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Meta-analysis of the effects of anti-epidermal growth factor receptor on recurrent/metastatic head and neck squamous cell carcinoma

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Abstract

Background: We performed a meta-analysis to compare the efficacy and safety of anti-epidermal growth factor receptor (EGFR) therapy and non-anti-EGFR therapy in recurrent/metastatic (RM) head and neck squamous cell carcinoma (HNSCC).

Methods: The Cochrane library, WanFang Data, PubMed, Medline, VIP, CBM, and EBSCO databases were searched for relevant studies. The objective response rate (ORR, defined as complete response or partial response according to RECTST version 1.1) and grade 3 to 4 adverse effects were used.

Results: Ten studies involving 2260 patients were included. Primary meta-analysis showed that anti-EGFR therapy improved the ORR [odds ratio (OR): 1.79, 95% confidence interval 1.44–2.21, $P < .00001$]. Subgroup analyses revealed that the ORR of patients with RM HNSCC could be improved by monoclonal antibodies (OR: 1.89, 1.46–2.45, $P < .00001$) and tyrosine kinase inhibitors (OR: 1.57, 1.07–2.31, $P = .02$). Analysis of grade 3 to 4 adverse effects demonstrated that diarrhea (3.15, [1.90, 5.20]), rash/desquamation (13.66, [6.86, 27.20]), hypomagnesemia (1.83, [1.28, 2.62]), vomiting (1.99, [1.00, 3.95]), anorexia (3.34, [1.45, 7.73]), dehydration (2.22, [1.19, 4.12]), and hypokalemia (1.63, [1.09, 2.42]) were significantly associated with anti-EGFR therapy.

Conclusion: Anti-EGFR therapy is recommended for patients with RM HNSCC. Adverse effects, such as diarrhea, anorexia, hypomagnesemia, and hypokalemia, should be carefully monitored during anti-EGFR therapy.

Abbreviations: CI = confidence interval, CT = chemotherapy, EGFR = epidermal growth factor receptor, FDA = Food and Drug Administration, HNSCC = head and neck squamous cell carcinoma, HPV = human papillomavirus, LA = locoregionally advanced, mAbs = monoclonal antibodies, MeSH = medical subject heading terms, OR = odds ratio, ORR = objective response rate, PS = performance status, RCTs = randomized controlled trials, RM = recurrent/metastatic, TKIs = tyrosine kinase inhibitors.

Keywords: anti-EGFR therapy, HNSCC, meta-analysis, metastatic, recurrent

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is a type of cancer that arises in the squamous epithelium of the aerodigestive tract, including the lip, the oral cavity, the pharynx (oropharynx, hypopharynx, and nasopharynx), the larynx, and the paranasal sinuses and holds about 5% to 10% of the whole body malignant tumors. The average incidence of this disease is 10 to 15/10 million,[1] which means that about 645,000 new cases of head and neck cancer occur each year. The global incidence of HNSCC is expected to rise by 17% in 2012 to 2022 years.[2] HNSCC is the seventh most common form of cancer in developed countries, and it occurs more frequently in men than women; more than 90% of head and neck cancers are squamous cell carcinoma, and an estimated 48,330 new cases occurred in the United States in 2016.[3] Aside from the abuse of alcohol and tobacco, recent evidence has indicated that human papillomavirus (HPV)-positive and HPV-negative HNSCC are clinically and biologically distinct in the primary disease setting.[4,5] The HPV-positive status is associated with increased overall survival in patients with oropharyngeal cancer, and HPV-16 is the most common infection virus.[6,7]

Given that the prognosis of metastatic HNSCC is highly similar to that of recurrent HNSCC, advanced HNSCC is often divided into locoregionally advanced (LA) stage and recurrent/metastatic (RM) stage.[8,9] The majority of HNSCC patients are diagnosed in the later stages of the disease, more than 50% patients at the time of diagnosis have LA HNSCC, approximately 12% of HNSCC cases are diagnosed with distant metastases,[10,11] and 55% of patients with LA disease develop incurable relapse.[12] Current treatment strategies include surgery, chemotherapy (CT), radiation, and molecular targeted therapy, which are designated by the American Joint Committee on Cancer. Molecular targeted therapy, which selectively interferes with

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signaling pathways associated with carcinogenesis, has emerged as a promising technique to improve patient outcome.[13] Two meta-analyses have reported the efficacy and toxicity of this technique and revealed that anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) are effective while tyrosine kinase inhibitors (TKIs) are unsuitable for RM HNSCC.[14–15] However, an increasing number of trials display that mAbs is associated with later high resistance[16] and that TKIs can improve patient outcome.[16–18]

EGFR, which is overexpressed in up to 90% of all HNSCC, initiates important signal transduction pathways in HNSCC carcinogenesis. It is a member of the ErbB family of receptors which, once activated, can promote cell survival and proliferation.[19] Upon ligand fixation, the homodimerization or heterodimerization of EGFR signaling molecules (Pegfr, pakt, and perk1/2) with another HER receptor occurs. This process leads to the activation of downstream signaling molecular pathways, such as the Ras/Raf/Mek/Erk and phosphatidylino-sitol-3-kinase/protein kinase pathways, which are involved in tumor proliferation, apoptosis, angiogenesis, and cell migration/invasion. EGFR is associated with disease progression, increased resistance to conventional approaches, and poor prognosis.[20–22] Thus, anti-EGFR agents are used in the clinic. The most extensively evaluated anti-EGFR agents that are approved by the US Food and Drug Administration (FDA) in the clinic are anti-EGFR mAbs, such as cetuximab and panitumumab, and low-molecular-weight TKIs, such as afatinib, gefitinib, lapatinib, vandetanib, and erlotinib.

Until now, cetuximab is the only target drug that has been approved by the US FDA to treat HNSCC;[23] other target agents remain to be verified. Cetuximab is an IgG1 mAb that inhibits ligand binding to EGFR and stimulates antibody-dependent cell-mediated cytotoxicity, which may influence the observed clinical activity and may partially explain why biomarkers focused on EGFR protein expression or gene amplification are not predictive. TKIs lack such a mechanism of action, which distinguishes them from the mAbs. A meta-analysis of randomized controlled trials (RCTs) found that mAbs including cetuximab, nimotuzumab, and zalutumumab are effective for both LA and RM HNSCC while TKIs containing lapatinib and gefitinib are unsuitable for the treatment of advanced HNSCC.[15] Nevertheless, several types of TKI drugs for HNSCC are still in clinical use. Clinical trials are ongoing, and information about anti-EGFR therapy is being updated. Thus, we hope to conduct a new meta-analysis to compare the benefits of anti-EGFR therapy with those of conventional CT and the difference of 2 types of anti-EGFR drugs.

2. Materials and methods

2.1. Search strategy

The search strategy consisted of a systematic review of the literature for RCTs over the last 10 years in English language in the Cochrane library, WanFang Data, PubMed, Medline, VIP, CBM, and EBSCO databases. Publications were searched from March 2007 to March 2017. The search terms contained "head and neck cancer," "head and neck squamous carcinoma," "EGFR," "monoclonal antibodies," "tyrosine kinase inhibitors," "cetuximab," "panitumumab," "zalutumumab," "gefitinib," "vandetanib," "afatinib," "erlotinib," and "lapatinib." Conference Proceedings from the American Society of Clinical Oncology and the European Society for Medical Oncology from 2007 to 2017 were also searched using the above terms. We combined both medical subject heading terms (MeSH) and free text words to identify relevant studies. ClinicalTrials.gov was also searched in March 2017 to check for updated data. Finally, the Web of Science database was searched for more studies. When studies were duplicated, we selected the most recent ones that meet all requirements for meta-analysis. Article selection was based on the methodology used in the RCTs. A total of 216 articles were identified.

2.2. Study selection

The inclusion criteria were as follows:

(1) studies presented in English,
(2) prospective RCTs,
(3) studies that involved biopsy-proven RM HNSCC patients,
(4) studies that compared the clinical benefits of anti-EGFR therapy (alone or in combination with conventional CT) and non-anti-EGFR therapy, and
(5) studies that reported the objective response rate (ORR) and grade 3 to 4 adverse effects.

Exclusion criteria were

(1) the nasopharynx or esophagus cancer (because of the difference in etiology, epidemiology, and potential treatment options between nasopharynx/esophagus cancer),
(2) trials with missing data, and
(3) duplicate reports, trials of poor methodological quality, and trials with obvious bias. Figure 1 shows the flow of selection (Fig. 1).

2.3. Data extraction

The relevant data from the included studies were independently extracted by all authors. Discrepancies regarding data extraction were resolved by discussion and consensus among the investigators. Data extractions included authors, intent-to-treat population size, phase of trials, treatment information, publication year, country, eligibility criteria for performance status (PS), median age, sex ratio, ORR, and grade 3 to 4 adverse effects. Adverse effects were graded in accordance with the National Cancer Institute Common Toxicity Criteria Version 3.0. The number of patients with grade 3 to 4 adverse effects was determined from the articles.

2.4. Data analysis

All statistical analyses were conducted using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). As dichotomous variables, outcomes were calculated as the odds ratio (OR), the 95% confidence interval (CI), and the outcomes (OR) were larger than 1. Statistical significance was considered at $P<.05$. The inconsistency index ($I2$) statistic and the Q statistic were used to test the heterogeneity between RCTs.[24] For outcomes with fine homogeneity ($P>.1$; $I2 \leq 50\%$), a fixed-effects model was used for secondary analysis; otherwise ($P<.1$; $I2>50\%$), a random-effects model was used.[24] The funnel plot, which was substantially symmetrical, was used to analyze the publication bias. In consideration that the meta-analysis involves a relatively small number of RCTs, a certain degree of publication bias exists.

3. Results

3.1. Search results

A number of cases with RM HNSCC have been reported in patients treated with anti-EGFR therapy in case reports, clinical

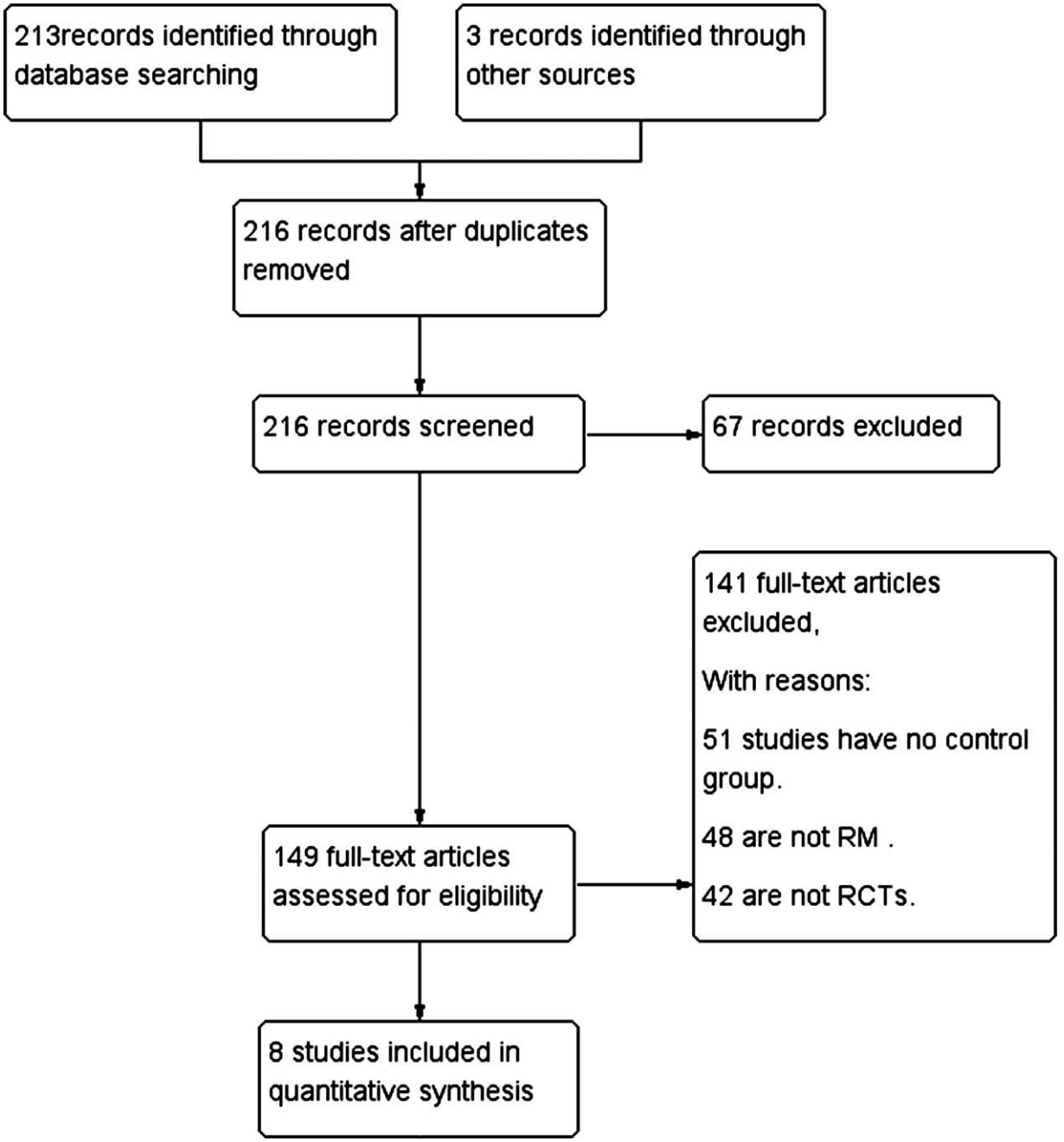

Figure 1. Outline of selection flow chart.

trials, and retrospective studies. A total of 216 publications on EGFR for head and neck cancer were originally extracted from the search databases after initial screening of the research object, treatments, research type, title, and abstract on the basis of the screening criteria. Only 8[16–18,25–29] of these studies, which involved 2621 patients, were included after considering the inclusion and exclusion criteria. The report of Stewart et al[15,26] comprised 3 arms: 2 gefitinib arms (250 and 500 mg/day) and 1 control arm (methotrexate). We considered Stewart's study as 2 independent trials, gefitinib of 250 mg/day and 500 mg/day versus methotrexate, because of the different dosages of anti-EGFR therapy. The report of Kushwaha et al[18] also comprised 3 arms: 1 gefitinib arm and 2 control arms (methotrexate, methotrexate+5FU). We divided Kushwaha's study as 2 independent trials: gefitinib versus methotrexate and gefitinib versus methotrexate+5FU. Therefore, we extracted 10 trials from the 8 included studies. The characteristics of the included RCTs are shown in Table 1, which in order report the first author, publication year (recent 10 years), participating country, phase of trials, eligibility criteria for Eastern cooperative oncology group or World Health Organization PS, and the time of trials from beginning to end. Table 2 presents the patient characteristics, including neoplasm staging, intent-to-treat population size, treatment and control information, sex ratio, and median age.

Table 1

Characteristics of included randomized controlled trials.

Authors Year	Country	Phase	PS criteria	Time
Vermorken et al 2008[25]	Multinational	III	NA	2004.12–2005.12
Stewart et al 2009[26]	Multinational	III	WHO PS≤2	2003.12–2006.1
Argiris et al 2013[16]	U.S.	III	ECOG PS≤2	2004.8–2008.11
Machiels et al 2011[27]	Multinational	III	WHO PS≤2	2006.11–2009.6
Vermorken et al 2013[28]	Multinational	III	ECOG PS≤1	2007.5–2009.3
Wirth et al 2016[29]	Multinational	II	ECOG PS≤1	2007.1–2012.6
Machiels et al 2015[17]	Multinational	III	ECOG PS≤1	2012.1–2013.12
Kushwaha et al 2015[18]	India	III	ECOG PS≤2	2010.6–2012.9

EOCG = eastern cooperative oncology group, NA = not available, PS = performance status, WHO = World Health Organization.

We can find that the age of people ranging from 55 to 60 has more risk in HNSCC, with males at higher risk than females (Tables 1 and 2).

3.2. Efficacy of anti-EGFR therapy for HNSCC

Anti-EGFR treatment for ORR: The 10 trials involving 2621 patients ($n=1543$ in the Anti-EGFR group; $n=1278$ in the conventional CT group) from the 8 reports provided ORR data. In the heterogeneity test, outcome was calculated using the fixed-effects model ($P=.68$, $I^2=0\%$), which has fine homogeneity. The ORR of the anti-EGFR therapy and conventional CT were 21.3% (329/1543) and 16.4% (210/1278), respectively, with significant difference (OR:1.79, 95% CI 1.44–2.21, $P<.00001$) (Fig. 2A) The funnel plot shows no obvious publication bias (Fig. 3A).

Subgroup analysis: We divided the trials into subgroups based on anti-EGFR drug types. The mAbs were analyzed in 4 studies, including 1397 patients ($n=743$ in the mAbs group; $n=654$ in the CT group). Four studies with 6 trials focused on TKIs ($n=800$ in the TKI group; $n=624$ in the CT group). Subgroup analysis showed that the heterogeneity test reveals good homogeneity. The outcomes of the fixed-effects model are (mAbs: $P=.37$, $I^2=4\%$) and (TKIs: $P=.72$, $I^2=0\%$) (Figs. 2B and C). The mAbs increased the ORR (OR:1.89, 95% CI 1.46–2.45, $P<.00001$) (Fig. 2B), and the TKIs also worked (OR:1.57, 95% CI 1.07–2.31, $P=.02$) (Fig. 2C). No obvious publication bias was found in the funnel plot (Figs. 3B and C).

3.3. Safety analysis

Table 3 8 reports[16–18,25–29] provided data on adverse reactions associated with anti-EGFR therapy. Considering the high frequency of grade 1 to 2 adverse reactions and the low frequency of grade 5 adverse reaction, we selected the middle frequency of the grade 3 to 4 adverse effects for this research. From the 8 articles, we selected grade 3 to 4 adverse effects with a frequency greater than or equal to 3 times. These adverse effects include diarrhea, fatigue, rash/desquamation, nausea, vomiting, stomatitis, neutropenia, thrombocytopenia, hypomagnesemia, weight loss, anemia, anorexia, dehydration, and hypokalemia. Most adverse effects analyses showed that the heterogeneity test has good homogeneity ($P>.1$; $I2\leq 50\%$). The fixed effects model was used.

Results showed that diarrhea (3.15, [1.90, 5.20]), rash/desquamation (13.66, [6.86, 27.20]), hypomagnesemia (1.83, [1.28, 2.62]), vomiting (1.99, [1.00, 3.95]), anorexia (3.34, [1.45, 7.73]), dehydration (2.22, [1.19, 4.12]), hypokalemia (1.63, [1.09, 2.42]), and anemia (0.68 [0.49, 0.96]) were significantly associated with anti-EGFR therapy. Furthermore, anemia reduced in varying degrees while others increased comparing anti-EGFR with non-anti-EGFR.

4. Discussion

This meta-analysis compared the efficacy and safety of anti-EGFR with conventional CT in patients with incurable LA RM HNSCC. We used ORR to evaluate the efficacy and safety of these treatments. The meta-analysis provided evidence that anti-EGFR including mAbs and TKIs significantly increase the ORR and cause diarrhea, rash/desquamation, hypomagnesemia, vomiting, anorexia, and other adverse events. The curative effect of molecular targeted therapy is mostly observed in practice. In a Chinese meta-analysis,[14] mAbs have been proven effective in the treatment of RM HNSCC. The EXTREME regimen (platinum, 5FU, and cetuximab) is currently considered the first-line

Table 2

Characteristics of the patients included in randomized controlled trials.

Authors Year	Stage	n(z/d)	Treatment	Sex (M/F)	Age (T/C)
Vermorken et al 2008[25]	RM	442(222/220)	CT ± cetuximab	399/43	56/57
Stewart et al 2009[26]	RM	486 (158/161)	Gefitinib 250 mg vs CT	396/90	NA
		(167/161)	Gefitinib 500 mg vs CT		
Argiris et al 2013[16]	RM	239 (126/129)	CT ± gefitinib	190/49	60.8/61.4
Machiels et al 2011[27]	RM	286 (191/95)	Zalutumumab vs BSC	252/34	57/58
Vermorken et al 2013[28]	RM	657 (327/330)	CT ± panitumumab	570/87	58/59
Wirth et al 2016[29]	RM	111 (56/55)	CT ± panitumumab	NA	58.2/58.9
Machiels et al 2015[17]	RM	483 (322/161)	Afatinib vs MTX	412/71	60/59
Kushwaha et al 2015[18]	RM	156 (39/40)	Gefitinib vs MTX	111/6	47/46.9
		(39/38)	Gefitinib vs MTX+5FU		

T/C = test arm/control arm, M/F = male/female, CT = chemotherapy, NA = not available; BSC = best supportive care.

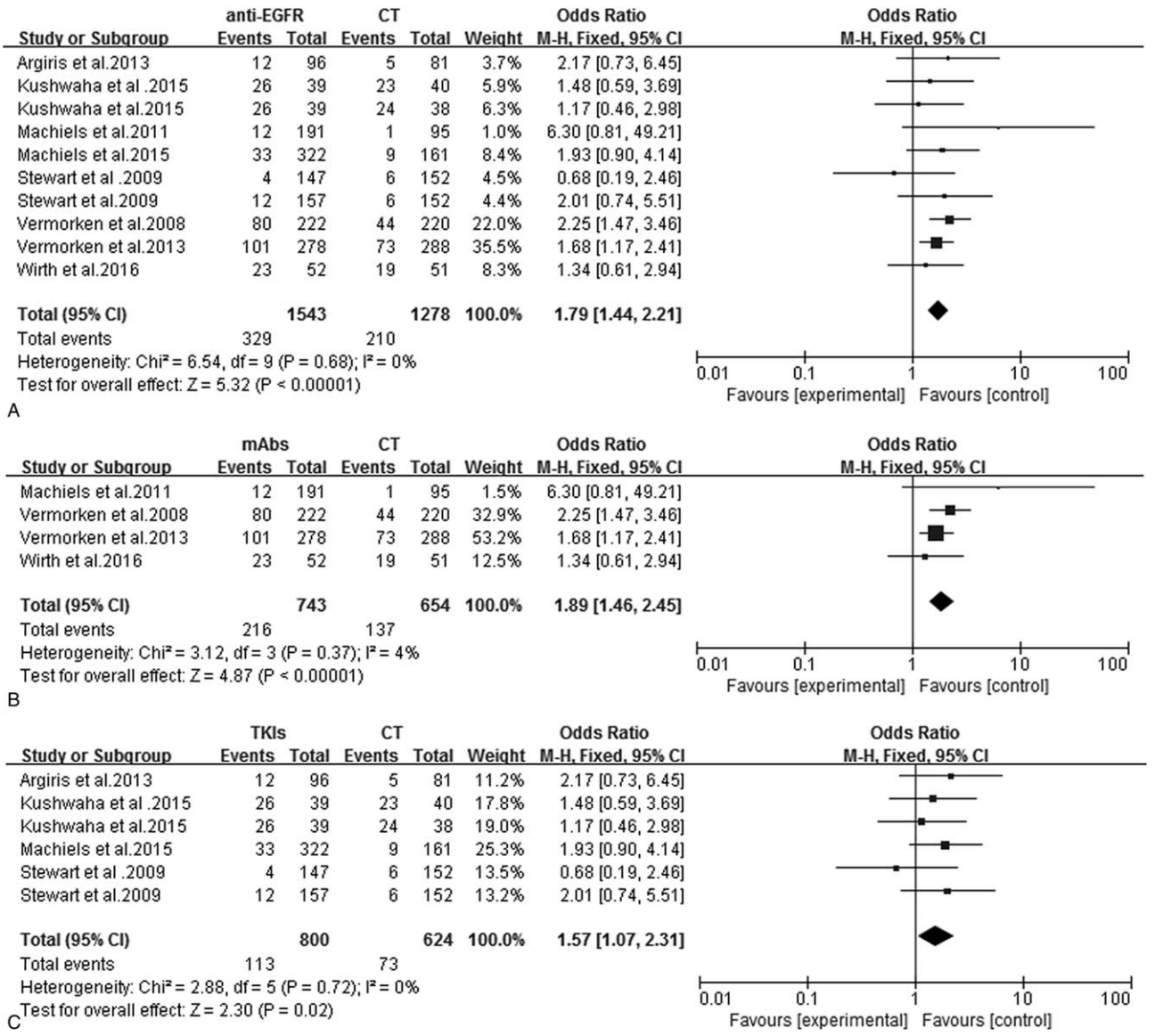

Figure 2. (A,B,C) Forest of OR for ORR comparing RM HNSCC patients undergoing anti-EGFR therapy (A:mAbs+TKIs,B:mAbs,C:TKIs) and those undergoing non-anti-EGFR therapy. EGFR = epidermal growth factor receptor, HNSCC = head and neck squamous cell carcinoma, OR = odds ratio, ORR = objective response rate, RM = recurrent/metastatic, TKIs = tyrosine kinase inhibitors.

standard option for this population with a level of evidence and grade of recommendation of IIA.[30] In the present study, a phase II trial evaluating 4 cycles of docetaxel in combination with cisplatin and cetuximab (termed TPEx) as the first-line treatment of RM HNSCC is proven to be feasible, convenient, and precociously active with a manageable safety profile.[31] Basing from on this study, Guigay et al reported a case of a patient with recurrent oropharyngeal carcinoma treated with cetuximab, docetaxel, and cisplatin (TPEx) as the first-line treatment followed by cetuximab maintenance and then provided a protocol that TPEx followed by cetuximab maintenance may lead to patient complete remission within the first year of treatment.[32] However, our primary results showed that the anti-EGFR TKIs cannot be confirmed to improve the ORR of patients with RM HNSCC,[15] which is consistent with our previous assumptions. We attribute this difference to the lack of studies on TKIs before. Phase II randomized, clinical trials of afatinib versus cetuximab in RM HNSCC have shown that Afatinib exhibits anti-tumor activity comparable to that of cetuximab in RM HNSCC, although other patients discontinued afatinib treatment due to adverse effects.[33] This conclusion further confirms our conclusion.

Complex connection in all ErbB-dependent signaling pathways in RM HNSCC and the numerous molecular and genetic changes result in the development of cetuximab resistance.[34] Acquired resistance is in connection with dysregulation of EGFR internalization or degradation, EGFR-dependent activation of human EGFR 2 (HER2; ErbB2), and ErbB3 and possibly with the increased signaling of alternative receptor tyrosine kinases.[35] To overcome this resistance, a sequential EGFR/ErbB treatment with afatinib and cetuximab provided sustained clinical benefit in patients after crossover, suggesting a lack of cross-resistance.[33]

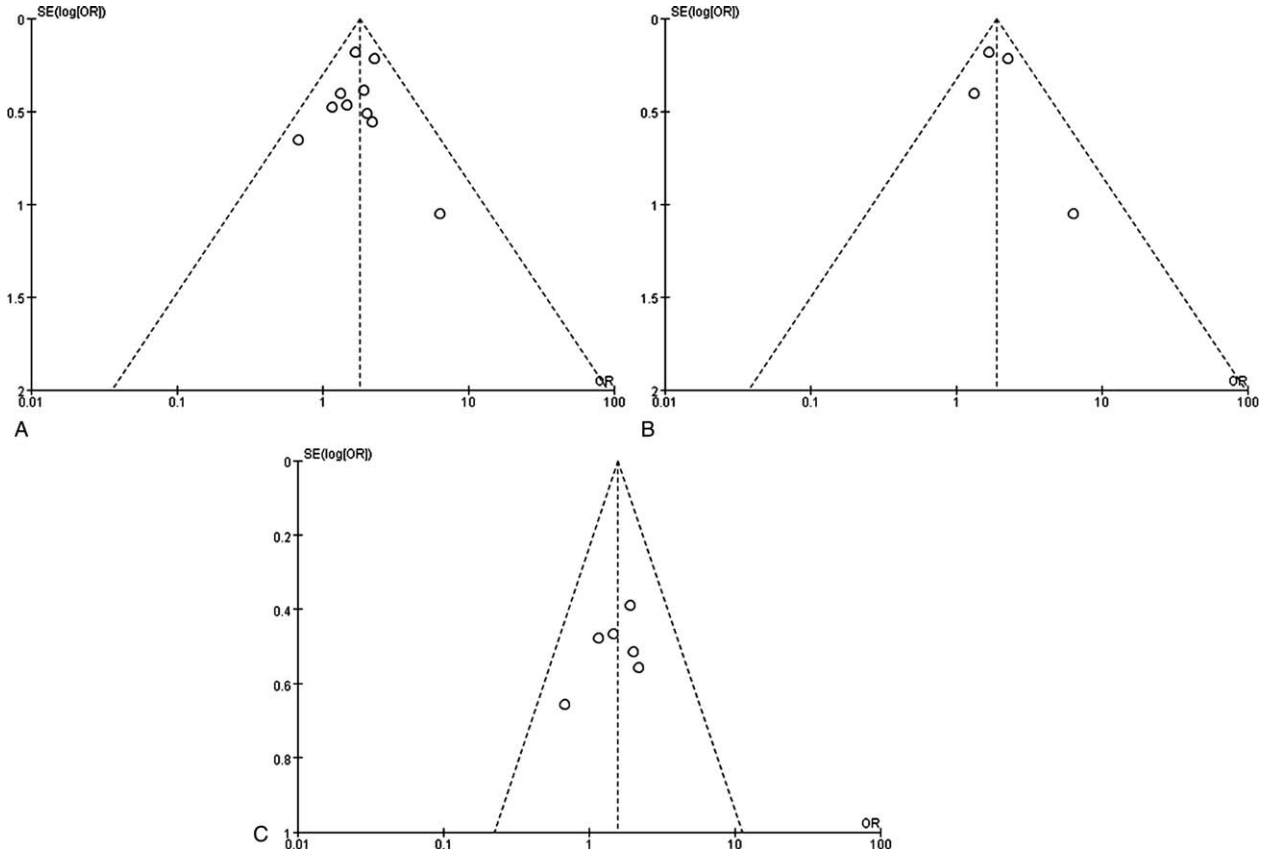

Figure 3. (A,B,C) Funnel plot of OR for ORR comparing RM HNSCC patients undergoing anti-EGFR therapy (A:mAbs+TKIs,B:mAbs,C:TKIs) and those undergoing non-anti-EGFR therapy. EGFR = epidermal growth factor receptor, HNSCC = head and neck squamous cell carcinoma, OR = odds ratio, ORR = objective response rate, RM = recurrent/metastatic, TKIs = tyrosine kinase inhibitors.

Therefore, sequential mAbs and TKIs may be a good choice for future treatment. Other several ideas include the following:

(1) Giving preventive anti-EGFR treatments to initial patients with HNSCC but anti-EGFR treatments as the last choice.
(2) Providing preoperative neoadjuvant targeted therapy referring to preoperative neoadjuvant CT.
(3) Combining COX inhibitor and anti-EGFR given that the EGF receptor (EGFR) and COX2 pathways are upregulated in HNSCC.[36]
(4) The combination therapy of targeted therapeutics against PI3K/mTORC signaling with anti-EGFR because of the ability of PI3K and mTORC inhibition to suppress the growth of HNSCC cells.[37]

Table 3

Adverse effects associated with anti-EGFR therapy.

					Heterogeneity	
Adverse effects	**No of reports**	**included patient, n**	**OR (95% CI)**	***P* value**	**I^2, %**	***P* value**
Diarrhea	7	2316	3.15 [1.90, 5.20]	<.00001	27	.22
Fatigue	6	1777	1.28 [0.85, 1.91]	.24	36	.17
Rash/desquamation	6	2329	13.66 [6.86, 27.2]	<.00001	0	.54
Nausea	6	2432	1.10 [0.58, 2.09]	.76	0	.42
Vomiting	6	1822	1.99 [1.00, 3.95]	.05	0	.66
Stomatitis	5	2049	0.50 [0.20, 1.23]	.13	70	.005
Neutropenia	4	1636	0.89 [0.75, 1.06]	.2	38	.18
Thrombocytopenia	4	1464	0.94 [0.65, 1.35]	.72	0	.54
Hypomagnesemia	4	1477	1.83 [1.28, 2.62]	.0009	77	.004
Weight loss	4	1399	0.69 [0.26, 1.84]	.46	0	.8
Anemia	4	1886	0.69 [0.53, 0.90]	.006	37	.16
Anorexia	3	1183	3.34 [1.45, 7.73]	.005	0	.88
Dehydration	3	1030	2.22 [1.19, 4.12]	.01	0	.56
Hypokalemia	3	1194	1.63 [1.09, 2.42]	.02	0	.46

CI = confidence interval, OR = odds ratio.

(5) Treatment with hypoxia and anti-EGFR.
(6) Seeking the compatible PD-1 drugs to enhance curative effect. Above all, the results of this meta-analysis provided a strong evidence to the efficacy of anti-EGFR and greater probability to treat RM HNSCC in the clinic.

In addition to the efficacy of anti-EGFR, further studies should investigate their adverse effects. In consideration that mAbs and TKIs both block EGFR signaling pathways, the close mechanisms cause their similar adverse effects. We analyzed the adverse effects of combining mAbs with TKIs. A 2012 meta-analysis[15] reported that only 3 types of adverse effects (rash, diarrhea, and anorexia) should be well monitored. Molecularly targeted therapies reduce the incidence rate of adverse effects. However, they inevitably initiate reactions in tissues that are crucially associated with EGFR signaling for normal function by blocking EGFR signaling pathways and the route of administration; these reactions include diarrhea, rash/desquamation, hypomagnesemia, vomiting, anorexia, dehydration, and hypokalemia. Diarrhea, vomiting, anorexia, dehydration are gastrointestinal reactions, whereas rash/desquamation are skin reactions. Hypomagnesemia and hypokalemia in the circulatory system were first reported in a systematic meta-analysis. Therefore, these events should be monitored in future clinical treatments. The route of administration may be changed to reduce the gastrointestinal reactions. In addition, specificity to EGFR can be enhanced. Third, the best dosage for reducing adverse effects on an anti-neoplastic basis should be identified.

This meta-analysis also had several limitations. As shown in Tables 1 and 2, only a limited number of eligible studies and a relatively small number of patients were analyzed. Each study used different drug doses, different anti-EGFR drugs, and different conventional CT programs. Given positive results are likely to be published, publication bias should also be considered. Eight studies were randomized, open-label trials. Investigators and participants were not blinded to the therapy assignment, but researchers accessing the outcomes were blinded to the therapy group. Considering outcomes objective, the lack of blinding of participants and investigators would not have caused significant bias.

In summary, our meta-analysis showed that anti-EGFR mAbs and TKIs can improve the ORR of patients with RM HNSCC. Thus, we recommend anti-EGFR mAbs and TKIs as a first- or second-line treatment for RM HNSCC and seeking more combination therapies to improve their curative effect. During treatment, skin reactions (rash), gastrointestinal reactions (diarrhea, vomiting, anorexia, and dehydration), electrolyte disturbances (hypomagnesemia and hypokalemia) should be carefully monitored.

Author contributions

YX and QY, CY participated in the design of the study. QY, FJ, WG, QH, LZ performed the statistical analysis, interpreted the data and drafted the manuscript. YX and JG contributed to the interpretation of the data and critical revision of the manuscript for important intellectual content. JG gave final approval of the version to be published and is accountable for all aspects of the work. All authors read and approved the final manuscript.

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References

[1] Peng W, Aiqing Z, Minghua G. Application of traditional Chinese medicine in the treatment of head and neck squamous cell carcinoma. Zhejiang J Integrat Tradit Chin West Med 2013;2:3–4.
[2] Siegel R, Ma J, Zou Z, et al. Cancer statistics. CA Cancer J Clin 2014;64:9–29.
[3] Xie M, Gupta MK, Archibald SD, et al. Marijuana and head and neck cancer: an epidemiological review. J Otolaryngol Head Neck Surg 2018;47:319–22.
[4] Ghasemi F, Black M, Vizeacoumar F. Repurposing Albendazole: new potential as a chemotherapeutic agent with preferential activity against HPV-negative head and neck squamous cell cancer. Oncotarget 2017;10:71512–9.
[5] Nickson CM, Moori P, Carter RJ, et al. Misregulation of DNA damage repair pathways in HPV-positive head and neck squamous cell carcinoma contributes to cellular radiosensitivity. Oncotarget 2017;8: 29963–75.
[6] Jin L, Sturgis EM, Zhang Y, et al. Association of tumor necrosis factor-alpha promoter variants with risk of HPV-associated oral squamous cell carcinoma. Mol Cancer 2013;12:80–1.
[7] Castellsague X, Alemany L, Quer M, et al. Human papillomavirus in head and neck cancer: a comprehensive biomarker evaluation of 3680 patients. J Natl Cancer Inst 2016;108:403–8.
[8] Papaspyrou G, Werner JA, Dietz A. Pharmacotherapy for squamous-cell carcinoma of the head and neck. Expert Opin Pharmacother 2011; 12:397–409.
[9] Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol 2007;4:156–71.
[10] Birkeland AC, Rosko AJ, Chinn SB, et al. Prevalence and outcomes of head and neck versus non-head and neck second primary malignancies in head and neck squamous cell carcinoma: an analysis of the surveillance, epidemiology, and end results database. ORL J Otorhinolaryngol Relat Spec 2016;78:61–9.
[11] Machiels JP, Licitra LF, Haddad RI, et al. Rationale and design of LUX-Head & Neck 1: a randomized, Phase III trial of afatinib versus methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who progressed after platinum-based therapy. BMC Cancer 2014;14:473–5.
[12] Chang JH, Wu CC, Yuan KS, et al. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. Oncotarget 2017;8:55600–12.
[13] Vatte C, Al Amri AM, Cyrus C, et al. Tyrosine kinase domain mutations of EGFR gene in head and neck squamous cell carcinoma. Onco Targets Ther 2017;10:1527–33.
[14] Song Q, Li X, Li B, et al. Anti-EGFR monoclonal antibodies in locally advanced head and neck squamous cell carcinoma: A Meta-analysis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2015; 29:815–21.
[15] Zhang S, Chen J, Jiang H, et al. Anti-epidermal growth factor receptor therapy for advanced head and neck squamous cell carcinoma: a meta-analysis. Eur J Clin Pharmacol 2012;68:561–9.
[16] Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. J Clin Oncol 2013;31:1405–14.
[17] Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 2015;16:583–94.
[18] Kushwaha VS, Gupta S, Husain N, et al. Gefitinib, Methotrexate and Methotrexate plus 5-Fluorouracil as palliativetreatment in recurrent head and neck squamous cell carcinoma. Cancer Biol Ther 2015;16: 346–51.
[19] Machiels JP, Schmitz S. Molecular-targeted therapy of head and neck squamous cell carcinoma: beyond cetuximab-based therapy. Curr Opin Oncol 2011;23:241–8.
[20] Szabó B, Nelhubel GA, Karpati A, et al. Clinical significance of genetic alterations and expression of epidermal growth factor receptor (EGFR) in head and neck squamous cell carcinomas. Oral Oncol 2011;47:487–96.

[21] Wiechec E, Hansson KT, Alexandersson L, et al. Hypoxia Mediates Differential Response to Anti-EGFR Therapy in HNSCC Cells. Int J Mol Sci 2017;18:943–9.
[22] Gehrke T, Scherzad A, Ickrath P, et al. Zinc oxide nanoparticles antagonize the effect of Cetuximab on head and neck squamous cell carcinoma in vitro. Cancer Biol Ter 2017;18:513–8.
[23] Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomized, open-label, phase 3 study. Lancet 2018;18:316–8.
[24] Hicks M, Macrae ER, Abdel-Rasoul M, et al. Neoadjuvant dual HER2-targeted therapy with lapatinib and trastuzumab improves pathologic complete response in patients with early stage HER2-positive breast cancer: a meta-analysis of randomized prospective clinical. Oncologist 2015;20:337–43.
[25] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
[26] Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27:1864–71.
[27] Machiels JP, Subramanian S, Ruzsa A, et al. Zalutumumab plus best supportive care alone in patients with recurrent or metastatic squamous cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. Lancet Oncol 2011;12:333–43.
[28] Vermorken JB, Stöhlmacher-Williams J, Davidenko I, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol 2013;14:697–710.
[29] Wirth LJ, Dakhil S, Kornek G, et al. PARTNER: An open-label, randomized, phase 2 study of docetaxel/cisplatin chemotherapy with or without panitumumab as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck. Oral Oncol 2016;61: 31–40.
[30] Grégoire V, Lefebvre J-L, Licitra L, et al. Group ObotEEEGWSquamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v184–6.
[31] Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. Ann Oncol 2015;26:1941–7.
[32] Guigay J, Even C, Mayache-Badis L, et al. Long-term response in patient with recurrent oropharyngeal carcinoma treated with cetuximab, docetaxel and cisplatin (TPEx) as first-line treatment followed by cetuximab maintenance. Oral Oncol 2017;68:114–8.
[33] Seiwert TY, Fayette J, Cupissol D, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Ann Oncol 2014;25:1813–20.
[34] Rogers SJ, Harrington KJ, Rhys-Evans P, et al. Biological significance of c-ErbB family oncogenes in head and neck cancer. Cancer Metastasis Rev 2005;24:47–69.
[35] Wheeler DL, Huang S, Kruser TJ, et al. Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. Oncogene 2008;27:3944–56.
[36] Gross ND, Bauman JE, Gooding WE, et al. Erlotinib, erlotinib-sulindac versus placebo: a randomized, double-blind, placebo-controlled window trial in operable head and neck cancer. Clin Cancer Res 2014;20:3289–98.
[37] Swick AD, Prabakaran PJ, Miller MC, et al. Cotargeting mTORC and EGFR signaling as a therapeutic strategy in HNSCC. Mol Cancer Ther 2017;16:1257–68.