REVIEW

Burkhard H. A. von Rahden
Marcus Feith
Hubert J. Stein

Carcinoma of the cardia: classification as esophageal or gastric cancer?

B. H. A. von Rahden · M. Feith ·
H. J. Stein (✉)
Chirurgische Klinik und Poliklinik,
Klinikum rechts der Isar der TU München,
Ismaningerstrasse 22, 81675 Munich,
Germany
e-mail: stein@nt1.chir.med.tu-muenchen.de
Tel.: +49-89-41404745
Fax: +49-89-41404940

Abstract *Introduction:* The cardia is the anatomical borderland between the esophagus and stomach. Carcinomas of the cardia are regarded to share features of both, esophageal and gastric cancers. Controversy exists concerning their appropriate classification and whether these tumors comprise—in respect to tumor biology, pathophysiology as well as clinical features—an entirely separate entity. *Classification:* In order to distinguish cardia carcinomas from other adenocarcinomas arising within the vicinity of the esophagogastric junction, a classification system has been introduced from a surgical viewpoint, and is now well established and increasingly used worldwide. According to the topography of the main tumor mass, cardia carcinomas (AEG II) are distinguished from adenocarcinomas of the distal esophagus (AEG I) and subcardiac gastric cancers (AEG III). The tumor-node-metastasis (TNM) staging system by the International Union Against Cancer (UICC) does not provide a separate classification for tumors of the esophagogastric junction. The use of the classification for esophageal or for gastric cancers is recommended, irrespective of the elementary differences in the classification of lymphatic spread implemented herein. *Discussion:* New aspects concerning this controversial debate are discussed based on current insights into the pathogenesis and the cellular origin of these entities. The controversies concerning the classification of cardia carcinomas and the failure of the current esophageal and gastric cancer staging systems to reflect the peculiarities of this entity accurately, present a strong argument in favor of a new classification system.

Keywords Esophageal cancer · Gastric cancer · Barrett's esophagus · Intestinal metaplasia · TNM classification

Introduction

Carcinomas of the cardia are localized in the topographical borderland between the esophagus and the stomach—the anatomical cardia. Controversy exists concerning their classification. Carcinomas of the cardia are regarded to share features of both, esophageal and gastric cancers. Neither from the pathogenetic nor from the clinical viewpoint the subsumption of cardia carcinomas is unequivocal.

In order to differentiate cardia carcinomas from other entities within the esophagogastric junction, a proper and unequivocal classification is of fundamental importance. In the meantime, a well-established model is in use, which is outlined in the first section of this article (Concept: adenocarcinomas of the esophagogastric junction).

Little is known about the *tumor biology* of cardia carcinomas, whether they share a cellular origin with adenocarcinomas of the distal esophagus, based on spe-

cialized intestinal metaplasia (IM), or if they have a similar pathogenetic basis to subcardiac gastric cancers [1]. These aspects are discussed in the second section (Biological controversy: cellular origin of cardia carcinomas).

The third section addresses the Clinical controversy: the *clinical*, prognosis-oriented tumor-node-metastasis (TNM) staging system by the International Union Against Cancer (UICC) [2] does not provide a separate classification for cardia carcinomas. It is recommended that staging of these tumors should be performed according to either the classification for gastric cancers or that for esophageal cancers, despite substantial differences between these two classifications.

Concept: adenocarcinomas of the esophagogastric junction

Most fundamental—for planning clinical therapeutic strategies and for obtaining comparable results from different institutions—is to unequivocally distinguish cardia carcinomas from other entities arising within the vicinity of the esophagogastric junction. Such a classification is essential for daily clinical practice (especially for choosing surgical approaches) as well as for comparing results from different institutions. For these purposes, a classification based on the topographic anatomy has been introduced [3, 4]. The localization of the main tumor mass—in relation to the anatomical cardia, defined by the proximal end of the gastric folds (Fig. 1)—is the major criterion for distinguishing true cardia carcinomas (AEG II), adenocarcinomas of the distal esophagus (AEG I), and subcardiac gastric cancers (AEG III; Fig. 2). A clinical rule defines 5-cm areas below and above the cardia as the primary topographical origin of AEG I, II, and III tumors (Fig. 2). In practice, the diagnosis and classification of
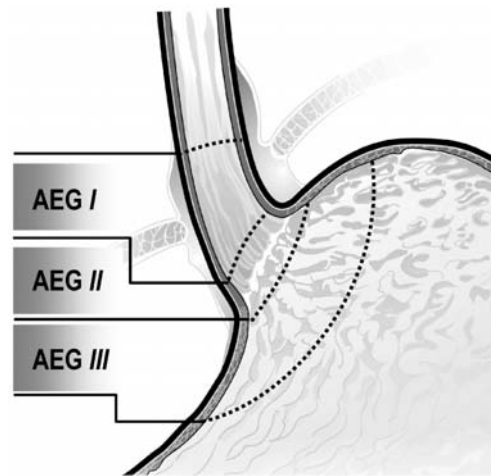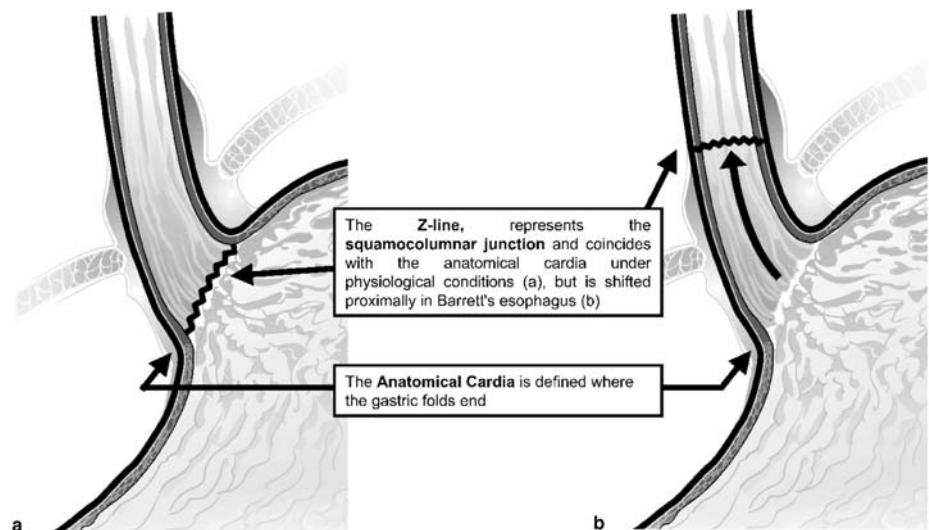

Fig. 2 Classification of adenocarcinomas of the esophagogastric junction according to Siewert et al. [3] and Siewert and Stein [4]. *AEG I* adenocarcinomas of the distal esophagus, *AEG II* cardia carcinomas, *AEG III* subcardiac gastric cancers

AEG tumors comprise a summary of different staging modalities (esophagoscopy + biopsy, pharyngo-esophagography, CT scan).

This classification system was accepted in 1997 by the consensus conference of the International Society for Diseases of the Esophagus and the International Gastric Cancer Association [4]. The classification is strongly recommended for international comparison of therapeutic results and is now increasingly accepted and used worldwide [5–8].

Initially introduced from a surgical viewpoint, current insights into pathogenesis reveal that the classification also reflects biologically different tumor entities, the latter especially in the light of the concept of Barrett's esophagus [1].

Fig. 1 Anatomy of the esophagogastric junction (EGJ) **a** under physiological conditions and **b** in patients with Barrett's esophagus

The **Z-line**, represents the **squamocolumnar junction** and coincides with the anatomical cardia under physiological conditions (a), but is shifted proximally in Barrett's esophagus (b)

The **Anatomical Cardia** is defined where the gastric folds end

Biological controversy: cellular origin of cardia carcinomas (the Barrett concept and intestinal metaplasia of the cardia)

Barrett's esophagus is the precancerous lesion for the development of Barrett's cancer. It is defined as specialized intestinal metaplastic epithelium in the distal esophagus—proximal to the anatomic cardia. The squamo-columnar junction (also known as the Z-line) is shifted proximally under this pathophysiological condition so that it is no longer at the same level as the anatomic cardia, which is defined by the proximal end of the gastric folds (Fig. 1) [9]. Barrett's esophagus is a combined endoscopic and histopathologic diagnosis, requiring both, endoscopic demonstration of the typical red- or salmon-colored mucosa and histological evidence of specialized IM.

The development of Barrett's esophagus, as well as the progression towards cancer, are regarded as the results of the chronically damaging effect of gastro-esophageal reflux. The latter promotes the IM through a metaplasia–intraepithelial neoplasia–carcinoma sequence toward Barrett's carcinoma [9, 10].

Almost all AEG I tumors are Barrett's carcinomas, developing on the basis of Barrett's esophagus. Formerly, a lower association (about 80%) between Barrett's esophagus and Barrett's cancer was assumed, but a recent investigation has shown that chemotherapy applied in a neoadjuvant setting may unmask Barrett metaplasia, which had been previously overgrown by the locally advanced cancer [11]. In this series the overall association of Barrett's mucosa with adenocarcinoma in the distal esophagus accounted for 97.4%.

By contrast to Barrett's esophagus and AEG I tumors, the role of histologically detected IM at the cardia, and its hypothetical pathogenetic link to AEG II tumors, is largely unknown and under intense controversial debate. Some authors report rather high rates of IM or short segments of Barrett's esophagus associated with AEG II tumors [12, 13]. They proclaim a common pathogenesis with Barrett's cancer. Some authors even regard IM of the cardia and Barrett's esophagus as a continuum of one and the same disease process [1, 14].

This theory is based on the concept that the cardia epithelium, previously regarded as physiologic, already constitutes the histopathologic appearance of an epithelium altered by reflux. Thus, the cardia epithelium, previously regarded as normal, is believed to be metaplastic by these authors. According to this theory, perpetuating reflux may either promote the cardia epithelium to IM with potential subsequent malignant transformation and progression to cardia carcinoma, or the IM "explodes" into the esophagus forming Barrett's esophagus, which may give rise to Barrett's cancer [14]. Thus, the supporters of this theory regard all adenocarcinomas at and in proximity to the cardia as a continuum of the same disease process.

This is, however, not proven. In our own experience (results of a retrospective analysis) we found an association of AEG II tumors with Barrett's esophagus in 10% [15]. A prospective analysis of primary resected AEG II early cancers showed an association with IM in 32% [1]. Predominantly, this IM was associated with the endoscopic aspect of (very) short segments of Barrett's esophagus or IM of the cardia without the endoscopic aspect of Barrett's esophagus (histological IM of the cardia).

The pathogenetic model—development of cardia carcinoma on the basis of IM—may thus only be valid for a minority of AEG II tumors. A predominant number of AEG II tumors have—in respect to epidemiology, morphological, and genetic aspects—more similarities with the subcardiac gastric cancers (AEG III) than with AEG I tumors [1]. Furthermore, the progression of microscopic foci of IM of the cardia toward Barrett's esophagus [16] and the longitudinal growth of Barrett's esophagus [12] has never been observed [1].

Clinical controversy

The prognosis-oriented TNM staging system by the UICC [2] does not provide a separate classification for carcinomas of the esophagogastric junction. No appropriate concept for discriminating these entities has been recommended, nor has an unequivocal recommendation for the use of a staging system been made. The UICC proposes to perform staging of cardia carcinomas according to the classification for either esophageal or gastric cancers.

This bears substantial difficulties due to the marked differences between these classifications. Esophageal and gastric cancers vary elementarily in their patterns of lymphatic tumor spread, with a predominant spread of esophageal cancers into the lower posterior mediastinum and the paracardial nodes, and the preference of gastric cancers for the abdominal compartment.

The TNM classification contributes to these substantial differences with the implementation of certain subclassifications of the N-category. In gastric cancer, the N-category is subclassified according to the number of involved lymph nodes: N1 (1–6 positive nodes), N2 (6–15 positive lymph nodes), and N3 (more than 15 positive lymph nodes). By contrast, for esophageal cancer the nodal involvement is merely classified as nodal positive (N1) and nodal negative (N0), irrespective of the number of lymph nodes involved. A peculiarity is that it is recommended that metastatic lymph nodes at the celiac axis be classified as systemic tumor spread (M1a) in esophageal cancers. By contrast, a subclassification of the M-category is not suggested for gastric cancers.

Further differences of the classification pertain to the staging of the primary tumor (T-category). The TNM classification for gastric cancers provides a subclassification for the T1 category (T1a = limited to mucosa, T1b = invasion of submucosa), which is (in clinical practice) also used for esophageal cancers as well. Subclassification of T2 tumors is again a special feature of gastric cancers, as T2a means "infiltration of muscularis propria" and T2b reflects "infiltration of subserosa or perigastric fat."

The pattern of lymphatic spread in cardia carcinomas is a controversial issue. Some authors have shown that these tumors tend to spread to both, abdominal and thoracic nodes [17, 18]. This is probably related to a wide definition of "cardia cancers." In our experience—with a proper and strict distinction of this entity based on published criteria [3, 4]—AEG II tumors are more likely to spread to the abdominal compartment and behave like gastric tumors in this respect [15]. The predominant localization of lymph node metastases in AEG II tumors are (in decreasing order of frequency of occurrence) the paracardial region, the lesser and greater curvature of the stomach, the celiac axis, the superior border of the pancreas, and the posterior lower mediastinum. By contrast, in AEG I tumors, the posterior mediastinum is more likely to be involved [19, 15]. In this respect, AEG II tumors are clearly different from AEG I tumors.

The appropriate classification for cardia carcinomas is of major importance for treatment. The mainstay of therapy for these tumors is surgical resection—provided staging does not show evidence of distant metastases and the patient is fit for a major surgical procedure [20]. The controversy regarding the classification of cardia carcinomas is closely related to the discussion about the appropriate surgical approach. A vast variety of techniques has been applied over the last few decades: abdominothoracic en bloc esophagogastrectomies, subtotal esophagectomies with resection of the proximal stomach, total gastrectomies with transhiatal resection of the distal esophagus (extended gastrectomy), and limited resections of the esophagogastric junction and proximal stomach. The main question is whether (sub)total removal of the esophagus and the mediastinal nodes and/or total removal of the stomach and upper abdominal nodes may be required.

Acceptable results with good 5- and 10-year survival rates can be obtained with a variety of approaches [15, 17, 21]. Nevertheless, it remains a question of major importance as to whether there is a need to remove the esophagus and perform a transthoracic approach, with its associated considerably higher morbidity [22], when similar results can be obtained with extended gastrectomy [15].

Conclusion

The controversies concerning the classification of cardia carcinomas and the failure of the current esophageal and gastric cancer staging systems to accurately reflect the peculiarities of this entity constitute a strong argument in favor of a new classification system. As such a system has not been devised so far, these tumors should be—according to the most important clinical feature, the pattern of lymphatic spread—currently classified as gastric cancers.

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