

HER2 discordance between paired primary gastric cancer and metastasis: a meta-analysis

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Background: A number of studies have examined human epidermal growth factor receptor 2 (HER2) status in primary gastric cancer (GC) and associated metastasis, some showed their great concordance in HER2 expression, but others demonstrated notable discordance. There is still little consensus on HER2 discordance, therefore, a systematic review and meta-analysis was conducted to assess the status on HER2 discordance between primary GC and its paired metastasis.

Methods: PubMed, EMBASE, ASCO and The Cochrane Library were searched for studies that explored the concordance between primary tumor and metastasis in patients with GC up to 10 March, 2014. Data of discordance of HER2 between primary GC and corresponding metastasis were extracted from the publications and random-effects models were used to estimate pooled discordance proportions.

Results: Eighteen articles including 1,867 patients were included for the meta-analysis in accordance with the selection criteria. Pooled discordance proportions were 7% [95% confidence interval (CI): 5-10%] for HER2 status. Pooled proportions of tumors shifting from positive to negative and from negative to positive were 17% (95% CI: 7-29%) and 4% (95% CI: 2-6%) respectively. No publication bias was found in the meta-analysis.

Conclusions: The discordance of HER2 status is not rare in primary and metastatic GC through our meta-analysis. Prospective studies are needed to testify the clinical significance of the discordance of HER2 status.

Keywords: Gastric cancer (GC); human epidermal growth factor receptor 2 (HER2); discordance; meta-analysis

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Introduction

Gastric cancer (GC) keeps being one of the leading types of cancers worldwide. Based on the statistic estimate, there are still about one million new cases and over 700,000 deaths each year (1). Human epidermal growth factor receptor 2 (erbB2, or HER2/neu, or HER2), a proto-oncogene, is an important prognostic biomarker and key driver of tumorigenesis in GC (2). According to a great number of studies, HER2 positivity is detected in 7% to 34% of patients in GC (3-6). The results of the phase III

ToGA (trastuzumab for gastric cancer) trials (7), indicated that trastuzumab plus chemotherapy became the standard regimen for patients with HER2 positive advanced GC. Therefore, it is now recommended that HER2 status should be evaluated in every GC patient eligible for trastuzumab treatment for most effective therapy. HER2 status was recommended to be tested by immunohistochemistry (IHC) first, followed by fluorescence in situ hybridization (FISH) for IHC 2+ patients, who was considered as cases with equivocal expression (8).

Probably since the tissues in metastatic sites are rarely

removed or biopsied before treatment, HER2 status is generally evaluated in the primary lesions only, although trastuzumab-based therapy is used to treat metastatic disease. Several studies reported HER2 status in primary GC and associated metastasis, the discordance rate marked among these studies (9-12). Based on these disparate results and different opinions, arguments for or against HER2 testing of metastasis have therefore been aroused. Does the HER2 discordance come from the tumor-related behavior or testing error? As yet, little consensus has been reached on this controversy. Therefore, we performed a systematic review and meta-analysis to evaluate the discordance rate of HER2 status between primary tumor and corresponding metastasis and its clinical significance of treatment.

Methods

Search strategy and selection criteria

A systematic review of published work was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Electronic searches were performed to search the literatures reporting HER2 status in primary GC and its paired metastasis in PubMed, EMBASE, ASCO and The Cochrane Library using the combined text words 'gastric' or 'stomach' or 'gastroesophageal' and 'cancer' or 'tumor' or 'neoplasm' or 'carcinoma' and 'HER2' or 'HER-2' or 'ERBB2' or 'ERBB-2' or 'c-erbb-2' or 'cerbb2' or 'neu'. The latest search was undertaken in 10 March, 2014. We also manually screened the reference lists of the retrieved articles to identify other relevant publications.

Studies which met the following criteria were eligible for this meta-analysis: (I) report HER2 status in primary GC and its paired metastasis with IHC or FISH or chromogenic in situ hybridization (CISH) or silver in situ hybridization (SISH) and etc.; (II) provide data of discordance rate of HER2 status (primary *vs.* metastasis), or the data can be derived from reported results. When there was more than one article using the overlapped populations, the latest publication was selected. Review articles, case reports, circulating tumor cells studies and studies that did not report needed data were excluded.

Data extraction

Data was extracted by two investigators (Zhi Peng and Jianling Zou) independently using a standard protocol. Any

discrepancies were resolved by discussion and consensus was reached finally. The following data elements were extracted from each study: first author, year of publication, time of collection, race or country, number of patients (male/female), tumor stage, type and site of relapse, technique to detect HER2 status, corresponding scoring criteria, HER2 discordance rate, the prevalence shifting from positive to negative and vice versa.

Statistical analysis

The discordance proportion of HER2 between primary GC and metastasis with 95% confidence intervals (CIs) was calculated for each study. The Freeman-Tukey double arcsine transformation was used for the calculation of pooled estimates and corresponding 95% CIs (13). The chi-square test of homogeneity was performed to detect statistical heterogeneity (14). The Mantel-Haenszel fixed effect model was adopted if no significant difference was found in the homogeneity test. Otherwise, the DerSimonian-Laird random-effect model (D-Lmethod) was adopted for calculations.

In our study, subgroup analyses were conducted according to race, technique of detecting HER2 status, type and time of metastasis, type of sampling respectively. The quality of each study included in the meta-analysis was independently assessed by two reviewers (Zhi Peng and Jianling Zou) according to the Newcastle-Ottawa scale (NOS) (15). Studies that received more than six stars were considered as high quality, analogous to other reviews. We specifically classified studies at elevated risk of bias (1-3 stars), intermediate risk of bias (4-5 stars), or low risk of bias (6-9 stars). Any disagreements in studies' quality assessment were resolved by a consensus discussion between the two reviewers. Furthermore, Publication bias was evaluated using funnel plots and the asymmetry test developed by Egger and colleagues (16). All analyses were carried out with the R software (<http://cran.r-project.org/>) with package 'meta'. All the reported P values were two sided.

Results

Study characteristics

Totally 1,763 articles were identified from electronic databases, of which 39 studies were potentially related to our issue. Finally, eighteen articles (9-12,17-30) were included for the meta-analysis in accordance with the

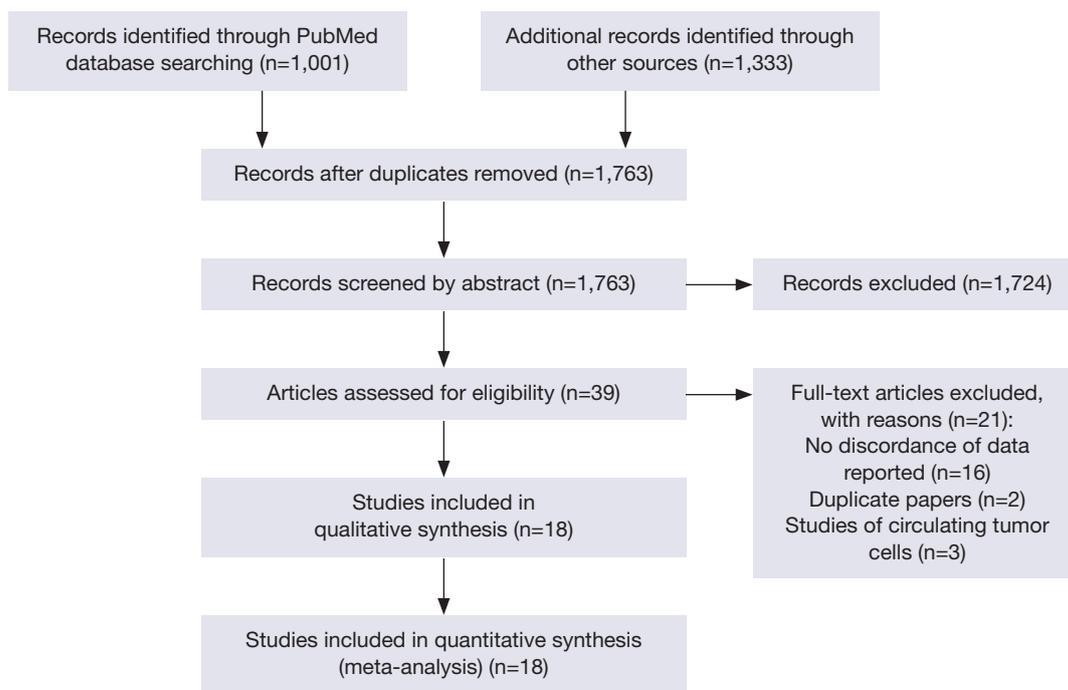


Figure 1 Flow chart of the eligible studies. Flow chart of the eligible studies for the meta-analysis of HER2 status in paired primary gastric cancer and metastasis.

selection criteria (*Figure 1*), which provided paired HER2 data for primary and metastasis tumor in 1,867 subjects, ranging from 34 to 250 patients per study. Among the 18 studies, 16 studies offered the full texts and the 2 studies (11,21) offered the abstracts with discordance rate between primary GC and the metastasis disease. Among the 14 studies with full texts, 2 were in Chinese with English abstracts (23,28).

Their main characteristics including year of publication, race or country, number of subjects, type of metastasis and sampling, time of metastasis, corresponding techniques are reported in *Table 1*. All studies were retrospective. Nine (9,11,20-22,25-27,30) of the 18 studies (1,186 patients, 63.5%) were performed in Asian populations, and the remaining 9 (10,12,17-19,23,24,28,29) studies (681 patients, 36.5%) were in Western populations. The techniques used in the studies included IHC, ISH, southern blot hybridization technique and (or) the combination of the two or three. The tissues were mainly collected from surgery, while there were still some with the mixed methods of surgery and biopsy, and Pigni *et al.* (30) reported the study used the both methods for all the patients. Most of the metastatic tumors are synchronous loco-regional lymph

nodes, whereas there were still several studies reporting the cases with synchronous or metachronous distant metastasis (22,25,30), and they mainly located in liver, abdominal wall, intestine, uterus and so on.

Meta-analysis of HER2 discordance between primary tumor and metastasis

Among all the studies, the discordance rates between primary and metastasis tumor ranged from 2% to 24% ($I^2 = 72.2\%$, $\tau^2 = 0.03$, $P < 0.0001$), and the pooled estimate of the proportion of the total studies was 7% (95% CI: 5-10%) (*Figure 2*). The proportions of patients whose HER2 status changed from positive to negative and from negative to positive were also conducted. The pooled proportion of negative conversion was 17% (95% CI: 7-29%) (*Figure 3A*), and the positive conversion was 4% (95% CI: 2-6%) (*Figure 3B*). The results reached significantly statistical difference ($P < 0.001$).

Stratified analysis was conducted according to the technique used to define HER2 status, site of relapse, the type to sampling and the time of metastasis. As it is shown in the *Table 2*, the pooled discordance proportion was 8% (95% CI: 6-11%) in studies using IHC alone, and 2% (95%

Table 1 Main characteristics of studies included in meta-analysis

First author	Year of publication	Time frame	Race or country	No. of subjects (male/female)	Median age [range age]	Regional or distant metastasis	Synchronous or metachronous metastasis	Type of sampling	Techniques to test HER2 status
Chariyalertsak S	1994	1990-1991	Thailand	97 (NR)	NR [NR]	Regional	Synchronous	Surgery or biopsy	IHC
Kim JS	1997	1992-1993	Korea	45 (NR)	NR [NR]	Regional	Synchronous	Surgery	Southern blot
Kim JH	2009	1995-2003	Korea	222 (NR)	55.4 [NR]	Regional	Synchronous	Surgery	IHC
Marx AH	2009	NR	Germany	51 (NR)	NR	Regional	Synchronous	Surgery	IHC and FISH
Kim JY	2010	NR	Caucasian	193 (NR)	NR [NR]	Regional	Synchronous	Surgery	IHC and FISH
Kim MA	2011	1990-2006	Korea	250 (NR)	NR	Regional and distant	Synchronous or metachronous	Surgery or biopsy	IHC and FISH
Geng YT	2011	2003-2005	China	110 (79/31)	63.5 [28-85]	Regional	Synchronous	Surgery	IHC
Bozzetti C	2011	NR	Italy	39 (NR)	NR [40-88]	Regional or distant	Synchronous and metachronous	Surgery or biopsy	IHC and FISH
Zhang YL	2012	2010-2011	China	112 (NR)	59 [30-79]	Regional	Synchronous	Surgery	IHC and FISH
Tsapralis D	2012	2004-2007	Athens	45 (NR)	NR [NR]	Regional	Synchronous	Surgery	IHC and CISH
Fassan M	2012	2000-2003	Italy	47 (38/9)	67.9 [49-87]	Regional	Synchronous	Surgery	IHC and CISH
Asioli S	2012	NR	Italy	60 (NR)	NR [NR]	Regional or distant	Synchronous	Surgery	IHC
Shinozaki E	2013	NR	Caucasian	58 (45/13)	NR [NR]	Distant	Synchronous and metachronous	Surgery	IHC
Pagni F	2013	2008-2011	Italy	34 (16/18)	68.5 [NR]	Regional or distant	Synchronous	Surgery and biopsy	IHC and FISH
Kochi M	2013	1990-2010	Japan	102 (82/20)	68 [29-86]	Regional	Synchronous	Surgery	IHC and FISH
Fusco N	2013	1996-2008	Italy	154 (NR)	NR [NR]	Regional	Synchronous	Surgery	IHC
Cho EY	2013	2000-2004	Korea	138 (NR)	NR [NR]	Distant	Synchronous and metachronous	Surgery	IHC and SISH
Geng Y	2014	2003-2005	China	110 (79/31)	63.5 [28-85]	Regional	Synchronous	Surgery	IHC

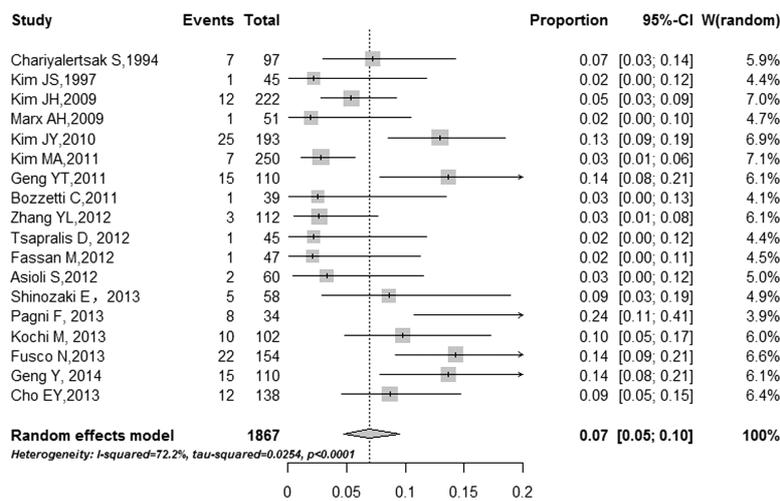


Figure 2 Forest plot for proportion of discordance HER2 status. Pooled estimate for HER2 discordant in studies reporting HER2 status in primary gastric cancer and paired metastasis. Weights are from random-effects analysis. Squares indicate the point estimates of the effect of study (proportion of discordance) and diamonds, the summary estimate from the pooled studies; 95% confidence intervals are indicated by horizontal bars and shown in square brackets.

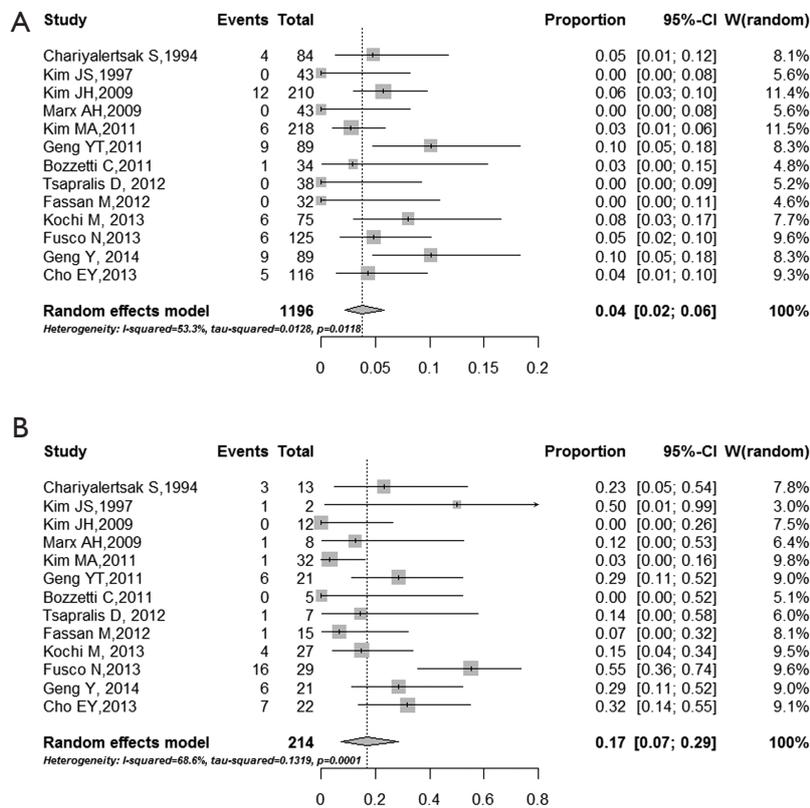


Figure 3 Forest plot for proportion of negative and positive conversion of HER2 status. The pooled proportions of patients whose HER2 status changed from positive to negative (A) and from negative to positive (B). Weights are from random-effects analysis. Squares indicate the point estimates of the effect of study (proportion of discordance) and diamonds, the summary estimate from the pooled studies; 95% confidence intervals are indicated by horizontal bars and shown in brackets.

Table 2 Subgroup analysis about HER2 discordant proportion	
Type of subgroups (No. of studies providing data for analysis, No. of subjects)	HER2 discordant% (95% CI)
Different race	
Asian population (9 studies, 1,186 subjects)	0.07 (0.03-0.12)
Western population (9 studies, 681 subjects)	0.07 (0.04-0.10)
Test used to determine HER2 status	
Immunohistochemistry (IHC) (16 studies, 1,788 subjects)	0.08 (0.06-0.11)
In situ hybridization (ISH) (8 studies, 902 subjects)	0.02 (0.01-0.05)
Immunohistochemistry (IHC)/in situ hybridization (IHC/ISH) (2 studies, 136 subjects)	0.15 (0.04-0.31)
Type of metastasis included in paired testing of primary cancer and metastasis	
Studies of loco-regional lymph nodes only (15 studies, 1,548 subjects)	0.07 (0.05-0.1)
Studies of distant metastasis only (3 studies, 225 subjects)	0.03 (0.00-0.09)
Studies of loco-regional lymph nodes and distant metastasis (3 studies, 162 subjects)	0.07 (0.00-0.21)
Metastasis synchronous or asynchronous to primary cancer	
Studies of synchronous metastasis (15 studies, 1,571 subjects)	0.07 (0.05-0.1)
Studies of asynchronous metastasis (1 study, 61 subjects)	0.00 (0.00-0.03)
Studies of synchronous or asynchronous metastasis (3 studies, 235 subjects)	0.07 (0.04-0.11)
Type of sampling	
Surgery only (15 studies, 1,481 subjects)	0.07 (0.05-0.1)
Biopsy only (1 study, 34 subjects)	0.26 (0.13-0.43)
Surgery or biopsy (3 studies, 386 subjects)	0.04 (0.01-0.07)
HER2, human epidermal growth factor receptor 2.	

CI: 1-5%) with studies using ISH alone, and 15% (95% CI: 4-31%) with studies using IHC and ISH. When it is about the site of relapse, the pooled discordance proportion was 7% (95% CI: 5-10%) for loco-regional lymph nodes only, and 3% (95% CI: 0-9%) for distant relapse only, and 7% (95% CI: 0-21%) for loco-regional lymph nodes or distant relapse. Different pooled discordance proportion was found when the time to metastasize was taken into account. When the relapse was synchronous to the primary cancer, the pooled discordance proportion was 7% (95% CI: 5-10%), and when asynchronous, the pooled discordance proportion was 0% (95% CI: 0-3%), and when mixed with synchronous and asynchronous, the pooled discordance proportion was 7% (95% CI: 4-11%). While the different pooled discordance of type of sampling was also analyzed, the pooled discordance proportion was 7% (95% CI: 5-10%) when the sampling was through surgery only, and 26% (95% CI: 13-43%) when the sampling was through biopsy only, and 4% (95% CI: 1-7%) when the studies was mixed with surgery and biopsy sampling. Influence analysis showed that removal any research would not cause a significant change in the results.

Risk of bias

In this review, we assessed the studies' quality according to the NOS guideline. Overall, 12 studies were assessed to be high-quality and 6 medium-quality; no studies was deemed to be low-quality (*Table S1*). For publication bias estimating, no visually and statistically significant asymmetry was found according to the inverted funnel plot (*Figure 4*) and Egger's test in all analyses ($P=0.835$), which means no publication bias was found between studies. We also tested the publication bias among the subgroups and no significant publication bias was observed either.

Discussion

The discordance of HER2 status between primary GC and metastasis and its clinical implications are still in debate. Accurate detection of HER2 will provide important information for determining whether trastuzumab therapy is needed. In this study, we synthesized the published data on HER2 status discordance between paired primary GC and corresponding metastasis. Our results showed that the

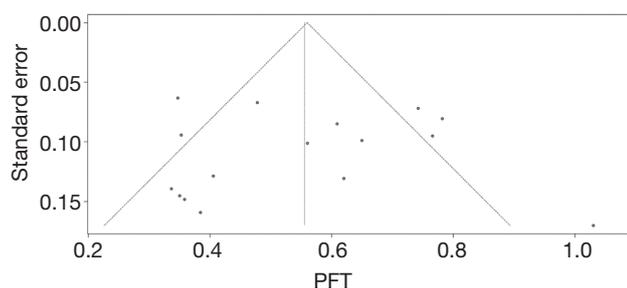


Figure 4 Funnel plots for the publication bias estimating. The dashed line represents 95% confidence intervals. Circles represent individual studies.

rates of HER2 discordance were 7% (95% CI: 5-10%).

The choice of systemic therapy in advanced GC is dependent on the appropriate targeting of HER2 receptor. The HER2 status of metastatic disease is usually assumed to be the same as that of the primary tumor, but there is evidence for discordance in receptor status between primary and metastatic tumor. In Japan, HER2 testing should be routinely performed in patients with metastatic or recurrent GC, which recommended by the Japanese Society of Pathology. Our data showed that the discordance of negative conversion is higher than that of positive conversion (0.17 vs. 0.04). The data imply 4% of patients may lose the chance of anti-HER2 therapy if they only detect primary GC site. Therefore, the HER2 testing should be performed in both primary and metastatic sites whenever possible for anti-HER2 therapy.

However, results of the meta-analysis should be interpreted with caution. The 'true' discordance rates may be lower than those reported in the literature. Firstly, debates still exist related to the intratumoral heterogeneity. Marx's study showed that HER2 amplification is highly homogenous in GC (20). However, Bilous *et al.* (31) and Grabsch *et al.* (32) indicated that there was heterogeneity among HER2 protein expression and amplification. It is suggested that HER2 testing in endoscopic biopsies before treatment is prone to false-negative results. Secondly, the limited discordant HER2 status found between the primary and the paired metastatic GC specimens might be partially due to the method of detection. HER2 overexpression in gastric tumor is heterogeneous and comprises a minority of tumor cells, which represent an important drawback for HER2 testing. It will produce low-reproducible results for HER2. In our meta-analysis, the pooled discordance is 8% using IHC, only 2% using ISH. It is consistent with

paired HER2 status in primary breast cancer and its paired metastasis, which generally suggested that the potentially greater accuracy of ISH relative to IHC (33). Previous studies have reported that variability in IHC testing, including variable types of fixation, different antigen retrieval methods, and subjectivities in observer analysis, might affect results (34). Other factors such as relatively small sample size, retrospective studies and without centralized evaluation are also need to be addressed.

In addition to intratumoral heterogeneity and technique issues, the true discordance of HER2 may be due to other factors, such as clonal selection, tumor progression and other unknown reasons. HER2 status may change during the metastatic process and tumorigenesis. It is suggested that biopsy of metastasis appears to be beneficial in breast cancer in a prospective study (35). Correspondingly, the inconsistent chemotherapy response usually exists in clinical. Our results underlie the therapeutic importance of HER2 testing in both primary and metastatic site in GC. In breast cancer, patients with receptor discordance between primary and recurrent tumor are associated with poor survival, which might lead to inappropriate targeted therapy (36). For breast cancer, guidelines recommend HER2 testing of primary breast cancer or at the time of metastatic relapse, and some recommend testing metastasis if HER2 status of the primary is unknown (37). However, to the best of our knowledge, there are no relevant data to elucidate the clinical significance for treatment change of HER2 status discordance between primary and metastasis in GC. Whether a finding of discordance altered management of metastatic disease and whether altered management improved patient outcomes need to be investigated in the future.

In clinical practice, there are also several factors need to be noted. Delaying systemic therapy to await biopsy of a metastatic lesion and its characterization is a concern. Biopsy of metastatic disease cannot be easy to be carried out due to potential complications and due to the need of surgical approaches. Patient's preference to undertake an invasive procedure is also concerned (35,38).

Conclusions

In conclusion, the discordance of HER2 status is not rare in primary and metastatic GC through our meta-analysis. Wherever possible, HER2 status testing is recommended to perform in both primary and metastatic sites. Prospective studies are needed to testify the clinical significance of the

discordance of HER2 status.

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Table S1 Assessment of study quality with Newcastle-Ottawa scale

Study ID	Year	Selection				Comparability		Exposure			No. of star
		S1	S2	S3	S4	C1	C2	E1	E2	E3	
Chariyalertsak S	1994	★	★	★		★		★	★		6
Kim JS	1997		★	★		★	★	★	★		6
Kim JH	2009	★		★	★	★	★	★	★	★	8
Marx AH	2009		★	★	★	★			★		5
Kim JY	2010			★		★	★	★	★		5
Kim MA	2011	★	★			★			★	★	5
Geng YT	2011			★	★	★	★	★	★	★	7
Bozzetti C	2011	★	★	★	★	★			★		6
Zhang YL	2012		★			★		★	★	★	5
Tsapralis D	2012			★	★	★	★	★	★		6
Fassan M	2012	★	★	★		★	★	★	★		7
Asioli S	2012		★		★	★		★	★		5
Shinozaki E	2013		★			★		★	★		4
Pagni F	2013	★			★	★	★		★	★	6
Kochi M	2013	★	★	★	★	★		★	★		7
Fusco N	2013	★	★		★	★	★	★	★	★	8
Cho EY	2013	★	★	★	★	★		★	★		7
Geng Y	2014	★		★	★	★	★		★		6

Selection contains four criteria: S1, is the case definition adequate? S2, representativeness of the cases; S3, selection of controls; S4, definition of controls. Comparability means: C1, comparability of cases; C2, controls on the basis of the design or analysis. Exposure contains three criteria: E1, ascertainment of exposure; E2, same method of ascertainment for cases and controls; E3, non-response rate.