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# Cetuximab or nimotuzumab in combination with chemotherapy for treating recurrent/metastatic nasopharyngeal carcinoma: A meta-analysis and systemic review

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**Abstract.** The present study aimed to evaluate the effectiveness and safety of cetuximab (CTX) or nimotuzumab (NTZ) in combination with chemotherapy for patients with recurrent and/or metastatic nasopharyngeal carcinoma (RM-NPC), and for this purpose, a single-group rate meta-analysis was performed. A systematic search of the Cochrane library, Pubmed, EMBASE, Chwina National Knowledge Infrastructure and WanFang databases for studies published until February 15, 2022 was performed. The 1-, 2-, 3- and 5-year overall survival (OS) rates were the primary endpoints. Complete response, partial response, stable disease, objective response rate, disease control rate and grade ≥3 toxicities were considered secondary endpoints. Cochran Q test and $I^2$ statistics were performed to assess the heterogeneity among studies. A total of nine studies comprising 435 patients were included in the analysis. The pooled 1-, 2-, 3- and 5-year OS rates were 81.0% [95% confidence interval (CI): 65.0-90.7%], 49.9% (95% CI: 35.3-64.5%), 46.3% (95% CI: 31.4-61.8%) and 31.0% (95% CI: 20.8-43.4%), respectively. The pooled disease control rate and objective response rate were 88.7% (95% CI: 78.4-94.5%) and 55.6% (95% CI: 39.9-70.1%), respectively. In addition, all grade 3-4 adverse events from the included studies were gathered. In conclusion, the use of CTX or NTZ in combination with chemotherapy may be a feasible and safe option for treating RM-NPC.

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*Abbreviations:* RM-NPC, recurrent and/or metastatic nasopharyngeal carcinoma; CTX, cetuximab; NTZ, Nimotuzumab; PCT, palliative chemotherapy; EGFR, epidermal growth factor receptor; mOS, median overall survival; PFS, progression-free survival; DFS, disease-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR (CR + PR), objective response rate; DCR (CR + PR + SD), disease control rate; SR, survival rate; AE, adverse event; CI, confidence interval; CSCO, Chinese Society of Clinical Oncology; CCRT, concurrent radiochemotherapy; NOS, Nottingham Ottawa Scale; GP, Gemcitabine + Platinum; PF, Fluorouracil + Platinum; TPF, Paclitaxel + Fluorouracil + Platinum; PC, Paclitaxel + Carboplatin; NA, not available; NR, no relevant statistical data

*Key words:* cetuximab, nimotuzumab, chemotherapy, nasopharyngeal carcinoma

## Introduction

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor of the nasopharynx that is common in Southeast Asia and North Africa (1). Distant metastases and local recurrence after primary curative treatment are the most common causes of treatment failure (2,3). For recurrent NPC and NPC with distant metastasis, the mainstream treatment option still remains palliative systemic chemotherapy. Platinum-containing two-drug or three-drug regimens were recommended as first-line chemotherapy for RM-NPC by The Chinese Society of Clinical Oncology (CSCO) in 2021 (1). Immunotherapy combined with chemotherapy has also proved to be a promising treatment approach, although it has always been controversial when combined with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (4).

The erb-b2 receptor tyrosine kinase 2 family of receptors includes epidermal growth factor receptor (EGFR). The EGFR signaling pathway is a critical regulator of cell differentiation, proliferation, migration, angiogenesis and apoptosis of cancer cells (5). Overexpression of EGFR is common in NPC (6) and certain studies have indicated that patients with high EGFR mRNA expression levels have worse prognoses than those with low expression levels (7). Furthermore, a study analyzing clinical samples from a cohort revealed a association between EGFR overexpression and the clinical stage, distant metastasis state and advanced tumor-node-metastasis stage of patients with NPC (8).

Anti-EGFR monoclonal antibodies including cetuximab (CTX) and nimotuzumab (NTZ) were discussed in the present study. A recombinant chimeric human/mouse IgG1 monoclonal antibody called CTX binds to EGFR and blocks the binding of EGF and other ligands through competitive binding. In contrast to NTZ, CTX binds to EGFR with greater specificity and affinity, competing for ligand binding and thereby blocking ligand-induced EGFR tyrosine kinase activation (5). Although NTZ is an IgG1 monoclonal antibody against

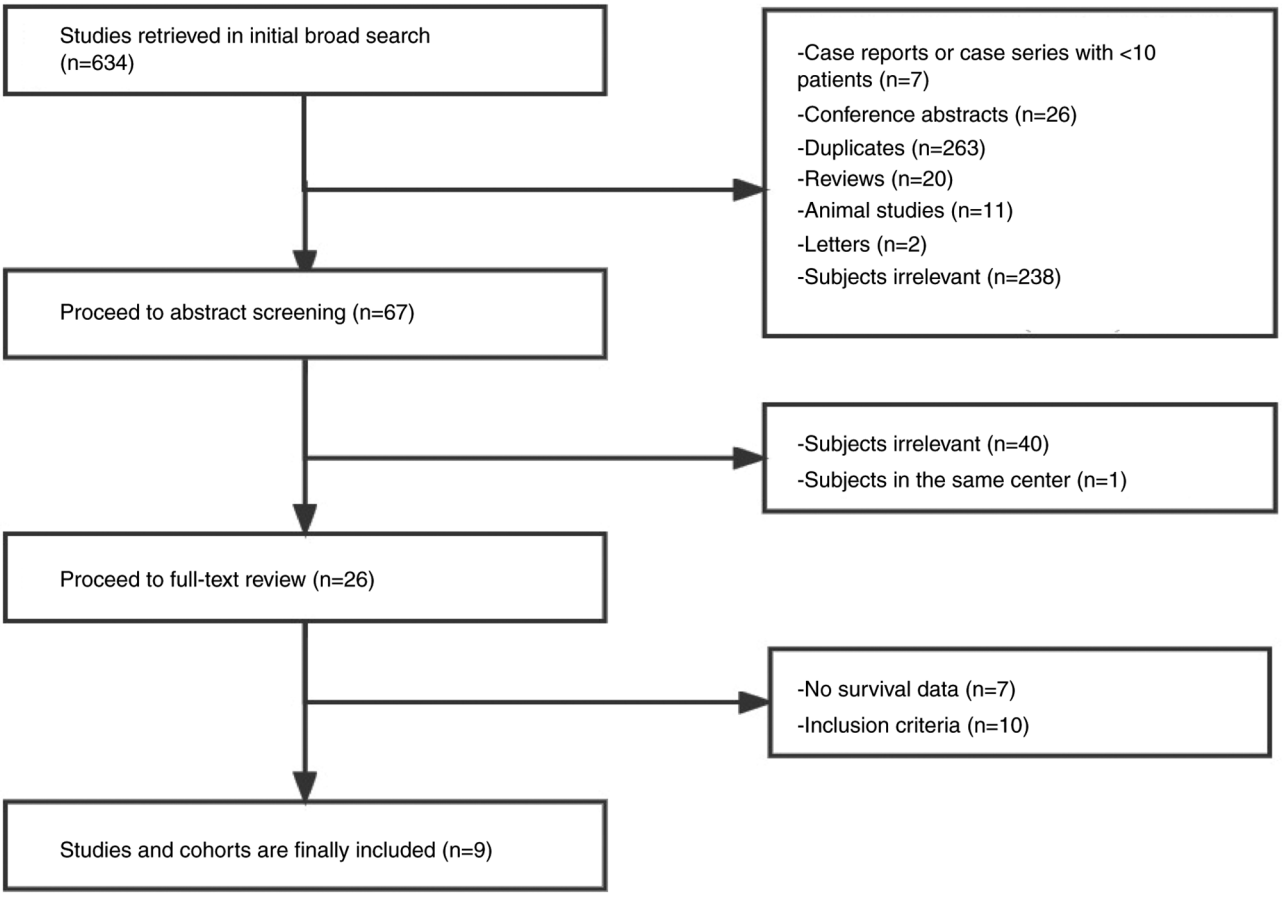


Figure 1. Process of selecting studies for final inclusion.

human EGFR, this humanization lessens the immunogenicity of the substance (9). Thus, combined use of CTX/NTZ with palliative chemotherapy (PCT) may be a therapeutic option for patients with recurrent and/or metastatic NPC (RM-NPC).

In comparison to chemotherapy alone, combination treatment with CTX was reported to improve response rates, progression-free survival (PFS) and overall survival (OS) of patients with recurrent and/or metastatic squamous cell head and neck cancer (10); however, primary NPC was an exclusion criterion in that study. In terms of biology, epidemiology, histology, natural history and therapeutic response, NPC is distinct from other head and neck malignancies (6). According to previous reports, the majority of NPC cases have high EGFR expression, which is independently associated with poor prognosis (11). To assess the effectiveness of EGFR-targeted therapies (CTX/NTZ) in combination with chemotherapy in RM-NPC, various retrospective studies have been conducted (12,13). Since 2004, a combination of CTX/NTZ and PCT has been trialed for treating RM-NPC and the results were documented in multiple case series. The median PFS (mPFS) was 8.9 months (95% CI: 7.7-10.0 months) and the median OS (mOS) was 29.1 months (95% CI: 23.5-34.6 months) in the study by Chen *et al* (12) including 203 patients with RM-NPC who underwent first-line chemotherapy with an anti-EGFR antibody. The PFS and OS rates at 1, 3 and 5 years were 35.5 and 79.6%, 15.2 and 42.5%, and 11.6 and 23.6%, respectively (12). Thus, this treatment appears to achieve promising antitumor activity with tolerable toxicity. However, the effectiveness of CTX/NTZ and PCT was comparable to that of single PCT treatment among de novo metastatic patients with NPC as per the propensity score reported by Sun *et al* (13). The addition of CTX to concurrent radiochemotherapy (CCRT) may worsen the acute mucositis and skin reactions, and the addition of anti-EGFR drugs to CCRT for patients with de novo metastatic NPC may not be beneficial.

In light of the clinical effect of CTX added to RM-NPC treatment, only a Phase III randomized, controlled, multi-center trial (NCT02633176) comparing cisplatin, docetaxel plus CTX with cisplatin and docetaxel has been reported (14). Thus, there appears to be a lack of credible evidence supporting the use of EGFR-targeted treatments for RM-NPC. Accordingly, the present study aimed to examine the available literature on the combined use of CTX/NTZ with PCT for RM-NPC.

## Materials and methods

*Study protocol*. Preferred Reporting Items for Systematic Reviews and Meta-Analysis standards were followed in the present study (15). Systematic searches in the Pubmed, EMBASE, the Cochrane library, WanFang Data and China National Knowledge Infrastructure databases were conducted up to February 15, 2022. All terms that may be used to refer to chemotherapy and RM-NPC were included in the search terms. Accordingly, searches were conducted in these databases using the following terms: ('recurrent/metastatic nasopharyngeal carcinoma' OR 'mNPC' OR 'recurrent/metastatic

nasopharynx cancer' OR 'recurrent/metastatic nasopharyngeal tumor' OR 'recurrent/metastatic nasopharyngeal neoplasms' OR 'advanced nasopharyngeal carcinoma') AND ('cetuximab' OR 'CTX' OR 'targeted therapy' OR 'anti-EGFR' OR 'nimotuzumab' OR 'NTZ') AND 'chemotherapy'. In addition, the reference lists of relevant articles were searched to identify further studies. English- and Chinese-language articles were included. Unpublished research was excluded from the search. XLN and HCY evaluated the included studies independently and sequent disagreements were resolved by discussion with a third investigator (DZ).

*Selection criteria*. All of the following criteria were required to be met by the studies to be eligible for inclusion in the present meta-analysis: i) Studies with at least 10 patients with RM-NPC; ii) clinical trials, prospective studies or retrospective research; and iii) containing information on at least one topic on survival (OS, PFS, 1-, 2-, 3- and 5-year OS rates), short-term effects [objective response rate (ORR), disease control rate (DCR)] and safety. The following were applied as the exclusion criteria: i) Letters, case reports, animal or *in vitro* research, reviews, conference articles and abstracts; ii) studies for which full-text articles could not be retrieved or those with insufficient data; and iii) duplicate reports.

After checking the titles of the studies that were searched, reviews, duplicates, animal or *in vitro* research, and case reports were removed. The studies were filtered to determine whether they met the inclusion criteria and to check for relevance to the study subject by reviewing the abstracts. When multiple studies had been published by the same center, the study with the greatest number of RM-NPC cases was included, as long as it met the inclusion criteria. Finally, a full-text review was performed on the filtered articles to determine whether they were relevant to the study subject and met all inclusion criteria. Two independent investigators performed the entire study selection process. Fig. 1 depicts the process of study selection.

*Data extraction*. The following data were independently extracted by two reviewers: i) First author, year of publication, country, design type, number of participants, inclusion period, age, sex, stage, treatment, NTZ/CTX, chemotherapy regimens and radiotherapy. The total relevant data and subgroup characteristics were extracted from noncomparative studies. ii) Antitumor efficacy indices [drug responses including complete response, partial response, stable disease, ORR and DCR; survival outcomes including mOS, mFPS, 1-, 2-, 3- and 5-year OS rate]. iii) All grade 3-4 adverse events (AEs) were also extracted. All original data were entered into related tables by XLN and HCY and a third reviewer (DZ) rectified any discrepancies.

*Quality assessment*. As the majority of the included studies were retrospective in nature, two authors (DZ and JY) evaluated the quality of the included studies using the Nottingham Ottawa Scale (NOS) (16). By analyzing three domains-selection, comparability and outcome for cohort studies, or exposure for case-control studies-the NOS rates the quality of clinical trials. A report with a NOS score of 7 to 9 was considered to be of high quality, whereas one with a score of 4 to 6 was considered medium quality.

*Statistical analysis*. Primary endpoints were mOS, mFPS, and 1-, 2-, 3- and 5-year OS rates. Secondary endpoints included ORR, DCR and toxicities at grade 3 or higher. Further, mOS, mFPS and toxicities were described in detail. To display the results of each analysis, a forest plot was drawn. Heterogeneity was defined as a P-value of the Cochran Q test being <0.1 and the $I^2$ statistic being >50% (17,18). If the data were significantly heterogeneous (P<0.1, $I^2$>50%), a random-effects model was used; otherwise, a fixed-effects model was used for analysis.

Publication bias for primary and secondary endpoints was assessed visually using the asymmetry of the funnel plot and quantitatively using Egger's test of intercept (19) and Duval and Tweedie's trim and fill test (20). If the two-tailed P-value in Egger's test was <0.1, Duval and Tweedie's trim test was performed. Comprehensive Meta-Analysis software version 3 was used for all statistical analyses (Biostat, Inc.).

## Results

*Study selection and features*. Following the initial broad search using the search terms, 634 studies were screened. The first screening eliminated 567 studies due to being duplicate studies, reviews, letters, animal studies, conference abstracts and case reports or case studies with 10 or fewer patients, or had an irrelevant topic. The titles and abstracts of the remaining 67 studies were then carefully reviewed and 40 studies with irrelevant topics were further excluded. One study was omitted because it was published by the same institute. The full-text contents of the remaining 26 studies were examined to determine whether they met all of the inclusion criteria. A total of 7 studies were eliminated because they only provided short-term efficacy with no survival data, and 10 studies were eliminated because they did not meet the inclusion criteria. Finally, 9 studies (12,21-28) comprising 435 patients (346 males and 89 females) were included in the present analysis.

A total of 8 studies were retrospective in nature and only 1 study was prospective. Of these 9 studies, 7 studies were published in English journals and 2 studies were from Chinese journals. The period of analysis of these studies was between 2004 and 2019. Overall, 207 patients were treated with NTZ, whereas 228 patients were treated with CTX. A total of 3 studies reported outcomes of combined treatment with NTZ and PCT, 5 studies reported outcomes of combined treatment with CTX and PCT, and only 1 of the 9 studies reported outcomes of combined treatment with NTZ/CTX and PCT. The treatment with CTX/NTZ ranged from 2 to 31 cycles, consistent with PCT. PCT regimens included Gemcitabine + platinum (GP), Fluorouracil + platinum (PF), Paclitaxel + fluorouracil + platinum (TPF) and Paclitaxel + carboplatin (PC). Furthermore, 2 studies also reported on combined radiotherapy with PCT. Tables I-III provide summaries of the baseline characteristics, clinical outcomes and grade 3-4 AEs of these included investigations, respectively. The quality levels of all nine studies fell into the medium quality range on the NOS scale (Table IV).

*OS*. Only 4 studies including 302 patients reported mOS and its range (12,21,24,25); the pooled mOS was 30.8 months (95% CI, 18.5-43.2, $I^2$=90.1%); 5 studies comprising 316 patients

Table I. Characteristics of included trials.

| First author, year | Country | Design type | Inclusion period | n | Age, years | Males, % | Stage | CTX/NTZ | Treatment (dose and cycles) | Chemotherapy | Radiotherapy | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhu, 2020 | China | Cohort | 2004-2018 | 49 | 49.08±10.72 | 81.6 | RM-NPC | NA | CT (5 cycles, range=2-8) | TP, GP, PF | NA | (21) |
| | | | | 21 | 48.81±13.32 | 100 | RM-NPC | NTZ (12 cycles, range=3-31) | CT (4 cycles, range=2-8) | TP, GP, PF | NA | |
| Zhang, 2020 | China | Prospective | 2006-2014 | 43 | 43 (23-63) | 83.7 | RM-NPC | CTX | CT (≤6 cycles) | TP | IMRT | (24) |
| Xu, 2015 | China | Retrospective | 2007-2011 | 30 | 44 (26-62) | 73.3 | RM-NPC | CTX (7 cycles, range=3-18) | NA | GP, TP, TPF, PC | IMRT | (28) |
| Ueda, 2020 | Japan | Retrospective | 2013-2019 | 14 | 59.6 (43-74) | 71.4 | RM-NPC | CTX continued until disease progression or unacceptable toxicities | CT (6 cycles) | PC | NA | (23) |
| Chen, 2020 | China | Retrospective cohort | 2007-2017 | 203 | 43 (12-72) | 82.8 | RM-NPC | CTX /NTZ | NA | GP, TP, TPF, PF | NA | (12) |
| Chan, 2005 | China | Phase II study | NA | 60 | 44.5 (23-64) | 77 | III, IV | CTX (10 cycles, range=1-30) | CT (≤8 cycles) | PF | NA | (22) |
| Zhao, 2019 | China | Phase II clinical trial | 2012-2015 | 35 | 44 (29-67) | 85.7 | RM-NPC | NTZ (12 cycles) | CT (6 cycles) | PF | NA | (25) |
| Gao, 2013 | China | Retrospective | 2009-2012 | 12 | 35 | 83.3 | IV | NA | CT (≥2 cycles) | GP | NA | (26) |
| | | | | 10 | 50 | 80 | IV | CTX | CT (≥2 cycles) | GP | NA | |
| Yao, 2013 | China | | 2009-2012 | 18 | 45.1 | 83.3 | NA | NA | CT (2 cycles) | GP | NA | (27) |
| | | | | 19 | 45.3 | 78.9 | NA | NTZ (2 cycles) | CT (2 cycles) | GP | NA | |

Age is presented as the median (range) or mean ± standard error. CTX, cetuximab; NTZ, Nimotuzumab; RM-NPC, recurrent and/or metastatic nasopharyngeal carcinoma; CT, chemotherapy; TP, paclitaxel + platinum; GP, Gemcitabine + platinum; PF, Fluorouracil + platinum; TPF, Paclitaxel + fluorouracil + platinum; PC, Paclitaxel + Carboplatin; IMRT, intensity-modulated radiation therapy; NA, not available.

Table II. Clinical results of included trials.

| First author, year | n | M follow up(months) | mOS | Survival outcomes | | | | | | Drug response, % | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | mPFS | OSR-1y | OSR-2y | OSR-3y | OSR-5y | CR | PR | SD | ORR | DCR | (Refs.) |
| Zhu, 2020 | 49 | 62 | 25.6 (18.9-32.4) | 7.5 (6.6-8.4) | NR | NR | 36.7 | 25.4 | 4.1 (2) | 55.1 (27) | 32.7 (16) | 59.2 (29) | 91.8 (45) | (21) |
| | 21 | 59 | 48.69 (35.6-61.6) | 8.5 (6.1-11.0) | NR | NR | 76.2 | 42.9 | 0 (0) | 57.1 (12) | 28.6 (6) | 57.1 (12) | 85.7 (18) | |
| Zhang, 2020 | 43 | NA | 32.9 (18.2-47.5) | 18.3 (10.6-26.0) | 88.4 | 60.5 | 48.8 | 34.9 | 34.9 (15) | 44.2 (19) | 14 (6) | 79.1 (66.9-91.2) | 93 (85.4-100) | (24) |
| Xu, 2015 | 30 | NA | 23.6 | NR | 100 | 53.3 | NR | NR | 10.0 | 60.0 | 23.3 | 70.0 | 93.3 | (28) |
| Ueda, 2020 | 14 | 23.8 | Not reached | 4.1 (2.6-5.6) | NR | NR | NR | NR | 16.7 (2) | 41.7 (5) | 33.3 (4) | 58.3 (7) | 91.7 (11) | (23) |
| Chen, 2020 | 203 | 34.3 | 29.1 (23.5-34.6) | 8.9 (7.7-10.0) | 79.6 | NR | 42.5 | 23.6 | 3.9 | 63.6 | 23.6 | 67.5 | 91.1 | (12) |
| Chan, 2005 | 60 | NA | 7.8 | 2.7 | NR | NR | NR | NR | 0 | 11.7 | 48.3 | 11.7 | 60.0 | (22) |
| Zhao, 2019 | 35 | 13.2 | 16.3 (11.4-21.3) | 7 (5.8-8.2) | 60.7 | 35.4 | 24.8 | NR | 3 | 68.6 | 14.3 | 71.4 | 85.7 | (25) |
| Gao, 2013 | 12 | NA | 46.43 | 7.07 | NR | NR | NR | NR | CR+PR, 16.7 | | 66.7 | 16.7 | 83.3 | (26) |
| | 10 | NA | 39.97 | 11 | NR | NR | NR | NR | CR+PR, 40.0 | | 60.0 | 40.0 | 100 | |
| Yao, 2013 | 18 | NA | 29.3 | 7 | NR | NR | NR | NR | NR | NR | NR | 16.7 | 77.8 | (27) |
| | 19 | NA | 40.2 | 11.2 | NR | NR | NR | NR | NR | NR | NR | 42.1 | 100 | |

M follow up, median follow up; mOS, median overall survival, mPFS, median progression-free survival; ORR, objective response rate; OSR-1y, 1-year overall survival rate; CR complete response; PR, partial response; SD, stable disease; DCR, disease control rate; NR, no relevant statistical data.

Table III. Grade 3-4 treatment-related adverse effects.

| First author, year | N | Neutropenia (%) | Leucopenia (%) | Anemia (%) | Thrombocytopenia (%) | Vomiting Nausea (%) | Decreased (%) (%) | Alopecia appetite | Neuropathy (%) | Acne-like (%) | Dermatitis rash (%) | (%) | (Ref.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhu, 2020 | 49 | 42.9 | 44.9 | 6.1 | NR | 4.1 | 4.1 | 0 | 10.2 | 2 | NR | NR | (21) |
| | 21 | 42.9 | 28.6 | 4.8 | NR | 4.8 | 0 | 4.8 | 19 | 4.8 | NR | NR | |
| Zhang, 2020 | 43 | 14 | 39.5 | 2.3 | 9.3 | 0 | 0 | NR | 0 | 0 | 11.6 | 0 | (24) |
| Xu, 2015 | 30 | 86.7 | NR | 26.7 | 10 | NR | NR | NR | NR | NR | 20 | NR | (28) |
| Ueda, 2020 | 14 | 21.4 | 28.3 | 0 | 0 | 7.1 | 7.1 | 0 | NR | 0 | 14.3 | NR | (23) |
| Chen, 2020 | 203 | NR | 43.4 | NR | 11.3 | 1 | 1 | 0 | NR | 0 | 1.5 | NR | (12) |
| Chan, 2005 | 60 | NR | 5 | 18.3 | 10 | NR | 6.7 | NR | NR | 6.7 | 11.7 | NR | (22) |
| Zhao, 2019 | 35 | NR | 62.9 | NR | NR | 22.9 | 25.7 | 17.2 | NR | NR | NR | NR | (25) |
| Gao, 2013 | 12 | NR | 33.3 | 0 | 16.7 | 0 | 0 | 0 | NR | NR | 0 | NR | (26) |
| | 10 | NR | 40 | 40 | 40 | 0 | 0 | 0 | NR | NR | 0 | NR | |
| Yao, 2013 | 18 | NR | 33.3 | 0 | 11.1 | 0 | 0 | NR | NR | NR | 0 | NR | (27) |
| | 19 | NR | 36.8 | 0 | 36.8 | 0 | 0 | NR | NR | NR | 0 | NR | |

NR, no relevant statistical data.

Table IV. Newcastle-Ottawa Scale assessment of the quality of studies included in the meta-analysis.

| First author, year | Selection | | | | Comparability | Exposure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Adequate definitions of the cases | Representativeness of the cases | Selection of controls | Definition of controls | control for important factor | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate | Scores | (Refs.) |
| Zhu, 2020 | ★ | ★ | - | - | ★ | ★ | ★ | ★ | 6 | (21) |
| Zhang, 2020 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (24) |
| Xu, 2015 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (28) |
| Ueda, 2020 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (23) |
| Chen, 2020 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (12) |
| Chan, 2005 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (22) |
| Zhao, 2019 | ★ | ★ | - | - | - | ★ | ★ | ★ | 5 | (25) |
| Gao, 2013 | ★ | - | ★ | ★ | ★ | ★ | - | - | 5 | (26) |
| Yao, 2013 | ★ | - | ★ | ★ | ★ | ★ | - | - | 5 | (27) |

reported mPFS and its range (12,21,23-25), and the pooled mPFS was 7.9 months (95% CI, 5.4-10.2, $I^2$=89.5%). The pooled 1-year OS rate for all four cohorts was 81.0% (95% CI: 65.0-90.7%). The pooled 2-year OS rates were available for all three cohorts, with a pooled rate of 49.9% (95% CI: 35.3-64.5%) (Table V), and the pooled 3-year OS rates for all four cohorts were available, with a pooled rate of 46.3% (95% CI: 31.4-61.8%), and the pooled 5-year OS rates for all three cohorts were also available, with a pooled rate of 31.0% (95% CI: 20.8-43.4%). Fig. 2 displays a forest plot containing the 1-, 3- and 5-year survival data. Table V provides an overview of the combined survival rates.

Pooled DCR and ORR rates were 88.7% (95% CI: 78.4-94.5%) and 55.6% (95% CI: 39.9-70.1%), respectively. Fig. 3 displays a forest plot of the ORR and DCR. Table V provides an overview of the pooled DCR and ORR. Due to the heterogeneity of the included trials, a random-effects model was used to calculate the ORR and DCR of the disease ($I^2$=78.79 and 85.20%, respectively; P<0.001 for both).

*Treatment toxicities*. A list of all 3-4 AEs from each included study was compiled (Table VI). Neutropenia (40.7%), leucopenia (32.6%), platelet count decrease (12.4%) and anemia (12.7%) were the most common AEs. Other AEs included nausea (3.5%), vomiting (4.0%), decreased appetite (2.5%), alopecia (6.3%), neuropathy (1.5%) and acne-like rash (6.0%).

*Publication bias*. Publication bias was found for 1-year OS (P=0.608), 5-year OS (P=0.036) and DCR (P=0.247) using Egger's regression test and on visual inspection of funnel plots (data not shown). Using Duval and Tweedie's method, trimmed data for these three rates were obtained (Table V). One study for 1-year overall survival, two for 5-year overall survival and four for response rate were trimmed.

## Discussion

To the best of our knowledge, the present study was the first single-group rate meta-analysis to pool the efficacy of the combination of CTX/NTZ and PCT in treating RM-NPC. Finally, 9 studies comprising 435 patients were included in the present study, wherein 207 patients were treated with NTZ and 228 patients were treated with CTX. These results mostly represent the efficacy and toxicities in the Asian population, notably in China, as the vast majority of the patients included in the present analysis had been treated in China. In addition, the male:female ratio of the pooled cohort of the present study was in line with that reported in the literature. The incidence of NPC is much higher in males than in females, with a ratio of ~2.5:1 in China in 2015 (1). RM-NPC is a set of heterogeneous disorders that are typically broken down into three categories: De novo metastasis, locoregional recurrence and locoregional recurrence with distant metastasis (1).

The pooled mOS and mPFS were 30.8 and 7.9 months in the present study, respectively, which appear higher than those observed with standard PCT (29,30). In 2021, a final OS analysis of the GEM20110714 phase III study: GP vs. FP as first-line therapy for RM-NPC, reported a median OS of 22.1 months with GP vs. 18.6 months with FP. The OS rate with GP vs.

Table V. Summary of pooled rates.

| | Rates, % (95% CI) | P-value, $I^2$ | Effect model | Publication bias | Trimmed result, % (95% CI) |
|---|---|---|---|---|---|
| OSR-1y | 81 (65-90.7) | 0.001, 76.21 | Random | Yes | 77.6 (59.1-89.3) |
| OSR-2y | 49.9 (35.3-64.5) | 0.090, 58.47 | Random | No | / |
| OSR-3y | 46.3 (31.4-61.8) | 0.005, 76.92 | Random | No | / |
| OSR-5y | 31 (20.8-43.4) | 0.078, 60.85 | Random | Yes | 23.6 (15.5-34.1) |
| DCR | 88.7 (78.4-94.5) | <0.001, 78.79 | Random | Yes | 85.9 (75.6-92.3) |
| ORR | 55.6 (39.9-70.1) | <0.001, 85.20 | Random | No | / |

OSR-1y, 1-year overall survival rate; DCR, disease control rate; ORR, objective response rate.

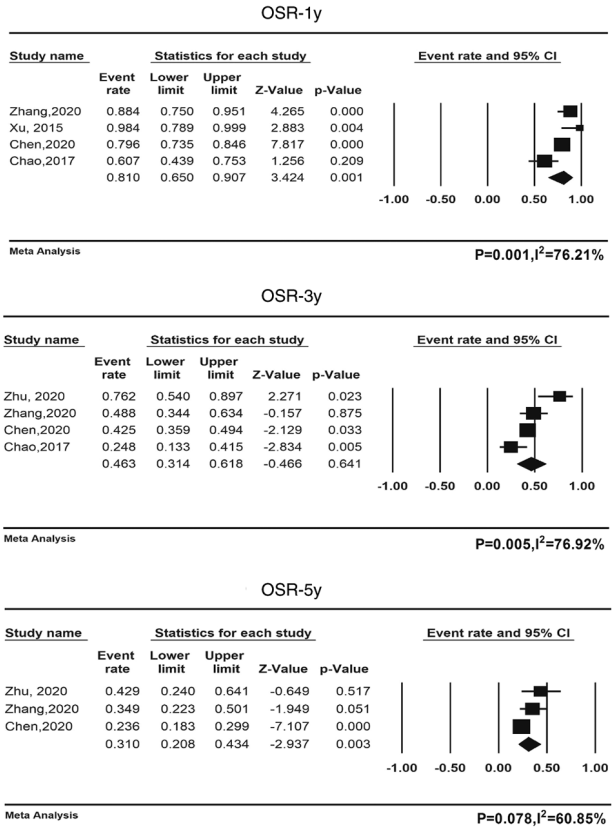


Figure 2. Forest plots of 1-, 3- and 5-year OS rate. 'Events' refers to mortalities. OSR-1y, 1-year overall survival rate.

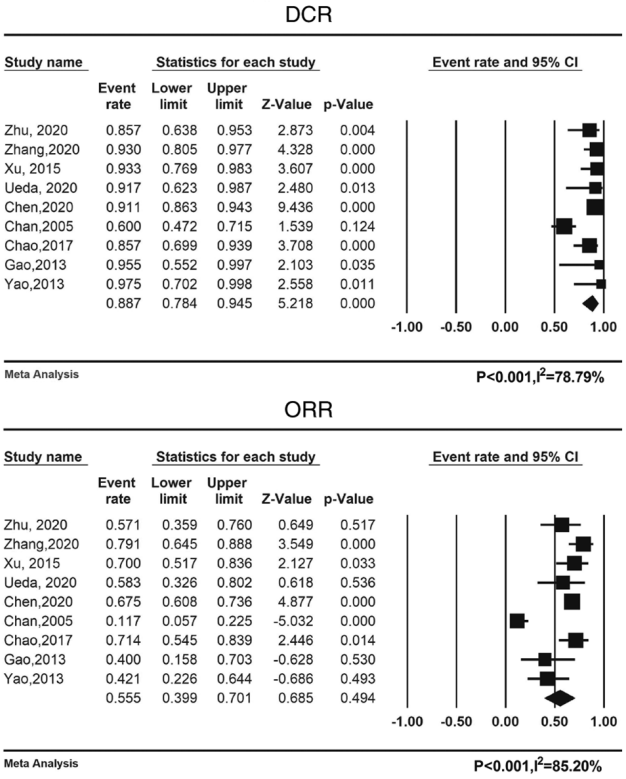


Figure 3. Forest plots of DCR and ORR. DCR, disease control rate; ORR, objective response rate.

FP at 1, 3 and 5 years was 79.9, 31.0 and 19.2% compared with 71.8, 20.4 and 7.8%, respectively (29). By contrast, in the present study, the pooled 1-, 2-, 3- and 5-year OS rates were 81.0, 49.9, 43.6 and 31.0%, respectively. The rate observed in the present study was also higher than that observed with standard PCT. There are several reasons for this, which may include the following: First, PCT was administered for 2-8 cycles or until unacceptable toxicities developed in included studies; CTX or NTZ was continued until disease progression or unacceptable toxicities developed in certain studies, wherein maintenance therapy may contribute to longer PFS or OS (31,32); however, more evidence is still required to confirm this in the future. Second, two out of nine studies (24,28) concluded that adding local radiation to chemotherapy significantly increased OS in patients with mNPC who were responsive to treatment (33). Other palliative first-line systemic treatment options included immunotherapy combined with gemcitabine plus cisplatin and other chemotherapeutic regimens in the 2021 CSCO guidelines. Yang *et al* (4) compared camrelizumab plus GP with placebo plus GP in a randomised phase 3 trial, and independent review committee-assessed PFS was significantly longer in the camrelizumab group (median, 9.7 months) than that in the placebo group (median, 6.9 months). Toripalimab was added to GP chemotherapy as a first-line treatment for patients with RM-NPC in a multicenter randomized phase 3 trial, which demonstrated better PFS compared with GP alone and a tolerable safety profile (34). Other chemotherapeutic regimens, targeted therapy and most recently immunotherapy have steadily developed as palliative systemic treatment

Table VI. Grade 3-4 AEs in included studies.

| AEs | Studies with reported AEs | Events/total | % |
|---|---|---|---|
| Hematological system AEs | | | |
| Neutropenia | 4 | 44/108 | 40.7 |
| Leucopenia | 8 | 132/405 | 32.6 |
| Anemia | 7 | 25/197 | 12.7 |
| Thrombocytopenia | 7 | 47/379 | 12.4 |
| Digestive system AEs | | | |
| Nausea | 7 | 12/345 | 3.5 |
| Vomiting | 8 | 16/405 | 4.0 |
| Decreased appetite | 5 | 7/283 | 2.5 |
| Others | | | |
| Alopecia | 2 | 4/64 | 6.3 |
| Neuropathy | 5 | 5/341 | 1.5 |
| Acne-like rash | 7 | 23/379 | 6.0 |
| Dermatitis | 1 | 0/43 | 0.0 |

AE, adverse event.

options in RM-NPC (35). In the present study, a thorough analysis of various conventional chemotherapy regimens was performed with an emphasis on contemporary chemotherapeutic strategies, as well as the most recent advancements in targeted medicine (4,34).

All grade 3-4 AEs reported in the included studies were also gathered in the present study. The most common grade 3-4 AEs were neutropenia (40.7%), leucopenia (32.6%), platelet count decrease (12.4%) and anemia (12.7%). Acne-like rash was another AE, which was observed at a frequency of 6%. Unlike CTX and small-molecule EGFR tyrosine kinase inhibitors, NTZ did not cause any acne-like rash. NTZ is able to preserve the equilibrium between the tethered and stretched EGFR conformations and does not obstruct EGFR signaling at the basal level, which is essential for the survival of healthy epithelial cells. These processes, along with the intermediate affinity of NTZ for other anti-EGFR antibodies, may account for the low level of side effects and low toxicity observed in clinical settings (9). Thus, NTZ may have a greater complete remission rate or overall remission rate of primary tumors in NPC compared with cetuximab, according to the findings of a network meta-analysis. However, there was no difference in the 1- and 2-year OS rates between NTZ and CTX (36).

The present study has a number of limitations. First, meta-analysis of observational studies is debatable (37) and heterogeneity among studies in terms of varying patient characteristics and study methods may have had an impact on pooled rates (38). Oncology does not always have solid evidence; thus, therapeutic decisions may be based on observational studies, numerous small trials or even just clinical experience alone. Although randomized controlled trials provide the strongest evidence, this is not always the case (39). A meta-analysis may be one of the few ways available to evaluate therapeutic efficacy and safety, as there are minimal observational study data regarding the combination of CTX/NTZ and PCT to date, despite the fact that RM-NPC is not an extremely rare disease. Second, most of the study participants were Chinese, which may have biased the results. Third, various therapy techniques had been used on the study participants. Fourth, the number of included articles and patients was small.

In conclusion, the current meta-analysis demonstrated that the combination of CTX/NTZ with PCT may be a feasible palliative treatment option for patients with RM-NPC. However, high-quality evidence with large sample sizes is needed to further validate the efficacy of EGFR-targeted therapies for RM-NPC.

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**Availability of data and materials**

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

**Authors' contributions**

Conceptualization: XN, JZ, DZ, JY, HY; data curation: XN, HY, DZ; formal analysis: XN, HY, DZ, JY; investigation: XN, HY, DZ, JY, QD; methodology: XN, HY; project administration: XN, JZ, DZ, JY, HY; software: XN, QD; supervision: XN, DZ, QD; writing-original draft: XN, JZ; writing-review and editing: XN, JZ, DZ, JY, HY, QD. XN and JZ confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare they have no competing interests.

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