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Comparison of loss of heterozygosity and microsatellite instability in adenocarcinomas of the distal esophagus and proximal stomach

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Abstract Adenocarcinoma of the gastroesophageal junction is rapidly rising in incidence. It has been proposed that these tumors be classified as three different types: distal esophageal (AEG I), cardia (AEG II), and subcardia (AEG III). Using comparative genomic hybridization (CGH) analysis, one recent study reported that the 14q chromosomal arm showed a significantly higher rate of deletion in esophageal than in cardia adenocarcinoma. Using a microsatellite analysis technique, we analyzed this area and regions in the vicinity of the *APC*, *DCC*, and *p53* genes. Tumor and normal tissues were microdissected from 54 cases (27 AEG I and 27 AEG III). DNA was extracted and then amplified using seven fluorescent-labeled microsatellite markers, one pair each on 5q, 18q, and 17p and four on 14q. The results were analyzed for loss of heterozygosity (LOH) and microsatellite instability (MSI). LOH varied from 20% to 30% at each locus except for the 17p locus, where it was slightly above 50% in both groups. No significant differences in LOH or MSI were found between the esophageal and gastric tumors, including the 14q chromosomal arm. These results fail to confirm the finding that abnormalities on the 14q chromosomal arm distinguish between distal esophageal and proximal gastric tumors.

Keywords Adenocarcinoma · Gastroesophageal unction · Loss of heterozygosity · Microsatellite instability

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Introduction

Adenocarcinoma of the gastroesophageal junction has the most rapidly rising incidence of all visceral malignancies in the industrialized Western world [1, 18, 27]. This is of particular concern since these tumors are often detected late and have a correspondingly poor prognosis [22]. The reasons for their rapid increase remain unknown, but is particularly striking in light of the fact that, in contrast, the incidence of gastric adenocarcinoma as a whole has seen a steady decline in the West for the past several decades [18]. Among other factors, this different epidemiology is one reason for the concept that tumors of the gastroesophageal junction, including distal esophageal, cardia and subcardial tumors, comprise a special group with distinct etiologic and biologic characteristics that distinguish them from tumors of the more distal stomach.

There is an ongoing discussion about the best means of classifying this group of tumors. At one end of the spectrum, some authors favor the concept that these are all essentially the same tumor type [6, 8]. Others, citing variations in epidemiology [7], their differing patterns of metastatic tumor cell spread, and the fact that they require different forms of surgical resection [23], favor a strict subdivision of these tumors into different types based on their location. One such proposal divides these adenocarcinomas of the esophagogastric junction (AEG) into distal esophagus tumors (AEG type I), cardia tumors (AEG type II), and subcardia tumors (AEG type III) [23].

Of these three AEG types, the carcinogenesis of tumors of the distal esophagus are the best understood, both in terms of the histopathology of the precursor lesions, but also, more recently, on the molecular genetic level as well. It is thought that practically all of these tumors arise in an intestinal metaplastic epithelium (Barrett's mucosa), in which low- and then high-grade dysplasia develops, followed by the transition to carcinoma. In contrast, the precursor lesions and carcinogenetic sequence of cardia and subcardial tumors are still poorly characterized, but may also be related to the process of intestinal metaplasia that takes place in response to gas-

troesophageal reflux or as a result of infection by *Helicobacter pylori* [2, 13, 22].

On the molecular biologic level, a variety of genetic changes have recently been described in tumors of the gastroesophageal junction. In particular, frequent allelic losses of 5q, 17p, and 18q [6, 28], rearrangement of 1p, 3q, 11p, and 22q and loss of the Y chromosome [12] have been described. Nearly all of these studies have found that these genetic changes are common in both distal esophageal and proximal gastric tumors, with no significant differences between them. However, one recent study, which compared groups of distal esophageal and proximal gastric tumors using comparative genomic hybridization (CGH), found that deletion of the distal portion (14q31–32.1) of chromosome 14q was common in esophageal, but not in proximal gastric tumors [25], a finding that might point to a basic difference in their carcinogenetic pathways.

In the present study, we examined loss of heterozygosity (LOH) of *APC*, *DCC*, and *p53* in patients with AEG type I and type III tumors of the gastroesophageal junction using microsatellite analysis. Based on the literature, we did not expect to find significant differences in the *APC*, *DCC*, or *p53* gene locations. However, using four sets of microsatellite markers on two areas of chromosome 14q (14q11–12 and 14q31–32.1), we hoped to confirm that this area was significantly more frequently involved in esophageal than in proximal gastric adenocarcinoma.

Materials and methods

Patient study group

The study involved the resection specimens from 54 patients with adenocarcinoma of the distal esophagus (AEG type I, *n*=27) or subcardial region of the proximal stomach (AEG type III, *n*=27) in the Department of Surgery of the Klinikum rechts der Isar, Technical University of Munich. The classification of the tumors as one of these two types was made according to a set of endoscopic, intraoperative, and pathologic macroscopic criteria as previously described [23]. In order to prevent potential overlap between the groups, AEG II tumors (adenocarcinoma of the true cardia) were not included. The clinicopathologic data of the two tumor groups are shown in Table 1.

Microsatellite analysis

Representative formalin-fixed, paraffin-embedded tissue blocks from tumor- and normal-appearing tissue areas were selected from each of the 54 specimens. Tissue sections (6-µm thick) were cut from these blocks, mounted on glass slides, and stained with a light hematoxylin solution. Matched tumor and normal tissue areas were microdissected either manually under microscopic control or, using a previously described method [26], with a ultra violet (UV) laser microbeam (P.A.L.M., Wolfratshausen, Germany). In the case of the tumor areas, at least 70% of the microdissected cells were estimated to be tumor cells. The microdissected material from each section was placed into 100 ml of buffer containing 50 mM Tris-HCl, pH 8.5, 1 mM ethylene diamine tetraacetic acid (EDTA), 0.5% Tween 20, 0.2 mg/ml proteinase K, 1 mg/ml for digestion at 55°C overnight. After inactivation of the proteinase K, the resulting DNA was used at a 1:10 dilution for polymerase chain reaction (PCR) amplification without purification, as previously described [9].

The seven loci shown in Table 2 were selected for microsatellite analysis, which was carried out according to a previously described method [9, 16]. These were D5S346 (5q21) in the vicinity of the *APC* gene, D18S34 (18q12.2) near the *DCC* gene, Tp53 near the *p53* gene, two loci, D14S80 and D14S75 on 14q12–13, and two loci on 14q31–32, D14S65, and D14S267. One oligonucleotide of each of the primer pairs was labeled with 6-FAM, TET, or HEX. An internal size standard, GS 500 (Applied Biosystems) was labeled with TAMRA. The PCR amplification reaction was performed in a 25-ml mixture containing 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 0.01% gelatin, 1.5 mM $MgCl_2$, 200 ml dNTPs, 0.4 mM of each primer, 1.25 U *Taq* polymerase, and 2 ml extracted DNA. Each PCR reaction consisted of initial denaturation at 94°C for 4 min, followed by 35 cycles of 94°C for 30 s, 55–60°C for 30 s, 72°C for 30 s, and a final extension at 72°C for 7 min. The resulting products were diluted (1:10–1:2), 1 ml was mixed with 2 ml formamide, 0.5 ml gel loading buffer, and 0.5 ml size standard. The products were then separated through gel electrophoresis on a Long Ranger Hydrolink gel (Biozym, Oldendorf, Germany) in 1× TBE (tris-borate plus EDTA) buffer in an automated fluorescent DNA sequencer, (ABI 377, Applied Biosystems, Norfolk Conn.). The data, including peak size, height, and area under the curve, were quantified and analyzed using Genescan software (Perkin Elmer Corp., Branchburg, N.J.). Microsatellite instability (MSI) was scored at a given locus when the carcinoma sample showed at least one peak that was not present in the corresponding normal sample. Allele ratios for the tumor samples were divided by the allele ratios of the corresponding normal samples and, if above 1.00, converted to a value ranging from 0.00–1.00. Values of 0.60 or below were scored as allelic imbalance, which were considered to represent LOH. Samples found to have MSI were not evaluated for LOH.

Table 2 The loci used for microsatellite analysis

Locus	Location	Length (bp)	Marker
D5S346	5q21	27	HEX
D18S34	18q12	17	FAM
Tp53	17p13	33	TET
D14S80	14q12–13	25	HEX
D14S75	14q12–13	19	TET
D14S65	14q31–32	25	TET
D14S267	14q31–32	32	FAM

Table 1 Patient data

Type	Esophagus	Stomach	Total
n	27	27	54
Age (years)	63.9 (34–76)	64.7 (26–84)	64.3 (26–84)
Male:female	26:1	20:7	46:8
T category[a](pT1:pT2:pT3:pT4)	18:3:6:0	4:15:7:1	22:18:13:1
pN0[b] *n* (%)	18 (66.7)	10 (37.0)	28 (51.9)
Differentiation (G1:G2:G3:G4)	0:11:14:2	0:14:12:1	0:25:26:3
Lauren type (intest:mixed:diffuse)	21:5:1	17:3:7	38:8:8

[a] P=0.00044
[b] P=0.02935

Statistical methods

The χ^2 and Fisher's exact test were used to compare results between groups. A P value of 0.05 or less was considered to be statistically significant.

Results

Histopathologic features

Overall, the patients had an average age of 64.3 years (range 26–84 years) and were predominantly male (85%). The tumors were classified with respect to stage according to the International Union Against Cancer (UICC) classification system [24]. Significant differences between the groups were seen with respect to the pT and pN categories, since the AEG III tumors were more advanced as a group. Histopathologically, the tumors of the two groups had similar proportions with respect to the degree of differentiation. A higher proportion of the AEG III tumors were of the diffuse or mixed types according to the Lauren classification [11] (37% AEG III vs 22% AEG I; P>0.05).

All of the AEG I cases had an associated Barrett's mucosa, and ten had chronic gastritis in the adjacent gastric mucosa, six of which had carditis. *H. pylori* was found in none of the AEG I cases. Among the 27 AEG III tumors, Barrett's mucosa was identified in none, 22 had at least some areas of chronic gastritis, of which 7 had gastritis involving the cardia. Only one AEG III case was proven to have had *H. pylori*.

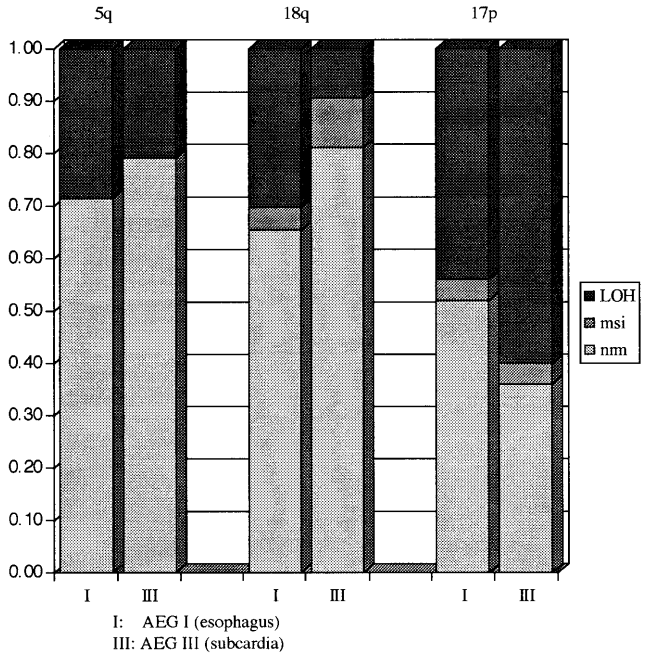

Fig. 1 The rates of loss of heterozygosity (LOH) and microsatellite instability are shown in comparison to tumor type, distal esophageal (AEG I) and subcardia (AEG III). Slightly higher rates of LOH are seen at 5q and 18q in the AEG type I tumors and at 17p in the AEG type III tumors, but none of the differences were significant

Table 3 The results of the microsatellite analysis. *AEG I* distal esophageal tumor type; *AEG II* cardia tumor type; *AEG III* subcardia tumor type; *LOH* loss of heterozygosity; *MSI* microsatellite instability

Locus	AEG I *n* (%)[a]	AEG III *n* (%)	Total *n* (%)
5q D5S346			
Informative	21	24	45
LOH	6 (29)	5 (21)	11 (24)
MSI	0 (0)	0 (0)	0 (0)
18q D18S34			
Informative	23	21	44
LOH	7 (32)	2 (11)	9 (22)
MSI	1 (4)	2 (7)	3 (6)
17p Tp53			
Informative	25	25	50
LOH	11 (46)	15 (63)	26 (54)
MSI	1 (4)	1 (4)	2 (4)
14q12 D14S80			
Informative	19	20	39
LOH	3 (18)	6 (33)	9 (26)
MSI	2 (8)	2 (7)	4 (8)
14q12 D14S75			
Informative	18	20	38
LOH	2 (13)	6 (32)	8 (23)
MSI	2 (8)	1 (4)	3 (6)
14q31 D14S65			
Informative	20	24	44
LOH	4 (21)	5 (23)	9 (22)
MSI	1 (4)	2 (7)	3 (6)
14q31 D14S267			
Informative	21	17	38
LOH	7 (35)	3 (20)	10 (29)
MSI	1 (5)	2 (10)	3 (7)

[a] Percentage for LOH calculated as: $n_{LOH}/(n_{informative}-n_{msi})$; percentage for MSI calculated as: $n_{msi}/n_{informative}$

Loss of heterozygosity

The results of the microsatellite analysis are summarized in Table 3, and the rates at the various loci are shown in Fig. 1 and Fig. 2. The highest rate of LOH overall was found at the 17p13 locus with 54%. All of the other loci had rates of LOH ranging from 22% to 29%, indicating that these chromosomal regions were also involved in the carcinogenesis of these lesions. Comparisons between the AEG I and AEG III tumors showed the greatest differences in rates of LOH at the D18S34 and D14S267 (more frequent in the AEG I tumors) and the Tp53 and D14S80 loci (more frequent in the AEG III tumors). However, none of the differences in rates of LOH was statistically significant (P values all greater than 0.05).

Microsatellite instability

With the exception of the D5S346 locus, which had no cases with microsatellite instability (MSI), all of the loci had two to four cases with MSI, for an overall percent-

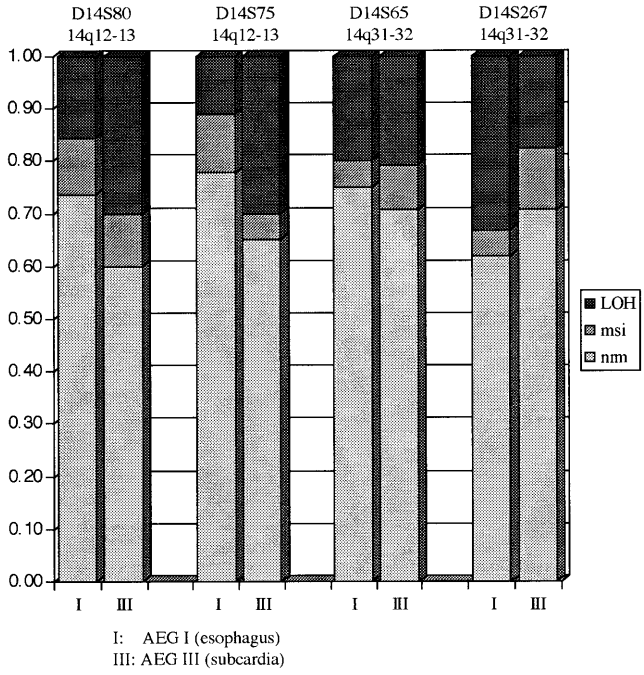

Fig. 2 The rates of loss of heterozygosity (LOH) and microsatellite instability shown in comparison to tumor type at the four 14q loci. At the two 14q12–13 loci, slightly higher rates of LOH were found in the subcardia (AEG type III) tumors and in the distal esophageal (AEG type I) tumors at one of the 14q31–32 loci, but none of the differences were statistically significant

age of less than 10%. There were no statistically significant differences in the rates of MSI between AEG I and AEG III tumors.

Discussion

APC, *p53*, *DCC;* MSI

Our results at the D5S346, Tp53, and D18S34 loci confirm those of previous studies that have shown that the 5q, 17p, and 18q loci are important for the carcinogenesis of adenocarcinomas of the gastroesophageal junction and that these show similar rates of abnormality between esophageal and proximal gastric tumors. Studies using CGH or microsatellite analysis have shown that 5q, 17p, and 18q are common regions of loss in these tumors and that there are no consistent differences between adenocarcinomas of the esophagus, esophagogastric junction, or stomach [6, 14]. Another study looked specifically at the question of whether there were differences with respect to *p53* or aneuploidy between distal esophageal and proximal gastric tumors [6]. One previous study found a rate of LOH at 17p of 79% in esophageal adenocarcinoma and a similar rate of 83% in tumors of the proximal stomach. The rates of *p53* mutations and aneuploidy were also similar for the two tumor types in that study. An additional area which has been studied is the chromosomal arm 17q, in which the rates of LOH in cardia and distal esophageal tumors were compared. Once again, however, no significant differences were found between these two tumor types [17]. Cytogenetic studies of the tumors of the gastroesophageal junction and esophagus have shown that deletions of 3q [20] and rearrangements of the 11p13–15 region [21] may be common events in both tumor types. In addition, interphase cytogenetics studies have shown a variety of changes in both esophageal and gastric tumors [19] but have not demonstrated any clear differences between them.

Compared with a previous study from our group that used microsatellite analysis to study tumors of the stomach as a whole [10], the rate of LOH at the D5S346 locus was similar between AEG III and all gastric tumors without a family history of gastric carcinoma (about 20%), was higher in the entire stomach compared with the AEG III tumors at 18q (about 25% compared with 11%), and was much higher at 17p in the AEG III tumors than in the stomach as a whole (63% vs 35%). This finding at 17p is interesting in light of the fact that tumors of the proximal stomach have been reported to have higher rates of p53 mutations than more distal tumors [3].

Despite the fact that we saw no significant differences in these three loci, it is interesting that the 18q locus had an almost three times higher rate of LOH in the AEG type I tumors, although these tumors were less advanced than the AEG type III group. The *DCC* gene is generally involved in the later stages of carcinogenesis in gastrointestinal tumors [4], and so this result is the opposite of what one might expect. Perhaps a larger number of cases might have shown that the difference between the two types at 18q was significant.

We found the rates of LOH at *APC*, *DCC*, and *p53* to be generally lower than has previously been found in adenocarcinomas of the esophagogastric junction. For instance, Wu et al. [28] found rates of LOH at 75% for 17p, 69% for 18q, and 46% for 5q. Our lower rates might be explained by the fact that our tumors, particularly the esophageal group, were less advanced and by the fact that other studies, such as that of Wu et al., have used multiple markers for each of the chromosomal arms, which increases the likelihood of being able to detect an LOH. The low rate of microsatellite instability that we found in this study is consistent with previous data that have shown that microsatellite instability is less common in tumors of the proximal than in the distal stomach [5].

14q

In contrast to the results of van Dekken et al. [25], who found a significant difference between esophageal and cardia carcinomas at 14q31–32 using CGH, we found no significant differences between the AEG I and AEG III tumors in our study. A direct comparison to the study of van Dekken is not absolutely possible since the defi-

nition of "cardia" carcinoma that he used was simply a carcinoma which "was clearly located in the proximal stomach", and tumors at the gastroesophageal junction were considered to be "nonclassifiable". Therefore, it appears that his "cardia" carcinoma was most closely equivalent to our AEG type III, and his "unclassifiable" tumors were most similar to the AEG type II tumors that we did not include. In van Dekken's study, only 1 of 10 cardia carcinomas, but 7 of 11 esophageal adenocarcinomas showed a deletion at 14q31–32, a significantly higher rate ($P<0.02$) among the esophageal tumors. In contrast, for our two loci at 14q31–32, one had a nearly identical rate of LOH in the esophageal and gastric tumors (21% and 22%) and the other a higher, but not significantly higher, rate in the esophageal tumors (35% vs 20%). At 14q12–13, we found an average rate of LOH of 33% in the subcardia carcinomas and only half that, 15%, in the esophageal adenocarcinomas at this site, a difference that was not significant. Abnormalities in this area were only seen in a total of four cases in the van Dekken study.

The differences between our studies at 14q12–13 could be easily explained on the basis that microsatellite analysis has a greater resolution and can detect areas of chromosomal loss that are not apparent when using CGH. However, at 14q31–32, we were unable to substantiate the high rate of deletion which van Dekken found in his esophageal carcinomas, although areas of deletion by means of CGH should be easily apparent using the microsatellite technique. The reason for this discrepancy is unclear, but we could not substantiate the concept that genes in this area (for example, TSHR) play an important role in the carcinogenesis of esophageal adenocarcinoma but not in the subcardia.

Summary

Based on our findings and those of most previous studies concerned with the molecular biology of adenocarcinomas of the esophagogastric junction, it appears that the basic sequence of carcinogenesis, with the involvement of genes, such as *APC*, *DCC*, and *p53*, are similar throughout the esophagogastric junction. Even additional, newly identified chromosomal areas, such as 17q or 11p [15], seem to be similarly important in esophageal and proximal gastric adenocarcinoma. It appears to be increasingly unlikely that gross chromosomal changes, which could be identified using a technique such as CGH, will be found that will allow differentiation of esophageal from cardia or subcardia adenocarcinomas. The differences in biologic and clinical behavior among these tumor types are more likely due to the differing anatomical relationships of these types or perhaps to discrete genetic changes which may only be apparent in terms of subtle differences in gene or protein expression.

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