

**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 Scheme**

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**Running Title:** Late toxicities in High-Dose-Rate Brachytherapy plus Weekly  
Cisplatin for Advanced Cervical Cancer Patients

## 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 group.

### **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 factors for rectal complication was the occurrence of bladder complication ( $p=0.01$ , hazard ratio 3.06). The

independent factors for bladder complication were, the use of CCRT ( $p=0.01$ , hazard ratio 2.08), and the occurrence of rectal complication ( $p=0.02$ , 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 5 fractions or 5.8 Gy in 6 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 4 fractions or 6 Gy in 5 fractions or 5.3 Gy in 6 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 need 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.

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 schedule. 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 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 with 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.

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<sup>2</sup> intravenously to give a total dose of up to 60 mg. The first cycle of cisplatin was initiated at the first radiotherapy (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 para-aortic 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 para-aortic 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 was calculated using the Kaplan-Meier method. Comparison of the categorical variables was performed using the  $\chi^2$  test. 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 complication 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 eleven 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 [13] 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 logistic-regression analysis, the independent factors for grade 2 or above rectal complication was the occurrence of bladder complication ( $p=0.01$ , hazard ratio 3.06, 95% CI 1.36~12.71). The independent factors for grade 2 or above bladder complication were, the use of CCRT ( $p=0.01$ , hazard ratio 2.08, 95% CI 1.02~5.43), and the occurrence of rectal complication ( $p=0.02$ , 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 complication, 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 [13]. There was no statistical difference of the mean bladder CBBEDs in the three periods (group A:109.2 Gy<sub>3</sub>; group B:113.2 Gy<sub>3</sub>; group C:111.7 Gy<sub>3</sub>).

## **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. In order 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 is 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.

While 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 include whether the addition of concurrent cisplatin with HDRICB increases or not the complication rate; this is because there is paucity in reporting late adverse effect 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% versus 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<sup>2</sup>/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 complication, which was demonstrated in 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 a 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 trial of the ICB scheme in CCRT era would seem to be essential if one is to achieve a better overall treatment outcome.

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### **Conflict of Interest Notification**

There were no actual or potential conflicts of interest in this study.

