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Differences of HER2 over-expression between proximal and distal gastric cancers in the Chinese population

**Fan XS *et al*. Expression of HER2 in gastric cancer**

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**Abstract：**

**AIM:** To investigate HER2 expression and its correlation with clinicopathological variables between proximal and distal gastric cancers (GC) in the Chinese population.

**METHODS:** Immunostaining of HER2 was performed and scored on a scale of 0 - 3 in 957 consecutive GC cases, according to the revised scoring criteria of HercepTest TM as used in the ToGA trial. Correlations between HER2 expression and clinicopathologic variables of proximal (*n* = 513) and distal (*n* = 444) GC were investigated.

**RESULTS:** Our results showed that HER2 expression was significantly higher in the proximal than distal GC (*P* < 0.05). HER2 expression was significantly higher in male patients (*P* < 0.01), the Lauren intestinal type (*P* < 0.001), low-grade (*P* < 0.001) and pM1 (*P* < 0.01) diseases, respectively. There was a significant difference in HER2 expression among some pTNM stages (*P* < 0.05). In contrast, HER2 expression in the distal GC was significantly higher in male patients (P < 0.001), low-grade histology (*P* < 0.001), the Lauren intestinal type（*P* < 0.001), pM1 (*P* < 0.001). In the proximal GC, however, higher HER2 expression scores were observed only in tumors with low-grade histology (*P* < 0.001) and the Lauren intestinal type (*P* < 0.001).

**CONCLUSIONS:** HER2 over-expression in GC of Chinese patients was significantly more common in the proximal than distal GC, and significantly correlated with the Lauren intestinal type and low-grade histology in both proximal and distal GC, and with pM1 disease and male patients with the distal GC.

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**Key words:** HER2; Gastric cancer; Immunohistochemistry; Clinicopathology

**Core tip:** In this study, immunostaining of HER2 was performed and scored according to the revised scoring criteria of HercepTest TM used in the ToGA trial in a very large cohort of GC (957 cases). Our results revealed that HER2 over-expression in GC of Chinese patients was significantly more common in the proximal than distal GC, and significantly correlated with the Lauren intestinal type and low-grade histology in both proximal and distal GC, and with pM1 disease and male patients with the distal GC.

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**INTRODUCTION**

*HER2* gene amplification and over-expression, which possibly represents a negative prognostical factor[1, 2] but a potential therapeutic target[3-7], was found in 6%-53.4% of gastric cancer (GC) in patients from Western countries[3, 8]. As such, it is now recommended that all patients with GC should have their tumors tested for the HER2 status at the time of initial diagnosis[9]. At present, the tests for HER2 over-expression by immunohistochemstry (IHC) and HER2 gene amplification by fluorescence in situ hybridization (FISH) are the most common methods. As demonstrated in the phase III ToGA trial, the patients with IHC 2+/FISH-positive or IHC 3+ tumors benefited from trastuzumab treatment, but cases with HER2 gene amplified tumors, revealed by the FISH test, without HER2 over-expression (IHC 0 or 1+) did not show any survival gain[5]. The characteristics of HER2 expression in GC were different from those in breast cancer[5, 10]. Therefore, in the phase III ToGA trial, the HER2 expression scoring system for breast cancer, which was proposed by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP), was modified for evaluation of HER2 expression in GC[11], requiring IHC for HER2 testing before use of the FISH test[9, 12, 13], because IHC seems to be more predictive of trastuzumab therapeutic responses than the FISH test alone in GC than in breast cancers[14].

In China, GC remains one of the leading cancers. Despite recent advances in treatment, the outcome of patients with advanced GCs is poor. Because there exist considerable differences in GC histopathology, environmental factors, and the Helicobacter pylori status between Western and Chinese patients[15], the need for a comprehensive investigation of the HER2 expression profile in GC of Chinese patients is urgent for better clinical management. Therefore, we carried out this study to fully investigate differences in HER2 expression and clinicopathologic features between proximal and distal GC with the same assessment criteria of IHC as used in the ToGA trial[11].

**MATERIALS AND METHODS**

***Case Selection***

We retrospectively searched a prospectively established electronic pathology database for GC resection cases with HER2 immunostaining results over the period from January 2007 to August 2009 at the affiliated Nanjing Drum Tower Hospital, Nanjing University Medical School in Nanjing, China. A total of 957 consecutive cases were identified, including 513 proximal and 444 distal GC, according to the surgical resection methods of GC and gross specimen description. Because our recent research results in the same group of Chinese GC patients suggested that almost all proximal GC with esophageal involvement also included Siewert II-III GC, which are regarded as esophageal origin and stage-grouped as esophageal cancers[16, 17], might be more accurately staged as gastric rather than esophageal cancers[18, 19]. Therefore, the proximal GC in this study included both GC with epicenters entirely below the gastroesophageal junction (GEJ) and those invading through the GEJ into the distal esophagus as a minor component. The distal GC was defined as tumors with epicenters in the region from the incisual angularis to the antrum-pylorus. The Lauren classification of GC was followed to subgroup all cases in histopathology. All cases were staged, according to the staging rules for GC set in the 7th edition of the American Joint Committee on Cancer Staging[20]. The patient demographic and pathologic information was retrieved from each pathology report. The patient private identification information was deleted and the study protocol was approved by the Medical Ethics Committee of the Hospital.

***Immunohistochemistry***

A conventional immunostaining protocol was used for all cases. Briefly, paraffin-embedded tumor tissue blocks were cut at 4-μm in thickness. Sections were deparaffinized, dehydrated, subjected to the antigen retrieval procedure, and then incubated with the primary rabbit antihuman HER2 polyclonal antibody (clone A0485, dilution: 1:2500, Dako, Denmark) for one hour at 37℃. The HER2 immunoreactivity was visualized after a brief treatment with the EnVision Plus system kit (Dako). Both positive and negative controls were included in each run.

Three experienced pathologists independently evaluated HER2-stained slides blindly without the knowledge of patient clinicopathologic information. The HER2 immunoreactivity of neoplastic cells was scored according to the revised ToGA scoring criteria of HercepTest TM for GC[5, 11], which was based on the intensity of membrane staining and quantity of positive neoplastic cells on a scale of 0-3. In brief, no membranous reactivity in less than 10% of tumor cell was scored as 0; faint/barely visible complete or basolateral membranous reactivity in 10% or more of tumor cells was scored as 1+; weak to moderate complete or basolateral membranous reactivity in 10% or more of tumor cells was scored as 2+; strong complete or basolateral membranous reactivity in 10% or more of tumor cells was scored as 3+. A score of 0 or 1+ was considered negative while scores 2+ and 3+ were positive.

***Statistical analysis***

The absolute and relative frequencies of qualitative variables were calculated in percentages. Chi-square tests for categorical variables were used and the differences were considered to be statistically significant if *P* values were less than 0.05. All analyses were performed using the SPSS version 20.0 software for Windows (SPSS Inc., Chicago, IL).

**RESULTS**

***Clinicopathologic features***

The patient mean age was 63 years (range: 17 – 89 years). As shown in Table 1, most patients were male (75%) with a male-female ratio of 3.0; 29% of patients were older than 70 years. Most tumors were the Lauren intestine type (59%), high-grade histology (66%), and at advanced stages of pIII and pIV (61%). About 54% of GC was located in the proximal stomach (Table 2). None of the patients received neoadjuvant therapy before surgical resections.

***Overall HER2 immunoreactivity in gastric cancer***

In general, HER2 immunoreactivity of neoplastic cells in GC was characterized by basolateral, lateral, and/or circumferential membranous, heterogeneous or diffuse, staining patterns (Figures 1-3). HER2 over-expression with score 3, and scores 2 and 3 were found in 9.5% (91/957) and 21.73% (208/957) of cases. Overall, HER2 expression with score 3 was significantly higher in male patients (10.24%, compared to 7.38% in the female, *P* < 0.01), the proximal GC (8.11%, compared to 10.72% in the distal GC, *P* < 0.05), the Lauren intestine type (14.79%, compared to 1.8% in the Lauren diffuse/mixed type, *P* < 0.001), histological low-grade histology (17.6%, compared to 5.37% in high-grade histology, *P* < 0.001), and pM1 (36.36%, compared to 8.88% in pM0, *P* < 0.01), respectively. Although there was a significant difference in HER2 expression between advanced and early GC, especially in stage pIV (pI: 2.7%; pII: 10.86%; pⅢ: 9.12%; pⅣ: 38.1%; *P* < 0.05), the correlation between HER2 and pTNM stage was not statistically significant (*P* > 0.05) (Table 1).

***Differences in HER2 Immunoreactivity between Proximal and Distal Gastric Cancers***

HER2 expression was higher in the proximal GC than in the distal (10.7%, compared to 8.1% with score 3; 25%, compared to 18.2% with scores 2 and 3; *P* < 0.05) (Table 2.). In the proximal GC, higher expression of HER2 with score 3 was found only in tumors with low-grade histology (17.24%, compared to 6.45%, *P* < 0.001), the Lauren intestine type (15.88%, compared to 0.58%, *P* < 0.001) than those with high-grade histology and the Lauren diffuse/mixed type (Table 3.). In the distal GC, however, HER2 over-expression with score 3 was significantly higher in male patients (9.09%, compared to 5.88%, *P* < 0.001), distant metastasis (50%, compared to 6.94%, *P* < 0.001), histological low-grade (18.18%, compared to 4.33%, *P* < 0.001), the Lauren intestine type（13.16%, compared to 2.87%, *P* < 0.001) GC than in female patients, pM0, high-grade histology, and the Lauren diffuse/mixed type (Table 4.).

**DISCUSSION**

In this retrospective study with the revised IHC scoring criteria of HercepTest TM for HER2 expression in GC of Chinese patients, we compared HER2 protein expression profiles along with clinicopathologic features between 513 proximal and 444 distal GC in Chinese patients. The data showed that HER2 over-expression was significantly more common in the proximal GC than in the distal, and significantly correlated with the Lauren intestine type and low-grade histology in both proximal and distal GC, and with pM1 disease and male patients with the distal GC.

In the recent literatures, the frequency of HER2 over-expression in GC, determined by IHC, ranges widely from 6.8% to 26.8%[21]. In this study, HER2 over-expression with score 2 and 3 was found in 21.73% of cases, which was higher than that (15.9%) in another recent study using the same antibody and the scoring criteria in Korean patients[8]. The discrepancy appears to result from the differences in tissue preparations because they used tissue microarray for HER2 immunostaining, which has a much lower sensitivity for HER2 immunnoreactivity because of the well-known heterogeneous expression of HER2 in GC[14, 21-24]. In addition, different primary antibody clones, various immunostaining protocols, and diverse immunoreactivity scoring schemes may also contribute to variations described among recent studies[8, 12, 25]. This inconsistency indicates an urgent need for standardized HER2 immunostaining in GC for better reporting and comparison of HER2 IHC results among different centers.

HER2 expression is known to differ among various clinicopathologic factors, such as patient gender, age, ethnicity, tumor location, type, and differentiation, etc. as shown in this and previous studies[26-28]. Our data showed high HER2 expression in GC with the low-grade histology and advanced pTNM stages. Similar to our results, a recent study in Japanese patients also described higher HER2 expression in male patients, tumors with the Lauren intestine type, pM1 stage[26]. With the multivariate analysis, Janjigian *et al*[29] reported a significantly higher frequency of HER2 immunopositivity in GC with liver metastasis and the Lauren intestine histology, but did not find significant differences in HER2 immunopositivity between resections and biopsies, or primaries and metastases. In that study, approximate 20% (78/381) of distant metastatic GC or GEJ cancer in Western patients were HER2-immunopositive (score 3+ or FISH-positive)[29], which is much lower than ours (38%, 8/21). However, the number of GC cases with distant metastasis was limited in this study and our results should be verified in studies with larger qualified cases. Nonetheless, our data suggested that HER2 over-expression was more often in GC with the Lauren intestine type, low-grade histology, advanced pTNM stage, and male patients.

In this study, we found a significantly higher frequency of HER2 over-expression in the proximal GC than in the distal. The result is similar to those reported recently in most of the other studies[30]. It must be pointed out that the vast majority of GEJ cancers in Chinese patients are not Barrett’s esophagus-related and originate primarily in the proximal stomach, invading into the distal esophagus with clinicopathologic features of GC, as we reported previously[31]. Despite similar HER2 over-expression characteristics between Western GEJ cancers and Chinese proximal GC, there exist a number of differences in HER2 over-expression features between proximal and distal GC of Chinese patients in the present study. For example, in the distal rather than proximal GC, HER2 over-expression in GC was more common in male patients, tumors staged at pM1 than in female patients, pM0 cases, respectively.

A major limitation in this observational study is the absence of the confirmatory FISH test for HER2 gene amplification. However, unlike in breast cancer, HER2 expression with an IHC score of 0 or 1+ but with FISH positivity in tumors did not play statistically significant role in the trastuzumab therapy[5]. GC with IHC 3+ of HER2 status was responded well to this treatment. Thus, the ToGA trial recommended testing HER2 gene amplification by the FISH method only in GC cases with an IHC score of 2+[5]. Therefore, a conformation FISH test might not be performed in GC with IHC 0, 1+ or 3+. Also, our cohort is large with 957 GC resection cases and differences in HER2 expression are dramatically significant in many important clinicopathologic parameters. Therefore, the validity of our results should be reasonably sound.

In summary, our data showed a significantly higher frequency of HER2 over-expression in the proximal GC than the distal. HER2 over-expression was significantly correlated with low-grade histology, the Lauren intestine type in both proximal and distal GC, male patients and distant metastasis in distal GC.

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**COMMENTS**

***Background***

*HER2* gene amplification and over-expression was a potential therapeutic target and found in 6%-53.4% of gastric cancer (GC) in patients from Western countries. As such, it is now recommended that all patients with GC should have their tumors tested for the HER2 status at the time of initial diagnosis. In China, GC remains one of the leading cancers. Because there exist considerable differences in GC between Western and Chinese patients, the need for a comprehensive investigation of the HER2 expression profile in GC of Chinese patients is urgent for better clinical management.

***Research frontiers***

The purpose of the present study was to investigate HER2 expression with the same assessment criteria of IHC as used in the ToGA trial and its correlation with clinicopathological variables between proximal and distal GC in the Chinese population.

***Innovations and breakthroughs***

Our study represented a very large cohort of GC. In this study, HER2 expression in the overall GC was significantly higher in male patients, the Lauren intestinal type, low-grade and pM1 diseases, respectively. There was a significant difference in HER2 expression among some pTNM stages. Similar to some Western study results, our data showed that HER2 expression was significantly higher in the proximal GC than in the distal. Also, HER2 expression in the distal GC was significantly higher in male patients, low-grade histology, the Lauren intestinal type, and pM1. In the proximal GC, however, higher HER2 expression scores were observed only in tumors with low-grade histology and the Lauren intestinal type.

***Applications***

Our data, derived from a comprehensive investigation of the HER2 expression profile with the same ToGA criteria in GC resection specimens in a large cohort of homogeneous Chinese patients, provide pathologists and oncologists with more accurate than tissue microarray study results on HER over-expression characteristics in both proximal and distal GC, which is essential for better clinical management of the patients with GC in the Chinese population.

***Terminology***

ToGA trial: An international, open-lable, randomized controlled, phase III trial of Herceptin (Trastuzumab) in combination with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer, which was undertaken in 122 centers in 24 countries; Lauren classification: the Lauren classification is based on the histological features of gastric adenocarcinomas, and divides gastric adenocarcinomas into 3 types: intestinal type (the tumor consists of neoplastic glands arranged in tubules, acini, and papillae), diffuse type (The tumor cells are discohesive and many show the signet-ring morphology ) and the mixed type.

***Peer review***

The authors reported statistically more frequent HER2 over-expression in the proximal than distal GC. HER2 over-expression was also associated with some clinicopathological characteristics, such as gender, the Lauren intestinal type, low-grade dysplasia, and pM1 diseases in GC. This is a valuable paper in which it represents a very large cohort of cancers (957 cases). This provides some real strength and confidence in the HER2 expression values. The data are consistent with but extend (for the Chinese population) the information already available.

**REFERENCES**

1 **Jørgensen JT**, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. *J Cancer* 2012; **3**: 137-144 [PMID: 22481979 DOI: 10.7150/jca.4090]

2 **Chua TC**, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. *Int J Cancer* 2012; **130**: 2845-2856 [PMID: 21780108 DOI: 10.1002/ijc.26292]

3 **Bang YJ**. Advances in the management of HER2-positive advanced gastric and gastroesophageal junction cancer. *J Clin Gastroenterol* 2012; **46**: 637-648 [PMID: 22751336 DOI: 10.1097/MCG.0b013e3182557307]

4 **Hicks DG**, Whitney-Miller C. HER2 testing in gastric and gastroesophageal junction cancers: a new therapeutic target and diagnostic challenge. *Appl Immunohistochem Mol Morphol* 2011; **19**: 506-508 [PMID: 22089490 DOI: 10.1097/PAI.0b013e31822c3a0f]

5 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. 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**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]

6 **Yamashita-Kashima Y**, Iijima S, Yorozu K, Furugaki K, Kurasawa M, Ohta M, Fujimoto-Ouchi K. Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. *Clin Cancer Res* 2011; **17**: 5060-5070 [PMID: 21700765 DOI: 10.1158/1078-0432.CCR-10-2927]

7 **Lordick F**. Trastuzumab: a new treatment option for HER2-positive metastatic gastric and gastroesophageal junction cancer. *Future Oncol* 2011; **7**: 187-199 [PMID: 21345138 DOI: 10.2217/fon.10.178]

8 **Cho EY**, Srivastava A, Park K, Kim J, Lee MH, Do I, Lee J, Kim KM, Sohn TS, Kang WK, Kim S. Comparison of four immunohistochemical tests and FISH for measuring HER2 expression in gastric carcinomas. *Pathology* 2012; **44**: 216-220 [PMID: 22437741 DOI: 10.1097/PAT.0b013e3283513e8b]

9 **Rüschoff J**, Hanna W, Bilous M, Hofmann M, Osamura RY, Penault-Llorca F, van de Vijver M, Viale G. HER2 testing in gastric cancer: a practical approach. *Mod Pathol* 2012; **25**: 637-650 [PMID: 22222640 DOI: 10.1038/modpathol]

10 **Rüschoff J**, Nagelmeier I, Baretton G, Dietel M, Höfler H, Schildhaus HU, Büttner R, Schlake W, Stoss O, Kreipe HH. [Her2 testing in gastric cancer. What is different in comparison to breast cancer?]. *Pathologe* 2010; **31**: 208-217 [PMID: 20443098 DOI: 10.1007/s00292-010-1278-1]

11 **Hofmann M**, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J, Henkel T. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; **52**: 797-805 [PMID: 18422971 DOI: 10.1111/j.1365-2559.2008.03028.x.]

12 **Park YS**, Hwang HS, Park HJ, Ryu MH, Chang HM, Yook JH, Kim BS, Jang SJ, Kang YK. Comprehensive analysis of HER2 expression and gene amplification in gastric cancers using immunohistochemistry and in situ hybridization: which scoring system should we use? *Hum Pathol* 2012; **43**: 413-422 [PMID: 21855114 DOI: 10.1016/j.humpath.2011.05.019]

13 **Fox SB**, Kumarasinghe MP, Armes JE, Bilous M, Cummings MC, Farshid G, Fitzpatrick N, Francis GD, McCloud PI, Raymond W, Morey A. Gastric HER2 Testing Study (GaTHER): an evaluation of gastric/gastroesophageal junction cancer testing accuracy in Australia. *Am J Surg Pathol* 2012; **36**: 577-582 [PMID: 22314190 DOI: 10.1097/PAS.0b013e318244adbb]

14 **Albarello L**, Pecciarini L, Doglioni C. HER2 testing in gastric cancer. *Adv Anat Pathol* 2011; **18**: 53-59 [PMID: 21169738 DOI: 10.1097/PAP.0b013e3182026d72]

15 **Bickenbach K**, Strong VE. Comparisons of Gastric Cancer Treatments: East vs. West. *J Gastric Cancer* 2012; **12**: 55-62 [PMID: 22792517 DOI: 10.5230/jgc.2012.12.2.55]

16 **Stephen B. Edge DRB**, Carolyn C. Compton, April G. Fritz, Frederick L. Greene, Andy Trotti, III. AJCC Cancer Staging Handbook. 7th. New York: Springer, 2009: 129-144

17 **R.D. Odze J-FF**, P. Boffetta, H. Hofler, E. Montgomery, S.J. Spchler: Tumours of the oesophagogastric junction. In: Fred T. Bosman FC, Ralph H. Hruban, Neil D. Theise. World Health Organization Classification of Tumours of the Digestive System. Lyon: IARC Press, 2010: 40-44

18 **Zhang YF**, Shi J, Yu HP, Feng AN, Fan XS, Lauwers GY, Mashimo H, Gold JS, Chen G, Huang Q. Factors predicting survival in patients with proximal gastric carcinoma involving the esophagus. *World J Gastroenterol* 2012; **18**: 3602-3609 [PMID: 22826627 DOI: 10.3748/wjg.v18.i27.3602]

19 **Huang Q**, Shi J, Feng A, Fan X, Zhang L, Mashimo H, Cohen D, Lauwers G. Gastric cardiac carcinomas involving the esophagus are more adequately staged as gastric cancers by the 7th edition of the American Joint Commission on Cancer Staging System. *Mod Pathol* 2011; **24**: 138-146 [PMID: 20852593 DOI: 10.1038/modpathol.2010.183]

20 **Stephen B. Edge DRB**, Carolyn C. Compton, April G. Fritz, Frederick L. Greene, Andy Trotti, III.AJCC Cancer Staging Handbook. 7th. New York: Springer, 2009: 145-152

21 **Kunz PL**, Mojtahed A, Fisher GA, Ford JM, Chang DT, Balise RR, Bangs CD, Cherry AM, Pai RK. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. *Appl Immunohistochem Mol Morphol* 2012; **20**: 13-24 [PMID: 21617522 DOI: 10.1097/PAI.0b013e31821c821c]

22 **Kim KC**, Koh YW, Chang HM, Kim TH, Yook JH, Kim BS, Jang SJ, Park YS. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. *Ann Surg Oncol* 2011; **18**: 2833-2840 [PMID: 21468783 DOI: 10.1245/s10434-011-1695-2]

23 **Yang J**, Luo H, Li Y, Li J, Cai Z, Su X, Dai D, Du W, Chen T, Chen M. Intratumoral heterogeneity determines discordant results of diagnostic tests for human epidermal growth factor receptor (HER) 2 in gastric cancer specimens. *Cell Biochem Biophys* 2012; **62**: 221-228 [PMID: 21927816 DOI: 10.1007/s12013-011-9286-1]

24 HER2 in gastric cancer: a digital image analysis in pre-neoplastic, primary and metastatic lesions. *Mod Pathol* 2013; [PMID: 23348899 DOI: 10.1038/modpathol.2012.228]

25 **Atkinson R**, Mollerup J, Laenkholm AV, Verardo M, Hawes D, Commins D, Engvad B, Correa A, Ehlers CC, Nielsen KV. Effects of the change in cutoff values for human epidermal growth factor receptor 2 status by immunohistochemistry and fluorescence in situ hybridization: a study comparing conventional brightfield microscopy, image analysis-assisted microscopy, and interobserver variation. *Arch Pathol Lab Med* 2011; **135**: 1010-1016 [PMID: 21809992 DOI: 10.5858/2010-0462-OAR]

26 **Kataoka Y**, Okabe H, Yoshizawa A, Minamiguchi S, Yoshimura K, Haga H, Sakai Y. HER2 expression and its clinicopathological features in resectable gastric cancer. *Gastric Cancer* 2013; **16**: 84-93 [PMID: 22410801 DOI: 10.1007/s10120-012-0150-9]

27 **Tafe LJ**, Janjigian YY, Zaidinski M, Hedvat CV, Hameed MR, Tang LH, Hicks JB, Shah MA, Barbashina V. Human epidermal growth factor receptor 2 testing in gastroesophageal cancer: correlation between immunohistochemistry and fluorescence in situ hybridization. *Arch Pathol Lab Med* 2011; **135**: 1460-1465 [PMID: 22032573 DOI: 10.5858/arpa.2010-0541-OA]

28 **Im SA**, Kim JW, Kim JS, Kim MA, Jordan B, Pickl M, Han SW, Oh DY, Lee HJ, Kim TY, Kim WH, Yang HK, Bang YJ. Clinicopathologic characteristics of patients with stage III/IV (M(0)) advanced gastric cancer, according to HER2 status assessed by immunohistochemistry and fluorescence in situ hybridization. *Diagn Mol Pathol* 2011; **20**: 94-100 [PMID: 21532492 DOI: 10.1097/PDM.0b013e3181fc02b7]

29 **Janjigian YY**, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jäger E, Altmannsberger HM, Robinson E, Tafe LJ, Tang LH, Shah MA, Al-Batran SE. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. *Ann Oncol* 2012; **23**: 2656-2662 [PMID: 22689179]

30 **Lee S**, de Boer WB, Fermoyle S, Platten M, Kumarasinghe MP. Human epidermal growth factor receptor 2 testing in gastric carcinoma: issues related to heterogeneity in biopsies and resections. *Histopathology* 2011; **59**: 832-840 [PMID: 22092394 DOI: 10.1111/j.1365-2559.2011.04017.x]

32 **Huang Q**, Fan X, Agoston AT, Feng A, Yu H, Lauwers G, Zhang L, Odze RD. Comparison of gastro-oesophageal junction carcinomas in Chinese versus American patients. *Histopathology* 2011; **59**: 188-197 [PMID: 21884197 DOI: 10.1111/j.1365-2559.2011.03924.x]

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**Figure 1 HER2 immunostaining in gastric cancers was scored as 1+, 2+ and 3+ in A, B and C, respectively.**

**Figure 2 Heterogeneous (A and B) or diffuse (C) expression pattern of HER2 protein was discovered in gastric cancers.**

**Figure 3 A rare diffuse and strong positive pattern of HER2 expression in the Lauren diffuse type gastric cancers.**

**Table 1 HER2 Expression in gastric adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n*** | **HER2 Score** | | | | **χ2** | ***P*** | **Univariate Analysis** | |
| **0** | **1** | **2** | **3** | ***rs*** | ***P*** |
| **Gender**  F  M | 244  713 | 149  366 | 58  176 | 19  98 | 18  73 | 10.106 | 0.001 | —— | —— |
| **Age (year)** ≤70  >70 | 682  275 | 370  145 | 164  70 | 82  35 | 66  25 | 1.347 | 0.418 | —— | —— |
| **pT** T1  T2  T3  T4 | 51  145  749  12 | 28  79  404  4 | 14  38  179  3 | 6  19  90  2 | 3  9  76  3 | 7.464 | 0.070 | —— | —— |
| **pN** N0  N1  N2  N3 | 243  140  205  369 | 138  63  104  210 | 60  34  50  90 | 27  23  31  36 | 18  20  20  33 | 13.591 | 0.335 | —— | —— |
| **pM** M0  M1 | 935  22 | 506  9 | 232  2 | 114  3 | 83  8 | 19.984 | 0.001 | 0.077  0.105 | 0.020  0.002 |
| **pTNM**  I  II  III  IV | 110  267  559  21 | 59  151  296  9 | 32  57  143  2 | 16  30  69  2 | 3  29  51  8 | 29.943 | 0.041 | 0.039 | 0.187 |
| **G** Low  high | 324  633 | 135  380 | 82  152 | 50  67 | 57  34 | 51.360 | 0.000 | —— | —— |
| **Lauren** intestinal  diffuse/mixed | 568  389 | 256  253 | 145  88 | 83  34 | 84  7 | 79.548 | 0.000 | —— | —— |

pTNM: Pathological tumor-node-metastasis; M: Male; F: Female.

**Table 2 Comparison of HER2 expression between proximal and distal gastric adenocarcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | ***n*** | **HER2 Score** | | | | **χ2** | ***P*** |
| **0** | **1** | **2** | **3** |
| Proximal | 513 | 260 | 126 | 72 | 55 | 6.691 | 0.011 |
| Distal | 444 | 255 | 108 | 45 | 36 |

**Table 3 HER2 Expression in proximal gastric adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n*** | **HER2 Score** | | | | **χ2** | ***P*** | **Univariate Analysis** | |
| **0** | **1** | **2** | **3** | ***rs*** | ***P*** |
| **Gender**  F  M | 108  405 | 57  203 | 28  98 | 13  59 | 10  45 | 0.884 | 0.232 | —— | —— |
| **Age (yr)** ≤70  >70 | 371  142 | 189  71 | 92  34 | 48  24 | 42  13 | 1.647 | 0.476 | —— | —— |
| **pT** T1  T2  T3  T4 | 10  61  439  3 | 4  30  226  0 | 3  16  107  0 | 1  11  59  1 | 2  4  47  2 | 15.026 | 0.472 | —— | —— |
| **pN** N0  N1  N2  N3 | 132  70  124  187 | 71  31  60  98 | 34  16  29  47 | 15  13  22  22 | 12  10  13  20 | 6.071 | 0.524 | —— | —— |
| **pM** M0  M1 | 503  10 | 255  5 | 125  1 | 70  2 | 53  2 | 1.959 | 0.269 | —— | —— |
| **pTNM**  I  II  III  IV | 43  129  332  9 | 20  74  161  5 | 14  26  85  1 | 6  16  49  1 | 3  13  37  2 | 6.790 | 0.133 | —— | —— |
| **G**  low  high | 203  310 | 84  176 | 52  74 | 32  40 | 35  20 | 19.924 | 0.000 | -0.179 | 0.000 |
| **Lauren** intestinal  diffuse/mixed | 340  173 | 150  110 | 85  41 | 51  21 | 54  1 | 39.351 | 0.000 | -0.210 | 0.000 |

pTNM: Pathological tumor-node-metastasis; M: Male; F: Female.

**Table 4 HER2 expression in distal gastric adenocarcinoma**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n*** | **HER2 Score** | | | | **χ2** | ***P*** | **Univariate Analysis** | |
| **0** | **1** | **2** | **3** | ***rs*** | ***P*** |
| **Gender** F  M | 136  308 | 92  163 | 30  78 | 6  39 | 8  28 | 11.510 | 0.000 | 0.148 | 0.000 |
| **Age (yr)** ≤70  >70 | 311  133 | 181  74 | 72  36 | 34  11 | 24  12 | 2.443 | 0.446 | —— | —— |
| **pT** T1  T2  T3  T4 | 41  84  310  9 | 24  49  178  4 | 11  22  72  3 | 5  8  31  1 | 1  5  29  1 | 3.983 | 0.131 | —— | —— |
| **pN** N0  N1  N2  N3 | 111  70  81  182 | 67  32  44  112 | 26  18  21  43 | 12  10  9  14 | 6  10  7  13 | 9.645 | 0.255 | —— | —— |
| **pM** 0  1 | 432  12 | 251  4 | 107  1 | 44  1 | 30  6 | 29.728 | 0.000 | 0.133 | 0.000 |
| **pTNM** I  II  III  IV | 67  138  227  12 | 39  77  135  4 | 18  31  58  1 | 10  14  20  1 | 0  16  14  6 | 39.702 | 0.164 | —— | —— |
| **G** low  high | 121  323 | 51  204 | 30  78 | 18  27 | 22  14 | 31.286 | 0.000 | -0.231 | 0.000 |
| **Lauren** intestinal  diffuse/mixed | 228  209 | 106  143 | 60  47 | 32  13 | 30  6 | 40.352 | 0.000 | -0.209 | 0.000 |

pTNM: Pathological tumor-node-metastasis; M: Male; F: Female.