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# A Comparative Study between Two Different Intracavitary High Dose Rate Brachytherapy Schedules with Concurrent External Beam Radiotherapy in Cervical Cancer Stage – II

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**Abstract**

**Background:** High Dose Rate (HDR) intracavitary Brachytherapy (ICBT) is essential for successful management of locally advanced cervical cancer. The quest is to interdigitate it with External Beam Radiotherapy (EBRT) to complete the treatment within 8 weeks and with fewer toxicities.

**Objective:** To compare and analyze results of Two HDR ICBT schedules of 6 Gray (Gy)/#(fractions) for 4 fractions (in Arm A), and 7.5 Gy/# for 3 fractions (in Arm B) given in concurrent form with EBRT to whole pelvis and weekly chemotherapy.

**Materials and Methods:** This study is a prospective randomized control trial performed in a regional cancer center located in Bikaner, Rajasthan from march 2017 to may 2018. Total of 42 cases of histologically proven squamous cell cancer of cervix satisfying our inclusion criteria were randomized into two arms. After completion of 20 Gy through EBRT cases in Arm A received 6 Gy / # for 4 # of HDR ICBT, while cases in Arm B received 7.5 Gy / # for 3# on every Saturday.

**Results:** The Median follow up period of study was 19 months. There is no significant difference in local control and late toxicities in both arms.

**Conclusion:** In our experience 7.5 Gy /# for 3# and 6 Gy /# for 4 # when given with EBRT produces equal results and are equally tolerated by patients, though these regimes required to be compared with conventional regimes (HDR ICBT followed by EBRT)

**Keywords:** cervical cancer, HDR intracavitary brachytherapy, dose fractionation,

## Introduction

The incidence of cervical cancer is on decreasing trend, as per recent data it is now 10th most common malignancy worldwide **[1].** Its more common in developing countries than developed countries. The Annual incidence rate of 122,844 is decreased to 96 922 and annual mortality is reduced from 67,477 females to 60 078 deaths due to

cervical cancer in India **[2][3].** It is now the third leading cause of female cancer and also 4th leading cancer cause of female deaths in India **[3].** Patients of cervical cancer in India usually present in FIGO stage II (35%), or in stage III (43%) with 88% of total cases having squamous histology **[4].** The American Brachytherapy Society (ABS) endorses the use of Brachytherapy (BT) as an integral component of the definitive treatment of locally advanced cervical cancer (IB2 – IVA) **[5].** The recommended treatment for locally advanced cervical cancer is EBRT with concurrent chemotherapy (CT) and HDR intracavitary brachytherapy (ICBT). The ABS recommends keeping the total treatment duration to less than 8 weeks because prolongation of total treatment duration can adversely affect local control and survival **[6].** ABS also recommend keeping individual fraction size to less than 7.5 Gy due to increase toxicities with larger fraction size **[7].** This makes it difficult to complete treatment in a specified duration of 8 weeks, the recommendation is, therefore, to interdigitate the implants during EBRT (but EBRT is not given on the day of HDR). Though there are multiple publications on optimum dose fractionation schedules in HDR ICBT for cervical cancer, a uniform consensus is still lacking **[8].**

This study was undertaken to examine the effectiveness of two ICBT regimes in cervical cancer, in terms of local control, Disease Free Survival (DFS), Overall Survival (OS) and toxicity. Patients are randomized on the basis of HDR dose fractionation schedules, in Arm A cases received 6 Gy/# for 4 fractions of HDR, while in Arm B cases received 7.5 Gy/# for 3 fractions.

**Materials and Methods**

This study is a prospective randomized control trial performed in a regional cancer center located in Bikaner, Rajasthan. A total of 42 patients of FIGO stage II A and II B with squamous cell histology were included. Cases were of age group between 35 to 70 years with a performance score of 0 to 2 (ECOG performance score) **[9].** All cases were treated with EBRT for a total dose of 50 Gy on $Co^{60}$ (Theratron -780c / Bhabhatron) units to the whole pelvis. The daily fraction of 2 Gy, 5 days/week with parallel – oppose fields. In addition, all patients received concurrent weekly 50 mg cisplatin (on every Sunday) for a total number of 3 – 5 cycles. Cases were randomized at the beginning in Arm A and Arm B. Arm A cases received 6 Gy/# for 4 fractions of HDR – ICBT on every Saturday in addition to EBRT and CT, similarly, Arm B cases received 7.5 Gy/# for 3 fractions of HDR – ICBT on every Saturday.

**Table I Patient characteristics in both arms of the study:**

| **Patient Characteristics** | **Arm A (No of patients)** | **Arm B (No of patients)** |
|---|---|---|
| Age group (years) | | |
| <50 years | 08 | 07 |
| >50 years | 13 | 14 |
| FIGO staging | | |
| II A | 05 | 03 |
| II B | 16 | 18 |
| Menopausal Status | | |
| Post-menopausal | 13 | 15 |
| Pre-menopausal | 08 | 06 |
| Residence | | |
| Rural | 19 | 15 |
| Urban | 02 | 06 |

FIGO – International Federation of Gynecology and Obstetrics

For comparison, Biological Effective Dose (BED) delivered to Point A in Arm A = $BED_{EBRT}$ + $BED_{ICBT}$ = 60 + 38.4 = 98.4 Gy, and BED in Arm B = 60 + 38.8 = 98.8 Gy. Equivalent dose in 2 Gy fraction (EQD2) to Point A in Arm A = BED / (1 + 2/10) = 82 Gy while EQD2 for Arm B = 82.3 Gy

**ICBT**

ICBT was performed on every Saturday in both arms once patient received 20 Gy from EBRT. Implants were placed under proper analgesia without the use of any anesthesia. Vaginal packing is done to reduce the dose to rectum and bladder. The simulation was done by using orthogonal AP (Antero – Posterior) and lateral X-ray films at each application. The dose was prescribed to Point A with keeping the dose to rectum and bladder to less than 80% of Point A, as per International Commission on Radiation Units (ICRU)– 38 guidelines. Treatment was delivered with bebig multisource 20 channel HDR – BT unit model 1322 – 0012 (Eckert and Ziegler), Germany using $Co^{60}$ source.

All cases completed the planned treatment. The mean duration of overall treatment time was 42 days. The mean duration of overall treatment time in Arm A and Arm B were 43 and 40 days. In all none of the case in any arm have completed the treatment in the recommended duration of 35 days, but only 2 cases took >56 days for treatment completion.

**Follow up**

All cases were followed up at 3, 6, 12 months after treatment completion. They were examined for any local, regional or distant failure and treatment-related toxicities. Toxicities (mainly bladder and rectal) were documented as per Radiation Therapy Oncology Group (RTOG) / European Organization for Research and Treatment of Cancer (EORTC) criteria **[10].**

Both arms were compared for local, regional or distant failure and treatment-induced toxicities. Local control, distant control, DFS, follow-ups were calculated from the beginning of treatment. Failure is classified as a locoregional failure and distant failure. All cases are alive at the end of one year follow up.

**Statistical Analysis**

For Statistical analysis IBM SPSS Statistics 25 software is used. Data were tabulated in MS Excel 2015. Statistical significance of the difference in proportions was calculated by the Chi-square test. Local control, disease-free survival, overall survival, and late complication rates were calculated by the Kaplan–Meier method, and the differences between the two arms were analyzed by log-rank test. p-value <0.05 was considered to be statistically significant.

**Results**

The median follow-up for all cases was 19 months (range: - 12 – 26 months). The median follow-up for Arm A was 19 months (range: - 13 – 26 months) and for Arm B, it was 18 months (range: - 12 – 25 months) respectively.

**Local Control**

One-year actuarial local control rates in Arm A and Arm B were 90.5% and 90.5%. (p value: - 0.520)

**Patterns of Failure**

**Table 2** Patterns of Failure

| Patterns of Failure | Arm A n (%) | Arm B n (%) | P value n (%) |
|---|---|---|---|
| Local failure alone | 2 (9.5%) | 1 (4.76%) | 0.549 |
| Distant failure alone | 2 (9.5%) | 2 (9.5%) | 1 |
| Both local and distant failure | 0 (0%) | 1 (4.76%) | 0.311 |
| Overall failure | 4 (19%) | 3 (14.3 %) | 0.703 |

**Disease Free Survival**

The one-year actuarial DFS in Arm A and B were 81% and 85.7% respectively, with overall DFS was 83.3%. Although the DFS is higher in Arm B, there was no statistical difference (p-value = .703) when compared to Arm A.

**Toxicities**

For grading of toxicities, RTOG / EORTC gradings were used.

**Table 3** Toxicities

| Patterns of Failure | Arm A n (%) | Arm B n (%) | P value n (%) |
|---|---|---|---|
| Local failure alone | 2 (9.5%) | 1 (4.76%) | 0.549 |
| Distant failure alone | 2 (9.5%) | 2 (9.5%) | 1 |
| Both local and distant failure | 0 (0%) | 1 (4.76%) | 0.311 |
| Overall failure | 4 (19%) | 3 (14.3 %) | 0.703 |

In total 19 cases developed late toxicities. Toxicities in Arm B were mostly Gd I and II but in Arm A, Gd III and IV toxicities were more common. Out of all study cases, 10 (23.8 %) cases developed grade III or IV toxicities. Though the number is higher for Arm A, it is nonsignificant if compared with Arm B (p-value = .741)

**Table 4** Late Toxicities

| Late Toxicities | Overall Cases n (%) | Arm A n (%) | Arm B n (%) | p-value |
|---|---|---|---|---|
| Toxicities of all grades | 19 (45.2) | 8 (38.1) | 11 (52.4) | .206 |
| Gd III IV toxicities | 10 (23.8) | 6 (28.5) | 4 (19) | .741 |

The risk of developing any grade of rectal toxicity was 35.7 % (23.8 % in Arm A and 47.6 % in Arm B), most toxicities were grade I and II. Grade I and II toxicities were more common in arm B (p-value = .006). No grade IV rectal toxicity is observed and risk of grade III rectal toxicity was equal for both arms. Grade I and II bladder toxicities were observed in 1 case in each arm. Two cases of Grade III bladder toxicity were seen in Arm B.

**Discussion**

ICBT with its characteristic rapid dose fall off is pivotal for completion of successful treatment of cervical cancer. BT allows for dose escalation of the tumor in a conformal manner that minimizes the toxicity of nearby organs at risk (OARs). This essential role of BT in the curative treatment paradigm has been confirmed by multiple reports, as it confers not only a local control but a survival advantage when compared to cohorts where EBRT is the only radiation treatment modality utilized **[11].** Low dose rate ICBT is now not used because of longer hospital stay and risk of radiation exposure to hospital staff **[12].** HDR ICBT is currently in use at most of the centers. The disadvantage of HDR therapy is its potential to increase late effects.

It has been demonstrated that individual fraction in HDR brachytherapy may be between 4 – 9 Gy **[13],** the prime importance is to reduce dose to rectum and bladder by proper vaginal packing.

The ABS recommended that individual fraction size should be kept < 7.5 Gy with 4 to 8 fractions. But they also added that these recommendations were not adequately tested and were not superior to clinical experience**.**

ABS has also recommended keeping the total treatment duration to less than 8 weeks, prolongation of treatment time is associated with local relapse and decrease survival. Fyles et al. reported approximately 1 % loss of tumor control per day of prolongation of treatment time beyond 30 days in cervical cancer patients who are treated with radiotherapy alone **[14].** Perez et al. in 1330 patients treated with definitive irradiation, noted a major impact of prolongation of treatment time on pelvic tumor control in stage IB, IIA, IIB. In stage III the relation was not statistically significant. Regression analysis in their study confirmed that prolongation of overall treatment time resulted in an increased failure rate of 0.59 % per day in stage IB and IIA and 0.86 % per day for Stage IIB disease. Many authors have published studies on optimum dose fractionation regimes for HDR ICBT, but most of those are used after completion of EBRT. HDR ICBT after EBRT may be associated with fewer toxicities but it makes it difficult to complete the treatment within 8 weeks because multiple sessions are required.

**Conclusion**

For the management of cervical cancer stage II, both the HDR dose fractionation schedules of 6 Gy/ # for 4# and

7.5 Gy / # for 3# produce equal local control. Although toxicities were more commonly seen in Arm B, they were mostly Grade I and II toxicities and there was no significant difference in grade III, IV toxicities in any arm. In Indian setting, it could result in better compliance of patients as less hospital stay is required, though further studies of this regimes with conventional schedules (HDR ICBT followed by EBRT) are required.

**Informed Consent**

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

**References**


1. GLOBOCAN 2018: Estimated cancer incidence, mortality and prevalence worldwide in 2018. http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
2. Burden of HPV related cancers. Human Papillomavirus and Related Diseases Report India. http://www.hpvcentre.net.
3. http://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
4. Jain A, Ganesh B, Bobdey SC et al. Sociodemographic and clinical profile of cervical cancer patients visiting in a TCH in India. Indian Journal of Medical and Paediatric Oncology 2017 jul – sep;38(3) : 291 – 295
5. Akila NV, Thomadsen B. et al. American Brachytherapy Society Cervical Cancer Brachytherapy Task Group, https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/file/public/guidelines/cervical_cancer_taskgroup.pdf
6. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles, https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/file/public/guidelines/Guidelines_Carcinoma_Cervix_Part1.pdf
7. Saptarshi Ghosh, Pamidimukalabramhananda Rao High-Dose-Rate Orthogonal Intracavitary Brachytherapy with 9 Gy/Fraction in Locally Advanced Cervical Cancer: Is it Feasible??. Journal of Obstetrics and Gynecology of India 66(Suppl 1):1-7 · December 2015
8. Gogia P, Dhull AK, Kaushal V. Weekly versus biweekly high-dose rate brachytherapy schedules in carcinoma cervix following concomitant chemoradiation with paclitaxel and carboplatin. Asian J Oncol [serial online] 2017 [cited 2018 Oct 13];3:12-6. Available from: http://www.asjo.in/text.asp?2017/3/1/12/209325
9. http://ecog-acrin.org/resources/ecog-performance-status
10. https://www.rtog.org/researchassociates/adverseeventreporting/rtogeortclateradiationmorbidityscoringschema.aspx
11. Tanderup et al. Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional. Int J Radiation Oncol Biol Phys, Vol. 88, No. 3, pp. 537 - 539, 2014 0360-3016/$
12. Bonala S R, Pranabandhu D et al. A Comparative Analysis of Two Different Dose Fractionation Regimens of High Dose Rate Intracavitary Brachytherapy in Treatment of Carcinoma of Uterine Cervix: A Prospective Randomized Study. Journal of Clinical and Diagnostic Research. 2017 Apr, Vol-11(4): XC01-XC05
13. Banerjee R, Kamrava M. Brachytherapy in the treatment of cervical cancer: a review. International Journal of Women's Health 2014:6 555–564

14. A N Viswanathan, B Thomadsen et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I General principles. Brachytherapy 11 (2012) 33-46