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Gastrointestinal Cancer

Clinicopathological Significance and Prognostic Role of Her2neu Protein Expression in Patients with Carcinoma Stomach: A Prospective Study from Northern India

Abhilash V. B.[1] Manas Kumar Behera[2] Shashikant C. U. Patne[3] Sunit Kumar Shukla[4] Vinod Kumar Dixit[4]

[1] ESIC Hospital, Varanasi, Uttar Pradesh, India
[2] Department of Hepatology, Srirama Chandra Bhanja (SCB) Medical College, Bhubaneswar, Odisha, India
[3] Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India
[4] Department of Gastroenterology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Address for correspondence Manas Kumar Behera, MD, DM, Department of Hepatology, SCB Medical College and Hospital, Cuttack, Odisha 753001, India (e-mail: manasbeherabhu@gmail.com).

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Abstract

Manas Kumar Behera

Background and Aims Gastric cancer is the third most common cause of cancer-related mortality worldwide after lungs and colorectum. Although controversial, Her2neu overexpression by immunohistochemistry is usually associated with poor prognosis in patients with carcinoma stomach. We conducted a prospective study to evaluate the prognostic role of Her2neu and its correlation with clinical, pathologic type, and stage of the disease.

Methods A prospective study was performed on paraffin blocks of 111 gastric cancer specimens (88 patients were biopsy specimens and 23 were gastrectomy specimens). The paraffin blocks were processed for Her2neu receptor immunohistochemical staining and fluorescence in situ hybridization, and scoring was done.

Results Her2neu overexpression was detected in 30 out of 111 (27%) patients. The mean age was 57.68 ± 12.82 years, with males constituting two-thirds of total patients. Tobacco addiction was found in 44% of the patients and smoking in 33% of the patients. Her2neu expression was similar in Lauren's intestinal and diffuse histologic type; however, proximal gastric tumors overexpressed Her2neu as compared with distal tumors. Her2neu 2+ or 3+ (odds ratio: 2.52, 95% CI: 1.61–3.95, $p = 0.001$) was the only independent predictor of survival in gastric cancer patients. Kaplan–Meir survival analysis showed that the survival of gastric cancer patients with Her2neu overexpression (Her2neu 2+ or 3+) was significantly lower than that of those with Her2neu nonexpression ($p = 0.001$).

Conclusion Her2neu positivity was a significant predictor of mortality in patients with carcinoma stomach, and Her2neu overexpression was associated with a lower overall survival rate compared with Her2neu nonexpression.

Keywords

- cancer stomach
- Her2neu
- immunohistochemistry

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Introduction

Gastric cancer is one of the aggressive tumors encountered in clinical practice, accounting for the third most common cancer-related death worldwide.[1] However, in India, it is the fifth most common cancer among males and seventh in females.[2,3] There is a wide topographical difference in the incidence of gastric cancer, with the highest incidence being reported from Japan and India being fortunate to be in the low-risk population for cancer stomach.[4] These variations are probably due to dietary habits and the prevalence of *Helicobacter pylori* infection.[5] Although there is a declining trend in the prevalence of gastric cancer worldwide due to improvement in food hygiene and preservation methods, the regional variation in India still persists with more prevalence of gastric cancer among the southern Indian population as compared with its northern counterpart, maybe due to dietary habits like pickled food, high rice intake, and spicy food rich in chilly.[6,7]

Although surgery is the only curative option in gastric cancer, unfortunately, most tumors present with locally advanced disease. In the advanced stage of the disease, surgical resection is not possible, and chemoradiation has limited success in the management of gastric cancer.[8] Hence, the chances of survival in advanced gastric cancer with currently available palliative chemotherapy are low, with an urgent need of new effective chemotherapeutic agents targeting molecular signaling cascades. One of these signaling cascades is a 185 KDa tyrosine kinase protein and a member of the epidermal growth factor receptors' family, Her2, regulating cell proliferation, differentiation, and cellular survival.[9]

The overexpression of Her2neu has been shown to affect prognosis and response to therapy in patients with breast cancer, and it has been also observed in tumor overgrowth.[10] However, this signaling molecule has gained popularity in patients with gastric cancer over one decade as a predictive marker of treatment response to trastuzumab in Her2neu-positive advanced gastric cancer along with conventional chemotherapeutic agents. The Trastuzumab for Gastric Cancer (TOGA) trial has clearly shown the benefits of anti- Her2 therapies in patients of gastric cancer with Her2neu overexpression.[11] Hence, accurately characterizing Her2neu status in carcinoma stomach patients may help to improve the outcome of trastuzumab therapy and its undesirable side effects. We conducted a cross-sectional study to evaluate the Her2neu expression in gastric cancer patients by immunohistochemistry and correlate the Her2neu overexpression with clinical, pathologic type, and stage of the disease. We also evaluated the prognostic role of Her2neu overexpression in the survival of carcinoma stomach patients.

Patients and Methods

Methodology

This is a prospective study conducted in the Institute of Medical Sciences, Banaras Hindu University, Varanasi, from March 2013 to November 2016. All the consecutive patients of gastric cancer who had undergone surgery or endoscopic biopsy were enrolled in the study. A complete history with respect to symptoms and risk factors was ascertained. A thorough clinical examination of the patient was also done. Complete blood count, blood sugar, liver function test, renal function test, and screening for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus were done. The informed consent was taken from all patients, and study approval was taken from the ethical committee of Banaras Hindu University.

Processing of the Specimens

The specimens were transferred to the histopathology unit after biopsy/gastrectomy in 10% neutral buffer formalin. Paraffin blocks were prepared after gross examination of the specimens for staining and microscopy. The differentiation, lymphovascular invasion, perineural invasion, and infiltration of tumor up to mucosa/submucosa/muscularis propria/ serosa were identified in the slides. The procedure of routine histopathology for gastric cancer has already been standardized in the Department of Pathology, IMS, BHU, Varanasi.

Her2neu Immunohistochemistry

After histopathological confirmation of adenocarcinoma of the stomach, the paraffin block was processed for Her2Neu receptor immunohistochemical staining. The slides were deparaffinized in xylene and rehydrated in gradient ethanol solution. The antigen retrieval was done by immersing the slides in 10-mM citric buffer (pH 6.0) and then heating them for 15 minutes, followed by cooling at room temperature for 20 minutes and washing with phosphate-buffered saline (PBS). Endogenous peroxidase was blocked with 3% H2O2 in methanol for 10 minutes. Preincubation of 10% fetal calf serum in PBS with 0.01% sodium azide was done to prevent nonspecific binding. Then, the slides were incubated with antibody against Her2neu HercepTest Kit (Thermo-Fischer) for 1 hour followed by amplifier and horseradish peroxidase complex for 20 minutes after washing three times in PBS and, then, visualized with diaminobenzidine and counterstained with hematoxylin. The primary antibody was replaced with PBS for negative controls. Breast cancer tissue exhibiting high levels of markers served as controls.

Two experienced pathologists reviewed the Her2neu-stained slides, and a score of 0 to 3+ was assigned as per the criteria recommended by Hoffman et al as per the membrane staining in at least 10% of the tumor cells in the Her2neu-stained slides.[12] Her2neu-negative status was given to those with scores of 0 and 1 +, while scores of 3+ or 2+ with FISH positivity were defined as Her2neu-positive status.

Statistical Analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS, Chicago, IL, United States).[13] The categorical variables were expressed as numbers with percentages and continuous variables as mean ± standard deviation or median. Continuous data were analyzed using

independent *t*-test and categorical variables with chi-square test and Fischer exact test whenever applicable. Cox multivariate regression was employed to estimate the predictive factors for survival of gastric cancer patients. Kaplan–Meir survival analysis was done to evaluate the cumulative survival as per Her2neu status. p-value <0.05 was considered as statistically significant.

Results

Demographics and Clinicopathological Parameters of Gastric Cancer Patients

A total of 111 gastric cancer patients were included in the study, 88 patients (79%) provided biopsy specimens and 23 (21%) gastrectomy specimens. ►Table 1 depicts the demographics and clinicopathological parameters of gastric cancer patients. The mean age was 57.68 ± 12.82 years, with males constituting 66% of patients. Weight loss was the most common symptom (61%), followed by vomiting (48%) and pain in abdomen (45%). Tobacco addiction was found in 44% of patients and smoking in 33% of patients. In upper GI endoscopy, ulcerating growth was found in 64% of patients, and polypoid and scirrhous morphology was detected in around 15% of patients. The distal growth was found in 50% of patients and proximal growth in 29%. Out of all patients, grade III was found in 59%, grade II in 31%, and grade I in 10% patients. Around 90% of total patients were in stage II and III diseases, and 9% of patients were in stage IV disease.

Table 1 Baseline clinicopathological and endscopic characteristics of carcinoma stomach patients

Parameters	Number of patients ($n = 111$)
Age in years	57.68 ± 12.82 (26–78)
Gender	Male 73 (65.8%)
	Female 38 (34.2%)
Clinical symptoms	Weight loss 68 (61%)
	Vomiting 53 (48%)
	Pain addomen 50 (45%)
	Early satiety 43 (39%)
	Dysphagia 29 (26%)
Addiction	Tobacco 49 (44%)
	Smoking 37 (33%)
	Alcohol 20 (18%)
Morphology	Polypoid 15 (13.5%)
	Ulcerating 71 (64%)
	Schirrous 17 (15.3%)
	Fungating 8 (7.2%)
Site of disease	Proximal 40 (29%)
	Distal 55 (50%)
	Both 23 (21%)
Tumor type	Intestinal 57 (51.4%)
	Diffuse 43 (38.7%)
	Mixed 11 (9.9%)
Grade of differentiation	Grade I 11 (10%)
	Grade II 34 (31%)
	Grade III 66 (59%)
Stage of disease	I 3 (2.7%)
	II 50 (45%)
	III 48 (43%)
	IV 10 (9%)

Clinicopathological and Endoscopic Parameters according to Her2neu Status

As shown in ►Table 2, age and gender distribution were similar in both groups of patients irrespective of Her2neu status. Polypoidal growth was more prevalent in Her2neu-positive tumors (26 vs. 9%, $p = 0.04$). There was no significant difference between Lauren's intestinal variety with Her2neu expression in gastric cancer. However, the Her2 neu was overexpressed in proximal gastric tumors (50 vs. 32%,$p = 0.002$) and less expressed in distal tumors (20 vs. 50%, $p = 0.002$). Her2neu expression was not statistically different in advanced stages (stage III and IV disease) of the disease.

Predictors of Mortality in Gastric Cancer

The median survival of gastric cancer patients, as shown in ►Fig. 1, revealed that stage IV gastric cancer had a median survival of 6 months, stage III had of 17 months, stage II had of 27 months, and stage I had of 38 months. The predictive factors of mortality in cancer stomach patients as assessed by Cox regression analysis as shown in ►Table 3, revealed that the age of patients (odds ratio [OR]: 1.02, 95% confidence interval [CI]: 1.01–1.04, $p = 0.03$) and Her2Neu 2+ or 3 + (OR: 2.68, 95%CI: 1.76–4.16, $p = 0.001$) were significant predictors of survival in univariate analysis. However, Her2-Neu 2+ or 3 + (OR: 2.52, 95%CI: 1.61–3.95, $p = 0.001$) was the only independent predictor of survival in multivariate analysis. Kaplan–Meir survival analysis, as depicted in ►Fig. 2, showed that survival of gastric cancer patients with Her2neu overexpression (Her2neu 2+ or 3 +) was a significantly lower than that of those with Her2neu nonexpression ($p = 0.001$).

Discussion

Gastric cancer is one of the top five common cancers in India, with the second most common cancer-related death among the Indian population.[14] High salt diet with an increase in the smoking habit in both males and females along with *Helicobacter pylori* infection is considered as significant risk factors for the development of gastric cancer in India.[15] The advanced stage of the disease, along with limited palliative chemotherapeutic modalities, increases morbidity and mortality of the patients with this deadly cancer. Her2neu overexpression in gastric cancer has been known for years as a therapeutic target as well as the antitumor activity of anti-Her2neu molecules.[16]

Table 2 Demographics, clinicopathological, and endoscopic parameters according to Her2neu status

Parameters	Her2neu 0 or 1+ ($n=81$)	Her2neu 2+ or 3+ ($n=30$)	*p*-Value
Age in years	59.30 ± 12.82	54.93 ± 13.80	0.06
Gender: M:F	56:25 (69%:31%)	17:13 (57%:43%)	0.26
History of smoking	32 (40%)	5 (17%)	0.02
Tumor morphology			
Polypoid	7(8.6%)	8 (26%)	0.04
Ulcerating	56 (69%)	15 (50%)	
Schirrous	11 (13.6%)	6 (20%)	
Fungating	7 (8.6%)	1 (3.3%)	
Site			
Proximal only	26 (32%)	15 (50%)	0.002
Distal only	41 (50%)	6 (20%)	
Both proximal and distal	14 (12%)	9 (30%)	
Tumor type			
Intestinal	42 (52%)	15 (50%)	0.76
Diffuse	32 (40%)	11(36%)	
Mixed	7 (6.3%)	4 (13%)	
Grade			
I	8 (10%)	3 (10%)	0.68
II	25 (31%)	10 (33%)	
III	48 (59%)	17 (57%)	
Stage of diseases			
I	3 (3.5%)	0	0.001
II	43 (53%)	7 (23%)	
III	33 (41%)	15 (50%)	
IV	2 (2.5%)	8 (27%)	

Note: Her2 2+ status with positive confirmatory FISH test.

In our study, we found that 30 out of 111 (27%) had Her2neu 2+ or 3+. One recent study from Assam reported 56% Her2neu positivity in their study.[16] Another study from Tamil Nadu reported a lower Her2neu positivity rate of 12%.[9] This variability of Her2neu positivity in various studies may be attributed to intratumoral heterogeneity of Her2neu, and also a selection of primary antibodies, either monoclonal or polyclonal, may also affect the result. Our study was at par

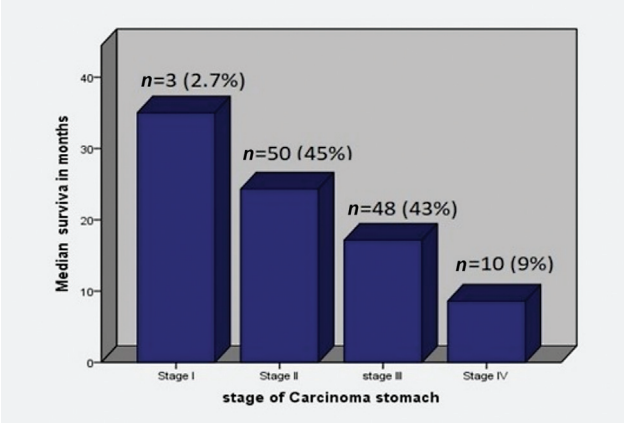

Fig. 1 Bar diagram showing the median survival of different stages of carcinoma stomach patients.

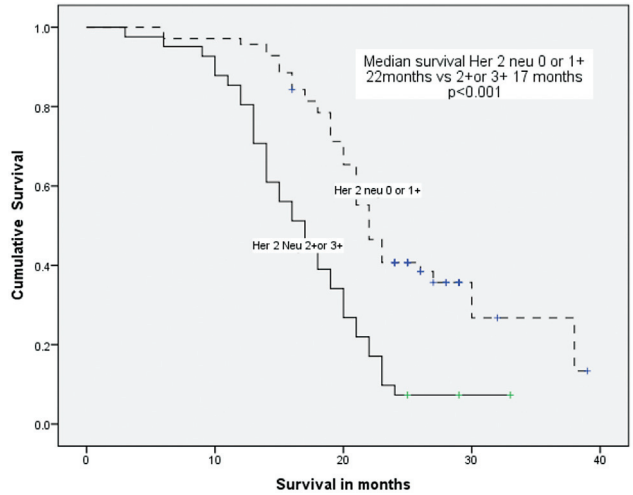

Fig. 2 Kaplan–Meir survival analysis of patients with carcinoma stomach, according to Her2neu staining.

Table 3 Cox regression analysis showing factors predicting survival in patients with carcinoma stomach

	Univariate analysis			Multivariate analysis		
Parameters	**OR**	**95% CI**	***p*-Value**	**AOR**	**95% CI**	***p*-Value**
Age of patient	1.02	1.01–1.04	0.03	1.01	0.99–1.03	0.16
Male gender	1.44	0.89–2.44	0.13	–	–	–
Intestinal type vs. diffuse type	1.25	0.87–1.87	0.22	–	–	–
Proximal tumor vs. distal tumor	1.16	0.84–1.88	0.25	–	–	–
Her2neu 2+ or 3+	2.68	1.76–4.16	0.001	2.52	1.61–3.95	0.001

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
Note: Her2 2+ status with positive confirmatory FISH test.

with the previously reported Her2neu positivity rate of 9 to 38%.[17,18] In addition, the proximal location of the tumor was also associated with Her2neu overexpression in the current study. The studies by Tanner et al and Gordon et al also found higher Her2neu expression among gastroesophageal junction favoring higher proximal predominance of Her2neu expression, as found in our study.[18,19]

In the current study, the Her2neu overexpression was not correlated with the pathologic type of tumor; the intestinal type had a similar Her2neu expression as the diffuse-type tumor. However, previous Korean studies had shown higher rates of Her2neu overexpression in Lauren's intestinal type of cancer than in diffuse cancers, and this higher Her2neu expression in intestinal-type cancer was also observed TOGA trial.[11,20] Hence, the preferential coexpression of Her2neu with intestinal phenotype tumor cells is responsible for Her2neu overexpression in intestinal phenotype than in diffuse variety.[20] In addition, Her2neu expression was inversely associated with E cadherin mutation found in diffuse histologic type, hence overexpression of Her2neu in intestinal-type rather than in diffuse variety. However, one Indian study from Hyderabad found a similar Her2neu expression rate among intestinal and diffuse histologic varieties, at par with our findings.[21] The grade of differentiation was not correlated with Her2neu expression in our study. Multiple studies had earlier shown a higher Her2neu positivity rate among well-differentiated gastric cancer than among poorly differentiated cancers.[9,22] The underlying molecular mechanisms of Her2neu positivity in different grades of differentiation are usually complex and need further evaluation.

The role of Her2neu as a prognostic factor in the survival of gastric cancer patients is highly controversial due to different results in different studies. In our study, Her2neu positivity was an independent predictor of mortality in patients with carcinoma stomach, and patients with Her2neu overexpression (Her2neu 2+ or 3+) had significantly lower survival than those with Her2neu nonexpression. Hence, gastric cancer patients with her2neu overexpression showed poor outcomes than Her2neu-negative patients. Previous studies had shown shorter overall survival rates with overexpression of Her2neu in gastric cancer patients.[23–25] A study from Bulgaria found that Her2neu positivity was associated with the worst outcome after surgical resection compared with Her2neu negativity.[26] Zhang et al, in their series of 102 gastric cancer patients, found decreased survival time among patients with Her2neu overexpression.[27] However, one large series by Yu et al of 1,143 gastric cancer patients did not show any correlation of survival time with Her2neu positivity.[28] However, the majority of publications had confirmed the association of Her2neu positivity with the worst outcome among gastric cancer patients, suggesting the predictive role of Her2neu in prognosticating patients with carcinoma stomach.[29,30] The major limitation of our study was the relatively small sample size. The prospective nature of the study and correlation of Her2 Neu with outcome were factors adding significant strength to our study.

In conclusion, Her2neu has a significant role in the tumor development and progression of disease in carcinoma stomach. Her2neu positivity was an independent predictor of mortality in patients with carcinoma stomach, and patients with Her2neu overexpression had significantly lower overall survival than those with Her2neu nonexpression. The proximal location of gastric cancer is more likely to have Her2neu positivity than the distal location. Her2neu testing should be recommended in all patients with early gastric cancer, and target therapy with trastuzumab may be considered after detection of Her2neu status in gastric cancer patients.

Conflicts of Interest

None declared.

References

1 Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol 2019;14(01):26–38
2 Rao DN, Ganesh B. Estimate of cancer incidence in India in 1991. Indian J Cancer 1998;35(01):10–18
3 Sharma A, Radhakrishnan V. Gastric cancer in India. Indian J Med Paediatr Oncol 2011;32(01):12–16
4 Mohandas KM, Jagannath P. Epidemiology of digestive tract cancers in India. VI. Projected burden in the new millennium and the need for primary prevention. Indian J Gastroenterol 2000; 19(02):74–78
5 Dikshit RP, Mathur G, Mhatre S, Yeole BB. Epidemiological review of gastric cancer in India. Indian J Med Paediatr Oncol 2011;32 (01):3–11
6 Pavithran K, Doval DC, Pandey KK. Gastric cancer in India. Gastric Cancer 2002;5(04):240–243

7 Malhotra SL. Geographical distribution of gastrointestinal cancers in India with special reference to causation. Gut 1967;8(04): 361–372
8 Yan SY, Hu Y, Fan JG, et al. Clinicopathologic significance of HER-2/neu protein expression and gene amplification in gastric carcinoma. World J Gastroenterol 2011;17(11):1501–1506
9 Sukanya JS, Raj PV, Thanka J. Role of HER2neu expression in gastric cancer. Indian J Pathol Microbiol 2021;64(01):58–64
10 Lastraioli E, Romoli MR, Arcangeli A. Immunohistochemical biomarkers in gastric cancer research and management. Int J Surg Oncol 2012;2012:868645
11 Bang YJ, Van Cutsem E, Feyereislova A, et al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376 (9742):687–697
12 Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008;52(07):797–805
13 Behera MK, Swain SN, Sahu MK, et al. Diastolic dysfunction is a predictor of poor survival in patients with decompensated cirrhosis. Int J Hepatol 2021;2021:5592376
14 GBD 2017 Stomach Cancer Collaborators. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol 2020;5(01):42–54
15 Roy PS, Nyodu T, Hazarika M, et al. Prevalence of HER2 expression and its correlation with clinicopathological parameters in gastric or gastroesophageal junction adenocarcinoma in North-East Indian population. Asian Pac J Cancer Prev 2019;20(04):1139–1145
16 Ishida T, Tsujisaki M, Hanzawa Y, et al. Significance of erbB-2 gene product as a target molecule for cancer therapy. Scand J Immunol 1994;39(05):459–466
17 Tokunaga A, Onda M, Okuda T, et al. Clinical significance of epidermal growth factor (EGF), EGF receptor, and c-erbB-2 in human gastric cancer. Cancer 1995;75(6, suppl):1418–1425
18 Tanner M, Hollmén M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with topoisomerase II alpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005;16(02):273–278
19 Gordon MA, Gundacker HM, Benedetti J, et al. Assessment of HER2 gene amplification in adenocarcinomas of the stomach or gastroesophageal junction in the INT-0116/SWOG9008 clinical trial. Ann Oncol 2013;24(07):1754–1761
20 Park DI, Yun JW, Park JH, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 2006; 51(08):1371–1379
21 Sekaran A, Kandagaddala RS, Darisetty S, et al. HER2 expression in gastric cancer in Indian population—an immunohistochemistry and fluorescence in situ hybridization study. Indian J Gastroenterol 2012;31(03):106–110
22 He C, Bian XY, Ni XZ, et al. Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer. World J Gastroenterol 2013; 19(14):2171–2178
23 Uchino S, Tsuda H, Maruyama K, et al. Overexpression of c-erbB-2 protein in gastric cancer. Its correlation with long-term survival of patients. Cancer 1993;72(11):3179–3184
24 Hilton DA, West KP. c-erbB-2 oncogene product expression and prognosis in gastric carcinoma. J Clin Pathol 1992;45(05): 454–456
25 Jaehne J, Urmacher C, Thaler HT, Friedlander-Klar H, Cordon-Cardo C, Meyer HJ. Expression of Her2/neu oncogene product p185 in correlation to clinicopathological and prognostic factors of gastric carcinoma. J Cancer Res Clin Oncol 1992;118(06):474–479
26 Ananiev J, Gulubova M, Manolova I, Tchernev G. Prognostic significance of HER2/neu expression in gastric cancer. Wien Klin Wochenschr 2011;123(13-14):450–454
27 Zhang XL, Yang YS, Xu DP, et al. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. World J Surg 2009;33(10):2112–2118
28 Yu GZ, Chen Y, Wang JJ. Overexpression of Grb2/HER2 signaling in Chinese gastric cancer: their relationship with clinicopathological parameters and prognostic significance. J Cancer Res Clin Oncol 2009;135(10):1331–1339
29 Xie SD, Xu CY, Shen JG, Jiang ZN, Shen JY, Wang LB. HER 2/neu protein expression in gastric cancer is associated with poor survival. Mol Med Rep 2009;2(06):943–946
30 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008;19(09): 1523–1529

