

# Concurrent Weekly Cisplatin vs Triweekly Cisplatin Alone with Radiotherapy for Treatment of Cervical Cancer: A Meta-Analysis

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**Abstract:** To confirm the difference on side effect and survival between Weekly cisplatin and Triweekly cisplatin combined radiotherapy for cervical cancer treatment. **Method** The searching strategy was developed in EMBASE, MEDLINE and Cochrane library from their earliest publication dates to May 2018. 8 studies were selected to compare weekly cisplatin and triweekly cisplatin combined radiotherapy. **Results** Of the 1134 research literatures, 8 were eligible for inclusion and included in the analysis. Our meta-analysis proved that there were no obvious difference on leukopenia (OR, 0.14;95% CI, 0.04-0.49,  $p=0.07$ ), Gastrointestinal toxicity (OR, 1.17;95% CI, 0.46-2.97,  $p=0.91$ ), and 5-Y OS (OR, 0.93, 95% CI, 0.74-1.17,  $P=0.54$ ) between Weekly cisplatin and Triweekly cisplatin combined radiotherapy, but Weekly cisplatin has the tendency to reduce the leukopenia happen. **Conclusion** Weekly cisplatin and Triweekly cisplatin combined radiotherapy have their own advantages, and there were no obvious difference between them. Patients can choose the treatment that suits themselves.

**Keywords:** Cervical Cancer, Cisplatin, Side Effects, Meta-Analysis, 5-Year OS

## Introduction

Cervical cancer (CC) is the third most common gynaecologic cancer in woman worldwide, with estimated 528000 new cases and 266000 deaths each year[1]. Sustaining infection by high risk human papillomavirus (HR-HPV) is widely recognized as the development of precancerous lesions and invasive carcinoma of CC[2]. Although several progresses such as screening, vaccination, diagnostic and treatment strategies have been made, the increasing morbidity of CC among women and the refractoriness of advanced CC arouse to be new problems. Currently, For the early CC is usually treated by surgery, which can effectively remove the focus, but most of patients have been attached to the advanced cancer stage, the main method usually through radiation therapy. But only used the treatment with simple radiation therapy has limited therapeutic effect and must be look for a scientific and effective treatment to improve patient survival. Nowadays, synchronous radiotherapy combined with cisplatin has been the mainstream treatment for CC, Several random tests show that treatment options combining radiation therapy and platinum-based chemotherapy annual overall survival rate and progression-free survival rate stage IIb ~ IVa cervical cancer patients[3]. Cisplatin treatment of CC is currently the most clinically common treatment options, but its with greater side effects. In 2002, weekly cisplatin gradually replaced cisplatin and

5-FU because of the reason was weekly cisplatin chemotherapy had less toxicity[4]. Platinum-based chemotherapy includes cisplatin, carboplatin, and neatazol. Cisplatin is a standard preparation for chemotherapy. Catano reported that weekly carboplatin combined with radiation therapy has a high efficacy with moderate progression-free survival and overall survival in advanced CC[5]. There has been reported that triweekly cisplatin 75mg/m<sup>2</sup> chemotherapy combined with radiotherapy was more effective and feasible than the conventional weekly cisplatin 40 mg/m<sup>2</sup> schedule may be a strong candidate for the optimal cisplatin dose and dosing schedule in the treatment of advanced CC[6]. So, which method is a better choice? We use sensory meta-analysis to better characterize the difference between weekly and triweekly cisplatin, which is beneficial to clinicians and patients. Our analysis was a comparison of adverse reactions and survival rates between drug regimens.

## Materials and Methods

### Search strategy and study selection

To get access to potentially eligible studies, The searching strategy was developed in EMBASE, MEDLINE and Cochrane library from their earliest publication dates to May 2018 with the key words with all the possible combinations: "weekly" "cisplatin" "cervical cancer" "triweekly".

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Published at: <http://www.ijsciences.com/pub/issue/2019-03/>

DOI: 10.18483/ijSci.1968; Online ISSN: 2305-3925; Print ISSN: 2410-4477



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### References of the identified articles were also checked.

All eligible studies were reviewed and collected according to the selection criteria by two researchers separately. Any disagreement between the two reviewers was resolved by discussion or consult to the third-party. The name of the first author and the year of publication for this article is used for identification purposes. The following data was extracted: adverse effect, the overall survival (OS). All resulting citation abstracts were reviewed for potential eligibility, and the full article texts were obtained for further evaluation in cases in which abstracts did not provide enough details for the determination of eligibility.

### Statistical analysis

Data were extracted from the primary articles and meta-analysis was calculated with the use of RevMan 5.3 software (Cochrane Collaboration, <http://community.cochrane.org/tools/reviewproduction-tools/revman-5/revman-5-download>). The results of adverse reactions were calculated by ratio and expressed by corresponding 95% confidence interval (CI). However, if we want to compare OS and DFS between weekly patients treated with cisplatin and patients treated with triweek of cisplatin and radiotherapy, it is usually problematic because the most appropriate summary statistics are usually not provided. Based on the Kaplan-Meier curve, the summary information of eligible studies was estimated to calculate the risk ratio (HR) and 95% confidence interval (CI).

### Results

**Study selection.** 1134 possible related references were identified by search. Further 14 possible related literatures were identified by reviewing the list of references. After reading the headlines and abstracts to exclude duplicate and irrelevant references, the number of articles that needed to be effectively read was 785. After reading the full text, 109 references were excluded due to the lack of valid data or due to lack of relevant data. Finally, 8 studies[4, 6-13] served as data sources for the present meta-analysis (Table 1). Figure 1 shows the flowchart of the search results.

### Side effects

At present, there are many side effects of chemotherapy or radiation therapy for CC. According to related literature reports, the longest side effect were leucopenia and gastrointestinal toxicity. Therefore, we mainly analyze the data of these two aspects.

### leukopenia

There were 6 studies reported the event of leukopenia were included in the meta analysis. There were no difference between Weekly cisplatin and Triweekly

cisplatin combined radiotherapy (OR, 0.14;95% CI, 0.04-0.49,  $p=0.07$ ), but there has obvious trend for Weekly cisplatin reduce the leukopenia. Figure 2 shows the forest plot for leukopenia rate. However, the heterogeneity of the results is high ( $\chi^2 = 31.72$ ;  $df=5$  ( $p < 0.00001$ );  $I^2=84\%$ ), and the credibility of the results is to be further studied in subsequent forest experiments.

### Gastrointestinal toxicity

There were 5 studies involved in the Gastrointestinal toxicity meta-analysis. From the picture 3, we can also find that there were no obvious different between Weekly cisplatin and Triweekly cisplatin combined radiotherapy (OR, 1.17; 95% CI, 0.46-2.97,  $p=0.91$ ).

### Survival rate

The combined OR of 5-year OS was 0.93 (95% CI, 0.74 to 1.17;  $P = 0.54$ ). Weekly cisplatin and Triweekly cisplatin combined radiotherapy showed no statistical difference in the 5-year OS rate. The Cochran tests for heterogeneity showed that  $\chi^2 = 4.46$ ,  $df = 2$  ( $P = 0.11$ );  $I^2 = 55\%$ , which showed that there is no significant inconsistency (Figure 4).

### Discussion

Cervical cancer is one of the major cause of death for woman in the world. In the past, radiotherapy was the first choice for treating advanced CC, but the failure rate was so high. Currently, chemoradiotherapy is the main treatment for local advanced CC, Chemotherapy prescription included cisplatin, platinum combined paclitaxel, fluorouracil, etc.

The purpose of our research was to evaluate the treatment efficiency of Weekly cisplatin and Triweekly cisplatin combined radiotherapy for patients. There were total 8 studies were included in this meta-analysis, 6 studies were randomized controlled clinical trials with a parallel design in advanced CC. however, Kinjyo and Lee were retrospective study in postoperative CC. Leukopenia occurs mainly with chemotherapy, the factors affecting the severity include: the dose of chemotherapy drugs, the number of chemotherapy courses, the toxicity degree of different chemotherapy drugs, and the dose of bone marrow exposure and so on[14]. It is known that cisplatin combined with radiotherapy has more toxicity than cisplatin alone. Although our results were not proved the difference between Weekly cisplatin and Triweekly cisplatin combined radiotherapy, but as the number of clinical trials increases, research deepens, the results may change. The single dose of cisplatin was 30-40  $mg/m^2$ , while combining dose was 75  $mg/m^2$ . Although has a three-week interval, the toxicity is still greater than that of single-week medication.

Acute toxic and side effects of chemoradiotherapy for CC also include digestive symptoms usually characterized by nausea, vomiting, abdominal pain, bloating, diarrhea, frequent urination, urgency, and hematuria. In our research there is no differentiation in gastrointestinal toxicity. It shows that the prescription of cisplatin combined with radiotherapy does not increase the risk of gastrointestinal toxicity compared with cisplatin alone.

Although patients prefer to choose Triweekly cisplatin because its more convenient and flexible, but Weekly cisplatin may has less side effect to human body because its shows lower risk hematologic toxicity for CC. For 5-year survival rate part, there were no obvious different between two treatment method, this result proved these treatments have no significant effect on longevity. Li reported that Weekly cisplatin chemotherapy group had the same effect as Triweekly cisplatin combined chemotherapy group, but had less toxicity[7]. From this research, we found that there have no difference between Weekly cisplatin and Triweekly cisplatin combined radiotherapy, they all have their own advantages, patients can choose appropriate treatment method according to their own needs. And we also look forward to further clinical trials to confirm which treatment method can better treat patients and

reduce the occurrence of side reactions.

### Conclusion

In conclusion, our analysis seems to support that weekly cisplatin and Triweekly cisplatin combined radiotherapy have their own advantages, and there were no obvious difference between them. Patients can choose the treatment that suits themselves.

### Availability of data and materials

The datasets analyzed during the current study are not publicly available due to further publications pending but are available from the corresponding author on reasonable request.

### Authors' contributions

Hong Yu reviewed the manuscript. Zhe Sun analyzed the data and wrote the manuscript. Xianfei Yan and Xiaolu Fang analyzed the data and wrote the manuscript.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

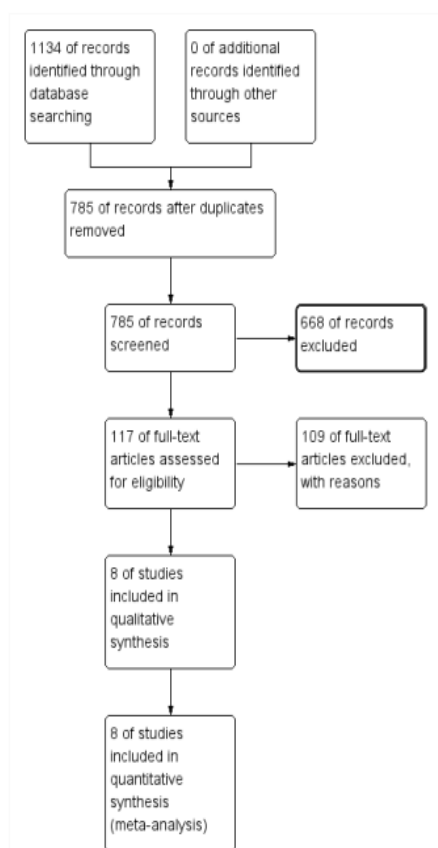


Figure 1. Flowchart of the process for the identification of relevant studies.

Table 1. Studies included in the present meta-analysis

| Author Year | Methods | Stage N(QW/Q3W) | Concurrent Chemotherapy   |
|-------------|---------|-----------------|---|
| Kumar 2017  | RCT     | Ia-IIIb 25/25   | QW: Cisplatin 35mg/m <sup>2</sup> , 5 cycles; Q3W: Cisplatin 75mg/m <sup>2</sup> , 2 cycles   |
| Kinjo 2017  | Retro   | Ib-IVa 75/110   | QW: Cisplatin 40mg/m <sup>2</sup> , 5 cycles; Q3W: Cisplatin 20mg/m <sup>2</sup> 5days, 2cycles   |
| Panda 2017  | RCT     | IIB-IVa 41/41   | QW: Cisplatin 40mg/m <sup>2</sup> , 5 cycles; Q3W: Cisplatin 75mg/m <sup>2</sup> , 3cycles  |
| Lee 2011    | Retro   | IB-IIB 71/130   | QW: Cisplatin 40mg/m <sup>2</sup> , 6 cycles; Q3W: Cisplatin 75mg/m <sup>2</sup> , 3 cycles Combined FU, Paclitaxel, etc  |
| Ryu 2011    | RCT     | IIIB-IVa 51/53  | QW: Cisplatin 40mg/m <sup>2</sup> , 6 cycles; Q3W: Cisplatin 75mg/m <sup>2</sup> , 3 cycles   |
| Torres 2008 | RCT     | I-IV 27/55      | QW: Cisplatin 40mg/m <sup>2</sup> , 6 cycles; Q3W: Cisplatin 75mg/m <sup>2</sup> , 3 cycles combined FU 4gm/m <sup>2</sup> /96h   |
| Rose 2007   | RCT     | IIB-IVa 176/173 | QW: Cisplatin 30mg/m <sup>2</sup> , 6 cycles; Q3W: Cisplatin 50mg/m <sup>2</sup> , 2 cycles combined FU 4gm/m <sup>2</sup> /96h, Hydroyurea 2gm/m <sup>2</sup> , twice per week |
| Rose 1999   | RCT     | IIB-IVa 176/173 | QW: Cisplatin 30mg/m <sup>2</sup> , 6 cycles; Q3W: Cisplatin 50mg/m <sup>2</sup> , 2 cycles combined FU 4gm/m <sup>2</sup> /96h, Hydroyurea 2gm/m <sup>2</sup> , twice per week |

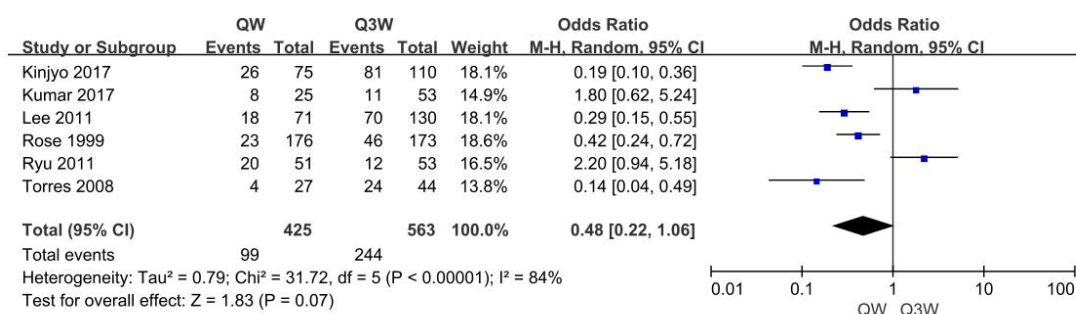


Figure 2 Funnel plot of this analysis, between Weekly cisplatin and Triweekly cisplatin combined radiotherapy (OR, 0.14; 95% CI, 0.04-0.49, p=0.07), the heterogeneity of the results is high (chi<sup>2</sup> = 31.72; df=5(p < 0.00001); I<sup>2</sup>=84%)

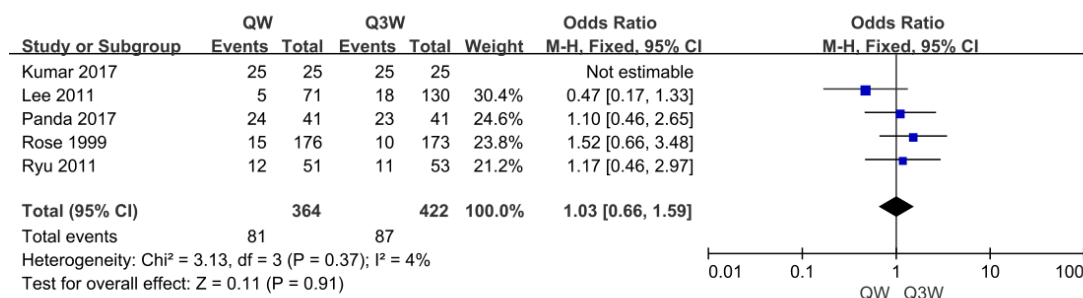


Figure 3 Funnel plot of this analysis. there were no obvious different between Weekly cisplatin and Triweekly cisplatin combined radiotherapy (OR, 1.17; 95% CI, 0.46-2.97, p=0.91).

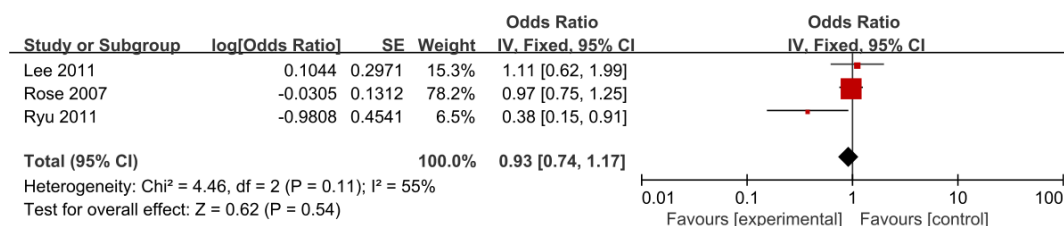


Figure 4 The combined OR of 5-year OS was 0.93 (95% CI, 0.74 to 1.17;  $P = 0.54$ ). Weekly cisplatin and Triweekly cisplatin combined radiotherapy showed no statistical difference in the 5-year OS rate. The Cochran tests for heterogeneity showed that  $\chi^2 = 4.46$ ,  $df = 2$  ( $P = 0.11$ );  $I^2 = 55\%$ ,

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