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ORIGINAL ARTICLE

Cetuximab versus nimotuzumab for the treatment of advanced nasopharyngeal carcinoma: A network meta-analysis

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Summary

Purpose: *We conducted a network meta-analysis to evaluate the efficacy and toxicity of cetuximab and nimotuzumab in the treatment of advanced nasopharyngeal carcinoma (NPC).*

Methods: *A systematic literature search was performed though Pubmed, Embase, Cochran Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical (CBM) and Wanfang databases. Totally, 19 randomized controlled trials (RCTs) (n=1201) met the study selection criteria and were incorporated in this network meta-analysis.*

Results: *Compared with cetuximab, the results of network meta-analysis indicated that nimotuzumab may achieve higher complete remission rate (CRR) or overall remission rate (ORR) of the primary tumor, but no difference was noticed in 1- and 2-year overall survival (OS) rate and certain toxicities such as myelosuppression, radiodermatitis, mucositis and gastrointestinal reactions. Although nimotuzumab increased the 3-year OS rate, compared with cetuximab, this result needs to be interpreted cautiously because of the studies' heterogeneity.*

Conclusion: *Even though we didn't find significant difference between cetuximab and nimotuzumab in terms of survival outcomes, nimotuzumab is more advantageous in short-term efficacy.*

Key words: *cetuximab, nasopharyngeal carcinoma, network meta-analysis, nimotuzumab*

Introduction

NPC linked to Epstein–Barr virus (EBV), is the most common malignant tumor in head and neck, distributed mainly in Southeast Asia, Southern China, Hong Kong and Taiwan [1]. According to reports, in 2010 the incidence and mortality rates in Southern China were 19.5 and 7.7 per 100,000 persons, respectively [2]. In recent years, combination of radiotherapy (RT) and chemotherapy (CT) is being used, gradually becoming the best method for the treatment of patients with advanced NPC. But even so, the 5-year overall survival rate is only 40-50% [3,4].

Fortunately, with the development of biological treatments, molecular targeted therapies have become another main therapy for malignant tumors. The epidermal growth factor receptor (EGFR) signalling pathway is highly correlated with invasion or metastasis of NPC and indirectly related to poor survival [5], which indicates EGFR may be an effective therapeutic target. A meta-analysis,

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performed by our team, confirmed that anti EGFR monoclonal antibodies, including cetuximab and nimotuzumab, improved the therapeutic effect of advanced NPC [6].

However, despite the potential advantages of anti EGFR monoclonal antibodies for NPC, it is still not clear which one benefits patients with NPC more, compared with cetuximab and nimotuzumab. Given the lack of enough randomized controlled trials (RCTs) to reveal the argument, this issue may be addressed by a network meta-analysis. Therefore, we performed this network meta-analysis, which provides useful information on comparisons of the two regimens (cetuximab+chemoradiotherapy (CRT)/RT and nimotuzumab+CRT/RT) by integrating indirect methods, to evaluate the efficacy of cetuximab and nimotuzumab, and to verify their efficacy in locoregionally advanced NPC.

Methods

Literature search strategy

A systematic literature search was performed through Pubmed, Embase, Cochran Library, CNKI, CBM and Wanfang databases, covering all articles published up to December 2016. We used the following terms: "Nasopharyngeal Neoplasm", "NPC", "epidermal growth factor receptor", "EGFR", "cetuximab", "nimotuzumab", "randomized controlled trials" and "RCT".

Study criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. The inclusion criteria for eligible studies were: (1) Studies should be prospective RCTs of NPC; (2) Patients were diagnosed with NPC by pathological examination, computed tomography or magnetic resonance imaging scan, and the majority of the enrolled patients had locoregionally advanced NPC; (3) Studies were included if the RCTs compared a CRT/RT to cetuximab+CRT/RT or nimotuzumab+CRT/RT; (4) The endpoints were complete remission rate (CRR) or overall remission rate (ORR) of the primary tumor, long-term overall survival (OS) rate and toxicities.

Data extraction

Two investigators (Cheng Yuan and Lu Xu) independently reviewed the articles and disagreements were resolved by discussion and consensus. The following information was extracted from each study: (1) First author's surname, publication year, stages, number of patients and average age; (2) Treatment regimens for each study; (3) Reported outcomes, including CRR or ORR of the primary tumor, OS rate and toxicities.

Statistics

The primary endpoint of this network meta-analysis was OS, defined as the time from random assignment to death. Secondary endpoints were CRR or ORR of the primary tumor, OS rate and toxicities.

The statistical software (STATA13.1) was used in this network meta-analysis, and the results were reported as odds ratios (ORs) and the 95% confidence interval (CI). For indirect comparisons, treatment effects of all treatment regimens were estimated by applying a two-stage network meta-analysis as follows: Firstly, the inconsistency test through node-splitting model and the fitting consistency model or inconsistency model were performed and presented through the network command. However, due to the inability of the network meta-analysis to perform loop comparison, inconsistency test would not be performed. So, fitting consistency model was performed and presented through the network command. Then, the pairwise comparisons were conducted by "intervalplot" command. Publication bias was evaluated though comparison-adjusted funnel plot. In addition, the purpose of the network meta-analysis was to compare the curative effect of cetuximab and nimotuzumab though indirect comparison, so ranking of interventions was not necessary to perform.

Results

Baseline characteristics of included studies

The initial database search broadly identified 198 studies. After reviewing the title and abstract, duplicate search results (n=57), letters or reviews (n=32) and cell or animal studies (n=50) were excluded. From the remaining 59 full-text articles, non-RCT (n=19), articles not associated with NPC or not related to the research topic (n=10) and retrospective study (n=11) were further eliminated by the screening process. Ultimately, 19 RCTs [8-26] met the study selection criteria and were incorporated in this network meta-analysis study.

These pooled 19 RCTs involved 1201 randomly assigned patients, of whom 609 received CRT or RT alone, 592 received cetuximab+CRT/RT or nimotuzumab+CRT/RT. RT regimens included two-dimensional RT, three-dimensional conformal RT and intensity modulated radiation therapy (IMRT). Chemotherapy regimens included TP regimen (paclitaxel+ cisplatin), cisplatin and nedaplatin. The baseline characteristics of the 19 included studies are displayed in Table 1. The different regimens reported in these studies are diverse and include various combinations of RT/CRT, cetuximab+CRT/RT and nimotuzumab+CRT/RT (Figure 1). Connecting line represents the head-to-head comparison between the two connected interventions and pairs of interventions without connections can be indirectly compared through network meta-analysis.

Table 1. Characteristics of published studies included in this network meta-analysis

Study [REF]	*Year*	*No. of patients*	*Tumor stage*	*Anti EGFR monoclonal antibody*	*Control group Chemoradiotherapy regimen*	*Tumor classification*	*Endpoints*
Cai [8]	2016	40	-	nimotuzumab	TP+IMRT	differentiated, undifferentiated	CRR;ORR
Cao [9]	2016	40	III-IV$_a$	cetuximab	Cisplatin+IMRT	undifferentiated	CRR;ORR 1-, 2- and 3-year OS rate
Chen [10]	2016	66	III-IV	nimotuzumab	IMRT	squamous cell carcinoma; undifferentiated	CRR;ORR toxicities
Cheng [11]	2016	80	III-IV	nimotuzumab	TP+3D-conformal RT	-	CRR;ORR toxicities
Fu [12]	2015	40	-	cetuximab	Cisplatin+IMRT	-	CRR;ORR 1-, 2- and 3-year OS rate toxicities
Huang [13]	2007	130	III-IV	nimotuzumab	RT	squamous cell carcinoma	CRR toxicities
Li [14]	2015	60	II-IV	nimotuzumab	Nedaplatin+3D -conformal RT	differentiated, undifferentiated	CRR;ORR toxicities
Lu [15]	2014	54	-	nimotuzumab	Cisplatin+RT	-	CRR;ORR toxicities
Shao [16]	2014	48	III-IV$_a$	nimotuzumab	Nedaplatin+3D -conformal RT	-	CRR; 1-, 2- and 3-year OS rate; toxicities
Sun [17]	2016	100	III-IV	cetuximab	Cisplatin+IMRT	-	CRR;ORR toxicities
Tang [18]	2013	110	II-IV	cetuximab	Cisplatin+IMRT	squamous cell carcinoma	CRR;ORR toxicities
Tang [19]	2012	63	III-IV$_a$	nimotuzumab	TP+3D-conformal RT	-	CRR; toxicities
Wang [20]	2016	78	I-IV	cetuximab	Cisplatin+RT	-	CRR;ORR 1-, 2- and 3-year OS rate toxicities
Wu [21]	2014	35	III-IV$_b$	nimotuzumab	RT	-	CRR;ORR toxicities
Xu [22]	2015	44	III-IV$_b$	cetuximab	Cisplatin+IMRT	-	CRR; 1-, 2- and 3-year OS rate;
Yang [23]	2016	45	III-IV$_a$	cetuximab	Cisplatin+IMRT	differentiated, undifferentiated, keratinized	CRR;ORR toxicities
Yu [24]	2014	44	III-IV$_b$	nimotuzumab	Cisplatin+RT	-	CRR;ORR toxicities
Zeng [25]	2015	60	-	nimotuzumab	Cisplatin+RT	-	CRR;ORR
Zhao [26]	2015	64	III-IV$_b$	cetuximab	Cisplatin+IMRT	-	CRR;ORR toxicities

CRR:complete remission rate, ORR:overall remission rate, OS:overall survival, IMRT:intensity modulated radiation therapy, RT:radiotherapy, 3D:three-dimensional, TP: paclitaxel+cisplatin

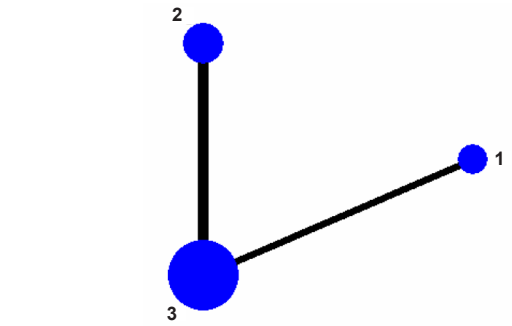

Figure 1. Relatioship between clinical trials of the three interventions. 1=nimotuzumab+RT/CRT, 2=cetuximab+RT/CRT, 3= RT/CRT alone.

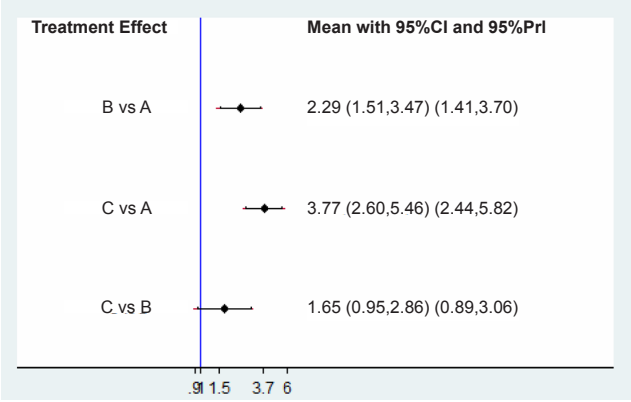

Figure 2. The 95% prediction interval (PrI) and 95% confidence interval (CI) in complete remission rate (CRR) of primary tumor. **(A)** nimotuzumab+RT/CRT, **(B)** cetuximab+RT/CRT, **(C)** RT/CRT alone. PRL=prediction interval.

The results of network meta-analysis

CRR and ORR of primary tumor

All the included studies compared the CRR of the primary tumor. The results of network meta-analysis showed that, compared with cetuximab, nimotuzumab achieved higher CRR of the primary tumor (ORs=2.29, 95%CI:1.51-3.47; Figure 2). Furthermore, 15 RCTs reported ORR of primary tumor further, and results showed that nimotuzumab also achieved higher ORR of the primary tumor (ORs=3.21, 95%CI:1.97-5.21; Figure 3).

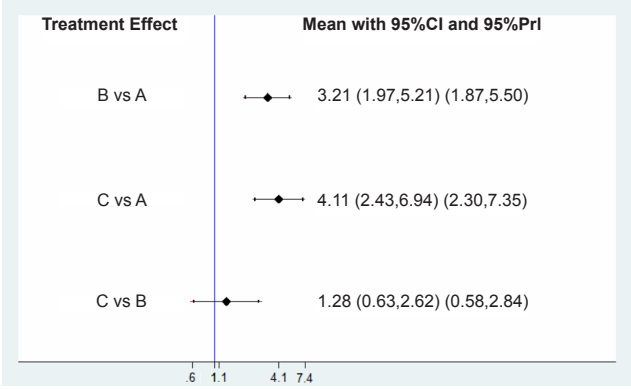

Figure 3. The 95% prediction interval (PrI) and 95% confidence interval (CI) in overall remission rate (ORR) of primary tumor. **(A)** nimotuzumab+RT/CRT, **(B)** cetuximab+RT/CRT, **(C)** RT/CRT alone.

Survival outcomes

Data available regarding the survival outcomes were limited. Although certain papers reported the results of metastasis-free survival (MSF), progression-free survival (PFS), disease-free survival (DFS) and recurrence-free survival (RFS), the reporting and occurrence of these events were rare. Therefore, we could only choose the results of OS to evaluate the survival outcomes.

There were 5 eligible studies that reported the endpoints of 1-year, 2-year and 3-year OS rate. The results of network meta-analysis found cetuximab and nimotuzumab had no difference in 1-year and 2-year OS rate of patients with advanced NPC (ORs=1.19, 95%CI: 0.51-2.78, Figure 4(A) and ORs=2.20,95%CI: 0.94-5.14,Figure 4(B),respectively),

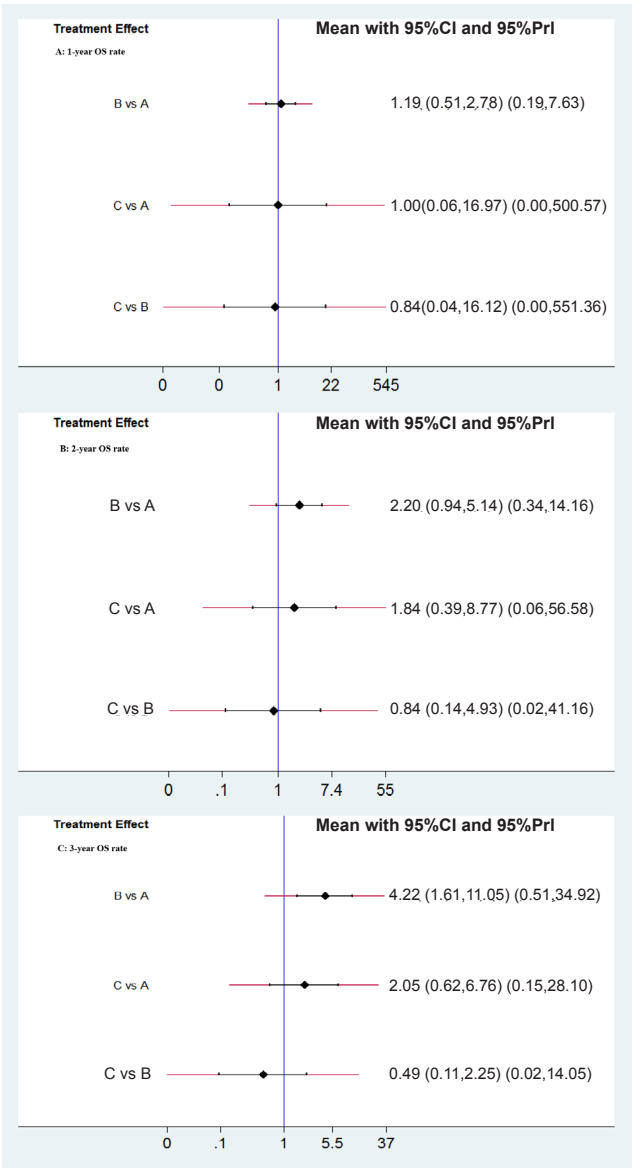

Figure 4. The 95% prediction interval (PrI) and 95% confidence interval (CI) in overall survival (OS) rate. **(A)** nimotuzumab + RT/CRT, **(B)** cetuximab + RT/CRT, **(C)** RT/CRT alone.

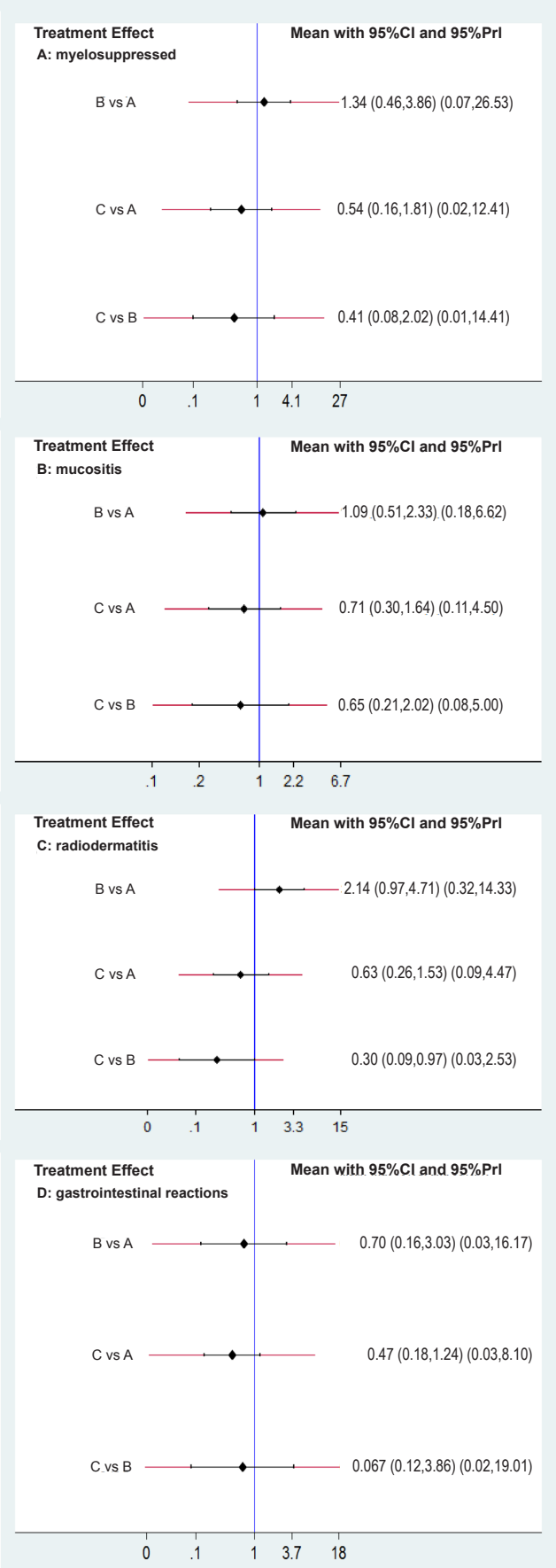

Figure 5. The 95% prediction interval (PrI) and 95% confidence interval (CI) in toxicities. **(A)** nimotuzumab + RT/CRT, **(B)** cetuximab + RT/CRT, **(C)** RT/CRT alone.

while nimotuzumab showed increased 3-year OS rate compared with cetuximab (ORs=4.21, 95%CI:1.61-11.05, Figure 4 (C)). However, it was worth noting that the 95% prediction interval (PrI) was wider than the 95%CI, and the former crosses the invalid line, which suggested that, due to the impact of heterogeneity, the current results may change in the future. Therefore, whether nimotuzumab was better than cetuximab in terms of 3-year OS rate remained to be further discussed.

Toxicities

Toxicities are the important indicators of drug evaluation, and in this network meta-analysis we evaluated the following most reported toxicities: myelosuppression, radiodermatitis, mucositis and gastrointestinal reactions. The results of the network meta-analysis illustrated that cetuximab and nimotuzumab had no difference in myelosuppression, radiodermatitis, mucositis and gastrointestinal reactions of patients with advanced NPC (ORs=1.34, 95%CI: 0.46-3.86; ORs=2.14, 95%CI: 0.97-4.71; ORs=1.09, 95%CI: 0.51-2.33; and ORs=0.70, 95%CI: 0.16-3.03; Figure 5).

Publication bias

Since all included studies reported CRR of primary tumor, publication bias would be evaluated by the CRR of primary tumor. Funnel plots are shown in Figure 6. Arrangement of data points did not reveal any evidence of obvious asymmetry.

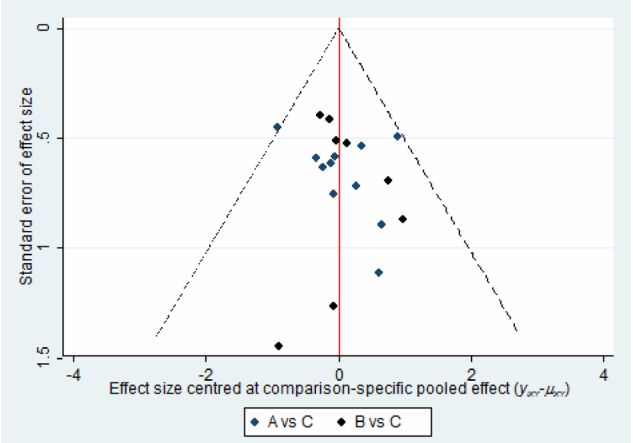

Figure 6. Comparison-adjusted funnel plot. **(A)** nimotuzumab + RT/CRT, **(B)** cetuximab + RT/CRT, **(C)** RT/CRT alone.

Discussion

During the past decades, despite the progress in technique evolution of RT, the long-term survival rate of NPC did not show fundamental improvement, so that developing new effective ther-

apeutic modalities is an urgent need. Anti-EGFR monoclonal antibodies provide new options of therapy for malignant tumors. Currently, the anti-EGFR monoclonal antibodies have been widely used in the clinical treatment of a variety of malignant tumors, including lung cancer, colorectal cancer, breast cancer and other malignancies [27-29]. Due to the rather unsatisfactory results of conventional therapy for advanced NPC, anti-EGFR monoclonal antibodies offer a new direction for the treatment of NPC [30]. Cetuximab and nimotuzumab are widely used in clinical treatment. But which one of them can benefit patients more is a problem that needs to be faced.

To our knowledge, this network meta-analysis is the first study to evaluate the efficacy and toxicity of the cetuximab versus nimotuzumab in the treatment of advanced NPC through indirect statistical comparisons based on all available information from the included RCTs. In this network meta-analysis we included 19 RCTs, involving 1201 randomly assigned patients, of whom 609 received CRT or RT alone, 592 received cetuximab+CRT/RT or nimotuzumab+CRT/RT. The results indicated that nimotuzumab may achieve higher CRR and ORR of the primary tumor compared with cetuximab, but without difference in 1-year and 2-year OS rate and certain toxicities such as myelosuppression, radiodermatitis, mucositis and gastrointestinal reactions. Although nimotuzumab increased 3-year OS rate compared with cetuximab, this result should be interpreted more cautiously. Although we found no significant difference between cetuximab and nimotuzumab in the survival outcomes, nimotuzumab was more advantageous in short-term efficacy.

The limitations of this study cannot be ignored. Firstly, as cetuximab and nimotuzumab monoclonal anti-EGFR antibodies share a common target. Given that the majority of the population included in this study was from China, domestic nimotuzumab was also widely used in clinical practice in China, which may lead to overestimation of the results of this network meta-analysis. Secondly, this study only refers to the results of indirect comparison, so that the results of statistics can not reflect the clinical reality completely. Thirdly, only articles in English and Chinese were included, which might lead to potential publication bias, although publication bias was not significant in this study.

In conclusion, despite the above limitations in the network meta-analysis, the results provide certain reference value. Compared with cetuximab, nimotuzumab might be more advantageous in the short-term, but without significant difference in the survival outcomes and toxicities.

Acknowledgement

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Conflict of interests

The authors declare no confict of interests.

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