A Prospective study to assess Prognostic factors for patients with Cervical cancer stage II treated with concurrent chemoradiotherapy

Authors
Dr Rahul Kumar Rai¹, Dr Rajesh Kumar²*, Dr Neeti Sharma³, Dr Neha Rawat⁴
Dr Narendra Kumar Gupta⁵, Dr H S Kumar⁶

¹,²,³,⁴ III-year PG Residents, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001
²Senior Resident, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001
³Professor, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001
⁶Senior 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 Rajesh Kumar
Senior Resident, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, Rajasthan, India, 334001

Abstract
Background: Concurrent chemoradiotherapy is standard of care for the management of cervical cancer.
Objective: In this study we try to explore various prognostic factors for management of cervical cancer, stage II. The main objective was to analyze impact of various factors on disease response and toxicities.
Methods: This is a prospective analysis of 50 patients of stage II cervical cancer, treated with concurrent chemoradiotherapy. The most common regime used was Concurrent EBRT (External Beam Radiotherapy) + HDR (High Dose Rate) ICBT (Intra cavitary Brachytherapy) + weekly cisplatin (40 mg/m²). The most common dose fractionation regime was 7.5 Gy X 3 fractions or 6 Gy X 4 fractions. A total dose of 50 Gy was delivered by EBRT.
Results: Of the 50 patients, 14 patients (28%) were in stage IIa while 36 (72%) were in stage IIb. 41 (82%) achieved CR.
Conclusion: Out of the various factors analyzed NLR (Neutrophil-Leucocyte Ratio), pre-treatment Hb (Hemoglobin) value, number of weekly cisplatin cycle received were the only factors with significant impact on prognosis.
Keywords: Cervical cancer, HDR intracavitary brachytherapy, Prognostic factors, 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.

Treatment of choice for most patients with early stage (IB&IIA) disease is either radiation therapy or surgery. NCCN have category one recommendations for surgery or radiotherapy in stage IB1 & IIA1 while concurrent chemoradiotherapy as category one for stage IB2 & IIA2 and onward\(^{(6)}\).

Radiotherapy is a combination of external beam irradiation and brachytherapy is used. External beam radiation is used to treat the central disease and to sterilize known or suspected regional metastases. Early stage non-bulky disease is suitable for simultaneous application brachytherapy and EBRT.

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 el al.)\(^{(7)}\). Total treatment duration (EBRT& ICBT) must be less than 8 weeks \(^{(8)}\). 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 \(^{(9)}\). ABS also recommend maintaining fraction size to < 7.5 Gy for each application of BT \(^{(10)}\) with 4 to 8 fractions, because higher dose per fraction are associated with higher toxicities. To achieve this, we used concurrent HDR ICBT with EBRT regimes only for the management of patients. The addition of concurrent cisplatin-based chemotherapy to radiotherapy reduced the risk of death by 30 percent to 50 percent.U.S. National Cancer Institute Bulletin about use of chemoradiotherapy has also advocated addition of chemotherapy with EBRT\(^{(11)}\). In this study we used weekly cisplatin with a dose of 40 mg/m\(^2\) on every Sunday.

This study compares the effects of various factors on disease response and toxicities in cervical cancer patients treated with concurrent HDR ICBT with EBRT and weekly cisplatin (40 mg/m\(^2\)).

**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/m\(^2\) wkly) + EBRT upto 50Gy to whole pelvis + HDR ICBT. The ICBT was started only when patient had received 20 Gy (10 fractions) of EBRT on wkly 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 of patients included in the study

| Patient Characteristics                  | Arm A | Arm B |
|------------------------------------------|-------|-------|
| Age Group (years): -                     |       |       |
| < 50 years                               | 14 (56%) | 15 (60%) |
| >50 years                                | 11 (44%) | 10 (40%) |
| FIGO staging: -                          |       |       |
| IIA                                      | 06 (24%) | 08 (32%) |
| IIB                                      | 19 (76%) | 17 (68%) |
| ECOG Performance Status\[^2\]:           |       |       |
| 0                                        | 19 (76%) | 21 (84%) |
| 1                                        | 06 (24%) | 04 (16%) |
| Menopausal Status: -                     |       |       |
| Pre-menopausal                           | 10 (40%) | 08 (32%) |
| Post-menopausal                          | 15 (60%) | 17 (68%) |
| Residence: -                             |       |       |
| Rural                                    | 21 (84%) | 21 (84%) |
| Urban                                    | 04 (16%) | 04 (16%) |
| Smoking History: -                       |       |       |
| Current Smokers                          | 03 (12%) | 03 (12%) |
| Former or Never Smokers                  | 22 (88%) | 22 (88%) |
| BMI (Body Mass Index): -                 |       |       |
| Normal or Underweight                    | 20 (80%) | 23 (92%) |
| Overweight                               | 05 (20%) | 02 (08%) |
| Age at Menarche: -                       |       |       |
| <13 years                                | 08 (32%) | 08 (32%) |
| >13 years                                | 17 (68%) | 17 (68%) |

Table 2: Various characteristics of patients included in study

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

Statistical Analysis
The primary outcome measure was DFS (Disease Free Survival), which was defined as the time from the starting date of initial treatment to any progression of disease. 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

Table 3: Various parameters of patients included in study

| S. No. | Parameter                      | Value       |
|--------|--------------------------------|-------------|
| 1      | Age:                           |             |
|        | 31-50 yrs                      | 27 (54%)    |
|        | >50 yrs                        | 23 (46%)    |
| 2      | ECOG:                          |             |
|        | 0                              | 40 (80%)    |
|        | 1                              | 10 (20%)    |
| 3      | Histology:                     |             |
|        | Well Differentiated            | 20 (40%)    |
|        | Moderately Differentated       | 19 (38%)    |
|        | Poorly Differentiated          | 11 (22%)    |
| 4      | Tumor morphology:             |             |
|        | Proliferative                  | 23 (46%)    |
|        | Ulcerative                     | 19 (38%)    |
|        | Infiltrative                   | 08 (16%)    |
| 5      | Pre-treatment Hb:              |             |
|        | <10 gm%                        | 19 (38%)    |
|        | >10 gm%                        | 31 (62%)    |
| 6      | Number of weekly cisplatin received: |     |
|        | 1 – 4                          | 22 (44%)    |
|        | 5                              | 28 (56%)    |
| 7      | NLR:                           |             |
|        | <2.95                          | 30 (60%)    |
|        | >2.95                          | 20 (40%)    |

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 3 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. Cases 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

| Response          | Arm A (No of Patients) | At Treatment Completion | At 1 Mth | At 3 Mths | At 6 Mths |
|-------------------|------------------------|-------------------------|----------|-----------|----------|
| Complete Response (CR) | 33                     | 38                      | 41       | 41        |          |
| Partial Response (PR)   | 17                     | 10                      | 06       | 05        |          |
| Stable Disease (SD)     | 00                     | 00                      | 00       | 00        |          |
| Progressive Disease (PD)| 00                     | 02                      | 03       | 04        |          |
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

To understand the effect of age on response rate, patients were divided into two groups. In group 1, patients with age between 31 to 50 years were included. In group II, patients with age group of >50 years were included. Total number of cases in group 1 were 27 and in group 2 were 23 respectively. 22 cases (81.5%) in Arm A and 19 cases (82.6%) in Arm B were able to achieve CR (p value = .112). Out of 40 patients with ECOG score of 0, 33 (82.5%) were able to achieve CR. Similarly, in 10 patients with ECOG score of 1, 08 (80%) were able to achieve CR (p value = .526). Results suggests that ECOG score of 0 or 1 does not affect the response rate in cervical cancer patients. The reason for this is that patients with ECOG score of 0 or 1 were able to receive complete treatment protocol as their general condition is good.

Out of 20 patients with Well Differentiated histology 17 patients (85%) were able to achieve CR. In 19 patients of Moderately Differentiated histology 15 patients (79%) attained CR, and in 11 patients with poorly differentiated histology 09 (82%) achieved CR.

The effect of tumor morphology on treatment response rate was also assessed. In 23 patients of proliferative morphology 19 (82.6%) patients were able to achieve CR. In 19 cases of ulcerative morphology 15 (78.9%) cases attained CR, and in 08 cases of infiltrative morphology 07 (87.5%) cases were able to attain CR.

To understand the effect of Hb on outcome, patients were divided into two groups; Group 1 with pre-treatment Hb value of <10 gm% and group 2 with Hb value of 11 gm% or above. A total of 19 patients were in group 1, of those 19 patients 14 (73.7%) were able to achieve CR. Group 2 had 31 patients, out of which all 31 (100%) were able to achieve CR (p value = .005). To assess the effect of number of weekly cisplatin (40 mg/m2) cycles on response rate, patients were divided into two groups. Those patients who due to complications received less than 5 weekly cisplatin cycles were included in group 1, while
those patients who were able to receive all 5 weekly cisplatin cycles included in group 2. A total of 22 patients were in group 1, while 28 were in group 2. Out of 22 patients only 14 were able to achieve CR in group 1. In group 2, 27 patients out of 28 were able to attain CR (p value = .05).
To assess the effect of pre-treatment NLR (Neutrophil to lymphocyte ratio), patients were divided into two groups; Group 1 contain patients with NLR value < 2.95 while group 2 with NLR value of > 2.95. Out of 50 patients 30 patients (60%) were in group 1 while remaining 20 (40%) were in group 2. In group 1, 28 patients were able to attain CR, while in group 2 CR was attained by 13 patients (p value = .036).

**Conclusion**
For patients of stage I cervical cancer treated with concurrent chemoradiotherapy with short overall treatment time (<8 weeks), pre-treatment Hb, number of weekly cisplatin cycles received and pre-treatment NLR were the most important prognostic factors associated with disease response.

**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. NCCN clinical practice guidelines in oncology: Cervical cancer [Internet] National Comprehensive Cancer Network; Version 2.2019. [cited November 30, 2018] Available from: http://www.nccn.org.
7. 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.
8. 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
9. 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.
10. Saptarshi Ghosh, Pamidimukalabramananda 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.
11. National Cancer Institute. Concurrent chemoradiotherapy for cervical cancer. Clinical announcement. Washington, DC: National Cancer Institute,1999.
12. 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.
13. RTOG FOUNDATION INC. RTOG/EORTC Late Radiation Morbidity Scoring Schema. 2018 Available from: https://www.rtog.org/researchassociates/adverseeventreporting/rtogeortclateradiationmorbidityscoringschema.aspx