

Original Article

Concurrent chemotherapy with or without nimotuzumab for treatment for locoregionally advanced nasopharyngeal carcinoma: a meta-analysis

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Abstract: Background: Nimotuzumab (NTZ) has been reported to improve outcomes of locoregionally advanced nasopharyngeal carcinoma (LANPC). The current meta-analysis was conducted to assess the efficacy and toxicities of adding NTZ to standard cisplatin-based concurrent chemoradiotherapy (CCRT) in LANPC. Methods: Present researchers systematically searched various electronic databases, including PubMed, Embase, Cochrane Library, and Web of Science, for publications from January 1, 1990, to July 31, 2018. Pooled hazard ratios (HRs) for overall survival (OS), distant metastasis-free survival (DMFS), loco-regional relapse-free survival (LRFS), disease-free survival (DFS), progression-free survival (PFS), and pooled risk ratios (RRs) for adverse events were meta-analyzed. Results: A total of 1,444 patients with LANPC, included in 4 retrospective cohort studies, were included for analysis. HRs between the CCRT plus NTZ group and CCRT group were 0.70 (95% confidence interval (CI) 0.44-1.12, $P=0.14$), 0.75 (95% CI 0.50-1.12, $P=0.16$), 0.60 (95% CI 0.33-1.08, $P=0.09$), 0.59 (95% CI 0.41-0.86, $P=0.006$), and 1.28 (95% CI 0.58-2.85) for OS, DMFS, LRFS, DFS, and PFS, respectively. However, subgroup analysis indicated that the CCRT plus NTZ group had higher 3-year OS (HR=0.44, 95% CI 0.25-0.79, $P=0.004$) and 3-year DMFS (HR=0.56, 95% CI 0.35-0.89, $P=0.01$). No differences in incidence of grade 3-4 hematological toxicities (anemia, leucopenia, neutropenia, and thrombocytopenia), and grade 3-4 non-hematological toxicities (mucositis, dermatitis, nausea, vomiting, and weight loss) were found. Conclusion: Adding NTZ to CCRT effectively improved 3-year survival rates in patients with LANPC, with no significant differences in adverse events, compared with CCRT alone.

Keywords: Locoregionally advanced nasopharyngeal carcinoma, nimotuzumab, concurrent chemoradiotherapy, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is an endemic in Southeast Asia, especially Southern China. Incidence is 20 to 30 cases per 100,000 people [1-4]. Previous studies have reported that 60% to 70% of patients with NPC were diagnosed with stage II-IVb NPC [5, 6]. Based on 2017 National Comprehensive Cancer network (NCCN) guidelines for locoregionally advanced NPC (LANPC), concurrent platinum-based chemoradiotherapy (CCRT) is the present standard treatment. However, approximately one third of patients with LANPC failed in the treatment, experiencing locoregional recurrence or distant metastasis [7, 8]. To improve survival rates of NPC, Sun and her colleagues conducted a pha-

se III randomized controlled trial (RCT). They reported that induction chemotherapy significantly improved overall survival (OS) and distant failure-free survival (DFS) rates of NPC patients [9]. However, incidence of locoregional recurrence and distant failure in LANPC was still 20% [9, 10]. Therefore, new regimens with tolerable adverse events are urgent for patients with LANPC.

Epidermal growth factor receptor (EGFR) has been shown to be greatly expressed in most human epithelial carcinomas, and in more than 80% of LANPC patients [11, 12]. Moreover, overexpression of EGFR has been correlated with poor clinical prognosis of LANPC [13, 14]. Anti-EGFR antibodies, such as cetuximab (CTX),

have been shown to improve survival rates of locoregionally advanced head and neck squamous cell carcinoma (HNSCC) patients [15]. Furthermore, several studies have reported that CCRT plus cetuximab for LANPC is a feasible and tolerable strategy [14, 16]. These findings indicate that patients with LANPC could benefit from the concurrent combination of chemoradiotherapy plus cetuximab. However, high rates of skin rashes, mucositis, and dermatitis have limited the pervasive application of cetuximab [14, 17].

Nimotuzumab (NTZ) is a humanized monoclonal antibody (mAb). It competitively binds to the extra-cellular domain of the EGFR [18]. In previous studies, NTZ was applied in various tumors, including the head and neck and gliomas, as well as colorectal, pancreatic, prostate, and non-small cell lung cancer [19-21]. It has been reported that NTZ combined with radiotherapy or chemoradiotherapy significantly improved OS in locally advanced HNSCC [11]. In NPC, adding NTZ to radiotherapy has shown promising outcomes in terms of survival and locoregional control [22, 23]. Striking outcomes from the use of NTZ include the absence of severe skin rashes, in sharp contrast to cetuximab [24]. Recently, several studies compared treatment outcomes of CCRT with or without NTZ in LANPC [25-28]. Yao and his colleagues retrospectively examined the benefits of CCRT plus NTZ, compared with CCRT alone, in patients with stage III-IVb NPC [26]. The CCRT plus NTZ group exhibited significantly increased 5-year OS, increased 5-year PFS, and improved 3-year DMFS. However, in a clinical trial conducted by Wang et al., 3-year OS, LRFS, and PFS rates of the CCRT plus NTZ group were comparable to the CCRT group [25]. Considering these results, adding NTZ to CCRT might be an alternative option for regionally advanced NPC.

Thus, there remains a debate over whether CCRT plus NTZ achieves potential benefits with tolerable toxicities in patients with LANPC. Therefore, the current meta-analysis was conducted to assess the efficacy and safety of CCRT plus NTZ in LANPC patients.

Material and methods

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [29].

Search strategy

To identify relevant studies, studies were searched using PubMed, Cochrane Library, Embase, and Web of Science (from January 1, 1990, to July 31, 2018). Search terms included “nasopharyngeal carcinoma” OR “nasopharyngeal neoplasms” OR “nasopharyngeal cancer” OR “nasopharyngeal tumor”, “concurrent chemoradiotherapy” OR “concurrent” OR “chemoradiotherapy” and “nimotuzumab”. They used to identify relevant studies with no restrictions on language. Finally, all eligible studies were retrieved. References were hand searched for other relevant publications.

Inclusion and exclusion criteria

Inclusion criteria: (1) The experimental arm was CCRT plus NTZ. NTZ should be administered concomitantly with CCRT. The control arm was CCRT alone; (2) Participants were diagnosed with local regionally advanced (stage II-IVb) NPC; (3) Studies were retrospectively controlled trials or matched-pair analyses; and (4) Blinded or unblinded randomized controlled trials were considered for evaluation. Exclusion criteria: Reviews, letters to editors, case reports, meeting abstracts, trial protocols, comments, and animal experiments.

Outcomes

Primary outcomes were OS, DMFS, LRFS, DFS, and PFS. Secondary outcomes were adverse events, including leukopenia, neutropenia, anemia, thrombocytopenia, mucositis, dermatitis, nausea, vomiting, and weight loss.

Quality assessment

Quality of included trials was assessed using the 9-star Newcastle-Ottawa Scale (NOS) (25) in 3 domains: selection, comparability, and outcomes for cohort studies or exposure for case-control studies. Scores with 7-9 points are defined as high quality, while scores < 7 are defined as low quality.

Data extraction

For all eligible studies, the following data was extracted: First author, year of publication, study type, inclusion period, number of patients, staging information, median follow up, outcomes, and adjusting factors (including age, gen-

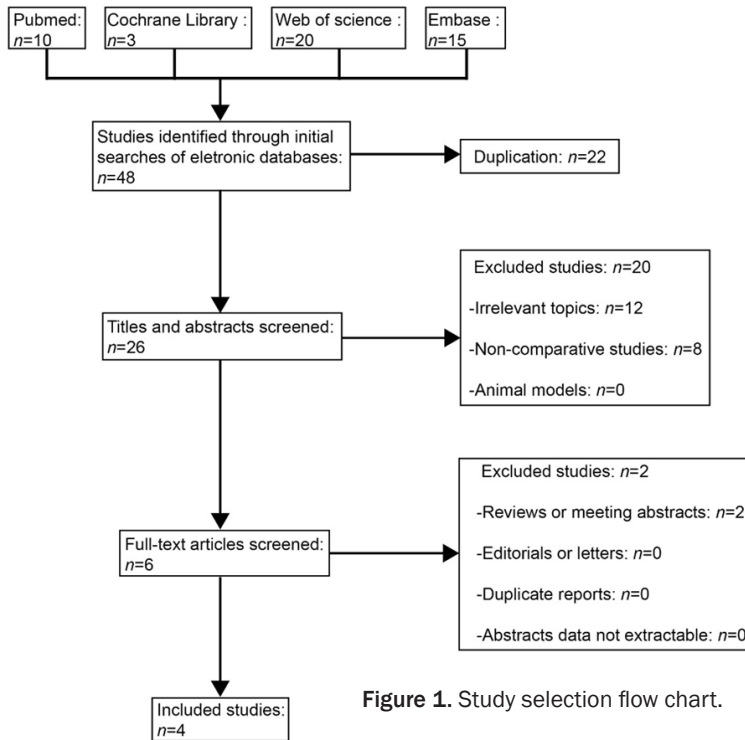


Figure 1. Study selection flow chart.

der, pathological type, T category, N category, clinical stage, Karnofsky performance status scores, and induction chemotherapy). After removal of duplicates, BC Wang and LL Shi, independently, reviewed abstracts. If an agreement could not be reached, disagreements were adjudicated by group consensus.

Statistical analysis

Endpoints were determined as OS, DMFS, LRFS, DFS, PFS, and adverse events. Time-to-event data from individual trials was assessed by hazard ratios (HR) and 95% confidence intervals (CI). Additionally, hematological and nonhematological toxicities were calculated as risk ratios (RRs) with two-sided 95% CIs. This meta-analysis used RevMan version 5.3 software (Cochrane Collaboration’s Information Management System) to calculate, synthesize, and analyze collected data from selected trials. Statistical heterogeneity of results was evaluated using forest plots and quantified with I^2 statistic percentages. Meta-analyses were performed using a fixed-effects model if heterogeneity testing showed no statistical significance ($P \geq 0.10$, $I^2 \leq 50\%$). Otherwise, a random-effects model of meta-analysis was used. Statistical significance testing was 2-sided, with $P < 0.05$ indicating significant outcomes. Subgroup anal-

ysis was performed according to 3-year or 5-year follow-up times.

Results

Search results and study characteristics

After preliminary screening and eligibility, a total of 48 records were identified from PubMed, Cochrane Library, Embase, and Web of Science databases. Moreover, 26 records were included after screening titles and abstracts. Of the remaining eligible studies, 22 were further excluded based on inclusion and exclusion criteria. Finally, a total of 4 retrospective controlled studies, including 1,444 patients (299 in the CCRT plus NTZ group and 1,145 in the CCRT group,

respectively), were eligible for this meta-analysis [25-28]. A flowchart of studies is shown in **Figure 1**. Characteristics of these 4 studies are summarized in **Table 1**. According to the 9-star NOS, 4 studies were classified as high-quality (**Table 2**).

Effects of intervention

Survival events

Overall survival: Data regarding OS was available from all selected studies [25-28], including 299 patients in the CCRT plus NTZ group and 1,145 patients in the CCRT group. Forest plots showed that the CCRT plus NTZ group had a lower risk of death, according to 3-year OS, compared to the CCRT group. However, there were no differences in 5-year OS between the CCRT plus NTZ group and CCRT group for LANPC patients (3-year OS: HR=0.44, 95% CI 0.25-0.76, $P=0.004$; 5-year OS: HR=2.15, 95% CI 0.91-5.06, $P=0.08$) (**Figure 2A and 2B**).

Distant metastasis failure-free survival

DMFS data was available for all studies [25-28]. Compared with CCRT alone, adding NTZ to CCRT showed a lower risk of distant metastasis in 3-year DMFS (3-year DMFS: HR=0.56, 95%

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Table 1. Characteristics of included studies in the meta-analysis

Author	Year	Country/City	Inclusion period	Group	Number of patients	Follow-up (months)*	Study type	Stage	Concurrent chemotherapy	Outcome	Adjusting factors
M Lin	2018	China/Guangzhou	2008-2013	CCRT+NTZ CCRT	61 274	57.0 55.0	Cohort	AJCC 7th edition III-IVb	Cisplatin greater than 200 mg/m ²	OS, DFS, LRFS, DMFS	1,2,4,5,6,7
FZ Wang	2018	China/Zhejiang	2008-2014	CCRT+NTZ CCRT	120 120	56.0 56.6	Cohort	AJCC 7th edition III-IVb	Cisplatin 80 mg/ m ² , d1-d3	OS, LRFS, DMFS, PFS	1,2,4,5,6,8
JJ Yao	2018	China/Guangzhou	2009-2012	CCRT+NTZ CCRT	31 62	59.2 57.4	Cohort	AJCC 7th edition III-IVb	Cisplatin 40 mg/m ² , weekly or 100 mg/m ² , tri-weekly	OS, LRFS, DMFS, PFS	1,2,3,4,5,6,7
R You	2017	China/Guangzhou	2009-2013	CCRT+NTZ CCRT	87 689	48.0 48.9	Cohort	AJCC 7th edition II-IVb	Cisplatin 100 mg/m ² , tri-weekly	OS, DFS, LRFS, DMFS	1,2,4,5,6,7

*, median follow up; 1 = age; 2 = gender; 3 = pathological type; 4 = T category; 5 = N category; 6 = clinical stage; 7 = Karnofsky performance status score; 8 = induction chemotherapy.

Table 2. Newcastle-Ottawa scale of studies included in the meta-analysis

Study	Selection				Comparability		Outcome			Scores
	1	2	3	4	5a	5b	6	7	8	
Cohort										
Lin 2018	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
Wang 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Yao 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
You 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8

Note: 1 indicates representativeness of the exposed cohort; 2 indicates drawn from the same community as the exposed cohort; 3 indicates ascertainment of exposure by surgical record or structured interview; 4 indicates outcome of interest was not present at start of study; 5a indicates cohorts comparable on basis of age; 5b indicates cohorts comparable on other factors; 6 indicates assessment of outcome by independent blind assessment or record linkage; 7 indicates follow-up (at least 3 year) was long enough for outcomes to occur; 8 indicates complete follow up of cohorts.

CI 0.35-0.89, $P=0.01$). However, there were no statistically significant differences in 5-year DMFS (5-year DMFS: HR=1.70, 95% CI 0.78-3.71, $P=0.18$) (Figure 2C and 2D).

Local-regional failure-free survival

Two selected studies [27, 28] were included in LRFS analysis, involving 148 patients in the CCRT plus NTZ group and 963 patients in the CCRT alone group. Compared with patients receiving CCRT alone, patients receiving CCRT plus NTZ showed no significant differences in 3-year LRFS (HR=0.60, 95% CI 0.33-1.08, $P=0.09$) (Figure 2E and 2F).

Disease-free survival

DFS data was available in 2 trials [27, 28]. Forest and funnel plots showed that the CCRT plus NTZ group had a lower risk of 3-year DFS than the CCRT group (HR=0.59, 95% CI 0.41-0.86, $P=0.006$) (Figure 2G and 2H).

Progression-free survival

Two trials were included in the analysis of PFS [25, 26]. There were no significant differences concerning risk of disease progression (HR=1.1, 95% CI 0.14-8.41, $P=0.92$) (Figure 2I and 2J).

Adverse events

Grade 3-4 hematological toxicities: All enrolled studies provided information regarding grade 3-4 hematological toxicities, including anemia, leucopenia, neutropenia, and thrombocytopenia [25-28]. Forest and funnel plots showed

no significant differences in hematological toxicities between the CCRT plus NTZ group and CCRT alone group (anemia RR=0.85, 95% CI 0.38-1.89, $P=0.68$; leucopenia RR=0.89, 95% CI 0.68-1.17, $P=0.41$; neutropenia RR=0.67, 95% CI 0.27-1.68, $P=0.39$; thrombocytopenia RR=1.52, 95% CI 0.80-2.88, $P=0.20$) (Figure 3).

Grade 3-4 skin reactions: All studies supplied data regarding grade 3-4 skin reactions, including muco-

stitis and dermatitis. There were no significant differences in risk of mucositis (RR=1.33, 95% CI 0.81-2.19, $P=0.26$) and dermatitis (RR=1.35, 95% CI 0.73-2.51, $P=0.034$) with the addition of NTZ to CCRT versus CCRT alone (Figure 4).

Grade 3-4 gastrointestinal reactions: Grade 3-4 nausea and vomiting data was available from all included trials. Compared to the CCRT alone group, the CCRT plus NTZ group appeared to have a similar risk of weight loss gastrointestinal reactions (nausea RR=0.83, 95% CI 0.50-1.36, $P=0.46$; vomiting RR=0.88, 95% CI 0.54-1.45, $P=0.62$) (Figure 5A-D).

Grade 3-4 weight loss: Two trials contributed information regarding grade 3-4 weight loss [27, 28]. There were no significant differences in risk of Grade 3-4 weight loss between the groups (RR=1.80, 95% CI 0.79-4.13, $P=0.16$) (Figure 5E and 5F).

Discussion

EGFR has been shown to be overexpressed in over 90% of NPC patients [30]. Previous studies have reported that EGFR-blocking agents significantly improved PFS and OS rates in the treatment of NPC [14]. This meta-analysis directly compared CCRT+NTZ and CCRT alone in LANPC patients, including 299 patients treated with CCRT plus NTZ and 1,145 patients treated with CCRT. Present data indicates that treatment with CCRT plus NTZ was associated with significantly improved 3-year OS, 3-year DMFS, and 3-year DFS, but not 5-year OS, 5-year DMFS, 3-year LRFS, and 5-year PFS in patients with LANPC.

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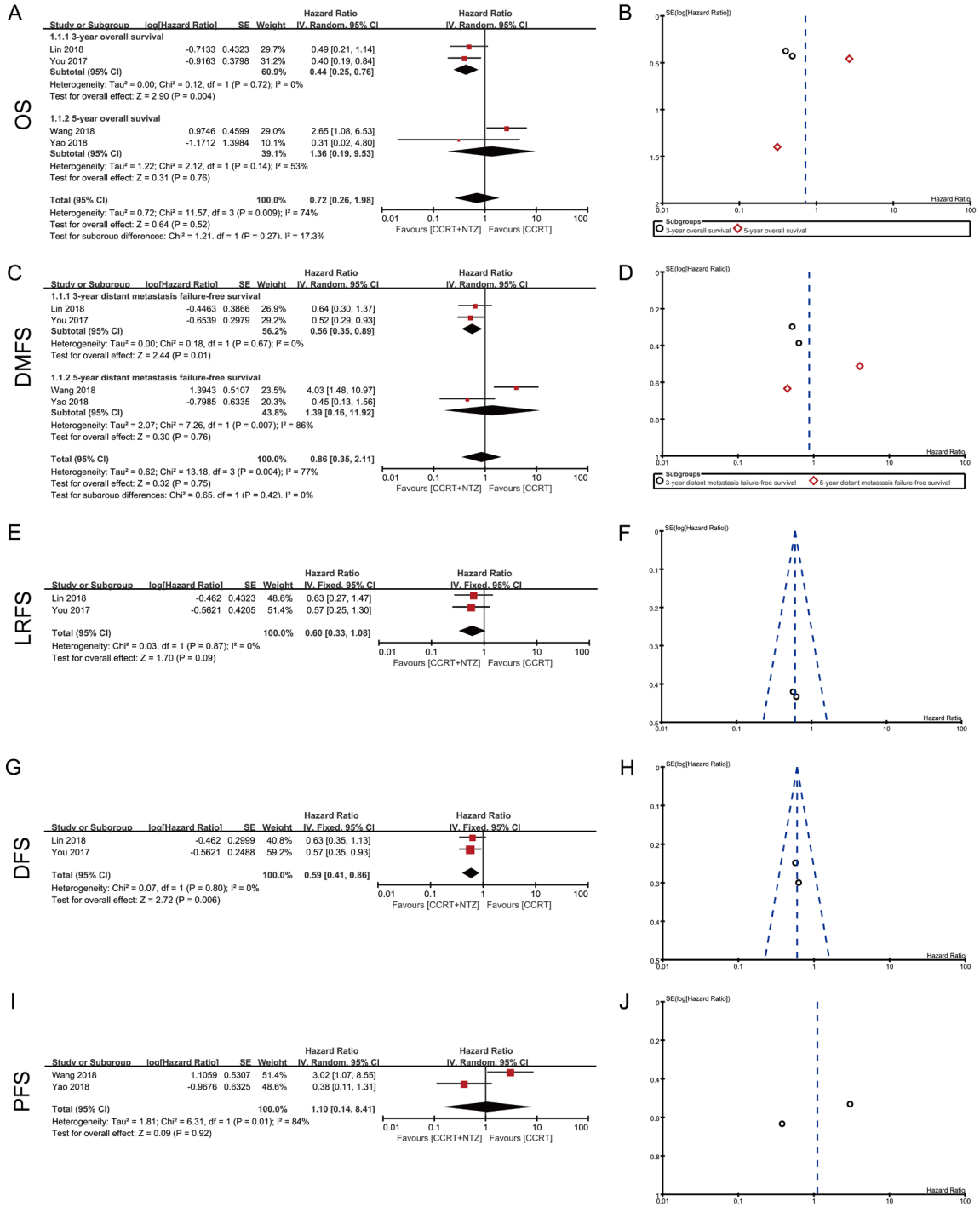


Figure 2. Forest and funnel plots of hazard ratios for 3-year and 5-year OS (A and B), 3-year and 5-year DMFS (C and D), 3-year LRFS (E and F), 3-year DFS (G and H), and PFS (I and J) in patients between the CCRT plus NTZ group and CCRT group. NTZ, nimotuzumab; CCRT, concurrent chemoradiotherapy; OS, overall survival; DMFS, distant metastasis-free survival; LRFS, loco-regional relapse-free survival; DFS, disease-free survival; PFS, progression-free survival; CI, confidence interval; I^2 , index of heterogeneity.

CTX is a chimeric mouse-human monoclonal antibody. It has high avidity target binding because of highly affinity constants, although EGFR expression is lowly expressed in healthy

tissues [31]. Thus, significant cutaneous toxic effects have limited the application of CTX, even though it has shown good therapeutic effects in the treatment of NPC. Newly EGFR-

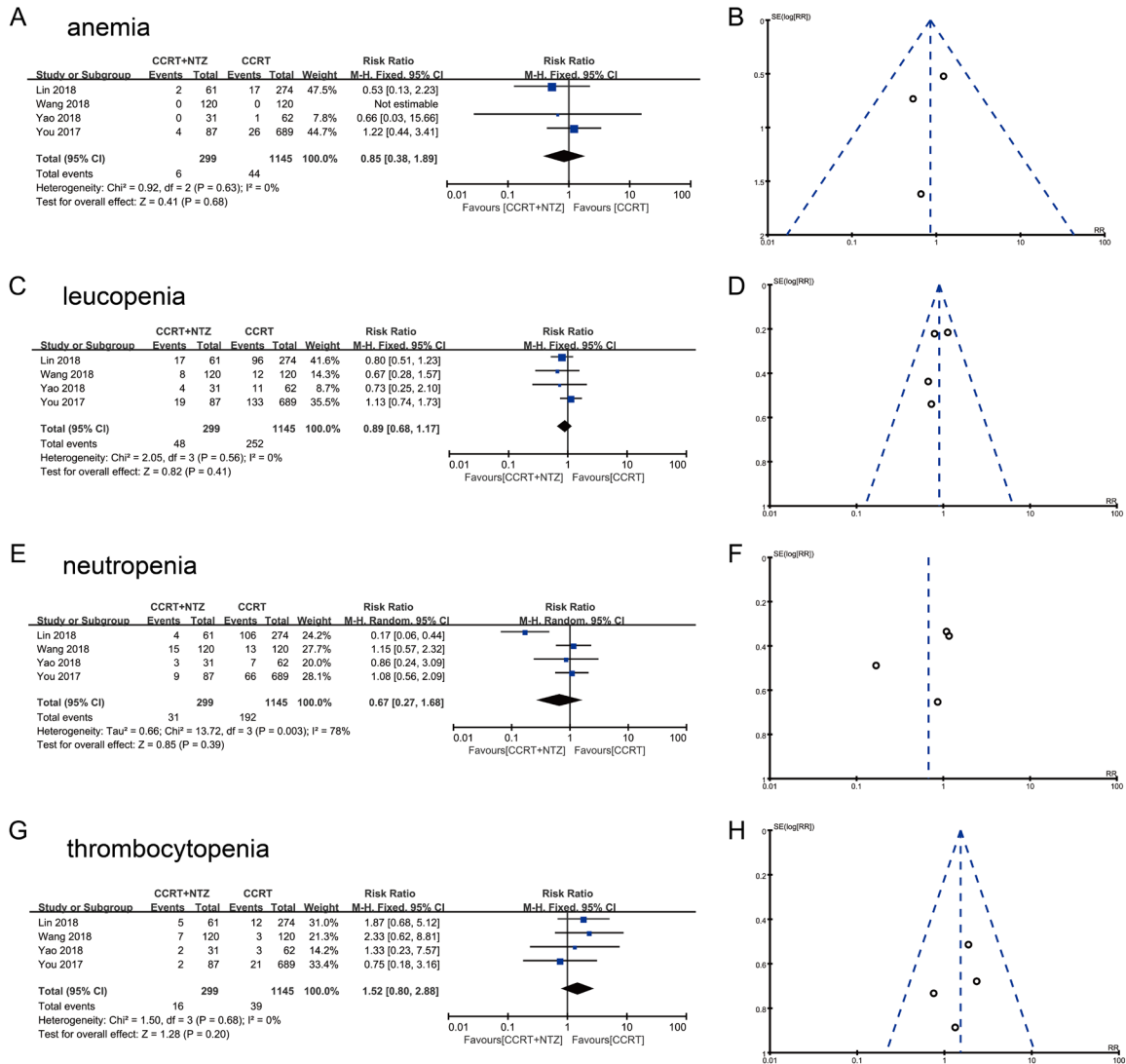


Figure 3. Forest and funnel plots of risk ratios for grade 3-4 hematological toxicities (anemia (A and B), leucopenia (C and D), neutropenia (E and F), and thrombocytopenia (G and H)) in the CCRT plus NTZ group and CCRT group.

targeted agents without cetuximab related toxicities are urgently needed.

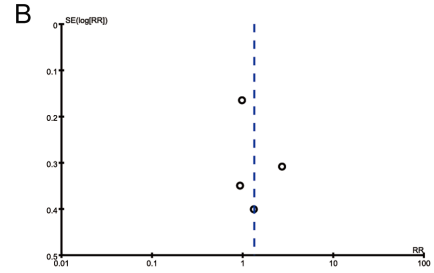
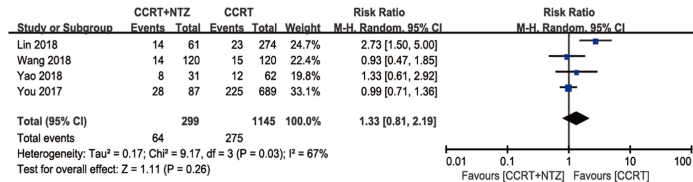
In contrast, NTZ has a lower affinity constant than CTX, allowing for high tumor uptake and low healthy tissue uptake [31]. Previously, NTZ was approved for treatment of unresectable HNSCC [11, 32]. Selected studies in this meta-analysis further confirmed that adding NTZ to CCRT could maximize survival rates of LANPC patients, compared to patients treated CCRT alone [25-28]. In the study of You [28], the CCRT plus NTZ group was superior to the CCRT group, resulting in a significantly higher 3-year OS rate (96.6% vs 92.9%, respectively, $P=0.015$), 3-year DFS rate (93.5% vs 86.9%,

$P=0.028$), and 3-year DMFS rate (94.6% vs 89.3%, $P=0.030$). In the study of Yao [26], concomitant NTZ and CCRT was significantly associated with superior 5-year OS rates (96.8% vs 82.3%, $P=0.001$), 5-year DMFS rate (90.3% vs 80.6%, $P=0.012$) and 5-year PFS rates (83.9% vs 71.0%, $P=0.006$), compared with CCRT alone. In addition, no significant differences in hematology and non-hematology parameters were found between the two groups.

In the present meta-analysis, there were no significant differences in LRFS between the CCRT plus NTZ group and CCRT group. Likewise, 5-year LRFS was comparable between the two groups. This result might be attributed to the

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A mucositis



C dermatitis

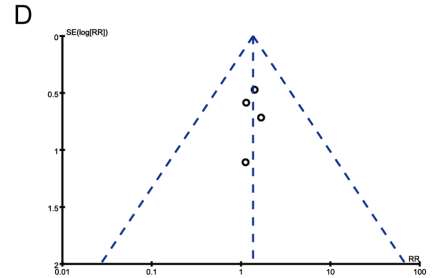
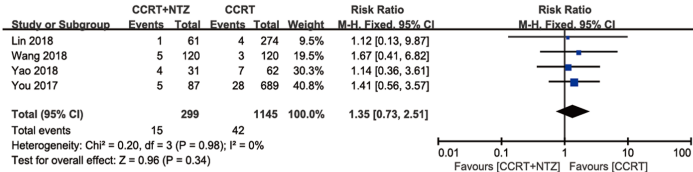
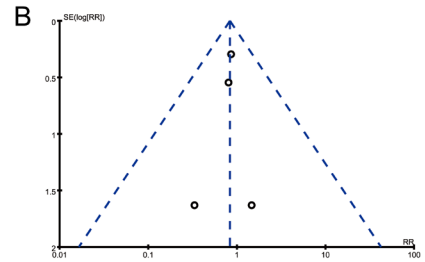
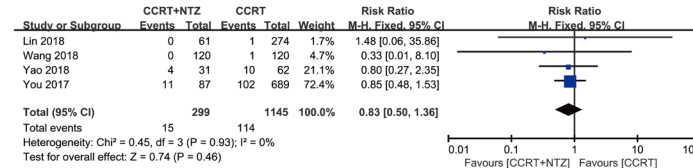
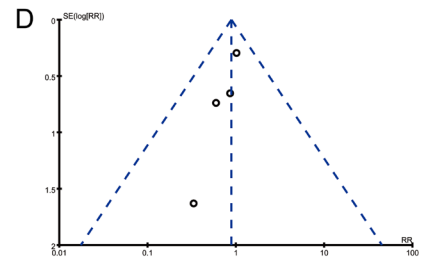
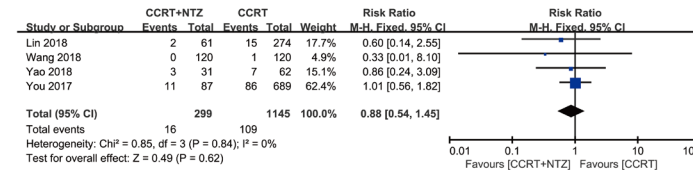


Figure 4. Forest and funnel plots of risk ratios for grade 3-4 mucositis (A and B) and dermatitis (C and D) in the CCRT plus NTZ group and CCRT group.

A nausea



C vomiting



E weight loss

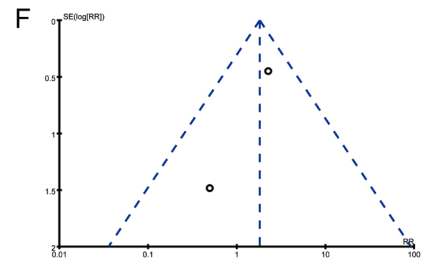
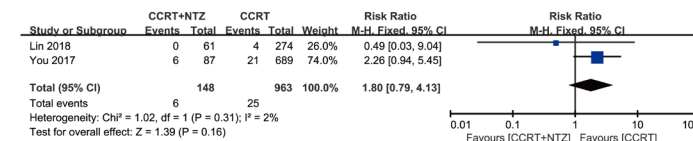


Figure 5. Forest and funnel plots of risk ratios for grade 3-4 nausea (A and B), vomiting (C and D), and weight loss (E and F) in the CCRT plus NTZ group and CCRT group.

development of radiation techniques, which have 90% control rates for patients with LANPC

[33, 34]. EGFR blocking agents have been reported to overcome resistant metastatic

tumor cells [35]. This might partially explain the significant increase in 3-year DMFS and 3-year DFS rates. Furthermore, significant increases in DMFS and DFS have translated into OS benefits. However, comparable risks of death, tumor metastasis, and tumor progression of 5-year OS, DMFS, and PFS between the two groups were observed. These results could be potentially explained by satisfactory salvage treatments, such as radio- or chemo-therapy interruption [36, 37] and selection biases in retrospective design.

There were some limitations to the current meta-analysis, however. First, all eligible selected studies were single-center and retrospective studies, originating in China. Second, even though the number of patients receiving CCRT plus NTZ in the meta-analysis was 299, it was still relatively low. Third, patients in the selected studies received different induction chemotherapy regimens. Fourth, there was significant heterogeneity found in the 5-year subgroup analysis. Fifth, studies conducted by You and Lin analyzed 3-year survival rates between CCRT alone and CCRT plus NTZ/CTX, but not CCRT plus NTZ.

In conclusion, the combination of NTZ with CCRT is more effective in extending survival times in patients with LANPC, compared with CCRT alone. Moreover, patients in the CCRT plus NTZ group experienced well-tolerated and less acute toxicity. Therefore, NTZ should be alternatively recommended for treatment of LANPC patients. More randomized clinical trials are necessary to verify therapeutic efficacy and safety levels.

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Disclosure of conflict of interest

None.

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