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Review Article

Platinum single-agent vs. platinum-based doublet agent concurrent chemoradiotherapy for locally advanced cervical cancer: A meta-analysis of randomized controlled trials

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HIGHLIGHTS

- A meta-analysis was conducted to compare treatment outcomes and adverse events of radiotherapy with concurrent platinum-based doublet/single-agent therapy.
- Concurrent RT with platinum-based doublet chemotherapy significantly improved the OS and PFS.
- Grade 3 or 4 vomiting, thrombocytopenia, and urinary system toxicity were more frequent in the polychemotherapy arm.

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ABSTRACT

Objectives. This study compared treatment outcomes and adverse events in patients with locally advanced cervical cancer undergoing radiotherapy (RT) with concurrent platinum-based doublet therapy vs. RT plus platinum single-agent therapy. The main outcomes were progression-free survival (PFS), overall survival (OS), and the occurrence of adverse events.

Methods. We comprehensively searched Medline, Embase, the Cochrane Library, China National Knowledge Web, Wanfang Database, and VIP database, and performed a systematic review and cumulative meta-analysis of all randomized controlled trials (RCTs) by using the fixed-effect or random-effect models. The primary endpoints were OS and PFS, reported as hazard ratios (HRs) and 95% confidence intervals (95% CIs). The meta-analysis was performed with RevMan 5.2.

Results. Seven randomized trials including 1503 patients were identified. The meta-analysis showed that, for locally advanced cervical cancer, concurrent RT with platinum-based doublet chemotherapy significantly improved the OS (HR 0.75, 95% CI 0.60–0.94, $p = 0.01$) and the PFS (HR 0.78, 95% CI 0.65–0.94, $p = 0.01$) compared to RT with cisplatin monotherapy. Grade 3 or 4 vomiting (related ratio [RR] = 3.19, 95% CI 1.85–5.49, $p < 0.0001$) and thrombocytopenia (RR = 2.75, 95% CI 1.39–5.44, $p = 0.004$) occurred more frequently in the polychemotherapy arm. The incidence of urinary system toxicity tended to be higher in the polychemotherapy arm (RR = 4.58, 95% CI 1.00–20.89, $p = 0.05$).

Conclusions. Under the premise of good tolerance, RT plus platinum-based doublet therapy improves survival compared to RT plus platinum single-agent therapy in patients with locally advanced cervical cancer.

Contents

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1. Introduction

Cervical cancer is the most common gynecological malignant tumor, preceded only by breast cancer in developing countries. It is the third most common cancer among women worldwide, after colorectal cancer and breast cancer; over 500,000 new cases are diagnosed and there are 250,000 deaths annually, 80% of which are in developing countries. In China, with the development of disease screening, the incidence of cervical cancer has dropped significantly, but it has recently started to increase in younger groups. In most developed countries, patients with cervical cancer are diagnosed in the early stage due to disease screening, and they then receive surgery or radical radiotherapy (RT). However, in developing countries, >80% of patients are diagnosed with locally advanced cervical cancer, including stage IIB–IVA, and have poor prognosis [1].

The National Comprehensive Cancer Network treatment guidelines recommend concurrent chemoradiotherapy (CCRT) as the standard treatment for stage IIB and higher cervical cancer. Although several studies [2–6] have compared RT with concurrent platinum-based doublet therapy and RT plus platinum single-agent therapy, it is still uncertain which of them is superior. Petrelli [7] et al. conducted a meta-analysis of 1500 patients with advanced cancer, including 4 randomized controlled trials (RCTs) and 4 retrospective analyses, and showed that concurrent RT with cisplatin-based doublet chemotherapy significantly improved the overall survival (OS) (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.51–0.81; $p = 0.0002$), progression-free survival (PFS) (OR, 0.71; 95% CI, 0.55–0.91; $p = 0.006$), and rate of locoregional relapse (OR, 0.64; 95% CI, 0.47–0.89; $p = 0.008$) compared to RT with concurrent weekly cisplatin alone. This indicated that platinum-based combination therapy plus RT should be the preferred treatment over weekly cisplatin plus RT for patients with advanced cervical cancer. However, the study by Petrelli et al. has limitations in the selection of statistical effect indicators and the heterogeneity of the included studies. Therefore, this study aimed to improve upon that study and include additional studies in the meta-analysis.

2. Methods

2.1. Search method

Medline, the Cochrane library, Embase, China National Knowledge Web, Wanfang, and VIP databases were searched for studies published through January 31, 2018. The following MeSH terms and their combinations were searched in the [Title/Abstract]: cervical cancer, cervical carcinoma, uterine cervix cancer; concurrent chemoradiotherapy, CCRT, concurrent radiotherapy and chemotherapy, and chemoradiotherapy. Reference lists of all retrieved studies and related articles were also examined.

2.2. Inclusion and exclusion criteria

All included studies were prospective RCTs that compared RT plus concurrent platinum-based doublet therapy and RT plus a platinum single agent. All patients were pathologically diagnosed with cervical adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma. The clinical International Federation of Gynecology and Obstetrics (FIGO) stage was stage IIB-IVA (advanced cervical cancer). All patients were under primary treatment with no contraindications for chemoradiotherapy. When multiple reports describing the same population were published, only the most recent or complete report was included.

We excluded studies in which patients (FIGO IB-IIB) received preoperative neoadjuvant chemoradiotherapy or postoperative adjuvant CCRT, those that excluded patients with recurrence or distant metastasis, and those that excluded patients with severe medical disease (PS ≥ 2). We excluded articles published neither in English nor Chinese. Case reports, reviews, and conference articles were also excluded.

2.3. Data extraction and outcomes of interest

Data from the included studies were extracted and summarized independently by two investigators (SYM and YYH). Any disagreement was resolved by the adjudicating senior author (WZ).

The outcome indicators were OS and PFS. Hazard ratios (HRs) and 95% CIs were extracted from complete survival curves and sufficient survival data. We also assessed chemoradiotherapy-related adverse events.

2.4. Quality assessment and statistical analysis

The quality of RCTs was assessed using the Cochrane risk of bias tool [8]. Review Manager 5.2 software was used to perform the meta-analysis. A fixed-effects or random-effects model was used for this meta-analysis. Statistical heterogeneity of the results of the studies was assessed using the chi-square test, expressed with the I^2 index or p-value. If the heterogeneity test result was $p > 0.10$ or $I^2 \leq 50\%$, it was considered that there was no obvious heterogeneity of the included studies, and the fixed-effect model was used. When heterogeneity was detected, a possible explanation was intensively pursued. If a reasonable cause was found, a subgroup analysis was then performed. Otherwise, a random-effects model was used. For time-to-event data, the HR was used as a summary statistic for effect outcomes (OS and PFS), and the 95% CI was calculated for each point estimate. An HR >1 represented a survival benefit favoring the platinum-based doublet therapy group. When HRs were not provided by the original text, we estimated them from survival curves using Engauge Digitizer 4.1 software with the method previously described by Jayne F Tierney [9]. The related ratio (RR) was used as a summary statistic for the side effect rate. An RR >1 represented that toxicity effects occurred more frequently in the polychemotherapy arm. Funnel plots were used to screen for potential publication bias.

3. Results

3.1. Literature search

A total of 2917 potential related articles were found by the defined search strategy. After excluding duplicates, 2126 reports remained, of

which 2095 were excluded after title and abstract review. The remaining 31 articles were fully reviewed, and 24 were excluded for the following reasons: 1 study was written in neither English nor Chinese, 17 studies had chemotherapy regimens that did not match, 6 studies were retrospective studies, and 1 study had obvious bias. Finally, 7 RCTs [3–5,10–13] with a total of 1503 patients were included: 748 patients received platinum-based CCRT and 755 patients received platinum single-agent therapy plus RT. Fig. 1 shows the details of the selection process.

3.2. Characteristics of the included studies

This study included 7 RCTs, including 2 phase III clinical studies, each of which was searchable in full. Table 1 shows the details of the studies.

3.3. Quality assessment

The quality of the 7 included RCTs was assessed using the Cochrane risk of bias tool. The studies by Dueñas-González, Wang, and Veerasarn were open-label trials with a high risk of allocation concealment. Nedovic grouped patients according to the order of occurrence, which did not conform to the principle of random allocation and was considered high-risk. Other than the study by Li, which included a detailed description that double-blind treatment used for researchers and patients, no explanation was found in other studies, and the risk of performance bias was unknown. The quality assessment for the included studies is shown in Supplementary Fig. 1 and Supplementary Fig. 2.

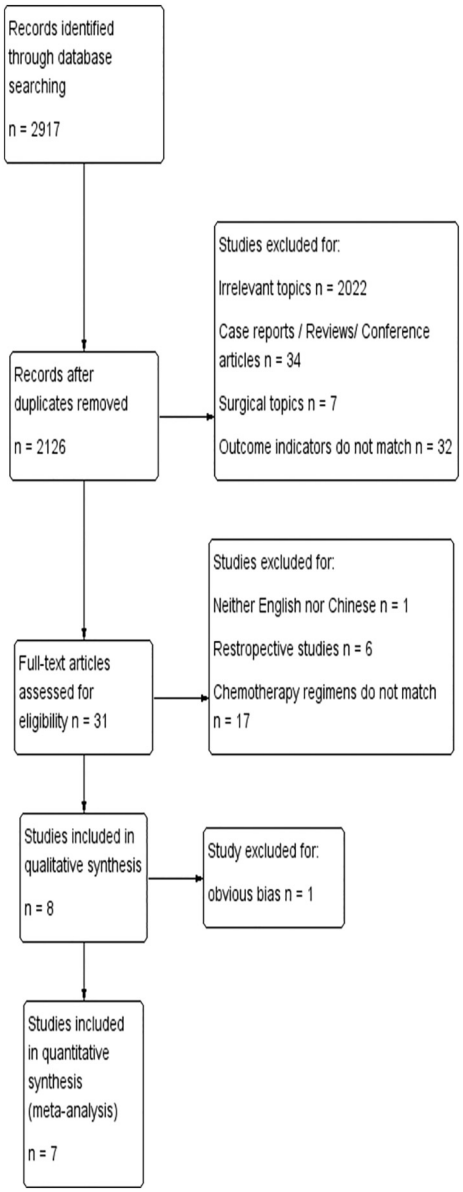

Fig. 1. Flowchart showing publication selection.

3.4. Outcomes: OS, PFS, and toxicity

The OS was reported in 7 studies, and the fixed-effect model was chosen as there was no heterogeneity ($p = 0.92$, $I^2 = 0\%$). The meta-analysis showed that, for locally advanced cervical cancer, concurrent RT with platinum-based doublet chemotherapy significantly improved the OS (HR = 0.75, 95% CI 0.60–0.94, $p = 0.01$; Fig. 2).

Data from 7 studies assessing the PFS showed no obvious heterogeneity between the two groups ($p = 0.26$, $I^2 = 22\%$). The meta-analysis revealed that concurrent RT with platinum-based doublet chemotherapy significantly improved the PFS (HR = 0.78, 95% CI 0.65–0.94, $p = 0.01$; Fig. 3).

The development of hematologic toxicities was reported in 5 studies. There was a significant heterogeneity between the two groups in the incidence of leukopenia ($p < 0.00001$, $I^2 = 87\%$) and anemia ($p = 0.05$, $I^2 = 61\%$). Considering the different side effects caused by different chemotherapy regimens, the patients were further subdivided into a gemcitabine group and a fluorouracil group, based on the type of chemotherapy combined with the platinum-based agent. The subgroup analysis showed that the heterogeneity of the gemcitabine subgroup was still significant (leukopenia $p < 0.00001$, $I^2 = 95\%$; anemia $p = 0.03$, $I^2 = 79\%$). The cause of heterogeneity was analyzed, including experimental design, measurement, chemotherapy and RT dose, average age and gender composition of the patients, period of treatment, and severity of disease. The possibility of radiation dose difference and racial difference were ultimately considered, and the random-effect model was used for statistical analysis. There was no evidence that concurrent RT with platinum-based doublet chemotherapy increased the risk of leukopenia (RR = 2.41, 95% CI 0.9–6.44, $p = 0.08$; Fig. 4) or anemia (RR = 1.35, 95% CI 0.41–4.44, $p = 0.63$; Supplementary Fig. S3) compared to the cisplatin monotherapy arm. However, the meta-analysis of 5 trials indicated that the platinum-based polychemotherapy arm increased the risk of thrombocytopenia (RR = 2.75, 95% CI 1.39–5.44, $p = 0.004$) with an acceptable heterogeneity ($p = 0.24$, $I^2 = 28\%$; Supplementary Fig. S4).

Non-hematologic toxicities were also reported. Data of 7 trials were assessed to evaluate the incidence of vomiting and showed a difference favoring the platinum single-agent therapy arm (RR = 3.19, 95% CI 1.85–5.49, $p < 0.0001$) with no obvious heterogeneity ($p = 0.88$, $I^2 = 0\%$) (Supplementary Fig. S5). The incidences of urinary system toxicity from the data of 4 trials tended to be higher in the polychemotherapy arm (RR = 4.58, 95% CI 1.00–20.89, $p = 0.05$) with no heterogeneity among the studies ($p = 0.88$, $I^2 = 0\%$) (Supplementary Fig. S6).

3.5. Publication bias

Fig. **5** shows a funnel plot of the studies included in this meta-analysis that reported OS. All of the studies lay inside the 95% CIs, with an even distribution around the vertical line, indicating no obvious publication bias.

4. Discussion

This meta-analysis of 7 RCTs including 1503 patients compared platinum single-agent and platinum-based doublet agent chemoradiotherapy for locally advanced cervical cancer; results showed that platinum-based doublet therapy plus RT improved survival as it significantly prolonged the OS and PFS. However, there was a higher incidence of

Table 1
Characteristics of included studies.

Author	Year	Type	Median age (exp/ctr)	Stage	Patients (exp/ctr)	CT regimens	RT doses
Veerasarn	2007	RCT	49.6/49.7	IIB-IVA	234/235	Tegafur-uracil + carboplatin/carboplatin	EBRT 40–50 Gy/20–25 F + ICRT(NR)
Kim	2008	RCT	60/57	IIB-IVA	79/79	5- FU + cisplatin/cisplatin	EBRT 41.4–50.4 Gy/23–28 F +ICRT 30–35 Gy/6–7 F
Dueñas-González	2011	RCT	45/46	IIB-IVA	259/256	Gemcitabine + cisplatin/cisplatin	EBRT 50.4 Gy/28 F +ICRT 30 Gy/6 F
Nedovic	2012	RCT	51/54	IIB-IVA	64/70	5-FU + cisplatin/cisplatin	EBRT 50.4–54 Gy/20–30 F +ICRT 30–34 Gy/5 F
CC Wang	2015	RCT	55/56	III-IVA	37/37	Gemcitabine + cisplatin/cisplatin	EBRT 45 Gy/25 F + ICRT 25.8 Gy/6 F
Z. Li	2015	RCT	51.7/49.8	IIB-IVA	36/36	S-1 + cisplatin/cisplatin	EBRT 50 Gy/25 F +ICRT 10 Gy/2 F
Thakur	2016	RCT	NR	IIA-IIIB	39/42	Paclitaxel + cisplatin/cisplatin	EBRT 50 Gy/25 F +ICRT 35 Gy/7 F

RCT, randomized control trial; NR, not reported; CT, chemical therapy; RT, radiotherapy; EBRT, external beam radiotherapy; ICRT, intracavitary radiotherapy.

grade 3 or 4 vomiting and thrombocytopenia, and urinary system toxicity tended to occur more frequently in the polychemotherapy arm.

The role of chemotherapy in CCRT is mainly to improve the sensitivity of RT. Chemotherapy sensitization corresponds to the 4R principle of oncologic radiobiology. Most single-regimen chemotherapies have limited effects owing to the dose limits. Therefore, combination chemotherapy can achieve effects that cannot be achieved with a single drug. In contrast, each drug can achieve maximum cell death within the tolerance of the human body even though tumor cells are heterogeneous. However, drug resistance could be prevented or decelerated by the combined administration of cell cycle-non-specific agents and cell cycle-specific agents. Therefore, platinum-based doublet therapy improves survival compared to platinum single-agent therapy, although it is accompanied by a higher incidence of toxic side effects, as hypothesized.

Considering the limited number of studies comparing platinum-based monotherapy and platinum-based combination chemotherapy as well as the quality of the trials, language, and type of research, we included only a limited number of studies in this analysis. Therefore, differences in RT and chemotherapy doses, combination regimens, and length of follow-up among studies were inevitable.

Cisplatin was the most common first-generation platinum single agent to be administered alongside RT in patients with advanced cervical cancer, and carboplatin has been more commonly used in recent studies. Sebastião [14] showed that single-agent cisplatin and carboplatin plus RT have similar survival benefits and toxicity. The study conducted by Nam [15] et al. also supports this conclusion. For patients who cannot receive cisplatin, carboplatin may be an alternative treatment. Combination chemotherapy regimens are generally platinum combined with docetaxel, paclitaxel, gemcitabine, and fluorouracil. The study by Sol [16] showed no significant difference in the 5-year OS and PFS between patients receiving cisplatin plus fluorouracil and those receiving cisplatin plus paclitaxel, underlining the opportunities in the selection of clinical medication.

The trials included in this study involved the combination of platinum and other chemotherapy drugs. However, there was no significant heterogeneity in the OS ($p = 0.92$, $I^2 = 0\%$) or PFS ($p = 0.26$, $I^2 = 22\%$) among the studies; therefore, subgroup analysis was not necessary. With regard to toxic effects, there was a significant heterogeneity in the occurrence of leukopenia ($p < 0.00001$, $I^2 = 87\%$) and anemia ($p = 0.05$, $I^2 = 61\%$) between the two arms in this meta-analysis. Considering the different side effects caused by different types of chemotherapy drugs, patients were divided into a gemcitabine group and a fluorouracil group. The gemcitabine subgroup proved to be markedly heterogeneous. The patients' age, tumor stage, chemotherapy regimens, and chemotherapy dose had no obvious differences; therefore, the possibility of radiation dose difference and racial difference was considered, as the RT dose (external beam RT + intracavity RT) difference was nearly 10 Gy, and we included studies from both North America and East Asia. In terms of toxicity and side effects, grade 3 or 4 vomiting and thrombocytopenia occurred more frequently in the polychemotherapy arm. The incidence of urinary system toxicity tended

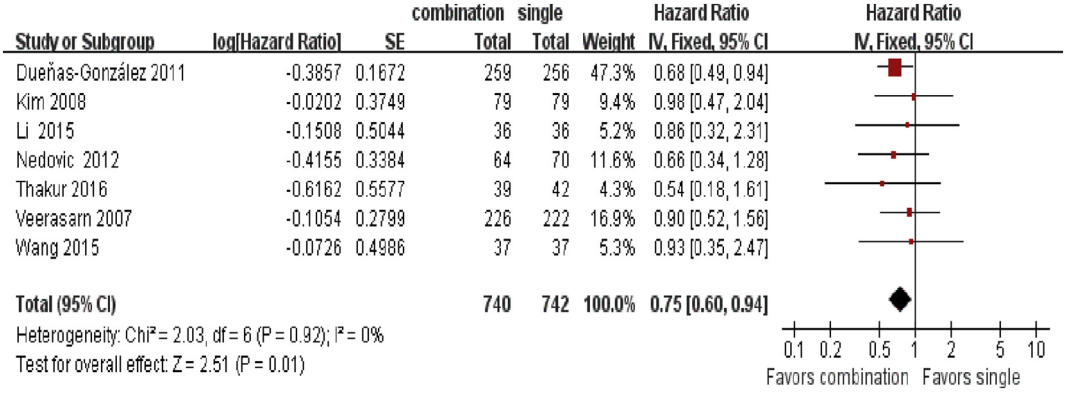

Fig. 2. Forest plot and meta-analysis of overall survival. SE: standard error; CI, confidence interval.

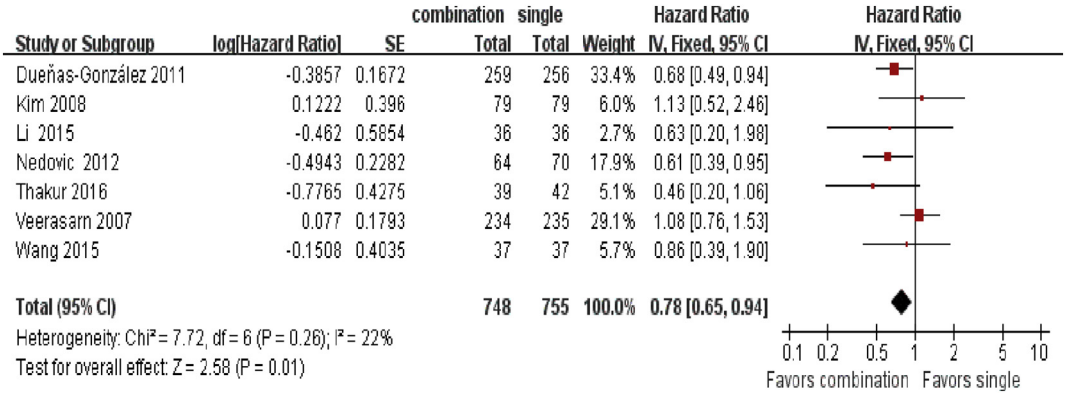

Fig. 3. Forest plot and meta-analysis of progression-free survival. SE: standard error; CI, confidence interval.

to be higher in the polychemotherapy arm. Thrombocytopenia caused by gemcitabine is very common in clinical practice, and in 2 of the 5 trials included in this study, cisplatin was administered combined with gemcitabine. More studies are needed to reduce the possibility of bias due to the large proportion of patients administered gemcitabine.

Petrelli et al. had conducted a meta-analysis of four RCTs and four retrospective analyses with statistical effect indicators as the ORs; they showed that platinum-based combination therapy plus RT should be the preferred treatment over weekly cisplatin plus RT for patients with advanced cervical cancer. However, Yang et al. pointed out that survival data is a type of time-to-event-data, which not only indicate the occurrence of events but also reflect the time elapsed from the occurrence of this result and consider the existence of censored data. The ratio of the incidence of an event is a dichotomous variable, which is not sufficient to describe the whole process of the actual event. At present, the clinical observation of cancer prognosis is mostly reflected by changes in OS and PFS in the form of survival curves. However, there are still many time-to-event-data that meta-analyses select as a specific time point for point estimation (OR or RR). The incomplete data obtained by this approach may lead to inappropriate conclusions. In our study, HRs were used as summary statistics for effect outcomes. On researching the published articles for outcomes of RT with concurrent platinum-based doublet therapy versus RT plus platinum single-agent therapy in patients with locally advanced cervical cancer, we found that all results were expressed as ORs. This study is the first to use the HR as an indicator. This meta-analysis made a breakthrough on the basis of previous research by using the HR as the statistical effect indicator and by including 7 RCTs, more than that used in the study by Petrelli et al., to yield a much higher evidence level.

The results of the incorporation of immunotherapy associated with chemotherapy and RT could change the treatment approach for cervical cancer. The JGOG study [17], a phase III placebo-controlled double-blind randomized trial of RT for stage IIB-IVA cervical cancer with or without the immunomodulator Z-100, indicated that the 5-year OS rates were 75.7% for Arm Z (Z-100) and 65.8% for Arm P (placebo), and the HR was 0.65 (95% CI 0.40–1.04). A survival benefit in Arm Z was observed regardless of whether patient received chemoradiation or radiation alone. The study conducted by Enwere et al. [18] aimed to determine the pre-treatment tumor expression of PD-L1 in locally advanced cervical cancer patients treated with radical chemoradiotherapy. The high percentage of cervical cancer tumor samples expressing PD-L1 in their study suggests that anti-PD-L1 or anti-PD-1 therapies are potential treatment options for this patient population. The US FDA has approved Keytruda (pembrolizumab) as a second-line treatment for patients with recurrent or metastatic cervical cancer, but there is no specific study to explore the effect of immunotherapy on chemotherapy regimen or dose in CCRT for cervical cancer. We firmly believe that the addition of immunotherapy will affect the treatment mode of CCRT. However, CCRT is still the first-line treatment for locally advanced cervical cancer currently.

Since escalation of the radiation dose is constrained by the increase in toxicity, more effective chemotherapy has been used to improve the efficacy of CCRT. There is currently no standard chemotherapy regimen for CCRT in locally advanced cervical cancer. Our study supports the conclusion that platinum-based doublet therapy plus RT has a clinically useful role in locally advanced cervical cancer compared to platinum single agent. It should be considered an option for patients receiving CCRT if they are able to tolerate it. With regard to radical CCRT, according to the principle of first-order kinetics, the

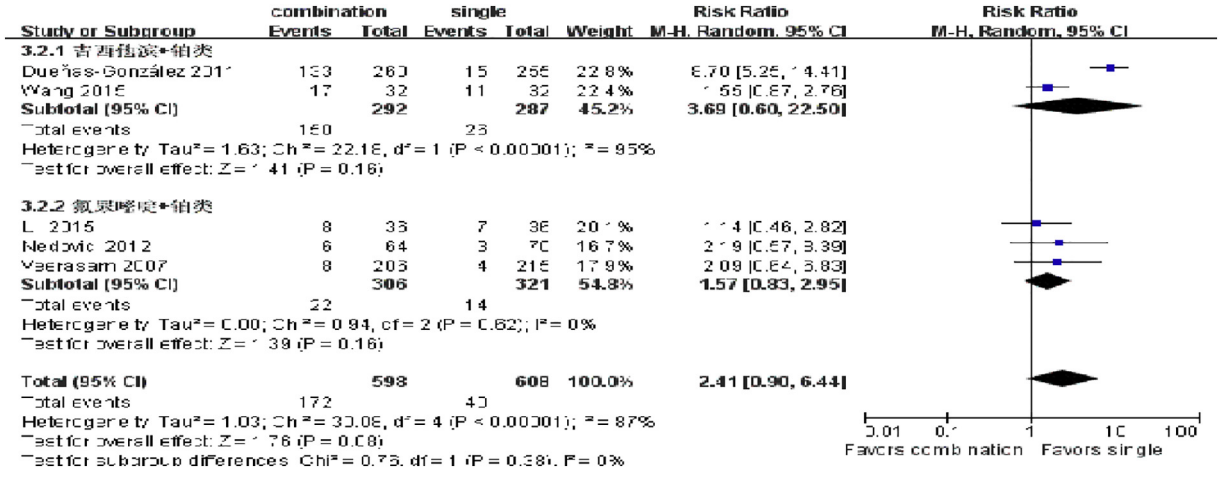

Fig. 4. Forest plot and meta-analysis of leukopenia occurrence. SE: standard error; CI, confidence interval.

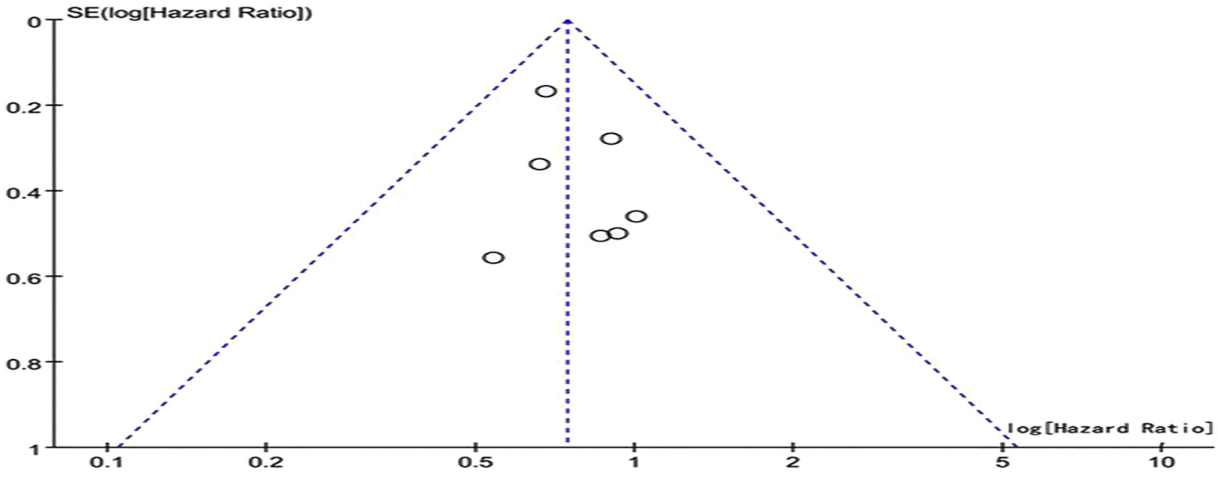

Fig. 5. Funnel plot illustrating the meta-analysis of overall survival. SE: standard error.

chemotherapy should be combined use and with sufficient intensity, which is consistent with our findings. As found in our study, grade 3 or 4 vomiting and thrombocytopenia occurred more frequently in the polychemotherapy arm, and the incidence of urinary system toxicity tended to be higher, but the incidence of grade 3 and 4 toxicities was low overall and considered clinically acceptable, in accordance with previous studies [19–21]. As a systematic review affected by many factors, our study recommends polychemotherapy plus RT in the clinic, and some such regimens have indeed proven to have good efficacy. However, further large multi-center randomized clinical trials are necessary to further demonstrate these results.

There are still some shortcomings of this study. Seven RCTs were included in this meta-analysis, only 2 of which were phase III clinical trials. Therefore, the number of included studies is still insufficient, and we should continue to pay attention to the most up-to-date information in this area.

5. Conclusions

Under the premise of good tolerance, platinum-based doublet therapy plus RT improves survival compared to platinum single-agent therapy plus RT in patients with locally advanced cervical cancer.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.04.013.

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Conflict of interest statement

There are no actual or potential conflicts of interest from the authors.

Author contributions

Wen Zou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wen Zou, Shuyun Ma.

Acquisition of data: Shuyun Ma, Yiyu Han.

Analysis and interpretation of data: Feng Guo, Caizhi Chen, Xishan Chen.

Drafting of the manuscript: Shuyun Ma, Wen Zou, Jingjing Wang.

Critical revision of manuscript for important intellectual content: Jingjing Wang.

Statistical analysis: Shuyun Ma; Jingjing Wang.

Obtaining funding: None.

Supervision: Wen Zou.

Other (specify): None.

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