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 stage-I 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...
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 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 I² 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>No. of inclusion patients</th>
<th>Inclusion period</th>
<th>Stage</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>IC</th>
<th>CC</th>
<th>AC</th>
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<tr>
<td>He et al., 2009</td>
<td>IC+CCRT</td>
<td>38</td>
<td>2004-4</td>
<td>2.0 Gy/Fx5wk, primary site:66-70Gy, positive nodes: 64-66Gy, the prevention dose for neck:50-55Gy.</td>
<td>Cisplatin 80 mg/m², d1, 5-fluorouracil 800 mg/m², q6wk for 5 cycles.</td>
<td>Cisplatin 40 mg/m², d1, qwk for 6 cycles.</td>
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<tr>
<td>Mu et al., 2008</td>
<td>IC+CCRT</td>
<td>49</td>
<td>2013-5</td>
<td>2.0 Gy/Fx5wk, primary site:56Gy/0.7Gy, the prevention dose for neck:50-55Gy.</td>
<td>Cisplatin 20 mg/m², d1-5, 5-fluorouracil 1000 mg/m², d1-5, qwk for 2 cycles.</td>
<td>Cisplatin 20 mg/m², d1-5, 5-fluorouracil 1000 mg/m², d1-5, qwk for 2 cycles.</td>
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<tr>
<td>Hui et al., 2009</td>
<td>IC+CCRT</td>
<td>34</td>
<td>2012-11</td>
<td>2.0 Gy/Fx5wk, nasopharyngeal-66Gy.</td>
<td>Dacarbazine 75 mg/m² q2wks and cisplatin 5 q3wks for 2 cycles.</td>
<td>Dacarbazine 40 mg/m²/qwk for 8 cycles.</td>
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<tr>
<td>Sun et al., 2009</td>
<td>IC+CCRT</td>
<td>76</td>
<td>2015-5</td>
<td>2.0 Gy/Fx5wk, primary site:50-60Gy, positive nodes: 60-70Gy, pharyngeal extension and residual nodes:50Gy.</td>
<td>IMRT: GTVnx: 66-70.4Gy, GTVnd: Docetaxel 75 mg/m² q2wks for 3 cycles.</td>
<td>Cisplatin 80 mg/m², 5-fluorouracil 1500 mg/m², q3wks for 2 cycles.</td>
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<tr>
<td>He et al., 2009</td>
<td>IC+CCRT</td>
<td>71</td>
<td>2008-9</td>
<td>2.0 Gy/Fx5wk, primary site:50-70Gy.</td>
<td>Cisplatin 20 mg/m², d1-4 and 5-fluorouracil 1000 mg/m², d4-7, q2wks for 3 cycles.</td>
<td>Cisplatin 20 mg/m², d1-4, 5-fluorouracil 1000 mg/m², d4-7, q2wks for 3 cycles.</td>
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<tr>
<td>He et al., 2011</td>
<td>IC+CCRT</td>
<td>14</td>
<td>2005</td>
<td>2.0 Gy/Fx5wk, primary site:70Gy.</td>
<td>Cisplatin 25 mg/m², d1-4 and 5-fluorouracil 1500 mg/m², d1-4, q2wks for 3 cycles.</td>
<td>Cisplatin 20 mg/m², d1-4, 5-fluorouracil 1500 mg/m², d1-4, q2wks for 3 cycles.</td>
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<tr>
<td>Xu et al., 2011</td>
<td>IC+CCRT</td>
<td>25</td>
<td>2008-8</td>
<td>2.0 Gy/Fx5wk, primary site:70Gy.</td>
<td>Dacarbazine 75 mg/m², d1, d3, 5-fluorouracil 2.5 mg/m², q3wks for 2 cycles.</td>
<td>Dacarbazine 40 mg/m², d1, d3, q3wks for 3 cycles.</td>
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<tr>
<td>He et al., 2012</td>
<td>IC+CCRT</td>
<td>50</td>
<td>2008-12</td>
<td>2.0 Gy/Fx5wk, primary site:70Gy.</td>
<td>Cisplatin 25 mg/m², d1-6, 5-fluorouracil 1000 mg/m², q2wks for 3 cycles.</td>
<td>Cisplatin 90 mg/m², d1, q2wks for 3 cycles.</td>
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<td>Fountzilas et al., 2012</td>
<td>IC+CCRT</td>
<td>2</td>
<td>2001-3</td>
<td>2.0 Gy/Fx5wk, primary site:66 GY.</td>
<td>Cisplatin 25 mg/m², q2wks for 3 cycles.</td>
<td>Cisplatin 40 mg/m², q2wks for 3 cycles.</td>
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<tr>
<td>Chen et al., 2012</td>
<td>IC+CCRT</td>
<td>30</td>
<td>2009-1</td>
<td>2.0 Gy/Fx5wk, primary site:70Gy.</td>
<td>5-fluorouracil 1000 mg/m², d1-4, q2wks for 2 cycles.</td>
<td>5-fluorouracil 1000 mg/m², d1-4, q2wks for 2 cycles.</td>
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<tr>
<td>Cai et al., 2012</td>
<td>IC+CCRT</td>
<td>35</td>
<td>2008</td>
<td>2.0 Gy/Fx5wk, primary site:70Gy.</td>
<td>Cisplatin 25 mg/m², d1-6, 5-fluorouracil 1000 mg/m², q3wks for 2 cycles.</td>
<td>The experimental group: Cisplatin 80 mg/m², q2wks for 8 cycles.</td>
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<td>Huang et al., 2012</td>
<td>IC+CCRT</td>
<td>100</td>
<td>2003-9</td>
<td>2.0 Gy/Fx5wk, primary site:66-70Gy, positive nodes: 60-70Gy, the prevention dose for neck:50-54Gy.</td>
<td>Cisplatin 80 mg/m², d1, q3wks for 3 cycles.</td>
<td>Cisplatin 40 mg/m², d1-5, q2wks for 7 cycles.</td>
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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, concomitant 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, Wanshang 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 were 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 replication, 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 regimen, patient number, inclusion period, AJCC (American Joint Committee on Cancer) performance status, UICC (Union for International Cancer Control) performance status, Chinese stage performance status, and Chinese stage performance status, and Chinese stage performance status.

Risk of bias of eligible studies (Figure 2)

Of eleven studies, six studies reported adequate reliability determined random sequence generation (He 2013). DOI:http://dx.doi.org/10.7314/APJCP.2013.14.1.515

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, I² = 59%). 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, I² = 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, I² = 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, I² = 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, I² = 23%).

Toxicity

Grade 3-4 leucopenia: Three eligible studies (He et al., 2009; Chen et al., 2012; Huang et al., 2012) had the data of grade 3-4 leucopenia 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, I² = 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 leucopenia in favor of the CCRT+/-AC group (RR 1.90 95%CI 1.24-2.92,
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 heterogeneity 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, I² = 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, I² = 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, I² = 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, I² = 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 (X²=3.96~8.26, 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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Induction Chemotherapy with or without Concurrent Chemoradiotherapy for NPC


