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

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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™ 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 in distal GC (P < 0.05). Overall, 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), and 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).

CONCLUSION: HER2 over-expression in GC of Chinese patients was significantly more common in proximal than in 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 gender in 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™ used in the ToGA trial in a very large cohort of gastric cancers (GC) patients (957 cases). Our results revealed that HER2 over-expression in GC of Chinese patients was significantly more common in proximal than in distal GC, and was significantly cor-
related with the Lauren intestinal type and low-grade histology in both proximal and distal GC, and with pM1 disease and male gender in 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], has been found in 6%-53.4% of gastric cancer (GC) in patients from Western countries[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 immunohistochemistry (IHC) and HER2 gene amplification by fluorescence in situ hybridization (FISH) are the most common methods. As demonstrated in the phase III ToGA trial, 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 are different from those in breast cancer[3,9]. 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[10,11], because IHC seems to be more predictive of trastuzumab therapeutic responses than the FISH test alone in GC, compared with 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[10].

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 Stewart III-IV GC, which are regarded as esophageal origin and stage-grouped as esophageal cancers[16,17], they 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. Distal GC was defined as tumors with epicenters in the region from the incisura 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 out in the 7th edition of the American Joint Committee on Cancer Staging[20]. The patient demographics and pathologic information were 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 °C. 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™ 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 cells 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.

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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, respectively. Overall, HER2 expression with score 3 was significantly higher in male patients (10.24% vs 7.38% in females, P < 0.01), the proximal GC (8.11% vs 10.72% in distal GC, P < 0.05), and the Lauren intestine type (14.79% vs 1.8% in the Lauren diffuse/mixed type, P < 0.001), histological low-grade histology (17.6% vs 5.37% in high-grade histology, P < 0.001), and pM1 (36.36% vs 8.88% in pM0, P < 0.01). Although there was a significant difference in HER2 expression between advanced and early GC, especially in stage pN (p I: 2.7%; p II: 10.86%; p III: 9.12%; p IV: 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 GCs

HER2 expression was higher in proximal GC than in distal GC (10.7% vs 8.1% with score 3; 25% vs 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% vs 6.45%, P < 0.001), the Lauren intestine type (15.88% vs 9.58%, 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% vs 5.88%, P < 0.001), distant metastasis (50% vs 6.94%, P < 0.001), histological low-grade (18.18% vs 4.33%, P < 0.001), the Lauren in-

### RESULTS

#### Clinicopathologic features

The mean patient 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 pT III and pN IV (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 GC

In general, HER2 immunoreactivity of neoplastic cells

| 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  |       |      |

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  |       |      |

Statistical analysis

The absolute and relative frequencies of qualitative variables were calculated in percentages. χ² 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, United States).

| Gender | n   | HER2 score | χ² | P   |
|--------|-----|------------|----|-----|
|        | 0   | 1  | 2  | 3   |    |
| F      | 244 | 149 | 58  | 19  | 18  | 10.106 | 0.001 |
| M      | 713 | 366 | 176 | 98  | 73  |        |      |

| Age (yr) | n   | HER2 score | χ² | P   |
|----------|-----|------------|----|-----|
|          | 0   | 1  | 2  | 3   |    |
| ≤ 70     | 682 | 370 | 164 | 82  | 66  | 1.347 | 0.418 |
| > 70     | 275 | 145 | 70  | 35  | 25  | 7.464 | 0.070 |

| pT       | n   | HER2 score | χ² | P   |
|----------|-----|------------|----|-----|
|          | 0   | 1  | 2  | 3   |    |
| T1       | 51  | 28  | 14  | 6   | 3   | 7.464 | 0.070 |
| T2       | 145 | 79  | 38  | 19  | 9   |        |      |
| T3       | 749 | 404 | 179 | 90  | 76  |        |      |
| T4       | 12  | 4   | 3   | 2   | 3   |        |      |

| pN       | n   | HER2 score | χ² | P   |
|----------|-----|------------|----|-----|
|          | 0   | 1  | 2  | 3   |    |
| N0       | 243 | 138 | 60  | 27  | 18  | 13.591 | 0.035 |
| N1       | 140 | 63  | 34  | 23  | 20  |        |      |
| N2       | 205 | 104 | 50  | 31  | 20  |        |      |
| N3       | 369 | 210 | 90  | 36  | 33  |        |      |

| pM       | n   | HER2 score | χ² | P   |
|----------|-----|------------|----|-----|
|          | 0   | 1  | 2  | 3   |    |
| M0       | 935 | 506 | 232 | 114 | 83  | 19.984 | 0.001 |
| M1       | 22  | 9   | 2   | 3   | 8   | 0.105  | 0.002 |
| pTNM     | n   | HER2 score | χ² | P   |
|          | 0   | 1  | 2  | 3   |    |
| I        | 110 | 59  | 32  | 16  | 3   | 29.943 | 0.041 |
| II       | 267 | 151 | 57  | 30  | 29  |        |      |
| III      | 558 | 296 | 143 | 68  | 51  |        |      |
| IV       | 22  | 9   | 2   | 3   | 8   |        |      |
| G        | n   | HER2 score | χ² | P   |
|          | 0   | 1  | 2  | 3   |    |
| Low      | 324 | 135 | 82  | 50  | 57  | 51.360 | 0.000 |
| High     | 633 | 380 | 152 | 67  | 34  |        |      |

| Lauren   | n   | HER2 score | χ² | P   |
|----------|-----|------------|----|-----|
| Intestinal | 568 | 256 | 145 | 83  | 84  | 79.548 | 0.000 |
| Diffuse/mixed | 389 | 253 | 88  | 34  | 7   |        |      |
DISCUSSION

In this retrospective study using the revised IHC scoring criteria of HercepTest™ 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 proximal GC than in distal GC, and significantly correlated with the Lauren intestine type and low-grade histology in both proximal and distal GC, and with pM1 disease and male gender in distal GC.

In the recent literature, 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 diffuse/mixed type (Table 4).
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 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 immunoreactivity 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

### Table 3 HER2 expression in proximal gastric adenocarcinoma

| Gender | n | HER2 score | \(x^2\) | P |
|--------|---|------------|---------|---|
| F      | 108 | 0 | 57 | 28 | 13 | 10 | 0.884 | 0.232 |
| M      | 405 | 0 | 203 | 98 | 59 | 45 | 1.647 | 0.476 |
| Age (yr) < 70 | 371 | 189 | 92 | 48 | 42 | 1.647 | 0.476 |
| pT T1 | 10 | 4 | 3 | 1 | 2 | 15.026 | 0.472 |
| T2 | 61 | 30 | 16 | 11 | 4 |
| T3 | 439 | 226 | 107 | 59 | 47 |
| pN N0 | 132 | 71 | 34 | 15 | 12 | 6.071 | 0.524 |
| N1 | 70 | 31 | 16 | 13 | 10 |
| N2 | 124 | 60 | 29 | 22 | 13 |
| N3 | 187 | 98 | 47 | 22 | 20 |
| pM M0 | 503 | 255 | 125 | 70 | 53 | 1.959 | 0.269 |
| M1 | 10 | 5 | 1 | 2 | 2 |
| pTNM I | 43 | 20 | 14 | 6 | 3 | 6.790 | 0.133 |
| II | 129 | 74 | 26 | 16 | 13 |
| III | 331 | 161 | 85 | 48 | 37 |
| IV | 10 | 5 | 1 | 2 | 2 |
| G Low | 203 | 84 | 52 | 32 | 35 | 19.924 | 0.000 |
| High | 310 | 176 | 74 | 40 | 20 |
| Lauren Intestinal | 340 | 150 | 85 | 51 | 54 |
| Diffuse/mixed | 173 | 110 | 41 | 21 | 1 |

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

### Table 4 HER2 expression in distal gastric adenocarcinoma

| Gender | n | HER2 score | \(x^2\) | P |
|--------|---|------------|---------|---|
| F      | 136 | 92 | 30 | 6 | 8 | 11.510 | 0.000 |
| M      | 308 | 163 | 78 | 39 | 28 |
| Age (yr) < 70 | 311 | 181 | 72 | 34 | 24 | 2.443 | 0.131 |
| pT T1 | 41 | 24 | 11 | 5 | 1 | 3.983 | 0.131 |
| T2 | 84 | 49 | 22 | 8 | 5 |
| T3 | 310 | 178 | 72 | 31 | 29 |
| pN N0 | 111 | 67 | 26 | 12 | 6 | 9.645 | 0.255 |
| N1 | 70 | 32 | 18 | 10 | 10 |
| N2 | 81 | 44 | 21 | 9 | 7 |
| N3 | 182 | 112 | 43 | 14 | 13 |
| pM 0 | 432 | 251 | 107 | 44 | 30 | 29.728 | 0.000 |
| 1 | 12 | 4 | 1 | 1 | 6 |
| pTNM I | 67 | 39 | 18 | 10 | 0 | 39.702 | 0.164 |
| II | 138 | 77 | 31 | 14 | 16 |
| III | 227 | 135 | 58 | 20 | 14 |
| IV | 12 | 4 | 1 | 1 | 6 |
| G Low | 121 | 51 | 30 | 18 | 22 | 31.286 | 0.000 |
| High | 323 | 204 | 78 | 27 | 14 |
| Lauren Intestinal | 228 | 106 | 60 | 32 | 30 |
| Diffuse/mixed | 209 | 143 | 47 | 13 | 6 |

pTNM: Pathological tumor-node-metastasis; M: Male; F: Female.
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 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, and pM1 stage[29]. With a multivariate analysis, Janjigian et al[30] 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, approximately 20% (78/381) of distant metastatic GC or GEJ cancers in Western patients were HER2-immunopositive (score 3+ or FISH-positive)[30], a figure which is much lower than ours (36.4%, 8/22). However, the number of GC cases with distant metastasis was limited in this study and our results should be verified in studies with more qualified cases. Nonetheless, our data suggested that HER2 over-expression was more often seen in GC with the Lauren intestine type, low-grade histology, advanced pTNM stage, and in male patients.

In this study, we found a significantly higher frequency of HER2 over-expression in proximal GC than in distal GC. The result is similar to those reported recently in most other studies[31]. 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[32]. 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 distal rather than proximal GC, HER2 over-expression in GC was more common in male patients and in tumors staged at pM1 than in female patients and in 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 GC tumors does not play a statistically significant role with regard to trastuzumab therapy[33]. GC with IHC 3+ HER2 status responds 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+[34]. Therefore, a confirmation FISH test might not be performed in GC with IHC 0, 1+ or 3+. However, 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 proximal GC than in distal GC. HER2 over-expression was significantly correlated with low-grade histology and the Lauren intestine type in both proximal and distal GC, and with male gender and distant metastasis in distal GC.

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**COMMENTS**

**Background**

HER2 gene amplification and over-expression is a potential therapeutic target and is 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 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. 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 proximal GC than in distal GC. 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 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 study results than tissue microarray regarding HER2 over-expression characteristics in both proximal and distal GC, which is essential for better clinical management of patients with GC in the Chinese population.

**Terminology**

ToGA trial: An international, open-label, 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 mixed type.

**Peer review**

The authors reported statistically more frequent HER2 over-expression in 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 pT1M1 diseases in GC. This is a valuable paper which represents a very large cohort of cancers (957 cases). This provides
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: 157-144 [PMID: 22481979 DOI: 10.7150/jca.4009]

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 gastrosophageal junction cancer. J Clin Gastroenterol 2012; 46: 637-648 [PMID: 22751336 DOI: 10.1097/MCG.0b013e3182573070]

4. Hicks DG, Whitney-Miller C. HER2 testing in gastric and gastrosophageal junction cancers: a new therapeutic target and diagnostic challenge. Appl Immunohistochem Mol Morphol 2011; 19: 506-508 [PMID: 22089490 DOI: 10.1097/PAL00138231283a09]

5. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Oumuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lebile M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastrosophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)6121-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 gastrosophageal junction cancer. Future Oncol 2011; 7: 187-199 [PMID: 21345138 DOI: 10.2217/fon.11.78]

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: 22477741 DOI: 10.1097/PAT.0b013e3283513e88]

9. Rüschoff J, Hanna W, Bilous M, Hofmann M, Osamura RY, Penna-Lloruca 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, Albray P, Pecciarini L, Doglioni C, HER2 testing in gastric cancer. Adv Anul Pathol 2011; 18: 53-59 [PMID: 21697385 DOI: 10.1097/PAP.0b013e31824a4d8b]

11. Albray P, Baretton G, Dietel M, Höfler H, Albray P, Pecciarini L, Doglioni C, HER2 testing in gastric cancer. Adv Anul Pathol 2012; 36: 577-582 [PMID: 22314190 DOI: 10.1097/PAP.0b013e318224a4d8b]

12. 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.2012.2.5.35]

13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging handbook. 7th ed. New York: Springer, 2009: 129-144

14. Ozde J-F, Fathi H, Spychler T. Tumours of the oesophagogastric junction. In: Fred T, Bosman FC, Roth H, Kluin-Nelemans HC, editors. World Health Organization classification of tumours of the digestive system. Lyon: IARC Press, 2010: 40-44

15. 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: 22862627 DOI: 10.3748/wjg.v18.i27.3602]

16. Huang Q, Jiang 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]

17. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging handbook. 7th ed. New York: Springer, 2009: 145-152

18. Kunz PL, Mojtahed A, Fisher GA, Ford JM, Chang DT, Balise RR, Bangs CD, Cherry AM, Pai RK. HER2 expression in gastric and gastrosophageal 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/PAL001382312821]

19. 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 4,144 cases of whole-tissue sections and 955 cases of tissue microarrays. Ann Surg Oncol 2011; 18: 2833-2840 [PMID: 21468783 DOI: 10.1245/s10434-011-1695-2]

20. 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/s12015-011-9286-1]

21. Fusco N, Rocco EG, Del Conte C, Pollegreni C, Bulfamante G, Di Nuovo F, Romagnoli S, Rosari S. HER2 in gastric cancer: a digital image analysis in pre-neoplastic, primary and metastatic lesions. Mod Pathol 2013; Epub ahead of print [PMID: 23438899 DOI: 10.1038/modpathol.2012.228]

22. 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/ajr.2010-0462-OAR]

23. 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/
Fan XS et al. Expression of HER2 in gastric cancer

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]

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.0b013e3181d87f7]

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]

Lee S, de Boer WB, Fermoye 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]

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]