

**Research Paper**

Establishing use of Concurrent HDR-ICBT with EBRT for management of Stage II cervical cancer at a Regional Cancer Center

Authors

**Dr Rahul Kumar Rai¹, Dr Neeti Sharma^{2*}, Dr Neha Rawat³
Dr Narendra Kumar Gupta⁴, Dr H S Kumar⁵**

^{1,3,4} III-year PG Residents, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001

² Professor, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001

⁵ Senior Professor and Head, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001

*Corresponding Author

Dr Neeti Sharma

Professor, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001

Abstract

Background: ABS (American Brachytherapy Society) necessitates use of BT (Brachytherapy) for successful completion of management of locally advanced cervical cancer. Multiple dose fractionation schedules are available but none is currently standardized.

Objective: To analyze two different concurrent HDR-ICBT (Intracavitary BT) schedules, their disease response, acute and late toxicities.

Materials and Methods: 50 cases of histologically proven stage II cervical cancer were randomized into two arms, Arm A and Arm B. Patients in both arms received 50 Gy (Gray) (2 Gy/ fraction, 25 fractions, Monday to Friday) of EBRT (External Beam Radiotherapy) to whole pelvis with weekly cisplatin (40 mg/m²) on every Sunday. Patients in Arm A received HDR-ICBT regime of 7.5 Gy/fraction for 3 fractions, in Arm B patients received 6 Gy/fraction for 4 fractions on every Saturday.

Results: Median follow up period of study was 14 months (range 7 – 20 months). There is no significant difference in local control and late toxicities in both arms.

Conclusion: Both regimes of concurrent HDR- ICBT were tolerated well and were safe to use. Results of disease response and toxicity profile were also similar in both regimes.

Keywords: cervical cancer, HDR intracavitary brachytherapy, dose fractionation, acute toxicity, late toxicity.

Introduction

Carcinoma of the uterine cervix (cervical cancer) is the second most common malignancy seen in

Indian females⁽¹⁾. In India 60000 death occur every year is caused by carcinoma cervix⁽²⁾. It is third leading cause of female cancer and 4th

leading cancer cause of female deaths in India⁽³⁾. Worldwide, it is overall tenth common malignancy⁽⁴⁾. Around 0.5 million new cases of carcinoma cervix are diagnosed annually in world. It is more common in rural (about 65 percent) than urban (about 35 percent).

Patients of cervical cancer in India usually present in FIGO (International Federation of Gynecology & Obstetrics) stage II (35%), or in stage III (43%) with 88% of total cases having squamous histology⁽⁵⁾. This allows to use surgery and RT (Radiotherapy) as the primary modality of treatment. Surgery has a role mainly in localized tumor of 4 cm or less size. RT is recommended in patients with primary tumor of >4 cm size or patient who either refuse or are not fit for surgery.

Any treatment of advanced cervical cancer (Ib – IVa) with RT is incomplete without the use of BT (Brachytherapy). ABS recommend use of BT whenever possible for completion of successful treatment of cervical cancer with radiotherapy (Nag S et al.)⁽⁶⁾. Total treatment duration (EBRT & ICBT) must be less than 8 weeks⁽⁷⁾. Several studies have suggested that there may be as much as 1% decrease in survival and local control for each extra day of treatment beyond a total treatment time of 55 to 60 day⁽⁸⁾. ABS also recommend to maintain fraction size to ≤ 7.5 Gy for each application of BT⁽⁹⁾ with 4 to 8 fractions, because higher dose per fraction are associated with higher toxicities. When following the recommendations of ABS and using 7.5 Gy schedule after completion of EBRT, the treatment time may go beyond 8 weeks as multiple sessions of brachytherapy will be required. ABS in after guidelines has allowed to use brachytherapy in concurrent form with EBRT, but still an optimum dosing schedule is missing. In an international survey from the Gynaecologic Cancer Intergroup, 28 different fractionation regimens were used by international cooperative group members⁽¹⁰⁾. Each institution should follow a consistent treatment policy, including complete documentation of treatment parameters and correlation with clinical

outcome (pelvic tumor control, survival, and complications).

This study compares two different HDR Dose Fractionation schedules of Intracavitary Brachytherapy in Carcinoma Cervix in stage-II patients in terms of their disease response, acute and late treatment related toxicity.

Materials and Methods

This is a prospective randomized control study carried in department of Radiotherapy at Acharya Tulsi Regional cancer treatment center Bikaner. 50 patients with biopsy proven cases of carcinoma cervix were included and received concurrent CT (inj. Cisplatin 40 mg/m² wkly) + EBRT up to 50Gy to whole pelvis + HDR ICBT. 25 patients of this 50 were randomized on one to one basis to each Arm (Arm A and B). Patients were prospectively randomized into two treatment schedules as follows:

- Arm-A: 3 fractions x 7.5 Gy
- Arm-B: 4 fractions x 6 Gy

The ICBT was started only when patient had received 20 Gy (10 fractions) of EBRT on wky schedule on every Saturday. Weekly chemotherapy was given on every Sunday.

Application of ICBT was performed on an outpatient basis with non-narcotic analgesics. For ICBT simulation, orthogonal films of anteroposterior and lateral views were taken with the applicators inserted, and the position of point A, bladder and rectal points were defined according to the Manchester method and ICRU (International Commission on Radiation Units and Measurement) 38 recommendations. The Linear Quadratic equation was used to calculate the dose to point A and the BED for Arm A was 98.4 Gy and for Arm B it was 98.8 Gy.

Table 1: Patient characteristics in both arms of the study

Patient Characteristics	Arm A No (% of Arm A)	Arm B No (% of Arm B)
Age Group (years):- ≤ 50 years >50 years	14 (56%) 11 (44%)	15 (60%) 10 (40%)
FIGO staging: - IIa IIb	06 (24%) 19 (76%)	08 (32%) 17 (68%)
ECOG Performance Status⁽¹⁾: 0 1	19 (76%) 06 (24%)	21 (84%) 04 (16%)
Menopausal Status: - Pre-menopausal Post-menopausal	10 (40%) 15 (60%)	08 (32%) 17 (68%)
Residence: - Rural Urban	21 (84%) 04 (16%)	21 (84%) 04 (16%)
Smoking History: - Current Smokers Former or Never Smokers	03 (12%) 22 (88%)	03 (12%) 22 (88%)
BMI (Body Mass Index): - Normal or Underweight Overweight	20 (80%) 05 (20%)	23 (92%) 02 (08%)
Age at Menarche: - ≤13 years >13 years	08 (32%) 17 (68%)	08 (32%) 17 (68%)

Age at Marriage: - <17 years >17 years	11 (44%) 14 (56%)	12 (48%) 13 (52%)
Age at First Child-birth: - <21 years >21 years	21 (84%) 04 (16%)	21 (84%) 04 (16%)
No of Full-term Pregnancies: - <3 >3	04 (16%) 21 (84%)	03 (12%) 22 (88%)
History of STDs: - Yes No	09 (36%) 16 (64%)	05 (20%) 20 (80%)

All patients were able to complete planned treatment in both Arms. The median time of follow-up was 14 months for whole study (range 7 – 20 months). Mean duration for treatment completion was 42.82 days (43.12 days for Arm A and 42.52 days for Arm B).

Follow up

All patients were followed up at 3 and 6 months after treatment completion for disease response and toxicities. Toxicities were analysed by using RTOG (Radiation Therapy Oncology Group)/ EORTC (European Organisation for Research and Treatment of Cancer) criteria.

Statistical Analysis

Data were tabulated in MS Excel 2016 and analysis IBM SPSS Statistics 25 software was used for statistical analysis. For statistical significance of the difference in proportions Chi-square test was used. Kaplan–Meier method was used to analyze local control, disease-free survival, overall survival, and late complication rates, and the differences between the two arms were analyzed by log-rank test. for significance of results, p value should be <0.05.

Results

Study has included patients from age of 33 to 60 years. Maximum number of patients were in 41 – 50-year age group. The mean age of study was 50.20 years. The mean age for Arm A and B was 50.64 and 49.76 years respectively.

The median time of follow-up was 14 months for whole study (range 7 – 20 months). Mean duration for treatment completion was 42.82 days (43.12 days for Arm A and 42.52 days for Arm B).

Table 2: - Response Evaluation in Study Population

Response	Arm A (No of Patients)				Arm B (No of Patients)			
	Treatment Completion	At 1 Mth	At 3 Mths	At 6 Mths	Treatment Completion	At 1 Mth	At 3 Mths	At 6 Mths
Complete Response (CR)	18	18	21	21	15	20	20	20
Partial Response (PR)	07	06	03	02	10	04	03	03
Stable Disease (SD)	00	00	00	00	00	00	00	00
Progressive Disease (PD)	00	01	01	02	00	01	02	02

Table 2 explains that at the end of 6 months, 41 patients (82%) had attained CR. CR rate was 84% for Arm A and 80% for Arm B (p value = .721). Overall 09 patients (18%) were in non-CR group (non-CR = patients with PR, SD or PD). The non-CR rate was 16% for Arm A and 20% for Arm B. Among 09 patients of non-CR group 05 had residual disease and 04 had failure at distant site. Residual disease was seen in 02 (08%) patients of Arm A and 03 (12%) patients of Arm B (p value = .608). Similarly, distant failure was seen in 02 (08%) patients of Arm A and 02 (08%) patients of Arm B (p value = .969). The most common site for distant metastasis was para-aortic node in both arms. Isolated para-aortic metastasis was seen in only one patient of Arm B though. In other three cases of distant metastasis, >1 sites of metastasis were there (most common being Lung). Median duration of distant metastasis development was 11.5 months. Case with residual disease or distant metastasis were treated with further chemotherapy.

Acute reactions are the most common sequel of Radiotherapy (EBRT + ICBT). These reactions were seen in both arms. Most of the acute reactions were grade I or II reactions. No grade IV acute toxicity was seen in any arm. Anemia, leukocytopenia, nausea and vomiting were all mostly of grade I or II. All grade I and II reactions were managed on OPD basis. 15 patients (30%) developed grade III skin toxicity. 7 patients in

Arm A (28%) and 8 patients (32%) in Arm B developed grade III toxicity (p value = .503). For the management of skin toxicity patient were advised to wear loose cotton cloths, maintain local hygiene and to use aloe-vera (except at the time of radiation delivery). In all patients skin reactions resolved after completion of treatment and no patient had grade III or higher reaction at 3-months follow-up. Grade III Diarrhea was seen in 8 patients (16%), 5 in Arm A (20%) and 3 in Arm B (12%) (p value = .684). All grade III reactions were managed by hospitalization and appropriate medical management. No patient suffered from any intra-procedural complication.

Late reactions were examined up to 6 months following Radiotherapy. The most common late complication observed was vaginal stenosis. Vaginal stenosis was seen in 20 cases (40%) of study population. Shorter treatment time (≤ 43 days, p value = .012) and older age (> 50 years, p value = .021) were two important factors associated with it. Though incidence of vaginal stenosis was higher in post-menopausal females (15 in 32), results were non-significant when compared with pre-menopausal females (5 in 18) (p value = .377). For vaginal stenosis patients were advised to continue sexual activity and frequent cervical dilatations.

Most of the rectal and bladder toxicities were grade I and II toxicities. One patient in each arm develop grade III rectal complication (p value =

.886). Grade I, II rectal complications were more common in Arm B (though p value = .430). Grade III bladder toxicity was seen in only 1 patient of Arm A. Grade I and II bladder toxicity was seen in 09 patients (18%) of study population. 04 cases in Arm A had grade I, II toxicity while 05 cases of Arm B had Grade I or II toxicity (p value = .375).

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 as explained by Tanderup et al. (2014) ⁽¹³⁾. Low dose rate ICBT is now not used at most of the center because of longer hospital stay and risk of radiation exposure to hospital staff, prolonged treatment time, mandatory hospitalization and applicator movement (Gaur R, et al ⁽¹⁴⁾), LDR-ICBT is now replaced by HDR-ICBT.

Brachytherapy for the management of cervical cancer is essential, though IMRT for the purpose of dose escalation has been tried but results were inferior to brachytherapy ⁽¹⁵⁾. Other options like helical tomotherapy and SBRT were also investigated but clinical data are very limited to support them ⁽¹⁶⁾⁽¹⁷⁾⁽¹⁸⁾⁽¹⁹⁾. When combining the two modalities of radiotherapy overall treatment time (OTT) becomes a major factor for pelvic tumor control ⁽²⁰⁾⁽²¹⁾⁽²²⁾. Direct comparisons between dose/fractionation schedules for cervical brachytherapy are limited ⁽²³⁾.

ABS recommend maintaining fraction size to ≤ 7.5 Gy for each application of Brachytherapy ⁽²⁴⁾ with 4 to 8 fractions, because higher dose per fraction are associated with higher toxicities, though they also suggested that these are not adequately clinically tested results and clinical experience should be use before treatment

planning. They also recommend keeping total treatment duration (EBRT & ICBT) for less than 8 weeks ⁽²⁵⁾. Several studies have suggested that there may be as much as 1% decrease in survival and local control for each extra day of treatment beyond a total treatment time of 55 to 60 day ⁽²⁶⁾. Many authors have published studies on optimum dose fractionation regimes for HDR ICBT, the optimal time–dose–fractionation scheme for HDR ICBT for cervical cancer has yet to be established. In an international survey from the Gynaecologic Cancer Intergroup, 28 different fractionation regimens were used by international cooperative group members ⁽¹⁰⁾. Each institution should follow a consistent treatment policy, including complete documentation of treatment parameters and correlation with clinical outcome (pelvic tumor control, survival, and complications).

Conclusion

Our study was started with an intention to explore disease response and toxicities when using concurrent HDR brachytherapy in two different fractionation schedules with EBRT (and weekly cisplatin) for management of Stage II. We observed no difference in the response rate in both arms. The number of patients with grade I and II late toxicities were more in Arm B, though the relationship was non-significant. Grade III late toxicity rate was similar in both arms. The rate of acute toxicity was also non-significantly different in both arms. Both regimes were safe and well tolerated by patients. So, any of the regime can be used depending upon patient factors and workload of the institute. Though for concrete assessment of disease response and toxicities, long follow-up and a large patient sample is required.

Informed Consent

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

References

1. Maheshwari A, et al. Gynecological cancers: A summary of published Indian

- data. South Asian J Cancer. 2016 Jul-Sep; 5(3): 112–120.
2. Burden of HPV related cancers. Human Papillomavirus and Related Diseases Report India. <http://www.hpvcentre.net>.
 3. GLOBOCON 2018. <http://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf>
 4. GLOBOCON 2018. <http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>
 5. 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.
 6. Nag S, et al. The American Brachytherapy Society recommendations for High-dose-rate brachytherapy for carcinoma of the cervix. Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 1, pp. 201–211, 2000.
 7. 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
 8. Petereit DG, Sarkaria JN, et al. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 1995; 32:1301–1307.
 9. Saptarshi Ghosh, Pamidimukalabrahamananda 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 2015;66(Suppl 1):1-7.
 10. Toita T, Kakinohana Y, Ogawa K, et al. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. Int J Radiat Oncol Biol Phys. 2003;56(5):1344–1353.
 11. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5:649-655.
 12. RTOG FOUNDATION INC. RTOG/EORTC Late Radiation Morbidity Scoring Schema. 2018 Available from: <https://www.rtog.org/researchassociates/adverseeventreporting/rtogeortclateradiationmorbidityscoringschema.aspx>
 13. Tanderup R, Eifel PJ, et al. Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional. Int J Radiation Oncol Biol Phys, Vol. 88, No. 3, 2014 pp. 537-539.
 14. Gaur R, Singh OP, et al. Comparison of Low- and High-dose Rate Brachytherapy in Carcinoma Cervix: Results from a Randomized Study. Indian Journal of Clinical Practice, Vol. 23, No. 4, September 2012.
 15. Kaled MA. Can intensity-modulated radiation therapy replace brachytherapy in the management of cervical cancer? Brachytherapy 1 (2002) 191–194
 16. Sethi RA, Jozsef G, Grew D, et al. Is there a role for an external beam boost in cervical cancer radiotherapy? Front Oncol 2013;33.
 17. Hsieh CH, Wei MC, Hsu YP, et al. Should helical tomotherapy replace brachytherapy for cervical cancer? Case Report. BMC Cancer. 2010; 10:637.
 18. Marnitz S, Kohler C, Budach V, et al. Robotic radiosurgery: Emulating brachytherapy in patients with locally advanced cervical carcinoma. Technique, feasibility and acute toxicity. Radiat Oncol. 2013;8(1):109.
 19. Haas JA, Witten MR, Clancey O, Episcopia K, Accordino D, Chalas E.

- CyberKnife boost for patients with cervical cancer unable to undergo brachytherapy. *Front Oncol.* 2012; 2:25.
20. Perez CA, Grigsby PW, Castro-Vita H, et al: Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 32:1275-1288, 1995.
21. Lanciano RM, Pajak TF, Martz K, et al: The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: A patterns-of-care study. *Int J Radiat Oncol Biol Phys* 25:391-397, 1993.
22. Grinsky T, Rey A, Roche B, et al: Overall treatment time in advanced cervical carcinoma: A critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys* 27:1051-1056, 1993.
23. Huang EY, Sun LM, Lin H, et al. A prospective cohort study to compare treatment results between 2 fractionation schedules of high-dose-rate intracavitary brachytherapy (HDR-ICBT) in patients with cervical cancer. *Int J Radiat Oncol Biol Phys.* 2013;85(1):123–128.
24. Saptarshi Ghosh, Pamidimukalabrahamananda 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* 2015;66(Suppl 1):1-7.
25. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles, [https://www.americanbrachytherapy.org/ABS/document-](https://www.americanbrachytherapy.org/ABS/document-server/?cfp=ABS/assets/file/public/guidelines/Guidelines_Carcinoma_Cervix_Part1.pdf)
- server/?cfp=ABS/assets/file/public/guidelines/Guidelines_Carcinoma_Cervix_Part1.pdf
26. Petereit DG, Sarkaria JN, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1995; 32:1301–1307.