REVIEW

Navigating the complexities of developing a classification of esophagogastric junction tumors suitable for preoperative setting

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ABSTRACT
Despite the worldwide decrease in the incidence of gastric cancer, the proportion of occurrence of carcinomas of the esophagogastric junction and proximal third of stomach is on the rise. The cause of this development is believed to lie in an increasing incidence of reflux esophagitis with Barrett´s metaplasia and successful eradication of *Helicobacter pylori* infection. The aim of this work is to present various views on the definition of the esophagogastric junction itself and to give an overview of tumor classification schemes being used *(Fig. 2, Ref. 54). Text in PDF www.elis.sk*
KEY WORDS: gastric cancer, esophagogastric junction, definition, classification.

List of abbreviations: AJCC – American Joint Committee on Cancer, BE – Barrett's esophagus, EGJ – esophagogastric junction, GEJ – gastroesophageal junction, IGCC – International Gastric Cancer Congress, ISDE – International Society of Diseases of the Esophagus, SCJ – squamocolumnar junction, UICC – International Union Against Cancer, WHO – World Health Organization

Introduction

In recent years, there has been a change in the predominant histological type of esophageal cancer, as well as in the localization of esophageal and stomach tumors. At present, in our latitudes, adenocarcinoma of the esophagus prevails over squamous cell carcinoma, mainly due to the increasing incidence of gastroesophageal reflux disease and associated intestinal (Barrett's) metaplasia of the distal esophagus. The incidence of adenocarcinoma of the esophagus increases annually by 5–10 % (1). In the stomach, on the other hand, there is an increase of proximally located tumors (2,3). The reason for this trend lies in the increasingly successful eradication of *Helicobacter pylori* infection (1). However,

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the incidence of adenocarcinomas in the area of transition of the esophagus into the stomach is increasing, as shown by numerous population studies based on data from oncology registries (4–6). In the literature, we come across different designations for tumors involved in this area. Most often, these are tumors of the esophagogastric or gastroesophageal transition or junction (EGJ or GEJ). Sometimes the tumors are labeled as carcinomas of the cardia, which, due to the "anatomical" definition of the cardia itself, does not quite accurately reflect the true extent of tumor involvement. The inconsistency in the designation also results from the large number of proposed classification schemes that try to classify these tumors. These efforts have been the subject of ongoing discussions as some professionals consider cancers in this location to be esophageal, while others categorize them as gastric. These differing viewpoints have significant implications for choosing an appropriate treatment strategy. The classification itself not only aids in comparing the results of treatment, but also plays a crucial role in determining the most suitable treatment procedure, including the type of operation. In real-world scenarios, making preoperative decisions can become intricate when the performed endoscopic examinations yield vague descriptions such as "bulky tumor of the cardia" without further elaboration on the extent of involvement. Such situations are not uncommon and far from ideal for both patients and the surgeons. In the literature, the terms esophagogastric and gastroesophageal transitions, junction or just cardia are encountered, while only a few works provide precise definitions of these terms. Without well-defined terminology, it becomes difficult to conduct comparative analyses of the results achieved across different workplaces. Determining the correct treatment procedure, especially for tumors in this area is particularly challenging because disparate views extend beyond

individual specialties (anatomists, physiologists, endoscopists or histologists) and no agreement can be reached even among individual specialists within these groups, as will be mentioned later. From a historical point of view, the mere designation of the cardia as the part of the stomach closest to the heart, which is referred to as "cardia" in ancient Greek adds to the confusion (7).

Anatomical and physiological view on EGJ

From a purely anatomical point of view, the EGJ or cardia is considered to be the site where the "tube-shaped" esophagus passes into the "pouch-shaped" stomach. Under physiological conditions, this site externally corresponds to the sharp His' angle. This anatomical definition of the EGJ also serves as the basis for the Siewert classification of tumors in this area, which is a classification system most widely used in the world today. Unfortunately, this anatomical view by itself is hardly useful in preoperative planning and deciding about the type of operation. Physiologists define the EGJ as the distal border of the lower esophageal sphincter. However, this cannot be determined without performing esophageal manometry (8). There is no doubt that the sphincter mechanism in the region of the distal esophagus is one of the main factors that prevent gastroesophageal reflux, but its exact anatomical determination is still unclear even today. Attempts to prove the existence of the lower esophageal sphincter were already made in the middle of the past century. According to Lerche, the smooth circular muscle of the wall of the distal esophagus begins to thicken at the point of attachment of the ascending sheet of the phrenoesophageal membrane (endoabdominal fascia from the lower surface of the diaphragm). This enhancement continues distally, where the circular course of muscle fibers shifts to oblique orientation, and the enhancement concludes at the anatomically defined EGJ (9). As early as 1966, attempts to identify the lower esophageal sphincter anatomically were made by Bombeck whose investigation was conducted on 33 cadavers. In 12 cases, he did not demonstrate any strengthening of the circular muscle in the distal esophagus. However, in 21 cases, he demonstrated a very significant strengthening reaching up to an average height of 4.6 cm (range 3–7 cm) above the squamocolumnar junction (SCJ). By microscopic measurement, he found that the circular muscle layer was 1.8 times thicker in this area compared to other segments of the esophagus (10). He tried to disprove objections that this augmentation was caused by smooth muscle spasms in the cadavers by introducing a wide dilatation probe into the esophagus, which was kept *in situ* until fixation. However, this raised further doubts about the accuracy of the measurement because the distal esophagus is not dilated under physiological *in vivo* conditions (11, 12). Nowadays, the lower esophageal sphincter is understood rather as a site of increased intraluminal pressure at the transition of the esophagus to the stomach. Consequently, the practical clinical utility of the physiologically defined EGJ appears to be minimal.

Endoscopic definition

From the point of view of current diagnosis and classification of EGJ tumors, endoscopic examination with biopsy for histologi-
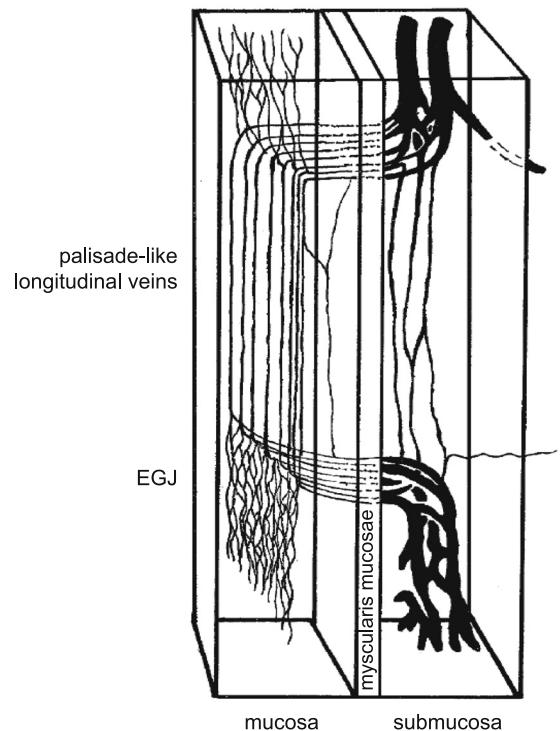

Fig. 1. Palisade-like longitudinal veins in mucosa of distal esophagus (freely according to Ishimura, 2009)

cal verification are the most relevant, yet controversial diagnostic procedures. The endoscopic definition of EGJ is twofold. Mainly in the Western world, it is defined as the proximal edge of the longitudinal mucosal cilia of the stomach (1, 13, 14). There is no exact determination for the distal border of the cardia. The SCJ is an endoscopically well-visible interface between the stratified squamous nonkeratinizing epithelium of the esophageal mucosa and the single-layered columnar epithelium of the gastric mucosa. However, according to many authors, this line (*linea serrata*, Z-line) does not correspond to the anatomically defined EGJ, not even in completely healthy individuals. Rather, it is displaced proximally by 3–11 mm (10, 15, 16). Bombeck published a study where the displacement averaged 11 mm (range 5–21 mm) in a total of 21 cases, while in Takuba's study, the displacement averaged 3 mm (range 0–10 mm) in 50 cases. These results also point to the fact that in the Western world, the incidence of columnar epithelium in the distal esophagus is higher than in Japan. Therefore, even in Japan, the SCJ is considered to be equivalent to the EGJ in most patients (17). A number of Japanese endoscopists find fault with the Western definition of the EGJ, specifically they find the description of it as the proximal border of the longitudinal gastric mucosa to be inaccurate. They particularly point to the fact that its position is influenced by the amount of air insufflated into the esophagus during endoscopy as well as by breathing, when it moves distally along with deep breath. With some exceptions (18), most Japanese endoscopists consider the distal edge of the palisade-like arranged

longitudinal veins that are present in the mucosa of the distal esophagus to be a more appropriate definition of the EGJ (Fig. 1) (19, 20). The veins in the esophageal submucosal layer run longitudinally and form into several main thick trunks. At the level of the diaphragmatic hiatus, they break through the lamina muscularis mucosae and form a palisade-like formation in the mucosa, which ends distally at the level of the anatomically defined EGJ, where it passes back into the submucosal layer and continues into the venous network in the submucosa of the stomach (19). This characteristic arrangement was also demonstrated by vasography (21). Based on these data, the Japanese Esophageal Society recommended using the distal edge of the palisade-like longitudinal veins in the mucosa as the endoscopic definition of the EGJ (22). However, even this definition of EGJ has its limits, especially in the presence of intestinal metaplasia of the epithelium of the distal esophagus. This caveat becomes more important due to the ever-increasing prevalence of Barrett's esophagus (BE), which ranges from 1.6 to 25 %, while the prevalence of long-segment BE is reported to be between 0.5 and 7.2 % and short-segment BE in the range of 1.1–17.2 % (23–28). Visualization may not be simple also due to insufficient distension of the distal esophagus during endoscopy or in the presence of a thick doubled muscularis mucosae. In the case of locally advanced EGJ tumors, often impenetrable to the endoscope, the endoscopic diagnosis becomes completely impossible.

Esophagogastric junction histology

Histologically, the cardia is characterized as an epithelial transition zone, i.e., SCJ. In this zone, tubular glands containing cells producing mainly mucus are present. In the short section between the cardia and the fundus of the stomach, there are also parietal (oxyntic) cells, either solitary or in small clusters. The extent of mucus-producing epithelium is variable (29). Cardia-type mucosa was not observed in 42.85 % of pediatric patients at autopsy (30). This led the author to hypothesize that cardia-type mucosa is an early histological manifestation of gastroesophageal reflux. The proximal edge of the gastric oxyntic mucosa should thus be defined as the „true" EGJ (31, 33). In other works, conversely, this specific mucosa was found in all cases in sets of dissected embryos, fetuses, or newborns (33–36). Its range varied from 0.3 mm shortly after birth to 4 mm in older children. Other authors describe the range of cardia-type mucosa, where cardiac glands are found, even larger, namely 3 – 15 mm (15, 37). The maximum length of the squamous epithelium under which these glands can occur has been reported to be between 1–5 mm (12). This is the reason why some surgeons tend to consider adenocarcinomas of the "true" cardia to be like tumors of the esophagus and choose the surgical procedure accordingly (32). The overview underscores the lack of a universally agreed-upon definition for EGJ. At the same time, the disparity in opinions on the etiology of carcinomas in the EGJ region remains persistent, which engenders complexities in establishing the preoperative diagnosis. This, at times, necessitates intraoperative adjustments to the intended surgical procedure, while the precise localization and extent of the tumor remain contingent upon post-examination of the resected specimen by the pathologist.

Classification of EGJ tumors

As with other locations, an unambiguous classification of tumors in the EGJ area is an essential prerequisite for the correct treatment strategy as well as for the possibility of conducting meaningful comparative analysis of achieved outcomes. Unfortunately, the vast majority of EGJ tumors are still diagnosed and treated at an advanced stage, and clinicians and pathologists are faced with the difficult decision as to whether the tumor originates primarily from the esophagus, stomach, or is a "true" cardiac tumor (1). Until recently, even the currently most widespread TNM system, the International Union Against Cancer (UICC), in agreement with the American Joint Committee on Cancer (AJCC), has not provided a completely clear solution to this question. In an effort to enhance clarity and achieve a general consensus, several classification systems have been developed, most of which are based on topographic-anatomical relationships. They are based on the localization of the center of the tumor or its predominant mass. The topographical classification of EGJ carcinomas was proposed by Ellis in 1980. He defined carcinomas of the cardia as tumors arising from the proximal third of the stomach and infiltrating the EGJ and the distal esophagus. Adenocarcinomas underlying Barrett's esophagus were not included, not even in case they infiltrated the EGJ (38–40). The so-called Liverpool classification of EGJ tumors was introduced in 1999 by Dolan (41). It was developed based on the analysis of more than 15,000 cases of cancer of the esophagus and stomach. In this classification, the EGJ is considered to be the proximal edge of the mucosal cilia of the stomach. Carcinomas that occupy the EGJ are classified as esophageal carcinomas in the EGJ subgroup. Esophageal carcinomas that do not progress to the EGJ are graded as esophageal in the distal third subgroup. Similarly, gastric carcinomas that are close to, but dot extend into the EGJ constitute a subgroup of carcinomas with a proximal gastric position. Carcinomas involving multiple parts of the stomach are considered gastric, even if they extend beyond the EGJ. Neither of these two classifications has gained wide acceptance. The definition of cardia (or tumors situated therein) that has been in use for a considerable period in Japan situates the proximal and distal margins of cardia 2 cm above and 2 cm below EGJ. EGJ itself is defined as the transition between the musculature of the esophagus and stomach. The definition is clinically diverse based on the criteria mentioned in the previous chapter. It just points to the fact that SCJ may not correspond to EGJ in some cases. Tumors in this area are classified as carcinomas of the cardia (regardless of their histological type) and are distinguished from tumors of the proximal third of the stomach. Their predominant direction of propagation is then the subject of a more detailed subclassification. In addition, the distance of the center of the tumor from the EGJ is recorded (12, 42, 43).

The TNM classification, in its 6th edition of 2002, differentiated between esophageal and gastric carcinomas, but lacked a separate classification of EGJ adenocarcinomas (44). In the sup-

plement of this edition, however, there was a recommendation to classify adenocarcinomas in the EGJ region as adenocarcinomas of esophagus, esophagogastric junctions, or cardia. The location of the main tumor mass was the decisive criterion. If more than 50 % of the tumor mass was in the cardia, then the tumor was designated as an adenocarcinoma of the cardia. In the case the main tumor mass located in the esophagus, it was considered esophageal. Additionally, it was specified that if a tumor in the EGJ region was associated with Barrett's metaplasia, its origin in the esophagus could be assumed (45). A weakness in this edition lies in inconsistent N staging for tumors of the esophagus and stomach. While for stomach tumors, the staging was based on the number of positive lymph nodes (N1–N3), for esophageal carcinomas, simple positivity or negativity of lymph nodes (N0 vs. N1) was evaluated. The 7th edition of the TNM underwent fundamental changes within the individual categories (46). The T category was modified and the N staging for tumors of the esophagus and stomach was unified. The pM1a classification for carcinomas of the esophagus and EGJ metastasizing to the lymph nodes in the region of the celiac trunk was canceled. Particularly noteworthy is that the inclusion of EGJ tumors in the schemes applicable to the esophagus and stomach was clarified. A tumor centered within 5 cm of the EGJ and extending into the esophagus is graded and staged using the esophageal scheme. Tumors centered in the stomach more than 5 cm from the EGJ or within 5 cm of the EGJ without spreading into the esophagus are classified and staged using the gastric scheme (46). Even with this clarification, not all possible cases are covered. As for locally advanced type III tumors, according to the Siewert classification (see below), no cases of T3 or T4 tumors can be classified according to the scheme for the esophagus. Instead, it would be more logical to use the scheme for the stomach. The revisions made in the 8th edition of the TNM classification represent a next step towards clarification, while even intercepting the latter logical inconsistency. In this edition, adenocarcinomas of the EGJ, specifically those with their center within 2 cm of the „anatomical" cardia (types I and II according to Siewert), are classified using the esophagus scheme. Carcinomas centered more than 2 cm distal to the cardia are also classified according to the scheme for the stomach (47) even in the case of EGJ involvement (type III according to Siewert). This latest modification in the globally accepted and extensively employed tumor classification aligns with the classification of EGJ adenocarcinomas, which was introduced by Siewert and Hölscher in 1987 and subsequently subjected to revisions (48–51). Their topographic-anatomic classification was unanimously adopted at the 7th meeting of the International Society of Diseases of the Esophagus (ISDE) in 1995 as well as at the 2nd International Gastric Cancer Congress (IGCC) in Munich in 1997 (52). Thus, the authors were the first to attempt to resolve the inconsistency and ambiguity in the classification of EGJ tumors by creating a third entity in addition to esophageal and gastric carcinomas (1). In this, so-called Siewert's classification, the term EGJ adenocarcinoma is used for tumors centered within a region defined by its proximal and distal boundaries, each 5 cm away from the anatomical EGJ and meet the condition of its infiltration (Fig. 2). Based on this definition, EGJ adenocarcinomas
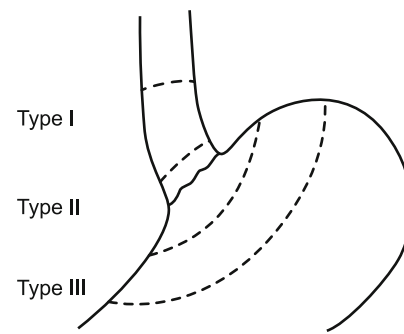

Fig. 2. Siewert´s classification of EGJ adenocarcinomas (freely according to Siewert and Stein, 1998).

are then categorized into 3 types according to their location. This classification plays a significant role in determining the type of surgery, where the first type is managed as esophageal and the third as gastric EGJ adenocarcinomas. For type II cases, there is no unanimous consensus regarding treatment. While extended total gastrectomy represents the prevalent approach in European countries, East Asian countries lean towards subtotal esophagectomy. It depends on the experience and habits of the workplace and also on the degree of involvement in the proximal direction of the esophagus.

Type I – adenocarcinoma of the distal esophagus with its center 1-–5 cm proximal to the EGJ. This type commonly originates from intestinal metaplasia of Barrett's esophagus and infiltrates the EGJ from tissue proximal to EGJ.

Type II – "true" adenocarcinoma of the cardia centered within an area delineated by its proximal and distal margins positioned 1 cm and 2 cm from the EGJ, respectively. This type originates from the cardia-type mucosa.

Type III – adenocarcinoma of the subcardiac part of the stomach centered 2–5 cm distal to the EGJ. This type infiltrates the EGJ and may extend to distal esophagus from tissue distal to EGJ.

The World Health Organization (WHO) provides its own classification (53). EGJ adenocarcinomas are defined as tumors extending across or "sitting" at the junction between the esophagus and the stomach, i.e., the definition is not based on the specific location of the main mass of the tumor. At the same time, the WHO classification advises against the misleading term "carcinoma of the cardia". Unlike other classifications, the WHO classification offers a more detailed categorization according to histopathological characteristics (54).

Conclusion

Currently, there is no universaly agreed-upon definition of esophagogastric junction. From a practical point of view, the classification systems based upon the combination of endoscopic and topographic-anatomical criteria seem to be the most useful option to date. The use of endoscopic definition may provide some preliminary information about the localization and extent of the

tumour prior to surgery. This preliminary understanding is then adjusted based on the actual topographic-anatomical site found peroperatively. Moreover this combination of criteria forms the base of the classification system developed by Siewert. The fact that it is the most widely used classification system allows for conducting meaningful comparative analyses of outcomes achieved across different medical settings.

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