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A meta-analysis of cisplatin-based concurrent chemoradiotherapy with or without cetuximab for locoregionally advanced nasopharyngeal carcinoma

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Abstract

Background: It is unclear whether cetuximab (CTX) plus cisplatin-based concurrent chemoradiotherapy (CCRT) delivers equivalent or improved results over standard CCRT in locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: The strategy involved searching the PubMed, Embase, Cochrane Library, and Web of Science. Pooled hazard ratios (HRs) for overall survival (OS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRFS), and disease-free survival (DFS), and pooled risk ratios for adverse events were meta-analyzed.

Results: In all, 1744 patients in 5 clinical trials were included in the analysis. Compared with CCRT group, CTX plus CCRT significantly improved DFS (HR = 0.59, 95% confidence interval [CI]: 0.41–0.86, $P = .006$) and distant metastasis failure-free survival (HR = 0.54, 95% CI: 0.38–0.76, $P = .0004$), rather than OS (HR = 0.70, 95% CI: 0.44–1.09, $P = .12$) and local-regional failure-free survival (HR = 0.82, 95% CI: 0.54–1.22, $P = .33$).

Conclusions: CTX plus CCRT might achieve higher DFS and DMFS with no significant difference in OS and LRFS. CTX plus CCRT group was associated with more grade 3-4 skin rash, mucositis and dermatitis. Large randomized trials were urgent to fully explore the usefulness of this treatment in the locally advanced NPC patients.

Abbreviations: CCRT = cisplatin-based concurrent chemoradiotherapy, CI = confidence interval, CTX = cetuximab, DFS = disease-free survival, DMFS = distant metastasis-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, LRFS = locoregional relapse-free survival, NPC = nasopharyngeal carcinoma, NTZ = nimotuzumab, OS = overall survival, RR = risk ratio.

Keywords: cetuximab, concurrent chemoradiotherapy, locoregionally advanced nasopharyngeal carcinoma, meta-analysis, survival

1. Introduction

Nasopharyngeal carcinoma (NPC) is highly prevalent in Southeast Asia and Southern China, especially in the Guangdong province, where the incidence ranges from 20 to 30 per 100,000 population.[1–3] Most patients presented with locoregionally advanced NPC.[4] According to the 2017 National Comprehensive Cancer Network guidelines for head and neck cancer, concurrent platinum-based chemoradiotherapy (CCRT) is the present basic treatment for patients diagnosed with locoregionally advanced NPC.[5–12] Cisplatin-based chemotherapy combined with intensity-modulated radiotherapy had been the most commonly used treatment regimen for these stage II-IVb NPC patients. However, there was increasing evidence showing that CCRT alone might be inadequate for these patients who had a high potential for locoregional recurrence and distant metastasis.[13] For the patient who relapsed with locoregional recurrence and distant metastasis, the prognosis was poor with reported median survival of 8 months.[6,9] Therefore, new systemic strategies are urgently demanded for the treatment of NPC.

Previous study revealed the molecular target, epidermal growth factor receptor (EGFR), was highly expressed in more than 80% of locoregionally advanced NPC patients and correlated with poor clinical outcome.[14,15] Cetuximab (CTX), an anti-EGFR antibody, had been proven to improve survival of locoregionally advanced head and neck squamous cell carcinoma patients when combined with radiotherapy.[16] When radiation increased the expression of EGFR in NPC cells, inhibition of EGFR signaling made tumor cells more sensitive to radiotherapy.[17] Ma and his colleagues had shown a single-arm phase II clinical trial and reported that addition of CTX to concurrent

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chemoradiotherapy for locoregionally advanced NPC was a feasible strategy.[18] He and his colleagues had observed that combination of CTX and chemoradiotherapy was effective and tolerated.[19] These findings prompted researchers to investigate whether patients of locoregionally advanced NPC could benefit from the concurrent combination of CTX plus chemoradiotherapy.

Recently, several studies compared efficacy and safety between CTX plus CCRT and CCRT alone in local-regionally advanced NPC.[20–24] You and his colleagues retrospectively examined the benefits of CTX and CCRT compared with CCRT alone in patients with stage II-IVb NPC.[23] The CTX plus CCRT group exhibited a significantly increased 3-year overall survival (OS), improved 3-year disease-free survival (DFS), and improved 3-year distant metastasis-free survival (DMFS). Nevertheless, in a clinical trial conducted by Lin et al, the 3-year OS, DFS, DMFS, and locoregional relapse-free survival (LRFS) rates of CTX with CCRT group were comparable to CCRT group.[20] Several other studies also compared the efficacies and toxicities in both groups, but none of those were sufficient to demonstrate the priority of combination of CTX with CCRT.

However, there has been a debate over whether CTX with CCRT can achieve survival outcomes comparable to CCRT without additional toxicities. Therefore, we performed this literature-based meta-analysis to investigate the efficacy and safety of CTX plus CCRT and CCRT alone in locoregionally advanced NPC patients.

2. Materials and methods

This meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines,[25] and based on published studies with ethical approvals. No original clinical raw data was collected in this analysis, thus ethical approval was not necessary.

2.1. Search strategy

The literature search was performed using the Pubmed, Embase, Cochrane Library, and Web of Science (up to May 2018). The search was performed using the following terms: "nasopharyngeal carcinoma" OR "nasopharyngeal neoplasms" OR "nasopharyngeal cancer" OR "nasopharyngeal tumor," "chemoradiotherapy" OR "concurrent" OR "concurrent chemoradiotherapy" and "cetuximab". All of the eligible articles were retrieved, and their references were checked for other relevant publications.

2.2. Inclusion and exclusion criteria

Trials should meet the following inclusion criteria:

(1) the participating patients were local regionally advanced NPC, including stage II-IVb patients,
(2) the patients were receiving cisplatin-based CCRT with or without CTX,
(3) the studies were retrospective controlled trials or matched-pair analyses,
(4) randomized controlled trials will be considered for evaluation and maybe blinded or unblinded.

However, we excluded reviews, letters, case reports, meeting abstracts, trial protocols, comments, and animal experiments.

2.3. Quality assessment

The included retrospective trials were evaluated by 2 authors (BCW and LLS) and their results assessed using 9 star Newcastle–Ottawa scale.[26] The Newcastle–Ottawa scale assesses trial quality by evaluating 3 domains: selection, comparability, and outcome for cohort studies or exposure for case-control studies. Selection and outcome or exposure domain that meets the criteria is given a star, while the comparability domain has a maximum of 2 stars. The maximum of stars is 9 points; scores 7 to 9 points were defined as high quality and scores <7 as low quality studies.

2.4. Data extraction

Following information was extracted from each study: first author, publication year, study type, inclusion period, number of patients, staging information, median follow up, adjusting factors, adverse reactions, and survival events. When CTX and nimotuzumab (NTZ) were both studied in the same article, CTX data was extracted as much and separately as possible. If agreement could not be reached between the 2 authors (BCW and LLS), the third investigator (GP) was consulted to resolve the discrepancies.

2.5. Statistical analysis

Endpoints were determined as OS, DFS, LRFS, DMFS, and adverse events. Time-to-event data from individual trials were assessed by hazard ratio (HR) and 95% confidence interval (CI). Additionally, hematological and nonhematological adverse events were calculated as risk ratios (RRs) with 95% CIs. All analyses were conducted using RevMan version 5.2 software (Cochrane Collaboration's Information Management System). We evaluated the heterogeneity of the results using the forest plots, Chi-squared (χ^2) tests, and I^2 statistic percentages. $P<.05$ was considered as significant outcomes. A fixed-effect model was applied if the heterogeneity test showed no statistical significance ($P\geq.10$, $I^2\leq 50\%$), otherwise, a random-effect model was used.

3. Results

3.1. Study selection and identification

The preliminary literature screening yielded 98 records from the 4 databases. 90 records were excluded after screening their titles and abstracts. Of the remaining 8 potentially eligible studies, 3 were further excluded based on the exclusion criteria. Finally, 5 retrospective controlled studies of 1744 patients (411 in CTX + CCRT group and 1333 in CCRT group, respectively) were eligible for the meta-analysis published from 2000 to 2018.[20–24] The flowchart of studies through the selection process was shown in Figure 1. The main characteristics of the 5 included studies are summarized in Table 1.

According to the 9-srat Newcastle–Ottawa scale, 5 studies were classified as high quality studies (Table 2).

3.2. Effects of interventions
3.2.1. Survival events

3.2.1.1. Overall survival. All selected studies[20–24] were included in the OS analysis, including 411 patients in CTX + CCRT group and 1333 patients in CCRT group. Forest plot showed no difference of 3- and 5-year OS between the CTX with CCRT and

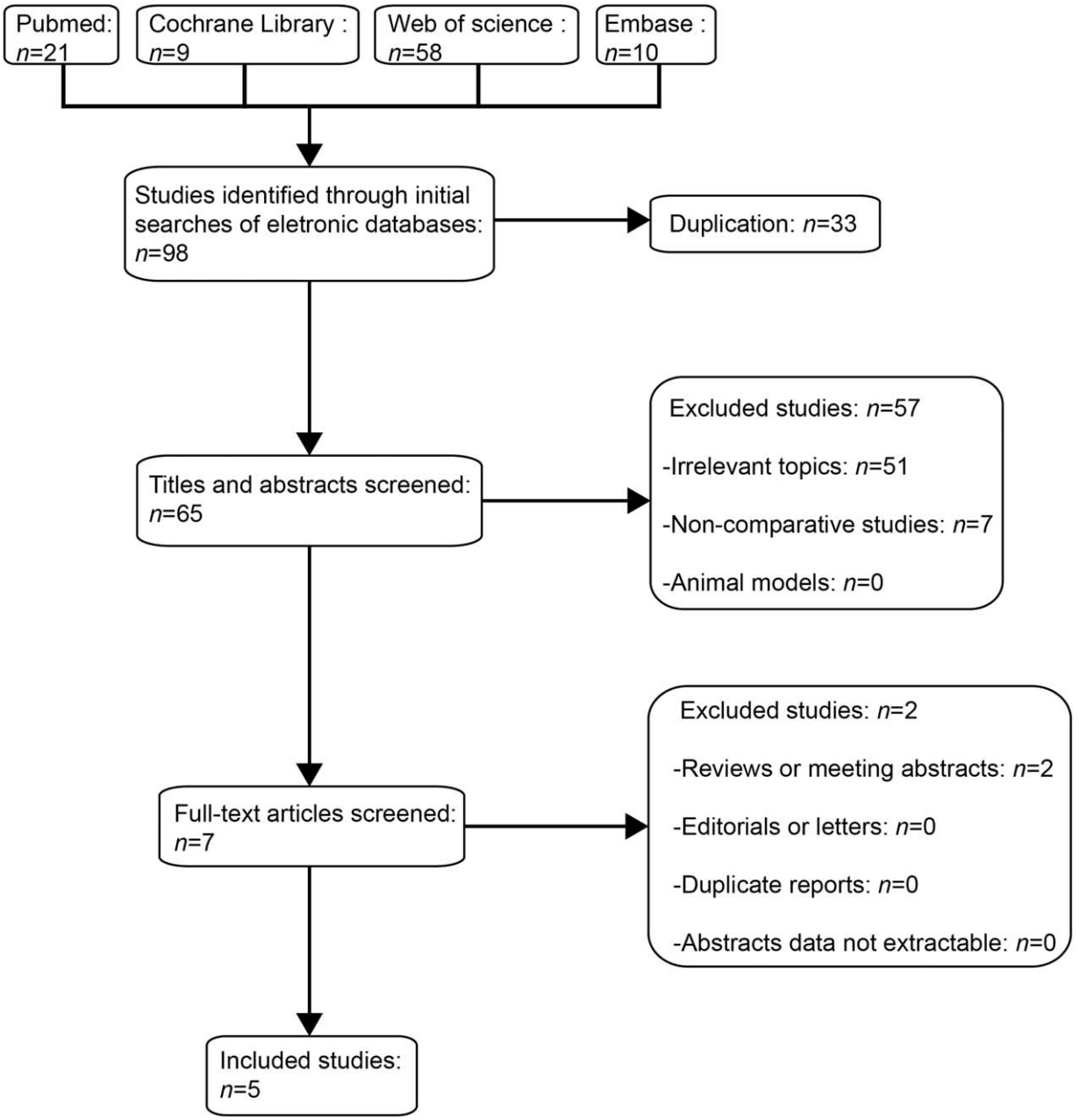

Figure 1. Study selection flow about the clinical controlled trials of concurrent chemoradiotherapy with or without cetuximab in patient with locoregionally advanced nasopharyngeal carcinoma.

CCRT alone for NPC patient (3-year OS: HR = 0.65, 95% CI: 0.31–1.38, $P = .26$; 5-year OS: HR = 0.71, 95% CI: 0.40–1.25, $P = .23$) (Fig. 2A).

3.2.1.2. Disease-free survival. Data regarding the DFS were available in 2 trials[20,23] involving 326 patients in the CTX + CCRT group and 963 patients in the CCRT group. No significant heterogeneity was detected ($I^2 = 0.0\%$, $P = .80$), therefore, a fixed-effects was used. The risk of disease progression among the patients treated with CTX plus CCRT was lower compared with patients treated with CCRT alone (3-year DFS: HR = 0.59, 95% CI: 0.41–0.86, $P = .006$) (Fig. 2B).

3.2.1.3. Local-regional failure-free survival. Five studies[20–24] were included in the LRFS analysis. There was no significant difference in the risk of locoregional relapse in the patients received CTX plus CCRT compared with patient received CCRT alone (3-year LRFS: HR = 0.76, 95% CI: 0.47–1.22, $P = .26$; 5-year LRFS: HR = 0.98, 95% CI: 0.45–2.13, $P = .97$) (Fig. 2C).

3.2.1.4. Distant metastasis failure-free survival. DMFS data were available in the 5 trials.[20–24] Compared with CCRT alone, the addition of CTX to CCRT showed lower risk of distant metastasis (3-year DMFS: HR = 0.59, 95% CI: 0.39–0.90, $P = .01$; 5-year DMFS: HR = 0.44, 95% CI: 0.24–0.81, $P = .008$).

Table 1

Baseline characteristics of the studies included in the meta-analysis.

Author	Year	Country/city	Inclusion period	Group	Number of patients	Follow-up, mo*	Study type	Stage	Median age, yr	Adjusting factors
LR Wu	2018	China/Nanjing	2010–2014	CTX + CCRT	75	41.0	Cohort	AJCC 7th edition	47.41	1,2,3,4,5,15,16,17,18,
				CCRT	150	43.6		III-IVb	47.86	
M Lin	2018	China/Guangzhou	2008–2013	CTX + CCRT	76	57.0	Cohort	AJCC 7th edition	45.00	1,2,4,5,6,10,
				CCRT	274	55.0		III-IVb	44.00	
WX Xia	2017	China/Guangzhou	2006–2013	CTX + CCRT	96	62.0	Cohort	AJCC 7th edition	43.90	1,2,4,5,11,12,13,14
				CCRT	96	62.9		III-IVb	44.00	
R You	2017	China/Guangzhou	2009–2013	CTX + CCRT	102	48.0	Cohort	AJCC 7th edition	44.70	1,2,4,5,6,10
				CCRT	689	48.9		II-IVb	45.60	
Y Li	2017	China/Guangzhou	2006–2014	CTX + CCRT	62	76.0	Case-control	AJCC 7th edition	46.32	1,2,3,4,5,6,7,8
				CCRT	124	76.0		II-IVb	46.05	

1 = age, 2 = sex, 3 = pathological type, 4 = T category, 5 = N category, 6 = disease stage, 7 = radiotherapy technique, 8 = Epstein-Barr virus DNA levels, 9 = Eastern Cooperative Oncology Group, 10 = Karnofsky performance status score, 11 = education, 12 = smoking, 13 = drinking, 14 = World Health Organization pathology, 15 = body mass index, 16 = titers of immunoglobulin A against early antigen, 17 = immunoglobulin A against viral capsid antigen of the Epstein-Barr virus, 18 = chemotherapy; CCRT = concurrent chemoradiotherapy, CTX = cetuximab.

* Median follow up.

Table 2

Newcastle–Ottawa scale.

Study	Selection				Comparability		Outcome			Scores
	1	2	3	4	5a	5b	6	7	8	
Cohort										
Wu et al [21]	☆	☆	☆	–	☆	☆	☆	☆	☆	8
Lin et al [20]	☆	☆	☆	–	☆		☆	☆	☆	8
Xia et al [24]	☆	☆	☆	–	☆	☆	☆	☆	☆	8
You et al [23]	☆	☆	☆	☆	☆	–	☆	☆	☆	8
Case-control										
Li et al [22]	☆	☆	☆	–	☆	☆	☆	☆	☆	8

For cohort studies, 1 indicates exposed cohort truly representative; 2 drawn from the same community as the nonexposed cohort; 3 ascertainment of exposure by secure record or structured interview; 4 outcome of interest was not present at start of study; 5a cohorts comparable on basis of age and gender; 5b cohorts comparable on other factors; 6 outcome assessment by independent blind assessment or record linkage; 7 follow-up long was enough for outcomes to occur (at least 2 yr); 8 complete follow up accounting for cohorts. For case-control study, 1 indicates the case is adequate definition; 2 the case is representative series of population; 3 community controls; 4 controls have no history of nasopharyngeal carcinoma; 5a study controls for age and gender; 5b study controls for additional factors; 6 ascertainment of exposure by blinded structured interview; 7 same method of ascertainment for cases and controls; 8 the same nonresponse rate for both cases and controls.

There was no heterogeneity between studies for the DMFS analyses (Fig. 2D).

3.3. Adverse events

Grade 3-4 adverse events were gathered from the enrolled studies, including hematological toxicities (anemia, neutropenia, thrombocytopenia, and leucopenia) and nonhematological toxicity, including skin rash, mucositis, dermatitis, nausea, vomiting, and weight loss.

3.3.1. Grade 3-4 hematological toxicities. Five enrolled studies provided the information regarding grade 3-4 anemia, neutropenia, thrombocytopenia, and leucopenia.[20–24] There was no significant difference in hematological toxicities between CTX + CCRT group and CCRT group, including anemia (RR = 0.79, 95% CI: 0.39–1.62, $P = .52$), neutropenia (RR = 0.88, 95% CI: 0.40–1.93, $P = .76$), thrombocytopenia (RR = 0.70, 95% CI: 0.32–1.52, $P = .36$), and leucopenia (RR = 0.86, 95% CI: 0.57–1.29, $P = .46$) (Fig. 3).

3.3.2. Grade 3-4 skin rash. Two studies supplied data of grade 3-4 skin rash[21,24] among which included 27 patients in the CTX + CCRT group and 171 patients in the CCRT group. Forest plot showed that addition of CTX to CCRT treatment significantly increased the risks of skin rash (RR = 38.09, 95% CI: 5.20–279.20, $P = .0003$). No heterogeneity was observed for skin rash analysis (Fig. 4A).

3.3.3. Grade 3-4 mucositis. Five studies with 1744 patients reported the incidence of grade 3-4 mucositis.[20–24] The addition of CTX to the CCRT significantly increased the risk of mucositis (RR = 2.75, 95% CI: 1.52–4.96, $P = .0008$) (Fig. 4B).

3.3.4. Grade 3-4 dermatitis. All eligible studies had the data for grade 3-4 dermatitis.[20–24] Patients treated with CTX plus CCRT seemed to be more prone to occur dermatitis than those with CCRT alone (RR = 6.41, 95% CI: 1.90–21.62, $P = .003$) (Fig. 4C).

3.3.5. Grade 3-4 gastrointestinal reactions. Two trials contributed information regarding grade 3-4 nausea in 178 patients in the CTX + CCRT group and 963 patients in the CCRT group,[20,23] and there was no significant difference in the grade 3-4 nausea for both groups (RR = 1.10, 95% CI: 0.69–1.77, $P = .69$) (Fig. 5A). All enrolled trials contributed information regarding grade 3-4 vomiting, and forest plot showed no difference between CTX + CCRT group and CCRT group (RR = 1.31, 95% CI: 0.62–2.75, $P = .48$) (Fig. 5B).

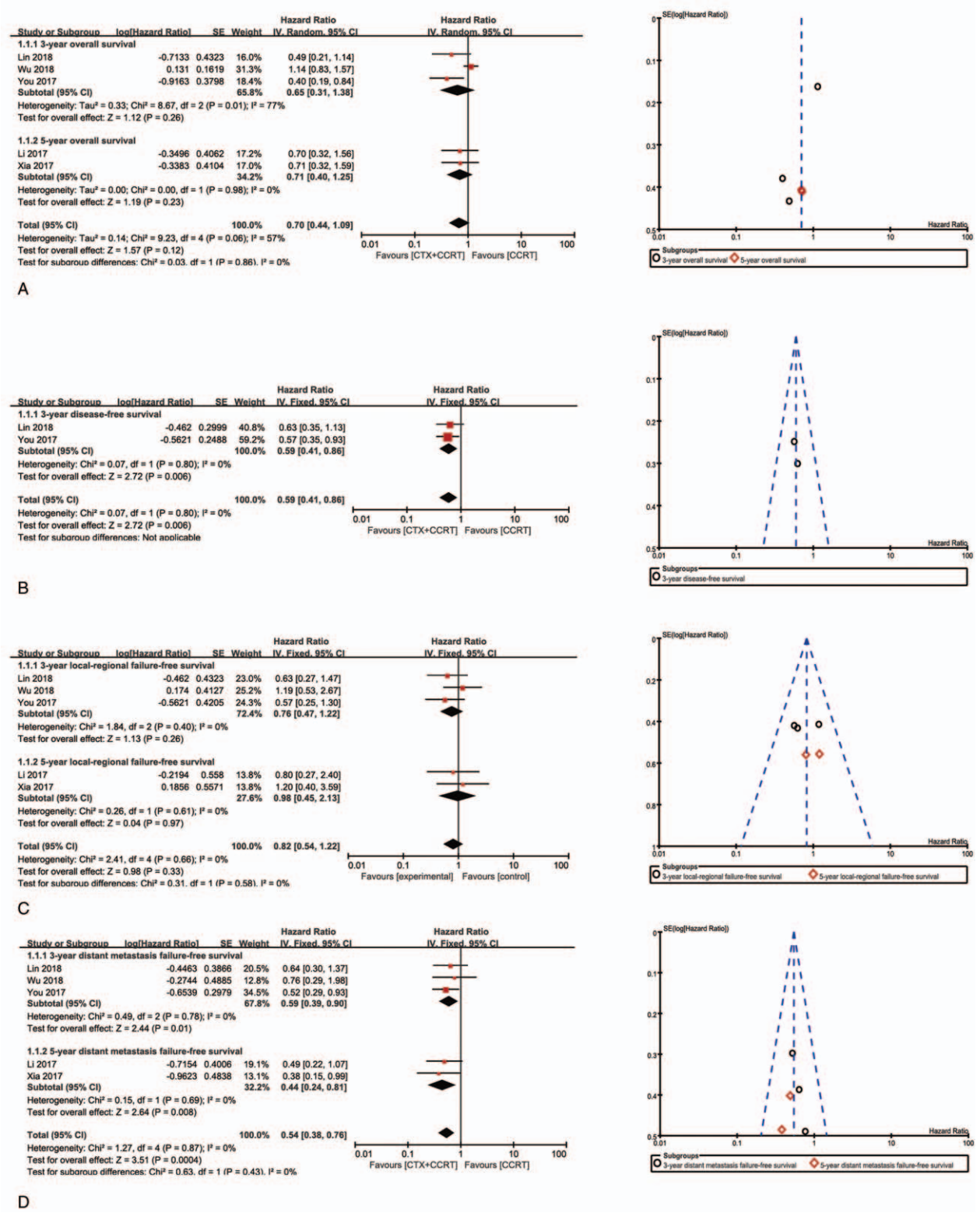

Figure 2. Forest plots and funnel plots of hazard ratios for 3-year and 5-year OS (A), DFS (B), LRFS (C), and DMFS (D) in patients between CTX + CCRT group and CCRT group. CI = confidence interval, CCRT = concurrent chemoradiotherapy, CTX = cetuximab, DFS = disease-free survival, DMFS = distant metastasis-free survival, I^2 = index of heterogeneity, LRFS = loco-regional relapse-free survival; OS = overall survival.

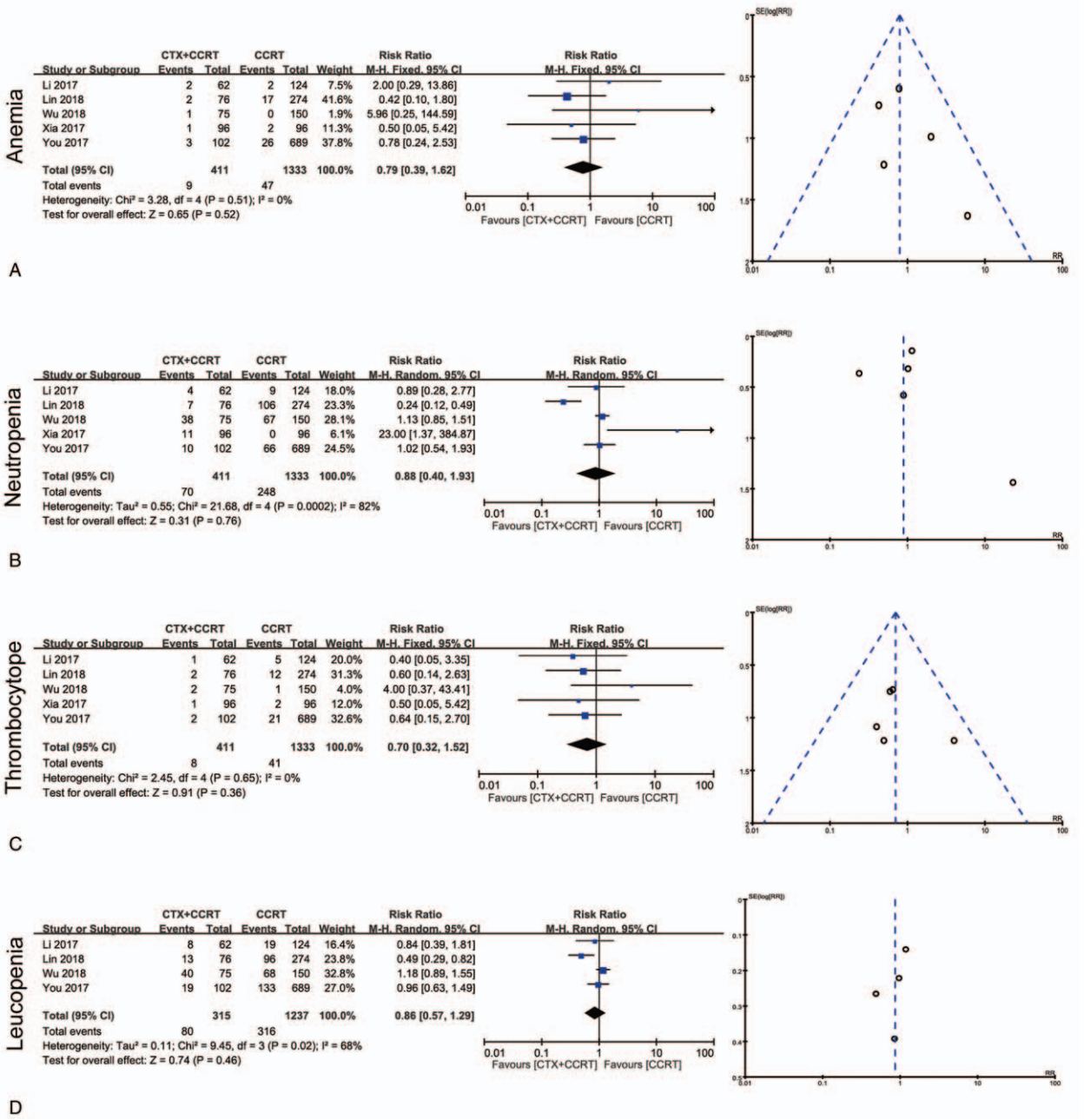

Figure 3. Forest plots and funnel plots of risk ratios for grade 3-4 hematological toxicities (amenia (A), neutropenia (B), thrombocytopenia (C), and leucopenia (D)) in CTX + CCRT group and CCRT group. CCRT = concurrent chemoradiotherapy, CTX = cetuximab.

3.3.6. Weight loss. All 5 trials reported information regarding grade 3-4 weight loss. The CTX + CCRT group appeared similar risk of weight loss compared to CCRT group, with an RR = 1.48, 95% CI: 0.95–2.33, $P = .08$. There was no heterogeneity between studies for the weight loss analyses ($I^2 = 0\%$, $P = .57$) (Fig. 5C).

4. Discussion

To the best of our knowledge, this study is the first meta-analysis to directly compare CCRT and concomitant CTX and CCRT treatments in patients with locoregionally advanced NPC. Our results indicated that the combination of CTX and CCRT was associated with significant improved DFS and DMFS, rather than OS and LRFS in staged II-IVb NPC. Although NTZ included in the studies of You and Lin and induction chemotherapy conducted in the study of Lin might increase the heterogeneity, the 5-year survival analyses based on Li and Xia showed that CTX plus CCRT significantly prolonged DMFS, rather than OS and LRFS. Owing to the patients in our analysis were treated in China, these results mainly represented the efficacy and toxicities in the Asian population, especially in China.

A combination treatment including CTX plus radiotherapy had been shown to improve survival in NPC patients.[16,27,28] In studies comparing CTX plus radiotherapy with CCRT, the

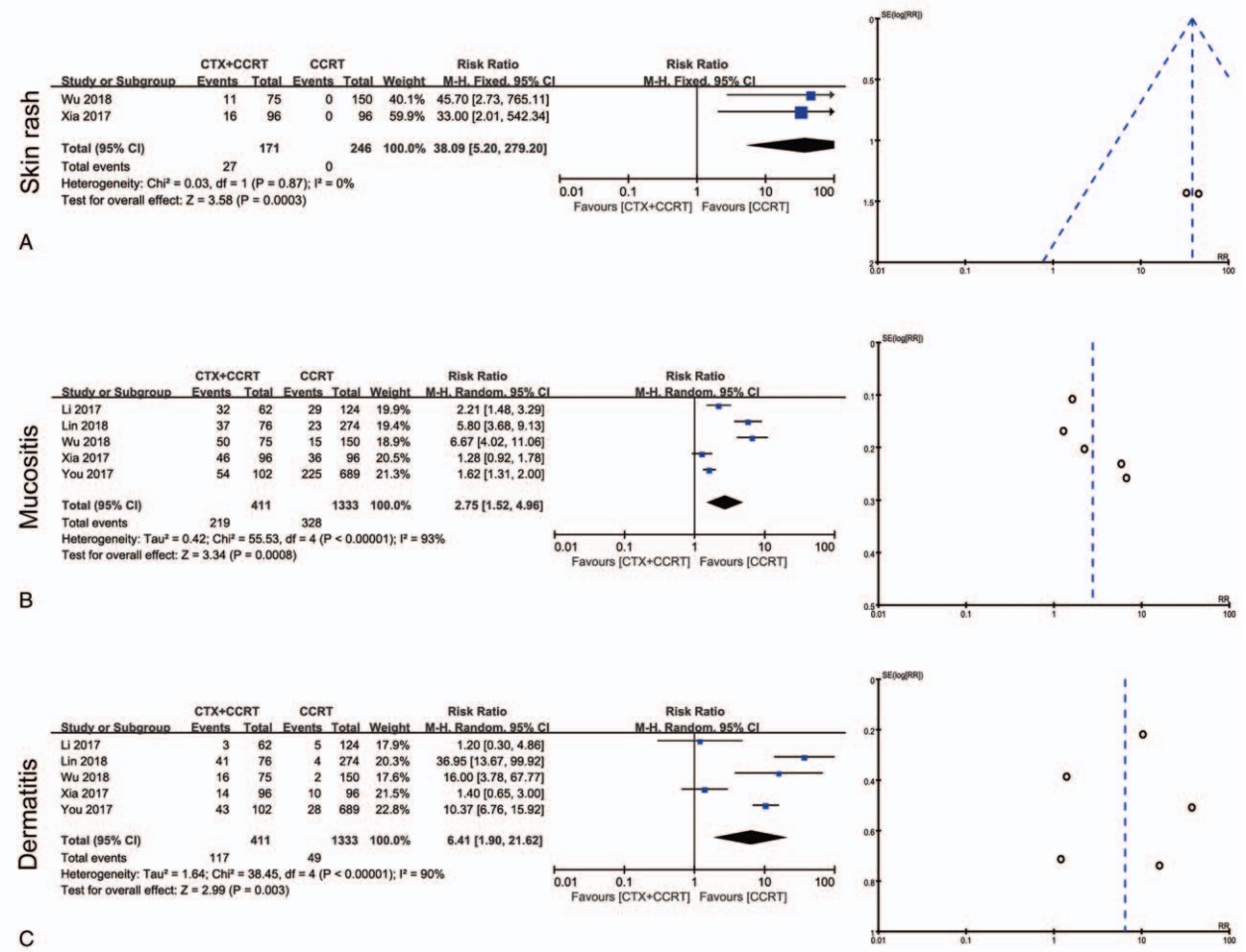

Figure 4. Forest plots and funnel plots of risk ratios for grade 3-4 skin rash (A), mucositis (B), and dermatitis (C) in CTX + CCRT group and CCRT group. CCRT = concurrent chemoradiotherapy, CTX = cetuximab.

primary interest was whether CTX could be used as an alternative to cisplatin-based CCRT in locoregionally advanced NPC. A retrospective analysis was conducted to examine the clinical efficacy and toxicity of the combination of CTX and CCRT compared with CCRT alone in patients with staged II-IVb NPC.[23] The results showed that the treatment with CTX plus CCRT was associated with a significantly increased 3-year OS, DFS, and DMFS rates comparing with CCRT. Wu et al showed that CTX plus CCRT was associated with significantly improved 3-year LRFS in staged III-IVb patients and 3-year OS among patients with T4 and/or N3 category comparing with CCRT.[21] Nevertheless, Li et al showed that adding CTX to CCRT did not significantly improve 5-year OS, LRFS, and DMFS, but exacerbate skin rash and mucositis.[22] Therefore, multicenter prospective randomized clinical trials are needed to compared CTX plus CCRT with CCRT in locoregionally advanced NPC.

Cunningham et al reported that CTX had clinical activity in overcoming resistance to previously administered chemotherapy.[29] Moreover, Vermorken et al exhibited that combination of CTX with platinum-based chemotherapy (platinum-fluorouracil) significantly improved OS and PFS when given as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma.[30] Cao reported that positive expression EGFR had a significantly poorer 5-year OS and DFS than negative expression in patients with stage III-IVa NPC.[31] Thus, we postulated that inhibition of EGFR might eradicate CCRT-resistant metastatic tumor cells. This could partially explain the significant increase in DFS and DMFS in CTX + CCRT group compared with CCRT group in the present study. In the present study, there was no significant difference in OS and LRFS between the CTX + CCRT group and CCRT group. However, considerably lower risk of death and tumor progression in OS and LRFS were observed. There are several potential explanation for this result. First, stage II/III patients were enrolled in the studies. In both studies conducted by Xu and Wu showed that CTX plus radiotherapy did not enhance OS rate compared with CCRT.[32,33] Second, CCRT had achieved satisfactory locoregional control, thus, LRFS rates in both group had been narrowed.[34] Moreover, patients with disease recurrence might be amenable to satisfactory salvage treatment such as re-irradiation, chemotherapy, and surgery, which might explain that the improvement in DFS and DMFS did not translate into an OS benefit.[35]

The present meta-analysis showed that skin rash, mucositis and dermatitis were the most serious adverse reactions. Patients with CTX plus CCRT experienced higher rates of grade 3-4 skin

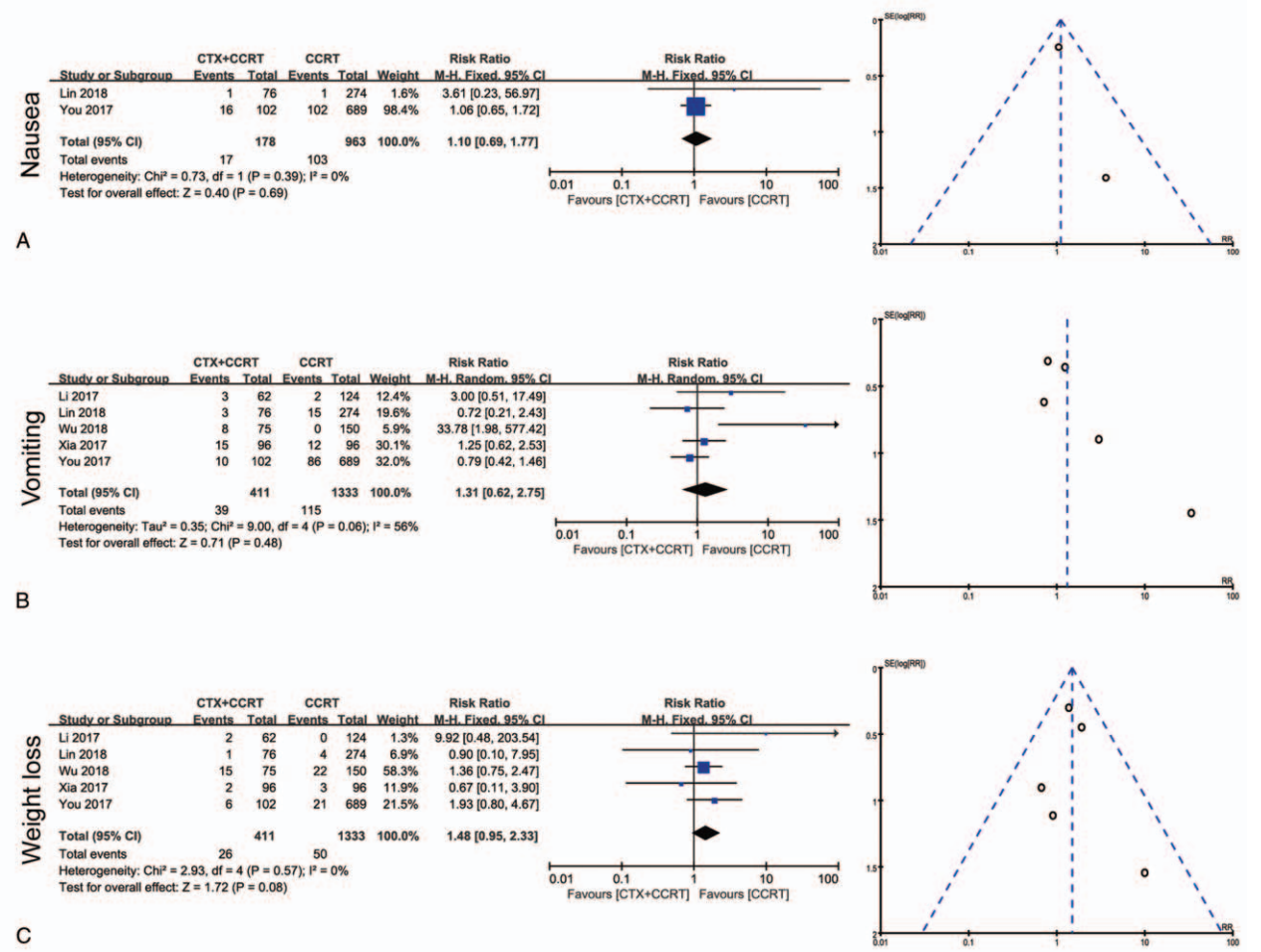

Figure 5. Forest plots and funnel plots of risk ratios for grade 3-4 nausea (A), vomiting (B), and weight loss (C) in CTX + CCRT group and CCRT group. CCRT = concurrent chemoradiotherapy, CTX = cetuximab.

rash, mucositis and dermatitis than those in CCRT alone group. In the phase II study, Ma et al reported that concurrent administration of CTX and chemoradiotherapy was a feasible regimen against locoregionally advanced NPC.[18] In the phase II multicenter study conducted by Baselga, they evaluated the toxicity of CTX plus CCRT in patients with recurrent or metastatic head and neck carcinoma and reported a well-toleration in treatment-related toxicities.[36] These results indicated that the addition of CTX to CCRT could be considered when treating the patients with locoregionally advanced NPC.

There are several inherent limitations to our study. First, this meta-analysis included a small number of retrospective studies. Second, patients in the studies were all from China, and this may result in selection bias. Third, there was a significant heterogeneity in the subgroup analyses. Fourth, patients in the studies received different treatment modalities. Fifth, 2 studies used both CTX and NTZ.

In conclusion, this meta-analysis demonstrated that the combination of CTX with CCRT improved the DFS and DMFS compared with CCRT alone in patients with locoregionally advanced NPC. However, the high rates of grade 3-4 skin rash, mucositis, and dermatitis should not be ignored. These results indicated that CTX might be an alternative regimen to standard CCRT in patients with locoregionally advanced NPC. More prospective studies are needed to verify our findings.

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References

[1] Wee JT, Ha TC, Loong SL, et al. Is nasopharyngeal cancer really a "Cantonese cancer"? Chin J Cancer 2010;29:517–26.
[2] Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 2002;12:421–9.
[3] Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005;365:2041–54.
[4] Mao YP, Xie FY, Liu LZ, et al. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2009;73:1326–34.
[5] Adelstein D, Gillison ML, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw 2017;15:761–70.
[6] Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol 1998;16:1310–7.
[7] Lin JC, Jan JS, Hsu CY, et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol 2003;21:631–7.
[8] Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. J Clin Oncol 2004;22:2643–53.
[9] Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002;20:2038–44.
[10] Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005;23:6730–8.
[11] Lee AW, Tung SY, Ngan RK, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. Eur J Cancer 2011;47:656–66.
[12] al-Sarraf M, Pajak TF, Cooper JS, et al. Chemo-radiotherapy in patients with locally advanced nasopharyngeal carcinoma: a radiation therapy oncology group study. J Clin Oncol 1990;8:1342–51.
[13] Lin JC, Liang WM, Jan JS, et al. Another way to estimate outcome of advanced nasopharyngeal carcinoma–is concurrent chemoradiotherapy adequate? Int J Radiat Oncol Biol Phys 2004;60:156–64.
[14] Ma BB, Poon TC, To KF, et al. Prognostic significance of tumor angiogenesis, Ki 67, p53 oncoprotein, epidermal growth factor receptor and HER2 receptor protein expression in undifferentiated nasopharyngeal carcinoma–a prospective study. Head Neck 2003;25:864–72.
[15] Feng HX, Guo SP, Li GR, et al. Toxicity of concurrent chemoradiotherapy with cetuximab for locoregionally advanced nasopharyngeal carcinoma. Med Oncol 2014;31:170.
[16] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
[17] Liang K, Ang KK, Milas L, et al. The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys 2003;57:246–54.
[18] Ma BB, Kam MK, Leung SF, et al. A phase II study of concurrent cetuximab-cisplatin and intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma. Ann Oncol 2012;23:1287–92.
[19] He X, Xu J, Guo W, et al. Cetuximab in combination with chemoradiation after induction chemotherapy of locoregionally advanced nasopharyngeal carcinoma: preliminary results. Future Oncol 2013;9:1459–67.
[20] Lin M, You R, Liu YP, et al. Beneficial effects of anti-EGFR agents, cetuximab or nimotuzumab, in combination with concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma. Oral Oncol 2018;80:1–8.
[21] Wu LR, Zhu HF, Xu J, et al. Effectiveness of cetuximab in combination with concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: a 1:2 propensity score-matched analysis. J Cancer 2018;9:1642–51.
[22] Li Y, Chen QY, Tang LQ, et al. Concurrent chemoradiotherapy with or without cetuximab for stage II to IVb nasopharyngeal carcinoma: a case-control study. BMC Cancer 2017;17:567.
[23] You R, Hua YJ, Liu YP, et al. Concurrent chemoradiotherapy with or without anti-EGFR-targeted treatment for stage II-IVb nasopharyngeal carcinoma: retrospective analysis with a large cohort and long follow-up. Theranostics 2017;7:2314–24.
[24] Xia WX, Liang H, Lv X, et al. Combining cetuximab with chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma: a propensity score analysis. Oral Oncol 2017;67:167–74.
[25] Stewart LA, Clarke M, Rovers M, et al. Group P-IDPreferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313:1657–65.
[26] Wells GASB, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[27] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.
[28] Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007;25:2191–7.
[29] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–45.
[30] 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.
[31] Cao XJ, Hao JF, Yang XH, et al. Prognostic value of expression of EGFR and nm23 for locoregionally advanced nasopharyngeal carcinoma. Med Oncol 2012;29:263–71.
[32] Xu T, Liu Y, Dou S, et al. Weekly cetuximab concurrent with IMRT aggravated radiation-induced oral mucositis in locally advanced nasopharyngeal carcinoma: results of a randomized phase II study. Oral Oncol 2015;51:875–9.
[33] Wu X, Huang J, Liu L, et al. Cetuximab concurrent with IMRT versus cisplatin concurrent with IMRT in locally advanced nasopharyngeal carcinoma: a retrospective matched case-control study. Medicine 2016;95:e4926.
[34] Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005;97:536–9.
[35] Cao SM, Yang Q, Guo L, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. Eur J Cancer 2017;75:14–23.
[36] Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23:5568–77.