Systematic Review and Meta-Analysis

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The efficacy and toxicity of induction chemotherapy plus concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma

A meta-analysis of randomized controlled trials

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Abstract

Background: A systemic review and meta-analysis of randomized controlled trials (RCTs) was performed to compare the efficacy, toxicity and safety of concurrent chemoradiotherapy (CCRT) with or without induction chemotherapy (IC) for locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: Research searching was performed in Web of Science, PubMed, The Cochrane Library, Embase, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chongqing VIP Database for Chinese Technical Periodicals and Wanfang Database. RCTs including patients diagnosed with locoregionally advanced NPC without metastasis and randomly treated with IC plus CCRT and CCRT alone were included. Survival and outcome data were extracted and meta-analysis was performed using the Revman 5.3.0 software.

Results: Ten RCTs (2280 patients) were selected and used for pooled meta-analysis. In comparison with CCRT, IC plus CCRT treatment significantly improved the overall survival (OS; HR = 0.70, 95%CI 0.56–0.87, $P = .002$), progression-free survival (PFS; HR = 0.75, 95%CI 0.65–0.87, $P < .0001$), distant metastasis failure-free survival (DMFS; HR = 0.71, 95%CI 0.58–0.85, $P = .0003$) and loco-regional failure-free survival (LFES; HR = 0.72, 95%CI 0.59–0.88, $P = .002$) of patients with locoregionally advanced NPC. Patients treated with IC and CCRT had higher incidence of grade 3–4 leucopenia and thrombocytopenia than patients treated with CCRT alone ($P < .0001$). No significant difference in other grade 3–4 adverse events and radiation toxicity was observed between the two groups. IC combined with CCRT improved the survival of patients with locoregionally advanced NPC.

Conclusions: Combined IC and CCRT therapy was an efficacy treatment regimen for locoregionally advanced NPC.

Abbreviations: CBD = Chinese Biomedical Database, CCRT = concurrent chemoradiotherapy, CNKI = Chinese National Knowledge Infrastructure, CQVIP = Chongqing VIP Database for Chinese Technical Periodicals, CTCAE = common terminology criteria for adverse events, DMFS = distant metastasis failure-free survival, DMFS = distant metastasis failure-free survival, EBV = Epstein–Barr virus, ECOG = Eastern Cooperative Oncology Group, IC = induction chemotherapy, LFES = locoregional failure-free survival, LFES = loco-regional failure-free survival, NPC = nasopharyngeal carcinoma, OS = overall survival, PFS = progression-free survival, PFS = progression-free survival, RCTs = randomized controlled trials, RT = favored radiotherapy, TNM = tumor node metastasis.

Keywords: combined IC and CCRT therapy, concurrent chemoradiotherapy, improved survival, induction chemotherapy, locally advanced nasopharyngeal carcinoma

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1. Introduction

Nasopharyngeal carcinoma (NPC) is an epidermoid original cancer which distinctly from head and neck cancers. Epstein-Barr virus (EBV) infection is a major character of NPC.[1] NPC is regionally distributed and the high incidences are reported in Eastern Asia, Northern Africa, Southern China, Micronesia and Polynesia.[2] The incidence of NPC is reported in 60.6 thousand people in China in 2015, with higher proportion (71.45%) in males and a mortality of 56.27%.[3] An urgent problem that desperately needs to be solved is the survival and quality of patients with locoregionally advanced NPC.

Radiotherapy is the first preferred alternative treatment for NPC. Concurrent chemoradiotherapy (CCRT) is an unquestionable treatment for early NPC.[4] The contribution of induction chemotherapy (IC) after CCRT, however, remains controversial for the treatment of locoregionally advanced NPC.[5–8] On the one hand, there were two different trial outcomes on the benefit of IC to CCRT (effective or noneffective). Some studies showed IC plus CCRT improved patients survival rate significantly, while the others showed no improvement on overall survival (OS).[5–8] On the other hand, IC resulted into higher incidence of grade 3–4 adverse events, including neutropenia, leucopenia and stomatitis.[5–9]

This meta-analysis will give us a summary on the efficacy of using IC plus CCRT in locoregionally advanced NPC and provide a reference for clinical management for locoregionally advanced NPC.

2. Materials and methods

This review of RCTs was designed and conducted following the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[10] This study does not include human tissue samples, and therefore an ethics committee approval is not applicable.

2.1. Search strategy

Eligible studies published in Web of Science, PubMed, The Cochrane Library, Embase, Chinese Biomedical Database (CBD), Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Database for Chinese Technical Periodicals (CQVIP) and Wanfang Database with the searching terms: "nasopharyngeal neoplasms" OR "nasopharyngeal tumors" OR "nasopharyngeal cancers" AND "clinical trials" OR "randomized controlled trial". Publications in both Chinese and English languages from the earliest record of the databases to July 15, 2018 were included. Publications with insufficient data were excluded, while additional eligible studies in references were identified and included as alternatives.

2.2. Inclusion and exclusion criteria

Inclusion criteria were patients

(1) diagnosed with locoregionally advanced NPC without metastasis;
(2) treated with IC plus with CCRT or CCRT alone;
(3) recruited in RCTs.

Publications were excluded if they were:

(1) duplicated publications;
(2) low quality reports or with incomplete information;
(3) RCTs only published as abstracts;
(4) cohort study;
(5) comments, reviews, case reports, or letters.

Three experts independently assessed the abstracts of studies that met the inclusion criteria. If there are different opinions, the three experts agree to be approved.

2.3. Data extraction and outcomes

Publication data including the title, first author information and publication data were collected. RCT quality was obtained. The baseline data of patients [including sex, age, (Tumor Node Metastasis (TNM) classification, histology stage, Eastern Cooperative Oncology Group (ECOG) performance status], treatment regimens (IC plus with CCRT or CCRT alone) and follow-up times were extracted. Outcome data, including overall survival (OS), progression-free survival (PFS), distant metastasis failure-free survival (DMFS), loco-regional failure-free survival (LFFS), radiation toxicity and advent events, were extracted from eligible studies. All data extracted from included RCTs were pooled separately for meta-analysis.

2.4. Quality assessment

The quality evaluation of the data extracted from the included studies was independently performed using the Cochrane Collaboration's tool for assessing risk of publication bias[11] and 5-point Jadad score system.[12]

2.5. Statistical analysis

Meta-analysis for the extracted data was performed using Revman 5.3.0 software. The 95% confidence interval (95% CI) and Peto odds ratio were used for meta-analysis. The number of incident events and total people was recorded. The expected number of deaths (O-E) was calculated based on the 5-year age groups and calendar periods as well as mortality rates of locoregionally advanced NPC patients. Publications' heterogeneity was assessed using I-square (I^2) test with χ^2 test. $I^2 \geq 50\%$ and $P < .1$were set as the threshold for heterogeneity, and homogeneity otherwise ($I^2 < 50\%$ and $P \geq .1$). Sensitivity analysis was performed for heterogeneity studies. Meta-analysis was conducted using fixed-effect and random-effect model of extracted data in homogeneity ($I^2 < 50\%$) and heterogeneity ($I^2 \geq 50\%$), respectively.

3. Results

3.1. Included studies

A total of 484 English and Chinese publications were searched from databases and 3 articles were obtained by manual retrieval the reference lists. After removing duplicated publications (n = 132) or publications met the exclusion criteria (meeting abstract, case reports and reviews, not RCTs or patients not assigned into treatment with IC and CCRT vs CCRT, n = 345), only 10 eligible studies[1,6–9,13–17] were included for the meta-analysis (Table 1). The PRISMA flow diagram of publication selection is shown in Figure 1. No publication bias was found in these publications (Fig. 2 and Figure S1, http://links.lww.com/MD/D908).

3.2. Baseline characteristics of included studies

A total of 2280 patients were randomly assigned into IC combined with CCRT treatment (n = 1145) and CCRT alone

Table 1

Characteristics of the 10 eligible studies included in this review.

Study	Clinical stage (TNM classification)	Histology (WHO classification)	Patients (IC and CCRT vs. CCRT)	Radiotherapy	Concurrent chemoradiotherapy	Induction chemotherapy	Median follow-up(month)	Jadad Score
Tan et al, 2015, Singapore[17]	UICC/AJCC5th editionT3–4NxM0or TxN2–3M0	I, III	86/86	IMRT: GTVnx:69.96/2.12Gy/33f; GTVnd:69.96/2.12Gy/33f; CTV1:60/1.82Gy/33f. (4patients) 2D-CRT: primary site 70/2Gy/35f; positive nodes70/2Gy/35f; pharyngeal extension and residual nodes 60/2Gy/30f	Cisplatin40mg/m2 d1, q1wk×8	Paclitaxel70mg/m^{2}d1, d8;Carboplatin AUC=2.5d1,d8; Gemcitabine1000mg/m^2 d1, d8; q3wks×3	40.8 (13.2- 100.8)	4
Fountzilas et al, 2012, New Zealan[1]	AJCC/UICC6th edition IIB-IVB	I-III	72/69	3D-CRT and 2D-CRT: 2.0Gy/F×5F/wk; primary site66–70Gy; positive nodes66–70Gy;pharyngeal extension and residual nodes 50Gy	Cisplatin40mg/m^2 d1, q1wk×8	Cisplatin75mg/m^{2}d1; Epirubicin75mg/m^2 d1;Paclitaxel175mg/m^2 d1; q3wks×3	55 (0.5–76.2)	5
Hui et al, 2009, Hong Kong, China[16]	UICC/AJCC5th edition III-IVB	NR	34/31	IMRT and 2D-CRT:2 Gy/F×5F/wk;total66Gy; residual boost of 7.5Gy	Cisplatin40mg/m^2 d1, q1wk×8	Docetaxel75mg/m^2 d1;Cisplatin75mg/m^2 d1; q3wk×2	51.6	5
Cao et al, 2017, China[8]	UICC/AJCC6th edition III-IVB excluding T3N0–1	II,III	238/238	IMRT and 2D-CRT: 2.0–2.33Gy/F×5F/wk; total 66Gy or more	Cisplatin 80 mg/m2 d1, q3wk×3	cisplatin (80mg/m^{2}d1) fluorouracil (800mg/m^2 civ d1–5) q3wk×2	50 (3–94)	5
Gao et al, 2013, China (in Chinese)[13]	1992 Fuzhou stage T3–4N2–3M0	II,III	57/55	2D-CRT:2.0Gy/F×5F/ wk; primary site70–74Gy; positive nodes 66–70Gy; pharyngeal extension and residual nodes 50Gy	Cisplatin40mg/m^2 d1, q1wk×7	Cisplatin30mg/m^{2}d1–3;Fluorouracil 450mg/m^{2}d1–3; q3wks×2	42	3
Huang et al, 2012, China (in Chinese)[15]	AJCC/UICC6th edition III-IVB	II,III	100/100	2D-CRT:2.0Gy/F×5F/wk; primary site 65–78Gy; positive nodes 60–70Gy; pharyngeal extension and residual nodes 50–54Gy	Caboplatin AUC=6 d7, d28, d49	Caboplatin AUC=6 d1; Fluorouracil750mg/m^2, d1–5; q3wks×2	46.8	5
Sun et al, 2016, China[9]	UICC/AJCC7th edition III-IVB (except T3–4N0)	II,III	241/239	IMRT (radical radiotherapy)	Cisplatin100mg/m^2 d1, q3wks×3	Docetaxel60mg/m^2 d1;Cisplatin60mg/m^2 d1;Fluorouracil600 mg/m^{2}d1–5; q3wks×3	45	4
Frikha et al, 2018 France and Tunisia[7]	AJCC/UICC6th edition IIB-IVB	I, II	40/41	70Gy/2Gy/35F/7wks 2D-CRT OR IMRT	Cisplatin40mg/m^2 d1, q1wk×7	Docetaxel75mg/m^{2}d1; cisplatin75mg/m^{2}d1; 5FU750mg/m^2/d1–5; q3wks×3	43.1	4
Hong et al, 2018, China[6]	UICC/AJCC5th IVA-IVB edition	II	239/240	(292patients)IMRT and (187patients)3D-CRT: 1.8–2.2Gy/F×5F/wk; total 70Gy or more	Cisplatin30mg/m^2 d1, q1wk×7	Mitomycin 8mg/m^2, epirubicin60mg/m^2, and cisplatin60mg/m^{2}on D1,5-FU450mg/m^2, and leucovorin30mg/m^{2}on D8(MEPFL) q3wks×3	72 (0.1–108)	5
He et al, 2009, China (In Chinese)[14]	1992Fuzhou III-IVA	III-IVA	38/36	2D-CRT: 2.0Gy/F×5F/wk; primary site 68–72Gy; positive nodes 64–66Gy; negative neck 50Gy/25f	Cisplatin40mg/m^2 d1, q1wk×6	cisplatin (80mg/m^2 d1) fluorouracil (800mg/m^2 civ d1–5) q3wk×2	26.7 (6–48)	3

2D-CRT=two-dimensional conformal radiotherapy, 3D-CRT=three-dimensional conformal radiotherapy, AJCC=American Joint Committee on Cancer, AUC=area under the cure, IMRT=intensity-modulated radiotherapy, UICC=union for international cancer control, WHO=world health organization.

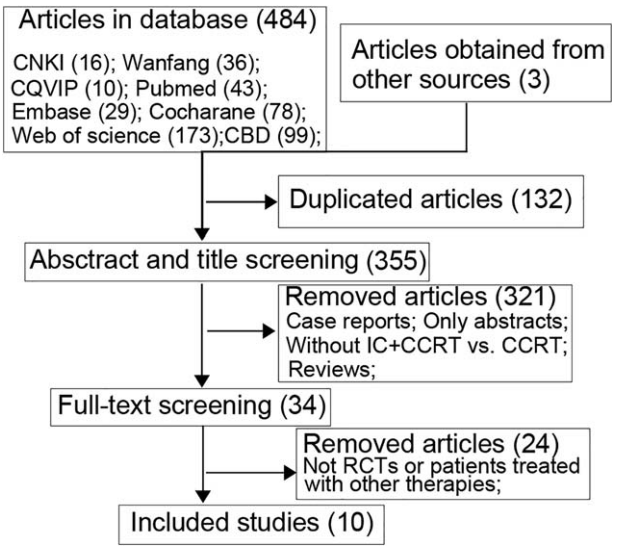

Figure 1. The PRISMA flow diagram of the identification and selection of relevant articles for this meta-analysis.

(n = 1135). Patients had locoregionally advanced NPC at TNM classification IIB ~ IVB or WHO classification I ~ IVA and were followed up for 23.7 to 72 median months. For CCRT, patients were mainly received cisplatin (30~100 mg/m^2 for one day, followed with different regimens). Nine drugs, including paclitaxel, carboplatin, gemcitabine, cisplatin, epirubicin, docetaxel, fluorouracil, mitomycin and leucovorin, were mentioned as the IC regimens in different articles, with different combinations (Table 1).

3.3. IC + CCRT treatment has higher efficacy than CCRT alone on locoregionally advanced NPC

All the 2280 patients in the selected 10 articles were used for the OS meta-analysis. Of which, 2206 (9 articles except for He[14]) were used for the PFS meta-analysis. And 2199 (9 articles except for Frikha[7]) patients were available for the DMFS and LFFS meta-analysis, respectively. In comparison with CCRT alone, locoregionally advanced NPC patients treated with combined treatment showed significantly higher rates of OS (HR = 0.70, 95% CI 0.56–0.87, $P = .002$, $I^2 = 0.0\%$, Fixed model; Fig. 3A), PFS (HR = 0.75, 95% CI 0.65–0.87, $P < .0001$, $I^2 = 0.0\%$, Fixed model; Fig. 3B), DMFS (HR = 0.71, 95% CI, 0.58 – 0.85, $P = .0003$; $I^2 = 0.0\%$, Fixed model; Fig. 3C) and LFFS (HR = 0.72, 95% CI, 0.59–0.88, $P = .002$; $I^2 = 0.0\%$, Fixed model; Fig. 3D). These results suggested that IC was in favor of the survival rate of CCRT-treated patients with locoregionally advanced NPC.

3.4. IC + CCRT improves adverse events than CCRT

No treatment-related death was reported in the two groups during the follow up. According to the Common Terminology Criteria for Adverse Events (CTCAE), the frequently recorded adverse events (grade 3–4) following IC prior to CCRT treatment were neutropenia (32%, available in 3 articles), leucopenia (30%, available in 3 articles), thrombocytopenia (12%, available in 3 articles) and nausea or vomiting (9%, available in 4 articles, Table 2). During the phase of CCRT, the incidences of grade 3–4 adverse events, including leucopenia ($P < .0001$) and thrombocytopenia ($P = .0006$), in patients treated with IC + CCRT were higher than that treated with CCRT alone (Table 3). No differences were seen in other adverse grade 3–4 adverse events (Table 3) and late radiation morbidity (Table 4) between the two groups.

4. Discussion

The addition of IC to CCRT could improve the survival time and rates of patients with advanced cancers.[18] Our meta-analysis study, including 10 eligible studies, showed that IC plus CCRT-treated patients with locoregionally advanced NPC had higher survival rates (OS, PFS, DMFS and LFFS) than patients only treated with CCRT. Although there were higher occurrence of grade 3–4 leucopenia and thrombocytopenia in IC and CCRT group, no difference in treatment-related death was found between the 2 groups. These results systemically suggested the efficacy and survival benefit of IC and CCRT for locoregionally advanced NPC.

Song et al[19] and Chen et al[20] separately performed a meta-analysis in 2015 enrolling 798 (4 RCTs) and 1988 (9 RCTs) patients with locoregionally advanced NPC randomly treated with IC or IC and CCRT, respectively. They both showed that the addition of IC to CCRT had no significant improvement in OS.[19,20] However, Song et al showed the benefit of IC addition for improving the DFS and DMFS of patients with locoregionally advanced NPC.[19] Yan et al performed a review of 25 RCTs and confirmed that IC did not favor CCRT in view of OS, but it favored radiotherapy (RT).[21] In addition, Yan showed that adjuvant chemotherapy (A) plus CCRT, IC plus CCRT, CCRT and IC+RT+A had similar probability (28%, 25%, 24%, and

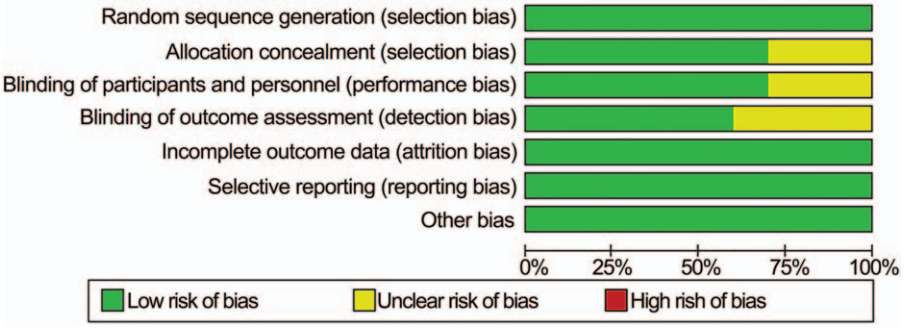

Figure 2. Publication bias of the 10 included articles.

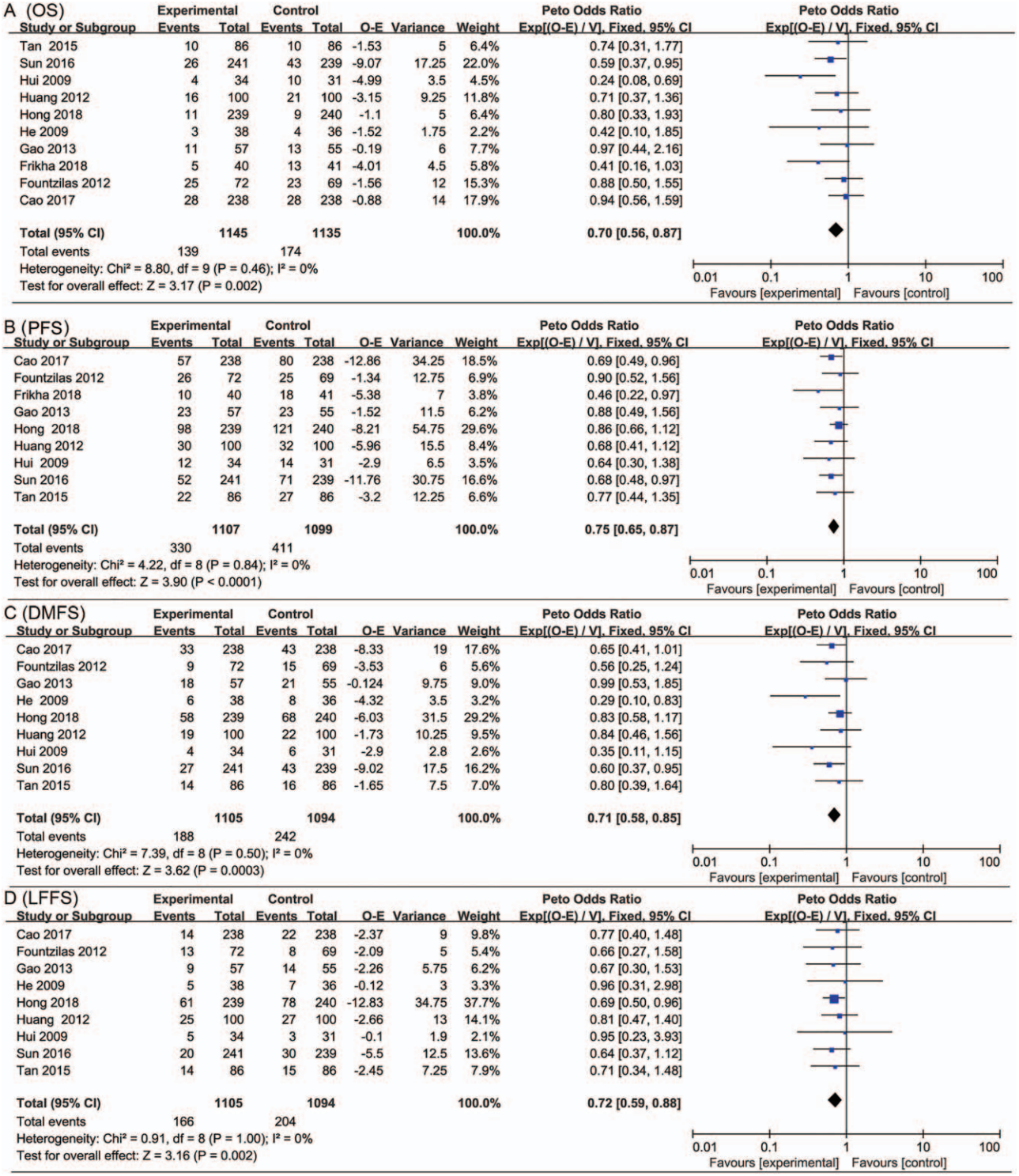

Figure 3. The forest plots for the effect of different therapies on induction chemotherapy the survival of patients with locoregionally advanced nasopharyngeal carcinoma. A to D, the overall survival (OS), progression-free survival (PFS), distant metastasis failure-free survival (DMFS) and loco-regional failure-free survival (LFFS) of patients with LA-NPC (locoregionally advanced nasopharyngeal carcinoma). Experiment group was treated with induction chemotherapy combined with concurrent chemoradiotherapy (IC + CCRT) and control group was treated with (concurrent chemoradiotherapy), respectively. CI = confidence interval, O-E = observed minus expected events.

21%, respectively) of being the best regimen, using a network meta-analysis.[21] Similar results were reported by Ribassin-Majed et al.[22] In comparison with these meta-analyses,[19–21] our study (enrolled 2280 patients in 10 eligible publications in both Chinese and English) confirmed that the addition of IC to CCRT showed significant benefit for the OS, PFS, DMFS, and LFFS of patients with locoregionally advanced NPC compared with CCRT alone (Fig. 3). We found patients showed higher

Table 2

Adverse events induction chemotherapy treatment.

Adverse event	Trials	Grade 3–4 (%, event/total)
Anemia	3	3.21% (18/561)
Neutropenia	3	32.40%(116/358)
Febrile neutropenia	2	5.17% (14/271)
Leucopenia	3	29.77%(167/561)
Thrombocytopenia	3	11.76% (66/561)
Nausea/vomiting	4	9.24% (55/595)
Hepatotoxicity	3	1.43% (8/561)
Nephrotoxicity	2	0 (0/238)
Mucositis	2	1.26% (6/475)

Adverse events are grade 3–4 hematological events according to the Common Terminology Criteria for Adverse Events. CCRT = concurrent chemoradiotherapy, IC = induction chemotherapy.

survival rate when treated with IC plus CCRT, compared with CCRT alone. These might due to the inclusion of three latest publications published in 2016,[9] 2017,[8] and 2018.[6]

Of the 3 latest published articles, Hong et al (n = 479) showed the addition of IC showed significant benefit to DFS and LFFS[6]; Sun et al (n = 480) showed the significant benefit of IC addition to OS, DFS and LFFS[9]; and Cao et al (n = 476) showed IC addition significantly improved DFS and a marginal significance in DMFS ($P < .056$).[8] A recently reported meta-analysis of RCTs and observational studies by Tan et al showed the similar significantly benefit of IC addition to CCRT for improving DFS and OS.[23] These data showed that the IC addition to CCRT is being advanced into clinical treatment of locoregionally advanced NPC. It has been widely reported that IC offers favor to eradicating the micrometastasis and improving patients' tolerability,[5,22] which might benefit for the better prognosis of patients treated with IC and CCRT.

Most of the included studies[6,8,9,13–17] and others[24] showed that the addition of IC regimens to CCRT induced higher rates of grade 3–4 adverse events, including leucopenia, neutropenia, thrombocytopenia and stomatitis/mucositis. These data suggested that the investigational IC arm showed more grade 3–4 toxicities. However, no difference was seen in the radiation toxicity between the two groups. Frikha et al[7] even showed there was no difference in the grade 3–4 adverse events between the two groups, suggesting the adjustable incidence of adverse events by adding different IC regimens.

5. Limitations

Several limitations exist in our study. First, 7 IC regimens were used in the 10 included studies, including TPF (docetaxel, cisplatin, and fluorouracil),[7,9] PF (cisplatin and fluorouracil),[8,13,14] DC (cisplatin and docetaxel),[16] CF (carboplatin and fluorouracil),[15] GCP (gemcitabine, carboplatin, and paclitaxel),[17] PET (epirubicin, paclitaxel and cisplatin)[1] and MEPFL (mitomycin C, epirubicin, cisplatin, and 5-fluorouracil (5-FU)/leucovorin).[6] The advantages of TPF to PF regimen had been reported in chemotherapy NPC and in other cancers.[6] TPF regimen showed significant benefit for the OS and DMFS of patients with locally advanced locoregionally advanced NPC[25]

Table 3

The pooled analyses of the grade 3–4adverse events during concurrent chemoradiotherapy between experimental and control groups.

Adverse event	Trials	Grade 3–4 (%, event/total)		95% CI	*P*
		IC+CCRT	CCRT		
Anemia	9	6.16% (67/1087)	2.23% (24/1076)	0.94–4.81	.07
Neutropenia	5	24.10% (159/660)	8.97% (59/658)	0.73–5.98	.17
Febrile neutropenia	4	1.94% (11/568)	0.71% (4/561)	0.39–6.93	.50
Leucopenia	8	31.05%(327/1053)	14.86%(156/1050)	1.87–4.40	<.0001
Thrombocytopenia	8	11.25%(118/1049)	0.87% (9/1040)	2.38–24.80	.0006
Nausea/vomiting	9	16.74%(182/1087)	15.52%(167/1076)	0.72–1.56	.76
Hepatotoxicity	6	1.99% (19/952)	1.17% (11/944)	0.78–3.75	.18
Nephrotoxicity	6	0.27% (2/728)	0.28% (2/726)	0.15–7.39	.96
Mucositis	8	28.47%(285/1001)	26.87% (266/990)	0.87–1.97	.20
Fatigue	3	9.29% (17/183)	3.30% (6/182)	0.42–11.19	.36
Neurotoxicity	3	0 (0/387)	0.25% (1/394)	0.01–9.12	.54
Skin reaction	5	5.77% (50/866)	5.48% (47/858)	0.68–1.57	.88
Diarrhea	2	0.66% (2/301)	0 (0/308)	0.27–121.70	.26

Adverse events are grade 3–4 hematological events according to the Common Terminology Criteria for Adverse Events. IC = induction chemotherapy.

Table 4

Late radiation toxicities (grade 3–4) according to RTOG morbidity grading.

Toxicity	Trials	IC + CCRT (%, event/total)	CCRT (%, event/total)	95% CI	*P*
Skin	3	1.99% (7/352)	2.65% (9/339)	0.23–1.79	.39
Subcutaneous tissue	3	3.69% (13/352)	1.18% (4/339)	0.88–8.42	.08
Mucous membrane	3	8.52% (30/352)	7.96% (27/339)	0.38–3. 03	.90
Salivary gland	3	5.40% (19/352)	6.49% (22/339)	0.36–1.45	.36
Esophagus	3	4.83% (17/352)	2.95% (10/339)	0.75–3.62	.22
Joint	2	1.26% (4/318)	0 (0/313)	0.48–167.39	.14
Larynx	2	3.77% (12/318)	2.24% (7/313)	0.66–4.44	.27

CCRT = concurrent chemoradiotherapy, IC = induction chemotherapy, RTOG = radiation therapy oncology group.

or other cancers.[26] In addition, TPF regimen is a standard induction regimen for locally advanced unresectable head and neck cancer[27,28] and larynx preservation.[29] These results suggested that different IC regimens might affect the prognosis of patients with locoregionally advanced NPC. The unification of IC regimens might confirm a more reliable efficacy of IC addition on CCRT survival years. Second, the follow-up period in some studies was less than 5 years,[13,14] which resulted into the limit data for the analysis of the long-time efficacy and safety of IC. Third, the frequencies of late radiation toxicities (grade 3–4) were only reported in few studies, which limited the evaluation for the long-term safety of using IC regimens in NPC.

6. Conclusion

This meta-analysis suggested the IC addition to CCRT improved the OS, DFS, DMFS and LFFS of patients with locoregionally advanced NPC significantly. Leucopenia, neutropenia, and mucositis were the most grade 3–4 adverse events in IC and CCRT arm. No difference was seen in the radiation toxicity between the two groups. The meta-analysis showed that IC addition arm significantly benefitted to the survival of patients with locoregionally advanced NPC in comparison with CCRT alone. This study provided important reference for clarifying the precise value of IC and CCRT in treatment of locoregionally advanced NPC.

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Validation: Peirong Wang, Chuanshu Cai.
Visualization: Peirong Wang, Chuanshu Cai.
Writing – original draft: Peirong Wang.
Writing – review & editing: Peirong Wang, Chuanshu Cai.

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