PD-1 Inhibitor Plus Chemotherapy Versus Chemotherapy for First-Line Treatment in Advanced Esophageal Cancer: A Systematic Review and Meta-Analysis.

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Research

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Abstract

Background: Immunotherapy combined with chemotherapy has recently changed the first-line treatment of several cancers. We perform a systematic meta-analysis to assess the efficacy and safety of PD-1 inhibitor plus chemotherapy for first-line treatment in advanced esophageal cancer.

Methods: Data were collected from eligible studies searched from PubMed, Web of Science, Cochrane Library, Embase, American society of clinical oncology (ASCO) and the European Society for Medical Oncology (ESMO). Pooled hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS), pooled odds ratio (OR) for objective response rate (ORR) and treatment-related adverse effects (TrAEs) were estimated to assess the efficacy and safety of PD-1 inhibitor plus chemotherapy versus chemotherapy. We performed several subgroup analyses to explore the variables on immunotherapy efficacy for esophageal cancer. The five-point Jadad scoring system and the bias risk assessment were used to evaluate the quality of studies, and sensitivity analyses were carried out to evaluate the robustness of the combined outcomes.

Results: Seven records involving 3754 participants were selected in our study. Compared to chemotherapy group, the OS (HR=0.72; 95% CI: 0.66-0.78, $P<0.01$), PFS (HR=0.62; 95% CI: 0.57-0.68, $P<0.01$) and ORR (OR=2.07; 95% CI: 1.76-2.43, $P<0.01$) were significantly longer in PD-1 inhibitor plus chemotherapy group. The overall survival benefit was observed in patients regardless of histology or PD-L1 combined positive score (CPS). OS and PFS were generally consistent across subgroups by clinical features. In safety analyses, PD-1 inhibitor plus chemotherapy had significantly higher incidence of TrAEs (OR=1.85; 95% CI: 1.21-2.84, $P<0.01$), but there was no statistical difference in grade 3 or higher TrAEs (OR=1.24; 95% CI: 1.00-1.55, $P=0.05$).

Conclusion: Compared with chemotherapy, PD-1 inhibitor plus chemotherapy has an improvement of anti-tumor activity and controllable TrAEs for first-line treatment of advanced esophageal cancer.

Background

The incidence and mortality of esophageal cancer (EC) rank 7th and 6th among all malignant tumors, respectively, and more than 500,000 people die of esophageal cancer every year[1]. Esophageal squamous cell carcinoma (ESCC) is predominant in China, while esophageal adenocarcinoma (EAC) is common in western countries[2-4]. The diagnosis typically occurs in patients with locally advanced unresectable or metastatic disease, while systemic chemotherapy is the first choice[5]. Although the application of surgery, radiotherapy, chemotherapy and targeted therapy in the comprehensive treatment of cancer is constantly updated, the 5-year survival rate of esophageal cancer is still low worldwide, about 30%-40%[6]. A large number of studies are being conducted to explore new treatment modalities to improve survival for patients with esophageal cancer[7-9].

In recent years, immunotherapy has continuously made new breakthroughs in various tumor types[10, 11], and immune checkpoint inhibitors have been used in a large number of clinical studies about

esophageal cancer and achieved certain results[12-14]. Programmed death-1 (PD-1) is an important immunosuppressive molecule that inhibits T cell activation by binding with programmed death ligand 1 (PD-L1)[15]. Inhibition of the PD-1/PD-L1 pathway has shown significant survival benefits in multiple tumor therapy[16]. PD-1 inhibitor, representative drugs of immunotherapy, has rapidly entered the field of esophageal cancer treatment, from the single-drug second-line treatment to the first-line treatment of combined chemotherapy in unresectable locally advanced or metastatic esophageal cancer [17]. Keynote-181 demonstrated superior efficacy of the PD-1 inhibitor pembrolizumab compared to chemotherapy in the treatment of relapsed or metastatic esophageal cancer[18]. In the Attraction-03 trial and ESCORT trial, the PD-1 inhibitor have shown effective antitumor activity for patients with advanced ESCC[14, 19]. Our previous meta-analysis has revealed that PD-1 inhibitor significantly prolonged the overall survival (OS) when compared with chemotherapy as second-line or later therapy in patients with esophageal cancer[20].

At the same time, immunotherapy has entered the exploration of first-line treatment of advanced esophageal cancer. The benefit of combining PD-1 inhibitor therapy with chemotherapy has been demonstrated in several studies. Keynote 590 is the first phase III study to achieve a survival benefit in first-line treatment for esophageal cancer[21]. The efficacy of immunotherapy combined with chemotherapy has also been further confirmed in Checkmate 648 and Escort-1st[22, 23], and studies such as Jupiter-06 and Orient-15 also have achieved survival benefit[24, 25]. However, the treatment-related adverse effects (TrAEs) caused by immunotherapy should not be ignored.

Currently, there are no meta-analyses exploring the safety and efficacy of PD-1 inhibitor plus chemotherapy in the first-line treatment of advanced esophageal cancers. We conducted this meta-analysis, which systematically combines all prospective clinical studies data to compare the efficacy and safety of PD-1 inhibitor plus chemotherapy as the first-line treatment for patients with advanced esophageal cancers. We performed a comprehensive analysis of the current data published from clinical trials to inform decision making and enable the development of optimal first-line treatment strategies for those patients.

Methods

Search strategy

Comprehensive searches published in English were carried out in PubMed, Web of Science, Cochrane Library, and Embase to collect all relevant citations. The date of the latest search was Sep 18, 2021. Meeting abstracts were also searched from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). Keywords were used for the search: ("immune checkpoint inhibitor" OR "ICI" OR "immunotherapy" OR "PD-1" OR "Nivolumab" OR "Pembrolizumab" OR "SHR-1210" OR "Camrelizumab" OR "Tislelizumab" OR "Toripalimab" OR "JS001" OR "Sintilimab") AND ("esophageal" OR "esophagus" OR "oesophageal" OR "oesophagus" OR "esophagogastric" OR "gastro-oesophageal" OR "gastroesophageal" OR "EGJ" OR "GEJ") AND ("cancer" OR "carcinoma" OR "tumor" OR

“neoplasm”). Literature searching was performed independently by two authors independently (Mengli Xu; Yalan Yang). All searched results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Selection criteria

Inclusion criteria: (1) randomized clinical trials in patients with advanced esophageal cancer or gastro-oesophageal junction carcinoma (GEJC); (2) random assignment of PD-1 inhibitor plus chemotherapy or chemotherapy; (2) previously untreated, locally advanced, unresectable or metastatic EC/GEJ; (3) study contained one or all of the following information: OS, progression-free survival (PFS), objective response rate (ORR) and TrAEs.

Exclusion criteria: (1) the clinical trial was designed for perioperative treatment, second-line or later therapy; (2) observational studies, editorials, study protocol, commentaries, reviews and case reports were excluded; (3) If datasets were duplicated or overlapped, only the most recent information was included.

The primary screening was done by reading the titles and abstracts of the studies to select relevant articles. The full texts of relevant articles were retrieved for eligibility. All the work above was accomplished by two authors independently to select included studies in the systematic review by searching the databases (Lulu Guan; Yu Chen). Disagreements were resolved by discussing it with all authors.

Data extraction

Study characteristics were extracted from each eligible study as follows: authors, publication year, trial name and phase, number of patients, treatment strategy, ORR, OS, PFS, the frequency of TrAEs, and some basic information, such as age, sex, region, Eastern Cooperative Oncology Group performance status (ECOG PS), histological type, tumor site, and PD-L1 status. Two authors extracted data with an information sheet, independently (Mengli Xu; Yuanyuan Yang). Discrepancies were resolved by all authors.

Statistical analysis

Pooled hazard ratio (HR) for OS and PFS, pooled odds ratio (OR) for ORR and TrAEs were estimated to assess the efficacy and safety of PD-1 inhibitor plus chemotherapy versus conventional chemotherapy. We performed several subgroup analyses to explore the variables on immunotherapy efficacy for esophageal cancer. We used Cochran’s Q test and Higgins I^2 statistic to evaluate heterogeneity. When high heterogeneity was detected ($I^2 > 50\%$), a random-effects model was adopted; otherwise, a fixed-effects model was adopted. The quality of included trials was assessed by two authors (Yao Lu; Lulu Guan) independently in accordance with the five-point Jadad scoring system[26]. The risk of bias of selected trials was evaluated by using the Cochrane Collaboration Tool[27]. The sensitivity analyses were used to evaluate the robustness of the combined outcomes. The meta-analysis was conducted according

to the Cochrane handbook for systematic reviews of interventions, and the forest figure were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corporation). All reported P -values were two-sided, and $P<0.05$ was considered statistically significant. The work was done independently by two authors (Yao Lu; Feng Wang). Disagreements were resolved by discussing it with all authors.

Results

Search Results

The literature screening process for this study was showed by flow diagram (Figure 1). A total of 1674 records were retrieved. 274 records were excluded for duplicates, 1391 records were excluded across exclusion criteria, 2 studies were excluded due to lack of the comparative data, and 7 randomized clinical studies which compared the efficacy and adverse events of PD-1 inhibitor plus chemotherapy with placebo plus chemotherapy as a first-line treatment in advanced or metastatic EC/GEJC[21-25, 28, 29].

The main characteristics of the included trials were summarized in Table 1. All literatures were randomized controlled trials (RCT) and published in 2021. The trials included a total of 3754 EC/GEJC patients. 4 trials enrolled patients with ESCC[22-25], and 1 trial enrolled patients with ESCC, EAC and GEJC[21]. We also extracted the patients' data with EAC and GEJC from 2 trials[28, 29].

Efficacy outcomes of PD-1 inhibitor plus chemotherapy

The pooled HR of OS and PFS, and the pooled OR of ORR were used to assess the efficacy of PD-1 inhibitor plus chemotherapy in first-line treating EC. In term of OS benefit, the PD-1 inhibitor plus chemotherapy led to a 28% reduction in the risk of death compared with chemotherapy (HR=0.72; 95% CI: 0.66-0.78, $P<0.01$), and there was no obvious heterogeneity ($I^2 = 0\%$, $P=0.435$) (Figure 2A). The pooled HR of PFS showed that PD-1 inhibitor plus chemotherapy significantly reduced the risk of disease progression compared with chemotherapy (HR=0.62; 95% CI: 0.57-0.68, $P<0.01$; and heterogeneity: $I^2 = 46.6\%$, $P=0.112$) (Figure 2B). In addition, the difference of ORR benefit was significantly between the PD-1 inhibitor plus chemotherapy group and chemotherapy group (OR=2.07; 95% CI: 1.76-2.43, $P<0.01$; and heterogeneity: $I^2 = 24.5\%$, $P=0.264$) (Figure 2C).

Association of histology and PD-L1 expression status with OS

Five studies had the result of OS for squamous cell carcinoma, and three studies had the result of OS for adenocarcinoma. The difference of OS benefit across histology subgroups obtained a near-significant trend ($P=0.054$) (Figure 3A). There were two studies assessed PD-L1 combined positive score (CPS). In the subgroup with PD-L1 CPS less than 10%, the pooled HR of OS was 0.76, and the OS benefit was the higher in patients with a PD-L1 CPS of at least 10% (HR=0.69). However, there was no statistically difference in terms of PD-L1 expression level ($P = 0.188$) (Figure 3B).

Subgroup analyses by clinical features

We performed subgroup analyses according to some basic information, including age, sex, ECOG PS. There was no significant interaction between treatment effect in terms of OS and clinical features (age: $P=0.236$; sex: $P=0.340$; ECOG: $P=0.593$) (Figure 4A). Same as before, the PFS benefit of PD-1 inhibitor plus chemotherapy compared to chemotherapy did not vary significantly across subgroups (age: $P=0.922$, sex: $P=0.390$, ECOG PS: $P=0.319$) (Figure 4B).

The Safety Evaluation of PD-1 inhibitor plus chemotherapy

The pooled OR of TrAEs was 1.85 (95% CI: 1.21-2.84, $P<0.01$; and heterogeneity: $I^2 = 9.9\%$, $P=0.350$), which showed that PD-1 inhibitor plus chemotherapy can increase the incidence of TrAEs, compared with chemotherapy (Figure 5A). In term of grade 3 or higher TrAEs, there was no statistical difference, but a near-significant trend (OR=1.24; 95% CI: 1.00-1.55, $P=0.05$) (Figure 5B).

Assessment of study quality and sensitivity analysis

All trials included in this study were multicenter and randomized clinical trial, and five trials were double blinded. The Jadad score ranged from 3 to 5, indicating that the quality was high (Table 1). The bias risk of the included studies was shown in Figure 6F. All trials included random sequence generation. Five trials were double blinded. Two trials were open label, and therefore these studies are at performance and detection bias. Two studies didn't report all data, so that they had risk for reporting bias. Nevertheless, all studies were felt to be low risk for attrition and other bias.

Sensitivity analysis was applied to evaluate the stability of our meta-analysis. The results showed that our meta-analysis were robust in term of pooled HR for OS (Figure 6A) and PFS (Figure 6B), pooled OR for ORR (Figure 6C), TrAEs (Figure 6D) and grade 3 or higher TrAEs (Figure 6E). No significant deviation from the overall results was detected.

Discussion

Chemotherapy and targeted therapy did not improve the survival of patients with esophageal cancer, and clinical trials of PD-1 inhibitors in the treatment of esophageal cancer have been gradually carried out[30, 31]. As far as the results were concerned, immunotherapy achieved a major breakthrough from the back line to the first line for patients with advanced esophageal cancer[17, 32]. Our previous meta-analysis has revealed that PD-1 inhibitors significantly prolonged the overall survival (OS) when compared with chemotherapy in previous systemic therapy patients with esophageal cancer. Perioperative immunotherapy for esophageal cancer is also beginning to recruit patients. In 2021, there were multiple studies reporting the results for advanced esophageal cancer in first-line therapy. KEYNOTE 590 announced global population data in Lancet, which was the first Phase 3 study to achieve a survival benefit, changing the landscape of first-line treatment for esophageal cancer[21]. The results from ESCORT-1st, published in JAMA, was a critical turning point in the treatment of ESCC[23]. The results of

nivolumab plus chemotherapy versus chemotherapy from Checkmate 648 were reported in 2021ASCO[22]. Orient-15 and Jupiter-06 were global, randomized, double-blind studies to evaluate the efficacy and safety of PD-1 inhibitor plus chemotherapy vs chemotherapy as first-line treatment in advanced ESCC, and also published the main data in 2021ESMO[24, 25]. Survival data related to GEJC were extracted from Checkmate 649 and Orient-16[28, 29]. Based on these data, a meta-analysis of prospective clinical trials was conducted. These included trials, which were all registered with ClinicalTrials.gov, were multicenter, randomized, phase 3 studies. Although some research results have yet to be published in a journal, data presented at ESMO or ASCO meeting met meta-analysis. To the best of our knowledge, this is the first meta-analysis that focuses on investigating the survival benefits in PD-1 inhibitor plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer.

Recent studies have shown that PD-1 inhibitor plus chemotherapy significantly improve survival benefit in first-line of treatment for advanced non-small cell lung carcinoma[33]. In our meta-analysis, we first compared the efficacy of PD-1 inhibitors plus chemotherapy versus chemotherapy as first-line therapy in advanced esophageal cancer patients. OS, PFS and ORR were selected as the primary endpoints. The results showed that PD-1 inhibitors plus chemotherapy significantly prolonged OS, PFS, and improve the ORR in advanced esophageal cancer. PD-1 inhibitor plus chemotherapy was associated with a 28% reduction in the risk of death, a 38% reduction in the risk of disease progression, and 2.07 times the probability of achieving an objective response compared with standard chemotherapy for first-line treatment. These results showed good clinical efficacy of immunotherapy plus chemotherapy, which can be used as a good choice for advanced esophageal cancer.

Previous studies have shown the expression level of PD-L1 as a predictive biomarker in cancer immunotherapy[34]. Therefore, we conducted a subgroup analysis to clarify the association between OS benefit with and different PD-L1 expression, the results showed a potentially better OS benefit in patients with baseline PD-L1 CPS of 10 or higher than in patients with a PD-L1 CPS of less than 10, but the test for interaction was not statistically significant. The same results were found in the Escort-1st study, which assessed the PD-L1 expression with cut-off value 1%. Histological types have an impact on survival of patients with esophageal cancer [35], and we also conducted a subgroup analysis to explore the OS difference between squamous cell carcinoma and adenocarcinoma. The OS benefit in patients with squamous cell carcinoma were superior than adenocarcinoma, but there was no statistical difference. This findings were consistent with data from previous studies where patients with esophageal cancer, typically with squamous cell carcinoma histology, had greater treatment benefit from immunotherapy[18, 36]. The Food and Drug Administration (FDA) of US has approved the pembrolizumab plus platinum and fluoropyrimidine-based chemotherapy for treatment of certain patients with locally advanced or metastatic EC/GEJC, regardless of PD-L1 expression.

We also showed the subgroup analyses by clinical features, which may be related to the efficacy of immunotherapy[37-39]. The OS and PFS benefits were similar in patients < 65 years old and ≥ 65 years old, patients ECOG PS 0 and 1. However, we found that greater OS and PFS benefits with PD-1 inhibitor

plus chemotherapy for male patients than for female patients, but there was no statistical difference. A recent meta-analysis also demonstrated that the relative benefit of immunotherapy was greater in male cancer patients than in female patients[39]. This finding also raises a clinically important question whether male has greater efficacy than female in advanced esophageal cancer patients with immunotherapy, which needs further studies.

Despite the success and ongoing promise of PD-1 inhibitor of advanced cancer, TrAEs, which have emerged as frequent complications of checkpoint blockade, remains a constraint of this type of therapy[40-42]. Therefore, we analyzed the incidence of total TrAEs events and grade 3 or higher TrAEs. Regarding the safety profile, PD-1 inhibitor plus chemotherapy was significantly associated with increasing risk of developing TrAEs, however, no significant difference was found in the incidence of grade 3 or higher TrAEs. All of these studies showed an acceptable safety profile in patients with PD-1 inhibitors plus chemotherapy.

Our results demonstrated that the combination of PD-1 inhibitor and chemotherapy can be considered as a new first-line treatment in patients with advanced esophageal cancer. Although some studies are searched from ASCO and ESMO meetings, the topic of this paper is still novel and the high quality of the data included in the meta-analysis, which provides a new direction for the first-line treatment of advanced esophageal cancer.

Conclusion

OS, PFS and ORR are all significantly improved in PD-1 inhibitors plus chemotherapy versus chemotherapy, with a manageable safety profile for first-line therapy in patients with advanced esophageal cancer. PD-1 inhibitor plus chemotherapy should be considered for patients with unresectable, metastatic esophageal cancer in the first-line setting.

Abbreviations

EC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; GEJC: gastro-oesophageal junction carcinoma; GEJAC: gastro-oesophageal junction adenocarcinoma; PD-1: Programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1; HR: Hazard ratio; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; DOR: Duration of response; CI: Confidence interval; TrAEs: treatment-related adverse effects; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status.

Declarations

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Authors' Contributions

Yao Lu: Statistical analysis, Writing-Original Draft, Assessment of study quality; Mengli Xu: Literature searching, Data extraction; Lulu Guan: Literature screening, Assessment of study quality; Yalan Yang: Literature searching; Yu Chen: Literature screening; Yuanyuan Yang: Data extraction; Feng Wang: Statistical analysis, Writing-Review and Editing, Funding acquisition.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

All datasets analyzed during the current study are available from PubMed, Web of Science, Cochrane Library, Embase and the meetings abstract of ASCO and ESMO.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agree the work published in this journal.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 0:1-41.
2. Short MW, Burgers KG, Fry VT. Esophageal cancer. *Am Fam Physician* 2017; 95:22-28.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in china, 2015. *CA Cancer J Clin* 2016; 66:115-32.
4. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in western and eastern countries. *World J Gastroenterol* 2015; 21:7933-43.
5. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2019, nccn clinical practice guidelines in oncology. *J Natl Compr Canc*

Netw 2019; 17:855-883.

6. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016; 66:271-89.
7. Zhang X, Jia J, Lu M, Wang X, Gong J, Li J, et al. Nimotuzumab plus paclitaxel and cisplatin as a 1(st)-line treatment for esophageal cancer: Long term follow-up of a phase ii study. *J Cancer* 2019; 10:1409-1416.
8. Chen Y, Wu X, Hao D, Cheng X, Zhang L, Zhang Y, et al. Neoadjuvant nimotuzumab plus chemoradiotherapy compared to neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma. *Oncotarget* 2019; 10:4069-4078.
9. Barsouk A, Rawla P. Targeted therapies and immunotherapies in the treatment of esophageal cancers. 2019; 7:
10. Gotwals P, Cameron S, Cipolletta D, Cremasco V, Crystal A, Hewes B, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer* 2017; 17:286-301.
11. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: A common denominator approach to cancer therapy. *Cancer Cell* 2015; 27:450-61.
12. Doi T, Piha-Paul SA, Jalal SI, Saraf S, Lunceford J, Koshiji M, et al. Safety and antitumor activity of the anti-programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. *Journal of Clinical Oncology* 2018; 36:61-67.
13. Huang J, Xu B, Mo H, Zhang W, Chen X, Wu D, et al. Safety, activity, and biomarkers of shr-1210, an anti-pd-1 antibody, for patients with advanced esophageal carcinoma. *Clinical Cancer Research* 2018; 24:1296-1304.
14. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (attraction-3): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; 20:1506-1517.
15. Tumei PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. Pd-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; 515:568-71.
16. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. Pd-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; 372:2509-20.
17. Schizas D, Charalampakis N. Immunotherapy for esophageal cancer: A 2019 update. *Immunotherapy* 2020; 12:203-218.
18. Kojima T, Shah MA. Randomized phase iii keynote-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *Journal of Clinical Oncology* 2020; Jco2001888.
19. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (escort): A multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* 2020; 21:832-842.

20. Lu Y, Guan L, Xu M, Wang F. The efficacy and safety of antibodies targeting pd-1 for treatment in advanced esophageal cancer: A systematic review and meta-analysis. *Translational Oncology* 2021; 14:
21. Sun J-M, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (keynote-590): A randomised, placebo-controlled, phase 3 study. *Lancet* 2021; 398:759-771.
22. Chau I, Doki Y, Ajani JA, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab (nivo) plus ipilimumab (ipi) or nivo plus chemotherapy (chemo) versus chemo as first-line (1l) treatment for advanced esophageal squamous cell carcinoma (escc): First results of the checkmate 648 study. *Journal of Clinical Oncology* 2021; 39:LBA4001.
23. Luo H, Lu J, Bai Y, Mao T, Wang J, Fan Q, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: The escort-1st randomized clinical trial. *Jama* 2021; 326:916-925.
24. Xu RH, Wang F, Cui C, Yao J, Zhang Y, Wang G, et al. 1373mo jupiter-06: A randomized, double-blind, phase iii study of toripalimab versus placebo in combination with first-line chemotherapy for treatment naive advanced or metastatic esophageal squamous cell carcinoma (escc). *Annals of Oncology* 2021; 32:S1041.
25. Shen L, Lu ZH, Wang JY, Shu YQ, Kong L, Yang L, et al. Lba52 sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: First results of the phase iii orient-15 study. *Annals of Oncology* 2021; 32:S1330.
26. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
27. 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.
28. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (checkmate 649): A randomised, open-label, phase 3 trial. *Lancet* 2021; 398:27-40.
29. Xu J, Jiang H, Pan Y, Gu K, Cang S, Han L, et al. Lba53 sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastroesophageal junction (g/gej) adenocarcinoma (orient-16): First results of a randomized, double-blind, phase iii study. *Annals of Oncology* 2021; 32:S1331.
30. Hirano H, Kato K. Systemic treatment of advanced esophageal squamous cell carcinoma: Chemotherapy, molecular-targeting therapy and immunotherapy. *Jpn J Clin Oncol* 2019; 49:412-420.
31. Alsina M, Moehler M, Lorenzen S. Immunotherapy of esophageal cancer: Current status, many trials and innovative strategies. *Oncol Res Treat* 2018; 41:266-271.

32. Vivaldi C, Catanese S, Massa V, Pecora I, Salani F, Santi S, et al. Immune checkpoint inhibitors in esophageal cancers: Are we finally finding the right path in the mist? *Int J Mol Sci* 2020; 21:
33. Zhou Y, Chen C, Zhang X, Fu S, Xue C, Ma Y, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: A systematic review and meta-analysis. *J Immunother Cancer* 2018; 6:155.
34. Patel SP, Kurzrock R. Pd-I1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* 2015; 14:847-56.
35. Xi M, Yang Y, Zhang L, Yang H, Merrell KW, Hallemeier CL, et al. Multi-institutional analysis of recurrence and survival after neoadjuvant chemoradiotherapy of esophageal cancer: Impact of histology on recurrence patterns and outcomes. *Ann Surg* 2019; 269:663-670.
36. Shah MA, Bennouna J, Shen L, Enzinger PC, Li Q, Csiki I, et al. Pembrolizumab (mk-3475) for previously treated metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: Phase ii keynote-180 study. *Journal of Clinical Oncology* 2016; 34:
37. Yang F, Wang YC, Nowakowski GS, Wang M, Chintakuntlawar AV, Halfdanarson TR, et al. Association of sex, age and ecog performance status with cancer immunotherapy efficacy in randomized controlled trials. *Journal of Clinical Oncology* 2019; 37:
38. Jiang Y, Su Z. Cancer immunotherapy efficacy and patients' age: A systematic review and meta-analysis. *Annals of Oncology* 2019; 30:
39. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, et al. Cancer immunotherapy efficacy and patients' sex: A systematic review and meta-analysis. *Lancet Oncology* 2018; 19:737-746.
40. Anderson R, Jing Y, Liu J, Ye Y. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Support Care Cancer* 2020; 11:4946.
41. Abdel-Wahab N, Alshawa A, Suarez-Almazor ME. Adverse events in cancer immunotherapy. *Nat Commun* 2017; 995:155-174.
42. Blidner AG, Choi J, Cooksley T, Dougan M, Glezerman I, Ginex P, et al. Cancer immunotherapy-related adverse events: Causes and challenges. *Supportive Care in Cancer* 2020; 28:6111-6117.

Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

The flowchart of studies selection process for the meta-analysis.

Figure 2

Pooled hazard ratio for overall survival (A), progression-free survival (B), and pooled odds ratio for objective response rate (C) in advanced esophageal cancer treated with PD-1 inhibitor plus chemotherapy versus chemotherapy. (HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; PD-1: Programmed cell death 1)

Figure 3

Forest plot of hazard ratios by histological type (A) and PD-L1 expression (B) comparing overall survival in patients who received PD-1 inhibitor plus chemotherapy versus chemotherapy.

A

B

Figure 4

Forest plot of hazard ratio in subgroup analysis by clinical information comparing overall survival (A) and progression-free survival (B) in patients who received PD-1 inhibitors plus chemotherapy versus chemotherapy. (HR: Hazard ratio; CI: Confidence interval; PD-1: Programmed cell death 1; ECOG PS: ECOG performance status)

Figure 5

Pooled odds ratio (OR) for the incidence of all treatment-related adverse effect (A) and grade 3 or higher treatment-related adverse effect (B). (OR: Odds ratio; CI: Confidence interval; and PD-1: Programmed cell death 1)

Figure 6

Sensitivity analysis of the hazard ratios of overall survival (A), progression-free survival (B), and the odds ratio for objective response rate (C), TrAEs (D) and grade 3 or higher TrAEs (E). The risk of bias was evaluated by using the Review Manager 5.3 (F).

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- [Table1.docx](#)