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Clinical efficacy analysis of preoperative neoadjuvant chemotherapy with high-dose dense paclitaxel plus cisplatin in Stages IB2, IIA2, IIB cervical cancer in Iran

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Summary

Purpose of investigation: In Iran, the authors use neoadjuvant chemotherapy (NACT) prior to surgery in cervical cancer due to limited access to the radiotherapy and very prolonged waiting time in accession to radiotherapy. The study was done to analyze the efficacy of the NACT with high dose-dense paclitaxel and cisplatin before radical surgery on cure rate, survival rate, and the progression of free survival rate of bulky tumor of cervical cancer in Stages IB2, IId A2, and IIB. *Materials and Methods:* Fifty-two patients with cervical cancer in Stages Ib2, IIA2, and IIB were selected, and responding patients to chemotherapy were scheduled to undergo radical hysterectomy and bilateral pelvic lymphadenectomy with or without para-aortic lymphadenectomy. *Results:* Fifty out of 52 patients with a median age of 50 years were evaluable for clinical response. Thirty-two patients (64%) responded to the NACT including six (12%) with a complete clinical response. There was no statistical relationship between clinical response, tumor stage and size, and parametrical involvement, however, patients with higher grade of tumor, adenocarcinoma or tumor in upper 2/3 of vagina showed a higher probability of no response to chemotherapy. Downstaging after NACT in all stages was statistically significant regarding pathologic findings and clinical response ($p = 0.002$). Five-year survival was 88% and factors affecting survival and disease-free survival were pathological response and tumor site based on cox-regression analysis. Overall recurrence rate was 20% and tumor size was the only significant relevant factor for recurrence ($p = 0.017$). *Conclusion:* Combined regimen of chemotherapy in locally advanced cervical cancer proved to be valuable and efficacious without any late complications.

Key words: Cervical cancer; Neoadjuvant chemotherapy; Radical surgery.

Introduction

The fourth common cancer in women is uterine cervical cancer with an estimated 528,000 new cases and 266,000 deaths in 2012. Over 85% of the global burden occurs in developing countries. On the other hand, more than 80% of women with cervical cancers at advanced stages are in these developing countries [1].

According to the International Federation of Gynecology & Obstetrics in 2009 (FIGO 2009) [2], bulky uterine cervical cancers in Stages IB2 and IIA2 are associated with deep stromal invasion and high lymph node involvement (35%-80%). Prognosis of these bulky stages are similar to Stage IIB cervical cancer and the five-year survival rates are 31%-48% [3] Therefore, different new optional treatments are investigated to increase the survival rate. After publication of five randomized clinical trials in 1999, the National Cancer Institute (NCI) approved concurrent cisplatin-based chemoradiation as a standard treatment in locally advanced cervical cancer with 15% increasing 5SR and decreasing 30%-50% death risk [4-7].

Due to limited technological development and difficulty in accessing radiotherapy in parts of Europe, Asia, and South America, neoadjuvant chemotherapy (NACT) before surgery is administered for locally advanced cervical cancer instead of prescribing concurrent chemoradiation.

The goal of NACT before surgery is to decrease the tumor size and increase the operability rate of tumor. This issue is challenging with many unanswered questions and especially with no standard drug regimen. There is no available data showing that NACT can be as standard as concurrent chemoradiotherapy in locally advanced cervical cancer. Currently two ongoing studies are being performed to compare these treatments: (EORTC 55994) and a study sponsored by the Department of Atomic Energy of India.

Somehow, in Iran, NACT has to be used prior to surgery for the following reasons: 1) limited access to the radiotherapy, 2) very prolonged waiting time in accession to radiotherapy, 3) preventing therapeutic delay, and 4) saving

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the patients.

This trial was performed to analyze the clinical efficacy of this new modality of treatment on cure rate, survival rate, and the progression of free survival rate of bulky tumor of cervical cancer in Stages IB2, IIA2, and IIB.

Materials and Methods

The authors studied 52 patients with locally advanced cervical cancer (clinical Stage Ib2, IIA2, and IIB). They were consecutively admitted at the Department of Gynecology-Oncology of the University of Tehran-Iran in Vali-Asr hospital from March 2008 to September 2013, prospectively. All patients consented prior to participating. All patients were sent for chemoradiotherapy primarily. They volunteered for the research if their schedule was too long, Cisplatin chemotherapy was free of charge but paclitaxel was charged by the patients. All patients who responded to the chemotherapy were scheduled to undergo radical hysterectomy and bilateral pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Cisplatin and taxol were provided to patients undergoing chemotherapy, from Tehran Medical University science pharmacy and with collaboration of social security insurance, while Ethical approval was provided by the Institutional Research Ethics Committee in accordance with the ethical standards of Helsinki Declaration.

Inclusion criteria

1) Invasive squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix; 2 Stage IB2, IIA2, and IIB according to the Federation of Gynecology and Obstetrics (FIGO); 3) age below 80 years; 4 Performance status < 2 according to the World Health Organization (WHO) criteria; 5) normal heart, hematological and respiratory, kidney functions; 6) absence of secondary malignancies; and 7) written informed consent by the patients.

Exclusion criteria

1) Prior therapy with cytotoxic drugs; 2) abnormal liver (transaminases > 1.5× upper limit of normal) and kidney (creatinine clearance < 60 ml/minute and/or serum creatinine > 1.5 mg/100 ml) functions; 3) severe infection, other systemic diseases or mental illness, prior to hysterectomy; 4) pregnancy; 5) refusal to participate in the study; and 6) abnormal bone marrow function (WBC < 3,000/ml and platelets < 100,000/µl, HB < 90 g/L).

Board-certified gynecologic oncologists examined all patients.Transvaginal ultrasonography, thoracic radiography, intravenous pyelography, proctosigmoidoscopy, magnetic resonance imaging, and computed tomography were performed appropriately, and then clinical staging was determined according to the FIGO 2009 criteria.

All enrolled patients received three cycles of NACT every ten days according to the scheme cisplatin 80 mg/m^2 and paclitaxel 60 mg/m^2. If hematologic or extra-hematologic toxicity > G3 occurred, cycle was delayed from one to two weeks and/or dosage was reduced by 25%. Chemotherapy-induced toxicity was determined according to the Modified from Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Evaluation of response to NACT

Tumor extension was assessed clinically and by MRI after three courses, and all patients considered operable underwent radical hysterectomy (type II-III) and pelvic lymphadenectomy within three or four weeks after finishing the third cycle. Para-aortic lymphadenectomy was optional. Patients with inoperable tumors (progression or stable disease groups) were offered concurrent chemoradiotherapy. Clinical responses were determined according to the RECIST criteria [8]. Complete response (CR): vanishing of all target lesions. Any pathological lymph nodes (whether target or non-target) reduced in short axis to < ten mm. Partial response (PR): at least a 30% reduction in the sum of diameters of target lesions; the baseline sum diameters were taken as reference. Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions; the smallest sum on study (this includes the baseline sum if that is the smallest on study) was taken as reference. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least five mm. (Note: the appearance of one or more new lesions was also considered as progression). Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; the smallest sum diameters while on study were taken as reference [8]. Generally, the FDA has defined objective response rate (ORR) as the sum of partial responses plus complete responses.

Evaluation of pathologic response

Pathological evaluation of tumor was done by a pathologist who was blinded to the treatment received by the patient. The entire cervix was included for analysis and the response was defined as follows: CR was defined as the complete vanishing of tumor in the cervix with negative lymph nodes complete pathologic response (CPR); optimal PR was defined as a persistent residual disease with less than three-mm stromal invasion including in situ carcinoma on the surgical specimen (PR1); and suboptimal response consisted of persistent residual disease with more than three mm stromal invasion on the surgical specimen (PR2). The three-mm threshold, used to set the lowest limit of the optimal response (OR) category, was chosen because it showed the maximal extension of FIGO Stage IA1 cervical tumor, which is cured after local resection, and the prognosis of it is good [9]. Then optimal pathological response was considered CPR+PR1.

Women with positive lymph nodes, parametrial involvement, cut-through or suboptimal pathologic response or optimal response but still with positive nodes underwent further treatment (radiochemotherapy). Patients who achieved a CR or PR received no more chemotherapy.

Follow-up after treatment

All patients followed every three months until the end of the second year and then every six months until the last follow-up.

Statistical analysis

Survival was calculated from the date of study entry to the date of death or the last visit. Disease-free survival was calculated from the date of surgery to the date of relapse or the last visit.

Overall survival was estimated by the Kaplan-Meier method from the date of diagnosis to the date of death or the last follow-up visit. The influence of variables on survival was analyzed by the Cox regression method. All statistical tests were two-sided with statistical significance defined as $p < 0.05$. Analysis was performed by the SPSS-19 software.

Results

Clinico-pathologic criteria

Fifty patients (median age 50 years, range 30-80) out of 52 enrolled for evaluation of clinical response. Two patients were excluded from the analysis. One patient had severe allergy to paclitaxel and was referred to the radiotherapy center to receive chemoradiotherapy. Another patient dis-

Table 1. — *Clinico-pathologic data of patients.*

	Number	Percentage
Mean parity (range)	4.21 (0-10)	
The first symptom:		
AUB[1]	25	48%
PMB[2]	18	35%
PCB[3]	4	8%
Vaginal discharge	3	6%
Pelvic pain	2	4%
Pathology:		
SCC	48	92%
Adenocarcinoma	4	8%
Grade of tumor differentiation:		
Grade I	18	34%
Grade II	20	39%
Grade III	14	27%
Mean tumor size (exam), range	5.09 cm (2-8 cm)	
Clinical stage (before chemotherapy):		
IB2	8	15%
IIA2	9	17%
IIB	35	67%

[1] Abnormal uterine bleeding. [2] Postmenopausal bleeding.
[3] Postcoital bleeding.

Table 2. — *Chemotherapy response of the patients.*

	Number	Percentage
Complete clinical response	6	12%
Partial clinical response	26	52%
Stable disease	17	34%
Progressive disease	1	2%
Objective response (complete + partial response)	32	64%

continued chemotherapy after the first cycle. Ninety-four percent of the patients received 100% of the planned chemotherapy dose. Other results of clinico-pathologic data are summarized in Table 1.

Response to chemotherapy

After finishing chemotherapy, 32 patients (64%) responded to the NACT of which six patients (12%) had a CR. Eighteen patients (36%) were non-responders to NACT and received concurrent chemoradiotherapy (Table 2).

Factors affecting clinical response of chemotherapy including pathological type, tumor stage, tumor size, tumor site in MRI, parametrical involvement, and tumor grade were evaluated with multiple regression analysis. There was no statistically significant relationship between clinical response and tumor stage, parametrical involvement, tumor size, whereas there was a higher probability of no response to chemotherapy for the patients with higher grade tumor, adenocarcinoma and tumor in upper two-thirds of vagina (Table 3).

Downstaging after NACT in all stages was statistically significant ($p = 0.002$). For example, Stages IB2, IIA2, and IIB converted to Stage IB1, respectively, 50%, 12.5%, and 41%. Overall downstaging was observed after summarizing NACT in Figure 1.

Toxicity

Toxic side effects induced by NACT were limited to grade I to II. None of the present patients were affected by grade III and IV side effects except one patient who had severe allergic reaction to paclitaxel (grade IV), so she was excluded from this study. The most complications of post-chemotherapy were transient flushing (96%) and leucopenia grade I (87.5%).

Surgical treatment & Pathologic response

All patients who responded to the chemotherapy (n=32, Table 2) underwent laparotomy. Radical hysterectomy (type II: 12; type III: 20) plus systematic para-aortic (in six cases) and pelvic (in 32 cases) were performed on all responding 32 cases (64%). If pelvic lymph node frozen result was positive for cancer, para-aortic lymphadenectomy was done. Mean number of all resected lymph nodes was 15.24 (+/- 1.53 SE). Surgical resection margins were disease free in all except four cases (three in Stage IIB, one in Stage IB2) with positive vaginal margins. Parametrical involvement was

Table 3. — *Factors affecting clinical response of chemotherapy.*

Variable		No. (%)	% Response	Odds ratio	95% Confidence interval	*p-value*
Pathology type:	SCC	46 (92)	58 (12 CR*)	8.70	2.43-14.98	*0.007*
	Adenocarcinoma	4 (8)	6 (0 CR)			
Tumor grade:	Grade I	18 (36)	100 (25 CR)	0.44	0.007-0.58	*0.04*
	Grade II	20 (40)	90 (10 CR)			
	Grade III	12 (24)	75 (0 CR)			
Tumor site in MRI:	Anterior cervical lip	4 (8)	100 (50 CR)	7.63	1.141-14.126	*0.021*
	Posterior cervical lip	4(8)	100 (50 CR)			
	Whole cervix	11 (23)	91 (18 CR)			
	2/3 upper vagina	23 (46)	56(8 CR)			

* Complete response.

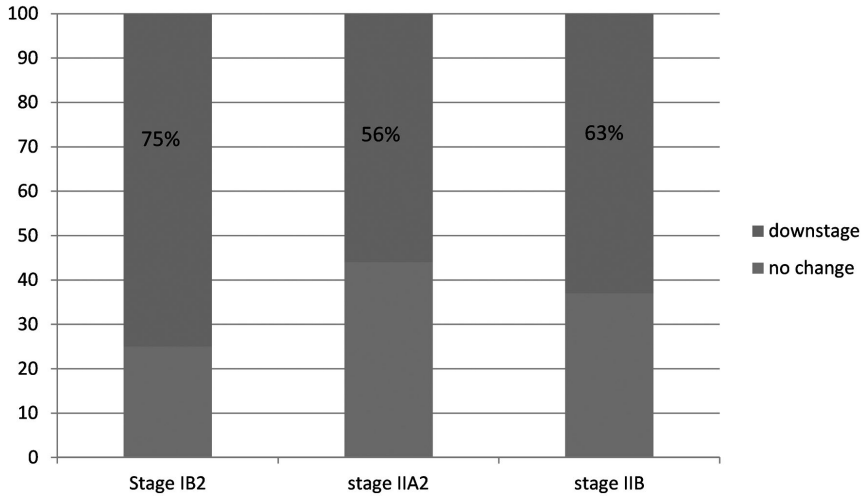

Figure 1. — Downstaging of carcinoma after chemotherapy.

Table 4. — *Evaluation of pathologic response.*

Variable	No.	Percentage
Complete pathologic response	9	28
PR1 (< 3mm stromal invasion)	3	9
PR2 (> 3mm stromal invasion) or suboptimal	20	63
Optimal pathologic response (complete pathologic response + PR1)	12	37

found in just one patient (in Stage IIB). Lymph node metastasis was detected in four (12%) cases, all belonging to Stage IIB and just found in pelvic lymph nodes, not in paraaortic nodes. The mean size of tumor in the cervical specimen was 1.3 cm (range: 0-5 cm). Lymphovascular invasion and deep stromal invasion were found respectively in nine (27%) and 15 (44%) of cases. There was no detectable disease in nine cases (28%). Other pathologic responses are summarized in Table 4.

There was statistically significant relationship between pathologic and CR ($p = 0.002$). Of complete pathologic response group (nine cases), there were three (34%) complete and six (66%) partial CR (100% optimal responses), but in suboptimal pathological response group (20 cases), there were one CR (10%), 17 partial CR (85%), and two stable diseases (5%). There was no statistically significant relation between pathologic response and histopathological type of tumor based on regression analysis.

Complications

There was no surgery -related morbidity or mortality except blood transfusions that were necessary in 18 cases (56%) due to blood loss during surgery.

Adjuvant therapy

In responding cases that were operated (n=32) 16 cases (51%) did not require any adjuvant therapy; the remaining patients (48%) received adjuvant therapy including chemoradiotherapy (15 cases, 48%) and one case (1%) lost to post-surgical follow-up.

Survival

The median follow up interval was 26.9 months. At the time of the present evaluation (during five-year follow-up), 44 patients (88%) are alive (97% in responder group *vs.* 72% in non-responder group), five patients in the non-responder group had died (10%) due to local recurrences in two cases and both local and systemic recurrences in three cases, and one patient was lost to the postsurgical follow-up (2%). Mean and median overall survival rate of the present patients were 27.55 ± 2.5 and 26.9 months, respectively. The mean overall survival in the CR group was significantly better than progressive disease group ($p = 0.0011$) (respectively: 29.43 ± 6.2 *vs.* 22.4 ± 0 months). Moreover, mean and median overall disease-free survival of the present patients were 26.36 ± 1.7 and 26.46 months, respectively. The mean overall disease-free survival in the CR group was significantly better than progressive disease group ($p = 0.002$) (respectively: 26.48 ± 7.13 *vs.* 18.13 months).

The mean overall survival and disease-free survival in non-responder group were less than responder group but was not significant ($p = 0.3$) (respectively: 23.5 ± 11.16, 21.11 ± 12.8 months *vs.* 26.05 ± 15.43, 25.3 ± 15.3 months).

In the cox-regression model, the authors analyzed clinical response, pathological response, tumor site, tumor size, tumor stage, parametrial involvement factors.

Based on the cox-regression analysis, factors affecting survival and disease-free survival were pathological response [RR = 2.36, CI (1.14 - 4.89)] and tumor site [RR = 0.31, CI (0.13 - 0.73)]. For example, if tumor site was in the cervix, 22% of the suboptimal pathologic response occurred but if

tumor site was in the upper two-thirds of vagina, 83% sub-optimal response occurred and hence these patients had poorer survival and disease-free survival.

Overall recurrence rate was 20% (ten cases) that all belonged to the non-responder group (six cases local recurrence and three cases systemic with local recurrence), except one case (2%) which was in the responder group and had local recurrence.

In logistic regression analysis of factors affecting recurrence rate, such as histopathologic type of tumor, tumor stage, pathological response, and tumor size, tumor size was the only statistically significant relevant factor to the recurrence rate ($p = 0.017$). Therefore, in recurrence cases, the mean tumor size was six cm ± one cm but in non-recurrence cases, the mean tumor size was 4.8 cm ± 1.3 cm.

Discussion

The present study suggests that NACT with taxol and cisplatin prior to a radical operation is a feasible compound treatment with acceptable side effects on curing cervical cancer in the local advanced stage and this is in line with the published data [3, 9-12]. Using dose dense chemotherapy (once every ten days), the toxicity of prescribing taxol with cisplatin was mild to moderate, and except one case, who showed severe sensitivity to taxol, there was no grade III or more than toxicity or death. Besides, in this study it was seen that NACT before operation would not increase the surgical side effects.

By using different NACT drugs, numerous phase II studies have reported 60% to 90% objective clinical responses [10, 11, 13] and 15% CRs. These results are comparable with those of this study in which the authors used combination of two drugs i.e. taxol and cisplatin. In the present study, objective and CRs were 64% and 12%, respectively.

In regression analysis for identifying predictive factors in tumor's response to the chemotherapy, it was shown that some factors such as tumor's grade, pathology, and site are highly determining for predicting tumor's response to the chemotherapy. Despite the results reported by others [11], there was no relation between tumor's response to the chemotherapy and patient's stage, tumor's primary size, and parametrical involvement.

Proved in Benedetti-Panici *et al.*'s study [11], grade and pathology are tumor's natural factors for determining their response to chemotherapy. In the present study, beside these factors, tumor's response to chemotherapy was related to its site. This difference is probably because of careful clinical checking, which is an indispensable criterion for determining the stage of cervix cancer, and accurate MRI for determining the exact place of tumor that was used in this study. Therefore, including MRI, in addition to clinical exam, can be helpful in determining the exact site of tumor and choosing a proper patient for receiving this kind of treatment modality.

In the present study, chemotherapy drugs, taxol 60 mg/m^2 and cisplatin 80 mg/m^2, were prescribed once every ten days intravenously; but generally chemotherapy drugs are repeated every three weeks. The latter one needs a period of nine to 12 weeks to obtain a definitive treatment, whereas a quick weekly prescribed diet not only reduces the time to the definite treatment but also prevents the rapid regrowth of tumor cells without increasing any side effects. According to a meta-analysis performed on 21 clinical trials in 2003, it was shown that using chemotherapy cycles shorter than 14 days or cisplatin dosage more than 25 mg/m^2/wk would lead to improved survival, otherwise NACT might have negative impact on patients' survival [14]. In this study, a dosage of 80 mg/m^2 cisplatin was used every ten days, and after three chemotherapeutical periods, 56%, 63%, and 75% of patients were downstaged to Stages IB2, IIB, and IIA2 , respectively, which is comparable with 50% downstage according to Singh *et al.* in which they used taxol and cisplatin chemotherapy every three weeks [15].

There are some disagreements on the difficulty of surgery and surgical vascularity after NACT, whereas in the present study, all responder patients, 64%, were able to be operated and dissected easier while the surgery. In spite of 6% cancellation of what (treatment) reported in Benedetti-Panici *et al.* study [11], there was no cancellation due to the difficulty of the surgery in the present study.

The optimal pathology response in the present study was 37% including 28% complete pathology response, whereas in Lissoni et *al.*'s study [16] in which they used two drugs of taxol and cisplatin once every three weeks with the dosage of 175 mg/m^2 and 75 mg/m^2, respectively, the optimal pathology response was 25% which was significantly less than the present study. Moreover, this 37% optimal pathology response is comparable with the 48% response, including 20% complete pathology response, reported by Buda *et al.* [9] in which they used three drugs of taxol, ifosfamide, and cisplatin, and the medicational side effects, reducing drug dosage, and delay in therapy were high in this study [9]. In fact, the present study showed that this high dose-dense chemotherapy regimen with two drugs of taxol and cisplatin, has the same effect of the therapeutic diet of once every three weeks of three drugs of taxol, cisplatin, and ifosfamide. It improves the safety profile without noticeable side effects of the three drugs therapeutic diet in Buda *et al.* study [9].

An important idea about NACT clinical trials on cervical cancer is that the pathology response of tumor as an independent factor in survival is supposed to be matched with the patient's survival. According to Cox-regression-analysis, it was shown in the present study that pathology response is an independent factor for predicting survival [PR = 2.36, CI 95% (1.14 - 4.89)].

Although there is no doubt about chemosensitivity of the cervical cancer, it is wondered whether using this kind of chemotherapy before a radical surgery leads to increase

the overall survival of patients suffering from cervical cancer in the locally advanced stage or not. Following treatment with radiotherapy with or without surgery, the overall survival of patients in Stages IB2 and IIA2 has a range from 60% to 70% and in Stage IIB has a range from 25% to 65%. Following treatment with simultaneous chemoradiotherapy, the overall survival of this group had another 10% increase; however, there is contradictory information whether this combined modality therapy, NACT and radical surgery, might lead to increase the overall survival of this group of patients or not. It might be answered when two studies of EORTC protocol 55994 and trial NCT 00193739, will be completed in the future. Nonetheless, the present study is the first long-term survival analysis in Iran on the patients suffering from the locally advanced cervical cancer. In this study, overall five-year-survival of our patients was 88%, whereas in Behtash *et al*.'s study [17] in which they used the therapeutic diet of cisplatin and vincristine one every ten days, the overall three-year-survival was reported as much as 56%. Moreover, the therapeutic diet of taxol and cisplatin in the present study survived 51% of patients from receiving adjuvant therapy, but 63% and 81% of patients in Duenas-Gonzalez *et al.* [18] and Behtash *et al.* [17] study received adjuvant therapy, respectively.

Similar to Benedetti-Panici et *al.*'s study [11], the chemotherapy response (both clinical and pathological) was meaningfully a potential factor for predicting survival, so that in the present study, all the cases of death and recurrence (both locally and systematically, except one case) belonged to non-respondent group. The recurrence rate in the present study was 20% which is similar to Chang *et al.* [19] who reported the rate to be 21%, whereas Behtash *et al.* reported it to be 47% [17]. However, local recurrence in the present study, similar to Benedetti-Panici et *al.*'s study considers special treatments.

Some risky factors such as the primary size of tumor, depth of tumor invasion, parametrical involvement, and metastasis of lymph nodes are reported as factors involved in recrudescence [11]. Hwang *et al.* [20] and Behtash *et al*. [17] have reported the involvement of lymph nodes as a factor of recrudescence, however, in the present study just the primary size of tumor was the important factor involved in recrudescence ($p = 0.017$).

Conclusion

Although the present study had the limitation of lack of control group (concurrent chemoradiotherapy group, as a standard treatment for cervical cancer), it proved the value and efficacy of this regiment of chemotherapy drugs. Furthermore most of the present patients are alive and without any late complications at long-term follow up.

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