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A PROSPECTIVE RANDOMIZED STUDY TO COMPARE THE CONCURRENT CHEMO-RADIATION VERSUS HYPO-FRACTIONATED CHEMO-RADIATION IN LOCALLY ADVANCED CERVICAL CANCER.

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ABSTRACT **Background:** Concurrent chemo-radiation is the standard treatment worldwide for locally advanced squamous Cell carcinoma cervix. However, conventional chemo-radiotherapy is also associated with unacceptable local and systemic failure rates for locally advanced disease. Biologically squamous cell carcinoma of head- neck cancer and cervical cancer behaves quite similarly in response to radiotherapy. So, it can be expected that, altered fractionation can increase the local control in case of squamous cell carcinoma cervix than conventional radiotherapy. There is no randomised control trial for carcinoma cervix till date, which compares conventional chemo-radiation with hypo-fractionated chemo-radiation.

Aims And Objectives: The present study was planned to compare local disease control and acute toxicity of conventional chemo-radiation with hypo-fractionated chemo-radiation in locally advanced carcinoma cervix.

Materials And Methods: In Conventional Chemo-radiation Arm A patients (n=30) received external beam radiotherapy 50 Gy in 25 fractions in 5 weeks accompanied by weekly intravenous Cisplatin 40mg/m2 followed by intracavitary brachytherapy 7 Gy per fraction once in a week for 3 weeks. The second group of hypo-fractionated Arm B received external beam radiotherapy 45 Gy in 20 fractions in 4 weeks accompanied by weekly intravenous Cisplatin 40mg/m2 followed by intracavitary brachytherapy 9 Gy per fraction once in a week for 2 weeks.

Results: Grade II diarrhea were seen more in Arm B 17 (56.66%) compare to Arm A 12(40%) and grade III diarrhea was seen 4 (3.33%) in Arm B and 2(6.66%) in Arm A. At 2 months and 6 months after completion of treatment Complete response were 25 (83.4%) in Arm A compare to 22 (73.3%) in Arm B and 20 (74.1%) in Arm A and 18 (72%) in Arm B respectively.

Conclusion: Hypo-fractioned radiotherapy may be used as an alternate protocol for treatment of locally advanced carcinoma cervix with acceptable toxicities.

KEYWORDS : Conventional radiotherapy, Hypo-fractionated radiotherapy, Carcinoma cervix

INTRODUCTION:

Cervical cancer is the fourth most common cancer affecting women worldwide [1]. Almost 70% of the global burden falls in areas with lower levels of development, and more than one fifth of all new cases are diagnosed in India [1]. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease [2]. It is the second most common cancer in women aged 15–44 years [2].

Squamous Cell carcinoma is the most common histology in carcinoma cervix [2]. It is a radiosensitive tumor and concurrent chemo-radiation with injection cisplatin is accepted as standard treatment worldwide for locally advanced cervical Carcinoma [3,4].The total dose is delivered by External Beam Radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) [5].

However, besides acute toxicities, conventional chemo-radiotherapy is also associated with unacceptable local and systemic failure rates for locally advanced disease. Thus, some form of treatment intensification is needed to improve the therapeutic ratio [6,7,8,9,10].There are several methods for radiotherapy intensification altered fractionation is one of this, which includes hyperfractionation, hypofractionation, accelerated fractionation, Continuous hyperfractionated accelerated radiation therapy, split course therapy. Hypothetically as per radiobiology altered fractionation should increase the local control than conventional radiotherapy, which may or may not bring survival advantage.

This hypothesis is already established in case of Head-Neck squamous cell carcinoma (SCC) [11], where altered fractionation like hyperfractionated or accelerated radiotherapy has increased the local control of the disease than conventional radiotherapy. Also in case of Non small cell lung carcinoma (SCC) [12,13,14], hypofractionation increased the local control. Biologically squamous cell carcinoma of head- neck cancer and cervical cancer behaves quite similarly in response to radiotherapy.So, it can be expected that, altered fractionation can increase the local control in case of squamous cell carcinoma cervix than conventional radiotherapy. It is also recommended that the whole treatment for carcinoma cervix should be completed within 8 weeks as increasing the total duration of treatment beyond this period decreases the response rate, local control and overall survival (OS) [15]. In hypofractionated treatment (>2 Gy/fraction) the overall treatment time is also reduced which should have a considerable effect on local control and survival. The chances of late complication increase with increasing dose per fractionation.

There is no randomised control trial for carcinoma cervix till date, which compares conventional chemo-radiation with hypo-fractionated chemo-radiation as per our knowledge. So, we have designed this study to compare conventional chemo-radiation with hypo-fractionated chemo-radiation in our set-up to compare local disease control, and acute toxicity of the two treatment protocols and to see which one is better suitable for our patient population.

MATERIALS AND METHODS:

This prospective randomized study was done on 60 patients with histologically proven squamous cell carcinoma in cervix, FIGO stage IB2 to IVA at department of radiotherapy, N.R.S Medical College and Hospital, Kolkata. The study accrual period was January 2014 to December 2014 and follow up period was till June 2015.The institutional ethical committee approved the study protocol and written informed consent was taken from each patient. Performance statuses of patients were 70% or more as per KPS Scoring. Patients with prior history of any form of anti-cancer treatment as well as patients with history of hysterectomy were excluded from the study.

Pre-treatment evaluation included detailed history taking and through physical examination, complete haematological and biochemical profile, biopsy from cervical lesion, chest x-ray PA view, USG of whole abdomen, cystoscopy and proctoscopy as and when indicated, biochemical and microbiological study of urine as and when indicated. CECT scan and MRI of abdomen and pelvis were done if required.

The patients were randomized into conventional chemo-radiation Arm A (n=30) and hypo-fractionated arm B (n=30). In Conventional Chemo-radiation Arm A patients received external beam radiotherapy to pelvis with a schedule of five days in a week, 2 Gy per fraction dose

to a total dose of 50 Gy in 25 fractions in 5 weeks accompanied by weekly intravenous Cisplatin 40mg/m^2. The second group of hypo-fractionated Arm B received external beam radiotherapy to pelvis in a schedule of five days in a week, 2.25 Gy per fraction to a total dose of 45 Gy in 20 fractions in 4 weeks accompanied by weekly intravenous Cisplatin 40mg/m^2.

Telecobalt machine (^{60}Co), Theratron 780E was used to deliver external beam Radiotherapy. All patients underwent computed tomography simulation for planning external beam radiotherapy followed by treatment planning using Oncentra planning system version 4. External beam radiotherapy was delivered through four field box technique. During external beam radiotherapy acute toxicities were assessed by weekly history taking, physical examination, study of blood parameters and toxicities were graded according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE V4.0) scale. Blood parameters were maintained by using oral iron supplementation and transfusion of blood and blood components whenever required.

After completion of external beam radiotherapy, the patients in the Conventional Arm received high dose rate (HDR) intracavitary brachytherapy with ^{192}Ir remote after loading system with a schedule of 7 Gy per fraction prescribed at point A, once weekly in 3 fractions to a total dose of 21 Gy and the patients in the Hypofractionated Arm received HDR intracavitary brachytherapy with same source with a schedule of 9 Gy per fraction prescribed at point A, once weekly in 2 fractions to a total dose of 18 Gy. Eclipse PLATO treatment planning system was used for brachytherapy Planning.

Disease response was assessed clinically after completion of external beam radiotherapy, at the time of last fraction of intracavitary brachytherapy and after 1month of treatment completion. Response was assessed by using the Response Evaluation Criteria in Solid Tumors (RECST). Acute toxicity was noted weekly during external beam radiotherapy and at first follow up. First follow up was done at 2 months after completion of treatment and thereafter at 6 months. Patients were followed up with detailed history, through physical and gynaecological examination per vaginal, per speculum, per rectal and appropriate imaging and blood test.

Statistical Analysis:

Statistical Analysis was conducted using IBM SPSS Statistics version 20. For normally distributed data, the mean values between the two arms were compared for test of significance using unpaired t test. Inter-arm mean differences were compared for test of significance using paired t test. For comparing proportions of different events in between the two arms Pearson's chi-square test was applied as test of significance.

RESULTS :

The mean age of the patients in our study was 50.63 yrs in Arm A and 49.77 yrs in Arm B [Shown in Table no.1]. Majority of the patients had Karnofsky Performance Score 80 or above. Most of the patients had FIGO stage IIB, 13 (43.33%) in Arm A and 17 (56.66%) in Arm B. Baseline comparison of different laboratory parameters including haemoglobin, total leucocyte count, Platelet count, weight and serum creatinine before starting treatment revealed no significant difference in both the groups. The mean treatment completion time for the total population was 59.25 days.

Treatment related acute toxicities [Shown in Table no.2] vomiting, diarrhea, dermatitis, anemia, urinary tract pain and anal mucositis were seen in both the groups but no statistical significant difference were seen in both the groups.

At 2 months after completion of treatment Complete response were 25 (83.4%) in Arm A compare to 22 (73.3%) in Arm B [shown in Table 3]. Partial response were 4 (13.3%) in Arm B compare to 6 (20%) in Arm B. Progressive disease were 2 (6.7%) in Arm B compare to 1 (3.3%) in Arm A. There was no stable disease in both the groups. Local response in two Arms were not statistically significant (p value 0.629). At 6 month after completion of treatment 1 patient in Arm A and 1 patients Arm B were dead due to disease progression and 2 patients in the Conventional Arm A and 4 patients in the Hypofractionated Arm B were lost of follow up. Local Response assessment of 52 patients (Arm A n= 27 and Arm B n=25) at 6th month of follow-up after completion of treatment [shown in Table 4]showed complete response was 20 (74.1%) in Arm A and 18 (72%) in Arm B. Partial response were 6 (22.2%) in Arm A and 6 (24%) in Arm B. Progressive disease were 1(3.7%) in Arm A and 1(4%) in Arm B. Local response in two Arms were not statistically significant (p value 0.985).

Table 1: Patients characteristics

Characteristics	Conventional Arm (A) (n=30)	Hypofractionated Arm (B) (n=30)
No. of patients	30	30
Mean Age (Age range 32yrs – 70yrs)	50.63 yrs	49.77 yrs
Parity		
< 3	18 (60%)	16 (53.3%)
>3	12 (40%)	14 (46.7%)
Socioeconomic status		
Low	22 (73.3%)	25 (83.3%)
Others	8 (26.7%)	5 (16.7%)
Karnofsky Performance Score (KPS)		
100	4 (13.3%)	8 (26.7%)
90	12 (40%)	8 (26.7%)
80	14 (46.7%)	14 (46.7%)
Stage of disease		
IIA	3 (10%)	1(3.33%)
IIB	13(43.33%)	17(56.66%)
IIIA	4(13.33%)	2(6.66%)
IIIB	10(33.33%)	10(33.33%)

Table 2: Comparing Treatment Related Acute Toxicities in both Arms

Toxicities		Conventional Arm A	Hypo-fractionated arm B	P Value
Vomiting				
Grade	I	10 (33.33%)	8 (26.66%)	
	II	5 (16.66%)	5 (16.66%)	0.551
	III	0	1 (3.33%)	
Diarrhea				
Grade	I	8 (26.66%)	5 (16.66%)	
	II	12 (40%)	17 (56.66%)	0.386
	III	2 (6.66%)	4 (3.33%)	
Anemia				
Grade	I	10 (33.33%)	9 (30%)	
	II	14 (46.66%)	18 (60%)	0.790
	III	2 (6.66%)	3 (10%)	
Acute Dermatitis				
Grade	I	10 (33.33%)	15 (50%)	
	II	6 (20%)	8 (26.66%)	0.719
	III	4 (13.33%)	3 (10%)	
Urinary Tract pain				
Grade	I	11 (36.66%)	13 (43.33%)	
	II	6 (20%)	9 (30%)	0.720
Anal Mucositis				
Grade	I	9 (30%)	10 (33.33%)	
	II	8 (26.66%)	11 (36.66%)	0.386
	III	0	1 (3.33%)	

Table 3: Disease response (as per RECIST criteria) at 2 months of treatment completion

Response	Conventional Arm A (n = 30)	Hypofractionated Arm B (n= 30)	P value
Complete Response	25 (83.4%)	22 (73.3%)	
Partial Response	4 (13.3)	6 (20%)	0.629
Stable Disease	0	0	
Progressive Disease	1 (3.3%)	2 (6.7%)	

Table 4: Disease response (as per RECIST criteria) at 6 months of treatment completion

Response	Conventional Arm A (n = 27)	Hypofractionated Arm B (n= 25)	P value
Complete Response	20 (74.1%)	18 (72%)	
Partial Response	6 (22.2%)	6 (24%)	0.985
Stable Disease	0	0	
Progressive Disease	1 (3.7%)	1 (4%)	

DISCUSSION:

Sixty patients of locally advanced squamous cell carcinoma of cervix of Federation of Gynecology and Obstetrics (FIGO) stage IIA–IIIB met the inclusion and exclusion criteria were included in our study. Thirty patients were randomized to concurrent ciplatin based conventional chemoradiation Arm A and thirty patients to hypofractionated chemoradiation Arm B. The background characteristics of the two groups were similar as shown in Table 1. The mean age of the conventional Arm A was 50.63 years and hypofractionated Arm B was 49.77 years. According to available literature the peak age for cervical cancer incidence is 45-54 years in India [2]. The mean age of our study, thus corresponds to the existing data for Indian Population. In both the groups most of the patients were in low socioeconomic status as per education and per capita monthly

family income. Majority of the patients had Karnofsky Performance Score 80 or above. Most of the patients had FIGO stage IIB, 13 (43.33%) in Arm A and 17 (56.66%) in Arm B.

The mean treatment completion time for the total population was 59.25 days. All patients completed treatment as per prescribed dose of Radiotherapy and Chemotherapy. The minimum time required to complete treatment was 42 days and maximum time taken to complete treatment was 79 days. 23 (76.7%) in Arm B patients could complete their treatment within 8 weeks and 30 (100%) in Arm A taken >8 weeks to complete their treatment. American Brachytherapy Society recommends treatment completion within 8 weeks to achieve better local control and overall survival as there is chance of failure of treatment as treatment is prolonged by each day after 8 weeks [4]. So we investigated the number of patients completing treatment within 8 weeks. 23 (38.33%) out of 60 patients who completed treatment could complete treatment within 8 weeks duration. The result that majority of patients (61.66%) could not complete the treatment within 8 weeks reflects the high incidence of acute toxicities during radiotherapy. 22 (36.66%) patients required treatment interruption during treatment due to grade III or above acute dermatological, gastrointestinal or haematological toxicities. Treatment interruption occurred in Patients with grade II anemia due to blood transfusion.

Radiation induced acute toxicities were graded weekly according to CTCAE (V4.0) scoring criteria and were compared between the two Arms of treatment (Table no. 2). Grade I toxicity was most common among dermatological toxicities in both Arms, 10 (33.33%) in the Conventional Arm A and 15 (50%) Hypofractionated Arm B. But the difference was not statistically significant (P value = 0.719). Grade II diarrhea was most common among in both Arms, 12 (40%) in the Conventional Arm A and 17 (56.66%) in Hypofractionated Arm B. But the difference was not statistically significant (P value 0.386). This can be explained by high dose per fraction in the Hypofractionated Arm B and the sensitizing effect of Cisplatin on the rapidly proliferating intestinal mucosa. There is also higher proportion of Grade II Anal mucositis in the Hypofractionated Arm B 11 (36.66%) compare to Conventional Arm A 8 (26.66%) but statistically not significant (P value = 0.386). Grade I toxicity was most common among urinary tract pain in both Arms, 11 (36.66%) in the Conventional Arm A and 13 (43.33%) Hypofractionated Arm B. But the difference was not statistically significant (P value = 0.720). The grade II Anemia was seen more in Hypofractionated Arm B 18 (60%) compare to conventional Arm A 14 (46.66%) and grade III Anemia was 3 (10%) in Hypofractionated Arm B compare to 2 (6.66%) in conventional Arm A but the difference was not statistically significant (P value = 0.790). Muckaden MA et al. at Tata Memorial Hospital shown in their study that 21 (44%) patients developed acute gastrointestinal toxicity of which 5 patients had grade III and 1 patient had grade IV toxicity and skin reactions were mainly grade I or grade II [16]. In our study grade II diarrhea was most common among in both Arms, 12 (40%) in the Conventional Arm A and 17 (56.66%) in Hypofractionated Arm B. But the difference was not statistically significant (P value 0.386). This can be explained by high dose per fraction in the Hypofractionated Arm B and the sensitizing effect of Cisplatin on the rapidly proliferating intestinal mucosa. There is also higher proportion of Grade II Anal mucositis in the Hypofractionated Arm B 11 (36.66%) compare to Conventional Arm A 8 (26.66%) but statistically not significant (P value = 0.386). Grade I toxicity was most common among urinary tract pain in both Arms, 11 (36.66%) in the Conventional Arm A and 13 (43.33%) Hypofractionated Arm B. But the difference was not statistically significant (P value = 0.720). The grade II Anemia was seen more in Hypofractionated Arm B 18 (60%) compare to conventional Arm A 14 (46.66%) and grade III Anemia was 3 (10%) in Hypofractionated Arm B compare to 2 (6.66%) in conventional Arm A but the difference was not statistically significant (P value = 0.790).

Local Response rates were assessed using the RECIST response assessment criteria at 2 months after completion of treatment and then at sixth month. At the end of 2 months follow up complete response were 25 (83.4%) in conventional Arm A compare to 22 (73.3%) in hypofractionated Arm B, Partial response 4 (13.3%) in Arm A compare to 6 (20%) in Arm B, Progressive disease was 1 (3.3%) in Arm A compare to 2 (6.7%) in Arm B but the difference was not statistically significant (p value = 0.629).

At 6 month after completion of treatment 1 patient in Arm A and 1 patients Arm B were dead due to disease progression and 2 patients in the Conventional Arm A and 4 patients in the Hypofractionated Arm B were lost of follow up. At 6th month after treatment completion 20 (74.1%) patients in Conventional Arm A and 18 (72%) patients in hypofractionated Arm B achieved complete response, 6 (22.2%) patients in conventional Arm A and 6 (24%) patients in hypofractionated Arm B achieved partial response, progressive disease was 1 (3.7%) patients in conventional Arm A and 1 (4%) patients in hypofractionated Arm B but the difference was not statistically significant (p value = 0.985).

In the developing country like India, there is a huge burden of Cervical Cancer patients and there is lack of sufficient numbers of radiation therapy units and other resources; patients have to wait longer period for radiotherapy to be initiated. Similar Hypofractionated radiotherapy protocol may be useful in such situations without compromising the response rate with manageable toxicity profile. The major limitation of the study was its short duration of follow-up and small sample size. Because of its short duration of follow-up overall survival, disease free survival or progression free survival could not be assessed. The impact of hypofractionated Radiotherapy on late radiation induced toxicity was also not assessed because of short duration. Further studies with higher number of patients and longer follow-up may be needed to establish these observations.

CONCLUSION:

It is evident from this study that treatment intensification by using altered fractionation like hypofractionated radiotherapy is equally effective in controlling the disease locally for locally advanced carcinoma cervix with slight higher rate of acute toxicities. But those toxicities are only of grade I or II and statistically insignificant also. It is also feasible to complete the treatment within the recommended time period and thus may confirm the higher chance of local control and overall survival. So, hypofractioned radiotherapy may be used as an alternate protocol for treatment of locally advanced carcinoma cervix with acceptable toxicity profile.

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