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Meta-analysis

The primary site of head and neck squamous cell carcinoma predicts survival benefits of EGFR inhibitors: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: To assess the survival benefits associated with epidermal growth factor receptor (EGFR) inhibitors in head and neck squamous cell carcinoma (HNSCC) according to the primary site.
Materials and methods: A systematic review and meta-analysis were conducted for randomized phase III trials comparing treatment with or without EGFR inhibitors in locoregionally advanced, recurrent, or metastatic HNSCC. The primary and secondary endpoints were overall survival (OS) and progression-free survival (PFS), respectively. Data were pooled using a random-effects model.
Results: Seven trials with a total of 3391 patients were included. The addition of EGFR inhibitors improved OS in patients with oral cavity-oropharyngeal carcinoma (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.67–0.87, $P < 0.001$) but not in patients with hypopharyngeal-laryngeal carcinoma (HR 0.94, 95% CI 0.82–1.08, $P = 0.398$). A significant interaction was found in favor of oral cavity-oropharyngeal carcinoma ($P = 0.029$). The addition of EGFR inhibitors increased PFS in both patients with oral cavity-oropharyngeal carcinoma (HR 0.67, 95% CI 0.52–0.85, $P = 0.001$) and patients with hypopharyngeal-laryngeal carcinoma (HR 0.81, 95% CI 0.69–0.94, $P = 0.005$). A trend towards significant interaction was found in favor of oral cavity-oropharyngeal carcinoma ($P = 0.161$). Comparable results were observed in the pre-specified subgroup analyses. Meta-regression analyses suggested that the primary site appeared to be a predictor of survival benefits in HNSCC patients who received treatment with EGFR inhibitors over those who did not.
Conclusion: Our meta-analysis suggests that the survival benefits of EGFR inhibitors might depend on primary sites in HNSCC. Further studies are needed to confirm this finding.

In clinical studies, medical oncologists generally group squamous cell carcinomas that originate in the oral cavity, oropharynx, hypopharynx, and larynx as the same disease, head and neck squamous cell carcinoma (HNSCC). The epidermal growth factor receptor (EGFR) is overexpressed in the overwhelming majority of HNSCC, and its overexpression is associated with poor prognosis [1]. Cetuximab, an antibody against EGFR, has been approved in combination with chemotherapy as the first-line treatment for recurrent or metastatic HNSCC [2]. The approval was based on the phase III EXTREME trial, in which the addition of cetuximab significantly prolonged the overall survival (OS) [3]. However, subgroup analyses suggested that the survival benefits were limited to HNSCC with primary site on the oral cavity [3]. Cetuximab was also shown to improve OS in locoregionally advanced disease when combined with radiotherapy in another phase III trial [4]. In this trial, oral cavity primaries were not included, and patients with oropharyngeal carcinoma appeared to benefit most from the addition of cetuximab [4]. To date, no studies have been adequately powered or designed to detect the differences in the treatment outcomes associated with cetuximab among primary sites in HNSCC.

We hypothesized that the OS benefits of EGFR inhibitors were limited to patients with oral cavity or oropharyngeal carcinoma

Abbreviations: CI, confidence interval; CNKI, China National Knowledge Infrastructure; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR, hazard ratios; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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of HNSCC. It would be interesting to study survival differences among all the primary sites, but a statistically sound investigation would have been unlikely due to availability of limited data from published literature. Here, we conducted a systematic review and meta-analysis of phase III randomized controlled trials in patients with locoregionally advanced, recurrent, or metastatic HNSCC who were treated with or without EGFR inhibitors. We aimed to assess the differences in the improvement of survival between patients with oral cavity-oropharyngeal carcinoma and those with hypopharyngeal-laryngeal carcinoma.

Materials and methods

We conducted this systematic review and meta-analysis by following the Preferred Reporting Items for Systematic Reviews and

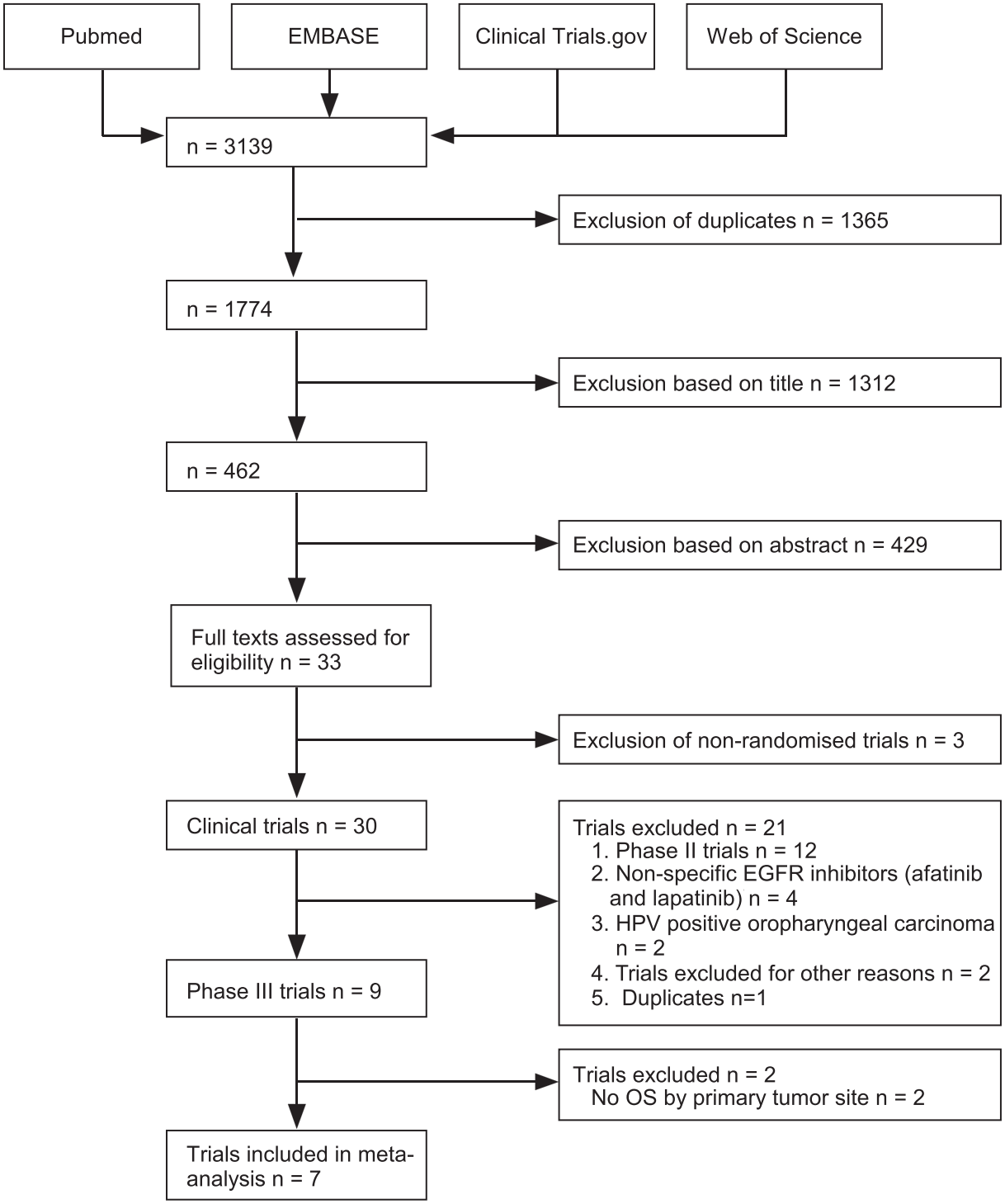

Fig. 1. Flow diagram of trial selection. Abbreviations: HPV, human papillomavirus; OS, Overall survival. Note: We did not identify an eligible randomized controlled trial in the Chinese databases.

Meta-Analyses guidelines [5]. Disagreements in the process of this meta-analysis were resolved by discussion among the authors, with reference to a third reviewer, if necessary.

Selection criteria

We searched the following bibliographic databases: PubMed, ClinicalTrials.gov, EMBASE, Web of Science, and Chinese databases (China National Knowledge Infrastructure [CNKI], Database for Chinese Technical Periodicals, and Wan Fang) for articles published before May 1, 2020. The main search terms were "(EGFR OR HER1 OR ErbB1 OR epidermal growth factor receptor OR cetuximab OR panitumumab OR zalutumumab OR nimotuzumab OR duligotuzumab OR afatinib OR dacomitinib OR tyrosine kinase inhibitor OR TKI OR gefitinib OR erlotinib) AND (head and neck OR oral cavity OR oropharynx OR hypopharynx OR larynx) AND (carcinoma OR cancer) AND trial." A full search strategy is presented in the Supplementary Materials and Methods. To ensure complete coverage, we manually searched the reference lists of the retrieved review articles and primary studies.

Inclusion criteria were: (1) phase III, randomized controlled trials; (2) locoregionally advanced, recurrent, or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; (3) the anti-EGFR agents used, either antibodies or tyrosine kinase inhibitors (TKIs), selectively targeted at EGFR rather than other members of the human EGFR family; (4) the study compared chemotherapy, radiotherapy, chemoradiotherapy, or best supportive care among treatment regimens with and without an EGFR inhibitor; and (5) the study provided the hazard ratios (HRs) with 95% confidence intervals (CIs) for OS according to primary sites, or reported information to calculate these. There were no language restrictions, and the most recently updated results were included if more than one publication was reported for a trial.

The exclusion criteria were: (1) studies with surgery as the curative treatment; (2) trials focusing on human papillomavirus (HPV)-positive HNSCC, because some evidence suggest that HPV-positive disease might not benefit from anti-EGFR treatment [6–8]; (3) trials in abstract forms; and (4) non-specific anti-EGFR inhibitors, such as afatinib [7] and lapatinib [9]. Patients enrolled in the specific EGFR inhibitor trials differed from those included in non-specific EGFR inhibitor trials. Specific EGFR inhibitor trials enrolled patients who had never received anti-EGFR therapy or patients who had undergone anti-EGFR therapy as part of an initial curative multimodality therapy completed more than 6 months prior to trial entry [3,4,6,10–13]. In contrast, non-specific EGFR inhibitors were designed to improve efficacy and overcome resistance to specific anti-EGFR inhibitors [14]. Non-specific EGFR inhibitor trials enrolled patients who had already been exposed to an EGFR targeted antibody [7,15]. In the phase III LUX-Head & Neck 1 and 3 trials [7,15], progression-free survival (PFS) benefit was unique to patients not previously treated with EGFR targeted antibodies. Therefore, the inclusion of patients previously treated with EGFR inhibitors may affect the validity and robustness of the conclusions drawn from the present meta-analysis.

Data extraction and risk of bias assessments

The following data were independently extracted by two authors from each trial: study design, inclusion and exclusion criteria, patient characteristics, number of patients, histology, TNM stage, performance status, treatment protocol, follow-up, EGFR inhibitors, clinical endpoints, HRs and their 95% CIs for OS and PFS. For randomization integrity, we assessed the patterns of treatment allocation and balance in baseline characteristics between patient groups. In case of missing data, we contacted the corresponding author via e-mail to request the provision of the missing information.

For this meta-analysis of subgroup data from trials, the risk of bias of each eligible study was assessed independently by two authors following the guidelines in the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions [16].

Statistical analysis

Our prespecified hypothesis was that the OS benefits of EGFR inhibitors would be limited to HNSCC with oral cavity and oropharynx primary sites. Therefore, we assessed differences in the improvement of survival between anti-EGFR beneficiary (oral cavity-oropharyngeal) carcinoma and anti-EGFR non-beneficiary (hypopharyngeal-laryngeal) carcinoma. This hypothesis was inferred from the results of subgroup analyses of two phase III trials, EXTREME [3] and IMCL-9815 [4], based on which cetuximab was approved for use in patients with HNSCC. The feasibility of this classification was also verified by a pilot study prior to the present meta-analysis. The pilot study included meta-analyses and meta-regression analyses by each primary cancer site (Fig. S1 and Table S1). An improved OS was observed in patients with oral cavity carcinoma (HR 0.64, $P = 0.004$) and patients with oropharyngeal carcinoma (HR 0.81, $P = 0.005$) who underwent treatment with EGFR inhibitors when compared to that in the control groups. In contrast, no OS benefit was observed in hypopharyngeal carcinoma (HR 0.89, $P = 0.372$) or laryngeal carcinoma (HR 1.01, $P = 0.938$). Meta-regression analyses showed no difference in OS benefits between oral cavity carcinoma and oropharyngeal carcinoma ($P = 0.095$) and a significant OS difference in favor of oral cavity carcinoma when compared to that in hypopharyngeal carcinoma ($P = 0.049$) or laryngeal carcinoma ($P = 0.003$). Therefore, it is feasible to combine oral cavity carcinoma with oropharyngeal carcinoma as anti-EGFR beneficiary carcinoma and hypopharyngeal carcinoma with laryngeal carcinoma as anti-EGFR non-beneficiary carcinoma for a meta-analysis.

All analyses were pre-specified in the protocol unless otherwise indicated. The primary and secondary endpoints were OS and PFS, respectively. Owing to the clinical heterogeneity among the trials identified a priori, the random-effects model was used to pool data [17]. HRs and their 95% CIs were calculated to assess the survival advantage of treatment with or without EGFR inhibitors. The Cochrane Q test and I^2 statistic were used to assess heterogeneity among trials [18]. The test of interaction proposed by Altman et al. [19] was used to compare treatment effects between patients with oral cavity-oropharyngeal carcinoma and those with hypopharyngeal-laryngeal carcinoma.

To assess the relationship between study level covariates, and the effect size of treatment with and without EGFR inhibitors, we performed the random-effects model meta-regression analysis in the overall population [20]. The covariates included primary site (oral cavity and oropharynx *vs*. hypopharynx and larynx), anti-EGFR agent (antibody *vs*. tyrosine kinase inhibitor), treatment line (first-line *vs*. subsequent-line), disease pattern (locoregionally advanced *vs*. recurrent and metastatic), agents approved by the Food and Drug Administration (FDA; cetuximab *vs*. non-cetuximab), and FDA-approval of regimens (approved *vs*. non-approved). In addition, subgroup analyses were conducted to evaluate whether the differences in survival benefits between primary sites (oral cavity-oropharynx *vs*. hypopharynx-larynx) were dependent on these covariates. To conduct a subgroup analysis, at least two trials were required. We conducted sensitivity analyses by excluding one trial at a time to explore whether the results were strongly influenced by a specific trial. Potential publication bias was graphically presented by funnel plots, and the asymmetry was assessed with linear regression tests.

All statistical analyses were performed using R version 3.5.2 (www.r-project.org). Statistical significance was defined as a 2-sided *P*-value of 0.05.

Results

A total of 7 phase III randomized controlled trials [3,4,6,10–13] were included in this meta-analysis (Fig. 1). We did not identify an eligible trial in the Chinese databases. Two phase III trials (Burtness et al., 2005 [21] and IMEX [22]) were excluded because the OS by primary sites were not reported.

The study characteristics are listed in Table 1. The experimental and control groups in all the trials were reported to be well balanced with respect to the patient baseline characteristics, including the primary site. Three trials [6,11,12], where the primary site was a planned stratification factor, were graded to have a low risk of bias; while the others [3,4,10,13] were graded to have a moderate risk of bias.

A total of 7 trials with 3391 patients were eligible for the meta-analysis of OS. Patients with oral cavity-oropharyngeal carcinoma who underwent treatment with EGFR inhibitors had an improved OS (HR 0.77, 95% CI 0.67–0.87, $P < 0.001$) compared to the control group (Fig. 2). In contrast, patients with hypopharyngeal-laryngeal carcinoma did not exhibit OS benefits through the addition of EGFR inhibitors (HR 0.94, 95% CI 0.82–1.08, $P = 0.398$). The interaction between the treatment effects on OS and the primary site was sta-

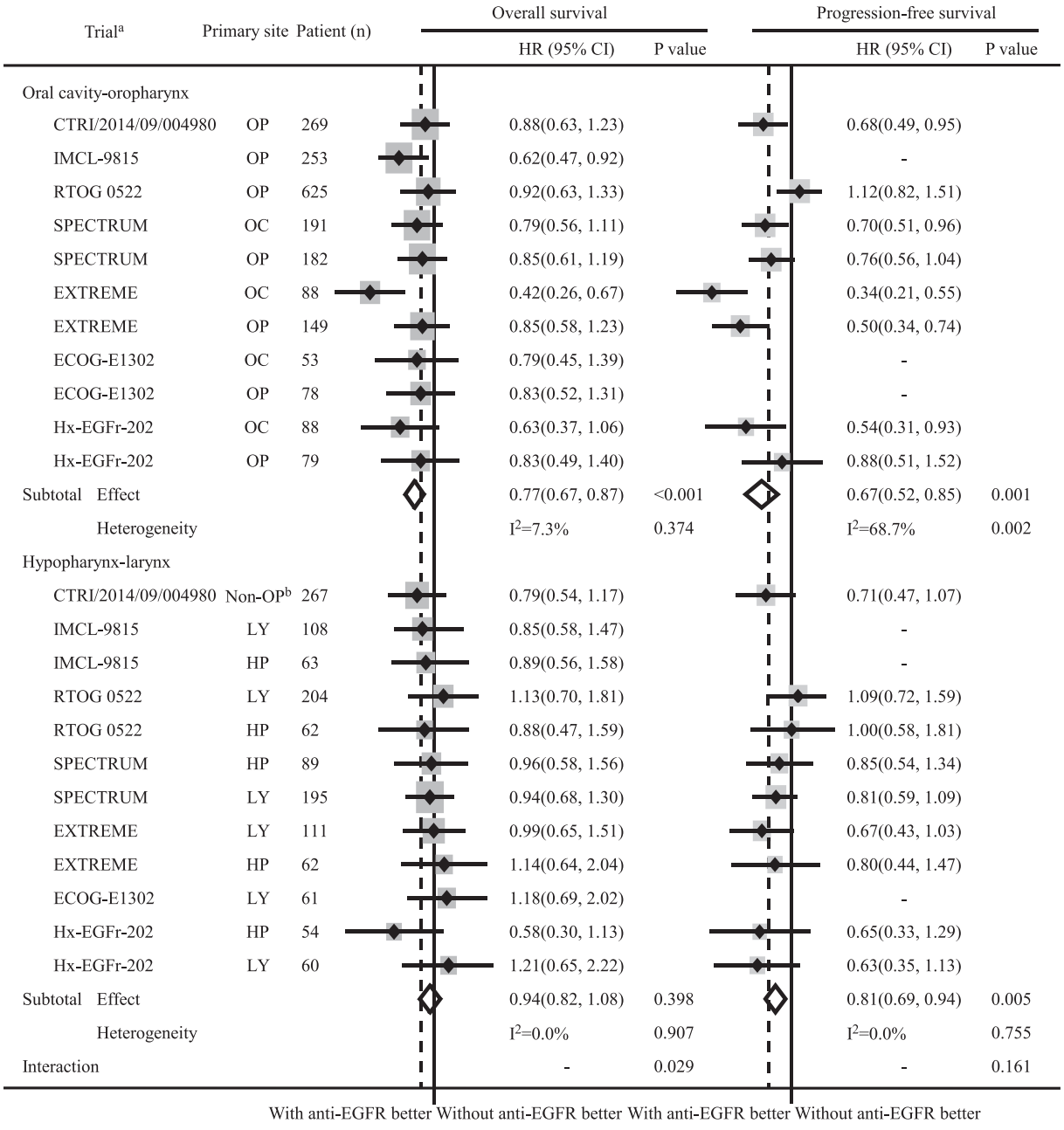

Fig. 2. Forest plot of survival benefits associated with anti-EGFR versus non-anti-EGFR treatments according to primary sites. Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; HP, hypopharynx; HR, hazard ratio; LY, larynx; OC, oral cavity; OP, oropharynx. [a]Two trials (IMCL-9815 and ECOG-E1302) did not report progression-free survival (PFS) according to the primary site. [b]Non-oropharynx group is the combination of patients with oral cavity carcinoma (n = 3, 1%) and hypopharyngeal-laryngeal carcinoma (n = 264, 99%).

Table 1
Characteristics of eligible trials in the meta-analysis.

Trial, publication year	Sample size[a]	Eligible criterion	Treatment	Inclusion period	Primary endpoint
SPECTRUM, 2013 [6]	657	First-line therapy for R/M HNSCC	Cisplatin and fluorouracil with or without panitumumab	2007–2009	OS
EXTREME, 2008 [3]	410[a]	First-line therapy for R/M HNSCC	Cisplatin or Carboplatin plus 5-Fluorouracil with or without cetuximab	2004–2005	OS
ECOG-E1302, 2013 [10]	192[a]	First- or subsequent-line therapy for R/M HNSCC	Docetaxel with or without gefitinib	2004–2008	OS
RTOG 0522, 2014 [11]	891	Previously untreated III to IVa,b HNSCC	Radiotherapy plus cisplatin with or without cetuximab	2005–2009	PFS
CTRI/2014/09/004980[b], 2019 [12]	536	Previously untreated III to IVa,b HNSCC	Radiotherapy plus cisplatin with or without nimotuzumab	2012–2018	PFS
IMCL-9815, 2009 [4]	424	Previously untreated III to IVa,b HNSCC	Radiotherapy with or without cetuximab	1999–2002	Duration of locoregional control
Hx-EGFr-202, 2011 [13]	281[a]	R/M HNSCC after failure of platinum-based chemotherapy	Best supportive care with zalutumumab versus best supportive care with optional methotrexate	2006–2009	OS

Abbreviations: HNSCC, head and neck squamous cell carcinoma; PFS, progression-free survival; R/M, recurrent or metastatic; OS, overall survival.
[a] A total of 84 patients with carcinomas not originating from the oral cavity, oropharynx, hypotharynx, or larynx were excluded from this meta-analysis (32 in EXTREME, 47 in ECOG-E1302, and 5 in Hx-EGFr-202).
[b] The primary carcinomas were classified into oropharyngeal and non-oropharyngeal carcinomas, and the latter included oral cavity carcinoma (n = 3, 1%) and hypopharyngeal-laryngeal carcinoma (n = 264, 99%).

tistically significant (P = 0.029). Heterogeneity was barely observed across trials. Five trials [3,6,16–18] with a total of 2775 patients were included in PFS analysis. The addition of EGFR inhibitors increased PFS in both patients with oral cavity-oropharyngeal carcinoma (HR 0.67, 95% CI 0.52–0.85, P = 0.001) and hypopharyngeal-laryngeal carcinoma (HR 0.81, 95% CI 0.69–0.94, P = 0.005). A trend towards a significant interaction was found in favor of oral cavity–oropharyngeal carcinoma (P = 0.161), and heterogeneity was observed across trials of oral cavity-oropharyngeal carcinoma.

The patients in all trials were combined for the meta-regression analysis. Among the covariates investigated, the primary site was the only significant predictor of OS benefits of anti-EGFR treatment compared to control group (univariate HR 1.23, 95% CI 1.02–1.48, P = 0.027; multivariate HR 1.23, 95% CI 1.03–1.48, P = 0.025; Table 2). Although no significant predictor was identified in the analysis of PFS, the primary site showed a trend towards significance.

Table 3 shows subgroup analyses. A significant difference in OS, or a trend towards a significant difference, was observed in most subgroups. Some heterogeneity was observed across studies on oral cavity-oropharyngeal carcinoma. Similarly, the subgroup analyses of PFS generated roughly comparable results with the main meta-analysis of PFS (Table S2). Sensitivity analyses (Table S3) yielded results that were consistent with the main analysis. Fig. 3 shows the funnel plots, which suggest absence of publication bias.

Discussion

Our meta-analysis assessed the impact of the primary site of locoregionally advanced, recurrent, or metastatic HNSCC on the OS benefit of EGFR inhibitors. The results showed that the addition of EGFR inhibitors improved the OS of patients with oral cavity-oropharyngeal carcinoma, but not that of patients with hypopharyngeal-laryngeal carcinoma. Controlling for all possible confounders made little difference to this finding.

This finding contradicts the standard of care for the use of EGFR inhibitors in HNSCC, which is independent of the primary site. The credibility of our meta-analysis was assessed based on the guidance by Sun et al. [23]. First, the main meta-analysis showed a significant difference in OS benefits between the primary sites after EGFR inhibitor treatment. The meta-regression analysis also suggested that the primary site is an effect modifier. Second, the subgroup analyses of OS demonstrated roughly consistent results with the main analysis. As for oral cavity-oropharyngeal carcinoma, the effect of EGFR inhibitors might depend on the agents (e.g., cetuximab or gefitinib) and treatment regimens (e.g., the addition of EGFR inhibitors to chemotherapy or radiotherapy). As a result, subgroup analyses yielded effects of varying quantities depending on the patient group. This implies that the addition of EGFR inhibitors is significantly associated with OS benefits (i.e., true positive), and that the change in inhibitors or treatment regimens has an influence on the effect. Third, a trend towards a significant interaction was found in favor of oral cavity-oropharyngeal carcinoma in the meta-analysis of PFS. Finally, consistent results were observed in the independent studies. In the SEER-medicare-based analysis of 2135 patients (median age: 73 years old) with squamous cell carcinoma of the oropharynx, hypopharynx, larynx, and nasopharynx, definitive radiotherapy with concurrent cetuximab was compared to chemoradiotherapy to evaluate OS. The benefits of radiotherapy with concurrent cetuximab on OS versus radiotherapy alone were shown in patients with oropharyngeal carcinoma but not in those with hypopharyngeal or laryngeal carcinoma [24]. In a prospective observational study of chemotherapy with or without cetuximab in recurrent or metastatic HNSCC, patients with oral cavity and oropharynx carcinomas had a significantly better response than patients with hypopharynx and larynx carcinomas [25]. Taken together, it is unlikely that the difference between the primary sites occurs by chance, so the finding is highly credible.

This study had several limitations. First, the objective response rate was not investigated due to the lack of data. Second, due to the lack of OS data according to primary tumor site, we had to exclude two phase III trials involving a total of 603 patients [21,22]. Compared to the sample size of our meta-analysis (7 trials with 3391 patients), the exclusion of these two trials should not have a significant impact on the real effect size. Third, the test of interaction analysis has limited power to detect interactions [19], especially on the PFS analyses, which have a much smaller sample size. These results on PFS should be considered cautiously. Fourth, there was substantial diversity in the included studies in terms of the treatment regimens and agents. This clinical heterogeneity could be considered a potential problem in interpreting the results of the present meta-analysis. Indeed, greater variability between studies was equivalent to adding "noise" to the analysis, making it unlikely

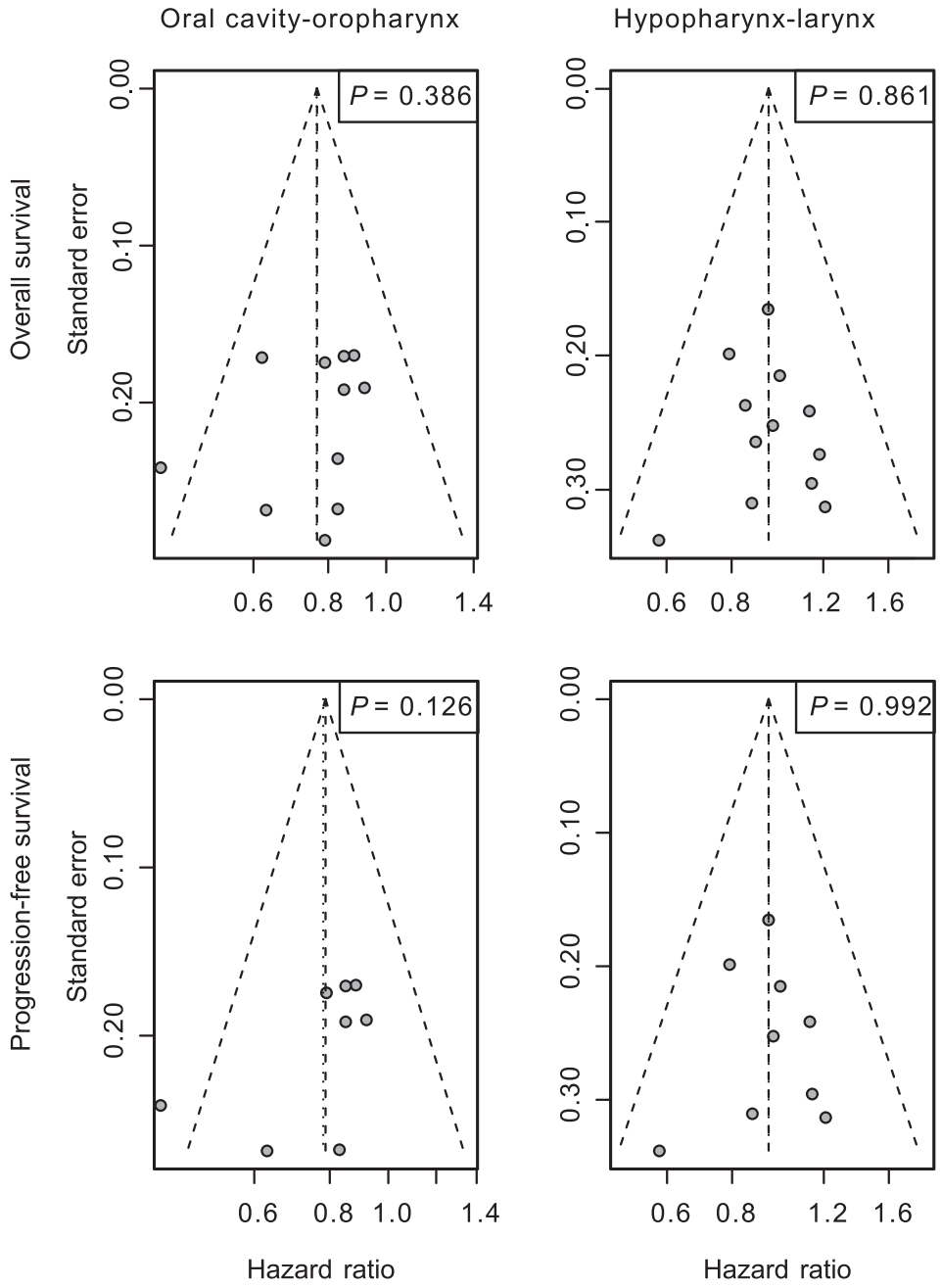

Fig. 3. Funnel plots of publication bias. Note: Each comparison in a trial was considered as a separate study.

Table 2
Meta-regression model for predictors of survival benefit in HNSCC after anti-EGFR versus non-anti-EGFR treatments.

Versus	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* effect	HR (95% CI)	*P* effect	HR (95% CI)	*P* effect	HR (95% CI)	*P* effect
HL vs. OO	1.23 (1.02–1.48)	0.027	1.23 (1.03–1.48)	0.025	1.19 (0.97–1.47)	0.095	1.19 (0.96–1.48)	0.120
Antibody vs. TKI[a]	1.10 (0.80–1.50)	0.558	1.19 (0.79–1.81)	0.390	N.A.	N.A.	N.A.	N.A.
Subsequent- vs. first-line[b]	1.00 (0.80–1.26)	0.990	0.88 (0.63–1.23)	0.476	0.90 (0.66–1.23)	0.511	0.89 (0.63–1.27)	0.532
Recurrent and metastatic vs. locoregionally advanced	1.01 (0.83–1.21)	0.953	1.06 (0.85–1.33)	0.595	0.92 (0.73–1.15)	0.452	1.04 (0.74–1.44)	0.838
Non-cetuximab vs. cetuximab	1.05 (0.87–1.26)	0.615	0.86 (0.62–1.21)	0.401	0.98 (0.78–1.22)	0.848	0.88 (0.60–1.29)	0.515
Non-approved vs. approved[c]	1.15 (0.94–1.39)	0.176	1.30 (0.93–1.82)	0.120	1.10 (0.87–1.37)	0.452	1.25 (0.77–2.04)	0.367

Abbreviation: CI, confidence interval; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; HL, hypopharyngeal-laryngeal carcinoma; N.A., not applicable; OO, oral cavity-oropharyngeal carcinoma; TKI, tyrosine kinase inhibitor.

[a] TKI was used as an anti-EGFR agent in one trial (ECOG-E1302), where the subgroup data of PFS was not reported.

[b] The ECOG-E1302 trial was a combination of first-line (26%) and subsequent-line (74%) treatment, and was classified into the subsequent-line group.

[c] Food and Drug Administration approved: IMCL-9815 and EXTREME.

Table 3
Differences in overall survival benefits between primary sites after anti-EGFR versus non-anti-EGFR treatments according to patient groups.

Groups	Trials (n)	Oral cavity-oropharynx carcinoma				Hypopharynx-larynx carcinoma				*P* interaction
		Patients (n)	HR (95%CI)	*P* effect	I^2 (%)	Patients (n)	HR (95%CI)	*P* effect	I^2 (%)	
Anti-EGFR agent[a]										
Antibody	6	1927	0.76 (0.65–0.88)	<0.001	25.0	1272	0.93 (0.80–1.07)	0.300	0.0	0.058
Treatment line[b]										
First-line	5	1760	0.76 (0.64–0.90)	0.002	40.0	1158	0.94 (0.80–1.09)	0.381	0.0	0.069
Disease pattern										
Locoregionally advanced	3	1150	0.79 (0.62–1.01)	0.064	35.0	701	0.89 (0.72–1.10)	0.288	0.0	0.478
Recurrent and metastatic	4	908	0.75 (0.64–0.88)	<0.001	8.0	632	0.98 (0.82–1.18)	0.837	0.0	0.029
Agents approved by FDA										
Cetuximab	3	1115	0.69 (0.50–0.94)	0.019	63.0	610	0.97 (0.79–1.19)	0.788	0.0	0.075
Non-cetuximab	4	943	0.81 (0.70–0.95)	0.009	0.0	723	0.92 (0.76–1.11)	0.367	0.0	0.308
FDA-approval of regimens[c]										
Approved	2	490	0.62 (0.43–0.89)	0.010	62.0	344	0.95 (0.75–1.21)	0.685	0.0	0.054
Non-approved	5	1568	0.83 (0.72–0.96)	0.010	0.0	989	0.94 (0.79–1.11)	0.455	0.0	0.275

Abbreviation: CI, confidence interval; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HR, hazard ratio.
[a] Because there is only one trial that used tyrosine kinase inhibitors (TKIs) as an anti-EGFR agent (ECOG-E1302), the subgroup analysis of trials on TKIs was not conducted (at least two trials were needed for a subgroup analysis).
[b] The ECOG-E1302 trial was a combination of first-line (26%) and subsequent-line (74%) treatment, and was excluded from either the first- or subsequent-line treatment subgroup.
[c] Food and Drug Administration approved: IMCL-9815 and EXTREME.

to convert a null result into a positive finding [26,27]. In contrast, it is more likely that a positive correlation between primary tumor site and OS benefit would be masked or weakened by this "noise". However, as suggested by the subgroup, meta-regression, and sensitivity analyses, the correlation is fairly stable, thereby suggesting that it may be a general feature of HNSCC in response to anti-EGFR treatment across different clinical situations. Finally, this meta-analysis was based on summarized data rather than individual patient data. However, results from summarized data are often consistent with individual patient data [28,29].

Conclusion

To our knowledge, this is the first study that examined the impact of HNSCC primary sites on the survival benefits of anti-EGFR treatment. Our meta-analysis supports the association between primary sites and OS benefits from anti-EGFR based treatments in patients with HNSCC. This is a hypothesis-generating study, and confirmation with prospective studies is required.

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Declarations of interest

None.

CRediT authorship contribution statement

Deheng Nie: Methodology, Software, Writing - review & editing. **Xin Wang:** Data curation, Investigation, Resources, Supervision, Validation, Writing - original draft. **Meiting Sun:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Zhenbang Feng:** Data curation, Methodology, Software. **Fengli Pei:** Conceptualization, Methodology, Visualization, Writing - original draft. **Wenhui Liu:** Data curation, Methodology, Software, Visualization. **Zonghan Wang:** Data curation, Methodology, Visualization, Writing - original draft. **Fujun Han:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.02.001.

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