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Gastric Carcinomas in Young (Younger than 40 Years) Chinese Patients

Clinicopathology, Family History, and Postresection Survival

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Abstract: Little is known about clinicopathological characteristics of gastric carcinoma (GC) in young (≤40 years) Chinese patients. We aimed in this study to analyze those features along with family history and prognostic factors after resection.

We retrospectively reviewed all 4671 GC resections (surgical and endoscopic) performed at our center from 2004 to 2014 and identified 152 (3.2%) consecutive young patients. Patient demographics, clinical results, family history, and endoscopic-pathological findings were analyzed along with the older (>41 years) GC controls recruited in the same study period. Clinicopathological factors related to postresection outcomes were assessed statistically.

The trend of GC resections in young patients was not changed over the study period. Compared to old GCs, the young GC cohort was predominant in women, positive family history, middle gastric location, the diffuse histology type, shorter duration of symptoms, and advanced stage (pIII+pIV, 53.3%). Radical resection was carried out in 90.1% (n = 137) with a better 5-year survival rate (70.3%) than palliative surgery (0%, n = 15). There was no significant difference in clinicopathological characteristics between familial GC (FGC, n = 38) and sporadic GC (SGC, n = 114) groups. Very young patients (≤ 30 years, n = 38) showed lower Helicobacter pylori (Hp) infection and significantly higher perineural invasion rates, compared to older (31–40 years) patients. Hp infection was more commonly seen in the Lauren's intestinal type and early pT stages (T1+T2). Independent prognostic

factors for worse outcomes included higher serum CA 72–4, CA 125 levels, positive resection margin, and stage pIII–pIV tumors. The 5-year survival rate was significantly higher in patients with radical resection than those without.

GCs in young Chinese patients were prevalent in women with advanced stages but showed no significant differences in clinicopathology between FGC and SGC groups. High serum CA 72–4 and CA 125 levels may help identify patients with worse outcomes. Radical resection improved postresection survival.

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Abbreviations: AJCC = American Joint Committee on Cancer, EOGC = early-onset gastric cancer, FGC = familial gastric cancer, GC = gastric carcinoma, SGC = sporadic gastric cancer.

INTRODUCTION

At present, the incidence of gastric carcinoma (GC) has steadily decreased worldwide due to effective Helicobacter pylori (Hp) screening and treatment, as well as early detection by upper endoscopy.[1] However, GC remains the third leading cause of cancer-related deaths in China.[2,3] In general, GC occurs primarily in elderly patients aged ≥60 years; only ~2.7% to 15% of patients are ≤40 years old,[4–6] as the early-onset gastric cancer (EOGC).[7] Previous studies show that EOGCs occur mainly in female patients with the histology diffuse type (Lauren's classification), advanced tumor stage, and high incurable rates.[4,8,9]

Although detailed pathogenesis mechanisms of GC remain elusive, environmental factors combined with specific genetic alterations in the vulnerable population play critical roles in GC tumorigenesis.[10–12] Because EOGC patients expose to environmental toxins much lesser than older patients, hereditary factors may be of more importance in EOGC tumorigenesis.[13] Indeed, ~10% to 25% of EOGC patients have a positive family history,[6,9,14,15] some of whom have hereditary GC syndromes, such as hereditary diffuse GC with 25% to 50% of cases harboring germline CDH1 gene mutations. However, the CDH1 gene mutation rate differs considerably between high- and low-incidence regions in the world. In a Japanese study on CDH1 gene mutations in 13 familial gastric cancer (FGC) families,[16] only 1 missense somatic mutation was identified. Most Chinese studies also revealed no truncating germline CDH1 gene mutations in FGC families or EODGC patients,[17–19] a feature different from that reported in Europeans.[20,21]

The reports on prognosis of EOGC patients after resection also show conflicting results.[5,8,9,22–25] Some studies demonstrate an unfavorable prognosis in very young (<30 years) GC patients, which was interpreted as a result of delayed diagnosis and rapid disease progression,[5,25] whereas others report no significant differences in survival between the very young

and older GC patient groups.[9,22–24] Some investigators have even described better survival rates in EOGC patients, compared to older GC patients.[8] However, few studies have focused on clinicopathologic features of young Chinese GC patients and those with a family history of GC in the first- or second-degree relatives. The aims of this study were to characterize clinico-pathology of EOGC, compared to old (>41 years) GCs, elucidate prognostic factors, especially in familial EOGC patients, and compare differences between very young (≤30 years) and older (31–40 years) EOGC patients groups in a homogeneous Chinese population.

METHODS

Patients

We searched GC resection cases in the electronic pathology databank stored in the Department of Pathology of the Nanjing Drum Tower Hospital over the period between January 2004 and December 2014. All pathology reports were retrieved and reviewed by 2 experienced pathologists. Inclusion criteria for the EOGC study were: (1) surgical or endoscopic GC resection, (2) patient age ≤40 years. Exclusion criteria consisted of: (1) GC diagnosed by endoscopic biopsy without resection, (2) no archival tissue blocks available for recuts, and (3) the patient lost to follow-up. The control group consisted of 250 older (>41 years) GC patients recruited from the same study period. Consent for GC resection and research was obtained from each patient before the resection procedure was taken place. The study protocol was approved by the Medical Ethics Committee of the Nanjing Drum Tower Hospital.

Data

Clinical features of each patient, extracted from the medical record, included demographics, symptoms and durations, body mass index (BMI), endoscopic findings (tumor site, macroscopic pattern defined by the WHO classification),[26] adjuvant therapy, tumor recurrence, and *Hp* infection status (determined by the rapid urease test). Grossly, early GC was categorized as protruded (type 0–I), superficially elevated (type 0–IIa), superficially flat (type 0–IIb), superficially depressed (type 0–IIc), and excavated (type 0–III) patterns, whereas advanced GC showed 4 patterns, including polypoid (type I), fungating (type II), ulcerated (type III), and flat infiltrative feature (type IV). Tabulated were laboratory test results on serum levels of albumin (normal range: 35–50 g/L), CA 72–4 (normal range: 0–6.9 U/mL), CA 125 (normal range: 0–30.2 U/mL), CA 19–9 (normal range: 0–39 U/mL), CA 242 (normal range: 0–15 U/mL), CEA (normal range: 0–10 ng/mL), and AFP (normal range: 0–10 ng/mL). Also analyzed were surgical resection methods, operative morbidity, and pathological details such as tumor size and 4 primary tumor locations: (1) proximal, including gastroesophageal junction and proximal third of the stomach, (2) middle (corpus), and (3) distal stomach, from the incidura, antrum to pylorus, and (4) whole stomach. Pathology features assessed were Lauren's classification, the WHO tumor histology type, WHO tumor differentiation, tumor stage (based on the 7th edition of the American Joint Committee on Cancer [AJCC7]),[27] lymphovascular invasion (LVI), perineural invasion (PNI) (defined as the process of neoplastic invasion of nerves),[28] and resection margin status. All selected patients were interviewed and followed-up through telephone or home visit by a trained gastroenterologist for detailed family history
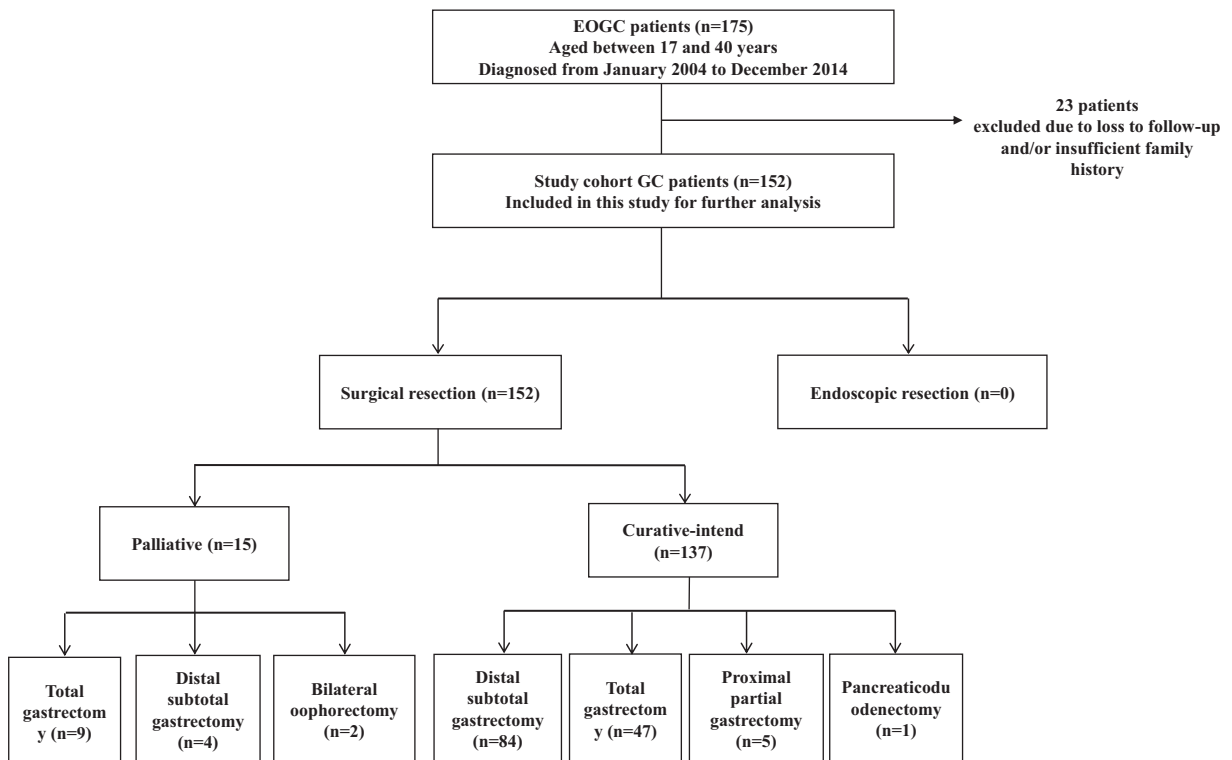

FIGURE 1. Flowchart showing early-onset gastric cancer study cohort and treatment modalities.

TABLE 1. Clinicopathologic Features of Early-Onset Gastric Carcinoma in Chinese Patients (Younger than 40 Years of Age) Versus Those in Patients 41 Years or Older

Features	Young Patients (N = 152)	Old Patients (N = 250)	P^*
Age	33.7 ± 5.54	62.9 ± 10.4	<0.01
Gender			<0.01
Male	53 (34.9%)	178 (71.2%)	
Female	99 (65.1%)	72 (28.8%)	
Positive familiar gastric cancer patients	38 (25.0%)	40 (16.0%)	0.027
Symptom at diagnosis			
Abdominal pain	73 (48.0%)	98 (39.2%)	0.083
Discomfort	37 (24.3%)	95 (38.0%)	<0.01
Alarming features	39 (25.7%)	48 (19.2%)	0.127
Gastrointestinal bleeding	19 (12.5%)	11 (4.4%)	
Distant metastasis	7 (4.6%)	5 (2.0%)	
Vomiting	7 (4.6%)	17 (6.8%)	
Dysphagia	6 (4.0%)	15 (6.0%)	
Diarrhea	2 (1.3%)	1 (0.4%)	0.560
Discovered at health check-up	1 (0.7%)	8 (3.2%)	0.162
Duration of symptom			<0.01
<1 year	125 (82.2%)	142 (56.8%)	
≥1 year	27 (17.8%)	108 (43.2%)	
Tumor site			
Proximal	8 (5.3%)	75 (30%)	<0.01
Middle	57 (37.5%)	53 (21.2%)	<0.01
Distal	75 (49.3%)	115 (46%)	0.515
Whole gastric	12 (7.9%)	7 (2.8%)	0.02
Macroscopic type			
0	31 (20.4%)	57 (22.8%)	0.572
0−I	4 (2.6%)	10 (4.0%)	
0−IIA	3 (2.0%)	9 (3.6%)	
0−IIB	12 (7.9%)	14 (5.6%)	
0−IIC	10 (6.6%)	14 (5.6%)	
0−III	2 (1.3%)	10 (4%)	
I	5 (3.3%)	35 (14.0%)	<0.01
II	34 (22.4%)	63 (25.2%)	0.520
III	66 (43.4%)	70 (28%)	<0.01
IV	16 (10.5%)	25 (10%)	0.866
Hp infection	70 (51.1%)	154 (61.6%)	0.045
Lauren's classification			
Diffuse	112 (79.4%)	73 (29.2%)	<0.01
Intestinal	13 (9.2%)	156 (62.4%)	<0.01
Mixed	16 (11.3%)	21 (8.4%)	0.475
Clinical staging			
0 (Tis)	0	12 (4.8%)	<0.01[†]
IA+IB	39 (25.7)	129 (51.6%)	<0.01
IIA+IIB	32 (21.1)	35 (14%)	0.066
III	66 (43.4)	52 (20.8%)	<0.01
IV	15 (9.9)	22 (8.8%)	0.719

* χ^2 test. † Fisher's exact test.

(living status of first- and second-degree relatives of the proband). According to the FGC diagnostic guideline of the Netherland Research Group,[29] the criteria for FGC included GC in 2 or more first- or second-degree relatives, with at least 1 having GC diagnosed before the age of 50 years or GC in 3 or more first- or second-degree relatives, independent of age. GC patients without a positive family history were grouped as spontaneous GC (SGC).

Statistical Analysis

Categorical variables were compared with Pearson's Chi-square (χ^2) test or Fisher's exact test; continuous variables were evaluated by Student's *t* test or Mann–Whitney *U* test. Correlations between various factors and *Hp* infection status were assessed by univariate and multivariate logistic regression analyses. Patient survival was estimated with the Kaplan–Meier method and a log-rank test. Postresection overall survival was analyzed by univariate and multivariate Cox proportional hazards regression models. Variables found to be statistically significant by the univariate analysis were further scrutinized backward stepwise by the multivariate analysis, in which the least significant variable was excluded sequentially. Independent risk factors were presented as the hazard ratio (HR) with 95% confidence interval (CI). All 2-tailed *P* values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics Version 22 (SPSS Inc, Chicago, IL).

RESULTS

Demographics and Baseline Characteristics

Among 175 EOGC patients with the median age of 33 years (range: 17–40), 23 patients were lost to follow-up or did not have a detailed family history and thus excluded from the analysis (Figure 1). A total of 152 young patients and 250 old patients were eligible for the study (Table 1). The mean follow-up time for surviving patients was 38.1 months. There was no significant change in the trend in EOGC resections observed over the 11-year study period (Figure 2A). The overall male-to-female ratio was 0.53:1, which was significantly lower than that of old patients (*P* < 0.01, Table 1). The female-to-male patient ratio increased dramatically in the 31 to 40 years groups, compared to that of very young (≤ 30 years) patient group (Figure 2B).

Clinical Findings

Overall, the symptom at diagnosis of all patients was nonspecific (Table 1). Only 25.7% EOGC and 19.2% old GC patients showed alarming clinical presentations, such as severe dysphagia, considerable gastrointestinal bleeding, and vomiting. Most young patients (82.2%) had a short duration of symptoms.

Upper Endoscopy

The most common EOGC location was in the distal (49.3%) stomach, followed by the middle (37.5%). Only 5.3% of cases occurred in the proximal stomach (Table 1). In contrast in old patients, GC tumors were significantly more common in the proximal stomach (*P* < 0.01), but significantly less frequent in the middle (*P* < 0.01), and similarly common in the distal stomach (Table 1). Macroscopically in EOGCs, the most common pattern was type III (43.4%), followed by type II

TABLE 2. Comparison in Clinicopathology Features Between Familial and Sporadic EOGC Patients

Clinicopathologic Characteristics		Total Number (n = 152) (%)	FGC (n = 38) (%)	SGC (n = 114) (%)	P^*
Gender					0.998
	Male	53 (34.9)	13 (34.2)	40 (35.1)	
	Female	99 (65.1)	25 (65.8)	74 (64.9)	
	Male/female ratio	0.53/1	0.52/1	0.54/1	
Age		33.6 ± 5.54	33.8 ± 5.21	33.6 ± 5.66	0.610†
Duration of symptom					0.391
	<1 year	125 (82.2)	33 (86.8)	92 (80.7)	
	≥1 year	27 (17.8)	5 (13.2)	22 (19.3)	
Tumor location					0.694
	Proximal	8 (5.3)	1 (2.6)	7 (6.1)	
	Middle	57 (37.5)	17 (44.7)	40 (35.1)	
	Distal	75 (49.3)	18 (47.4)	57 (50.0)	
	Linitis plastica	12 (7.9)	2 (5.3)	10 (8.8)	
Size (cm)					0.203†
	Overall	4.6 ± 2.9	4.2 ± 2.1	4.7 ± 3.1	
	Range	0.3–15.0	1.2–8.0	0.3–15.0	
Hp infection					0.074
	Positive	70 (51.1)	17 (48.6)	53 (52.0)	
	Negative	67 (48.9)	18 (51.4)	49 (48.0)	
Lauren's classification					0.537
	Diffuse	112 (79.4)	27 (75.0)	85 (81.0)	
	Intestinal	13 (9.2)	5 (13.9)	8 (7.6)	
	Mixed	16 (11.3)	4 (11.1)	12 (11.4)	
Clinical Staging					0.665
	IA+IB	39 (25.7)	11 (28.9)	28 (24.6)	
	IIA+IIB	32 (21.1)	10 (26.3)	22 (19.3)	
	III	66 (43.4)	14 (36.8)	52 (45.6)	
	IV	15 (9.9)	3 (7.9)	12 (10.5)	
LVI		85 (55.9)	18 (47.4)	67 (58.8)	0.220
PNI		94 (61.8)	21 (55.3)	73 (64.0)	0.335
LN metastasis		99 (65.1)	21 (55.3)	78 (68.4)	0.140
Metastasis		15 (9.9)	3 (7.9)	12 (10.5)	0.875
Adjuvant treatment		118 (77.6)	29 (76.3)	89 (78.1)	0.822
Relapse		51 (33.6)	13 (34.2)	38 (33.3)	0.921
Dead		42 (27.6)	10 (26.3)	32 (28.1)	0.834
Survival Rate					0.433‡
	1 year	82.4	84.8	81.7	
	3 years	71.6	73.0	71.1	
	5 years	64.0	67.4	62.9	
Overall survival					
	Month after surgery	80.23 ± 4.93	86.43 ± 9.54	76.87 ± 5.66	

EOGC = early-onset gastric cancer, FGC = familial gastric cancer, LN = lymph node, LVI = lymphovascular invasion, PNI = perineural invasion, SGC = sporadic gastric cancer.
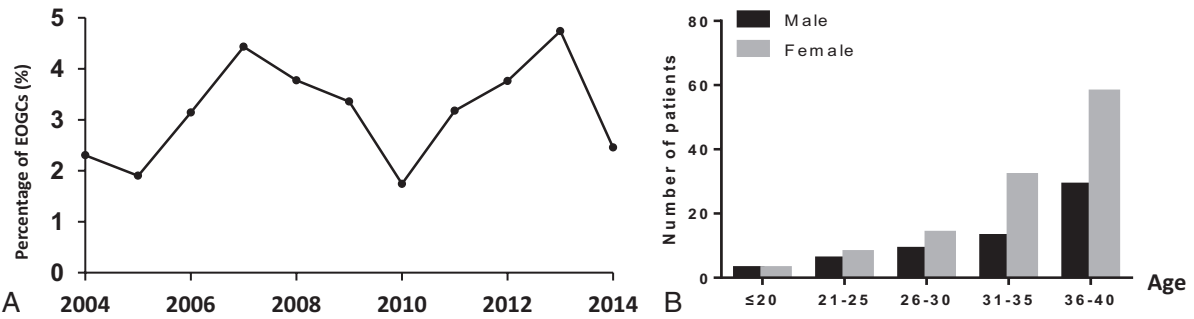* χ^2 test. † t test. ‡ Log-rank test.

FIGURE 2. Percentage of EOGC patients treated annually and frequency of male vs female patients; (A) percentage of EOGC patients operated annually over the period from 2004 to 2014. (B) Number of male and female patients in different age groups. EOGC = early-onset gastric cancer.

and type 0; the type I pattern was the least (3.3%) frequent, and whole stomach involvement was found in 16 patients (10.5%). In type 0 GCs, type IIB and IIC lesions were most common (7.9% and 6.6%). In comparison in old GCs, the type I pattern was significantly more common ($P < 0.01$) and the type III pattern was significantly less frequent ($P < 0.05$). Interestingly, the EOGC group had significantly lower frequent *Hp* infection rate than the old GC ($P < 0.05$, Table 1).

Histopathology

According to Lauren's classification, the diffuse type (79.4%) was significantly more common in young GCs ($P < 0.01$), whereas the intestinal type was significantly more common in old GCs (62.4%) ($P < 0.01$). As shown in Table 1, 43.4% of young patients were significantly more frequently diagnosed at advanced stage (pIII, $P < 0.01$), compared with 20.8% in old patients. In EOGCs, tumor distant metastasis ($n = 15$) was limited to abdominal organs, mainly to the ovary ($n = 6$), peritoneum ($n = 4$), colon ($n = 4$), and pancreas ($n = 1$).

Clinicopathological Characteristics of Familial EOGC

Detailed family cancer history was available in all 152 patients (Table 2 and Figure 3). Thirty-eight (25%) GC cases met the FGC diagnostic criteria, whereas the majority ($n = 114$, 75%) were classified as SGC. Among typical pedigrees of FGC, the autosomal dominant hereditary pattern was most common. The most common organ with cancer in the relatives was, in the descending order, the stomach, esophagus, liver, lung, and colorectum (Table 3). In contrast, esophageal, hepatic, and pulmonary cancers were significantly more frequently found in the SGC group. However, the difference in overall clinicopathology between the 2 groups was not statistically significant.

Differences in Clinicopathology between Very Young ($\leq$ 30 years) and Older (31–40 years) EOGC Patient Groups

To investigate the biological behavior of EOGCs, we further divided the cohorts into 2 groups, according to age (Supplementary Table 1, http://links.lww.com/MD/A718). The very young EOGC ($\leq$30 years) group, compared to the older (31–40 years) group, was significantly more likely to have more frequent PNI (76.3% vs 57.0%, $P = 0.034$). No other significant differences in clinicopathology were found between the 2 groups.

Hp Infection Status

Hp infection was detected in 51.1% of EOGC cases. The clinicopathological difference between *Hp*-positive and -negative patients was shown in Supplementary Table 2, http://links.lww.com/MD/A719. Interestingly, the *Hp* infection rate was significantly higher in the older (31–40 years, 55.1%) GC group, Lauren's intestinal type, and longer symptom duration, but significantly lower in patients staged at pIII and pIV ($P = 0.002$) and PNI ($P = 0.001$). Consequently, the survival rate in patients with *Hp* infection was significantly higher than those without. Univariate logistic regression analysis showed that patient age, advanced macroscopic pattern (i.e. local or infiltrating, ulcerative, whole gastric involvement), Lauren's intestinal type, larger tumor size >4.0 cm, advanced tumor stage (cIII and cIV), pT stage, and PNI were significantly associated with *Hp* infection, whereas Lauren's intestinal type and early pT stage (pT1 and pT2) were the independent risk factors for *Hp* infection by multivariate analysis (Table 4).

Prognostic Factors for Overall Survival

In the cohort, 137 EOGC patients (90.1%) underwent radical R0 surgical resection with curative intent. Tumor palliative resection was carried out in 15 (9.9%) (R1 resection) patients. Two EOGC patients underwent endoscopic submucosal dissection with subsequent additional open surgical resection with nodal dissection because of signet-ring cell carcinoma. One patient had severe postoperative complications with multiple organ failure and died of extensive abdominal metastasis. Of 152 EOGC patients, 42 (27.6%) died of cancer-specific causes. Univariate analysis (Table 5) identified poor prognostic factors including lower BMI (<18.5 kg/m^2), the absence of *Hp* infection, lower serum levels of albumin, higher levels of CA 72–4, CA 125, and CA 19–9, larger tumor size of >4 cm, whole stomach involvement, advanced macroscopic patterns (type pIII–pIV),[30] palliative R1 surgical resection, advanced pathologic stage (pIII and pIV), LVI, PNI, and resection margin involvement. By multivariate analysis (Table 5), independent worse prognostic factors included higher serum levels of CA 72–4 (HR: 7.673, 95% CI: 2.475–23.791, $P < 0.001$), higher CA 125 (HR: 3.903, 95% CI: 1.121–13.590, $P = 0.032$), positive resection margin (HR: 11.081; 95% CI: 3.957–31.028, $P = 0.017$), and advanced tumor stage pIII (HR: 12.851), 95% CI: 1.601–103.122, $P = 0.016$) and pIV (HR: 72.516, 95% CI: 7.750–678.516, $P < 0.001$). Kaplan–Meier survival curves for EOGC patients, according to independent prognostic factors, were exhibited in Figure 4.
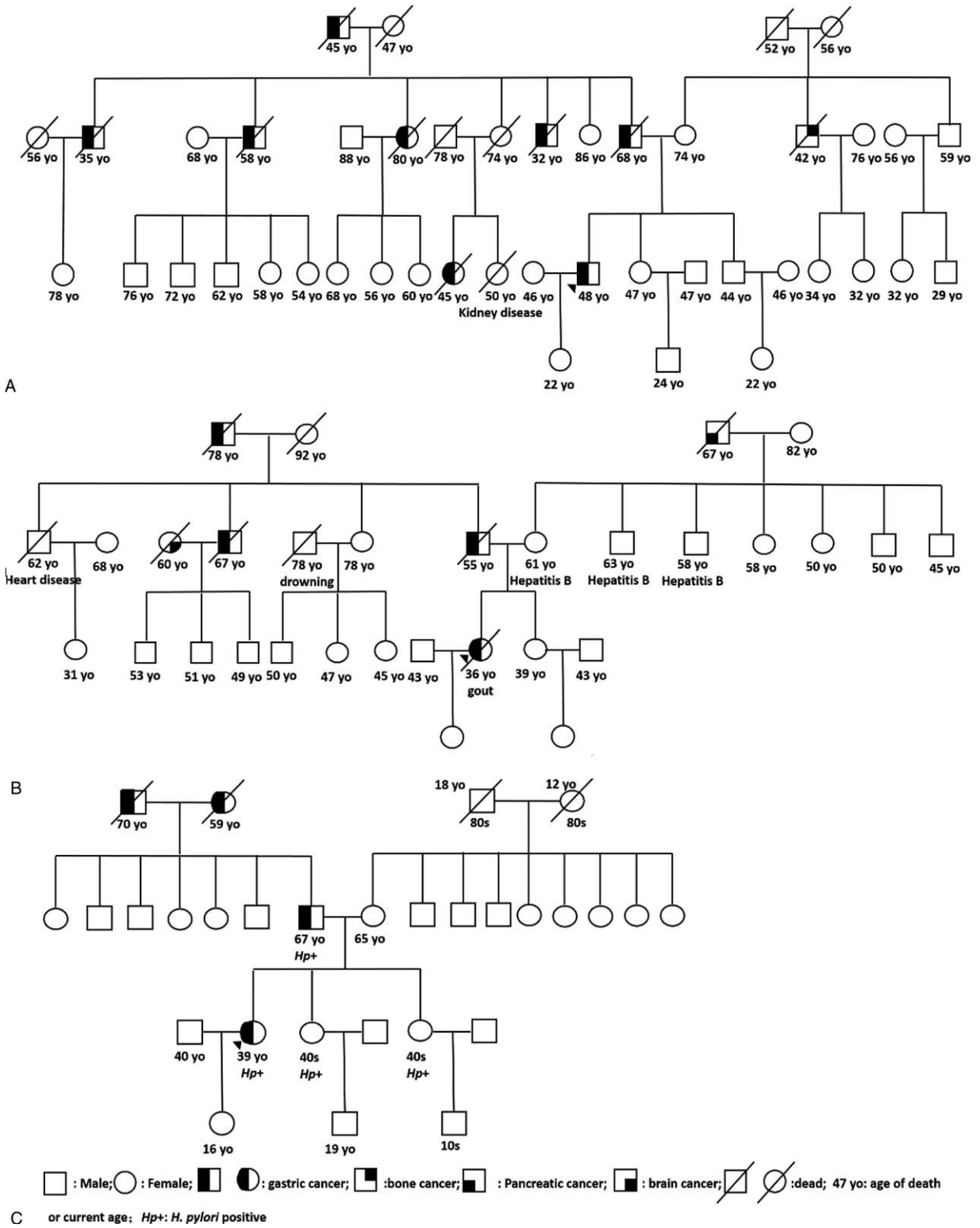
FIGURE 3. Typical pedigree of familiar gastric carcinoma patient.

TABLE 3. Cancers Among the First- and Second-Degree Relatives of Early-Onset Gastric Carcinoma Patients Between Familial and Sporadic Groups

| Cancer Site | Total Number (%) | First- and Second-Degree Relative | | P^* |
		FGC (%)	SGC (%)	
Total	145	85	60	
Stomach	56 (38.6)	56 (100)	0 (0)	
Esophagus	20 (13.8)	6 (30.0)	14 (70.0)	0.005
Liver	17 (11.7)	5 (29.4)	12 (70.6)	0.009
Lung	13 (9.0)	3 (23.1)	10 (76.9)	0.006
Colorectum	10 (6.9)	6 (60.0)	4 (40.0)	0.927
Pancreas	5 (3.4)	1 (20.0)	4 (80.0)	0.186
Gallbladder	3 (2.1)	3 (100)	0	0.267†
Bone	3 (2.1)	1 (33.3)	2 (66.7)	0.759
Leukemia	2 (1.4)	0	2 (100)	0.170†
Breast	2 (1.4)	1 (50.0)	1 (50.0)	1.000†
Uterus	2 (1.4)	0	2 (100)	0.170†
Nasal pharyngeal cancer	1 (0.7)	1 (100)	0	1.000†
Melanoma	1 (0.7)	1 (100)	0	1.000†
Brain	1 (0.7)	0	1 (100)	0.414†
Kidney	1 (0.7)	0	1 (100)	0.414†
Prostate	1 (0.7)	1 (100)	0	1.000†
Bladder	1 (0.7)	0	1 (100)	0.414†
Lymphoma	1 (0.7)	0	1 (100)	0.414†
Unknown	5 (3.4)	0	5 (100)	0.011†

FGC = familial gastric cancer, SGC = sporadic gastric cancer.
* χ^2 test. † Fisher's exact test.

DISCUSSION

In line with previous similar investigations in other ethnic populations,[4,22,31,32] our study reveals that EOGCs in Chinese patients treated at our hospital are also female predominant and show mainly the diffuse histology type. Although FGC accounts for only 25% of the EOGC cohort, there are no significant differences in clinicopathology between FGC and SGC groups. However, very young (≤ 30 years) patients have a significantly lower *Hp* infection rate, but a higher PNI rate than older patients, the findings that have not been described before.[33,34] To our surprise, high serum levels of CA 72−4 and CA 125, along with palliative resection, are identified as independent risk factors for worse outcomes in EOGC patients, which may be clinically useful for patient management, if confirmed by additional clinical studies with larger samples from other centers.[35,36]

EOGC is uncommon and found in only 3.2% of all GC resections in our cohort, which is consistent with previous studies (2−8%).[15,37−39] Although the true incidence of EOGC in China remains unknown, a recent American study, based on the data of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program in the United States, shows a significantly increased incidence trend from 0.27 to 0.45 per 100,000 person-years for both female and male patients aged between 25 and 39 years.[40] However, that study is limited to noncardiac GC only and carried out in a low GC risk population. In contrast, a significantly decreased EOGC incidence for male patients has been reported by Korean investigators under the Population-Based Regional Cancer Registry (PBCR) program in Korea,[41] which is a high GC risk population, as the Chinese.

In general, family cancer aggregation is more common in EOGC patients than in older age GC groups, as also shown in our study. In our cohort, FGC accounted for 25% of EOGCs, a percentage similar to that reported by Umeyama et al in Japan,[6] but slightly higher than that described by investigators from Shanghai in China[9] and in Korea.[15,35] Our studies show that the EOGC tumor location is more frequent in the middle stomach, which is consistent with that reported previously in Chinese[9] and Japanese[42] studies, suggesting underlying unique, probably hereditary, pathogenesis mechanisms that are different from those in the proximal or distal stomach. Nevertheless, the published data indicate an important role of hereditary factors in tumorigenesis of EOGC in both

TABLE 4. Univariate and Multivariate Analyses (Logistic Regression) of Clinicopathological Features in Relation to *Hp* Infection in Early-Onset Gastric Cancer Patients

| Factors | Univariate Analysis | | Multivariate Analysis | |
	Risk Ratio (95% CI)	P	RR (95% CI)	P
Age (≥30 years)	1.083 (1.012−1.160)	0.021		
Macroscopic type				
Early GC				
Advanced GC	0.296 (0.121−0.724)	0.008		
Tumor size (>4.0 cm)	0.862 (0.758−0.981)	0.024		
Lauren's classification				
Diffuse/mixed				
Intestinal	12.868 (1.608−102.969)	0.016	18.896 (1.693−210.871)	0.017
Perineural invasion	0.303 (0.147−0.625)	0.001		
Clinical tumor stage				
I+II				
III+IV	0.476 (0.240−0.941)	0.033		
Advanced pT stage (pT3 and pT4)	0.207 (0.096−0.445)	<0.001	0.044 (0.005−0.382)	0.005

CI = confidence interval, GC = gastric carcinoma, RR = risk ratio.

TABLE 5. Uni- and Multivariate Analyses (Cox Regression) on Prognosis of EOGC Patients

Factors	Univariate Analysis		Multivariate Analysis	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Female	1.322 (0.692–2.528)	0.397		
Age (≤30 y)	1.139 (0.570–2.274)	0.713		
Positive family history	0.745 (0.355–1.561)	0.435		
Higher body mass index	0.193 (0.096–0.391)	<0.001		
Positive *Hp* infection	0.460 (0.233–0.909)	0.026		
Laboratory findings				
Higher albumin level	0.362 (0.137–0.961)	0.041		
Higher CA 72–4	3.287 (1.401–7.716)	0.006	7.673 (2.475–23.791)	<0.001
Higher CA 125	3.276 (1.222–8.781)	0.018	3.903 (1.121–13.590)	0.032
Higher CA 19–9	3.863 (1.724–8.653)	0.001		
Larger tumor size (cm)	1.453 (1.314–1.608)	<0.001		
Tumor location				
Proximal				
Middle	0.421 (0.132–1.343)	0.144		
Distal	0.624 (0.212–1.837)	0.392		
Whole gastric	3.671 (1.078–12.501)	0.037		
Macroscopic type*				
Early GC				
Advanced GC	31.298 (1.467–667.893)	0.027		
Surgical resection				
Radical				
Palliative	6.942 (3.381–14.253)	<0.001		
Lauren's classification				
Diffuse (and mixed)				
Intestinal	0.186 (0.025–1.356)	0.097		
Positive resection Margin	6.679 (3.329–13.398)	<0.001	11.081 (3.957–31.028)	<0.001
Staging (AJCC 7)				
I				
II	2.515 (0.228–27.771)	0.452		
III	26.814 (3.626–198.293)	0.001	12.851 (1.601–103.122)	0.016
IV	76.699 (9.603–612.577)	<0.001	72.516 (7.750–678.516)	<0.001
Lymphovascular invasion	10.005 (3.540–28.281)	<0.001		
Perineural invasion	8.955 (3.152–25.435)	<0.001		

AJCC = American Joint Committee on Cancer, CI = confidence interval, EOGC = early-onset gastric cancer, GC = gastric carcinoma, RR = risk ratio.

Western and Asian populations. Compared with SGC, the FGC group does show more frequent esophageal, liver and lung cancers in the proband first- and second-degree relatives. Interestingly, those cancers rank the highest in incidence among other organ types of cancer in the general population in China,[3] suggesting a hereditary component(s) in those cancers. A recent genomic study[43] points out that germline mutation of the *CDH1*, *CTNNA1,* or *MAP3K6* genes may be involved in the tumorigenesis of some FGCs. Further investigations are needed to reveal genomic mechanisms of hereditary GC in Chinese patients. In contrast in the SGC group, lung and liver, but not esophageal, cancers are predominant, a finding consistent with the data from the Chinese National Central Cancer Registry (NCCR) published in 2011.[3] Apparently, EOGC in the SGC group may be part of common cancer syndromes but the hereditary relationship may exist between esophageal and gastric cancers in the Chinese population, as alluded by the most recent meta-analysis of GC genomics.[44]

GC is more common in men with a male/female ratio ranging from 1.62:1 to 2:1.[45,46] However, most surveys on EOGC, including our own, have shown a female dominance with the male/female ratio ranging from 0.64:1 to 0.87:1.[15,35,47] This observation suggests the potential role of estrogen in EOGC pathogenesis. According to a prospective study on Spanish women,[48] the risk of GC increased in women who had oophorectomy, indicating the protective effect of estrogen against GC development, which has been confirmed by 2 large-scale studies in Japan[49] and in China.[50] Further investigation to illustrate molecular mechanisms by which estrogen plays in EOGC tumorigenesis is needed.

Hp infection has been proven to be carcinogenic in GC development but conveys a favorable survival outcome in GC patients with *Hp* infection, compared to those without *Hp* infection,[51] which is also our experience in EOGC. Moreover, we show that very young (≤ 30 years) GC patients are less likely to be infected with *Hp* and less exposure to environmental toxins,[52] suggesting that hereditary factors may be of more
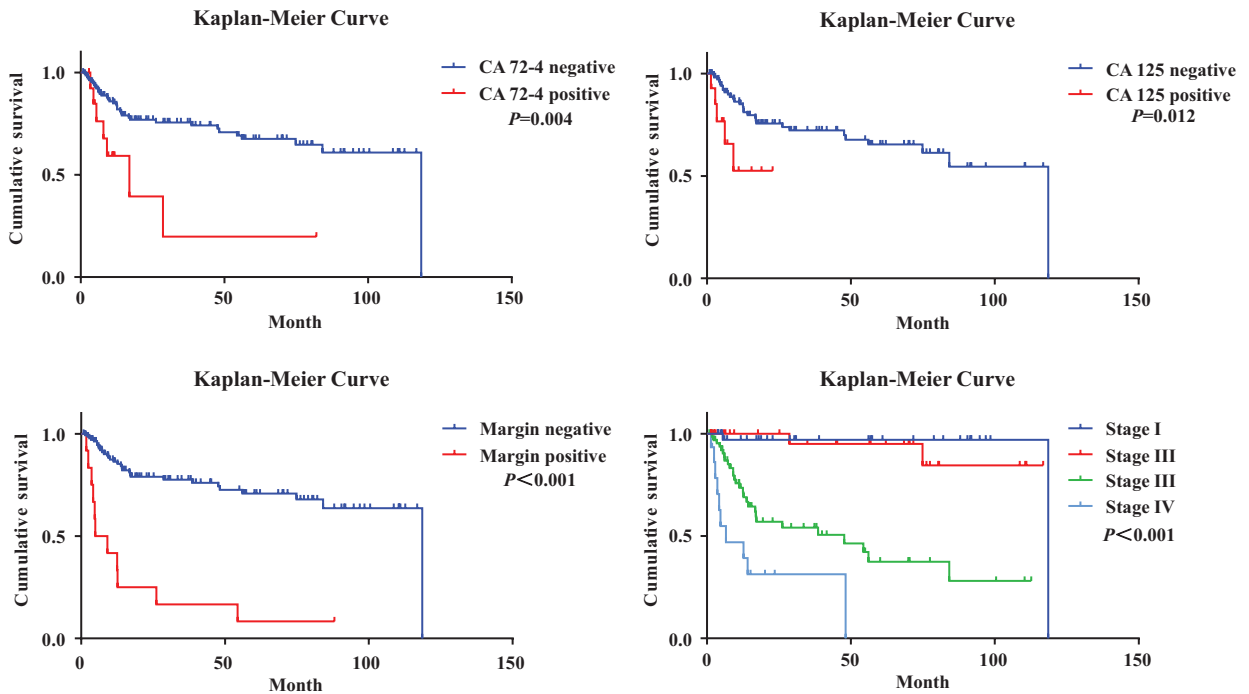
FIGURE 4. Kaplan–Meier curve showing the probability of overall survival for EOGC patients, according to CA 72–4 level, CA 125 level, resection margin, and pathology stage (log-rank test). EOGC = early-onset gastric cancer.

importance than *Hp* infection in tumorigenesis of EOGC. We showed that the absence of *Hp* infection was associated with a shorter symptom duration, more advanced tumor stage, and more frequent PNI, which are consistent with those reported in 1995 by a research group from Taiwan.[51] Lee et al first reported that *Hp* seropositive GC patients with localized Borrmann types showed better survival than *Hp*-negative counterparts.[51] Recently, *Hp* infection was found to be an independent prognostic factor for relapse-free survival and overall survival.[53,54] The immune response activated by *Hp* infection could lead to genesis of gastric adenocarcinoma (activation of Th17 pathway),[55] but meanwhile can also modulate antitumor immunity.[54] The molecular interplay between *Hp* infection and host genetic vulnerability is essential for illustration of EOGC pathogenesis mechanism.

The postresection survival of EOGC patients remains elusive.[56] In our study, the 5-year survival rate in EOGC patients was 64%, which is much higher than that reported by Korean and Japanese investigators.[9,35] The discrepancy may be related to several factors. First, we included only the patients who underwent surgical or endoscopic resection with additional surgical nodal dissection. This indirectly suggests that if young GC patients diagnosed at a resectable stage, the prognosis would be favorable. Second, most patients in our cohort have undergone radical resection that demonstrates a significant survival advantage than those with palliative surgery only.

A major limitation of our study is the retrospective study design. As a result, not all cases have a complete dataset for analysis. In addition, we rely on patient self-reporting family history, which might have contributed to under-reporting of second-degree positive family history and under-diagnosed FGC. Although those variables are difficult to be controlled in the present study, we are currently conducting a robust prospective clinical investigation with a major focus on hereditary GC diseases at our center.

CONCLUSION

We show that family aggregation in GC is more common in EOGC patients but FGC patients have clinicopathological features similar to SGC patients; early detection of high serum levels of CA 72–4 and CA 125 and subsequent radical, rather than palliative, resection could improve survival outcomes, especially for those with positive family history. Further genomic studies of EOGC especially FGC may help reveal molecular tumorigenesis mechanisms to provide EOGC patients with optimal individualized precision management strategy.

REFERENCES

1. Herrero R, Parsonnet J, Greenberg ER. Prevention of gastric cancer. *JAMA.* 2014;312:1197–1198.

2. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 10 October 2014.

3. Chen W, Zheng R, Zeng H, et al. Annual report on status of cancer in China, 2011. *Chin J Cancer Res.* 2015;27:2–12.

4. Hsieh FJ, Wang YC, Hsu JT, et al. Clinicopathological features and prognostic factors of gastric cancer patients aged 40 years or younger. *J Surg Oncol.* 2012;105:304–309.

5. Theuer CP, de Virgilio C, Keese G, et al. Gastric adenocarcinoma in patients 40 years of age or younger. *Am J Surg.* 1996;172:473–476; discussion 476–477.

6. Umeyama K, Sowa M, Kamino K, et al. Gastric carcinoma in young adults in Japan. *Anticancer Res.* 1982;2:283–286.

7. Corso G, Pedrazzani C, Pinheiro H, et al. E-cadherin genetic screening and clinico-pathologic characteristics of early onset gastric cancer. *Eur J Cancer.* 2011;47:631–639.

8. Qiu MZ, Wang ZQ, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of gastric cancer in the young adult in China. *Tumour Biol.* 2011;32:509–514.

9. Bai Y, Li ZS. Endoscopic, clinicopathological features and prognosis of very young patients with gastric cancer. *J Gastroenterol Hepatol.* 2011;26:1626–1629.

10. Fang C, Lu L, Shi J, et al. Risk factors of early proximal gastric carcinoma in Chinese diagnosed with the WHO criteria. *J Dig Dis.* 2015;16:327–336.

11. Mocellin S, Verdi D, Pooley KA, et al. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. *Gut.* 2015;64:1209–1219.

12. Graham DY. *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology.* 2015;148:719–731; e713.

13. Tavares A, Gandra A, Viveiros F, et al. Analysis of clinicopathologic characteristics and prognosis of gastric cancer in young and older patients. *Pathol Oncol Res.* 2013;19:111–117.

14. Kokkola A, Sipponen P. Gastric carcinoma in young adults. *Hepatogastroenterology.* 2001;48:1552–1555.

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

16. Shinmura K, Kohno T, Takahashi M, et al. Familial gastric cancer: clinicopathological characteristics, RER phenotype and germline p53 and E-cadherin mutations. *Carcinogenesis.* 1999;20:1127–1131.

17. Zhang YY, Li JT, Zhu M, et al. Association of the germline mutations of E-cadherin gene (CDH1) in gastric cancer. *Carcinogen, Teratog Mutagen.* 2005;17:350–353.

18. Zhu ZG, Yu YY, Zhang Y, et al. CDH1 mutational analysis and pathologic study of a Chinese familial cancer syndrome with diffuse type gastric cancer/breast cancer proband. *Chin J Digestion.* 2004;24:344–348.

19. Yanjun X, Wenming C, Lisha Y, et al. Detection of CDH1 gene variants in early-onset diffuse gastric cancer in Chinese patients. *Clin Lab.* 2014;60:1823–1830.

20. Corso G, Carvalho J, Marrelli D, et al. Somatic mutations and deletions of the E-cadherin gene predict poor survival of patients with gastric cancer. *J Clin Oncol.* 2013;31:868–875.

21. Kaurah P, MacMillan A, Boyd N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA.* 2007;297:2360–2372.

22. Ramos-De la Medina A, Salgado-Nesme N, Torres-Villalobos G, et al. Clinicopathologic characteristics of gastric cancer in a young patient population. *J Gastrointest Surg.* 2004;8:240–244.

23. Yokota T, Takahashi N, Teshima S, et al. Early gastric cancer in the young: clinicopathological study. *Aust N Z J Surg.* 1999;69:443–446.

24. Lo SS, Kuo HS, Wu CW, et al. Poorer prognosis in young patients with gastric cancer? *Hepatogastroenterology.* 1999;46:2690–2693.

25. Smith BR, Stabile BE. Extreme aggressiveness and lethality of gastric adenocarcinoma in the very young. *Arch Surg.* 2009;144:506–510.

26. Lauwers G, Carneiro F, Graham DY, et al. Gastric carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO Classification of Tumours of the Digestive System.* Lyon: IARC; 2010:48–68.

27. Edge S, Byrd DR, Compton CC, et al. Cancer Staging Manual. 7th ed. New York: Springer-Verlag; 2010:XV, 648.

28. Liebig C, Ayala G, Wilks JA, et al. Perineural invasion in cancer: a review of the literature. *Cancer.* 2009;115:3379–3391.

29. Kluijt I, Sijmons RH, Hoogerbrugge N, et al. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. *Fam Cancer.* 2012;11:363–369.

30. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011;14:101–112.

31. Isobe T, Hashimoto K, Kizaki J, et al. Characteristics and prognosis of gastric cancer in young patients. *Oncol Rep.* 2013;30:43–49.

32. Lim S, Lee HS, Kim HS, et al. Alteration of E-cadherin-mediated adhesion protein is common, but microsatellite instability is uncommon in young age gastric cancers. *Histopathology.* 2003;42:128–136.

33. Takatsu Y, Hiki N, Nunobe S, et al. Clinicopathological features of gastric cancer in young patients. *Gastric Cancer.* 2015[Epub ahead of print].

34. Xu JB, He YL, Wu H, et al. Clinicopathological features and prognosis of young patients with gastric cancer. *Chin J Gastrointest Surg.* 2013;16:160–162.

35. Park HJ, Ahn JY, Jung HY, et al. Clinical characteristics and outcomes for gastric cancer patients aged 18–30 years. *Gastric Cancer.* 2014;17:649–660.

36. Chung HW, Noh SH, Lim JB. Analysis of demographic characteristics in 3242 young age gastric cancer patients in Korea. *World J Gastroenterol.* 2010;16:256–263.

37. Matley PJ, Dent DM, Madden MV, et al. Gastric carcinoma in young adults. *Ann Surg.* 1988;208:593–596.

38. Bloss RS, Miller TA, Copeland EM 3rd. Carcinoma of the stomach in the young adult. *Surg Gynecol Obstet.* 1980;150:883–886.

39. Tso PL, Bringaze WL 3rd, Dauterive AH, et al. Gastric carcinoma in the young. *Cancer.* 1987;59:1362–1365.

40. Anderson WF, Camargo MC, Fraumeni JF Jr et al. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA.* 2010;303:1723–1728.

41. Song M, Kang D, Yang JJ, et al. Age and sex interactions in gastric cancer incidence and mortality trends in Korea. *Gastric Cancer.* 2015;18:580–589.

42. Nakamura T, Yao T, Niho Y, et al. A clinicopathological study in young patients with gastric carcinoma. *J Surg Oncol.* 1999;71:214–219.

43. Kakiuchi M, Nishizawa T, Ueda H, et al. Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. *Nat Genet.* 2014;46:583–587.

44. Mocellin S, Verdi D, Pooley KA, et al. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. *Gut.* 2015;64:1209–1219.

45. Sipponen P, Correa P. Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis. *Gastric Cancer.* 2002;5:213–219.

46. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64:9–29.

47. Yu J, Li Z. The sex ratio and age of onset features of gastric cancer patients in hereditary diffuse gastric cancer families. *Fam Cancer.* 2011;10:573–579.

48. Duell EJ, Travier N, Lujan-Barroso L, et al. Menstrual and reproductive factors, exogenous hormone use, and gastric cancer risk in a cohort of women from the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol.* 2010;172:1384–1393.

49. Persson C, Inoue M, Sasazuki S, et al. Female reproductive factors and the risk of gastric cancer in a large-scale population-based cohort study in Japan (JPHC study). *Eur J Cancer Prev.* 2008;17:345–353.

50. Freedman ND, Chow WH, Gao YT, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut.* 2007;56:1671–1677.

51. Lee WJ, Lin JT, Shun CT, et al. Comparison between resectable gastric adenocarcinomas seropositive and seronegative for *Helicobacter pylori*. *Brit J Surg.* 1995;82:802–805.

52. Milne AN, Sitarz R, Carvalho R, et al. Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. *Curr Mol Med.* 2007;7:15–28.

53. Meimarakis G, Winter H, Assmann I, et al. *Helicobacter pylori* as a prognostic indicator after curative resection of gastric carcinoma: a prospective study. *Lancet Oncol.* 2006;7:211–222.

54. Kang SY, Han JH, Ahn MS, et al. *Helicobacter pylori* infection as an independent prognostic factor for locally advanced gastric cancer patients treated with adjuvant chemotherapy after curative resection. *Int J Cancer.* 2012;130:948–958.

55. Amedei A, Munari F, Bella CD, et al. *Helicobacter pylori* secreted peptidyl prolyl cis, trans-isomerase drives Th17 inflammation in gastric adenocarcinoma. *Intern Emerg Med.* 2014;9:303–309.

56. Karim S. Clinicopathological and p53 gene alteration comparison between young and older patients with gastric cancer. *Asian Pac J Cancer Prev.* 2014;15:1375–1379.