Combination immunochemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: a systematic review and meta-analysis

Qiudong Xu,1,2 Shuang Huang,2 Kai Yang 2

ABSTRACT

Objective To evaluate the efficacy and safety of combination immunochemotherapy regimens for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Design Meta-analysis and systematic review.

Data sources PubMed, Embase, Web of Science and Cochrane library and the Clinicaltrials.gov clinical trials registry were searched up to 14 March 2022.

Eligibility criteria for selecting studies We included randomised controlled trials that compared combination immunochemotherapy with conventional chemotherapy for R/M HNSCC. Primary outcomes of interest were overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse effects (AEs).

Data extraction and synthesis Two reviewers independently extracted data and assessed the risk of bias of the included studies. The HR and its 95% CI were used as the effect analysis statistic for survival analysis, while the OR and its 95% CI were used as the effect analysis statistic for dichotomous variables. These statistics were extracted by the reviewers and aggregated using a fixed-effects model to synthesise the data.

Results A total of 1214 relevant papers were obtained after the initial search, and five papers that met the inclusion criteria were included; these studies included a total of 1856 patients with R/M HNSCC. Meta-analysis showed that the OS and PFS of patients with R/M HNSCC in the combination immunochemotherapy group were significantly longer than those in the conventional chemotherapy group (HR=0.84; 95% CI 0.76, 0.94; p=0.002; HR=0.67; 95% CI 0.61, 0.75; p<0.0001), and the ORR was significantly higher (OR=1.90; 95% CI 1.54, 2.34; p<0.0001). The analysis of AEs showed that there was no significant difference in the overall incidence rate of AEs between two groups (OR=0.80; 95% CI 0.18, 3.58; p=0.77), but the rate of grade III and IV AEs was significantly higher in patients in the combination immunochemotherapy group (OR=3.58; 95% CI 1.12, 1.73; p<0.003).

Conclusions Combination immunochemotherapy prolonged OS and PFS in patients with R/M HNSCC and improved the ORR; while this approach did not increase the overall incidence of AEs in patients, it increased the rate of grade III and IV AEs.

PROSPERO registration number CRD42022344166.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was based on strict inclusion and exclusion criteria and a comprehensive search of existing databases to ensure the comprehensiveness of the research.

⇒ All included studies were open-label trials and did not employ blinding.

⇒ The number of included studies was limited and did not meet the criteria for publication bias assessment.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) ranks as the sixth most common cancer worldwide, with over 740,000 new cases and more than 360,000 deaths annually.1 2 The main treatment options for patients with HNSCC are surgery, radiotherapy, chemotherapy and combination therapy.3 4 However, most patients with HNSCC already have locally advanced or metastatic disease at the time of diagnosis5 and more than 50% of patients with locally advanced HNSCC who undergo surgery develop local recurrence or distant metastases within 2 years after surgery.6 8 Surgery is often difficult for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), and systemic chemotherapy is the main treatment option for these patients.9

Platinum-based anticancer drug regimens (platinum+5-fluorouracil, platinum+docetaxel or paclitaxel) are the standard first-line treatment for patients with R/M HNSCC. Compared with single-agent chemotherapy regimens, platinum-based chemotherapy regimens significantly improve the remission rate in patients with R/M HNSCC,10 11 but do not show a significant advantage in prolonging patient survival, with the overall survival (OS) in patients with R/M HNSCC treated by platinum-based
chemotherapy regimens usually not exceeding 6 months.\textsuperscript{12,13}

As the role of the immune system in the development and progression of HNSCC has been further investigated, immune drugs in combination with traditional platinum-based chemotherapy regimens have begun to gain increasing attention. In 2006, the US Food and Drug Administration approved cetuximab, a chimeric monoclonal antibody targeting epidermal growth factor receptor (EGFR), for the treatment of patients with R/M HNSCC. A phase III clinical trial by Vermorken et al.\textsuperscript{14} showed that the use of cetuximab in combination with platinum-based chemotherapy (the EXTREME regimen: cetuximab+cisplatin/carboplatin+5-fluorouracil) significantly improved the survival time of patients with R/M HNSCC. The median survival time of patients treated with EXTREME was increased to 10 months from 6 months with platinum-based chemotherapy.\textsuperscript{14} Based on the results of this clinical trial, the EXTREME regimen has become the new standard chemotherapy option for the first-line treatment of R/M HNSCC.\textsuperscript{15,16}

Currently, a number of randomised controlled clinical trials related to combination immunochemotherapy regimens are ongoing, and some results have been reported.\textsuperscript{14,17–23} However, the efficacy and adverse effects of different combination immunochemotherapy regimens are inconsistent, and current clinical guidelines on the use of combination immunochemotherapy regimens are mostly based on the results of individual randomised controlled clinical trials with small caseloads and distinct study centres. Therefore, there is a need for a systematic evaluation and meta-analysis of the efficacy and safety of combination immunochemotherapy regimens compared with conventional chemotherapy regimens for the treatment of R/M HNSCC.

In this study, a systematic review and meta-analysis of the published studies related to combination immunochemotherapy regimens was conducted. The effectiveness and safety of combination immunochemotherapy regimens compared with conventional chemotherapy regimens in the treatment of R/M HNSCC were analysed in terms of OS, progression-free survival (PFS) and objective response rate (ORR) as outcome indicators of effectiveness and incidence of AEs and grade III and IV AEs as the outcome indicator of safety. We expect to provide a reference and guidance for the clinical application of combination immunochemotherapy regimens in the treatment of R/M HNSCC.

**Materials and Methods**

**Protocol**

The reporting of this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.\textsuperscript{24}

**Search strategy**

The PubMed, Embase, Cochrane Library(Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Review) and Web of Science databases were searched for this study. Searches were conducted using a combination of subject terms and free words: “Squamous Cell Carcinoma of Head and Neck”, “Recurrent or Metastatic”, “Immunotherapy”, “Combination” and “Randomized Controlled Trial”. Each database was searched from inception to 14 March 2022. No language restrictions on literature search strategy. In addition, Clinicaltrials.gov was searched to include ongoing randomised controlled trials (RCTs). The detailed search strategy is shown in online supplemental table 1.

**Inclusion and exclusion criteria**

Inclusion criteria: (1) study participants: patients with histologically or cytologically confirmed R/M HNSCC that cannot be surgically resected; (2) study type: RCT; (3) intervention: trial group treated with at least one immunological agent in combination with a traditional platinum-based anticancer drug chemotherapy regimen; and (4) outcome measures (including at least one of the following outcome measures): OS (time from randomisation to death from any cause); PFS (time from randomisation to first progression or death); ORR (the proportion of patients achieving a complete response or partial response based on RECIST version 1.1\textsuperscript{25}); and incidence of AEs (the unwanted or harmful effects associated with a treatment or disease) and grade III and IV AEs (severe or life-threatening side effects associated with a treatment or disease, as per the Common Terminology Criteria for Adverse Events grading system).

Exclusion criteria: (1) studies focusing on patients with R/M HNSCC receiving surgery or radiotherapy in conjunction with combination immune therapy; (2) retrospective studies, single-arm trials and animal studies; (3) studies with incomplete trial study designs; (4) studies with insufficient data and (5) studies focusing on patients with nasopharyngeal carcinoma, which, although part of HNSCC, has a different pathogenesis and treatment options than HNSCC.

**Study selection and data extraction**

Two researchers (QX and SH) independently screened all titles and abstracts and obtained full texts of literature that potentially met the inclusion criteria. The researchers applied the inclusion/exclusion criteria to the full-text articles. Any disagreements were resolved through consensus or with the assistance of a third researcher (KY).

Both researchers independently extracted data that included general information: title, author, country of study, funding, publication year, registration number; study details: objective, design, inclusion and exclusion criteria, randomisation methods and allocation; study population: age, gender, race, sample size, ECOG (Eastern Cooperative Oncology Group) score, tumour
site, pathological staging; intervention characteristics: type, duration, dose, follow-up time points, compliance and outcomes: OS, PFS, ORR, and incidence of AEs and grade III and IV AEs.

Risk of bias assessment
The two aforementioned researchers independently completed risk of bias assessments using the Cochrane Collaboration’s tool for assessing risk of bias in randomised trials (ROB1). Any discrepancies were cross-checked, and any disagreements were resolved with the help of a third researcher (KY). The Cochrane Risk of Bias tool assesses the risk of bias in RCTs across several criteria, including: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other sources of bias.

Statistical analysis
Analyses were conducted using Review Manager V.5.4 (Cochrane Collaboration). The HR and its 95% CI were used as the effect analysis statistic for survival analysis, and the OR and its 95% CI were used as the effect analysis statistic for dichotomous variables. The $\chi^2$ test was used to test the heterogeneity of the included studies, and I² was used to quantify the heterogeneity: if $p>0.1$ and $I^2 \leq 50\%$, the heterogeneity among studies was considered low, and a fixed-effect model analysis was used; if $p\leq0.1$ and $I^2>50\%$, the heterogeneity among studies was considered high, and a random-effect model analysis was used; for the effect sizes with large heterogeneity, sensitivity analysis was used to evaluate study reliability.

Patient and public involvement
Patients and the public were not involved in any way.

RESULTS
Included studies
A total of 1214 relevant papers were obtained after completing the preliminary search according to the given search strategy, and 282 duplicate papers were removed. A total of five studies (E1305, CHANGE-2, EXTREME, SPECTRUM, PARTNER) were finally included. The literature screening process and results are shown in figure 1.

Characteristics of the included studies/trials
The eligible articles for inclusion criteria were published or updated between 2008 and 2021. The total number of participants in the trials ranged from 111 in PARTNER to 657 in SPECTRUM. All studies had a 1:1 allocation ratio between the experimental and control groups, except for CHANGE-2, which used a 2:1 ratio. The median follow-up time varied from 11 months in SPECTRUM to 40 months in E1305.

All five studies were multicentre trials, with E1305 conducted in the USA and South Africa, CHANGE-2 conducted in China, EXTREME conducted in...
Europe, SPECTRUM\(^{22}\) conducted in the Asia Pacific, North America, South America, Western Europe and Eastern Europe and PARTNER\(^{23}\) conducted in the USA and Europe. Two studies\(^{14,20}\) used cetuximab in combination with platinum-based chemotherapy regimens, two studies\(^{22,23}\) used panitumumab in combination with platinum-based chemotherapy regimens and one study\(^{17}\) used bevacizumab in combination with platinum-based chemotherapy regimens.

All five studies\(^{14,17,20,22,23}\) were open-label, RCTs, with four being phase III clinical trials\(^{14,17,20,22}\) and one being a phase II clinical trial.\(^{23}\) E1305\(^{17}\) was supported by the National Cancer Institute, while EXTREME\(^{14}\) and CHANGE-2\(^{20}\) were supported by Merck. SPECTRUM\(^{22}\) and PARTNER\(^{23}\) were supported by Amgen Inc.

Except for E1305,\(^{17}\) all studies provided baseline data including age, gender, primary tumour site and recurrence/metastasis status. The median age of the overall population of participants across all trials ranged from 57 to 59 years, with the proportion of male participants ranging from 84\% to 92\%. Significantly more male patients than female patients were present in all five studies.\(^{14,17,20,22,23}\)

The characteristics of the included studies can be found in table 1, while a comprehensive overview is available in online supplemental table 2.

### Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Sample size (n)</th>
<th>Median Age (y)</th>
<th>Male (%)</th>
<th>Primary tumour site</th>
<th>Intervention arm</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral cavity (n)</td>
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<td></td>
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<td></td>
<td>Oropharynx (n)</td>
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<td></td>
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<td></td>
<td>Hypopharynx (n)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention arm</td>
<td></td>
</tr>
<tr>
<td>Argiris 2019 (E1305)(^{17})</td>
<td>III</td>
<td>203/200</td>
<td>NA</td>
<td>87/84</td>
<td>41/44</td>
<td>87/76</td>
</tr>
<tr>
<td>Guo 2021 (CHANGE-2)(^{20})</td>
<td>III</td>
<td>164/79</td>
<td>57/57</td>
<td>89/85</td>
<td>46/21</td>
<td>25/17</td>
</tr>
<tr>
<td>Vermorken 2008 (EXTREME)(^{14})</td>
<td>III</td>
<td>222/220</td>
<td>57/57</td>
<td>89/92</td>
<td>46/42</td>
<td>80/69</td>
</tr>
<tr>
<td>Vermorken 2013 (SPECTRUM)(^{22})</td>
<td>III</td>
<td>327/330</td>
<td>58/59</td>
<td>87/87</td>
<td>89/102</td>
<td>86/96</td>
</tr>
<tr>
<td>Wirth 2016 (PARTNER)(^{23})</td>
<td>II</td>
<td>56/55</td>
<td>57/58</td>
<td>85/90</td>
<td>19/13</td>
<td>15/26</td>
</tr>
</tbody>
</table>

### Risk of bias

All five included studies\(^{14,17,20,22,23}\) reported sufficient information regarding the methods used to generate the random sequence, so we consider these trials to have a low risk of bias. Except for PARTNER,\(^{23}\) all studies\(^{14,17,20,22}\) reported a method of allocation concealment, so we also consider these trials to have a low risk of bias. However, due to the lack of sufficient information regarding the allocation concealment procedure in PARTNER,\(^{23}\) we consider the risk of bias in this trial to be unclear.

All five included studies\(^{14,17,20,22,23}\) were open-label trials and did not employ any blinding for the implementers or participants. Therefore, we consider their performance bias to be high risk. Four of them,\(^{14,20,22,23}\) with the exception of E1305,\(^{17}\) reported independent radiological review, so we consider the detection bias risk to be low in CHANGE-2,\(^{20}\) EXTREME,\(^{14}\) SPECTRUM\(^{22}\) and PARTNER,\(^{23}\) However, due to the lack of reporting information, the detection bias risk of E1305\(^{17}\) is unclear.
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Figure 2  Summary of results from the assessment of studies using the Cochrane Risk of Bias tool.

included studies14 17 20 22 23 provided complete reporting of outcome data, indicating low risk of attrition bias. However, only EXTREME14 reported outcome data in a prespecified way, according to its published protocol, so we consider that EXTREME14 has low reporting bias. For the remaining four studies17 20 22 23 we consider the reporting bias was unclear.

Risk of bias assessment of each individual study is summarised in figure 2 which shows that all included studies had mixed risks with unclear or high risks of bias. High risk of bias was concentrated in allocation blinding of participants and personnel, which was high risk for all included studies.14 17 20 22 23

Efficacy outcomes

The efficacy outcome indicators include OS, PFS and ORR. Five studies14 17 20 22 23 were included in the analysis for all three outcome measures, and there was no significant heterogeneity among the studies as determined by the heterogeneity tests (p=0.49, I²=0%; p=0.09, I²=50%; p=0.53, I²=0%), therefore a fixed-effect model was used for the efficacy outcome indicators. OS and PFS data of the included studies are provided in online supplemental table 3.

Overall survival

A total of 972 patients in the combination immunonotherapy group and 884 patients in the conventional chemotherapy group were included. The OS of patients in the combination immunonotherapy group was significantly longer than that in the conventional chemotherapy group (HR=0.84; 95% CI 0.76, 0.94; p=0.002) (figure 3A). Subgroup analysis was performed for different immunological agents, and the results showed that patients in the cetuximab combination chemotherapy group had a significantly longer OS than those in the conventional chemotherapy group (HR=0.76; 95% CI 0.64, 0.91; p=0.003), but the panitumumab combination chemotherapy group (HR=0.90; 95% CI 0.76, 1.07; p=0.23) and the bevacizumab combination chemotherapy group (HR=0.87; 95% CI 0.70, 1.08; p=0.21) were not significantly different from the conventional chemotherapy group in terms of OS (figure 3B).

Further subgroup analyses were performed for patient sex, ECOG score, primary tumour location, tumour recurrence and metastasis status, and tumour differentiation status. The results showed that patient sex, ECOG score and tumour primary location had a significant effect on OS. In the male subgroup (HR=0.79; 95% CI 0.65, 0.95; p=0.01), ECOG=1 subgroup (HR=0.84; 95% CI 0.72, 0.99; p=0.03) and tumour primary in the oral subgroup (HR=0.64; 95% CI 0.52, 0.80; p=0.0001), the combination immunocombination chemotherapy regimens significantly prolonged OS compared with conventional chemotherapy regimens (online supplemental figures 1 and 2). Subgroup analysis according to tumour recurrence or metastasis status and tumour differentiation showed that tumour recurrence or metastasis status and tumour differentiation indicated that these factors had no significant effect on OS (online supplemental figure 3).

Progression-free survival

A total of 972 patients in the combination immunonotherapy group and 884 patients in the conventional chemotherapy group were included. The analysis showed that patients in the combination immunonotherapy group had a significantly longer PFS time than those in the conventional chemotherapy group (HR=0.67; 95% CI 0.61, 0.75; p<0.0001) (figure 4A).

Objective response rate

A total of 919 patients in the combination immunonotherapy group and 838 patients in the conventional chemotherapy group were included. The analysis showed that the ORR was significantly higher in patients in the combination immunonotherapy group than in the
conventional chemotherapy group (OR=1.90; 95% CI 1.54, 2.34; p<0.00001) (figure 4B).

Safety outcomes
The safety outcome indicators included overall incidence of AEs and grade III and IV AEs. Two studies20 23 were included in the analysis of overall incidence of AEs, and five studies14 17 20 22 23 were included in the analysis of grade III and IV AEs. There was no significant heterogeneity among the studies (p=0.53, I²=0%; p=0.34, I²=11%), therefore a fixed-effect model was used for the safety outcome indicators.

Overall AE incidence
A total of 214 patients in the combination immunochemotherapy group and 129 patients in the conventional chemotherapy group were included. The analysis showed that no significant difference was found in overall AE incidence between the combination immunochemotherapy group and the conventional chemotherapy group (OR=0.80; 95% CI 0.18, 3.58; p=0.77) (figure 5A).

Grade III and IV AEs
A total of 956 patients in the combination immunochemotherapy group and 870 patients in the conventional chemotherapy group were included. The analysis showed that the incidence of grade III and IV AEs was significantly higher in the combination immunochemotherapy group than in the conventional chemotherapy group (OR=1.39; 95% CI 1.12, 1.73; p=0.003) (figure 5B). Further subgroup analysis showed that the incidence of grade III and IV hypokalaemia (p=0.006), hypomagnesemia (p<0.00001) and dehydration (p=0.0004) was significantly higher in the combination immunochemotherapy group than in the conventional chemotherapy group. However, there was no significant difference between the two groups in the incidence of grade III and IV neutropenia (p=0.17), anaemia (p=0.68), thrombocytopenia (p=0.68), leukopenia (p=0.09), neutropenic fever (p=0.17) or diarrhoea (p=0.06) (table 2).

Publication bias test and sensitivity analysis
Because of the limited number of included studies for the outcome indicators analysed in this study (n<10), Egger
and Begg tests were not used to evaluate publication bias. There were differences in baseline data between the included studies, such that E130517 included significantly fewer people than the remaining studies, the CHANGE-2 experimental group to control group ratio was set at 2:1, and the duration of follow-up ranged from 11 to 40 months. We used sensitivity analysis to assess the impact of these differences on the meta-analysis. Sensitivity analysis of the outcome indicators with significant heterogeneity revealed that the excluding individual studies one by one did not affect the results, suggesting that the conclusions of each outcome indicator were stable and reliable, so we concluded that these differences in baseline data did not have an impact on the results of the meta-analysis.

**DISCUSSION**

This study is the first systematic review and meta-analysis to investigate the effectiveness and safety of immune combination chemotherapy in the treatment of R/M HNSCC. It is noteworthy that the study includes the inclusion of the CHANGE-2 trial, which focuses on the previously neglected or under-researched Asian population. This important addition enhances the generalisability of the results.
the results and provides a more comprehensive understanding of the effectiveness of this treatment approach for different patient populations.

The most widely used cancer immunotherapy is monoclonal antibody-based immunotherapy, including regimens targeting tumour antigen (TA), cytokines and tumour necrosis factor receptor family costimulation as well as immune checkpoint inhibitor therapy.27 Of the five papers14 17 20 22 23 included in this paper on combination immunochemotherapy for R/M HNSCC, four papers14 20 22 23 had a trial group using TA-targeted therapy, an anti-EGFR monoclonal antibody (cetuximab or panitumumab) combined with platinum-based chemotherapy, and one paper17 had a trial group using cytokine-targeted therapy, an anti-VEGF (vascular endothelial growth factor) monoclonal antibody (bevacizumab) combined with a platinum-based chemotherapy regimen.

EGFR, a glycoprotein receptor with tyrosine kinase activity located on the cell membrane surface, belongs to the ErbB receptor family.28 29 EGFR is overexpressed in 80%–90% of HNSCC tumour cells, and when EGFR ligands bind to the extracellular ligand binding region, the receptor can homodimerize or heterodimerize, activating intracellular tyrosine kinases and further activating downstream signalling pathways.30 31 This leads to tumour cell proliferation and invasion, resulting in poor patient prognosis.32 Anti-EGFR monoclonal antibodies specifically bind to the extracellular structural domain of human EGFR, thereby competitively inhibiting epidermal growth factor binding to EGFR, blocking EGFR phosphorylation and thus inhibiting downstream signalling.33–35 The VEGF family plays an extremely important role in the regulation of neovascularisation and lymphatic vessel formation. VEGF secreted by tumour cells and the surrounding stroma is able to stimulate the proliferation of vascular endothelial cells, leading to the formation of new blood vessels in tumour tissue, which may result in abnormal tumour architecture as well as local invasion of tumour cells.36–39 VEGF is overexpressed in most human tumours and is strongly associated with tumour aggressiveness, vascular density, metastasis, recurrence and prognosis.40–43

This study contains an analysis of the efficacy and safety of five combination immunochemotherapy regimens in comparison with those of conventional chemotherapy for R/M HNSCC. Since OS is the most important outcome indicator in the assessment of treatment efficacy in patients with malignancy, it was also studied as the main outcome indicator in this study. The meta-analysis results showed that OS was significantly longer in the combination immunochemotherapy group of R/M HNSCC patients than in the conventional chemotherapy group. According to Wirth et al23 and Vermorken et al,22 panitumumab combined with conventional platinum-based chemotherapy regimens was more effective in prolonging PFS (6.9 months vs 5.5 months and 5.8 months vs 4.6 months, respectively) and improving the ORR (44% vs 37% and 37% vs 26%, respectively) in patients with R/M HNSCC but did not prolong OS (12.9 months vs 13.8

<table>
<thead>
<tr>
<th>Subgroup analysis of grade III and IV adverse effects (AEs)</th>
<th>Included studies (n)</th>
<th>Events/total</th>
<th>OR (M-H, random, 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>24/793</td>
<td>1.45 (0.85–2.49)</td>
<td>0.17</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4</td>
<td>9/793</td>
<td>1.94 (0.85–4.40)</td>
<td>0.08</td>
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<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>5/793</td>
<td>0.92 (0.51–1.66)</td>
<td>0.68</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>8/793</td>
<td>0.92 (0.61–1.38)</td>
<td>0.68</td>
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<td>Hypokalaemia</td>
<td>3</td>
<td>8/793</td>
<td>0.92 (0.51–1.38)</td>
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<tr>
<td>Hypomagnesemia</td>
<td>3</td>
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<td>0.92 (0.51–1.38)</td>
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<td>4</td>
<td>21/793</td>
<td>1.60 (0.86–2.98)</td>
<td>0.12</td>
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<tr>
<td>Dehydration</td>
<td>3</td>
<td>2/490</td>
<td>2.56 (1.52–4.39)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Bold rows indicate statistical significance at p<0.05.
months and 11.1 months vs 9.0 months, respectively). In this study, a subgroup analysis of different immunologic agents showed that, compared with panitumumab and bevacizumab, cetuximab in combination with chemotherapy significantly prolonged OS in patients with R/M HNSCC. According to the reports by Vermorken et al.\(^1\) and Guo et al.,\(^2\) the OS of patients receiving cetuximab combined with chemotherapy was 10.1 months versus 7.4 months and 11.1 months versus 8.9 months compared with those receiving traditional chemotherapy regimens, respectively. And the subgroup analysis also showed that immunotherapy in combination with chemotherapy significantly prolonged OS in male patients, patients with an ECOG score of 1, and patients with primary tumours in the oral cavity. It is worth noting that in the subgroup analysis of OS, only the difference between groups was significant (p=0.05, \(I^2=60.6\%\)) for the primary tumour location, while the difference between groups for the remaining subgroups was not significant, and therefore the results of the subgroup analysis should be interpreted with caution.

The consideration of treatment options for patients with R/M HNSCC is based not only on studies analysing effectiveness but also on those evaluating safety. In this study, there was no significant difference in the overall incidence of adverse events between combination immunchemotherapy and conventional chemotherapy, but combination immunchemotherapy significantly increased grade III and IV AEs including hypokalaemia, hypomagnesemia and dehydration, which are considered acceptable in light of the efficacy benefits of combination immunchemotherapy regimens and can be mitigated by symptomatic treatment.

We consider the quality of the five included RCTs\(^3\)\(^4\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\) to be moderate. Although only five studies were included, the total number of participants was considerable (n=1856), indicating a sufficient sample size. Furthermore, while all five studies\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\) were open-label trials, four of them,\(^3\)\(^4\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\) with the exception of E1305,\(^13\) reported independent radiological review. Therefore, we consider the results of these trials to be reliable.

The limitations of this study are as follows: (1) the number of trials included in the studies was small (n<10) and did not meet the criteria for publication bias assessment, so publication bias assessment was not performed. And some immunological agents, such as PD-1 and PD-L1 immune checkpoint inhibitors,\(^3\)\(^4\)\(^7\)\(^8\)\(^9\)\(^10\) combined with platinum-based chemotherapy regimens were excluded because the trial control group setting and trial type did not meet the inclusion criteria; (2) the human papillomavirus (HPV) infection status of patients has important implications for prognosis guidance. However, in the literature included, only one study\(^22\) reported on the HPV status of patients, so it was not possible to perform subgroup analysis of patients according to their HPV infection status.

In summary, combination immunchemotherapy significantly prolonged OS and PFS and improved ORRs in patients with R/M HNSCC compared with conventional platinum-based chemotherapy regimens, without increasing the overall incidence of adverse events, although an increase in grade III and IV adverse events was observed, which is acceptable.

**Contributors** OX is the first author, and KY is the corresponding author responsible for the overall content of the manuscript as the guarantor. OX and KY designed the study. OX and SH performed systematic searches, retrieved literature, and conducted data extraction. OX and SH conducted data analysis. OX wrote the first draft of the article. KY contributed to the important intellectual content, provided critical expertise, and made revisions to the manuscript. All authors have given final approval of the version to be published.

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