

# Compare Two Different Fractionated Regimes of HDR Intracavitary Brachytherapy after Concomitant Chemoradiation in Carcinoma Cervix: A Prospective Study

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## Abstract

**Background:** Cervical cancer is the common cancer cause of death among women in developing countries. High Dose Rate (HDR) intracavitary brachytherapy that is given with or sequential after EBRT, is an integral component in the treatment of carcinoma of the cervix. In recent years, High Dose Rate (HDR) brachytherapy in combination with External Beam Radiotherapy (EBRT) has been popular in the management of carcinoma of the cervix. **Objectives:** To evaluate treatment response post 3 and 6 months after treatment completion and treatment-related toxicities during treatment in weekly v/s biweekly HDR intracavitary brachytherapy after concomitant chemoradiation in squamous cell carcinoma cervix patients. **Methods:** A total of 60 cervical cancer patients fulfilling the inclusion criteria were selected. Patients were randomly assigned to the weekly and Biweekly HDR ICBT using the chit-box method with replacement. Arm A (Study arm): 30 patients with concurrent EBRT (50 Gy/25 fractions with 2 Gy per fraction) with weekly cisplatin (35 mg/m<sup>2</sup>) followed by HDR-ICBT 5 Gy \* 5 fractions biweekly after completion of EBRT. Arm B (Control arm): 30 patients with concurrent EBRT (50 Gy/25 fractions with 2 Gy per fraction) with weekly cisplatin (35 mg/ m<sup>2</sup>) followed by HDR - ICBT 7.5 Gy \* 3 fractions weekly after completion of EBRT. **Results:** Patients were assessed at 3 and 6 months to determine the local disease response and the incidence of any toxicities assessed during the treatment. All responses were graded as either CR (complete response), PR (partial response), SD (stable disease), or PD (progressive disease). 30 patients were assessed for therapy response using the WHO criteria. At 3 months arm A showed 86% CR and arm B showed 90% CR. 2 patients in arm A and 1 patient in arm B had PR. In both arms 2 patients had progressive disease. At 6 months 1 patient in both arms who had progressive disease converted into partial response after taking post RT chemotherapy. **Conclusions:** To sum up, brachytherapy is a vital aspect of the process of treating cervical cancer. Several centers have experimented with various doses and fractionation regimes. Patients in the current trial reported no safety concerns or intolerability issues across any treatment protocol. Arm A had treatment completion before arm B with comparable disease response and toxicities. Therefore, the choice of treatment plan depends on the individual patient's circumstances and the institution's demands. nonetheless, longer follow-ups and a bigger patient sample are needed for a solid evaluation of disease response and toxicity.

**Keywords:** Concomitant Chemoradiation- High dose rate intracavitary brachytherapy- Cervical Cancer- Treatment Response

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## Introduction

As per GLOBOCAN 2020 data of cancer incidence and mortality given by the International Agency for Research on Cancer (IARC) worldwide approx. 19.3 million new cases and almost 10 million cancer deaths occurred in 2020, in which approx. 9 million females had

cancer cases and around 6 lakhs among them had cervical cancer [1]. Cervical cancer is the fourth most common cancer, in females across the world, and the 8<sup>th</sup> most common cancers overall [1]. Cervical carcinoma is the 2<sup>nd</sup> most common cancer in India and leading cause of deaths

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also [2, 3]. The main treatment for advanced stage cervical cancer is chemoradiation followed by brachytherapy [4-7]. High dose rate (HDR) Intracavitary Brachytherapy (ICBT) for carcinoma cervix is now well established because of their much advantages. A combination of EBRT and brachytherapy can improve tumor control [8, 9]. There are a smaller number of studies based totally on the optimum fractionation and dosage in intracavitary brachytherapy in carcinoma cervix. Individual fraction sizes of less than or equal to 7.5 Gy in 4 to 8 fractions, depending on the dose in keeping with fraction, were advised by means of the American Brachytherapy Society (ABS) [9]. In contrast to ABS, studies have shown that HDR Intracavitary Brachytherapy is safe and effective while the dosage per fraction is even greater than 7.5 Gy [8-11]. We are practicing the HDR - ICBT schedule of 7.5 Gy per fraction per week for three fractions in our institute. So, this prospective study was conducted with the aim to evaluate the feasibility and tolerability between two different dose fractionations of HDR-ICBT consisting of 7.5 Gy per fraction per week for 3 fractions and 5.5 Gy per fraction 2 times in a week for 5 fractions in terms of complete response, partial response, stable disease and progressive disease and toxicities during treatment. As external Beam Radiotherapy for Carcinoma cervix spans over 5-6 weeks, lowering fraction size and frequency of fractionations of Brachytherapy results in a reduction in the standard treatment time.

## Materials and Methods

This study is a Hospital-Based, Prospective, randomized performed in the regional cancer center PBM Hospital, Bikaner Rajasthan.

Data collection was done for 6 months from February 2022 - August 2022 or when the sample size is achieved. It was taken 1 month to process and analyze the data and write the report. The study included newly diagnosed patients with histologically confirmed squamous cell carcinoma of the cervix, attending the department of RADIOTHERAPY, ATRCTRI Bikaner. All patients included in the study, registered at the Department of RADIOTHERAPY. The cases were distributed randomly among the two groups.

### Inclusion Criteria

- FIGO Stage - IIA - IIIC of carcinoma cervix
- ECOG PERFORMANCE status 0-2.
- Age 18 -70 years
- Adequate baseline organ function (Hematological, Renal, and Liver function Test)

-Patient willing to give informed written consent.

### Exclusion Criteria

- Previously treated patients (post-hysterectomy, post RT to pelvis)
- Distant metastasis
- Patients with Double malignancy
- Patients unfit for HDR

-Patient having other comorbidities: (uncontrolled Hypertension, uncontrolled Diabetes mellitus, severely immunocompromised).

### Method of Randomization

Randomization was done after giving 50 Gy in 25 fractions of EBRT using chit and box method with replacement.

### Assessment of Toxicities

Toxicities were scored according to the RTOG criterion in both groups of patients.

### Procedure

A Urinary catheter was placed in the Bladder and installed with a radiopaque solution and a rectal tube with a wire marker put into the rectum. Vaginal packing was applied to move the bladder and rectum away from the applicator.

-Applicator compose of 1 intrauterine tandem and 2 ovoids, and the same tandem curvature used throughout all the fractions.

-ICBT Simulation Orthogonal X-ray film with front and back views following applicator insertion.

### Patients Selection

-A total of 60 cervical cancer patients fulfilling the inclusion criteria were selected.

-Patients were randomly assigned to the weekly and Biweekly HDR ICBT using chit box method with replacement.

### -Arm A (Study arm)

30 patients with concurrent EBRT (50 Gy/25 fractions with 2 Gy per fraction) with weekly cisplatin (35 mg/m<sup>2</sup>) followed by HDR-ICBT 5.5 Gy 5 fractions biweekly after completion of EBRT.

### -Arm B (Control arm)

30 patients with concurrent EBRT (50 Gy/25 fractions with 2 Gy per fraction) with weekly cisplatin (40 mg/m<sup>2</sup>) followed by HDR-ICBT 7.5 Gy 3 fractions weekly after completion of EBRT.

### Analysis

For Statistical analysis, IBM SPSS Statistics 25 software is used. The statistical significance of the difference in proportions was calculated by the Chi-square test. p-value <0.05 was considered statistically significant.

## Results

A total of sixty patients with histopathological confirmed squamous cell carcinoma of cervical cancer were included in the study over the study period. Patients were assigned to one of two arms using a chit-and-box method. The maximum number of patients in both groups was found to be in the age group of 51-60 years in the first arm 13 (39%) and in the second arm 12 (36%) as shown in Table No. 1. The minimum number of patients

Table 1. Age Incidence

Age Group	No. of Patients n =60	
	First Arm n=30 (100%)	Second Arm n=30 (100%)
18-40 yrs.	3 (10)	6 (20)
41-50 yrs.	8 (27)	7 (23)
51-60 yrs.	13 (43)	12 (40)
61-70 yrs.	6 (20)	05 (17)

Table 2. Ecog Performance Scale

ECOG GROUP	No. of Patients (%)	
	First Arm n=30 (100%)	Second Arm n=30 (100%)
0	11 (37)	12 (40)
1	15 (50)	14 (47)
2	4 (13)	4 (13)

Table 3. Figo Stage

FIGO STAGE	No. of patients (%)	
	First Arm	Second Arm
	30 (100)	30 (100)
II	18 (60)	17 (56)
III	12 (40)	13 (44)

in both groups were found to be in the age group of 18-40 years in First arm 3 (10%) and second arm 6 (19%). The distribution of patients according to the ECOG scale was shown in Table 2. Study population ECOG Performance Scale ranged from 0-2. The study population had a median ECOG of 1. Most of the population had ECOG PS 1. The distribution of patients is shown in Table 3 according to the FIGO scale. Study population FIGO Performance Scale staging ranged from II -III. Treatment compliance is shown in Table 4. Study population shows Chemotherapy (3<sup>rd</sup> Treatment compliance is shown in Table No. 4. Study population shows Chemotherapy (3<sup>rd</sup> Cycle completed) in both arms. First Arm and Second Arm received 30 (100%), and 28 (87 %) respectively. Chemotherapy (4<sup>th</sup> Cycle completed) in First Arm, and Second Arm was found to be 28 (87%), and 26 (79%) respectively. Patients were assessed at 3, and 6 months to measure the local response of the illness and the incidence of any toxicities during treatment. Patients were classified as having either a CR, PR, SD or progressing illness. RTOG graded the responses of normal tissue. 30 patients in each arm were evaluated for treatment response using WHO criteria: - At 3 months 26 (86%) out of 30 of those in Arm A had complete response whereas 27 patients (90%) of those in Arm B had PR. 2 patients in arm A and 1 patient in arm B had PR. In both arms 2 patients had progressive disease. At 6 months 1 patient in both arms who had progressive disease changed into partial response after taking post RT chemotherapy. Results of both arms were statistically insignificant. (p=0.86) (Table 5). As observed in Table No. 6 during treatment, during radiation, acute

toxicities were evaluated according to the National Cancer Institute; Common Terminology Criteria of Adverse Event (CTCAE) version 4. Acute toxicities related to hematologic profiles, gastrointestinal and genitourinary toxicity were evaluated. No patient showed grade 4 toxicity in terms of the hematologic, gastrointestinal, or genitourinary systems. All acute toxicities were relieved spontaneously or controlled with medications. 4 patients in the first arm and 3 patients in the second arm had grade I gastrointestinal toxicities. 3 patients in Arm A and 2 patients in Arm B had grade 2 rectal toxicities and all patients were treated conservatively. In the first arm, no patients had rectal toxicities of grade III, but one patient in the second arm did. No patient had rectal toxicity of grade IV. 4 patients in the first arm and 3 individuals in the second arm had an increase in urinary frequency and 2 among 4 in arm A had UTI symptoms and were treated with antibiotics. 2 patients in Arm A and 1 patient in Arm B had bladder toxicity of grade II severity. No patients had grade 3 and 4 bladder toxicities. All values are statistically insignificant.

## Discussion

Combined radiotherapy technique in the form of EBRT with intracavitary brachytherapy has been customary as the use of radical treatment in uterine cervical cancer worldwide. With brachytherapy, we can increase the cure rates by using dose escalation after EBRT and turning in high doses directly to the tumor with sparing surrounding normal tissues. HDR brachytherapy additionally has some benefits of low radiation exposure to radiation workers, and dose optimization but also in addition of late toxicity because of the large dose per fraction. A study was completed by Orton et al., who did a study and obtained statistics from 56 institutions treating a total of over 17,000 cervix cancer patients. Most cancers patients with HDR-ICBT found that affected person morbidity rates were due to toxicities had been lower for point A with less than 7 Gy in comparison with greater than 7 Gy for both types of toxicities (1.28% vs. 3.44%) and moderate + severe toxicities (7.58% vs. 10.51%) [12]. They showed that fractionation of HDR brachytherapy can influence toxicities. However, this observation did not take BED values into concerns and additionally, it was also retrospective [12]. In further analysis, Orton et al., additionally stated that 4 to 9 Gy may be appropriate but proper packing method in ICBT needs to be considered. Peterit et al., reviewed 24 articles on excessive Dose rate brachytherapy for carcinoma cervix the use of

Table 4. Compliance of Patients

Parameter	No of Patients (%)	
	First Arm (%)	Second Arm
Chemotherapy	30 (100)	30 (100)
(3 <sup>rd</sup> Cycle completed)	30 (100)	28 (94)
Chemotherapy	28 (94)	26 (87)
(4 <sup>th</sup> Cycle completed)		

Table 5. Treatment Response

Disease Response	Arm A (out of 30)		Arm B (out of 30)	
	At 3 <sup>rd</sup> Month	At 6 <sup>th</sup> Month	At 3 <sup>rd</sup> Month	At 6 <sup>th</sup> Month
Complete Response (CR)	26 (86 %)	26 (86%)	27	27
Partial Response (PR)	2	3	1	2
Stable Disease (SD)	0	0	0	0
Progressive Disease (PD)	2	1	2	1

Table 6. Toxicities During Treatment

Toxicity Group	Grade I		Grade II		Grade III		Grade IV	
	First Arm	Second Arm	First Arm	Second Arm	First Arm	Second Arm	First Arm	Second Arm
Rectal toxicities (diarrhea)	4	3	3	2				
Bladder toxicities	4	3	2	1	0	0	0	0

distinctive regimens attempted to correlate BED10 and BED3 to pelvic control and complications, respectively [13]. However, no dose response relationship for normal tissue complications and tumor control probability had been given. They discovered that the approach and experience of individual centers would possibly have performed an extra important role than attempts to optimize fractionation.

The American Brachytherapy Society recommends individual fraction sizes of less than 7.5 Gy per fraction using 4 to 8 fractions. However, ABS additionally consist of caution that these recommendations are no alternative for clinical experience and need to be tested in a clinical setting. Numerous [14-18] studies used distinctive fractionation schedules in HDR-ICRT, however the doses of EBRT to the complete pelvis range in their research. Consequently, a simple evaluation of fraction size and total physical dose might also lead to the wrong interpretation of outcomes. Since the idea of BED was accepted within the clinical field, some have stated upon the outcomes of diverse combos of EBRT and ICBT fractionations in terms of BED10 or BED3. Ferrigno et al. observed that the 5 yr late bladder complication rate was better when treated with BED3 greater than 125 Gy at the bladder reference point, although the difference was no longer statistically significant (17% vs. 9%,  $p = 0.27$ ) [19]. Toita et al., additionally encouraged that in HDR brachytherapy the rectal dose BED3 needs to keep under 100-120 Gy [20]. Patel et al. did a prospective randomized study in 104 cervical cancer patients who were treated with EBRT with HDR [21], in ARM A he chooses 9 Gy for two fractions, and in ARM B he used 6.8 Gy for 3 fractions. He gave each fraction weekly. In his result, the 3 – 12 months risk of developing any grade three late toxicity was 7.47% with 9 Gy and 3.57% with 6 Gy ( $p = 0.3$ ). However not statistically significant. He also stated that using a high dose per fraction (9 Gy per fraction), the incidence of late toxicity was much less because of brachytherapy application under general anesthesia and effective vaginal packing. They concluded that a smaller number of fractions are extra economical and may lessen the health facility admissions frequencies.

To compare with all studies in our study both the fractions are comparable in terms of disease response and toxicities but arm A had less treatment completion time than arm B.

#### Limitation

Small sample size and short follow-up.

In conclusion, brachytherapy should be considered a cornerstone of cervical cancer treatment. Several centers have experimented with various doses and fractionation regimes. Patient safety and tolerability were not an issue in this trial between the two treatment groups. Toxicities and illness responses indicated that Arm B was more effective than Arm A. Yet, there was no statistically significant difference. Thus, the choice of treatment plan depends on the individual needs of the patient and the demands of the institutions. Though for a concrete assessment of disease response and toxicities, longer follow-ups and a larger patient sample are required.

#### Informed Consent

Research involving human participants – Informed consent was obtained from all individual participants included in the study.

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