Meta Analysis

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Effect of neoadjuvant chemotherapy followed by surgery for FIGO stage I–II cervical cancer: a meta-analysis

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Abstract

Objective: In this meta-analysis, we aimed to evaluate the oncological outcomes of preoperative neoadjuvant chemotherapy followed by radical surgery compared with radical surgery alone for treatment of International Federation of Gynecology and Obstetrics (FIGO) stage I–II cervical cancer.

Method: We searched for studies comparing the safety and efficacy of neoadjuvant chemotherapy plus surgery versus surgery alone in treatment outcomes of locally advanced cervical cancer. Meta-analysis was used to calculate the pooled odds ratios with corresponding 95% confidence intervals (CI).

Results: Sixteen studies were included in our analysis. Pooled analysis of overall survival rate [odds ratio (OR) = 1.09, 95% CI: 0.83–1.43] and progression-free survival rate (OR = 1.10, 95% CI: 0.77–1.57) showed that preoperative neoadjuvant chemotherapy did not have a benefit compared with surgery alone in terms of survival rates. The pooled results for postoperative parameters indicated that preoperative neoadjuvant chemotherapy followed by radical surgery was associated with a high rate of vascular space involvement (OR = 0.25, 95% CI: 0.17–0.35) and parametrial infiltration (OR = 0.60, 95% CI: 0.45–0.79).

Conclusions: This meta-analysis indicated that surgery following neoadjuvant chemotherapy for FIGO stage I–II cervical cancer and surgery alone had similar oncological outcomes.

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Introduction

Cervical cancer is a frequent cancer-related cause of death in women in developing countries.[1] For patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ia–Ib1 cervical cancer, radical surgery is recognized as the standard therapy, and the 5 year survival rate of patients may be as high as 80% to 90%.[2,3] Pelvic relapse is the most common negative outcome after radical surgery for cervical carcinoma. Patients with disease at FIGO stage Ib2 and above undergo radiation therapy rather than radical surgery because of the potential for postoperative complications such as parametrial involvement, lymph node metastases, and positive surgical margins. Although radiotherapy can have the same effect as surgery, injury to surrounding tissues caused by radiation may harm ovarian function and sexual capacity, which significantly affects patients' quality of life.

With the goal of improving efficacy for patients with cervical cancer, previous trials have been conducted to compare neoadjuvant therapy with surgery alone.[4–6] Neoadjuvant chemotherapy (NACT) followed by radical surgery therapy (RST) has become a popular option for treatment of cervical cancer.[7]

NACT, also called early or prechemotherapy, is used to reduce tumor volume before surgery or radiotherapy. For advanced-stage cervical cancer, two to three cycles of NACT can help increase the success rate of surgical resection. Previous trials have indicated that NACT can eliminate tumor micro-metastases, shrink tumor volume, improve the resection rate, and achieve surgical down-staging of patients.[8] A previous meta-analysis[9] revealed that neoadjuvant chemotherapy with radical surgery increased survival rates and decreased local and distant recurrence rates in patients with stage Ib2–IIb cervical cancer. However, some studies have failed to show benefits of neoadjuvant therapy, and, in some cases, have shown unfavorable effects on efficacy.[10,11] To date, there is no agreement on whether NACT significantly improves the prognosis of patients with cervical cancer.

The aim of our study was to compare the efficacy of NACT followed by RST with RST alone in patients with stage I to II cervical cancer.

Materials and methods

Ethical approval

The study did not require ethical board approval because it did not include human or animal trials.

Search strategy

We conducted a systematic screening using the electronic databases PubMed, Embase, and Cochrane Library up to September 2019. The process was based on MeSH terms and keywords "cervical cancer," "neoadjuvant chemotherapy," and "surgery". We also searched the references

of eligible publications that dealt with the topic of interest to identify additional relevant studies. We performed the current meta-analysis based on the *Cochrane Handbook for Systematic Reviews of Interventions*[12] and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[13] Meanwhile, we did not register our study with PROSPERO before screening studies for inclusion.

Eligibility criteria

Inclusion criteria were articles relating to (1) studies focused on comparing NACT + RST and RST; (2) reports of patients clinically diagnosed with early or locally advanced (stage I–II) cervical cancer; (3) studies that included data on surgery-related outcomes and postoperative specimens for both groups; (4) and studies with full texts available.

Quality assessment

Study quality was assessed separately by two investigators using the "Risk of bias" assessment tool from the Cochrane Collaboration for further justification.[14]

Data extraction

Two authors independently extracted the relevant data from each trial based on the inclusion criteria. Differences were settled by consensus. We extracted the following information: name of the first author; year of publication; number of recruited participants; country; study period; histological type of the patients; tumor stage; results of interest including intraoperative parameters, complications, and pain scores.

Statistical analysis

The meta-analysis was conducted using Review Manager version 5.3 software (Revman; Cochrane Collaboration, Oxford, UK). A sensitivity analysis was conducted depending on the degree of heterogeneity across the included trials. Heterogeneity of the trial results was assessed using the I^2 statistic to select the ideal analysis model.[14] Studies with an $I^2 \geq 50\%$ suggested high heterogeneity, and those with $I^2 < 50\%$ indicated low heterogeneity.[15] When there was low heterogeneity among trials, the fixed-effects model was used. Otherwise, the random effects model was used. A P-value < 0.05 was used to identify a statistically significant difference.

Results

Overview of literature search and study characteristics

In total, 392 publications were initially identified. According to the criteria described in the methods, 22 articles were evaluated in more detail but some failed to provide detailed results. Finally, 16 studies[16–31] were included in this meta-analysis. Table 1 provides a brief description of these studies. Figure 1 shows the search process, and Figure 2 and Figure 3 summarize the quality assessment processes.

Clinical and methodological heterogeneity

Survival and recurrence rates. Data on rates of survival are shown in Figure 4a and 4b. The results showed that preoperative neoadjuvant chemotherapy plus surgery (NACT+RST) was not better than RST alone; the groups did not differ in overall survival rate [odds ratio (OR) = 1.09, 95% confidence interval (CI): 0.83–1.43] or progression-free survival rate (OR = 1.10, 95% CI: 0.77–1.57).

The fixed-effects model was used to pool recurrence rate data because there was low heterogeneity across the studies. The pooled data showed that there was no significant difference between NACT+RST and RST

Table 1. Primary characteristics of the eligible studies.

Author	Country	Research period (year/month)	Tumor stage	Number of patients		Mean age (years)		Historical type	Treatment regimen	Type of study
				NACT+ RST	RST	NACT+ RST	RST			
Serur et al., 1997[24]	USA	1987/1–1993/12	Ib2	20	32	47.8	48.7	SCC	BP, LP	PS
Behtash et al., 2006[17]	Iran	1996/3–2004/3	Ib-IIa	22	160	48	52	SCC+ACC	VP	RS
Cai et al., 2006[25]	China	1999/1–2001/12	Ib	52	54	45.6	44.8	SCC+ACC	5 FU–cisplatin	RCT
Eddy et al., 2007[22]	USA	1996/12–1999/1	Ib	145	143	—	—	SCC+ACC+ASC	NACT	RCT
Sardi et al., 1997[23]	Argentina	1987/5–1992/12	Ib	102	103	39	41	SCC	BOMP	RCT
Chen et al., 2008[18]	China	1999–2004	Ib2-IIb	72	70	44	44	SCC+ACC+ASC	MP	RCT
Cho et al., 2009[30]	Korea	1999/11–2007/9	Ib2-IIa	51	35	47.8	44.8	SCC+ACC+ASC	IP, TP	RS
Lee et al., 2011[21]	Korea	2000/1–2006/12	Ib-IIa	33	41	47.5	47.3	SCC+ACC+ASC	TP, 5 FU–cisplatin	RS
Wang et al., 2011[26]	China	2006/1–2010/2	Ib2-IIb	68	42	45.7	49.1	SCC+ACC+ ASC+other	BP, TP	RS
Kim et al., 2011[28]	Korea	2000–2008	Ib1-IIa	451	73	50.6	49.4	SCC+ACC+ ASC+other	TP, 5 FU–cisplatin	RS
Wen et al., 2012[29]	China	2006/1–2009/12	Ib2-IIa	31	31	45.68	44.97	SCC+ACC	5 FU–cisplatin	RCT
Prueksaritanond et al., 2012[20]	Thailand	2000/1–2009/12	Ib2-IIa	40	40	42.98	43.13	SCC+ACC	TP	RS
Katsumata et al., 2013[19]	Japan	2001/12–2005/7	Ib2–IIb	67	67	47	46	SCC+ASC	BOMP	RCT
Bogani et al., 2014[27]	Italy	2007/2–2014/3	Ia-IIb	20	40	46.5	46.7	SCC+ACC+ ASC+other	IP, TP	PS
Yang et al., 2016[16]	China	2010/9–2012/7	Ib-IIb	109	110	47	48	SCC+ACC+ ASC+other	IP, TP	RCT
Zhao et al., 2019[31]	China	2009/1–2016/12	Ib2/IIa2	178	125	45.1	45.7	SCC+ACC+ASC	IP, BP, BOMP	RS

NACT, neoadjuvant chemotherapy treatment; RST, radical surgery treatment; SCC, squamous carcinoma cell; ACC, adenocarcinoma; ASC, adenosquamous carcinoma; 5 FU, 5-fluorouracil; IP, irinotecan combined with cisplatin; TP, paclitaxel combined with cisplatin; VP, vincristine combined with cisplatin; MP, mitomycin combined with cisplatin; BP, bleomycin combined with cisplatin; LP, leucovorin combined with cisplatin; BOMP, bleomycin + vincristine + mitomycin combined with cisplatin; NACT, vincristine-cisplatin chemotherapy; PS, prospective study; RS, retrospective study; RCT, randomized controlled trial.

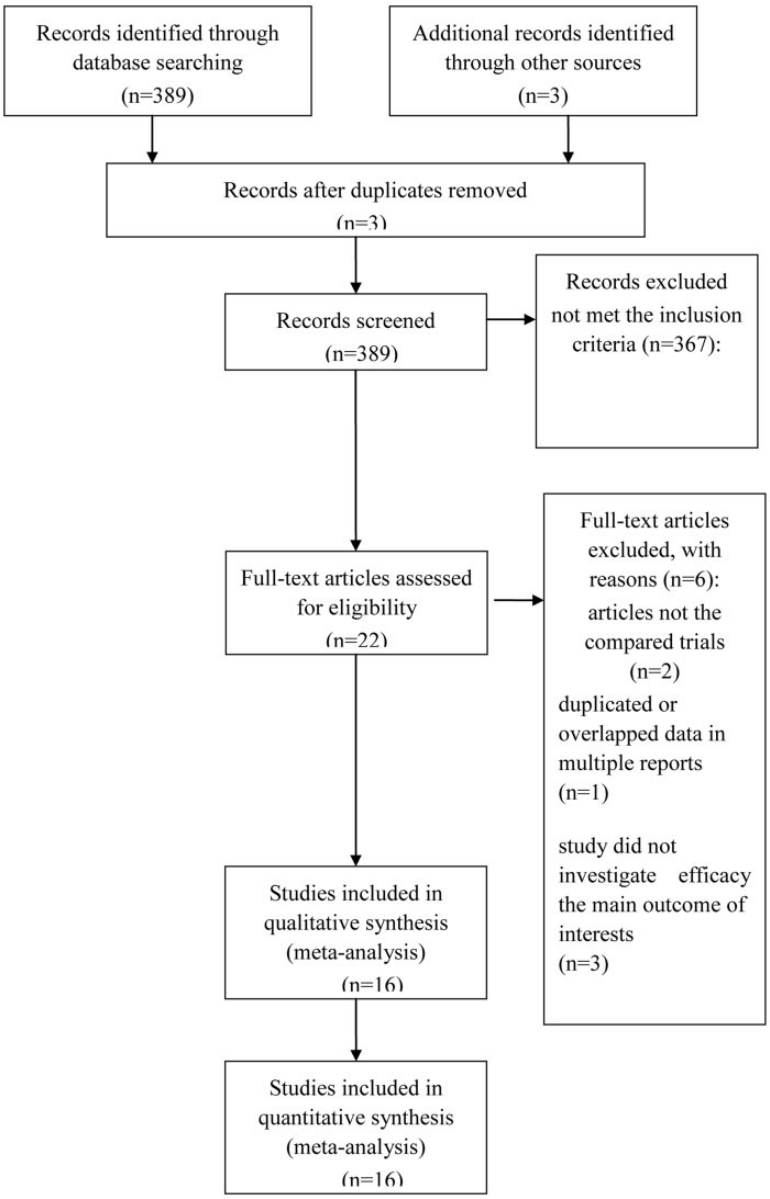

Figure 1. The PRISMA flowchart of the selection process to identify studies eligible for pooling.

groups (OR = 0.98, 95% CI: 0.74–1.32) (Figure 4c).

Duration of surgery and blood loss. The pooled data showed no difference in duration of surgery [mean difference (MD) = 0.10, 95% CI: −0.04 to 0.24) between the NACT+RST and RST groups (Figure 4d). The blood loss rate was available for eight trials. No significant differences were observed between the NACT+RST group and the RST group in terms of blood loss

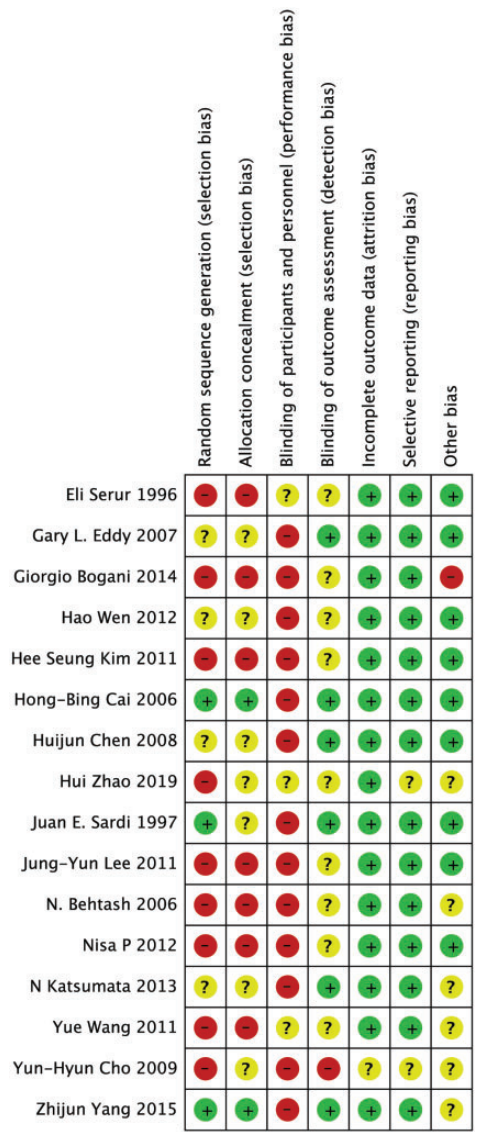

Figure 2. Quality assessment summary for included studies: + indicates low risk of bias, − indicates high risk of bias, and ? indicates unclear risk of bias.

rate (MD = 25.21, 95% CI: −76.47 to 126.90) (Figure 4e).

Vascular space involvement, parametrial infiltration, and lymph node metastasis. For the incidence of vascular space involvement, we found that NACT+RST was better than RST alone (OR = 0.25, 95% CI: 0.17–0.35; $P < 0.00001$) (Figure 4f). The pooled results indicated that there was a significant difference in the rate of parametrial infiltration between the two groups, and NACT+RST was better than RST alone (OR = 0.60, 95% CI: 0.45–0.79; $P = 0.0004$) (Figure 4g). In the analysis of the rate of lymph node metastasis, no significant difference was found between the NACT+RST and RST groups (OR = 0.65, 95% CI: 0.39–1.06) (Figure 4h).

Discussion

Cervical cancer is the most commonly diagnosed tumor in developing countries and is the fourth leading cause of cancer-related death among women.[1,32] For early-stage cervical carcinoma (stages Ia, Ib1, IIa1), surgery is accepted as the most effective therapeutic treatment. However, the use of surgery is limited to patients with locally advanced cervical cancer (LACC, stages Ib2, IIa2, IIb).[33]

Since the late 1980s, NACT before surgery has been an effective option for LACC, being effective in shrinking tumor volume, preventing micro-metastases, improving surgical feasibility, and decreasing the disease stage of patients.[8,34,35] Nevertheless, recent studies that compared NACT+RST with RST alone have shown different results,[18,22,25] and the efficacy of NACT remains unclear. Thus, the present meta-analysis aimed to evaluate the effectiveness and safety of NACT and RST by pooling data from published studies and providing a reference for cervical cancer patients.

Many previous studies have shown that NACT reduces the risk of pathologic factors, thereby reducing the rate of postoperative radiation and chemotherapy[30,36–38] and improving patients' quality of life. Our data were consistent with these

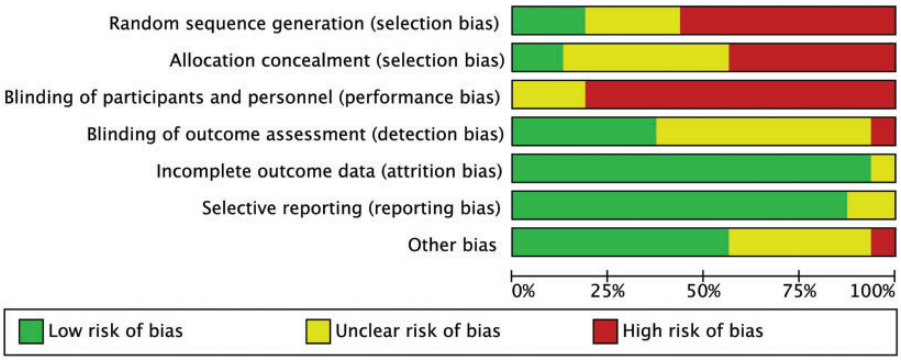

Figure 3. Methodological quality assessment for included studies.

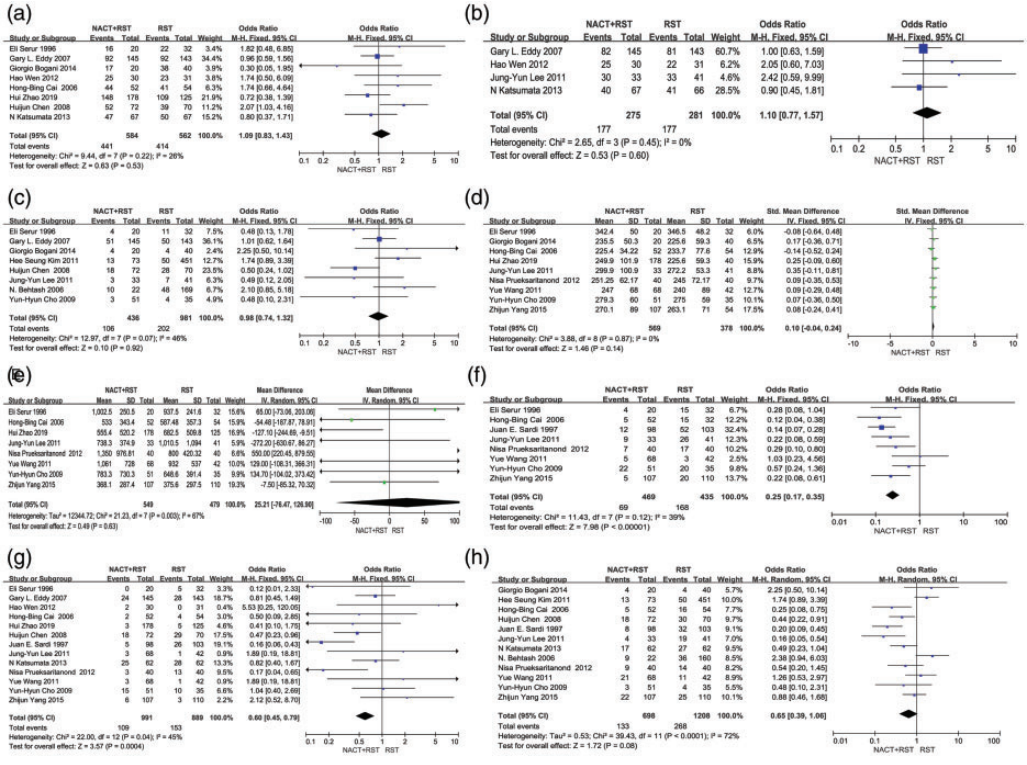

Figure 4. Pooled analysis of (a) overall survival rate; (b) progression-free survival rate; (c) recurrence rate; (d) duration of surgery; (e) blood loss; (f) vascular space involvement; (g) parametrial infiltration; and (h) lymph node metastasis for NACT+RST versus RST. The box indicates the weight of the study, the lines indicate 95% CI, and the diamond indicates the total effect. NACT, neoadjuvant chemotherapy treatment; RST, radical surgery treatment.

pathologic risk factors, and no significant differences in lymph node metastasis, duration of surgery, intraoperative blood loss, or recurrence rate were found between the NACT+RST group and the RST group, showing that NACT could reduce the surgical risk of LACC, without increasing the difficulty of surgery.[39,40] In clinical practice, a surgeon often finds local adhesions surrounding the uterine artery and ureter, which can increase the difficulty of the surgery. Nevertheless, this phenomenon is not observed in all patients. One possible explanation is that the combination treatment was mainly used in patients with more severe local lesions, in whom artery embolization blocked tumor blood supply and thus controlled local bleeding, enabling clear exposure, and without prolonging the duration of surgery.[26] The other reason may be that NACT shrinks the tumor volume before surgery, which makes surgery easier.

The improvement in survival rates with NACT plus RST was not statistically significant. One explanation for this may be the variation in effectiveness of different neoadjuvant regimens.[19] The trials included in our meta-analysis used cisplatin-based chemotherapy combined with irinotecan, paclitaxel, vincristine, mitomycin, vincristine, bleomycin, or 5-fluorouracil. To clarify the benefits of neoadjuvant chemotherapy, more potent regimens of chemotherapy, with various chemotherapy cycles, dose intensity, and diversity, should be explored. Additionally, the clinical response to NACT may depend on the pathological types of the cervical cancers, which include squamous cell carcinoma and adenocarcinoma. Some studies have indicated that poor outcomes are observed in adenocarcinoma.[41] Recently, several new drugs have been developed and sensitivity has been improved.[42,43] Moreover, the rate of postoperative adjuvant chemo-radiotherapy was lower in the NACT+RST group than in the RST group, which may have an effect on the long-term outcomes of NACT clinical responders.

Our study has several limitations. First, because of the retrospective nature of the study, clinical heterogeneity existed, such as different histological types and treatments, which may affect comparison of the clinical results. Second, data were pooled from studies with different inclusion criteria, and there was heterogeneity among the included studies. Future research should include subgroup analysis to further evaluate these two methods.

Conclusion

The findings of this study indicated that administration of NACT before radical surgery is an optimal treatment strategy for locally advanced cervical cancer, yielding an advantage in terms of reducing surgical risk without increasing difficulty of surgery or decreasing survival rate. Larger prospective trials with different neoadjuvant approaches are warranted to clarify the potential benefits of NACT.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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