



### Original Article

## A comparison of Dosimetry and Efficacy between two fractionation schedules of HDR brachytherapy using Fletcher–suit-delclos-applicator in patients with locally advanced Carcinoma Cervix- A Single Institution Randomised Prospective Study

Authors

Subhendu Gangopadhyay, Bidyut Mandal\*, Janmenjoy Mondal,  
Shinjini Chakrabarty, Debjit Ghosh, Abhishek Basu

\*Corresponding Author

Bidyut Mandal (Assistant Prof)

Department of Radiotherapy, Medical College Kolkata, India

### Abstract

**Purpose:** Cervical cancer is the second most common cancer in women in India with annual mortality of around 60,000. Brachytherapy is an integral part of treatment of CA Cervix. Single Institutional, Open label randomised clinical trial was performed to compare & evaluate clinical outcomes using two different dose fractionation but same applicator in ICBT for Cancer Cervix in term of better locoregional control with acceptable bladder, rectal toxicity & late toxicity.

**Material & Methods:** 60 patients were accrued between January 2018 & June 2019 & treated with ICBT using FLETCHER – SUIT – DELCLOS applicator with HDR after loader unit. All patients received 50Gy/25# whole pelvis EBRT with concurrent Inj Cisplatin. They were allotted in 2 arms (n= 30) & received 9 Gy ×2# and 7 Gy ×3 # respectively. Response and Radiation induced toxicities were assessed and graded. Disease free survival was estimated based on the duration from the date of completion of treatment to the date of last follow up/recurrence of tumour/ death in the patients who have achieved Complete Response. During treatment, patients were reviewed weekly. After treatment completion, patients were reviewed at 6 weeks, 3 months, 6 months, 9 months and 12 months.

**Results:** Patients in both the arms had equivalent response (local control) with 80% local control in study arm as compared to 63.3% in control arm. 1 year actuarial DFS in study arm is 60% as compared to 52% in control arm. Median DFS was better in study arm (14 months v/s 12 months) with a trend of significant benefit. Improved DFS in the study arm was probably be explained by reduction of overall treatment time. Few Grade 1 & 2 late rectal, bladder and vaginal toxicities were present over there without any Grade 3 or 4 toxicity.

**Conclusion:** 9 Gy/# × 2 HDR Brachytherapy is an effective and safe alternative to equivalent response in terms of dose fractionation and manageable toxicity for treating locally advanced CA cervix that can be used in developing countries with excessive patient load.

**Keywords:** Carcinoma Cervix, Intracavitary Brachytherapy, Fractionation, Fletcher applicator.

### Purpose

Cervical cancer is the second most common cancer after Breast cancer in women of India with annual mortality of around 60,078.<sup>[1]</sup> Brachytherapy is an integral part of treatment of CA Cervix. In developing countries like India, most of the cases are detected in an advanced stage, i.e., in the International Federation of Gynecology and Obstetrics (FIGO) Stage IIB- IVA.<sup>[2]</sup> In the locally advanced stage disease, external beam radiotherapy (EBRT) along with concurrent chemotherapy (cisplatin as radio sensitizer, at a dose of 40 mg/m<sup>2</sup> as per institutional protocol) followed by high dose rate (HDR) intracavitary brachytherapy (with minimising doses to organs at risk) becomes the treatment of choice. Dose of EBRT ranges from 4000 to 5000 cGy in 20–30 fractions, 180–200 cGy per fraction over a period of 5 weeks, five fractions per week delivered using conventional or conformal radiotherapy technique.<sup>[3]</sup> Brachytherapy plays an anchor role in management of cervical cancer and forms an integral part of radiation therapy. Intracavitary brachytherapy remains the most commonly practiced form of brachytherapy for cervical cancer.<sup>[4]</sup>

The conventional Fletcher's applicator has a stainless steel tandem and two colpostats or ovoids which are fixed to hollow handles for loading of radioactive sources. The rigid tandem used in Fletcher's applicators has curvatures like 15°, 30°, or 45°. <sup>[5]</sup> 3D image based ICBT is currently the standard mode of treatment in cervical cancer which is being practised in our institution (MCH, Kolkata) with dose prescribed to Point A. Total treatment duration in our institution using conventional ICBT doses i.e. 7Gy per fraction per week in 3 fractions is 8-9wks depending on logistics & patient's complianace. On the contrary, treatment duration using higher doses of ICBT (9Gy per fraction per week in 2 fractions) is 8 weeks. Several studies have described lower pelvic control and survival rates with prolongation of treatment duration. In short it

can be said that overall disease free survival can be maximised by reducing treatment time by giving large dose per ICBT fraction. This is a prospective study was undertaken with the aim of assessing the feasibility and tolerability to evaluate the effects of treatment duration shortening by means of higher doses (9Gy/fraction/week for 2 fractions) per fraction of ICBT comparing with conventional (7GY/fraction/week for 3 fractions) doses with respect to local control rate (tumour response), disease free survival, overall survival & acceptable bladder and rectal toxicity and late toxicity of rectum, bladder, skin, vaginal mucous membrane, GI & Hematological system toxicity in case of locally advanced carcinoma of cervix.

### Material & Methods

Conventionally, brachytherapy is delivered after completion of EBRT and most procedures related to HDR BT use conventional doses of 7 Gy per fraction for 3 fractions. This prospective open label randomised clinical trial included (Table 1) 60 patients of biopsy proven cases of locally advanced Carcinoma cervix attending Radiotherapy OPD, treated with HDR brachytherapy using fletcher–suit-delclos-applicator during the period January 2018 to June 2019, and traced till September 2019. All these patients were treated with combination of EBRT followed by intracavitary brachytherapy with either 9Gy ×2# or 7Gy×3#. All patients had routine workup and All patients were given external beam radiotherapy dose of 50Gy in 25 fraction with 2Gy /#, five days a week schedule to whole pelvis using anterior and posterior parallel opposed portals on 780C Theratron Telecobalt. All these patients are randomly allotted (Fig 1)& treated with ICBT using FLETCHER – SUIT – DELCLOS applicator (Tandem with ovoids) by iridium 192 with HDR afterloader unit with VARIAN ECCLIPSE Treatment Planning System (TPS). They were allotted in 2 arms (n= 30) & received 9 Gy ×2# and 7 Gy ×3 # respectively. Response was assessed using the RECIST version

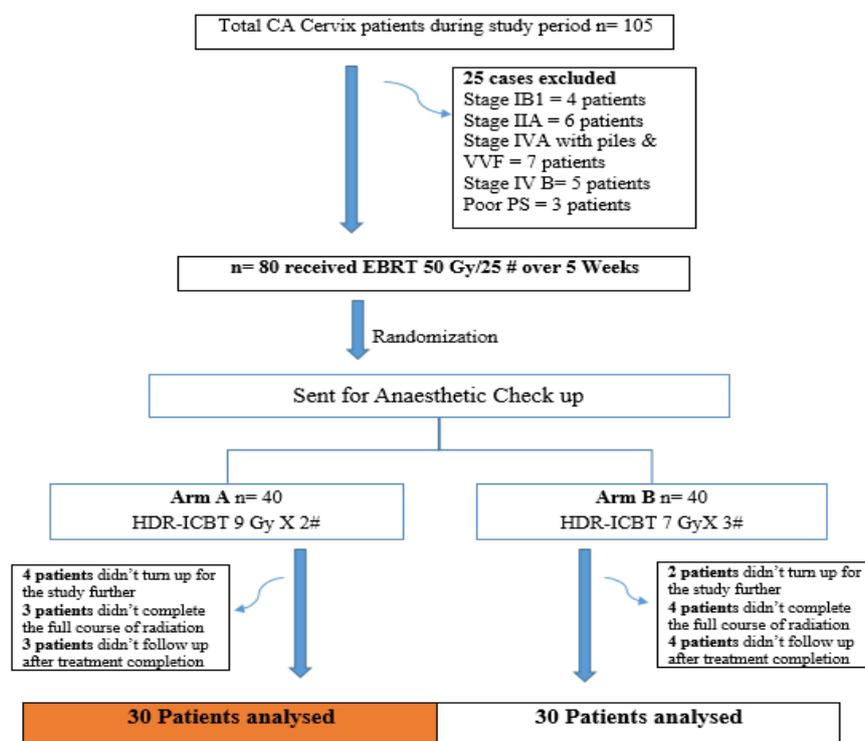
1.1. Radiation induced toxicities was assessed and graded. Disease free survival was estimated based on the duration from the date of completion of treatment to the date of last follow up/recurrence of tumour/ death in the patients who have achieved Complete Response. During treatment patients were reviewed weekly. After treatment completion, patients were reviewed at six weeks, then at 3 months, 6 months, 9 months and 12 months. Radiation induced toxicities was assessed and graded according to RTOG/ EORTC acute and late toxicity grading criteria. All the data was

compiled, tabulated & analysed using Unpaired T test & Chi-square test to compare numerical & categorical variables, using IBM Statistical Package for Social Sciences (SPSS), Version 23. Local pelvic control rate and disease free survival (DFS)&overall survival (OS) were calculated using Kaplan–Meier analysis, and log-rank test was used for comparison. A p value  $\leq 0.05$  was considered significant.

**Ethical Clearance:** IEC of Medical College, Kolkata approved; MC/ Kol/ IEC/ Non-spon/ 640/ 11-2017

**Table 1:** Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<b>i.</b> Age 25 - 70yrs	<b>i.</b> Pregnant and lactating women
<b>ii.</b> Histo-pathologically proved carcinoma cervix cases	<b>ii.</b> Previous History of hysterectomy and pelvic irradiation
<b>iii.</b> International Federation of Gynaecology and Obstetrics (FIGO) stage IIB to IVA cases	<b>iii.</b> Patient with any benign rectal or bladder disorder
<b>iv.</b> Karnofsky performance status above 70	<b>iv.</b> Patient with genital prolapse or with deformities of the knee or Hip
<b>v.</b> Patient who has given approved Informed consent of Hospital Ethical Committee	<b>vi.</b> Patients not willing to have anaesthesia



**Fig 1:** Scheme of selection, randomization and allocation of patients into two arms

## Results

Both the arms are comparable on demographic characteristic (table 2). The overall treatment time was shorter in study arm (9 Gy) with a mean value of 57.4 days compared to 63.2 days in control arm (7 Gy). [p <0.01, i.e. statistically significant]. Stage wise disease distribution, EBRT & BT gap and final response are comparable in both arms. Dosimetry of Brachytherapy was also comparable in both arms (Table 3). In the dosimetric analysis, mean 2 cc bladder dose in the study arm is significantly low as compared to control arm (p = 0.01). Mean point A dose and mean 2 cc rectal doses are also lower in study arm as compared to control arm but it was statistically not significant. Hence there were less chance of bladder & rectal toxicity without affecting therapeutic goal. Mean duration of follow up was 14 month (range 12-16month). The median follow up for the whole group was 13 months. The median follow-up for Study arm was 15 months and for Control Arm, it was 14 months. 1yr tumour control in both the arms has equivalent results showing 80% in study arm v/s 63.3% in control arm. Response was not significantly better in study arm (p = 0.347) but ORR (Overall response rate) was similar (93.3% vs 90%) in both the arms. Comparing from

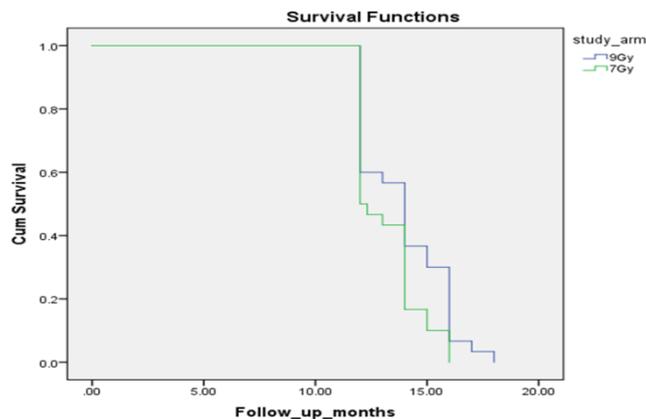
Kaplan Meir DFS curve the 1 year disease free survival rate was 60% for study arm and 52% for control arm (Fig 2). The Median DFS was better in study arm (14 months vs 12 months). As there is no death in both the arms during study, overall survival remains the same in both the arms. Multivariate analysis showed that overall treatment time was an important prognostic factor in local control and DFS (p = 0.006). Better 1 year disease-free-survival (DFS) in study arm was significantly related to less overall treatment time. The major reason for poor results in patients receiving three fractions of HDR ICBT is the prolongation of treatment time in control arm as most patients completed treatment beyond 8 weeks. Few Grade 1 & 2 late rectal and bladder toxicities were present over there without any Grade 3 or 4 toxicity (Table 5). Both acute (mucositis) & late (dyspareunia) vaginal toxicity were greater in the study arm, statistically insignificant. However there were no Grade 3 & Grade 4 vaginal toxicity in any arm at any stage of follow-up. There was no life threatening grade 3 or 4 haematological toxicity in either of the arms. Acute skin toxicity was present in few patients but late skin toxicity was not present in both the arms during such short follow up period.

**Table 2** Demographic characteristics of study population

Demographic Parameters	Study Arm (9 Gy) (n=30)	Control Arm (7 Gy) (n= 30)	P Value
Age (Mean Value) [Yrs]	49.6	53.1	0.228
Age of Menarche (Mean Value) [Yrs]	11.8	11.7	0.081
Stage (Most common)	IIB	IIB	0.68
Age at 1 <sup>st</sup> Pregnancy (Mean) [Yrs]	23.4	22.9	0.22
Pre-treatment Hb% (Mean)	9	8.9	0.177
ECOG- PS (Most Common)	1	1	0.119

**Table 3** Dosimetry comparison between two Arms

PARAMETERS	Study Arm (9 Gy)	Control Arm (7 Gy)	P value
Point A dose(Gy) EQD2 [Mean Value]	79.59 ± 2.59	80.62 ± 2.51	0.126
2CC Bladder dose(Gy) EQD2 [Mean Value]	73.31 ± 6.5	78.63 ± 8.77	0.01
2CC Rectal dose(Gy) EQD2 [Mean Value]	71.82 ± 3.99	73.64 ± 5.78	0.16



**Fig 2:** Kaplan Meir survival curve showing Disease free Survival (DFS) in two groups

### Discussion

Intracavitary brachytherapy (ICBT) is a very important and integral component of definitive treatment by radiotherapy for carcinoma of the cervix. ICBT enhances the curative potential of radiotherapy by delivering a very high dose of radiation to the tumour while sparing the normal tissues. With the advent of HDR Brachytherapy, high dose of radiation can be delivered in a shorter period of time, thereby reducing patient discomfort and inconvenience. Despite its practical advantages HDR Brachytherapy has experienced considerable resistance due to its potential late toxicity and theoretical radiobiologic disadvantages of greater probability of late effects for a given level of tumour control. Fractionation and dose adjustment of the total dose are crucial factors in lowering the frequency of complications without compromising the treatment results.

Several studies have described lower pelvic control and survival rates with prolongation of treatment duration. Data by Orton et.al. demonstrated that late complication rates were significantly lesser with HDR fraction size of  $\leq 7$  Gy as compared with  $> 7$  Gy, but effects of dose per fraction on cure rates are equivocal.<sup>[6]</sup>

Patel et al, (2005, 2011) demonstrated that two applications of HDR ICBT with 9 Gy per fraction was both safe and effective with good local tumour control and minimum toxicity. The actuarial 5 yr local control rate was 74.5%.<sup>[7]</sup>

An American study found that two fractions of HDR ICBT with 9 Gy per fraction or even with 9.4 Gy per fraction, survival rates after 2, 3, and 5 years were 83%, 78%, and 78%, respectively.<sup>[8]</sup>

In a prospective institutional study in southern India, from 1<sup>st</sup> June 2012 to 31<sup>st</sup> July 2014, 76 patients of cervical cancer were treated with concurrent chemoradiation followed by ICBT with 9 Gy per fraction in two fractions, 7 days apart. Median follow up period was 24 months. The 2 year actuarial local control rate, disease free survival and overall survival were 88.1%, 84.2% & 81.8% respectively.<sup>[9]</sup> The ABS recommended that the individual fraction size in HDR brachytherapy should be  $<7.5$  Gy with a total of 4 to 8 applications, But they also added that these recommendations were not adequately tested and was inferior to clinical experience. (Nag etal; 2000).<sup>[10]</sup>

Present study results are in concordance with the results of earlier studies. So 9 Gy/# HDR Brachytherapy is an effective and safe dose fractionation with equivalent response and manageable toxicity that can be used in developing countries with excessive patient load. The most likely reason for this is the prolongation of overall treatment time when we use three fractions instead of two after external beam radiation. As the toxicity is not significantly high with higher dose per fraction, decreasing the number of fractions is a more practical approach in our set up, provided a favourable application is possible.

### Conclusion

In a developing country like India, keeping the patient compliance and convenience in mind, two fractions of 9 Gy can be safely administered in ICBT for Locally advanced carcinoma cervix. This is a practical approach when desired dosimetry has achieved as this reduces multiple exposure to anaesthetic drugs & multiple admissions in Indoor, thus coping with the fairly large patient load in a busy Government Hospital. Further large Prospective, multi institutional,

randomised studies are needed for validation for benefit the entire mankind & future direction.

## References

1. Bray, F., Ferlay, J. , Soerjomataram, I. , Siegel, R. L., Torre, L. A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:[10.3322/caac.21492](https://doi.org/10.3322/caac.21492).
2. Nandwani PK, Vyas RK, Neema JP, Suryanarayan UK, Bhavsar DC, Jani KR. MUPIT in locally advanced gynecological malignancy. J Cancer Res Ther 2007;3:111- 5.
3. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high risk cervical cancer: an update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. J Clin Oncol. 2004;22(5):872–80.
4. Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIg). *Int J Radiat Oncol Biol Phys*. 2012;82(1):250–255. doi:[10.1016/j.ijrobp.2010.10.030](https://doi.org/10.1016/j.ijrobp.2010.10.030)
5. Khan FM, Gibbons JP. Chapter 23: High-Dose-Rate Brachytherapy. In: *The Physics of Radiation Therapy*. 5<sup>th</sup> ed. USA: Lippincott Williams & Wilkins; Wolters Kluwer; 2014. p. 476
6. Orton GC. Width of the therapeutic window: What is the optimal dose-per-fraction for high dose rate cervix cancer brachytherapy? *Int J Radiat Oncol Biol Phys* 1995;31:1011e1013.
7. Patel FD, Kumar P, Karunanidhi G, Sharma S.C, Kapoor R, et al. Optimization of high – dose- rate intracavitary brachytherapy schedule in the treatment of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011;10: 147e153
8. Sood BM, Gorla G, Gupta S, et al. Two fractions of high-dose-rate brachytherapy in the management of cervix cancer: Clinical experience with and without chemotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:702e706
9. High Dose Rate Brachytherapy in Two 9 Gy Fractions in the Treatment of Locally Advanced Cervical Cancer - a South Indian Institutional Experience. Ghosh S<sup>1</sup>, Rao PB, Kotne S.
10. Nag S, Erickson B, Thomadsen B, et al. The American Brachytherapy Society (ABS) Recommendations for High-Dose-Rate Brachytherapy for Carcinoma of the Cervix. *Int J Radiat Oncol Biol Phys* 2000;48:201–211.