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- 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) and, since 1998 this regimen had become the standard therapy for advanced nasopharyngeal carcinoma.

However, in this standard treatment, whether AC was essential for advanced nasopharyngeal carcinoma had not been established. Now several randomized controlled trials (RCTs) compared the therapy of CCRT followed by AC with CCRT alone (Kwong et al., 2004; Xu et al., 2008; Ding et al., 2011; Chen 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 CCRT followed by AC with CCRT alone.
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 July 2012. The text search term was: (((nasopharyngeal carcinoma) OR (nasopharyngeal cancer) OR (nasopharyngeal neoplasms)) AND (chemotherapy OR cisplatinum OR carboplatin OR nedaplatin) 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 neoplasms) AND (chemotherapy) 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 CCRT followed by AC versus CCRT alone. (3) RCTs. Reports were excluded by the following criteria: (1) Incompletion of important information. (2) Less rigorous of studies, such as errors in data. (3) Literature published repeatedly. (4) 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) (Jpt 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. Reviews 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 regimen, patient number, inclusion period, World Health Organization (WHO) status, AJCC (American Joint Committee on Cancer) performance status, and Chinese stage (2008) performance status. The outcomes were overall survival (OS), failure-free survival (FFS), 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, FFS, LFFS and DMFS 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 CCRT followed by AC group versus the CCRT alone 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 I² ≥ 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 performed by excluding the trials which potentially 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 5 studies involving 7 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 2186 citations were searched. After adjusting for duplicates 1151 remained. Of these, 1139 studies were discarded because after reviewing the titles and the abstracts it appeared that these papers clearly didn’t meet the criteria. Of the last 12 articles, three articles were discarded.

Table 1. Inclusion Criteria of Eligible Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>No. of patients</th>
<th>Inclusion period</th>
<th>Histology (WHO grade No.)</th>
<th>Stage</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwong et al, 2004</td>
<td>CCRT+AC</td>
<td>57</td>
<td>1995.5-2001.10</td>
<td>I 7 II 45 III 50</td>
<td>The 5th ACC stage III-IV</td>
<td>2.5GyFx5Fwk/primary site-68Gy, nodes-66Gy, +10Gy boost dose was given for pharyngeal extension and residual nodes</td>
<td>CCRT:200mg tid on days 1-7</td>
<td>UFT:200mg tid on days 1-7</td>
</tr>
<tr>
<td>Xue, 2008</td>
<td>CCRT+AC</td>
<td>30</td>
<td>2007.3-2007.11</td>
<td>I 7 II 45 III 50</td>
<td>The 6th ACC stage III-IVb</td>
<td>2.5GyFx5Fwk/primary site-68Gy, nodes-66Gy, +10Gy boost dose was given for pharyngeal extension and residual nodes</td>
<td>CCRT:200mg tid on days 1-7</td>
<td>UFT:200mg tid on days 1-7</td>
</tr>
<tr>
<td>Ding et al, 2011</td>
<td>CCRT+AC</td>
<td>28</td>
<td>2006.1-2009.12</td>
<td>I 7 II 45 III 50</td>
<td>The 5th ACC stage III-IVb</td>
<td>70GyFx(2GyFx5Fwk)</td>
<td>CCRT:200mg tid on days 1-7</td>
<td>UFT:200mg tid on days 1-7</td>
</tr>
<tr>
<td>Huang et al, 2012</td>
<td>CCRT+AC</td>
<td>28</td>
<td>2008.5-2010.5</td>
<td>I 7 II 45 III 50</td>
<td>Chinese stage (2008) II-IV</td>
<td>2.5GyFx5Fwk +5-Fu(800mg/m2/day)</td>
<td>CCRT:200mg tid on days 1-7</td>
<td>UFT:200mg tid on days 1-7</td>
</tr>
<tr>
<td>Chen et al, 2012</td>
<td>CCRT+AC</td>
<td>28</td>
<td>2011.5</td>
<td>I 7 II 45 III 50</td>
<td>The 6th ACC stage III-IVb</td>
<td>2.2-2.7GyFx5Fwk, primary site-66Gy or greater, the involved neck area-60-66Gy, all potential sites-50Gy or greater.</td>
<td>CCRT:200mg tid on days 1-7</td>
<td>UFT:200mg tid on days 1-7</td>
</tr>
</tbody>
</table>

CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; 3DRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; C, cisplatin; 5-Fu, 5-fluorouracil; UFT, uracil and tegafur in 4:1 molar ratio; VBM, vincristine 2mg, bleomycin 30mg, methotrexate 150mg/m2; WHO, world health organization; AJCC, American Joint Committee on Cancer

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

Figure 2. Risk of Bias Graph: Review Authors’ Judgements about Each Risk of Bias Item Presented as Percentages Across all Included Studies

(Kwong et al., 2006; Kwong et al., 2008). At last, a total of 793 patients of 5 clinical studies were available for analysis, with 394 patients in the CCRT group and 399 patients in the CCRT alone 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, World Health Organization (WHO) status, AJCC (American Joint Committee on Cancer) performance status, and Chinese stage (2008) performance status administered in the studies.

Risk of bias for studies (Figure 2 and Figure 3)

Of 5 studies, all satisfied the criteria of complete outcome data, while three RCTs didn’t correspond with the item of selective reports. Only one (Chen et al., 2012) reported adequate reliability determined random sequence generation, allocation concealment, binding of participants and personnel, and binding of outcome assessment. There was no other bias found in these 5 studies.
Efficacy (Figure 4)

OS: Two eligible studies (Kwong et al., 2004, Chen et al., 2012) had the data of three years OS which included 308 patients in the group of CCRT followed by AC and 310 patients in the group of CCRT alone. There was no significant difference in 3 years OS in favor of the group of CCRT plus AC (RR 1.02 95% CI 0.89-1.15, heterogeneity P = 0.41, I² = 0.0%).

FFS: Two eligible studies (Kwong et al., 2006; Chen et al., 2012) had the data of five years FFS which included 308 patients in the group of CCRT followed by AC and 310 patients in the group of CCRT alone. There was no significant difference in 5 years FFS in favor of the group of CCRT plus AC (RR 0.93 95% CI 0.72-1.21, heterogeneity P = 0.60, I² = 0.0%).

LFFS: Two eligible studies (Kwong et al., 2006; Chen et al., 2012) had the data of two years LFFS which included 308 patients in the group of CCRT followed by AC and 310 patients in the group of CCRT alone. There was no significant difference in 5 years LFFS in favor of the group of CCRT plus AC (RR 1.07 95% CI 0.87-1.32, heterogeneity P = 0.96, I² = 0.0%).

DMFS: Two eligible studies (Kwong et al., 2006; Chen et al., 2012) had the data of two years DMFS which included 308 patients in the group of CCRT followed by AC and 310 patients in the group of CCRT alone. There was no significant difference in 5 years DMFS in favor of the group of CCRT plus AC (RR 0.95 95% CI 0.80-1.13, heterogeneity P = 0.58, I² = 0.0%).

Toxicity: There were no treatment-related deaths in both groups of five studies. Hematologic and gastrointestinal toxicity were the most significant for patients during AC. Chen et al. (2012) reported that during AC, grade 3-4 toxic effects occurred in 87(42%) of 205 patients. The most commonly recorded grade 3-4 non-haematological adverse events were stomatitis, nausea, and vomiting. Grade 3-4 leucopenia or neutropenia was recorded in 35 patients, with the next most common events
being thrombocytopenia and anaemia. Kwong et al. (2004) observed some increased late toxicity probably associated with AC, such as moderate to severe soft tissue fibrosis with neck stiffness and limitation in neck movement. In addition to hematologic and gastrointestinal toxicity, Xu et al. (2008) found that weight loss, hearing loss, phlebitis, and alopecia of the outside of radiation field were also more significant for the group of CCRT followed by AC.

Quality of evidence: There were 4 outcomes in efficacy of this meta-analysis. OS was critical results; FFS, LFFS and DMFS were all important results. The quality of the evidence of every result was low (Table 2).

Discussion

To our knowledge, this article is the first meta-analysis to evaluate the efficacy and toxicity of the therapy of CCRT followed by AC versus CCRT alone for locoregionally advanced nasopharyngeal carcinoma. A total of 793 patients from 5 studies, with 394 patients in the group of CCRT followed by AC and 399 patients in the group of CCRT alone were analyzed.

In this meta-analysis, there were no significant differences in three years OS, five years FFS, five years LFFS, and five years DMFS between two groups. There were no treatment-related deaths in both groups. Hematologic and gastrointestinal toxicity were the most significant for patients during AC. Based on the GRADE system, the level of evidence was low.

In theory, it was expected to improve survival by reducing recurrence and distant metastasis. However, it had been proved that compared with CCRT alone, CCRT followed by AC couldn’t significantly improve LFFS and DMFS in this study. In 2002, Chi et al. (2002) reported a randomized Phase III trial comparing radiotherapy (RT) followed by adjuvant chemotherapy to RT alone in patients with advanced NPC. In this trial, 157 patients with Stage IV, M0 (UICC/AJCC, 1992) advanced NPC disease were randomized to receive standard radiotherapy, with or without 9 weekly cycles of 24-h infusional chemotherapy (20 mg/m^2 cisplatin, 2,200 mg/m^2 (2) 5-fluorouracil, and 120 mg/m^2 (2) leucovorin) after RT. With a median follow-up of 49.5 months, the 5-year overall survival and relapse-free survival rates were 60.5% vs. 54.5% (p = 0.5) and 49.5% vs. 54.4% (p = 0.38) for the two groups, respectively. They concluded that adjuvant chemotherapy after RT for patients with advanced NPC has no benefit for overall survival or relapse-free survival. Similar conclusion was got in another trial (Rossi et al., 1988).

Cisplatin and fluorouracil were mostly used as the AC regimen in studies included in this meta-analysis. Platinum-based combinations with new agents, including gemcitabine and paclitaxel, showed promising efficacy against metastatic NPC (Ma et al., 2005). Capecitabine combined with cisplatin were also active in first line as shown in a phase II study, which gave an overall response rate of 62.5% (95% CI, 49.1–76.4%) with manageable toxicity (Li et al., 2008). However, these studies mainly focused on the recurrent or metastatic disease. Perhaps new agents with more effective antineoplastic activities and less toxicity profile need to be explored in previously untreated NPC.

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=3.96–8.26, P<0.05) (Yu et al., 2012). Thephamongkhhol et al. (2004) conducted a meta-analysis of CCRT versus RT alone in NPC treatment which included 101 RCTs, 3-year OS and 5-year OS were improved significantly in the CCRT alone group (Odds Ratio 0.37, 95%CI 0.46–0.72 and Odds Ratio 0.68, 95%CI 0.46–0.99). Another meta-analysis also confirmed similar conclusion (Zhang et al., 2010). A greater improvement of treatment results with CCRT alone might have narrowed any potential gain in overall survival offered by AC.

For the toxicity during AC, we should monitor hemogram, so that we could take measures timely when neutropenia occurred. Of course, we should also prevent the nausea, vomiting, and other adverse effects.

There were several limitations in this meta-analysis. Firstly, because individual patient data couldn’t be got, publication data and selection bias might occurred, which would affect the level of evidence. Secondly, the quality of trials of this study was not high. Only one study reported adequate reliability determined random sequence generation, allocation concealment, binding of participants and personnel, and binding of outcome assessment (Chen et al., 2012). Thirdly, not all articles had the available data of OS, FFS, LFFS and DMFS. Finally, the sample size was still small.

In conclusion, our research indicated that compared with CCRT alone, CCRT in combination with AC couldn’t significantly improve prognosis. More toxicities were found during AC. Larger and multicenter RCTs are required to assess whether CCRT followed by AC is superior to CCRT alone for locoregionally advanced NPC. Moreover, trials about new chemotherapy agents need to be explored in previously untreated NPC, so that new chemotherapy regimens with more effective antineoplastic activities and less toxicity can be used for untreated NPC.

References


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