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Efficacy and safety of weekly versus triweekly cisplatin concurrent with radiotherapy in nasopharyngeal carcinoma

A meta-analysis

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Abstract

Background: Cisplatin-based concurrent chemoradiotherapy is a standard of care for locally advanced nasopharyngeal carcinoma (NPC), and weekly and triweekly cisplatin are both alternative regimens based on the results of squamous cell carcinoma of the head and neck. However, there is a lack of direct evidence on the efficacy and safety of weekly versus triweekly cisplatin concurrent with radiotherapy in NPC alone. This meta-analysis aimed to identify which regimen is more superior between weekly and triweekly cisplatin in patients with NPC treated with concurrent chemoradiotherapy.

Methods: The PubMed, Embase, and Cochrane Library were searched for eligible literatures. Clinical outcome measures including 1-year overall survival (OS), 3-year OS, 5-year OS, 5-year loco-regional failure-free survival, 5-year distant metastasis-free survial and the most common 3 grade or higher acute toxicities (hematological toxicity, mucositis and nausea and vomiting) were analyzed by RevMan 5.4 software; significance level was 0.05.

Results: Seven clinical controlled studies with 1795 patients were included in the meta-analysis. There were no significant differences between weekly and triweekly cisplatin in 1-year OS, 3-year OS, 5-year OS, 5-year loco-regional failure-free survival, and 5-year distant metastasis-free survial) (all $P > .05$). Grade 3 or higher mucositis and nausea and vomiting showed similar between the 2 arms. However, grade 3 or higher hematological toxicity of weekly cisplatin was significantly higher than that of triweekly cisplatin (1.55; 95% CI, 1.22–1.98, $P = .0004$).

Conclusions: Weekly cisplatin resulted in similar survival benifit as triweekly cisplatin, but with higher hematological toxicity.

Abbreviations: CCRT = concurrent chemoradiotherapy, DFS = disease-free survival, LRFFS = loco-regional failure-free survival, NPC = nasopharyngeal carcinoma, OS = overall survival, SCCHN = squamous cell carcinoma of the head and neck.

Keywords: chemoradiotherapy, cisplatin, efficacy and safety, meta-analysis, nasopharyngeal carcinoma

1. Introduction

Nasopharyngeal carcinoma (NPC) is 1 of the most common malignant tumors in South China, Southeast Asia and the Mediterranean region disease.[1] Because of the occult onset and no obvious early symptoms, most patients were on the locally advanced disease when diagnosed.[2] Although the overall prognosis was relatively good for early-or locally advanced NPC, most patients underwent treatment failure because of locoregional recurrence or distant metastasis.[1,3] Concurrent chemoradiotherapy (CCRT) has been proved as the standard treatment for locally advanced NPC with significant improved OS, disease-free survival (DFS), locoregional and distant control compared to radiotherapy alone.[4–7]

Currently, cisplatin-based CCRT is the most commonly used regimen, which is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as the first-line treatment for early stage to locally advanced NPC.[4,8] In clinical practice, sigle agent cisplatin was usually used once per week (30–40 mg/m^2) or once every 3 weeks (80–100 mg/m^2) for CCRT, and these clinical strategies were widely used in head and neck cancers for decades.[9–12] With regards to weekly and triweekly cisplatin, evidence has demonstrated that the efficacy and safety of weekly cisplatin showed similar to those of triweekly cisplatin in squamous cell carcinoma of the head and neck (SCCHN). A comparative analysis by Mohamed et al[13] including 3668 patients from 39 prospective studies reported that weekly and triweekly cisplatin concurrent with radiotherapy showed similar toxicities, locoregional control, 2-year progression-free survival, and 2-year OS in locally advanced SCCHN. Another meta-analysis by Jacinto et al[14] reported that weekly cisplatin was not

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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superior to triweekly cisplatin in 5-year progression-free survival and 5-year OS in locally advanced SCCHN. Similar to SCCHN, some studies reported that weekly cisplatin concurrent with radiotherapy resulted in similar efficacy and toxicity as triweekly cisplatin in patients with NPC.[15–19] However, the results were not reported consistent in NPC. The study by Wang et al[20] reported that the 5-year DFS and 5-year OS of weekly cisplatin were significantly better than those of triweekly cisplatin (96.7% vs 88.3%, $P = .036$ and 90.7% vs 80.5%, $P = .028$, respectively) in NPC. Another large cohort study by Zhu et al[21] reported that weekly cisplatin was associated with significantly improved DMFS and lower rates of grade 3 to 4 mucositis, nausea and vomiting compared with triweekly arm in locally advanced NPC, but with significantly higher rates of grade 3 to 4 thrombocytopenia. Therefore, although weekly and triweekly cisplatin concurrent with radiotherapy showed similar efficacy and safety in SCCHN, evidence in NPC is not sufficient, and which regimen is more superior remains controversial.

In order to evaluate the clinical efficacy and safety of weekly versus triweekly cisplatin concurrent with radiotherapy in NPC, we perform this meta-analysis to examine the survival benefit and toxicities in patients with early-or locally advanced NPC, and provide more evidence for clinical use of these treatment strategies.

2. Methods

2.1. Identification of trials

Databases including PUBMED, EMBASE and Cochrane Library were systematically searched from inception until June 2022. Clinical studies were identified using any of the following key words: nasopharyngeal carcinoma, nasopharyngeal cancer, nasopharynx cancer, weekly, triweekly, once a week, every 3 weeks, cisplatin, concurrent, chemoradiotherapy. The search was not limited to controlled or randomized trials, to minimize the chances of missing a study. A manual search of the relevant references was performed to identify other relevant trials. This meta-analysis was limited to human studies published in English.

Both prospective and retrospective clinical controlled studies that assessed efficacy and safety of weekly versus triweekly cisplatin concurrent with radiotherapy in NPC were included. Non controlled trials, systematic reviews, meta-analysis, letters, case reports and non English publications were excluded. Besides, clinical trials with unclear data on treatment related effectiveness and safety were aslo excluded. The studies identified through the search were independently screened by 2 authors (C.L. and L.Y.C.) for inclusion. Any disagreements were arbitrated by a third author (H.M.).

2.2. Types of outcome measures

The outcomes evaluated in this meta-analysis were 1 years OS, 3 years OS and 5 years OS, 5-year loco-regional failure-free survival (LRFFS), 5-year DMFS, and the most common ≥ 3 grade toxicities (hematological toxicity, mucositis and nausea and vomiting). Other outcomes including DFS and objective response rate were not available because most included studies did not provide relevant information.

2.3. Data extraction and quality assessment

Two authors independently extracted data concerning author details, year, country, study design, radiation dose, the number and dose of weekly and triweekly cisplatin using a data extraction form. When multiple publications of the same trial were identified, data was extracted and recorded as a single trial. Discrepancies were resolved by discussion and consensus. Qualification in all included studies were evaluated by 2 authors (Z.S.J. and Y.Q.W.) independently based on the Newcastle-Ottawa Scale[22] and the Cochrane Handbook. We use the Newcastle-Ottawa Scale to assess the quality of non-Randomied Controlled trails and the Cochrane Handbook for Systematic Evaluation of Intervention to the quality of Randomied Controlled trails.

2.4. Statistical analysis

Meta-analysis was performed using RevMan software version 5.4 (Nordic Cochrane Centre, Copenhagen). Pooled odd ratios (ORs) using the Mantel-Haenszel method were calculated for dichotomous data. Heterogeneity between trials was assessed through the Cochrane's Q-statistic and I^2 index in the meta-analysis. The heterogeneity was regarded as low (I^2 value between 25% and 50%), moderate (I^2 value between 50% and 75%) and high (I^2 value > 75%). For statistically significant heterogeneous data, a random-effects model was used; otherwise, a fixed-effects model was applied. $P < .05$ was considered statistically significant.

3. Results

3.1. Search results and study characteristics

A total of 315 references were identified. The reference flow is shown in Figure 1. Seven clinical studies including a total of 1795 patients were included.[15–21] Among the 7 studies, 4 studies were from China[18–21] and another 3 were from Turkey, British and Korea.[15–17] Six of them were retrospective studies[15,16,18–21] and another was prospective randomized controlled trial.[17] All patients were diagnosed with nasopharyngeal carcinoma by pathology. Most studies used a cisplatin dose of 30–40 mg/m^2 in weekly arm and 80–100 mg/m^2 in triweekly arm,[16–21] and only 1 study used a slightly higher cisplatin dose of 50mg/m^2 in weekly arm.[15] Across these 7 studies, 1-year OS, 3-year OS and 5-year OS, 5-year LRFFS, 5-year DMFS and the most common grade 3 or higher toxicities (hematological toxicity, mucositis and nausea and vomiting) were extracted and recorded in detail. All articles were published between 2014 and 2019. Studies including patients with only NPC or those that enrolled more than 10 patients were included. Studies using either weekly or triweekly cisplatin in combination with radiotherapy, and a total radiation dose of at least 60 Gy were required. Studies were excluded if immunotherapy, targeted agents or other chemotherapy drugs were used during the course of treatment with CCRT. Important details about the included studies are shown in Table 1.

3.2. Efficacy

The OS was mentioned in all the 7 included studies. All studies reported 1 to 3 year OS (N = 640 patients in weekly vs 1155 in triweekly), and only 5 studies reported 5-year OS (N = 542 patients in weekly vs 1071 in triweekly). As shown in Figure 2, the analysis for 1-year OS, 3-year OS, and 5-year OS of weekly and triweekly cisplatin regimens did not show statistical differences (odds ratio, 1.09; 95% CI, 0.55–2.15, $P = .8$; odds ratio, 0.85; 95% CI, 0.57–1.26, $P = .41$ and odds ratio, 0.92; 95% CI, 0.66–1.29, $P = .63$, respectively).

Data on LRFFS and DMFS was extracted from 4 publications. As shown in Figure 3, there were no significant differences in 5-year LRFFS and 5-year DMFS between weekly and triweekly cisplatin regimens (odds ratio, 1.10; 95% CI, 0.73–1.67, $P = .64$ and odds ratio, 0.81; 95% CI, 0.54–1.22, $P = .32$, respectively).

3.3. Safety

The most common grade 3 or higher treatment related adverse events reported in the 7 included studies were hematological

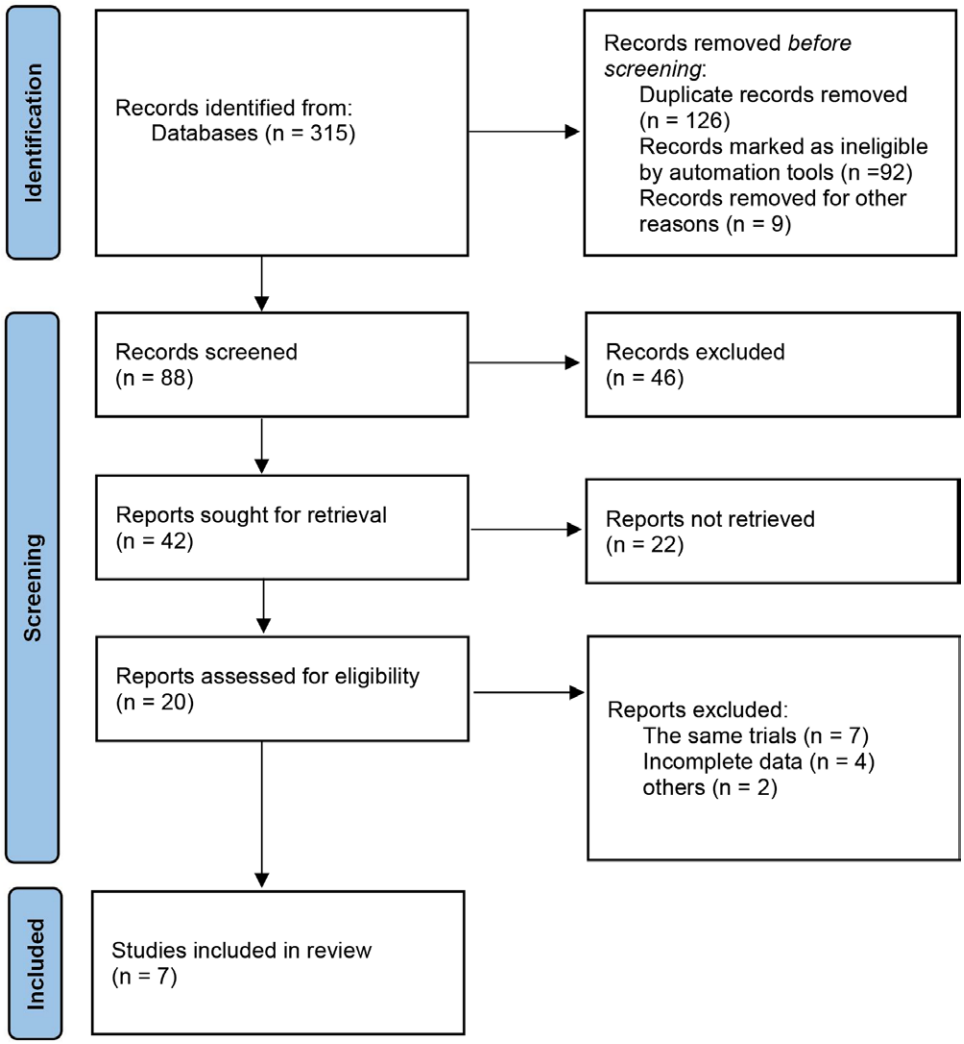

Figure 1. Flow chart of articles identified, included and excluded.

Table 1

Characteristics of the included studies.

					Weekly cisplatin		Triweekly cisplatin	
Study	**Country**	**Design**	**Stage**	**RT**	**N**	**Dose**	**N**	**Dose**
Gundog 2019[15]	Turkey	Retrospective	II to IVa	70 Gy	61	50 mg/m²	37	100 mg/m²
Jagdis 2014[16]	British	Retrospective	II to IVb	66–70 Gy	45	40 mg/m²	28	100 mg/m²
Lee 2015[17]	Korea	Prospective	II to IVb	66–70 Gy	53	40 mg/m²	56	100 mg/m²
Meng 2018[18]	China	Retrospective	III to IVb	66–72 Gy	90	30–40 mg/m²	90	80 mg/m²
Tao 2014[19]	China	Retrospective	II to IVb	68 Gy	73	30–40 mg/m²	81	80 mg/m²
Wang 2019[20]	China	Retrospective	I to IVa	66–72 Gy	93	30–40 mg/m²	229	80–100 mg/m²
Zhu 2018[21]	China	Retrospective	III to IVb	68 Gy	225	40 mg/m²	634	100 mg/m²

Gy = gray, RT = radiotherapy.

toxicity, mucositis and nausea and vomiting. The forest plot of these toxicities are showed in Figures 4, 5 and 6. Weekly cisplatin significantly increased the incidence of grade 3 or higher hematological toxicity (odds ratio, 1.55; 95% CI, 1.22–1.98, $P = .0004$, Fig. 4) compared with triweekly cisplatin. With regards to non-hematological toxicity, there were no significant differences between the 2 arms in the risk of grade 3 or higher mucositis (odds ratio, 0.76; 95% CI, 0.58–1.01, $P = .06$, Fig. 5) and nausea and vomiting (odds ratio, 0.72; 95% CI, 0.31–1.66, $P = .43$, Fig. 6).

3.4. Quality of the included studies

The risks of bias in the studies included in this meta-analysis are detailed in Tables 2 and 3. The methodological quality was high in all the 7 studies.

4. Discussion

Previous studies had demonstrated that weekly and triweekly cisplatin concurrent with radiotherapy showed no differences

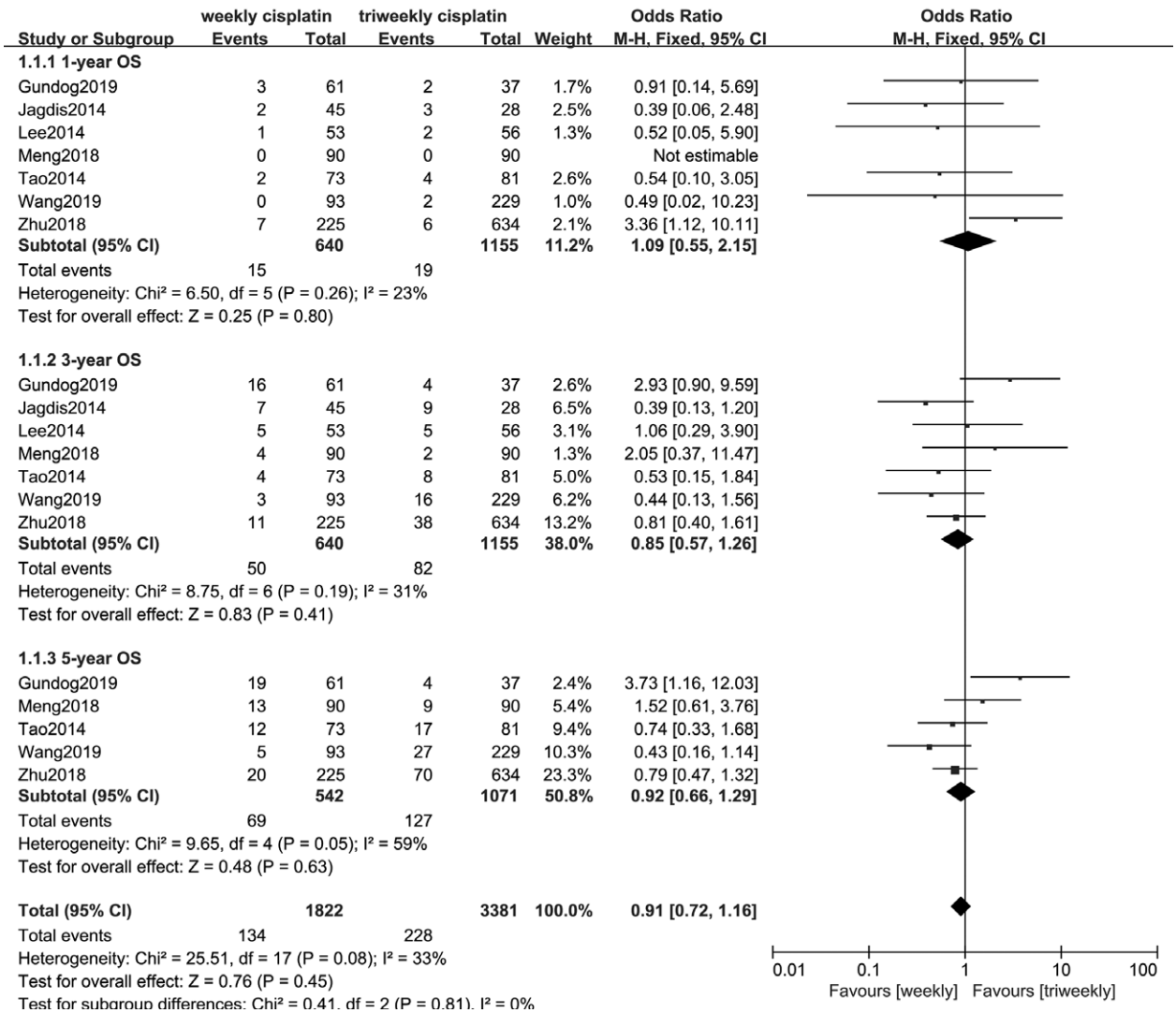

Figure 2. Forest plot of the OS. OS = overall survival.

in efficacy and toxicity in SCCHN.[13,14] However, due to the differences in tumor heterogeneity between NPC and other head and neck cancers, such as invasiveness, treatment sensitivity and prognosis, whether the same conclusion can be made in NPC worths our great concern. Thus, we performed this meta-analysis to evaluate the efficacy and safety of weekly and triweekly cisplatin concurrent with radiotherapy in patients with NPC.

Our study synthesizes results from 7 clinical controlled studies of weekly versus triweekly cisplatin concurrent with radiotherapy in patients with NPC. To our knowledge, this is the first meta-analysis to directly compare the efficacy and safety of weekly with triweekly cisplatin in NPC alone. The results show that no statistical differences were observed in 1-year OS, 3-year OS, 5-year OS, 5-year LRFFS, and 5-year DMFS between the 2 arms, which were consistent with those reported in the previous studies of SCCHN,[13,14,23–25] and confirm the conclusion that the efficacy of weekly cisplatin was similar to that of triweekly cisplatin in NPC.

With regards to toxicities, we analyzed the most common grade 3 or higher adverse events between the 2 arms in our study. We found that the grade 3 or higher mucositis and nausea and vomiting between weekly and triweekly groups showed no significant differences (both $P > .05$), and the results were also consistent with those of SCCHN in the previous studies.[11,13,14] In terms of grade 3 or higher hematologic toxicity, the results of this meta-analysis demonstrated that weekly cisplatin significantly increased the risk of hematological toxicity compared with triweekly cisplatin (1.55; 95% CI, 1.22–1.98, $P = .0004$). Because hematologic toxicity is a severe problem in patients receiving CCRT in NPC, which often resulting in delayed or missed chemotherapy treatments and even impacting the prognosis,[3,26] our meta-analysis suggests that the significant difference in hematologic toxicity may be the key factor affecting the choice of chemotherapy regimens in the case of similar survival benifit. Moreover, triweekly cisplatin is obviously more convenient when using, which may reduce the length of hospital stay or treatment time where compared with weekly cisplatin. Therefore, our results suggest triweekly cisplatin may be a better choice.

Our study has several limitations. First, significant heterogeneity exists among the included studies, such as tumor stage, experimental design, radiotherapy dose, cisplatin dose and method, etc. The study by Wang et al[20] enrolled some patients with stage I, so our results are not restricted to locally advanced patients, but rather reflect the overall efficacy and safety of cisplatin in patients with early-or locally advanced NPC. Second, the number of the included studies is small and most studies are retrospective researches. Third, data of the total grade 3 or higher adverse events was not available, because most studies did not provide enough detailed information. Finally, toxicities among all the included studies were

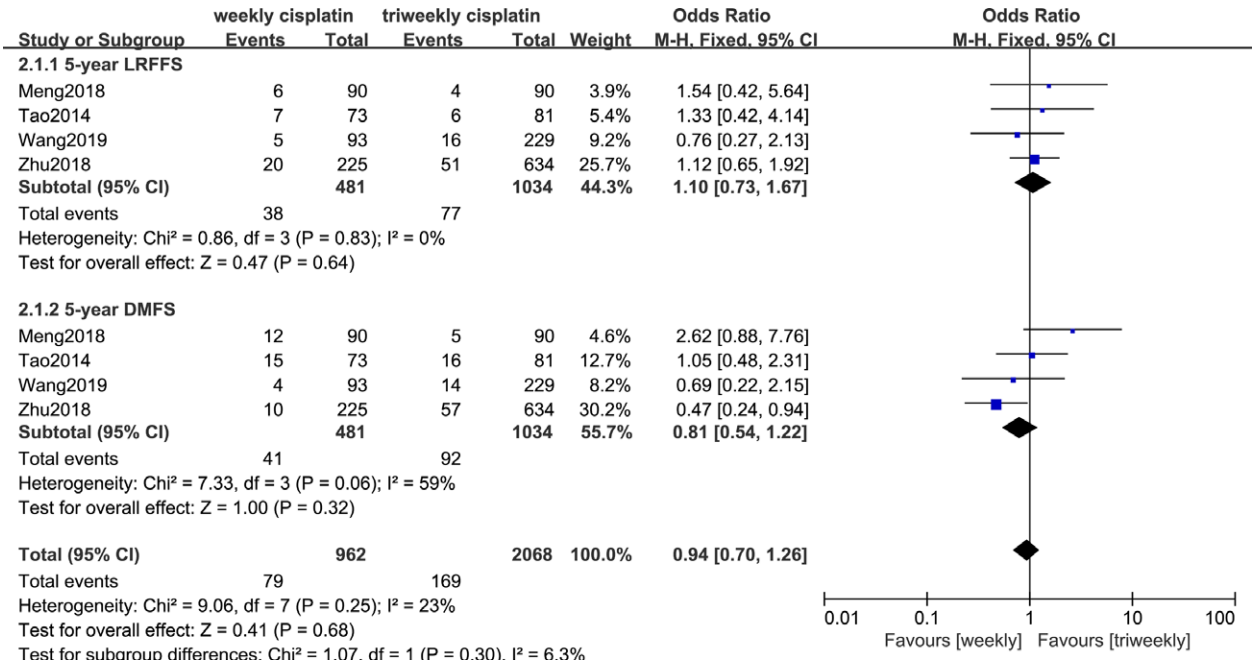

Figure 3. Forest plot of the 5-year LRFFS and DMFS. DMFS = distant metastasis-free survial, LRFFS = loco-regional failure-free survival.

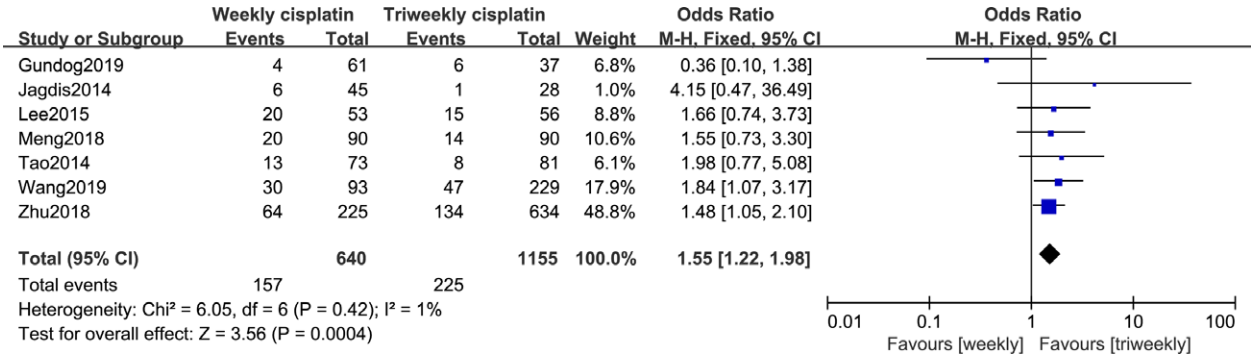

Figure 4. Forest plot of hematological toxicity.

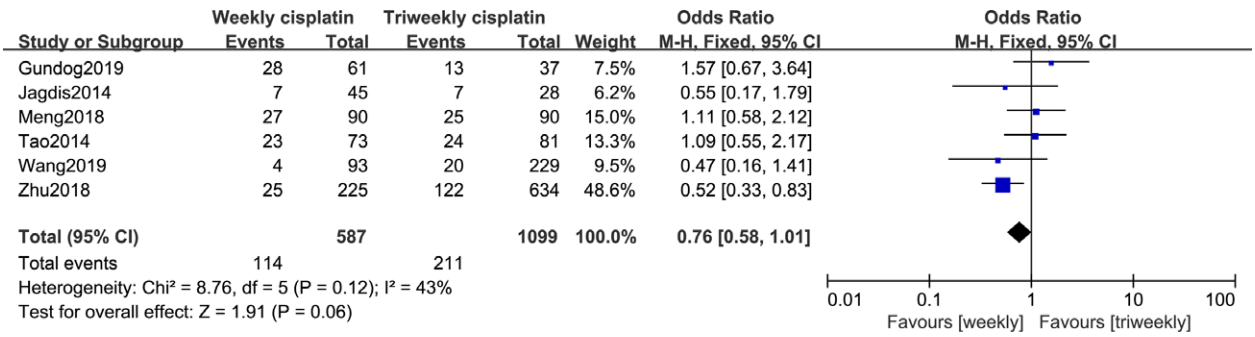

Figure 5. Forest plot of mucositis.

not assessed by unified evaluation criteria, which might lead to an overestimation of totoxic results in this study.

In conclusion, this meta-analysis showed no differences in survival outcomes between weekly and triweekly cisplatin in terms of LRRFS, DMFS and OS. However, triweekly cisplatin showed significantly lower grade 3 or higher hematological toxicity versus weekly cisplatin. Therefore, our study suggests triweekly cisplatin may be a superior treatment option in patients with NPC treated with CCRT. Further investigations are required, because of the risk of limitations.

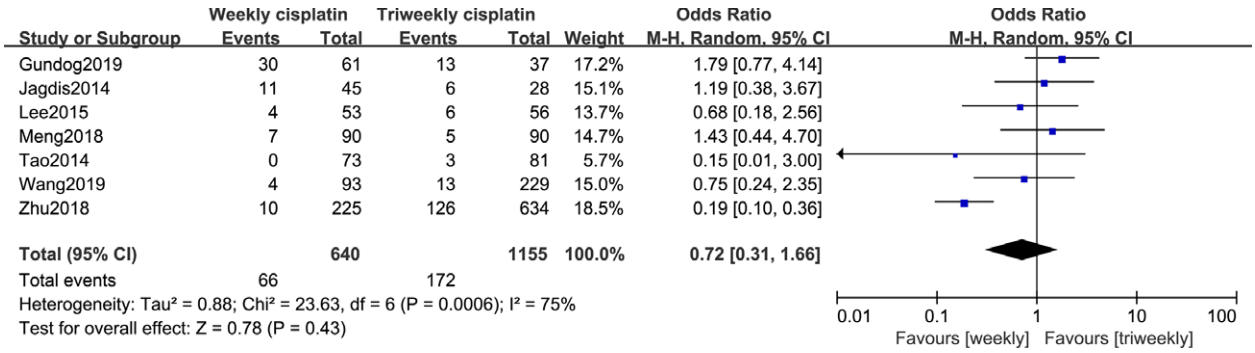

Figure 6. Forest plot of nausea and vomiting.

Table 2

The quality of the included non-RCTs was assessed based on the Newcastle-Ottawa Scale.

Study	Selection star	Comparability star	Outcome star	Total star	Study quality
Gundog 2019	3	2	3	8	High
Jagdis 2014	3	2	2	7	High
Meng 2018	3	2	3	8	High
Tao 2014	3	2	3	8	High
Wang 2019	3	2	3	8	High
Zhu 2018	3	2	3	8	High

RCT = randomied controlled trail.

Table 3

The quality of the included RCTs was assessed according to the Cochrane Intervention Systematic Review Manual.

Study	Sequence generation of randomization	Allocation concealment	Blinding of patients	Blinding of personnel	Blinding of outcome	Study quality
Lee 2015	Yes	Yes	Unknow	Unknow	Unknow	High

RCT = randomied controlled trail.

Author contributions

C.L. and L.Y.C. contributed to the study design and writing.
C.L., L.Y.C., and H.M. carried out the data collection and selection. Z.S.J. and Y.Q.W. carried out the data analysis. All authors read and approved the final manuscript.
Conceptualization: Long Chen, Yi-Chang Li.
Data curation: Min Hu, Yi-Chang Li, Long Chen.
Formal analysis: Shi-Jie Zhao, Qiang-Wei Yang.
Investigation: Min Hu.
Software: Shi-Jie Zhao, Qiang-Wei Yang.
Writing – review & editing: Long Chen, Yi-Chang Li.

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