

ORIGINAL ARTICLE

The efficacy of traditional Chinese Medicine as an adjunctive therapy in nasopharyngeal carcinoma: A systematic review and meta-analysis

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Summary

Purpose: The purpose of this systematic review was to assess the efficacy of traditional Chinese Medicine (TCM) as an adjunctive therapy to radiotherapy (RT) and/or chemotherapy (CT) for patients with nasopharyngeal carcinoma (NPC).

Methods: Randomized controlled trials (RCTs) with TCM to treat NPC were extensively searched in eight databases. Two researchers independently assessed the quality and validity of the included trials and extracted outcome data. Thirteen RCTs were included for analysis.

Results: Compared to using RT and/or CT, TCM combined with conventional cancer therapy had significantly improved Karnofsky performance status (KPS) [odds ratio (OR) 4.81, 95% confidence interval (CI) 3.06-7.56]. TCM as

an adjunctive therapy significantly reduced the serious adverse effects of RT to the oral mucosa and skin so that grade I+II prevailed [OR 2.19, 95% CI 1.31-3.66; OR 8.63, 95% CI 3.28-22.70, respectively]. The combined therapy significantly enhanced immunoregulation, improving the levels of CD3, CD4 T cells (OR 10.08, 95% CI 1.38-18.78; OR 7.08, 95% CI 2.41-11.74, respectively).

Conclusions: This systematic review suggests that TCM as a therapy adjunctive to RT and/or CT vs only RT and/or CT has significant efficacy in terms of improvement of quality of life (QoL), alleviation of acute adverse effects, and enhancement of immunoregulation.

Key words: adjunctive therapy, meta-analysis, nasopharyngeal carcinoma, systematic review, traditional Chinese medicine

Introduction

NPC is a disease with distinct ethnic and geographic distribution. This tumor is relatively rare in the Western world, but represents a significant disease burden in Southern China and Southeast Asia, with an annual incidence rate of about 20 per 100,000 people in endemic areas [1,2]. Globally, NPC accounts for 80,000 new cases and 50,000 deaths annually [2]. Megavoltage RT is the primary treatment modality. Recent data demonstrated that 15–19% of all NPC patients fail with distant metastases, while current results using intensity-modulated radiotherapy (IMRT) rarely yield any local or regional lymph node recurrences [3-5]. These results clearly indicate that NPC is no

longer a problematic disease from a locoregional control standpoint and research priorities should lie in the development of innovative strategies in order to prevent distant dissemination, prolonging remission in patients with metastatic disease and minimizing treatment toxicities. A key area for improvement in the management of the locoregional setting of NPC is to maintain excellent disease control while incorporating novel therapeutic strategies that can potentially minimize toxicity. Thus, there is an increasing awareness to maximize tumor control, prolong overall survival, minimize side-effects and improve QoL.

In complementary and alternative medicine (CAM), TCM has become increasingly popular for patients with NPC. Data from the 2002 National

Health Interview Survey (N=31,044) found that 62% of US adults reported using at least one type of CAM in a year [6]. The types of CAM used by patients with cancer vary among countries. In US and Europe, the most commonly used CAMs tend to be naturopathy and homeopathy [7,8], whereas in patients with Chinese background, TCM is popular among cancer patients [9]. According to World Health Organization (WHO) report in 2001, TCM accounted for 30-50% of the total medical consumption in mainland China and up to 60% of Hong Kong population with severe acute respiratory syndromes, either for treatment of disease or maintenance of health [10]. In the past 50 years, TCM combined with the conventional therapy has been used to alleviate clinical symptoms, prolong survival, and minimize the adverse effects in Asia [11].

Previous clinical studies have suggested that TCM could have potential roles in three main aspects. Firstly, it can improve the patients' immune function [12] and prevent recurrence and metastasis; secondly, it may prevent or reduce toxicity of anticancer agents [13]; and thirdly, it can improve QoL [14]. However, albeit a number of studies being published in Chinese, the evidence on the efficacy of TCM as adjunctive therapy to conventional therapy is not well demonstrated in the Western world. Thus, the aim of this study was to carry out a comprehensive systematic review about the efficacy of TCM as an adjunctive therapy for NPC over QoL, adverse effects, and immune function.

Methods

In the present study, we examined whether the combined use of TCM with RT and/or CT could increase immediate tumor response, reduce the risk of RT-related adverse effects, and improve the therapeutic efficacy of RT and CT administered as adjunctive treatment compared with conventional cancer therapy for NPC patients. Databases, conference papers, and theses were searched by using both electronic and manual methods.

Search strategy

The terms retrieved in databases were as follows: nasopharyngeal carcinoma or nasopharyngeal cancer or NPC; and Chinese medicine or traditional Chinese medicine or Chinese herbal medicine or Chinese herbal drug or traditional herbal medicine or herbal medicine. The terms in Chinese adopted from the above terms were retrieved from Chinese databases.

Databases

The databases in English language included EM-

BASE (1974 to May 2013), MEDLINE (1946 to May 2013), AMED (from 1985 to May 2013), EBM Reviews included in Cochrane Database of Systematic Reviews (2005 to May 2013), ACP Journal Club (1991 to May 2013), Health Technology Assessment (May 2013), and NHS Economic Evaluation Database (September 2012). The databases in Chinese included CNKI (China Knowledge Resource Integrated Database, China Academic Journals, Conference Proceedings and Theses; 1979 to May 2013). Retrieved studies were independently reviewed by two reviewers. Only studies satisfying the selection criteria were included. Discrepancies were resolved by discussion with a third reviewer.

Inclusion criteria

Studies complying with the following criteria were included: i) Participants: NPC patients undergoing RT and/or CT, with cytologically or pathologically confirmed NPC; ii) Type of studies: only randomized controlled trials were eligible; iii) Type of intervention: studies comparing RT and/or CT combined with or without TCM. For studies using other agents as third arm, only the two arms using TCM and/or conventional cancer therapy were included for analysis; iv) Type of outcome measurements: reduction in adverse effects of RT was the main outcome measurement; other outcome measurement included tumor response, improvement in clinical symptoms and immunoregulation.

Exclusion criteria

Clinical trials were excluded if they did not meet the above mentioned criteria. In addition, studies with the followings were also excluded: i) TCM was used in both the intervention group and control group; ii) Non-original research (e.g. review article, letter to the editor); iii) Duplicated publications.

Outcome measures

Outcomes that were thought to be the most clinically valuable in assessing the efficacy of TCM for NPC patients receiving RT and/or CT included:

- Determination of the efficacy of TCM on the number of patients with improved or stable KPS (100 refers to a normal patient with no complaints, 70 refers to a patient unable to carry on normal activity, 50 refers to a patient who requires considerable assistance, 40 refers to a disabled patient and 30 refers to a hospitalization-recommended patient).
- Assessment of the efficacy of TCM on relieving the adverse effects of RT by grading its acute and subacute toxic effects [15], including acute radiation reaction of the skin and acute oropharyngeal mucositis.
- Assessment of the efficacy of TCM on the immunostimulatory activity, i.e. the mean values of CD3 and CD4.

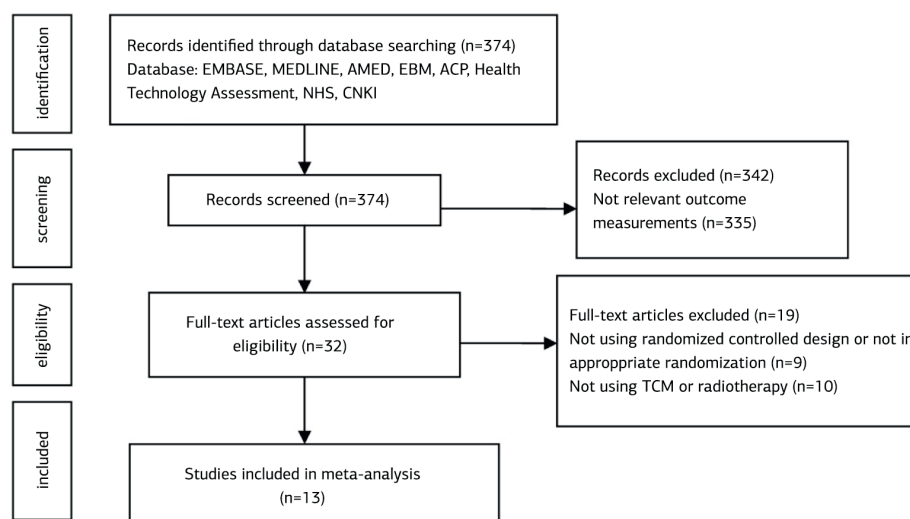


Figure 1. Flow diagram of study selection. TCM: traditional Chinese Medicine.

Quality assessment

Methodological quality of RCTs was assessed using the 5-point Jadad scale [16]: i) description of randomization; ii) adequate and appropriate randomization method; iii) description of single- or double-blindness; iv) assessors blinded to treatment conditions; and v) description of withdrawals and dropouts. In addition, allocation concealment, mask assessment of outcomes, intent-to-treat analysis and dropouts were also taken into the assessment.

The quality of each article was also assessed by the Cochrane format [17], using a grading scheme for each of four main aspects, each classified into three grades (A,B and C): i) quality of randomization; ii) quality of allocation concealment; iii) quality of blinding; and iv) quality of the description of withdrawals and dropouts. The grades were assigned as follows: (A) adequate, with correct procedures; (B) unclear, without a description of methods; and (C) inadequate procedures, methods, or information. Based on these four criteria, the studies could be divided into three groups: group A had low risk of bias for studies with A grades for all items; group B had moderate risk of bias for studies with one or more B grades; or group C with high risk of bias for studies with one or more C grades.

Data analyses

All analyses were performed with RevMan (version 5) to quantify and compare the efficacy outcomes of the treatment group vs the control group. Dichotomous data were reported as odds ratio (OR) whereas continuous data were reported as mean difference (MD)±standard deviation (SD). The random-effects model was employed using the DerSimonian and Laird methods to calculate 95% confidence interval (CI) resulting in wider interval and also to give more importance to trials with smaller sample size [18]. Study of

heterogeneity was assessed using the χ^2 test; significant difference for heterogeneity was considered when $p < 0.01$. The Z-test was used to compare the overall effects of the treatment groups and the control groups, and differences were considered to be statistically significant when $p < 0.05$.

Results

Overall, 374 studies were retrieved in this review. There were 335 studies not investigating outcome of interest (such as only investigating TCM syndrome scales) and 7 studies were literature reviews, so only 32 studies satisfied the selection criteria, among which 9 studies were not RCTs and 10 studies did not use TCM combined with RT as interventions. Thus, finally 13 RCTs were included in this meta-analysis [12-14,19-28] (Figure 1).

Studies retrieved for meta-analysis

With electronic search, 13 studies were retrieved, based on the selection criteria. In the TNM staged studies, 6 studies recruited patients at TNM II/III/IV, 4 studies recruited patients with TNM III/IV stages, 2 studies recruited patients with TNM I-IV, and one study recruited patients with TNM II/III. The duration of CAM in the retrieved studies ranged from 6.5 to 8 weeks. Analyzable KPS scores were reported in 4 studies. Extractable T lymphocytes scores were available in 4 studies while acute side effects of cancer therapy (RT and/or CT) were reported in 6 studies. Characteristics and quality evaluation of the included trials are listed in Tables 1 and 2 [12-14,19-28].

Table 1. The quality evaluation of included trials

<i>Study</i>	<i>Quality</i>			<i>Withdrawal/ dropout assessment</i>	<i>Total scores</i>	<i>Reference no.</i>
	<i>Randomization</i>	<i>Allocation concealment</i>	<i>Blindness</i>			
Wang et al., 2006	B	C	C	C	C	12
Xie et al., 2001	B	C	C	C	C	14
Zhu et al., 2000	A	C	C	B	B	19
Chen, 2005	A	C	B	B	B	20
Huang et al., 2003	B	C	C	B	B	13
Zhou et al., 2006	B	C	C	B	B	21
Wu et al., 2003	B	C	C	B	B	22
Wu et al., 2003	A	C	C	B	B	23
Zhou et al., 2008	B	C	C	B	B	24
Tang et al., 2012	B	C	C	C	C	25
Wang et al., 2012	B	C	C	B	B	26
Yuan et al., 2000	A	C	C	A	B	27
Zhou et al., 2012	A	C	C	B	B	28

For A, B, C see text

Table 2. Characteristics of included studies

<i>No. of participants/ No. of drop outs</i>	<i>TNM stage</i>	<i>Treatment group interventions</i>	<i>Control group interventions</i>	<i>TCM formula</i>	<i>Outcome assessment</i>	<i>Duration (weeks)</i>	<i>Jadad scale</i>	<i>Reference no.</i>
150/0	III-IV	TCM+ CR+RT	CR+RT	Yanshu Injec- tion	KPS,CD3,CD4	8-12	3	12
89/0	II-IV	TCM+ RT	RT	Antike capsule	KPS,AEs,C- D3,CD4	6.5-7	4	14
120/0	II-IV	TCM+ RT	RT	Shenlong oral liquid	CD3,CD4	8	3	19
71/0	II-IVa	TCM+ RT	RT	AiDi injection	KPS,CD3,CD4	8	3	20
101/0	III-IVa	TCM+ RT	RT	TCMs based on syndrome differentiation	AEs	8	3	13
160/0	III-IV	TCM+ RT	RT	Selaginella	AEs	6-7	4	21
76/0	II-III	TCM+ RT	RT	TCMs based on syndrome differentiation	AEs	7	4	22
120/0	I-IV	TCM+ RT	RT	Ditto	AEs	8	4	23
180/27 dropout	III-IVa	TCM+ RT	RT	Selaginella	AEs	6-7	4	24
67/0	I-IV	TCM+ RT	RT	TCMs based on syndrome differentiation	AEs	8	3	25
100/0	II-IV	TCM+ RT	RT	Ditto	AEs	6-7	3	26
80/0	II-IV	TCM+ RT	RT	Modified decoc- tion	KPS	7-8	3	28

AEs: adverse effects, TCM: traditional Chinese medicine, RT: radiotherapy, CT: chemotherapy, KPS: Karnofsky performance status, TNM: tumor-node-metastasis

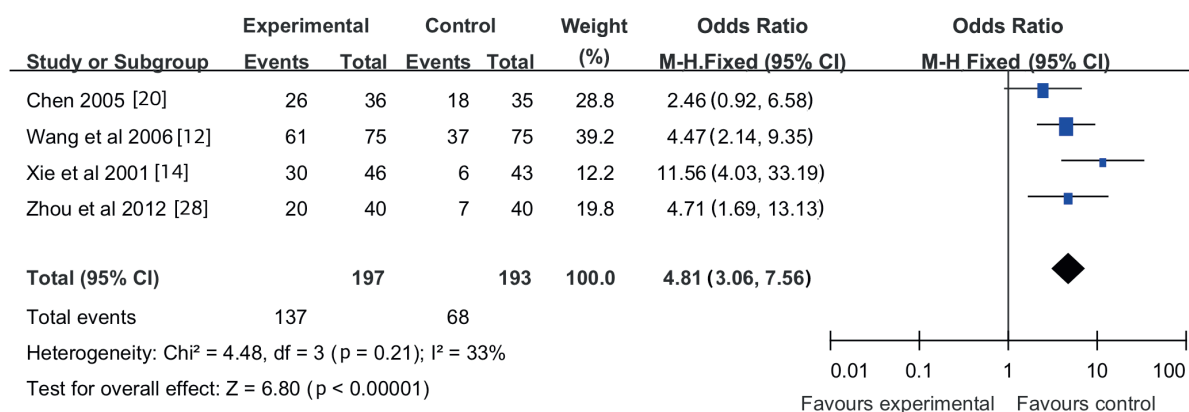


Figure 2. Overall efficacy estimated from meta-analysis of pairwise comparisons in patients with traditional Chinese Medicine (TCM, experimental group) vs patients without TCM (control group): number of patients with non-deterioration of Karnofsky performance score. M-H: Mantel-Haenszel method.

Karnofsky performance status

The QoL changes on KPS were examined in 9 studies. These studies assessed the non-deterioration status in 649 NPC patients. There were 69% (137/197) of the patients reporting non-deterioration in the treatment groups, while in the control groups this figure was 35% (68/193) ($p < 0.01$; Figure 2). The results showed that parallel use of CT and TCM was significantly and positively correlated with improved QoL (OR 4.81, 95%CI 3.06-7.56; $p < 0.01$; Figure 2). There was no significant heterogeneity among these studies.

Reduction in therapy side effects

Compared to acute oropharyngeal mucositis, acute radiation reaction of the skin was infrequent in NPC patients. The change of the skin in the acute radiation reaction grade of I+II in patients with TCM therapy was significantly increased (OR 2.19, 95% CI 1.31-3.66, $p < 0.01$, 3 studies, 349 patients, Figure 3A). No significant heterogeneity among these studies was recorded, which showed the combined TCM therapy relieved the acute radiation reaction of the skin.

Acute oropharyngeal mucositis and acute radiation reaction of the skin are common side effects of RT. A significant improvement of acute oropharyngeal mucositis and radiation reaction of the skin grade I+II in the treatment group compared to RT group was found (OR 8.63, 95% CI 3.28-22.70, 6 studies, 624 patients) (Figure 3B) ($p < 0.01$). The heterogeneity test indicated a significant difference ($p < 0.01$) among the pooled 6 studies, which might be due to different TCM regimens used in different studies.

Immunoregulation

A significant rise in CD3 and CD4 T cell number was reported in patients treated with RT and TCM (OR 10.08, 95% CI 1.38-18.78; OR 7.08, 95% CI 2.41-11.74, 4 studies, 365 patients) ($p = 0.003$) (Figure 4 A,B). However, the heterogeneity test indicated a significant difference ($p = 0.003$) among the pooled 4 studies, which might be due to different TCM regimens used in different studies. It was obviously the combined TCM therapy that enhanced the immunoregulation in NPC patients.

Discussion

Emerging evidence showed that TCM could suppress the proliferation of NPC cells and activate apoptosis via different mechanisms [29-31]. However, the efficacy of the combined use of TCM and RT on NPC remains controversial. TCM is especially popular among CAM users as palliative care for cancer, but the efficacy of the combined use of CAM and RT in NPC remains under exploration due to language barrier of many studies reported in Chinese language. Meta-analysis is a powerful statistical analysis method of results from individual studies, which increases the precision of a treatment effect and settles controversial studies [32]. In the present study, the pooled data with NPC has shown that combined therapy significantly improved performance status, immune function, and survival of NPC patients. We also found that, when compared with RT alone, the combined TCM therapy significantly reduced adverse effects associated with radiotherapeutic interventions, including acute oropharyngeal mucositis and acute radiation reaction of the skin (Figure 3).

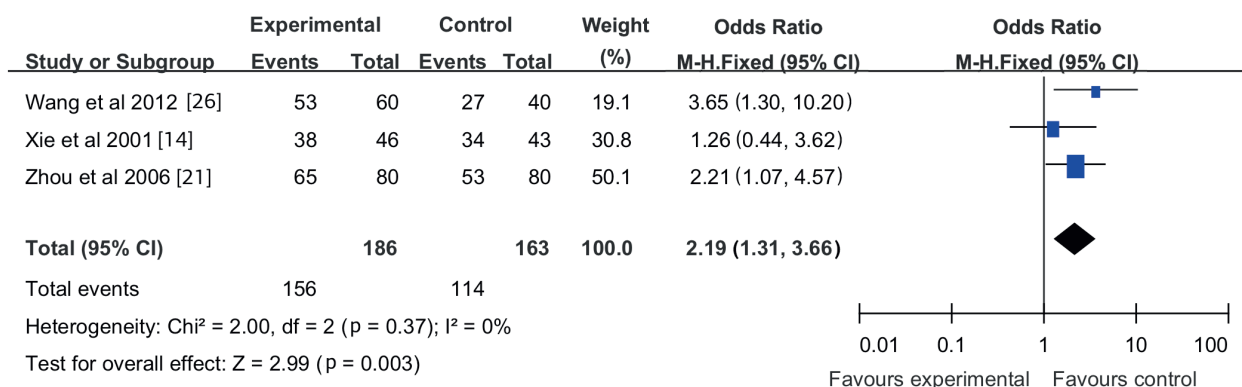
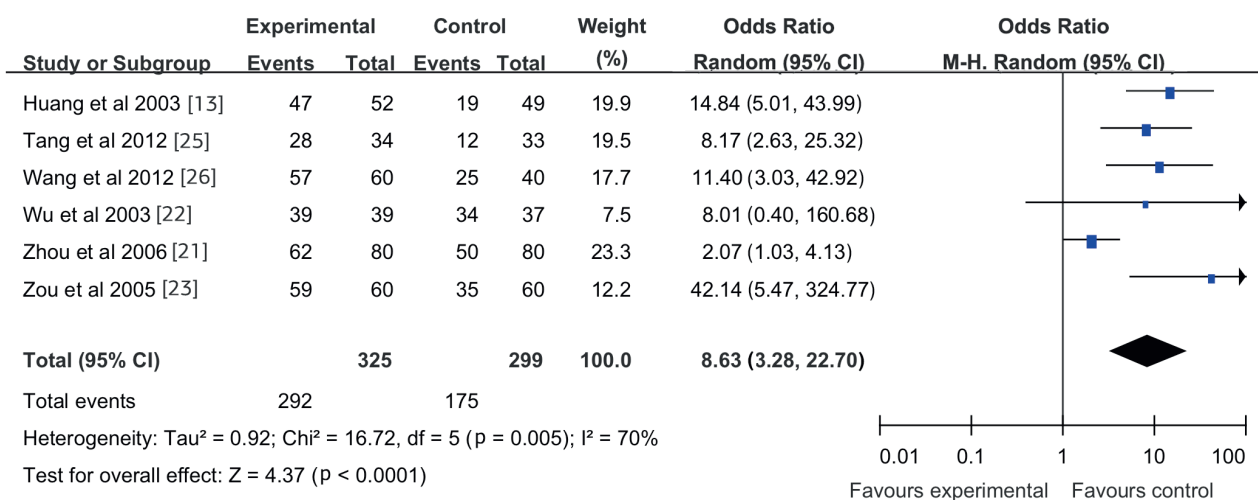
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Figure 3. Reduction of adverse effects estimated from meta-analysis of pairwise comparisons in patients with traditional Chinese Medicine (TCM, experimental group) versus patients without TCM (control group): **(A)**: number of patients with acute radiation reaction of the skin grade I+II; **(B)**: number of patients with acute oropharyngeal mucositis grade I+II. M-H: Mantel-Haenszel method.

In contrast to most of the previous meta-analyses in this area, our systematic review set the inclusion criteria with Jadad score ≥ 3 to increase the study quality and classified studies with grade I+II to minimize the heterogeneity among the studies. It is also encouraging to see that the adjunctive use of TCM with RT may improve the immune function in NPC patients. On the other hand, RT-related adverse effects will lead to intolerance of RT and patients may be forced to stop further treatment. Our results showed that RT-related side effects appear to be less frequent and milder with the use of concomitant CAM treatment, which suggests CAM may enhance the compliance to RT and eventually result in improving the KPS of the patients. The efficacy of TCM as an adjuvant therapy for NPC is in line with the published systematic reviews in colorectal cancer, hepatocellular carcinoma and non-small cell lung cancer [33-35]. Evidence from these reviews and our analyses all

suggest that conventional therapy combined with TCM is advantageous in a variety of cancers.

According to Chinese medicine theory, illness is caused by the disharmony of yin and yang, and Chinese medicine aims to restore the balance of yin and yang to alleviate the disease symptoms. TCM has been commonly used in Asia for thousands of years. Using the holistic and harmonic approaches, Chinese medicine emphasizes the effort to strengthening the body resistance against cancer. It attaches importance to the selfhealing ability of human body to remove pathogenic factors and recover health. Many of its cancer therapies are employed for enhancing this power. Experimental studies revealed that TCM may help improve the immune function in cancer patients [36-40]. The mechanisms of the properties effects of most TCMs remain unknown, but it is well-confirmed that a number of anticancer TCMs have been found to be effective in boosting and stim-

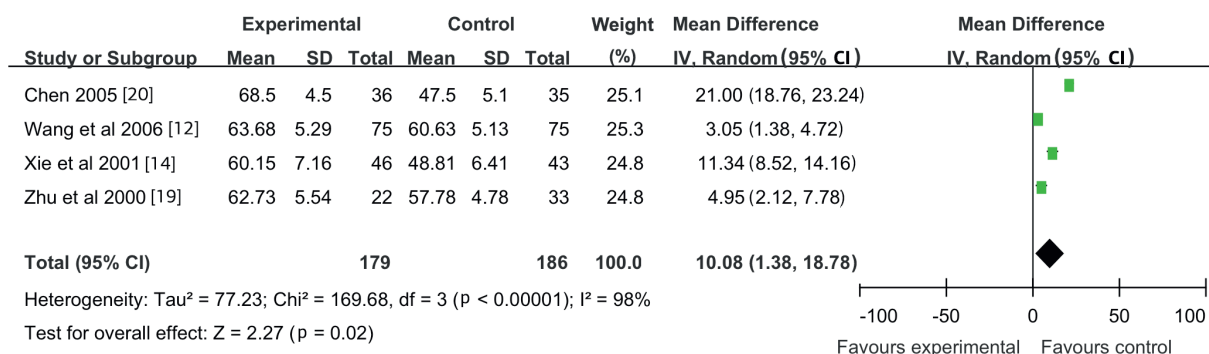
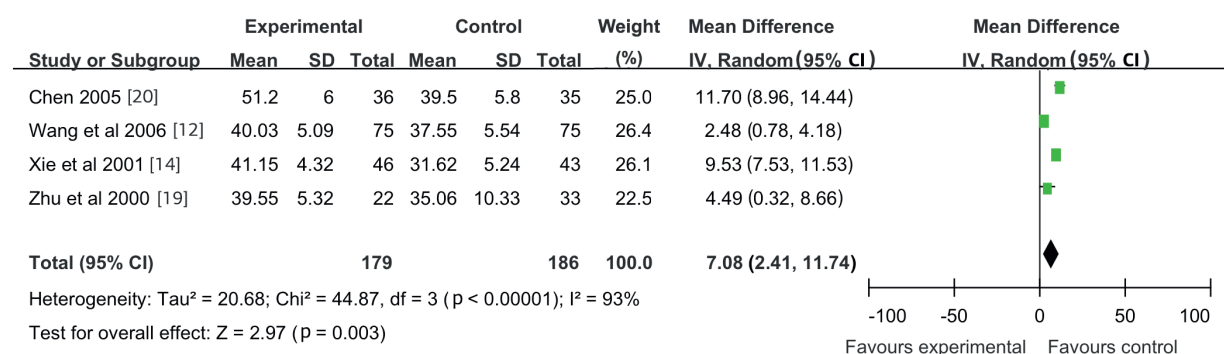
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Figure 4. Immune effect estimated from meta-analysis of pairwise comparisons in patients with traditional Chinese Medicine (TCM, experimental group) versus patients without TCM (control group): **(A)**: mean difference between post-treatment CD3 T cell levels of patients treated by with TCM and without TCM; **(B)**: mean difference between post-treatment CD4 T cell levels of patients treated by with TCM and without TCM. IV: inverse variance method.

ulating the immune system [41,42]. This may explain why adjunctive TCM can not only alleviate the adverse effects of RT and improve the QoL, but also enhance the tumor response by significantly stimulating the immune system.

KPS, RT-related adverse effects, immune function and survival are the four major outcomes in the analyzed studies. However, not all of the studies simultaneously reported the three outcomes. For example, Xie et al. [14] reported three outcomes while Huang et al. [13] reported the reduction of adverse effects only. Nevertheless, we analyzed all available data in these reports without any subjective selection.

There are several limitations in the present meta-analysis. Firstly, clinical trials in the studies were not strictly designed and published following the gold standard, which may put the results of meta-analysis at risk. Allocation concealment and blinding were not clearly described in most of the included trials, which may result in the emergence of bias and overestimation of the ef-

ficacy of the treatment group [43]. None of the included trials conducted was placebo-controlled, double-blind style. Secondly, there are variations among the studies in terms of interventions, TCM composition (single or combination herbs), dosage preparation, and manufacturing standards, which may contribute to heterogeneity among the studies. Thirdly, publication bias may exist in the present meta-analysis. Most of the findings presented in the included studies displayed positive results. Some negative results might be unreported and therefore not included in the review. Finally, similarly to all previously published meta-analyses of TCM combined with conventional therapy, most of the trials included in this study did not provide enough information on demography and methodology [44], such as disease duration, random sequence, intention-to-treat analyses, and drop-out rate. Because of the lack of such information, we could not analyze the associations of treatment effects with demographic factors and potential biases derived from methodological flaws.

In conclusion, the evidence from the included studies in the present meta-analysis shows that TCM as adjunctive therapy offers advantages to NPC patients. However, due to the complex nature of TCM interventions, particular attention

should be paid to apply appropriate and rigorous research methodologies to investigate TCM as a holistic system [45]. Therefore, a large-scale RCT integrating the Chinese Medicine methodology of diagnosis and treatment is warranted.

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