

ORIGINAL ARTICLE

## Gastric adenocarcinoma under the age of 40; more metastatic, less differentiated

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### Summary

**Purpose:** Gastric carcinoma is relatively rare under the age of 40 years, and the mean age at presentation is 65 years. Histologically, adenocarcinoma prevails. Previous studies state that gastric adenocarcinoma under 40 is more aggressive. The present retrospective study was undertaken to clarify the clinicopathological characteristics of gastric adenocarcinoma in patients under 40 and to compare their clinical features with the patients over 40 years of age.

**Methods:** All of the patients with histologically diagnosed gastric adenocarcinoma who had applied to our department from March 2001 to September 2009 were retrospectively evaluated. Patients were stratified according to their age at diagnosis ( $\leq 40$  years; group 1, and  $> 40$  years;

group 2). Their clinical, laboratory, and pathological characteristics were analyzed.

**Results:** 251 patients were studied. Sixty-eight percent of those under 40 and 46% over 40 had poorly differentiated histology ( $p=0.036$ ). Fifteen (60%) patients under 40 and 73 (32.3%) over 40 had metastatic diseases ( $p=0.007$ ).

**Conclusion:** Younger patients with gastric adenocarcinoma have less differentiated, more advanced and metastatic disease. Patients' complaints, tumor localization, metastatic sites and smoking did not differ significantly between the groups. Controversy for survival parameters still exists.

**Key words:** age under 40, differentiation, gastric adenocarcinoma, metastasis

### Introduction

Gastric carcinoma is relatively rare in patients under the age of 40, and the mean age at diagnosis is 65 years according to some studies [1,2]. The incidence is nearly 10/100,000 for men and 5/100,000 for women [3,4]. Adenocarcinomas comprise 90-95% of all malignant gastric tumors, with the remaining consisting of lymphomas, stromal tumors, and other rare tumors such as gastric carcinoids [5].

Patients with gastric cancer may present with a variety of symptoms and the two most common symptoms are weight loss and abdominal pain. The other symptoms are early satiety, nausea, vomiting, and non-specific dyspepsia [6]. The two main histological types of gastric adenocarcinoma are the intestinal and the diffuse types by the Lauren's classification, and as expanding and infiltrating types according to the Ming's classification [7,8]. The less well-differentiated diffuse (infiltrating) type is considered an endemic type, and is more common in

women and younger patients [5]. Gastric carcinoma under the age of 40 was reported to be less differentiated and more aggressive in previous studies [2,5].

Upper gastrointestinal system endoscopy is the cornerstone for diagnosis of gastric carcinoma, and is more sensitive and specific than barium radiography. Endoscopy also helps make a biopsy and histologic evaluation. Measurement of serologic markers like CEA, CA 72-4, and CA 19-9 are of little importance and use for diagnosis or screening of gastric cancer and are not helpful in the evaluation and management of this disease.

Tumor stage and location play a critical role in determining the treatment of gastric cancer. The most common staging system used for gastric cancer is the one of the American Joint Committee on Cancer. This TNM staging system incorporates tumor depth (T), nodal stage (N), and presence of distant metastases (M) [9]. Computed tomography, abdominal ultrasonography and endoscopic ultrasonography are mostly utilized for the detection of distant metastasis, lymph node involve-

ment and depth of tumor invasion. Hundahl et al. demonstrated that 65% of gastric cancers in the USA present at an advanced stage (T3/T4), with nearly 85% of tumors accompanied by nodal metastasis at the time of diagnosis [10]. More than 50% of patients present with unresectable, locally advanced or metastatic gastric adenocarcinoma [11].

The risk factors for the development of gastric adenocarcinoma are chronic atrophic gastritis with intestinal metaplasia, gastric ulcer, subtotal gastric resection and adenomatous gastric polyps. *Helicobacter pylori* is also known to be a risk factor for the development of gastric adenocarcinoma [12].

This retrospective study was undertaken to clarify the clinicopathological characteristics of gastric adenocarcinoma in patients under 40 years of age and to compare their features with the patients over 40 years.

## Methods

All patients with a diagnosis of gastric adenocarcinoma who had applied to our department from March 2001 to September 2009 were retrospectively evaluated. A total of 251 patients with histological diagnosis of gastric adenocarcinoma was collected. Patients were stratified according to their age at diagnosis ( $\leq 40$  years; group 1, and  $> 40$  years; group 2). Their clinical, laboratory, and pathological characteristics were analyzed.

### Statistical analysis

Distribution of the continuous variables was determined by the Student's t-test for the independent variables, and One-Way ANOVA test for the dependent variables. All numeric variables were expressed as mean $\pm$ SD, and categorical variables were expressed

as percentages. The significance of correlations was assessed by Pearson's correlation analysis. For all statistics, a two-sided p-value  $< 0.05$  was considered statistically significant. SPSS for Windows, version 15.0 statistical package, was used.

## Results

### Patient characteristics

Of a total of 251 patients with gastric adenocarcinoma, 25 (9.96%) were under 40 (group 1) and 226 (90.4%) over 40 years of age (group 2). Thirteen patients under 40 (52%) were female and 12 (48%) male. The median age of 251 patients was 59 years (range 26-87). The median age of group 1 patients was 37 years (range 26-40) and of group 2 62 years (range 41-87). Co-morbidities included hypertension (22 patients, 8.76%), diabetes mellitus (15 patients, 5.97%), and coronary artery disease (14 patients, 5.57%). Two (8%) patients in group 1 and 28 (12.38%) in group 2 had a history of malignancy in their first-degree relatives ( $p=0.720$ ). Sixteen (64%) patients in group 1 and 140 (61.9%) in group 2 were non-smokers ( $p=0.280$ ) (Table 1).

The most usual complaint of group 1 patients was epigastric pain (56%), vomiting (24%) and difficulty at swallowing (8%). The complaints of group 2 patients were similar but weight loss was more common (13.4%). Concerning tumor localization, in group 1 patients corpus was the most usual localization (44%), while the distal part of the stomach (36%) and the cardia (16%) were less frequent localizations. The results of group 2 patients were similar (Table 2).

### Grade of differentiation

Fifty (19.9%) of 251 patients had well differentiat-

**Table 1.** Patient characteristics

Characteristics	Under 40 years n (%)	Over 40 years n (%)	Total	p-value
No. of patients	25 (10)	226 (90)	251	
Age, years, median (range)	36 (26-40)	62 (41-87)	59 (26-87)	
Sex				
Male	12 (48)	162 (71.6)	174	
Female	13 (52)	64 (28.4)	77	
Malignancy in first-degree relatives	2 (8)	28 (12.3)	30	NS
Non smokers	16 (64)	140 (61.9)	156	NS
Localization				NS
Cardia	4 (16)	26 (11.5)		
Corpus	11 (44)	111 (49.1)	226	
Distal stomach	9 (36)	59 (26.1)		
Others	1 (4)	20 (8.8)		

NS: nonsignificant

**Table 2.** Main patient complaints in the two groups

Complaint	Under 40 years n (%)	Over 40 years n (%)	Total n (%)	p-value
Gastric bleeding	1 (4)	13 (57.5)	14 (55.7)	NS
Epigastric pain	14 (56)	135 (59.7)	149 (59.3)	NS
Weight loss	1 (4)	33 (14.4)	34 (13.5)	NS
Anemia	0 (0)	2 (0.88)	2 (0.79)	NS
Difficulty in swallowing	2 (8)	4 (1.76)	6 (2.4)	NS
Vomiting	6 (24)	28 (12.4)	34 (13.5)	NS

NS: nonsignificant

ed, 80 (31.8%) moderately differentiated and 123 (49%) poorly differentiated adenocarcinoma. Sixteen percent of the patients in group 1 and 21.2% in group 2 had a well differentiated histology ( $p=0.032$ ). Sixteen percent of group 1 patients and 33.6% of group 2 had a moderately differentiated histology ( $p=0.025$ ). Sixty-eight percent of group 1 patients and 46% of group 2 had poorly differentiated histology ( $p=0.036$ ). In other words, 32% of patients under 40 and 54% over 40 years did not have a poorly differentiated histology ( $p=0.025$ ; Table 3).

#### Metastatic disease

Of all group 1 and 2 patients 88 (35.06%) had metastatic disease at presentation (15; 60% in group 1, and 73; 32.3% in group 2;  $p=0.007$ ). Locally advanced tumor (T4) was surprisingly seen in 20% of group 1 and 15.3% of group 2 patients ( $p=0.728$ ). This also means that 80% of the patients in group 1 and 47.6% of the patients in group 2 had unresectable disease at the time of diagnosis ( $p=0.025$ ). The most frequent metastatic sites were the liver (40%) and the peritoneum (33.3%) in group 1 and the liver (60.3%) and the peritoneum (22.06%) in group 2 (nonsignificant differences between groups). Other metastatic sites (only in group 2) included lungs and bones (Table 4).

## Discussion

In this study 25 patients with gastric adenocarcinoma aged 40 years or less were studied. We found that these patients had less differentiated tumors and more metastatic disease compared with older patients. Eighty percent of younger patients presented with an unresectable tumor.

Gastric adenocarcinoma is mostly diagnosed at the 7th decade of life and the mean age at diagnosis is 65 years [1,13]. The median age of our patients was 59 years (range 26-87). Nearly 5.5% of all gastric adenocarcinomas occur under the age of 40; in our study this ratio was 9.96%. A slight female predominance in the group under 40 years was registered, which coincides with previous studies [14,15].

To our knowledge most of the previous trials imply that tumor differentiation is lower in younger patients [16,17]. In the present study 68% of the patients under 40 had poorly differentiated adenocarcinomas, significantly more than in patients over 40 ( $p=0.036$ ). Signet-ring cell carcinomas, diffuse histology, aggressive behavior, and higher grade of malignancy is more frequent in patients under 40 years [18,19].

In our study no differences between the groups concerning tumor localization was found. However,

**Table 3.** Grade of differentiation in the two groups

Grade	Under 40 years n (%)	Over 40 years n (%)	Total	p-value
Well differentiated	4 (16)	48 (21.2)	52	0.032
Moderately differentiated	4 (16)	76 (33.6)	80	0.025
Poorly differentiated	17 (68)	102 (45.1)	119	0.036
Total	25 (100)	226 (100)	251	

**Table 4.** Metastatic disease

	Under 40 years n (%)	Over 40 years n (%)	Total (%)	p-value
Metastasis +	15 (60)	73 (32.3)	88 (35)	0.007
Metastasis -	10 (40)	153 (67.6)	163 (64.9)	
Total	25 (100)	226 (100)	251 (100)	

literature data suggest that gastric adenocarcinoma in younger patients is more likely to develop in the body of the stomach rather than the antrum or gastro-esophageal junction [13].

Younger patients were less likely to be diagnosed with localized or regional gastric carcinoma than older patients. Eighty percent of the younger patients presented with unresectable tumor. According to several authors one possible explanation is the higher proportion of poorly differentiated carcinomas observed in young patients that would be more likely to metastasize. Also, young patients may have not equal access to medical care, or may have lower socioeconomic status preventing them to seek prompt medical evaluation of symptoms of gastric carcinoma. It is also possible that physicians may order less tests to diagnose the disease because of the overall rarity of gastric carcinoma in young people [13,17,19]. A study of gastric carcinoma patients in Los Angeles indicated that clinicians were more likely to establish a preoperative diagnosis of gastric carcinoma in older than in younger patients, indicating that standard tests used to diagnose this cancer were less sensitive in younger patients [19]. A delay in diagnosis may allow gastric carcinoma cases in the young to reach a more advanced stage before definitive diagnostic tests.

Younger patients have more advanced disease. In the present study 60% of these patients had metastatic disease and 20% had T4 tumor, while the percentage of metastatic disease in the older group was 32.3% and T4 tumor 15.3% ( $p=0.007$ ). Kim et al. reported that 80.3% of patients under 36 years had advanced disease [17], similar to our findings.

The most frequent site of metastasis in both groups was the liver (40 and 60.3% in group 1 and 2, respectively) and the peritoneum (33.3 and 22.06% in group 1 and 2, respectively), in concordance with the relevant literature [20,21]. No hereditary cases were detected in our patients of both groups. Also, although smoking is reported as a risk factor for gastric adenocarcinoma, most of the patients in both groups were non-smokers.

In conclusion, younger patients with gastric adenocarcinoma have less differentiated, more advanced and metastatic disease. Patients' complaints, tumor localization, metastatic sites and smoking did not differ significantly between the groups. Controversy for survival parameters still exists.

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