Am J Cancer Res 2022;12(6):2757-2769
www.ajcr.us /ISSN:2156-6976/ajcr0142901

Original Article

The clinicopathological characteristics of early-onset gastric cancer and its evolutionary trends: a retrospective study

Xiaodong Qu[1], Xingyu Zhao[1], Yuhuan Liu[2], Na Wang[1], Luyao Zhang[1], Xiaojing Zhu[1], Qiang Dong[1], Junye Liu[3], Yongquan Shi[1]

[1]State Key Laboratory of Cancer Biology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, China; [2]Xi'an Medical University, Xi'an, Shaanxi, China; [3]Department of Radiation Protective Medicine, Fourth Military Medical University, Xi'an, Shaanxi, China

Received March 15, 2022; Accepted May 23, 2022; Epub June 15, 2022; Published June 30, 2022

Abstract: Although gastric cancer (GC) is most common in the elderly population, the rate of early-onset gastric cancer (EOGC) is increasing each year. In this study, the clinicopathological information of 9,406 patients who underwent GC resection in our institution from 2000 to 2019 was collected. We compared the clinicopathological characteristics between the EOGC group, in which patients were younger than 40, and the control group, summarizing the evolutionary trends of the EOGC group's characteristics. Then, we focused on the characteristics of EOGC in different sex groups and the evolutionary trends of female EOGC patients' clinicopathological characteristics. The results showed that a greater proportion of the EOGC group was female (47.32% vs. 23.53%), had poorly differentiated adenocarcinoma (84.78% vs. 64.11%), gastric antrum cancer (59.38% vs. 50.72%) and signet ring cell carcinoma (21.13% vs. 8.51%). Over the past 20 years, the proportion of EOGC patients with T4 stage (10.71% to 41.74%), N3 stage (0 to 30.73%) and poorly differentiated adenocarcinoma (70.37% to 92.23%) has increased. In the female EOGC group, there were more patients with stage III-IV disease (57.23% vs. 43.22%), T4 stage (35.85% vs. 22.60%), and poorly differentiated adenocarcinoma (91.88% vs. 78.68%). Additionally, the proportions of T4 stage (16.13% to 50.50%), N3 stage (0% to 31.68%), and poorly differentiated adenocarcinoma (69.23% to 98.97%) gradually increased. In conclusion, our study not only identified unique clinicopathological characteristics of EOGC but also revealed the evolutionary trends of these indicators, which may provide some theoretical basis for the prevention and diagnosis of EOGC.

Keywords: Early-onset gastric cancer, clinicopathological characteristics, evolutionary trends, sex, adenocarcinoma

Introduction

The Global Cancer Statistics 2020 report released by the International Agency for Research on Cancer (IARC) showed that the global incidence and mortality of gastric cancer (GC) ranked fifth and third among malignant tumors [1]. As one of the most common malignant tumors, GC poses a serious threat to human health. GC frequently occurs in middle-aged and elderly people, with the highest incidence in people aged 50 to 70 [2]. The incidence of GC is relatively low among young people, and previous studies have shown that young GC patients account for approximately 4.6%-14.8% of the study population [3-8]. Nevertheless, in recent years, there has been a rising trend in GC cases among young people [9]. Some studies have reported that younger patients have a significantly worse prognosis than older patients [10, 11]. In contrast, other studies claimed that the survival rates for younger GC patients are similar to those of elderly patients [2, 5, 7]. Numerous studies have confirmed that early-onset gastric cancer (EOGC) has unique clinicopathological characteristics, such as a higher proportion of female patients, poor differentiation, and more advanced clinical stage [12, 13]. However, the results of these studies on the characteristics

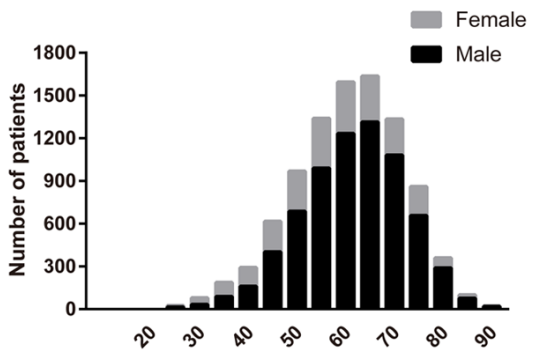

Figure 1. Age and sex histograms for all patients with gastric cancer.

of EOGC are not entirely consistent. More importantly, few studies have focused on the evolutionary trends of the clinicopathological characteristics of EOGC over time; therefore, we believe that the clinicopathological characteristics of EOGC still need further study.

Materials and methods

Inclusion and exclusion criteria

This study retrospectively included medical records of patients who underwent gastrectomy for GC at Xijing Hospital from January 2000 to December 2019. The inclusion criteria were (1) underwent surgical treatment (including open and laparoscopic surgery), (2) pathologically confirmed primary GC, and (3) complete, available medical records. The exclusion criteria were (1) previous gastrectomy for other diseases; (2) the presence of other malignant tumors (except metastatic cancer of gastric origin); and (3) the presence of tumors of nonepithelial origin in the stomach, such as malignant lymphoma, mesenchymal tumor, sarcoma, etc.; (4) surgical approach of endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), with pathology only suggestive of intraepithelial neoplasia; and (5) missing key data. Ultimately, 9,406 patients met the criteria and were therefore included in the study.

Definition of patients with EOGC and experimental grouping

In East Asian countries where the prevalence of GC is high, such as Japan and Korea, the age of GC screening is set at 40 years [14]. In China, the incidence of GC in people over 40 years of age has increased significantly, so experts recommend 40 years as the starting age for early GC screening [15]. Therefore, in this study, patients with EOGC were defined as those younger than 40 years old. The remaining GC patients older than 40 years of age were defined as the control group. From 2000 to 2019, 672 patients (7.14%) were assigned to the EOGC group, and 8734 patients (92.86%) were assigned to the control group. In addition, we divided the EOGC patients into four chronological groups according to the year of diagnosis: 2000-2004 (period A), 2005-2009 (period B), 2010-2014 (period C) and 2015-2019 (period D). **Figure 1** shows the histogram of the age and sex distribution of 9,406 patients.

Data collection

Patient age, sex, family history of GC, weight, tumor size and location, history of smoking, drinking, gastric ulcer, and chronic gastritis, diabetes, clinical stage (established according to guidelines of the 7th edition of the AJCC), depth of infiltration (T stage), lymph node metastasis (N stage), distant metastasis (M stage), histological type and degree of differentiation of the adenocarcinoma were collected. Based on the location of the center of the lesion, tumors were considered cardia fundus cancer, gastric body cancer, gastric antrum cancer (including incisura angularis and pylorus) or entire GC (a tumor that invaded 2/3 or more of the stomach wall), and the tumor size was based on the largest diameter. According to the classification developed by the Japanese Gastric Cancer Association, the histological type of GC was classified as adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma or other [16]. Due to the lack of data, the positivity rate of tumor markers was recorded from 2005 to 2019, and CEA>5 ng/ml, CA19-9>30 U/ml, CA125>24 U/ml, and AFP>7 ng/ml were considered positive.

Statistical analysis

Statistical analysis was performed to assess the differences in clinicopathological characteristics between the EOGC group and the control group and the evolutionary trends of clinicopathological characteristics of EOGC over time. Measurement data are expressed as the mean ± standard deviation (x ± SD) and were com-

pared by Student's t test, Mann-Whitney U test or Kruskal-Wallis test. Count data are expressed as percentages, and the chi-square test or Fisher's exact test was used for comparisons between groups. All data were analyzed using SPSS software (version 22.0, USA), and two-sided P<0.05 was regarded as statistically significant.

Results

Demographic characteristics of participants

Of all 9,406 patients in this study, the majority were from the five northwestern provinces of China (87.02%), mainly from Shaanxi (62.41%) and Gansu (19.05%) provinces, and the remaining patients (12.98%) came from many other provinces of China. The median age was 58.3 years (range, 20-92), and there were 7,033 (74.77%) male patients and 2373 (25.23%) female patients. Among all patients, 672 patients were 40 years old or younger with a median age of 35.4 years, and 8,734 patients were more than 40 years old with a median age of 59.3 years. In general, both EOGC group patients and control group patients were primarily male, but the proportion of females in the EOGC group was much higher than that in the control group (47.32% vs. 23.53%, P<0.001).

Clinicopathological characteristics of participants

Table 1 illustrates the clinicopathological characteristics of the two groups. Although both EOGC and non-EOGC occurred predominantly in the antrum, the proportion of antrum cancer was greater in the EOGC group (59.38% vs. 50.72%), and the proportion of cardia fundus cancer was significantly lower in the EOGC group (5.65% vs. 19.77%, P<0.001). In addition, the tumor size was smaller in the EOGC group (4.44±2.74 vs. 4.78±2.52, P=0.002). More patients in the EOGC group had a family history of GC (6.55% vs. 4.73%, P=0.035) and a history of gastric ulcers (17.11% vs. 10.24%, P<0.001). Patients in the control group were more likely to have a history of smoking (37.55% vs. 20.54%, P=0.004) and diabetes (6.10% vs. 0.60%, P<0.001). In terms of the proportion of patients with a history of drinking and chronic gastritis, the EOGC group did not differ significantly from the control group. The proportions of patients with stage I disease (30.36% vs. 26.21%, P=0.02) and T1 stage (25.30% vs. 19.14%, P=0.002) were higher in the EOGC group, while there was no significant difference in the rates of N stage and M stage. Regarding the histological type, the EOGC group had a significantly higher proportion of signet ring cell carcinoma cases than the control group (21.13% vs. 8.51%, P<0.001). In addition, given the predominance of adenocarcinoma in GC, we compared the degree of adenocarcinoma differentiation between the two groups, and the results showed that poorly differentiated adenocarcinoma was significantly more common in the EOGC group (84.78% vs. 64.11%, P<0.001). In connection with the positive staining rate of tumor markers, the positive rates of CEA (7.95% vs. 19.91%, P<0.001) and CA19-9 (10.58% vs. 17.79%, P<0.001) staining were significantly lower in the EOGC group, and the positive rate of CA125 staining (15.46% vs. 10.85%, P=0.001) was higher in the EOGC group than in the control group.

Since there were significant differences in several clinical characteristics between EOGC patients and control patients, we performed univariate and multivariate analyses and found independent risk factors for EOGC. As shown in **Table 2**, among these clinical characteristics, female sex and history of gastric ulcers were independent risk factors for EOGC, and females had the highest OR value. Therefore, we divided the EOGC group into male and female EOGC subgroups. According to the results shown in **Table 3**, the mean tumor size, diabetes, histological type, tumor location and family history of GC in the female group were not significantly different from those in the male group. Males were more inclined to have a history of smoking (38.98% vs. 0%, P<0.001), drinking (29.10% vs. 1.26%, P<0.001), and gastric ulcer (20.34% vs. 13.52%, P=0.019). However, females had a higher percentage of patients with a history of chronic gastritis (27.40% vs. 17.61%, P=0.003). The female group was more likely to be diagnosed with poorly differentiated adenocarcinoma (91.88% vs. 78.68%, P<0.001). Additionally, there were statistically significant differences between the two groups in terms of clinical stage, depth of tumor infiltration and lymph node metastasis (P<0.001). The proportions of T4 (35.85% vs. 22.60%) and N3 (30.50% vs. 20.34%) stage

Table 1. Comparison of demographic and clinicopathologic characteristics between the EOGC group and the control group

Characteristics	EOGC group (n=672, %)	Control group (n=8734, %)	*P*-value
Median age	35.4	59.3	
Sex			<0.001
Male	354 (52.68)	6679 (76.47)	
Female	318 (47.32)	2055 (23.53)	
Family history of GC			0.035
Yes	44 (6.55)	413 (4.73)	
No	628 (93.45)	8321 (95.27)	
Weight (kg; x ± SD)	59.3±11.5	63.1±10.8	<0.001
Tumor size (cm; x ± SD)	4.44±2.74	4.78±2.52	0.002
History of smoking			0.004
Yes	138 (20.54)	3228 (37.55)	
No	534 (79.46)	5454 (62.45)	
History of drinking			0.726
Yes	107 (15.92)	1436 (16.44)	
No	565 (84.08)	7298 (83.56)	
History of gastric ulcer			<0.001
Yes	115 (17.11)	894 (10.24)	
No	557 (82.89)	7840 (89.76)	
History of chronic gastritis			0.886
Yes	153 (22.77)	1969 (22.54)	
No	519 (77.23)	6765 (77.46)	
Diabetes			<0.001
Yes	4 (0.60)	533 (6.10)	
No	668 (99.40)	8201 (93.90)	
Location			<0.001
Cardia fundus	38 (5.65)	1727 (19.77)	
Body	200 (29.76)	2266 (25.94)	
Antrum	399 (59.38)	4430 (50.72)	
Entire	35 (5.21)	311 (3.56)	
Clinical stage			0.020
I	204 (30.36)	2289 (26.21)	
II	133 (19.79)	2057 (23.55)	
III-IV	335 (49.85)	4388 (50.24)	
Depth of infiltration			0.002
T1	170 (25.30)	1672 (19.14)	
T2	99 (14.73)	1329 (15.22)	
T3	209 (31.10)	2980 (34.12)	
T4	194 (28.87)	2753 (31.52)	
Lymph node metastasis			0.818
N0	249 (37.05)	3353 (38.39)	
N1	141 (20.98)	1864 (21.34)	
N2	113 (16.82)	1451 (16.61)	
N3	169 (25.15)	2066 (23.65)	
Distant metastasis			0.069
M0	623 (92.71)	8245 (94.40)	
M1	49 (7.29)	489 (5.60)	

Histological type			<0.001
Adenocarcinoma	506 (75.30)	7543 (86.36)	
Mucinous adenocarcinoma	21 (3.13)	365 (4.18)	
Signet ring cell carcinoma	142 (21.13)	743 (8.51)	
Others	3 (0.45)	83 (0.95)	
Degree of adenocarcinoma differentiation			<0.001
Well differentiated	25 (4.94)	693 (9.19)	
Moderately differentiated	52 (10.28)	2014 (26.70)	
Poorly differentiated	429 (84.78)	4836 (64.11)	
CEA			<0.001
>5 ng/ml (Positive)	42 (7.95)	1431 (19.91)	
≤5 ng/ml (Negative)	486 (92.05)	5755 (80.09)	
CA 19-9			<0.001
>30 U/ml (Positive)	55 (10.58)	1251 (17.79)	
≤30 U/ml (Negative)	465 (89.42)	7032 (82.21)	
CA 125			0.001
>24 U/ml (Positive)	79 (15.46)	754 (10.85)	
≤24 U/ml (Negative)	432 (84.54)	6198 (89.15)	
AFP			0.137
>7 ng/ml (Positive)	26 (5.07)	472 (6.76)	
≤7 ng/ml (Negative)	487 (94.93)	6509 (93.24)	

Note: AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA 19-9, cancer antigen 19-9; CA 125, carbohydrate antigen 125; EOGC, early-onset gastric cancer; GC, gastric cancer.

Table 2. Results of univariate and multifactorial analyses of clinical characteristics of EOGC

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female	2.920	2.490-3.424	<0.001	2.461	2.059-2.942	<0.001
Family history of GC	0.858	0.600-1.225	0.398			
History of smoking	0.446	0.369-0.540	<0.001	0.661	0.534-0.818	<0.001
History of drinking	0.926	0.747-1.150	0.488			
History of gastric ulcer	1.933	1.516-2.465	<0.001	2.024	1.579-2.593	<0.001
History of chronic gastritis	1.069	0.889-1.286	0.479			
Diabetes	0.139	0.062-0.312	<0.001	0.148	0.066-0.334	<0.001

Note: CI, confidence interval; GC, gastric cancer; OR, odds ratio.

diseases were significantly higher in the female group, and similarly, the proportion of III-IV stage disease (57.23% vs. 43.22%) was also higher in the female group.

Trends in the evolution of the clinicopathological characteristics of EOGC

To explore the evolutionary trends in the clinicopathological characteristics of EOGC over the past two decades, we performed a statistical analysis of periods A, B, C, and D. Patients with EOGC accounted for 8.99% in period A, 8.62% in period B, 8.03% in period C, and 5.55% in period D. As summarized in **Table 4**, it seems that the proportion of male patients with EOGC increased slightly over time (44.64% to 53.67%), but the difference was not statistically significant. In addition, there were no statistically significant changes in the family history of GC, weight, tumor size and location, clinical stage or distant metastasis. The clinicopathological characteristics of patients with EOGC changed significantly in terms of smoking and drinking history (P=0.004, P=0.025, respectively), degree of infiltration, lymph node metastasis and histological type (P<0.001, respectively). The T4 stage, which represents a high

Table 3. Comparison of clinicopathologic characteristics between the male EOGC group and the female EOGC group

Characteristics	Male (n=354, %)	Female (n=318, %)	*P*-value
Tumor size (cm; x ± SD)	4.52±2.51	4.37±2.93	0.501
Family history of GC			0.496
Yes	21 (7.23)	23 (5.93)	
No	333 (92.77)	295 (94.07)	
History of smoking			<0.001
Yes	138 (38.98)	0 (0.00)	
No	216 (61.02)	318 (100.00)	
History of drinking			<0.001
Yes	103 (29.10)	4 (1.26)	
No	251 (70.90)	314 (98.74)	
History of gastric ulcer			0.019
Yes	72 (20.34)	43 (13.52)	
No	282 (79.66)	275 (86.48)	
History of chronic gastritis			0.003
Yes	56 (17.61)	97 (27.40)	
No	262 (82.39)	257 (72.60)	
Diabetes			0.057
Yes	0 (0.00)	4 (1.13)	
No	318 (100.00)	350 (98.87)	
Location			0.438
Cardia fundus	20 (5.65)	18 (5.66)	
Body	100 (28.25)	100 (31.45)	
Antrum	219 (61.86)	180 (56.60)	
Entire	10 (4.24)	20 (6.29)	
Clinical stage			<0.001
I	129 (36.44)	75 (23.58)	
II	72 (20.34)	61 (19.18)	
III-IV	153 (43.22)	182 (57.23)	
Depth of infiltration			<0.001
T1	108 (30.50)	62 (19.50)	
T2	59 (16.67)	40 (12.58)	
T3	107 (30.23)	102 (32.07)	
T4	80 (22.60)	114 (35.85)	
Lymph node metastasis			<0.001
N0	156 (40.07)	93 (29.25)	
N1	60 (16.95)	81 (25.47)	
N2	66 (18.64)	47 (14.78)	
N3	72 (20.34)	97 (30.50)	
Histological type			0.673
Adenocarcinoma	272 (76.84)	234 (73.58)	
Mucinous adenocarcinoma	11 (3.11)	10 (3.14)	
Signet ring cell carcinoma	69 (19.49)	73 (22.96)	
Others	2 (0.56)	1 (0.31)	
Degree of adenocarcinoma differentiation			<0.001
Well differentiated	19 (6.99)	6 (2.56)	
Moderately differentiated	39 (14.34)	13 (5.56)	
Poorly differentiated	214 (78.68)	215 (91.88)	

Note: GC, gastric cancer.

Table 4. Clinicopathological characteristics of EOGC at different time periods

Characteristics	Period A (n=56, %)	Period B (n=114, %)	Period C (n=284, %)	Period D (n=218, %)	*P*-value
Median age	35.8	36.8	35.6	34.2	
Sex					0.655
Male	25 (44.64)	60 (52.63)	152 (53.52)	117 (53.67)	
Female	31 (55.36)	54 (47.37)	132 (46.48)	101 (46.33)	
Weight	Missing	59.0±11.6	58.5±11.3	60.5±11.7	0.165
Family history of GC					0.074
Yes	1 (1.79)	3 (2.63)	21 (7.39)	19 (8.72)	
No	55 (98.21)	111 (97.37)	263 (92.61)	199 (91.28)	
Tumor size (cm; mean ± SD)	4.58±2.31	4.46±2.33	4.47±2.70	4.36±3.08	0.946
History of smoking					0.004
Yes	4 (7.14)	15 (13.16)	69 (24.30)	50 (22.94)	
No	52 (92.86)	99 (86.84)	215 (75.70)	168 (77.06)	
History of drinking					0.025
Yes	9 (16.07)	13 (11.40)	59 (20.77)	26 (11.93)	
No	47 (83.93)	101 (88.60)	225 (79.23)	192 (88.07)	
Location					0.257
Cardia fundus	1 (1.79)	7 (6.14)	17 (5.99)	13 (5.96)	
Body	19 (33.93)	35 (30.70)	85 (29.93)	61 (27.98)	
Antrum	34 (60.71)	68 (59.65)	173 (60.92)	124 (56.88)	
Entire	2 (3.57)	4 (3.51)	9 (3.17)	20 (9.17)	
Clinical stage					0.265
I	14 (25.00)	43 (37.72)	79 (27.82)	68 (31.19)	
II	9 (16.07)	17 (14.91)	58 (20.42)	49 (22.48)	
III-IV	33 (58.93)	54 (47.37)	147 (51.76)	101 (46.33)	
Depth of infiltration					<0.001
T1	8 (14.29)	24 (21.05)	70 (24.65)	68 (31.19)	
T2	11 (19.64)	26 (22.81)	43 (15.14)	19 (8.72)	
T3	31 (55.36)	49 (42.98)	89 (31.34)	40 (18.35)	
T4	6 (10.71)	15 (13.16)	82 (28.87)	91 (41.74)	
Lymph node metastasis					<0.001
N0	21 (37.50)	55 (48.25)	87 (30.63)	86 (39.45)	
N1	29 (51.79)	35 (30.70)	44 (15.49)	33 (15.14)	
N2	6 (10.71)	20 (17.54)	55 (19.37)	32 (14.68)	
N3	0 (0.00)	4 (3.51)	98 (34.51)	67 (30.73)	
Distant metastasis					0.131
M0	48 (85.71)	104 (91.23)	265 (93.31)	206 (94.50)	
M1	8 (14.29)	10 (8.77)	19 (6.69)	12 (5.50)	
Histological type					<0.001
Adenocarcinoma	27 (48.21)	71 (62.28)	202 (71.13)	206 (94.50)	
Mucinous adenocarcinoma	6 (10.71)	5 (4.39)	8 (2.82)	2 (0.92)	
Signet ring cell carcinoma	23 (41.07)	36 (31.58)	73 (25.70)	10 (4.59)	
Others	0 (0.00)	2 (1.75)	1 (0.35)	0 (0.00)	
Degree of adenocarcinoma differentiation					<0.001
Well differentiated	3 (11.11)	11 (15.49)	9 (4.46)	2 (0.97)	
Moderately differentiated	5 (18.52)	10 (14.08)	23 (11.39)	14 (6.80)	
Poorly differentiated	19 (70.37)	50 (70.42)	170 (84.16)	190 (92.23)	

Note: GC, gastric cancer.

infiltration depth, showed an increasing trend from period A to period D (10.71% to 41.74%). For lymph node metastasis, the proportion of cases of N1 stage disease showed a decreasing trend (51.79% to 15.14%), while the proportion of cases of N3 stage disease continually increased (0.00% to 30.73%). Over time, more patients were diagnosed with adenocarcinoma, and this type even became dominant over other types (48.21% to 94.50%); in contrast, the proportions of cases of mucinous adenocarcinoma and signet ring cell carcinoma gradually decreased (10.71% to 0.92%, 41.07% to 4.59%, respectively). Among adenocarcinoma patients, the proportion of cases of poorly differentiated adenocarcinoma showed an increasing trend from period A to period D (70.37% to 92.23%). Since female patients seemed to have more severe disease than male patients, we paid extra attention to the changes in the clinicopathological characteristics of female patients with EOGC during the study period. As shown in **Table 5**, female patients showed no statistically significant changes in terms of family history of GC, tumor location, or clinical stage. There were significant differences in the depth of tumor infiltration, lymph node metastasis, histological type, degree of adenocarcinoma differentiation (all $P<0.001$), and distant metastasis ($P=0.041$). From period A to period D, the proportion of female patients with T4 stage disease increased from 16.13% to 50.50%, and the proportion of patients with N3 stage disease increased from 0% to 31.68%. The proportion of females diagnosed with adenocarcinoma increased from 41.94% to 96.04%. Moreover, the proportion of patients with poorly differentiated adenocarcinoma gradually increased with time, and by period D, 98.97% of female patients were diagnosed with poorly differentiated adenocarcinoma, accounting for the majority of cases in females. In contrast, the percentage of female patients with signet ring cell carcinoma decreased significantly from 51.61% to 2.97%.

Discussion

As the fifth most prevalent malignant tumor, GC accounted for approximately 800,000 deaths in 2020 [1], indicating that it poses a serious medical burden on humanity. GC is most prevalent in elderly people, especially those aged 50-70 [2]; however, recent studies have shown that the incidence of GC in people under the age of 50 is increasing, both in high-risk and low-risk areas [17, 18]. Although there is some controversy, many previous retrospective studies have shown that EOGC has distinct clinicopathological characteristics, such as predominantly female patients, more advanced disease, worse prognosis, and poor differentiation [2, 10, 12, 13, 19].

In our study, 672 patients aged ≤40 years were included in the EOGC group, with slightly more males than females (52.68% vs. 47.32%). However, the proportion of females in the EOGC group was obviously higher than that in the control group (patients >40) (47.32% vs. 23.53%), and the results of multivariate analysis revealed that female sex was an independent risk factor for EOGC. Therefore, we grouped all patients and patients with EOGC by sex to investigate whether there were differences in clinicopathological characteristics. For male and female GC patients (Table S1), the differences in clinicopathological characteristics were not as great, except for the proportion of patients with cardia fundus cancer and patients with a history of smoking and drinking, which were higher in males than in females. Nevertheless, there were significant differences in the clinicopathological characteristics of male and female EOGC patients. The results showed that females with EOGC tended to have a higher proportion of chronic gastritis history, deeper tumor infiltration, more lymph node metastases, higher tumor stage, and poorer differentiation in adenocarcinoma. Moreover, over a 20-year period, the condition of women with EOGC appeared to worsen, and the progressive increase in T4 stage, N3 stage and the proportion of poorly differentiated adenocarcinomas is strong evidence for this indication. However, the previous results of Ławniczak et al. showed no differences between male and female EOGC patients [6]. Although female EOGC patients are much less likely to have a history of smoking, which is a risk factor for GC [20], than male EOGC patients, females seem to have more severe cancer, probably suggesting that EOGC pathogenesis differs between women and men. Hye et al. found that among women, older age at first delivery (>35 years), lack of lactation history and nulliparity were significantly associated with an increased risk of GC [21], indicating

Table 5. Clinicopathological characteristics of female EOGC patients at different time periods

Characteristics	Period A (n=31, %)	Period B (n=54, %)	Period C (n=132, %)	Period D (n=101, %)	*P*-value
Median age	34.4	35.9	34.4	33.9	
Family history of GC					0.417
Yes	1 (3.23)	2 (3.70)	10 (7.58)	10 (9.90)	
No	30 (96.77)	52 (96.30)	122 (92.42)	91 (90.10)	
Location					0.088
Cardia fundus	0 (0.00)	3 (5.56)	7 (5.30)	8 (7.92)	
Body	9 (29.03)	19 (35.19)	43 (32.58)	29 (28.71)	
Antrum	21 (67.74)	30 (55.56)	78 (59.09)	51 (50.50)	
Entire	1 (3.23)	2 (3.70)	4 (3.03)	13 (12.87)	
Clinical stage					0.113
I	4 (12.90)	17 (32.08)	34 (25.76)	20 (21.05)	
II	5 (16.13)	5 (9.43)	25 (18.94)	26 (27.37)	
III-IV	22 (70.97)	32 (58.49)	73 (55.30)	55 (51.58)	
Depth of infiltration					<0.001
T1	1 (3.23)	7 (12.96)	31 (23.48)	23 (22.77)	
T2	4 (12.90)	12 (22.22)	17 (12.88)	7 (6.93)	
T3	21 (67.74)	24 (44.44)	37 (28.03)	20 (19.80)	
T4	5 (16.13)	11 (20.37)	47 (35.61)	51 (50.50)	
Lymph node metastasis					<0.001
N0	9 (29.03)	20 (37.04)	34 (25.76)	30 (29.70)	
N1	19 (61.29)	22 (40.74)	19 (14.39)	21 (20.79)	
N2	3 (9.68)	9 (16.67)	17 (12.88)	18 (17.82)	
N3	0 (0.00)	3 (5.56)	62 (46.97)	32 (31.68)	
Distant metastasis					0.041
M0	24 (77.42)	48 (88.89)	124 (93.94)	92 (91.09)	
M1	7 (22.58)	6 (11.11)	8 (6.06)	9 (8.91)	
Histological type					<0.001
Adenocarcinoma	13 (41.94)	34 (62.96)	90 (68.18)	97 (96.04)	
Mucinous adenocarcinoma	2 (6.45)	1 (1.85)	6 (4.55)	1 (0.99)	
Signet ring cell carcinoma	16 (51.61)	18 (33.33)	36 (27.27)	3 (2.97)	
Others	0 (0.00)	1 (1.85)	0 (0.00)	0 (0.00)	
Degree of adenocarcinoma differentiation					<0.001
Well differentiated	1 (7.69)	3 (8.82)	1 (1.11)	1 (1.03)	
Moderately differentiated	3 (23.08)	1 (2.94)	9 (10.00)	0 (0.00)	
Poorly differentiated	9 (69.23)	30 (88.24)	80 (88.89)	96 (98.97)	

Note: GC, gastric cancer.

that sex hormones possibly play a role in the development of EOGC.

In addition, a slightly greater proportion of patients with EOGC had a family history of GC (6.55% vs. 4.73%, P=0.035), and the proportion of patients with EOGC who had a family history of GC showed an increasing trend over the study period, although this change was not statistically significant (1.79% to 8.72%, P=0.074). Previous studies have reported that hereditary diffuse gastric cancer (HDGC) is an autosomal dominant disease and was shown to be associated with CDH1 (E-cadherin)-inactivating mutations in 1998 [22]. The median age at diagnosis of HDGC is 38 years, and there are more female GC patients than male patients [23]. Similarly, considering that EOGC is also characterized by an earlier age of onset, higher incidence in women, and a family history of GC, we

speculate that the unique characteristics of EOGC are related to genetic factors.

Concerning the tumor location, Bai et al. and Takatsu et al. reported that young patients had a predominance of gastric body cancer (or the middle third of the stomach) and a significantly higher proportion than controls [2, 19]. However, other studies claimed that EOGC occurred mainly in the lower third of the stomach, but the proportion of tumors at this site was lower than that in the control group [12, 13]. Similarly, our study found that most tumors were found in the gastric sinus regardless of whether they were early-onset or not, but distinct from the control group, a higher proportion of patients with EOGC had gastric sinus cancer (59.38% vs. 50.72%), and a lower proportion had gastric fundic cancer (5.65% vs. 19.77%).

In terms of pathological characteristics, patients with EOGC differed from the control group in terms of clinical stage, depth of infiltration, and histological type. The proportion of EOGC patients with T1 stage disease was higher than that of patients in the control group (25.30% vs. 19.14%), but there was no significant difference between the groups in terms of lymph node metastasis and distant metastasis. In contrast, Al-Refaie et al. showed a significant difference in lymph node metastasis and distant metastasis in younger patients versus middle-aged and older patients [24]. The results of Sandeep et al., which are consistent with ours, also showed a higher proportion of T1 stage cases in younger patients than in middle-aged and older patients, but in their study, clinical stage did not differ between groups [11]. Histologically, although the proportion was not as high as that in the control group, both the EOGC group and the control group were dominated by adenocarcinoma. The proportion of patients with poorly differentiated adenocarcinoma was significantly higher in the EOGC group (84.78% vs. 64.11%). There was a higher proportion of patients with signet ring cell carcinoma (21.13% vs. 8.51%) in the EOGC group. This proportion was generally consistent with the findings of Bergquist et al [25]. However, the results of Rona et al. showed a much higher proportion of young GC patients with signet ring cell carcinoma, reaching nearly 90% [26].

Tan et al. chronologically studied GC in North China and obtained changes in the clinicopathological characteristics of GC in the region over a 30-year period [27]. Although many studies have examined the unique clinicopathologic characteristics of EOGC, few investigators have examined the evolution of the clinicopathologic characteristics of EOGC over time. We observed the clinicopathological characteristics of patients with EOGC at our institution over a two-decade period in chronological order. The indicators that changed significantly during these two decades were a history of smoking and drinking (P=0.004, P=0.025, respectively), depth of tumor infiltration, lymph node metastasis, histological type and degree of adenocarcinoma differentiation (P<0.001). The proportion of patients with a history of smoking increased significantly from period A to period D (7.14% to 22.94%), but no significant trend was observed for the history of drinking. Regarding the depth of tumor infiltration, the percentage of patients with T4 stage disease increased from 10.71% to 41.74%, indicating a trend of increasingly deeper tumor infiltration. For lymph node metastasis, the percentage of patients with N1 stage disease decreased from 51.79% to 15.14%, and the percentage of patients with N3 stage disease increased from 0% to 30.73%. In terms of histological type, the proportion of patients with signet ring cell carcinoma decreased (41.07% to 4.59%), while adenocarcinoma was the dominant type, and its proportion increased year by year (48.21% to 94.50%). What is more concerning is that the percentage of patients with poorly differentiated adenocarcinoma increased, with 70.37% of patients with adenocarcinoma in period A and 92.23% in period D. These results seem to indicate that EOGC is progressing to more severe disease during the study period. Finally, although our results showed a decreasing trend in the proportion of EOGC, we believe that this may be related to our exclusion of patients treated with ESD or EMR. ESD and EMR are increasingly accepted as effective means of treating early gastric cancer (i.e., gastric cancer with infiltration depth not exceeding T1 stage) [28, 29]. The proportion of EOGC patients in the T1 stage also increased during the study period, so it is possible that more EOGC patients in the early stage were excluded because they were

treated with ESD or EMR, which led us to the result that the proportion of EOGC decreased.

Our results differed somewhat from those of previous studies, and we considered that this may be due to differences in the study population and cutoff values for the age of EOGC in different studies (e.g., disease occurrence at less than 35, 40, 45 or 50 years of age [6, 19, 26, 30]). As a single-center retrospective study, there is inevitable case selection bias. Most of the patients who underwent ESD or EMR were only diagnosed with intraepithelial neoplasia, and patients who could not undergo surgical resection lacked pathological information. Considering these reasons, we excluded these two types of cases, but this may lead to partial loss of information. However, since our institution is one of the largest first-class hospitals at Grade 3 in China and the source of patients is not limited to the local area, sufficient and extensive case information can increase the representativeness of our conclusions to a certain extent. Additionally, our study also has a longer review period than other retrospective studies [2, 4-8, 10, 11, 13, 19, 21, 26], and the results may be more representative if they can be analyzed in conjunction with data from other multicenter sites. Since the EOGC group and control group showed a significant difference in sex ratio, we grouped the EOGC group by sex and found differences in the clinicopathological characteristics of patients. We also grouped patients with EOGC by diagnosis year to observe changes in their clinicopathological characteristics during our study period, which, to our knowledge, has not been studied before.

In conclusion, our findings reveal unique clinicopathological characteristics of EOGC, including higher proportions of female patients, early-stage disease at diagnosis, antrum tumor site, poorer differentiation and signet ring cell carcinoma cases. For female EOGC patients, the tumors are more advanced at the time of diagnosis, and their prognosis may be worse. However, the EOGC group showed increasing trends in terms of invasion depth, lymph node metastasis, and proportion of poorly differentiated adenocarcinoma in the last two decades, indicating that EOGC is progressing to a more serious disease state.

Therefore, more attention should be given to the screening and prevention of EOGC, especially early screening for female patients and those with gastric ulcers and injuries to the distal stomach. Patients with family genetic factors and hormone level disorders should be screened more intensively as well.

Acknowledgements

This work was supported by grants from National Natural Science Foundation of China (No. 8217031045 and No. 81873554 to YQS).

Disclosure of conflict of interest

None.

Address correspondence to: Yongquan Shi, State Key Laboratory of Cancer Biology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, No. 15 West Changle Road, Xi'an 710032, Shaanxi, China. Tel: +86-029-84771534; Fax: +86-862982539041; E-mail: shiyquan@fmmu.edu.cn

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[2] Takatsu Y, Hiki N, Nunobe S, Ohashi M, Honda M, Yamaguchi T, Nakajima T and Sano T. Clinicopathological features of gastric cancer in young patients. Gastric Cancer 2016; 19: 472-478.

[3] Koea JB, Karpeh MS and Brennan MF. Gastric cancer in young patients: demographic, clinicopathological, and prognostic factors in 92 patients. Ann Surg Oncol 2000; 7: 346-351.

[4] Theuer CP, Kurosaki T, Taylor TH and Anton-Culver H. Unique features of gastric carcinoma in the young: a population-based analysis. Cancer 1998; 83: 25-33.

[5] Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Jedrys J and Szczepanik AM; Polish Gastric Cancer Study Group. Clinicopathological profile and long-term outcome in young adults with gastric cancer: multicenter evaluation of 214 patients. Langenbecks Arch Surg 2008; 393: 37-43.

[6] Ławniczak M, Gawin A, Jaroszewicz-Heigelmann H, Rogoza-Mateja W, Białek A, Kulig J, Kaczmarczyk M and Starzyńska T. Analysis of clinicopathologic characteristics of gastric can-

cer in patients ≤40 and ≥40 years of age. Scand J Gastroenterol 2020; 55: 62-66.
[7] Tekesin K, Emin Gunes M, Tural D, Akar E, Zirtiloglu A, Karaca M, Selcukbiricik F, Bayrak S and Ozet A. Clinicopathological characteristics, prognosis and survival outcome of gastric cancer in young patients: a large cohort retrospective study. J BUON 2019; 24: 672-678.
[8] Ramos-De la Medina A, Salgado-Nesme N, Torres-Villalobos G and Medina-Franco H. Clinicopathologic characteristics of gastric cancer in a young patient population. J Gastrointest Surg 2004; 8: 240-244.
[9] Yin J, Song JN, Bai ZG, Cai J, Zhang J, Zheng Z, Wu HW, Ye PP, Gao X and Zhang ZT. Gastric cancer mortality trends in China (2006-2013) reveal increasing mortality in young subjects. Anticancer Res 2017; 37: 4671-4679.
[10] Nakamura R, Saikawa Y, Takahashi T, Takeuchi H, Asanuma H, Yamada Y and Kitagawa Y. Retrospective analysis of prognostic outcome of gastric cancer in young patients. Int J Clin Oncol 2011; 16: 328-334.
[11] Sandeep B, Huang X, Li Y, Mao L, Gao K and Xiao ZW. Gastric carcinoma in young patients and its clinicopathological characteristics and prognosis. Gastroenterol Res Pract 2020; 2020: 7378215.
[12] Park HJ, Ahn JY, Jung HY, Lim H, Lee JH, Choi KS, Kim DH, Choi KD, Song HJ, Lee GH and Kim JH. Clinical characteristics and outcomes for gastric cancer patients aged 18-30 years. Gastric Cancer 2014; 17: 649-660.
[13] Huang Q, Zheng XF, Jiao Y, Lei YN, Li XY, Bi F, Guo FK, Wang G and Liu M. A distinct clinicopathological feature and prognosis of young gastric cancer patients aged ≤45 years old. Front Oncol 2021; 11: 674224.
[14] Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, Wu KC, Wu DC, Sollano J, Kachintorn U, Gotoda T, Lin JT, You WC, Ng EK and Sung JJ; Asia Pacific Working Group on Gastric Cancer. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol 2008; 9: 279-287.
[15] Li ZS, Wang GQ, Zhang ST and Linghu EQ. China experts consensus on the protocol of early gastric cancer screening (2017, Shanghai). Chin J Health Manage 12: 8-13.
[16] Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd english edition. Gastric Cancer 2011; 14: 101-112.
[17] Arnold M, Park JY, Camargo MC, Lunet N, Forman D and Soerjomataram I. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut 2020; 69: 823-829.
[18] Heer EV, Harper AS, Sung H, Jemal A and Fidler-Benaoudia MM. Emerging cancer incidence trends in Canada: the growing burden of young adult cancers. Cancer 2020; 126: 4553-4562.
[19] Bai Y and Li ZS. Endoscopic, clinicopathological features and prognosis of very young patients with gastric cancer. J Gastroenterol Hepatol 2011; 26: 1626-1629.
[20] Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R and Lunet N. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 2008; 19: 689-701.
[21] Chung HW, Noh SH and Lim JB. Analysis of demographic characteristics in 3242 young age gastric cancer patients in Korea. World J Gastroenterol 2010; 16: 256-263.
[22] Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A and Reeve AE. E-cadherin germline mutations in familial gastric cancer. Nature 1998; 392: 402-405.
[23] Yu JX and Li ZF. The sex ratio and age of onset features of gastric cancer patients in hereditary diffuse gastric cancer families. Fam Cancer 2011; 10: 573-579.
[24] Al-Refaie WB, Hu CY, Pisters PW and Chang GJ. Gastric adenocarcinoma in young patients: a population-based appraisal. Ann Surg Oncol 2011; 18: 2800-2807.
[25] Bergquist JR, Leiting JL, Habermann EB, Cleary SP, Kendrick ML, Smoot RL, Nagorney DM, Truty MJ and Grotz TE. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. Surgery 2019; 166: 547-555.
[26] Rona KA, Schwameis K, Zehetner J, Samakar K, Green K, Samaan J, Sandhu K, Bildzukewicz N, Katkhouda N and Lipham JC. Gastric cancer in the young: an advanced disease with poor prognostic features. J Surg Oncol 2017; 115: 371-375.
[27] Tan YE, Wang PL, Yin SC, Zhang C, Hou WB and Xu HM. Thirty-year trends in clinicopathologic characteristics and prognosis after gastrectomy for gastric cancer: a single institution in Northern China. J Cancer 2020; 11: 1056-1062.
[28] Kato M. Endoscopic submucosal dissection (ESD) is being accepted as a new procedure of endoscopic treatment of early gastric cancer. Intern Med 2005; 44: 85-86.

[29] Kim JJ, Lee JH, Jung HY, Lee GH, Cho JY, Ryu CB, Chun HJ, Park JJ, Lee WS, Kim HS, Chung MG, Moon JS, Choi SR, Song GA, Jeong HY, Jee SR, Seol SY and Yoon YB. EMR for early gastric cancer in Korea: a multicenter retrospective study. Gastrointest Endosc 2007; 66: 693-700.

[30] Bacani J, Zwingerman R, Di Nicola N, Spencer S, Wegrynowski T, Mitchell K, Hay K, Redston M, Holowaty E, Huntsman D, Pollett A, Riddell R and Gallinger S. Tumor microsatellite instability in early onset gastric cancer. J Mol Diagn 2005; 7: 465-477.

Table S1. Comparison of clinicopathologic characteristics between the male and female GC patients

Characteristics	Male (n=7033, %)	Female (n=7033, %)	*P*-value
Tumor size (cm; x ± SD)	4.76±2.54	4.76±2.56	0.994
Family history of GC			0.421
Yes	349 (4.96)	108 (4.55)	
No	6684 (95.04)	2265 (95.45)	
History of smoking			<0.001
Yes	3343 (47.53)	23 (0.97)	
No	3690 (52.47)	2350 (99.03)	
History of drinking			<0.001
Yes	1519 (21.60)	24 (1.01)	
No	5514 (78.40)	2349 (98.99)	
History of gastric ulcer			0.207
Yes	526 (7.48)	159 (6.70)	
No	6507 (92.52)	2214 (93.30)	
History of chronic gastritis			0.894
Yes	1589 (22.59)	533 (22.46)	
No	5444 (77.41)	1840 (77.54)	
Diabetes			0.001
Yes	433 (6.16)	104 (4.38)	
No	6600 (93.84)	2269 (95.62)	
Location			<0.001
Cardia fundus	1515 (21.54)	250 (10.54)	
Body	1813 (25.78)	653 (27.52)	
Antrum	3461 (49.21)	1368 (57.65)	
Entire	245 (3.48)	101 (4.26)	
Clinical stage			0.503
I	1882 (26.76)	611 (25.75)	
II	1643 (23.36)	547 (23.05)	
III-IV	3508 (49.88)	1215 (51.20)	
Depth of infiltration			0.001
T1	1339 (19.04)	503 (21.20)	
T2	1104 (15.70)	324 (13.65)	
T3	2435 (34.62)	754 (31.77)	
T4	2155 (30.64)	792 (33.38)	
Lymph node metastasis			0.120
N0	2726 (38.76)	876 (36.92)	
N1	1511 (21.48)	494 (20.82)	
N2	1165 (16.56)	399 (16.81)	
N3	1631 (23.19)	604 (25.45)	
Histological type			<0.001
Adenocarcinoma	6106 (86.82)	1943 (81.88)	
Mucinous adenocarcinoma	288 (4.09)	98 (4.13)	
Signet ring cell carcinoma	568 (8.08)	317 (13.36)	
Others	71 (1.01)	15 (0.63)	

Note: GC, gastric cancer.