Original Article

Effectiveness of cervical cancer therapy using neoadjuvant chemotherapy in combination with radical surgery: a meta-analysis

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Background: Cervical cancer is the fourth of most common cancers, and also the fourth cause of women death in the world. Neoadjuvant chemotherapy (NACT) combined with conventional radical surgery (RS) has been proposed to be able to eradicate the micro metastasis for advanced cervical tumors so that improve the survival of cancer patients. However, the effectiveness of combined treatment of both NACT and RS is still a debate. Results from different studies are usually inconsistent, even contradictory.

Methods: To evaluate the advantage of the combination of NACT and RS over RS alone for cervical cancer, we performed a meta-analysis, which involved eight case-control studies. Two-year and 5-year disease-free survival (DFS) and overall survival (OS) were compared with stratification analysis in each group with regard to the surgical-pathologic high risk factors including lymph node metastasis, positive surgical margin, parametric infiltration, lymphovascular invasion, cervical stromal depth and positive pelvic nodes.

Results: Our study showed that cervical cancer patients with additive NACT treatment may have no additional benefit for the long-term OS and DFS than RS alone group [2-year OS: odds ratios (ORs) =1.008; 95% confidence intervals (CIs), 0.832–1.220; P=0.937; 5-year OS: OR =1.054; 95% CI, 0.860–1.292; P=0.913; 2-year DFS: OR =1.015; 95% CI, 0.853–1.207; P=0.870; 5-year DFS: OR =1.001; 95% CI, 0.816–1.228; P=0.992]. Further subgroup meta-analysis of adjuvant therapy and stratification adjustment with six surgical–pathologic risk factors also drew the same conclusion.

Conclusions: These results suggested that NACT might not be effective enough to elongate patients survival as been reported by some studies, further confirmation needs to be done by more profound analyses.

Keywords: Chemotherapy; cervical cancer; meta-analysis; radical surgery (RS); neoadjuvant therapy

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Introduction

Cervical cancer represents a common gynecologic malignancy in developed and developing countries (1). Approximately 500,000 new cases of cervical cancer are diagnosed each year with 70% of them diagnosed at an advanced stage (2). Both the size of the lesion and depth of stromal invasion are reported to have an important effect on survival, and thus the lesion diameter becomes the most important prognostic factor during cervical cancer treatment (3,4). According to the staging of cervical

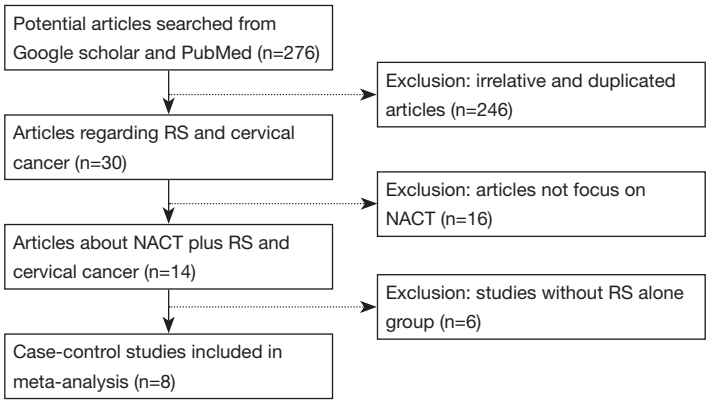

Figure 1 Flow diagram of article collection. Seven studies were selected as the objects of this study.

cancer by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, cancers at stages IB-IIA (tumor size more than 4 cm) and FIGO stage IIB and above, are characterized by bulky tumor volume, deep cervical stromal invasion, and a high rate of lymph node metastasis (35–80%), having a high rate of recurrence after conventional radical surgery (RS) alone (5). These patients have a very poor prognosis with an overall 5-year survival rate of around 40% after conventional treatments. These facts have posed great challenge to the treatment of cervical cancer (6).

Recently, neoadjuvant chemotherapy (NACT) prior to surgery or radiotherapy has been proposed as a new therapeutic option for bulky or locally advanced cancers (6). NACT has been reported to be able to improve the pelvic control and eradicate the micrometastasis for advanced cervical tumor, and be regarded as an effective method in tumor volume reducing, which could greatly facilitate the surgical removal (7).

So far, numerous studies have been conducted to evaluate the effectiveness of combined treatment using both NACT and RS (8-24). However, the results of these studies are so contradictory. Specifically, Eddy *et al*. suggested that the combination of NACT and RS provided no additional objective benefit for cervical cancer patients than using the RS alone, and this conclusion was further validated by other studies (11,25,26). In contrast, other studies indicated that the combined treatment could improve the long-term disease-free survival (DFS) and overall survival (OS) (17,27). Therefore, no conclusion has been drawn on whether NACT combined with operational therapy, can improve the recurrence rate of cervical cancer. With the rapid accumulation of studies in these years, we performed a meta-analysis in this study, which involved as many reports as possible, to investigate the improvement of a combination of NACT and RS than RS alone for cervical cancer patients.

Methods

Identification of eligible publication and acquisition

PubMed and Google Scholar database were searched with the following medical subject terms: "cervical cancer/carcinoma/tumor/neoplasm", "NACT" and "RS". The search included literature published from Jan. 2000 to Sep. 2016. Totally 276 results (108 from PubMed and 168 from Google Scholar) were acquired initially. Among these results, 246 literatures of irrelative or duplicated articles were excluded, resulting in 30 articles regarding RS and cervical cancer; Then 16 articles were eliminated due to irrelevance to NACT. Six articles without RS alone were further deleted. Therefore eight studies focusing on NACT plus RS and cervical cancer met with our requirement and were acquired altogether. Articles not focusing on NACT, RS and/or cervical cancer were excluded. Finally eight studies were employed in our meta-analysis. For each literature, the following data were extracted: the first author's last name, year of publication, country, ethnicity, number of patients, ANCT and surgery performed, adjuvant therapy, DFS and OS rates (for both 2- and 5-year), and information on surgical-pathologic risk factors. The procedure of article collection was shown in *Figure 1*.

Statistical methods

STATA software (version 12.0) was used to analyze the

Table 1 Characteristics of literatures included in the meta-analysis

Author	Year	Country	No. of patient (case/control)	Age (mean/sd)	Stage	Type of study	Ethnicity	NACT			Surgery
								Chemotherapy	IVDs	Cycles	
Liu *et al*. (12)	2013	China	102/96	48/11	IB2 & IIA2	Retrospective	Asian	Na			Na
Katsumat *et al.* (14)	2013	Japan	62/62	46/Na	IB2, IIA2 & IIB	Prospective	Asian	B: 7 mg/m^2 (D1-D5); V: 0.7 mg/m^2 (D5); MMC: 7 mg/m^2 (D5); CP: 14 mg/m^2 (D1–D5)	21	2 or 4	RS III or RS IV
Gong *et al.* (13)	2012	China	202/212	43.1/8	IB2-IIB	Retrospective	Asian	Va	Va	1–3	RS III, LE
Cho *et al.* (10)	2009	Korea	51/35	47.8/10.8	IB2-IIA	Retrospective	Asian	PTX: 135 mg/m^2 (D1); CP: 75 mg/m^2 (D1) or CBP AUC 5 (D1)	21	2	RS III, PLE, PALE
Chen *et al.* (9)	2008	China	72/70	44/Na	IB2-IIB	NA	Asian	CP: 100 mg/m^2 (D1); MMC: 4 mg/m^2 (D5); 5FU: 24 mg/m^2 (D5)	14	2	RS III, PLE
Eddy *et al.* (11)	2007	USA	145/143	Na	IB	Prospective	Mixed	V: 1 mg/m^2 (D1); CP: 50 mg/m^2 (D1)	10	3	RS, PLE, PALE
Behtash *et al.* (8)	2006	Iran	19/160	48/Na	IB-IIA	NA	Caucasian	CP: 50 mg/m^2 (D1); V: 1 mg/m^2 (D1)	10	3	RS III, PLE, PALE, UVLE
Gong *et al.* (18)	2016	China	411/389	43.72/7.94	IB2-IIB	Retrospective	Asian	Va	Va	1–3	RS III, LE

NA, not available; B, bleomycin; V, vincristine; M, mitomycin; CP, cisplatin; PTX, paclitaxel; CBP, carboplatin; MMC, mitomycin C; 5FU, 5-Fluorouracil; Va, Various; IVDs, interval days; LE, lymphadenectomy; PLE, pelvic lymphadenectomy; PALE, para-aortic lymphadenectomy; UVLE, upper vaginectomy lymphadenectomy; NACT, neoadjuvant chemotherapy.

collected data in this study. The improvement between case group and control group was evaluated using all databases by pooled odds ratios (ORs) with 95% confidence intervals (CIs). The heterogeneity assumption was assessed by I^2 index. $I^2 \leq 25\%$ was assumed no significant heterogeneity between pooled data, while $I^2 > 75\%$ was regarded as significant heterogeneous. We used Mantel-Haenszel (M-H) fixed-effect model for calculations unless there was a significant heterogeneity, in which DerSimonian and Laird (D-L) random-effected model was applied instead. ORs were calculated with each model within 95% confidence intervals. Forest plots were generated to visualize the results. Begg's funnel plots and Egger's regression asymmetry test was employed to evaluate potential publication bias. All P values were two-sided, and $P<0.05$ was considered statistically significant.

Results

Characteristic of data collected

In our study, eight eligible case-control studies were collected, and characteristics of these studies were shown in *Table 1*. These studies involved 654 cases and 998 controls in total, whose ages are usually around 45 excluding study from Chen *et al*. (9) without relevant data. All data were recorded at late stage with bulk cancer volume (IB-IIA or above). Among all the studies, five focused on Asian population, while other two involved with Caucasian people. NACT was different among most studies except two studies (8,11), which performed the same NACT (intravenous vincristine 1 mg/m^2 and cisplatin 50 mg/m^2 every 10 days for three cycles). Surgery was performed according to RS III with different lymphadenectomy in

Table 2 Clinical data of all included literatures in this study

Author	OS		DFS		Adjuvant therapy	Lymph node metastasis	Positive surgical margin	Parametric infiltration	Lymphovascular invasion	Deep cervical stromal >0.5	Positive pelvic nodes
	2-year	5-year	2-year	5-year							
Liu *et al*. (12) [2013]	–	83/79	84/84	80/78	NA	–	–	–	–	–	–
Katsumata *et al*. (14) [2013]	55/52	14/14	45/43	14/12	RT	–	–	25/28	–	–	17/27
Gong *et al*. (13) [2012]	193/206	–	189/200	–	NA	56/59	10/12	14/11	80/74	142/142	–
Cho *et al*. (10) [2009]	50/33	47/32	49/30	47/28	RT, CRT	18/17	2/0	15/10	22/20	33/32	–
Chen *et al*. (9) [2008]	–	–	16/19	14/18	RT	18/30	–	18/29	–	–	–
Eddy *et al*. (11) [2007]	103/100	55/48	86/83	47/39	RT	–	13/15	24/28	–	–	47/56
Behtash *et al*. (8) [2006]	–	6/93	–	6/91	RT	8/36	–	–	–	–	–
Gong *et al*. (18) [2016]	–	333/305	–	330/315	RT, CT, CRT	–	–	–	–	–	–

NA, not available; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy; DFS, disease-free survival; OS, overall survival.

seven studies and to RS III or IV in one study (14). Clinical data of all these studies were shown in *Table 2*. The overall and DFS rates were analyzed for 2 and 5 years separately. Survival data which are not available in some studies were shown as blank. In total, four studies possess 2-year OS data, of which all comes from Asian people; and six studies have 5-year OS data. Meanwhile, DFS were available in seven of the total studies. The subgroup meta-analyses by adjuvant therapy (RT, CT or CRT) are 3, 5, 4, and 6 studies for 2-year OS, 5-year OS, 2-year DFS, and 5-year DFS, respectively. To acquire complete understanding about the clinical efficacy of the treatment, we also included in this study with six surgical-pathologic risk factors including lymph node metastasis, positive surgical margin, parametric infiltration, lymphovascular invasion, cervical stromal depth and positive pelvic nodes.

Meta-analysis on comparison of NACT combined with RS vs. RS alone treatment

In order to assess the combination effect of NACT and RS treatment, we performed systemic survival analysis on available clinical data. The results of the overall and DFS rates between case (NACT combined with RS treatment) and control group (RS treatment alone) were shown in *Table 3*, and forest plot for each survival rate was shown in *Figure 2*. For all survival rates, I^2 indexes were consistently equal to 0% with no statistically significant heterogeneity (P>0.05). In this regard, we used fixed-effect model for the calculation for all of them. Overall, we found no significant survival rate improvement for the combination of NACT and RS over the RS alone group (2-year OS: OR =1.008; 95% CI, 0.832–1.220; P=0.937; *Figure 2A*; 5-year OS: OR =1.054; 95% CI, 0.860–1.292; P=0.913; *Figure 2B*; 2-year DFS: OR =1.015; 95% CI, 0.853–1.207; P=0.870; *Figure 2C*; 5-year DFS: OR =1.001; 95% CI, 0.816–1.228; P=0.992; *Figure 2D*). Besides, we also found that there was no significant publication bias based on funnel plot for 2- and 5-year survival rates (as were shown in *Figure 3*). This was further confirmed by results of both Egger's and Begg's test, with P value larger than 0.05 in all cases, which was shown in *Table 3*. *Figure 4* shows subgroup meta-analyses of the efficacy of NACT and FS on cervical cancer therapy according to adjuvant therapy. There was also no significant efficacy on

Table 3 Results of meta-analysis for overall and DFS rates

Analysis model	Analysis method	Heterogeneity		OR				Publication bias	
		I^2 (%)	P value[#]	Overall	Lower	Upper	P value*	Begg	Egger
OS									
2-year	Fixed	0.0	0.995	1.008	0.832	1.220	0.937	0.308	0.086
5-year	Fixed	0.0	0.762	0.988	0.770	1.268	0.923	0.462	0.198
DFS									
2-year	Fixed	0.0	0.989	1.015	0.853	1.207	0.870	0.060	0.058
5-year	Fixed	0.0	0.771	1.014	0.791	1.300	0.911	0.133	0.423

[#], P value from heterogeneity test; *, P value from OR test. DFS, disease-free survival; OS, overall survival.

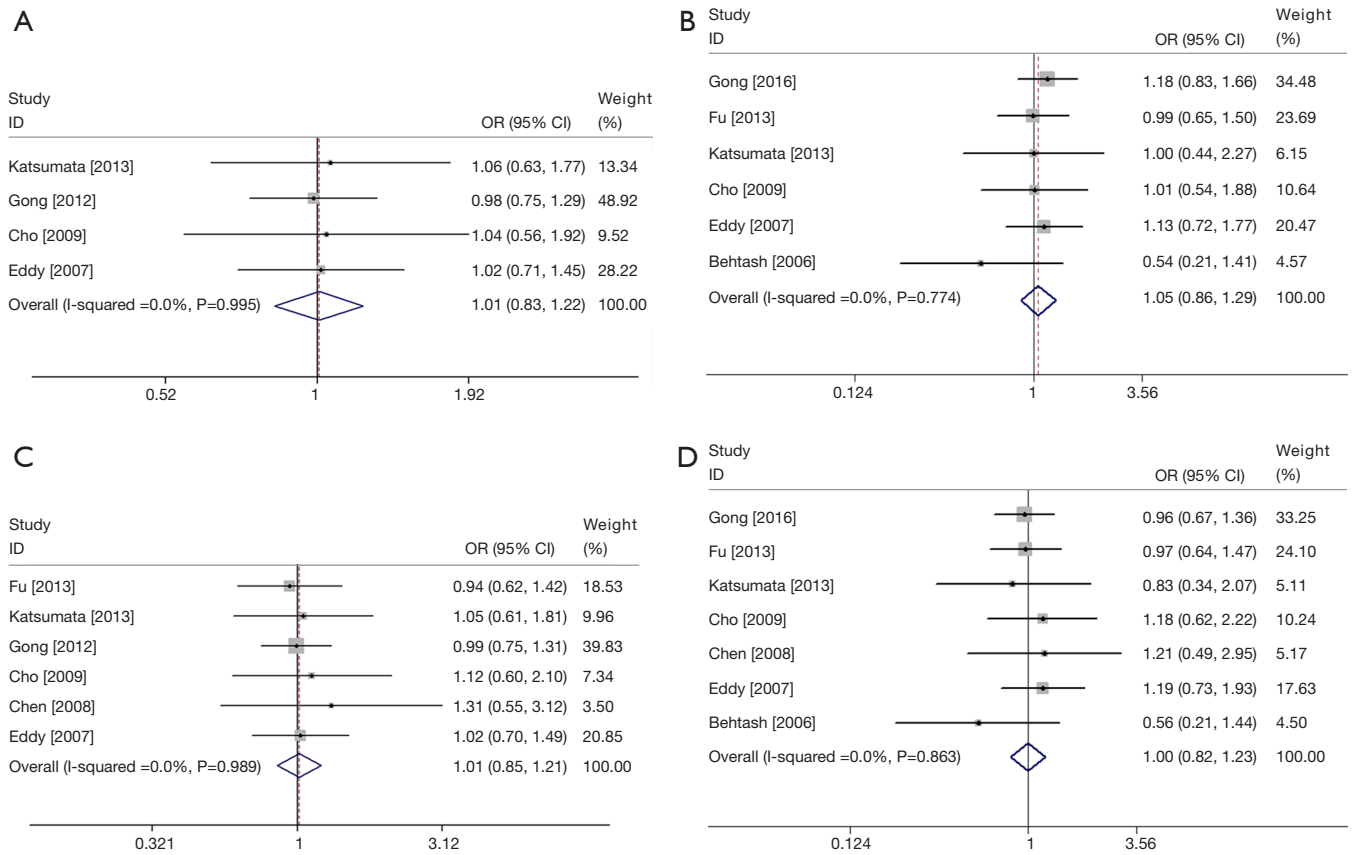

Figure 2 Forest plot showed no significant improvement of the survival for the combined treatment of NACT and RS compared with RS alone group. (A) 2-year OS; (B) 5-year OS; (C) 2-year disease free survival; (D) 5-year DFS. NACT, neoadjuvant chemotherapy; RS, radical surgery; DFS, disease-free survival; OS, overall survival.

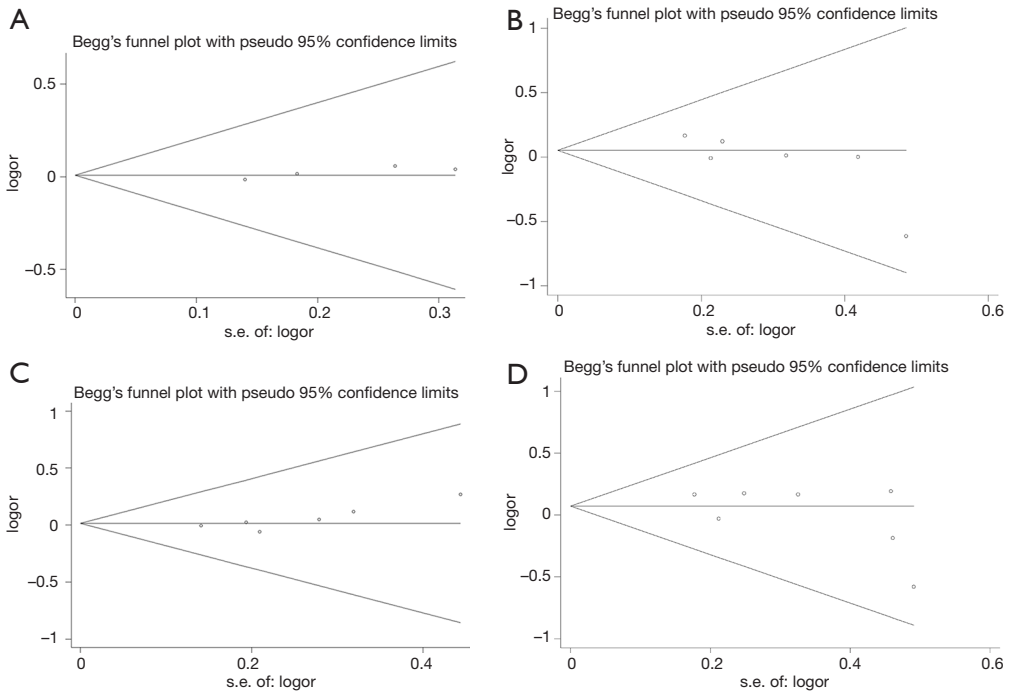

Figure 3 Funnel plot showed no significant publication bias for all comparisons in this study. (A) 2-year OS; (B) 5-year OS; (C) 2-year DFS; (D) 5-year disease free survival. DFS, disease-free survival; OS, overall survival.

OS or FDS in subgroup meta-analyses by adjuvant therapy. These results indicated that the cervical cancer patients with the additive treatment of NACT may have not any beneficial effect on survival rate than RS treatment alone.

Moreover, to broaden the clinical implication of this comparison, we performed surgical-pathologic risk factors analysis, and results were shown in *Table 4*. Due to the insignificant statistics of the heterogeneity of I^2 indexes, fixed model was used in this analysis. The lack of significant heterogeneity (P>0.05) found in all analysis, indicated the reliability of the results with no significant publication bias. Pooled analysis showed all p values were more than 0.05 for OR tests, suggesting that compared with control group, case group demonstrated little statistically significant improvement regarding each individual risk factor, including lymph node metastasis, positive surgical margin, parametric infiltration, lymphovascular invasion, cervical stromal depth and positive pelvic nodes. All these analyses further confirmed the previous conclusion, and demonstrated that the combination of NACT and RS combination therapy could have no improvement on RS treatment alone for cervical cancer therapy.

Discussion

In this study, we presented a meta-analysis to investigate the improvement of the combination of NACT plus RS over RS alone in the treatment of cervical cancer. This systematic review and meta-analysis of clinical trial showed that patients with additive NACT treatment may have no additional benefit for the long-term OS and DFS than using RS alone. Subgroup meta-analysis by adjuvant therapy and further assessments on six surgical-pathologic risk factors also confirmed this conclusion.

The rational that some researchers believe why NACT can enhance the clinical treatment of cervical cancer is apparent. The stage of the cervical cancer strongly decides the treatment of this cancer, of which the tumor size and volume have both been regarded as important prognostic factors for early cervical cancer. However, majority of cervical cancer patients have already reached late or advanced stage at diagnosis, which cannot be effectively eradicated by traditional radical surgeries (28). The potential advantages of NACT was thought to lies in its effectiveness in minimize tumor size, decreasing the number of micro metastases (29) and widening uninfiltrated

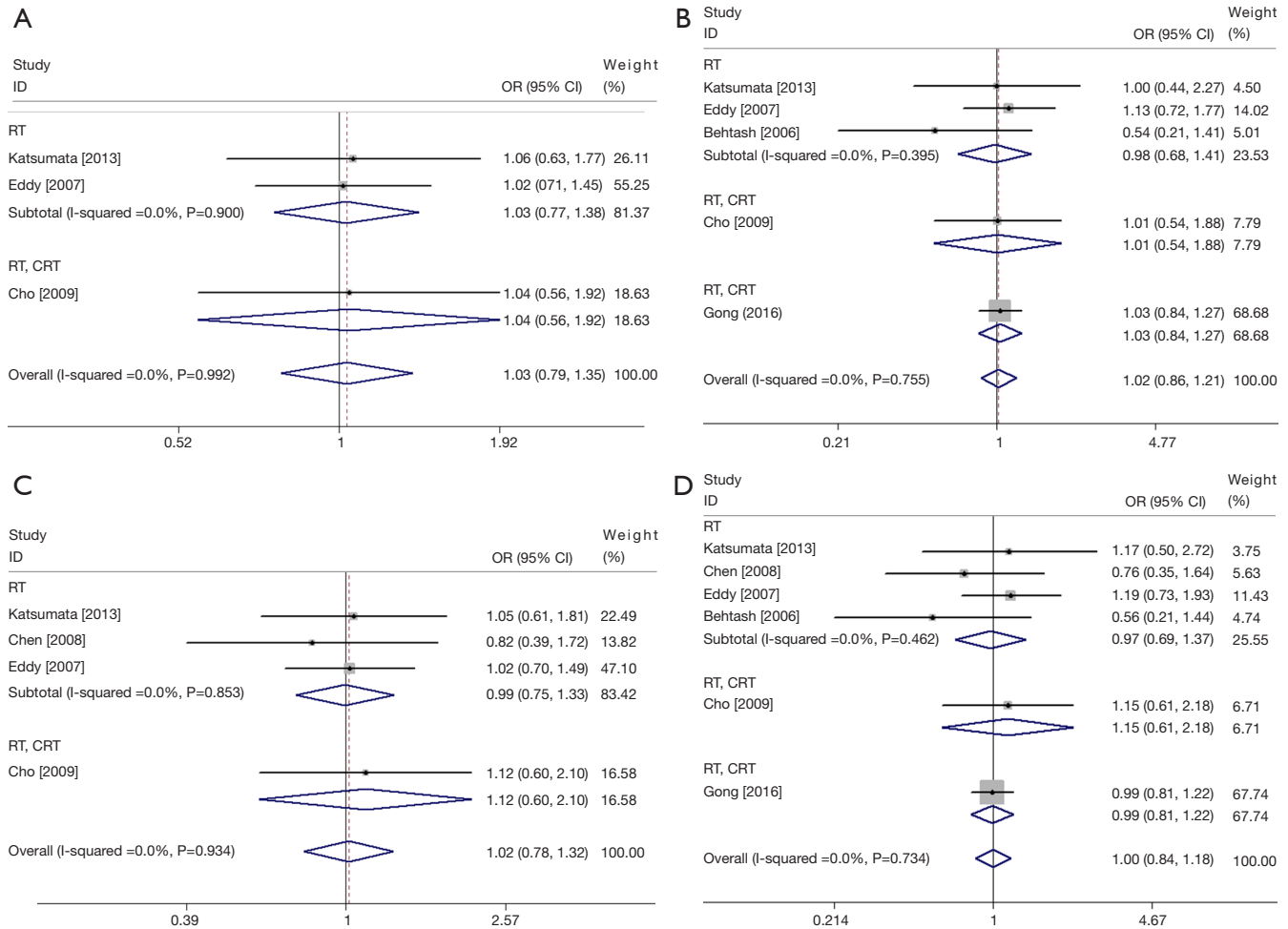

Figure 4 Forest plot showed no significant improvement of the survival for the combined treatment of NACT and RS compared with RS alone group in subgroup meta-analysis by adjuvant therapy. (A) 2-year OS; (B) 5-year OS; (C) 2-year DFS; (D) 5-year DFS. NACT, neoadjuvant chemotherapy; RS, radical surgery; DFS, disease-free survival; OS, overall survival.

Table 4 Results of meta-analysis for surgical-pathologic risk factors

Risk factor	Analysis method	Heterogeneity		OR			
		I^2 (%)	P value[#]	Overall	Lower	Upper	P value*
Lymph node metastasis	Fixed	35.4	0.200	0.907	0.670	1.227	0.527
Positive surgical margin	Fixed	0.0	0.683	0.922	0.526	1.615	0.776
Parametric infiltration	Fixed	0.0	0.672	0.872	0.639	1.190	0.388
Lymphovascular invasion	Fixed	0.0	0.336	1.046	0.751	1.457	0.788
Deep cervical stromal >0.5	Fixed	14.0	0.281	0.978	0.744	1.286	0.875
Positive pelvic nodes	Fixed	0.0	0.520	0.763	0.523	1.115	0.163

[#], P value from heterogeneity test; *, P value from OR test.

resection area (6). Another advantage of NACT followed by surgery relies on the removal of potential chemo-resistant foci (30) diminishing the need for adjuvant treatment (31). Therefore it has been widely suggested that preoperative NACT could reinforce the efficacy of treatment for patients who do not meet the criteria for surgery (28,32).

However, in compliance with our study, objections to the usage of preoperative neoadjuvant therapy still exist since the application of NACT in clinical trial. The following reason might be able to explain how the discrepancy presents among different studies. First, many clinico-pathological factors, such as clinical stage, histological type and grade, physical condition, etc., can also determine the recurrence of cervical cancer. Patients subjected to the studies were at different stages and have different pathological characteristics (33). To some extent, the heterogeneity of the data will compromise the statistical significance of the study. Moreover, it is also suggested that the efficacy of NACT in different subtypes of cervical cancer can be of huge distinction, no matter short-term or long-term outcomes are investigated (6). Second, the criteria and strategy for adjuvant therapy (including the chemo-agents, dosage, cycle-length, etc.) could be different among groups, which might have great influence on the evaluation of the NACT efficacy. Third, the sample size and study design varies among each trial (6,34).

Actually, more and more attention has been drawn to the disadvantages of NACT recently. It was reported that some patients do not respond to neoadjuvant therapy at all. Hence, the delay in treatment, the development of radio-resistant cellular clones caused by NACT and so forth, could all worsen the effectiveness of the treatment (6). Another drawback of NACT is that it is thought to increase the difficulties of surgical dissection of tumor-affected pelvic tissues, in particular, which hinders the usage of robotic techniques to perform RS after NACT (35). Due to these reasons, the combination therapy of NACT and RS will not present satisfactory or better effect compared with RS alone.

Moreover, it is suggested that among the patients with pelvic lymph node metastases who were free of parametrial extension, those who received postoperative chemo-radiotherapy had significantly better DFS (P=0.021) and OS (P=0.030) than those who received no adjuvant therapy (36). However, it is also indicated that extended chemotherapy could not show advantages in terms of DFS and OS (37). Thus, we did a subgroup meta-analysis by adjuvant therapy to assess its effect on this study. There was also no significant efficacy on OS and DFS in subgroup meta-analyses conforming our results.

Ours result is consistent with many previous studies (38) by summarizing numerous previous studies and provides a quantitative assessment of the effectiveness of NACT when adding into RS treatment. We believe our study will shed new lights on future cervical cancer treatment researches. Although the sample size is small, which may possibly lead to bias in the conclusion. Further investigation would be helpful to confirm this issue by taking substantial efforts to obtain relevant data from more randomized controlled trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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