5 Differences in the Molecular Biology of Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

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Abstract Adenocarcinoma of the distal esophagus, gastric cardia, and upper gastric third are grouped in type I-III by the Siewert classification. This classification is based on the endoscopic localisation of the tumor center, and is the most important diagnostic tool to group these tumors. On a molecular level, there is currently no marker that would allow to differentiate the three different types. Furthermore, the Siewert classification was not uniformly used in the recent literature, making interpretation and generalization of these results difficult. However, several potential targets have been identified that may help to separate these tumors by molecular markers, and are summarized in this chapter.

5.1 Introduction

The incidence of cancer at the gastroesophageal junction is rising in the US and in Europe (Devesa et al. 1998). The increase of these junction tumors was accompanied by a simultaneous decrease of noncardia tumors of the stomach (Botterweck et al. 2000). A clinical classification of carcinomas of the gastroesophageal junction exists according to Siewert, distinguishing between type I (distal esophagus), type II (true cardia), and type III (subcardial tumors) (Siewert and Stein 1998). This classification is based on endoscopic appearance and defines the cardia as a zone of 2 cm at the proximal end of the longitudinal folds.

The clinical management of type I tumors includes, as for esophageal carcinomas, a transthoracic esophageal resection and a mediastinal and coeliacal lymphadenenectomy. Type II and III tumors are treated by abdominal, transhiatal extended gastrectomy with a D2 lymphadenenctomy (Stein et al. 2000; von Rahden et al. 2006).

Known prognostic factors are a complete (R0) resection and involvement of lymph nodes. Type I tumors metastasize to lymph node compartments in the mediastinum, whereas type II and III tumors spread mainly into the celiac compartment. A study with 145 patients found a significantly increased rate (24% vs. 7%) of micrometastasis in type II and III tumors compared with type I tumors (Mueller et al. 2000). A significant impact on survival for micrometastasis was observed in type I and II tumors in a series of 85 patients (Schurr et al. 2006).

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5.2 Microsatelite Instability (MSI) and Loss of Heterozygosity (LOH)

By comparing MSI and LOH by genomic hybridization, a significant difference was found on locus 14q31–32.1. This mutation occured more often in Barrett-related adenocarcinoma than in cardia cancer (van Dekken et al. 1999). This result was not confirmed by a following study and many others did not succeed in demonstrating any significant differences by genomic hybridization (El-Rifai et al. 2001; Marsman et al. 2004; Menke-Pluymers et al. 1996; Weiss et al. 2003; Yanagi et al. 2000). A comparative analysis using microarrays showed some differences between the two types but concrete and reproducible results must follow (Chang et al. 2004).

5.3 Difference in Phenotype on Histology and Immunohistochemistry

A prospective analysis of 1,346 patients observed intestinal metaplasia (Barrett's esophagus) adjacent to the tumor in 76.9% of the specimens and in 97.4% after neoadjuvant chemotherapy. In contrast, only 2% of the type III tumors exhibited this growth pattern. Similarly, 81% of the type I but only 39% of the type III tumors had an intestinal growth pattern (Siewert et al. 2005) (Table 5.1).

Cytokeratin (CK) 7 and 20 are structural proteins of the cytoskeleton. Intestinal cells express CK20, lining the glandular surfaces and crypts. CK7 is a marker of differentiated intestinal cells. A typical CK20/CK7 expression pattern was observed in long-segment Barrett's esophagus compared to the gastric cardia (Couvelard et al. 2001; Ormsby et al. 1999). This pattern was not seen in intestinal metaplasia in the stomach (Shen et al. 2002). The expression rate of the CK7/CK20 pattern may be lower in patients with a short-segment Barrett's esophagus (Liu et al. 2005). For the distinction of benign lesions, the value of the CK7/CK20 expression pattern is still under discussion (Nurgalieva et al. 2007).

For the differentiation of junctional carcinomas, the literature is also controversial; a positive predictive value of 87% was found for the CK7/CK20 phenotype in 85 cases. This sharp edged difference is supported by other studies (Mattioli et al. 2007; Taniere et al. 2002). But in several publications, no important difference in CK7/20 staining between esophageal and cardia cancer was observed (Driessen et al. 2004; Flucke et al. 2003; van Lier et al. 2005).

Mucin peptide core antigens were identified as markers for the progression of dysplasia in Barrett's esophagus (Arul et al. 2000). MUC1

Table 5.1 Clinical differences between esophagogastric junction tumors according to Siewert's classification

Clinical Phenotype	Type I	Type II	Type III
age	60	61	64
male/female ratio	10:1	5:1	2:1
intestinal metaplasia	76-97%	6%	1%
high grade (G3-4) tumors	54%	60%	73%
intestinal growth pattern (Laurén)	81%	55	38%
lymph node spread	mediastinal	celiac	celiac
pN+	55%	66%	79%
micrometastases	24%	24%	7%
gastroesophageal reflux	strong	+	weak
Helicobacter pylori	none	+	strong
previous cancer	++	+	++
survival after 5/10 years	50/40%	40/35%	25/20%

and MUC6 helped to differentiate intestinal metaplasia originating from a Barrett's esophagus only in some studies (Flucke et al. 2003; Glickman et al. 2003).

5.4 Differences in the Hallmarks of Cancer

Self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion are called the hallmark capabilities of cancer cells (Hanahan and Weinberg 2000). The tumor cell achieves these capabilities in a multistep process by mutation of genes leading to a gain or loss of function of gene products. Candidate genes for progression of Barrett's esophagus to adenocarcinoma have been described (Fitzgerald 2006; Morales et al. 2002). In the following sections, we will discuss important candidate genes and factors that are involved and may be different between type I, II, and III tumors of the esophagogastric junction (Table 5.2).

Table 5.2 Molecular differences between esophagogastric junction tumors according to Siewert's classification. A stronger association is represented by (+), and a weaker association by (–)

Molecular Markers	Type I	Type II	Type III
CK7/20 pattern	+		–
MUC 1/6	+		–
p53	+	+	–
COX-2	+	–	
APC hypermethylation		+	–
loss of p16	+	+	–
phosphorylated Rb		+	–
MAPK	–	+	+
b-catenin redistribution	+	–	

5.5 Self-Sufficiency in Growth Signals

In gastric cancer, chronic infection with *Helicobacter pylori* (Hp) is a known risk factor for the development of gastric carcinoma. Chronic Hp infection induces mitogen-activated protein kinase (MAPK) activity and subsequently activates mitogenic pathways (Kacar et al. 2007). Type II esophagogastric carcinomas showed a significantly higher rate of gastric Hp infection, compared to type I carcinomas (Mattioli et al. 2007). In contrast, chronic gastric Hp infection was associated with a statistically reduced risk for esophageal carcinoma and was not associated with cardia cancer in other studies (Anderson et al. 2008; Kamangar et al. 2006; Ye et al. 2004).

In Barrett's esophagus, repeated exposure to bile salts induces an increased proliferation (Kaur et al. 2000). Activation of proliferative signals by bile exposure involves inflammation-associated signaling pathways I kappaB kinases beta (IKK beta), tuberous sclerosis complex 1 (TSC1), and mammalian target of rapamycin (mTOR) downstream effector S6 kinase (S6K1) (Yen et al. 2008) or nuclear factor kappa B (Abdel-Latif et al. 2004) and c-myc (Tselepis et al. 2003). Bile reflux is also associated with intestinal metaplasia in the gastric cardia (Dixon et al. 2002). The localization of metaplasia may be related to the severity of reflux and the function of the lower esophageal sphincter (Csendes et al. 2002).

5.6 Insensitivity to Antigrowth Signals

Antigrowth pathways block proliferation or can induce a quiescent stage. Hypermethylation of the p16 gene, controlling the transition of the G2/S

phase, is a mechanism of neoplastic progression in esophageal neoplasia (Bian et al. 2002; Klump et al. 1998). Loss of p16 staining on immunohistochemistry was also significantly more frequent in cardia compared to noncardia gastric cancer (Kim et al. 2005). Hypermethylation of the APC locus may also contribute to esophageal cancer progression (Eads et al. 2000). APC mutations were observed to be significantly more in cardia than in distal gastric carcinomas (Tajima et al. 2007). Studies comparing the differences among all three types of junctinal tumors are lacking.

5.7 Evasion of Apoptosis

An important cell cycle control mechanism and potential switch to apoptosis is mediated by p53 (Levine 1997). Mutation-positive status for p53 has been shown to be a marker of progression to malignancy and an independent prognostic factor for patients after complete resection of a Barrett's carcinoma (Schneider et al. 1996, 2000). Mutations of p53 seem to occur in a similar frequency in distal esophageal and cardia carcinomas (Ireland et al. 2000). In more distal gastric carcinomas, this mutation is much less common (Flejou et al. 1999).

Increased expression of cyclooxygenase Type 2 (COX-2) is an important prognostic factor in Barrett's carcinoma (Buskens et al. 2002; Wilson et al. 1998). This expression was significantly weaker in cardia carcinoma than in the distal esophagus (Buskens et al. 2003; Marsman et al. 2004).

The enzyme 15-Lipoxygnase (15-LOX-1) showed a decreased expression in esophageal carcinoma. An upregulation of the enzyme and induction of apoptosis by NSAIDs could be demonstrated in vitro (Shureiqi et al. 2001). In gastric carcinoma cells, inhibition of 15-LOX-1 also induced apoptosis by upregulation of the enzyme (Wu et al. 2003).

5.8 Limitless Replicative Potential

Normal cells lack telomerase, the enzyme required to replicate the last 50–200 basepairs of the genome. Thus, every replication cycle shortens this region, finally inducing a growth-arrested G0 stage. Most human cancer cells reactivate telomerase; this was also observed in esophageal adenocarcinoma (Morales et al. 1998) and in gastric carcinomas (Gulmann et al. 2005). No difference was observed for the expression in both types of cancers and a diagnostic value seems improbable as this mutation occurs early in carcinogenesis (Barclay et al. 2005).

5.9 Sustained Angiogenesis

Expression of vascular endothelial growth factor (VEGF) is an essential and early step in the carcinogenesis of Barrett's adenocarcinoma (Auvinen et al. 2002; Couvelard et al. 2000). This was also shown for early gastric cancer (Cabuk et al. 2007). Expression of VEGF was a marker of progression and had a prognostic impact on disease free survival and overall survival in patients with gastric cancer (Kolev et al. 2007). There is a correlation of COX-2 expression and VEGF. Inhibition of COX-2 resulted in a decreased lymphangiogenesis in an experimental model (Iwata et al. 2007).

5.10 Tissue Invasion

The glycoprotein e-cadherin on the cell surface mediates the anchoring of cells via intracellular catenins and the actin cytoskeleton. Significant reduction of e-cadherin expression is a step in the dysplasia-adenocarcinoma sequence of Barrett's

esophagus (Bailey et al. 1998). Beta-catenin plays a structural role by binding to cadherins at the intracellular cell surface. It also has a role in downstream signaling by the wnt pathway and mediates transcriptional activation in a complex with lymphoid enhancer factor/T cell factor (Lef/Tcf) (Novak and Dedhar 1999). One study showed a significantly increased nuclear accumulation of beta-catenin in patients with esophageal adenocarcinoma, compared to patients with gastric cardia cancer (Marsman et al. 2004).

5.11 Conclusion

The anatomical classification by Siewert is safe and easily applicable and translates in a different surgical strategy for type I compared to type II and III carcinomas. The classification is nowadays widely, but not uniformly used. This makes interpretation of some results difficult.

Two major risk factors are identified for the development of adenocarcinoma in the gastroesophageal region: Gastroesophageal reflux and Hp infection. Gastroesophageal reflux has clear association with Barrett's carcinoma, the association with cardia carcinoma is only suspected. For gastric adenocarcinoma – and type III tumors are considered as such – there is a clear association with chronic Hp infection. This association seems less probable for type II carcinomas.

At the moment, the literature fails to show a clearcut molecular differentiation between the three types. Differences between distal esophageal (type I) and gastric (type III) carcinomas are partially established. These genes include p16 and p53. Cardia carcinomas (type II) differ from type I tumors in the expression of COX-2 and from type III tumors in APC mutational status.

Immunohistochemical discrimination by cytokeratin (CK7 and CK20) or mucin phenotype is considered to be controversial, although some studies showed promising results.

Further molecular differentiation of the three tumor types is mandatory and should follow a uniform classification.

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