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Research Article

A PROSPECTIVE COMPARATIVE STUDY OF CONCURRENT VERSUS SEQUENTIAL INTRACAVITRARY BRACHYTHERAPY WITH EXTERNAL BEAM RADIOTHERAPY IN CERVICAL CANCER

Rakesh Gocher, Shantanu Sharma*, Subhash C Bairwa, Kartick Rastogi, Pawan Jangir, R S Gothwal, Sandeep Jain and Shivani Gupta

Department of Radiation Oncology, SMS Medical College & Hospitals, Jaipur, Rajasthan (India)

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A B S T R A C T

Aim: To compare concurrent versus sequential Intracavitary brachytherapy with External Beam Radiotherapy in Cervical Cancer stage II B & III B in terms of acute reactions and treatment response.

Methods and Materials: Fifty patients of carcinoma cervix (FIGO- II B/IIIB) were randomly divided into two groups: the study group treated with concomitant EBRT and HDR-ICBT (EBRT = 50–50.4 Gy/25–28 Fr, HDR 7 Gy in 3 Fr during the 3rd, 4th, and 5th weeks), EBRT and weekly cisplatin were not given on the day of HDR-ICBT; and the control group treated with EBRT followed by HDR-ICBT and weekly cisplatin. Acute reactions and local disease response were compared after treatment and at 6-month follow-up by using RTOG 4 POINT scale and WHO criteria respectively.

Results: The response of treatment in both the groups was assessed by WHO criteria. Complete Response was seen in 80% patients of study group and 68% patients of control group. Partial Response was seen in 16% patients of study & 20% of control group. Stable disease was seen in 0% patients of study group and 8% patients of No patient of either group had progressive disease. Acute skin reactions and diarrhea and bladder toxicity were within acceptable range.

Conclusion: It is concluded that concurrent External beam irradiation with Intracavitary brachytherapy, was found to be a better treatment regimen for management of carcinoma cervix stage IIB to IIIB and lead to better local pelvic disease control with shorter overall treatment time than External beam irradiation followed by intracavitary brachytherapy. This was not statistically significant in the present study and results were encouraging

INTRODUCTION

Worldwide, cervix cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women accounts for 3.2 % of all sites and no of death is 3.3% of all the site across the world based on 2018 GLOBOCAN estimates.[1] In India, cervical cancer is second most common cancer in females and accounts for almost 14%. As per the latest Globocan 2018 reports; the incidence, 5-year prevalence and mortality of cancer cervix in India is 122844 (22.9%), 308901 (27.4%) and 67477 (20.7%) respectively.[2] Cervical cancer is a major health problem of Indian women. The age-adjusted incidence rate is 27.0 per 100,000 female population and age-adjusted mortality rate per 10,000 population is reported to be 12.4.[3] Squamous cell carcinomas is most common type of histology and accounts for 90% of all cervix cancer[4] Less common histologies are adenocarcinona, small cell and adenosquamous.

Corresponding author:* **Shantanu Sharma
Department of Radiation Oncology, SMS Medical College & Hospitals, Jaipur, Rajasthan (India)

In epidemiological risk factors human papillomavirus (HPV) type16 & 18[5] are most common association with early age at marriage, multiple sexual partners, multiple pregnancies, poor genital hygiene, malnutrition, use of oral contraceptives, and lack of awareness. The earliest symptom of invasive cervical cancer is usually abnormal vaginal bleeding, often following coitus or vaginal douching. This may be associated with a clear or foul-smelling vaginal discharge. Besides FIGO stage, prognosis is also influenced by general condition, anemia, clinical tumor diameter presence of medial versus lateral parametrial involvement, presence of unilateral versus bilateral parametrial or pelvic wall involvement lymph node metastasis, size of the largest node, and the number of involved pelvic lymph nodes. [6] At an early stage, disease can be cured by either surgery or radiotherapy but in advance stage or when medically inoperable, radiotherapy with concurrent chemotherapy is the definitive line of treatment. The radiotherapy of cervical cancer involves a judicious use of teletherapy and brachytherapy. So this study has been conducted with the aim to compare Concurrent versus Sequential Intracavitary Brachytherapy with External Beam

Radiotherapy in Cervical Cancer in favour of to assess and compare local disease control ,acute toxicities in terms of skin reaction, bowel toxicity, rectal toxicity and bladder toxicity.

MATERIALS AND METHODS

It was a hospital based quantitative prospective follow-up study which was conducted in from June 2018 to May 2019 in a tertiary care center of north- west India. After approval of institutional Review Board/ Ethical committee, histopathological proven Squamous cell carcinoma cervix (FIGO- II B/IIIB) and ready to give informed written consent were included in this study. Sample size is calculated at 80% study power and α error of 0.05 assuming 60% bladder toxicity in group A and 12% in group B in first five weeks of treatment as found in reference article. Following above assumption, 19 cases in each arm are required as sample size for statistical analysis of present study. Therefore sample size is increased to 25 cases in each group as final sample size for present study expecting 25% dropouts/ lost to follow up/ accretion in 6 months follow up period.

Randomization: Eligible Patients were randomized after giving 10 fractions EBRT: Study group: concurrent EBRT (50 Gy/25fractions with 2Gy per fraction) with weekly cisplatin (30 mg/m^2) and integrated 3 fractions of HDR-ICBT of 7 Gy per fraction in the 3rd, 4th and 5th weeks of EBRT. Control group: concurrent EBRT (50 Gy/25 fractions with 2Gy per fraction) with weekly cisplatin (30 mg/m^2) followed by 3 fractions of HDR-ICBT of 7Gy per fraction

RT Technique: All patients were treated over dual energy Linear Accelerator by 3-dimensional conformal radiation therapy (3DCRT) technique in supine position with immobilization using four field technique with EBRT of 50Gy were delivered in 25 fractions with 6 MV beam energy,2Gy per fraction in both the groups. All patients will be given weekly cisplatin at dose of 30 mg/m^2 IV as per the schedule. Intracavitary brachytherapy was delivered with HDR technique with 6MV average beam energy. In control group it was delivered after completion of EBRT, whereas in study group it was integrated with EBRT during 3rd, 4th, and 5th week. On the day of HDR-ICBT in study group, neither EBRT nor concurrent cisplatin were given. The plan of the treatment were to prescribe total dose of 85-90 Gy at point A. Dose calculations for rectum and bladder was made according to the ICRU—38 recommendations

Evaluation: Patients were accessed during treatment for local disease response and development of any acute skin reactions and diarrhea and bladder toxicity and followed up at the 1st, 3rd, and 6th months after treatment. Response will be evaluated in terms of stable disease (SD), partial response (PR), progressive disease, or complete response (CR) according to WHO Clinical Response Criteria[3]. Grading of normal tissue reactions will be done by Radiation Therapy Oncology Group toxicity criteria

Statistical analysis: Quantitative data were expressed in means with standard deviation and qualitative data were expressed in percentage proportions. Significance of difference in means of two groups were inferred with unpaired T test. Significance of difference in proportion in two groups was inferred with Chi-square test .For significance P- value less than 0.05 was considered as significant

OBSERVATIONS AND RESULTS

Patient criteria: Both arms were well balanced regarding age, sex, socio economic status, co morbidity, ECOG- PS, HB level and histopathology. Moderately differentiated Squamous cell carcinoma was most common histology. (Table: 1)

Response evolution

Acute Skin Reaction: Acute Skin Reaction (RTOG Grade) was not significantly different in both groups during and after treatment. (Figure:1)

Acute diarrhea: Acute diarrhea was not significantly different in both groups during and after treatment. (Figure: 2)

***Bladder Toxicity*:** Bladder toxicity was not significantly different in both groups during and after treatment. (Figure: 3)

Distribution of the cases according to Disease control (WHO)*:* No significant difference observed among the groups. (Figure: 4)

Distribution of the cases according to End of treatment: At the completion of study, Complete Response was seen in 80% patients of study group and 68% patients of control group. Partial Response was seen in 16% patients of study & 20% of control group. Stable disease was seen in 8% patients of control group. The response in study group was better than control group**.** (Table: 2)

Table 1 Distribution of the cases according to Differentiation of Tumor

Differentiation	Control Group N (%)	Study Group N (%)	Total	p-value
Moderately differentiated	12(48%)	12(48%)	24(48%)	0.73NS
Poorly differentiated	6(24%)	8(32%)	14(48%)	

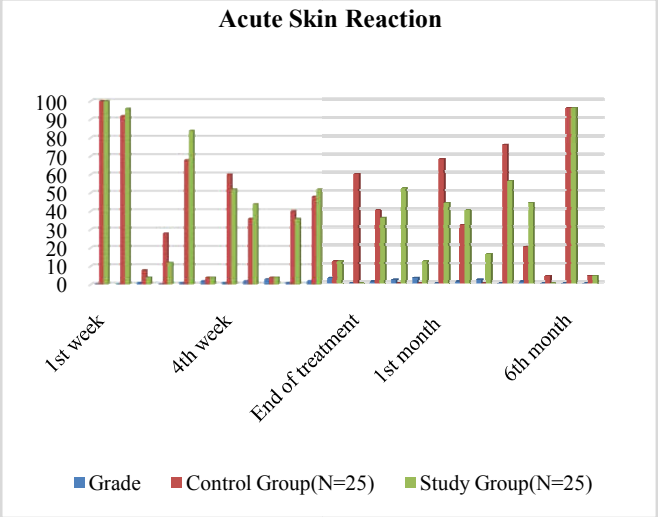

Figure 1 Acute skin reaction

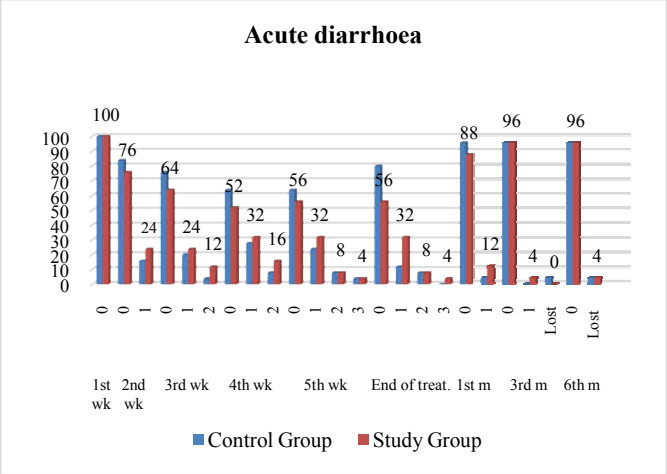

Figure 2 Acute Diarrhea

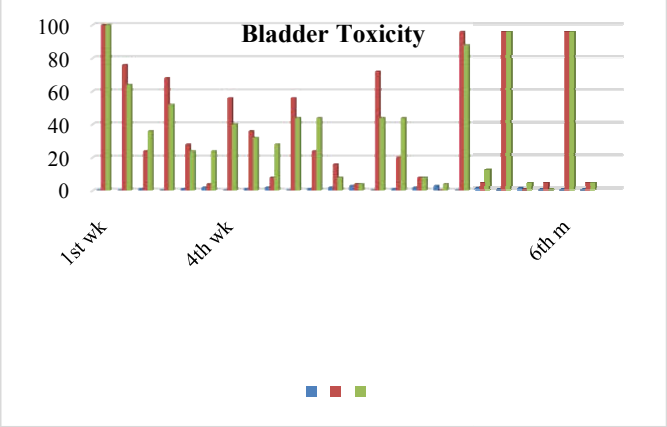

Figure 3

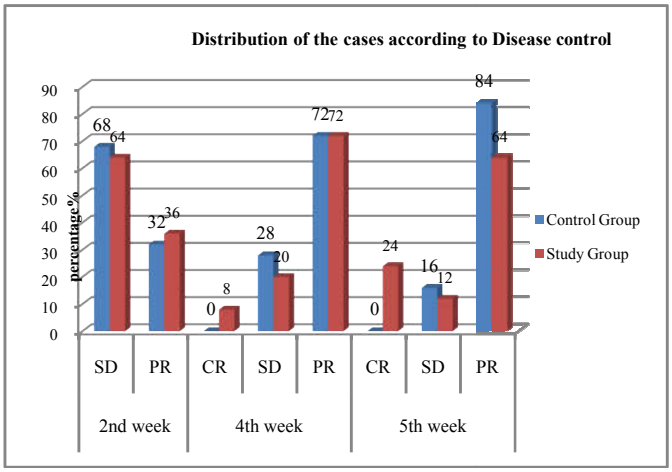

Figure 4 Distribution of the cases according to Disease control

Table 2 Distribution of the cases according to End of treatment

End of treatment	Control Group	Study Group	Total	P-VALUE
	N(%)	N(%)	N(%)	
CR	3(12%)	6(24%)	9(18%)	0.53NS
SD	4(16%)	3(12%)	7(14%)	
PR	18(72%)	16(64%)	34(68%)	
	1st month			
CR	13 (52%)	14 (56%)	27 (54%)	0.58NS
SD	3(12%)	1(4%)	4(8%)	
PR	9(36%)	10(40%)	19(38%)	
	3rd month			
CR	16(64%)	18(72%)	34(68%)	0.73NS
Lost	1(4%)	0	1(2%)	
SD	2(8%)	0	2(4%)	
PR	6(24%)	7(28%)	13(26%)	
	6th month			
CR	17 (68%)	20(80%)	37(74%0	0.68NS
Lost	1(4%)	1(4%)	2(94%)	
SD	2(8%)	0	2(4%)	
PR	5(20%)	4(16%)	9 (18%)	
Total	25(100%)	25(100%)	50 (100%)	

DISCUSSION

Radiotherapy, with combination of External beam irradiation and Intracavitary brachytherapy, is a well recognized effective treatment modality for early stage Carcinoma Cervix. The importance of overall treatment time on pelvic tumor control & survival rates has been well documented. The aim of this prospective study was to evaluate the role of of Concurrent versus Sequential Intracavitary Brachytherapy with External Beam Radiotherapy in Cervical Cancer. In our study acute skin reaction was the most common sequelae of radiotherapy seen in patients of both study and control group which was not statistically significant. At the end of the treatment, grade 2 (16%) and 3 (12%) reactions were more in study group while grade 0 (76%) and 1 (20%) reactions were more in control group.

Acute diarrhea was observed in both study and control group. Grade 4 reactions were seen in none of the patients recruited in the study. Grade 1(24%) and 2(12%) reactions were significantly more in study group at end of 3rd week of treatment (p = 0.51) because the study group was receiving concomitant Intracavitary brachytherapy with External beam irradiation and while the control group was receiving only External beam irradiation at that time. Similar to this, grade 2 reactions were significantly more in the study group at the end of 4th week of treatment (p = 0.59). At the end of treatment, grade 1(32%), 2(8%) and 3(4%) reactions were more in study group but not statistically significant (p = 0, 0.228). The diarrhea got normalized at the end of study in both study and control group**.** Similar with the study conducted by *Frank C.S.Wong et* al [7]: who reported results and complications of High Dose Rate Intracavitary brachytherapy in cancer cervix. The 5-year actuarial major complication rates (Grade 3 or above) were as follows: proctitis, 1.0%; 0.5%; enteritis, 1.3%; and overall, 2.8%. The two HDR fractionation schedules were not a significant prognosticator in predicting disease control and complications.

Grade 1(24%) and 2(24%) acute cystitis was significantly more in study group at end of 3th week of treatment (p =0.124) because the study group was receiving concomitant Intracavitary brachytherapy with External beam irradiation and while the control group was receiving only External beam irradiation at that time. Similar to this, grade 2 reactions were significantly more in the study group at the end of 4th week of treatment (p =0.173). At the end of treatment, grade 1(4%), 2(0%) and 3(0%%) reactions were more in study group but not statistically significant (p = 0, 0.228). The cystitis got normalized at the end of study in both study and control group. *H.U.Ghoriet al.* [8] They found that patients showed good response to the treatment. After follow up at one year, patient showed slightly better control with slightly increased toxicities of rectum & bladder in study group. Treatment response was observed better in study groups than the control.

The overall treatment time was approximately 6 weeks in study group and 8 weeks for the control group. So it was convenient for patients as well as favorable. These

observations were matched with other studies too *Sandhya Sood et al* [9]*:* reported impact of treatment time on outcome in cancer cervix. In this study, for Stage III patients, relapse were 15.55%, 20%, 12.5% when overall treatment time was up to 7.9 weeks, 7.9 to 9.9 weeks and more than 9.9 weeks respectively. She concluded that for Stage III patients, though not statistically significant but there is a decreasing trend in survival rate on increasing overall treatment time**.** *Takashi Nakano et al* [10] reported efficacy and late toxicity of High Dose Rate - Intracavitary brachytherapy for cervical carcinoma. The overall treatment time was approximately 6 weeks. *Chen SW et al* [11], reported the adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy .*Chen SW et al* [11] in their study observed that two groups of patients with treatment time less than 63 days and equal to or greater than 63 days reported pelvic control rate 83% and 72% respectively. These findings were significant for stage Ib / IIa [97% and 79% (P=0.01), and 100% and 87% (P=0.02), respectively).The results in this study were better than in present study it may be due to small In our study at the completion, Complete Response was seen in 80% patients of study group and 68% patients of control group. Partial Response was seen in 16% patients of study & 20% of control group. Stable disease was seen in none patients of study group and 8% patients of control group. No patient of study group or control group had progressive disease. The response in study group was better than control group. Results are nearly similar as observed in other published studies. *Robson Ferrignoet al* [12] who found 62% local control at 5 years, and overall treatment time up to 50 days as the only statistically significant adverse variable for overall survival and actuarial local control. In our study local control at end of study is better than above mentioned study which may be due to early stage, overall treatment time less than 40 days and higher cumulative dose to point A. The studies which correlate well with the control group are described as follows. *SandhyaSood et al* [9]**:** reported no statistically significant difference but decreasing trend in survival rate on increasing overall treatment time. *J Vandana et al* [13] reported the 5-year disease-free mean survival rate was 58%, 44%, for stages I, II, respectively at a median 59 month post treatment follow up. The results of this study were worse than present control group; it may be because of much longer follow up in the study. *Potter R et al*[14] reported the actuarial pelvic control and disease-specific survival rates at three years , This study had better results than present control group despite of almost same dose given by External beam irradiation and Intracavitary brachytherapy which may be due to more number of patients in this particular study, while only 25 patients in present control group. *Eiichi et al* [15] reported results of cervical cancer patients treated with High Dose Rate Intracavitary brachytherapy combined with External beam irradiation. For stage III patients, 5-year cause-specific survival rates were 53% and also similar finding was observed in *Firuza Patel et al*. [16] So it may be concluded that EBRT with concurrent Intracavitary brachytherapy is better for the treatment of the cervical cancers.

CONCLUSIONS

At the completion of study, Complete Response was seen in 80% patients of study group and 68% patients of control group. Partial Response was seen in 16% patients of study & 20% of control group. Stable disease was seen in 0% patients of study group and 8% patients of No patient of either group had progressive disease. The response in study group was better, but statistically not significant, than control group. Acute skin reactions and diarrhea were within acceptable range. It is hereby concluded that concurrent External beam irradiation with Intracavitary brachytherapy, was found to be a better treatment regimen for management of carcinoma cervix stage IIB to IIIB and lead to better local pelvic disease control with shorter overall treatment time than External beam irradiation followed by intracavitary brachytherapy. This was not however statistically significant in the present study. However, the results were encouraging and it shall require larger number of patients and longer follow up in order to arrive at a concrete conclusion as far as disease free survival, cause specific survival, pelvic control rate, and long term sequelae or complications are concerned.

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