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Original Article

Efficacy of concurrent single-agent chemotherapy using radiotherapy in patients with cervical cancer: a meta-analysis

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Abstract: Concurrent chemoradiotherapy has proven to be more effective on patients with advanced cervical cancer than radiotherapy alone. Although cisplatin has been recommended to be the standard agent in chemotherapy, it has some limitations in clinical use because of its strong side effects. Moreover, the optimal chemotherapy regimen remains unclear. A comprehensive electronic search was conducted via the Internet retrieval system to identify eligible trials. The ending points included response, overall survival (OS), local recurrent, and distant metastasis rates. Odds ratios and 95% confidence interval were calculated to compare the effects. Fifteen trials with 1142 patients were eligible. With regard to the response rate, only nedaplatin showed a significant improvement compared with cisplatin. Docetaxel, pacitaxel, fluoropyrimidine, paclitaxel liposome, and irinotecan did not show any advantages. When targeted on OS or local recurrent rate, no significant advantage was found when these single-drug regimens were compared with cisplatin. However, when aimed at distant metastasis rate, fluoropyrimidine showed a disadvantage to cisplatin, whereas others showed equal efficacy. Nedaplatin, docetaxel, pacitaxel, and fluoropyrimidine showed a better effect on reducing chemotherapy toxicity than cisplatin. Single-drug chemotherapy concurrent with radiotherapy, except for nedaplatin, may have no advantage on clinical outcomes when compared with cisplatin but showed a better effect on reducing chemotherapy toxicity, which could be used as an alternative to patients who can not tolerate the side effects of cisplatin. Nedaplatin is also effective and safe, and may be highly valuable in clinical applications.

Keywords: Cervical cancer, concurrent chemotherapy, single-drug chemotherapy, meta-analysis

Introduction

Cervical cancer is one of the major cancer diseases in the world. It has the second highest morbidity among females, only next to breast cancer, accounting for 15% of the cancer patients; most cases occurred in developing countries with no effective screening system [1]. The current treatments for cervical cancer are mainly operation and radiotherapy, which can produce satisfactory therapeutic effects in the early stage of cervical cancer; however, combined treatment should be adopted when the disease severity worsens. Radiotherapy alone has a higher cure rate for small-size cervical cancer, but curing large-volume tumors is difficult [2]. Therefore, comprehensive treatment combined with radiotherapy and chemotherapy is neccesary for advanced cervical cancer.

In 1999, the GOG, RTOG, and SWOG for periods of five random III clinical studies confirmed that chemoradiotherapy can decrease the rate of local recurrence and distant metastasis of cervical cancer, thereby improving the survival rate of cervical cancer by 30% to 50% [3-6]. The meta-analysis results of 18 randomized studies in 2008 showed that the application of concurrent chemoradiotherapy in cervical cancer patients for five years caused the survival rate to increase by 6% [7]. These results encouraged the use of chemoradiotherapy in the comprehensive therapy of cervical cancer. In the

NCCN guidelines, cisplatin is strongly recommended as the standard single agent for chemoradiotherapy, and it has been widely used in the comprehensive treatment of cervical cancer; cisplatin was also proven to improve the outcomes in nearly all trials for cervical cancer [8, 9]. However, given the strong side effects of cisplatin, such as vomiting, ototoxicity, and nephrotoxicity, some scholars both in China and abroad began to study other chemotherapy drugs to seek alternative treatment regimens with higher efficiency and lower toxicity. Recently, reports have surfaced on several drugs that were used singly in concurrent with chemoradiotherapy for cervical cancer. However, the results are contradictory, and the optimal chemotherapy regimen is not yet under a certain criteria.

A meta-analysis of data from published literature was conducted in this study to provide a theoretical basis for making clinical decisions. The differences between other chemotherapy drugs and cisplatin were also characterized to determine which is more beneficial for clinicians and patients. This study compared the efficacy and safety between the different drug regimens in the chemoradiation system for cervical cancer.

Subjects and methods

Search strategy

This meta-analysis was reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis statement [10]. A comprehensive electronic search of PubMed, Embase, Medline, Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure was performed via the Internet retrieval system. No language limitation was indicated, and the cut-off date of the included articles was 1 November, 2014. The search terms included the follow: "cervical cancer/carcinoma", "chemoradiation", "radiochemotherapy", "concurrent chemotherapy/radiotherapy", and "cisplatin". The titles and abstracts of initially selected trials were manually examined to exclude irrelevant studies. The full texts of the remaining articles, which were closely related to the topic, were reviewed for further study. When multiple publications with the same or overlapping patient population, from the same institution were identified, only the published report with the largest series was included.

Inclusion and exclusion criteria

Studies were eligible for our meta-analysis if: (1) they were randomized controlled trials, and randomization was clearly demonstrated in the articles; (2) patients were divided into at least two groups, and one group was treated with radiotherapy combined with single-drug chemotherapy of cisplatin, and another group used radiotherapy concurrent with non-cisplatin but another single drug (e.g., nedaplatin, docetaxel, and paclitaxel); and (3) they reported at least one primary outcome to measure the effect of the treatments. Studies considered ineligible for the meta-analysis were as follows: reviews, conference abstracts, editorials, or case reports; research on cervical cancer treated by multi-drug regimen; articles that reported a single cohort study without a control group, non-randomized trials, and pseudo-randomized trials with alternate allocation of subjects; and studies with incorrect or unavailable data analysis method.

Data extraction

Data extraction was independently completed by two authors (ZY and YZC) and checked by a third reviewer (LYY). Any disagreement was resolved through discussion. The following data were extracted from each eligible study: first author's name, publication year, journal, location, experience design, eligible patients' criteria (age, TNM stage, and histological type), sample size (total, eligible, and per group), follow-up time, chemotherapy regimens (drug, usage, dosage and the completion rate), and radiotherapy (types and dosimetry). The outcomes of interest were as follows: the response rate of concurrent radiochemotherapy, overall survival (OS) rate, local recurrent rate, distant metastasis rate, and adverse effects.

Qualitative assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS), as recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used to assess the quality of the randomized controlled trials that were included in our meta-analysis [11, 12]. According to the NOS, the studies were evaluated in four broad aspects: selection of the case and control groups (four criteria, one star for each), comparability of the case and control groups (one criterion, one star), assessment of exposure (one

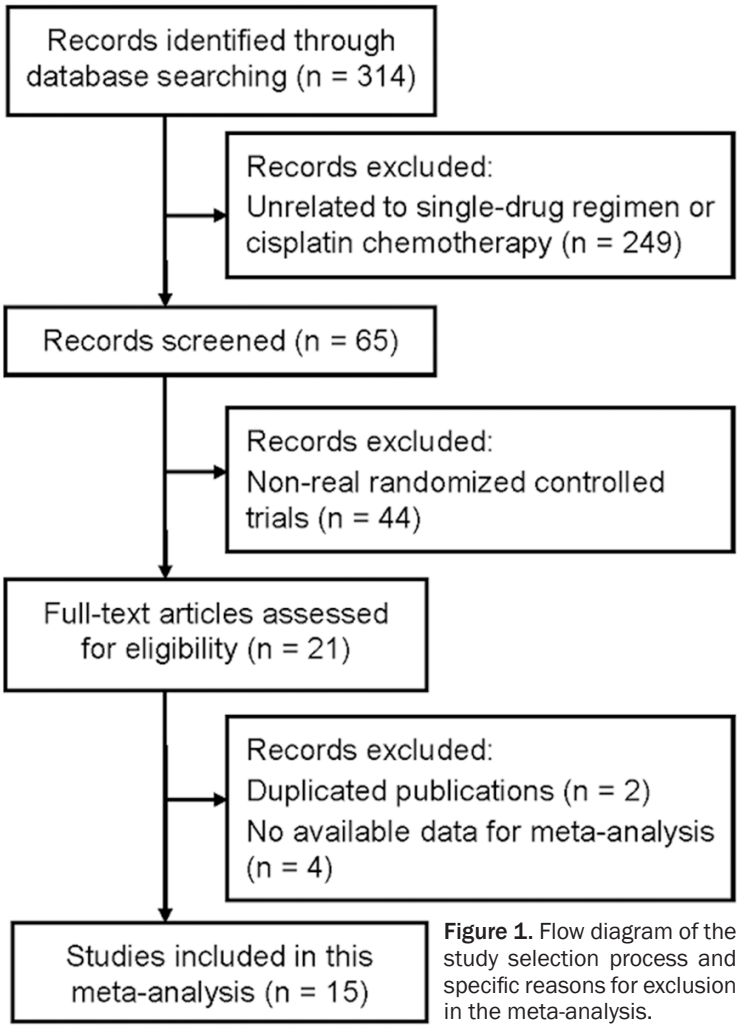

Figure 1. Flow diagram of the study selection process and specific reasons for exclusion in the meta-analysis.

criterion, two stars), and outcome of study participants (two criteria, one star for each). The total score ranged from 0 to 9. Articles that garnered five stars or more were considered high-quality studies, and only these papers were included in our meta-analysis.

Statistical analysis

The meta-analysis was spontaneously performed using STATA 11.0 (STATA Corporation, College Station, TX, USA). The results of each randomized controlled trial were treated as dichotomous frequency data. For all the outcomes of interest, event numbers were extracted from each individual study, and odds ratios (*OR*s) and 95% confidence interval (*CI*) were calculated before data pooling. Combined *OR*s and 95% *CI* were used to estimate the response rate of single-drug chemoradiotherapy with cisplatin compared with other single-drug regimens; the comparisons of other clinical results, such as OS, local recurrent rate, distant metastasis rate, and adverse effects, were similar to this method [13].

Heterogeneity was validated using the chi-squared test based *Q* statistic for statistical significance [14]. Heterogeneity was considered statistically significant for $P < 0.10$, and graphical presentations were drawn prior to data consolidation. Between-study heterogeneity was determined by I^2 statistic inconsistency, which was not interfered by the number of studies used in the meta-analysis ($I^2 < 25\%$, no heterogeneity; $I^2 = 25\%$ to 50%, moderate heterogeneity; $I^2 > 50\%$, extreme heterogeneity). A fixed-effect model was applied when no between-study heterogeneity was found by the Mantel-Haenszel method, and a random-effect model based on the method of DerSimonian and Laird was used when significant heterogeneity existed [15].

The robustness of the meta-analysis outcomes was confirmed, and sensitivity analysis was performed by omitting one individual study each time using the "metainf" STATA command. Begg's rank correlation and Egger's linear regression method were used to evaluate potential publication bias [16], which was also graphically assessed by funnel plots. Egger's test results were statistically significant at $P < 0.10$. All reported *P* values were two-sided.

Results

Eligible studies and main characteristics

Fifteen trials met our inclusion criteria for meta-analysis [17-31]. The detailed steps of our liter-

Table 1. Characteristics of the included studies

Author (year)	Location	Research time	TNM stage	Histological type	Follow-up time	No. of pts (exp/ctr)	CT schedules (exp/ctr)	RT dose GY/BT dose GY	CT completion (%) (exp/ctr)	Score
Wang et al. (2011)	China	2006.6~2007.7	III_A~III_B	SCC	Up to 2010.7	34/34	wNDP: 40 mg/m^2×6/ wCDDP: 40 mg/m^2×6	EBRT 46~56/BT 36~46	85/79	6
Cheng et al. (2011)	China	2005.1~2007.12	II_B~III	ADC+SCC	3 years	32/32	wNDP: 30 mg/m^2×6/ wCDDP: 40 mg/m^2×6	EBRT 40~50/BT 36~42	NR	6
Lou et al. (2011)	China	2004.5~2006.10	≥II_B	ADC+SCC	Up to 2009.9	31/31	wNDP: 40 mg/m^2×3/ wCDDP: 40 mg/m^2×3	EBRT 50/BT 30~40	81/55	5
Wang et al. (2014)	China	2011.1~2012.3	III~IV	NR	NR	35/35	wNDP: 40 mg/m^2×4/ wCDDP: 40 mg/m^2×4	EBRT 50/BT 40	NR	7
Li et al. (2014)	China	2010.10~2013.10	II_B~III_B	ADC+SCC+ASC	1 year	48/48	wNDP: 40 mg/m^2×4/ wCDDP: 40 mg/m^2×4	NR	NR	6
Jiang et al. (2009)	China	2000.1~2003.12	II_B~III	ADC+SCC	Up to 2007.12	34/30	wDCT: 25 mg/m^2×6/ wCDDP: 40 mg/m^2×6	EBRT 50~60/BT 18	NR	6
Li et al. (2011)	China	2008.6~2009.12	II_B~IV_A	ADC+SCC	Up to 2011.1	16/22	wDCT: 25 mg/m^2×6/ wCDDP: 30 mg/m^2×6	EBRT 50/BT 36	94/100	5
Geara B et al. (2010)	Lebanon	2000.5~2004.5	I_B~IV_A	ADC+SCC	5 years	15/16	wPAC: 50 mg/m^2×5/ wCDDP: 40 mg/m^2×5	EBRT 40/BT 26~34	80/87	8
Wang et al. (2011)	China	2004.3~2005.3	≥II_B	SCC	Up to 2009.3	30/28	wPAC: 60 mg/m^2×6/ wCDDP: 30 mg/m^2×6	EBRT 48~54/BT 35~42	NR	6
Narayanan et al. (2012)	Kenya	2006.2~2007.2	II_B~III_B	ADC+SCC	NR	19/16	wPAC: 50 mg/m^2×5/ wCDDP: 40 mg/m^2×5	EBRT 50/BT 21	NR	7
Nagai et al. (2001)	Japan	1991.1~1998.12	≥II	ADC+SCC+ASC	4 years	28/32	d5-FU:200 mg/d×4/ tmCDDP:120 mg/ m^2×4	EBRT 50/BT 18~20	NR	7
Lanciano et al. (2005)	America	1997.10~2000.7	II_B~IV_A	ADC+SCC+ASC	4 years	157/159	5d/w5-FU: 225 mg/m^2×6/ wCDDP: 40 mg/m^2×6	EBRT 45/BT 30~40	72/56	8
Xin et al. (2014)	China	2009.10~2011.6	I_B~IV_A	ADC+SCC+ASC	NR	47/53	wPTL: 45 mg/m^2×4~6/ wCDDP: 40 mg/m^2×4~6	EBRT 45~50/BT 24~32	NR	6
Coronel et al. (2013)	Mexico	NR	I_B~IV_A	ADC+SCC+ASC	29 months	19/20	wVCR: 60 mg/m^2×6/ wCDDP: 40 mg/m^2×6	EBRT 50.4/BT 30~35	NR	7
Wang et al. (2012)	China	2008.6~2010.12	II_B~III	ADC+SCC	NR	40/40	wCPT-11: 40 mg/ m^2×5/wCDDP: 25 mg/m^2×5	EBRT 46/BT 32~45	NR	5

NR: none reported; pts: patients; exp: experimental group; ctr: control group; CT: chemotherapy; RT: radiotherapy; EBRT: external beam radiotherapy; BT: brachytherapy; ADC: adenocarcinoma; SCC: squamous cell carcinoma; ASC: adenosquamous carcinoma; wCDDP: weekly cisplatin; tmCDDP: twice per month cisplatin; wNDP: weekly nedaplatin; wDCT: weekly docetaxel; wPAC: weekly paclitaxel; w5-FU: weekly fluorouracil; 5 d/w5-FU: 5 days per week fluorouracil; wPTL: weekly paclitaxel liposome; wVCR: weekly vinorebine; wCPT-11: weekly irinotecan.

Table 2. Main outcomes of the eligible studies

Strategy	Study (year)	Response rate (events/total) (exp vs. ctr)	OS (events/total) (exp vs. ctr)	Local recurrent rate (events/total) (exp vs. ctr)	Distant metastasis rate (events/total) (exp vs. ctr)
NDP vs. CDDP	Wang et al. (2011)	NR	26/34 vs. 24/34	NR	NR
	Cheng et al. (2011)	32/32 vs. 31/32	22/32 vs. 23/32	4/32 vs. 4/32	2/32 vs. 2/32
	Lou et al. (2011)	31/31 vs. 31/31	22/31 vs. 20/31	NR	NR
	Wang et al. (2014)	19/35 vs. 10/35	NR	NR	NR
	Li et al. (2014)	46/48 vs. 38/48	44/48 vs. 41/48	6/48 vs. 15/48	3/48 vs. 11/48
DCT vs. CDDP	Jiang et al. (2009)	34/34 vs. 29/30	25/34 vs. 17/30	2/34 vs. 3/30	2/34 vs. 2/30
	Li et al. (2011)	14/16 vs. 18/22	16/16 vs. 21/22	2/16 vs. 4/22	1/16 vs. 2/22
PAC vs. CDDP	Geara B et al. (2010)	10/15 vs. 15/16	6/15 vs. 8/16	6/15 vs. 3/16	5/15 vs. 4/16
	Wang et al. (2011)	29/30 vs. 27/28	23/30 vs. 19/28	2/30 vs. 3/28	3/30 vs. 4/28
	Narayanan et al. (2012)	18/19 vs. 12/16	NR	1/19 vs. 4/16	NR
5-FU vs. CDDP	Nagai et al. (2001)	25/28 vs. 28/32	13/28 vs. 16/32	NR	NR
	Lanciano et al. (2005)	NR	86/157 vs. 102/159	22/157 vs. 25/159	46/157 vs. 29/159
Others vs. CDDP	Xin et al. (2014)	46/47 vs. 50/53	NR	NR	NR
	Coronel et al. (2013)	NR	15/19 vs. 14/20	NR	NR
	Wang et al. (2012)	26/30 vs 24/30	NR	NR	NR

NR: none reported; exp: experimental group; ctr: control group; CDDP: cisplatin; NDP: nedaplatin; DCT: docetaxel; PAC: paclitaxel; 5-FU: fluorouracil; PTL: paclitaxel liposome; VCR: vinorebine; CPT-11: irinotecan.

Table 3. Main results of the meta-analysis for response rate, OS, local recurrent rate and distant metastasis rate

Categories	Outcome	No. (cases)	OR (95% CI)	Z	P	I^2 (%)	P_h
NDP vs. CDDP	Response rate	4 (292)	3.71 (.66~8.29)	3.20	0.001	0.0	0.749
	OS	4 (290)	1.27 (0.73~2.22)	0.85	0.397	0.0	0.831
	Local recurrent rate	2 (160)	0.46 (0.20~1.06)	1.85	0.068	35.9	0.212
	Distant metastasis rate	2 (160)	0.34 (0.12~1.01)	1.94	0.052	31.2	0.228
DCT vs. CDDP	Response rate	2 (102)	1.928 (0.396~9.379)	0.81	0.416	0.0	0.668
	OS	2 (102)	2.142 (0.789~5.820)	1.49	0.135	0.0	0.963
	Local recurrent rate	2 (102)	0.602 (0.163~2.227)	0.76	0.447	0.0	0.920
	Distant metastasis rate	2 (102)	0.783 (0.164~3.741)	0.31	0.759	0.0	0.868
PAC vs. CDDP	Response rate	3 (124)	0.892 (0.290~2.743)^R	0.20	0.842	62.1	0.072
	OS	2 (89)	0.653 (0.285~1.496)^R	1.01	0.314	80.4	0.024
	Local recurrent rate	3 (89)	0.850 (0.320~2.260)	0.33	0.745	52.7	0.121
	Distant metastasis rate	2 (89)	1.008 (0.335~3.033)	0.01	0.989	0.0	0.476
5-FU vs. CDDP	Response rate	1 (60)	1.190 (0.242~5.844)	0.21	0.830	-	-
	OS	2 (376)	0.705 (0.467~1.065)	1.66	0.097	0.0	0.663
	Local recurrent rate	1 (316)	0.873 (0.471~1.625)	0.43	0.669	-	-
	Distant metastasis rate	1 (316)	1.858 (1.094~3.154)	2.29	0.022	-	-
PTL vs. CDDP	Response rate	1 (100)	2.760 (0.277~27.483)	0.87	0.387	-	-
VCR vs. CDDP	OS	1 (39)	1.607 (0.373~6.919)	0.64	0.524	-	-
CPT-11 vs. CDDP	Response rate	1 (60)	1.625 (0.408~6.469)	0.69	0.491	-	-

All pooled *OR*s were derived from fixed-effects model except for cells marked with (random^R). CDDP: cisplatin; NDP: nedaplatin; DCT: docetaxel; PAC: paclitaxel; 5-FU: fluorouracil; PTL: paclitaxel liposome; VCR: vinorebine; CPT-11: irinotecan; *P*: *P* value for statistical significance based on *Z* test; P_H: *P* value for heterogeneity based on *Q* test; -: unable to calculate.

ature search are shown in **Figure 1**. 15 studies with a total of 1142 patients and a sample size that ranged from 31 to 316 were published from 2001 to 2014. Ten of them originated in China [17-23, 25, 29, 31], and the rest in Lebanon [24], Kenya [26], Japan [27], the

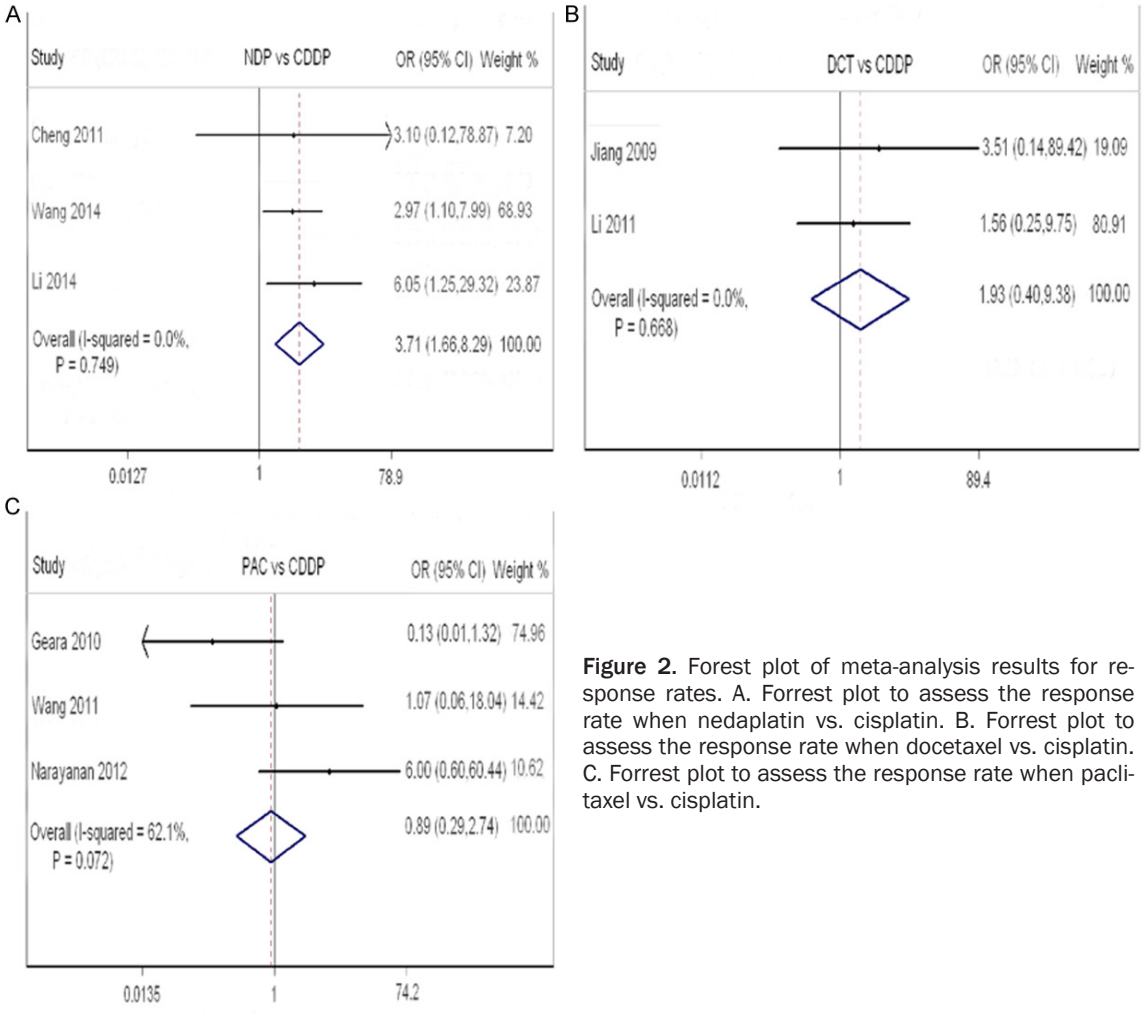

Figure 2. Forest plot of meta-analysis results for response rates. A. Forrest plot to assess the response rate when nedaplatin vs. cisplatin. B. Forrest plot to assess the response rate when docetaxel vs. cisplatin. C. Forrest plot to assess the response rate when paclitaxel vs. cisplatin.

United State [28], and Mexico [30]. Five studies included patients at stages II to II [18, 21, 22, 26, 31], three at stages I to IV [24, 29, 30], three at stages > II [19, 25, 27], and the other at stage III or stage II to IV. Seven of the 15 eligible studies focused on adenocarcinoma and squamous cell carcinoma [18, 19, 22, 23, 24, 26, 31]; five of them contained adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma [21, 27-30]; and two included only squamous cell carcinoma [17, 25]. Five trials used nedaplatin in the observation group [17-21], three used paclitaxel [22-24], two used docetaxel [25, 26], two used fluoropyrimidine [27, 28], and the other three used paclitaxel liposome [29], vinorelbine [30], and irinotecan [31]. The quality scores of the included studies ranged from five to eight stars. Twelve of the eligible trials had reported the response rate for the main outcome [18-27, 29, 31], and 11 had reported OS [17-19, 21-25, 27, 28, 30]. However, only eight and seven had reported the local recurrent [18, 21-26, 28] and the distant metastasis rates [18, 21-25, 28], respectively. **Table 1** shows the main characteristics of the 15 eligible trials, and **Table 2** shows the main outcomes of the studies through stratification by different drug schemes.

Main results of response rate

The response rates reported by the 12 trials ranged from 54.29% to 100% in the non-cisplatin group, and 28.57% to 100% in the cisplatin group. After stratification by different chemotherapy regimens, only nedaplatin showed a higher response rate than cisplatin (*OR* = 3.71; 95% *CI*, 1.66 to 8.29, *P* = 0.001; fixed-effect model; **Table 3**), with data from four trials on 292 patients. When docetaxel, paclitaxel, fluo-

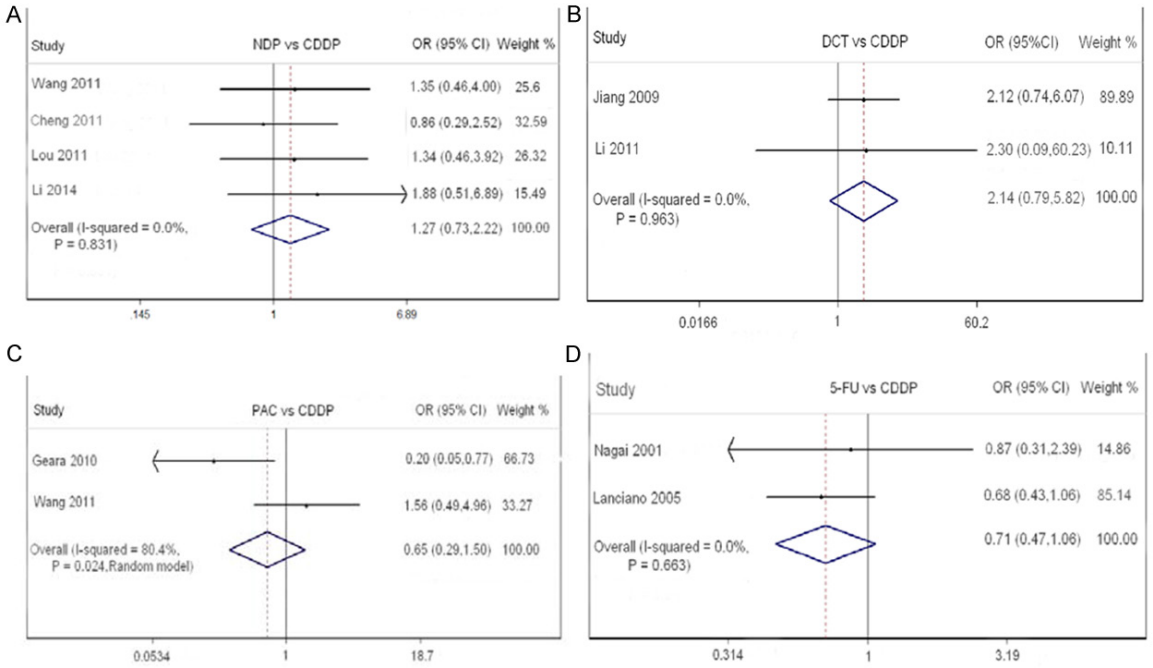

Figure 3. Forest plot of meta-analysis results for the overall survival rate. A. Forrest plot to assess the overall survival rate when nedaplatin vs. cisplatin. B. Forrest plot to assess the overall survival rate when docetaxel vs. cisplatin. C. Forrest plot to assess the overall survival rate when paclitaxel vs. cisplatin. D. Forrest plot to assess the overall survival rate when fluorouracil vs. cisplatin.

ropyrimidine, paclitaxel liposome, and irinotecan were compared with cisplatin, no statistical significance was found on the response rate (**Table 3**). No heterogeneity existed among the studies for these outcomes, except paclitaxel treatment (I^2 = 62.1%, P_h = 0.072). A forest plot for response rate in different drug regimens is shown in **Figure 2**.

Main results of OS, local recurrent rate, and distant metastasis rate

When the research focused on OS or local recurrent rate, no significant advantage existed when the other single-drug regimen was used in the concurrent chemoradiotherapy compared with cisplatin. However, when the research was aimed at distant metastasis rate, fluoropyrimidine showed a disadvantage in controlling disease metastasis with only one report in 316 patients (*OR* = 1.858; 95% *CI*, 1.094 to 3.154, *P* = 0.022; fixed-effect model; **Table 3**), which indicated that cisplatin demonstrated a better rate than fluoropyrimidine in reducing distant metastasis for cervical cancer. No extreme heterogeneity existed among the studies for these outcomes, except paclitaxel treatment for OS (I^2 = 80.4%, P_h = 0.024). The main results for these indexes are shown in **Table 3**. Forest plots for these outcomes in different drug regimens are shown in **Figures 3**-**5**.

Main results of toxicity

A summary of WHO grade 1 or greater drug-related toxicities is shown in **Table 4**. Considerable variability in the completeness of toxicity reporting was found among the included studies. Overall, nedaplatin therapy showed a significant advantage in reducing the risk of nausea and vomiting (*OR* = 0.21; 95% *CI*, 0.13 to 0.36, *P* < 0.001; fixed-effect model), renal dysfunction (*OR* = 0.41; 95% *CI*, 0.23 to 0.74, *P* = 0.003; random-effect model), liver dysfunction (*OR* = 0.40; 95% *CI*, 0.19 to 0.86, *P* = 0.019; fixed-effect model), and diarrhea (*OR* = 0.41; 95% *CI*, 0.19 to 0.91, *P* = 0.027; random-effect model). However, it acted as a promoting factor in thrombocytopenia (*OR* = 1.84; 95% *CI*, 1.14 to 2.97, *P* = 0.012; random-effect model). When docetaxel treatment was used in the concurrent chemoradiotherapy, it protected against myelosuppression (*OR* = 0.21; 95% *CI*, 0.09 to 0.47, *P* < 0.001; random-effect model)

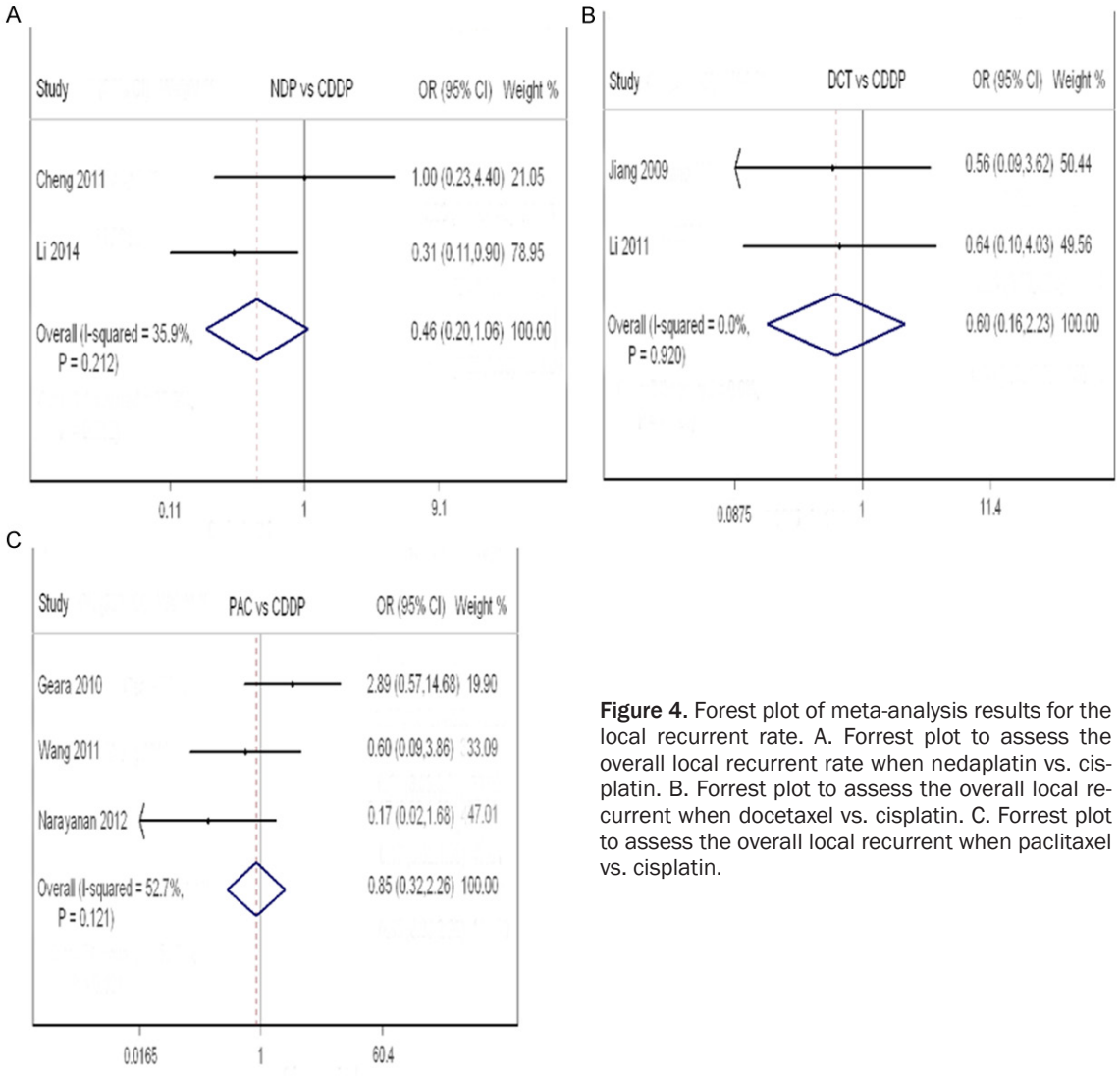

Figure 4. Forest plot of meta-analysis results for the local recurrent rate. A. Forrest plot to assess the overall local recurrent rate when nedaplatin vs. cisplatin. B. Forrest plot to assess the overall local recurrent when docetaxel vs. cisplatin. C. Forrest plot to assess the overall local recurrent when paclitaxel vs. cisplatin.

and gastrointestinal toxicity (*OR* = 0.19; 95% *CI*, 0.08 to 0.44, *P* < 0.001; fixed-effect model). Paclitaxel and fluoropyrimidine both showed a protective effect on myelosuppression (*OR* = 0.37, 95% *CI*: 0.17 to 0.81, *P* = 0.013, random-effect model; *OR* = 0.24, 95% *CI*: 0.14 to 0.43, *P* < 0.001, fixed-effect model), and paclitaxel showed a significant superiority in decreasing the risk of nausea and vomiting (*OR* = 0.40, 95% *CI*: 0.17 to 0.92, *P* = 0.030; random-effect model). Meanwhile, two studies with a total of 376 patients reported that fluoropyrimidine therapy was associated with a significant reduction in the risk for overall Grades III to IV toxicity (*OR* = 0.34, 95% *CI*: 0.22 to 0.52, *P* < 0.001; random-effect model). Heterogeneity among individual studies was found in some toxicity analyses, possibly because of the different treatment regimens.

Sensitivity analysis and publication bias

Sensitivity analyses were conducted by individually excluding studies and analyzing the effects of such exclusion on the remaining studies to assess the robustness of the results. No individual study significantly affected the OR for response, OS, local recurrent or distant metastasis rates. Funnel plot analysis and Egger's test were also performed to evaluate publication bias. The results showed no publication bias in each test for each endpoint analysis.

Discussion

In the past, radiotherapy was the first choice for treating advanced cervical cancer, but 30% to 40% treatment failure always occurred. The

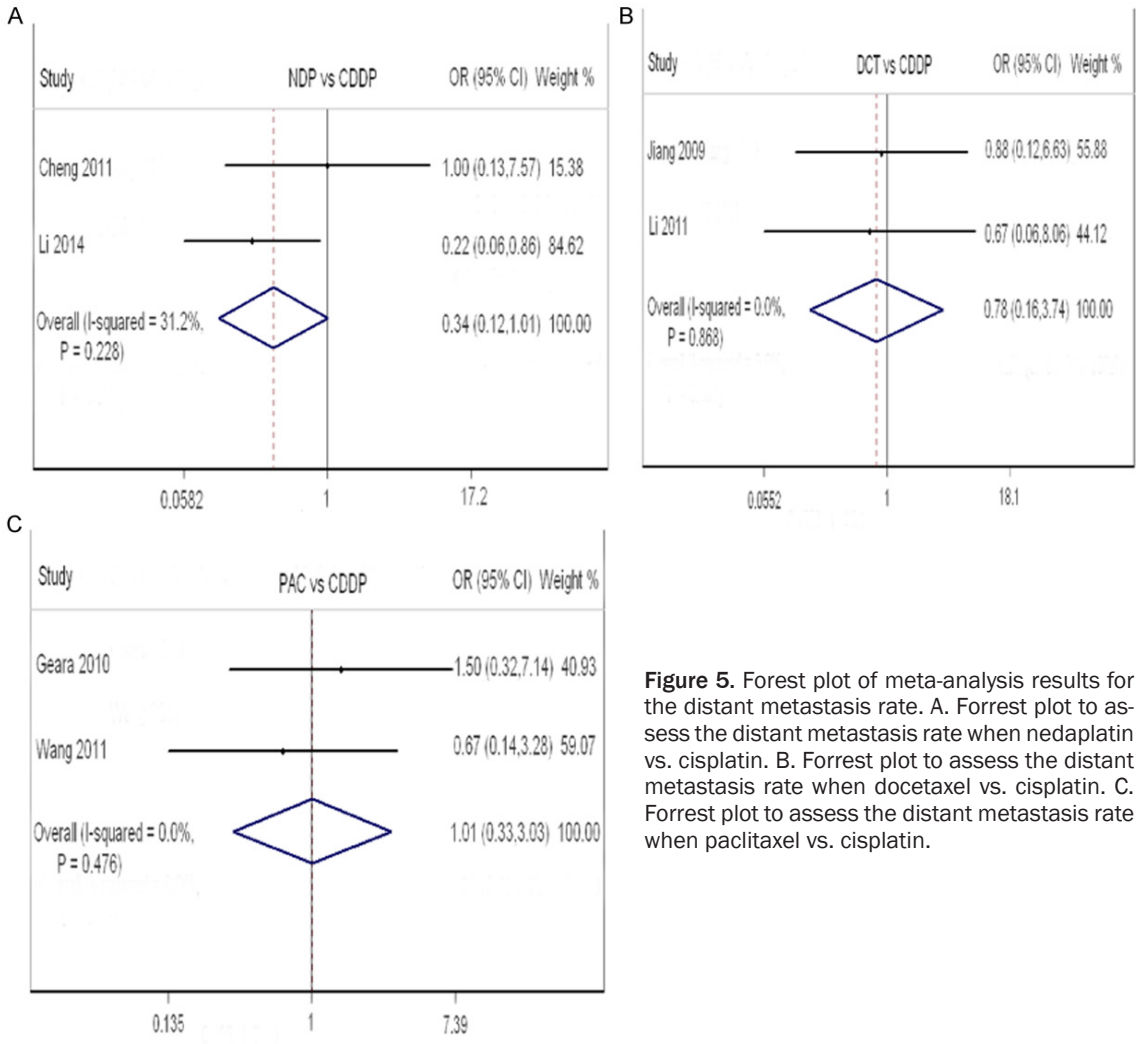

Figure 5. Forest plot of meta-analysis results for the distant metastasis rate. A. Forrest plot to assess the distant metastasis rate when nedaplatin vs. cisplatin. B. Forrest plot to assess the distant metastasis rate when docetaxel vs. cisplatin. C. Forrest plot to assess the distant metastasis rate when paclitaxel vs. cisplatin.

main cause of treatment failure was the loss of local control and relapse of the tumor, which was followed by lymph node metastasis and distant spread, which were related to certain reasons, such as enormous tumor volume, hypoxic cells and parametrical infiltration insensitive to radiotherapy, or radiotherapy could not control the radiation field outside the sub-infiltration lesions [22]. Concurrent chemoradiotherapy shows some theoretical advantages of avoiding any delay in the initiation of radiotherapy, which is the main treatment method, shortening the overall treatment time, preventing the tumor from relapse and cross resistance to therapy, and radiosensitizing the effect of chemotherapeutic agents compared with neoadjuvant therapy [32, 33]. Concurrent chemoradiotherapy does not only strengthen the control of local lesions, but also considers the treatment for systemic micrometastasis [34]. Concurrent chemoradiotherapy is presently the main treatment method for local advanced cervical cancer. Chemotherapy drugs act as a radiation sensitizer, and a synergistic effect combined with radiotherapy is revealed.

Currently, the most commonly used regimen for concurrent chemoradiotherapy is the multi-drug combination scheme, especially the cisplatin-based regimen. However, the multi-drug combination scheme has shown its limitations in multiple trials. Kim et al. [35, 36] found that the addition of fluorouracil to cisplatin in chemoradiation for locally advanced cervical cancer results in higher acute complication and poorer compliance without any clear improvement in treatment outcomes; the cisplatin alone regimen also has the advantage of not

Table 4. Main results of the meta-analysis for toxicity

Strategy	Outcomes	*No.* of studies (patients)	*OR* (95% *CI*)	*P*	I^2 (%)	P_H
NDP vs. CDDP	Nausea and vomiting	5 (360)	0.21 (0.13~0.36)	< 0.01	0.0	0.754
	Leucopenia	4 (290)	0.84 (0.48~1.49)^R	0.560	58.9	0.063
	Thrombocytopenia	4 (290)	1.84 (1.14~2.97)^R	0.012	84.0	< 0.01
	Renal dysfunction	5 (360)	0.41 (0.23~0.74)^R	0.003	74.4	0.004
	Liver dysfunction	3 (200)	0.40 (0.19~0.86)	0.019	3.5	0.355
	Diarrhea	2 (158)	0.41 (0.19~0.91)^R	0.027	85.7	0.008
DCT vs. CDDP	Myelosuppression	2 (102)	0.21 (0.09~0.47)^R	< 0.01	88.1	0.004
	Gastrointestinal toxicity	2 (102)	0.19 (0.08~0.44)^R	< 0.01	69.4	0.071
	Renal dysfunction	2 (102)	0.46 (0.10~2.20)	0.330	0.0	0.369
PAC vs. CDDP	Myelosuppression	3 (124)	0.37 (0.17~0.81)^R	0.013	66.5	0.051
	Nausea and vomiting	2 (93)	0.40 (0.17~0.92)	0.030	0.0	0.799
	Diarrhea	3 (124)	1.07 (0.46~2.50)	0.873	0.0	0.497
5-FU vs. CDDP	Myelosuppression	2 (376)	0.24 (0.14~0.43)	< 0.01	0.0	0.730
	Nausea and vomiting	2 (376)	0.70 (0.43~1.14)	0.155	0.0	0.990
	Overall Grade III to IV toxicity	2 (376)	0.34 (0.22~0.52)	< 0.01	0.0	0.892

All pooled *OR*s were derived from fixed-effects model except for cells marked with (random^R). CDDP: cisplatin; NDP: nedaplatin; DCT: docetaxel; PAC: paclitaxel; 5-FU: fluorouracil; P_H: *P* value for heterogeneity based on *Q* test; *P*: *P* value for statistical significance based on *Z* test; -: unable to calculate.

requiring hospitalization. When paclitaxel was added into the cisplatin-based scheme, quality of life did not significantly improve, but Grades 3 to 4 toxicity was more common [37]. The sequential chemotherapy of paclitaxel plus carboplatin in high-risk cervical cancer did not show any significant benefit to the survival rate, but more phenomena of toxicity occurrence and a higher frequency of early treatment termination appeared than the cisplatin alone regimen [38]. Thus, there is not enough evidence to prove that multi-drug chemotherapy with radiotherapy has any advantage compared with single-agent concurrent chemoradiotherapy; however, the latter can significantly reduce the side effects, and is easily accepted by patients. Thus, it is more suitable for the treatment of cervical cancer.

Cisplatin is a broad-spectrum anticancer drug, which mainly acts on the target cell DNA, influences the interlinking interchain or internal chain, and interferes with DNA replication and the synthesis of nuclear protein or cytoplasmic protein [39]. As one of the earliest researched and the most commonly used sensitizer for radiotherapy, cisplatin has an affirmative effect on concurrent chemoradiation, but it also has some limitations in clinical use because of its strong side effects. Therefore, some other chemotherapy drugs have been researched to seek an alternative. In this meta-analysis, 15 trials that covered seven chemotherapeutics were searched as a comparison with cisplatin. Unfortunately, three of the sevev chemotherapeutics failed to conduct data synthesis because of only one report on them. Based on the results of meta-analysis of the remaining trials, no advantage was found in response, OS, local recurrent, or distant metastasis rates, except for nedaplatin in the response rate. This result indicated that nedaplatin displayed a similar or even better clinical efficacy to the single-cisplatin regimen. However, this conclusion should be regarded with caution because of the small sample size.

Toxicity is an important indicator for evaluating the safety and tolerance of pharmaceuticals. From the composite results that were collected from the eligible cases, some toxicity was found to be more severe in patients who received the single-cisplatin treatment. By contrast, nedaplatin, docetaxel, paclitaxel, or fluorouracil showed superiority in reducing the risk of overall toxicity. However, nedaplatin displayed a disadvantage to thrombocytopenia, which was a main constraint for dose limitation. In particu-

lar, the toxicity of thrombocytopenia caused by nedaplatin was mainly in Grade I or II, and could be rapidly eased by applying the granulocyte colony-stimulating factor; thus, the treatment process was unaffected [17]. To sum up, nedaplatin, docetaxel, paclitaxel, or fluorouracil may be used as an alternative for patients who cannot tolerate the side effects of cisplatin.

The technique and dosage of radiotherapy, in this study, were different in individual trials. The outcome of therapeutic efficacy and toxicities should be regarded as a comprehensive response of the whole treatment. Thus, the superiority of one regimen over the other depends on when either radiotherapy or the radiosensitizer is used. Some other limitations also existed in our meta-analysis. 1) Considering the limitation on the quality and quantity of the eligible trials in this meta-analysis, the conclusions should be regarded with caution. 2) The included studies are mainly in China, so only the research status of China is reflected. 3) Other factors may influence heterogeneity, such as the timing or approach of drug delivery and surgery. Unfortunately, this information could not be accessed.

In conclusion, concurrent chemoradiotherapy has a treatment history of nearly 20 years for cervical cancer, and many patients have benefited from it. Given the considerable side effects of this chemotherapy drug, choosing drugs with better curative effects and less toxicity as radiosensitizers is the trend in concurrent chemoradiation. The data in our meta-analysis indicated that single-drug chemotherapy with nedaplatin, paclitaxel, docetaxel, or fluorouracil may be the direction of concurrent chemoradiotherapy in the future. Future studies requires randomized controlled experiments with more multi-centers, large sample, proper design, and long follow-up time to prove a more effective and tolerable scheme.

Disclosure of conflict of interest

None.

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References

[1] Zhou H, Peng YP, Yu J and Lin ZQ. Interpretation of the clinical practice guidelines for cervical cancer by NCCN (2014). Chin J Pract Obstet and Gyneco 2014; 30: 422-425.

[2] Zhang L, Tang J and Zhang JJ. Meta analysis of chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma. Chin J Clinicians (Electronic Edition) 2014; 18: 2827-2832.

[3] Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL and Gersell D. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage B cervical carcinoma. N Engl J Med 1999; 340: 1154-1161.

[4] Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, Rotman M, Gershenson DM and Mutch DG. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999; 340: 1137-1143.

[5] Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W Jr and Alberts DS. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18: 1606-1613.

[6] Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, Clarke-Pearson DL and Liao SY. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999; 17: 1339-1348.

[7] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008; 26: 5802-5812.

[8] Petrelli F, De Stefani A, Raspagliesi F, Lorusso D and Barni S. Radiotherapy with concurrent cisplatin-based doublet or weekly cisplatin for cervical cancer: a systematic review and meta-analysis. Gynecol Oncol 2014; 134: 166-171.

[9] Eigel PJ. Concurrent chemotherapy and radiation therapy as the standard of care for cervical cancer. Nat Clin Pract Oncol 2006; 3: 248-255.

[10] Moher D, Liberati A, Tetzlaff J, Altman DG; and PRISMA Group. Preferred reporting items for

systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.
[11] Wells GA, Shea B, O'Connell D and Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Health Research Institute Wed Site 2012.
[12] Maxwell L, Santesso N, Tugwell PS, Well GA, Judd M and Buchbinder R. Method guidelines for Cochrane Musculoskeletal Group systematic reviews. J Rheumatol 2006; 33: 2304-2311.
[13] Deeks J, Higgins JP. Analysis data and undertaking meta-analyses: Cochrane Handbook for Systematic Reviews of Interventions 5.0.0. (Assessed on July 15, 2011 at http: //www. cochrane- handbook.org).
[14] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[15] Mantel N and Haenszel E. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[16] Egger M, Davey SG, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[17] Wang HR, Yu CH, Zhu WG and Li T. Comparison of the effect of nedaplatin and cisplatin in the concurrent chemoradiotherapy of cervical cancer. Chin J Pract Obstet and Gyneco 2011; 27: 771-774.
[18] Cheng XW, Yang YX and Yu XY. A comparative study of concurrent chemo- radiotherapy with cisplatin versus nedaplatin for patients with middle-advanced stage uterine cervical cancer. Chin J Tumor 2011; 31: 662-664.
[19] Lou PR, Tao QS, Guo JX, Yu QB, Dong YE, Wang YH, Xu ZY and Yuan ZG. Clinical study of concurrent cisplatin or nedaplatin-based chemoradiation for locally advanced cervical cancer. J Chin Oncol 2011; 17: 93-96.
[20] Wang CX, Lv HQ, Zhu SM, Zhang FQ and Shang CJ. Comparison of the clinical efficacy between nedaplatin and cisplatin concurrent chemoradiotherapy in the treatment of advanced cervical carcinoma. Anti-tumor Pharm 2014; 4: 290-293.
[21] Li L. Evaluation of curative effect of nedaplatin concurrent chemoradiotherapy in the treatment of 48 cases of cervical cancer. Chin J Med Front 2014; 6: 74-76.
[22] Jiang L, Hao Q and Wang HY. Curative effect of three chemotherapy programs in concurrent with radiotherapy on medium and advanced stage cervical cancer. Chin J Pract Obstet Gyneco 2009; 25: 293-295.
[23] Li QF, Jin GW, Bai XJ and Jiang CH. Effect of cisplatin and docetaxel concurrent chemotherapy and radiotherapy in local advanced cervical cancer. Modern Oncol 2011; 19: 1827-1830.
[24] Geara FB, Shamseddine A, Khalil A, Abboud M, Charafeddine M and Seoud M. A phase II randomized trial comparing radiotherapy with concurrent weekly cisplatin or weekly paclitaxel in patients with advanced cervical cancer. Radiat Oncol 2010; 23: 84.
[25] Wan YH, Zhang ZC, Li YX, Li X, Wang XL and Li SW. Curative effect of cisplatin or paclitaxel in concurrent chemoradiotherapy for cervical cancer: a report of 58 cases. J Chin Tradit Chin Med Inform 2011; 3: 162.
[26] Narayanan V, Bista B and Sharma S. External beam therapy in a four-field box technique with paclitaxel versus a two-field technique with cisplatin in locally advanced carcinoma cervix: a phase II monocentric trial. ISRN Oncol 2012; 2012: 390193.
[27] Nagai N, Oshita T, Murakami J, Shigemasa K, Hirokawa Y and Ohama K. Radiotherapy combined with transcatheter arterial infusion of cisplatin versus oral fluoropyrimidine anticancer agent for locally advanced carcinoma of the uterine cervix: a prospective follow-up study. Oncol Rep 2001; 8: 119-125.
[28] Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA 3rd, Moore DH, Monk BJ and O'Connor DM. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. J Clin Oncol 2005; 23: 8289-8295.
[29] Xin SB, Lin BH, Lin SF and Li HJ. Comparison of the effect between weekly paclitaxel liposome and weekly cisplatin in concurrent radiotherapy in advanced cervical cancer. J Guangdong Med 2014; 35: 761-763.
[30] Coronel JA, Cetina Ldel C, Cantú D, Cerezo O, Hernández CS, Rivera L, Chacón AP and Duenas-Gonzalez A. A randomized comparison of cisplatin and oral vinorelbine as radiosensitizers in aged or comorbid locally advanced cervical cancer patients. Int J Gynecol Cancer 2013; 23: 884-889.
[31] Wang HJ and Shu CR. Irinotecan combined with radiotherapy for locally advanced cervical carcinoma. J Nanchang Univ (Med Sci) 2012; 52: 52-57.
[32] Perez CZ, Grigsby PW and Chao CK. Chemotherapy and irradiation in locally advanced squamous cell carcinoma of the uterne cervix: A review. Semin Radiat Oncol 1997: 7 Suppl 2: 45-65.
[33] Fu KK. Biological basis for the interactions of chemotherapeutic agents and radiation therapy. Cancer 1985; 55 Suppl: 2123-2130.

[34] Lu JL and Yang F. Clinical pharmacokinetic study of cisplatin in enhancing cervical cancer radiosenstivity. J South Med Univ 2006; 26: 1170-1172.

[35] Kim YS, Shin SS, Choi EK, Kim JH, Ahn SD, Lee SW, Park HJ, Kim YT, Mok JE and Nam JH. A preliminary results of a randomized trial comparing monthly 5-flourouracil and cisplatin to weekly cisplatin alone combined with concurrent radiotherapy for locally advanced cervical cancer. Cancer Res Treat 2005; 37: 37-43.

[36] Kim YS, Shin SS, Nam JH, Kim YT, Kim YM, Kim JH and Choi EK. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecol Oncol 2008; 108: 195-200.

[37] McQuellon RP, Thaler HT, Cella D and Moore DH. Quality of life (QOL) outcomes from a randomized trial of cisplatin versus cisplatin plus paclitaxel in advanced cervical cancer: a gynecologic oncology group study. Gynecol Oncol 2006; 101: 296-304.

[38] Sehouli J, Runnebaum B, Fotopoulou C, Blohmer U, Belau A, Leber H, Hanker LC, Hartmann W, Richter R, Keyver-Paik MD, Oberhoff C, Heinrich G, du Bois A, Olbrich C, Simon E, Friese K, Kimmig R, Boehmer D, Lichtenegger W and Kuemmel S. A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO intergroup study. Ann Oncol 2012; 23: 2259-2264.

[39] Hashemi FA, Akbari EH, Kalaghchi B and Esmati E. Concurrent chemoradiation with weekly gemcitabine and cisplatin for locally advanced cervical cancer. Asian Pac J Cancer Prev 2013; 14: 5385-5389.