RESEARCH ARTICLE

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The Endoscopic and Clinicopathological Characteristics of Early-onset Gastric Cancer in Vietnamese Patients

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Abstract

Aim: To assess the endoscopic and clinicopathological features of early-onset gastric cancer (EOGC) in Vietnamese, a population with intermediate risk of gastric cancer. **Patients and methods:** Consecutive patients diagnosed with gastric adenocarcinoma were prospectively recruited. The demographic, clinical data in each patient were collected. The location and macroscopic type of all gastric lesions suspected to be malignant were reported according to the Japanese classification. The histologic tumor type of gastric cancer (GC) was classified according to the Lauren classification. *Helicobacter pylori (H. pylori)* infection were diagnosed by rapid urease test and urinary *H. pylori* antibody test. The infection was diagnosed when at least one of the two tests was positive. **Results:** The rate of EOGC (i.e. ≤ 40 years of age) was 16.3% (23/141). The median age of patients with EOGC was 35 (range 28 – 40) years and the male-to-female was 1:1.09. Compared to the older group (i.e. ≥ 50 years of age), the rates of positive family history, *H. pylori* infection and alarm features in the EOGC group were not significantly different (0.0% vs. 5.4%, p = 0.581; 73.9% vs. 66.3%, p = 0.620; and 60.8% vs. 79.3%, p = 0.100; respectively). The EOGC group had significantly higher rate of tumor extending to entire stomach (21.7% vs. 3.4%, p = 0.003); but the rate of diffuse-type GC between the two groups were not significantly different (87.0% vs. 71.7%, p = 0.181). **Conclusions:** Vietnamese patients with EOGC had higher rate of tumor extending to entire stomach compared to the older group. But the family history of GC, *H. pylori* infection and the pathological characteristics were not significantly different between the two groups. Environmental factors which play important roles in the development of EOGC in Vietnam should be investigated in future study.

Keywords: Early-onset- gastric cancer- carcinoma- Vietnam- *Helicobacter pylori*

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Introduction

Gastric cancer (GC) is the fifth most common malignancy worldwide, and accounts for a notable proportion of cancer (McLean and El-Omar, 2014). But it is not commonly diagnosed at young age. Depending on the cutoff age, early-onset gastric cancer (EOGC) has been reported in 3.7 – 15.5% of patients with gastric carcinoma (Maeta et al., 1995; Kim et al., 2008; Al-Refaie et al., 2011; Dhobi et al., 2013; Isobe et al., 2013; Seker et al., 2013; Kandel et al., 2016; Lee et al., 2016; Takatsu et al., 2016; Wang et al., 2016; Zhou et al., 2016; Rona et al., 2017). The occurrence of EOGC remains largely unexplained. The complex combinations and interactions between many environmental factors including *Helicobacter pylori (H. pylori)* infection, and genetic factors may affect the risk of gastric carcinoma (Milne and Offerhaus, 2010). Genetic factors are presumed to be more important in EOGC than in older patients because younger patients have less exposure to environmental carcinogens. In fact, several studies reported that the rate of positive family history of GC in patients with EOGC was significantly higher than that in older patients (Bai and Li, 2011; Punjachaipornpon et al., 2016). However, an inherited component was reported to contribute to only less than 3% of all GCs (McLean and El-Omar, 2014). Although *H. pylori* is likely to involve a smaller percentage of EOGC than the older group, it still plays a pivotal role in the pathogenesis of GC in a large number of young patients (Rugge et al., 1999; Haruma et al., 2000).

Interestingly, the rates of EOGC and the age-standardized incidence rate (ASR) of GC in many countries are not parallel. Using the same cutoff age of ≤ 40, the rates of EOGC in countries with high ASR such as Korea, Japan and China are generally lower compared to those in developing countries with low ASR such as Nepal and India (2.8% - 3.7% vs. 10.0% - 13.2%, respectively) (Dhobi et al., 2013; Kandel et al., 2016; Lee et al., 2016; Takatsu et al., 2016; Zhou et al., 2016). This discrepancy is worth investigating further to clarify. Up to now, there has been no data on EOGC in Vietnam, a country with intermediate-to-high risk of GC. The aim of this study was to investigate the endoscopic and clinicopathological

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features of EOGC in Vietnamese population.

Materials and Methods

Patients

From February 2016 to December 2016, consecutive patients aged ≥ 18 years who were diagnosed with gastric adenocarcinoma at the Department of Endoscopy, University Medical Center, Hochiminh City, Vietnam, were prospectively recruited. Patients with gastric carcinoid tumor, gastric lymphoma, gastrointestinal stromal tumor or prior history of gastrectomy were excluded. Written informed consents were obtained from all patients. This study was approved by the ethical committee of the University of Medicine and Pharmacy at Hochiminh City, Vietnam.

Data collection

The demographic and clinical data in each patient were collected, which included age, gender, smoking status, family history of GC, chief complaints and alarm features (i.e. weight loss ≥ 10% over a 6-month period, anemia, dysphagia, gastrointestinal bleeding, loss of appetite, Virchow's node and abdominal mass on examination). All of the upper gastrointestinal endoscopy procedures were performed by experienced endoscopists. During the procedures, the upper gastrointestinal tract was carefully inspected. The location and macroscopic type of all gastric lesions, which were suspected to be malignant, were reported according to the Japanese classification (Japanese Gastric Cancer, 2011). All of these lesions were taken biopsy. The final diagnosis was confirmed by experienced pathologists of the Department of Pathology, University Medical Center. The histologic type of gastric adenocarcinoma was examined according to the Lauren classification. *H. pylori* infection was diagnosed by rapid urease test (PyloriTek, Serim Research Corp., Elkhart, Ind., USA) and urinary *H. pylori* antibody tests (Rapirun® *H. pylori* Antibody Stick, Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan). The infection was diagnosed when at least one of the two above-mentioned tests was positive.

Data analysis

All patients with adenocarcinoma during the studying period were recruited. Characteristics of the EOGC group (≤ 40 years of age) and the older group (≥ 50 years of age) were compared. Categorical data between the two groups were compared by chi-squared test with continuity correction or Fisher's exact test if appropriate. Continuous variables were expressed as mean ± standard deviation (SD) and ranges, and were compared by the Student's t-test. Statistical analysis of the data was performed with Microsoft Excel, and SPSS 20.0 for Windows (Statistical Product and Service Solutions, Chicago, IL, USA). Two-tailed p-values less than 0.05 were considered statistically significant.

Results

A total of 141 patients were diagnosed with gastric carcinoma at the University Medical Center, Hochiminh City during the studying period. There were 37 (26.2%) patients under 45, and 23 (16.3%) under 40 years of age. The patients' demographic and clinical characteristics are shown in Table 1. Median age of patients in the EOGC group was 35 (range 28 – 40) years and the male-to-female was 1:1.09. The most common presenting symptoms of patients with EOGC were abdominal pain (78.2%), heartburn (73.9%) and postprandial fullness (47.8%). Even though all patients in our study had advanced endoscopic lesions, alarm features were present in only 60.8% of patients in the EOGC group and 79.3% of patients in the older group (p = 0.100).

The patients' endoscopic and pathologic characteristics are shown in Table 2. The primary tumor most commonly involved the lower third of the stomach in both groups. But the EOGC group had significantly higher rate of tumor extending to entire stomach compared to the older group (21.7% vs. 3.4%, p = 0.003). The most common endoscopic appearance of GC in both groups was type 1 according to the Japanese classification; and there was no significant difference between the two groups. In addition, the rate of diffuse type carcinoma in the EOGC group was also not significantly different from that in the older group (87.0% vs. 71.7%, respectively, p = 0.181).

There were only 7 (4.9%) patients with positive family history of GC in our study (4 male and 3 female patients). The rates of positive family history between two groups

Table 1. Demographic and Clinical Characteristics of the Study Population

	Early-onset group (≤ 40 years) (n = 23)	Older group (≥ 50 years) (n = 92)	p value
Age (years)			
Mean (SD)	35.2 (4.4)	62.9 (9.9)	
Median	35	59.5	
Minimum	28	50	
Maximum	40	86	
Sex n (%)			
Male	11 (47.8)	55 (59.8)	0.350
Female	12 (52.2)	37 (40.2)	
BMI			
Mean (SD)	21.3 (2.7)	21.7 (3.6)	0.266
Family history of GC n (%)	0 (0)	5 (5.4)	0.581
Clinical symptoms and findings n (%)			
Dysphagia	1 (4.3)	9 (9.8)	0.864
Heartburn	17 (73.9)	47 (51.1)	0.061
Abdominal pain	18 (78.2)	71 (77.2)	1.000
Postprandial fullness	11 (47.8)	60 (65.2)	0.152
Early satiation	5 (21.7)	44 (47.8)	0.033
Significant weight loss	5 (21.7)	40 (43.5)	0.061
Gastrointestinal bleeding	3 (13.0)	12 (13.0)	1.000
Loss of appetite	8 (34.8)	45 (48.9)	0.251
Anemia	2 (8.7)	39 (42.4)	0.003
Abdominal mass	3 (13.0)	15 (16.3)	1.000
Alarm features (%)	14 (60.8)	73 (79.3)	0.100
H. pylori positive (%)	17 (73.9)	61 (66.3)	0.620

BMI, Body mass index

Table 2. Endoscopic and Pathologic Characteristics of the Study Population

	Early-onset group (≤ 40 years) (n = 23)	Older group (≥ 50 years) (n = 92)	p value
Tumor location n (%)			
Upper	2 (8.7)	10 (10.8)	
Middle	8 (34.8)	18 (19.5)	0.003
Lower	8 (34.8)	61 (66.3)	
Entire	5 (21.7)	3 (3.4)	
Endoscopic appearance (%)			
0	0	0	
1	15 (65.2)	43 (46.7)	
2	6 (26.1)	29 (31.5)	0.074
3	0 (0)	17 (18.5)	
4	2 (8.7)	3 (3.3)	
5	0	0	
Histological type (%)			
Diffuse	20 (87.0)	66 (71.7)	0.181
Intestinal	3 (13.0)	26 (28.3)	

were not significantly different (0.0% vs. 5.4%, p = 0.581) (Table 1). All of patients with positive family history had diffuse type adenocarcinoma. And all of the relatives with GC diagnosis were their fathers or siblings. The detailed characteristics of these patients are presented in Table 3.

Discussion

The two most common cutoff ages which are used to define EOGC are equal or less than 40 or 45 years. According to the Asian Consensus on functional dyspepsia, a new-onset dyspepsia in the subjects over 40, 45 and 50 years of age should be considered as an alarm feature in population with high, intermediate or low prevalence of upper gastrointestinal malignancy, respectively (Miwa et al., 2012). As Vietnam is a country with intermediate-to-high prevalence of GC, we decided the cutoff age of EOGC in this study was equal or less than 40.

Our study showed that patients with EOGC in Vietnamese shared several clinical, endoscopic and histologic characteristics with those reported in other populations. Nearly half of patients with EOGC in our study were female. Studies in other populations reported similar result or even a female predominance in patients with EOGC (Maeta et al., 1995; Bani-Hani, 2005; Bai and Li, 2011; Isobe et al., 2013; Wang et al., 2016). Interestingly, a retrospective study in Japan on 2,325 consecutive GC patients between 1966 and 1990 reported that the male-to-female ratio in the young group was with more female predominating as the age of patients decreased (Maeta et al., 1995). In addition, this study also showed a significantly higher frequency of Borrmann type 4 cancer, poorly differentiated adenocarcinoma with the scirrhous type of growth and peritoneal metastasis in the pregnancy-associated patients. Therefore, the female predominance in EOGC may be partially due to hormonal factors (Maeta et al., 1995; Milne and Offerhaus, 2010).

Patients with EOGC in our study had significantly higher rate of tumor extending to the entire stomach compared to patients in the older group (21.7% vs. 3.4%, respectively, p = 0.003).

Although all patients had advanced endoscopic lesions, the rate of alarm features in EOGC group was only 60.8%. A previous Chinese study on 210 patients with GC who were under 35 years of age also showed that only one third of patients presented with alarm features (Bai and Li, 2011). Therefore, the diagnosis of EOGC is very challenging, and alarm features should not be considered as sensitive indicators to prompt young patients for upper gastrointestinal endoscopy.

There are very limited data about genetic susceptibility of the host in Vietnamese population. Family history could indirectly show the potential effect of genetics on GC risk though it may be partially affected by shared environmental risk factors (Karimi et al., 2014). In our study, there were no patients with EOGC having family history of GC. In addition, the rates of positive family history were also not significantly different between EOGC and the older group. Therefore, the results of this study do not support genetic susceptibility as an important factor for EOGC in Vietnam.

The *H. pylori* virulence in Vietnamese has been extensively studied. A recent study reported that the prevalence of quadruple-positive for cagA, vacA s1, vacA m1, and jhp0562-positive/β-(1,3)galT-negative was significantly lower in Vietnam than in Bhutan and correlated with GC incidence (Trang et al., 2015). In addition, gastritis-staging scores measured by histology of gastric mucosa were significantly higher in

Table 3. Clinicalpathological Characteristics of Patients with Family History of GC

	Sex	Age	First class relative with GC			Histologic characteristics	
			n	Age at onset*	Relationship	Location	Phenotype
1	Male	43	1	42	Sibling	Lower	Diffuse
2	Male	48	1	67	Father	Entire	Diffuse
3	Female	50	1	68	Father	Middle	Diffuse
4	Male	54	1	36	Father	Lower	Diffuse
5	Male	54	1	64	Father	Lower	Diffuse
6	Female	58	2	54*	Father, sibling	Middle	Diffuse
7	Female	72	1	54	Sibling	Upper	Diffuse

* The age of GC onset was recorded according to the youngest age of the relatives when GC was diagnosed.

quadruple-positive strains. However, there have been no studies to compare the bacteria virulence between EOGC and late-onset GC in Vietnam. In our study, *H. pylori* infection rates between the two groups were not significantly different. There may be concerns about the underestimated positive rate of *H. pylori* infection as only two diagnostic tests were applied in this study. However, previous local studies published in Vietnamese which applied a combination of several *H. pylori* test methods including rapid urease test, serum test, urine test, histology and culture reported a positive rate of around 80%. Therefore, we think that the H. pylori- negative GC rate in Vietnamese is high compared to the international literature, and other environmental factors may play important roles in the development of GC in Vietnam.

This study has some limitations. Firstly, this is a single-center study with limited number of patients during a short studying period and, therefore, can not represent for the whole population. Although previous Vietnamese studies published in local journals also reported similars rate of EOGC, a large multi-center study needs to be conducted in the future. Secondly, pathologic findings of the background gastric mucosal in patients with EOGC, which may help to better understanding the pathogenesis of EOGC, have not been examined. Thirdly, as *H. pylori* infection was determined by antibody method and/or rapid urease test and most of patients in our study were with advanced GC stage, the true rate of *H. pylori* infection might be underestimated.

In conclusion, our study showed that Vietnamese patients with EOGC had higher rate of tumor extending to entire stomach compared to the older group. The low rates of positive family history and *H. pylori* infection suggest that other environmental factors play important roles in the development of EOGC in Vietnam, which should be investigated in future study.

Statement Of Interests

Declaration of personal interests: No
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