Late toxicities in concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy plus weekly cisplatin for locally advanced cervical cancer: a historical cohort comparison against two previous different treatment schemes

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Summary

Purpose: To determine the long-term toxicity of concurrent chemoradiotherapy (CCRT), using high-dose rate intracavitary brachytherapy (HDRICB) compared to radiation (RT) alone in patients with advanced cervical cancer using a control-cohort study. *Methods:* A total of 332 cases of Stage IIB-III disease were included in this comparative study. Seventy-three patients were treated with a 3-insertion schedule and labeled group A, whereas the other 146 patients with a 4-insertion schedule became group B. One hundred and thirteen patients treated by a 4-insertion protocol with concurrent weekly cisplatin were labeled group C. *Results:* The cumulative rate of grade 2 or above rectal complication was 13.7% for group A, 9.6% for the group B and 15.9% for group C ($p = 0.76$), whereas the grade 3 to 4 non-rectal radiation-induced intestinal injury was 6.8% for group A, 6.2% for group B and 9.7% for group C ($p = 0.20$). Grade 2 to 4 late bladder toxicity was higher in group C, with the cumulative rate being 5.5% for group A, 4.8% for group B and 15.0% for group C ($p = 0.004$). The independent factor for a rectal complication was the occurrence of a bladder complication ($p = 0.01$, hazard ratio 3.06). The independent factors for bladder complications were the use of CCRT ($p = 0.01$, hazard ratio 2.08), and the occurrence of rectal complications ($p = 0.02$, hazard ratio 2.77). *Conclusions:* When treating advanced cervical cancer, HDRICB consisting of four 6 Gy insertions and weekly cisplatin shows a trend of increasing late bladder complications. The interval between drug administration and HDRICB should be kept long enough to avoid any synergistic effect of both regimens.

Key words: Carcinoma of the cervix; Radiotherapy; Concurrent chemoradiotherapy; High-dose rate brachytherapy; Complications.

Introduction

The routine use of high-dose rate intracavitary brachytherapy (HDRICB) has been questioned because of the presence of a narrow therapeutic window and a lack of consensus on fractionation [1]. Despite some skepticism, HDRICB has been widely used for the management of cervical cancer since it allows the application of brachytherapy during outpatient visits. Orton et al. has suggested that an increase in the fraction number accompanied by a decreasing fraction size reduces the incidence of complications [2]. However, there is no consensus as to the optimum fractionation regimen that should be used; such a consensus is available with the low-dose-rate (LDR) regimen. The American Brachytherapy Society (ABS) dose recommendation for the radiation treatment of advanced cervical cancer is 45 Gy of external beam radiotherapy (EBRT) to the entire pelvis in combination with a prescribed dose of 6.5 Gy to point A in five fractions or 5.8 Gy in six fractions. Other alternatives that have been proposed and these include an EBRT of 50.4 Gy to the pelvis together with 7 Gy to point A in four fractions or 6 Gy in five fractions or 5.3 Gy in six fractions [3]. The prescribed doses that make up these schedules, when calculated, range from 90.5 to 99 Gy of the LDR equivalent when using the LDR/HDR conversion factor [2, 4]. More clinical datasets are required to compare the outcomes of the different fractionation schedules because these schedules have not been thoroughly tested in a clinical situation.

The American National Cancer Institute made a strong recommendation that those patients with invasive cervical cancer who require RT should be treated concurrently with cisplatin-based chemotherapy. To avoid prolongation of the overall treatment time, HDRICB should be initiated after tumor regression. Thus, HDRICB is always interspersed with EBRT when weekly cisplatin is given. The potential risk of increased late toxicity when combining chemotherapy and HDRICB also needs to be further investigated. While HDRICB treatment allows better custom-tailoring of the dose distributions compared to LDR, it also requires more attention in order to achieve a precise and accurate dose distribution calculation and treatment delivery because there is a loss in the biological therapeutic ratio. Although retrospective studies of HDR and concurrent chemotherapy have demonstrated toxicity rates similar to those with LDR [5-10], these investigations have involved only limited numbers of patients and there is also a lack of long-term follow-up.

Revised manuscript accepted for publication November 4, 2009

Table 1. — *Patient characteristics*.

Characteristic	group A no = 73	group B no = 146	group C no = 113	χ^2 test *p* value
Age (years)	35 ~ 85 (median 61)	35 ~ 82 (median 60)	33 ~ 83 (median 58)	ns
< 45	6 (8.2%)	22 (15.1%)	15 (13.3%)	
45-65	44 (60.3%)	84 (57.5 %)	71 (62.8 %)	
> 65	23 (31.5 %)	40 (27.4 %)	27 (23.9 %)	
Stage				ns
IIB	43 (58.9%)	106 (72.6%)	80 (70.8%)	
III	30 (41.1%)	40 (27.4%)	33 (29.2%)	
Tumor size	> 0.10			
< 4 cm	13 (17.8%)	27 (18.5%)	21 (18.6%)	
≥ 4 cm	60 (82.2%)	119 (81.5%)	92 (81.4%)	
Pelvic lymph node				ns
Negative	64 (87.7%)	130 (89.0%)	100 (88.5%)	
Positive	9 (12.3%)	16 (11.0%)	13 (11.5%)	
Pathology				ns
squamous cell ca.	67 (91.8%)	136 (93.2%)	102 (90.3%)	
adenocarcinoma/adenosquamous	6 (8.2%)	10 (6.8%)	11 (9.7%)	
RT duration (days)	50 ~ 121 (median 63)	49 ~ 115 (median 59)	39 ~ 108 (median 55)	ns
Whole pelvis dose (Gy)	44 ~ 46 (median 44)	40 ~ 50 (median 44)	39.6 ~ 50.4 (median 45)	
Parametrial dose (Gy)	58 Gy	58 Gy	57.6 Gy	
Number of insertion	3	4	4	
Point A dose (Gy)	7.2	6.0	6.0	
Follow-up (months)	11 ~ 110 (median 62)	18 ~ 101 (median 58)	19 ~ 90 (median 54)	

The definition of a parametrial dose is the summation of external beam irradiation dose before and after central shielding. It represents the cumulative dosage to the bilateral parametria; ns = non significant.

In this study, we compared the late complications among patients with advanced cervical cancer who had been treated with HDRICB over three distinct treatment systems through a historical cohort control. Since this study was retrospective and CCRT has become an established treatment policy for locally advanced cervical cancer, the aim was to analyze the late toxicities rather than to compare the survival curves.

Materials and Methods

Patient characteristics

Between January 1993 and December 2006, a total of 451 patients with previously untreated cervical cancer completed curative-intent RT at the China Medical University Hospital. Before January 2000, most of our patients were treated with RT alone using two different ICB schedules. After January 2000, the routine use of CCRT for advanced tumors became the standard pattern of care and a total of 153 patients were treated in this later period. The inclusion criteria were:

1) Stage IIB-III disease with a homogeneous EBRT dose to the pelvis and brachytherapy protocol. Patients with Stage IB-IIA disease were excluded because the optimal RT policy for bulky IB-IIA tumors was not consistently reproducible across the different treatment periods.

2) The patients had three sessions of HDRICB with either a prescribed dose of 7.2 Gy per fraction to point A (before December 1995) or four sessions of HDRICB with 6.0 Gy to point A (after January 1996).

3) The patients completed at least two years of regular follow-up and laboratory studies.

A total of 332 cases were included in this comparative study. No studied subjects received extended field irradiation. Seventy-three patients were treated with a 3-insertion schedule and were labeled as group A. Another 146 patients underwent a 4-insertion schedule and were labeled group B. Finally, the remaining 113 patients were treated with a 4-insertion ICB protocol and concurrent weekly cisplatin and these were labeled as group C. No patient in either group A or B had been treated with combination chemotherapy. All the patients were treated by the same radiation oncology team. The patient characteristics of the three groups are summarized in Table 1.

Radiotherapy

Irradiation treatment consisted of EBRT followed by HDRICB. Initially, the whole pelvis was treated with 10 MV X-rays via anterior and posterior parallel fields or box variants where the AP diameter was over 18 cm. The standard prescribed dose was 44 to 45 Gy, which consisted of 22 to 25 fractions four to five weeks apart. The radiation dose for patients diagnosed as FIGO Stage IIB-III bilateral parametrial disease was boosted to 50.4 to 59.4 Gy with 4-cm wide mid-line shielding.

After adequate tumor regression, HDRICB was performed using an Ir-192 remote after-loading technique at 1-week intervals and this was carried out concurrently with parametrial boosting. The total prescribed point A doses (EBRT + HDRICB) ranged from 65.6 to 69 Gy (median, 68 Gy). The details of the radiotherapy techniques are listed in Table 2.

Table 2. — *Outcome and survival across the treatment groups*.

Survival		group A	group B	group C
5-year CSS	IIB	77%	75%	78%
	III	55%	68%	72%
5-year PRFS	IIB	89%	91%	92%
	III	71%	79%	81%
5-year DMFS	IIB	74%	75%	80%
	III	64%	70%	68%

The values in parentheses represent patient number.
CSS = cause-specific survival; PRFS = pelvis relapse-free survival; DMFS = distant metastasis-free survival.

Table 3. — *Chronic complications across the three treatment groups*.

Category of complication	group A (no = 73)	group B (no = 146)	group C (no = 113)	χ^2 test *p* value
Radiation proctitis				
Grade 2-4	10 (13.7%)	14 (9.6%)	18 (15.9%)	0.70
Grade 3-4	4 (5.8%)	3 (2.1%)	3 (2.7%)	0.48
Median duration (range)	14 months (5-28)	12 months (6-26)	11 months (7-22)	
NRRIII Grade 3-4	5 (6.8%)	9 (6.2%)	11 (9.7%)	0.20
Median duration (range)	17 months (9-23)	18 months (6-39)	13 months (7-28)	
Radiation cystitis				
Grade 2-4	4 (5.5%)	7 (4.8%)	17 (15.0%)	0.004
Grade 3-4	2 (2.7%)	3 (2.1%)	6 (5.3%)	0.30
Median duration (range)	22 months (11-43)	26 months (8-41)	15 months (3-27)	
Lower leg edema	2 (2.7%)	5 (3.4%)	4 (3.5%)	0.79
Renal insufficiency	0	1 (0.7%)	5 (4.4%)	–
Renal failure (need dialysis)	0	1 (0.7%)	1 (0.9%)	–
Electrolyte imbalance	0	0	4 (3.5%)	–
Ureteral stenosis	1 (1.3%)	3 (2.1%)	2 (1.7%)	–
Bone marrow failure	0	0	1 (0.9%)	–

The values in parentheses represent the percentage of patients with chronic complications.
NRRIII = non-rectal radiation-induced intestinal injury.

Table 4. — *Interval between brachytherapy and weekly cisplatin in group C*.

Grade 2 to 4 bladder complication	Negative (No = 85)	Positive (No = 28)	χ^2 test *p* value
No course with the interval interval less than 24 hours	60	15	0.07
At least one course with the interval < 24 hours	25	13	
one course	18	9	
two courses	5	3	
three courses	2	1	
four courses	0	0	

After January 2000, most patients with advanced disease were treated with concurrent chemotherapy. The chemotherapy consisted of cisplatin delivered weekly at a dose of 40 mg/m^2 intravenously to give a total dose of up to 60 mg. The first cycle of cisplatin was initiated at the first RT treatment. In accordance with the duration of the RT, the treatment plan thus included a total of five to six cycles of cisplatin. The details of the drug administration protocol have been described in our previous study [11].

During the RT course, weekly monitoring of hemoglobin levels was required. Blood transfusion was mandatory if the hemoglobin level fell below 1000/dl. In addition, to reduce the risk of aspiration when conscious sedation was used, HDRICB was delivered before the administration of chemotherapy when both modalities were given simultaneously.

Treatment planning and the rules of the source dwell

For patients treated with the two-field technique, the EBRT dose was calculated at the midplane, while the dosimetry of the box field was calculated using computer-based software and the doses were prescribed to the isocenter. The HDRICB dosimetry was calculated using orthogonal films exposed during each insertion. The HDRICB isodose curves were reviewed by physicians to ensure that the residual tumors were fully irradiated within the high-dose area. The applicator for the brachytherapy was a Henschke's type. The detailed method of modulating the weight of the dwell time has been reported in the study of Wang *et al*. [12].

During each insertion, the posterior and anterior vagina was packed with radio-opaque gauze to reduce rectal and bladder exposure and to visualize the posterior vaginal septum. The detailed method used to calculate the rectal and bladder reference doses has been described elsewhere [13].

Follow-up and complication analysis

We assessed the treatment response four weeks after completion of treatment. If residual disease was suspected, a biopsy was performed. Patients underwent regular follow-up examinations every one to two months for the first year and then every three months thereafter. A pelvic examination was performed during each follow-up visit. Tumor markers (squamous cell and carcinoembryonic antigens) were checked every three to six months and radiographical examinations (a chest X-ray and abdominopelvic computed tomography (CT) scanning) were conducted yearly. Pelvic recurrence was confirmed if the disease was detected in the irradiated field. Distant metastases were confirmed if tumors occurred in the paraaortic lymph nodes or elsewhere outside the pelvis. Once central recurrence was noted at follow-up, a salvage operation would be performed if possible. Otherwise, palliative RT with or without chemotherapy would be administered to treat the metastatic paraaortic lymph nodes or painful recurrent tumors.

Patients who had bloody stools or hematuria underwent endoscopy to identify the site of the bleeding and a blood count every two to four weeks for surveillance of the severity of complications. Rectal and bladder complications and non-rectal gastrointestinal sequelae (small bowel complications) were scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading scale [14]. Non-rectal radiation-induced intestinal injury (NRRIII) was defined as RT-induced gastrointestinal sequelae other than rectal complications and has been described in our previous study [15]. Due to a concern that less than comprehensive history-taking might not give a correct score for low-grade NRRIII, only grade three or above complications were entered into our analysis.

Statistical analysis

Patient survival was measured from the date of initiation of therapy to the date of the last follow-up examination. Survival

Table 5. — *Results of various HDRICB studies with concurrent chemotherapy in locally advanced cervical cancer.*

First author	Patient no.	Stage	ICB schedule	Drug regimen	End point/Outcome	Late complications
Souhami [7]	50	IIA-IVA 30 Gy/3Fr	EBRT 46 Gy	cisplatin 30 mg/m^2 weekly	complete remission 88%	rectal ulcer 20% rectovaginal fistula 4% small bowel obstruction 4%
Sood [6]	49	IB-IIIB	EBRT 45 Gy 18 Gy/2Fr	cisplatin 20 mg/m^2/day x 5 days week1 and 5	5-year OS 78%	grade 2-4 all toxicity 5%
Novetsky [9]	77	IB2-IV	EBRT 45 Gy 18 Gy/2Fr	cisplatin 40 mg/m^2 weekly or cisplatin 20 mg/m^2/day every 3 weeks	5-year LCR IB2/II 88%; III/IV 68% 5-year DFS IB2/II 83%; III-IV 61%	grade 3-4 all toxicity: 6%
Toita [10]	40	IB2-IVA	EBRT 40 Gy 18 Gy/3Fr	cisplatin 20 mg/m^2/day x 5 days every 3 weeks	3-year PCR 91% 3-year DFS 67% 3-year OS 79%	proctitis (all grade) 9% enterocolitis (all grade) 15%
Tseng [5]	60	IIB-IIIB	EBRT 44 Gy 25.8 Gy/6Fr	cisplatin + vincristine + bleomycin every 3 weeks for 4 courses	3-year DFS 50% 3-year OS 62%	proctitis (no grading) 10% cystitis (no grading) 3.3% intestinal obstruction 3.3%
Present study	113	IIB-IIIB	EBRT 45 Gy 24 Gy/4Fr	cisplatin 40 mg/m^2 weekly	5-year CSS IIB 78%; III 72% 5-year PRFS IIB 92%; III 81% 5-year DMFS IIB 80%; III 68%	proctitis (grade 2-4) 15.9% proctitis (grade 3-4) 2.7% cystitis (grade 2-4) 15% cystitis (grade 3-4) 5.3% NRRIII (grade 3-4) 9.7%

EBRT = external beam radiotherapy; OS = overall survival; LCR = local control rate; DFS = disease-free survival; CSS = cause-specific survival; PRFS = pelvis relapse-free survival; DMFS= distant metastasis-free survival; NRRIII = non-rectal radiation-induced intestinal injury.

was calculated using the Kaplan-Meier method. Comparison of the categorical variables was performed using the chi square test. The logistic regression test was utilized for assessment of the patient and treatment factors associated with the occurrence of late complications. Statistical significance was considered to be present when the *p* value was less than 0.05. All calculations were performed with SPSS 13.0 for Windows (SPSS Inc, Chicago, Ill).

Results

The median duration of follow-up for all groups was 57 months (group A: 62 months; group B: 58 months; group C: 53 months). The outcomes and survival for the three groups of patients are listed in Table 2.

Table 3 summarizes the late complications and latency for the three treatment groups. Forty-two patients (12.7%) had grade 2 to 4 rectal complications and ten patients (3.0%) had grade 3 to grade 4. The cumulative rate of grade 2 or above rectal complications was 13.7% for group A, 9.6% for the group B and 15.9% for group C ($p = 0.76$). The cumulative rate of grade 3 to 4 NRRIII was 6.8% for group A, 6.2% for group B and 9.7% for group C ($p = 0.20$). Thus, there was no substantial increase in the incidence of grade 2 to 4 or major gastrointestinal complications across the three treatment groups. However, four patients (5.5%), who were members of group A, died of treatment-related gastrointestinal bowel perforation or ischemia due to lack of optimum salvage during the earlier part of the period covered in this study.

Twenty-eight patients (8.4%) had grade 2 to 4 bladder complications and 11 patients (3.3%) were categorized as grade 3 to grade 4. The introduction of cisplatin-based CCRT significantly increased the incidence of grade 2 to 4 bladder complications. The cumulative rate of grade 2 to 4 complications was 5.5% for group A, 4.8% for group B and 15.0% for group C ($p = 0.004$). In addition, there seemed to be a slight increase in grade 3 to 4 complications ($p = 0.30$) and a trend towards decreasing latency among the group C patients. In our previous study, we detected a trend towards a close association between gastrointestinal and genitourinary injuries reported [14] and therefore the cumulative incidence of complications of any kind was also analyzed. The cumulative rate of grade 3 to grade 4 injuries was 8.2% for group A, 6.8% for group B and 12.4% for group C group ($p = 0.14$).

Some further irreversible adverse effects were also noted in the group C. Five patients (4.4%) developed renal insufficiency and one needed hemodialysis. Four patients developed persistent electrolyte imbalance and one patient developed irreversible bone marrow failure.

From the logistic-regression analysis, the independent factor for grade 2 or above rectal complications was the occurrence of bladder complications ($p = 0.01$, hazard ratio 3.06, 95% CI 1.36~12.71). The independent factors for grade 2 or above bladder complications were the use of CCRT ($p = 0.01$, hazard ratio 2.08, 95% CI 1.02~5.43), and the occurrence of rectal complications ($p = 0.02$, hazard ratio 2.77, 95% CI 1.07~6.29). No patient or treatment-related factor was associated with grade 3 or above NRRIII.

To clarify the risk factors of bladder complications, further analysis of the interval between the HDRICB and weekly cisplatin was carried out (Table 4). The result showed that the interval was less than 24 hours in 13 of the 28 patients with grade 2 or above complications, compared to 25 of the 85 patients without obvious complications ($p = 0.07$). Furthermore, the cumulative bladder biologically effective dose (CBBED) from the different treatment periods was calculated as the formula reported in our previous study [14]. There was no statistical difference of the mean bladder CBBEDs in the three periods (group A: 109.2 Gy_3; group B: 113.2 Gy_3; group C: 111.7 Gy_3).

Discussion

It is interesting to compare the data from the patients treated with HDRICB and LDRICB, with or without addition of cisplatin-based chemotherapy; this is because a small gain in local control through CCRT might be counteracted by the possibility of increased morbidity through the combination of HDRICB and chemotherapy. Furthermore, there might be dilution due to the unpredictable biological effects of the two different dose rates. To clarify these possibilities it would be necessary to conduct a phase III randomized trial. However, such a study is difficult to conduct since combination treatment has become the standard pattern of care. Thus, the utilization of control-cohort analysis from different treatment periods would seem to be a feasible way to examine the concept that late toxicities with CCRT plus HDRICB are equivalent to that of RT alone. The studies available for a combination of CCRT with HDRICB are summarized in Table 5. The outcomes for our CCRT patients are also comparable to other similar investigations. However, considering the prescribed doses of HDRICB for the three studies using three or more brachytherapy fractions are obviously lower than those suggested by the ABS, the current ABS recommendations needed to be tested clinically.

HDRICB treatment allows better custom-tailored dose distributions compared to LDR. However, irreparable mistakes can happen very quickly and quality assurance of the treatment plan has proved to be much more important than with LDR. For those institutions performing CCRT, one of the questions that remains unanswered includes whether the addition of concurrent cisplatin with HDRICB increases or not the complication rate; this is because there is paucity in reporting late adverse effects due to a lack of long-term follow-up with some patients. This is especially true for late urological sequelae, which may occur regularly up to 20 years later [16, 17]. Although four LDR trials reported no significant difference in the incidence of long-term toxicity [18-21], one HDR trial [5] reported that treatment-related late toxicity did appear to be higher with CCRT compared with RT alone (23.4% vs 12.9%, $p = 0.13$). Souhami *et al*. [7] also reported a higher late gastrointestinal complication rate with CCRT when compared to other non-CCRT HDR series. In contrast, Sood *et al*. [6] found no evidence of an increase in bladder or rectum toxicity when applying two courses of HDRICB (9 Gy to point A per fraction) plus two cycles of cisplatin (20 mg/m^2/days for five days). As summarized in Table 5, the late complications of our study were clearly classified and the major sequelae appear to be higher than with the other series. In addition, there is a trend toward a higher incidence and a shorter latent period for bladder complications compared to non-CCRT patients. Specifically, the reduction in latency might imply an increased severity of tissue damage and, as a consequence, a subsequent increase in the incidence of late complications might thus be anticipated. Further optimization of the EBRT protocol and/or the HDRICB fractionation scheme for CCRT patients needs to be performed in order to obtain an increase in the therapeutic gain.

In this study, the finding of close association between rectal and bladder complications was addressed in our previous report [13]. The reason for the higher incidence of bladder complications in our group C might be attributable to the possibility of a concurrent rapid decrease of both the tumor and the thickness of the uterus after CCRT; this may contribute to an increase in the irradiated volume during HDRICB. Thus, for patients receiving higher ICRU bladder doses, modification of the ICB fraction size should be done to reduce the risk of bladder sequelae [13]. Furthermore, the use of 3D image-based dosimetry for HDRICB is becoming increasingly more common and it may increase the feasibility of further optimizing ICB planning [8]. Finally, the interval between drug administration and HDRICB should be kept long enough to avoid any synergistic effect of both regimens as there was a trend that the short interval might be associated with grade 2 or above complications, which was demonstrated in the current study.

On the other hand, Ferrigno *et al*. [22] reported the incidence of grade 3 to 4 small bowel complications with RT alone was 7.2%, which is similar to our NRRIII incidence across all group patients. They also recommended limiting the total parametrial dose to 54 Gy (45 Gy to the whole pelvis with a 9 Gy boost to the parametrium). In this study, the majority of pelvic failures originated from recurrence of the central disease. Therefore, it should be possible to reduce the parametrial dose in order to decrease the risk of NRRIII.

Conclusion

HDRICB consisting of four 6 Gy insertions and concurrent weekly cisplatin has similar efficacy when compared to the other HDRICB series. Nonetheless, this regimen did demonstrate an increase in late bladder complications. The best results from HDRICB plus CCRT treatment are probably achieved by two approaches. The interval between drug administration and HDRICB should be kept long enough. Furthermore, more prospective trials of the ICB scheme in the CCRT era would seem to be essential if a better overall treatment outcome is to be achieved.

References

[1] Petereit D.G., Fowler J.F.: "High-dose-rate brachytherapy: High-dose, high-tech, and high-results". *Int. J. Radiat. Oncol. Biol. Phys*., 2003, *55*, 1159.

[2] Orton C.G., Seyedsadr M., Somnay A.: "Comparison of high and low-dose rate remote afterloading for cervfical cancer and the importance of fractionation". *Int. J. Radiat. Oncol. Biol. Phys*., 1991, *21*, 1425.

[3] Nag S., Erickson B., Thomadsen B., Orton C., Demanes J.D., Petereit D.G.: "The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix". *Int. J. Radiat. Oncol. Biol. Phys*., 2000, *48*, 201.

[4] Nag S., Gupta N.: "A simple method of obtaining equivalent doses for use in HDR brachytherapy". *Int. J. Radiat. Oncol. Biol. Phys*., 2000, *46,* 507.

[5] Tseng C.J., Chang C.T., Lai C.H., Soong Y.K., Hong J.H., Tang S.G. *et al*.: "A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix". *Gynecol. Oncol*., 1997, *66*, 52.

[6] Sood B., Gorla G., Gupta S., Gorla G., Malhotra H., Guha C. *et al*.: "Two fractions of high-dose rate brachytherapy in the management of cervix cancer: Clinical experience wth and without chemotherapy". *Int. J. Radiat. Oncol. Biol. Phys*., 2002, *53,* 702.

[7] Souhami L., Seymour R., Roman T.N., Stanimir G.W., Trudeau M., Clark B.G. *et al*.: "Weekly csplatin plus external beam radiotherapy and high-dose rate brachytherapy in patients with locally advanced carcinoma of the cervix". *Int. J. Radiat. Oncol. Biol. Phys*., 1993, *27,* 871.

[8] Potter R., Dimopoulos J., Bachtiary B., Sissolak G., Klos B., Rheinthaller A. *et al*.: "3D conformal HDR-brachy- and external beam therapy plus simultaneous cisplatin for high-risk cervical cancer: Clinical experience with 3-year follow-up". *Radiol. Oncol*., 2006, *79,* 80.

[9] Novetsky A.P., Einstein M.H., Goldberg G.L., Hailpern S.M., Landau E., Fields A.L. *et al*.: "Efficacy and toxicity of concomitant cisplatin with external beam pelvic radiotherapy and two high-dose-rate brachytherapy insertions for the treatment of locally advanced cervical cancer". *Gynecol. Oncol.,* 2007, *105,* 635.

[10] Toita T., Moromizato H., Ogawa K., Kakinohana Y., Maehama T., Kanazawa K. *et al*.: "Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer". *Gynecol. Oncol*., 2005, *96,* 665.

[11] Chen S.W., Liang J.A., Hung Y.C., Yeh L.S., Chang W.C. *et al*.: "Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications". *Int. J. Radiat. Oncol. Biol. Phys*., 2006, *66*, 1370.

[12] Wang C.J., Leung S.W., Chen H.C., Sun L.M., Fang F.M., Changchien C.C. *et al*.: "High-dose-rate intracavitary brachytherapy in treatment of cervical carcinoma". *Int. J. Radiat. Oncol. Biol. Phys*., 1997, *38,* 391.

[13] Chen S.W., Liang J.A., Yeh L.S., Yang S.N., Shiau A.C., Lin F.J.: "Comparative study of reference points by dosimetric Analyses for Late complications following uniform external radiotherapy and high-dose-rate brachytherapy for cervical cancer". *Int. J. Radiat. Oncol. Biol. Phys*., 2004, *60*, 663.

[14] Cox J.D., Stetz J., Pajak T.F.: "Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)". *Int. J. Radiat. Oncol. Biol. Phys*., 1995, *31*, 1341.

[15] Chen S.W., Liang J.A., Yang S.N., Hung Y.C., Yeh L.S., Shiau A.C. *et al*.: "Radiation injury to intestine following hysterectomy and adjuvant radiotherapy for cervical cancer". *Gynecol. Oncol*., 2004, *95*, 208.

[16] Kirwan J.M., Symonds P., Green J.A., Tierney J., Collingwood M., Williams C.J.: "A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer". *Radiother. and Oncol*., 2003, *68*, 217.

[17] Eifel P.J., Levenback C., Oswald M.J.: "The time course and incidence of late complications in patients treated with radiation therapy for FIGO Stage IB carcinoma of the uterine cervix". *Int. J. Radiat. Oncol. Biol. Phys*., 1994, *30,* 212.

[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] Keys H.M., Bundy B.N., Stehman F.B., Muderspach L.I., Chafe W.E., Suggs C.L. *et al*.: "Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage IB cervicak carcinoma". *N. Engl. J. Med.,* 1999, *340,* 1154.

[20] Whitney C.W., Sause W., Bundy B.N., Malfetano J.H., Hannigan E.V., Fowler W.C. *et al*.: "Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in Stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A gynecology Oncology Group and Southwest Oncology study". *J. Clin. Oncol*., 1999, *17*, 1339.

[21] Peters W.A., Liu P.Y., Barrett R.J., Stock R.J., Monk B.J., Berek J.S. *et al*.: "Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation alone as adjuvant therapy after radical surgery in high-risk early - stage cancer of the cervix". *J. Clin. Oncol*., 2000, *18,* 1606.

[22] Ferrigno R., dos Santos Novaes P.E., Pellizzon A.C., Maia M.A., Fogarolli R.C., Gentil A.C. *et al*.: "High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications". *Int. J. Radiat. Oncol. Biol. Phys*., 2001, *50*, 1123.

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