Neoadjuvant Chemotherapy Followed by Surgery/Chemoradiotherapy Versus Radical Chemoradiotherapy in Stage IB2, IIA2, IIB Locally Advanced Cervical Carcinoma: A Retrospective Multicenter Study of 388 Patients

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Abstract

Purpose: The present study aimed to compare the oncologic outcomes and side effects between neoadjuvant chemotherapy followed by surgery/chemoradiotherapy and radical chemoradiotherapy for locally advanced cervical carcinoma (LACC).

Methods: We conducted a retrospective review of patients with LACC (IB2, IIA2 and IIB stages) from six hospitals between June 2007 and January 2017.

Results: A total of 388 patients were included, in which 278 patients received radical chemoradiotherapy (Standard group), and 110 patients received neoadjuvant chemotherapy. 65 patients of the 110 received radical hysterectomy (Surgery group), and 45 received chemoradiotherapy (Neo-Ra group). The 5-year overall survival (OS) in Surgery group (92.5%) was similar to that of the Standard group (84.9%), but both groups had higher OS rates than Neo-Ra group (75.6%). The 5-year disease-free survival (DFS) and progression-free survival (PFS) showed no differences among the three groups, respectively. There were no significant differences for grades 1-3 gastrointestinal and genitourinary toxicities among the three groups. No patient had grade 4 adverse effects. In multivariate analysis, tumor regression (CR vs. PR+SD+PD), pathological type (squamous cancer vs. non-squamous cancer) and lymph node metastasis (positive vs. negative) were considered as independent predictors of OS. Furthermore, besides above factors, the maximum diameter of tumors and adjuvant chemotherapy were also considered as significant prognostic factors for DFS and PFS.

Conclusion: These findings showed that neoadjuvant chemotherapy followed by radical hysterectomy as a feasible and reliable therapy, resulting in encouraging oncologic outcomes and low side effects when compared to those obtained by standard chemoradiotherapy for IB2, IIA2, IIB stage cervical carcinoma patients.

Introduction

Cervical carcinoma is a public health issue globally, and it is currently the fourth most common cancer in women. About 80% of cervical cancers occur in individuals of low- and middle-income countries, where the health systems cannot provide well-known effective prevention network. Furthermore, cervical cancer remains the third main cause of death due to its malignancy in women worldwide^{1, 2}. Since 1999, cisplatin-based concurrent chemoradiotherapy (CCRT) is the standard primary treatment used for treating patients with locally advanced cervical carcinoma (LACC) with 3- and 5-year survival rates of 69% and 62% for IB to IVA stages, respectively³. The benefits of CCRT have been evaluated by several randomized trials including the Morris *et al.* study, which reported conduction of radiotherapy with cisplatin and 5 fluorouracil. The 5-year overall survival (OS) rate significantly reached to 67% when compared with 40% with radiotherapy alone. Furthermore, the rates of both distant metastases and locoregional recurrences were significantly higher among patients treated with radiotherapy alone⁴.

Surgery, which is the primary mode of treatment for cervical carcinoma, is increasingly being used in China. For LACC FIGO stages IB2, IIA2 and IIB, the use of neoadjuvant chemotherapy (NACT) followed by radical surgery could be an alternative choice to chemoradiotherapy for treating LACC based on a 5-year OS rate range of 45–83%^{5–7}. For NACT followed by CCRT approach in LACC, A meta-analysis study by conducted Tierney *et al.* included 2074 patients from 18 trials with NACT followed by local therapy (mainly radiotherapy), and the results revealed neither higher response rates nor longer survival rates⁸. Narayan *et al.* have reported NACT followed by CCRT demonstrated a significantly superior disease-free survival (DFS) when compared to definitive CCRT in bulky stage IB2 and locally advanced (stages II–IVA) in cervical carcinoma⁹. The INTERLACE is the only randomized phase 3 trial that evaluated NACT followed by CCRT versus CCRT alone and is still recruiting patients¹⁰.

In contrast, a direct comparison of NACT followed by surgery versus CCRT is still lacking as the standard treatment offered considerable efficacy. The purpose of this retrospective multicenter study was to compare the clinical outcomes and side effects of cervical cancer patients who underwent platinum-based NACT followed by radical hysterectomy or CCRT versus CCRT alone. Also the prognostic factors that have more effect for over a long period of time with regard to survival outcomes were analyzed using univariate and multivariate analyses.

Methods

Patients

This retrospective study is approved by the participating centers of the Institutional Review Board, and all patients provided written informed consent prior to the study entry. Inclusion criteria were as follows: patients aged 18–65 years; with pathologically diagnosed disease (stages IB2, IIA2 and IIB) according to the Federation International of Gynecology and Obstetrics (FIGO) 2009 classification; with no evidence of distant metastasis; with Karnofsky performance score of ≥ 70 (adequate hepatic, renal, and cardiopulmonary function were verified). All pertinent clinical data were obtained from patients, and they completed the full course of radiotherapy.

The study included 388 patients with FIGO stage IB2, IIA2, IIB cervical carcinoma between June 2007 and January 2017 from six centers. Of these, 278 (72%) patients received radical chemoradiotherapy with cisplatin based external beam radiotherapy plus high-dose-rate brachytherapy (Standard group). The remaining 110 (28%) received NACT with a combination of 3–4 cycles of cisplatin plus paclitaxel regimen. Of the 110 patients, 65 (16%) patients received NACT followed by radical hysterectomy and adjuvant radiotherapy (Surgery group) and 45 patients (12%) did not undergo radical surgery after NACT received CCRT (Neo-Ra group).

Standard group

The patients in the Standard group received a mean dose of 44 ± 10.5 Gy pelvic external-beam radiation therapy (EBRT) with a three-dimensional conformal radiotherapy (3D-CRT) technique (18 patients) or

intensity-modulated radiotherapy (IMRT) technique (77 patients) before image guided high-dose-rate brachytherapy (once a week) with a mean dose of 25 ± 8 Gy (2–7 fractions). Chemotherapy was given during EBRT with intravenous cisplatin of 40 mg/m^2 once a week for 5 weeks in all patients. Adjuvant chemotherapy is administered after radical radiotherapy for some patients.

Surgery group/Neo-Ra group

The 110 patients in the Surgery group/ Neo-Ra group received two TP cycles chemotherapy, cisplatin ($50\text{--}60 \text{ mg/m}^2$ intravenous infusion on day 1) and paclitaxel ($135\text{--}150 \text{ mg/m}^2$ intravenous infusion on day 1), were administered at an interval of 3 weeks. 65 patients (Surgery group) who require radical operation after NACT underwent radical hysterectomy according to the Piver–Rutledge classification with pelvic lymphadenectomy within 3–6 weeks from the last cycle of chemotherapy. Postoperative adjuvant radiotherapy was considered for high risk patients with positive surgical margins, metastatic lymph nodes or parametrial involvement. 45 patients (Neo-Ra group) received CCRT after NACT due to bad response to chemotherapy and still amenable to undergo radical surgery.

Patient assessment and follow-up

Clinical evaluation of therapeutic effectiveness was based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1¹¹. Acute and late adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Adverse events that occur after 6 months were considered late toxicity. The patients were periodically followed-up with clinical and radiological examinations every 3 months for the first 3 years, every 6 months for the fourth and fifth years, and every year thereafter until death or until January 2017. The time from the first treatment till the detection of recurrence or death was defined as DFS. Progression-free survival (PFS) was calculated from the date of recruitment till the date of progressive disease according to the RECIST criteria. The time from the first treatment to death or last observation was defined as OS. DFS, PFS and OS were calculated each year.

Statistical methods

Statistical analysis was performed using SPSS 22.0 software (IBM, Armonk, NY). The continuous variables were presented as means $\pm$ standard deviations (SD). The categorical variables were presented as counts or percentages. One-way ANOVA, chi-square test, and Kruskal-Wallis H-test were used to compare and analyze patient characteristics in the three groups. Moreover, log-rank test using the Kaplan–Meier method was performed to compare DFS, PFS and OS among the three groups. *P* values of < 0.05 were considered to be statistically significant.

Results

Patient characteristics

Between June 2007 and January 2017, 388 patients with LACC who underwent treatment in 6 cancer centers were retrospectively analyzed. The patient and tumor characteristics are summarized in Table 1. The mean $\pm$ SD age of these patients was 51.3 ± 9.5 years. FIGO stage was IB2 in 35 patients (9%), IIA2 in 47 patients (12%), and IIB in 306 patients (79%). The histological type squamous cell carcinoma was observed in 336 patients. Radical chemoradiotherapy with cisplatin based EBRT plus brachytherapy was received by 278 patients. All patients completed the full course of radiotherapy and two cycles of concurrent chemotherapy. 287 patients received no further adjuvant chemotherapy after CCRT.

NACT involved a combination of 3–4 cycles of cisplatin plus paclitaxel regimen in all 110 patients. Using this treatment, 65 patients received radical hysterectomy, whereas 45 patients received chemoradiotherapy. No significant differences were found between the two groups in baseline characteristics.

Clinical response

After 3–4 cycles of NACT with cisplatin plus paclitaxel, 9 patients (7%) had complete response (CR) and 79 (72%) had partial response (PR). The CR and most PR patients who required radical operation received radical resection. For patients with stages IB2 and IIA, 77.5% (31/40) received surgery, whereas only 51.4% (36/70) received surgery for IIB stage. The patients with PR and stable disease (SD) were not considered amenable to receive radical surgery, and so received CCRT as radical treatment. Three months after radiotherapy, the CR and PR were 98.3% (115/117) in the Standard group, 100% (65/65) in the Surgery group, and 97.7% (44/45) in the Neo-Ra group (Table 2) ($p > 0.05$).

Patterns of treatment failure

The median follow-up of survivors was 66.5 months (range 8-212 months). For 5-year follow-up period, locoregional relapse occurred in 3.2% in Standard group, 1.5% in Surgery group and 11.1% in Neo-Ra group ($p > 0.05$), whereas a disseminated relapse occurred in 14.4% patients in Standard group, 7.7% in Surgery group and 11.1 % in Neo-Ra group, where were considered similar (Table 2) ($p > 0.05$).

Late toxicities

Acute toxicities during radiotherapy were well tolerated by entire group of patients. Hematological and gastrointestinal toxicities were most commonly observed adverse events. The most common side effect that occurs due to late toxicity was gastrointestinal toxicity, which occurred in 24.5% of patients. Most of them were grade 1 or 2 adverse events. The grade 1–3 gastrointestinal toxicities were seen in 23% cases in Surgery group, 18% cases in Neo-Ra group, and 26% cases in Standard group, respectively, showing no significant difference. No patient had grade 4 adverse events. Genitourinary toxicities were the second most common late side effects, which occurred in 14% of patients. Most of them were grade 1–2, and grade 1–3 genitourinary toxicities were seen in 11% cases in Surgery group, 4% cases in Neo-Ra group, and 16% cases in Standard group, respectively, which showed no significance either (Table 2). Other less common late side effects included vaginal dehiscence and dyspareunia, but are less observed.

Survival analysis

The 5-year OS was observed in 92.5% patients in Surgery group, and in 84.9% in Standard group, which showed no significant differences, but both groups had higher rates than that of 75.6% patients in Neo-Ra group ($p < 0.05$). The 5-year DFS and PFS were 89.2% and 87.7 % in Surgery group, 77.8% and 77.8% in Neo-Ra group, and 81.7% and 80.9% in Standard group, respectively, and showed no significant differences among any groups (Fig. 1 A-C).

Subgroup analysis showed that, for IB2 and IIA2 stage, the 5-year OS was 90.3%, 88.9% and 83.3%, the DFS was 87.1%, 88.9% and 85.7%, and PFS was 84.1%, 88.9% and 83.3% for Surgery group, Standard group and Neo-Ra group, respectively, showing no significant differences among any groups for the three alternative modalities (Fig. 1 D-F). For IIB stage, the 5-year OS in the Neo-Ra group (72.2%) was significantly lower than the Surgery group (94.1%) and the Standard group (85.5%). The 5-year DFS was 91.2%, 75.0%, 80.9% and PFS was 91.2%, 75.0%, 80.5% for Surgery group, Standard group and Neo-Ra group, showing no significance among any groups (Fig. 1 G-I). The results of IIB stage were similar with the results of the whole group.

Prognostic factors

The various potential prognostic factors for predicting DFS, PFS and OS rates included age, maximum diameter of tumors, treatment days and mean D90 HRCTV (EQD2₁₀), SCC, CA125, WHO histology, overall stage, tumor regression, lymph node metastasis, parametrial involvement and adjuvant chemotherapy. In multivariate analysis, tumor regression (CR vs. PR + SD + PD), pathological type (squamous cancer vs. non-squamous cancer) and lymph node metastasis (positive vs. negative) were found as independent predictors of OS. Furthermore, besides the above factors, the maximum diameter of tumors and adjuvant chemotherapy were considered as significant prognostic factors for DFS and PFS (Table 3–5).

Discussion

The present study demonstrated that NACT followed by surgery resulted in similar outcomes in terms of 5-year OS, PFS and DFS rates compared with radical chemoradiotherapy for LACC. Subgroup analysis demonstrated that NACT has an excellent high conversion rate, which converted patients with IB2, IIA2 stage from inoperable to operable state, and their 5-year OS, DFS and PFS showed no significant differences among any groups. So, NACT followed by radical hysterectomy was considered feasible and reliable therapy, especially for IB2, IIA2 stage LACC patients, and also salvage radiotherapy remains to be effective even if the response of NACT was not satisfactory. But for patients with stage IIB, the NACT conversion rate of patients from inoperable to operable states was much lower than those with stage IB2, IIA2. The study revealed that only less than half of the patients benefitted from NACT with stage IIB, and unfortunately the remaining patients (Neo-Ra group) who cannot receive the surgery had the lowest OS. Actually, patients who did not receive surgery because of bad pathological response had a 7.4-fold higher risk of recurrence and a 4.7-fold higher risk of death than those who received surgery according to our

study results. In the present study, no significant differences were observed in grade 1–3 late gastrointestinal genitourinary toxicities among the three different treatment groups. However, NACT followed by radical surgery have been used to reduce the long-lasting adverse effects of radical radiotherapy, because of adjuvant radiotherapy after surgery has the lower prescription irradiation dose compared with CCRT. NACT in LACC patients showed no meaningful improvement in the decrease of gastrointestinal and genitourinary late toxicities based on our studies.

The standard treatment for CCRT followed by brachytherapy for LACC acts as an essential independent treatment factor for improving the pelvic control^{12, 13}. Whereas NACT followed by radical hysterectomy is performed in some institutions of Europe and Asia. NACT before local therapy showed unexpected results in reducing tumor mass before definitive therapy. The effect of NACT can be evaluated immediately. Most of the chemotherapy is administered after surgery when patients lacked a measurable disease. When chemotherapy precedes surgery, one might measure the primary tumor directly or evaluate the surgical specimen for histological evidence of response to therapy¹⁴. The experience with regard to efficacy for this approach has now well documented by large randomized clinical trials¹⁵. Nowadays, including our studies, NACT followed by radical hysterectomy is considered as an interesting alternative therapeutic option to CCRT for patients with stage IB2-IIIB cervical cancer^{16–19}. Some retrospective studies have evaluated the contribution of NACT for patients with LACC beyond IIB stage. The most extensive series conducted by Sardi *et al.* reported that 151 patients were treated with vincristine, bleomycin and cisplatin according to the “Buenos Aires” protocol^{20–22}. When compared with nonrandomized historical control group patients who received conventional radiation therapy alone, a statistically significant advantage in terms of 2-year DFS favoring the chemotherapy-surgery group was demonstrated for patients with stage IIB and IIIB. But Benedetti-Panici *et al.*²³ have reported significant survival benefits for neoadjuvant chemotherapy and radical surgery versus radiotherapy in stage IB2-IIIB LACC but not for stage III disease. Bloss *et al.*²⁴ have designed a Phase II trial of bleomycin, cisplatin, and vincristine administration prior to radical surgery and/or radiotherapy. The results showed a positive impact on the survival rate in 30 women with FIGO stage IIB-IVA disease, concluding that the NACT regimen was ineffective in converting patients from inoperable to operable state. So, based on these studies, the doctors should make a discrete decision in choosing NACT for beyond IIB stage. There are many chemotherapy regimens available till date. However, the guidelines failed to identify the combination that offers the best result. All the regimens achieved comparable results with many combinations and with cisplatin as the main agent²⁵.

Several studies have demonstrated that positive lymph nodes, large tumor burden, close surgical margins, advanced stage and parametrial infiltration are associated with a greater risk of local recurrence or death for LACC^{26–28}, and the FIGO clinical stage has no prognostic significance. Previous FIGO staging system does not take into account the influence of clinicopathological factors. In particular, numerous investigators have identified pelvic and/or para-aortic lymph node metastases as the most important influential factor for survival^{29, 30}. In this scenario, our analysis confirmed the literature data that a statistically significant difference can be observed for lymph node metastasis. The FIGO Committee

added IIIC1P and IIIC2P to FIGO 2018 staging criteria by taking into consideration the effect of lymph node metastasis on prognosis³¹. In this trial, the addition of adjuvant chemotherapy improved the DFS and PFS. Despite the proven efficacy of chemotherapy that is delivered concurrently with conventional radiation, the literature data on adjuvant treatments are still confusing and heterogeneous, lacking the results to make more difficult in selecting the appropriate therapy. A larger survival advantage occurs when adjuvant chemotherapy is administered after CCRT^{32–34}. But for those who had adjuvant chemotherapy in chemo-surgical treatment, optimal responders after surgery for IB2-IIB stage required no further treatment. Additional cycles of chemotherapy could be of benefit for patients with suboptimal response and intra-cervical residual disease³⁵.

However, there are some limitations to our study. Firstly, due to the retrospective nature of the study, there is a possibility of lack of some relevant clinical data, and the inclusion of patients treated for over a long period of time, which might in turn affect disease staging as well as supportive therapy. Another major limitation of this study was that the Neo-Ra group all included patients with selective resistance to chemotherapy, leading to worst oncologic outcomes. Some studies have obtained the good response to NACT, making subsequent local treatment (radiation or surgery) more effective³⁶, while bad response of NACT provided evidence after platinum cross-resistance with radiotherapy, inducing the development of radioresistant cellular clones¹⁸.

Conclusion

The results of the present retrospective analysis showed that chemo-surgical approach as a feasible and reliable therapy, resulting in encouraging oncologic outcomes and low side effects when compared to those obtained by standard chemoradiotherapy for IB2, IIA2, IIB stage cervical carcinoma patients.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**(2): 87-108.
2. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. *Lancet* 2017; **389**(10071): 847-60.
3. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002; **20**(4): 966-72.
4. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; **340**(15): 1137-43.
5. Angioli R, Plotti F, Montera R, et al. Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer. *Gynecologic oncology* 2012; **127**(2): 290-6.
6. Park DC, Kim JH, Lew YO, Kim DH, Namkoong SE. Phase II trial of neoadjuvant paclitaxel and cisplatin in uterine cervical cancer. *Gynecologic oncology* 2004; **92**(1): 59-63.
7. Eddy GL, Manetta A, Alvarez RD, Williams L, Creasman WT. Neoadjuvant chemotherapy with vincristine and cisplatin followed by radical hysterectomy and pelvic lymphadenectomy for FIGO

- stage IB bulky cervical cancer: a Gynecologic Oncology Group pilot study. *Gynecologic oncology* 1995; **57**(3): 412-6.
8. Collaboration. NCfLACCM. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. *Eur J Cancer* 2003; **39**: 2470-86.
 9. Narayan S, Sharma N, Kapoor A, et al. Pros and Cons of Adding of Neoadjuvant Chemotherapy to Standard Concurrent Chemoradiotherapy in Cervical Cancer: A Regional Cancer Center Experience. *Journal of obstetrics and gynaecology of India* 2016; **66**(5): 385-90.
 10. de Azevedo CR, Thuler LC, de Mello MJ, Ferreira CG. Neoadjuvant Chemotherapy Followed by Chemoradiation in Cervical Carcinoma: A Review. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2016; **26**(4): 729-36.
 11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer* 2009; **45**(2): 228-47.
 12. Lanciano RM, Martz K, Coia LR, Hanks GE. Tumor and treatment factors improving outcome in stage III-B cervix cancer. *International journal of radiation oncology, biology, physics* 1991; **20**(1): 95-100.
 13. Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. *International journal of radiation oncology, biology, physics* 2013; **87**(1): 111-9.
 14. Tewari K, Cappuccini F, Gambino A, Kohler MF, Pecorelli S, DiSaia PJ. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. *Cancer* 1998; **82**(8): 1529-34.
 15. 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. *Gynecologic oncology* 1997; **67**(1): 61-9.
 16. Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration C. Neoadjuvant chemotherapy for locally advanced cervix cancer. *Cochrane Database Syst Rev* 2004; (2): CD001774.
 17. Buda A, Fossati R, Colombo N, et al. Randomized trial of neoadjuvant chemotherapy comparing paclitaxel, ifosfamide, and cisplatin with ifosfamide and cisplatin followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study. *J Clin Oncol* 2005; **23**(18): 4137-45.
 18. Gonzalez-Martin A, Gonzalez-Cortijo L, Carballo N, et al. The current role of neoadjuvant chemotherapy in the management of cervical carcinoma. *Gynecologic oncology* 2008; **110**(3 Suppl 2): S36-40.
 19. Lissoni AA, Colombo N, Pellegrino A, et al. A phase II, randomized trial of neo-adjuvant chemotherapy comparing a three-drug combination of paclitaxel, ifosfamide, and cisplatin (TIP) versus paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced squamous cell

- cervical carcinoma: the Snap-02 Italian Collaborative Study. *Annals of oncology : official journal of the European Society for Medical Oncology* 2009; **20**(4): 660-5.
20. Sardi JE, di Paola GR, Giaroli A, et al. Results of a phase II trial with neoadjuvant chemotherapy in carcinoma of the cervix uteri. *Gynecologic oncology* 1988; **31**(2): 256-61.
 21. Sardi J, Sananes C, Giaroli A, Maya G, di Paola G. Neoadjuvant chemotherapy in locally advanced carcinoma of the cervix uteri. *Gynecologic oncology* 1990; **38**(3): 486-93.
 22. Sardi J, Sananes C, Giaroli A, et al. Results of a prospective randomized trial with neoadjuvant chemotherapy in stage IB, bulky, squamous carcinoma of the cervix. *Gynecologic oncology* 1993; **49**(2): 156-65.
 23. Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. *J Clin Oncol* 2002; **20**(1): 179-88.
 24. Bloss JD, Lucci JA, 3rd, DiSaia PJ, et al. A phase II trial of neoadjuvant chemotherapy prior to radical hysterectomy and/or radiation therapy in the management of advanced carcinoma of the uterine cervix. *Gynecologic oncology* 1995; **59**(1): 105-10.
 25. Osman M. The role of neoadjuvant chemotherapy in the management of locally advanced cervix cancer: a systematic review. *Oncol Rev* 2014; **8**(2): 250.
 26. Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstetrics and gynecology* 1975; **46**(5): 507-10.
 27. Fuller AF, Jr., Elliott N, Kosloff C, Lewis JL, Jr. Lymph node metastases from carcinoma of the cervix, stages IB and IIA: implications for prognosis and treatment. *Gynecologic oncology* 1982; **13**(2): 165-74.
 28. Mohar A, Frias-Mendivil M. Epidemiology of cervical cancer. *Cancer investigation* 2000; **18**(6): 584-90.
 29. Thar TL, Million RR, Daly JW. Radiation treatment of carcinoma of the cervix. *Seminars in oncology* 1982; **9**(3): 299-311.
 30. Chung CK, Nahhas WA, Stryker JA, Curry SL, Abt AB, Mortel R. Analysis of factors contributing to treatment failures in stages IB and IIA carcinoma of the cervix. *American journal of obstetrics and gynecology* 1980; **138**(5): 550-6.
 31. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2018; **143 Suppl 2**: 22-36.
 32. Chemoradiotherapy for Cervical Cancer Meta-Analysis C. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(35): 5802-12.
 33. Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin

versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(13): 1678-85.

34. Abe A, Furumoto H, Nishimura M, Irahara M, Ikushima H. Adjuvant chemotherapy following concurrent chemoradiotherapy for uterine cervical cancer with lymphadenopathy. *Oncology letters* 2012; **3**(3): 571-6.

35. Landoni F, Sartori E, Maggino T, et al. Is there a role for postoperative treatment in patients with stage Ib2-IIb cervical cancer treated with neo-adjuvant chemotherapy and radical surgery? An Italian multicenter retrospective study. *Gynecologic oncology* 2014; **132**(3): 611-7.

36. Singh RB, Chander S, Mohanti BK, et al. Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma: a pilot study. *Gynecologic oncology* 2013; **129**(1): 124-8.

Tables

Table 1. Patient and tumor characteristics of 388 patients in different treatment groups

Characteristics	Standard group (n=278)	Surgery group (n=65)	Neo-Ra group (n=45)
Age, years	51.9±9.6	48.7±8.4	51.6±9.8
Tumor size, cm	4.6±1.4	4.8±1.1	4.4±1.4
Treatment days	57.6±38.6 ^a	75.3±43.8	62.5±16.8
SCCAg	7.3±11.4 ^a	3.0±7.0	6.9±9.3
CA125	40.6±67.9 ^{a b}	21.2±23.1	21.1±8.0
EQD ₂ , Gy	83.1±13.2 ^a	64.3±13.6 ^c	85.8±15.4
FIGO stage [*]			
ⅡB2	15(5.4)	19(29.2)	1(2.2)
ⅡA2	27(9.7)	12(18.5)	8(17.8)
ⅡB	236(84.9)	34(52.3)	36(80.0)
Tumor histology			
Squamous cell carcinoma	237(85.3)	58(89.2)	41(91.1)
Others	41(14.7)	7(10.8)	4(8.9)
Lymph node metastasis [*]			
Negative	151(54.3)	51(78.5)	37(82.2)
Positive	127(45.7)	14(21.5)	8(17.8)
Parametrial invasion			
Negative	218(78.4)	51(78.5)	30(66.7)
Positive	60(21.6)	14(21.5)	15(33.3)
Adjuvant chemotherapy [*]			
No	203(73.0)	42(64.6)	42(93.3)
Yes	75(27.0)	23(35.4)	3(6.7)
Post-radiotherapy effect			
CR	135(48.6)	62(95.4)	33(73.3)
PR	135(48.6)	3(4.6)	11(24.4)
SD	4(1.4)	0(0)	0(0)

PD	4(1.4)	0(0)	1(2.2)
Recurrence [*]			
No	269(96.8)	64(98.5)	40(88.9)
Yes	9(3.2)	1(1.5)	5(11.1)
Distant metastasis			
No	238(85.6)	60(92.3)	40(88.1)
Yes	40(14.4)	5(7.7)	5(11.9)

^a Standard group vs. Surgery group $P<0.05$

^b Standard group vs. Neo-Ra group $P<0.05$

^c Surgery group vs. Neo-Ra group $P<0.05$

^{*} $P<0.05$

SCCAg = Squamous Cell Carcinoma Antigen

CA125 = carbohydrate antigen 125

FIGO = International Federation of Gynecology and Obstetrics

Table 2. Clinical efficacy, 5-year recurrence and distant metastasis and late toxicity (CTCAEv4.0) rates in patients with LACC in different treatment groups

Characteristics	Standard group (n=278)	Surgery group (n=65)	Neo-Ra group (n=45)
Post-radiotherapy effect			
CR	135(48.6)	62(95.4)	33(73.3)
PR	135(48.6)	3(4.6)	11(24.4)
SD	4(1.4)	0(0)	0(0)
PD	4(1.4)	0(0)	1(2.2)
Recurrence *			
No	269(96.8)	64(98.5)	40(88.9)
Yes	9(3.2)	1(1.5)	5(11.1)
Distant metastasis			
No	238(85.6)	60(92.3)	40(88.1)
Yes	40(14.4)	5(7.7)	5(11.9)
Lower gastrointestinal toxicity			
G0	50(76.9)	37(82.2)	206(74.1)
G1-2	14(21.5)	8(17.8)	68(24.5)
G3	1(1.6)	0(0)	4(1.4)
Genitourinary toxicity			
G0	58(89.2)	43(95.6)	232(83.5)
G1-2	7(10.8)	2(4.4)	45(16.2)
G3	0(0)	0(0)	1(0.3)

* $P < 0.05$

CR = complete response

PR = partial response

SD = stable disease

PD = progressive disease

Table 3. Predictive variables of OS by univariate analysis in patients with LACC

Univariate Analysis of Continuous Variables

	Outcome	Censored	Wals χ^2	<i>P</i>
Age	50.7±10.9	54.4±9.2	0.15	0.703
Treatment days	55.2±26.3	62.2±39.9	0.62	0.433
Tumor size	5.2±1.7	4.5±1.3	13.02	<0.001
SCC	11.2±15.0	5.7±9.5	15.39	<0.001
CA125	46.1±95.3	31.9±50.2	4.37	0.037
EQD ₂	81.6±14.3	80.0±15.5	0.28	0.600

Univariate Analysis of Classified Variables

	Outcome	Censored	χ^2	<i>P</i>
Post-radiotherapy effect			23.78	<0.001
CR	12(5.7)	199(94.3)		
PR+ SD+ PD	46(26.0)	131(74.0)		
Tumor histology			21.63	<0.001
Squamous cell carcinoma	40(11.9)	296(88.1)		
Others	18(34.6)	34(65.4)		
FIGO stage			0.92	0.631
ⅢB2	6(17.1)	29(82.9)		
ⅢA2	5(10.6)	42(89.4)		
ⅢB	47(15.4)	259(84.6)		
Lymph node metastasis			23.39	<0.001
Negative	17(7.1)	222(92.9)		
Positive	41(27.5)	108(72.5)		
Parametrial invasion			0.01	0.926
Negative	46(15.4)	253(84.6)		
Positive	12(13.5)	77(86.5)		
Adjuvant chemotherapy			4.07	0.044
No	50(17.4)	237(82.6)		
Yes	8(7.9)	93(92.1)		
Treatment			14.7	0.001
Standard group	42(15.1)	236(84.9)		
Surgery group	5(7.7)	60(92.3)		
Neo-Ra group	11(24.4)	34(75.6)		

Multivariate analysis

	β	S.E.	Wald χ^2	HR (95%CI)	P
SCC	0.03	0.01	10.13	1.03 [1.01, 1.04]	0.001
Post-radiotherapy effect					
CR				1.00	
PR+ SD+ PD	1.11	0.34	10.62	3.03 [1.56, 5.90]	0.001
Tumor histology					
Squamous cell carcinoma				1.00	
Others	1.46	0.30	24.13	4.32 [2.41, 7.75]	<0.001
Lymph node metastasis					
Negative				1.00	
Positive	0.89	0.31	8.37	2.43 [1.33, 4.43]	0.004

Table 4. Predictive variables of DFS by univariate analysis in patients with LACC

Univariate Analysis of Continuous Variables

	Outcome	Censored	Wals χ^2	P
Age	51.2±10.2	51.3±9.3	0.02	0.879
Treatment days	54.6±28.8	62.5±39.8	1.63	0.201
Tumor size	5.2±1.6	4.5±1.3	16.83	<0.001
SCC	10.0±14.1	5.8±9.6	10.22	0.001
CA125	43.8±54.3	32.0±60.1	3.75	0.053
EQD ₂	82.1±13.8	79.9±15.6	1.14	0.286

Univariate Analysis of Classified Variables

	Outcome	Censored	χ^2	<i>P</i>
Post-radiotherapy effect			36.42	<0.001
CR	13(6.2)	198(93.8)		
PR+ SD+ PD	55(31.1)	122(68.9)		
Tumor histology			11.18	0.001
Squamous cell carcinoma	51(15.2)	285(84.8)		
Others	17(32.7)	35(67.3)		
FIGO stage			1.42	0.492
ⅢB2	6(17.1)	29(82.9)		
ⅢA2	5(10.6)	42(89.4)		
ⅢB	57(18.6)	249(81.4)		
Lymph node metastasis			38.73	<0.001
Negative	18(7.5)	221(92.5)		
Positive	50(33.6)	99(66.4)		
Parametrial invasion			0.06	0.801
Negative	52(17.4)	247(82.6)		
Positive	16(18.0)	73(82.0)		
Adjuvant chemotherapy			9.48	0.002
No	61(21.3)	226(78.7)		
Yes	7(6.9)	94(93.1)		
Treatment			4.4	0.113
Standard group	51(18.3)	227(81.7)		
Surgery group	7(10.8)	58(89.2)		
Neo-Ra group	10(22.2)	35(77.8)		

Multivariate analysis

	β	<i>S.E.</i>	<i>Wald</i> χ^2	<i>HR (95%CI)</i>	<i>P</i>
Tumor size	0.19	0.09	4.92	1.21 [1.02, 1.43]	0.027
Post-radiotherapy effect					
CR				1.00	
PR+ SD+ PD	1.20	0.33	13.54	3.30 [1.75, 6.24]	<0.001
Tumor histology					
Squamous cell carcinoma				1.00	
Others	0.86	0.28	9.10	2.35 [1.35, 4.11]	0.003
Lymph node metastasis					
Negative				1.00	
Positive	0.89	0.31	8.37	2.43 [1.33, 4.43]	0.004
Adjuvant chemotherapy					
No				1.00	
Yes	-0.92	0.40	5.23	0.40 [0.18, 0.88]	0.022

Table 5. Predictive variables of PFS by univariate analysis in patients with LACC

Univariate Analysis of Continuous Variables

	Outcome	Censored	Wals χ^2	<i>P</i>
Age	50.5±10.6	51.5±9.2	0.64	0.425
Treatment days	55.2±28.5	62.5±40.0	1.50	0.220
Tumor size	5.3±1.6	4.4±1.3	21.78	<0.001
SCC	9.9±13.9	5.8±9.6	10.39	0.001
CA125	52.0±92.3	30.0±48.3	10.64	0.001
EQD ₂	82.1±14.3	79.9±15.5	1.26	0.262

Univariate Analysis of Classified Variables

	Outcome	Censored	χ^2	<i>P</i>
Post-radiotherapy effect			34.07	<0.001
CR	15(7.1)	196(92.9)		
PR+ SD+ PD	56(31.4)	121(68.4)		
Tumor histology			12.24	<0.001
Squamous cell carcinoma	53(15.8)	283(84.2)		
Others	18(34.6)	34(65.4)		
FIGO stage			2.17	0.338
ⅢB2	8(22.9)	27(77.1)		
ⅢA2	5(10.6)	42(89.4)		
ⅢB	58(19.0)	248(81.0)		
Lymph node metastasis			39.96	<0.001
Negative	19(7.9)	220(92.1)		
Positive	52(34.9)	97(65.1)		
Parametrial invasion			0.01	0.966
Negative	55(18.4)	244(81.6)		
Positive	16(18.0)	73(82.0)		
Adjuvant chemotherapy			7.27	0.007
No	62(21.6)	225(78.4)		
Yes	9(8.9)	92(91.1)		
Treatment			3.5	0.175
Standard group	53(19.1)	225(80.9)		
Surgery group	8(12.3)	57(87.7)		
Neo-Ra group	10(22.2)	35(77.8)		

Multivariate analysis

	β	<i>S.E.</i>	<i>Wald</i> χ^2	<i>HR (95%CI)</i>	<i>P</i>
Tumor size	0.03	0.01	10.13	1.03 [1.01, 1.04]	0.001
CA125	0.01	0.01	5.60	1.00 [1.00, 1.01]	0.018
Post-radiotherapy effect					
CR				1.00	
PR+ SD+ PD	1.04	0.31	11.37	2.83 [1.55, 5.19]	0.001
Tumor histology					
Squamous cell carcinoma				1.00	
Others	0.99	0.28	12.28	2.69 [1.55, 4.67]	<0.001
Lymph node metastasis					
Negative				1.00	
Positive	1.01	0.29	12.36	2.75 [1.56, 4.83]	<0.001
Adjuvant chemotherapy					
No				1.00	
Yes	-0.80	0.38	4.52	0.45 [0.22, 0.94]	0.034

Figures

Figure 1

Kaplan-Meier estimates of the survival of patients with LACC treated by neoadjuvant chemotherapy followed by radical hysterectomy/chemoradiotherapy and radical chemoradiotherapy. (A, B, C) OS, DFS and PFS in patients with stage IB2, IIA2, IIB LACC. (D, E, F) OS, DFS and PFS in patients with stage IB2, IIA2 LACC. (G, H, I) OS, DFS and PFS in patients with stage IIB LACC.