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Research Article

TOXICITY AND TREATMENT OUTCOME OF ACCELERATED FRACTIONATION RADIOTHERAPY VERSUS CONVENTIONAL FRACTIONATED CONCOMITANT CHEMORADIATION IN LOCALLY ADVANCED CERVICAL CARCINOMA: A PROSPECTIVE STUDY

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ABSTRACT

Objectives: The benefit of concurrent chemoradiation is often not achievable due to poor tolerance due to increased toxicity, which is a common problem in our setting, where a significant portion of carcinoma cervix patients presents at an elderly age, with medical comorbidities, and with poor performance status. In addition, many patients refuse chemotherapy. Accelerated radiation therapy remains one of the possible alternatives there. Hence, we would like to perform a prospective study to compare treatment results between Pure Accelerated Radiation versus Concomitant Chemoradiation in Locally Advanced Squamous Cell Carcinoma of Cervix.

Methods: After the initial investigative work, a total of 62 histologically confirmed squamous cell carcinoma of cervix locally advanced stage (FIGO-stage IB2 to IVA.) with ECOG performance status 0–2 patients were randomized into two arms: Arm A (Study arm, n=30) – Patients received Six fractions per week of External Beam Radiotherapy without chemotherapy and Arm B (Control arm, n=32) patients received concurrent chemoradiation with Five fractions per week of radiation with Weekly Injection of Cisplatin at the dose of 40 mg/m^2.

Results: Overall response rates between the two arms were similar and statistically not significant (p=0.352). All acute late toxicities are similar in both arms except acute renal toxicity which is more in the control arm and the difference is statistically significant (p=0.005).

Conclusions: In developing countries like India with limited treatment facilities, pure accelerated RT with brachytherapy, without concurrent chemotherapy, may be a good option and it can be viewed as an equally effective option for the elderly patients, the patients who refuse, those who have contraindications for chemotherapy, or have comorbidities. Further, multicenter, controlled, and Phase III trials will be needed to prove the benefit of the shortening overall treatment time and compare the efficacy with chemoradiation.

Keywords: Accelerated fractionation, Chemoradiation, Cervical cancer.

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INTRODUCTION

With an estimated 96,922 new cases in 2018, as per GLOBOCAN 2018, cervical cancer is the fourth most common cancer in women, after breast, colorectal, and lung cancers, and the seventh overall [1]. Cervical cancer is a very important public health issue in a developed country like India. Due to ignorance, lack of infrastructure, and less access to screening facilities in remote areas lead to the majority of patients being diagnosed in the advanced stage [2]. As there are survival advantages, presently locally advanced carcinoma cervix cases are treated with concurrent chemoradiation with platin-based chemotherapy [3-7]. In the setting of Radiotherapy (RT) or concurrent chemoradiotherapy (CRT), local disease control is affected badly by overall treatment time (OTT) prolongation. Hence, total treatment duration as short as possible and ideally treatment should be completed within 8 weeks [8]. The benefit of concurrent chemoradiation is often not achievable due to poor tolerance due to increased toxicity, which is a common problem in our setting where a significant portion of carcinoma cervix patients presents at an elderly age, with medical comorbidities, and with poor performance status. In addition, many patients refuse chemotherapy. Accelerated radiation therapy remains one of the possible alternatives there. Hence, the objective of our prospective study is to compare treatment results between Pure Accelerated Radiation versus Concomitant Chemoradiation in Locally Advanced Squamous Cell Carcinoma of Cervix.

METHODS

After obtaining approval from the Institutional Ethics Committee (IEC), between December 2017 and April 2019, a total of 62 histologically confirmed squamous cell carcinoma of cervix locally advanced Stage (FIGO-stage IB2 to IVA.) with ECOG performance status 0–2 were included for single institutional, prospective, and parallel randomized study. After the initial investigative workup, patients were randomized into two arms: Arm A (Study arm, n=30) – Patients received six fractions per week of External Beam RT (EBRT) without chemotherapy from every Monday to Saturday (one extra fraction of EBRT on Saturdays, that is, Pure Accelerated RT) and Arm B (Control arm, n=32) – patients received concurrent chemoradiation with five fractions per week of radiation from every Monday to Friday along with Weekly Injection of Cisplatin at the dose of 40 mg/m^2 IV with necessary pre-medications and adequate hydration will be administered on every Monday before external radiation.

EBRT technique

Bladder protocol was followed for all patients. Patients were asked to void their bladder completely and then drink 250 ml of water 30 min before the simulation and the same will be followed every day before RT on the EBRT machine Theratron 780ETelecobalt machine (Theratronics International Ltd., Canada). To treat patients, a standard four field Box technique using Anteroposterior, posterior-anterior, and two lateral parallel opposed portals were used.

Brachytherapy

After completion of EBRT, brachytherapy is delivered by Fletcher-Suit applicator system (tandem and two ovoids) with microSelectron remote after loading the machine using Ir192 isotope. Three consecutive

weekly applications of 700 cGy each to point A (a point 2 cm lateral to the center of the uterine canal and 2 cm above from the mucous membrane of the lateral fornix of the vagina in the plane of the uterus) were done. Simple sterile gauze packing was introduced to ensure optimal separation between the applicators and the bladder anteriorly and rectum posteriorly.

Patients of the study arm received EBRT only, 6# per week, from every Monday to Saturday (one extra fraction of EBRT on Saturday, that is, pure accelerated RT). Considering starting day of EBRT as Day 0 (Monday), 50 Gy in 25# was completed on Day 28. (4 weeks and 1 day). Patients of the control arm received conventional RT (EBRT), five fractions per week, from every Monday to Friday. Considering starting day as Day 0, 50 Gy in 25# was completed on Day 32(5 weeks). In the study arm, 1st session (#) of brachytherapy was done on Day 29 (Tuesday), 2nd session on Day 36, and 3rd session on Day 43. Hence, OTT was 43 days in the case of the study arm. In the control arm, 1st # on Day 35 (Monday) and 2nd and 3rd # were given 1-week intervals on Day 42 and Day 49. OTT was 49 days in the control arm.

Calculation of biological equivalent dose (BED)

Considering tumor repopulation at a continuous (exponential) rate throughout treatment, the net effect depends on total treatment duration (T) and the potential doubling time (Tpot). As a consequence of this, the formula of BED will be as below:

$$BED=nd\ [1+d/\alpha/\beta]-(In\ 2/\alpha.Tpot)\ (T-Tk) \quad (1)$$

Here

- n is the number of fractions
- d is the dose per fraction
- α and β are the parameters of the LQ model. α/β (often called fractionation sensitivity) is a measure of how a specific tissue will respond to fractionation and dose rate.
- T is the Total duration of treatment considering that the first fraction was given on Day 0 and
- Tk is the time from when repopulation starts. It is called kick-off time.
- Tpot is the potential doubling time of clonogenic cell.

The entity $0.693/\alpha$. Tpot can be simply expressed as a constant K, the required dose equivalent of repopulation per day. For rapidly proliferating tumors, like cervical cancers, the value of K is approximately 0.6 Gy/day (considering In 2=0.693 α=0.3 Gy-1 and Tpot=3.5–5 days). There is controversy regarding values of Tk, although 21 days is probably most appropriate, as there is evidence of a time effect for tumor control beyond 3 weeks. The simplified formula will therefore be as below:

$$BED=nd\ [1+d/\alpha/\beta]-0.6(T-21) \quad (2)$$

Chemotherapy equivalent biologic effective dose – This predicts a 2 Gy equivalence for each cycle of chemotherapy such as single-agent Cisplatin when used weekly during RT, although such a conclusion seems over-simplified. This would mean a 10 Gy advantage for chemoradiation patients of the control arm, thereby increasing the BED. Again, this proves the benefit of using accelerated fractionation (AF) which can achieve a BED similar (although slightly lesser) to chemoradiation than using radiation alone, which would most likely have been used in this setting.

After completion of treatment, patients were followed up with detailed gynecological examination, complete systemic examination, and appropriate blood examinations and/or imaging studies, after treatment, 1 month, 3 months, and then every 3 monthly with a minimum follow-up period of 6 months. Patients were examined for acute and late toxicities of renal, bladder, and bowel using RTOG/CTCAE criteria version 4.

RESULTS

The general characteristics such as age, ECOG, stage of the total study population, as well as in between study arms and control arms were comparable and statistically not significant.

Response assessment

Response was assessed using the Response Evaluation in Solid Tumors (RECIST v1.1). The median follow-up duration was 13 months in both arms (range -10–16 months). Although CR remained higher among control arm patients (75% vs. 56.66% in study arm), CR+PR was almost similar (control arm 90.62% vs. study arm 80.0%). Overall response rate (CR+PR+SD) was 96.87%, 86.66% for patients in control arm and study arm, respectively (ORR Table 1 and Fig. 1). Overall response rates between the two arms were similar and statistically not significant (p=0.352). One patient each in both arms had Progressive Disease. At such a small period of follow-up, no comment can be made about overall survival.

Acute toxicities

Acute skin toxicity

(Table 2 and Fig. 2) were similar in both the arms and statistically not significant (p-0.816).

Hematological toxicity

The number of patients who developed Grade I and Grade II toxicity were 40.625% and 36.67%, respectively, for the control arm and study arm. About 12.5% of patients in the control arm developed Grade 3 toxicity, and 6.67% of patients in the study arm developed Grade 3 toxicity. Hematological toxicity was seen in 46.87% of patients in the control arm and 56.66% of patients in the study arm, respectively, and was statistically not significant. Grade 4 toxicity was not seen in any arm. The acute hematological toxicity is depicted in Table 3 and Fig. 3.

Acute renal toxicity

Grade I and Grade II toxicity is 53.12% in the control arm and 13.33% in the study arm with p-value of 0.005 which indicates renal toxicity is significantly higher in the control arm than study arm (Table 4 and Fig. 4). Furthermore, Grade 3 toxicity was found in 3.12% of patients of the control arm, which is absent in the patients of the study arm.

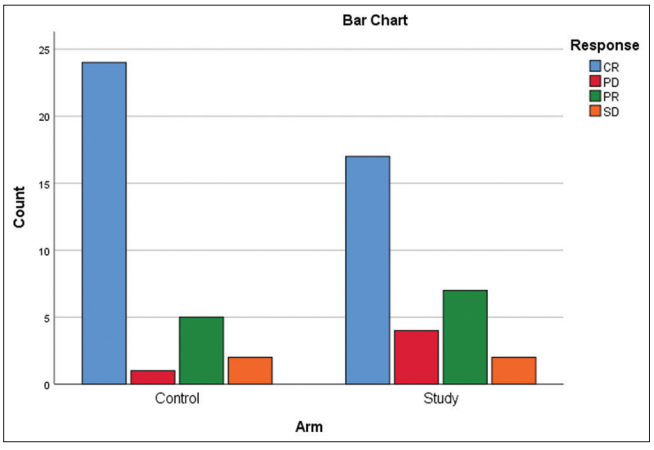

Fig. 1: Overall response between arms

Table 1: Overall response between arms

Response	CR	PD	PR	SD	Total	p-value
Control arms study	24	1	5	2	32	0.352
	17	4	7	2	30	
Total	41	5	12	4	60	

Acute bladder toxicity

There was not any significant difference in Acute Bladder Toxicity in the two arms (p=0.841). Grade 1 and Grade 2 toxicity in the Control arm is 46.87%, and in the study, the arm is 40%. No Grade 3 toxicity was found in any of the arms (Table 5 and Fig. 5).

Acute rectal toxicity

There was not any significant difference in Acute Rectal Toxicity in the two arms (p=0.866). Grade 1 and Grade 2 toxicity in the Control arm is 12.5%, and in the study, the arm is 10%. No Grade 3 or 4 toxicity was found in any arm (Table 6 and Fig. 6).

Late bladder and rectal toxicities were similar in both arms with statistically insignificant p values.

DISCUSSION

Despite cervical malignancies are not more radiosensitive than other epithelial malignancies, the relative success of radiation therapy has been seen mainly due to (i) relatively higher radiation tolerance of the adjacent structures, like the rectum and bladder, (ii) orderly progression of lymph node involvement, that is, paracervical, iliac, and then para-aortic node, (iii) the suitable anatomy for brachytherapy, and (iv) early or locally advanced stages at the time diagnosis. The most significant development in the treatment of carcinoma cervix has been the introduction of chemoradiation. After the NCI alert in 1999, cisplatin-based CRT has become the standard treatment of locally advanced carcinoma cervix [9]. This study was done to evaluate the feasibility and compare the efficacy of six fractions per week of accelerated EBRT (with conventional fraction size), versus concomitant chemoradiation (five fractions per week), followed by intracavitary brachytherapy for patients with locally advanced squamous cell carcinoma of the cervix (FIGO stage IB2-IVA).

The study intended to see the results between the two treatment arms by shortening the OTT. The OTT was 43 days in the study arm and 49 days in the control arm. Our results indicate that the AF of RT given 6 days a week was feasible in patients with locally advanced carcinoma of the cervix with acceptable morbidity. At the initial examination by the end of treatment, the local response was found to be better in the CRT arm, but on subsequent follow-up examinations, the difference was not seen. Although the complete response was relatively higher in control arm than in the study arm (75% in the control arm, 56% in the study arm), at the end of the median follow-up of 13 months, the overall response rate (CR+PR+SD) was similar between the two arms and statistically not significant (p=0.352).

Table 2: Showing acute skin toxicity

Grade	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Total	p-value
Control arms	2	17	11	2	32	0.816
Study arms	2	14	10	4	30	
Total	4	31	21	6	62	

Table 3: Showing acute hematological toxicity

Grade	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Total	p-value
Control arms	15	9	4	4	32	0.707
Study arms	17	9	2	2	30	
Total	32	18	6	6	62	

Table 4: Showing acute renal toxicity

Grade	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Total	p-value
Control arms	14	10	7	1	32	0.005
Study arms	26	3	1	0	30	
Total	40	13	8	1	62	

Table 5: Showing acute bladder toxicity

Grade	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Total	p-value
Control arms	17	12	3	0	32	0.841
Study arms	18	10	2	0	30	
Total	35	22	5	0	62	

Table 6: Showing acute rectal toxicity

Grade	Gr. 0	Gr. 1	Gr. 2	Gr. 3	Total	p-value
Control arms	28	2	2	0	32	0.866
Study arms	27	2	1	0	30	
Total	55	4	3	0	62	

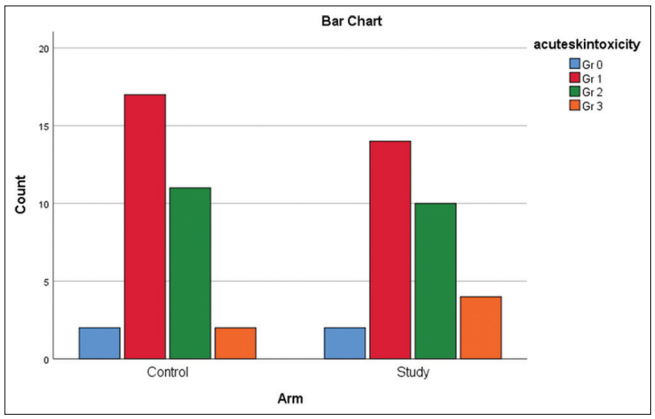

Fig. 2: Bar diagram showing skin toxicity

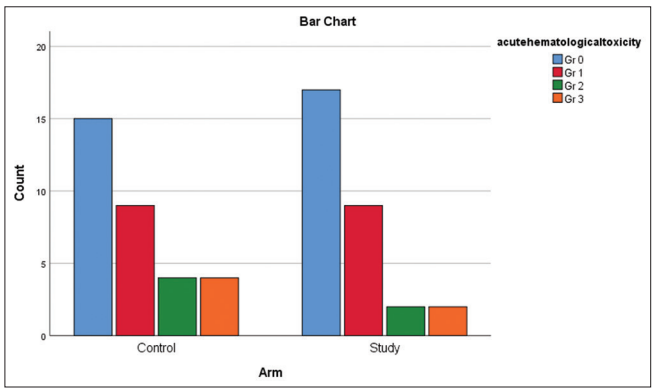

Fig. 3: Bar diagram showing acute hematological toxicity

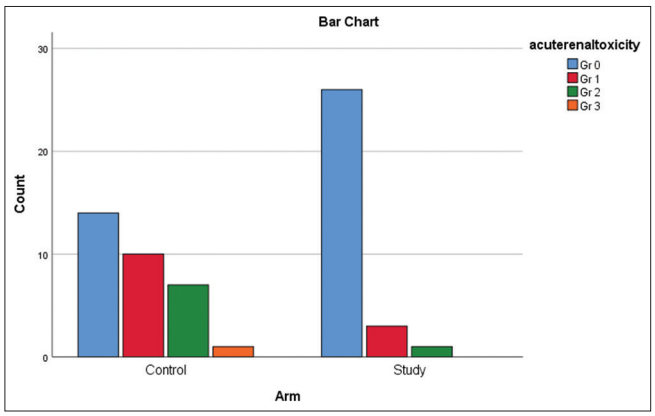

Fig. 4: Showing acute renal toxicity

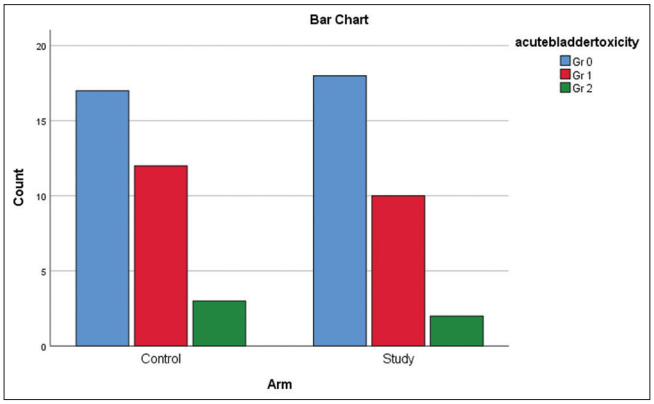

Fig. 5: Bar diagram showing acute bladder toxicity

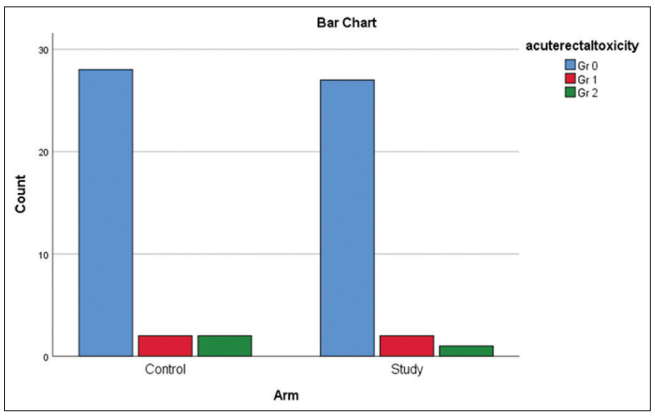

Fig. 6: Bar diagram showing acute rectal toxicity

Acute renal toxicity was significantly high in the control arm (CRT) compared to the study arm (6#/week) (p=0.005), 3.12% of Grade 3 toxicity was found in the control arm. The rest of the acute and late toxicities in the study arm was comparable to the control arm and statistically, not significant. Grade 3 hematological toxicity was found to be almost double (12.15%) in the control arm than study arm (6.67%). Green *et al*. concluded that concomitant chemotherapy results in improved overall survival (HR 0.71; p<0.0001) and progression-free survival (HR 0.61; p<0.0001). -- The absolute overall survival benefit was 12%, and a greater beneficial effect was seen in trials that included a higher proportion of stage II and II patients. (p=0.009). Patients receiving chemoradiation had a higher incidence of Grade 3 or 4 hematologic and gastrointestinal toxicities [10]. A Study by Basu *et al*. from Kolkata showed that pure accelerated radiation therapy is an effective alternative to conventional concurrent CTRT with the same 3 years locoregional response, median DFS, and late toxicities with less acute toxicities [11]. However, the one limitation of this study was different inclusion criteria for two arms with more elderly populations were offered the accelerated treatment. Another Phase III trial by Sharma *et al*. reported no significant difference between pure accelerated radiation therapy and conventional CTRT in terms of locoregional response, overall Survival (OS), and disease-free survival (DFS) [12]. In another study by Roy *et al*., the early responses of the AF were comparable to concurrent chemoradiation and this AF regime had shown lesser toxicities. The DFS was comparable between the two arms [13].

Overviewing all these studies and our study, it seems that pure accelerated RT can be a choice to circumvent the two issues. By shortening treatment time, without any alteration of total dose or dose per fraction, treatment can be effectively completed earlier and with lesser toxicities. This benefit should ideally be extended to those in whom concomitant chemotherapy is not possible, because it gives them a tangible benefit over conventional radiation by reducing OTT. In a developing country like ours, where delivering treatment under limited resource constraints is a major challenge, shortening treatment time is beneficial so that earlier initiation of treatment for more patients by reducing the waiting period and ensures optimization of limited resources.

Our study has some drawbacks including (i) small sample size, (ii) short follow-up period, and (iii) due to the short duration of follow-up, overall survival (OS), and DFS or progression-free survival could not be assessed. However, our trial offers an exciting prospect that might be an alternative option in selected patients who have contraindications to concurrent chemoradiation, and our results will be validated in larger trials in the future to better serve these patients.

CONCLUSIONS

The pure AF regime of six fractions per week of EBRT followed by intracavitary brachytherapy seems to be equally efficacious as concurrent chemoradiation with less acute renal toxicity and it is a comparable alternative treatment option for carcinoma cervix. In developing countries like India with limited treatment facilities, pure accelerated RT with brachytherapy, without concurrent chemotherapy, may be a good option and it can be viewed as an equally effective option for the elderly patients, the patients who refuse, those who have contraindications for chemotherapy, or have comorbidities. Further, multicenter, controlled, and phase III trials will be needed to prove the benefit of the shortening OTT and compare the efficacy with chemoradiation.

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AUTHOR CONTRIBUTIONS

Dr. Sharmistha Daripa: Conceptualization, drafting of work, data collection, data interpretation, statistical analysis, review, and approval of the final version of the manuscript. Dr. Saptarshi Banerjee: Conceptualization, drafting of work, data collection, data interpretation, statistical analysis, review, and approval of the final version of the manuscript. Dr. Aparajita Sadhya: Conceptualization, drafting of work, data collection, data interpretation, review, and approval of the final version of the manuscript. Dr. Anjan Bera: Conceptualization, drafting of work, data collection, data interpretation, review of statistical analysis, writing, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

All the declares no conflicts of interest in publishing this article.

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