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Expression of HER2 and Ki-67 in gastric cancer and its correlation with clinicopathological features

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Abstract: *This study investigates the expression of HER2 and Ki-67 in gastric cancer and their relationship with clinicopathological features, as well as explores the association between these markers and the clinical development and invasiveness of gastric cancer. We conducted a retrospective study involving 118 hospitalized patients with gastric cancer diagnosed by gastroscopic biopsy or pathological examination after gastric cancer surgery at the Fifth Affiliated Hospital of Zhengzhou University from March 2020 to December 2023. Baseline and immunopathological data were collected and analyzed, dividing the patients into low and high expression groups based on Ki-67 expression levels. We examined the relationships between HER2 and Ki-67 expressions and the clinicopathological characteristics of gastric cancer. The results showed that the positive and high expression rate of HER2 in gastric cancer was 13.6% (16/118), while the high expression rate of Ki-67 (>30%) was 78.8% (93/118). HER2 expression was positively correlated with the maximum diameter of gastric cancer (correlation coefficient: 0.182, P = 0.049) and the degree of differentiation of gastric cancer (correlation coefficient: 0.280, P = 0.049). Ki-67 expression showed significant differences related to tumor maximum diameter, stage (early vs. advanced), histological type, location, depth of invasion, lymph node invasion stage, and pTNM stage (P < 0.05). However, there was no significant correlation between HER2 and Ki-67 expressions in gastric cancer patients (r = 0.127, P = 0.171). In summary, the expressions of HER2 and Ki-67 are closely related to the clinicopathological features of gastric cancer. Larger tumor diameter and better differentiation are associated with higher HER2 positive grades, while Ki-67 is closely related to the occurrence, development, and invasiveness of gastric cancer. There is no significant correlation between the expressions of HER2 and Ki-67 in gastric cancer tissues.*

Keywords: *Gastric cancer; HER2; Ki-67; Clinicopathological features*

1. Introduction

Gastric cancer is one of the most common malignant tumors in the world. In China, the incidence of gastric cancer ranks second only to lung cancer, making it the second most common malignant tumor overall. Each year, there are 400,000 to 500,000 new cases, and although the incidence and mortality rates are showing a downward trend, they still remain relatively high globally. For patients with advanced gastric cancer, traditional treatment methods such as surgery, chemotherapy, and radiotherapy are limited, while immunotherapy and targeted therapy are gradually being recognized and applied in clinical practice. In 2010, HER2 was identified as the first precise treatment target for gastric cancer. Chemotherapy combined with anti-HER2 targeted drugs has become the standard treatment for HER2-positive advanced gastric cancer. A multicenter retrospective study of 40,842 cases of gastric adenocarcinoma in China showed that HER2 positivity is related to tumor location, differentiation degree, and specimen type. Another study in China showed that HER2 overexpression is significantly positively correlated with tumor differentiation and Lauren classification. Therefore, there is currently no definitive conclusion on the relationship between HER2 and the clinical pathological characteristics of gastric cancer, making the relationship between HER2 and the clinical pathological characteristics of gastric cancer a hot topic of research.

With the popularization and extensive application of tissue analysis gene testing, the molecular characteristics of tumors are receiving increasing attention. A study of 693 patients with T3 stage gastric cancer who underwent surgical resection showed that Ki-67 may represent a poor prognostic biomarker for resected T3 gastric cancer. However, there are also some studies with completely opposite results,

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showing that patients with low Ki-67 have a higher mortality rate. Therefore, the clinical pathological characteristics of gastric cancer patients in relation to Ki-67 are still unclear, and this retrospective study aims to explore the association between the clinical development, invasiveness, and HER2 and Ki-67 in gastric cancer.

2. Materials and Methods

2.1 General Information

A retrospective study was conducted, selecting 118 inpatients diagnosed with gastric cancer through gastroscopic biopsy or pathological examination of gastric cancer surgery specimens at the Fifth Affiliated Hospital of Zhengzhou University from March 2020 to December 2023. Among them, there were 83 males (70.3%) and 35 females (29.7%), with ages ranging from 25 to 90 years and a median age of 65 years. Based on imm unohistochemistry results, they were divided into HER2-positive group (n=16) and negative group (n=102), as well as low Ki-67 expression group (≤0.30, n=25) and high expression group (>0.30, n=93). This study was approved by the Ethics Committee of Zhengzhou University Fifth Affiliated Hospital (Approval No.: 2023051).[1]

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Complete clinical and immunohistochemical data; (2) No concomitant malignant tumors of other organs; (3) Pathological data were original data before treatment.

Exclusion Criteria: (1) Metastatic gastric cancer or concomitant tumors of other systems; (2) Incomplete medical record information or data; (3) Severe systemic diseases such as renal or hepatic failure; (4) Data obtained after treatment.[2]

2.3 Immunohistochemical Detection of HER2 Status and Ki-67 Expression Levels

Our hospital assessed HER2 expression according to the HER2 testing guidelines (2011 version, 2016 version) (Table 1). In this study, HER2 2+ and HER2 3+ were considered high expression.

Table 1: Specimen Type and Grading

grading	0(Negative)	1+(Negative)	2+(Indeterminate)	3+(Positive)
specimen				
surgical specimen	No staining or <10% tumor cell membrane staining	Weak or faint membrane staining in ≥10% of tumor cells, with staining observed in only some cells	Weak to moderate basal/lateral/complete membrane staining in ≥10% of tumor cell	Strong basal/lateral/complete membrane staining in ≥10% of tumor cells
biopsy specimen	No membrane staining in any tumor cells	Faint or faintly visible membrane staining in clusters of tumor cells (regardless of the percentage of stained tumor cells in the entire tissue)	Weak to moderate basal/lateral/complete membrane staining in clusters of tumor cells (regardless of the percentage of stained tumor cells in the entire tissue, but with at least 5 clustered tumor cells stained)	Strong basal/lateral/complete membrane staining in clusters of tumor cells (regardless of the percentage of stained tumor cells in the entire tissue, but with at least 5 clustered tumor cells stained)

Ki-67 (positive) result determination: At least 3 representative areas under high-power microscopy (×400) were selected for counting. In each representative area, cells showing brownish-yellow or brown deposits in the nucleus were considered Ki-67-positive cells. Cells counted exceeded 500 in a representative area. The ratio of positive cells to total cells is the Ki-67 proliferation index. According to the characteristics of the data, the Ki-67 index is divided into two groups: ≤30% for the low expression group and >30% for the high expression group.[3]

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2.4 Statistical Methods:

Statistical analysis of the data was performed using SPSS 27.0 statistical software. Count data were expressed as cases or percentages (%). Between-group comparisons were performed using the $\chi 2$ test, chi-square correction test, Fisher's exact test, and Spearman correlation analysis to study the correlation between HER2 and Ki-67 and the clinical development and invasiveness of gastric cancer. A significance level of $P<0.05$ was considered statistically significant.

3. Results

3.1 HER2 Expression Status

According to immunohistochemistry results, among the 118 gastric cancer patients, 102 cases (86.5%) were negative (IHC 0, IHC 1+), and 16 cases (13.5%) were positive (IHC 2+, IHC +3), with a HER2 positivity rate of 13.5% (Table 2).[4-6]

Table 2: HER2 Immunohistochemistry Results at Different Levels

HER2 Expression status	0	1+	2+	3+	Total
Number of cases	71	31	10	6	118
Percentage	60.2%	26.3%	8.4%	5.1%	100%

3.2 Correlation Analysis between HER2 Status and Clinicopathological Features of Gastric Cancer:

Among the 118 patients, 16 were HER2-positive and 102 were HER2-negative. Compared with the HER2-negative group, HER2 protein-positive expression showed no significant statistical differences in patient age, gender, smoking history, alcohol consumption, family history of gastric cancer, tumor size, stage (early stage, advanced stage), histological type, degree of differentiation, depth of invasion, lymph node metastasis, tumor location, pTNM stage, or elevated levels of CA199 and CEA (Table 3).[7-10]

Table 3: Comparison of Clinicopathological Features in Different HER2 Status

Grouping		HER2 (2+,3+)(0,1+)		Number of cases	Positive rate(%)	χ^2	P
Age						3.176	0.075
	<60	1	32	33	3.0		
	≥60	15	70	85	17.6		
Gender						0.021	0.885
	Male	12	71	83	14.5		
	Female	4	31	35	11.4		
Smoking						0.944	0.331
	Yes	8	38	46	17.4		
	No	8	64	72	11.1		
Alcohol consumption						0.126	0.723
	Yes	5	24	29	17.2		
	No	11	78	89	12.4		
Family history						0.002	0.965
	Yes	3	15	18	16.7		
	No	13	87	100	13.0		
Tumor diameter						1.319	0.251
	<4cm	6	54	60	10.0		
	≥4cm	10	48	58	17.2		
Staging						0.000	1.0
	Early stage	3	21	24	12.5		
	Advanced stage	13	81	94	13.8		
Histological type						4.030	0.127
	Pure adenocarcinoma	11	71	82	13.4		
	Mixed	5	16	21	23.8		

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	adenocarcinoma						
	Other types	0	15	15	0		
Site						3.133	0.383
	Esophagogastric junction	7	38	45	15.6		
	Gastric antrum	2	31	33	6.1		
	Gastric body	5	18	23	21.7		
	Mixed type	2	15	17	11.8		
Differentiation degree						1.493	0.563
	Poorly differentiated	11	80	91	12.1		
	Moderately differentiated	5	19	24	20.8		
	Well differentiated	0	3	3	0		
Depth of infiltration						0.131	0.718
	T1+T2	6	30	36	16.7		
	T3+T4	10	72	82	12.2		
Lymph node involvement						1.494	0.222
	N0+N1	10	47	57	17.5		
	N2+N3	6	55	61	9.8		
Distant metastasis						0.005	0.942
	M0	12	81	93	12.9		
	M1	4	21	25	16.0		
Staging						0.820	0.365
	I+II	9	45	54	16.7		
	III+IV	7	57	64	10.9		

Table 4: Expression of HER2 (0, 1+, 2+, 3+) and the Correlation Analysis of Ki67 with Clinicopathological Features of Gastric Cancer

Clinicopathological characteristics	Total number of cases	HER2		Ki67	
		Correlation coefficient	P value	Correlation coefficient	P value
T-Staging(T1,T2,T3,T4)	118	0.022	0.814	0.357	<0.001
NS-taging(N0,N1,N2,N3)	118	0.071	0.443	0.297	0.001
M-Staging(M0,M1)	118	-0.062	0.502	0.104	0.263
Maximum tumor diameter (cm)	118	0.182	0.049	0.310	<0.001
Tumor location (esophagogastric junction, gastric body, gastric antrum, mixed type)	118	-0.097	0.296	-0.126	0.174
Differentiation grade (poorly differentiated, moderately-low differentiated, moderately differentiated, moderately-high differentiated, well differentiated)	118	0.280	0.002	0.115	0.213
pTNM-Staging(I,II,III,IV)	118	0.014	0.881	0.335	<0.001
CA199	118	0.181	0.050	0.075	0.419
CEA	118	0.169	0.067	0.198	0.031
Ki67	118	0.127	0.171		

3.3 Spearman Correlation Analysis of HER2 with Clinicopathological Parameters of Gastric Cancer

The expression of HER2 showed a strong correlation with the maximum diameter of gastric cancer tissue (correlation coefficient: 0.182, P value: 0.049); it also showed a strong correlation with the degree of tumor differentiation (correlation coefficient: 0.280, p=0.002). However, there was no significant correlation between HER2 expression and tumor T stage, N stage, M stage, tumor location, pTNM stage, or CEA (Table 4).

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3.4 Association of Ki-67 Expression Level with Clinicopathological Features of Gastric Cancer

Table 5: Comparison of Ki-67 Expression Levels with Clinicopathological Features [n(%)]

Grouping		Ki-67 ≤ 30%	Ki-67 >30%	Number of cases	High expression rate(%)	χ^2	P
Age						0.000	0.997
	<60	7	26	33	78.8		
	≥60	18	67	85	78.8		
Gender						0.042	0.838
	Male	18	65	83	78.3		
	Female	7	28	35	80		
Smoking						0.650	0.420
	Yes	8	38	46	82.6		
	No	17	55	72	76.4		
Alcohol consumption						0.201	0.654
	Yes	7	22	29	75.9		
	No	18	71	89	79.8		
Family history						0.553	0.457
	Yes	5	13	18	72.2		
	No	20	80	100	80.0		
Tumor diameter						8.029	0.005
	<4cm	19	41	60	68.3		
	≥4cm	28	6	52	89.7		
Staging						24.897	<0.001
	Early stage	14	10	24	41.7		
	Advanced stage	11	83	94	88.3		
Histological type						9.168	0.009
	Pure adenocarcinoma	13	69	82	84.1		
	Mixed adenocarcinoma	4	17	21	81.0		
	Other types	8	7	15	46.7		
Site						12.045	0.005
	Esophagogastric junction	3	42	45	93.3		
	Gastric antrum	12	21	33	63.6		
	Gastric body	7	16	23	69.6		
	Mixed type	3	14	17	82.4		
Differentiation grade						3.947	0.110
	Poorly differentiated	17	74	91	81.3		
	Moderately differentiated	6	18	24	75.0		
	Well differentiated	2	1	3	33.3		
Depth of infiltration						13.013	<0.001
	T1+T2	15	21	36	58.3		
	T3+T4	10	72	82	87.8		
Lymph node involvement						9.743	0.002
	N0+N1	19	38	57	66.7		
	N2+N3	6	55	61	90.2		
Distant metastasis						1.603	0.205
	M0	22	71	93	76.3		
	M1	3	22	25	88.0		
TNMStaging						11.685	<0.001
	I+II	19	35	54	64.8		
	III+IV	6	58	64	90.6		

There were 25 cases (21.2%) of low Ki-67 expression and 93 cases (78.8%) of high Ki-67 expression

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in gastric cancer patients. The rates of high Ki-67 expression in the tumor diameter <4cm group and ≥4cm group were 68.3% and 89.7%, respectively.(χ^2=8.029,P=0.005);The rates of high Ki-67 expression in the cardia-fundus group, gastric antrum group, gastric body group, and mixed type group were 93.3%, 63.6%, 69.6%, and 82.4%, respectively.(χ^2=12.045,P=0.005);The rates of high Ki-67 expression in early-stage gastric cancer group and advanced-stage gastric cancer group were 41.7% and 88.3%, respectively.(χ^2=24.897,P<0.001);The rates of high Ki-67 expression in the pure adenocarcinoma group, mixed adenocarcinoma group, and other types group were 84.1%, 81.0%, and 46.7%, respectively.(χ^2=9.168,P=0.009);The rates of high Ki-67 expression in the T1+T2 group and T3+T4 group were 58.3% and 87.8%, respectively.(χ^2=13.013,P<0.001);The rates of high Ki-67 expression in the N0+N1 group and N2+N3 group were 66.7% and 90.2%, respectively.(χ^2=9.743,P=0.002);The rates of high Ki-67 expression in the stage I+II group and stage III+IV group were 64.8% and 90.6%, respectively.(χ^2=11.685,P<0.001), All differences were statistically significant (Table 5).[11]

3.5 Spearman Correlation Analysis of Ki-67 with Gastric Cancer Related Indicators

The expression of Ki-67 was significantly correlated with tumor T stage (correlation coefficient: 0.357, P<0.001), N stage (correlation coefficient: 0.297, P=0.001), tumor maximum diameter (correlation coefficient: 0.310, P<0.001), TNM stage (correlation coefficient: 0.335, P<0.001), and CEA (correlation coefficient: 0.198, P=0.031). However, there was no significant correlation between Ki-67 expression and M stage, tumor location, tumor differentiation degree, or CA199 (Table 4).

4. Discussion

Dai Xiaomin et al. [8] assessed the HER2 status of 461 gastric cancer tissue specimens using IHC and FISH, and found a HER2 positivity rate of 16% (74/461). In this study, only IHC was used to detect HER2 expression levels, with IHC 2+ and IHC 3+ considered positive, without FISH detection. The HER2 positivity rate was 13.5%, which should theoretically be higher, but the result was similar to the aforementioned study, possibly due to the small number of cases, indicating a need to increase the sample size. Yoshiki et al. [9] conducted a retrospective study including 213 patients, with 25 cases (11.7%) of HER2-positive gastric cancer. HER2-positive cases were more common in males, elderly patients, and those with histological type classified as intestinal type (P=0.0048, 0.0309, and 0.0001, respectively). In contrast, our study found no significant correlation between HER2 protein-positive expression and patient age, gender, tumor size, stage (early stage, advanced stage), histological type, degree of differentiation, depth of invasion, lymph node metastasis, or pTNM stage compared with the negative group. However, when HER2 expression was classified into 0, 1+, 2+, and 3+ groups, Spearman correlation analysis revealed a positive correlation between HER2 expression and tumor maximum diameter (correlation coefficient: 0.182, P=0.049), indicating that the larger the tumor diameter, the higher the HER2 protein-positive grade, and the stronger the proliferative ability. At the same time, the expression of HER2 protein is positively correlated with the degree of tumor differentiation, which indicates that the expression of HER2 protein is related to the occurrence of gastric cancer and promotes the differentiation of tumor cells.

Ki-67 is a commonly used indicator for describing cell proliferation. A study including 5600 cases of gastric cancer found that high Ki-67 expression was significantly correlated with Lauren classification and tumor size [10]. Another study showed that Ki-67 expression was significantly correlated with tumor cell differentiation, depth of tumor cell invasion, and lymph node metastasis (P<0.05) [11]. In our study, high Ki-67 expression was associated with tumor size, stage (early stage, advanced stage), histological type, T stage, N stage, and pTNM stage, indicating that changes in tumor cell proliferation activity are related to the progression of gastric cancer, with higher Ki-67 expression indicating higher tumor invasiveness. In addition, in our study, there was a statistically significant difference in Ki-67 protein proliferation index expression between tumor locations (χ2=12.045, P=0.005), indicating that cancer cells in the cardia and gastric fundus have higher proliferation activity than those in other locations, suggesting the necessity of performing Ki-67 immunostaining in the cardia and gastric fundus in clinical practice. A study on breast cancer in Vietnam showed a significant correlation between HER2 gene amplification and the proliferation index Ki-67 (p=0.024) . However, our study results showed no significant correlation between Ki-67 expression in gastric cancer tissue and HER2 expression (correlation coefficient: 0.127, P=0.171>0.05). The reason for the different results may be the influence of tumor heterogeneity on gastric cancer, and there may be a risk of sampling errors in tissue biopsy.

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5. Conclusion

In conclusion, HER2 and Ki-67 expression are closely related to the clinicopathological characteristics of gastric cancer. The larger the tumor diameter and the higher the degree of differentiation, the higher the HER2 positivity grade. Ki-67 expression is closely related to the occurrence, development, and invasiveness of gastric cancer. There was no significant correlation between HER2 and Ki-67 in gastric cancer tissue.

Conflict of Interest Statement

All authors declare no conflicts of interest.

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