

Original Article

The safety and efficacy of the preoperative neoadjuvant chemotherapy for patients with cervical cancer: a systematic review and meta analysis

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Abstract: Objective: To evaluate the safety and efficacy of the preoperative neoadjuvant chemotherapy for patients with cervical cancer. Methods: A systematic literature search was conducted using the PubMed, EMBASE and Cochrane databases. Studies comparing combined neoadjuvant chemotherapy treatment (NACT)/radical surgery treatment (RST) with RST alone in patients with cervical cancer were eligible for inclusion. Results: Eight studies were finally included in this meta analysis, involving a total of 1302 patients. Meta analysis shows that NACT might have lower lymph node metastasis than RST [OR=0.57, 95% CI (0.41, 0.79), P=0.0008]. However, there are no differentiation between two groups in operation time [SMD=0.16, 95% CI (-0.08, 0.48), P=0.19], intraoperative estimated blood loss [SMD=0.20, 95% CI (-0.19, 0.58), P=0.48], intraoperative and postoperative complication rates [OR=1.33, 95% CI (0.45, 3.92), P=0.60], overall survival rate [OR=1.07, 95% CI (0.48, 2.41), P=0.86] and recurrence rate [OR=1.06, 95% CI (0.56, 2.03), P=0.85]. Conclusions: The safety and efficacy of two treatments are similarly. However, NACT can reduce the rate of lymph node metastasis, which is an independent risk factor for cervical cancer prognosis and may improve the prognosis of cervical cancer.

Keywords: Cervical cancer, preoperative neoadjuvant chemotherapy, NACT, radical surgery treatment, RST, meta analysis

Introduction

Cervical cancer is the most common Gynecologic malignancy, that the overall survival rate of patients with is about 55%~80% [1-3]. The pathogeny of cervical cancer are still fully unknown, which may be related to sexual frequency, the age of first-time sex < 16, early delivery, productivity, human papilloma virus (HPV) infection and so on. According to the World Health Statistics Yearbook 2008 statistics, there are 53 million new cases of cervical cancer each year, and 27.5 million deaths related cervical cancer [4]. In the past, patients with cervical cancer were suggested to accept operation in phase IA1-IIA or radiation in other phases [5]. Chemotherapy is used as adjuvant therapy. Since the late 1980s, the preoperative neoadjuvant chemotherapy (adjuvant chemotherapy combined with radical surgery, NACT) are applied to locally advanced cervical cancer and shown positive significance, which is reduc-

ing tumor volume, eliminating micro-metastases and subclinical lesions, and prolonging survival time [6]. Results of current research about the efficacy of NACT remain controversial. However, many single center study have statistical limitations due to the small sample size, and hard to evaluate the advantages and disadvantages of efficacy and safety of NACT, objectively. Therefore, the present systematic review aimed to evaluate the efficacy of NACT and radical surgery (RST) by pooling available data from published studies, and provide a reference for medical.

Materials and methods

Literature search strategy

Relevant publications were identified by conducting a literature search in The Cochrane Library, PubMed and Embase databases using the following search terms: cervical cancer, and

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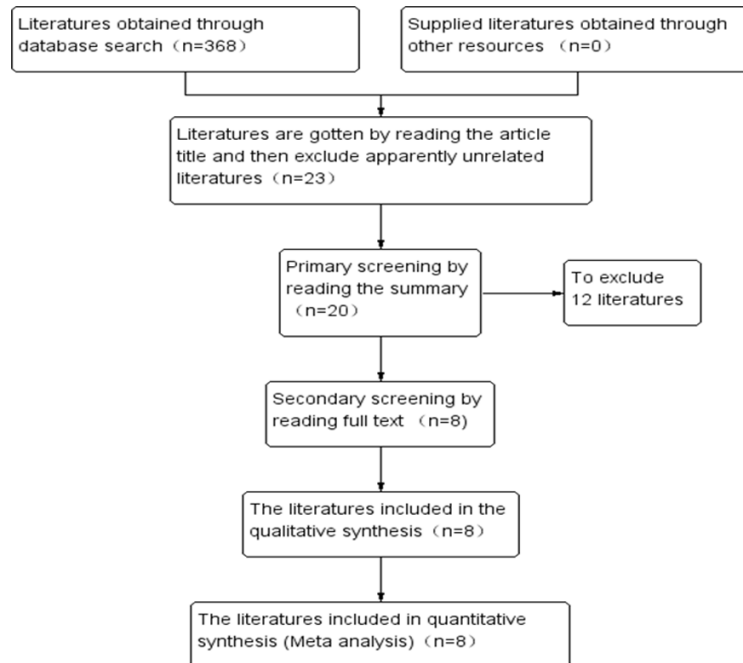


Figure 1. Flow chart showing the document screening process and results.

neoadjuvant chemotherapy or NACT, and radical surgery or radical hysterectomy or RST. The last search was updated on January 25, 2015. The reference lists of reviews and retrieved articles were also screened to find additional eligible studies by two investigators. Search results were limited to studies published in English.

Inclusion and exclusion criteria

Candidate studies could be included in our analysis if the following criteria were satisfied: (1) cohort or case control focused on the relationship between NACT and RST; (2) all patients met the diagnostic criteria for cervical cancer; (3) sufficient original data were provided to estimate the odds ratio (OR) and a corresponding 95% confidence interval (95% CI). Studies were excluded if the following criteria were satisfied: (1) not case-control study; (2) duplicate of previous publications; (3) no usable data reported; (4) missing ethics board approval.

Data extraction

According to the PRISMA guidelines, two investigators independently reviewed eligible studies and extracted and tabulated information from the following data: name of first author; year of publication; country or region of origin;

ethnicity; the clinical stage of cancer; number of cases and controls; indicators of efficacy including survival rate, the lymph node metastatic rate and recurrence rate; indicators of safety including operation time (min), intraoperative and postoperative complication rates (urethral trauma, vascular injury, infection, pelvic abscess, fistula, intestinal obstruction, urethral stricture, etc) and intraoperative estimated blood loss (mL). Disagreements between the two investigators were resolved by discussing the results with a third investigator.

Statistical analysis

Data analysis and bias risk assessment was performed with Revman 5.1 software from the Cochrane collaboration. Using odds ratios (OR) as the statistic analysis of count data, and using weighted mean difference (WMD) as the statistic analysis of continuous data. If the same variable with different measurement units, using standardized mean differences (SMD) to analyze it. A statistical test to judge heterogeneity between studies was performed using Q-test and I^2 test. When $P < 0.05$ in Q-test or $I^2 < 50\%$ in I^2 test, indicating the absence of heterogeneity, a fixed-effect model was used to estimate pooled odds ratios (OR) and 95% confidence intervals (CI). Otherwise, a random-effect model was applied. Sensitivity analyses were performed to assess the stability of pooled results. We use funnel plots to judge publication bias. All of the P values were two-tailed. Uses GRADEpro3.6 software to analyze the evidence quality levels and give the recommended level.

Results

General situation and baseline characteristics of included studies

We searched primarily from the above databases, with 368 citations screened. A flow chart about the selection process and specific reasons for exclusion are shown in **Figure 1**. Finally,

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Table 1. The General Information of Included Studies

Researchers	Location	Research time	FIGOI staging	Therapy	number	The diameter of tumor (cm)	outcome
Chi-An Chen 2002 [15]	Taiwan	1991.7-1999.6	IB2 or IIA	NACT	31	4.6±0.8	③②
Hee Seung Kim 2011 [16]	Seoul	2000-2008	IB1-IIA	NACT	73	3.5±0.2	③②
				RST	451	2.9±1.9	
Huijun Chen 2008 [9]	Wuhan	1999-2004	IB2-IIB	NACT	72	> 4	③⑤
				RST	70	> 4	
Jung-Yun Lee 2010 [12]	Seoul	2000.1-2006.11	IB-IIA	NACT	33	4.6±0.6	①②③④⑤⑥
				RST	41	4.8±0.8	
N.Katsumata 2013 [13]	Japan	2001.11-2005.8	IB2, IIA2, IIB	NACT	67	4.1±3.0	①②
				RST	67	6.6±3.3	
N.Behtash 2006 [10]	Teheran	1996.3-2004.3	IB-IIA	NACT	22	> 4	①③
				RST	160	> 4	
Nisa Prueksaritanond 2012 [11]	Bangkok	2000.1-2009.11	IB2-IIA	NACT	40	5.1±0.4	②④⑤⑥
				RST	40	5.2±0.6	
Yue Wang 2011 [14]	Beijing	2006.1-2010.11	IB2-IIB	NACT	68	> 4	④⑥
				RST	42	> 4	

Indicators of efficacy: ① survival (survival rate), ② the lymph node metastatic rate, and aim at recurrence rate. Indicators of safety: ④ operation time (min), ⑤ intraoperative and postoperative complication rates (urethral trauma, vascular injury, infection, pelvic abscess, fistula, intestinal obstruction, urethral stricture, etc), ⑥ intraoperative estimated blood loss (ML).

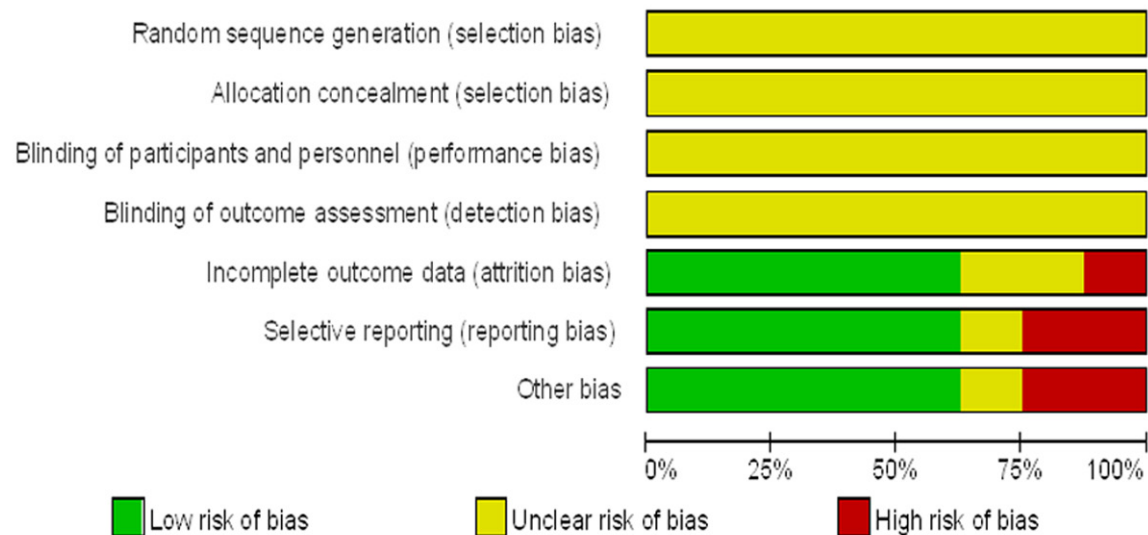


Figure 2. The risk of bias of all the included studies the percentage of project judging.

in accordance with the inclusion criteria, full-text papers of 8 studies were included [9-16]. The 8 studies included 1,302 patients in total, with 406 cases in NACT group and 896 cases in RST group. The general situation and baseline characteristics of included studies are presented in **Table 1**. The results of homogeneity testing about patient age, tumor size, clinical stages and pathological types in included stud-

ies, the difference was not statistically significant ($P > 0.05$).

Evaluation of the risk of bias from included studies

According to the recommended methods of Cochrane [7], we assessed the risk of bias from all included studies. The baselines of all includ-

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chi-An Chen	?	?	?	?	-	-	+
Hee Seung Kim	?	?	?	?	?	-	?
Huijun Chen	?	?	?	?	+	+	+
Jung-Yun Lee	?	?	?	?	+	+	-
N.Behtash	?	?	?	?	+	+	+
Nisa Prueksaritanond	?	?	?	?	+	+	+
N Katsumata	?	?	?	?	?	?	+
Yue Wang	?	?	?	?	+	+	-

Figure 3. Risk of bias: authors of all included studies each project risk of bias in judgment.

ed studies are comparable, but it still had a different degree bias, as shown in **Figures 2 and 3**. All studies did not adopted blind methods, and two of them were references to “random” but did not describe the random method. All studies reported complete results without selecting. Finally, our results are obtained that three studies [9-11] have low risk of biases, three studies [12-14] have moderate risk of biases and two studies [15, 16] have high risk of biases.

The results of meta analysis

Analysis of relevant indicators in efficacy between NACT and RST: Four studies [12-14] compared overall survival rates between two groups, as shown in **Figure 4**. We used a ran-

dom effects model for analysis, taking into account heterogeneity between studies ($P=0.02$, $I^2=69\%$), which may be caused by regional differences and data processing method. The result of meta analysis didn't show a significant difference between two groups in overall survival rates [OR=1.07, 95% CI (0.48, 2.41), $P=0.86$]. Six studies [12-14] compared the rate of lymph node metastasis between two groups, as shown in **Figure 5**. We used a fixed effects model for analysis because there are no heterogeneity between studies ($P=0.14$, $I^2=40\%$). The result of meta analysis showed a significant difference between two groups in the rate of lymph node metastasis [OR=0.57, 95% CI (0.41, 0.79), $P=0.0008$], which means NACT might have lower lymph node metastasis than RST. There is no publication bias in comparison of the rate of lymph node metastasis between NACT group and RST group, according to the funnel chart, as shown in **Figure 6**.

Analysis of relevant indicators in safety between NACT and RST: Three Researches [12-

14] compared the operating time (min) between two groups, as shown in **Figure 7**. We used a fixed effects model for analysis because there are no heterogeneity between studies ($P=0.65$, $I^2=0\%$). The result of meta analysis showed a significant difference between two groups in the operating time [SMD=0.16, 95% CI (-0.08, 0.48), $P=0.19$]. Three studies [12-14] compared the intraoperative estimated blood loss (ML) between two groups, as shown in **Figure 8**. We chose SMD as the merge statistics and used a random effects model for analysis, taking into account heterogeneity between studies ($P=0.007$, $I^2=80\%$), which may be caused by different measurement tools and data processing method. The result of meta analysis didn't show a significant difference between two groups in

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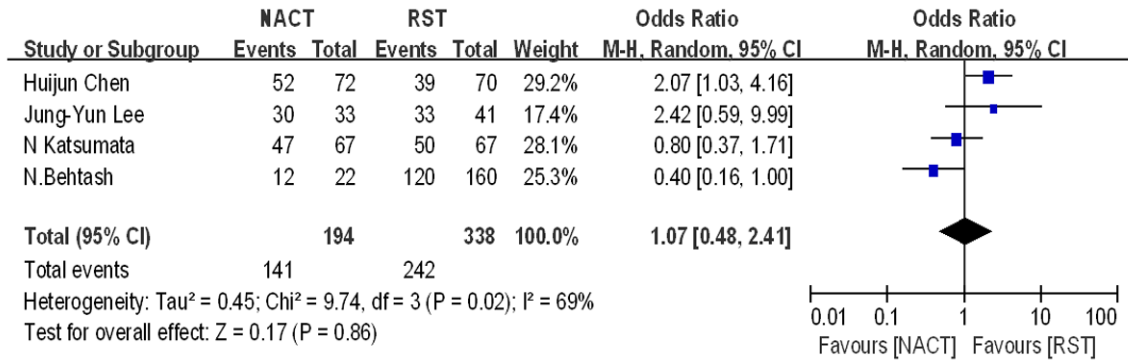


Figure 4. Comparison of overall survival rates between NACT group and RST group.

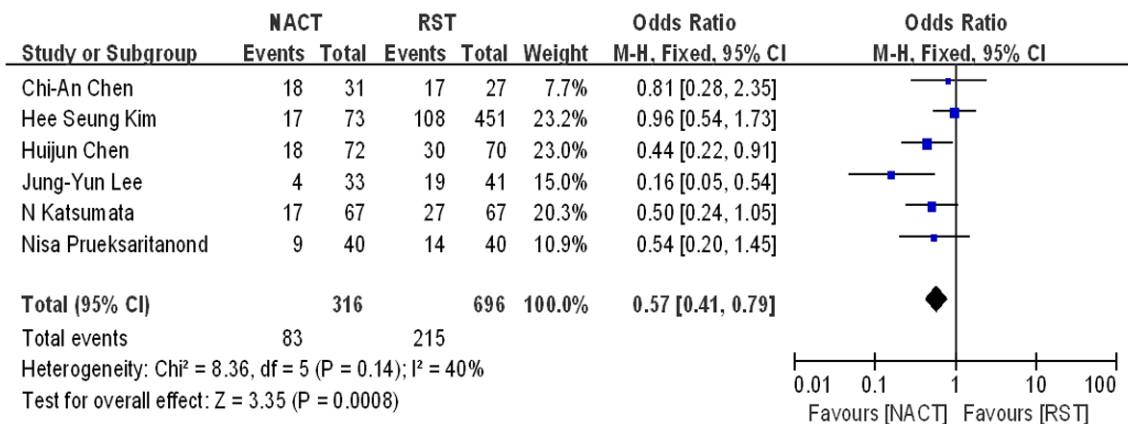


Figure 5. Comparison of the rate of lymph node metastasis between NACT group and RST Group.

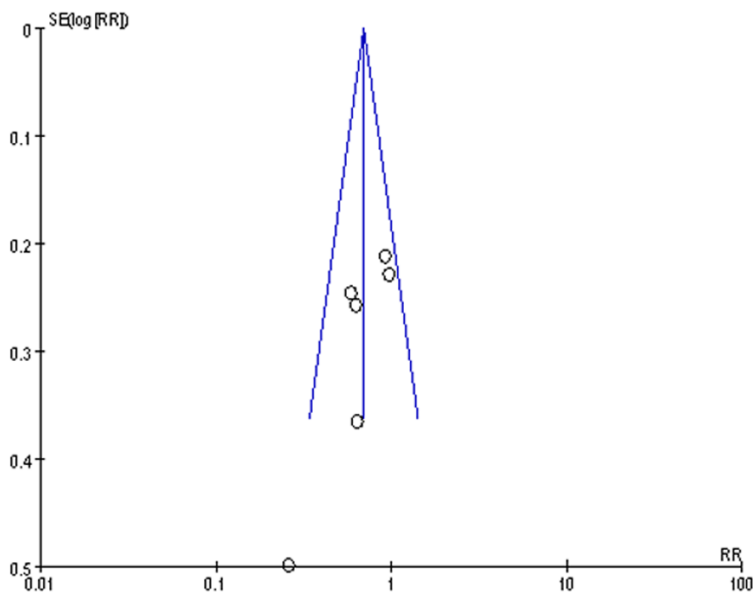


Figure 6. Funnel plot for checking publication bias.

the intraoperative estimated blood loss [SMD=0.20, 95% CI (-0.35, 0.76), P=0.48]. Three studies [12-14] compared the intraoperative and postoperative complication rates between two groups, as shown in Figure 9. We used a random effects model for analysis, taking into account heterogeneity between studies (P=0.05, I²=67%), which may be caused by regional differences and data processing method. The result of meta analysis didn't show a significant difference between two groups in the intraoperative and postoperative complication rates [OR=1.26, 95% CI (0.41, 3.85), P=0.68]. Five

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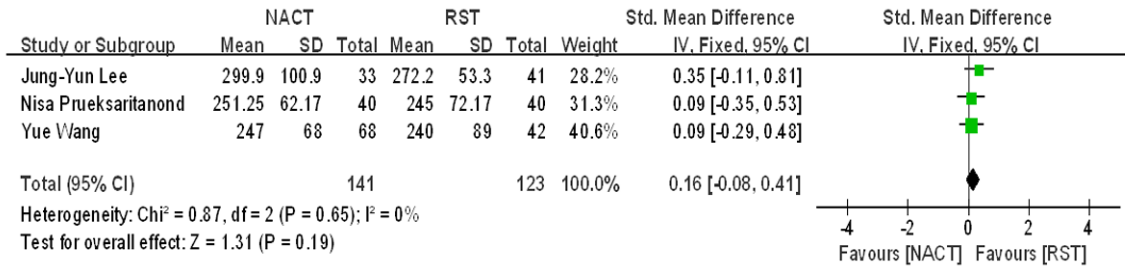


Figure 7. Comparison of operation time between NACT group and RST group.

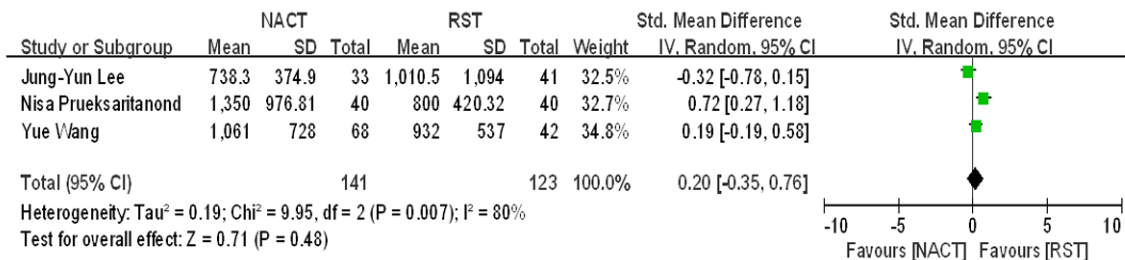


Figure 8. Comparison of the estimated intraoperative blood loss between NACT group and RST group.

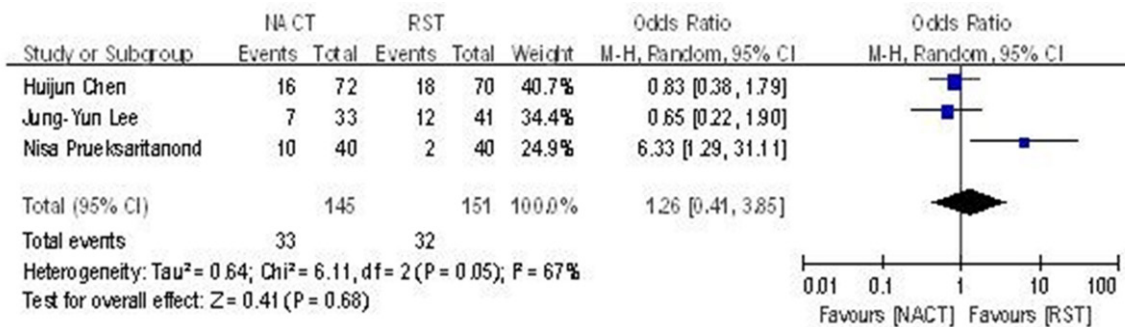


Figure 9. Comparison of the intraoperative and postoperative complication rates between NACT group and RST group.

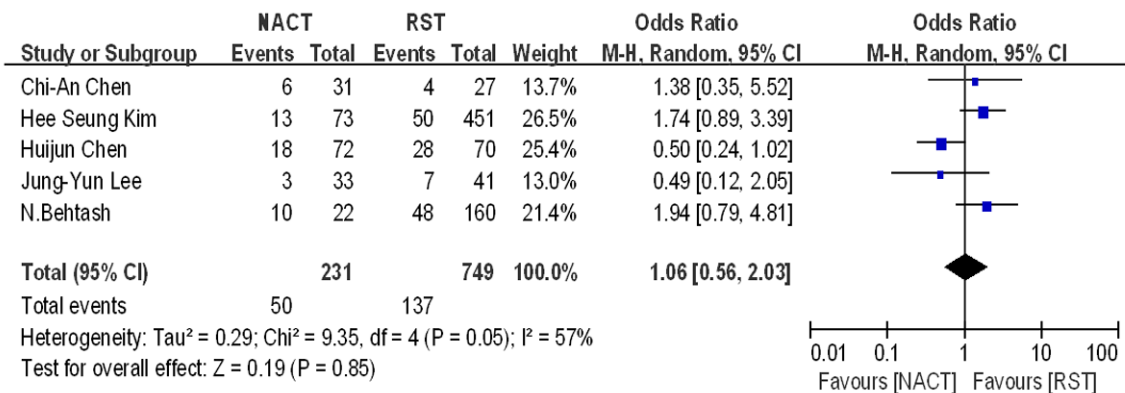


Figure 10. Comparison of recurrence rate between NACT group and RST group.

studies [12-14] compared the recurrence rate after treatment between two groups, as shown in **Figure 10**. We used a random effects model for analysis, taking into account heterogeneity between studies ($P=0.05$, $I^2=57\%$), which may be caused by regional differences and data processing method. The result of meta analysis didn't show a significant difference between two groups in the recurrence rate [OR=1.06, 95% CI (0.56, 2.03), $P=0.85$].

The quality of GRADE evidence

This meta-analysis have six outcome measures. Evidence grade of observational studies belongs to medium level, judging by GRADE (data not shown). The above results are low grade evidence, because: ① retrospective study without blind method, ② sample size of the two groups are quite different in some included studies, ③ some results exist publication bias. Therefore, clinicians should ensure that patients should be treated in line with their values and aspiration.

Discussion

This meta-analysis shows that there are significant differences between two groups in the lymph node metastatic rate, and not significant differences in survival and recurrence rates. And another article compared on neoadjuvant chemotherapy with radiotherapy [20] considered patients' survival rate has not improved in two groups. There are no significant difference between two groups in operation time, intraoperative and postoperative complication rates and intraoperative estimated blood loss, although researches of Burghardt E [17] and Chang [18] think neoadjuvant chemotherapy can narrowed tumor volume and make surgery easier. It may be related to the sample size of studies and the FIGO staging of patients. But the speculation still needs further tests to verify.

However, we think these conclusions should be received with caution, due to the meta analysis was limited by the quality and quantity of included studies. We use the way of Hozo [21] to estimate the operation time and intraoperative estimated blood loss of Nisa's study, which difference with other articles on the statistical description. In addition, although no statistical significance of publication bias was found in this

study, the underlying bias may be produced when only English publications were included.

In conclusion, the present meta-analysis indicated that application of NACT can reduce the rate of lymph node metastasis, which is an independent risk factor for cervical cancer prognosis and may improve the prognosis of cervical cancer. Even the relationship between NACT and survival rate, recurrence rate, incidence of complications, operative time and bleeding volume cannot be demonstrated by this meta-analysis, we believe it might be positively discovered if more rigorously controlled clinical trials would be preferred for future study. However, this study did not make a further study of different neoadjuvant chemotherapy and not demonstrated that all neoadjuvant chemotherapy cannot improve the survival rate or reduce the recurrence rate. Further studies should be conducted on broader scale in order to investigate the safety and efficacy between different neoadjuvant chemotherapy. Although limited by the study quality, NACT may provide beneficial effect for cervical cancer patients.

Disclosure of conflict of interest

None.

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References

- [1] Rettenmaier MA, Casanova DM, Micha JP, Moran MF, Ramsanghani NS, Syed NA, Puthawala A, DiSaia PJ. Radical hysterectomy and tailored postoperative radiation therapy in the management of bulky stage 1B cervical cancer. *Cancer* 1989; 63: 2220-3.
- [2] Piver MS and Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstet Gynecol* 1975; 46: 507-10.
- [3] Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1994; 29: 9-16.
- [4] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.

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- [5] Kanayama N, Isohashi F, Yoshioka Y, Baek S, Chatani M, Kotsuma T, Tanaka E, Yoshida K, Seo Y, Suzuki O, Mabuchi S, Shiki Y, Tatsumi K, Kimura T, Teshima T, Ogawa K. Definitive radiotherapy for primary vaginal cancer: correlation between treatment patterns and recurrence rate. *J Radiat Res* 2015; 56: 346-53.
- [6] Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, Snaidas L, Vighi S, Gomez Rueda N, di Paola G. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. *Gynecol Oncol* 1997; 67: 61-9.
- [7] Gonzalez-Martin A, González-Cortijo L, Carballo N, Garcia JF, Lapuente F, Rojo A, Chiva LM. The current role of neoadjuvant chemotherapy in the management of cervical carcinoma. *Gynecol Oncol* 2008; 110 (3 Suppl 2): S36-40.
- [8] Zeng XT, L WD, Li S. How to understand and use GRADE system correctly? A briefly outline. *Chinese Journal of Evidence-Based Medicine* 2011; 11: 985-990.
- [9] Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. *Gynecol Oncol* 2008; 110: 308-15.
- [10] Behtash N, Nazari Z, Ayatollahi H, Modarres M, Ghaemmaghami F, Mousavi A. Neoadjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage IB-IIA cervical cancer. *Eur J Surg Oncol* 2006; 32: 1226-30.
- [11] Prueksaritanond N, Chaisarn P and Yanaranop M. The efficacy of neoadjuvant paclitaxel-carboplatin chemotherapy followed by radical hysterectomy compared to radical hysterectomy alone in bulky stage IB2-IIA cervical cancer. *J Med Assoc Thai* 2012; 95 Suppl 3: S55-61.
- [12] Lee JY, Kim YH, Kim MJ, Kim K, Chung HH, Park NH, Song YS, Kang SB. Treatment of stage IB2, IIA bulky cervical cancer: a single-institution experience of neoadjuvant chemotherapy followed by radical hysterectomy and primary radical hysterectomy. *Arch Gynecol Obstet* 2011; 284: 477-82.
- [13] Katsumata N, Yoshikawa H, Kobayashi H, Saito T, Kuzuya K, Nakanishi T, Yasugi T, Yaegashi N, Yokota H, Kodama S, Mizunoe T, Hiura M, Kasamatsu T, Shibata T, Kamura T; Japan Clinical Oncology Group. Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102). *Br J Cancer* 2013; 108: 1957-63.
- [14] Wang Y, Wang G, Wei LH, Huang LH, Wang JL, Wang SJ, Li XP, Shen DH, Bao DM, Gao J. Neoadjuvant chemotherapy for locally advanced cervical cancer reduces surgical risks and lymph-vascular space involvement. *Chin J Cancer* 2011; 30: 645-54.
- [15] Chen CA, Cheng WF, Wei LH, Su YN, Hsieh CY. Radical hysterectomy alone or combined with neoadjuvant chemotherapy in the treatment of early stage bulky cervical carcinoma. *J Formos Med Assoc* 2002; 101: 195-202.
- [16] Kim HS, Kim JH, Chung HH, Kim HJ, Kim YB, Kim JW, Park NH, Song YS, Kang SB. Significance of numbers of metastatic and removed lymph nodes in FIGO stage IB1 to IIA cervical cancer: Primary surgical treatment versus neoadjuvant chemotherapy before surgery. *Gynecol Oncol* 2011; 121:551-7.
- [17] Burghardt E and Pickel H. Local spread and lymph node involvement in cervical cancer. *Obstet Gynecol* 1978; 52: 138-45.
- [18] Chang HC, Lai CH, Chou PC, Tseng CJ, Chang TC, Hsueh S, Ho YS, Soong YK. Neoadjuvant chemotherapy with cisplatin, vincristine, and bleomycin and radical surgery in early-stage bulky cervical carcinoma. *Cancer Chemother Pharmacol* 1992; 30:281-5.
- [19] Wen H, Wu X, Li Z, Wang H, Zang R, Sun M, Huang X, Zhang Z, Cai S. A prospective randomized controlled study on multiple neoadjuvant treatments for patients with stage IB2 to IIA cervical cancer. *Int J Gynecol Cancer* 2012; 22: 296-302.
- [20] Lee DW, Lee KH, Lee JW, Park ST, Park JS, Lee HN. Is neoadjuvant chemotherapy followed by radical surgery more effective than radiation therapy for stage IIB cervical cancer? *Int J Gynecol Cancer* 2013; 23: 1303-10.
- [21] Selvaggi L, Loizzi V, Di Gilio AR, Nardelli C, Cantatore C, Cormio G. Neoadjuvant chemotherapy in cervical cancer: a 67 patients experience. *Int J Gynecol Cancer* 2006; 16: 631-7.