3 Histopathologic Classification of Adenocarcinoma of the Esophagogastric Junction

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3.1 Introduction

In contrast to squamous cell carcinomas of the esophagus as well as adenocarcinomas of the distal or middle third of the stomach, the incidence of adenocarcinomas in the distal esophagus or EG junction increased continuously during the last decades. Initially, most of these cancers were thought to represent either esophageal or gastric carcinomas (especially the so-called "carcinomas of the cardia"). However, it became clear that the pathogenesis of these cancers exhibits differences. While most of the "true" adenocarcinomas of the distal esophagus arise predominantly on the basis of Barrett's metaplasia developing in the clinical setting of gastroesophageal reflux disease, the etiology of cancers of the cardia and the subcardial stomach remained unclear. In addition, the histopathological discrimination of these three types of adenocarcinoma remained difficult and arbitrary in a substantial part of the cases, especially if residual Barrett's epithelium could not be detected. On the other hand, surgical experience led to the conclusion that differentiated surgical approaches may be necessary depending on tumor stage and localization (Stein et al. 2000, 2003). On this background, Siewert et al. (Siewert et al. 1987; Siewert and Stein 1998) introduced a clinical topographic classification of carcinomas of the esophagogastric junction, which was based on the combination of contrast radiogram, endoscopy with orthograde and retroflexed view of the esophagogastric junction, computer tomography, as well as intraoperative observations. According to this classification, adenocarcinomas of the esophagogastric junction were defined as tumors which have their center within 5 cm proximal or distal to the endoscopic cardia. They are divided into three types (I–III) according to their location. Type I represents adenocarcinomas of the distal esophagus with the tumor center located more than 1 cm above the endoscopic esophageal junction. Type II carcinomas ("true" carcinomas of the cardia) are those having their center located within 1 cm oral and 2 cm aboral of the junction. Type III represents subcardial adenocarcinomas with the tumor center located more than 2 cm below the esophagogastric junction.

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3.2 Definition of the Esophagogastric Junction

The classification of the adenocarcinomas of the esophagogastric junction mainly depends on the definition of the esophagogastric junction itself. Anatomically, it represents the region where the tubular esophagus joins the stomach. Endoscopically, the esophagogastric junction is defined as the level of the most proximal end of the gastric folds (Boyce 2000). On the other hand, the esophagogastric junction is histologically defined as the squamocolumnar junction (SCJ or Z-line). However, the junction between squamous epithelium of the esophagus and gastric (cardiac) epithelium may occur at or up to about 2 cm above the anatomical junction. While in normal individuals the tubular esophagus is lined by squamous epithelium, it may also be lined by columnar epithelium especially in patients with hiatus hernia and gastroesophageal reflux disease. During the last years, controversies started with regard to the gastric cardia. According to the traditional definition, the gastric cardia starts at the squamocolumnar junction; however, its distal end is ill-defined.

Histologically, it is characterized by tubular glands containing mucus-secreting cells. In the transition zone between cardia and gastric fundus, parietal (oxyntic) cells are also present as solitary cells or as small cell groups. Therefore, the extent of the exclusively mucus-secreting epithelium is variable (de Nardi and Riddell 1997). These traditional definitions were questioned by Chandrasoma and coworkers in several studies. In one of them (Chandrasoma et al. 2000), a cardia-type mucosa was not observed in 3/7 pediatric patients at autopsy. The authors developed the hypothesis that cardia-type mucosa represents an early histologic manifestation of gastroesophageal reflux. According to their theory, an abnormal columnar-lined esophagus is characterized by the presence of cardia-type mucosa, oxynto-cardia-type mucosa, and intestinal metaplastic epithelium between gastric oxyntic mucosa and esophageal squamous epithelium (Chandrasoma et al. 2001). In consequence, the proximal limit of gastric oxyntic mucosa defined by histology should represent the true esophagogastric junction (Chandrasoma et al. 2006). However, in numerous further autopsy studies on embryos, fetuses, and infants (Kilgore et al. 2000; Glickman et al. 2002; Derdoy et al. 2003; de Hertogh et al. 2003), a columnar epithelium representing fetal or infant cardia-type mucosa could be observed in all individuals investigated. Its length was rather short (0.3–0.6 mm) at or after birth (de Hertogh et al. 2003) and varied in pediatric patients between 1–4 mm (Kilgore et al. 2000) or 0.1–3 mm (Derdoy et al. 2003). These data underline that cardia-type mucosa represents a normal histological structure at least during fetal and infant development. The length of cardia-type epithelium, especially in adults, may increase in patients with gastroesophageal reflux disease and extend proximally above the level of the anatomic esophagogastric junction into the distal esophagus (Glickman et al., 2002; Odze 2005). Apart from this controversy, if cardia-type mucosa represents a normal or a metaplastic epithelium, further aspects make the definition of "true carcinomas of the cardia" as a special subgroup problematic. In this context, the observations that cardia-type mucosa can also be found in the distal esophagus, that it rarely extends more than 2–3 mm below the squamocolumnar junction (Ormsby et al. 2000; Kilgore et al. 2000), and that the proximal stomach is predominantly lined by oxyntic epithelium (Chandrasoma 1997; Oberg et al. 1997) have to be mentioned. Therefore, an adenocarcinoma located in the anatomical region of the cardia must not be histogenetically derived from true cardia-type epithelium. Taking into consideration the discussion of these problems and controversies, a new WHO classification of tumors of the esophagogastric junction was introduced in 2000.

3.3 WHO Classification of Tumors of the Digestive System

3.3.1 General Principles

The WHO Classification of Tumors of the Digestive System (Hamilton and Aaltonen 2000) defines adenocarcinomas of the esophagogastric junction as "adenocarcinomas that straddle the junction of the esophagus and stomach." Adenocarcinomas confined to the distal esophagus, which are mostly Barrett's carcinomas, are designated as "adenocarcinomas of the esophagus." Gastric adenocarcinomas have to be confined to the stomach and do not cross the esophagogastric junction. In summary, the definition of these three tumor types is now based on their localization.

According to the WHO classification, the following guidelines should be applied:

1. "Adenocarcinomas that cross the esophagogastric junction are called adenocarcinomas of the EG junction, regardless of where the bulk of the tumor lies.
2. Adenocarcinomas located entirely above the esophagogastric junction as previously defined are considered esophageal carcinomas.
3. Adenocarcinomas located entirely below the esophagogastric junction are considered gastric in origin. The use of the ambiguous and often misleading term "carcinoma of the cardia" is discouraged. Depending on their size, these should be called carcinoma of the proximal stomach or carcinoma of the body of the stomach."

3.4 Histopathologic Subtypes

Adenocarcinomas of the distal esophagus derive from Barrett's mucosa in the vast majority of the cases. Histologically, they typically exhibit a tubular and/or papillary pattern and are mostly well or moderately differentiated (Paraf et al. 1995). However, signet-ring cell carcinomas and mucinous adenocarcinomas also occur in a minority of the cases.

Four types of adenocarcinomas of the esophagogastric junction are described in the WHO classification: papillary, tubular, mucinous, and signet-ring cell carcinomas. The latter two types are only rarely observed in the esophagus and the EGJ, and their frequency is considerably higher in the stomach (Wang et al. 1986). As a special tumor type, "pylorocardiac carcinoma" characterized by tall epithelial cells with a clear or pale cytoplasm and basal or central nuclei was described earlier (Mulligan and Rember 1954), but other authors found this pattern difficult to distinguish from other types of gland-forming adenocarcinomas (Stubbe Teglbjaerg and Vetner 1977). Two other rare types of carcinomas have to be encountered: the adenosquamous carcinoma seems to result from a dual differentiation leading to a mixture of glandular and squamous elements. Furthermore, the mucoepidermoid carcinoma of the esophagus should be distinguished. It arises from the mucous paraesophageal glands and resembles salivary gland tumors. The two components are more separated and the nuclear pleomorphism is increased.

3.5 Precancerous Lesions and Histogenetic Aspects

With regard to the etiology of adenocarcinoma of the distal esophagus, the decisive role of chronic gastroesophageal reflux and the consecutive development of Barrett's mucosa and Barrett's-associated intraepithelial neoplasia has been established (Lagergren et al. 1999; Mueller et al. 2000; Goldblum 2003; Fléjou 2005).

According to the WHO classification (Hamilton and Aaltonen 2000), all specimens

containing Barrett's epithelium should be assessed as negative, positive, or indefinite for intraepithelial neoplasia (formerly the so-called "dysplasia"). If intraepithelial neoplasia is present, it should be classified as "low-grade" (synonymous with mild or moderate dysplasia) or "high-grade" (synonymous with severe dysplasia and carcinoma in situ). The criteria applied for the grading of intraepithelial neoplasia comprise cytological as well as architectonical features (Schmidt et al. 1985; Antonioli and Wang 1997; Hamilton and Aaltonen 2000; Odze 2006). Since interobserver agreement on the grading of intraepithelial neoplasia is poor, in some European and most Far Eastern countries (Odze 2006) the so-called Vienna classification (Schlemper et al. 2000) has also been applied (Table 3.1). In the esophagogastric junction, intestinal metaplasia and intraepithelial neoplasia of the cardia-type epithelium are also observed and have been regarded as precancerous conditions (DeMeester and DeMeester 2000, DeMeester 2006). Obviously, both may also be related to gastroesophageal reflux disease. However, intestinal metaplasia of the cardia is only observed in a minority of the patients with Barrett's esophagus (Pereira et al. 1998). Furthermore, columnar epithelium-lined esophagus with specialized intestinal metaplasia was most commonly seen in Caucasian patients with reflux, whereas intestinal metaplasia at the esophagogastric junction was found in Caucasians with reflux and in African Americans without reflux with similar frequencies (Chalasani et al. 1997). Demographically, patients with intestinal metaplasia at the esophagogastric junction are different from patients with Barrett's esophagus. They have a higher prevalence of *Helicobacter pylori* infection and a lower prevalence of dysplasia as compared to Barrett's esophagus (Hirota et al. 1999; Sharma et al. 2000). Especially, the role of intestinal metaplasia in the context of Helicobacter infection remains unclear at the moment, particularly if it is concomitant with gastroesophageal reflux (Vigneri et al. 2000; Voutilainen and Sipponen 2001; Malfertheiner and Peitz 2005; Odze 2006). In summary, at least some clinical and pathological features indicate that Barrett's mucosa and intestinal metaplasia of the cardia-type epithelium represent two potentially different clinical processes. Barrett's mucosa and intestinal metaplasia of the cardia can be usually distinguished on the basis of H&E sections (Sarbia et al. 2004). In addition, various attempts were made in the past to evaluate whether additional immunohistochemical markers (especially cytokeratins or mucins) can help to discriminate both conditions. In 1999, Ormsby et al. reported that Barrett's mucosa shows a typical superficial CK20 staining as well as a strong CK7 staining of both superficial and deep glands in nearly all cases. On the other hand, this pattern was not observed in gastric cardia specimens with the evidence of intestinal metaplasia. During the following years, numerous other groups performed similar immunohistochemical investigations. As reviewed recently (Nurgalieva et al. 2007), only 8 of 15

Table 3.1 Vienna classification of gastrointestinal epithelial neoplasia (Schlemper et al. 2000)

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Noninvasive high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Noninvasive carcinoma (carcinoma in situ)[a]
	4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia
	5.1 Intramucosal carcinoma[b]
	5.2 Submucosal carcinoma or beyond

[a]Noninvasive indicates absence of evident invasion

[b]Intramucosal indicates invasion into the lamina propria or muscularis mucosae

comparative studies reported significant differences in cytokeratin staining patterns between Barrett's esophagus and intestinal metaplasia of the cardia with a high sensitivity (89–100%) and specificity (83–100%) for long-segment Barrett's esophagus and lower estimates for short-segment Barrett's esophagus, and seven studies showed no significant differences and a very low sensitivity. In conclusion, the role of cytokeratin immunohistochemistry in differentiating Barrett's esophagus, especially short-segment Barrett's esophagus, from intestinal metaplasia of the cardia remains controversial. In this context the definition of "positivity" and the subjectivity in the interpretation of the results obviously play an important role (Younes 2005).

Furthermore, adenocarcinomas of the distal esophagus, esophagogastric junction, and proximal stomach were also investigated immunohistochemically in order to evaluate possible histogenetic differences. However, most of them exhibited a $CK7^+/CK20^+/MUC1^+$ phenotype irrespective of the presence or absence of Barrett epithelium, which suggests a similar histogenesis of these tumors (Flucke et al. 2003). Other authors also observed that CK 7/20 profiles have no role in distinguishing tumors of the three locations (Gulmann et al. 2003), whereas another group (Taniere et al. 2002) reported that a $CK7^+/CK20^-$ pattern is highly suggestive of an esophageal origin as compared to an origin from the proximal stomach. Similarly, a $CK7^+/CK20^-$ profile was shown in 87.5% of type I, but only 35% of type II adenocarcinomas according to the Siewert classification (Mattioli et al. 2007). On the other hand, Driessen et al. (2004) observed an identical cytokeratin expression pattern $CK7^+/CK20^-$ in most esophageal and cardia adenocarcinomas. Therefore, the question of a particular histogenesis of the different types of adenocarcinomas of the EGJ as reflected by cytokeratin expression remains controversial.

3.6 Prognostic Aspects of Histopathologic Classification

In an analysis of 96 patients with Barrett's-associated adenocarcinoma (Torres et al. 1999), older patient age, higher pathologic stage (including depth of invasion and lymph node status), infiltrative growth pattern, perineural invasion, vascular invasion, and the absence of a peritumoral lymphoid infiltrate were associated with shortened survival according to univariate survival analysis in the entire cohort and in patients without chemoradiation, with the exception of infiltrative growth pattern (in the nonchemoradiation group). Subcategorization of lymph nodes according to the number involved with metastases had no further effect on prognosis. However, subcategorization of T1 tumors into T1a and T1b reflected differences in prognosis. Using multivariate analysis, only older patient age and the absence of a peritumoral lymphoid infiltrate were found to be statistically associated with poor survival independent of stage.

Another study (Fontana et al. 2003) involving 100 patients with carcinomas of the esophagogastric junction (5 type I, 54 type II, and 41 type III according to the Siewert classification) investigated the prognostic value of various histopathological classifications, Siewert's topographical classification as well as TNM classification. Summarized, histopathologic lassifications according to WHO, Laurén (1965) and Goseki et al. (1992) as well as Siewert's topographical classification did not reveal any differences with regard to survival probability. Only the TNM staging system, and particularly lymph node positivity, represented predictors of survival. Previously, Jakl et al. (1995) identified only residual tumor and depth of penetration as independent predictors of survival in multiple regression analysis of a series of 125 patients with resected "carcinomas of the cardia," whereas lymph node involvement and Laurén's classification did not

show additional significance. As compared with distal gastric carcinomas, the poor prognosis of proximal gastric cancers relied on the more advanced age and tumor stage at the moment of presentation as well as on the higher postoperative morbidity (Pacelli et al. 2001).

3.7 UICC Classification and Grading

Adenocarcinomas of the esophagus or stomach should be staged according to the new seventh edition of the UICC classification (Sobin et al. 2010), as shown in Tables 3.2 and 3.3. Carcinomas of the esophagogastric junction the epicenter of which is within 5 cm of the esophagogastric junction and thus also extend into the esophagus are classified and staged using the esophageal scheme. Tumors with an epicenter in the stomach greater than 5 cm from the esophagogastric junction are classified and staged using the gastric carcinoma scheme (Sobin et al. 2010). Compared to the previous sixth edition of the TNM classification, some pT and pN categories of the classifications of both esophageal and gastric cancers were revised. Furthermore, metastases of esophageal and esophagogastric junction carcinomas to celiac lymph nodes are no longer staged as pM1a.

Differentiation of adenocarcinomas of the distal esophagus, esophagogastric junction, or stomach should be graded as well, moderately or poorly differentiated.

Table 3.2 UICC classification of carcinomas of the esophagus and EG junction (7th edn 2010)

T – primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
	T1a Tumor invades lamina propria or muscularis mucosae
	T1b Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
	T4a Tumor invades pleura, pericardium, or diaphragm
	T4b Tumor invades other adjacent structures such as aorta, vertebral body, or trachea
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

3.8 Histopathologic Regression Grading after Neoadjuvant Therapy

During the last years, the concept of neoadjuvant (radio-)chemotherapy with regard to carcinomas of the esophagus, esophagogastric junction, and the stomach has developed rapidly (Schneider et al. 2005; Cunningham et al. 2006; Halliday et al. 2007; Ott et al. 2008). Recently, the United Kingdom National Cancer Research Institute (NRCI) Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated a significantly improved progression-free and overall survival for patients with operable gastric or lower esophageal adenocarcinomas, who received a perioperative regimen of infused epirubicin,

Table 3.3 UICC classification of carcinomas of the stomach (7th edn 2010)

T – primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa
T4	Tumor perforates serosa or invades adjacent structures
T4a	Tumor perforates serosa
T4b	Tumor invades adjacent structures
N – regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

cisplatin, and fluorouracil (ECF) (Cunningham et al. 2006). Consequently, perioperative chemotherapy in stage II and stage III esophageal and gastric cancers is suggested as a new standard of care in the Western World (Ott et al. 2008; Siewert et al. 2007). Since clinical response evaluations according to WHO criteria applying endoscopy, endoscopic ultrasound, and re-biopsy (Schneider et al. 2008) have been shown to be highly inaccurate, an objective morphologic response evaluation should be performed after surgery. In 1994, Mandard et al. established a tumor regression grading system using five grades: TRG1 (complete regression) with the absence of residual cancer and fibrosis extending through the different layers of the esophageal wall; TRG2 characterized by the presence of rare residual cancer cells scattered through the fibrosis; TRG3 exhibiting an increase in the number of residual cancer cells, but fibrosis still predominating; TRG4 shows residual tumor outgrowing fibrosis; and TRG5 is characterized by the absence of regressive changes. Subsequently, systems of tumor regression were introduced for gastric (Becker et al. 2003) as well as esophageal (Baldus et al. 2004; Schneider et al. 2005) cancer, which are based on the estimated percentage of vital residual tumor cells (VRTC). In the latter study, the degree for histomorphologic regression was classified into four categories (Schneider et al. 2005): grade I, >50% VRTCs; grade II, 10–50% VRTCs (partial response); grade III, nearly complete response (NCR) with <10% VRTCs; and grade IV, complete response (pCR, ypT0). Both studies demonstrated that tumor regression was significantly correlated with prognosis. With regard to gastric carcinoma, the accuracy of regression grading may be improved by adding additional staging variables such as tumor size and lymphatic vessel involvement. Regarding esophageal cancer, lymph node status represented an additional prognostic parameter for patients with complete resections (R0) following neoadjuvant radiochemotherapy. Therefore, a response classification system including tumor regression as well as lymph node metastases was proposed (Schneider et al. 2005), as shown in Table 3.4. In conclusion, the application of a regression classification based

Table 3.4 Response Classification System proposed for Esophageal Cancer (Schneider et al. 2005)

Class I	Minor histomorphologic regression (VRTC >10%)
a	With lymph node metastases
b	Without lymph node metastases
Class II	Major histomorphologic response (VRTC <10%)
a	With lymph node metastases
b	Without lymph node metastases

on two parameters could lead to an improved objective evaluation of the effectiveness of treatment protocols, accuracy of staging and restaging modalities, as well as molecular response prediction.

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