

Does the use of targeted agents in advanced gastroesophageal cancer increase complete response? A meta-analysis of 18 randomized controlled trials

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Purpose: We aimed to investigate whether the use of targeted agents (TAs) in advanced gastroesophageal cancer (GEC) increased the complete response (CR) and to assess the surrogate endpoints for survival in the targeted treatment of GEC by using a meta-analysis of randomized controlled trials (RCTs).

Methods: Eligible studies were identified using Medline, PubMed, and meeting abstracts. Searches were last updated on April 30, 2018. We calculated the incidence and Peto odds ratio (Peto OR) of CR events in patients assigned to TAs compared with controls. Simple linear regression models were fitted for median overall survival (OS) and each surrogate [median progression-free survival (PFS), CRs, objective response rate (ORR), and disease control rate (DCR), respectively].

Results: A total of 7,892 GEC patients from 18 RCTs were included for analysis. The incidence of CR in GEC patients treated with TAs was 2.0% (95% CI, 1.3%–3.0%) compared with 1.7% (95% CI, 1.0%–2.7%) in the control arms. The use of TAs in advanced GEC had a tendency to improve the possibility of achieving CR (Peto OR 1.42; 95% CI, 0.98–2.04; $P=0.064$) compared with controls. Subgroup analysis according to treatment TAs showed that the addition of anti-epidermal growth factor receptor (EGFR) agents to chemotherapy in GEC significantly improved the CR rate in comparison with control (Peto OR 1.77; 95% CI, 1.02–3.09; $P=0.044$), but not for other molecular TAs ($P=0.49$ for angiogenesis inhibitors, $P=0.66$ for mesenchymal-epithelial transition inhibitors). We also found that the addition of TAs to first-line therapy (Peto OR 1.41; 95% CI, 0.94–2.11; $P=0.098$) had a tendency to increase the chance of obtaining a CR, but not for second-line therapy (Peto OR 1.47; 95% CI, 0.60–3.55; $P=0.40$). In addition, correlation analysis indicates that PFS, ORR, and DCR were strongly correlated with OS for GEC patients receiving TAs ($r=0.85$ for PFS; $r=0.86$ for ORR; $r=0.81$ for DCR). No marked correlation was found between OS and CRs ($r=0.43$; $P=0.18$).

Conclusion: Although the CR is a rate event in advanced GEC patients, adding the TAs to therapies, especially for anti-EGFR agents, increases the chance of achieving CR in comparison with the controls. PFS, ORR, and DCR are significantly correlated with OS and could be used as surrogate endpoints in patients with GEC who have received TA therapy, but not for CR.

Keywords: gastroesophageal carcinoma, systematic review, novel molecular agents

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Introduction

Gastroesophageal cancer (GEC), which comprises tumors arising from the gastroesophageal junction and the stomach, is the fourth most common malignant disease

and the second leading cause of cancer mortality worldwide, accounting for 8% (989,600 million) of the total new cancer cases and 10% (738,000) of the total cancer deaths in 2008.^{1,2} Substantial geographic variation exists in incidence, with the highest incidence rates occurring in Asia, South America, and Eastern Europe.³ Until now, the only curative treatment of GEC is surgical resection; however, the majority of GEC (approximately 50%) are regarded as incurable at initial diagnosis. In addition, most of GEC often relapse even after curative surgery. Doublet or triplet combination chemotherapy containing a platinum–fluoropyrimidine, such as FOLFOX regimen (fluorouracil, leucovorin calcium and oxaliplatin), remains the backbone of treatment for advanced GEC resulting in superior survival outcomes and symptom control and consequently improved quality of life compared with best supportive care.^{4–6} For gastric cancer overexpressing human epidermal growth factor-2 (HER2), trastuzumab plus chemotherapy is the current standard treatment.⁷ However, the prognosis of GEC patients remains poor, with median survival <1 year.⁸ Thus, there is an urgent unmet need to develop novel efficient agents for advanced GEC patients.

During the past decades, the emergence of molecularly targeted agents (TAs), including angiogenesis inhibitors, antiepidermal growth factor receptor (EGFR) agents, or MET inhibitors, has provided another strategy for the treatment of advanced GEC patients.^{9,10} Currently, two TAs, including trastuzumab and ramucirumab, have been approved for the treatment of advanced GEC patients. Additionally, a number of novel agents have been extensively investigated in clinical trials. Indeed, multiple meta-analyses have demonstrated that the addition of TAs to chemotherapies in advanced GEC significantly improves overall survival (OS) and progression-free survival (PFS) when compared with chemotherapy alone.^{11–14} Although these agents have shown greater activity, in terms of PFS or OS, compared with controlled therapies, specifically when compared with placebo, a clinically relevant increase in complete response (CR) was not reported and the role of TAs in increasing the curability of this cancer remains unclear. We thus conducted this meta-analysis of published reports about TA-containing regimens vs placebo or chemotherapy to investigate the incidence rates and relative risk of CR in advanced gastroesophageal cancer patients.

Methods

Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adheres to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.¹⁵

Definition of outcomes

Treatment with TAs was considered as the experimental arms and the other treatments as the standard comparators. CRs were considered as the main outcomes, and the analysis was conducted in order to find a significant difference between the two arms. CRs were defined as disappearance of all target lesions. Any pathological lymph nodes (whether targeted or nontargeted) must have reduction in short axis to <10 mm according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. OS was defined as the period from starting targeted therapy until death or last follow-up. Time to progression/PFS was defined as the period from starting targeted therapy until progression or last follow-up; objective response rate (ORR) was defined as the rate of partial responses and CRs, and disease control rate (DCR) was defined as the rate of partial responses, CR, and stabilization.

Selection of studies

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including Embase, PubMed/Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to April 2018. The search was limited to human studies and randomized controlled trials (RCTs). No language restriction was imposed. If more than one publication was found for the same trial, the most recent was considered for analysis. Abstracts of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology Congress since 2002 (ESMO), and the World Gastrointestinal Congress since 2006 were also searched manually.

Data extraction

Two authors conducted the data extraction independently. It was performed according to the PRISMA statement,¹⁶ and any types of discrepancies were resolved by consensus. The data extracted for each trial were first author's name, year of publication, number of enrolled patients, dose of TAs, median age, median OS, and median PFS.

Statistical method

For calculating the incidence, the number of patients with CR and the number of patients treated in each arm were extracted from the efficacy profile of the selected trials. The proportion of patients with CR and the derived 95%

CI were calculated for each study. We also calculated the Peto odds ratio (Peto OR) and the CIs of events in patients assigned to TAs compared with the controlled patients in the same study. To calculate the 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method.¹⁷ Between-study heterogeneity was estimated using the χ^2 -based Q -statistic.¹⁸ Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.1$. When substantial heterogeneity was observed, the pooled estimate, calculated based on the random-effects model, was reported using the method described by Dersimonian and Laird,¹⁹ which considered both within- and between-study variations. We also conducted the prespecified subgroup analyses according to treatment line and treatment regimens. We assessed the potential publication bias by visual inspection of the symmetry of funnel plots and with tests described by Begg and Mazumdar²⁰ and Egger et al.²¹ Study quality was assessed by using the Jadad five-item scale that included the randomization, double blinding, and withdrawals; the final score was reported between 0 and 5.²² All data were collected using

Microsoft Office Excel 2003; and meta-analysis was performed using version 2 of the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA).

Results

A total of 550 studies were identified from the database search [PubMed/Medline (n=320), ASCO (n=120), ESMO (n=50), and World Gastrointestinal Congress (n=60)], of which 70 were duplicates and 430 did not meet the inclusion criteria and were therefore excluded. Of these, 50 reports were retrieved for full-text evaluation. A total of 18 trials met the inclusion criteria and were included in this systematic review (Figure 1).^{23–40} The characteristics of patients and studies were listed in Table 1. Overall, a total of 18 studies with 7,892 GEC patients were included. The median number of patients included in each study was 549 patients (range: 60–904 patients). Fourteen studies compared TAs plus chemotherapy with or without placebo,^{23–25,27,29–36,38,40} other four studies compared TAs alone with placebo.^{26,28,37,39} Dosages for each molecule are

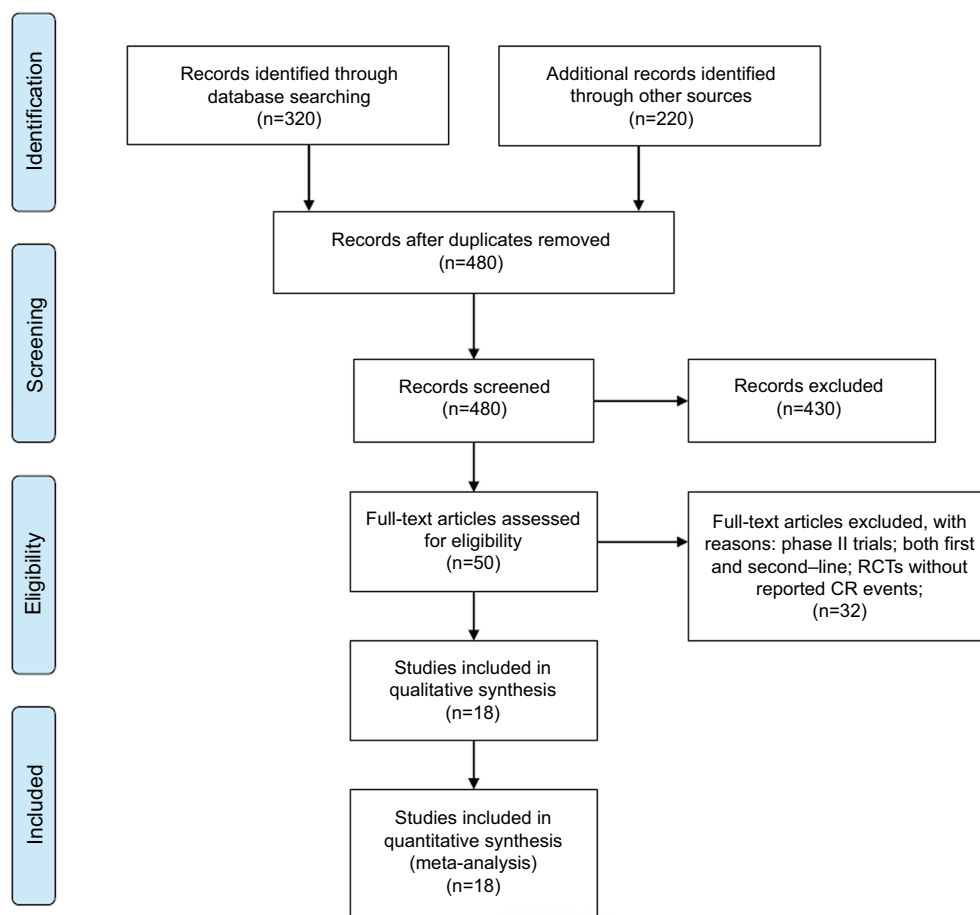


Figure 1 Selection process for RCTs included in the meta-analysis.

Abbreviations: CR, complete response; RCT, randomized controlled trials.

Table 1 Baseline characteristic of included 18 trials for analysis

Authors	Treatment line	Total	Treatment arms	Median age (years)	Median PFS	Median OS	CR	No. for analysis	Jadad score
Shah et al (2017) ³²	First line	562	Onartuzumab 10 mg/kg + FOLFOX	60	6.8	11	4	217	5
			Placebo + FOLFOX	58	6.7	11.3	4	207	
Catenacci et al (2017) ³³	First line	609	Rilotumumab 15 mg/kg + epirubicin + DDP + capecitabine	61	6.05	8.8	3	262	5
			Placebo + epirubicin + DDP + capecitabine	59	7.06	10.7	8	267	
Bang et al (2017) ³⁴	Second line	643	Olaparib 100 mg + PTX	58	3.6	8.8	4	263	5
			Placebo + PTX	59	5.5	6.9	1	262	
Yoon et al (2016) ³⁵	First line	168	Ramucirumab 8 mg/kg + FOLFOX	64.5	6.4	11.7	6	84	5
			Placebo + FOLFOX	60	6.7	11.5	5	84	
Shah et al (2016) ³⁶	First line	123	Onartuzumab 10 mg/kg + FOLFOX	58.5	6.77	10.61	4	62	5
			Placebo + FOLFOX	57	6.97	11.27	1	61	
Pavlikis et al (2016) ³⁷	Second line	152	Regorafenib 160 mg	63	2.6	5.8	3	97	5
			Placebo	62	0.9	4.5	1	50	
Moehler et al (2016) ³⁸	Second line	90	Sunitinib + FOLFIRI	62	3.5	10.4	0	45	5
			Placebo + FOLFIRI	57	3.3	8.9	5	45	
Li et al (2016) ³⁹	Second line	267	Apatinib	58	2.6	6.5	4	176	5
			Placebo	58	1.8	4.7	0	91	
Hecht et al (2016) ⁴⁰	First line	545	Lapatinib 1,250 mg + CapeOx	61	6	12.2	6	249	5
			Placebo + CapeOx	59	5.4	10.5	4	238	
Du et al (2015) ³¹	First line	60	Nimotuzumab 200 mg/m ² + chemotherapy	58	4.8	10.2	1	31	3
			Chemotherapy	53	7.2	14.3	0	31	
Fuchs et al (2014) ²⁸	Second line	335	Ramucirumab 8 mg/kg	60	NR	5.2	1	238	5
			Placebo	60	NR	3.8	0	117	
Wilke H. et al (2014) ³⁰	First line	655	Ramucirumab 8 mg/kg + PTX	61	4.4	9.6	2	330	5
			Placebo + PTX	61	2.9	7.4	1	335	
Shen et al (2015) ²⁹	Second line	202	Bevacizumab 2.5 mg/kg/wk + capecitabine + DDP	54.2	6	11.4	1	86	5
			Placebo + capecitabine + DDP	55.5	6.3	10.5	0	81	
Waddell et al (2013) ²⁷	First line	553	Panitumumab 9 mg/kg + EOC	63	7.4	11.3	8	254	3
			EOC	62	6	8.8	5	238	
Ohtsu et al (2013) ²⁶	Second line	656	Everolimus 10 mg/d	62	1.7	5.4	1	379	5
			Placebo	62	1.4	4.3	0	191	
Lordick et al (2013) ²⁵	First line	904	Cetuximab 400 mg/m ² followed by 250 mg/m ² + capecitabine + DDP	60	4.4	9.4	2	455	3
			Capecitabine + DDP	59	5.6	10.7	2	449	
Ohtsu et al (2011) ²⁴	First line	774	Bevacizumab 2.5 mg/kg/wk + capecitabine + DDP	58	6.7	12.1	5	387	5
			Placebo + capecitabine + DDP	59	5.3	10.1	3	387	
Bang et al (2010) ²³	First line	594	Trastuzumab 8 mg/kg followed by 6 mg/kg + chemotherapy	59.4	6.7	13.8	16	294	3
			Chemotherapy	58.5	5.5	11.1	7	290	

Abbreviations: CapeOx, cisplatin plus oxaliplatin; CR, complete response; DDP, cisplatin; EOC, epirubicin plus oxaliplatin plus capecitabine; FOLFIRI, 5Fu/Lv plus irinotecan; FOLFOX, 5Fu/Lv plus oxaliplatin; NR, not reported; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel.

reported in Table 1. Among the included trials, the role of trastuzumab and lapatinib was investigated in HER2-positive GEC patients, and onartuzumab and rilotumumab were assessed in advanced MET-positive GEC patients,

while other TAs were investigated in unselected GEC patients. The quality of each included study was roughly assessed according to Jadad scale, and 14 trials had Jadad score of 5, and four trials had Jadad scores of 3.

Incidence of CR

CRs were reported in 71 of 3,909 patients in the experimental arm, with an incidence of 2.0% (95% CI, 1.3%–3.0%; Figure 2) compared with 47 of 3,424 patients treated in the control arm, with an incidence of 1.7% (95% CI, 1.0%–2.7%).

Peto OR of CR

A total of 7,892 patients from 18 RCTs were included for analysis. The Peto OR of CR was 1.42 (95% CI, 0.98–2.04;

$P=0.064$) in patients treated with TAs compared with the controls, according to the fixed effects model ($P=0.89$; $I^2=0\%$). We then performed the subgroup analysis according to treatment line and showed that the addition of TAs to first-line therapy had a tendency to increase the chance of achieving CRs (Peto OR 1.41; 95% CI, 0.94–2.11; $P=0.06$; Figure 3), but not for second-line therapy (Peto OR 1.47; 95% CI, 0.60–3.55; $P=0.40$). Of note, the occasional wide variation in the CIs might indicate that using TAs as a second-line therapy might also substantially increase the Peto OR of

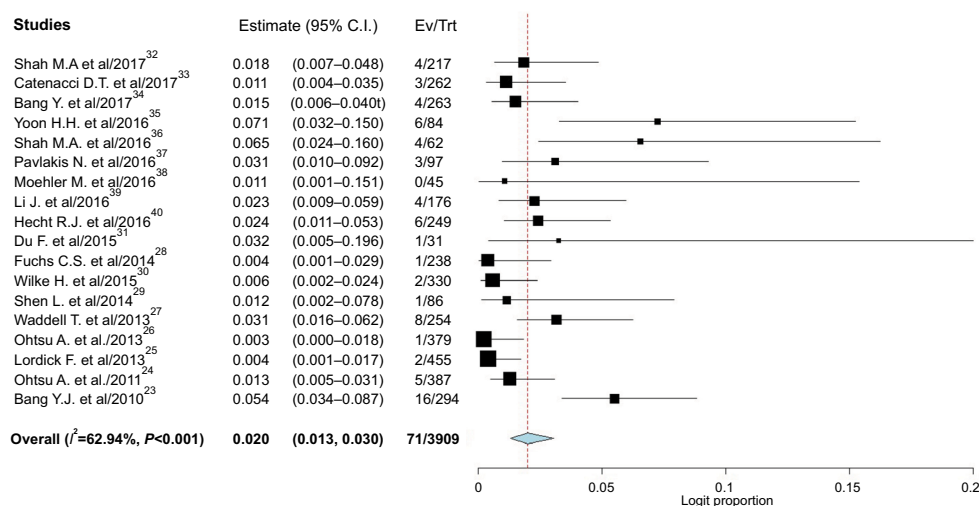


Figure 2 Pooled incidence of complete response associated with targeted agents.

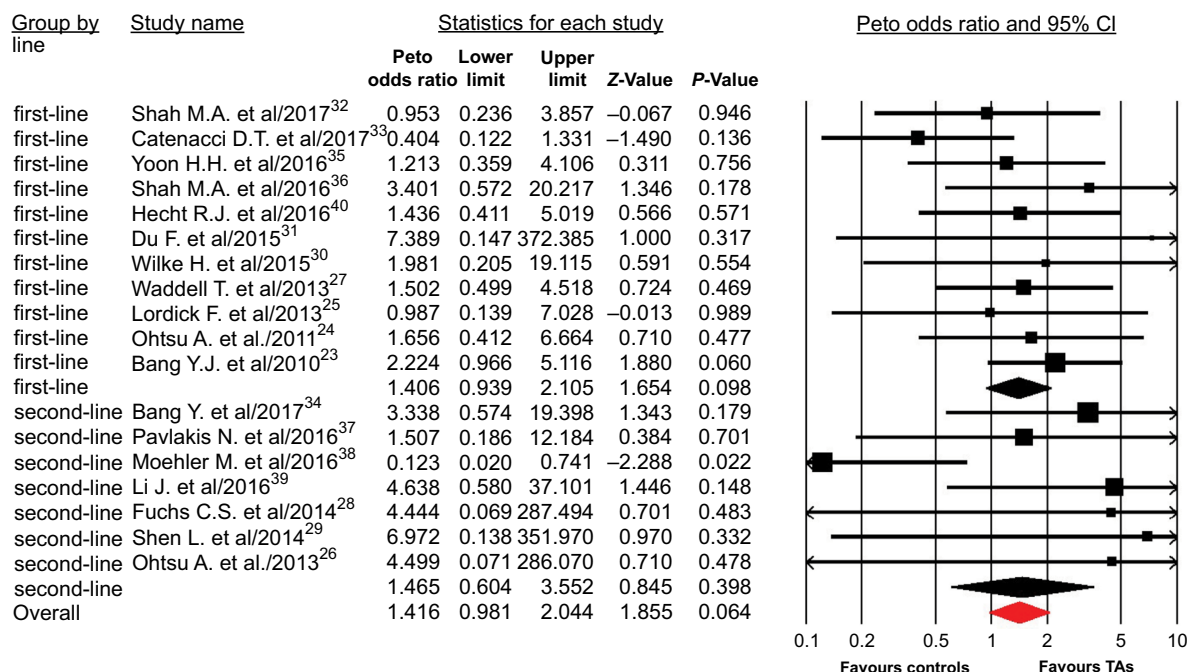


Figure 3 Subgroup analysis based on treatment line for Peto odds ratio of complete response associated with TAs vs controls.

Abbreviation: TA, targeted agent.

CRs, but there was lack of statistical power to demonstrate a significant difference. In addition, subgroup analysis to specific TAs showed that the addition of anti-EGFR agents to chemotherapy in GEC significantly improved the CR rate in comparison with control (Peto OR 1.77; 95% CI, 1.02–3.09; $P=0.044$), but not for other molecular TAs ($P=0.49$ for angiogenesis inhibitors, $P=0.66$ for MET inhibitors, Figure 4).

Publication bias

No evidence of publication bias was detected for the Peto OR of CRs in this study by funnel plots (Figure S1), Begg's test ($P=0.36$), and Egger's test ($P=0.37$).

Correlation between OS and PFS/ORR/DCR/CR

Data from 18 cohorts were available for correlation analysis between OS and PFS. There was a strong correlation between median OS and median PFS ($r=0.85$), and this correlation was statistically significant ($P<0.001$; Figure 5). Data from 18 cohorts were available for correlation analysis between median OS and ORR/DCR/CR. A significant correlation between median OS and ORR/DCR was also observed ($r=0.86$ and $r=0.81$, respectively), and this correlation was statistically significant ($P<0.0001$ and $P<0.0001$; Figure S2).

No marked correlation was found between median OS and CRs ($r=0.43$, $P=0.18$; Figure S2).

Discussion

Despite the major advances in chemotherapy during the past decades, only a small number of GEC patients receiving chemotherapy can achieve CR. Although several case reports have been published, overall incidence and likelihood of achieving a CR in GEC receiving TAs has not been systematically determined.^{41–43} In addition, obtaining a CR is independently associated with improved survival not only for GEC but also for other solid and hematologic malignancies.^{44–46} As a result, it is of particular importance to determine whether the use of TAs would increase the CR events in GEC patients.

Our meta-analysis included a total of 7,892 patients from 18 RCTs and demonstrated that the overall incidence of CR in patients treated with TAs is 2.0% (95% CI, 1.3%–3.0%) compared with 1.7% (95% CI, 1.0%–2.7%) in the control arms. In addition, we also found that adding TAs has a tendency to improve the possibility of achieving CR (Peto OR 1.42; 95% CI, 0.98–2.04; $P=0.064$) compared with controls. Subgroup analysis showed that the addition of TAs to first-line therapy has a tendency to increase the chance of achieving CRs (Peto

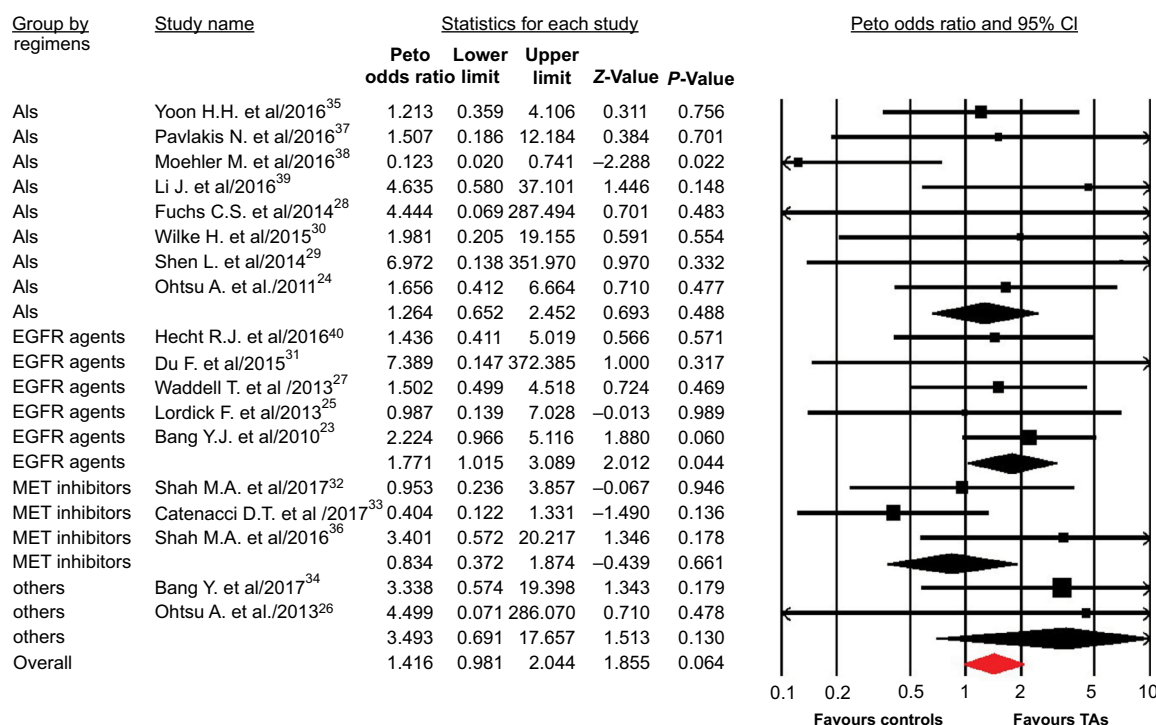


Figure 4 Subgroup analysis based on specific TAs for Peto odds ratio of complete response associated with TAs vs controls.

Abbreviations: Als, angiogenesis inhibitors; EGFR, epidermal growth factor receptor; TAs, targeted agents.

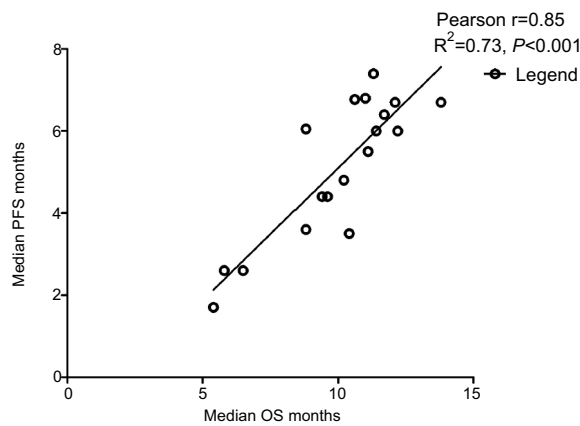


Figure 5 Correlation between median OS and PFS in gastroesophageal cancer patients received targeted agents.

Abbreviations: OS, overall survival; PFS, progression-free survival.

OR 1.41; 95% CI, 0.94–2.11; $P=0.06$), but not for second-line therapy (Peto OR 1.47; 95% CI, 0.60–3.55; $P=0.40$). In addition, subgroup analysis to specific TAs showed that the addition of anti-EGFR agents to chemotherapy in GEC significantly improved the CR rate in comparison with control (Peto OR 1.77; 95% CI, 1.02–3.09; $P=0.044$), but not for other molecular TAs ($P=0.49$ for angiogenesis inhibitors; $P=0.66$ for MET inhibitors). For patients with GEC, a common question is whether the patient needs chemotherapy plus TAs in first-line treatment. It is always difficult to make a decision because of the unclear survival benefit, potential toxicities, and high cost. The present study results supported the addition of anti-EGFR agents to first-line chemotherapy as initial treatment for unresectable metastatic GEC in order to pave the way for potentially radical surgery of the primary and metastatic sites. In addition, using the most active and well-tolerated therapy could provide a reduction of neoplastic mass and, as a consequence, result in the need for less aggressive surgery.

We also investigated the potential surrogate points for OS in GEC patients receiving TAs. We found that there is strong correlation between OS and PFS ($r=0.85$), and this correlation is statistically significant ($P<0.001$; Figure 5). In addition, a statistically significant correlation between ORR/DCR and OS is observed ($r=0.86$, $P<0.001$; $r=0.82$, $P<0.001$, respectively), while no marked correlation is found between OS and CR ($r=0.43$, $P=0.18$). Based on our findings, both PFS/ORR/DCR appears to be good surrogate endpoints for OS in GEC patients receiving TAs, although OS remains the historical and primary endpoint for studies in advanced GEC patients, and CR could not be a surrogate endpoint for OS.

The results of our meta-analysis represent the largest amount of evidence that adding TAs, especially anti-EGFR

agents, is effective in increasing the rate of CR in GEC when compared with controls. The quality of this evidence is based on the high rate of the mean Jadad score for the included studies. Nevertheless, several limitations need to be mentioned. First of all, this meta-analysis only considers published literature, and lack of individual patient data prevents us from adjusting the treatment effect according to disease and patient variables. Second, we include GEC patients who received different TAs due to the limited sample size of patients treated with any single TAs, which would increase the clinical heterogeneity among included trials. Third, CR events are prospectively collected for each clinical trial, but our study is retrospective, and there are potentially important differences among the studies, which could be another source of heterogeneity. However, the pooled analysis indicates that there is no significant heterogeneity among the included trials. Finally, due to different types of treatment modalities investigated (oral vs intravenous), some of the included trials are open-label, with an inherent risk of bias. Although the literature search is comprehensive, the possibility of relevant publications remains might not be identified.

Conclusion

Although the CR is a rate event in advanced GEC patients, adding the TAs to therapies, especially for anti-EGFR agents, increases the chance of achieving CR in comparison with the controls. Further studies are still needed to investigate whether treatment with TAs can be discontinued in these patients. In addition, PFS, ORR, and DCR are significantly correlated with OS and could be used as surrogate endpoints in patients with GEC who received TA therapy, but not for CR.

Ethics approval and consent to participate

This meta-analysis was approved by the institutional review board; the need for informed patient consent for inclusion was waived.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

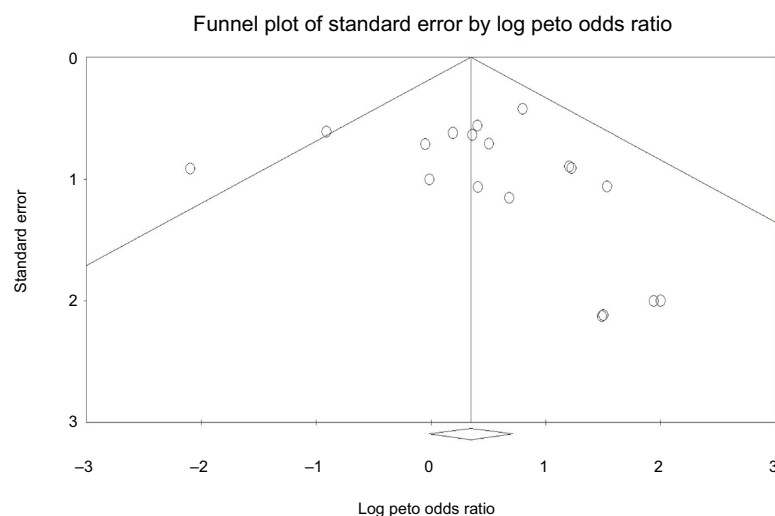


Figure S1 Publication bias of Peto odds ratio associated with targeted agents.

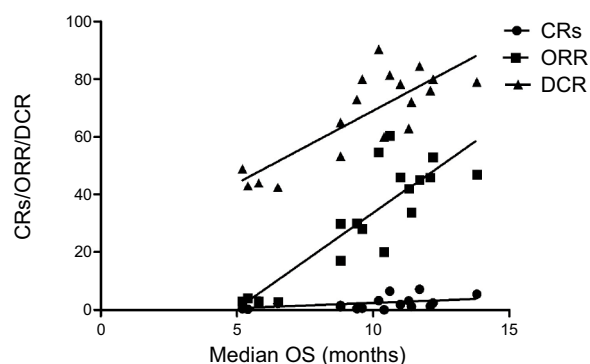


Figure S2 Correlation between median OS and ORR/DCR/CR in gastroesophageal cancer patients received targeted agents.

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; OS, overall survival.

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