The expression of epidermal growth factor receptor 1 and human epidermal growth factor receptor 2 based on tumor location affect survival in gastric cancer

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Abstract

To investigate the different expression of epidermal growth factor receptor 1 (EGFR) and human epidermal growth factor receptor 2 (HER2) in gastric cancer based on tumor locations and its impact on patients survival.

Gastric cancer is heterogeneous disease, recent years have established a molecular classification and described distribution of molecular subtypes in stomach. However, the difference of EGFR and HER-2 expression among tumor location is still unknown.

Between January 2010 and August 2014, 2477 consecutive patients with gastric cancer were treated in our surgery department. The tumor locations were classified into 4 groups: cardia, fundus, corpus, and antrum. Based on tumor locations, the clinicopathologic characteristics, EGFR and HER-2 expression, and follow-up data were analyzed by univariant analysis and Kaplan-Meier analysis retrospectively.

There were difference of gender, age, Borrmann type, pathological type, differentiation, T-stage, tumor size, gastrectomy method, and complications among the locations. The positive rate of EGFR expression in fundus was 18.18%, which was lower than cardia (46.21%), corpus (43.62%), and antrum (48.83%) ($P < .001$). The 5-year survival rate in EGFR positive patients was 50.8%, which was significantly lower than EGFR negative patients (64.0%, $P = .021$). The positive rate of HER-2 expression in cardia was 48.15%, which was significantly higher than fundus (37.5%), corpus (35.45%), and antrum (38.54%) ($P = .009$), but HER-2 expression did not correlate with 5-year survive ($P = .548$).

Our results suggest that there exist difference of EGFR and HER-2 expression based on tumor locations, and the distribution of EGFR impact on patients survival. Emphasizing the role of EGFR and HER-2 in the context of location contribute to make appropriate treatment strategy and improve prognosis of gastric cancer.

Abbreviations: EGFR = epidermal growth factor receptor 1, GC = gastric cancer, HER-2 = human epidermal growth factor receptor 2.

Keywords: clinicopathological characteristic, epidermal growth factor receptor 1, gastric cancer, human epidermal growth factor receptor 2, tumor location

1. Introduction

Gastric cancer (GC) ranks third for morbidity and second for morality worldwide. The 5-year survival was 25% to 39% in most countries.[1] The Cancer Genome Atlas project propose a molecular classification dividing gastric adenocarcinomas into 4 subtypes: tumors positive for Epstein-Barr virus; microsatellite unstable tumors; genomically stable tumors and tumors with chromosomal instability. Identification of these subtypes provides a roadmap for patient stratification and trials of targeted therapies.[2] Through the molecular and genomic basis of GC, the distribution of molecular subtypes in tumors has obtained. These advances are making it feasible to integrate genome-based and phenotype-based diagnostic and therapeutic methods, and apply them to individual GC patients.[3–5]

The molecular subtype and its different distribution in GC suggest that clinicopathologic characteristic and prognosis are closely correlate with the tumor locations. Sheikh demonstrate about one half of the GCs are located in the lower stomach, and remaining is located in the corpus and fundus of the stomach (20%), lesser curvature (20%), cardia (10%), and greater curvature (3%).[6] Cristescu has established 4 clinically relevant molecular subtypes, they find Microsatellite-unstable tumors are

frequently occurred in the antrum,[7] Birkman show Epstein-Barr virus positive intestinal-type tumors are more often found in the gastric corpus and the majority of the intestinal-type tumors with TP53 aberrations are proximally located.[8] However, the distribution of GC maybe changed with time, it has reported that the proportion of cardia/fundus cancer remain stable, but that of body cancer increase in Korea, and in the distribution of disease extent, the proportion of localized disease increase, and regional and distant disease decrease in all tumor locations.[9] Thereby, the distribution of GC should be emphasized in clinic.

Epidermal growth factor receptor 1 (EGFR) and human epidermal growth factor receptor 2 (HER2) are receptors for members of the epidermal growth factor family (EGF family).[10] EGFR overexpression is associated with development, metastasis and prognosis of GC,[10–12] EGFR tyrosine kinase inhibitors has been confirmed to cure some patients with non-small cell lung cancer, which induce a paradigm shift from "empiric" treatment to what can be called an "integrated" approach in 2009.[13] HER-2 is over-expressed in approximately 7% to 34% of patients with GC.[14,15] The identification of EGFR and HER-2 as oncogenes has led to develop a series of targeting therapeutic agents, such as gefitinib,[16] cetuximab,[17] and erlotinib for EGFR, and lapatinib,[18] trastuzumab,[19] and apatinib[20] for HER2. EGFR-positive patients have shown a 60% response rate, which exceeds the response rate for conventional chemotherapy,[21] and EGFR-target therapy could benefit a group of patients with low plasma levels of EGFR.[22] Similarly, HER-2 positive GC have been proved to benefit from trastuzumab treatment,[23] and except for HER2 amplification, no biomarker is available for predicting treatment response of trastuzumab in the individual patient.[24]

However, till now, the distinct expression of EGFR and HER-2 expression among tumor locations is unknown in GC. Therefore, in this study, based on tumor location, we investigated the correlation between the expression of EGFR and HER-2 and prognosis of GC.

2. Methods

2.1. Patient enrollment

Between January 2010 and August 2014, 4420 consecutive patients with GC underwent gastrectomy by the First Department of Digestive Surgery of XiJing Hospital, Fourth Military Medical University (Xi'an, China). For this retrospective cohort study, all patient data were evaluated by 2 researchers and the patient inclusion criteria were as follows:

(1) patients were diagnosed as gastric adenocarcinoma according to pathologic characteristics;
(2) patients underwent gastrectomy or explorative surgery, the tumor locations were clearly recorded by surgeons;
(3) tumor locations were classified as cardia, fundus, corpus, and antrum, tumor only located in 1 area were included, whereas patients with transregional tumors were excluded;
(4) patients had not severe basic disease and were at the level of I or II according to the American Society Anesthesiology Physical Status Classification System.

This study was approved by the Ethics Committee of the Fourth Military Medical University. All patients received verbal and written information regarding the study and provided informed consent before surgery.

2.2. Demographic and perioperative data

Demographic data, including sex, age, symptom, positive sign, history of past illness, and preoperative data, including routine hematological, biochemical tests, and X-rays, were collected to enable subsequent analysis of the comparability of the groups. Postoperative data included pathological type, Borrmann type, grade of differentiation, and tumor size. The histological subtype and pathological stage were determined using the Union for International Cancer Control and Tumor-Lymph Node-Metastasis (TNM) classification for GC. EGFR and HER-2 were stained postoperatively by immunohistochemistry in the pathological department, and the results were judged as positive staining or negative staining. These data were evaluated by 2 pathologists and collected from pathologic records for analysis.

2.3. Immunohistochemistry

Paraffin-embedded tumor tissues were sliced into 5-μm thick sections and mounted on glass. Slides were deparaffinized and rehydrated in 10 minutes through a graded alcohol series to deionized water in 1% Antigen Unmasking Solution (Vector Laboratories, Burlingame, CA) and microwaved to enhance antigen retrieval. Tissue samples were sequentially incubated with anti-mouse immunoglobulin coupled to horseradish peroxidase. Slides were incubated with the specific primary mouse anti-human EGFR (MAB-0196; MXB, Fuzhou, China) and mouse anti-human HER-2 monoclonal antibodies with a dilution 1:200, then incubated with an horseradish peroxidase-conjugated secondary antibody (KIT-9710; MXB), and then stained with 3,3-diaminobenzidine and counterstained with hematoxylin. In addition, slides stained without primary antibody or without secondary antibody were used as the control. Two pathologists independently observed and interpreted the results of the immunohistochemical staining.

2.4. Assessment of staining

Staining of EGFR and HER-2 was evaluated according to the percentage of positive cells under an optical microscope (Leica Microsystems, GmbH, Wetzlar, Germany; magnification, ×20). Staining intensity was classified as the following: Negative (−), no immunopositive staining or <10% of positive cells observed; weak to moderate (+), 10% to 30% positive cells; high (++), 30% to 70% positive cells; and strong (+++), >70% positive cells.

2.5. Follow-up data

All patients were followed for 5 years from the beginning of operation. And at the end of follow-up, the status of patients was recorded, which included survival, death, and lost follow-up.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 17 software (SPSS Inc., Chicago, IL). Differences among groups consisted of measurement data were analyzed by Student t test, and when unequal variance existed, the adjust-T test was used; Differences in expression rate among groups were analyzed by Pearson Chi-squared (χ^2) test. The Fisher exact test was used to assess the difference of positive rate when the number of total cases was less than 40. P-value <.05 was considered statistically significant. Survival analysis were used by Kaplan-Meier.
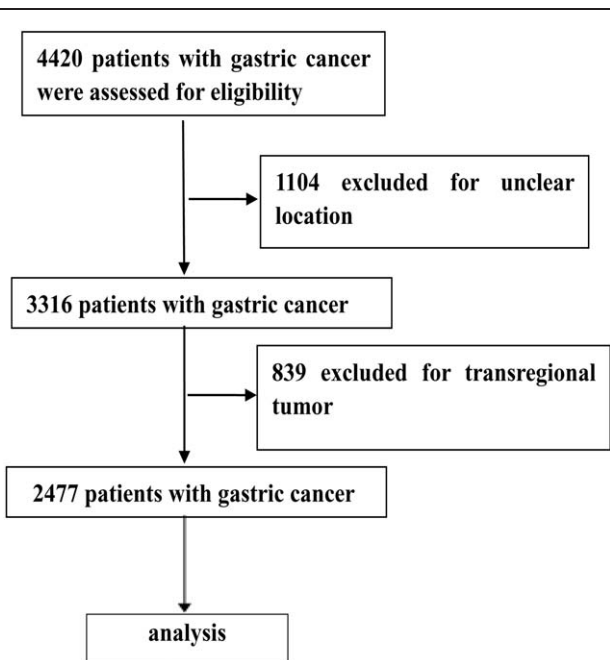
Figure 1. Flow diagram of patients enrollment.

significant differences among the locations regarding preoperative variables, such as age, sex, symptoms, positive sign, and blood test. The difference of pathological type, histological subtype, Borrman type, tumor differentiation, and TNM stage was also found among the 4 groups (Table 2).

3.2. The EGFR and HER-2 expression in different location

The staining levels of EGFR and HER-2 was shown in Figure 2. We found the positive rate of EGFR expression in fundus was 18.18%, which was significantly lower than that in cardia (46.21%), corpus (43.62%), and antrum (48.83%) ($P = .001$). The positive rate of HER-2 expression in cardia was 48.15%, which was significantly higher than that in fundus (37.5%), corpus (35.45%), and antrum (38.54%) ($P = .009$) (Table 3). By correlation analysis, we found the EGFR and HER-2 expression was closely correlated. $R^2 = 0.02$, $P = .001$.

3.3. Five-year survival rate of GC in different location

A total of 2145 cases had complete follow-up data, and average flow-up time was 27.28 ± 17.48 months (ranged from 0.3 to 66.73 months). We found the 5-year survival rate of GC in fundus was $73.7\% \pm 0.11\%$, higher than in cardia ($61.1\% \pm 0.04\%$), corpus ($56.3\% \pm 0.03\%$), and antrum ($58.1\% \pm 0.02\%$), but the difference was not statically significant ($P = .323$) by Kaplan-Meier analysis (Fig. 3A and B).

3.4. The correlation between the expression of EGFR and HER-2 and prognosis of GC

We also found EGFR expression was negatively correlated with 5-year survival, the survival rate in patients with EGFR positive was $50.8\% \pm 0.06\%$, which was significantly lower than that in

3. Results

3.1. Baseline characteristics

A total of 2477 cases met the inclusion criteria in this cohort study (Fig. 1), of those, 452 (18.3%), 54 (2.2%), 797 (32.2%), and 1174 (47.4%) cases were distributed in cardia, fundus, corpus, and antrum, respectively. The comparison of baseline data among the 4 locations was described in Table 1. There were

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Table 1

Characteristics of patients with gastric cancer according to tumor locations.

	Location				
Feature	Cardia	Fundus	Corpus	Antrum	P-value
No.	452	54	797	1174	
Male/female	392/60	48/6	565/232	847/327	.001
Age (yr)	60.42 ± 9.34	58.15 ± 10.32	55.4 ± 11.83	55.75 ± 11.72	.001
Symptom					
Abdominal pain (%)	187 (41.7)	33 (61.1)	596 (75.0)	804 (68.6)	.001
Abdominal distension (%)	121 (26.9)	41 (31.5)	303 (38.1)	580 (49.6)	.001
Vomit (%)	15 (3.3)	2 (3.7)	40 (5.0)	152 (13.0)	.001
Dysphagia (%)	187 (41.7)	14 (25.9)	27 (3.4)	11 (0.9)	.001
Sour regurgitation (%)	46 (10.3)	11 (20.4)	121 (15.2)	230 (19.6)	.001
Positive sign (%)	94 (21.4)	14 (26.4)	231 (29.5)	287 (24.8)	.012
Weight loss (kg)	3.17 ± 3.85	3.51 ± 4.93	2.68 ± 3.43	3.25 ± 4.18	.029
Family history of tumor (%)	31 (6.9)	5 (9.3)	55 (7)	96 (8.2)	.655
Heart disease (%)	11 (2.5)	0	15 (1.9)	24 (2.1)	.654
Hypertension (%)	69 (15.4)	10 (18.5)	83 (10.4)	119 (10.2)	.006
Others (%)	57 (12.8)	8 (15.1)	78 (9.8)	122 (10.4)	.291
Blood test					
WBC (10e9/L)	5.97 ± 1.68	6.21 ± 2.45	6 ± 2.28	5.92 ± 1.93	.693
HGB (g/L)	130.86 ± 24.69	128.63 ± 22.98	124.61 ± 27.78	125.51 ± 28.6	.001
GRA (%)	0.63 ± 0.38	0.61 ± 0.11	0.71 ± 2.35	0.61 ± 0.11	.430
RBC (10e12/L)	4.57 ± 4.45	4.4 ± 0.62	4.74 ± 8.26	4.52 ± 6.08	.901
TP (g/L)	67.42 ± 7.42	68.14 ± 7.33	66.54 ± 7.12	66.03 ± 7.24	.002
ALB (g/L)	42.45 ± 5.29	41.44 ± 4.36	42.04 ± 5.51	41.7 ± 5.38	.068

Student t test was used to analyze age and blood test, and Chi-square test were used to analyze categorical variables, respectively.
ALB = albumin, GRA = granulocyte, HGB = hemoglobin, L = litre, RBC = red blood cell count, SD = standard deviation, TP = serum protein, WBC = white blood cell count.

Table 2

Pathological characteristics of patients with gastric cancer according to locations.

Feature	Location				P-value
	Cardia	Fundus	Corpus	Antrum	
Tumor size (mean ± SD, cm)	4.37 ± 1.88	4.42 ± 2.37	4.81 ± 2.62	4.51 ± 2.31	.009
Borrman type					
I	16	4	39	46	.001
II	56	10	158	362	
III	106	14	230	305	
IV	18	2	89	104	
Pathological type					
Ulcer	285	28	479	796	.001
Infiltrate	27	2	45	51	
Mucus	14	2	30	37	
High-grade GIN	7	0	7	16	
Fungating	13	1	14	19	
Signet ring cell	4	0	22	11	
Other	15	1	25	25	
Grade of differentiation					
Well	71	9	79	143	.001
Moderate	108	17	195	310	
Poor	45	10	221	313	
T stage					
I	6	1	34	35	.001
II	59	11	92	190	
III	180	18	238	325	
IV	5	1	8	11	
Lymph node involvement					
N0	154	19	248	347	.397
N1	88	17	127	194	
N2	68	5	125	187	
N3	5	0	6	7	

Student t test was used to analyze tumor size, Chi-square test and The Fisher exact test were used to analyze categorical variables.

cm = centimeter, GIN = intraepithelial neoplasia, N = lymph node, N0 = no nodal metastasis, N1 = 1-3 peri-gastric lymph nodes involved, N2 = 4 or more peri-gastric lymph nodes involved, SD = standard deviation, T = tumor, T1 = tumor invades submucosa, T2 = tumor invades muscularis propria, T3 = penetration through muscularis propria into subserosa, T4 = invasion of other organs or involvement of free peritoneal cavity.
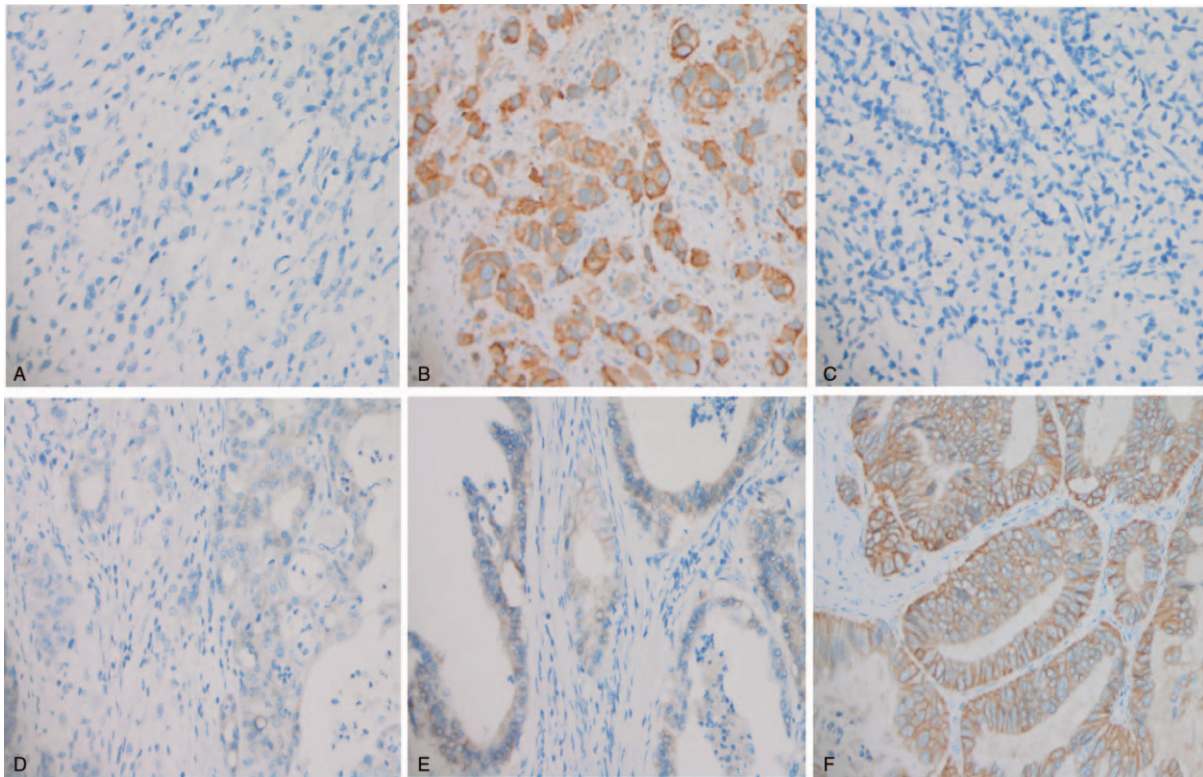
Figure 2. Immunohistochemical analysis of expression of EGFR and HER-2 in GC tissues. (A) Negative expression of EGFR; (B) Positive expression of EGFR was observed in GC. The main staining site was located in cytoplasm; (C) Negative expression of HER-2 in GC; (D) Weak to moderate positive expression of HER-2 in GC; (E) High expression of HER-2 in GC; (F) Strong expression of HER-2 in GC, The main staining site was located in membrane. The cells with brown yellow staining were positive (magnification, ×20). EGFR = epidermal growth factor receptor, GC = gastric cancer, HER-2 = human epidermal growth factor receptor 2.

Table 3

The expression of EGFR and HER-2 in different locations.

Location	EGFR			HER-2		
	Negative no. (%)	Positive no. (%)	P-value	Negative no. (%)	Positive no. (%)	P-value
Total	825 (53.68%)	712 (46.32%)		574 (60.80%)	370 (39.19%)	
Cardia	149 (53.79%)	128 (46.21%)	.001	84 (51.85%)	78 (48.15%)	.009
Fundus	18 (81.82%)	4 (18.18%)		10 (62.5%)	6 (37.5%)	
Corpus	265 (56.38%)	205 (43.62%)		193 (64.55%)	106 (35.45%)	
Antrum	393 (51.17%)	375 (48.83%)		287 (61.46%)	180 (38.54%)	

Chi-square test and the Fisher exact test were used to analyze categorical variables.
EGFR = epidermal growth factor receptor 1, HER-2 = human epidermal growth factor receptor 2.

patients with EGFR negative (64.0% ± 0.03%, $P=.002$) (Fig. 4A and B). But we did not find HER-2 expression correlated with 5-year survive, the survival rate in patients with HER-2 positive was 63.1% ± 0.06%, which was similar to that in patients with HER-2 negative (62.9% ± 0.03%, $P=.548$) by Kaplan-Meier analysis (Fig. 4A and C).

3.5. Combined effect of tumor location with EGFR expression on 5-year survival rate of GC

Combined analysis of location and EGFR expression, we found the 5-year survival rate was 37.9% in patients with tumor located in non-cardia and with positive EGFR expression. The prognosis of the patients was significantly worse than those patients with tumor in other locations ($P=.002$) (Fig. 5A and B).

4. Discussion

The aim of the present study was to investigate the difference of clinicopathologic and prognosis of GC according to the expression of EGFR and HER-2 in different tumor locations. We found EGFR and HER-2 expression level were significantly different according to tumor locations, and the 5-year survival was correlated with EGFR expression and the interaction between tumor location and EGFR expression.

It has reported the positive expression of EGFR and HER-2 was associated with male gender, older age, intestinal type, Borrmann classification of 0 or 1 tumors, and higher stage.[23,25–27] In our

study, EGFR and HER-2 expression were found statistically different among locations. Our results showed a decreasing expression rate of EGFR in fundus (18.18%) and an increasing expression rate of HER-2 in cardia (48.15%). The result of HER-2 expression in this study was higher than the result reported by other investigators, who demonstrate the overexpression of HER-2 in gastroesophageal junction adenocarcinomas is 12.5%,[28] the divergence of HER-2 expression may attribute to the different positive judgement standard and detective procedure.[29,30] Our results supplemented for the distribution of EGFR and HER-2 in GC.

Several studies have reported that the prognosis of GC were influenced by tumor size, depth of invasion, lymph node metastasis, early detection, chemotherapy, and radical resection.[31,32] In this study, we found the 5-year survival in EGFR negative group was significantly higher than it in EGFR positive group, our result was consistence with the previous report that the patients with EGFR positive GC had an unfavorable prognosis,[25] but was distinct from a study demonstrated EGFR family had not prognostic influence in GC according to analysis by a parametric model.[33] Our data provided powerful evidence for the prognostic value of EGFR and supported it as a therapeutic target in GC.[34]

We did not find the difference of 5-year survival rate according to tumor locations. However, we found the patients with tumor located in non-cardia and with positive EGFR expression had the worst prognosis. In addition, we found the lowest rate of EGFR expression and the best prognosis in fundus. Our results were
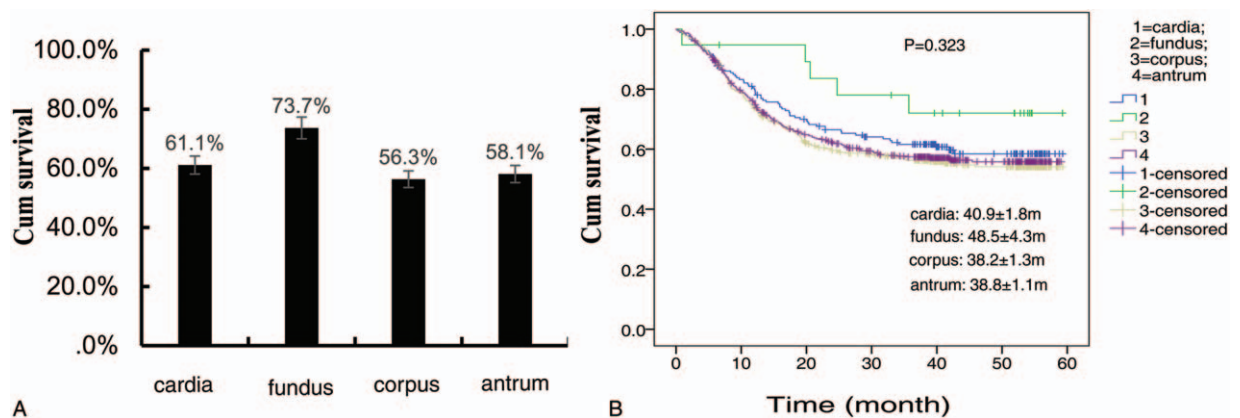
Figure 3. The survival difference among tumor locations in patients with gastric cancer. (A) The 5-survival rate was not statically different among tumor locations. (B) 5-yr survival curve of patients with gastric cancer in different tumor locations.
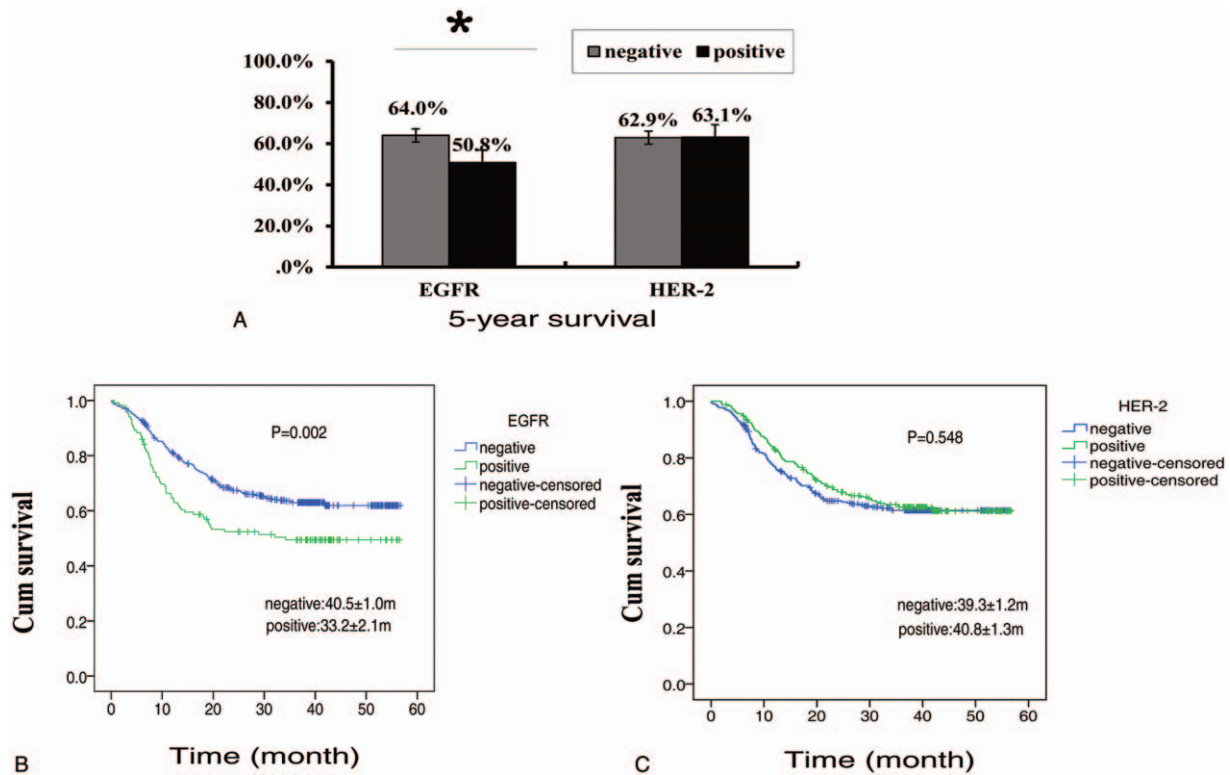
Figure 4. The effect of EGFR and HER-2 expression on prognosis of gastric cancer. (A). the difference of 5-survival rate between EGFR-positive group and EGFR-negative group, and between HER-2 positive group and HER-2 group. * Denoted there was a statistically difference between the 2 groups, *P*-value < .05. (B) 5-yr survival curve of patients with EGFR-positive and with EGFR-negative. (C) 5-yr survival curve of patients with HER-2 positive and with HER-2 negative. EGFR = epidermal growth factor receptor 1, HER-2 = human epidermal growth factor receptor 2.

similar to the report showed microsatellite-unstable tumors are hyper-mutated intestinal-subtype tumors occurring in the antrum, and the tumors have the best overall prognosis and the lowest frequency of recurrence.[7] Combined with molecular classification of GC, our result underscored that the interaction between tumor locations and EGFR expression play an important role of in the prognosis of GC, and suggested tumor location may represent relevant molecular subtypes.

HER-2 is one of the most effective targets for its outstanding performance in prognosis.[35] Combined with standard first-line chemotherapy, trastuzumab significantly improves the prognosis.[36] However, we did not find the correlation between HER-2
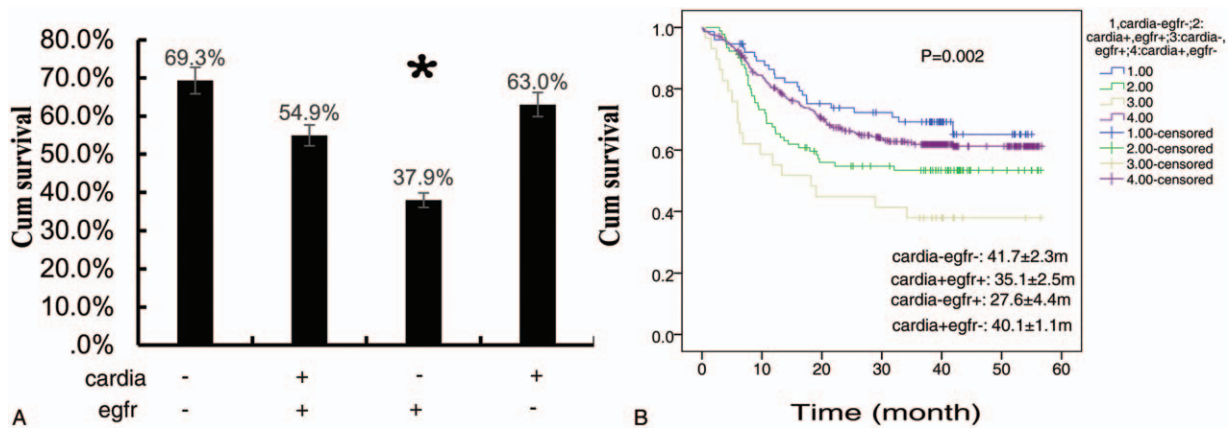
Figure 5. Combined effect of tumor location with EGFR expression on 5-yr survival rate of gastric cancer. (A) Combined analysis of the effect of tumor location and EGFR expression, the difference of 5-yr survival rate of gastric cancer was statically significant. * Denoted there was a statistically difference between the 2 groups, *P*-value < .05. "+" mean with; "−" mean without; (B) 5-yr survival curve of 4 combinations of location and EGFR expression in patients with gastric cancer. EGFR = epidermal growth factor receptor 1.

and prognosis of GC, our results was consistent with the study showed only EGFR amplification had a prognostic impact, while HER-2 amplification was not prognostically relevant in advanced GC.[11] But a close correlation between EGFR and HER-2 was also found in this study, suggested that HER-2 did not affect prognosis directly. Our results supported the view that HER-2 alteration is not an independent prognostic factor for curatively resectable GC.[25]

In conclusion, our results revealed there exist difference of EGFR and HER-2 expression based on tumor locations. These findings supplemented for the distributing characteristics of GC and underscored the need for further studies on the influence of biomarker expression in the context of location, as this may influence treatment strategy as well as prognosis.

Acknowledgments

Author contributions

Li GC: conceiving and designing the study, and writing the manuscript; Jia XC: Immunohistochemical analysis; Zhang HW and Zhao QC: providing critical revisions; Yang P: analyzing and interpreting the data; Pang FN, Xu LL and Sun JB: collecting the literatures; All authors approved the final version of the manuscript.

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