

## RESEARCH ARTICLE

# High Dose Rate Brachytherapy in Two 9 Gy Fractions in the Treatment of Locally Advanced Cervical Cancer - a South Indian Institutional Experience

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### Abstract

**Background:** Although 3D image based brachytherapy is currently the standard of treatment in cervical cancer, most of the centres in developing countries still practice orthogonal intracavitary brachytherapy due to financial constraints. The quest for optimum dose and fractionation schedule in high dose rate (HDR) intracavitary brachytherapy (ICBT) is still ongoing. While the American Brachytherapy Society recommends four to eight fractions of each less than 7.5 Gy, there are some studies demonstrating similar efficacy and comparable toxicity with higher doses per fraction. **Objective:** To assess the treatment efficacy and late complications of HDR ICBT with 9 Gy per fraction in two fractions. **Materials and Methods:** This is a prospective institutional study in Southern India carried on from 1<sup>st</sup> June 2012 to 31<sup>st</sup> July 2014. In this period, 76 patients of cervical cancer satisfying our inclusion criteria were treated with concurrent chemo-radiation following ICBT with 9 Gy per fraction in two fractions, five to seven days apart. **Results:** The median follow-up period in the study was 24 months (range 10.6 - 31.2 months). The 2 year actuarial local control rate, disease-free survival and overall survival were 88.1%, 84.2% and 81.8% respectively. Although 38.2% patients suffered from late toxicity, only 3 patients had grade III late toxicity. **Conclusions:** In our experience, HDR brachytherapy with 9 Gy per fraction in two fractions is an effective dose fractionation for the treatment of cervical cancer with acceptable toxicity.

**Keywords:** High dose rate brachytherapy - two fractions - treatment efficacy - late toxicity - cervical cancer

*Asian Pac J Cancer Prev*, 16 (16), 7167-7170

### Introduction

Cervical cancer is the fourth most common malignancy in females worldwide (Globocan, 2012: <http://www.globocan.iarc.fr>). Cervical cancer in locally advanced stages are treated by external beam radiotherapy (EBRT) along with concurrent chemotherapy, followed by high-dose-rate (HDR) intracavitary brachytherapy (ICBT). Although, image based brachytherapy is now the standard of treatment in most of the advanced centres in the world, orthogonal brachytherapy is still performed in the developing countries due to financial reasons.

Though there are more than many decades of published literature on the dose fractionation schedules in HDR ICBT for the treatment of cervical cancer, there is no uniform consensus on it (Sood et al., 2002). The American Brachytherapy Society (ABS) recommended an individual fraction size of less than 7.5 Gy in four to eight fractions depending on the dose per fraction. But they have also cautioned that the recommendation has not been thoroughly tested (Nag et al., 2000).

Few studies have demonstrated that HDR ICBT is also quite safe and equally effective if the dose per fraction is

as high as 9 Gy, as opposed to the ABS (Sood et al., 2002; Patel et al., 2005; Patel et al., 2011). Hence, the current study was undertaken to assess the efficacy and rate of late complications with 9 Gy per fraction of HDR ICBT in two applications.

### Materials and Methods

This is a prospective study undertaken in a South Indian institution from 1<sup>st</sup> June 2012 to 31<sup>st</sup> July 2014 with 76 patients of locally advanced cervical cancer. Patients included in the study were of the age group between 35-70 years with International Federation of Gynecology and Obstetrics (FIGO) Stage IIB to IIIB with squamous cell histology. All the patients underwent EBRT with 50.4 Gy to the whole pelvis in two parallel-opposed anteroposterior fields (1.8 Gy per fraction, 5 fractions/week, with 6 MV photons via Linear Accelerator, in 28 fractions). In all the patients, central shielding was done after 25 fractions (45 Gy) to spare the rectum and bladder while maximizing dose to the parametrium and pelvic nodes. Along with EBRT, all the study patients were treated with at least four cycles of concurrent weekly Cisplatin 40 mg/m<sup>2</sup> as

radiosensitizer. Institutional ethical committee approval was taken.

Following EBRT, all patients underwent two applications of HDR ICBT with 9 Gy per fraction, each one week apart. The basic characteristics of the study patients are depicted in Table 1.

The total biological equivalent dose (BED) delivered to Point A in the study was 87.3 Gy.

### EBRT

EBRT was delivered with 6 MV photons via linear accelerator at 1.8 Gy per fraction, 5 fractions per week in two parallel opposed anteroposterior fields up to a total dose of 50.4 Gy with central shielding done after 45 Gy. The radiation field was designed with superior border at the L4-L5 junction. The inferior border was kept at the lower border of the obturator foramen or still lower depending on the inferior extent of the disease. The lateral borders were planned 1.5-2 cm away from the lateral pelvic brim so as to include the pelvic nodes.

### Chemotherapy

Along with EBRT, at least four cycles of concurrent weekly Cisplatin at 40 mg/m<sup>2</sup> were delivered.

### ICBT

ICBT were performed in the minor operation theatre under proper analgesic coverage, without anaesthesia. The time gap between completion of EBRT and the starting of ICBT was kept between four days to one week. Adequate vaginal packing was done to minimize dose to the rectum and bladder. Orthogonal anteroposterior and lateral simulation X-ray films were taken after each ICBT application. Dose was prescribed to Point A and dose to bladder and rectum were calculated as per the International Commission on Radiation Units and Measurements (ICRU) Report 38 recommendations (ICRU Report # 38, 1985). The dose to the rectum and bladder were kept below 80% of the dose to the Point A, without compromising the Point A dose. Treatment was delivered using HDR

MicroSelectron machine using Ir192 source and Oncentra planning system.

The mean duration of overall treatment time was 59.2 days. 21 patients completed their overall treatment within 56 days.

### Follow up

All the study patients were followed up after every 3 months in the first two years and after every 6 months thereafter. The patients were evaluated for local or distant failures and any treatment related toxicities. Apart from a thorough clinical evaluation, proctoscopy and cystoscopy, other investigations like X-rays, CT scans, MRI scans, and recto sigmoidoscopy were performed whenever indicated. Rectal and bladder toxicity were documented according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria (Cox et al., 1995).

### Statistical analysis

Local disease control, disease-free survival and overall survival were calculated from the date of treatment initiation. Treatment failures were classified as local pelvic failures or distant failures (extra-pelvic lymph nodal metastases, bones, viscera). All data were tabulated in MS Excel 2013. Statistical analysis was done using SPSS Version 20. Statistical correlation between two variables were calculated by the Chi-square test. Local control, disease-free survival, overall survival and late complication rates were calculated by Kaplan-Meier method. p-value <0.05 was considered to be statistically significant.

## Results

### Local control

The 2 year actuarial local disease control rate was found to be 88.1% (Figure 1). On correlating all the variables with the local control rate of the disease, a significant correlation (p-value 0.048) was found with total treatment time.

### Failure patterns

A total of nine (11.8%) patients presented with local failure on follow up. Out of these, one patient had distant metastatic disease along with local failure. Overall failure was seen in 15.8% of the study patients (Table 2).

### Survival

The 2 year actuarial disease-free survival was found to be 84.2% (Figure 2). The 2 year actuarial overall survival among the study patients was found to be 81.8% (Figure 3). A total of 13 patients in the present study died during the follow up period. Four of these patients did not have any local or distant failure at their last follow up and died of other causes.

### Late toxicity

29 (38.2%) patients suffered with some form of late toxicity. Out of these 29 patients, 24 patients had late rectal toxicity and 13 patients had late bladder toxicity. Only

**Table 1. Study Patient Characteristics**

Patient Characteristics	Number of patients (%)
Age of the patients	
< 50 years	19 (25)
≥ 50 years	57 (75)
FIGO Stage of the patients	
Stage IIB	23 (30.3)
Stage IIIA	4 (5.3)
Stage IIIB	49 (64.5)
Pre-treatment Haemoglobin	
< 10 gm/dl	34 (44.7)
≥ 10 gm/dl	42 (55.3)
Number of Cycles of Weekly Cisplatin	
4	26 (34.2)
5	42 (55.3)
6	8 (10.5)
Total treatment time	
≤ 56 days	21 (27.6)
> 56 days	55 (72.4)

FIGO – International Federation of Gynecology and Obstetrics

three patients had Grade III late toxicity, while none of the study patients had any Grade IV late toxicity. Out of these three patients, two patients had Grade III rectal toxicity for which surgical exploration was done. One patient had Grade III bladder toxicity with severe frequency, dysuria,

generalized telangiectasia and frequent macroscopic hematuria. The mean time duration of developing late rectal toxicity and late bladder toxicity were 9.6 months and 21.8 months respectively.

## Discussion

Cervical carcinoma is one of the major contributors of cancer related morbidity and mortality in women all over the world (Shruthi et al., 2014). Chemoradiation with platinum compounds like Cisplatin as radiosensitizer is the treatment of choice in locally advanced cervical cancer (Kumaran et al., 2014). Although studies (Madan et al., 2014; Hashim et al., 2015) have demonstrated the underestimation of dose to the organs at risk and overestimation of target volume coverage with 2D orthogonal HDR ICBT, many centres in developing countries still practice this traditional approach due to financial constraints.

Orton GC (Orton GC, 1995) found that though individual fraction size in HDR brachytherapy may be between 4-9 Gy, it was of prime importance to minimize the dose to the rectum and bladder by means of proper vaginal packing or retraction. The ABS recommended that the individual fraction size in HDR brachytherapy should be < 7.5 Gy with a total of four to eight applications. But they also added that these recommendations were not adequately tested and was inferior to clinical experience (Nag et al., 2000).

An American study (Sood et al., 2002) found that two fractions of HDR ICBT with 9 Gy per fraction or even with 9.4 Gy per fraction, were safe and effective in the management of cervical cancer. They also concluded that the use of two fractions of brachytherapy did not lead to increased bladder or rectal toxicity. Patel et al. (2005), demonstrated that two applications of HDR ICBT with 9 Gy per fraction in the management of cervical cancer was both safe and effective with good local tumor control and minimum toxicity. The actuarial 5-year local control rate was 74.5% and the actuarial risk of developing Grade III or worse late toxicity was 3.31%. In 2011, Patel FD et al. (2011) concluded that two applications of HDR ICBT with 9 Gy per fraction was safe and effective with good local tumor control, good survival rates and manageable toxicity.

In the present study, the 2 year actuarial local tumor control rate, disease-free survival and overall survival were 88.1%, 84.2% and 81.8% respectively. Grade III late toxicity was seen in only three patients in the study. These results are in concordance with the earlier studies, and demonstrate that HDR ICBT with two applications of 9 Gy per fraction is effective in terms of tumor control and survival. Also this is a safe fractionation with manageable late toxicity, and can be practised.

In conclusion, HDR orthogonal ICBT with 9 Gy per fraction in two applications is an effective and safe dose fractionation for the treatment of cervical carcinoma. Hence, it can be used in developing countries, where – there is an excessive load of patients when compared to the centres; ICBT cannot be interdigitated with EBRT due to the increased acute toxicity in the patients, leading to

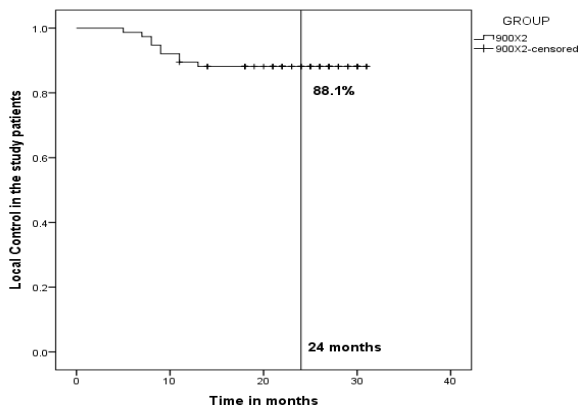


Figure 1. The 2 year Actuarial Local Disease Control was 88.1% in the Study Patients

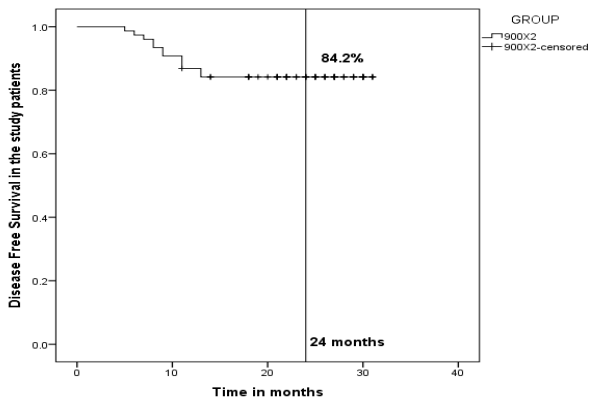


Figure 2. The 2 year Actuarial Disease Free Survival in the Study Patients was 84.2%

Table 2. Patterns of Failure in the Study Patients

Patterns of Failure	Number of patients (%)
Local failure alone	8 (10.5%)
Distant failure alone	3 (3.9%)
Local along with distant failure together	1 (1.3%)
Overall failure	12 (15.8%)

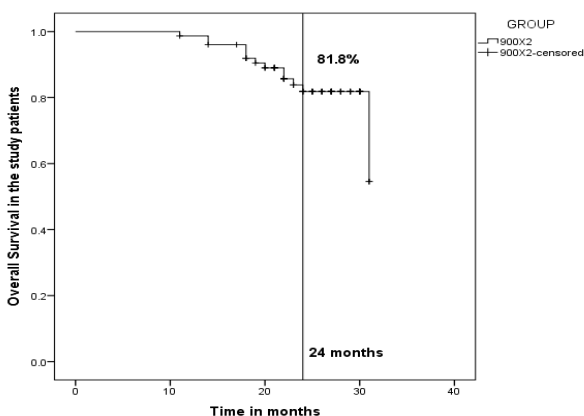


Figure 3. The 2 year Actuarial Overall Survival in the Study Patients was 81.8%

increase in total treatment time; patients are apprehensive and do not turn up properly for multiple (four to eight) brachytherapy applications, leading to incomplete treatment.

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