ORIGINAL RESEARCH

Concurrent cisplatin-based chemoradiotherapy versus exclusive radiotherapy in high-risk cervical cancer: a meta-analysis

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Objective: To evaluate the efficacy and safety of cisplatin-based concurrent chemoradiotherapy (DDP-CCRT) in patients with high-risk cervical carcinoma (CC) compared with exclusive radiotherapy (RT).

Materials and methods: Databases were searched for randomized controlled trials (RCTs) and cohort studies comparing DDP-CCRT with RT alone. Risk of bias assessment for RCTs was performed using the Cochrane Collaboration's tool, and the Newcastle–Ottawa quality scale was used to perform quality assessment for cohort studies. Meta-analysis was conducted using Review Manager 5 and Stata 12.0 software.

Results: Finally, eight RCTs and three cohort studies containing 2,130 subjects were included. Analysis on total failures revealed a statistically significant difference in favor of DDP-CCRT (risk ratio =0.77, 95% confidence intervals [CIs]: 0.67–0.89). No significant heterogeneity was detected for pooled analysis concerning overall survival; the result of which demonstrated the superiority of DDP-CCRT over RT alone (hazard ratio =0.68, 95% CI: 0.57–0.80), and stable and established accumulative effects were observed in cumulative meta-analysis. Similar results were observed for progression-free survival (hazard ratio =0.63, 95% CI: 0.50–0.76). In terms of treatment-related Grade 3 and 4 adverse events, our pooled analysis with a fixed-effects model showed significantly enhanced toxicity in the DDP-CCRT group compared with that in the RT group (odds ratio =3.13, 95% CI: 2.37–4.13).

Conclusion: Solid and stable beneficial effects are associated with DDP-CCRT, and its superiority over comparative RT in patients with high-risk CC is confirmed. DDP-CCRT should be considered one of the frontline treatment options for high-risk CC patients without contraindications. However, enhanced toxicity associated with DDP-CCRT should never be ignored.

Keywords: cervical carcinoma, concurrent chemoradiotherapy, meta-analysis, cisplatin, radiotherapy, survival

Introduction

Cervical cancer (CC) is one of the most common malignancies among females worldwide, with 400,000–500,000 new cases identified annually; the incidence of which varies across different countries and regions.[1] In developing and undeveloped countries, a much more severe prevalence of this malignancy is associated with a generally worse economical and sanitary condition, lack of effective screening, as well as underimplemented prevention strategy, where a lot of women were exposed to the risk of, or already affected by, high-risk CC, which remains a major health problem for women in these countries, though important advancement and progress has been witnessed in the last few years.[2,3]

In CC patients without distant metastasis, several factors have been demonstrated as directly associated with a worse prognosis, including locally advanced disease, bulky tumor, deeply invasive disease, and pelvic lymph node or parametrial involvement. Patients with the aforementioned characteristics are at higher risk of recurrence and generally have a shorter survival period.[4–8] Primarily applied conventional treatment modality for high-risk CC is radiotherapy (RT) with or without hysterectomy; however, inefficient local control and lymph node metastasis remain the major causes of treatment failure.[6,9,10] Therefore, treatment strategy combining RT with chemotherapy has been evaluated in a lot of clinical trials, initially in several pilot studies published ~15 years ago, most of which were randomized controlled trials (RCTs).[11–18] In these trials, concurrent chemoradiotherapy (CCRT) was the experimental treatment mode most widely assessed. Chemotherapy, at first, was applied exclusively as palliative care for patients with unfavorable prognosis. Among the drugs used for chemotherapy in advanced CC, cisplatin was one of the most effective agents.[19] Thus, cisplatin was primarily selected as one of the drugs tested in trials investigating CCRT. Among early researches comparing cisplatin-based concurrent chemoradiotherapy (DDP-CCRT) with RT, results with apparent discrepancies were reported. Four studies reported positive results, with a maximum risk reduction of 49% for estimated 4-year overall survival (OS), which supported the superiority of DDP-CCRT.[11,14,17,18] However, no significant benefits in favor of DDP-CCRT concerning survival outcomes and toxicity profile were revealed in two other studies.[12,16] These differences might be attributed to different study designs, subjects enrolled, control settings, regimens used, and duration of follow-up.

In 2002, a meta-analysis summarized these pilot studies, which presented positive results and comments recognizing improved outcomes achieved by DDP-CCRT, as well as evident toxic effects possibly enhanced by treatment combination.[20,21] However, the results of the meta-analysis showed that interventions for control groups were not totally consistent among the included studies.[11–15,17,18] Without considering surgical treatment performed in two studies as part of the local interventions for both experimental and control arms,[15,18] exclusive RT were set as control in four studies;[12,14,15,18] however in another two studies,[11,13] hydroxyurea, a widely used cytotoxic agent with antitumor activity targeting a variety of malignancies, was combined with RT as control group treatment.

Afterward, several similar studies comparing DDP-CCRT with RT alone were conducted, with different results reported.[22–28] Although more than 2 decades have passed since the initial application of DDP-CCRT in treating high-risk CC patients, during which time new agents and modalities have been developed, tested, and utilized, DDP remains in the first-line drug list for this specific population. Most recently, an RCT conducted in Brazil again evaluated the difference in treatment effects between DDP-CCRT and exclusive RT in advanced CC, using patients with International Federation of Gynecology and Obstetrics (FIGO) Stage III disease as the targeted population.[22] With accumulated and updated data from relevant studies available for a new pooled analysis, we performed this meta-analysis with refined design and analytical methods to provide more definitive evidence for clinical guidance.

Materials and methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[29]

Eligibility criteria

According to the PICOS,[29] the following criteria were used for study selection:

Participants: We included CC patients with high-risk factors; the definitions of which were provided in previous studies.[4–8]

Intervention: DDP-CCRT.

Comparator: CRT.

Outcomes: In this study, survivals were chosen as primary outcome measures for combined analyses, including OS and progression-free survival (PFS); OS was defined as the time from randomization till death caused by any cause, and PFS was defined as the time from randomization till local recurrence/progression, metastasis, or death by any cause. Secondary outcome measures consisted of treatment failure, early efficacy, and toxicity profile. Treatment failure included three aspects, ie, locoregional refractory/recurrent disease, distant metastasis, and combined local–distant failure. Early efficacy focused on complete response (CR) and partial response (PR). Treatment-related Grade 3 and 4 adverse events were chosen as the index to illustrate toxicity profile.

Study design: RCTs and comparative cohort studies.

We excluded the study based on the following exclusion criteria: 1) lack of full text – we contacted the author and got no response; 2) lack of important information – we contacted the author and got no response; 3) duplicate reports of single studies; and 4) radiation modalities were different in experimental and control groups. It should be noted that adjuvant surgical interventions consistent in both arms would

not affect the eligibility of studies that met all the selection criteria. If complementary valuable information was found in multiple reports of one trial, it was possible that different reports of a single study were included with different parts of data extracted for subsequent analyses.

Information source and search strategy

Computerized databases, such as PubMed, Embase, and the Cochrane Library, were searched using keywords "cervical cancer", "cervical carcinoma", "cisplatin", "chemoradiotherapy", "radiotherapy" with all possible combinations, for studies comparing DDP-CCRT with RT alone. The full search strategy is included in the "Supplementary material" section. The reference lists of the studies identified, relevant systemic reviews, and practice guidelines were also examined for additional potentially related studies.

Data extraction

All the titles and abstracts obtained from the results of the search strategy were screened to select potentially eligible articles. After full-text papers were independently reviewed by two investigators, the eligibility of these articles was further verified to ensure that they met all the selection conditions. Data from studies eligible for meta-analysis were independently extracted by two investigators. These data included the name of the first author, year of publication, country, study design, number of patients, clinical–pathological stage, and follow-up information. For survival outcomes, hazard ratio (HR) with corresponding 95% confidence interval (CI) was extracted. Risk ratio (RR) calculated by Cox model was considered identical to HR. If HR was not available in the text, survival curves provided in the article would be used to calculate HR and 95% CI, according to previously published methods.[30–32] Disagreement was thoroughly verified by a third investigator.

Risk of bias assessment

Risk of bias was assessed according to prespecified criteria from the Cochrane Collaboration's tool.[32,33] Briefly, the following items were evaluated: sequence generation, allocation concealment, blinding, completeness of outcome data, and other source of bias.

The quality of cohort studies was assessed using the Newcastle–Ottaw scale (NOS). This quality assessment tool covered the following aspects: selection of study groups (0–4 stars), comparability between groups (0–2 stars), and ascertainment of outcome of interest (0–3 stars) for cohort studies, respectively.

Statistical analysis

Statistical analyses were performed using the Review Manager 5 and Stata SE 12.0 software. HRs and 95% CIs were computed for survival statistics. Heterogeneity among studies was assessed using the χ^2 test and I^2 statistic, and a statistical heterogeneity of <25%, 25%–50%, and >50% was defined as low, moderate, and high, respectively.[34] If no significant heterogeneity was detected, a fixed-effects model would be used; otherwise, a random-effects model would be used. We carried out cumulative meta-analyses based on the order of publication year for survival outcomes. Subgroup analyses and metaregression analyses were conducted to further explore potential confounding bias of studies reporting survival. For all the statistical analyses, a P-value <0.05 was set as the level of significance. The publication bias was examined using the funnel plot; the results of which were further verified with Begg's test.[35]

Results

Characteristics of included studies

A total of 316 citations were retrieved, and is represented by a search flowchart as shown in Figure 1. After a refined selection according to the inclusion criteria, eight RCTs and three cohorts trials were finally included.[12,15,16,18,22–28] A total of 2,230 patients were involved, 1,098 of whom had received radiation and DDP-CCRT regimen. The majority of the eligible trials reported primary outcome measures, ie, OS and PFS. Details of the eleven included articles are provided in Table 1.
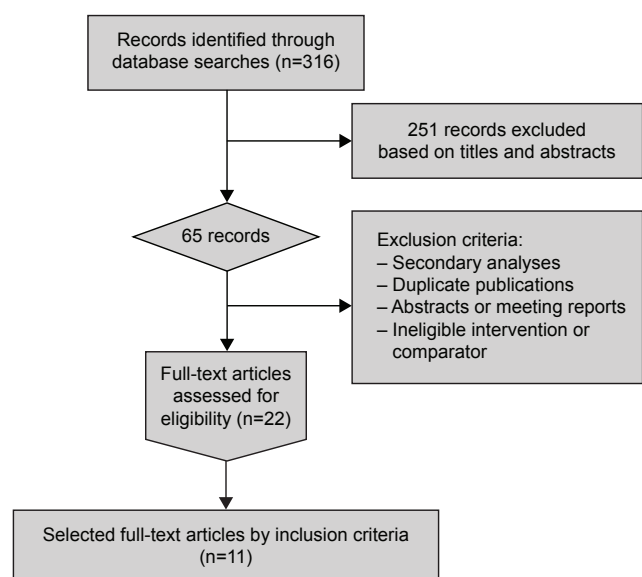

Figure 1 Flow diagram of meta-analysis.

Table I Characteristics of eligible studies in meta-analyses

Source	Region	Study type	No of Patients (CRT/RT)	Age (yr), mean (range)	Stage	Histology	Median follow-up (mo)	RT-regimen	CT-regimen	HR estimate	End points
Tseng et al[12]	Taiwan	RCT	122 (60/62)	57.5 (33–69)	IIb/IIIb	SCC	46.8	EBRT + HDRICB	Cisplatin + Vincristine + Bleomycin (q3w)	Calculated	TR, FP, OS, PFS, AE
Keys et al[18]	USA	RCT	369 (183/186)	41.5	Ib	CC	36	EBRT + LDRICB	Cisplatin (qw)		AE
Peters et al[15]	USA	RCT	243 (127/116)	39.6	Ia2–IIa	CC	42	EBRT	Cisplatin +5-FU (q3w)	Calculated	OS, PFS, AE
Pearcey et al[16]	Canada	RCT	253 (127/126)	(18–75)	Ib–IVa	SCC	82	EBRT + RICB	Cisplatin (qw)	Reported	OS, PFS
Chen et al[28]	Taiwan	Cohort	171 (70/101)	59.5 (33–79)	IIb–III	SCC and ADC	58	EBRT + HDRICB	Cisplatin (qw)	Calculated	OS, PFS, FP
Han and Kong[27]	People's Republic of China	Cohort	197 (97/100)	46 (25–81)	Ib–IVa	SCC and ADC	–	EBRT + HDRICB	Cisplatin +5-FU (q4w)		TR
Stehman et al[24]	USA	RCT	369 (183/186)	41.5	Ib	CC	101	EBRT + LDRICB	Cisplatin (qw)	Reported	OS, PFS, FP
Nagy et al[25]	Romania	RCT	566 (282/284)	46 (24–68)	IIb–IIIb	SCC	62.8	EBRT + HDRICB/XRA	Cisplatin (c5d/q3w)	Surv curv	TR, FP, OS, AE
Torbe et al[23]	Poland	Cohort	106 (52/54)	53.8 (27–78)	IIa–IVa	SCC and ADC	–	EBRT + LDRICB	Cisplatin (qw)	Surv curv	TR, OS, PFS, AE
Ke et al[26]	People's Republic of China	RCT	56 (28/28)	54 (33–65)	IIb–IVa	SCC and ADC	–	EBRT + HDRICB	Cisplatin + Taxotere (qw)		TR
Zuliali et al[22]	Brazil	RCT	147 (72/75)	–	IIIb	SCC	43.2	EBRT + HDRICB	Cisplatin (qw)		OS, PFS, FP

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; RCT, randomized controlled trial; SCC, squamous cell carcinoma; CC, cervical cancer; EBRT, external beam radiotherapy; ICB, intracavitary brachytherapy; 5-FU, 5-fluorouracil; HR, hazard ratio; Surv curv, survival curve; TR, tumor response; FP, failure patterns; OS, overall survival; AE, adverse effects; yr, years; mo, months; qd, once a week; q3w, every three weeks; q4w, every four weeks; c5d, 5 days a cycle; HDR, high-dose rate; LDR, low dose-rate; XRA, X radiation.

Quality assessment

As listed in Table 2, according to the Cochrane Collaboration bias assessment tool, all of the eight RCTs were adequately randomized (Figure S1). Only one study[22] described the allocation concealment. All of the included RCTs had not reported their blinding methods (either for participants or for appraisers). In addition, incomplete data were provided in one study,[18] while another study[26] selectively reported tumor response.

As evaluated by the NOS tool, the three cohort studies were considered high quality (8 stars, 7 stars, and 8 stars for Chen et al's,[28] Han and Kong's,[27] and Torbe et al's[23] reports, respectively).

Early efficacy

Data on early efficacy, ie, tumor response, were reported in five studies.[12,23,25–27] Among these studies, Nagy et al[25] only provided data on CR, while Torbe et al[23] only reported CR + PR. Statistically significant heterogeneity was observed, with an I^2 of 77% and 74% for CR and CR + PR, respectively. The pooled analysis with a random-effects model showed that statistical significance was reached in none of these comparisons (RR and 95% CI were 1.02 [0.77–1.34] and 0.96 [0.83–1.11] for CR and CR + PR, respectively; Figure 2).

Treatment failures

Patterns of treatment failure were evaluated in four RCTs and one cohort study.[12,22,24,25,28] Apart from the trial of Zuliani et al,[22] which only provided the total number of treatment failures, the other four studies separately provided the number of local failure, distant failure, and combined failure (local + distant). In particular, in Nagy et al's[25] report, combined failures were observed in none of the involved patients. The I^2 value was 34%, 63%, 0%, and 0% for total failure, local failure, distant failure, and combined failure, respectively. In our meta-analyses, although no significant differences were demonstrated for the three subtotal comparisons (local: RR =0.75, 95% CI: 0.47–1.20 [Figure 3B]; distant: RR =0.93, 95% CI: 0.68–1.27 [Figure 3C]; and combined: RR =0.84, 95% CI: 0.41–1.73 [Figure 3D]), analysis for total treatment failures revealed a statistically significant difference in favor of CRT (RR =0.77, 95% CI: 0.67–0.89; Figure 3A).

Survival outcomes

As shown in Figure 4A, there were eight studies[12,15,16,22–25,28] evaluating the OS, and no significant heterogeneity (I^2=0.0%, P=0.636) was found among these studies. The pooled analysis with a fixed-effects model showed a statistically

Table 2 Risk of bias assessment

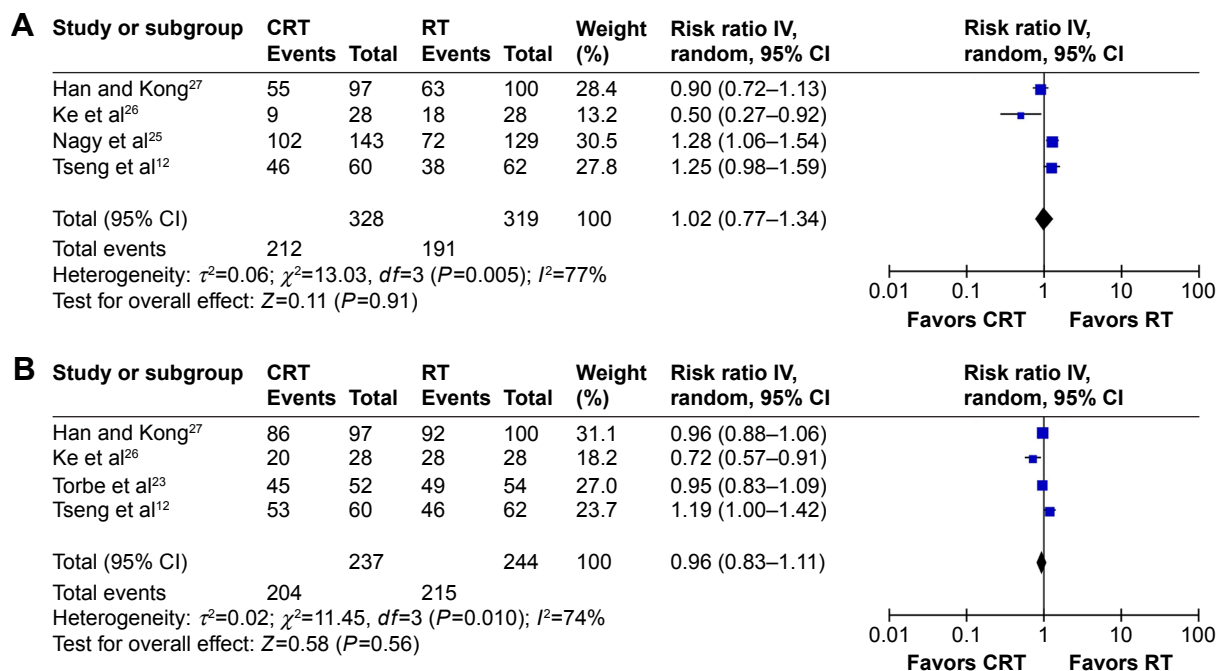| Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
Tseng et al[12]	Y	U	N	N	N	N
Keys et al[18]	Y	U	U	Y	N	N
Peters et al[15]	Y	U	N	N	N	N
Pearcey et al[16]	Y	U	N	N	N	N
Stehman et al[24]	Y	U	N	N	N	N
Nagy et al[25]	Y	U	N	N	N	N
Ke et al[26]	Y	U	N	N	Y	N
Zuliali et al[22]	Y	Y	N	N	N	N

Abbreviations: Y, yes; N, no; U, unclear.

significant difference in favor of CRT group over RT group (HR =0.68, 95% CI: 0.57–0.80). Although several RCTs with large sample size were designed to evaluate the OS after 2002, cumulative meta-analysis indicated that stable pooled effect was already established with the three earliest RCTs[12,15,16] (a total of 618 patients were involved) published in 1997, 2000, and 2002 (interim HR =0.68, 95% CI: 0.48–0.88), and further cumulative analyses with subsequent trials added resulted only in slightly changed point estimates and continuously narrowed 95% CIs (Figure 4B).

Similar results were observed for PFS. Minor heterogeneity among the included six studies[12,15,16,22–24] was observed (I^2=21.4%, P=0.273). Our meta-analysis demonstrated significantly better PFS in the CRT group (HR =0.63, 95% CI: 0.50–0.76; Figure 5A). The cumulative

meta-analysis of three RCTs[12,15,16] conducted before 2002 revealed an apparently better outcome of CRT group (interim HR =0.65, 95% CI: 0.47–0.84). Further cumulative analyses with subsequent trials added resulted only in narrowed 95% CIs and slightly changed pooled effect size (Figure 5B).

Adverse effects

To evaluate the adverse effects, the treatment-related Grade 3 and 4 adverse events were chosen as the effect size index, and totally five trials[12,15,18,23,25] with no significant heterogeneity (I^2=0.0%, P=0.79) were included. Among them, only one study[15] provided the number of patients with Grade 4 toxicity. Our pooled analysis with a fixed-effects model showed significantly enhanced toxicity in the CRT group compared with the RT group (OR =3.13, 95% CI: 2.37–4.13; Figure 6).

A

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio IV, random, 95% CI
Han and Kong[27]	55	97	63	100	28.4	0.90 (0.72–1.13)
Ke et al[26]	9	28	18	28	13.2	0.50 (0.27–0.92)
Nagy et al[25]	102	143	72	129	30.5	1.28 (1.06–1.54)
Tseng et al[12]	46	60	38	62	27.8	1.25 (0.98–1.59)
Total (95% CI)		328		319	100	1.02 (0.77–1.34)
Total events	212		191			

Heterogeneity: τ^2=0.06; χ^2=13.03, df=3 (P=0.005); I^2=77%
Test for overall effect: Z=0.11 (P=0.91)

B

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio IV, random, 95% CI
Han and Kong[27]	86	97	92	100	31.1	0.96 (0.88–1.06)
Ke et al[26]	20	28	28	28	18.2	0.72 (0.57–0.91)
Torbe et al[23]	45	52	49	54	27.0	0.95 (0.83–1.09)
Tseng et al[12]	53	60	46	62	23.7	1.19 (1.00–1.42)
Total (95% CI)		237		244	100	0.96 (0.83–1.11)
Total events	204		215			

Heterogeneity: τ^2=0.02; χ^2=11.45, df=3 (P=0.010); I^2=74%
Test for overall effect: Z=0.58 (P=0.56)

Figure 2 Forest plots and meta-analyses of tumor response.
Notes: (**A**) CR. (**B**) CR + PR.
Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; CI, confidence interval; CR, complete response; PR, partial response; df, degrees of freedom.
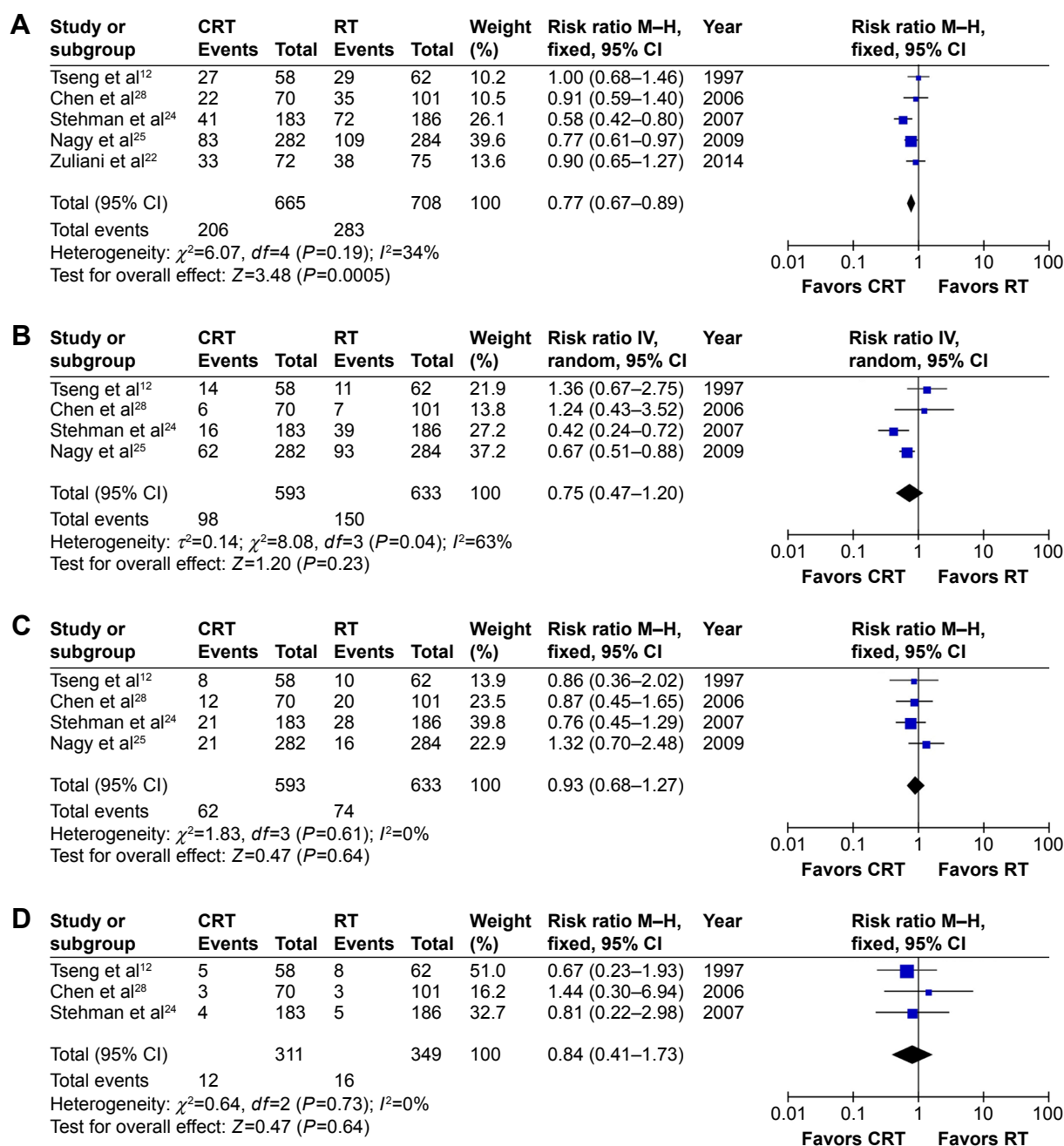
A

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Tseng et al[12]	27	58	29	62	10.2	1.00 (0.68–1.46)	1997
Chen et al[28]	22	70	35	101	10.5	0.91 (0.59–1.40)	2006
Stehman et al[24]	41	183	72	186	26.1	0.58 (0.42–0.80)	2007
Nagy et al[25]	83	282	109	284	39.6	0.77 (0.61–0.97)	2009
Zuliani et al[22]	33	72	38	75	13.6	0.90 (0.65–1.27)	2014
Total (95% CI)		665		708	100	0.77 (0.67–0.89)	
Total events	206		283				

Heterogeneity: $\chi^2=6.07$, $df=4$ ($P=0.19$); $I^2=34\%$
Test for overall effect: $Z=3.48$ ($P=0.0005$)

B

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio IV, random, 95% CI	Year
Tseng et al[12]	14	58	11	62	21.9	1.36 (0.67–2.75)	1997
Chen et al[28]	6	70	7	101	13.8	1.24 (0.43–3.52)	2006
Stehman et al[24]	16	183	39	186	27.2	0.42 (0.24–0.72)	2007
Nagy et al[25]	62	282	93	284	37.2	0.67 (0.51–0.88)	2009
Total (95% CI)		593		633	100	0.75 (0.47–1.20)	
Total events	98		150				

Heterogeneity: $\tau^2=0.14$; $\chi^2=8.08$, $df=3$ ($P=0.04$); $I^2=63\%$
Test for overall effect: $Z=1.20$ ($P=0.23$)

C

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Tseng et al[12]	8	58	10	62	13.9	0.86 (0.36–2.02)	1997
Chen et al[28]	12	70	20	101	23.5	0.87 (0.45–1.65)	2006
Stehman et al[24]	21	183	28	186	39.8	0.76 (0.45–1.29)	2007
Nagy et al[25]	21	282	16	284	22.9	1.32 (0.70–2.48)	2009
Total (95% CI)		593		633	100	0.93 (0.68–1.27)	
Total events	62		74				

Heterogeneity: $\chi^2=1.83$, $df=3$ ($P=0.61$); $I^2=0\%$
Test for overall effect: $Z=0.47$ ($P=0.64$)

D

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Tseng et al[12]	5	58	8	62	51.0	0.67 (0.23–1.93)	1997
Chen et al[28]	3	70	3	101	16.2	1.44 (0.30–6.94)	2006
Stehman et al[24]	4	183	5	186	32.7	0.81 (0.22–2.98)	2007
Total (95% CI)		311		349	100	0.84 (0.41–1.73)	
Total events	12		16				

Heterogeneity: $\chi^2=0.64$, $df=2$ ($P=0.73$); $I^2=0\%$
Test for overall effect: $Z=0.47$ ($P=0.64$)

Figure 3 Forest plots and meta-analyses of failure patterns.
Notes: (**A**) Total failure patterns. (**B**) Local failure patterns. (**C**) Distant failure patterns. (**D**) Combined (local + distant) failure patterns.
Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; CI, confidence interval; M–H, Mantel–Haenszel; *df*, degrees of freedom.

Sensitivity analysis and metaregression analysis

Sensitivity analysis was performed to verify the reliability and stability of the evidence when significant heterogeneity was detected. In this study, high heterogeneity was detected for the tumor response outcome, and sensitivity analysis by excluding certain study did not significantly change the result. Because of the limited number of trials included for tumor response evaluation and potential inconsistency in study characteristics, such as study design, sample size, and CCRT and RT regimen, we did not perform any subgroup analysis to further explore the source of heterogeneity. For survival outcomes, several subgroup analyses were performed (Table 3). In terms of OS, important inconsistency was detected for subcomparisons stratified by region and study design, showing that no significant pooled difference existed between DDP-CCRT and RT in studies conducted in Asia or studies with non-RCT design (HR =0.89, 95% CI: 0.46–1.32,
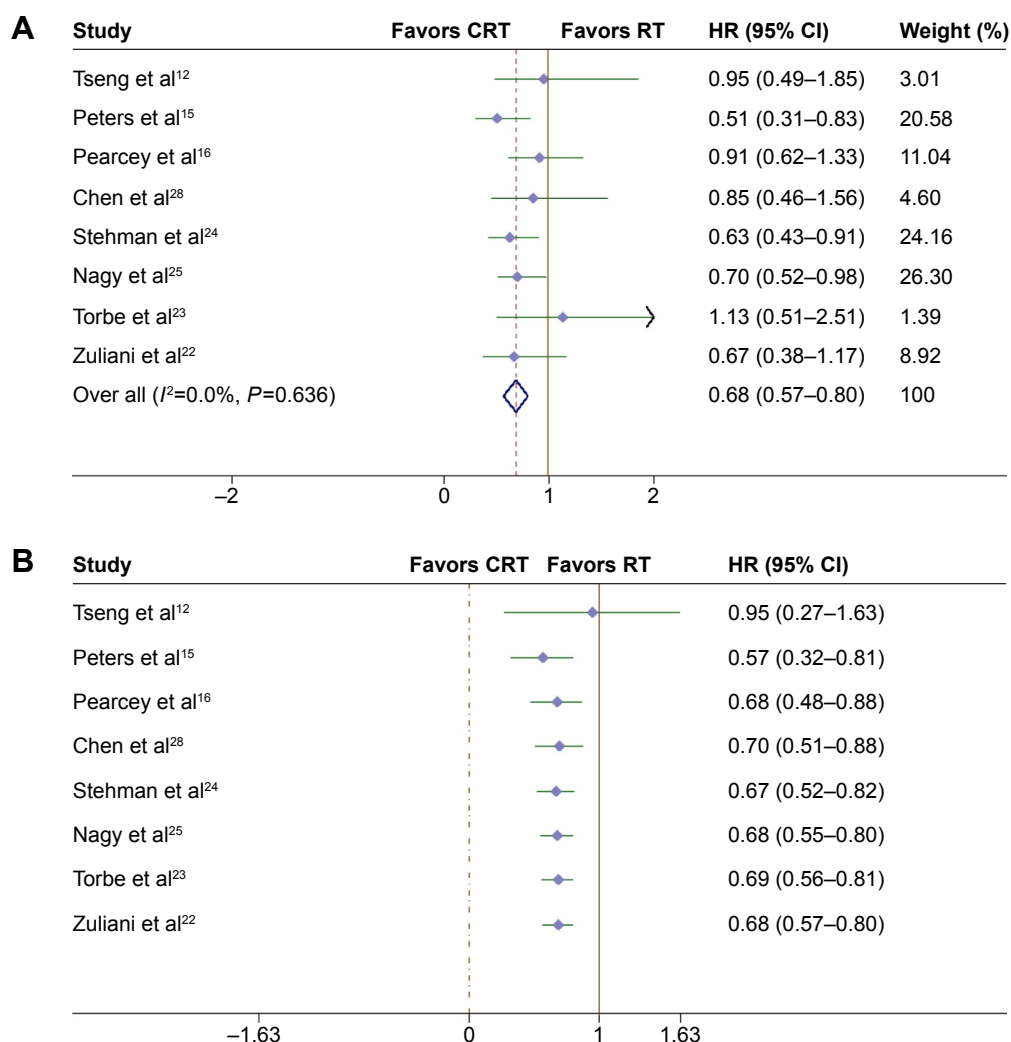
A

Study	Favors CRT	Favors RT	HR (95% CI)	Weight (%)
Tseng et al[12]			0.95 (0.49–1.85)	3.01
Peters et al[15]			0.51 (0.31–0.83)	20.58
Pearcey et al[16]			0.91 (0.62–1.33)	11.04
Chen et al[28]			0.85 (0.46–1.56)	4.60
Stehman et al[24]			0.63 (0.43–0.91)	24.16
Nagy et al[25]			0.70 (0.52–0.98)	26.30
Torbe et al[23]			1.13 (0.51–2.51)	1.39
Zuliani et al[22]			0.67 (0.38–1.17)	8.92
Over all (I^2=0.0%, P=0.636)			0.68 (0.57–0.80)	100

−2   0   1   2

B

Study	Favors CRT	Favors RT	HR (95% CI)
Tseng et al[12]			0.95 (0.27–1.63)
Peters et al[15]			0.57 (0.32–0.81)
Pearcey et al[16]			0.68 (0.48–0.88)
Chen et al[28]			0.70 (0.51–0.88)
Stehman et al[24]			0.67 (0.52–0.82)
Nagy et al[25]			0.68 (0.55–0.80)
Torbe et al[23]			0.69 (0.56–0.81)
Zuliani et al[22]			0.68 (0.57–0.80)

−1.63   0   1   1.63

Figure 4 Forest plots of OS.
Notes: (**A**) Meta-analysis of OS. (**B**) Cumulative meta-analysis of OS. Weights are from fixed-effects analysis.
Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; RT, radiotherapy.

and HR =0.92, 95% CI: 0.43–1.40, respectively). However, in terms of PFS, no subgroup analysis showed interesting results. The metaregression analysis was only feasible for OS, and the L'Abbé graph adjusted by age showed an overall trend that with the increasing age, patients' survival was shortened more frequently in the CRT group than the RT group (Figure 7).

Publication bias

The funnel plots of included articles were symmetrical, indicating the absence of publication bias, which was later confirmed by Begg's test (P=0.376; Figure 8).

Discussion

After the results of five pivotal trials were published in 1999,[11,14,15,17,18] with an alert issued by the National Cancer Institute recommending chemoradiation instead of radiation alone for the treatment of CC, DDP-CCRT has been extensively applied and investigated in clinical practice.[36] A meta-analysis published in 2002 summarized the comparison between cisplatin-based CRT and RT; however, several important problems exist in this very study.[20] First, for OS comparisons, the RR of each study was calculated with the number of events by the end of the research without considering the time-to-event information; thus, the results of the combined analyses were not as reliable as those using HR as effect size index. Second, apparent inconsistency existed among the control group settings of each study. Although major heterogeneity was not detected, this inconsistency may possibly introduce certain confounding effects into the results of pooled analyses; moreover, from our perspective, studies comparing DDP-CCRT with RT + HU should be considered
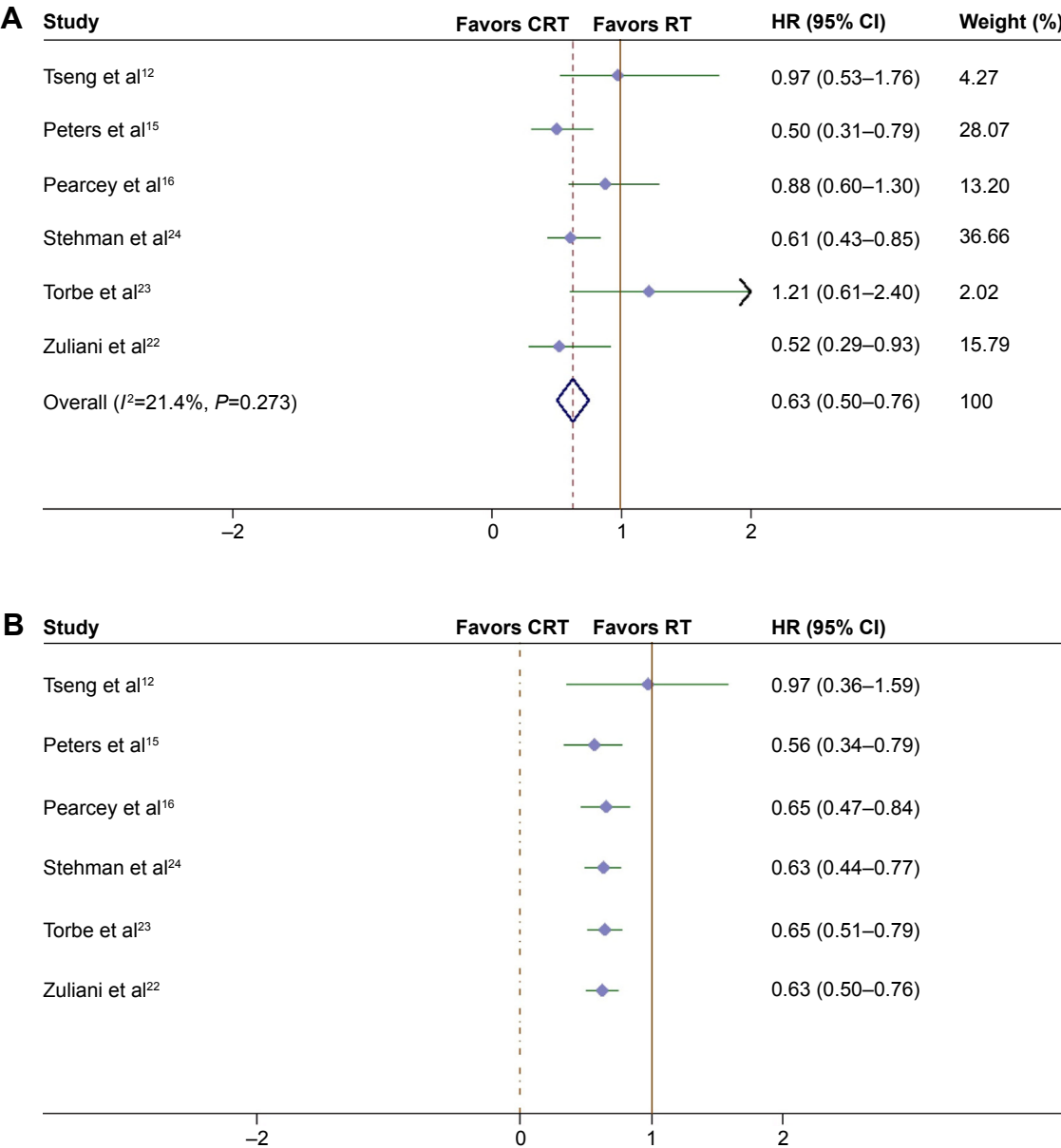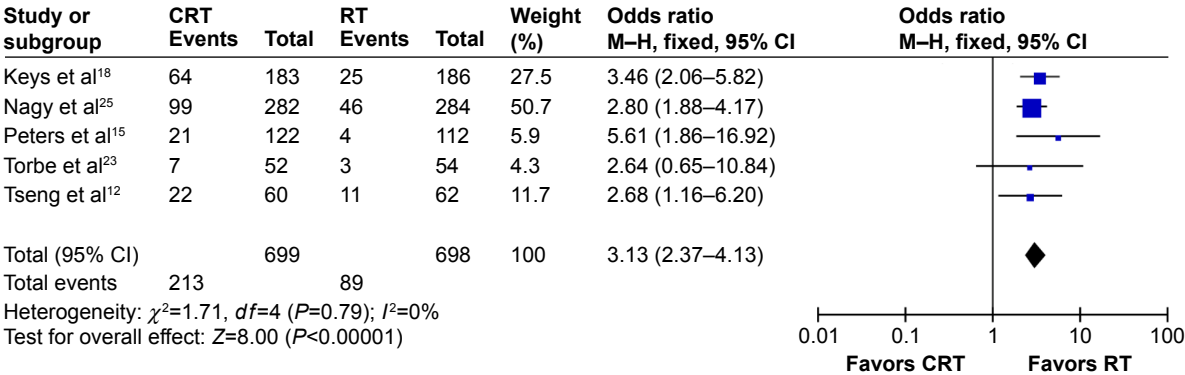
A

Study	Favors CRT / Favors RT	HR (95% CI)	Weight (%)
Tseng et al[12]		0.97 (0.53–1.76)	4.27
Peters et al[15]		0.50 (0.31–0.79)	28.07
Pearcey et al[16]		0.88 (0.60–1.30)	13.20
Stehman et al[24]		0.61 (0.43–0.85)	36.66
Torbe et al[23]		1.21 (0.61–2.40)	2.02
Zuliani et al[22]		0.52 (0.29–0.93)	15.79
Overall (I^2=21.4%, P=0.273)		0.63 (0.50–0.76)	100

B

Study	Favors CRT / Favors RT	HR (95% CI)
Tseng et al[12]		0.97 (0.36–1.59)
Peters et al[15]		0.56 (0.34–0.79)
Pearcey et al[16]		0.65 (0.47–0.84)
Stehman et al[24]		0.63 (0.44–0.77)
Torbe et al[23]		0.65 (0.51–0.79)
Zuliani et al[22]		0.63 (0.50–0.76)

Figure 5 Forest plots of PFS.
Notes: (**A**) Meta-analysis of PFS. (**B**) Cumulative meta-analysis of PFS. Weights are fixed-effects analysis.
Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; RT, radiotherapy.

Study or subgroup	CRT Events	Total	RT Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Keys et al[18]	64	183	25	186	27.5	3.46 (2.06–5.82)	
Nagy et al[25]	99	282	46	284	50.7	2.80 (1.88–4.17)	
Peters et al[15]	21	122	4	112	5.9	5.61 (1.86–16.92)	
Torbe et al[23]	7	52	3	54	4.3	2.64 (0.65–10.84)	
Tseng et al[12]	22	60	11	62	11.7	2.68 (1.16–6.20)	
Total (95% CI)		699		698	100	3.13 (2.37–4.13)	
Total events	213		89				

Heterogeneity: χ^2=1.71, df=4 (P=0.79); I^2=0%
Test for overall effect: Z=8.00 (P<0.00001)

Figure 6 Forest plot and meta-analysis of toxicity.
Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; CI, confidence interval; M–H, Mantel–Haenszel; df, degrees of freedom.

Table 3 Subgroups analyses of survival outcomes

End points (no of study)	Subgroup	Study	Heterogeneity		Meta-analysis	
			I^2 (%)	P-value	Effect size	95% CI
OS (8)	Country	Western	0.00	0.552	0.67	0.55–0.79
		Eastern	0.00	0.823	0.89	0.46–1.32
	Study design	RCT	0.00	0.545	0.67	0.55–0.79
		Non-RCT	0.00	0.631	0.92	0.43–1.40
	Stage	Early (≤IIb)	0.00	0.518	0.60	0.43–0.77
		Advanced (≥IIIa)	0.00	0.742	0.77	0.60–0.93
	Histology	CC	0.00	0.506	0.57	0.40–0.75
		SCC	0.00	0.695	0.76	0.59–0.92
		SCC and ADC	0.00	0.631	0.92	0.43–1.40
	CT-regimen	Cisplatin alone	0.00	0.763	0.72	0.59–0.86
		Cisplatin combined	28.70	0.236	0.57	0.32–0.81
	RT-regimen	EBRT + HDRICB	0.00	0.864	0.73	0.55–0.91
		EBRT + LDRICB	0.00	0.341	0.66	0.42–0.89
PFS (6)	Stage	Early (≤IIb)	0.00	0.499	0.56	0.40–0.72
		Advanced (≥IIIa)	25.40	0.259	0.75	0.53–0.96
	Histology	CC	0.00	0.499	0.56	0.40–0.72
		SCC	31.90	0.230	0.72	0.50–0.94
	CT-regimen	Cisplatin alone	23.50	0.270	0.66	0.50–0.81
		Cisplatin combined	48.60	0.163	0.56	0.34–0.79
	RT-regimen	EBRT + HDRICB	38.20	0.203	0.62	0.33–0.90
		EBRT + LDRICB	38.90	0.201	0.64	0.44–0.85

Abbreviations: CI, confidence interval; OS, overall survival; RCT, randomized controlled trial; CC, cervical cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; CT, chemotherapy; RT, radiotherapy; EBRT, external beam radiotherapy; ICB, intracavitary brachytherapy; LDR, low dose-rate; HDR, high dose-rate; PFS, progression-free survival.

comparisons between two different types of CRT rather than comparisons between DDP-CCRT and exclusive RT, and therefore should not be included for meta-analysis comparing DDP-CCRT with exclusive RT. On the other hand, including such studies into metacomparisons between DDP-CCRT and exclusive RT would preclude a reasonable interpretation for the pooled data. Third, the quality of original studies and risk of bias was not assessed. And finally, statistical analysis was not performed for data on toxicity. After the publication of

this 2002 meta-analysis, updated data with different results addressing this issue are available for an updated evaluation. In 2010, the Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC) published an individual patient data (IPD) meta-analysis to reduce uncertainties about the effects of CCRT for CC; the results of which supported the superiority of platinum-based (OS: HR =0.83, P=0.017) and nonplatinum-based chemoradiotherapy (OS: HR =0.77, P=0.009) over RT.[37] In this IPD meta-analysis, pooled
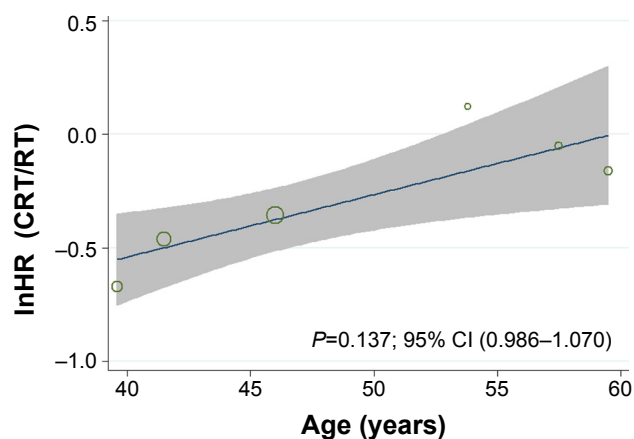
Figure 7 Representative l'Abbé plot shows the correlation of OS with age.
Note: Each green circle represents one study, and the blue line represents the fitted regression line.
Abbreviations: OS, overall survival; CRT, chemoradiotherapy; RT, radiotherapy; CI, confidence interval.
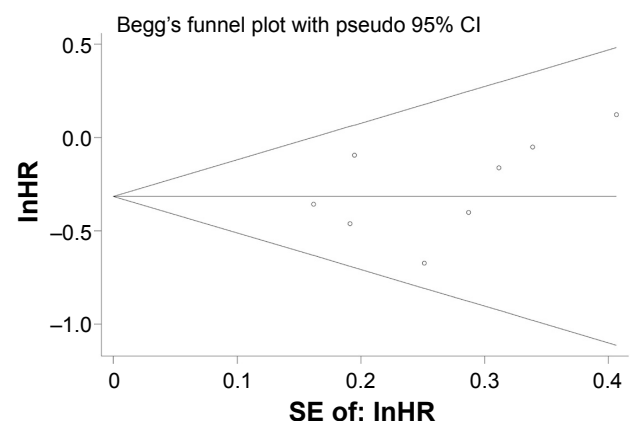
Figure 8 Funnel plot of studies reporting OS.
Abbreviations: OS, overall survival; SE, standard error; CI, confidence interval.

analyses were conducted for studies investigating CCRT versus the same RT (13 trials), and toxicity comparisons were conducted. Although this CCCMAC work used IPD from single studies (published and unpublished) to obtain more reliable results, certain interesting points should be noted. For example, the latest study included in this IPD study was finished in 2005; however, according to the results of our search strategy, additional data from at least two studies published during 2005–2010 with 737 patients were potentially available for combined analysis.[25,28] In addition, as to studies finished before 2005, at least one study with 122 patients was potentially useful for combined analysis.[12] Therefore, it is very likely that potentially available data, especially later ones, were not fully utilized in this IPD study. Why were certain potentially eligible studies not included in this IPD study? A possible reason was that the CCCMAC was unable to obtain IPD for those studies. Of course, IPD meta-analysis is a proposed method to perform meta-analyses, especially for those investigating time-to-event end points. However, obtaining complete original data of individual patients is never easy and always time consuming, and so cannot be widely performed by researchers. In addition, statistical methods and tools for IPD meta-analysis were more complicated than those of traditional meta-analysis. If certain data (especially recent ones) available for traditional meta-analysis could not be used for IPD due to methodological barriers, the results of IPD may be no more reliable and no superior than traditional meta-analysis.

Therefore, noting the limitations in these two aforementioned meta-analyses, we performed this study with more recent data and refined the study design to make a complementary contribution to the evidence-based medicine on CC treatment. The beneficial effects of cisplatin, which is the most widely used agent for CCRT in CC patients, whether alone or in combination with other drugs, were not independently reported in the CCCMAC study.[37] Our study focused on the comparisons between DDP-CCRT and exclusive RT to form a definitive conclusion for this issue. Moreover, only patients with high-risk disease, such as locally advanced cancer or bulky tumor, were investigated in this study. To the best of our knowledge, this is the first metacomparison for DDP-CCRT versus exclusive RT focusing on this specific subgroup of patients with CC. Furthermore, for the first time, cumulative meta-analyses addressing this topic were performed in our study, with stable and reliable results shown in the cumulative processing for survival outcomes.

In this study, combined analysis for the early efficacy (tumor response) was for the first time performed, and the results revealed major heterogeneity, which could not be successfully interpreted by sensitivity analysis and subgroup analysis. Since only four studies were included for analysis concerning CR[12,25–27] as well as CR + PR,[12,23,26,27] the heterogeneity detected could be attributed to relatively limited sample size. Obviously, the end point of tumor response was not as fully investigated as survival outcomes in previously published trials. Tumor response definitions based on the World Health Organization criteria were adopted in two studies, and the tumor response was evaluated by physical examination and tumor size measured with imaging techniques.[12,27] In Nagy et al's[25] report, the tumor response was evaluated pathologically. Evaluation criteria were not clarified in two studies; however, it could be inferred that the tumor response was evaluated clinically.[23,26] Different evaluation criteria may have contributed to the heterogeneity. Only Ke et al[26] reported a significantly better early efficacy in the DDP-CCRT group, and the pooled effects demonstrated no significant differences between CRT and RT for CR and CR + PR both. Because only 28 patients were enrolled in Ke et al's[26] study and the new agent Taxotere® was combined with DDP, the particular finding revealed in Ke et al's[26] study needs further investigation.

As to treatment failures, significant difference in favor of DDP-CCRT was detected exclusively for the total failure. The result for total treatment failure was consistent with the result for PFS, and both supported the superiority of DDP-CCRT. Interestingly, on the other hand, negative results were observed for all the three subtotal comparisons, ie, for local failure, distant failure, and combined failure. Of course, local recurrence-free survival and distant recurrence-free survival could be better indices to reflect the status of disease control; however, since few data on these two indices were available, regrettably a meta-analysis could not be performed. Further investigation addressing posttreatment local and distant relapsed disease is needed.

Significantly improved OS and PFS in DDP-CCRT-treated patients were demonstrated in our pooled analysis. Moreover, solid and stable beneficial effects were established through cumulative meta-analyses for the first time in our study. The pooled HR and 95% CI for OS and PFS were 0.68 (0.57–0.80) and 0.63 (0.50–0.76), respectively; according to the results of our cumulative meta-analyses, OS and PFS data from additional trials will only result in minimally changed HR and narrowed 95% CI. In the 2010 IPD meta-analysis, the pooled HR and 95% CI of OS were 0.84 (0.72–0.98) and 0.76 (0.62–0.94), respectively, for platinum-based CCRT and nonplatinum-based CCRT against control, and the pooled HR and 95% CI of overall PFS were 0.78 (0.70–0.87) for CCRT against RT. Comparing these statistics, it is not unreasonable

to speculate that the DDP may have better efficacy than other agents. Of course, this speculation should be further verified in future trials. Subgroup analyses were conducted for OS. According to analysis stratified by region, no significant difference of pooled OS between DDP-CCRT and RT was found for studies performed in Asian countries. Because only two studies with a total of 293 patients were categorized into this subgroup, including one RCT and one cohort trial both reporting negative results,[12,28] the pooled result may not be solid. However, interestingly, in the report of Han and Kong,[27] although survival curve and data on HR were not provided, no significant differences were found for the 3-year OS rate and 5-year OS rate between DDP-CCRT and RT. Moreover, in the CCCMAC IPD meta-analysis, only two Asian studies[38,39] concerning platinum-based CCRT with a total of 169 patients were included, both with negative OS results.[37] It is very interesting to note that almost all the Asian studies reported negative results. The racial difference could be an important underlying factor contributing to the evident inconsistency between the results of Asian studies and those of Western studies, and additional studies with emphasis on this issue are in need.

Limitations

First, concealment and blinding methods were not reported in most of the included RCTs. In fact, for the comparisons between DDP-CCRT and RT, concealment and blinding was almost impossible. Second, limited data on early efficacy, treatment failure, and toxicity profile were available for meta-analysis; therefore, to obtain more reliable results, further evaluation with additional data is necessary. Third, the value of HR and 95% CI for survival outcomes was not reported in certain studies; calculated statistics using time-to-event survival data or survival curves were utilized for meta-analysis. Although the statistic methods for these calculations are already established, minor deviations were inevitable during the process. However, according to our cumulative meta-analysis, the influence of these deviations was of minor importance.

Conclusion

To summarize, although high-risk CC patients form a heterogeneous population, solid and stable beneficial effects associated with DDP-CCRT compared with comparative RT alone in this special subgroup are further confirmed in our meta-analysis. For treatment decisions, CC patients with high-risk characteristics (eg, bulky tumor, deeply invasive disease, advanced disease, etc) could be considered an entity that would benefit from DDP-CCRT, which should

be considered one of the frontline treatment options for high-risk CC patients without contraindications. On the other hand, enhanced toxicity associated with DDP-CCRT should never be ignored. According to the results of our cumulative meta-analyses, further comparisons on OS and PFS between DDP-CCRT and RT are of minor importance. Investigations on tumor response, survival comparisons stratified by tumor response, large RCTs on potential racial difference, and intercomparisons between different CCRT regimens could be subjects for future studies.

Disclosure

The authors report no conflicts of interests in this work.

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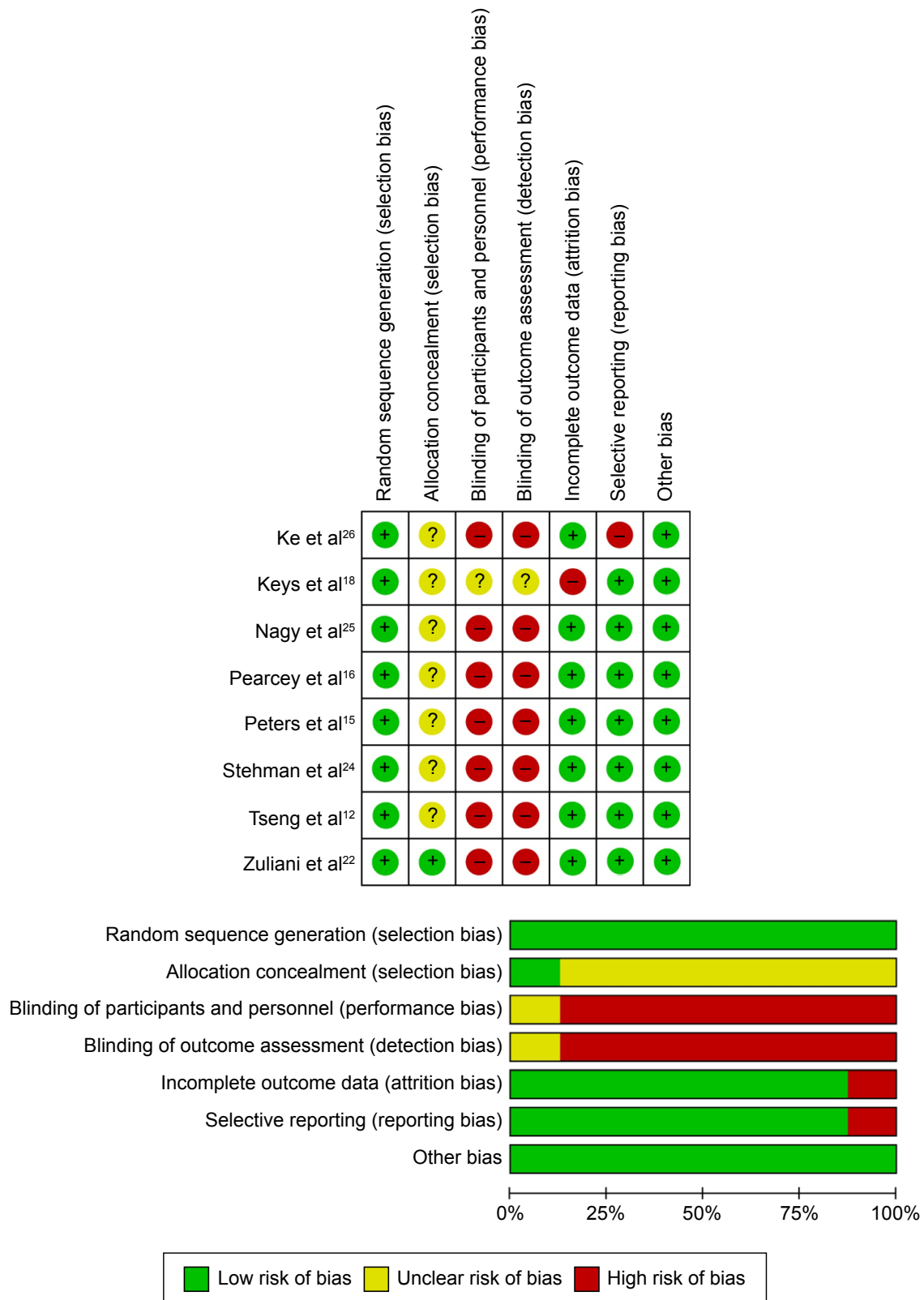
Supplementary material

Figure S1 Risk of bias assessment.