HER2 expression in gastric and oesophageal cancer: a meta-analytic review

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Background: Since the advent and the success of adjuvant medical therapy for human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the form of trastuzumab there has been increasing interest in the development of similar therapies in other solid organ malignancies including gastric cancer and oesophageal cancer. Over the years, multiple observational studies have been inconsistent. Several meta-analyses have been published looking at the association between HER2 and gastric cancer and oesophageal cancer. This review aims to summarize the meta-analytic evidence for the association between HER2 in gastric and oesophageal cancer.

Methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane Library, Google Scholar, Science Direct, and Web of Science.

Results: Of the articles selected, only nine studies met full criteria. Six of them reviewed the role of HER2 in gastric cancer and the remaining three reviewed its role in oesophageal cancer.

Conclusions: The current evidence regarding the role of HER2 is unclear. However, it clearly plays a key role in the pathogenesis of gastric and oesophageal carcinomas. Targeted therapy towards this subgroup (despite variable frequency and association with survival) would offer a mortality benefit and improve survival.

Keywords: Human epidermal growth factor receptor 2 (HER2); gastric cancer; esophageal cancer

Introduction

Recently, several meta-analyses have been published regarding the role of human epidermal growth factor receptor 2 (HER2) oncogene in gastric and oesophageal cancer. HER2 encrypts for a 185 KD transmembrane glycoprotein receptor with intracellular tyrosine kinase activity and is positioned at the long arm of human chromosome 17 (17q12) (1), and was first discovered in breast cancer and has become an important prognostic factor (2,3). Since the advent and the success of adjuvant medical therapy for HER2-positive breast cancer in the form of trastuzumab there has been increasing interest in the development of similar therapies in other solid organ malignancies. It has been assessed in

various other solid organ malignancies including gastric cancer (4), oesophageal cancer (5), colorectal cancer (6-8), osteosarcoma (9), ovarian cancer (10,11), prostate cancer (12), lung cancer (13), pancreatic cancer (14), bladder cancer (15), and uterine cancer (16). In gastric and oesophageal cancer the incidence of HER positive tumours range from 4% to 53% (17) and 9% to 64% (18). However, multiple observational studies have been inconsistent with regards to its correlation with survival. A major breakthrough in targeted therapy in gastric cancer was the ToGA trial (19). This multicentre randomized trial of 594 gastric cancer patients demonstrated an increase of 2.7 months in the median overall survival (OS) with trastuzumab and a recent meta-analysis (20) of randomized control trials suggested
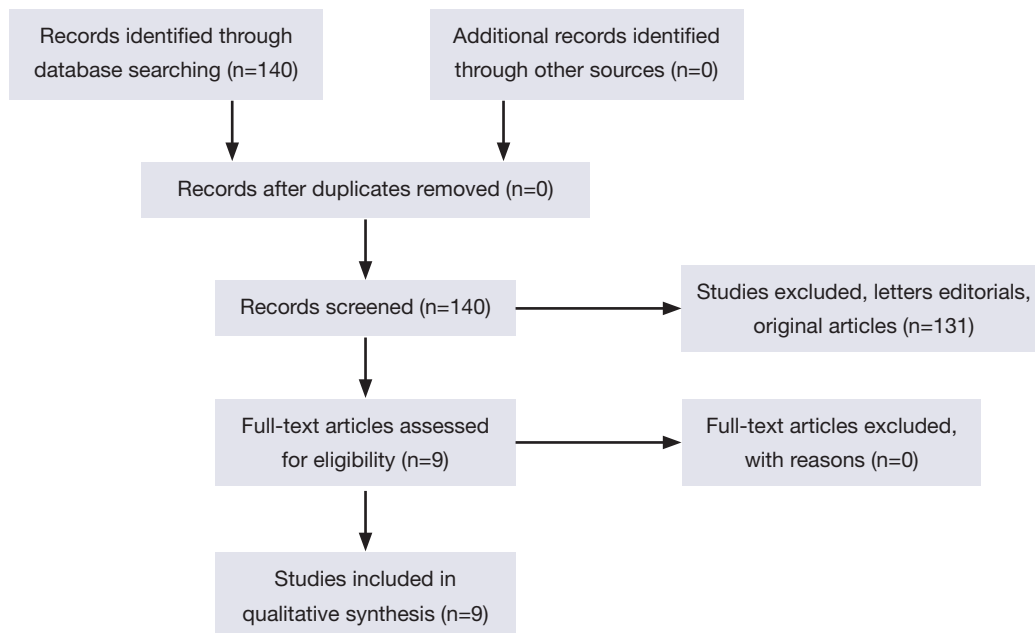
Figure 1 Flow of included studies.

an improvement in overall and progression free survival with the addition of trastuzumab to chemotherapy. The most important issue is that some of the subsequent meta-analyses published produce conflicting results. This review aims to summarize the meta-analytic evidence for the association between HER2 in gastric and oesophageal cancer.

Methods

Search strategy

The search strategy involved the major computer databases, including Medline, PubMed, EMBASE and Current Contents (January 1983 to November 2014). The search methodology involved using combinations of the following keywords: HER2, gastric cancer/carcinoma/adenocarcinoma, stomach cancer, meta-analysis, systematic review, oesophageal cancer/carcinoma/adenocarcinoma/squamous cell carcinoma. Additional manual searches were made using the reference lists from the selected articles to retrieve other papers relevant to the topic. No language restriction was placed on any of the literature searches.

Inclusion criteria

We included studies that met the following inclusion criteria:

❖ Meta-analyses and systematic reviews on the role of HER2 in gastric and oesophageal cancer.

Results

Overall

The original search strategy retrieved 140 citations (*Figure 1*). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only 9 studies (4,5,17,18,21-25) met full criteria for analysis and are summarised in *Table 1*. The years of publication ranged from 2011 to 2014.

HER2 and gastric cancer

There have been six systematic reviews published so far regarding the role of HER2 in gastric cancer (4,17, 21-23,25). Most of the studies were from China (*Table 1*). A recent meta-analysis of eight studies (22) reported that HER2 had significant predictive ability for estimating OS with a hazard ratio (HR: 1.43; 95% CI: 1.09-1.88) and was associated with moderate heterogeneity (I^2=52.90, P=0.038) and no publication bias (P=0.256). Similarly, Wang *et al.* (4) included 4,342 gastric cancer cases which suggested that HER2 was poor prognostic feature with a HR of 1.59 (95% CI: 1.20-2.12) and was associated with moderate

Table 1 Summary of all systematic review/meta-analyses regarding the association between HER2 and gastric cancer oesophageal cancer

Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Jorgensen et al. 2012 (25)	Journal of Cancer	Gastric	Denmark	PubMed from 1986 to August 2011	(I) The number of patients studied should be ≥100 and the HER2 status should have been determined by IHC or ISH such as FISH or CISH; (II) the selected articles should include an analysis of the association between the HER2 status and survival, e.g., OS and/or DFS and/or relevant clinicopathological characteristics such as serosal invasion, vascular invasion, lymph node involvement, distant metastases, disease stage, etc.	English articles only	Systematic review only	Systematic review only	Systematic review only	42	12,749	HER2-postive status was associated with poor survival	Serosal invasion, lymph node metastases, disease stage, or distant metastases	HER2 as a negative prognostics factor in gastric cancer

Table 1 *(continued)*

Table 1 *(continued)*

Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Chen et al. 2013 (22)	Archives of Medical Research	Gastric	China	PUBMED (2007 May 1, 2013), MEDLINE (2007–May 1, 2013) and EMBASE (2007–May 1, 2013), Cochrane Library (no date restriction)	(I) Proven diagnosis of GC in humans; (II) HER2 evaluation using special methods (e.g., PCR, IHC and FISH); and (III) correlation of HER2 with OS	English articles only	STATA 11.0	Egger's test	Fixed effects model	8	2,376	HR 1.43 (95% CI: 1.09-1.88)	Not performed	HER2 have significant predictive ability for estimating OS
Gu et al. 2014 (23)	Tumor Biology	Gastric	China	EMBASE (Jan 2008 to Nov 2013), Medline (Jan 2008 to Nov 2013), PubMed (Jan 2008 to Nov 2013), and Scopus (Jan 2008 to Nov 2013)	(I) patients had a diagnosis of GC; (II) OS and/or RFS were analyzed/ stratified by HER2 status; (III) The HER2 expression was detected by IHC and ISH approaches, with HER2 expression (positivity) defined as IHC score of 3+ or IHC score of 2+ plus HER2 gene amplification as detected by FISH or other ISH methods	English articles only	RevMan 5.2 analysis software (Cochrane Collaboration, Copenhagen, Denmark)	Funnel plot	Random effects model	11	4,569	HR 0.97; (95% CI: 0.84-1.12) univariate analysis, 1.01; (95% CI: 0.75-1.35) multivariate analysis	ORs (95% CIs) for HER2 positivity were 2.31 (95% CI: 1.59-3.36) for male patients, 1.80 (95% CI: 1.38-2.35) for tumor location at upper location or GEJ adenocarcinoma, 5.32 (95% CI: 3.95-7.17) for well/moderately differentiated tumor, and 5.55 (95% CI: 4.01-7.67) for intestinal-type tumor	HER2 expression based on ToGA criteria is not related to the survival in patients with gastric cancer

Table 1 *(continued)*

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Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Liang et al. 2014 (21)	Tumor Biology	Gastric	China	PubMed, Ovid, Web of Science, and Cochrane from 1990 to July 31, 2013	(I) proven diagnosis of gastric cancer; (II) HER2 expression evaluation using special methods such as IHC, FISH or other methods; (III) provided information on clinicopathological results and OS; and (IV) either one of the higher quality or the most recent study was included when two studies were published by the same institution or authors	English articles only	STATA 12.0	Begg's funnel plot and Egger's test	Random effects model	15	5,290	HR, 1.56; 95% CI: 1.05-2.07	Bormann type (OR: 1.76; 95% CI: 1.19-2.59; Z=2.85; P=0.004), tumor differentiation (OR: 3.14; 95% CI: 1.91-5.17; Z=4.49; P= 0.000), Lauren's classification (OR: 6.25; 95% CI: 4.29-9.10; Z=9.54; P=0.000), lymph node metastasis (OR: 1.43; 95% CI: 1.15-1.77; Z=3.23; P=0.001), venous invasion (OR: 1.69; 95% CI: 1.15-2.48; Z=2.67; P=0.008), and lymphovascular invasion (OR: 1.57; 95% CI: 1.21-2.04; Z=3.4; P=0.001)	HER2 overexpression had an unfavourable prognostic role for patients with gastric cancer. HER2-positive expression was associated with Bormann type, Lauren's classification, tumour differentiation, lymph node status, venous invasion, and lymphovascular invasion

Table 1 (*continued*)

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Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Chua et al. 2012 (17)	International Journal of Cancer	Gastric	Australia	MEDLINE and PubMed databases January 1990 to January 2011	HER2 protein expression evaluation in primary gastric cancer tissue (surgical or biopsy specimens) as opposed to serum or metastatic tissue. Metastatic tissues were excluded as there are insufficient data in the literature correlating the overexpression of metastases versus the primary tumor and the potential effects of chemotherapy on augmentation of HER2 expression. HER2 protein expression evaluated by any method, gastric cancer evaluated using conventional histopathological diagnosis, correlation of HER2 protein overexpression with clinicopathologic markers and the association of HER2 protein overexpression on DFS and OS	English articles only	Systematic review only	Systematic review only	Systematic review only	49	11,337	In patients with and without HER2 overexpression, the median 3-year DFS rate was 58% (range, 50-88%) and 86% (range, 62-97%), respectively	Of the 35 studies reporting the impact of HER2 overexpression on survival, 20 studies (57%) reported no difference in OS, two studies (6%) reported significantly longer OS in patients with HER2 overexpression and 13 studies (37%) reported significantly poorer OS in patients with HER2 overexpression. The median OS and 5-year survival rate was 21 (range, 10-57) months and 42%, and 33 (range, 13-80) months and 52% in patients with and without HER2 overexpression, respectively	HER2 overexpression appears to be associated with poorer survival and with intestinal-type gastric cancer in this group of patients for whom majority undergone curative gastrectomy

Table 1 (*continued*)

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Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Wang et al. 2011 (4)	*Asian Pacific Journal of Cancer Prevention*	Gastric	China	MEDLINE, PubMed, EMBASE and Chinese database of National Knowledge Infrastructure (CNKI) and WANFANG DATA search	(I) Patients included had surgery and their disease was identified as gastric cancer by postoperative pathological check; (II) the endpoint investigated was disease specific or OS; (III) the study reported a HR survival rate or data sufficient to estimate the HR; (IV) all publications are limited to using English and Chinese	English and Chinese	STATA 11.0	Egger's and Begg's test	Random effects model	19	4,342	HR, 1.58, 95% CI: 1.20-2.12	Not performed	HER-2/neu over-expression is related to poor prognosis of gastric cancer but has a modest effect on survival in gastric cancer as an independent prognosis factor
Gowryshankar et al. 2014 (5)	*Journal of Gastrointestinal Oncology*	Oesophageal	Australia	MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), PubMed (from 1950), and Current Contents Connect (from 1980) through to 2013	(I) HER2 positivity was measured in subjects with BE; (II) HER2 positivity was measured in subjects with EC; (III) diagnostic method was reported; (IV) prevalence of HER2 in BE or EC was reported	No language restrictions	Comprehensive Meta-analysis (version 2.0)	Egger's test	Random effects model	23	2,319	HR, 1.45; 95% CI: 0.85-2.48	Not performed	HER2+ appears to decrease the survival time of EC patients

Table 1 *(continued)*

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Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Chan et al. 2012 (18)	*Journal of Gastrointestinal Surgery*	Oesophageal	United Kingdom	Medline and Embase (January 1990 to November 2011)	Translational studies comparing OS outcomes in patients with operable oesophageal cancer with and without HER2 overexpression or gene amplification	English articles only	ReviewManager 5.1	Funnel plot	Random effects model	14	1,464	Five-year mortality was significantly higher in HER2-positive patients (OR: 1.43; 95% CI: 1.04-1.95; P=0.03. Analysis related to histological cell type demonstrated significantly higher 5-year mortality in HER2-positive squamous cell carcinoma (OR: 2.88; 95% CI: 1.34-6.17; P=0.006) and adenocarcinoma (OR: 1.91; 95% CI: 1.15-3.17; P=0.01) on sensitivity analysis of higher-quality studies	Not performed	HER2 overexpression and gene amplification in operable oesophageal cancer was an indicator of poor prognosis

Table 1 (*continued*)

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Author	Journal	Cancer	Country	Literature search	Inclusion criteria	Language	Software	Publication bias	Model	Number of studies	Sample size	Correlation of HER2 with survival	Correlation of HER2 with clinicopathological parameters	Conclusions
Chen et al. 2013 (24)	BMC Cancer	Oesophageal	China	PubMed	Criteria used to determine study eligibility were as follows: (I) a prospective or retrospective cohort design with a well-defined study population and justification for all excluded eligible cases; (II) assay of the primary EC specimens; (III) a clear description of methods for specimen handling and testing, including selection and preparation of reagents or kits, as well as visualization techniques; (IV) clear statements on the choice of positive/present and negative/absent controls and on assay validation; (V) statistical analysis using multivariable proportional hazards modeling that adjusted for clinical prognostic factors; and (VI) reporting of the resultant adjusted HRs and their 95% CIs, or provision of data available for statistical estimation of HRs	No language restrictions	STATA SE 11.0 software	Begg's adjusted rank correlation test and by Egger's regression asymmetry test	Random effects model	6	1,162	HER2 expression in adenocarcinoma and had a pooled HR of 2.15 (95% CI: 1.39-3.33) with no evidence of heterogeneity. Two studies assessed HER2 expression in an oesophageal cancer setting with a pooled HR of 0.91 (95% CI: 0.73-1.12)	Not performed	HER2 potential predictor of outcome

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; FISH, fluorescence in situ hybridization; CISH, chromogenic in situ hybridization; DFS, disease-free survival; OS, overall survival; RFS, relapse-free survival; HR, hazard ratio; GEJ, gastroesophageal junction; OR, odds ratio.

heterogeneity (I^2=48.10, P=0.019) and no publication bias (P=0.081). Liang *et al*. (21) suggested that HER2 overexpression was linked with Bormann type (I + II), well differentiated, intestinal type, lymph node metastasis, venous invasion, and lymphovascular invasion. Nevertheless, it had no relationship with depth of invasion, tumour size and stage. On the contrary, HER2 was significantly associated with patients' OS. A recent multicentre study consisting of 1,148 gastric cancer patients who underwent gastrectomy in eleven institutes across Japan found HER2 overexpression to be an important predictive factor in patients with any stage of operable gastric cancer (26).

A robust publication from Gu *et al*. (23) included only publications that classified HER2 expression based on ToGA criteria (27). This study demonstrated that relapse-free survival (RFS) as well as OS was not related to HER2 expression. The heterogeneity among the studies was low to moderate. The pooled odds ratio (OR) for HER2 positivity was linked to being male (OR: 2.31; 95% CI: 1.59-3.36), well/moderately differentiated tumour (OR: 5.32; 95% CI: 3.95-7.17), and for intestinal-type tumour (OR: 5.55; 95% CI: 4.01-7.67). Jørgensen *et al*. (25) published a systematic review with 12,749 patients which suggested HER2 positive tumours were associated with poor survival, serosal invasion, lymph node metastases and distant metastases. Finally, Chua *et al*. (17) published an excellent review of 49 studies. Out of which 35 studies reported the influence of HER2 overexpression on survival. Among these only two studies stated considerably longer OS in patients with HER2 overexpression and 13 studies reported significantly poorer OS in patients with HER2 overexpression.

HER2 and oesophageal cancer

The role of HER2 has also been well investigated in oesophageal cancer. Chan *et al*. (18) reviewed the effect of HER2 expression in surgically resectable oesophageal carcinoma which included 1,464 patients. The 5-year mortality rate was considerably greater in HER2-positive patients with an OR of 1.43 (95% CI: 1.04-1.95). However, there was significant heterogeneity among the studies and publication bias was evident. The effect of HER2 positivity was greater in squamous cell carcinoma (OR: 2.88; 95% CI: 1.34-6.17; I^2=0.00; P=0.52) compared to adenocarcinoma (OR: 1.91; 95% CI: 1.15-3.17; I^2=78.00; P=0.001) with respect to 5-year mortality. A recent meta-analysis of 2,319 oesophageal cancer patients of all stages demonstrated that HER2 positive tumours

survived 7 months less than HER2 negative tumours (5), however, this was not statistically significant.

Discussion

Gastric and oesophageal cancers result in 700,000 and 386,000 deaths every year respectively (28). HER2 plays an important role in the aggressiveness and progression of gastric (21,29) and oesophageal cancer (18). The overall direction of the meta-analyses for gastric cancer (4,17,21-23) suggests HER2 as a poor prognostic factor and is associated with poor OS. However, Gu *et al*. (23) published that RFS and OS were not related to HER2 expression. Gu *et al*. (23) included only publications that classified HER2 expression based on ToGA criteria making the analysis robust (27). As per Hofmann *et al*. (27) the definition for HER2 positivity was reclassified from IHC 2+ or 3+ or amplification in FISH to IHC 3+ or IHC 2+ and hence the conclusion from Gu *et al*. (23) were significantly different from the other meta-analyses. HER2 positive tumours are more likely to be well differentiated, intestinal-type, with lymphovascular invasion and more common in men. As far as oesophageal cancer is concerned (5,18), HER2 positive tumours have negative impact on survival and have a higher 5-year mortality rate.

Strengths and limitations

Gu *et al*. (23) searched the multiple databases including PubMed, EMBASE, Scopus, Medline between the dates Jan 2008 to Nov 2013 only, a significant drawback of the meta-analysis. Similarly, Chen *et al*. (22) searched only from 2007-May 1, 2013. Chen *et al*. (24), Chua *et al*. (17), and Chan *et al*. (18) explored only one or two databases for studies. The search strategy could explain the variability in the number of studies included among the meta-analyses and the inconsistency of the ORs for the various outcomes and heterogeneity among the meta-analyses. Gu *et al*. (23) did not describe a search strategy was and manual searches were not stated openly. Publication language in these meta-analyses was restricted to English only which introduces a language bias (17,21-23,25).

A strict inclusion/exclusion criterion was lacking in Gu *et al*. (23). The publication bias in these meta-analyses (18,23) was assessed by visual examination of the funnel plot which was unsuitable as the number of studies were less than ten and this was acknowledged only by Chan *et al*. (18). Inverse variance (IV) random-effects model was utilized in this meta-analysis which does not consider

both within- and between-study variations (23) and Chen *et al.* (22) used fixed effects model. The authors suggest that the DerSimonian and Laird random-effects model (30) should be utilised to obtain a more accurate estimate and the confidence interval. Lastly, only three meta-analyses (17,21,23) performed stratified analysis according to the clinicopathological parameters of tumours this could be due to insufficient information acquired from the included studies.

Conclusions

It is essential for a good meta-analysis to have a through database search (preferably multiple) and avoid language bias. With the available data the authors suggest that future prospective studies should use ToGA criteria (27) to assess the HER2 status and large studies are the need of the hour to confirm the evidence. HER2 status clearly plays a key role in the pathogenesis of gastric and oesophageal carcinomas. Targeted therapy towards this subgroup (despite variable frequency and association with survival) would offer a mortality benefit and improve survival.

Acknowledgements

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