Systematic Review/Meta-Analysis

Comparative effectiveness and tolerability of targeted agents combined with chemotherapy in patients with HER2-positive gastroesophageal cancer: A network meta-analysis

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Abstract

Background: Gastric cancer (GC) or gastroesophageal junction (GEJ) cancer with HER2 overexpression is highly invasive, with a poor prognosis. With the development of new targeted agents, which agents have ideal therapeutic effects must be determined. This network meta-analysis analyzed the effectiveness and tolerability of targeted agents combined with chemotherapy in HER2-positive GC/GEJ cancer.

Methods: Public databases were searched from the date of inception to October 22, 2020. Randomized controlled trials (RCTs) on targeted agent-related regimens for HER2-positive advanced GC or GEJ cancer were included. Subgroup analyses based on publication language, first-line treatment, second/third-line treatment, and HER2 staining intensity were performed.

Results: In total, 13 articles were included. The trastuzumabderuxtecan (TraD) and pertuzumab plus trastuzumab and chemotherapy (PerTraChemo) regimens were considered to have high effectiveness but low tolerability. In the subgroup analysis, PerTraChemo still had high effectiveness with low tolerability as the first-line therapy. As the second- or third-line therapy, TraD and lapatinib plus chemotherapy (LapChemo) had high effectiveness and moderate tolerability. In terms of overall survival (OS) time, PerTraChemo had a relative advantage in the immunohistochemistry (IHC) 2+/*in situ* hybridization (ISH)+ population, whereas TraD, PerTraChemo, and trastuzumab plus chemotherapy (TraChemo) had a relative advantage in the IHC3+ population.

Conclusion: TraD had relative advantages as the second- or third-line therapy and in the IHC3 + population. PerTraChemo is a potential first-line therapy, but it requires further confirmation because the JACOB phase III clinical trial failed to confirm the superiority of PerTraChemo over TraChemo with regard to OS.

Keywords: Gastric cancer, gastroesophageal junction cancer, HER2, meta-analysis

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer type and the third leading cause of cancer-related death worldwide.[1] The risk factors include *Helicobacter pylori* (HP) infection, age, a high-salt diet, and a diet low in vegetables and fruits.[2] It is an important public health problem

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worldwide because of its wide geographical distribution, aggressive behavior, high incidence and mortality rates.[3,4] However, with the improvement of living habits and active eradication of HP infection, the incidence of GC has decreased steadily.[5] With the promotion of endoscopic screening, the incidence seems to have increased, but GC-related mortality has greatly decreased.[6] In addition, the management of gastroesophageal junction (GEJ) cancer generally follows the guidelines for GC management.[7]

Human epidermal growth factor receptor 2 (HER2) is a growth-promoting protein that is widely recognized for its tumorigenic potential.[8] Overexpression of HER2 plays an important role in the development of GC.[9] Approximately 20% of gastroesophageal cancer (GOC) patients show HER2 amplification.[10] HER2-positive GOC is an important molecular subclass because of its stronger invasiveness and poorer prognosis compared to that of other subclasses.[11] HER2 inhibitors are considered important therapeutic agents for HER2-overexpressing GOC. However, HER2 inhibition has not achieved the same success in GC treatment as it has in breast cancer treatment.[12] Trastuzumab (Tra) is still the only approved HER2 inhibitor for GOC.[13] Trastuzumabderuxtecan (TraD) has the potential to be the next promising drug.[9]

A previous meta-analysis showed that second-line treatment with Tra in patients who progressed after first-line Tra-based treatment could prolong the progression-free survival (PFS) period without bringing more safety issues but could not prolong the overall survival (OS) period or improve the objective response rate (ORR). However, only cohort studies and a small sample randomized controlled trial (RCT) were included in this meta-analysis.[14] Therefore, whether Tra should be continuously used in second-line therapy for GOC patients still needs to be further studied. With the development of new target agents for HER2-positive GOC patients, there are still questions that need to be answered. For example, the effect of Tra in second- and third-line treatment of HER2-positive patients is still unclear, and whether other new targeted agents have better potential therapeutic effects also needs to be explored. Therefore, this work further analyzes the effectiveness and tolerability of targeted agents combined with chemotherapy in HER2-positive GOC by network meta-analysis.

METHODS

Search strategy

We performed a systematic review and network of randomized controlled trials according to PRISMA guidelines. The study protocol was approved by the Medical Ethics Committee of the study center and PROSPERO (CRD42021254305). We performed searches in public databases, namely PubMed, EmBase, Cochrane Central Register of Controlled Trials, Scopus, EBSCO host (including CINAHL), and MD Clinical Key, from the date of their inception to October 22, 2020, with no language restrictions. We used the following search terms: "HER2," "human epidermal growth factor receptor 2," "advanced," "late stage," "metastatic," "metastases," "unresectable," "gastric," "stomach," "gastroesophag*," "gastrooesophag*," "malignant," "neoplasms," "cancer," "tumor," "carcinoma," "adenocarcinoma," "squamous," "random*," "randomized," and "randomized". The electronic database searches were supplemented with a manual search for published and unpublished trials. Reference lists of the included studies and previous reviews were also screened to avoid omission.

Selection criteria

We included RCTs about HER2-positive advanced GC or GEJ cancer. The intervention arm was a target agent-related regimen, and control was another target agent-related regimen or chemotherapy alone. Studies reported the PFS and/or OS outcomes. The exclusion criteria included studies that did not include HER2-positive populations or did not report HER2+ populations as subgroup analysis results and repeated reports or posthoc studies. Two authors performed a search process independently.

Data extraction and outcomes

The extraction data included first author, publication year, research location, treatment stage, sample size, age of patients, trial abbreviation, register number, HER2 detection, intervention, control regimen, and follow-up period. The primary outcomes were PFS and OS based on Cox regression models. The second outcomes were ORR and serious adverse events (SAEs of grade ≥3) based on frequency event results. We assessed studies' risk of design bias in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[15] Then, we further assessed the certainty of evidence contributing to network estimates of the outcomes with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.[16]

Statistical analysis

We used hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PFS and OS results that were based on the Cox regression model and odds ratios (ORs) with 95% CIs for ORR and SAE outcomes. Effect sizes were synthesized using a frequentist framework random-effect

network meta-analysis.[17] We used loop-specific methods and design-by-treatment models to evaluate local and global inconsistency. Statistical heterogeneity in the entire network was estimated by common τ^2.[18] To rank the treatment for each outcome, we used the surface under the cumulative ranking curve (SUCRA), and the interventions and results were hierarchically clustered by k-means methods.[19] Comparison-adjusted funnel plots were used to assess the potential small-study effects. We performed subgroup analysis to assess nongray published English articles, first-line treatment, second/third-line treatment, and HER2-positive intensities based on immunohistochemistry (IHC)/*in situ* hybridization (ISH) detection. Stata software (version 14.0), the netmeta package of the R program (version 4.0.1), and RevMan (version 5.3) were used in all analyses.

RESULTS

Literature search

The study selection process is shown in Figure 1. A total of 1773 items were retrieved from the database search, and 1339 remained after removing duplications. After screening the titles and abstracts, 190 items remained. After full-text screening, the following articles were excluded: studies on HER2-negative patients (59 items), repeated or posthoc studies (38 items), reviews (30 items), protocols (20 items), studies without HER2-positive subgroup analysis (13 items), studies without randomization design (9 items), studies not reporting survival primary results (6 items), comments (1 item), and studies not related to advanced GC or GEJ cancer patients (1 item). Finally, 13 articles were included in the meta-analysis[20-32] [Figure 1].

Among the included studies, the publication time was from 2010 to 2020. Some of the studies were multicenter studies; there were also studies focusing on the populations of Japan, Korea, China, and the US [Table 1]. There were four gray articles, namely one Chinese-language study[23] and three conference reports.[26,28,29] The targeted agents included pertuzumab (Per), Tra, TraD (DS-8201a), trastuzumabemtansine (TraE, T-DM1), lapatinib (Lap), and MM-111 (MM111). There was also a study comparing the high-dose trastuzumab (HTra) regimen and the standard-of-care Tra regimen. Seven studies involved first-line treatments,[22,23,25-27,29,32] and the rest involved second- or third-line treatments. In terms of research quality, three studies applied blinding methods to prevent deviations caused by subjective factors,[22,27,29] and one gray study did not use a suitable random sequence generation method.[23] In addition, although 92.3% of the studies carried out complete protocol design and registration, selective reporting bias still existed. However, in terms of the primary survival outcome, the design quality of the included studies was acceptable [Figure 2].

The intervention methods in the network meta-analysis of PFS included chemotherapy alone (Chemo), HTraChemo, Lap, LapChemo, MM111TraChemo, PerTraChemo, TraChemo, TraD, and TraE [Figure 3a]. In pairwise comparisons, compared to Chemo, LapChemo (HR: 1.08; 95%CI: 1.01, 1.16), PerTraChemo (HR: 1.29; 95%CI: 1.17,1.42), TraChemo (HR: 1.13; 95%CI: 1.05, 1.20), and TraD (HR: 1.39; 95%CI: 1.16, 1.66) had significant advantages in terms of prolonging the PFS period. In addition, TraChemo was better than MM111TraChemo (HR: 1.37; 95%CI: 1.07, 1.76) but worse than PerTraChemo (HR: 0.87; 95%CI: 0.81, 0.94) [Table 2]. When the interventions were ranked based on the surface under the cumulative ranking curve (SUCRA) method, TraD (96.4%) and PerTraChemo (90.2%) ranked higher than the others.

Chemo, HTraChemo, Lap, LapChemo, MM111TraChemo, PerTraChemo, TraChemo, TraD, and TraE were included in the analysis of OS [Figure 3b]. In pairwise comparisons, PerTraChemo (HR: 1.19; 95%CI: 1.07, 1.33), TraChemo (HR: 1.10; 95%CI: 1.02, 1.20), and TraD (HR: 1.26; 95%CI: 1.05, 1.50) led to better OS than Chemo. TraChemo led to significantly better OS than MM111TraChemo (HR: 1.39; 95%CI: 1.00, 1.92) but worse OS than PerTraChemo (HR: 0.92; 95%CI: 0.86, 1.00) [Table 2]. The ranking results showed that TraD (91.0%) and PerTraChemo (86.5%) had high rankings.

Chemo, HTraChemo, Lap, LapChemo, PerTraChemo, TraChemo, TraD, and TraE were included in the assessment of the ORR results as the secondary outcome [Figure 3c]. In pairwise comparisons, LapChemo (OR: 0.45; 95%CI: 0.29, 0.70), PerTraChemo (OR: 0.41; 95%CI: 0.22, 0.74), TraChemo (OR: 0.62; 95%CI: 0.40, 0.96), and TraD (OR: 0.16; 95%CI: 0.06, 0.40) had significantly higher ORRs than Chemo [Table 2]. TraD (97.7%) and PerTraChemo (75.2%) had relative advantages over the other regimens.

Chemo, HTraChemo, Lap, LapChemo, MM111TraChemo, PerTraChemo, TraChemo, TraD, and TraE were included in the assessment of SAEs [Figure 3d]. In pairwise comparisons, no significant difference was found and the quality of evidence for most results was low due to inaccuracy [Table 2]. In the ranking results, TraE (86.6%) and Chemo (80.4%) had relative advantages over the

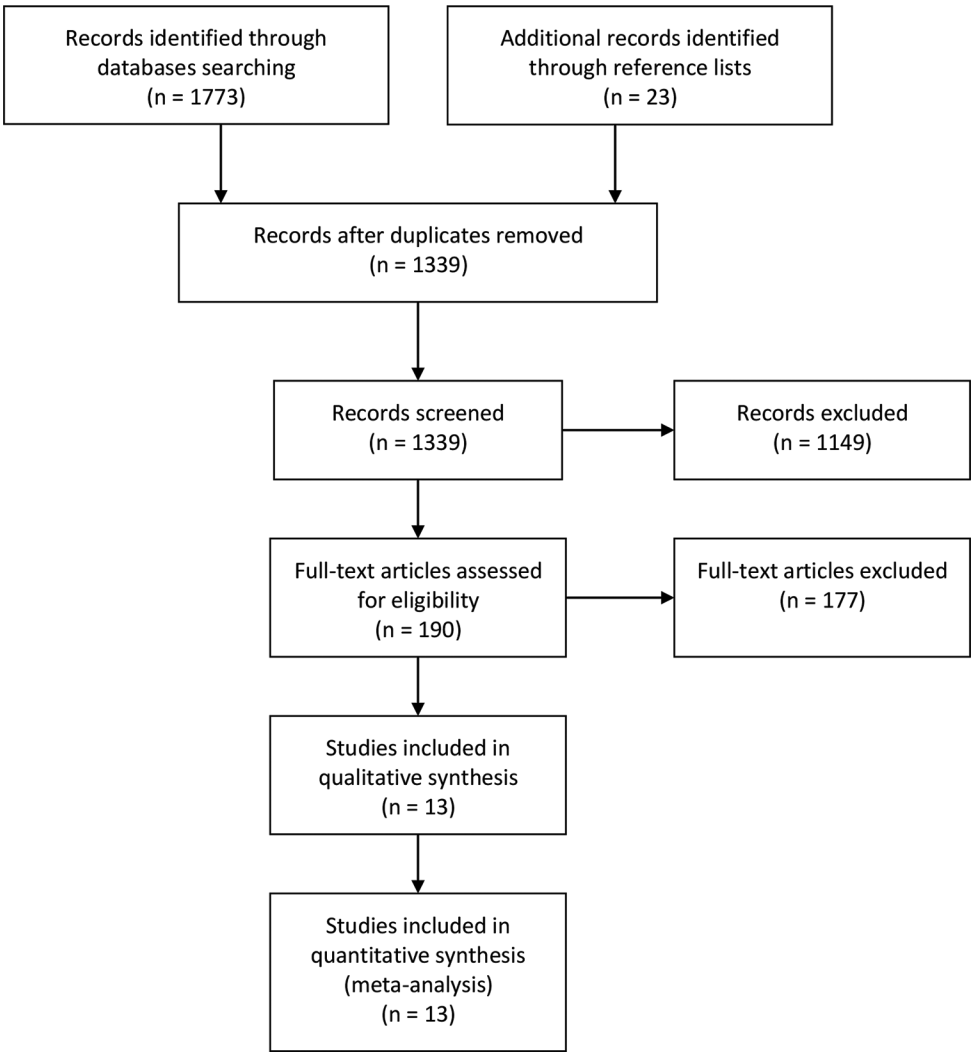

Figure 1: Flow chart illustrating the selection process in the study.

other regimens. No obvious statistical heterogeneity, inconsistency, or funnel plot asymmetry was found in the aforementioned network meta-analysis.

K-means cluster analysis was performed on the SUCRA results of the four above-mentioned analyses. The results showed that TraD and PerTraChemo exhibited high effectiveness but low tolerance. HTraChemo, TraChemo, and LapChemo had moderate effectiveness and safety. However, Lap, TraE, and Chemo had low effectiveness but high tolerability. MM111 TraChemo had low effectiveness and safety [Figure 4a].

The analysis focused on peer-reviewed published articles and excluded gray articles, such as non-English articles and conference abstracts. A total of eight intervention methods were included in the analysis, and the results showed that TraD and PerTraChemo still had relatively high effectiveness but low tolerability, even in a large dataset. Lap, Chemo, and TraE had relatively low effectiveness but high tolerability. LapChemo, HTraChemo, and TraChemo had moderate effectiveness and tolerability [Figure 4b]. Subgroup analyses were also performed according to the treatment line. In the first-line treatment results, only PerTraChemo had high effectiveness but low tolerability. TraChemo, HTraChemo, and LapChemo had moderate effectiveness and safety. The Chemo treatment had low effectiveness and relatively high tolerability [Figure 4c]. In second- and third-line treatments, TraD and LapChemo had relatively high effectiveness and moderate tolerability, while Lap and TraChemo had relatively moderate effectiveness and tolerability. Chemo and TraE had moderate effectiveness and high tolerability [Figure 4d].

Finally, the samples from the OS analysis were classified by HER2 IHC status and analyzed. In the IHC2+/ISH+ population, the interventions included Chemo, LapChemo, PerTraChemo, TraChemo, TraD, and

Table 1: The characteristics of the included studies

Author	Location	Treatment stage	Sample size	Age[#]	Trial Abbr.	Register No.	HER2 detection	Intervention[¶]	Control[¶]	Follow-up
K. Shitara 2020[20]	Japan/ Korea	Third-Line	187	65 (28-82)	DESTINY-Gastric01	NCT03329690	IHC 3+ or IHC 2+/ISH+	TrastuzumabDeruxtecan (TraD)	Irintecan/Paclitaxel (Chemo)	5 years
Akitaka Makiyama 2020[21]	Japan	Second-line	91	67 (33-89)	WJOG7112G/ T-ACT	UMIN000009297	IHC 3+ or IHC 2+/ISH+	Trastuzumab; Ppaclitaxel (TraChemo)	Paclitaxel (Chemo)	54 months
JosepTabernero 2018[22]	Multicenter	First-line	780	61 (54-69)§	JACOB	NCT01774786	IHC 3+or IHC 2+/ISH+	Pertuzumab; Trastuzumab; Cisplatin; Capecitabine/5-fluorouracil (PerTraChemo)	Placebo; Trastuzumab; Cisplatin; Capecitabine/5-fluorouracil (TraChemo)	42 months
Yongli Xin 2017[23]	China	First-line	30	45 (18-68)	NA	NA	IHC 1+to 3+	Lapatinib; Paclitaxel (LapChemo)	Paclitaxel (Chemo)	3 years
PC Thuss-Patience 2017[24]	Multicenter	Second-line	345	62 (19-80)	GATSBY	NCT01641939	IHC 3+or IHC 2+/ISH+	TrastuzumabEmtansine (TraE)	Docetaxel/Paclitaxel (Chemo)	33 months
MA. Shah 2017[25]	Multicenter	First-line	248	62 (26-83)	HELOISE	NCT01450696	IHC 3+or IHC 2+/ISH+	High-dose Trastuzumab; cisplatin; capecitabine (HTraChemo)	Standard of Care Trastuzumab; Cisplatin; Capecitabine (TraChemo)	32 months
PETRARCA-AIO 2017[26]	Multicenter	First-line	81	60 (NA)	PETRARCA-AIO	NCT02581462	IHC 2+/3+and ISH+	Trastuzumab; Pertuzumab; Docetaxel; Oxaliplatin; Leucovorin; 5- fluoruracil (PerTraChemo)	Docetaxel; Oxaliplatin; Leucovorin; 5-fluoruracil (Chemo)	2 years
JR. Hecht 2015[27]	Multicenter	First-line	545	61 (19-86)	TRIO-013/LOGiC	NCT00680901	IHC 3+or ISH+	Lapatinib; Capecitabine; Oxaliplatin (LapChemo)	Capecitabine; Oxaliplatin (Chemo)	48 months
CS. Denlinger 2017[28]	US	Second-line	84	63 (31-81)	NA	NCT01774851	HER2 Gene Amplification	MM-111; Trastuzumab; Paclitaxel (MM111TraChemo)	Trastuzumab; Paclitaxel (TraChemo)	56 weeks
MH. Moehler 2016[29]	Multicenter	First-line	28	NA	EORTC 40071	NCT01123473	IHC 2/3+or EGFR1 ISH+	Lapatinib; Epirubicin; Cisplatin; 5-fluoruracil/Capecitabine (LapChemo)	Placebo; Epirubicin; Cisplatin; 5-fluoruracil/ Capecitabine (Chemo)	2 years
S. Lorenzen 2015[30]	Multicenter	Second-Line	37	56 (44-75)	AIO	NCT01145404	IHC3+or 2+	Lapatinib; Capecitabine (LapChemo)	Lapatinib (Lap)	18 months
T. Satoh 2014[31]	Japan	Second-line	261	61 (22-80)	TyTAN	NCT00486954	ISH+	Lapatinib; Paclitaxel (LapChemo)	Paclitaxel (Chemo)	45 months
YJ. Bang 2010[32]	Multicenter	First-line	594	59±11	ToGA	NCT01041404	IHC 3+or ISH+	Trastuzumab; Cisplatin; Capecitabine/5-fluoruracil (TraChemo)	Cisplatin; Capecitabine /5-fluoruracil (Chemo)	36 months

EGFR1: Epidermal growth factor receptor 1; IHC: immunohistochemistry; ISH: *in situ* hybridization; NA: Not available. [#]Age was present as Median (minimum-maximum) or Mean±Standard Deviation. [§]Median (interquartile range). [¶]Targeted agents and cytotoxic drug used in treatment, and the abbreviations list in brackets for meta-analysis

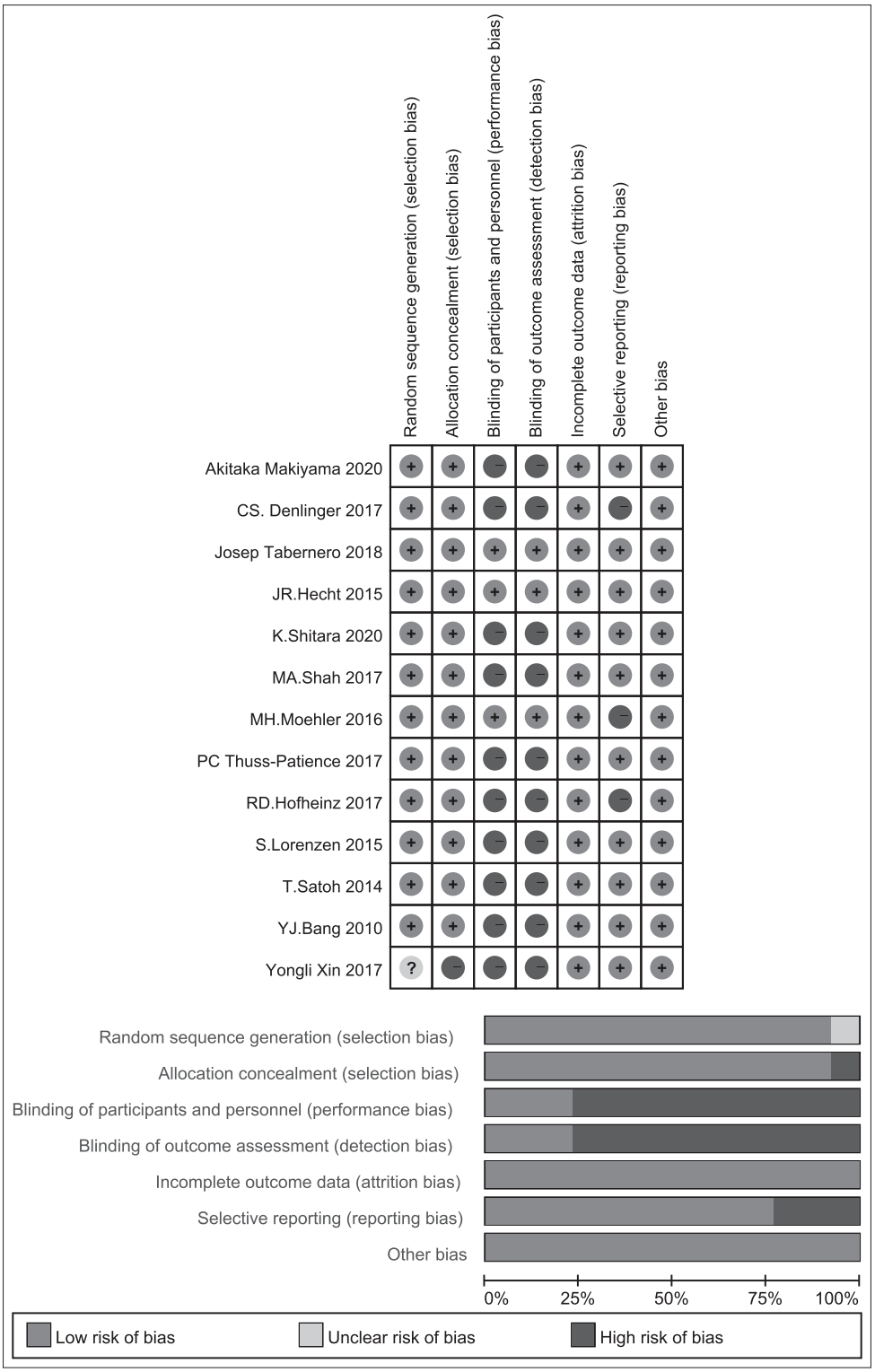

Figure 2: Risk of bias graph for each included study.

TraE. PerTraChemo (92.0%), TraChemo (68.5%), and LapChemo (63.8%) had relative advantages in terms of prolonging the OS period. In the IHC3 + population, the same interventions were included. The ranking results showed that TraD (80.9%), PerTraChemo (78.4%), and TraChemo (65.0%) had relative advantages over the other regimens.

DISCUSSION

This study analyzed the efficacy and tolerability of chemotherapy and targeted agent treatment for GC or GEJ cancer patients with HER2 overexpression or amplification by network meta-analysis. The TraD and PerTraChemo

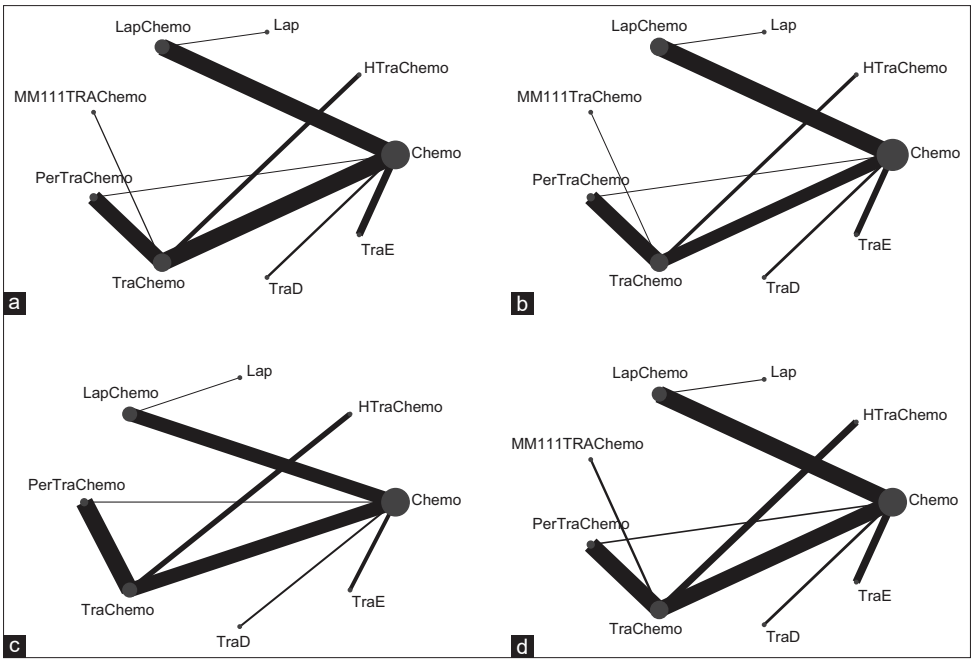

Figure 3: Network comparisons for the strategies included in the analyses. (a): Progression-free survival; (b): overall survival; (c): objective response rate; (d): serious adverse event.

regimens are considered to have high effectiveness but low tolerability. In the subgroup analysis, PerTraChemo had high effectiveness and low tolerability, and TraChemo and LapChemo were considered alternative regimens with moderate effectiveness and tolerability for first-line therapy. In second- and third-line therapy, TraD and LapChemo had high effectiveness and moderate tolerability. Finally, when patients were stratified according to the intensity of HER2 expression, PerTraChemo had a relative advantage in the IHC2+/ISH+ population and TraD, PerTraChemo, and TraChemo had a relative advantage in terms of OS in the IHC3+ population.

HER2 is a transmembrane protein and has tyrosine kinase activity after activation of intracellular region proteins. Thus, it can activate multiple signaling pathways to inhibit cancer cell apoptosis, promote cancer cell growth and metastasis, and promote neovascularization.[33] For GC cells, HER2 overexpression is involved in cancer proliferation and invasion through the Ras/MAPK and PI3K/Akt/PKB pathways.[34] Therefore, HER2 overexpression is considered a prognostic biomarker for GC patients and often predicts a poor prognosis.[35,36] At present, Tra is the only approved agent for the treatment of HER2-positive GC patients. Tra is a HER2 monoclonal antibody that acts on the extracellular region of HER2 to inhibit the activation of HER2 and downstream pathways and to inhibit tumor growth and invasion. However, among the regimens included in this analysis, TraChemo only had moderate effectiveness and safety as the first-line treatment. Increasing the Tra dose (HTraChemo) did not improve its effectiveness. The TraD and PerTraChemo regimens based on Tra showed were markedly more effective, but they resulted in more serious side effects.

With regard to Tra, the phase 3 ToGA study demonstrated the advantages of TraChemo over Chemo as the first-line treatment with regard to the OS (median: 13.8 months vs. 11.1 months) (HR: 0.74; 95%CI: 0.60–0.90; $P = 0.0046$).[32] However, increasing the Tra dose when it was used as a first-line treatment did not improve the effectiveness; indeed, higher-dose Tra resulted in a shorter OS duration than the standard-of-care (median: 10.6 months vs. 12.5 months).[26] After treatment failure with Tra plus fluoropyrimidine and platinum, Tra plus paclitaxel as a second-line treatment did not significantly prolong the OS time (median: 10 months vs. 10 months) or PFS time (median: 3.7 months vs. 3.2 months) compared to paclitaxel.[21] TraD is a conjugate of Tra and the cytotoxic topoisomerase I inhibitor deruxtecan that can inhibit HER2 protein activation and bring cytotoxic drugs directly to HER2-overexpressing cancer cells.[37,38] TraD has been approved for the treatment of HER2-positive breast cancer.[39,40] In the DESTINY-Gastric01 study, TraD yielded a superior ORR than Chemo (51% vs. 14%). TraD also resulted in a higher OS rate (80% vs. 66% at 6 months and 52% vs. 29% at 12 months) and a higher PFS rate (43% vs. 21% at 6 months and 30% vs. 0% at 12 months) than Chemo. However, the side effects of interstitial lung disease and pneumonitis need attention.[20] In this study, it was also

Table 2: Results for the treatment strategies according to their relative effect and the data reliability/quality

Outcomes	Comparisons	No. of studies	Direct Comparisons		Indirect Comparisons		Network Comparisons	
			HR/OR (95%CIs)	Quality	HR/OR (95%CIs)	Quality	HR/OR (95%CIs)	Quality
PFS	Chemo vs.							
	LapChemo	3	**1.08 (1.01, 1.16)**	H			**1.08 (1.01, 1.16)**	H
	PerTraChemo	1	1.27 (0.94, 1.73)	M†	**1.29 (1.17, 1.43)**	H	**1.29 (1.17,1.42)**	M#
	TraChemo	2	**1.13 (1.05, 1.21)**	H	1.11 (0.81, 1.52)	M†	**1.13 (1.05,1.20)**	M#
	TraD	1	**1.39 (1.16, 1.66)**	H			**1.39 (1.16,1.66)**	H
	TraE	1	0.95 (0.86, 1.05)	M†			0.95 (0.86,1.05)	M†
	HTraChemo vs.							
	TraChemo	1	1.02 (0.89, 1.16)	M†			1.02 (0.89,1.16)	M†
	Lap vs.							
	LapChemo	1	1.33 (0.99, 1.79)	M†			1.33 (0.99,1.79)	M†
	MM111TraChemo							
	TraChemo	1	**1.37 (1.07, 1.76)**	H			**1.37 (1.07,1.76)**	H
	PerTraChemo vs.							
	TraChemo	1	**0.87 (0.81, 0.94)**	H	0.89 (0.65, 1.21)	M†	**0.87 (0.81,0.94)**	M#
OS	Chemo vs.							
	LapChemo	4	1.06 (0.99, 1.14)	M*			1.06 (0.99,1.14)	M*
	PerTraChemo	1	1.29 (0.85, 1.96)	M†	**1.19 (1.06, 1.33)**	H	**1.19 (1.07,1.33)**	M#
	TraChemo	2	**1.10 (1.01, 1.20)**	H	1.19 (0.78, 1.83)	M†	**1.10 (1.02,1.20)**	M#
	TraD	1	**1.26 (1.05, 1.50)**	H			**1.26 (1.05,1.50)**	H
	TraE	1	0.94 (0.83, 1.06)	M†			0.94 (0.83,1.06)	M†
	HTraChemo vs.							
	TraChemo	1	1.10 (0.94, 1.29)	M†			1.10 (0.94,1.29)	M†
	Lap vs.							
	LapChemo	1	1.03 (0.63, 1.68)	M†			1.03 (0.63,1.68)	M†
	MM111TraChemo vs.							
	TraChemo	1	**1.39 (1.00, 1.92)**	H			**1.39 (1.00,1.92)**	H
	PerTraChemo vs.							
	TraChemo	1	**0.93 (0.86, 1.00)**	H	0.85 (0.56, 1.31)	M†	**0.92 (0.86,1.00)**	M#
ORR	Chemo vs.							
	LapChemo	3	**0.45 (0.29, 0.70)**	H			**0.45 (0.29,0.70)**	H
	PerTraChemo	1	**0.26 (0.08, 0.87)**	H	**0.47 (0.23, 0.94)**	H	**0.41 (0.22,0.74)**	H
	TraChemo	2	0.66 (0.41, 1.06)	M†	0.36 (0.10, 1.35)	M†	**0.62 (0.40,0.96)**	M#
	TraD	1	**0.16 (0.06, 0.40)**	H			**0.16 (0.06,0.40)**	H
	TraE	1	0.94 (0.45, 1.95)	M†			**0.94 (0.45,1.95)**	M†
	HTraChemo vs.							
	TraChemo	1	0.92 (0.48, 1.78)	M†			0.92 (0.48,1.78)	M†
	Lap vs.							
	LapChemo	1	0.17 (0.01, 3.89)	L‡			0.17 (0.01,3.89)	L‡
	PerTraChemo vs.							
	TraChemo	1	1.41 (0.85, 2.34)	M†	2.56 (0.70, 9.41)	L‡	1.52 (0.95,2.44)	M†
SAE	Chemo vs.							
	LapChemo	3	0.48 (0.18, 1.28)	L*†			0.48 (0.18,1.28)	L*†
	PerTraChemo	1	0.23 (0.04, 1.40)	M†	0.32 (0.04, 2.27)	M†	0.26 (0.07,1.01)	M†
	TraChemo	2	0.47 (0.14, 1.63)	M†	0.33 (0.03, 3.60)	L‡	0.44 (0.14,1.31)	M†
	TraD	1	0.19 (0.03, 1.01)	M†			0.19 (0.03,1.01)	M†
	TraE	1	1.59 (0.33, 7.58)	L‡			1.59 (0.33,7.58)	L‡
	HTraChemo vs.							
	TraChemo	1	1.06 (0.22, 5.08)	L‡			1.06 (0.22,5.08)	L‡
	Lap vs.							
	LapChemo	1	0.89 (0.12, 6.38)	L‡			0.89 (0.12,6.38)	L‡
	MM111TraChemo vs.							
	TraChemo	1	1.34 (0.24, 7.51)	L‡			1.34 (0.24,7.51)	L‡
	PerTraChemo vs.							
	TraChemo	1	1.48 (0.32, 6.77)	L‡	2.08 (0.23, 18.99)	L‡	1.65 (0.47,5.78)	L‡

CIs: confidence intervals; HR: hazard ratio; OR: odds rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; SAE: serious adverse event. PFS and OS outcomes reported HR (95%CIs); ORR and SAE outcomes reported OR (95%CIs); Quality level: H: high; M: moderate; L: low. Bold means statistic difference ($P<0.05$). *Study limitation; †Imprecision; ‡Severe Imprecision; #Incoherence.

confirmed that it has high effectiveness as a second- and third-line treatment and in the IHC3+ population. However, TraE, a conjugate of Tra and the tubulin inhibitor emtansine, has also been explored. In HER2-positive breast cancer cells, TraE can release emtansine-containing catabolites in the cell to affect cell mitosis and promote apoptosis.[41] However, the effectiveness of TraE is not ideal, which may be related to the insensitivity of GC cells to microtubule-inhibiting agents. It showed that the use of TraE as a second-line treatment did not prolong

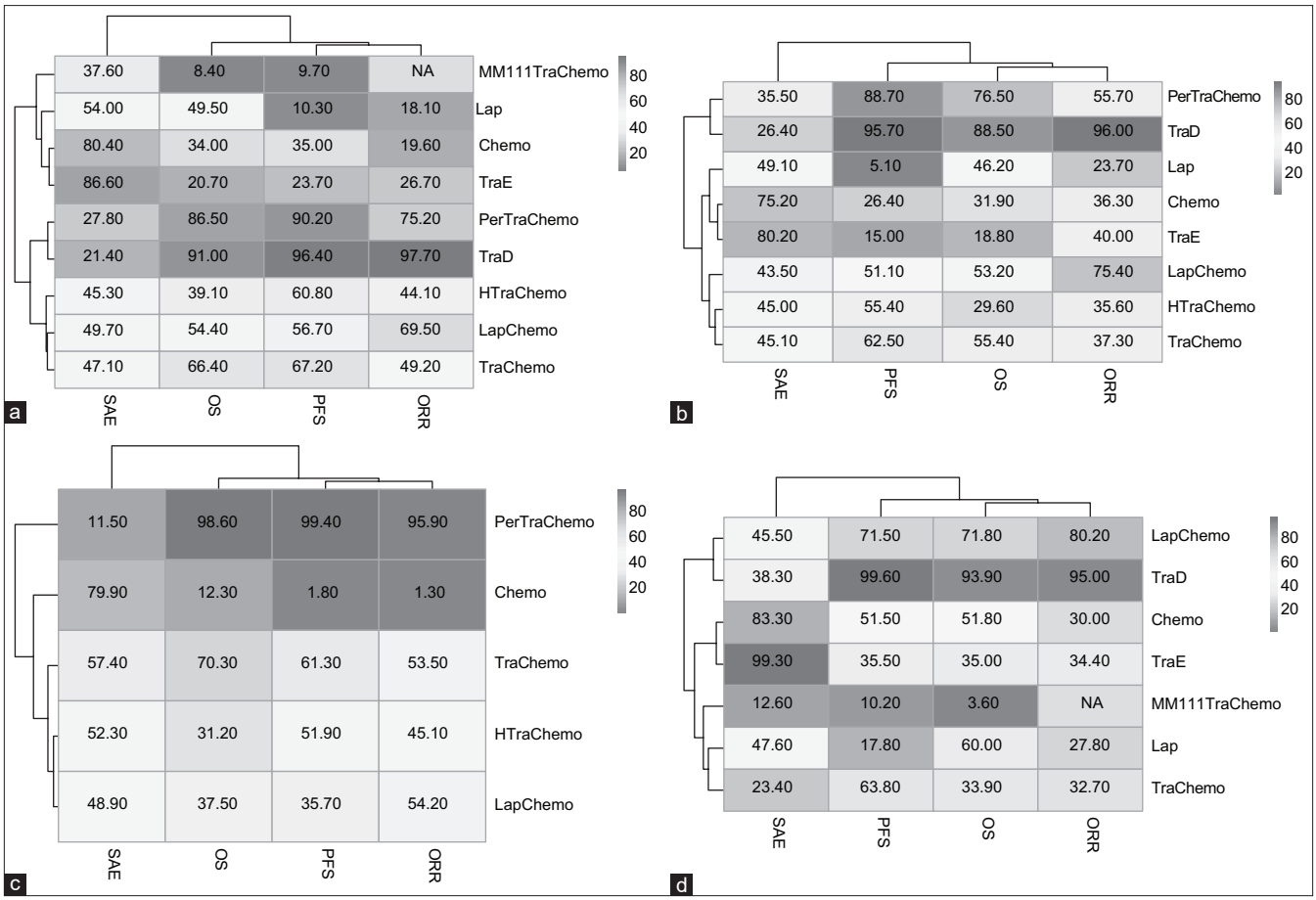

Figure 4: The hierarchical clustering of outcomes based on the surface under the cumulative ranking curve. (a): Overall results; (b): subgroup analysis of peer-reviewed published articles; (c): subgroup analysis of first-line treatment; (d): subgroup analysis of second/third-line treatment.

OS (median: 7.9 months vs. 8.6 months) or PFS (median: 2.7 months vs. 2.9 months) compared to Chemo.[24]

Per is a second-generation human monoclonal HER2 antibody that combines with the extracellular region of HER2 to block downstream signal transduction.[42] In the JACOB study, with regard to first-line treatment, there was no significant difference in OS between PerTraChemo and TraChemo (median: 17.5 months vs. 14.2 months). Coxregression also showed no significant difference (HR: 0.84; 95%CI: 0.71–1.00, $P = 0.057$). However, a trend toward therapeutic activity was possible.[22] In the PETRARCA study, with regard to first-line treatment, PerTraChemo on the basis of FLOT (docetaxel 50 mg/m^2; oxaliplatin 85 mg/m^2; leucovorin 200 mg/m^2; 5-FU 2600 mg/m^2, q2w) significantly improved the primary outcome, which was the pCR rate (35% vs. 12%). The median OS had not yet been reached. At 24 months, the OS rate of the PerTraChemo group was 84% and that of the Chemo group was 77%.[26] In this research, similar to TraD, PerTraChemo had obvious advantages in treatment effectiveness as a first-line treatment and in the ICH2+/ISH+ population, which indicated its potential as a treatment regimen for patients with HER2-positive GC and GEJ cancer. Lap is a dual tyrosine kinase receptor inhibitor of epidermal growth factor receptor (EFGR) and HER2, that blocks downstream signaling pathways not only by inhibiting the HER2 and EGFR intracellular tyrosine kinases but also by binding to their extracellular segments.[43] Although Lap showed therapeutic advantages in the treatment of HER2 + breast cancer, for HER2 + GC and GEJ cancer, LapChemo only had moderate effectiveness and tolerance as the first-line treatment and relatively high effectiveness as the second-line treatment. However, overall, Lap was not considered an advantageous agent based on this work.

In addition, a previous meta-analysis indicated that changes in HER2 status from primary GC to metastatic GC are not rare. Therefore, whether it is necessary to track HER2 status changes during the therapeutic period to modify the treatment strategy immediately, still needs to be clarified.[44] Due to the characteristic heterogeneity of gastric tumor cells, targeted agent and cytotoxic drug combinations are being used to improve survival outcomes according to

the characteristics of tumor cell biomarkers in individual patients, and this strategy needs to be further explored in the future.[45,46]

Advantages and limitations

This study included the following advantages: Almost all included studies registered the research protocol. Subgroup analyses based on treatment line and HER2 status also provided further precise interpretation of the results. As for the limitations of this study, patients with advanced HER2-positive GC and GEJ cancer received both targeted agents and chemotherapy drugs, but the chemotherapy regimens were different among studies and even within studies. Therefore, it was difficult to analyze the potential impact of various cytotoxic drugs on the outcomes. In addition, the overall accuracy of the SAE pairwise comparisons was low, which reduced the credibility of the evidence and had a nonrobust effect on the choice of drugs in practical applications for safety considerations.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ansari S, Gantuya B, Tuan VP, Yamaoka Y. Diffuse gastric cancer: A summary of analogous contributing factors for its molecular pathogenicity. Int J Mol Sci 2018;19:2424. doi: 10.3390/ijms19082424.
2. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396:635-48.
3. Martin-Richard M, Carmona-Bayonas A, Custodio AB, Gallego J, Jimenez-Fonseca P, Reina JJ, *et al*. SEOM clinical guideline for the diagnosis and treatment of gastric cancer (GC) and gastroesophageal junction adenocarcinoma (GEJA) (2019). Clin Transl Oncol 2020;22:236-244.
4. Kauppila JH, Ohtonen P, Karttunen TJ, Kokkola A, Laine S, Rantanen T, *et al*. Finnish National Esophago-Gastric Cancer Cohort (FINEGO) for studying outcomes after oesophageal and gastric cancer surgery: A protocol for a retrospective, population-based, nationwide cohort study in Finland. BMJ Open 2019;9:e024094.
5. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, *et al*. Association between *helicobacter pylori* eradication and gastric cancer incidence: A systematic review and meta-analysis. Gastroenterology 2016;150:1113-24 e5.
6. Zhang X, Li M, Chen S, Hu J, Guo Q, Liu R, *et al*. Endoscopic screening in Asian countries is associated with reduced gastric cancer mortality: A meta-analysis and systematic review. Gastroenterology 2018;155:347-54 e9.
7. Chau I, Le DT, Ott PA, Korytowsky B, Le H, Le TK, *et al*. Developing real-world comparators for clinical trials in chemotherapy-refractory patients with gastric cancer or gastroesophageal junction cancer. Gastric Cancer 2020;23:133-41.
8. Bluemel L, von Wahlde MK, Tio J, Kiesel L, Bernemann C. Reverse engineering of triple-negative breast cancer cells for targeted treatment. Maturitas 2018;108:24-30.
9. Erickson BK, Zeybek B, Santin AD, Fader AN. Targeting human epidermal growth factor receptor 2 (HER2) in gynecologic malignancies. Curr Opin Obstet Gynecol 2020;32:57-64.
10. Lote H, Valeri N, Chau I. HER2 inhibition in gastro-oesophageal cancer: A review drawing on lessons learned from breast cancer. World J Gastrointest Oncol 2018;10:159-71.
11. Jorgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer-A systematic analysis of data from the literature. J Cancer 2012;3:137-44.
12. Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, *et al*. Safety, pharmacokinetics, and antitumour activity of trastuzumabderuxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophagealtumours: A phase 1 dose-escalation study. Lancet Oncol 2017;18:1512-22.
13. Hierro C, Alsina M, Sanchez M, Serra V, Rodon J, Tabernero J. Targeting the fibroblast growth factor receptor 2 in gastric cancer: Promise or pitfall? Ann Oncol 2017;28:1207-16.
14. Ter Veer E, van den Ende T, Creemers A, de Waal L, van Oijen MG, van Laarhoven HW. Continuation of trastuzumab beyond progression in HER2-positive advanced esophagogastric cancer: A meta-analysis. Acta Oncol 2018;57:1599-604.
15. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi: 10.1136/bmj.d5928.
16. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, *et al*. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36-44.
17. Lin JZ, Ma SK, Wu SX, Yu SH, Li XY. A network meta-analysis of nonsmall-cell lung cancer patients with an activating EGFR mutation: Should osimertinib be the first-line treatment? Medicine (Baltimore) 2018;97:e11569.
18. Turner RM, Dominguez-Islas CP, Jackson D, Rhodes KM, White IR. Incorporating external evidence on between-trial heterogeneity in network meta-analysis. Stat Med 2019;38:1321-35.
19. Zhang JJ, Liu X. Aspirin plus dipyridamole has the highest surface under the cumulative ranking curves (SUCRA) values in terms of mortality, intracranial hemorrhage, and adverse event rate among 7 drug therapies in the treatment of cerebral infarction. Medicine (Baltimore) 2018;97:e0123.
20. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, *et al*. TrastuzumabDeruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419-30.
21. Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y, *et al*. Randomized, phase ii study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). J Clin Oncol 2020;38:1919-27.
22. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, *et al*. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): Final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol 2018;19:1372-84.
23. Xin Y, Pan X. Immune function and prognosis of patients with HER2-positive advanced gastric cancer following lapatinib combined with paclitaxel therapy. J Pract Oncol 2017;32:525-9.
24. Thuss-Patience PC, Shah MA, Ohtsu A, Van Cutsem E, Ajani JA, Castro H, *et al*. Trastuzumabemtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): An international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol 2017;18:640-53.
25. Shah MA, Xu RH, Bang YJ, Hoff PM, Liu T, Herraez-Baranda LA, *et al*. HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal

growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2017;35:2558-67.
26. Hofheinz RD, Haag GM, Ettrich TJ, Borchert K, Kretzschmar A, Teschendorf C, *et al*. Perioperative trastuzumab and pertuzumab in combination with FLOT versus FLOT alone for HER2-positive resectableesophagogastric adenocarcinoma: Final results of the PETRARCA multicenter randomized phase II trial of the AIO. J Clin Oncol 2020;38:4502.
27. Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, *et al*. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC--A randomized phase III trial. J Clin Oncol 2016;34:443-51.
28. Denlinger CS, Maqueda MA, Watkins DJ, Sym SJ, Bendell JC, Park SH, *et al*. Randomized phase 2 study of paclitaxel (PTX), trastuzumab (T) with or without MM-111 in HER2 expressing gastroesophageal cancers (GEC). J Clin Oncol 2016;34:4043.
29. Moehler MH, Schad A, Mauer ME, Messina CG, John JM, Lang I, *et al*. Lapatinib combined with ECF/x as first-line metastatic gastric cancer (GC) according to HER2 and EGFR status: A randomized placebo controlled phase II (EORTC 40071). J Clin Oncol 2015;33:80.
30. Lorenzen S, RieraKnorrenschild J, Haag GM, Pohl M, Thuss-Patience P, Bassermann F, *et al*. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: A randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur J Cancer 2015;51:569-76.
31. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, *et al*. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol 2014;32:2039-49.
32. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, *et al*. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
33. Oku N. HER2-positive gastric cancer. Gastric Cancer 2014;17:1-12.
34. Curea FG, Hebbar M, Ilie SM, Bacinschi XE, Trifanescu OG, Botnariuc I, *et al*. Current targeted therapies in HER2-positive gastric adenocarcinoma. Cancer BiotherRadiopharm 2017;32:351-63.
35. Lei YY, Huang JY, Zhao QR, Jiang N, Xu HM, Wang ZN, *et al*. The clinicopathological parameters and prognostic significance of HER2 expression in gastric cancer patients: A meta-analysis of literature. World J Surg Oncol 2017;15:68.
36. Kanayama K, Imai H, Usugi E, Shiraishi T, Hirokawa YS, Watanabe M. Association of HER2 gene amplification and tumor progression in early gastric cancer. Virchows Arch 2018;473:559-65.
37. Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] TrastuzumabDeruxtecan (DS-8201a), for HER2 cancer therapy. Chem Pharm Bull (Tokyo) 2019;67:173-85.
38. Andrikopoulou A, Zografos E, Liontos M, Koutsoukos K, Dimopoulos MA, Zagouri F. TrastuzumabDeruxtecan (DS-8201a): The latest research and advances in breast cancer. Clin Breast Cancer 2021;21:e212-9. doi: 10.1016/j.clbc. 2020.08.006.
39. Tamura K, Tsurutani J, Takahashi S, Iwata H, Krop IE, Redfern C, *et al*. Trastuzumabderuxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion, phase 1 study. Lancet Oncol 2019;20:816-26.
40. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, *et al*. TrastuzumabDeruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-21.
41. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, *et al*. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617-28.
42. Wuerkenbieke D, Wang J, Li Y, Ma C. miRNA-150 downregulation promotes pertuzumab resistance in ovarian cancer cells via AKT activation. Arch GynecolObstet 2015;292:1109-16.
43. Mu Y, Sun D. Lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) and HER-2, enhances radiosensitivity in mouse bladder tumor line-2 (MBT-2) cells *in vitro* and *in vivo*. Med SciMonit 2018;24:5811-9.
44. Peng Z, Zou J, Zhang X, Yang Y, Gao J, Li Y, *et al*. HER2 discordance between paired primary gastric cancer and metastasis: A meta-analysis. Chin J Cancer Res 2015;27:163-71.
45. Gao JP, Xu W, Liu WT, Yan M, Zhu ZG. Tumor heterogeneity of gastric cancer: From the perspective of tumor-initiating cell. World J Gastroenterol 2018;24:2567-81.
46. Lazar DC, Avram MF, Romosan I, Cornianu M, Taban S, Goldis A. Prognostic significance of tumor immune microenvironment and immunotherapy: Novel insights and future perspectives in gastric cancer. World J Gastroenterol 2018;24:3583-616.