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Effects of S-1 combined with radiotherapy in the treatment of nasopharyngeal cancer: a meta-analysis based on randomized controlled trials

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Abstract: The aim of this meta-analysis was to evaluate the effects and toxicity of S-1 combined with radiotherapy in the treatment of nasopharyngeal cancer (NPC). Through a search of the databases of PubMed, Embase, the Chinese Biomedicine Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang system and Chongqing VIP Information (CQVIP), the efficacy and side effects data of S-1 combined with radiotherapy in the treatment of NPC patients from open published randomized controlled trials (RCTs) were collected. The pooled complete response (CR), partial response (PR), objective response rate (ORR), 2-year survival rate and treatment related toxicity were analyzed by Stata12.0 software. Eight RCTs with 599 cases were included and analyzed in this meta-analysis. The general quality of the 8 studies were deemed as having moderate risk of bias. Adequate sequence generation was reported in 4 studies. Incomplete outcome data address was reported in 7 publications. Five studies indicated to be free of selective reporting. Seven studies reported the treatment complete response (CR) between S-1 combined with radiotherapy and radiotherapy alone. With significant heterogeneity, the data was pooled by random effect model. The pooled results indicated that S-1 combined with radiotherapy can significant increase the CR rate compared to radiotherapy alone (RR=1.52, 95%CI:1.33-1.74, P<0.05). Eight studies reported the partial response (PR) rate between the combined treatment and radiotherapy alone. The pooled results showed that there was no statistical difference for PR between combined treatment and radiotherapy alone (RR=0.85, 95%CI:0.62-1.16, P>0.05). For the effect size of objective response rate (ORR), pooled results indicated that S-1 combined with radiotherapy can significantly increased the ORR by random effect model (RR=1.39, 95%CI:1.23-1.57, P<0.05). The pooled results showed that S-1 combined with radiotherapy significant increase the risk of developing bone marrow suppression (RR=1.94, 95%CI:1.40-2.69, P<0.05) and gastrointestinal reaction (RR=1.81, 95%CI:1.38-2.38, P<0.05) with fixed effect model. However, the pooled oral mucositis (RR=1.22, 95%CI:0.99-1.50, P>0.05) and radiodermatitis (RR=0.93, 95%CI:0.77-1.12, P<0.05) were not statistically different. Two studies reported the 2-year survival rate between the two groups. The pooled results showed the combined treatment significantly increased the 2-year survival rate for patients with nasopharyngeal carcinoma (RR=1.14, 95%CI:1.01-1.28, P<0.05). The funnel plot demonstrated significant publication bias for complete response, partial response, objective response rate and oral mucositis. The egger's line regression test indicated significant publication bias for complete response (t=5.98, P=0.002) and objective response rate(t=6.23, P=0.003). Conclusion S-1 combined with radiotherapy can significant improve the clinical efficacy with more treatment related toxicity compared to radiotherapy alone in the treatment of nasopharyngeal carcinoma.

Keywords: Nasopharyngeal carcinoma; S-1; Radiotherapy; Meta-analysis

1 Introduction

The southern part China has one of the highest incidence rates of nasopharyngeal carcinoma (NPC) in the world [1]. According to the global registry of cancer incidence, NPC ranked 11th among all malignant tumors in China in 2008, with an incidence rate of 2.8/100,000 person-years in men

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and 1.9/100,000 person-years in women [2]. NPC is sensitive to radiation. So, most of the nasopharyngeal cancer patients were recommended for radiotherapy as the first-line treatment strategy. S-1 is an oral combination chemotherapy drug consisting of 5-fluorouracil prodrug tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate [3]. S-1 was initially used for gastric cancer chemotherapy with relative good response, and it was recommended in the NCCN guideline. We searched the database and found that several studies reported its clinical efficacy for nasopharyngeal carcinoma combined with radiation versus radiation alone [4, 5]. S-1 is a kind of chemotherapy drug which is widely used clinically for advanced NPC. However, the sample size of each study was relatively small with weak statistical power. Therefore, we pooled all the open published studies related to S-1 combined with radiation versus radiation alone in the treatment of NPC in order to further evaluate its clinical value.

2 Material and methods

2.1 Publication searching

Through a search of the databases of PubMed, Embase, the Chinese Biomedicine Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang system and Chongqing VIP Information (CQVIP), the efficacy and side effect data of S-1 combined with radiotherapy in treatment the nasopharyngeal cancer patients from open published randomized controlled trials (RCTs) were collected. The searching terms were used as follows: "nasopharyngeal cancer/NPC", "nasopharyngeal carcinoma", "radiation", "radiotherapy" "radiation therapy", "three-dimensional conformal radiotherapy/3D-CRT", "intensity modulated radiotherapy/IMRT" ,"s-1", " tegafur" or "TS-1". The searches were limited to human beings without language restriction. All references of relevant articles were scanned for additional analysis.

2.2 Data extraction

The data for authors, year of article publication, country, sample size of cases and controls, radiation technique, S-1 dosage, complete response (CR) rate, partial response (PR) rate, objective response rate (ORR), treatment-related toxicities and 2-year survival rate of each included study were extracted independently by two reviewers and cross checked.

2.3 Quality assessment

The methodological qualities of the included studies were assessed by two reviewers according to the Cochrane Reviews Handbook 5.0. There were six questionnaires for evaluation the general quality of the RCTs. They were (1) adequate sequence generation? (2)allocation concealment? (3) blinding? (4) incomplete outcome data addressed? (5) free selective reporting? (6) free of other bias?. For the questionnaires, "yes" meant low risk, "unclear" meant moderate risk and "no" meant high risk.

2.4 Statistical analysis

Review Manager (RevMan 5.0 provided by The Cochrane Collaboration) and Stata 12.0 (Stata Corporation, College Station, TX) were used to do the statistical analysis. Dichotomous data were calculated as the risk ratio (RR) with the 95% confidence interval (CI). Statistical heterogeneity across the included studies were evaluated by chi-square (χ^2) test [6]. The funnel plot and egger's line regression test were used for evaluation the potential publication bias.

3 Results

3.1 General characteristics

After searching the associated databases, fifty five publications were initially found. After reading the title and abstract, 12 studies were screened and only 8 randomized controlled trials [4, 5, 7-12] were finally included for meta-analysis after reading the full text paper. The publication inclusion flow chart was demonstrated in Figure 1. Eight RCTs with 599 cases were included and analyzed in this meta-analysis. For the included 8 studies, 6 publications included the patients with locally advanced stage and other 2 studies with early stage patients. Three studies use IMRT radiation technology, 2 studies use 3DCRT radiation technology and the left 3 studies use regular radiation process for nasopharyngeal cancer radiotherapy. The S-1 dosage range from 80mg/day to 80mg/day•m^2. The general information of the included studies were showed in Table 1.

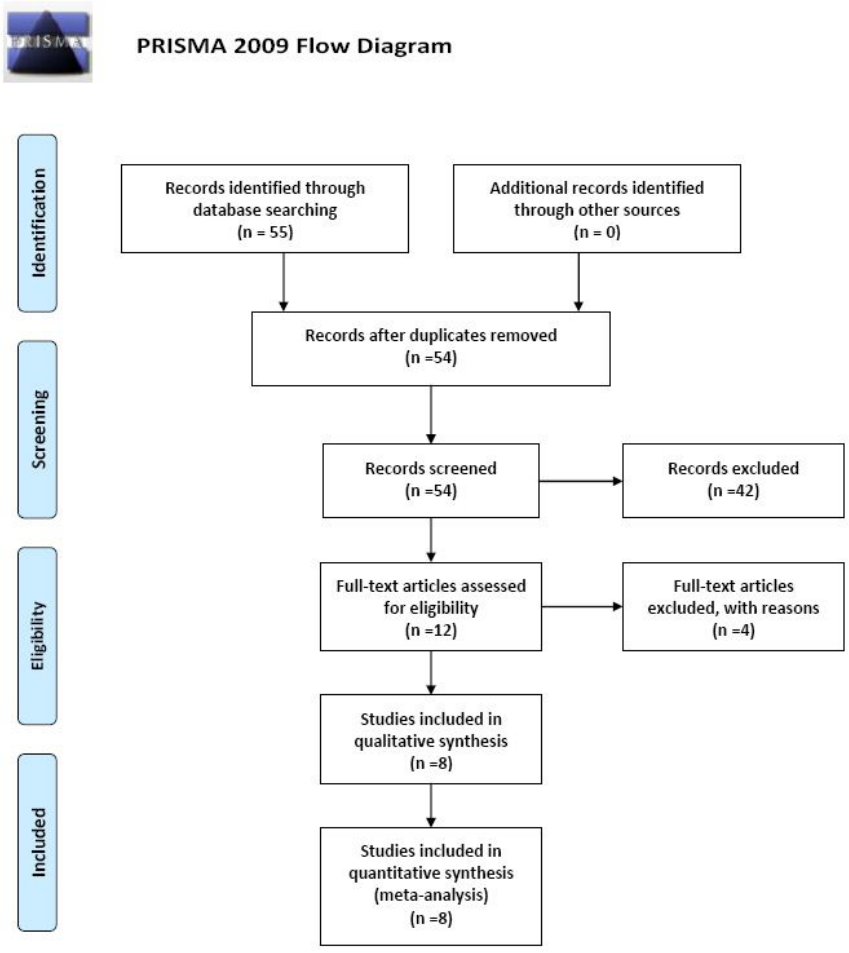

Figure 1: The paper searching flow chart

Table 1: The general information of included studies

Author	Year	Stage	n(E/C)	Treatment	Control	Outcome
Zheng ZH	2015	Locally advanced	60/60	IMRT+S-1(40-60mg,bid×14 day with 7 days interval until end of radiation)	IMRT	(1),(2),(3),(4),(5)
Palita•MTX	2014	Early stage	34/34	3DCRT+S-1(60mg, bid×14 days with 7 days interval until end of radiation)	3DCRT	(1),(2),(3)
Wang ZW	2014	Locally advanced	30/30	IMRT+S-1(80mg/day•m2, bid×14 days with 7 days interval until end of radiation)	IMRT	(1),(2),(3),(4),(5),(6),(7)
Li ZY	2013	Locally advanced	54/41	Radiation+S-1(60mg, bid×28days with 14 days interval until end of radiation)	Radiation	(1),(2),(3),(4),(5),(6),(7)
Wang L	2013	Locally advanced	31/32	IMRT+S-1(60mg,bid×14 day with 7 days interval until end of radiation)	IMRT	(1),(2),(3),(4),,(6),(7)
You CW	2012	Locally advanced	30/30	Radiation+S-1(60mg, bid×28days with 14 days interval until end of radiation)	Radiation	(2),(5)
Yang J	2012	Early stage	44/44	3DCRT+S-1(60mg, bid×14 days with 7 days interval until end of radiation)	3DCRT	(1),(2),(3)
Wu HL	2012	Locally advanced	22/23	Radiation+S-1(40mg/day•m2, bid×28 days with 14 days interval until 14 days after radiation)	Radiation	(1),(2),(3),(4),(5),(6),(7)

3.2 Quality assessment

The methodological quality of the included 8 studies were assessed by a six-question process introduced by Cochrane Reviews Handbook 5.0. The general quality of the 8 studies were deemed as moderate risk of bias. Adequate sequence generation was reported in 4 studies. Incomplete outcome data address was reported in 7 publications. 5 studies reported the free of selective reporting. The detailed information for methodological quality assessments were showed in Figure 2.

3.3 Clinical efficacy assessment

Seven studies reported the treatment complete response (CR) comparing S-1 combined with radiotherapy to radiotherapy alone. With significant statistical heterogeneity, the data was pooled by random effect model. The pooled results indicated that S-1 combined with radiotherapy can significant increase the CR rate compared to radiotherapy alone (RR=1.52, 95%CI:1.33-1.74, P<0.05). 8 studies reported the partial response (PR) rate between the combined treatment and radiotherapy alone. The pooled results showed that there was no statistical difference for PR (RR=0.85, 95%CI:0.62-1.16, P>0.05). For the effect size of objective response rate (ORR), pooled results indicated that S-1 combined with radiotherapy can significantly increase the ORR by random effect model (RR=1.39,95%CI:1.23-1.57, P<0.05), Figure 3.

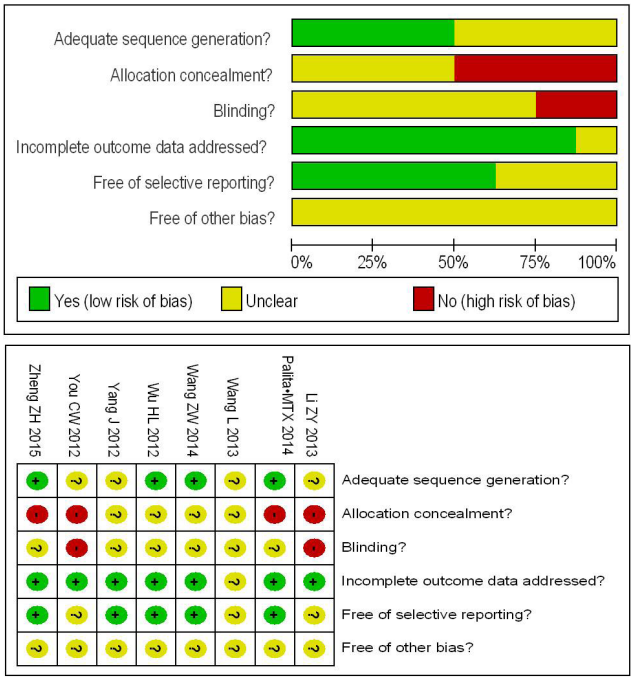

Figure 2: The methodology quality of the included studies, (+:low risk; ?:moderate risk; - high risk)

3.4 Treatment related toxicities

The pooled results showed that S-1 combined with radiotherapy significant increased the risk of developing bone marrow suppression (RR=1.94,95%CI:1.40-2.69, P<0.05) and gastrointestinal reaction (RR=1.81, 95%CI:1.38-2.38, P<0.05) with fixed effect model. However, the oral mucositis (RR=1.22, 95%CI:0.99-1.50, P>0.05) and radiodermatitis (RR=0.93, 95%CI:0.77-1.12, P>0.05) between the two groups were not statistical different, Figure 4.

3.5 2-year survival analysis

Two studies reported the 2-year survival rate between S-1 combined with radiotherapy and radiotherapy alone in the treatment of nasopharyngeal cancer. The pooled results showed the combined treatment significant increase the 2-year survival rate for patients with nasopharyngeal carcinoma (RR=1.14, 95%CI:1.01-1.28, P<0.05), Figure 5.

3.6 Publication bias

The publication bias were evaluated by funnel plot and egger's line regression test. The funnel plot demonstrated significant publication bias for complete response, partial response, objective response rate and oral mucositis, Figure 6. The egger's line regression test indicated significant publication bias for complete response (t=5.98, P=0.002) and objective response rate (t=6.23, P=0.003).

4 Discussion

Nasopharyngeal carcinoma is the most common cancer originating in the nasopharynx and one of the most diagnosed malignant squamous cell carcinomas of the head and neck [13]. It is vastly more common in certain regions of East Asia and Africa than elsewhere, with viral, dietary and genetic factors implicated in its causation. And it is more common in males than females [14]. The prognosis of nasopharyngeal carcinoma is relative favorable with a high 5-year survival rate for early stage patients. However, for patients with advanced stage or locally advanced

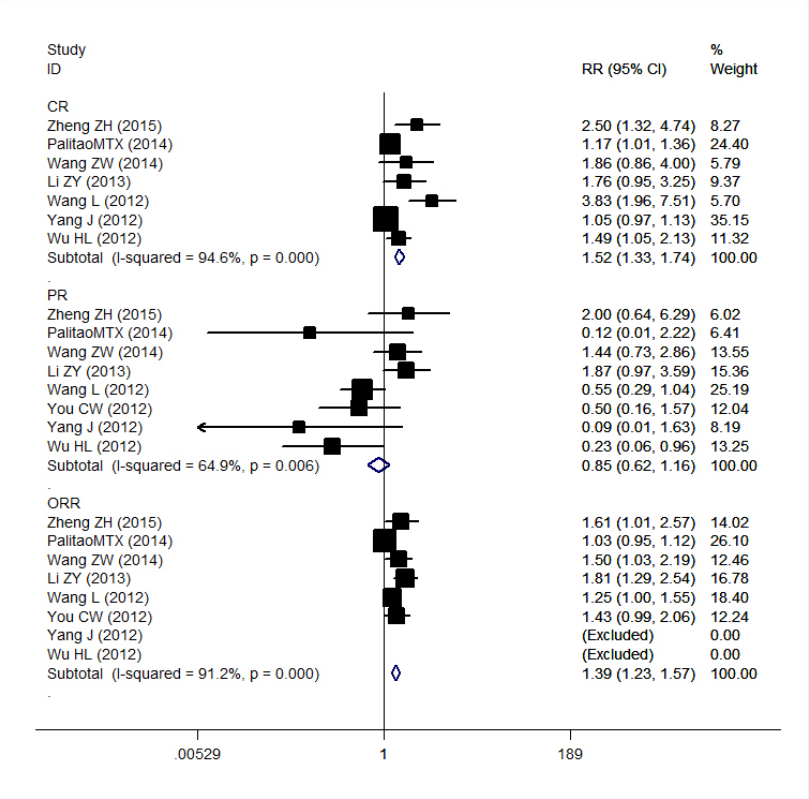

Figure 3: Forrest for clinical efficacy of S-1 combined with radiotherapy versus radiotherapy alone

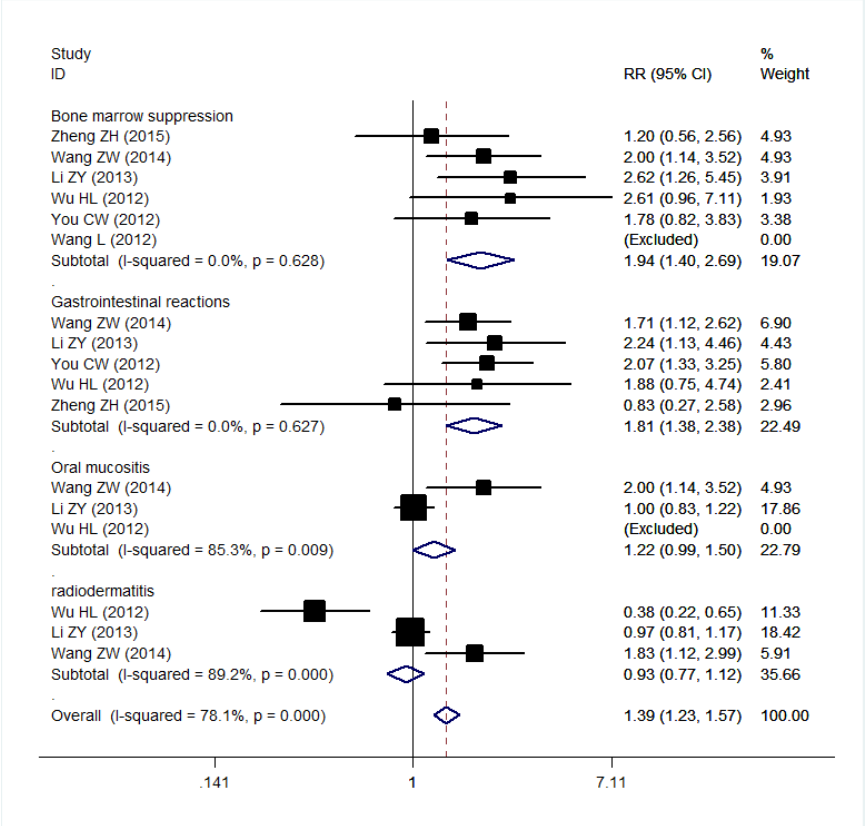

Figure 4: Forrest plot evaluation treatment related toxicity of S-1 combined with radiotherapy versus radiotherapy alone

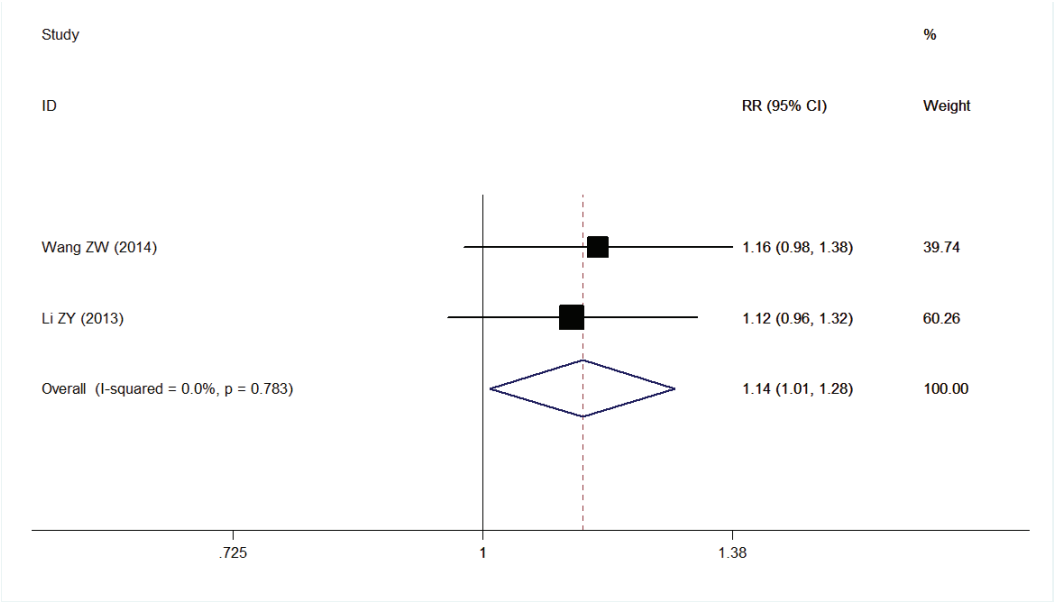

Figure 5: Forrest plot evaluation 2-year survival rate of S-1 combined with radiotherapy versus radiotherapy alone

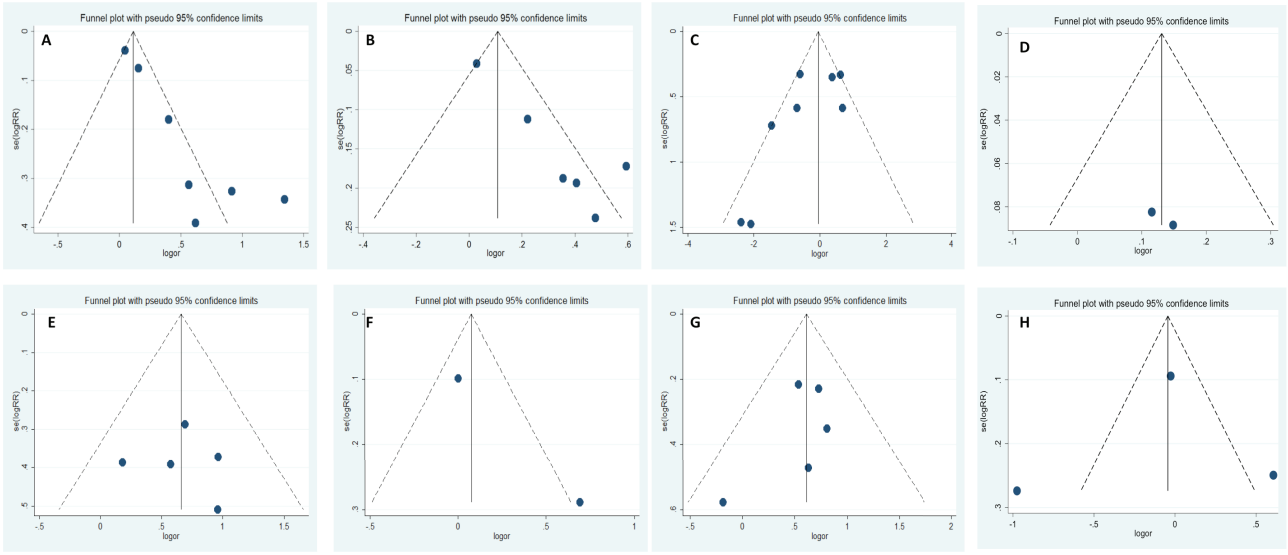

Figure 6: Funnel plot for evaluation the publication bias (A: complete response; B: partial response; C: objective response rate; D:2-year survival; E: bone marrow suppression; F: oral mucositis; G: gastrointestinal reaction; H: radiodermatitis)

disease, the prognosis is poor. Most of the cases of nasopharyngeal carcinoma are poorly differentiated squamous cell carcinoma which is sensitivity to radiation. Therefore, the first-line treatment strategy is radiotherapy. However, the 5-year survival rate is only 50% for patients receiving radiotherapy alone with the recurrence rate of 17%-42% [14].

Concomitant radiochemotherapy has been recently used for nasopharyngeal carcinoma treatment as reported in several published studies with a relatively favorable response and good long term survival. Recently, Blanchard[15] and his colleges published an update meta-analysis related to chemotherapy and radiotherapy in nasopharyngeal carcinoma. The results confirmed that the addition of concomitant chemotherapy to radiotherapy significantly improves survival in patients with locoregionally advanced nasopharyngeal carcinoma.

S-1 was an oral combination chemotherapy drug consisting of 5-fluorouracil prodrug tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate. S-1 was initially used for gastric cancer with relative well response. And several studies have demonstrated that S-1 was also effective for nasopharyngeal carcinoma. Wen et al [16] performed a phase II clinical trial of concurrent chemoradiotherapy with S-1 versus weekly cisplatin for locoregionally advanced nasopharyngeal carcinoma. In this prospective

study, the author recruited 105 locally advanced nasopharyngeal carcinoma and randomly divided into chemoradiotherapy plus S-1 group and cisplation group. The patients in the chemoradiotherapy plus S-1 group received regular radiation and 40-60 mg S-1 twice daily for 4 consecutive week. Patients in the cisplation chemotherapy group received cisplation plus radiation treatment. After treatment, they found that concomitant radiochemotherapy with S-1 was similar in efficacy but less toxicity compared to the standard concomitant radiochemotherapy with weekly cisplatin.

Recently, several studies have evaluated the clinical efficacy and toxicity of concomitant radiochemotherapy plus S-1 versus radiation alone for nasopharyngeal carcinoma treatment [4, 7]. However, the conclusion was not in accordance with each other with small sample size. In this meta-analysis, we searched the databases and included the open published studies related to concomitant radiochemotherapy plus S-1 versus radiation alone for nasopharyngeal carcinoma. In this meta-analysis, we included eight randomized controlled trials. We found that S-1 combined with radiotherapy can significant improve the clinical efficacy with more treatment related toxicity compared to radiotherapy alone in the treatment of nasopharyngeal carcinoma. The 2-year survival rate, objective response rate and complete response rate in the concomitant radiochemotherapy group was superior to that of radiation alone group. However, the treatment related toxicity such as bone marrow suppression and gastrointestinal reaction incidence rate was significant higher in combination group than radiation alone group. Many researchers have carried out stratified analysis on the side effects and have distinguished the degree of the side effects, which is helpful to elucidate the therapeutic effect [17,18]. However, the included original studies in our present meta-analysis did not provided enough data to do stratified analysis. So, we did not perform these subgroup analysis. Among these 8 included studies, two publications included patients with early stage NPC and the other six included patients with locally advanced NPC. This is a source of clinical heterogeneity. The subgroup analysis according to disease stage seems to be needed. However, the effects of CR, PR, ORR and toxicity are based on ratio, and the S-1 dosage was not significantly different for early or advanced stages disease. So, the stage had little effect on the results. Since there are only two studies including patients with advanced stage disease, the usefulness of subgroup analysis is limited.

Several limitations were found in our present meta-analysis: (1) The general methodological quality was relatively poor for the included 8 studies, and the sample size of the studies was relatively small which limited the statistical power. This is an important drawback of the original studies. We further searched the Google Scholar databases and found some related studies. However, after reading the whole paper, we found that the papers from the Goole Scholar did not meet the inclusion criteria.; (2) Statistical heterogeneity was found is the aspects of complete response, partial response, objective response, oral mucostitis and raitodermatitis; (3) significant publication bias were existed in the effects size of complete response and objective response rate. Publication bias usually occurs when the outcome of an experiment or research study influences the decision whether to publish or otherwise distribute it. The reason for publication bias was that the negative results were general not easy to publish. Studies with a null result can be of the same standard as studies with significant results with respect to quality and design. However, statistically significant results are three times more likely to be published than papers with null results, this lead to the significant publication bias.

Conflict of interest statement: Authors state no conflict of interest

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