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Efficacy of neoadjuvant cisplatin and 5-flourouracil prior to surgery in FIGO stage IB2/IIA2 cervical cancer

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Abstract. Cervical cancer is currently the first or second leading cause of cancer-related mortality among women in developing countries. This study was conducted in order to determine whether neoadjuvant cisplatin and 5-flourouracil (NAPF) prior to surgery is superior to primary surgical treatment (PST) as a treatment option for patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB2/IIA2 cervical cancer. A retrospective review of 195 patients with early-stage bulky cervical cancer was performed. The patients were divided into two groups, according to whether they received NAPF prior to surgery. The surgical profiles and complications, risk factors of recurrence and survival were compared between the groups. The response rate to NAPF was found to be 61.2%. There were no differences in operative time and intra-operative complications between the two groups, whereas the estimated blood loss in the NAPF and PST groups were 620.1±394.9 and 434.8±233.7 ml, respectively (P=0.000). When compared with PST, NAPF remarkably reduced tumor size (22.5 vs. 93.3%, P=0.000). Furthemore, the ratio of deep stromal invasion was significantly lower in responders to NAPF compared with that in non-responders (46.7 vs. 76.3%, respectively; P=0.004) and in the PST group (46.7 vs. 70.0%, respectively; P=0.004). No reduction of high-risk factors (HRFs) was observed. The NAPF group, even the responder subgroup, exhibited no significant improvement in progression-free survival (PFS) and overall survival (OS) compared to the PST group. In conclusion, despite the reduction of intermediate-risk factors (IRFs), neoadjuvant chemotherapy (NAC) with the NAPF regimen prior to radical surgery (RS) did not improve the prognosis in patients with FIGO stage IB2/IIA2 cervical cancer.

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Key words: neoadjuvant chemotherapy, primary surgical treatment, early-stage bulky cervical cancer, survival

Introduction

Despite the availability of effective screening methods, cervical cancer remains the first or second leading cause of cancer-related mortality among women in developing countries (1). For patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB/IIA cervical cancer, radical surgery (RS) or radiotherapy, with or without concurrent chemotherapy, may be the primary treatment option. However, patients with a lesion >4 cm in greatest dimension exhibit a poorer prognosis compared to those with a tumor ≤4 cm in greatest dimension, regardless of treatment selection (2). Therefore, the optimal management for patients with stage IB2/IIA2 cervical cancer remains controversial.

Neoadjuvant chemotherapy (NAC) prior to RS has been widely used in bulky cervical cancer since the mid-1980s, with the purpose of reducing tumor size, lowering the difficulty of operation, reducing the risk factors of recurrence and, thus, improving prognosis. However, NAC has not been considered to be the standard treatment option, since different studies reported conflicting results. Although neoadjuvant cisplatin and 5-flourouracil (NAPF) treatment prior to RS was previously compared to primary surgical treatment (PST) in patients with cervical cancer (3), to the best of our knowledge, it has not been investigated in patients with early-stage bulky disease only. Based on these facts, we performed this study to evaluate the short- and long-term efficacy of NAPF in patients with FIGO stage IB2/IIA2 cervical cancer.

Materials and methods

Study population. A database of 2,284 cervical cancer patients who were admitted to Peking Union Medical College Hospital (Beijing, China) between January, 2002 and December, 2011 was reviewed. Approval by the Institutional Review Board of Peking Union Medical College Hospital was obtained in advance and the requirement of patient informed consent was waived, since this study was retrospective. Patients with primary, previously untreated, histologically confirmed squamous cell carcinoma or adenocarcinoma of the cervix, with FIGO stage IB2/IIA2 disease, were considered eligible for inclusion this study. The patients were also required to have a performance status of 0 or 1, normal organ function and no

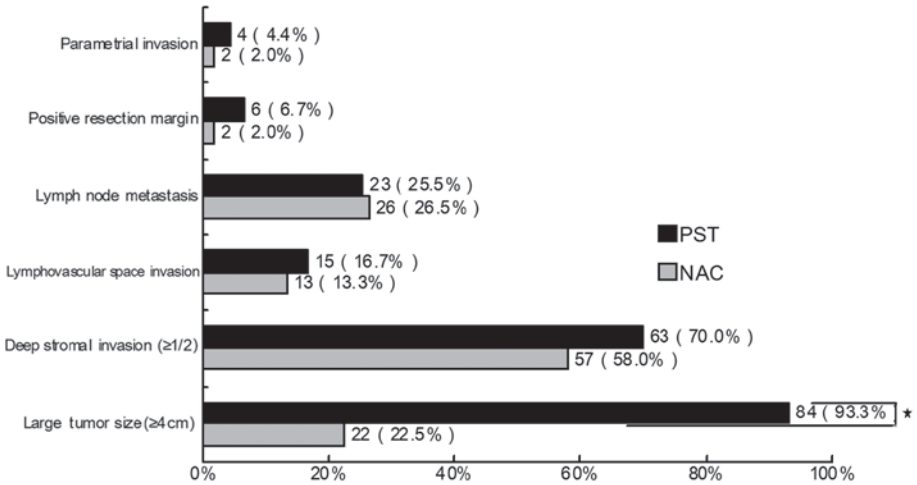

Figure 1. Comparison of intermediate- and high-risk factors between neoadjuvant chemotherapy (NAC) with cisplatin and 5-flourouracil and primary surgical treatment (PST) groups in International Federation of Gynaecology and Obstetrics stage IB2/IIA2 cervical cancer (*P<0.01).

Table I. Patient characteristics.

Characteristics	NAPF	PST	P-value
Age (years)			
≥40	62	60	0.469
<40	41	32	
FIGO stage			
IB2	78	62	0.197
IIA2	25	30	
Histology			
Squamous cell carcinoma	91	82	0.863
Adenocarcinoma	12	10	
Grade			
I-II	48	47	0.532
III	55	45	

NAPF, neoadjuvant cisplatin and 5-flourouracil; PST, primary surgical treatment; FIGO, International Federation of Gynaecology and Obstetrics.

complicating diseases that would affect survival. Patients who had received primary radiotherapy were excluded.

Treatment. Neoadjuvant chemotherapy consisted of 2-3 cycles of cisplatin (70 mg/m^2 on day 1) with 5-flourouracil (1,000 mg/m^2 for 4 consecutive days) every 3 weeks. The response to NAPF was evaluated by tumor size measured at initial diagnosis and immediately prior to surgery, according to the Response Evaluation Criteria in Solid Tumors (RECIST) (4). Complete response (CR) was defined as no visible lesion, partial response (PR) as ≥30% decrease of the greatest dimension, progressive disease (PD) as ≥20% increase of the greatest dimension or appearance of new lesions and stable disease (SD) as the status between PR and PD. Following NAPF, the patients were clinically reassessed and those with normal organ function and good performance status were identified as eligible for RS.

Type III radical hysterectomy plus bilateral pelvic lymphadenectomy was performed within 2 weeks after diagnosis in the PST group and within 3 weeks after the last administration of chemotherapy in the NAPF group. Para-aortic lymphadenectomy was also performed when there was a suspicion of metastasis. Furthermore, postoperative concurrent chemoradiation or radiotherapy alone was administered to patients with at least one high-risk factor (HRF) or at least two intermediate-risk factors (IRFs) identified in surgical specimens. HRFs included lymph node metastasis, parametrial invasion, or positive resection margin, whereas IRFs included large tumor size (≥4 cm), deep stromal invasion (≥1/2), lymphovascular space invasion, or poor differentiation.

Statistical analyses. Statistical analyses of categorical variables were performed using the Chi-square test, with continuity correction, or the Fisher's exact test. The operation time and estimated blood loss were compared with the Student's t-test. The Kaplan-Meier analysis with the log-rank test and the multivariate Cox's proportional hazards analysis were used to evaluate the prognostic factors affecting survival. All data were analyzed with the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 195 patients were enrolled in this study, with 103 patients in the NAPF and 92 patients in the PST group. The patient characteristics are summarized in Table I. There were no significant differences in age at diagnosis, FIGO stage, histology and grade between the two groups.

Clinical response to NAPF. The overall response rate to NAPF was 61.2%, including CR in 2 patients and PR in 61 patients. A total of 40 patients were assessed as having SD, whereas no PD was observed. The NAPF group was then subdivided

Table II. Multivariate Cox's proportional hazards analysis for prognostic factors.

	Progression-free survival			Overall survival		
Prognostic factors	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Age (years)						
<40	Reference			Reference		
≥40	0.748	0.358-1.564	0.440	0.803	0.348-1.852	0.607
FIGO stage						
IB2	Reference			Reference		
IIA2	0.848	0.359-2.002	0.707	0.883	0.343-2.271	0.796
Histology						
Squamous cell carcinoma	Reference			Reference		
Adenocarcinoma	1.314	0.454-3.799	0.614	1.579	0.530-4.702	0.412
No. of IRFs						
≤1	Reference			Reference		
≥2	1.185	0.287-4.894	0.815	1.716	0.327-8.995	0.523
No. of HRFs						
0	Reference			Reference		
≥1	4.094	1.888-8.881	0.000	4.343	1.789-10.542	0.001
Treatment						
PST	Reference			Reference		
Responders	0.793	0.266-2.364	0.678	1.018	0.313-3.307	0.976
Non-responders	1.802	0.769-4.221	0.175	2.127	0.799-5.661	0.131

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynaecology and Obstetrics; IRFs, intermediate-risk factors; HRFs, high-risk factors; PST, primary surgical treatment.

into intravenous chemotherapy (IVC) and intra-arterial chemotherapy (IAC) groups and the response rates of the two subgroups were not found to differ significantly.

Surgical profiles and complications. Of the 103 patients in the NAPF group, 3 patients received concurrent chemoradiation due to the toxicity of chemotherapy or other reasons. A total of 2 patients in the NAPF and 2 patients in the PST group were diagnosed with inoperable disease during surgery and the radical procedure was abandoned. The remaining 188 patients underwent RS and were included in the following analysis.

The operative time between the two groups did not exhibit a statistically significant difference (194.2±33.8 vs. 192.3±33.5 min, respectively; P=0.678). Intra-operative complications (ureter or bladder injury) occurred in 7.1% of the patients in the NAPF and 3.4% of those in the PST group, although the difference was insignificant (P=0.402). However, the estimated blood loss in the NAPF group was significantly higher compared to that in the PST group (620.1±394.9 vs. 434.8±233.7 ml, respectively; P=0.000). Analyses comparing these aspects between the IVC and IAC groups were performed and no difference was observed.

Intermediate- or high-risk factors. The patients in the NAPF group exhibited a lower rate of each IRF, whereas a significant difference was only observed in tumor size (22.5 vs. 93.3%, P=0.000). The frequencies of the HRFs were similar in the two groups (Fig. 1). To identify whether responders had significantly lower rates of IRFs or HRFs, we subdivided the NAPF group into the subgroups of responders and non-responders. Following subdivision, a remarkable decrease in an additional

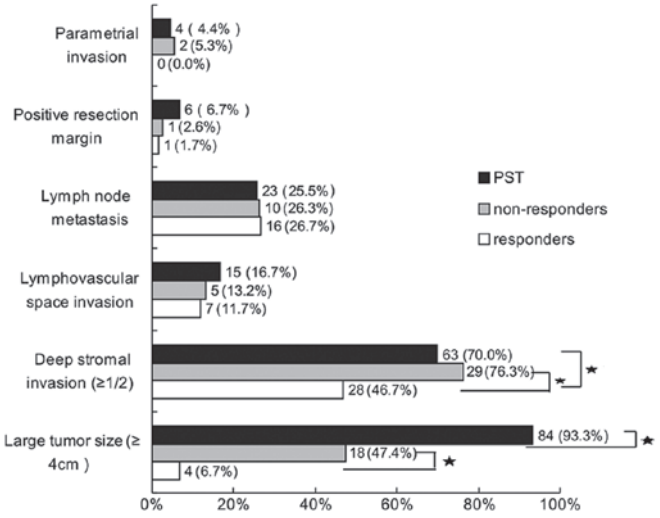

Figure 2. Comparison of intermediate- and high-risk factors among responders, non-responders and the primary surgical treatment (PST) group (*P<0.01).

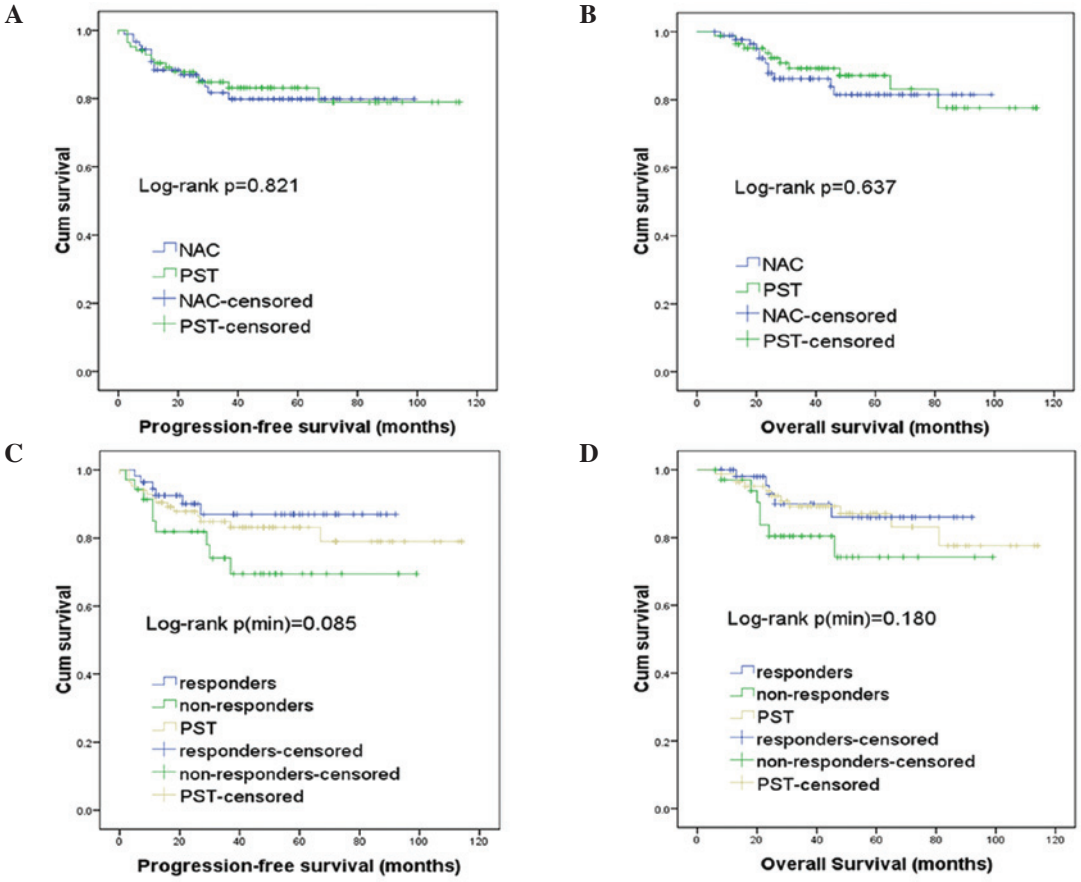

Figure 3. (A and B) Comparison of progression-free survival (PFS) and overall survival (OS) between the neoadjuvant chemotherapy (NAC) with cisplatin and 5-flourouracil and the primary surgical treatment (PST) groups. (C and D) Comparison of PFS and OS among responders, non-responders and the PST group.

IRF, deep stromal invasion, was detected in responders compared to non-responders (46.7 vs. 76.3%, respectively; P=0.004) and the PST group (46.7 vs. 70.0%, respectively; P=0.004), whereas the reduction of HRFs in responders was insignificant (Fig. 2).

There was no difference in the rate of adjuvant radiotherapy between the NAPF and PST groups (94.9 vs. 95.6%, respectively; P=1.000). The frequency of adjuvant radiotherapy tended to be lower in responders compared to that in non-responders, althought the difference was not statistically significant (93.3 vs. 97.4%, respectively; P=0.679).

Survival analysis. During this procedure, 14 patients were excluded due to loss of contact. The overall follow-up rate was 92.6% and the median follow-up time was 41 months (range, 6-114 months). As shown in Fig. 3A and B, the progression-free survival (PFS) was similar in the two groups. Similar results were observed regarding overall survival (OS). Although non-responders tended to be associated with worse outcomes compared to the other two groups, responders exhibited no improvement of PFS and OS compared to the PST group (Fig. 3C and D).

Furthermore, a multivariate Cox's proportional hazards analysis was performed, including the following variables: age at diagnosis, FIGO stage, histology, number of IRFs, number of HRFs and treatment selection (Table II). Only the presence of at least one HRF was found to be an independent predictor of poor PFS and OS (P=0.000 and 0.001, respectively).

Recurrence. Of the remaining 174 cases, 27 patients developed recurrences (15 patients in the NAPF and 12 in the PST group). The recurrence rates of the two arms did not differ significantly (16.7 vs. 14.3%, respectively; P=0.665). Furthermore, there was no significant difference in the rate of distant recurrence (14.4 vs. 9.5%, respectively; P=0.319) or pelvic failure (2.2 vs. 4.8%, respectively; P=0.616) between the two groups.

Discussion

Although NAC prior to RS has been widely applied in patients with early-stage or locally-advanced cervical cancer since the mid-1980s, only 6 randomized controlled trials (RCTs) comparing NAC plus RS to RS alone have been conducted and reported controversial results (3,5-9). A total of 3 RCTs concluded that NAC decreased HRFs (3,5,6), whereas the other 3 RCTs reported the opposite (7-9). The Eddy *et al* GOG trial (7) and the Katsumata *et al* JCOG trial (8) demonstrated no survival benefit with NAC, whereas the remaining trials reported improved survival. In addition, inconsistent outcomes were also reported by non-RCTs (10-13). One matched-case comparison of NAC prior to surgery and PST in FIGO stage IB/IIA cervical cancer concluded that NAC prior to surgery conferred no survival benefit over PST and may lead to poor prognosis in FIGO stage IIA disease, despite the reduction in IRFs and adjuvant radiotherapy (10), whereas another matched-case study reported that NAC, compared to primary surgery, significantly decreased IRFs and increased the 5-year

disease-free survival (DFS) and OS rates in patients with stage IB2 disease (11).

The factors affecting the efficacy of NAC in cervical cancer have not been determined. A Cochrane meta-analysis of the above-mentioned 6 RCTs demonstrated that total cisplatin dose, chemotherapy cycle length and FIGO stage could not sufficiently explain the differences among individual trials (14). However, the rate of postoperative radiotherapy within each of the individual trials ranged between 36.1 and 100% and this difference may contribute to the variation in the individual trial results (14). Since the rate of adjuvant radiotherapy was high in the present study, there is a possibility that the differences in PFS and OS between the two groups caused by NAPF are diminished by adjuvant radiotherapy. Furthermore, the failure of NAC in reducing HRFs, which were shown to be the independent prognostic factor for poor PFS and OS in the present study, may reflect the role of potential underlying factors. Recently, there has been increasing interest in the identification of biomarkers able to predict response to treatment and survival of patients with cervical cancer, such as the clusterin protein, which was reported by Watari *et al* (15) to be significantly associated with poor response to platinum-based NAC.

Although the improvement of survival in responders was of no statistical significance compared to that in non-responders and the PST group in our study, previously published studies reported better prognosis for responders. Hu *et al* (11) reported that the 5-year DFS and OS rates in responders were favorably increased in comparison to those in non-responders and the PST group. A retrospective study suggested that the response to NAC was an independent prognostic factor for prolonged survival in patients with bulky stage IB2/IIA2 cervical cancer (16). Whether the prognosis of NAC-responders is significantly better compared to that of patients receiving primary surgery requires further investigation.

Analyses of surgical profiles revealed that the estimated blood loss was significantly increased in the NAPF compared to that in the PST group. A possible explanation for this phenomenon is the occurrence of necrosis and subsequent angiogenesis following chemotherapy.

In this study, NAPF followed by RS was compared to PST in women with early-stage bulky cervical cancer. We observed that neoadjuvant chemotherapy with the NAPF regimen prior to RS did not improve prognosis, despite the reduction in tumor size or deep stromal invasion (only in responders). The strengths of this study included sole neoadjuvant regimen, homogeneous subjects and high follow-up rate. However, large RCTs may be required to compare NAC followed by RS to RS alone. Furthermore, comparison of NAC prior to RS and cisplatin-based chemoradiation is warranted, since the latter is currently the standard treatment for cervical cancer. To the best of our knowledge, three prospective randomized trials on this subject (EORTC55994, NCT00193739 and NCT01000415) have been initiated and the results are keenly awaited.

References

1. Jemal A, Bray F, Center MM, *et al*: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
2. Landoni F, Maneo A, Colombo A, *et al*: Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 350: 535-540, 1997.
3. Cai HB, Chen HZ and Yin HH: Randomized study of preoperative chemotherapy versus primary surgery for stage IB cervical cancer. J Obstet Gynaecol Res 32: 315-323, 2006.
4. Eisenhauer EA, Therasse P, Bogaerts J, *et al*: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
5. Chen H, Liang C, Zhang L, *et al*: Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. Gynecol Oncol 110: 308-315, 2008.
6. Sardi JE, Giaroli A, Sananes C, *et al*: 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 67: 61-69, 1997.
7. Eddy GL, Bundy BN, Creasman WT, *et al*: Treatment of ('bulky') stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. Gynecol Oncol 106: 362-369, 2007.
8. Katsumata N, Yoshikawa H, Kobayashi H, *et al*; 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 108: 1957-1963, 2013.
9. Napolitano U, Imperato F, Mossa B, *et al*: The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): a long-term randomized trial. Eur J Gynaecol Oncol 24: 51-59, 2003.
10. Kim HS, Kim JY, Park NH, *et al*: Matched-case comparison for the efficacy of neoadjuvant chemotherapy before surgery in FIGO stage IB1-IIA cervical cancer. Gynecol Oncol 119: 217-224, 2010.
11. Hu T, Li S, Chen Y, *et al*: Matched-case comparison of neoadjuvant chemotherapy in patients with FIGO stage IB1-IIB cervical cancer to establish selection criteria. Eur J Cancer 48: 2353-2360, 2012.
12. Xiong Y, Liang LZ, Cao LP, *et al*: Clinical effects of irinotecan hydrochloride in combination with cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. Gynecol Oncol 123: 99-104, 2011.
13. Lee JY, Kim YH, Kim MJ, *et al*: 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 284: 477-482, 2011.
14. Rydzewska L, Tierney J, Vale CL, *et al*: Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev 12: CD007406, 2012.
15. Watari H, Kanuma T, Ohta Y, *et al*: Clusterin expression inversely correlates with chemosensitivity and predicts poor survival in patients with locally advanced cervical cancer treated with cisplatin-based neoadjuvant chemotherapy and radical hysterectomy. Pathol Oncol Res 16: 345-352, 2010.
16. Li R, Lu ST, Si JG, *et al*: Prognostic value of responsiveness of neoadjuvant chemotherapy before surgery for patients with stage IB(2)/IIA(2) cervical cancer. Gynecol Oncol 128: 524-529, 2013.