Pathol. Oncol. Res. (2013) 19:111–117
DOI 10.1007/s12253-012-9530-z

METHOD

Analysis of Clinicopathologic Characteristics and Prognosis of Gastric Cancer in Young and Older Patients

Amelia Tavares · Antonio Gandra · Fernando Viveiros · Cassilda Cidade · Jorge Maciel

Received: 6 December 2011 / Accepted: 27 March 2012 / Published online: 10 May 2012

Abstract
Background The worldwide incidence of gastric cancer is gradually declining, however it remains the fourth highest in cancer incidence and the second leading cause of cancer death. Gastric cancer in young people is a disturbing problem and the routine screening does not include people less than 35 years. The clinicopathological features of gastric carcinoma are said to differ between young and elderly patients and it is thought that the prognosis of this disease is worse for younger patients. It is also suggested that the diagnosis is usually made later or have a more aggressive behaviour. Although, others report that tumor staging and prognosis for young patients is similar to older patients and depends on whether the patients undergo a curative resection. All these data need more investigation and studies. Although Portugal has a high incidence of gastric cancer, no studies have yet been performed comparing the clinicopathologic features and prognosis of young and elderly patients with gastric cancer.
Aims This study intend to assess whether the clinicopathological features and prognosis of gastric cancer in young patients (YGC) is similar to older ones (OGC).
Methods Between 2000 and 2005, 406 patients with histological diagnosis of primary gastric cancer, treated in the Departments of Surgery and Oncology at the Centro Hospitalar of Vila Nova de Gaia / Espinho, were regularly followed at least for five years after surgery. These were reviewed retrospectively. Several variables were analyzed in young patients and compared with the elder ones. We used the chi-square and Fisher to evaluate the statistical association between categorical variables and *t*-test for numeric variables. Survival was estimated by the Kaplan-Meier method and used the log-rank test to assess differences in survival among different subgroups of patients. The criteria for statistical significance was $p<0.05$. Data analysis was performed using the SPSS 18.
Results and Conclusions With regard to resectability, 78 % of the tumors were resected in the group of younger patients, the surgery more frequently achieved was total gastrectomy with anastomosis in Y of Roux. In the elder group, about 62 % of the tumors were resected and BII gastrectomy was the most frequent surgery. The diffuse adenocarcinoma was the most frequent histological type in younger patients, whereas in older patients was intestinal adenocarcinoma. With regard to the stage in the first group there was a predominance of stages: IA and IV (26.1 %) in the second: IV (25.8 %). The survival for stage III e IV was significantly worst in YGC compared with OGC.

Keywords Cancer gastric · Prognostic · Age

Introduction

The worldwide incidence of gastric cancer is gradually declining, however it remains the fourth highest in cancer incidence and the second leading cause of cancer death (10.4 % of cancer deaths) [1]. Every years, 900,000 new cases of gastric cancer are diagnosed, and 700,000 die of this disease, worldwide. Over 70 % of cases occur in developed countries [2]. Portugal is one of the European countries with the highest incidence of this pathology, especially in the northern region. In our country, according to data from Globocan 2008, gastric cancer is the malignant neoplasm with the third highest incidence (2889/100000) and mortality rate (2423/100000).

A. Tavares (✉) · A. Gandra · F. Viveiros · C. Cidade · J. Maciel
Centro Hospitalar de Vila Nova de Gaia/Espinho,
Vila Nova de Gaia, Portugal
e-mail: ameliassbtavares@gmail.com

It is thought that gastric cancer results from a combination of environmental factors and the accumulation of generalized and specific genetic alterations, and consequently affects mainly older patients after a long period of atrophic gastritis. The most common cause of gastritis is infection by *Helicobcter Pylori,* which is the single most common cause of gastric cancer and has been classified by the World Health organization as a class I carcinogen [3, 4]. The risk of infection varies with age, geographical location and ethnicity, but overall 15–20 % of infected patients develop gastric or duodenal ulcer disease and less than 1 % will develop gastric adenocarcinoma [5]. The response to *H. pylori* infection and the subsequent pattern of gastritis depends on the genotype of the patient [6]. Multifocal atrophic gastritis is usually accompanied by intestinal metaplasia and leads to cancer via dysplasia, and thus intestinal metaplasia is considered to be a dependable morphological marker for gastric cancer risk. Unlike intestinal gastric cancer, the diffuse type typically develops following chronic inflammation without passing through the intermediate steps of atrophic gastritis or intestinal metaplasia [7]. The contribution of the infection to the development of gastric cancer in young patients has not been elucidated, simply because the incidence of gastric cancer is low in the young. Even in pathological investigations, there have been only sparse data regarding the characteristics of the background gastric mucosa in young patients [28].

Gastric cancer in young people is a disturbing problem and the routine screening does not include people less than 35 years. This condition is difficult to diagnose in young asymptomatic even in advanced stages. The proportion of patients with gastric cancer under the age of 40 years varies between 2 and 9 %, and most present with an age over 35 years. Thus, this disease rarely appears in patients under 30 years. Thereafter it increases rapidly and steadily to reach the highest rates in the oldest age groups, both in males and females. The intestinal type rises faster with age than the diffuse type and is more frequent in males than in females. Young patients more frequently develop diffuse lesions, which often arise on the background of histologically "normal" gastric mucosa. It is postulated that genetic factors may be more important in young than in older patients as younger patients have less exposure to environmental carcinogens [7, 8].

The clinicopathological features of gastric carcinoma are said to differ between young and elderly patients and it is thought that the prognosis of this disease is worse for younger patients [9, 10, 29, 32]. It is also suggested that the diagnosis is usually made later or have a more aggressive behaviour. Although, others report that tumor staging and prognosis for young patients is similar to older patients and depends on whether the patients undergo a curative resection [11–13]. Little is known about the clinicopathological features and prognosis of gastric cancer in young European adults [31]. In other regions of the world (Japan, Taiwan, Korea, USA, Mexico and South Africa), young patients have a female preponderance, and a more frequent occurrence of diffuse cancer and less intestinal Metaplasia, comparing with older patients [14–16, 31]. This predominance of females is considered by some to be due to hormonal factors (some investigators defend a harmful role of estrogens) [17, 18, 29]. *Chung* et al. reported that their results may imply that excessive exposure to estrogen without counter exposure of progesterone is related to an increase in the development of gastric cancer in young female patients. Cancers in young patients are more often multifocal than in older patients [19]. Approximately 10 % of young gastric cancer patients have a positive family history [15], some of which are accounted for by inherited gastric cancer predisposition syndromes. Although the underlying genetic events are not always known, it can involve *CDH1* germline mutations, encoding an aberrant form of E-cadherin, resulting in hereditary diffuse gastric cancer (HDGC) [20, 21]. The 90 % without a family history emphasizes that the occurrence of gastric cancer in young patients remains largely unexplained, and is probably caused by a predisposing genotype that has facilitated cancer development due various environmental triggers [5]. Genetic alterations, such as activation of oncogenes K-*ras* and B-*raf* and inactivation of tumor suppressor gene *p53*, play important roles in the development of gastric cancers [22]. Dysfunction of DNA mismatch repair genes, which leads to microsatellite instability (MSI), also plays a crucial role [26]. Gastric cancer can occur as a hereditary non-polyposis colorectal cancer, whereby alterations in the mismatch repair genes (*hMLH1*, *hMSH2*, *hMSH6*, etc.) are responsible for colorectal, gastric, and endometrial tumor formation. Disrupted function of mismatch repair genes manifests as MSI and has been reported in 15–39 % of sporadic gastric cancer [27].

All these data need more investigation and studies. Although Portugal has a high incidence of gastric no studies have yet been performed comparing the clinicopathologic features and prognosis of young and elderly patients with gastric cancer.

Methods

Between 2000 and 2005, 406 patients with histological diagnosis of primary gastric cancer, treated in the Departments of Surgery and Oncology at the Centro Hospitalar of Vila Nova de Gaia / Espinho, were regularly followed at least for 5 years after surgery. These were consecutively reviewed retrospectively. Patients were followed up regularly every 6 months and examined by upper endoscopy and

CT scan at least once a year. The following patients were excluded from the study: cases of gastric cancer other than adenocarcinoma, patients in which the 5-year follow-up after surgery weren't possible and patients who died of other causes not related with gastric pathology. The study was approved by the Ethical Committee of the institution and all patients included in the study gave their consent.

We divided our population into two groups according to age with the cut-off of 40 years. The patients records were analyzed for gender, symptoms, histological features, treatment and survival, and compared between the 2 groups. We used the chi-square and Fisher to evaluate the statistical association between categorical variables and *t* test for numeric variables. Survival was estimated by the Kaplan-Meier method and used the log-rank test to assess differences in survival among different subgroups of patients. The criteria for statistical significance was $p<0.05$. Data analysis was performed using the SPSS 18.

Results

Clinicopathological Characteristics of Patients (Tables 1 and 2)

Of the 406 patients, 383 were classified as adenocarcinoma and the highest number of cases were in 2005 (Table 1). The incidence of gastric cancer showed a tendency to increase with age until the seventies and then decrease from eighties (Fig. 1). Of the group of gastric adenocarcinoma 23 patients presented with an age less than 40 years.

The male to female ratios in the YGC and OGC were 1:0.92 and 1:0.74 respectively, with a small higher incidence of females in YGC group.

The presence of co-morbid conditions was always higher in the OGC group, being the most frequent pathologies including hypertension, diabetes and heart disease. Risk factors for gastric cancer were more prevalent in OGC group, except drinking habits, Helicobacter pylori infection and family history that were more frequent in YGC group (Table 2).

The clinical presentation was similar between the two groups, it was found a duration of symptoms to diagnosis

Table 1 Gastric tumors diagnosed between 2000 and 2005

	2000	2001	2002	2003	2004	2005	Total
Adenocar.	65	64	55	49	67	83	383
Lymphoma	1	5	3	1	0	2	12
GIST	1	3	0	2	0	1	7
Neuroend. T.	0	0	0	0	2	1	3

Table 2 Clinicopathological characteristics of patients included in the study

	≤40 Years		> 40 Years		*P* value
	N	%	N	%	
Gender					
Male	12	52,2 %	207	57,5 %	NS
Female	11	47,8 %	153	42,5 %	
Risk Factors					
Obesity	0	0 %	14	4 %	NS
Drinking habits	4	17 %	47	13 %	NS
Previous gastric Surg	0	0 %	22	6 %	NS
Chronic gastritis	8	35 %	172	48 %	NS
HP infection	2	9 %	14	4 %	NS
Intestinal metaplasia	5	23 %	108	30 %	NS
Smoking	8	35 %	65	18 %	NS
Familial history	2	9 %	14	4 %	NS
Symptoms					
Anorexia	8	34,8 %	186	51,7 %	<0,05
Abdominal pain	12	52,2 %	160	44,4 %	NS
Bleeding	3	13 %	100	27,8 %	NS
Nausea	8	34,8 %	83	23,1 %	NS
Histological type					
Intestinal adenocarcinoma	8	34,8 %	255	70,8 %	<0,0001
Difuse adenocarcinoma	15	65,2 %	105	29,2 %	
Differentiation					
Well	4	17,4 %	56	15,6 %	<0,05
Moderate	7	30,4 %	215	59,7 %	
Poor	12	52,2 %	89	24,7 %	
T					
1a	6	26,1 %	23	6,4 %	0,036
1b	1	4,3 %	29	8,1 %	
2	3	13 %	54	15 %	
3	1	4,3 %	17	4,7 %	
4a	5	21,7 %	72	20 %	
4b	7	30,4 %	165	45,8 %	
N					
0	8	34,8 %	99	27,5 %	NS
1	4	17,4 %	33	9,2 %	
2	2	8,7 %	34	9,4 %	
3a	3	13 %	34	9,4 %	
3b	1	4,3 %	21	5,8 %	
Not possible	5	21,7 %	139	38,6 %	
TNM					
IA	6	26,1 %	47	13,1 %	0,05
IB	0	0 %	29	8,1 %	
IIA	4	17,4 %	16	4,4 %	
IIB	2	8,7 %	27	7,5 %	
IIIA	1	4,3 %	24	6,7 %	
IIIB	0	0 %	42	11,7 %	
IIIC	3	13 %	39	10,8 %	
IV	6	26,1 %	97	26,9 %	
Not possible	1	4,3 %	39	10,8 %	

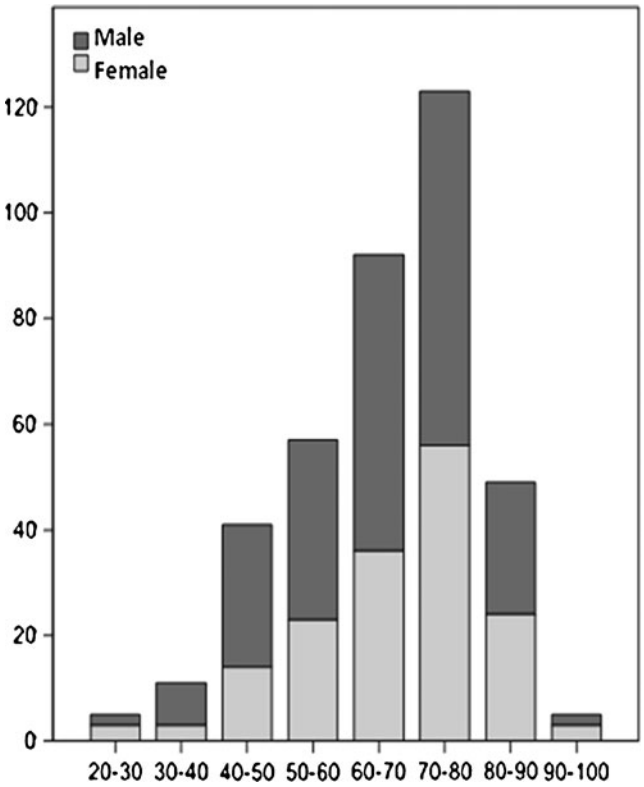

Fig. 1 Distribution of population by sex and age groups

of 6.9 months in the YGC group and 5.4 in OGC. This data can indicate that, athough the symptons, the young patients appeal the medical services later than older ones.

The resectability rate was higher in YGC with 83 % of resectable tumors versus 63 % in group OGC. The most common surgical procedure was a total gastrectomy (43.5 %) in the YGC group, while in the OGC group was the parcial gastrectomy with gastro-jejunal anastomosis BII (36.7 %) (Fig. 2), which can translate a more aggressive tumors in the first group.

As expected by greater incidence of co-morbidities in the OGC group, about 94 % of the overall postoperative morbidity occurred in this group, with respiratory infection as the most common complication. Similarly, 98 % of the overall postoperative mortality occurred in the OGC group (98 %, $p=0.013$).

With regard to histological type, we obtained statistically significant differences. The most frequent type in the OGC group was intestinal adenocarcinoma (71 %), while in the YGC group was diffuse adenocarcinoma (65 %). Besides the diffuse type had been more frequent in the YGC group, which in general has a poorer prognosis in relation to the intestinal, in this group, most tumors were undifferentiated (52.2 %) (Fig. 3), which also entails an increased aggressiveness. In OGC group tumors were mostly moderately differentiated (59.7 %). There was no statistical difference in tumor location, tumor size, macroscopic type, lymphatic permeation and vascular invasion between the two groups.

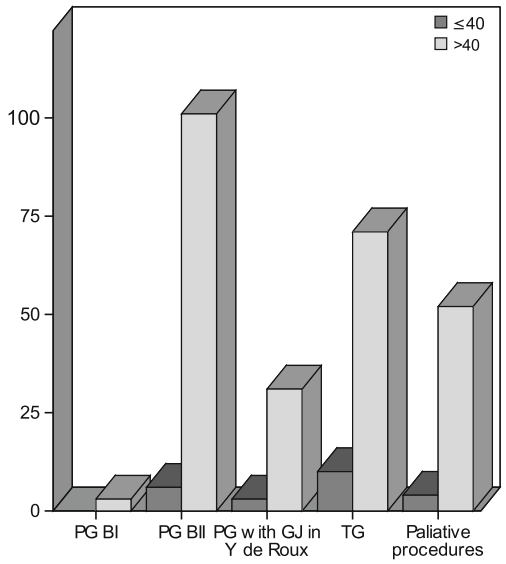

Fig. 2 Type of surgical procedures performed in young patients and older ones

Patients were staged according the AJCC Cancer Staging Manual, 7th edition. Locally, tumors in both groups were more often diagnosed in advanced stages (T4b), 30.4 % in the YGC group and 45.6 % in the OGC group. Interestingly, in the YGC group, the second most common T stage, was the 1a, while in the other group was the 4a. This does not seem to support the hypothesis that gastric cancer would be diagnosed in more advanced stages in young. With regard to lymph node metastasis, there was a significant percentage of patients in whom it was not possible to ascertain (those who did not undergo surgery). There was no statistical difference between YGC and OGC patients concerning the presence of lymph node metastasis. In both groups, most patients were staged at stage IV, 26.1 % of patients in YGC and 26.9 % in the OGC group (Fig. 4). Still there is no evidence that there is a delay in the diagnosis of younger patients compared with the older ones.

Prognosis according to Pathological Stage

No patients received neoadjuvant QT or RT. After surgery, 40 % of YGC received adjuvant QT versus 24 % in OGC patients. The global mortality rate was 43,5 % and 58,6 % in YGC and OGC groups, respectively. However, when we

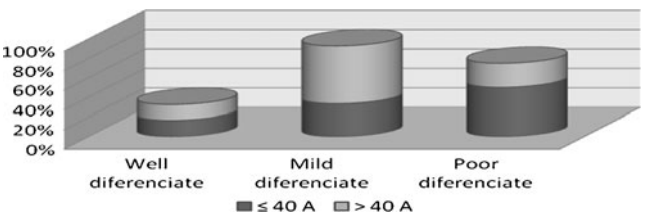

Fig. 3 Histological differentiation in young patients and older ones

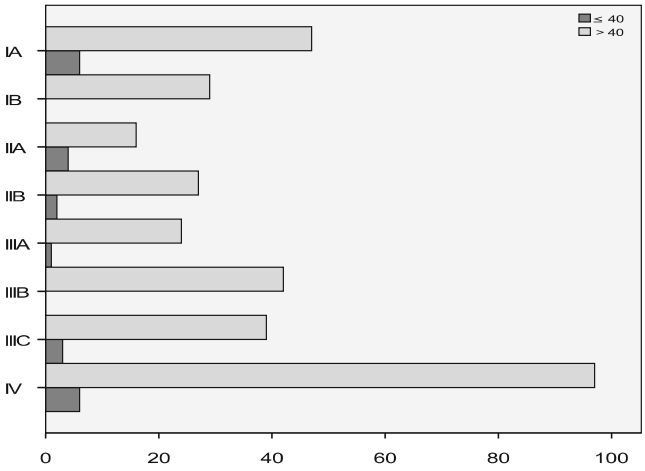

Fig. 4 Staging of patients (AJCC Cancer Staging Manual, 7th edition) according to age

exclude the cases of postoperative mortality and mortality associated with other causes than gastric cancer, the mortality rate shall be amended to 42.9 % and 35.6 % respectively in YGC and OGC. Five-year survival for YGC (Fig. 5) and OGC (Fig. 6) patients was 47,6 % and 23,1 %, respectively (p=0,016). Survival was determined according to stages in YGC and OGC patients. Five-year survival for YGC and OGC stage I patients was 83,3 % and 49.6 %, respectively; and for stage II patients was 62,7 % and 39,7 %, respectively. For stage III e IV, the five-year survival of YGC and OGC patients was 0 % e 8,53–4,1 %, respectively. So, in stages I e II the YGC group presented a better five-year survival comparing with OGC group, but a worse five-year survival in stage III e IV.

For patients who were treated with curative intent, there was locoregional recurrence in 22.2 % and 20.2 % in the OGC and YGC group, respectively; metastasis in 11.1 %

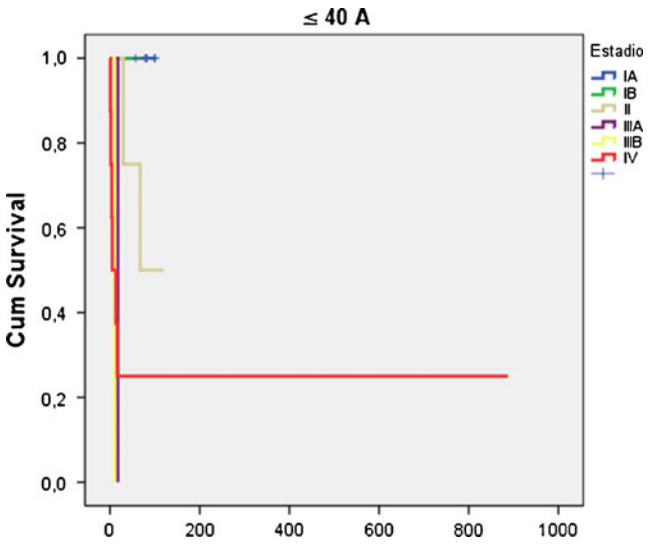

Fig. 5 Survival in the YGC group of patients with gastric cancer

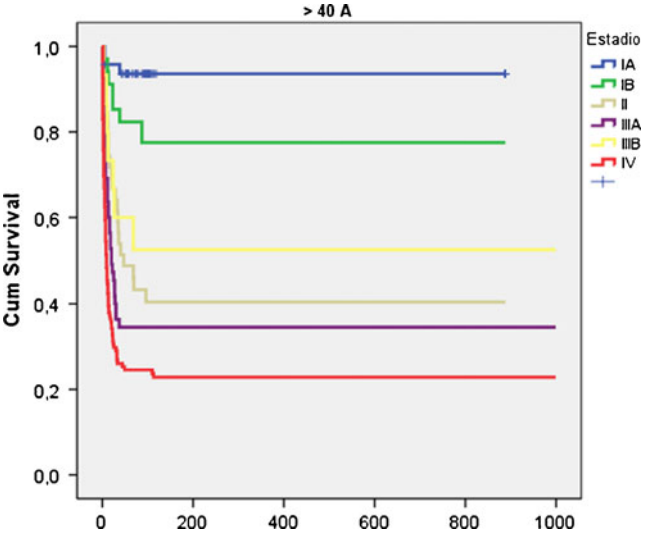

Fig. 6 Survival in the OGC group of patients with gastric cancer

and 19.1 %, respectively, and locoregional recurrence with metastases in 5.6 % and 6.2 % respectively (p=0.77). In general, the recurrence of disease was more frequent in YGC group. In these patients with recurrence, the average time disease free was 25 months in YGC and 17 months in OGC (p=0.36). Of the patients who had metastases during the course of their disease, 75 % of the YGC group, were in the peritoneum, and 46.7 % of the OGC group were in the liver (Table 3). The presence of peritoneal dissemination was statically different between the YGC and OGC patients. Like others studies [23], these results shows that in the YGC group, there is a tendency to easily penetrate the serosa, resulting in peritoneal dissemination.

Discussion

Gastric carcinoma, despite medical progresses in detection and treatment, continues a major cause of death by cancer. Although, the advances accomplished in the understanding of the biology of this pathology, it's fundamental to develop efficient and effective cancer-specific drugs and an accurate

Table 3 Type of metastasis, in patients with recurrence of the disease, according to age

MTT	≤40 Years		> 40 Years		*P* value
	N	%	N	%	
Peritoneal metastases	3	75 %	10	22,2 %	NS
Liver metastases	1	25 %	21	46,7 %	
Bones metastases	0	0 %	6	13,3 %	
Lung metastases	0	0 %	3	6,7 %	
Multiple metastases	0	0 %	4	8,9 %	

prediction of disease outcome for various patients. It is important to know whether some personal characteristics such as age may influence the biological behavior of cancer, towards improving disease control. Nakumara et al.demonstrated that one of the prognostic factors for gastric cancer is age, and patients younger than 34 years was statistically worse than patients older than 34 years. Nakumara et al. demonstrated that one of the prognostic factors for gastric cancer is age, and patients younger than 34 years had statistically significant worse prognosis than patients older than 34 years. Also, Lai et al., in a multivariate analysis showed that young age was an independent negative prognostic factor. This suggests that very young patients have gastric cancer with potentially biologically aggressive features.

It has been suggested that gastric cancer in young patients has different clinicopathological profile than conventional gastric carcinomas. These features include poorly differentiated diffuse adenocarcinoma which is associates with genetic abnormalities. This suggests that it represents a separate entity within gastric carcinogenesis and indeed evidence at a molecular genetics level supports this. Altough, *Hirahashi* et al. suggest that H. *pylori* infection contributes to the development of gastric cancer of poorly differentiated type in the young. Their pathological analysis revealed that *H. pylori* infection was strongly related to the development of gastric cancer in young patients. This observation strongly supports an additional pathway of H. pylori-related gastric carcinogenesis, that is, independent of glandular atrophy or intestinal metaplasia. Additionally, young patients also have been shown to have a high incidence of the *cagA*-positive genotype of *H. pylori* infection that is known to be more virulent than infection by bacterial strains not harboring the gene. Several studies have indicated that the *cagA*-positive genotype *H. pylori* infection substantially increases the odds ratio for cancer development compared with *cagA*-negative genotype *H. pylori* infection [30].

Many authors advocate a more aggressive progression of gastric cancer in younger patients. There have been some reports that the aggressive nature of gastric cancer in young patients was reflected by the high rates of nodal and distant metastases found at diagnosis, and by the frequency of plastic linitis [24, 25].

In this study, diffuse and poorly differentiated adenocarcinoma was seen in most young gastric cancer. Furthermore, in YGC patients, most recurrences were in the form of peritoneal dissemination. The tendency for peritoneal dissemination in YGC may reflect a genetic susceptibility, such as the CDH1, that can be responsible for a more aggressive biological behavior. The survival for stage III e IV was significantly worst in YGC compared with OGC. In this study we haven't found evidence that the diagnosis in YGC was delayed. As reported by others authors, we observed different characteristics of gastric cancer in young patients comparing with older ones. We think that is important to understand the causes for these differences in the sense of better treatment of these patients. Further studies are needed to investigate the different genetic pathways in young and older patients with a view to provide tools for prevention and early diagnosis.

References

1. Parkin DM (2004) International variation. Oncogene 23:6329–6340
2. Parkin DM, Bray FI, Devesa SS (2001) Cancer burden in the year 2000, the global picture. Eur J Cancer 37:S4–S66
3. Forman D, Newell DG, Fullerton F, Yarnell JW, Stacey AR, Wald N, Sitas F (1991) Association between infection with Helicobacter Pylori and risk of gastric cancer: evidence from a prospective investigation. BMJ 302:1302–1305
4. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK (1991) Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 325:1127–1131
5. Milne AN, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJ (2007) Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. Curr Mol Med 7:15–28
6. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS (2000) Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 404:398–402
7. Milne AN, Offerhaus GJA (2010) Early-onset gastric cancer: Learning lessons from the young. World J Gastrointest Oncol 2 (2):59–64
8. Correa P, Shiao YH (1994) Phenotypic and genotypic events in gastric carcinogenesis. Cancer Res 54:1941s–1943s
9. Maehara Y, Emi Y, Tomisaki S, Oshiro T, Kakeji Y, Ichiyoshi Y, Sugimachi K (1996) Age-related characteristics of gastric carcinoma in young and elderly patients. Cancer 77:1774–1780
10. Theuer CP, de Virgilio C, Keese G, French S, Arnell T, Tolmos J, Klein S, Powers W, Oh T, Stabile BE (1996) Gastric adenocarcinoma in patients 40 years of age or younger. Am J Surg 172:473–476
11. Hamilton SR, Aaltonen LA. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Digestive System. Lyon, France: IARC Press, 2000: 204
12. Ramos De la Medina A, Salgado-Nesme N, Torres-Villalobos G, Medina-Franco H (2004) Clinicopathologic characteristics of gastric cancer in a young patient population. J Gastrointest Surg 8:240–244
13. Medina-Franco H, Heslin MJ, Cortes-Gonzalez R (2000) Clinicopathological characteristics of gastric carcinoma in young and elderly patients: a comparative study. Ann Surg Oncol 7:515–519
14. Matley PJ, Dent DM, Madden MV, Price SK (1988) Gastric carcinoma in young adults. Ann Surg 208:593–596
15. Kokkola A, Sipponen P (2001) Gastric carcinoma in young adults. Hepatogastroenterology 48:1552–1555
16. Lim S, Lee HS, Kim HS, Kim YI, Kim WH (2003) Alteration of E-cadherin-mediated adhesion protein is common, but microsatellite instability is uncommon in young age gastric cancers. Histopathology 42:128–136
17. Maeta M, Yamashiro H, Oka A, Tsujitani S, Ikeguchi M, Kaibara N (1995) Gastric cancer in the young, with special reference to 14

pregnancy-associated cases: analysis based on 2,325 consecutive cases of gastric cancer. J Surg Oncol 58:191–195
18. Derakhshan MH, Liptrot S, Paul J, Brown IL, Morrison D, McColl KE (2009) Oesophageal and gastric intestinal-type adenocarcinomas show the same male predominance due to a 17 year delayed development in females. Gut 58:16–23
19. Furukawa H, Iwanaga T, Imaoka S, Hiratsuka M, Fukuda I, Kabuto T, Ishikawa O, Sasaki Y (1989) Multifocal gastric cancer in patients younger than 50 years of age. Eur Surg Res 21:313–318
20. Suriano G, Oliveira C, Ferreira P, Machado JC, Bordin MC, De Wever O, Bruyneel EA, Moguilevsky N, Grehan N, Porter TR, Richards FM, Hruban RH, Roviello F, Huntsman D, Mareel M, Carneiro F, Caldas C, Seruca R (2003) Identification of CDH1 germline missense mutations associated with functional inactivation of the E-cadherin protein in young gastric cancer probands. Hum Mol Genet 12:575–582
21. Suriano G, Yew S, Ferreira P, Senz J, Kaurah P, Ford JM, Longacre TA, Norton JA, Chun N, Young S, Oliveira MJ, Macgillivray B, Rao A, Sears D, Jackson CE, Boyd J, Yee C, Deters C, Pai GS, Hammond LS, McGivern BJ, Medgyesy D, Sartz D, Arun B, Oelschlager BK, Upton MP, Neufeld-Kaiser W, Silva OE, Donenberg TR, Kooby DA, Sharma S, Jonsson BA, Gronberg H, Gallinger S, Seruca R, Lynch H, Huntsman DG (2005) Characterization of a recurrent germ line mutation of the E-cadherin gene: implications for genetic testing and clinical management. Clin Cancer Res 11:5401–5409
22. Carneiro F, Oliveira C, Suriano G, Seruca R (2008) Molecular pathology of familial gastric cancer, with an emphasis on hereditary diffuse gastric cancer. J Clin Pathol 61:25–30
23. Nakamura R, Saikawa Y, Takahashi T, Takeuchi H, Asanuma H, Yamada Y, Kitagawa Y (2011) Retrospective analysis of prognostic outcome of gastric cancer in young patients. Int J Clin Oncol 16 (4):328–334
24. Ramos-De la Medina A, Salgado-Nesme N et al (2004) Clinicopathologic characteristics of gastric cancer in a young patient population. J Gastrointest Surg 8(3):240–244
25. Koea JB, Karpeh MS, Brennan MF (2000) Gastric cancer in young patients: demographic, clinicopathological, and prognostic factors in 92 patients. Ann Surg Oncol 7(5):346–351
26. Hiyama T, Tanaka S, Yoshihara M, Sasao S, Kose K, Shima H, Tuncel H, Ueno Y, Ito M, Kitadai Y, Yasui W, Haruma K, Chayama K (2004) Chromosomal and microsatellite instability in sporadic gastric cancer. J Gastroenterol Hepatol 19:756–760
27. Wu M, Semba S, Oue N, Ikehara N, Yasui W, Yokozaki H (2004) BRAF/K-ras mutation, microsatellite instability, and promoter hypermethylation of hMLH1/MGMT in human gastric carcinomas. Gastric Cancer 7:246–253
28. Hirahashi M, Yao T, Matsumoto T, Nishiyama K, Oya M, Iida M, Tsuneyoshi M (2007) Intramucosal gastric adenocarcinoma of poorly differentiated type in the young is characterized by Helicobacter pylori infection and antral lymphoid hyperplasia. Mod Pathol 20(1):29–34
29. Chung HW, Noh SH, Lim JB (2010) Analysis of demographic characteristics in 3242 young age gastric cancer patients in Korea. World J Gastroenterol 16(2):256–263
30. Smith BR, Stabile BE (2009) Extreme aggressiveness and lethality of gastric adenocarcinoma in the very young. Arch Surg 144 (6):506–510
31. Santoro R, Carboni F, Lepiane P, Ettorre GM, Santoro E (2007) Clinicopathological features and prognosis of gastric cancer in young European adults. Br J Surg 94(6):737–742
32. Lai JF, Kim S, Li C, Oh SJ, Hyung WJ, Choi WH, Choi SH, Wang LB, Noh SH (2008) Clinicopathologic characteristics and prognosis for young gastric adenocarcinoma patients after curative resection. Ann Surg Oncol 15(5):1464–1469