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Clinical effects of comprehensive treatments for FIGO Stage IIB adenocarcinoma/adenosquamous carcinoma of the cervix

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Summary

To evaluate the clinical effects of comprehensive treatments for the FIGO Stage IIB adenocarcinoma (AC) / adenosquamous carcinoma (ASC) of cervix of patients from four institutions between 2000 and 2009 with Stage IIB AC/ASC of cervix that were included and divided into two groups. Both groups received initial cisplatin-based neoadjuvant chemotherapy (NACT) treatment. Radical surgery (RS, n=70) group subsequently underwent surgery followed by adjuvant chemo-radiotherapy, while the radiotherapy (RT, n=70) group received the standard concurrent chemo-radiotherapy alone. Differences in outcomes were compared. Multivariate analysis was used. The overall survival (OS) was 74.3% *vs*. 52.9% ($p = 0.002$) and progression free survival (PFS) rates were 64.3% *vs*. 44.3 %($p = 0.007$) in each group. Complications in the RS group were acceptable. Presence of lymph node metastasis was a significant factor in determining OS. The authors conclude that NACT combined with RS followed by adjuvant chemo-radiotherapy is a promising treatment option for Stage IIB AC/ASC of the cervix.

Key words: Cervical cancer; Concurrent chemo-radiation; FIGO stage IIB; Adenocarcinoma/adenosquamous carcinoma; Radical surgery; Prognostic factors.

Introduction

Cervical cancer is the most common gynecological malignancy in the world. Historically, 90% to 95% of cervical cancer was squamous cell carcinoma (SCC) variety. However, in the past few years, the incidence of adenocarcinoma (AC) has increased approaching 20% [1]. Since no difference was found in epidemiology, treatment, modality or outcome, adenosquamous carcinoma (ASC) could be regarded as one subtype of AC [2].

The standard treatment for International Federation of Gynecology and Obstetrics (FIGO) Stage IIB cervical cancer suggested by National Comprehensive Cancer Network (NCCN) clinical practice guidelines is concurrent chemoradiation [3] while radical hysterectomy plus adjuvant radiotherapy has been recommended in Germany (the German Arbeitsgemeinschaft Gynaekologische Onkologie guidelines, GOG) [4] and Japan [5, 6]. A GOG study demonstrated that there were no statistically differences regarding the recurrence-free interval among histological types for Stage IB cervical cancer patients [7]. Therefore, NCCN guidelines also suggested that the AC/ASC were administrated to receive a similar treatment to SCC [3]. However, recent studies reported that the AC patients of Stage II suffered worse prognosis compared with SCC patients [2,5]. The five-year survival rate of Stage IIB cervical AC is less than 50% compared with 60-70% for SCC [8]. AC had shown more sensitive to chemotherapy than to radiotherapy, which suggested clinical tailored treatment strategies [9]. In addition, Mabuchi *et al.* showed that carboplatin-paclitaxel had significantly higher activity in patients with AC histology [10, 11].

In recent years, neoadjuvant chemotherapy (NACT) followed by radical hysterectomy was suggested to be a treatment trend for the locally advanced cervical cancer. Minig *et al.* reported that it was an effective option with FIGO Stage IIB cervical cancer patients [12]. NACT cannot improve the five-year OS. The purpose of NACT was to reduce the lesion size for achieving radical operability, and to reduce the number of patients who require postoperative radiotherapy [13]. However some other studies found that without NACT radical surgery and radical radiotherapy showed the same progression free survival (PFS) and overall survival (OS), which was not statistically significant

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[14]. However, more than 90% of the cases in these studies of FIGO Stage IIB cervical cancer were SCC.

To the present authors' knowledge, there is no international agreement on how AC/ASC cervical cancer patients with Stage IIB should be treated currently. Most studies of Stage IIB treated with NACT followed by radical surgery were based on SCC [15, 16]. Due to the worse prognosis and higher sensitivity to chemotherapy of AC, the present study focused on the clinical effects on AC/ASC cervical cancer patients from Chinese population with FIGO Stage IIB that underwent cisplatin-based NACT, followed by radical hysterectomy versus followed by concurrent chemoradiotherapy.

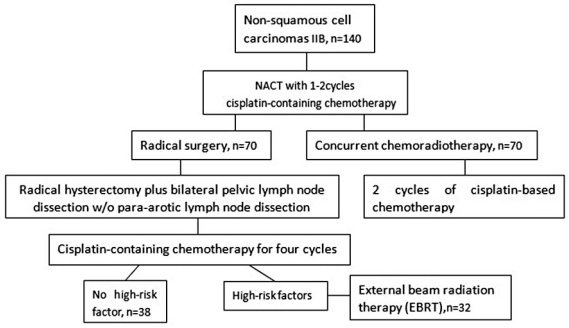

Figure 1. — Therapeutic strategy in this study.

Materials and Methods

All patients with FIGO Stage IIB AC/ASC of the cervix that underwent treatment in four medical institutions (Hunan Cancer Hospital, Jingzhou People's Hospital, The First Hospital of Huaihua, and The First Hospital of Loudi)) between March 2000 and December 2009 were enrolled in this retrospective study. Eligibility criteria were as follows: a primary pathology-confirmed cervical cancers of AC and ASC carcinoma, Stage IIB defined by FIGO guidelines and based on clinical criteria (determined by the assessments of three senior gynecologists; positive parametrial invasion proven by CT/MRI evidence), no evidence of other cancers, GOG performance status ≤ 3, adequate bone marrow, renal, and hepatic function, and absence of physical diseases that cannot tolerate chemotherapy. All patients had undergone pre-treatment clinical examination, which included: ultrasound examination, and CT or MRI of the chest/abdomen to evaluate lymph node involvement. Data was collected from patient medical records. All signed informed consents were approved by the Ethics Committee of the Hunan Cancer Hospital and the other three institutions.

The patients were divided into two groups according to the two different treatments modalities that they received (Figure1). Initially, all patients received cisplatin-containing chemotherapy intravenous infusion for one or two cycles. Two weeks after the last chemotherapy, patients were evaluated by gynecologic examination and received two different treatments.

Patients in the RS group were underwent a type III radical hysterectomy with bilateral pelvic lymph node dissection. A type III radical hysterectomy is defined as a resection of the uterus with a margin of 1/4 to 1/3 of the upper vagina, cardinal ligaments removal from the pelvic sidewall, and detachment of the uterosacral ligaments from their sacral origin. Patients with positive radiologic imaging or positive para-aortic /common iliac lymph nodes underwent para-aortic lymph node dissection. Postoperative therapy was tailored based on the pathologic high-risk factors (the authors defined high-risk factors as lymph node metastasis, parametrial invasion, and positive surgical margin). Patients without high-risk factors were administered cisplatin-based chemotherapy at 21 days intervals for four cycles. In addition, those patients with high-risk factors received pelvic radiotherapy of 42-46 Gy four weeks after their last cycle of chemotherapy. External beam radiation therapy (EBRT) of 42-46 Gy after radical surgery was delivered to the pelvis by anteroposterior and postero-anterior parallel ports in 21-23 fractions of 2.0 Gy with a 6-MV proton (five days /week). The pelvic field extended from the upper margin of L5 to the midpoint of the obturator foramen vertically, and 1.5 cm or 2 cm beyond the lateral margins of the bony pelvic wall horizontally. Intensity-modulated radiation therapy was not permitted in this study. Patients received concurrent chemotherapy (cisplatin alone 40 mg/m^2) during the time of EBRT. The extended-field radiotherapy was administrated if para-

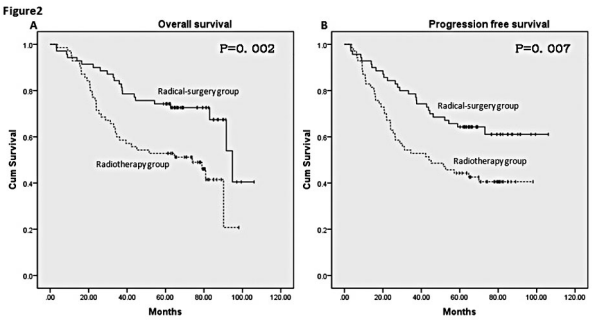

Figure 2. — Kaplan-Meier overall survival (A) curves and progression free survival (B) curves for the radical-surgery (RS) group and radiotherapy (RT) group. The solid line represents RS. The dashed line represents RT.

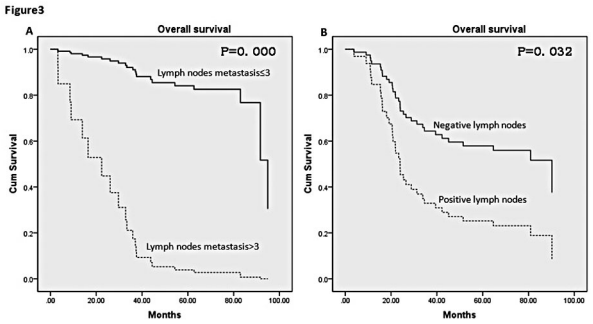

Figure 3. — Overall survival curves of two different lymph nodes metastasis in radical-surgery group (A) and radiotherapy group (B). The solid line in A represents lymph nodes metastasis ≤3. The dashed line represents lymph nodes metastasis > 3. The solid line in B represents negative lymph nodes by imaging. The dashed line represents positive lymph nodes by imaging.

Table1. — *Patient characteristics.*

Characteristic	Radical surgery group n=70		Radiotherapy group n=70		*p*
	No.	%	No.	%	
Age, years					0.081
Median	45		51		
Range	30-68		32-76		
Differentiated degree					0.101
High	19	27.1	6	8.6	
Moderate	37	52.9	51	72.8	
Poorly	14	20.0	13	18.6	
Histology					1.000
Adenocarcinoma	61	87.1	61	87.1	
Adenosquamous carcinoma	9	12.9	9	12.9	
Lesion size					
< 4cm	12	17.1	16	22.9	0.400
≥ 4cm	58	82.9	54	77.1	
Pelvic lymph node (radiological evidence)					
Positive	12	17.1	14	20.0	
Negative	58	82.9	56	80.0	0.665

aortic or common iliac lymph nodes were positive.

Standard concurrent chemoradiation for the patients in group RT was described as previously [17]. Briefly, external-beam radiotherapy was delivered using linear accelerator with a 6-MeV photons and administered before intracavitary iridium exposure. The total dose of external-beam radiotherapy was 46-48 Gy at point B in a two-field arrangement, given in a daily dose of 2 Gy, five times a week for four to five consecutive weeks. The target volumes were standard and designed to include the primary tumor and uterus, parametria, vagina, and the local regional lymph nodes. The superior border was placed at the L4-5 interspace. The inferior border was placed at the bottom of the obturator foramen or lower, depending on the extent of vaginal involvement of the tumor. The lateral margin was placed 2 cm lateral to the bony pelvis on each side. If patients had positive para-aortic lymph nodes by imaging, extended-field radiotherapy was administered. Central shielding was performed to protect against over-irradiation of centrally located pelvic tissue after the dose of 24 Gy had been delivered. Intracavitary application of iridium at a dose of 6 Gy was performed twice per week. The first iridium application was scheduled after the completion of 24 Gy external-beam irradiation. External-beam radiotherapy and intracavitary brachyradiotherapy could not be performed at the same day. The radiation scheme aimed at delivering 42 Gy to point A and 46-48 Gy to point B [18]. Cisplatin (40 mg/m^2) was administered for five weeks during external radiation, beginning on the first day of radiation. Patients in RT also underwent two cycles of cisplatin-based chemotherapy after primary concurrent chemoradiation.

Chemotherapeutic regimens used included: TP (paclitaxel 135 mg/m^2, day 1, cisplatin: 70mg/m^2, day 2), TC (paclitaxel 135 mg/m^2, day1; carboplatin AUC4, day 2), CF (cisplatin: 70 mg/m^2 day1; fluorourcil: 600 mg/ m^2, day 2).

During treatment, patients were evaluated before each cycle of chemotherapy or weekly in the period of radiotherapy. After treatment, all patients were evaluated every three months for the first year, every six months for the second year, and annually thereafter. Gynecologic examination, chest X-ray, and ultrasound examination were obtained at each follow up visit. CT/MRI or PET-CT was also obtained if necessary. The median follow-up was 85.16 (range: 60-129) months. The acute or late complications associated with chemo-radiotherapy were defined according to NCIC common toxicity criteria.

Statistical Package for Social Scientists (SPSS, version 20.0) was used in all statistical analyses. The characteristics of both groups were assessed using χ^2 test or Mann-Whitney U test. Survival curves were estimated by the Kaplan-Meier method and were compared using log-rank testing. Multivariate analysis was computed using the Cox proportional hazard model to determine the effects of prognostic factors. A $p < 0.05$ was considered a statistically significant difference.

Results

One hundred forty patients were enrolled in this retrospective study; 70 patients were in the in the RS group and 70 patients were in the RT group (Figure 1). The median ages of these two groups were 45 (30-68) years and 51 (32-76) years, respectively. The histological types included AC and ASC. Fifty-eight (82.9%) patients in the RS group and 54 (77.1%) patients in the RT group had large lesion size (diameter ≥ 4 cm). The characteristics of both groups are summarized in Table 1; there were no statistically significant differences in the characteristics between the two groups.

Two weeks after the NACT, most patients in these two groups had a decrease in the size of the lesion or an improvement in parametrial condition. In the RS group, no patients had positive surgical margins by pathology, but 27 patients had positive parametrial invasion. Thirty-eight (54.3%) patients without high-risk factors received only four cycles of adjuvant cisplatin- containing chemotherapy while 32 (45.7%) patients with high-risk factors received four cycles of adjuvant cisplatin-containing chemotherapy followed by EBRT in the RS group. One patient in the RT group and two patients in the RS group received para-aor-

Table 2. — *Multivariate analysis of prognostic factors in two groups.*

Characteristic	Radical-surgery group		Radiotherapy group	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, years	0.680(0.262-1.762)	0.427	0.961 (0.440-2.098)	0.920
Pathology	1.832(0.433-7.748)	0.411	1.230(0.416-3.642)	0.708
Differentiated degree	1.060(0.522-2.150)	0.873	0.783(0.394-1.555)	0.485
Lesion size	0.518(0.157-1.715)	0.282	1.201(0.492-2.929)	0.687
Lymph node metastasis	18.755(6.436-54.655)	0.000	2.523(1.085-5.864)	0.032

Table 3. — *Side effects in two groups.*

	Radical-surgery group		Radiotherapy group
	n=70		n=70
Operating time, minutes	190(110-365)		/
Blood loss, ml	400(100-1400)		/
Blood transfusion	17/70(24.3%)		2/70(2.86%)
Urinary retention	7/70(10.0%)		/
Vaginal stump unhealing	1/70(1.43%)		/
Small bowel obstruction	1/70(1.43%)		/
Acute complication			
Hematology		$p = 0.000$	
Grade 0	16/70(22.86%)		38/70(54.29%)
Grade 1	14/70(20.00%)		21/70(30.00%)
Grade 2	20/70(28.57%)		11/70(15.71%)
Grade 3	19/70(27.15%)		/
Grade 4	1/70(1.43%)		/
Nausea and vomiting		$p = 0.000$	
Grade 0	49/70(70.00%)		68/70(97.14%)
Grade 1	18/70(25.71%)		2/70(2.86%)
Grade 2	3/70(4.29%)		/
Diarrhea		$p = 0.555$	
Grade 0	68/70(97.14%)		69/70(98.57%)
Grade 1	1/70(1.43%)		1/70(1.43%)
Grade 2	1/70(1.43%)		/
Late complication			
Skin abnormalities	/		6/70(8.57%)
Edema	1/70(1.43%)		8/70(11.43%)
Radiation proctitis	/		6/70(8.57%)
Radiation cystitis	/		3/70(4.29%)
Cost	$8887.78		$5353.69

tic lymph node radiotherapy.

At the final endpoint of the study, 48 (68.6%) patients in the RS group and 32 (45.7%) patients in the RT group were alive. Five-year OS were 74.3% in RS group and 52.9% in RT group. Kaplan-Meier analysis revealed the patients in the RS group had significantly better OS when compared with those in the RT group (log-rank test, $p = 0.002$) (Figure 2A). Five-year PFS were 64.3% in RS group and 44.3% in RT group, a significant difference (log-rank test, $p = 0.007$) (Figure 2B). During the follow-up period, 26 (37.1%) patients and 41 (58.6%) patients in each group suffered tumor recurrence. The sites of recurrence included pelvis, vagina, lung, bone, abdomen, supraclavicular lymph node, thymus, etc. There were more patients in RT group than in RS group suffering distant recurrences (23/70 *vs*. 7/70), which was statistically significant ($p = 0.02$).

Prognostic factors (age, pathology, differentiated degree, lesion size, and lymph node metastasis) were evaluated in multivariate analysis using Cox regression hazard model. The involvement of > 3 lymph nodes metastases was associated with poor OS in radical-surgery group (Table 2, Figure 3A). Similarly, positive lymph node proven by radiological imaging were confirmed to be a significant prognostic factor and presented worse OS in the radiotherapy group (Table 2, Figure 3B).

As shown in Table 3, the median operating time was 190 (range 110-365) minutes, and the median blood loss was 400 (range 100-1400) ml. Seventeen of 70 patients (24.3%) and two of 70 patients (2.86%) received blood transfusion. In the RS group, there were seven patients developing post-

operative urinary retention, one patient experiencing poor vaginal stump healing, and one patient suffering from small bowel obstruction during the postoperative recovery period. Known radio-chemotherapy toxicities include myelosuppression, gastrointestinal reactions, liver and renal injuries, heart toxicity, neurotoxicity, etc. The acute chemoradiation complications (especially hematology, nausea, and vomiting) occurred more frequently in group RS (p = 0.000). However, the frequency of late complications was higher in group RT. Six patients suffered radiation proctitis and three patients experienced radiation cystitis in the radiotherapy group. All complications were tolerated in both groups. There was no treatment-related death in both groups. Only one patient in group RS had grade IV toxicity in hematology, which delayed the treatment. The mean cost of treatment in each group was $8887.78 (RS) and $5353.69 (RT).

Discussion

The present study focused on a NACT-based therapeutic strategy. Due to the NACT, AC/ASC of cervix with FIGO Stage IIB could achieve the effect of down-staging. The lesion size decreased and the extent of parametrial invasion improved, which allowed for operable radical surgery. In both groups, it had been confirmed by the assessments of three senior gynecologists. Although all patients in RS group had positive parametrial invasion proven by CT/MRI evidence, due to the NACT they received, only 27 of them had positive parametrium by pathology after surgery; 38/70 patients had no high-risk factors and received four cycles of cisplatin-based chemotherapy after operation without further radiotherapy. It showed great benefits for patients. Although the intensity-modulated radiation therapy (IMRT) can minimize the dose to the critical normal structures, patients could not completely avoid suffering complications of radiotherapy and sexual functions loss, especially for young patients.

AC/ASC types cervical cancers have a worse prognosis, often because they are diagnosed at later stages, with deep muscle infiltration, parametrial invasion, and lymphovascular space invasion [19, 20]. In recent studies, lymph node metastasis was recognized as a significant prognostic factor [21, 22], which is similar to the present outcome. Positive lymph node diagnosed by pathology or imaging indicated poor survival in both groups and the number of positive lymph node > 3 showed worse survival rate in RS group. The present authors saw that postoperative lymph node metastasis could be a major significant prognostic factor.

In this retrospective study, RS group had significant better five-year OS and PFS rates compared with RT group. Although more acute complications occurred, all the side effects were either self-limited or cured by regular treatments and the cost was affordable. The most important was that five-year OS and PFS for AC/ASC Stage IIB cervical cancer that improved more significantly by this combined treatment. AC/ASC may be less sensitive to radiotherapy than SCC [23]. Patients with AC/ASC undergoing adjuvant radiotherapy recurred in pelvic cavity significantly more frequently compared with SCC [6]. It is not clear whether cisplatin-based concurrent chemoradiation has the same effect on AC/ASC as on SCC, but a study showed that AC/ASC patients under radiotherapy had a higher distant metastasis rate than SCC patients in the high-risk groups, even though more concurrent chemoradiation was given for the former cohort [24]. The present data indicated group RS had a better five-year OS due to the lower incidence of distant recurrences (7/70 *vs*. 23/70), which was improved by effective chemotherapy. At the same time, radical surgery with EBRT was effective in controlling the local recurrence. Due to the fibrosis after radiotherapy, the effect of adjuvant chemotherapy may be decreased in RT group, and because of the suppression of bone marrow caused by radiotherapy, most patients receiving concurrent chemoradiation could not tolerate more than two cycles of adjuvant chemotherapy. However radiotherapy cannot be substituted. It provided benefits for the elderly, those with poor physical condition, and those intolerant to chemotherapy. Moreover, intracavitary brachytherapy was good for decreasing lesion size; extended-field RT was used to some local metastasis [25].

Acknowledgments

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References

[1] Smith H.O., Tiffany M.F., Qualls C.R., Key C.R.: "The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study". *Gynecol. Oncol.*, 2000, *78*, 97.

[2] Chen J.L., Huang C.Y., Huang Y.S., Chen R.J., Wang C.W., Chen Y.H., *et al.*: "Differential clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma/adenosquamous carcinoma and squamous cell carcinoma of cervix treated with definitive radiotherapy". *Acta Obstet. Gynecol. Scand.*, 2014, *93*, 661.

[3] Koh W.J., Greer B.E., Abu-Rustum N.R., Apte S.M., Campos S.M., Chan J., *et al.*: "Cervical cancer". *J. Natl. Compr. Canc. Netw.*, 2013, *11*, 320.

[4] Chai Y., Wang T., Wang J., Yang Y., Gao Y., Gao J., *et al.*: "Radical hysterectomy with adjuvant radiotherapy versus radical radiotherapy for FIGO stage IIB cervical cancer". *BMC Cancer*, 2014, *14*, 63.

[5] Kasamatsu T., Onda T., Sawada M., Kato T., Ikeda S.: "Radical hysterectomy for FIGO stage IIB cervical cancer: clinicopathological characteristics and prognostic evaluation". *Gynecol. Oncol.*, 2009, *114*, 69.

[6] Shimada M., Nishimura R., Nogawa T., Hatae M., Takehara K., Yamada H., *et al.*: "Comparison of the outcome between cervical adenocarcinoma and squamous cell carcinoma patients with adjuvant radiotherapy following radical surgery: SGSG/TGCU Intergroup Surveillance". *Mol. Clin. Oncol.*, 2013, *1*, 780

[7] Look K.Y., Brunetto V.L., Clarke-Pearson D.L., Averette H.E., Major F.J., Alvarez R.D., *et al.*: "An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 1996, *63*, 304.
[8] Irie T., Kigawa J., Minagawa Y., Itamochi H., Sato S., Akeshima R., *et al.*: "Prognosis and clinicopathological characteristics of Ib-IIb adenocarcinoma of the uterine cervix in patients who have had radical hysterectomy". *Eur. J. Surg. Oncol.*, 2000, *26*, 464.
[9] Rose P.G., Java J.J., Whitney C.W., Stehman F.B., Lanciano R., Thomas G.M.: "Locally advanced adenocarcinoma and adenosquamous carcinomas of the cervix compared to squamous cell carcinomas of the cervix in gynecologic oncology group trials of cisplatin-based chemoradiation". *Gynecol. Oncol.*, 2014, *135*, 208.
[10] Mabuchi S., Morishige K., Isohashi F., Yoshioka Y., Takeda T., Yamamoto T., *et al.*: "Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors". *Gynecol. Oncol.*, 2009, *115*, 482.
[11] Mabuchi S., Morishige K., Fujita M., Tsutsui T., Sakata M., Enomoto T., *et al.*: "The activity of carboplatin and paclitaxel for recurrent cervical cancer after definitive radiotherapy". *Gynecol. Oncol.*, 2009, *113*, 200.
[12] Minig L., Colombo N., Zanagnolo V., Landoni F., Bocciolone L., Cardenas-Rebollo J.M., *et al.*: "Platinum-based neoadjuvant chemotherapy followed by radical surgery for cervical carcinoma international federation of gynecology and obstetrics stage IB2-IIB". *Int. J. Gynecol. Cancer*, 2013, *23*, 1647.
[13] Bogani G., Cromi A., Serati M., Di Naro E., Casarin J., Marconi N., *et al.*: "A prospective case-control study on the impact of neoadjuvant chemotherapy on surgery-related outcomes of laparoscopic radical hysterectomy". *Anticancer Res.*, 2014, *34*, 5703.
[14] Mabuchi S., Okazawa M., Isohashi F., Matsuo K., Ohta Y., Suzuki O., *et al.*: "Radical hysterectomy with adjuvant radiotherapy versus definitive radiotherapy alone for FIGO stage IIB cervical cancer". *Gynecol. Oncol.*, 2011, *123*, 241.
[15] Katsumata N., Yoshikawa H., Kobayashi H., Saito T., Kuzuya K., Nakanishi T., *et al.*: "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.
[16] Choi Y.S., Sin J.I., Kim J.H., Ye G.W., Shin I.H., Lee T.S.: "Survival benefits of neoadjuvant chemotherapy followed by radical surgery versus radiotherapy in locally advanced chemoresistant cervical cancer". J. Korean Med. Sci., 2006, *21*, 683.
[17] Tang J., Tang Y., Yang J., Huang S.: "Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma". *Gynecol. Oncol.*, 2012, *125*, 297.
[18] Morris M., Eifel P.J., Lu J., Grigsby P.W., Levenback C., Stevens R.E., *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*, 1137.
[19] Lee Y.Y., Choi C.H., Kim T.J., Lee J.W., Kim B.G., Lee J.H., *et al.*: "A comparison of pure adenocarcinoma and squamous cell carcinoma of the cervix after radical hysterectomy in stage IB-IIA". *Gynecol. Oncol.*, 2011, *120*, 439.
[20] Farley J.H., Hickey K.W., Carlson J.W., Rose G.S., Kost E.R., Harrison T.A.: "Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma". *Cancer*, 2003, *97*, 2196.
[21] Tsubamoto H., Yamamoto S., Kanazawa R., Sakane R., Honda O., Kobayashi K., *et al.*: "Prognostic factors for locally advanced cervical cancer treated with neoadjuvant intravenous and transuterine arterial chemotherapy followed by radical hysterectomy". *Int. J. Gynecol. Cancer*, 2013, *23*, 1470.
[22] Intaraphet S., Kasatpibal N., Sogaard M., Khunamornpong S., Patumanond J., Chandacham A., *et al.*: "Histological type-specific prognostic factors of cervical small cell neuroendocrine carcinoma, adenocarcinoma, and squamous cell carcinoma". *Onco. Targets Ther.*, 2014, *7*, 1205.
[23] Niibe Y., Kenjo M., Onishi H., Ogawa Y., Kazumoto T., Ogino I., *et al.*: "High-dose-rate intracavitary brachytherapy combined with external beam radiotherapy for stage IIIb adenocarcinoma of the uterine cervix in Japan: a multi-institutional study of Japanese Society of Therapeutic Radiology and Oncology 2006-2007 (study of JASTRO 2006-2007)". *Jpn. J. Clin. Oncol.*, 2010, *40*, 795.
[24] Huang Y.T., Wang C.C., Tsai C.S., Lai C.H., Chang T.C., Chou H.H., *et al.*: "Clinical behaviors and outcomes for adenocarcinoma or adenosquamous carcinoma of cervix treated by radical hysterectomy and adjuvant radiotherapy or chemoradiotherapy". *Int. J. Radiat. Oncol. Biol. Phys*., 2012, *84*, 420.
[25] Vargo J.A., Boisen M.M., Comerci J.T., Kim H., Houser C.J., Sukumvanich P., *et al.*: "Neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy for locally advanced endometrial cancer clinically extending to the cervix or parametria". *Gynecol. Oncol.*, 2014, *135*, 190.

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