis esophagectomy also concern dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries.

2) The McKeown transthoracic esophagectomy is like Ivor Lewis procedure but contemplates an anastomosis in the cervical region and should be considered for EGJ cancers with large involvement of upper and middle esophagus.

3) Trans-hiatal esophagectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions [14]. This procedure is completed through the abdominal incision, and the gastric conduit is drawn through the posterior mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis.

Siewert type III EGJ cancers should be treated as gastric cancer, so the surgical treatment involves a total gastrectomy, an esophageal resection with a cancer-free margin, a D2 lymphadenectomy with removal of the lymph nodes of the lower mediastinum and para-aortic lymph nodes, and an esophageal-jejunal anastomosis. For Siewert type II tumors, there is still no standardization of surgical intervention. Many surgeons believe that to achieve an R0 resection both in terms of extension of esophagogastric resection than in terms of adequacy of lymphadenectomy, the only abdominal approach could be not adequate, and a concomitant transthoracic approach should be used such as the Ivor-Lewis's esophageal-gastric resection [15]; in some cases, a total gastrectomy with intra-thoracic esophago-digiunal anastomosis is preferred to a partial gastrectomy with plastic of the stomach. In this case of EGJ cancers, no significant differences were described, in terms of oncological radicality achieving and in terms of oncologic outcome [16,17], between trans-thoracic and abdominal approach for esophageal-gastric resection, while an higher rate of post-operative morbidity was described with trans-thoracic approach [18,19]. So, the choice of the approach should be considering the tumor and patient characteristics and the experience of the surgeon with one of the two approaches [15].

Interestingly, the Japanese surgical strategy for EGJ cancer suggest choosing the correct type of procedure according to the extension of esophageal and gastric involvement [20]:

1) Esophageal invasion of 3cm or more: Ivor Lewis esophagectomy with upper or middle mediastinal lymphadenectomy.

2) Esophageal invasion of 3cm or less and distal invasion not exceeding the upper third of the stomach: trans-hiatal extended proximal gastrectomy with lower mediastinum lymphadenectomy.

3) Esophageal invasion of 3cm or less and distal invasion exceeding the upper third of the stomach: trans-hiatal extended total gastrectomy with lower mediastinal lymphadenectomy.

Also, in surgery for EGJ mini-invasive approaches seem to be associated to a lower post-operative morbidity, quicker functional recovery and better quality of life at 1-year from surgery. About oncological outcome, mini-invasive approaches seem at least non-inferior to open approach [21-24]. A fundamental criterion in surgical management of EGJ cancer is that these kinds of surgical procedures, both open than mini-invasive, should always be performed in high-volume centers by experienced surgeons [25]. In experienced centers, mini-invasive approach is recommended as the surgical approach of choice [5].

Clinical management of locally advanced EGJ cancer (cT2-T4 or cN1-N3 M0)

While in the setting of early-stage EGJ cancer (cT1 cN0 cM0) surgery alone represents the treatment of choice, in the locally advanced disease (cT2-T4 or cN1-3 M0) a neoadjuvant or perioperative treatment is recommended by international guidelines [5,10,26-28]. Preoperative chemoradiation approach in resectable disease was introduced according to the results of CROSS trial [29] in which patients affected by locally advanced operable esophageal and EGJ carcinoma, both squamous cell and adenocarcinomas, where randomized to receive neoadjuvant chemoradiation therapy versus surgery alone; patients affected by EGJ lesion represents about 25% of recruited cohort. The results of this study shown a better 3- and 5- years overall survival rates, a lower incidence of pathological nodal involvement and an interesting rate of pathologic complete response (pCR, 29%) for the combined treatment. Radiotherapy total dose was of 41.2Gy in conventional fractionation and the concomitant chemotherapy schedule consisted of weekly carboplatin and paclitaxel.

The role of preoperative chemotherapy in this setting was evaluated on the bases of the following studies:

1) Burmeister et al. [30], in a phase II trial randomized 75 patients o receive chemotherapy versus 35Gy of chemoradiotherapy and achieved a higher pathological response rate and R1 resection rates in the chemoradiation modality.

2) Stahl et al. [31], that randomized in a phase III trial 126 patients affected by adenocarcinoma of lower esophagus and cardia (Siewert I-III) to receive chemotherapy versus chemotherapy and chemoradiation in preoperative setting documenting an improvement of the pCR rate and a tumor-free lymph-node rate.

The perioperative chemotherapy is another reported approach, especially in Siewert III EGJ adenocarcinoma [5,26], according to the results of the MAGIC trial [32] that randomized patients affected by gastric, EGJ or lower esophageal cancer to receive an epirubicin, cisplatin, and infused fluorouracil-based schedules of chemotherapy versus surgery alone. This approach leads to an advantage in overall and progression-free survival. Regarding the choice between preoperative chemoradiation versus perioperative chemotherapy, currently, NCCN guidelines distinguish patients with EGJ Siewert I and II adenocarcinoma, for whom neoadjuvant radiochemotherapy treatment is recommended [10], from patients with Siewert III EGJ adenocarcinoma, for whom perioperative chemotherapy treatment is recommended, following the gastric cancer guidelines [26]. Similarly, ESMO guidelines published in 2022 [5] and dealing with the issue in the context of esophageal cancers, propose both options of choice suggesting that, although in the absence of a clear evidence, some centers encourage preoperative chemoradiation therapy treatment in patients with Siewert I and II while proposing perioperative chemotherapy for Siewer III patients. This indication is based on the study of Anderegg et al. [33] where patients affected by esophageal or EGJ cancer who underwent to neoadjuvant chemoradiation or perioperative chemotherapy, with the same R0 surgery rate and median overall survival, were retrospectively analyzed showing that neoadjuvant chemoradiation therapy treatment patients had a better compliance and lower severe toxicities. Although there is no distinction of the patients recruited in this study according to Siewert classification, the fact that only one patient in this study had a surgical approach with total gastrectomy allows to assume that all the remaining EGJ cases had a Siewert I and II cancer and, consequently, we should consider the suggestions of a chemoradiation mainly in this setting. Currently ongoing randomized clinical trials are addressing this issue. For patients affected by locally advanced cM0 EGJ cancer with unresectable disease or without surgery indication for patient's clinical conditions, definitive chemoradiotherapy is the treatment of choice with a recommended total dose of 50-50.4Gy in conventional fractionation [10].

Adjuvant treatment of EGJ cancer

After surgery, curative approaches vary depending on the margins provided at the histopathologic examination after surgery and whether (or not) neoadjuvant therapy is performed preoperatively. The role of adjuvant chemoradiotherapy decreases the local recurrence rate, especially in the presence of positive surgical margins, occurrence of a pT3 disease or positive nodes, perivascular/perineural invasion and high differentiation grading, if the patient did not received any preoperative treatment [10,28,34]. American guidelines [10] propose differences in postoperative clinical management between squamous cell carcinoma and adenocarcinomas patients. In fact, in the case of patients affected by squamous cell carcinoma that did not underwent to a neoadjuvant treatment, an adjuvant fluoropyrimidine-based chemoradiation is considered only in the case of positive margins. Patients affected by adenocarcinoma should be evaluated for adjuvant chemoradiation also in the case of R0 resection in the case of positive nodes or pT3-pT4a stage. In the case of pT2 stage adjuvant chemoradiation is only suggested in the case of very high-risk EGJ adenocarcinoma (poor differentiation, high grade cancer, lymphovascular and or perineural invasion) or very young patient (age <50 years). After neoadjuvant chemoradiotherapy and surgery, adjuvant nivolumab should be proposed only in the case of R0 resection ypT positive and or ypN positive. In the case of R1-2 resection of squamous cell carcinoma observation until progression or best supportive care are recommended. Regarding EGJ adenocarcinoma treated with perioperative chemotherapy, the R0 resection should be followed by the completion of chemotherapy. After R1 resection of EGJ adenocarcinoma chemoradiation if not received preoperatively or, alternatively, re-resection can be considered. R2 resected EGJ adenocarcinoma should be proposed for chemoradiation therapy if not previously received or palliative management. A total dose of 45-50.4Gy in conventional fractionation is suggested by NCCN guidelines [10].

Ongoing trials

The aforementioned evidence has reinforced the role of the multimodal approach in the management of EGJ malignancies. In this context, numerous trials have been designed to define the optimal treatment modality in different settings; (Table 1) summarizes their main features. The main area of interest of ongoing trials is the management of neoadjuvant therapy of EGJ neoplasms. Ongoing studies aim to identify the best treatment approach by comparing perioperative chemotherapy (periCT) and neoadjuvant chemoradiation therapy (nCRT), evaluating the potential of integrating periCT and nCRT as well as the optimal chemotherapy in different clinical presentations. The phase III ESOPEC study compares nCRT with periCT followed by surgery, in terms of OS [35]. In the periCT arm, patients undergo four cycles of preoperative CRT and four cycles of postoperative CRT according to the FLOT protocol. In the nCRT arm, patients are randomised to receive CRT according to the CROSS protocol followed by surgery. In the multicentre randomised phase III trial, Neo-AEGIS, the survival benefit is compared between periCT according to the modified MAGIC scheme or nCRT according to the CROSS protocol [36]. The comparison between periCT and nCRT is also investigated in the PREACT study using S1 and oxaliplatin-based pharmacological schemes [37].

The randomised phase III RACE trial is studying progression-free survival in multimodality treatments for resectable EGJ malignancies [38]. In the experimental arm, preoperative induction of CT by the FLOT scheme is followed by nCRT (45Gy RT with weekly oxaliplatin with concomitant chemosensitization by 5-FU); whereas in the considered control arm, patients undergo four cycles of preoperative CT according to the FLOT scheme. In both arms, patients undergo resection and four cycles of postoperative FLOT. The TOPGEAR trial also compares periCT according to the ECF scheme with a multimodal approach based on ECF administration before and after fluoropyrimidine-based CRT [39]. The PROTECT Trial, a prospective multicentre randomised phase II study, is evaluating the short-term complete resection rate and safety of two different concomitant CT schedules (FOLFOX versus Paclitaxel and Carboplatin) in nCRT for oesophageal cancer and EGJ (Siewert I-II) [40]. The introduction of immunotherapy in the multimodal management of many neoplasms has radically changed clinical practice. A prospective phase III study is analysing the impact of immunotherapy in the multimodal treatment associated with CRT of oesophageal neoplasms and EGJ in the definitive setting. The KEYNOTE975 trial compares the use of Pembrolizumab in combination with CRT with FOLFOX or Cisplatin+5-FU [41].

Conclusions and Future Perspectives

The combination of surgical, CT and RT in the multimodal management of EGJ malignancies is the established approach in major international guidelines, therefore, the treatment of these diseases requires multidisciplinary evaluation and management. Ongoing studies aim at optimizing the integration of the different approaches by identifying modalities, drugs, and timing. The implementation of new and modern radiotherapy techniques and the combination with latest-generation drug therapies may open new perspectives for the management of these neoplasms.

Declarations

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Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

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Disclosures

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Conflicts of Interest

None.

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