RESEARCH ARTICLE

Induction Chemotherapy Followed by Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy with or without Adjuvant Chemotherapy for Locoregionally Advanced Nasopharyngeal Carcinoma: Meta-analysis of 1,096 Patients from 11 Randomized Controlled Trials

Zhong-Guo Liang, Xiao-Dong Zhu*, Ai-Hua Tan, Yan-Ming Jiang, Song Qu, Fang Su, Guo-Zeng Xu

Abstract

Purpose: To evaluate the efficacy and toxicity of induction chemotherapy followed by concurrent chemoradiotherapy (the treatment group) versus concurrent chemoradiotherapy with or without adjuvant chemotherapy (the control group) for locoregionally advanced nasopharyngeal carcinoma. Methods: The search strategy included Pubmed, Embase, the Cochrane Library, China National Knowledge Internet Web, Chinese Biomedical Database and Wanfang Database. We also searched reference lists of articles and the volumes of abstracts of scientific meetings. All randomized controlled trials were included for a meta-analysis performed with RevMan 5.1.0. The Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) was used to rate the level of evidence. Results: Eleven studies were included. Risk ratios of 0.99 (95%CI 0.72-1.36), 0.37 (95%CI 0.20-0.69), 1.08 (95%CI 0.84-1.38), 0.98 (95%CI 0.75-1.27) were observed for 3 years overall survival, 3 years progression-free survival, 2 years loco-regional failure-free survival and 2 years distant metastasis failure-free survival. There were no treatment-related deaths in either group in the 11 studies. Risk ratios of 1.90 (95%CI 1.24-2.92), 2.67 (95%CI 0.64-11.1), 1.04 (95%CI 0.79-1.37), 0.98 (95%CI 0.27-3.52) were found for grade 3-4 leukopenia, grade 3-4 thrombocytopenia, grade 3-4 mucous membrane, and grade 3-4 hepatic hematologic and gastrointestinal toxicity, the most significant toxicities for patients. Conclusion: Compared with the control group, induction chemotherapy followed by concurrent chemoradiotherapy was well tolerated but could not significantly improve prognosis in terms of overall survival, loco-regional failure-free survival or distant metastasis failure-free survival.

Keywords: Nasopharyngeal carcinoma - induction chemotherapy - chemoradiotherapy - adjuvant chemotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southern China, south-east Asia and north Africa. The incidence in southern China is reported to be about 80 cases per 100,000, which brings great threat to the local people (Chan et al., 2002). Because the early clinical symptoms are not obvious, at least 60% of patients with NPC present with locally advanced disease, while about 5–8% present with distant metastases at diagnosis (Fong et al., 1996; Heng et al., 1999). Radiation therapy is the main treatment for nasopharyngeal carcinoma. The 5-year survival rate had been reported to be about 85% for stageI- II NPC, while patients with locoregionally advanced NPC (Stage III and Stage IV disease) were reported to have a 5-year survival rate of only 55% (Teo et al., 1996). For advanced NPC, the Intergroup 0099 study showed that concurrent chemoradiotherapy (CCRT) with adjuvant chemotherapy (AC) provided a 31% increase in 3 year overall survival (Al-Sarraf et al., 1998). Concurrent chemoradiotherapy with or without adjuvant chemotherapy have become the standard therapy for advanced NPC.

At the Medical Oncology Outpatient/Inpatient unit of the Philippine General Hospital, 30 patients with stage III to IVb were randomized to receive induction chemotherapy (IC) followed by CCRT or CCRT with AC (Ruste et al., 2011). There was no significant difference between the two groups in terms of 3-year overall survival (IC+CCRT, 36%, CCRT + AC, 25.4%, Hazard ratio=0.92, $P = 0.889$). Now there were also several other randomized controlled trials (RCTs) compared the therapy of IC

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followed by CCRT and the therapy of CCRT with or without AC in advanced NPC (He et al., 2009; Ma et al., 2009; Sun et al., 2009; He et al., 2011; Xu et al., 2011; Chen et al., 2012; Cui et al., 2012; Fountzilas et al., 2012; Huang et al., 2012), but none of them were large enough to show a statistically significant effect. This meta-analysis was conducted to give an overview of all eligible RCTs comparing the therapy of IC+CCRT with the therapy of CCRT +/- AC in advanced NPC.

Materials and Methods

Search strategy

Studies were identified by searching electronic databases, scanning reference lists of articles and the volumes of abstracts of scientific meetings. Pubmed, Embase, and the Cochrane Library were searched until October 2012. The text search term was: ((nasopharyngeal carcinoma) OR (nasopharyngeal cancer) OR (nasopharyngeal neoplasms)) AND (chemotherapy OR cisplatinum OR carboplatin OR nedaplatin OR drug therapy) AND ((Randomized Controlled Trials) OR (Random*)). The Chinese periodical databases of China National Knowledge Internet Web (CNKI), Chinese Biomedical Database (CBM), and Wanfang Database were used for Chinese articles with the search term: ((nasopharyngeal carcinoma) OR (nasopharyngeal neoplasm)) AND (chemotherapy OR platinum) AND((Randomized Controlled Trials) OR (Random)) (in Chinese).

Inclusion and exclusion criteria

Literatures selected from this initial search were subsequently screened for eligibility using the following criteria: (1) Participating patients with locoregionally advanced nasopharyngeal carcinoma but no distant metastases at diagnosis. (2) Studies combined therapy with IC followed by CCRT versus CCRT with or without AC. (3) RCTs. Reports were excluded by the following criteria: (1) No RCTs. (2) Literature published repeatedly. (3) Any review, comment, letter, or case report. Eligibility assessment was performed independently in an unblinded standardized manner by 2 reviewers. Disagreements between reviewers were resolved by consensus.

Assessment of risk of bias in included studies

With the guidance of Cochrane handbook (5.1.0) (Julian et al., 2011), we assessed the risk of bias by using the following criteria: adequate reliability determined random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessment, incomplete outcome data, selecting reporting and other bias. High risk, low risk, or unclear were used to evaluate the risk of bias.

Quality of evidence

The quality of the evidence was a judgement about the extent to which we could be confident that the estimates of effect were correct. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the level of evidence and the strength of recommendation for each outcome (Zeng et al., 2011). The judgements were based on the risk of bias, limitations, the Indirectness, the consistency of the results across studies, the precision of the overall estimate across studies, and other considerations. For each outcome, the quality of the evidence was rated as high, moderate, low or very low using the following definitions: (1) Further research was very unlikely to change our confidence in the estimate of effect. (2) Further research was likely to have an important impact on our confidence in the estimate of effect and may change the estimate. (3) Further research was very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. (4) We were very uncertain about the estimate. The methodological quality of the studies included in the meta-analysis was ascertained with GRADEpro 3.6 by two reviewers. If disagreements occurred between the two reviewers, a third author would make decision through discussion.

Data extraction

A structured form was used to extract relevant data from the trials. Extraction was performed completely independently by two reviewers. Reviewers were not blinded to authors or journals. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned a third author would decide. The following information was sought from each article, although some articles did not contain all the information as followed: first author, publication year, treatment regiment, patient number, inclusion period, American Joint Committee on Cance (AJCC) performance status, Union for International Cancer Control (UICC) performance status, 1992 Fuzhou stage performance status, and Chinese stage (2008) performance status. The outcomes were overall survival (OS), progression-free survival (PFS), loco-regional failure-free survival (LFFS), distant metastasis failure-free survival (DMFS), haematological and non-haematological advent events.

Data analysis

Analysis was performed according to intention-to-treat. The outcomes data of OS, DFS, PFS, LFFS, DMFS, haematological and non-haematological advent events were analyzed quantitatively using Revman 5.1.0. Risk ratio (RR) and 95% confidence interval (CI) were calculated. RR represented the risk of an event occurring in the IC followed by CCRT group versus the CCRT with or without AC group. RR less than 1 indicated that the results favored the IC+CCRT group. When $P< 0.05$ and 95% CI did not include the value 1, the point estimate of the RR was statistically significant. Heterogeneity was assessed by I^2 statistic, which estimates the percentage of variability across studies not due to chance. The values of $I^2 \geq 50\%$ were considered to indicate a substantial level of heterogeneity. If no heterogeneity existed, the fixed-effect model was considered for pooled analysis. If any heterogeneity existed, the following techniques were employed to explain it: (1) Sensitivity analysis was performed by excluding the trials which potentially

Table 1. Inclusion Criteria of Eligible Trials

Study	Group	No. of patients	Inclusion period	Stage	Radiotherapy	Chemotherapy IC	Chemotherapy CC	Chemotherapy AC
He et al., 2009	IC+CCRT CCRT	38 36	2004.4-2006.5	1992 Fuzhou stage III-IVa	2.0Gy/F×5F/wk, primary site:68-72Gy, positive nodes: 64-66Gy, the prevention dose for neck: 50Gy.	Cisplatin 80 mg/m^2 d1, 5-fluorouracil 800 mg/m^2, d1-5, q3wks for 2 cycles.	Cisplatin 40 mg/m^2 d1, qwk for 6 cycles.	\
Ma et al., 2009	IC+CCRT CCRT	49 49	2003.5-2006.8	1992 Fuzhou stage III-IVa	2.0Gy/F×5F/wk, primary site:70Gy,the prevention dose for neck:50-55Gy.	Taxol 135 mg/m^2 d1, cisplatin 20 mg/m^2, d1-5 and 5-fluorouracil 1000 mg/m^2,d1-5, q3wks for 2 cycles.	Cisplatin 20 mg/m^2 d1-5, 5-fluorouracil 1000 mg/m^2, d1-5, for 2 cycles.	\
Hui et al., 2009	IC+CCRT CCRT	34 31	2002.11-2004.11	1997 UICC stage III-IVb	2.0Gy/F×5F/wk, nasopharyngeal-66Gy.	Docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, q3wk for 2 cycles	Cisplatin 40 mg/m^2/wk for 8 cycles	\
Sun et al., 2009	IC+CCRT(A) IC+CCRT(B) CCRT(C)	76 66 71	2005.5-2008.9	1992 Fuzhou stage III-IVa	Conventional radiotherapy: 2.0Gy/F×5F/wk, primary site-70Gy, positive nodes-66-70Gy, pharyngeal extension and residual nodes-50Gy. IMRT: GTVnx:68Gy,GTVnd:60-66Gy, CTV1:60Gy,CTV2:54Gy.	Group A: Cisplatin 80 mg/m^2, 5-fluorouracil 3 g/m^2, q3wks for 2 cycles. Group B: Taxol 135 m/m^2, Carboplatin (AUC=6), q3wks for 2 cycles.	Cisplatin80 mg/m^2, q3w for 2 cycles.	\
Ruste et al., 2011	IC+CCRT CCRT+AC	14 16	2005-2007	1997 UICC stage III-IVb	2.0Gy/F×5F/wk, primary site:70Gy, N0 disease:50Gy, nodes<2cm: 66 Gy, nodes greater than 2cm:70Gy	Cisplatin 20 mg/m^2 d1-4 and 5-fluorouracil 1000 mg/m^2 d1-4, q4wks for 3 cycle.	Cisplatin 25 mg/m^2 d1-4 q3wks for 3 cycle.	Cisplatin 20 mg/m^2 d1-4 and 5-fluorouracil 1000 mg/m^2 d1-4, q4wks for 3 cycle.
Xu et al., 2011	IC+CCRT CCRT	25 20	2008.8-2009.7	Chinese stage (2008) III-IVa	IMRT: GTVnx: 70.4-76.4Gy, GTVnd: 68Gy, CTV1: 60-62Gy, CTV2: 54-57Gy.	Docetaxel 75 mg/m^2,cisplatin 75 mg/m^2 d1, 5-fluorouracil 2.5 mg/m^2, CIV120h, q3wks for 2 cycles.	Cisplatin(40 mg/m^2), qwk for 5 cycles.	\
He et al., 2011	IC+CCRT CCRT	50 50	2008.12-2010.1	2002 AJCC stage III-IVa	Total dose: 70Gy	Docetaxel 75 mg/m^2 and cisplatin 25 mg/m^2 d1-3, 5-fluorouracil 800 mg/m^2, CIV96h, q3wks for 3 cycles.	Cisplatin 90 mg/m^2 d1, q3wks for 3 cycles.	\
Fountzilas et al., 2012	IC+CCRT CCRT	72 69	2003.10-2008.2	2002 AJCC stage IIb-IVb	2.0Gy/F×5F/wk, 66 Gy to clinically involved nodes <3 cm, 70 Gy to nodes≥3 cm and 50 Gy to uninvolved cervical and supraclavicular areas.	Cisplatin 75 mg/m^2, epirubicin 75 mg/m^2 and paclitaxel 175 mg/m^2, q3wks for 3 cycles.	Cisplatin 40 mg/m^2, qwk	\
Chen et al., 2012	IC+CCRT CCRT	30 30	2009.1-2010.1	Chinese stage (2008) III-IVa	IMRT: GTVnx: 66-70.4Gy, GTVnd: 66-70.4Gy, CTV1:6 0-64Gy, CTV2: 50-54Gy.	Docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 d1, and 5-fluorouracil 500 mg/m^2, d1-5, q3wks for 2 cycles.	Cisplatin 40 mg/m^2, qwk	\
Cui et al., 2012	IC+CCRT CCRT+AC	35 35	2008.5-2009.12	2002 AJCC stage III-IVb	2.0Gy/F×5F/wk, primary site:68-74Gy, positive node: 66-70Gy, the prevention dose for neck: 54-60Gy.	Nedaplatin 80 mg/m^2 d1, 5-fluorouracil 500 mg/m^2, d1-5, q3wks for 2 cycles.	The experimental group: Nedaplatin 80 mg/m^2 d1,q3wk The control group: cisplatin 100 mg/m^2, q3wk	Cisplatin 80 mg/m^2 d1, 5-fluorouracil 500 mg/m^2, d1-5, q3wks for 2 cycles.
Huang et al., 2012	IC+CCRT CCRT	100 100	2003.9-2006.5	1992 Fuzhou stage III-IVa	2.0Gy/F×5F/wk, primary site:66-78Gy, positive nodes: 60-70Gy, the prevention dose for neck 50-54Gy.	Carboplatin (AUC=6), 5-fluorouracil 750 mg/m^2,d1-5, q3wks for 2 cycles.	Carboplatin (AUC=6), q3wks for 3 cycles.	\

IC, introduction chemotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; IMRT, intensity-modulated radiotherapy; CC, concommitant chemotherapy

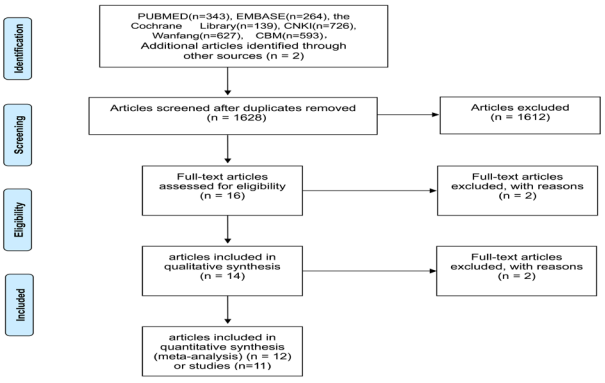

Figure 1. Process of Identification and Selection of Relevant Articles in This Meta-analysis

biased the results. (2) The random effect model was used after efforts were made to explore the cause of the heterogeneity.

Results

A total of 11 studies involving 12 articles were identified for inclusion in the meta-analysis. Through the databases of Pubmed, Embase, the Cochrane Library, CNKI, CBM, Wanfang databases and Manual Retrieval, a total of 2694 citations were searched. After adjusting for duplicates 1628 remained. Of these, 1612 citations were discarded because after reviewing the titles and the abstracts it appeared that these papers clearly didn't meet the criteria. Then, two articles was discarded because one was a retrospective trial (Yamazaki et al., 2011), and for the other trial, the therapy of experimental and the control groups were all IC followed by CCRT but with different chemotherapy regimens (Wang et al., 2011). Of the last 14 articles, two trials were almost the same in design and data with different authors (Sun et al., 2009; Zhong et al., 2011), and then zhong et al's trial (Zhong et al., 2011) was discarded. Another two trials (Chan et al., 2005; Hui et al., 2009) were the same in design and data with almost the same authors but different numbers of patients, and in order to avoid data reduplication, then Chan et al's trial (Chan et al., 2005) was discarded. Two trials (Fountzilas et al., 2009; Fountzilas et al., 2012) were from the same study but were reported in different follow-ups. They were both included. At last, a total of 1096 patients of 11 clinical studies were available for analysis, with 589 patients in the IC+CCRT group and 507 patients in the CCRT+/-AC group.

The process of identification and selection of the relevant studies according to the inclusion and exclusion criteria was depicted in Figure 1.

Table 1 showed the inclusion criteria of each trial regarding first author, publication year, treatment regiment, patient number, inclusion period, AJCC (American Joint Committee on Cancer) performance status, UICC (Union for International Cancer Control) performance status, 1992 Fuzhou stage performance status, and Chinese stage (2008) performance status administered in the studies.

Risk of bias of eligible studies (Figure 2)

Of eleven studies, six studies reported adequate reliability determined random sequence generation (He

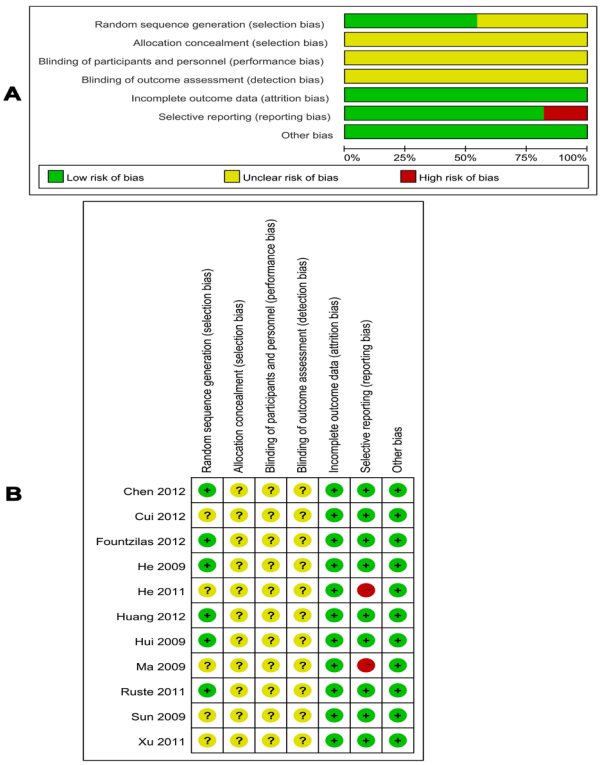

Figure 2. Risk of Bias Graph (A): review authors' judgements about each risk of bias item presented as percentages across all included studies; Risk of bias summary (B): review authors' judgements about each risk of bias item for each included study

et al., 2009; Hui et al., 2009; Ruste et al., 2011; Chen et al., 2012; Fountzilas et al., 2012; Huang et al., 2012). All satisfied the criteria of complete outcome data (He et al., 2009; Hui et al., 2009; Ma et al., 2009; Sun et al., 2009; He et al., 2011; Ruste et al., 2011; Xu et al., 2011; Chen et al., 2012; Cui et al., 2012; Fountzilas et al., 2012; Huang et al., 2012), two studies didn't satisfied the item of selective reports (Ma et al., 2009; He et al., 2011). There were no studies reporting allocation concealment, binding of participants and personnel, and binding of outcome assessment. There was no other bias found in these 11 studies.

Efficacy (Figure 3)

OS: Four eligible studies (Hui et al., 2009; Ruste et al., 2011; Fountzilas et al., 2012; Huang et al., 2012) had the data of 3 years OS which included 220 patients in the IC+CCRT group and 216 patients in the CCRT+/-AC group. There was no significant difference between the two groups (RR 0.85 95%CI 0.63-1.16). However, significant heterogeneity existed among trials (P = 0.06, I^2 = 59%). According to the results of sensitivity analysis, one trial (Hui et al., 2009) was excluded, there was no significant difference in 3 years OS between the two groups (RR 0.99 95%CI 0.72-1.36, heterogeneity P = 0.49, I^2 = 0.0%).

PFS: Three eligible studies (Hui et al., 2009; Ruste et al., 2011; Fountzilas et al., 2012) had the data of 3 years PFS which included 120 patients in the IC+CCRT group and 116 patients in the CCRT+/-AC group. There was significant difference in favor of the IC+CCRT group (RR 0.69 95%CI 0.48-0.97). However, significant heterogeneity

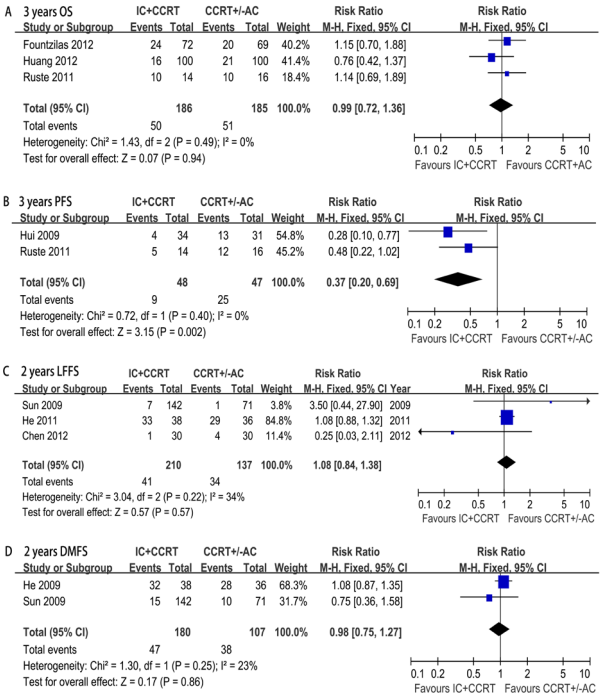

Figure 3. Forest Plot of the Risk Ratio of 3 years OS, 3 Years PFS, 2 Years LFFS, 2 Years DMFS

existed among trials (P = 0.04, I^2 = 70%). According to the results of sensitivity analysis, one trial (Fountzilas et al., 2012) was excluded, There was significant difference in 3 years PFS in favor of the IC+CCRT group (RR 0.37 95%CI 0.20-0.69, heterogeneity P = 0.40, I^2 = 0.0%).

LFFS: Three eligible studies (Sun et al., 2009; He et al., 2011; Chen et al., 2012) had the data of 2 years LFFS which included 210 patients in the IC+CCRT group and 137 patients in the CCRT+/-AC group. There was no significant difference in 2 years LFFS between the two groups (RR 1.08 95%CI 0.84-1.38, heterogeneity P = 0.22, I^2 = 34.0%).

DMFS: Three eligible studies (Sun et al., 2009; He et al., 2011; Chen et al., 2012) had the data of 2 years DMFS which included 210 patients in the IC+CCRT group and 137 patients in the CCRT+/-AC group. There was no significant difference between the two groups (RR 0.84 95%CI 0.65-1.10). However, significant heterogeneity existed among trials (P = 0.02, I^2 = 76%). According to the results of sensitivity analysis, one trial (Chen et al., 2012) was excluded, There was also no significant difference in 2 years DMFS between the two groups (RR 0.98 95%CI 0.75-1.27, heterogeneity P = 0.25, I^2 = 23%).

Toxicity

Grade 3-4 leukopenia: Three eligible studies (He et al., 2009; Chen et al., 2012; Huang et al., 2012) had the data of grade 3-4 leukopenia which included 168 patients in the IC+CCRT group and 166 patients in the CCRT+/-AC group. There was significant difference in favor of the CCRT+/-AC group (RR 2.86 95%CI 1.90-4.31). However, significant heterogeneity existed among trials (P = 0.02, I^2 = 74%). According to the results of sensitivity analysis, one trial (Huang et al., 2012) was excluded, There was also significant difference in grade 3-4 leukopenia in favor of the CCRT+/-AC group (RR 1.90 95%CI 1.24-2.92,

heterogeneity $P = 0.32$, $I^2 = 0.0\%$).

Grade 3-4 thrombocytopenia: Two eligible studies (Chen et al., 2012; Huang et al., 2012) had the data of grade 3-4 thrombocytopenia which included 130 patients in the IC+CCRT group and 130 patients in the CCRT+/-AC group. There was significant difference in favor of the CCRT+/-AC group (RR 3.00 95%CI 1.35-6.67). However, significant heterogeneity existed among trials ($P = 0.09$, $I^2 = 64\%$). Then random effect model was used. There was no significant difference in grade 3-4 thrombocytopenia between the two groups (RR 2.67 95%CI 0.64-11.1, heterogeneity $P = 0.09$, $I^2 = 64\%$).

Grade 3-4 mucous membrane: Four eligible studies (He et al., 2009; Hui et al., 2009; Sun et al., 2009; Huang et al., 2012) had the data of grade 3-4 mucous membrane which included 314 patients in the IC+CCRT group and 238 patients in the CCRT+/-AC group. There was no significant difference in grade 3-4 mucous membrane between the two groups (RR 1.04 95%CI 0.79-1.37, heterogeneity $P = 0.25$, $I^2 = 27\%$).

Grade 3-4 hepatic: Two eligible studies (Hui et al., 2009; Huang et al., 2012) had the data of grade 3-4 hepatic which included 134 patients in the IC+CCRT group and 131 patients in the CCRT+/-AC group. There was no significant difference in grade 3-4 hepatic between the two groups (RR 0.98 95%CI 0.27-3.52, heterogeneity $P = 0.41$, $I^2 = 0.0\%$).

In all, hematologic and gastrointestinal toxicity were the most for patients in both groups, and there were no treatment-related deaths in both groups of 11 studies. In addition to the adverse events above, there were also some other events reported, such as grade 3-4 hearing, grade 3-4 subcutaneous tissue, grade 2-3 neuropathy, grade 3-4 secondary cancer and so on. In Hui et al's trial (Hui et al., 2009), for the group of CCRT alone, one patient was found central nervous system hemorrhage, one patient suffered second cancer in primary site. However, for the IC+ CCRT group, two patients experienced second cancer in primary site, no patients suffered central nervous system hemorrhage.

Quality of evidence

There were 8 outcomes in efficacy and toxicity of this meta-analysis. OS was critical results. PFS, LFFS, DMFS, grade 3-4 leukopenia, grade 3-4 thrombocytopenia, grade 3-4 mucous membrane, and grade 3-4 hepatic were all important results. Based on the GRADE system, the level of evidence in grade 3-4 mucous membrane was moderate, while it was low in 3 years overall survival, 3 years progression-free survival, 2 years loco-regional failure-free survival, 2 years distant metastasis failure-free survival, grade 3-4 leukopenia, and grade 3-4 hepatic. It was very low in grade 3-4 thrombocytopenia.

Discussion

To our knowledge, this article is the first meta-analysis to evaluate the efficacy and toxicity of the therapy of IC followed by CCRT versus CCRT with or without AC for locoregionally advanced nasopharyngeal carcinoma. A total of 1096 patients from 11 studies, with 589 patients in the IC+CCRT group and 507 patients in the CCRT+/-AC group were analyzed.

In theory, induction chemotherapy could reduce burden of tumor, in which way the radiosensitivity was increased. What's more, it might kill subclinical micrometastasis. Therefore, it was expected to improve survival. However, it had been proved that compared with the CCRT+/-AC group, IC followed by CCRT couldn't significantly improve OS, LFFS and DMFS in this study. Perhaps, this might be related with the fact that induction chemotherapy delayed the time of radiotherapy. In 2002, Hareyama et al (Hareyama et al., 2002) reported a randomized Phase III trial comparing neoadjuvant chemotherapy followed by radiotherapy with radiotherapy alone in patients with advanced NPC. With a median follow-up of 49 months, no significant differences were found in 5-year overall survival (60% versus 48%) and 5-year disease free survival (55% versus 43%).

Docetaxel, platinum, and 5-fluorouracil (TPF) were used as the IC regiment in 5 studies (Ma et al., 2009; He et al., 2011; Xu et al., 2011; Chen et al., 2012; Fountzilas et al., 2012) included in this meta-analysis. The combination of platinum and fluorouracil (PF) or the combination of docetaxel and platinum (TP) were used as the IC regiment in other studies. No significant difference in survival was found in most studies included in this meta-analysis. However, in Hui et al's trial (Hui et al., 2009), significant improvement was found in 3-year OS for the IC+CCRT group. The regiment of IC in this study was docetaxel 75 mg/ m2 and cisplatin 75 mg/ m2 every 3 weeks for two cycles. Might the regiment of TP be superior to that of TPF or PF? In 2009, Sun (Sun et al., 2009) reported a phase II study comparing IC followed by CCRT with CCRT alone in patients with advanced NPC. In this study, patients were randomized to three groups: (1) PF every 3 weeks for two cycles, followed by CCRT every 3 weeks for two cycles, (2) TP every 3 weeks for two cycles, followed by CCRT, or (3) CCRT alone. They found there was significant difference in 2-year DMFS in favor the PF+CCRT group when compared with the TP+CCRT group. However, the baseline of these two groups was not comparable in Nodal classification. More patients of stage N3 were classified into the TP+CCRT group, who were easily suffered metastasis. So these results couldn't prove that PF was superior to TP in this study.

In 2012, Yu et al reported a trial involving a total of 95 patients who suffered from NPC (Stage III~IVa). Patients were divided into two groups: concurrent radiochemotherapy (Group CCRT, n=49) and radiotherapy (Group RT, n=46). Significant differences were found in 5-year OS and metastasis-free rates in favor of Group CCRT ($X^2 = 3.96 \sim 8.26$, $P < 0.05$) (Yu et al., 2012). Zhang et al (Zhang et al., 2010) conducted a meta-analysis of CCRT versus RT alone in NPC treatment which included 7 RCTs (totally 1608 patients), 2,3 and 5 years OS were improved significantly in the CCRT alone group (Risk ratio 0.63, 95%CI 0.50-0.80, Risk ratio 0.76, 95%CI 0.61-0.93, and Risk ratio 0.74, 95%CI 0.62-0.89). A greater improvement of treatment results with CCRT might have narrowed any potential gain in overall survival offered by IC.

There were no treatment-related deaths in both groups.

Hematologic and gastrointestinal toxicity were the most significant for patients of the two groups. During the period of chemotherapy and radiotherapy, we should monitor hemogram regularly, so that we could take measures timely when neutropenia or thrombocytopenia occurred. Of course, we should also prevent the nausea, vomiting, and other adverse effects. What's more, we oncologists should take great importance on the follow-up so that late morbidity and events were diagnosed early. In this way, patients might experienced a better quality of life and live for a long time.

There were several limitations in this meta-analysis. Firstly, because individual patient data couldn't be got, publication data and selection bias might occurred. These would affect the level of evidence. Secondly, the quality of trials of this study was not high. No study reported allocation concealment, binding of participants and personnel, and binding of outcome assessment .Two studies didn't reported the follow-up time (Ma et al., 2009; He et al., 2011), and five studies didn't reported adequate reliability determined random sequence generation (Ma et al., 2009; Sun et al., 2009; He et al., 2011; Xu et al., 2011; Cui et al., 2012). Thirdly, not all articles had the available data of OS, PFS, LFFS and DMFS. Finally, the sample size was still small.

In conclusion, our research indicated that compared with the CCRT+/-AC group, IC followed by CCRT could improve PFS but couldn't improve OS, LFFS, DMFS significantly. Grade 3-4 leukopenia occurred more in the IC+CCRT group. Larger and multicenter RCTs are required to assess whether IC followed by CCRT is superior to CCRT with or without AC for locoregionally advanced NPC. Moreover, RCTs comparing different regimens of IC such as TP, PF, and TPF were also needed to be explored in previously untreated NPC.

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We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service or company that could be construed as influencing the position presented in, or the review of the present study.

References

Al-Sarraf M, LeBlanc M, Giri PG, et al (1998). Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol,* **16**, 1310-7.

Chan AT, Teo PM,Johnson PJ (2002). Nasopharyngeal carcinoma. *Ann Oncol*, **13**, 1007-15.

Chan AT, Hui E, Ma B, et al (2005). A randomized phase II study of concurrent cisplatin-radiotherapy (RT) with or without neoadjuvant chemotherapy using docetaxel (Taxotere) and cisplatin in advanced nasopharyngeal carcinoma (NPC). 41st Annual Meeting of the American Society of Clinical Oncology (ASCO), *J Clin Oncol,* Abstract No. 5544.

Chen XJ, Qiu RL, Yang CL, Liu YQ (2012). Study of TPF neoadjuvant chemotherapy followed by concurrent intensity modulated radiochemotherapy in the treatment for 30 cases with locally advanced nasopharyngeal carcinoma. *Chin J Clin Oncol Rehabil*, **19**, 201-4.

Cui JD, Long GN, Zhang Y, et al (2012). Study of TPF neoadjuvant chemotherapy followed by concurrent intensity modulated radiochemotherapy in the treatment for 30 cases with locally advanced nasopharyngeal carcinoma. *Chin Clin Oncol*, **17**, 524-9.

Fong KW, Chua EJ, Chua ET, et al (1996). Patient profile and survival in 270 computer tomography-staged patients with nasopharyngeal cancer treated at the Singapore General Hospital. *Ann Acad Med Singapore*, **25**, 341-6.

Fountzilas G, Ciuleanu E, Kalogera-Fountzila A, et al (2009). Induction chemotherapy (IC) followed by concomitant chemoradiotherapy (CCRT) versus CCRT alone in patients with locally advanced nasopharyngeal carcinoma (LA-NPC) - A randomized phase II study of the Hellenic Cooperative Oncology Group. *Eur J Cancer*, **7**, 471.

Fountzilas G, Ciuleanu E, Bobos M, et al (2012). Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: A randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol*, **23**, 427-35.

Hareyama M, Sakata K, Shirato H, et al (2002). A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. *Cancer*, **94**, 2217-23.

He AJ (2011). Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy in the treatment of locally advanced nasopharyngeal carcinoma. *Hebei Med J*, **33**, 2115-6.

He QD, Yang L, Nie YH,Kang HB (2009). A phase ¢ò study of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma. *Chin Clin Oncol*, **14**, 1011-4.

Heng DM, Wee J, Fong KW, et al (1999). Prognostic factors in 677 patients in Singapore with nondisseminated nasopharyngeal carcinoma. *Cancer*, **86**, 1912-20.

Julian PTH and Sally G (2011). Cochrane handbook for systematic review of interventions version 5.0.1[updated March 2011].The cochrane collaboration 2011,available from www.cochranehandbook.org.

Huang S, Deng G, Huang G, et al (2012). Efficacy of induction chemotherapy combined with concurrent chemoradiotherapy for advanced nasopharyngeal carcinoma. *Chin J Clin Oncol,* **39**, 788-91.

Hui EP, Ma BB, Leung SF, et al (2009). Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*, **27**, 242-9.

Ma HM, Yuan X, Huang YL, Lin YF, Liu CX (2009). Paclitaxel and cisplatin, 5-fluorouracil (TPF) programme neoadjuvant chemotherapy for advanced nasopharyngeal carcinoma. *Mod Oncol*, **17**, 1233-5.

Ruste SA, Dizon DS, Ramirez F, et al (2011). Induction chemotherapy followed by concurrent chemoradiotherapy vs concurrent chemoradiotherapy followed by chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma. *Phil J Intern Med,* **49**, 1-7.

Sun R (2009). Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy with or without adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma [master].

Teo P, Yu P, Lee WY, et al (1996). Significant prognosticators

after primary radiotherapy in 903 nondisseminated nasopharyngeal carcinoma evaluated by computer tomography. *Int J Radiat Oncol Biol Phys*, **36**, 291-304.

Wang XJ, Shou T, Diao XM, et al (2011). Neoadjuvant chemotherapy with vinorelbine followed by concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma. *J Pract Med*, **27**, 4451-3.

Xu MJ, Ye JM, Wu LQ,Wang XC (2011). Study of TPF neoadjuvant chemotherapy followed by concurrent chemoradiotherapy with cisplatin in locally advanced nasopharyngeal carcinoma. *J Pract Oncol*, **26**, 291-4.

Yamazaki T, Ishiki H, Okano S, et al (2011). Impact of induction chemotherapy on local control for locally advanced nasopharyngeal cancer. *Eur J Cancer*, **47**, S569.

Yu H-S, Wang X, Song AQ, et al (2012). Concurrent chemoradiotherapy versus radiotherapy alone for locoregionally advanced nasopharyngeal carcinoma. *Asian Pacific J Cancer Prev*, **13**, 3961-5.

Zeng XT, Leng WD, Li S, Guo Y, Wang P (2011). How to understand and use GRADE system correctly? A brief outline. *Chin J Evid-Based Med*, **11**, 985-90.

Zhang L, Zhao C, Ghimire B, et al (2010). The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials. *BMC Cancer*, **10**, 558.

Zhong WH, Feng HX, Jiang HH, Zhang LP (2011). Clinical observation and nursing of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy with or without adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. *Chin Med Innov*, **20**, 162-4.