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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinicopathologic and molecular features associated with patient age in gastric cancer

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Abstract

AIM: To compare characteristics and prognosis of gastric cancer based on age.

METHODS: A retrospective study was conducted on clinical and molecular data from patients (n = 1658) with confirmed cases of gastric cancer in Seoul National University Bundang Hospital (Seoul, South Korea) from 2003 to 2010 after exclusion of patients diagnosed with lymphoma, gastrointestinal stromal tumor, and metastatic cancer in the stomach. DNA was isolated from tumor and adjacent normal tissue, and a set of five markers was amplified by polymerase chain reaction to assess microsatellite instability (MSI). MSI was categorized as high, low, or stable if $\geqslant$ 2, 1, or 0 markers, respectively, had changed. Immunohistochemistry was performed on tissue sections to detect levels of expression of p53, human epidermal growth factor receptor (HER)-2, and epidermal growth factor receptor. Statistical analysis of clinical and molecular data was performed to assess prognosis based on the stratification of patients by age ($\leqslant$ 45 and > 45 years).

RESULTS: Among the 1658 gastric cancer patients, the number of patients with an age $\leqslant$ 45 years was 202 (12.2%; 38.9 ± 0.4 years) and the number of patients > 45 years was 1456 (87.8%; 64.1 ± 0.3 years). Analyses revealed that females were predominant in

the younger group ($P < 0.001$). Gastric cancers in the younger patients exhibited more aggressive features and were at a more advanced stage than those in older patients. Precancerous lesions, such as atrophic gastritis and intestinal metaplasia, were observed less frequently in the older than in the younger group ($P < 0.001$). Molecular characteristics, including overexpression of p53 ($P < 0.001$), overexpression of HER-2 ($P = 0.006$), and MSI ($P = 0.006$), were less frequent in gastric cancer of younger patients. Cancer related mortality was higher in younger patients ($P = 0.048$), but this difference was not significant after adjusting for the stage of cancer.

CONCLUSION: Gastric cancer is distinguishable between younger and older patients based on both clinicopathologic and molecular features, but stage is the most important predictor of prognosis.

Key words: Age; Gastric cancer; Microsatellite instability; Molecular pathology; Prognosis; Stage

Core tip: Whether gastric cancer exhibits distinguishable characteristics based on age remains controversial. In this original article, results are presented that highlight differences in clinical characteristics, pathology, and molecular features of younger and older gastric cancer patients. In particular, the pathologic degree of precancerous lesions associated with each group illuminated potential differences in the pathogenesis of the disease. Although gastric cancer in younger patients presented with more aggressive features, the primary factor in predicting the prognosis of patients with the disease was the stage of the cancer, and not the age of the patient.

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INTRODUCTION

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer related death worldwide[1,2]. Due to successful screening, the detection of early gastric cancer and the cure rate of gastric cancer have increased annually[1,2]. Regardless of this effort however, mortality of gastric cancer remains high, particularly in East Asian countries.

In general, the peak incidence for gastric cancer is in patients aged 65-74 years[3], with only approximately 3%-10% of gastric cancers overall occurring in patients younger than 40 years[4]. Some case series have focused specifically on younger patients and have reported the cases to be highly advanced gastric cancers (AGC) with poor prognoses[5]. Intriguingly, these gastric cancers were found to be more common in women, frequently diffusely spread in the stomach, more poorly differentiated, and more advanced in stage than gastric cancers from older patients[6,7]. These findings remain controversial[6,8], particularly with regard to patient survival, but have raised the possibility of a disease course that is potentially distinct from that in older patients. Some studies report a better prognosis in younger patients[9,10], while others have found poorer prognoses in young gastric cancer patients relative to older patients[4,11]. Still others have demonstrated no significant differences at all in survival between the two age groups[6-8].

While the majority of reports have focused only on the clinical or pathologic features of gastric cancer in younger patients[4,6-11], molecular characteristics that may distinguish tumors between the two age groups have not been well described. Therefore, this study aimed to determine whether differences in clinicopathologic and molecular characteristics exist in gastric cancer based on age.

MATERIALS AND METHODS

Ethics statement

This study protocol was approved by the Ethical Committee at the Seoul National University Bundang Hospital (SNUBH; IRB number: B-1403/244-116), and conformed to the provisions of the Declaration of Helsinki. Informed consent was exempted by the committee.

Study population

A retrospective cohort study was conducted to identify differences between young (age ⩽ 45 years) and older (age > 45 years) patients with gastric cancer. The study was performed on patients who had been diagnosed with gastric cancer in SNUBH from June 2003 to December 2010. Exclusion criteria were the following: (1) patients < 20 years of age; (2) patients diagnosed with gastric mucosa-associated lymphoid tissue lymphoma, gastrointestinal stromal tumor, or other metastatic cancer located in the stomach; (3) patients for whom a pathologic diagnosis of gastric cancer was not confirmed; (4) patients who did not undergo a stage workup of gastric cancer; (5) patients who were lost in follow-up from SNUBH after diagnosis; or (6) patients who were not initially diagnosed with gastric cancer during the search period.

Data collection and pathologic examination

Demographic factors of patients, characteristics of gastric cancer, pathology, stage, molecular features, *Helicobacter pylori* (*H. pylori*) status, treatment, recurrence, and mortality were reviewed from electro-

nic medical records. Location of the primary tumor was assigned to the proximal, middle, or distal third of the stomach. Gastric cancer that extended into more than two of the three sections was defined as diffusely located[8]. The type of early gastric cancer followed Paris classification (Ⅰ to Ⅲ)[12], and the type of AGC followed Borrmann classification (Ⅰ to Ⅳ)[13]. Gastric cancer was staged according to the 7th edition of the American Joint Committee on Cancer TNM staging system[14].

The pathology of gastric cancers was categorized as intestinal, diffuse, or mixed by Lauren's classification[15]. The degree of *H. pylori* infection, neutrophil infiltration, mononuclear cell infiltration, atrophic gastritis, and intestinal metaplasia was scored as 0 (absent), 1 (mild), 2 (moderate), or 3 (marked) for statistical analysis, according to the Updated Sydney System[16].

Immunohistochemistry

Paraffin-embedded sections (4 μm) were deparaffinized and incubated with monoclonal antibodies against p53, human epidermal growth factor receptor (HER)-2, and epidermal growth factor receptor (EGFR). Detection of primary antibodies and amplification of signal was performed with the streptavidin-biotin method as previously described[17,18]. Staining was recorded as positive or negative expression[17,18]. Overexpression of p53 in > 10% of tumor cells, which generally reflects an underlying mutation in the p53 gene, was as considered positive[19]. Scoring for HER-2 protein expression was performed as previously reported: 0, membrane staining of less than 10% of tumor cells; 1+, faint partial membrane staining in > 10% of tumor cells; 2+, weak to moderate staining of whole membranes in > 10% of tumor cells; and 3+, strong staining of whole membranes in > 10% of tumor cells. Scores of 2+ and 3+ were classified as HER-2 overexpression[18]. A similar scoring method was applied to immunohistochemistry (IHC) staining for the EGFR protein, with scores of 2+ and 3+ classified as overexpression[18].

Microsatellite instability analysis

Tumor and normal DNAs were extracted from paraffin-embedded tissue. Five markers (BAT-25, BAT-26, D2S123, D5S346, and D17S250) were used following the guidelines of the International Workshop of the National Cancer Institute. Marker sequences from tumor and matched normal DNAs were amplified with polymerase chain reaction and compared. Tumors with two or more novel markers were classified as microsatellite instability (MSI)-high, whereas tumors with one marker shift were classified as MSI-low. Microsatellite stability was defined as when all markers were identical in tumor and normal DNAs[20].

Evaluation of outcomes

The primary and secondary outcomes that were compared in this study were mortality and recurrence. Cause of death was categorized as one of the following three scenarios: (1) gastric cancer-related death or mortality due to the progression of gastric cancer; (2) treatment-related death, including severe complications due to surgery or infection after chemotherapy; or (3) other causes not directly related to gastric cancer. Time to recurrence was estimated for those who were cured after endoscopic or surgical resection of gastric cancer.

Statistical analysis

Values are expressed as the mean ± SD for continuous variables and as frequencies (percent) for categorical variables. A Fisher's exact test, χ^2 analysis, and a Student's *t*-test were used for analyzing characteristics of gastric cancer. Independent risk factors for mortality were analyzed with univariate and multivariate analyses using the Cox proportional hazards model. Variables with $P < 0.05$ in univariate analyses were included in multivariate analyses. Overall survival and recurrence-free survival was estimated using the Kaplan-Meier method and the log-rank test. A $P \leqslant 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS, version 18.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Baseline characteristics

Patients (n = 2416) with a diagnosis of gastric cancer were identified from electronic records from June 2003 to December 2010 at SNUBH. The following patients (n = 758) were excluded from further analysis: < 20 years of age (n = 1); diagnosis of gastric mucosa-associated lymphoid tissue lymphoma (n = 87), gastrointestinal stromal tumor (n = 18), metastatic cancer in the stomach (n = 3), pathologic diagnosis of gastric cancer was not confirmed (n = 11), did not undergo a staging workup (n = 32), lost in follow-up (n = 89), and diagnosed with gastric cancer and receiving treatment (n = 517) (Figure 1). The remaining patients (n = 1658) were analyzed.

The number of younger patients (⩽ 45 years) was 202 (12.2%), and the number of older patients (> 45 years) was 1456 (87.8%). The mean age of diagnosis was 61.0 ± 0.3 years for all patients, 38.9 ± 0.4 years for younger patients, and 64.1 ± 0.3 years for older patients. A summary of the baseline characteristics for all patients is presented in Table 1. Analyses revealed that the number of female patients was predominant in the younger group ($P < 0.001$). The majority of younger patients requested medical examination because of symptoms (56.9%). In contrast, gastric cancer was detected in about half of the older patients as a result of screening (49.7%). Older patients had more comorbid diseases ($P < 0.001$). Gastric cancer in younger patients was more frequently diffusely spread in the stomach ($P < 0.001$) with more incidences of Borrmann type Ⅳ AGC ($P < 0.001$). There were no

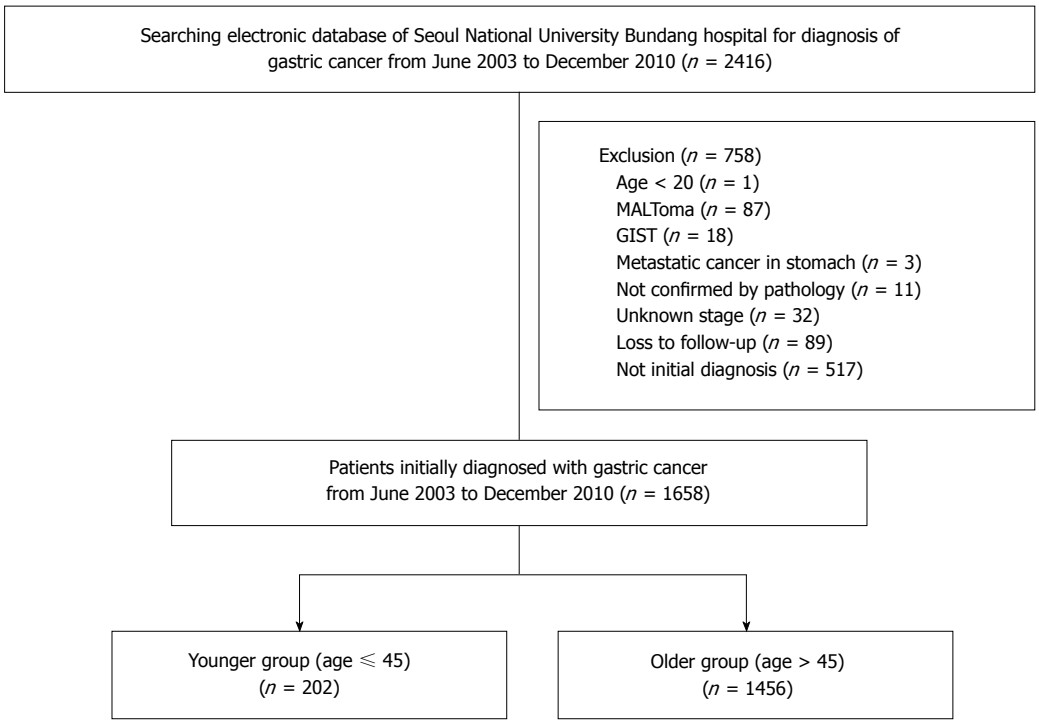

Figure 1 Flow chart for selection criteria of patients.

Table 1 Baseline characteristics of the study population *n* (%)

Characteristic	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)	*P* value
Gender			< 0.001
Male	111 (55.0)	1023 (70.3)	
Female	91 (45.0)	433 (29.7)	
Reason for medical checkup			< 0.001
Screening	70 (34.7)	724 (49.7)	
Symptoms[1]	115 (56.9)	613 (42.1)	
Bleeding/anemia	13 (6.4)	105 (7.2)	
Weight loss	4 (2.0)	14 (1.0)	
Comorbidity			< 0.001
No	188 (93.1)	1200 (82.4)	
Yes	14 (6.9)	256 (17.6)	
Size, cm	4.0 ± 0.3	3.7 ± 0.1	0.083
CEA	1.8 ± 0.2	4.5 ± 1.1	0.631
CA 19-9	38.3 ± 13.0	30.7 ± 6.5	0.090
Synchronous gastric cancer			0.226
No	193 (95.5)	1414 (97.1)	
Yes	9 (4.5)	42 (2.9)	
Location			< 0.001
Proximal	20 (9.9)	132 (9.1)	
Middle	88 (43.6)	433 (29.7)	
Distal	59 (29.2)	753 (51.7)	
Diffuse	35 (17.3)	138 (9.5)	
EGC type	116 (57.4)	889 (61.1)	0.084
I	1 (0.5)	50 (3.4)	
II	113 (55.9)	820 (56.3)	
III	2 (1.0)	19 (1.3)	
AGC type (Borrmann)	86 (42.6)	567 (38.9)	< 0.001
I	0 (0)	22 (1.5)	
II	6 (3.0)	118 (8.1)	
III	47 (23.3)	334 (22.9)	
IV	31 (15.3)	71 (4.9)	

[1]Symptoms included abdominal discomfort, abdominal pain, soreness, indigestion, anorexia, nausea, or vomiting. AGC: Advanced gastric cancer; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; EGC: Early gastric cancer.

differences in the size of the tumor, or expression of carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA 19-9) based on age.

Pathology and stage of gastric cancer

The pathology and the stages of gastric cancer for all patients are presented in Table 2. Statistical analyses revealed that more tumors in younger patients were diagnosed as diffuse based on Lauren's classification ($P < 0.001$) (Table 2). Depth of invasion, frequency of distant metastasis, and final stage were all higher in the younger patient group ($P = 0.001$). The pathologic features of venous ($P = 0.024$) and perineural invasion ($P = 0.043$) were also more frequently observed in gastric cancers from younger patients. In contrast, baseline adenoma occurred less often in these patients ($P < 0.001$).

Treatment and clinical outcomes of gastric cancer

Treatment for gastric cancer varied among patients of the study. For example, not all patients underwent curative resection. The various treatment strategies utilized are presented in Table 3. A significantly higher percentage of younger patients received palliative resection for AGC ($P = 0.018$), N3 dissection ($P = 0.017$), and chemotherapy ($P < 0.001$) compared to older patients.

The clinical outcomes are summarized in Table 4. The mean time for follow-up was 35.4 ± 23.7 mo. The mean time to recurrence was 17.8 ± 4.1 in younger patients, and 16.9 ± 1.3 mo in older patients. The recurrence rate for cured patients was similar in both age groups, with peritoneal metastasis as the most common site of recurrence. Furthermore,

Table 2 Pathology and stage of gastric cancer *n* (%)

Variable	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)	*P* value
Pathology (Lauren)			< 0.001
Intestinal	39 (19.3)	870 (59.8)	
Diffuse	157 (77.7)	526 (36.1)	
Mixed	6 (3.0)	60 (4.1)	
Depth of invasion			0.001
T1	117 (57.9)	876 (60.2)	
T2	10 (5.0)	143 (9.8)	
T3	15 (7.4)	186 (12.8)	
T4	33 (16.3)	146 (10.0)	
Lymph node metastasis			0.052
N0	122 (60.4)	962 (66.1)	
N1	8 (4.0)	127 (8.7)	
N2	15 (7.4)	74 (5.1)	
N3	25 (12.4)	155 (10.6)	
Distant metastasis			< 0.001
M0	153 (75.7)	1267 (87.0)	
M1	49 (24.3)	189 (13.0)	
Stage			< 0.001
Ⅰ	122 (60.4)	954 (65.5)	
Ⅱ	10 (5.0)	149 (10.2)	
Ⅲ	21 (10.4)	166 (11.4)	
Ⅳ	49 (24.3)	187 (12.8)	
Lymphatic invasion			0.612
No	121 (59.9)	902 (62.0)	
Yes	50 (24.8)	408 (28.0)	
Venous invasion			0.024
No	149 (73.8)	1207 (82.9)	
Yes	22 (10.9)	102 (7.0)	
Perineural invasion			0.043
No	125 (61.9)	1042 (71.6)	
Yes	46 (22.8)	264 (18.1)	
Baseline adenoma			< 0.001
No	165 (81.7)	1101 (75.6)	
Yes	4 (2.0)	195 (13.4)	

Table 3 Treatment of gastric cancer *n* (%)

Variable	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)	*P* value
Endoscopic resection	9 (4.5)	192 (13.2)	0.516
EMR	6 (3.0)	104 (7.1)	
ESD	3 (1.5)	88 (6.0)	
Operation	172 (85.1)	1160 (79.7)	0.018
Curative resection	157 (77.7)	1108 (76.1)	
Palliative resection	15 (7.4)	52 (3.6)	
LN dissection			0.017
Not performed	9 (4.5)	24 (1.6)	
N1	62 (30.7)	404 (27.7)	
N2	95 (47.0)	714 (49.0)	
N3	6 (3.0)	18 (1.2)	
Radiation			0.101
No	197 (97.5)	1440 (98.9)	
Yes	5 (2.5)	16 (1.1)	
Chemotherapy			< 0.001
No	132 (65.3)	1194 (82.1)	
Yes	70 (34.7)	261 (17.9)	

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LN: Lymph node.

Table 4 Mortality and recurrence of gastric cancer *n* (%)

Variable	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)
Mean follow-up duration, mo	36.9 ± 25.5	35.2 ± 23.5
Mean time to recurrence, mo[1]	17.8 ± 4.1	16.9 ± 1.3
Cured patients	162 (80.2)	1246 (85.6)
Recurrence	17 (10.5)	127 (10.2)
Mortality		
Survival	116 (57.4)	838 (57.6)
Death	26 (12.9)	159 (10.9)
Loss to follow-up	60 (29.7)	459 (31.5)
Cause of death		
Gastric cancer-related death	21 (10.4)	87 (6.0)
Treatment-related death	2 (1.0)	13 (0.9)
Other causes[2]	0 (0)	21 (1.4)
Not available	3 (1.5)	38 (2.6)

[1]Calculated only for cured patients; [2]Other causes of death included malignancy other than gastric cancer, infection not related to treatment of gastric cancer, myocardial infarction, hepatic failure, and trauma.

gastric cancer-related death was the most common cause of death in both groups. Mortality occurred in 26 (12.9%) and 159 (10.9%) of younger and older patients, respectively. Cumulative probabilities of overall mortality were not different between the two age groups (Figure 2). The cumulative rate of gastric cancer-related death was significantly higher in the younger age group (P = 0.048) (Figure 3). However, when adjusted for the stage, gastric cancer-related death was not significantly different between the two age groups (P = 0.191). The cumulative rate of treatment-related death was not different between the two age groups.

Molecular pathology and H. pylori status

The results of molecular pathology are shown in Table 5. Gastric cancer in the younger age group had significantly less positive staining for p53 (P < 0.001), HER-2 overexpression (P = 0.006), and MSI (P = 0.006). EGFR protein expression, however, did not differ between the two groups (P = 0.899).

The status of *H. pylori* and related changes of the stomach are presented in Table 6. The level of *H. pylori* in pathologic specimens was higher in younger patients (P = 0.012). The pathologic degrees of atrophic gastritis and intestinal metaplasia were, however, significantly higher in older patients (P < 0.001).

Predictors of overall survival

Risk factors for overall mortality in gastric cancer patients were analyzed using a Cox proportional hazards model (Table 7). In univariate analyses, the following were significant risk factors for mortality: non-curative resection, elevated CEA, elevated CA 19-9, larger size of gastric cancer, diffuse pathology, higher T, N, or M stage, final stage, and lymphatic, venous, and perineural invasion (all P < 0.001). Multivariate analyses demonstrated that only M stage (adjusted HR = 6.70; 95%CI: 1.58-24.49; P = 0.010) and final stage (adjusted HR = 10.78; 95%CI: 2.69-43.22; P = 0.001)

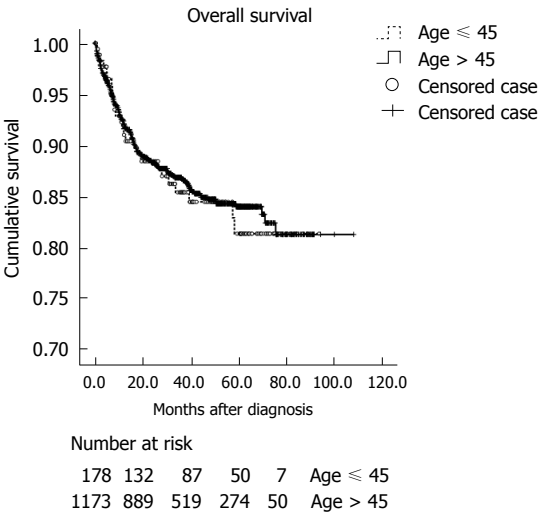

Figure 2 Cumulative probabilities of overall survival based on age (log-rank test, *P* = 0.780).

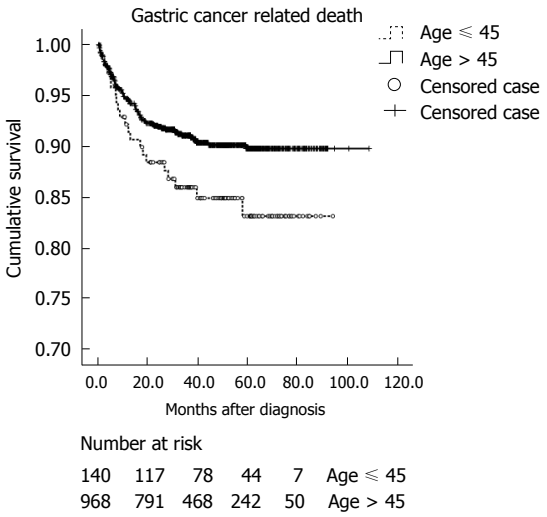

Figure 3 Cumulative probabilities of cancer-related death based on age (log-rank test, *P* = 0.048).

Table 5 Molecular pathology of gastric cancer *n* (%)

Variable	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)	*P* value
p53			< 0.001
Negative	123 (60.9)	681 (46.8)	
Positive	44 (21.8)	560 (38.5)	
MSI			0.006
Stable	85 (42.1)	566 (38.9)	
MSI-L	4 (2.0)	43 (3.0)	
MSI-H	1 (0.5)	79 (5.4)	
HER-2 status			0.006
Negative	78 (38.6)	528 (36.3)	
Positive	6 (3.0)	125 (8.6)	
EGFR status			0.899
Negative	94 (46.5)	674 (46.3)	
Positive	12 (5.9)	99 (6.8)	

EGFR: Epidermal growth factor receptor; HER-2: Human epidermal growth factor receptor-2; MSI: Microsatellite instability; MSI-H: MSI-high; MSI-L: MSI-low.

Table 6 *Helicobacter pylori* and associated changes of gastric cancer

Variable	Age ⩽ 45 yr (*n* = 202)	Age > 45 yr (*n* = 1456)	*P* value
Helicobacter pylori grade	0.8 ± 1.0	0.6 ± 0.9	0.012
Neutrophil infiltration	1.4 ± 0.9	1.4 ± 0.9	0.866
Mononuclear cell infiltration	1.9 ± 0.5	1.9 ± 0.5	0.679
Atrophic gastritis	0.5 ± 0.7	1.0 ± 0.9	< 0.001
Intestinal metaplasia	0.5 ± 0.7	1.0 ± 0.8	< 0.001

Scored according to the Updated Sydney System: 0 (absent), 1 (mild), 2 (moderate), and 3 (marked).

were independent risk factors for mortality.

DISCUSSION

This retrospective study of 1658 gastric cancer patients indicates that clinicopathologic features, such as being female, Borrmann type Ⅳ AGC, and diffuse type pathology, were more commonly associated with the younger group of patients. Gastric cancers from patients ⩽ 45 years of age exhibited more advanced stages than from patients > 45 years, but younger patients received more aggressive treatment such as palliative resection and chemotherapy. These findings are in agreement with previous studies[6-8,11].

One of the most intriguing implications of the results is that the pathogenesis of gastric cancer may differ between age groups. *H. pylori* infection is most commonly acquired in children[21], and with increasing age, the stomach changes stepwise from atrophic gastritis, intestinal metaplasia, p53 alteration, and dysplasia, to intestinal-type gastric adenocarcinoma; this transition is known as Correa's cascade[22]. Therefore, the presence of higher degrees of atrophic gastritis and intestinal metaplasia, and increased incidence of p53 overexpression, adenoma, and intestinal-type gastric cancer observed in older patients of this cohort largely corroborates this model. Higher grade *H. pylori* infection in the absence of precancerous changes in younger patients from the cohort, however, does not support this model. In the majority of cases from this cohort, the grade of *H. pylori* infection was evaluated from resected cancer specimens, which were primarily located in the distal third of the stomach of older patients (51.7%). As atrophic gastritis and intestinal metaplasia were more common in older patients, the degree of *H. pylori* infection as determined from pathologic specimens could be underestimated[23]. In fact, positivity of *H. pylori* determined from serology, pathology, and the rapid urease test did not differ between age groups (64.7% *vs* 62.4% in younger and older patients, respectively). The results of the current study indicate that gastric cancer in older patients tends to progress through a series of sequential changes starting with

Table 7 Univariate and multivariate analyses of predictors for mortality

Parameter	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≤ 45/> 45 yr)	1.10 (0.72-1.66)	0.664		
Gender (male/female)	0.87 (0.63-1.19)	0.384		
Curative resection (no/yes)	6.38 (4.33-9.40)	< 0.001		
CEA	1.00 (1.00-1.00)	< 0.001		
CA19-9	1.00 (1.00-1.00)	< 0.001		
Size, cm	1.24 (1.20-1.28)	< 0.001		
Pathology				
Intestinal	1.00 (reference)			
Diffuse	2.77 (2.03-3.78)	< 0.001		
Mixed	1.95 (0.89-4.26)	0.095		
T stage (Ⅲ, Ⅳ *vs* Ⅰ, Ⅱ)	26.07 (16.42-41.40)	< 0.001		
N stage (N+ *vs* N-)	21.29 (12.81-35.36)	< 0.001		
M stage (M+ *vs* M-)	42.17 (30.75-57.84)	< 0.001	6.70 (1.58-24.49)	0.010
Stage (Ⅲ, Ⅳ *vs* Ⅰ, Ⅱ)	46.39 (30.75-69.98)	< 0.001	10.78 (2.69-43.22)	0.001
Lymphatic invasion (yes/no)	11.84 (7.45-18.83)	< 0.001		
Venous invasion (yes/no)	14.75 (9.95-21.87)	< 0.001		
Perineural invasion (yes/no)	14.34 (9.42-251.85)	< 0.001		
Atrophic gastritis	1.06 (0.77-1.45)	0.736		
Intestinal metaplasia	1.00 (0.76-1.30)	0.977		
p53 (positive/negative)	1.45 (0.99-2.12)	0.058		
MSI (MSI-L *vs* stable)	1.30 (0.53-3.21)	0.565		
MSI (MSI-H *vs* stable)	0.82 (0.53-1.76)	0.602		
HER-2 (positive/negative)	0.57 (0.26-1.25)	0.158		
EGFR (positive/negative)	0.66 (0.27-1.65)	0.377		

CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; EGFR: Epidermal growth factor receptor; HER-2: Human epidermal growth factor receptor-2; MSI: Microsatellite instability; MSI-H: MSI-high; MSI-L: MSI-low.

H. pylori infection and leading to intestinal-type gastric cancer. In younger patients, however, a gastric cancer of a diffuse pathology was more prevalent. To the best of our knowledge, this study is the first to reveal potential age-associated biologic differences in gastric cancer and its development.

The results also highlight important differences in the molecular pathology of gastric cancer from the two groups. First, a higher incidence of MSI was detected in tumors from older patients. These results agree with a previous report that demonstrated an increased frequency of MSI specifically in gastric cancers with an antral location, intestinal pathology, and lower incidence of lymph node metastasis[17]. Second, while overexpression of HER-2 has been reported to predict poor prognosis in gastric cancer patients[24,25], an association between HER-2 and age has not yet been identified. The results of the current study indicate that overexpression of HER-2 in gastric cancer is in fact more common in older patients.

Interestingly, while younger patients exhibited a more advanced stage of gastric cancer, the overall mortality rate did not differ between the two age groups in this cohort. Younger patients did have a higher cumulative rate of cancer-related death compared to the older age group. However, this difference between the two age groups was not statistically significant once the data was adjusted for the stage of gastric cancer. Thus, these findings suggest that survival is not associated with age, which is in agreement with previous studies[6-8]. At the same time, treatment differences do exist between the two groups. For example, in spite of the higher stage of gastric cancer, younger patients received more palliative resections than older patients. Because it is possible that palliative gastrectomy could improve overall survival[26,27], aggressive treatment in younger patients might have extended their overall survival. However, despite potential advantage in treatment strategies in younger patients, gastric cancer-related death did not differ between the two groups when adjusted by stage. Further support for this conclusion is gained from the results that only stage and distant metastasis could predict mortality, whereas age was not found to be an independent risk factor in a Cox proportional hazards model. Therefore, other factors, such as the diffuse pathology or size, might more strongly influence overall survival.

Several limitations are inherent in this study, primarily because of the retrospective design. First, molecular pathology was not performed on all tumors. Results for MSI are particularly inconsistent, as the method described here has been applied to tumor samples starting only in the year 2007. Second, fluorescence *in situ* hybridization (FISH) is required to validate IHC scores of 2+ for the accurate diagnosis of the overexpression of HER-2[28]. As FISH was not performed on tumor sections from most patients, overexpression of HER-2 was determined based on IHC results alone. Third, the influence of chemotherapeutic treatment or specific protocol was not evaluated. A greater proportion of younger patients received

chemotherapy than older patients, and furthermore, different regimens could affect survival.

Nevertheless, our study presents several novel findings. To the best of our knowledge, this study is the first to identify differences based on age in the molecular pathology and *H. pylori*-associated precancerous changes of gastric cancer. Therefore, a novel concept on the basis of these results is that the disease pathogenesis differs between the two groups. However, additional studies are necessary to validate the role of *H. pylori* in disease progression, as well as the accompanying molecular changes in gastric cancer, of younger patients.

In conclusion, gastric cancer in younger and older patients differed in clinical characteristics, pathology, and molecular pathology. Although gastric cancer in younger patients often presented with more aggressive features, the primary factor in predicting prognosis was the stage of the gastric cancer and not the age of the patient.

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COMMENTS

Background

Clinicopathologic features differ between young and old patients with gastric cancer. Young patients predominantly are female, and their cancers display a more poorly differentiated pathology and advanced stage compared to older patients.

Research frontiers

Molecular differences and *Helicobacter pylori* (*H. pylori*)-associated changes, such as atrophic gastritis and intestinal metaplasia, have not yet been elucidated based on age. Whether prognosis is related to age also remains controversial. Therefore, this study aimed to illuminate differences in clinicopathologic, molecular, and biologic characteristics of gastric cancer associated with age.

Innovations and breakthroughs

Although gastric cancers in younger patients displayed more aggressive features than in older patients, cancer-related mortality did not differ between the two age groups after adjustment for the stage of cancer. Gastric cancer in younger patients was less frequently associated with atrophic gastritis, intestinal metaplasia, overexpression of p53, and microsatellite instability than in older patients.

Applications

The significant differences in the pathologic degree of precancerous lesions and in molecular pathology indicated a distinct pathogenesis of the disease associated with age. The results are consistent with the model that gastric cancer in older patients tends to follow a dynamic series of sequential changes initiated by *H. pylori* infection and leading to intestinal-type gastric cancer. As diffuse-type gastric cancer predominated in younger patients, molecular changes due to factors other than *H. pylori* infection may be more important in pathogenesis in patients ⩽ 45 years of age. Based on these results, prevention or tailored therapy based on age could be considered in the future.

Terminology

Gastric cancer patients were stratified as younger or older according to the age of 45 years.

Peer-review

This is a very interesting article that discusses a little population studied in gastric cancer where was observed an increase in the disease especially in the West. A population of a considerable volume center was analyzed, complementing clinical aspects with molecular variables and even preneoplastic lesions.

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