RESEARCH ARTICLE

Comparison of Concurrent Chemoradiotherapy Followed by Adjuvant Chemotherapy Versus Concurrent Chemoradiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma: a Meta-analysis of 793 Patients from 5 Randomized Controlled Trials

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Abstract

Purpose: The main objective of the present study was to evaluate the efficacy and toxicity of concurrent chemoradiotherapy followed by adjuvant chemotherapy compared with concurrent chemoradiotherapy alone in the treatment of 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. Randomized controlled trials (RCTs) that compared concurrent chemoradiotherapy followed by adjuvant chemotherapy with concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma were included. Meta-analysis was 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: Five studies were included. Risk ratios of 1.02 (95%CI 0.89-1.15), 0.93 (95%CI 0.72-1.21), 1.07 (95%CI 0.87-1.32), 0.95 (95%CI 0.80-1.13) were observed for 3 years overall survival, 5 years failure-free survival, 5 years loco-regional failure-free survival and 5 years distant metastasis failure-free survival. There were no treatment-related deaths in both groups of five studies. Hematologic and gastrointestinal toxicity were the most significant for patients during adjuvant chemotherapy. The level of evidence was low. Conclusion: Compared with concurrent chemoradiotherapy alone, concurrent chemotherapy followed by adjuvant chemotherapy did not improve prognosis. More toxicity was found during adjuvant chemotherapy.

Keywords: Nasopharyngeal carcinoma - 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% pres¬ent 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) 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.

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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. 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, 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 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 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

Study	Group	No. of patients	Inclusion period	Histology (WHO grade No.) I	II	III	Stage	Radiotherapy	Chemotherapy Concurrent	Adjuvant
Kwong et al, 2004	CCRT+AC CCRT	57 53	1995.5-2001.10	0 1	7 7	50 45	The 5th AJCC stage II-IV	2.5Gy/F×5F/wk,primary site-68Gy,Nodes-66Gy,+ 10Gy boost dose was given for pharyngeal extension and residual nodes	UFT(200mg tid on days 1-7)	C(100mg/m2 /d d1) +5-Fu(1000mg/m2 /day on days 1-3) +VBM(on day 1), q3wk for 6cycle
Xu, 2008	CCRT+AC CCRT	30 28	2007.3-2007.11		30 28		The 6th AJCC stage III-IVb	conventional radiotherapy: 70-76Gy(2Gy/F,5F/wk) IMRT:GTVnx:70.4Gy, GTVnd:60.4Gy,CTV1:60Gy, CTV2:54Gy.	C(40mg/m2/d d1 qwk×7)	C(80mg/m2 /day d1) +5-Fu(800mg/m2 /day on days 1-5), q4wk for 3 cycle
Ding et al, 2011	CCRT+AC CCRT	28 28	2006.1-2009.12		28 28		The 5th AJCC stage III-IVb	70Gy(2Gy/F,5F/wk)	C(40mg/m2/d d1 qwk×7)	C(80mg/m2 /day d1) +5-Fu(800mg/m2 /day on days 1-5), q4wk for 3 cycle
Huang et al, 2012	CCRT+AC CCRT	28 33	2008.5-2010.5	24 30	4 3		Chinese stage (2008) II-IV	conventional radiotherapy or 3DRT:2.5Gy/Fx5F/wk, primary site-70-76Gy, positive nodes-66-70Gy, negative nodes-50Gy IMRT:GTVnx:70Gy/30f, GTVnd:66-70Gy/30f, CTV1:60Gy/30f,CTV2:54Gy/30f	C(30mg/m2/d d1 qwk×6-7)	C(80mg/m2 /day d1) +5-Fu(800mg/m2 /day on days 1-5), q4wk for 3 cycle
Chen et al, 2012	CCRT+AC CCRT	251 257	2006.6-2010.3		508		The 6th AJCC stage III-IVb	2-2.27Gy/Fx5F/wk, primary site-66Gy or greater, the involved neck area-60-66Gy,all potential sites-50Gy or greater.	C(40mg/m2 /day qwk×7)	C(80mg/m2 /day d1) +5-Fu(800mg/m2 /day on days 1-5), q4wk for 3 cycle

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/m^2; WHO, world health organization; AJCC, American Joint Committee on Cancer

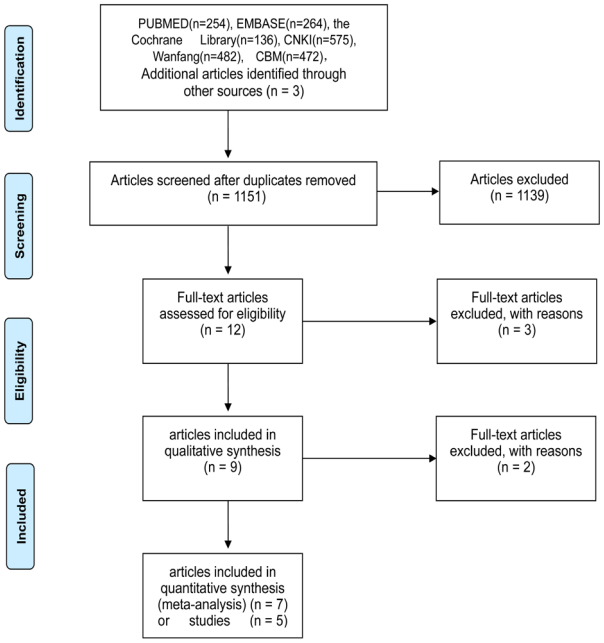

Figure 1. Process of Identification and Selection of Relevant Articles in This Meta-analysis

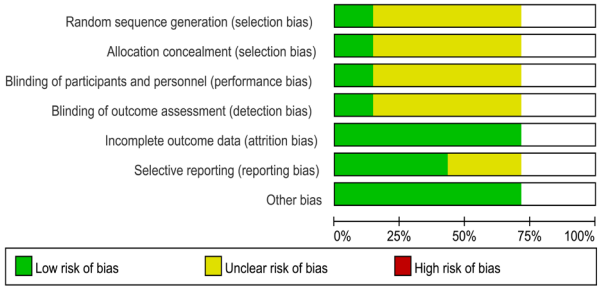

Figure 2. Risk of Bias Graph: Review Authors' Judgements about Each Risk of Bias Item Presented as Percentages Across all Included Studies

because one was not randomized controlled trial (Xu et al., 2011), one lacked essential data (Wen et al., 2007), one had obvious errors in data (Chen et al., 2010). Then, Of the last 9 articles, three trials were from the same research centers (Liang et al., 2008; Chen et al., 2009; Chen et al., 2012) and in order to avoid data reduplication, we only included the latest one (Chen et al., 2012). The other three trials (Kwong et al., 2004; Kwong et al., 2006; Kwong et al., 2008) were from the same study but were reported in different follow-ups by the University of Hong Kong and Queen Mary Hospital of Hong Kong. And one was published with full text (Kwong et al., 2004), while the other two were published with abstracts of conferences (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 followed by AC 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 regiment, 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 of eligible 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.

Table 2. Quality Measures of of the Randomized Controlled Trials

Quality assessment							Summary of findings				Importance
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other conside-rations	CCRT+AC	CCRT	Relative (95% CI)	Absolute	Quality
Three year OS (follow-up median 37.4 months)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	183/308 (59.4%)	180/310 (58.1%) 0%	RR 1.02 (0.89 to 1.15)	12 more per 1000[a] 0 more per 1000[b]	ÅÅOO LOW	CRITICAL
Five year FFS (follow-up median 51.4 months)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/308 (12.7%)	39/310 (12.6%) 0%	RR 0.93 (0.72 to 1.21)	9 fewer per 1000[c] 0 fewer per 1000[b]	ÅÅOO LOW	IMPORTANT
Five year LFFS (follow-up median 51.4 months)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/308 (15.6%)	42/310 (13.5%) 0%	RR 1.07 (0.87 to 1.32)	9 more per 1000[d] 0 more per 1000[b]	ÅÅOO LOW	IMPORTANT
Five year DMFS (follow-up median 51.4 months)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/308 (15.6%)	47/310 (15.2%) 0%	RR 0.95 (0.8 to 1.13)	8 fewer per 1000[e] 0 fewer per 1000[b]	ÅÅOO LOW	IMPORTANT

[1]Only one study introduced adequate sequence generation, Allocation concealment, binding of participants and personnel, binding of outcome assessment; [2]sample size is so small; [a]from 64 fewer to 87 more; [b]from 0 fewer to 0 more; [c]from 35 fewer to 26 more; [d]from 18 fewer to 43 more; [e]from 30 fewer to 20 more

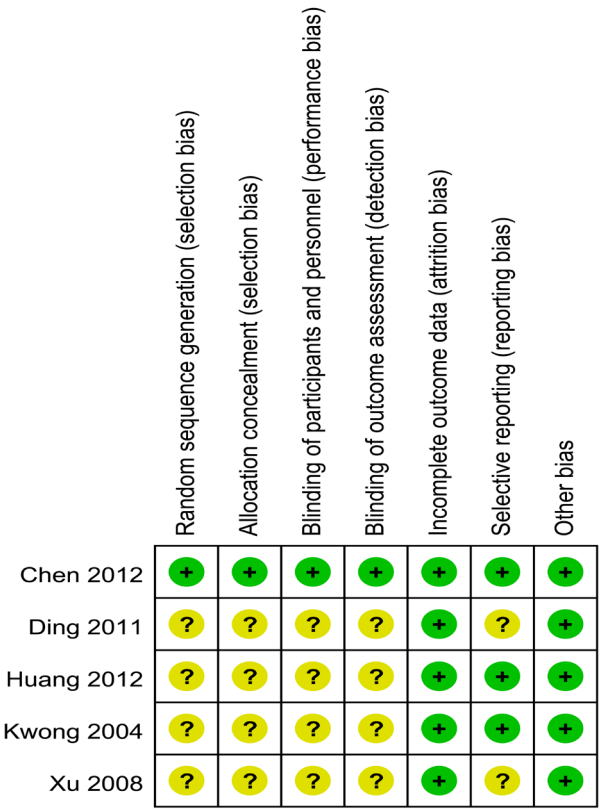

Figure 3. Risk of Bias Summary: Review Authors' Judgements About Each Risk of Bias Item for Each Included Study

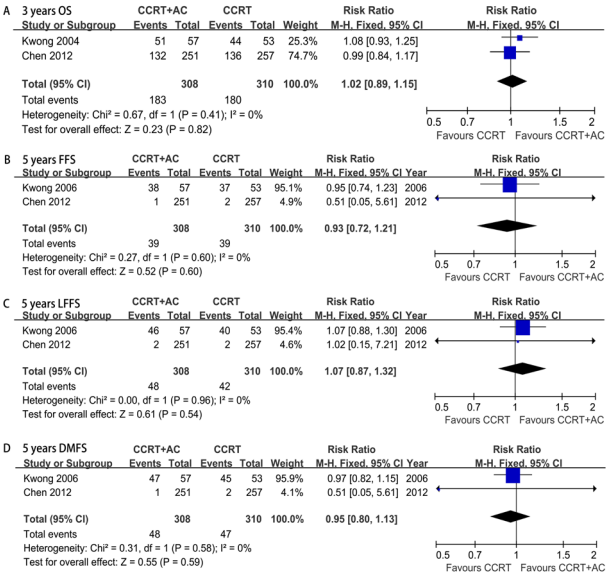

Figure 4. Forest Plot of the Risk Ratio of 3 Years OS, 5 Years FFS, 5 Years LFFS, 5 Years DMFS

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, I^2 = 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, I^2 = 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, I^2 = 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, I^2 = 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 (17%) of 205 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, M(0) (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) 5-fluorouracil, and 120 mg/m(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 regiment 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). Thephamongkhol 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 0.57, 95%CI 0.46-0.72 and Odds Ratio 0.68, 95%CI 0.46-0.99). Another meta-analysis also conformed 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

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.

Chen L, Hu CS, Chen XZ, et al (2012). Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*, **13**, 163-71.

Chen L (2009). Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china, **71**, 1356-64.

Chen Y, Liang ZB, Wang SY, et al (2010). A clinical study of acute toxicities of concurrent chemoradiotherapy plus adjuvant chemotherapy in patients with locoregionally advanced carcinoma. *Chin Pract Med*, **5**, 29-31.

Chi KH, Chang YC, Guo WY, et al (2002). A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys*, **52**, 1238-44.

Ding ZL (2011). Clinical analyses about the adverse reaction in the trial of combination with concurrent chemoradiotherapy and adjuvant chemotherapy for local regionally advanced nasopharyngeal carcinoma. *Clin Med*, **31**, 82-3.

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.

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

Huang HC, Xu HY, Wu SX (2012). Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *Jilin Med J*, **33**, 2037-40.

Jpt H, S G (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The cochrane collaboration, available from www.cochranehandbook.org.

Kwong DL, Sham JS, Au GK, et al (2004). Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol*, **22**, 2643-53.

Kwong DL, Sham JS, Au GK (2006). Five-year update on a randomized factorial study on concurrent and adjuvant chemotherapy for advanced nasopharyngeal carcinoma. *Int J Radiat Oncol*, **66**, S15-6.

Kwong DL, Sham JS, Au GK, et al (2008). Long-term results of concurrent and adjuvant chemotherapy for advanced nasopharyngeal carcinoma. *J Clin Oncol*, **26**, 6056.

Liang SB (2008). A multicenter prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy to concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma [master].

Li YH, Wang FH, Jiang WQ, et al (2008). Phase II study of capecitabine and cisplatin combination as first-line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma. *Cancer Chemoth Pharm*, **62**, 539-44.

Ma BB, Chan AT (2005). Recent perspectives in the role of chemotherapy in the management of advanced nasopharyngeal carcinoma. *Cancer*, **103**, 22-31.

Rossi A, Molinari R, Boracchi P, et al (1988). Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol*, **6**, 1401-10.

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.

Thephamongkhol K, Browman G, Wang R, et al (2004). Chemo-radiotherapy versus radiotherapy alone for nasopharyngeal carcinoma: A meta-analysis of 78 randomized controlled trials (RCTs) from English and non-English databases. *Proc Am Soc Clin Oncol*, **23**, 491.

Wen H, Lang JY, Li ZL (2007). A Prospective study on concurrent conventional Chemoradiotherapy Plus Adjuvant Chemotherapy in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma. *Sixth Acad Confer Nat Rad Oncol*, **80**.

Xu TT (2008). Prospective randomized clinical trial of combination with concurrent chemoradiotherapy and adjuvant chemotherapy for local regionally advanced nasopharyngeal carcinoma [master].

Xu TT, Hu CS, Wang XS, et al (2011). Comparing treatment outcomes of different chemotherapy sequences during radio-chemotherapy for stage N3 nasopharyngeal carcinoma. *Chin J Radiat Oncol*, **20**, 181-5.

Yu HS, Wang X, Song AQ, et al (2012). Concurrent Chemoradiotherapy Versus Radiotherapy Alone for Locoregionally Advanced Nasopharyngeal Carcinoma. *Asian Pac J Cancer Prev,* **13**, 3961-5.

Zeng XT, Leng W, Li S, et al (2011). How to Understand and Use GRADE System Correctly? A Briefly 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.