



## Current Definitions and Therapeutic Strategies for Esophagogastric Cancer: A Medical Oncologist's Perspective

Jian Ming Xu

Jian Ming Xu, Affiliated Hospital Cancer Center (307 Hospital of PLA), Academy of Military Medical Sciences, Beijing 100071, China

Correspondence to: Jian Ming Xu, Affiliated Hospital Cancer Center (307 Hospital of PLA), Academy of Military Medical Sciences, Beijing 100071, China

Email: [jmxu2003@yahoo.com](mailto:jmxu2003@yahoo.com)

Received: June 25, 2013

Revised: October 4, 2013

Accepted: October 10, 2013

Published online: February 18, 2014

### ABSTRACT

Gastroesophageal junction carcinoma is a challenge to medical oncologist due to issues in staging and classification and uncertainties regarding optimal treatment approach. As a comprehensive review of Status of Arts in gastroesophageal junction carcinoma, this article discusses its anatomical, histological, and endoscopic definition, classification, and advances in surgery, neoadjuvant therapy, adjuvant therapy, and innovative molecular targeting therapy. In general, anatomical and histological definitions are important for diagnosis and treatment of gastroesophageal junction carcinoma. Combination of surgery and adjuvant therapy is more beneficial for patients with gastroesophageal junction carcinoma than surgery alone.

© 2014 ACT. All rights reserved.

**Key words:** Gastroesophageal junction carcinoma; Definition; Therapeutic strategy

Xu JM. Current Definitions and Therapeutic Strategies for Esophagogastric Cancer: A Medical Oncologist's Perspective. *Journal of Tumor* 2014; 2(2): 83-86 Available from: URL: <http://www.ghrnet.org/index.php/JT/article/view/601>

The prevalence of distal gastric carcinomas (GC) has decreased worldwide; in contrast, the prevalence of proximal GCs including esophagogastric junction (EGJ) carcinoma and distal esophageal adenocarcinoma (EAC) has dramatically increased over the past two decades<sup>[1]</sup>. EGJ carcinoma is quite similar to distal EAC in age distribution, sex predilection, and pathological characteristics.

However, whether it is a subtype of EAC or GC remains controversial. It has been also suggested that carcinoma of EGJ be regarded as an independent entity equivalent to EAC and distal GC. Although radical resection remains to be the only curable treatment, approximately 3/4 of proximal GC carcinoma patients are in their later-stage upon diagnosis, which are not suitable for surgery. And proximal GC tends to be more malignant with poorer differentiation and prognosis than GC in general. Diagnosis and treatment of proximal GC including EGJ carcinoma are reviewed in this article.

### DEFINITION OF EGJ

#### Anatomical and histological definitions

Proximal GC usually refers to carcinoma located in the proximal third of gastric mucosa, i.e. the C-zone, and is generally termed as cardiac carcinoma (CC). This definition may not be precise, because the precise definition of gastric cardia is not clear. Is it merely a strip that separates the esophagus from the stomach or a particular region? In fact, both strip and region definitions can be found in literatures. According to the Cancer Principles & Practice of Oncology<sup>[2]</sup>, the cardia is the portion of the stomach surrounding the esophagogastric connection, characterized by the absence of acid cells; and its mucosa, a few centimeters in extension, is a continuation of transitional mucosa descending from the squamous columnar junction (SCJ). However, this conception has been challenged. Three large-scale studies on the distribution of cardiac mucosa at EGJ argued that the extension of cardiac mucosa descending from SCJ is less than 4 mm<sup>[3]</sup>. EGJ is anatomically defined as the junction of tubular esophagus and saccate stomach. From a histopathological perspective, EGJ carcinoma refers to the malignant tumor located at the zigzag junction where the stratified squamous epithelium of the distal esophagus meets the simple columnar epithelium of the stomach, i.e. carcinoma near the cardia. In normal conditions, anatomical EGJ coincides with histological SCJ or Z-line<sup>[4]</sup>. In many circumstances, however, particularly in adults with gastroesophageal reflux disease (GERD), slightly up-shifting or irregular Z line was frequently found, and the histological SCJ was usually above the anatomical EGJ. In such a context, this small portion of intestinal epithelium, which is composed of pure mucous glands or a mixture of mucous and gastric glands, histologically mimics the true cardia<sup>[5-7]</sup>. Biopsies from this region can be mistaken as the gastric



cardia, but actually they were specialized intestinal metaplasia originated from the distal esophagus.

#### Endoscopic definition

Endoscopy is the most common tool for EGJ carcinoma diagnosis<sup>[8,9]</sup>. Western researchers prefer proximal gastric plicae as the anatomical landmark for identification of esophagogastric boundary during endoscopy<sup>[10]</sup>. They believe that paliform blood vessels are sometimes indistinguishable from other vessels, and in some situations these vessels are even undetectable<sup>[11,12]</sup>. However, Japanese endoscopists argue that location of the proximal gastric plicae can be affected by inflation or respiration, particularly in cases of deep inspiration (the plicate boundary markedly shifts downwards). Then the judgment of precise tumor location will be misled. They argue the lower edge of paliform vessels provides a more definite boundary between the esophagus and stomach<sup>[13,14]</sup>.

## DEFINITION AND CLASSIFICATION OF EGJ CARCINOMA

According to the World Health Organization (WHO) classification of gastrointestinal tumors (2000), EGJ carcinoma is defined as adenocarcinoma affecting the EGJ area irrespective of its primary origin. By this definition, adenocarcinoma entirely located above EGJ is EAC while that entirely located below EGJ is GC<sup>[15]</sup>. This definition is rather simple for clinical practice but it is not helpful for determination of primary origin. Primary origin is difficult to be determined especially for tumor occupying both the lower esophagus and EGJ, or EGJ and proximal stomach, or even all the three sites.

The etiology, pathogenesis, and progress mechanism of EGJ carcinoma remains poorly understood, and the carcinoma has two different lymph node (LN) metastatic routes (spread to the thorax or to the epigastrium). In 1998, in order to objectively evaluate the efficacy of surgery and chemo-radiotherapy, the International Gastric Carcinoma Association (IGCA) and the International Society for Disease of the Esophagus (ISDE) guidelines jointly announced the definition and classification of EGJ carcinoma<sup>[16]</sup>. According to IGCA/ISDE guidelines, adenocarcinoma at EGJ (AEG, adenocarcinoma of the esophagogastric junction) was defined as the adenocarcinoma with epicenter located between 5 cm proximal and distal to the anatomical cardia. The tumors were further classified into three types. Type I AEG is the adenocarcinoma arising at the distal esophagus, which is usually derived from the specialized intestinal metaplasia (SIM) of esophageal epithelium, e.g. the Barrett's esophagus, which usually infiltrates the proximal esophagus. Type II AEG is derived from the true anatomical cardia or the short segment of intestinal metaplasia at the EGJ, which is also named "junction adenocarcinoma". And type III AEG refers to the subcardial GC which infiltrates the EGJ and distal esophagus.

Although different types of AEGs share many epidemiological and morphological features, latest researches have demonstrated differences in their pathology and biological behavior. For example<sup>[16]</sup>: (1) Type I AEG is more predominant in male patients than types II and III; (2) Patients with type I AEG are more likely to have hiatal hernia with a prolonged history of GERD; (3) SIM of distal esophagus (Barrett's esophagus) may progress to high-grade dysplasia, which has been identified as a main precancerous lesion for distal esophagus adenocarcinoma; but dysplasia is rare for intestinal metaplasia of the cardia and subcardia mucosa; (4) Cytokeratin expression and P53 mutation are more common in the adenocarcinoma at or above the gastric cardia; (5) Lymphangiography

has revealed different patterns of lymphatic spread: distal esophageal adenocarcinomas (EAC) mainly spread to the mediastinum in cephalad and to the celiac artery in caudad, while carcinomas at or below gastric cardia tend to invade the celiac artery, splenic hilum and the area besides abdominal aorta. This classification, which divides AEGs into distal esophagus carcinoma (type I), narrowly defined gastric cardia adenocarcinoma (type II), and subcardial gastric adenocarcinoma (type III), well favors the surgical decision as well as researches on pathogenesis and pathological behavior of AEGs.

Since EGJ as an area is difficult to be determined by endoscopy or autopsy, researchers argue that deviding esophagus from stomach with a strip is more practical. Based on the WHO definition and IGCA/ISDE classification, EGJ boundary can be defined with either the proximal gastric plicae or the lower edge of paliform vessel in the distal esophagus. Therefore, the clinical phrase "gastric cardia carcinoma" and anatomical term "EGJ carcinoma" are two distinct concepts: cardiac carcinoma is confined to a smaller region, equal to the IGCA-ISDE Type II tumor, and EGJ carcinoma includes all 3 types of IGCA-ISDE AEGs.

## TREATMENT

### Surgery

There has been little improvement in overall survival (OS) of EGJ carcinoma in recent decades, because 80% of patients had lymphatic metastases upon diagnosis. However, it is worth noting that the five-year rate of surgical resection alone has exceeded 35% to 50% in some surgical centers. Moreover, 5-year survival rate in Stage III carcinoma (T3-4N1) also reached 25%-35%. According to a meta-analysis, surgical resection alone can achieve a 5-year survival rate of more than 35% with less lymph nodes (LN) involved; once number of LNs involved exceed more than 6 or existence of distal LN metastases, the rate will drop to lower than 10%<sup>[17]</sup>.

### Neoadjuvant therapy

Currently, there is a general consensus that surgery alone may not be the treatment of choice even for resectable gastric carcinoma. MAGIC trial is regarded as the milestone study in aspect of treatment compliance, in which distal esophagus and EGJ adenocarcinomas accounted for 26% of the samples<sup>[18]</sup>. In the study, most patients completed full-dose preoperative neoadjuvant therapy, while only about 40% completed full-dose postoperative adjuvant therapy. The well tolerance is one of the factors contributing to preference of neoadjuvant therapy. In the CROSS study, a multi-center clinical trial conducted in France, patients underwent surgical resection plus preoperative concurrent chemoradiotherapy had a better survival than those treated with surgery alone<sup>[19]</sup>, which also supports the use of preoperative neoadjuvant therapy in resectable EGJ carcinoma.

Although preoperative neoadjuvant therapy can induce pathological complete remission in 20% patients and a higher 5-year survival rate than surgery alone, there are still more than 50% of patients fail to respond. It is worth noting that of those non-responders, the 5-year survival rate will drop to 12%. Currently there is no biological marker for reliable prediction of response. Some even suspect that the course of the therapy, usually lasts 3-4 months, reduce the opportunity of resection by postponing surgery. Therefore, targeted patients who may benefit from therapy remains to be the focus. Previous studies demonstrated that decline of tumor glucose uptake showed by PET after chemotherapy can be a predictor of response. Study of Lordick *et al* found that metabolic response (defined as decrease of 35% or more in tumor glucose SUV) after 2

weeks of induction chemotherapy is associated with the long term efficacy after several cycles of chemotherapy. The MUNICON trial, a prospective study involving 110 patients with EGJ carcinoma, showed that 49% of patients had initial metabolic response, who continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic non-responders discontinued chemotherapy and switched to surgery. Results showed that the median event-free survival was 29.7 months in metabolic responders, significantly longer than that of non-responders (14.1 months)<sup>[20]</sup>.

#### Adjuvant therapy

Although there have been numerous researches on adjuvant therapy published in the past three decades, the role of the therapy in the treatment of GC remains uncertain until the early 21<sup>st</sup> century. The intergroup 0116 study established adjuvant 5Fu/LV chemoradiotherapy as the standard of care of GC and EGJ adenocarcinoma in the USA<sup>[21]</sup>. However, this strategy has not been accepted outside the USA due to the associated toxicity, especially for patients who have undergone D2 dissection, radiotherapy is widely considered to be unnecessary. Attitude for adjuvant therapy shifted based on three evidences: (1) Four recent meta-analyses concluded patients underwent adjuvant therapy benefited more than those reported in the meta-analysis by Hermans in 1993<sup>[22]</sup>; (2) In ACTS-GC study<sup>[23]</sup>, a Japanese phase III clinical trial including 1,059 patients with stage II or III gastric carcinoma having gastrectomy with extended (D2) lymph-node dissection were randomly assigned to receive adjuvant therapy with S-1, an oral fluoropyrimidine, or surgery alone. Results showed that the three-year survival rate in S1 group was 80.5%, markedly higher than that in surgery alone group (70.1%); In addition, adjuvant chemotherapy reduced 32% of mortality risk. (3) In another Asian Classic study, 1,035 stages II/III GC patients who underwent D2 surgery were treated with or without XELOX (Capecitabine plus Oxaliplatin), an adjuvant chemotherapy regimen. Results showed that three-year survival rate was 83% in XELOX group, significantly higher than that (78%) in the control arm<sup>[24]</sup>. Asian physicians are more positive towards adjuvant therapy in the treatment of GC than their counterparts in western countries, who emphasize more on individualized treatment decisions. In general, therapeutic strategy in the treatment of EGJ carcinoma is accustomed to the preoperative neoadjuvant therapy—surgery—adjuvant therapy model.

#### Emerging treatment

Recently, increased awareness about tumor biology and molecular mechanisms responsible for tumor proliferation and growth have resulted in the development of active drugs that targeted in such mechanisms. These agents include the EGFR with subtypes Her-1, Her-2, Her-3 and Her-4, VEGF and its receptor(VEGFR), and mammalian target of rapamycin (mTOR)<sup>[25-29]</sup>. However, most of these agents had not demonstrated significantly improved OS and PFS of advanced GC and EGJ cancer. The recent ToGA (Trastuzumab for Gastric Carcinoma) is a milestone clinical trial which studied Trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or EGJ carcinoma<sup>[25]</sup>. It should be emphasized that this is the first regimen which has induced more than 1-year survival in patients with advanced GC. Particularly in this study, a stratification analysis revealed that the positive rate of HER-2 was significantly higher in EGJ carcinomas than that in GCs, suggesting that patients with advanced EGJ carcinoma may benefit more from the combination. In the near future, new pathways with more specific biological rationales in EGJ cancer need to be explored. Promising

new targets, such as HGF/MET pathway, is under evaluation.

## PROGNOSIS

It is traditionally recognized that the prognoses of EGJ carcinoma, GC and EAC as well as their gene expression profiles vary significantly. However, according to a meta-analysis of four clinical studies involving 1,775 subjects, significant difference exists in neither response nor survival rate among patients with advanced stages of esophageal adenocarcinoma, EGJ adenocarcinoma, or gastric adenocarcinoma, who received fluorine pyrimidines and/or platinum treatment<sup>[30]</sup>. It seems that the primary tumor origin is a less important prognostic factor for patients with metastasis; whereas gene mutation and activation of signal transduction pathway all contribute to the similar poor outcome of advanced diseases.

## SUMMARY

Both anatomical and histological definitions are important for diagnosis and treatment of AEGs. Medical oncologists, surgeons, pathologists, and endoscopists should devote much more time and efforts to EGJ carcinoma studies.

Combination of adjuvant therapy and surgery is more beneficial for patients with AEGs than surgery alone.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

## REFERENCES

- 1 Pera M. Epidemiology of esophageal cancer, especially adenocarcinoma of the esophagogastric junction. *Recent Results Cancer Res* 2000; **155**: 1-14
- 2 Posner MC, Minsky BD, Ilson DH. Cancer of the Esophagus. *Cancer Principles & Practice of Oncology*. 9th, 2012 Vincent T. Devita, Jr., Theodore S. Lawrence, Steven A. Rosenberg.
- 3 Dent J, Chir B. Pathogenesis and classification of cancer around the gastroesophageal junction—not so different in Japan. *Am J Gastroenterol* 2006; **101**: 934-936
- 4 Hayward J. The lower end of the oesophagus. *Thorax* 1961; **16**: 36-41
- 5 Chandrasoma PT, Der R, Ma Y, Dalton P, Taira M. Histology of the gas-troesophageal junction. An autopsy study. *Am J Surg Pathol* 2000; **24**: 402-409
- 6 Zhou H, Greco MA, Daum F, Kahn E. Origin of cardia-mucosa: Ontogenic consideration. *Ped Dev Pathol* 2001; **4**: 358-363
- 7 Sarbia M, Donner A, Gabbert HE. Histopathology of the gastroesophageal junction. A study on 36 operation specimens. *Am J Surg Pathol* 2002; **26**: 1207-1212
- 8 Chandrasoma PT, Der R, Ma Y, Peters J, Demeester T. Histologic classification of patients based on mapping biopsies of the gastro-sophageal junction. *Am J Surg Pathol* 2003; **27**: 929-936
- 9 Glickman JN, Fox V, Antonioli DA, Wang HH, Odze RD. Morphology of the cardia and significance of carditis in pediatric patients. *Am J Surg Pathol* 2002; **26**: 1032-1039
- 10 Takubo K, Vieth M, Aida J, Sawabe M, Kumagai Y, Hoshihara Y, Arai T. Differences in the definitions used for esophageal and gastric diseases in different countries: endoscopic definition of the esophagogastric junction, the precursor of Barrett's adenocarcinoma, the definition of Barrett's esophagus, and histologic criteria for mucosal adenocarcinoma or high-grade dysplasia. *Digestion* 2009; **80**: 248-257
- 11 Sharma P, Dent J, Armstrong D, Bergman JJ, Gossner L,

- Hoshihara Y, Jankowski JA, Jung-hard O, Lundell L, Tytgat GN, Vieth M. The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C&M criteria. *Gastroenterology* 2006; **131**: 1392-1399
- 12 Takubo K, Arai T, Sawabe M, Miyashita M, Sasajima K, Iwakiri K, Mafune KI. Structures of the normal esophagus and Barrett's esophagus. *Esophagus* 2003; **1**: 37-47
- 13 Aoki T. Report on research committee of definition on Barrett's esophagus (epithelium). *Chiba: Japanese Society of Esophageal Diseases* 2000; 20-23
- 14 Hoshihara Y, Kogure T. What are longitudinal vessels? Endoscopic observation and clinical significance of longitudinal vessels in the lower esophagus. *Esophagus* 2006; **3**: 145-150
- 15 Mönig SP, Schröder W, Beckurts KT, Hölscher AH. Classification, diagnosis and surgical treatment of carcinomas of the gastroesophageal junction. *Hepatogastroenterology* 2001; **48**: 1231-1237
- 16 Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85**: 1457-1459
- 17 Lerut T, Moons J, Coosemans W, Decaluwé H, Decker G, De Leyn P, Naftoux P, Van Raemdonck D. Multidisciplinary treatment of advanced cancer of the esophagus and gastroesophageal junction: a European center's approach. *Surg Oncol Clin N Am* 2008; **17**: 485-502
- 18 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20
- 19 Gaast AV, Van Hagen P, Hulshof M, Richel D, Berge Henegouwen MI, Nieuwenhuijzen GA, Plukker JT, Bonenkamp JJ, Steyerberg EW, Tilanus HW, Cross Study Group. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study. *J Clin Oncol(Meeting Abstracts)*2010; **28**: 15 suppl 4004
- 20 Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet* 2007; **8**: 797-805
- 21 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730
- 22 Menges M, Hoehler T. Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction. *J Cancer Res Oncol* 2009; **135**: 29-38
- 23 Sakuramoto S, Sasako M, Yamaguchi TA, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820
- 24 Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim, Noh SI Noh, Cho JY, Mok YJ, Kim YH, Ji JF, Yeh TS, Button, Sirzén F, Noh SH, for the CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321
- 25 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697
- 26 Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M; Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499
- 27 Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976
- 28 Nam HJ, Ching KA, Kan J, Kim HP, Han SW, Im SA, Kim TY, Christensen JG, Oh DY, Bang YJ. Evaluation of the antitumor effects and mechanisms of PF00299804, a pan-HER inhibitor, alone or in combination with chemotherapy or targeted agents in gastric cancer. *Mol Cancer Ther* 2012; **11**: 439-451
- 29 Ohtsu A, Ajani JA, Bai YX, Bang Y, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh K, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated patients with advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; [Epub ahead of print]
- 30 Chau I, Norman AR, Cunningham D, Oates J, Hawkins R, Iveson T, Nicolson M, Harper P, Seymour M, Hickish T. The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma – individual patient data from 1775 patients in four randomised controlled trials. *Ann Oncol* 2009; **20**: 885-891

**Peer reviewer:** Angelo Paradiso, Head Experimental Medical Oncology, National cancer institute, IRCCS Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco, 65, 70124 - BARI, Italy.