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Clinicopathological factors associated with HER2-positive gastric cancer
A meta-analysis

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Abstract

Background: The treatment of patients with advanced gastric cancer remains a most challenging task in the clinical practice. Recently, targeted therapies have significantly impacted the treatment strategy for many common malignancies. The use of trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2), plus chemotherapy proved to improve median overall survival in patients with advanced gastric cancer, compared with chemotherapy alone in Trastuzumab for Gastric Cancer (ToGA) trial. However, the prognostic value of HER2 status in gastric cancer remains controversial. Therefore, the aim of this study was to investigate the clinical pathology significance of HER2 overexpression in resectable gastric cancer for selecting the right patients with gastric cancer who may benefit from trastuzumab treatment.

Methods: Publications reported the clinicopathological factors associated with HER2 status in gastric cancer from 2012 to 2017 were collected. The literature databases, such as "Cochrane Library", "Sciencedirect", "Springer", "PubMed", "Embase", were extensively searched to retrieve the clinical studies of HER2 expression in gastric cancer. The major outcomes measures were odds ratios (ORs) and their 95% CIs. Statistical analysis was carried out by Revman software 5.3. The Newcastle–Ottawa scale was used to assess the quality of evidence.

Result: Fifteen studies met our inclusion criteria. This study demonstrated that the pooled OR for HER2 positivity was associated with being male (OR: 1.42; 95% CI: 1.23–1.64), well/moderately differentiated tumor (OR: 2.76; 95% CI: 1.72–4.45), and for intestinal-type tumor (OR: 0.31; 95% CI: 0.25–0.38). However, it had no correlation with depth of tumor ($P=.07$), venous invasion ($P=.82$), and lymphovascular invasion ($P=.24$).

Conclusion: HER2-positive expression was associated with male gender, intestinal type, and well/moderate cell differentiation. We recommend that those gastric cancer patients who may benefit from trastuzumab treatment should be subjected to targeted therapies. However, detecting HER2 status may contribute to the target therapy for gastric carcinoma using trastuzumab. This would be strengthened by further studies incorporating comorbidity data, and outcomes from centralized programs.

Abbreviations: OR = odds ratio, ToGA = Trastuzumab for Gastric Cancer.

Keywords: HER2, meta-analysis, prognostic, stomach neoplasm

1. Introduction

Targeted therapy is a new trend in cancer treatment to improve overall survival in patients with cancer. In regard to gastric cancer, molecular targeted therapy is also gaining status. Human epidermal growth factor receptor 2 (HER2) is a growth factor receptor that mediating cell growth and differentiation.[1]

Consequently, HER2-positive tumors likely have a poor prognosis compared with HER2-negative tumors. Various reports have shown that HER2-positive breast tumors demonstrate aggressive characteristics compared with HER2-negative breast tumors.[2] This has encouraged the investigation of its antitumor activity in patients with HER2-positive gastric adenocarcinomas. HER2 is overexpressed in approximately 10% to 30% of gastric cancers.[3] Due to the importance of targeted adjuvant chemotherapy, previous studies have evaluated the HER2 status in gastric cancer to correlate HER2 expression with clinical pathology features and to predict prognosis.[4,5] And the results of the ToGA trial have been very encouraging, opening a new channel of hope for the treatment of advanced gastric cancer.[6] Key prognostic factors have been defined to account for the staging and proper therapeutic strategies in GA. However, the factors are imprecise, and patients with similar GA stage prognosis may actually be at different stages. This may be the major source of controversies surrounding the prognostic value of HER2 overexpression. Therefore, studies are needed to constitute new prognostic factors. We conducted the study to examine both expression and amplification of Her2/neu in tumors of curatively resected gastric cancer and correlated these measurements to the clinicopathological of the patients.

2. Materials and methods

2.1. Search strategy

Two independent investigators searched electronic databases: Pubmed, Embase, Cochrane library up to January 2017. The following search items were used: "Stomach neoplasm" AND "human epidermal receptor-2" AND "Prognostic", and relevant Medical Subject Heading (MeSH) terms were utilized. References cited in the publications were hand-searched to identify additional relevant publications.

2.2. Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: patients were identified as gastric cancer at the first treatment whether they had surgery or the pathological check; HER2 expression evaluation using special methods such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or dual-color in situ hybridization (DISH); positivity for HER2 was defined as either IHC3 (+) or IHC2 (+) with DISH (+). Study provided information on clinical pathology results; all publications are limited to using English. We excluded the studies: duplicate data; they were case reports, nonoriginal articles, or articles with insufficient data; and they were published in non-English language.

2.3. Quality assessment

Two investigators independently rated the quality of the retrieved studies. We using the Newcastle–Ottawa Quality assessment scale recommended by The Cochrane Handbook for Systematic Reviews of Interventions.

2.4. Data extraction

Two investigators independently extracted the following information from each study. Disagreement was resolved by consensus. From each of the eligible studies, the following information was collected: first author family name, publication year, gender (female/male), median (age), provided information on clinic-pathological results.

2.5. Statistical analysis

Odds ratios (ORs) and their 95% CIs were combined to evaluate the association between HER2 overexpression and clinical pathology factors, such as gender, Lauren type, histologic grade, depth of tumor invasion, venous invasion, and Lymphatic invasion. The association between clinical pathology factors and gastric cancer is basing on the data from retrospective trials. The endpoints of interest in the pooled analysis were ORs and their 95% CIs data, and the endpoint outcome was considered as a weighted average of individual estimate of the hazard ratios (HRs) in every included study, using the inverse variance method.

A sensitivity analysis was also conducted to examine the impact on the overall results, depending on the heterogeneity between the included studies. Heterogeneity was investigated by use of the I^2 statistic.[7] Studies with an I^2 of 25% to 50%, 50% to 75%, or >75% were considered to have low, moderate, or high heterogeneity, respectively.[8] Only when there was low heterogeneity among studies, the fixed-effects model was used. Meanwhile, the rest pooled HRs were calculated using randomized-effects model. A P-value less than .05 was considered statistically significant. All the statistical tests in this meta-analysis were performed with Review Manager version 5.3 software (Revman; The Cochrane Collaboration, Oxford, United Kingdom). Findings of our meta-analysis were shown in forest plots.

2.6. Ethical approval

Ethical approval was not required because this study is a meta-analysis.

3. Results

3.1. Overview of literature search and study characteristics

A total of 267 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 17 publications were evaluated in more detail, but 2 did not meet the inclusion criteria. Therefore, a final total of 15 studies with included (9–23). The search process is described in Fig. 1.

All included studies in this study were considered to be of moderate quality at least. Table 1 describes the primary characteristics of the eligible studies in more detail.

3.2. Clinical and methodological heterogeneity
3.2.1. Pooled analysis of OR for the association of HER2 overexpression with the gender. A total of 15 studies[9–23] reported the rates in gender (Fig. 2). The aggregated results
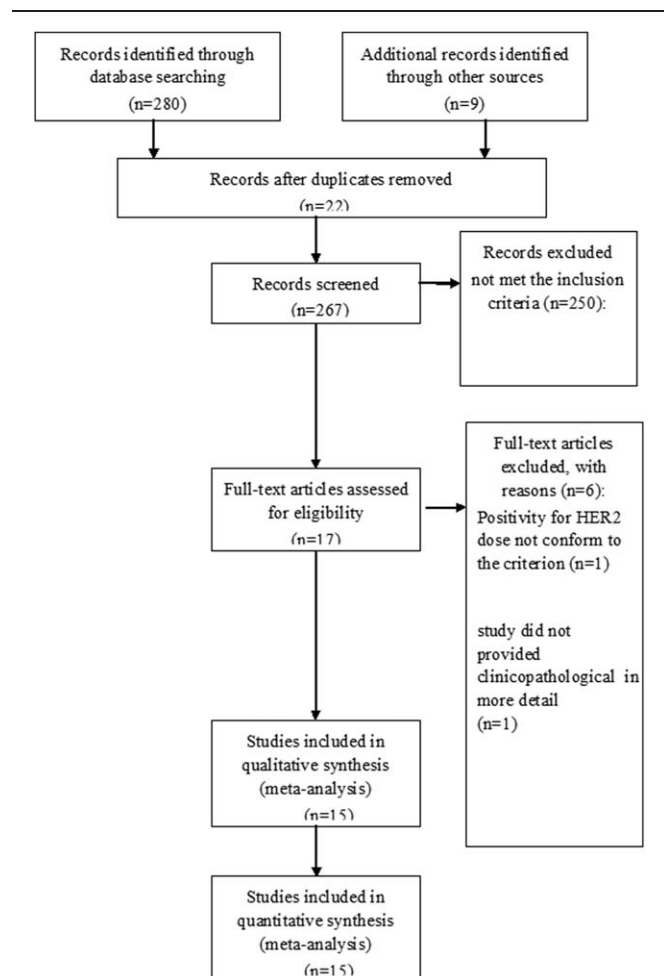
Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

Table 1

The primary characteristics of the eligible studies in more detail.

Refs.	Year	Country	N	Gender (F/M)	Age (median)	HER2%	Method	TNM
Tewari et al[9]	2015	India	70	20/50	52.97	21.4	IHC	I–IV
Kataoka et al[10]	2013	Japan	213	70/143	HER2(+)71.2, HER2(−)66.2	11.7	IHC FISH	DISH IB–IV
He et al[11]	2013	China	197	65/132	62	18.3	IHC FISH	
Tang et al[12]	2014	China	121	36/85	NA	28.1	IHC	II–IV
Zhou et al[13]	2012	China	227	70/157	60	11.89	IHC FISH	I–III
Shen et al[14]	2016	China	1562	386/1176	60	35.08	IHC	I–III
Otsu et al[15]	2015	Japan	360	118/242	63.5	10	IHC	I–IV
Son et al[16]	2014	Korea	139	49/90	HER2(+)60.71, HER2(−)60.16	15.1	IHC	I–III
Qiu et al[17]	2014	China	838	284/554	59	11.2	IHC FISH	I–IV
Ugras et al[18]	2014	Turkey	56	40/16	HER2(+)63, HER2(−)62	50	IHC	I–IV
Uprak et al[19]	2015	Turkey	135	47/88	61	8.1	IHC FISH	I–IV
Chong et al[20]	2106	Brunei	103	37/66	HER2(+)70.6, HER2(−)64.2	13.6	IHC	I–IV
Liu et al[21]	2016	China	678	224/454	59	40.3	IHC	I–IV
Yildiz et al[22]	2016	Turkey	143	46/97	57.3	9.1	IHC	I–IV
Kurokawa et al[23]	2015	Japan	1148	358/790	HER2(+)67.5, HER2(−)67	15.7	IHC	I–IV

DISH = dual-color in situ hybridization, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, NA = not applicable, TNM = tumor node metastasis.
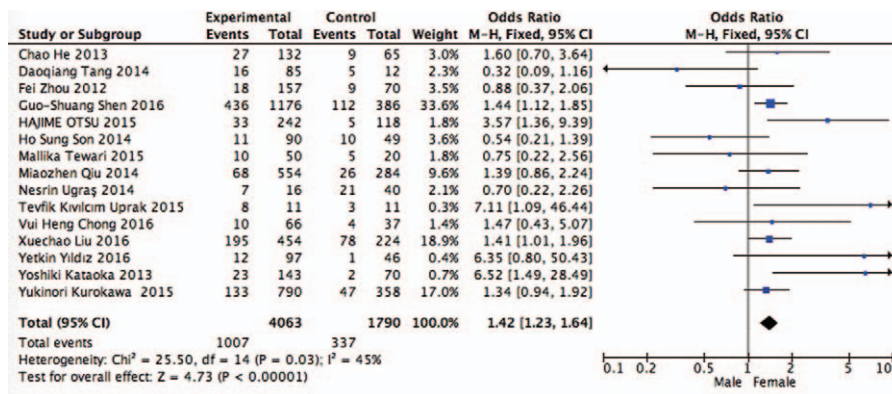

Figure 2. Pooled analysis of OR for the association of HER2 overexpression with the gender.

suggested that there was a higher HER2-positive rate with being male (OR: 1.42; 95% CI: 1.23–1.64, $P < .00001$).

3.2.2. Pooled analysis of OR for the association of HER2 overexpression with the Lauren type. In the analysis of OR for the association of HER2 overexpression with the Lauren type, 10 studies[9–13,19–23] were included, data are shown in Fig. 3. A higher HER2-positive rate was seen in the intestinal type.

3.2.3. Pooled analysis of OR for the association of HER2 overexpression with the Grade. OR for the association of HER2 overexpression with the Grade was available for 9 RCTs[9,11,13–17,20,21] (Fig. 4). The aggregated results suggested that the higher HER2-positive rate was seen in the well/moderately differentiated tumor (OR: 0.31; 95% CI: 0.25–0.38, $P < .0001$).
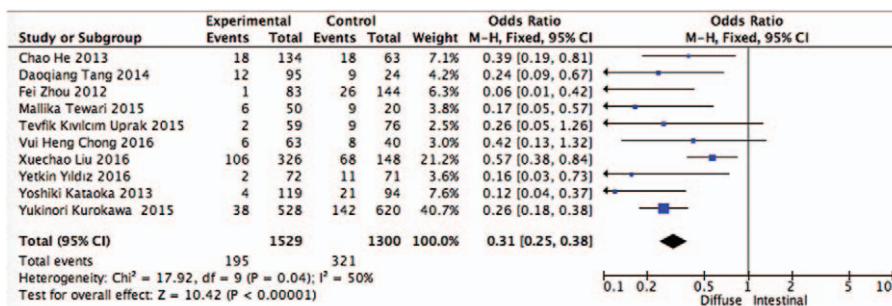

Figure 3. Pooled analysis of OR for the association of HER2 overexpression with the Lauren type.
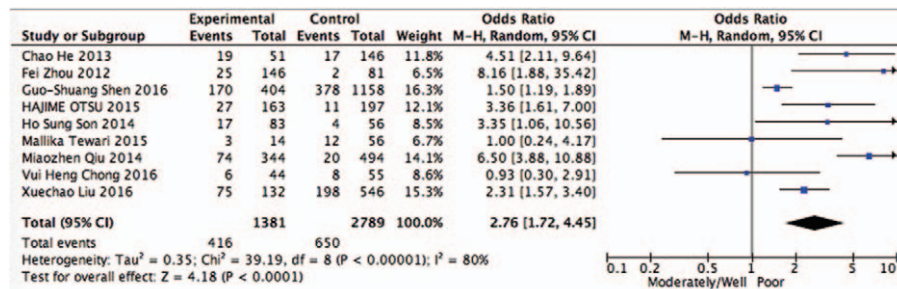
Figure 4. Pooled analysis of OR for the association of HER2 overexpression with the Grade.

4. Discussion

A treatment of patients with advanced gastric cancer remains a most challenging task in the clinical practice. Recent significant advances in understanding the gastric cancer disease process from both biological and genomic perspective have brought target-oriented therapy for advanced gastric cancer into clinical research and practice. HER2 overexpression plays an important role in the proliferation, apoptosis, and angiogenesis of many solid tumors.[24] HER2 gene amplification in gastric cancer would result in tumors having both greater invasive and proliferative capacity.

In the ToGA trial led to the conclusion that trastuzumab should be used to treat patients with Her2/neu overexpression, consisting with the results and analyses before. We wonder more trials are needed to identify at-risk patients for the addition of trastuzumab for advanced gastric cancer.

Considering evidences regarding the ToGA trial, the criteria for HER2/neu overexpression is IHC 3+ or IHC 2+ with amplification, instead of IHC 2+ or 3+ before, which means that clinical heterogeneity among trials should be taken into consideration in the interpretation of our findings.

In our analysis, we define the positivity for HER2 was either IHC3 (+) or IHC2 (+) with DISH (+) according to the ToGA study, we found that there is no relationship was observed between HER2 positivity and depth of tumor invasion, and venous invasion and lymphatic invasion ($P > .05$). However, male, intestinal-type and moderately/well-differentiated gastric cancer cases showed a higher HER2-positive rate than female, diffuse/mixed-type, and poorly differentiated cancer cases. This finding is in keeping with similar data from the ToGA trial and other published studies.

HER2 overexpression appears to be associated with intestinal-type gastric cancer.[25] Intestinal cancer is usually well differenti-ated, but diffuse cancer is poorly differentiated, which means that overexpression/amplification of HER2/neu are correlated with WHO classification and Lauren classification.

Given the fact that the reason why HER2/neu is associated with intestinal cancer did not achieve consensus, while the understanding the mechanisms of molecular differences is increasing. For example, E-cadherin has been reported to be correlated with the processing of the diffuse cancer.

The underlying molecular mechanisms behind the varying HER2 positivity rates in the different histological GC subtypes are clearly complex and require further investigation.

From the above results, it has been suggested that gastric cancer should be divided into subgroups in order to select a more tailored treatment strategy. As clinical surgeons, we should be readily and accurately able to identify which patients are suitable for Herceptin treatment. An accurate and reliable HER2 scoring system, together with clinical information, may help us to better determine whether a gastric cancer patient is a potential candidate for targeted therapy using Herceptin.

Several important limitations of the study should not be ignored. First, the present studies are almost performed in Asian, clinical heterogeneity among trials should be taken into consideration. Second, as this study consider papers published just in recent 5 years, and the range is very narrow, which might have led to potential bias. Prospective randomized trials with more patients around the world are required to be able to comment on this. A better understanding of HER2 expression in gastric adenocarcinoma may improve the staging strategies and influence new treatment modalities.

As our understanding improves and newer targeted therapies become available, future treatment options will provide better outcomes. The final decision for the optimal treatment of a patient with gastric carcinoma can be substantiated by a personalized treatment model.

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