

Adenocarcinoma of esophagogastric junction requires a clearer definition

Aiwen Wu, Jiafu Ji

Department of Gastrointestinal Surgery, Beijing Cancer Hospital and Institute, Peking University School of Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Beijing, China

Corresponding to: Jiafu Ji, MD, FACS. Department of Surgery, Peking University Cancer Hospital, Beijing Cancer Hospital & Institute, China. Email: jifbj@yeah.net.

Abstract: The past few years have witnessed two facts in gastric cancer research: the morbidity and mortality of gastric cancer has shown a significant downward trend worldwide; and the incidence of the adenocarcinoma of esophagogastric junction (AEG) has gradually increased in Western countries, which may be explained by the high prevalence of obesity and gastroesophageal reflux disease among the Western populations. AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will facilitate future scientific research and academic exchanges.

Key Words: Adenocarcinoma of the esophagogastric junction (AEG); staging; surgery



Submitted May 13, 2013. Accepted for publication May 31, 2013.

doi: 10.3978/j.issn.2224-4778.2013.05.41

Scan to your mobile device or view this article at: <http://www.amepc.org/tgc/article/view/2062/2844>



Jiafu Ji

Introduction

The past few years have witnessed two facts in gastric cancer research: the morbidity and mortality of gastric cancer has shown a significant downward trend worldwide (1); and the incidence of the adenocarcinoma of esophagogastric junction (AEG) has gradually increased in Western countries (2), which may be explained by the high prevalence of obesity and gastroesophageal reflux disease among the Western populations (3). The prevalence of gastric cancer is high in China, and the mortality of gastric cancer remains high in the rural areas; although the incidence of distal gastric cancer has slightly declined in the urban areas, the overall 5-year survival has not remarkably increased. Meanwhile, along with the rapid socioeconomic development in China, the lifestyles of many urban residents have increasingly been similar as those in the Western countries. As more people become obese, the high prevalence of AEG will also occur in China - in fact, such a trend has been reported (4). AEG has a poor overall prognosis, and its treatment needs to be improved (5).

The diagnosis and, particularly, treatment of cancers at the “gastroesophageal junction” had been highly controversial; the introduction of AEG has brought more problems and quarrels. In our opinion, defining the concept of AEG is the prerequisite for determining the research subjects, whereas more high-level clinical trials that are able to resolve these questions/quarrels are key to the improved treatment of AEG.

Defining the concept of AEG

Gastroesophageal junction is the structure that connects the esophagus and the stomach. Anatomically, it is known as the gastric cardia, which has no visible border with the other parts of the stomach. Malignancies located at this site have various names including AEG, cancer of cardia and stomach fundus, proximal gastric cancer, gastric cardia cancer, and distal esophageal carcinoma. In fact, the pathologic types of malignancies at the site also vary, which may include adenocarcinoma, squamous cell carcinoma, and, particularly, AEG. The concept of AEG, initially proposed by German surgeon Siewert, refers to the adenocarcinomas with epicenter located within 5 cm proximal or distant to the Z-line (6). He noted this phenomenon because the prevalence of AEG was high in Western countries and is constantly growing. In fact, many Chinese doctors have noted this disease and conducted many relevant studies. However, due to its relatively confusing definition, AEG remains particularly controversial or lacks specialized research. A standardized definition will be critical for academic research on AEG. The World Health Organization (WHO) classification refuse the term “gastric cardia cancer” since it is ambiguous and sometimes misleading; rather, it recommends “proximal gastric cancer” or “gastric body cancer” based on the tumor size, although no clear definition of tumors at this site has been proposed. Similarly, the Union for International Cancer Control (UICC) tumor classification also does not distinguish the gastric cardia cancer from other gastric cancers. It has been widely accepted in China that AEG includes both the distal esophageal adenocarcinoma and gastric cardia adenocarcinoma. However, the so-called “gastric cardia adenocarcinoma” has also not clearly defined, and its relationship with the gastric cancer cannot be identified.

In our opinion, the esophageal cancer and the gastric cancer differ dramatically in terms of pathogenesis, biological behaviors, and treatment, whereas the adenocarcinomas above and below the cardia have similar biological behaviors as the proximal gastric cancer and distal esophageal carcinoma. Therefore, a uniform consideration in terms of diagnosis, treatment, and prevention will be more feasible. According to Siewert, the epicenter of AEG is located within 5 cm proximal or distant to the Z-line. We believe that the proximal edge is easy to determine, because the esophagus has relatively fixed length; in contrast, the distal edge is more likely to be affected by the stomach size. Generally speaking, in an adult, a moderately filled

stomach has a mean length (from the fundus to the lower part of greater curvature) of 25-30 cm, and the size and morphology of the stomach vary as the stomach filling degree, body position, and body shape change. In addition, measurements of the in vivo and in vitro specimens often yield dramatically different results; distance alone can not reliably define the tumor type. In contrast, the Japanese Gastric Cancer Association (JGCA) gastric cancer classification is more useful in this regard. According to the Japanese Classification of Gastric Carcinoma (3rd edition), the stomach is anatomically divided into three portions, the upper (U), middle (M), and lower (L) parts, by the lines connecting the trisected points on the lesser and greater curvatures. Therefore, we recommend that, by combining the Japanese classification and Siewert definition, AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will for sure facilitate scientific research and academic exchanges.

Unique features of AEG in China

The AEG, particularly the distal esophageal carcinoma, has shown increasingly prevalence in the Western countries. In the United States, the incidence of distal esophageal carcinoma has increased by 6 times in the past decades, and this carcinoma became the main esophageal cancer type since the late 1990s. Similarly, the proportion of the proximal gastric cancer among gastric cancers has also dramatically increased since 1970s, whereas the distal gastric cancer declined (7). The increased incidence of distal esophageal carcinoma may be related with gastroesophageal reflux disease and Barrett's esophagus; nevertheless, there is much controversy on the etiology of gastric cardia cancer (8). Esophageal squamous cell carcinoma is highly prevalent in China, similar as the gastric cardia cancer. The gastroesophageal junction connects the end of the esophagus and the beginning part of the stomach. It roughly equals to the lower edge of the lower sphincter, but is not consistent with the Z-line (i.e. the border between the squamous epithelium and cylindrical epithelium at the lower part of the esophagus). A survey conducted in a region with high esophageal and cardiac cancer incidences in Henan Province showed that, the rate of the upward shift in Z-line (≥ 3 cm), irregular histopathology, and unclear

histopathology was 12%, 10%, and 1% under endoscope. In patients with the upward shift in Z-line, the frequencies of basal cell hyperplasia and anaplasia at the lower part of the esophagus remarkably increased. Meanwhile, the incidences of cardiac chronic superficial gastritis and chronic atrophic gastritis associated with intestinal metaplasia were significantly higher than those without upward shifted Z-line. Among the normal subjects in the highly prevalent region, the detection rates of Barrett's esophagus and reflux esophagitis were 0.5-2.4% and 5.0-6.0%, respectively. Among the cardiac cancers, the intestinal type accounted for over 60%, which was mainly seen in patients with intestinal metaplasia, atrophic gastritis, active gastritis, or gastric cardia inflammation (9). As shown in the clinical reports, the overall proportions of proximal gastric cancer, cardiac cancer, and distal esophageal carcinoma accounted for about 30-40% of gastric cancer in China and Western countries, which were far higher than those in Japan and Korea (10,11). Therefore, AEG in China has unique etiologies when compared with the Western countries and also remarkably differs from those in Japan, Korea, and other Eastern Asian countries/regions with high prevalence of gastric cancer.

Typing of AEG and its surgical implications

AEG should be typed from the perspectives of basic research and clinical application. According to Siewert classification, tumors with the epicenter 1-5 cm proximal to the esophago-gastric junction (EGJ) was classified as type I tumor (adenocarcinoma of the distal esophagus); tumors with the epicenter 1 cm proximal to EGJ and 2 cm distal to EGJ was classified as type II tumor, which is the "true" cardiac cancer; tumors with the epicenter 2-5 cm distal to EGJ was classified as Siewert type III (inferior cardiac cancer). This classification assumes that the tumors grow in a symmetric manner, which obviously has certain limitations. Furthermore, it is often challenging to distinguish the subtypes of an advanced tumor. Anyway, the Siewert classification remains the most commonly accepted system. As reported by Siewert *et al.* (12), the types I, II, and III accounted for 35.9%, 28.7%, and 35.4%, respectively. Bai *et al.* (13) reported 203 cases and found that the types I, II, and III AEG accounted for 14.3%, 39.4%, and 46.3%, respectively. In our series, we summarized the data of 471 patients and found that the type I AEG accounted for only 4.7% (14), which is consistent with the findings in Japan and Korea (15). It has been widely agreed that the distribution of Siewert types of AEG differs between Asian

countries and the Western countries. Data have shown that the high AEG prevalence in Western countries is related with gastroesophageal reflux disease, and its risk factors include alcoholism, obesity, and smoking. The pathogenic mechanism of AGE significantly differs between the Eastern Asian countries and Western countries, although remained unclear.

In terms of survival, most studies believe that the prognosis of patients with Siewert type I AEG is poorer than those of patients with type II and type III (16), whereas the type II and type III have similar prognoses. Fang *et al.* (17) reported that among 231 patients with Siewert type II and III AEG, the 5-year survival was 59.6% and 63.5%, respectively ($P=0.947$). Our studies have also yielded the same conclusions. Obviously, the Siewert type II and type III AGE are more alike, and meanwhile are different from type I. In fact, it has increasingly recognized that Siewert type I AGE is more similar to esophageal cancer, whereas the type II and type III close to the gastric cancer.

Also, there is no consensus on the surgical approaches for AEG. The conventional surgical procedures for AEG include Ivor-Lewis operation, transhiatal esophagectomy, surgical resection of left transthoracic approach, and thoracoabdominal approach. These methods have their unique advantages and disadvantages, and are preferred by different doctors. The surgical resection of left transthoracic approach can ensure the complete dissection of the posterior mediastinal lymph nodes and achieve negative esophageal resection margin, but has shortcomings including insufficient dissection of abdominal lymph nodes and high incidences of post-operative complications. The abdominal surgeries also have their limitations: they can not sufficiently cut off the esophagus and completely dissect the lower mediastinal lymph nodes. Siewert *et al.* (12) reported that, in patients with Siewert type I AEG, the proportion of lower mediastinal lymph node metastasis accounted for 50% of the total number of lymph node metastasis, whereas in type II and type III AEG, it accounted for 11% and 5%, respectively. According to Ichikura *et al.* (18), the rate of mediastinal lymph nodes involvement was 14% in Siewert type II AEG, while the metastasis rates in lymph nodes near the cardia, lesser curvature, and left gastric artery were 76%, 48%, and 33%, respectively. Although the metastasis rates differed among different studies, a basic fact is that abdominal lymph node metastasis remains the main finding in patients with Siewert type II and type III AEG. Therefore, a thorough dissection of abdominal lymph nodes is warranted. The JCOG9502 trial, a multi-center randomized controlled study,

enrolled totally 167 patients, with an aim to compare the left thoracoabdominal approach (LTA) with the abdominal-transhiatal approach (TH) in the treatment of the gastric cancer of the cardia or subcardia. Its main follow-up endpoint was the overall survival. LTA does not improve survival after TH and leads to increased morbidity in patients with cancer of the cardia or subcardia, LTA cannot be justified to treat these tumours; it is not recommended for Siewert type II and type III AEG (19). Therefore, the following consensus has been reached concerning the surgical approaches for AEG: the Siewert type I AEG should be treated as esophageal cancer. For Siewert type I and type III AEG, abdominal surgery is recommended; however, efforts should be recommended to ensure the complete dissection of the posterior mediastinal lymph nodes and achieve negative esophageal resection margin; meanwhile, the lower mediastinal lymph nodes should also be dissected. Compared with the surgical approaches, the D2 dissection of abdominal lymph nodes is more important, which has also been a priority in the standardized surgical treatment for gastric cancer.

The 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria for gastric adenocarcinoma has included AEG in esophageal cancer, which has caused a lot of controversy. Huang *et al.* (20) retrospectively analyzed 142 AEG patients with esophageal involvement and found that the gastric cancer staging can better predict the patient's prognosis. Some Korean scholars reviewed the clinical data of 4,534 cases from a single center and found that, among 497 AEG cases (all were Siewert type II and type III), the esophageal cancer staging criteria could not provide accurate staging for AEG (21). Currently the 8th edition of AJCC TNM staging criteria for gastric adenocarcinoma is under preparation, during which this issue is expected to be further discussed.

Conclusions

In China and many other East Asian countries/regions, whether AEG should be classified as an independent cancer remains controversial in terms of pathogenesis, population differences, surgical techniques, and staging. The proportion of Siewert type I AEG is low in China; anatomically, it belongs to esophageal cancer, so does its diagnosis and treatment. The Siewert type II and type III AEG are more likely to be gastric cancer, and their clinical features, diagnosis, and treatment are similar; also, they can not be strictly distinguished from the proximal gastric

cancer or cancer of the cardiac part of gastric fundus. However, most Siewert type II and type III AEGs are already in the advanced stages and large in size, and it is often difficult to accurately distinguish them. In summary, AEG can be the collective name of the adenocarcinomas located in the proximal 1/3 of the stomach and in the lower part of the esophagus (within 5 cm above the Z-line). It covers the gastric cardia cancer, distal esophageal carcinoma, proximal gastric cancer, and cancer of the cardiac part of gastric fundus. A standardized definition of AEG will facilitate future scientific research and academic exchanges.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (81071983) and Beijing Science and Technology Nova Project (2007-B057).

Disclosure: The authors declare no conflict of interest.

References

1. Crew KD, Neugut AI. Epidemiology of upper gastrointestinal malignancies. *Semin Oncol* 2004;31:450-64.
2. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049-53.
3. Souza RF, Spechler SJ. Concepts in the prevention of adenocarcinoma of the distal esophagus and proximal stomach. *CA Cancer J Clin* 2005;55:334-51.
4. He YT, Hou J, Chen ZF, et al. Trends in incidence of esophageal and gastric cardia cancer in high-risk areas in China. *Eur J Cancer Prev* 2008;17:71-6.
5. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84.
6. Szántó I, Vörös A, Gonda G, et al. Siewert-Stein classification of adenocarcinoma of the esophagogastric junction. *Magy Seb* 2001;54:144-9.
7. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142-6.
8. Ding YB, Xia TS, Wu JD, et al. Surgical outcomes for gastric cancer of a single institute in southeast China. *Am J Surg* 2012;203:217-21.
9. Wang LD, Zheng S, Fan ZM, et al. Changes of Z-line at the gastroesophageal junction in symptom-free subjects from high-incidence area for esophageal cancer in Henan.

- Journal of Zhengzhou University (Medical Sciences) 2002;37:733-6.
10. Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg* 2010;251:640-6.
 11. Wu A, Ji J, Yang H, et al. Long-term outcome of a large series of gastric cancer patients in China. *Chin J Cancer Res* 2010;22:167-75.
 12. Siewert JR, Feith M, Stein HJ. Biologic and clinical variations of adenocarcinoma at the esophago-gastric junction: relevance of a topographic-anatomic subclassification. *J Surg Oncol* 2005;90:139-46; discussion 146.
 13. Bai JG, Lv Y, Dang CX. Adenocarcinoma of the Esophagogastric Junction in China according to Siewert's classification. *Jpn J Clin Oncol* 2006;36:364-7.
 14. Yang H, Wu AW, Ji JF, et al. Adenocarcinoma of the esophagogastric junction according to Siewert classification: a clinical study of 471 cases. *Chinese Journal of Practical Surgery* 2012;32:310-5.
 15. 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;19:677-83.
 16. Chung JW, Lee GH, Choi KS, et al. Unchanging trend of esophagogastric junction adenocarcinoma in Korea: experience at a single institution based on Siewert's classification. *Dis Esophagus* 2009;22:676-81.
 17. Fang WL, Wu CW, Chen JH, et al. Esophagogastric junction adenocarcinoma according to Siewert classification in Taiwan. *Ann Surg Oncol* 2009;16:3237-44.
 18. Ichikura T, Ogawa T, Kawabata T, et al. Is adenocarcinoma of the gastric cardia a distinct entity independent of subcardial carcinoma? *World J Surg* 2003;27:334-8.
 19. Sasako M, Sano T, Yamamoto S, 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.
 20. Huang Q, Shi J, Feng A, et al. Gastric cardiac carcinomas involving the esophagus are more adequately staged as gastric cancers by the 7th edition of the American Joint Commission on Cancer Staging System. *Mod Pathol* 2011;24:138-46.
 21. Suh YS, Han DS, Kong SH, et al. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. *Ann Surg* 2012;255:908-15.

Cite this article as: Wu A, Ji J. Adenocarcinoma of esophagogastric junction requires a clearer definition. *Transl Gastrointest Cancer* 2013;2(S1):5-9. doi: 10.3978/j.issn.2224-4778.2013.05.41