ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 01 | January - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARISON OF SIX FRACTIONS RADIOTHERAPY PER WEEK WITH FIVE FRACTIONS PER WEEK CONCOMITANT CHEMORADIATION IN CARCINOMA CERVIX.

Oncology

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ABSTRACT

Aim: To compare and evaluate six fractions of radiotherapy in a week alone versus five fractions of radiotherapy with weekly ciplatin in locally advanced carcinoma cervix **Material and methods:** The study was conducted on 60 patients of locally advanced carcinoma cervix. The study group (Group I) received 50 Gy in 25 fractions, 6 fractions per week, over 4.1 weeks and the control group (Group II) received 50 Gy/25 fractions over 5 weeks by external beam radiotherapy with weekly injection cisplatin 40mg/m2. This was followed by Intracavitary High Dose Rate Brachytherapy 7Gy to point A, once in a week for 3 weeks for both groups. All the patients were followed up monthly up to a period of 6 months. The statistical method used for analysis was chi-square test. **Results:** The acute toxicities i.e Grade 3 haematological (0 vs 3%), Grade 2 renal(0 vs 7%), Grade 2 metabolic (0 vs 3%), Grade 3 upper gastrointestinal (0 vs 3%)and Grade 2 genitourinary(7% vs 10%) was observed less in group I than group II except Grade 3 acute skin reactions (17% vs 10%), Grade 3 acute mucosal reactions (20% vs 13%) and Grade 3 acute lower gastrointestinal toxicities (27 vs 20 %) which was observed more in group I than group II, though the observations were not statistically significant. The tumour response at the end of treatment and at six months of treatment was similar in both the groups and the observations were not statistically significant. **Conclusion:** The six fractions per week accelerated fractionation regimen in cervix may be a treatment option in selected patients of locally advanced carcinoma cervix.

KEYWORDS

Radiation, Carcinoma, Cervix, Accelerated

INTRODUCTION

Cancer of the cervix is a major public health problem worldwide and is a leading cause of mortality among women. As per GLOBOCAN 2018, cancer cervix is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in India.[1] Concurrent chemoradiation with cisplatin is the standard of care in locally advanced carcinoma of cervix.[2] However cisplatin is poorly tolerated by patients who have abnormal liver function tests and kidney function test, also patients in the older age group. The cost of treatment of the toxicity which develops after concomitant chemoradiation with cisplatin is also sometimes a burden on the poor patient. The financial difficulties faced by the patient and family members for treatment of toxicity following chemoradiation is also high for patient from rural India. Some centres in developing countries do not have all the radiation facilities. Moreover the treatment delays and interruptions will affect the overall survival of the patient.

Various methods were tried in the past to improvise on the treatment outcome in cases of carcinoma cervix. Altered fractionation is also one method in which an improvement in therapeutic ratio was noted. Various altered fractionation schemes used to increase the local control rate in malignancies are: Accelerated Hyperfractionation, Continuous Hyperfractionated Accelerated Radiotherapy (CHART) and Concomitant Boost Radiotherapy.

A Radiotherapy course duration of more than 8 weeks results in decreased cause specific survival and overall survival (OS). [3] It has been suggested that OS decreases by 0.6% per day and pelvic control by 0.7% per day for each additional day of treatment beyond 55 days. [4,5] Retrospective analysis of patients whose treatment duration lasted more than 8 weeks have shown worse progression free survival and overall survival.[6] It is hypothesized that clonogenic accelerated repopulation a phenomenon in which there is increase proliferation of tumour cells in response to treatment induced killing is responsible for the decreased tumour control with prolonged treatment.[7]

The present study has been carried out to compare six fractions per week radiotherapy alone versus five fractions of radiotherapy with weekly cisplatin and evaluate them in terms of tumour control and treatment induced toxicities.

Material And Methods: The study was conducted on 60 patients of locally advanced carcinoma cervix, previously untreated, histopathologically proven, attending the Department of Radiation Oncology at Pt. B. D. Sharma Post Graduate Institute of Medical sciences. The study group (Group I) received 50 Gy in 25 fractions, 6 fractions per week, over 4.1 weeks and the control group(Group II) received 50 Gy/25 fractions over 5 weeks by external beam radiotherapy with weekly injection cisplatin 40mg/m^2. This was followed by Intracavitary High Dose Rate Brachytherapy 7Gy to point A, once in a week for 3 weeks for both groups. During the course of treatment each patient was evaluated weekly for treatment induced reactions. The reactions were graded according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria. At the end of treatment, the response of the tumor was assessed based on World Health Organization Response Criteria. All the patients were followed up monthly up to a period of 6 months. The statistical method used for analysis was chi-square test.

Results: Both the groups were comparable with respect to clinicopathological parameters. Patient characteristics are shown in table 1. Acute toxicities in both the groups are shown in table 2. Acute skin reactions, acute mucosal reactions and lower gastrointestinal toxicity was seen more in group I than group II, though the observations were not statistically significant.

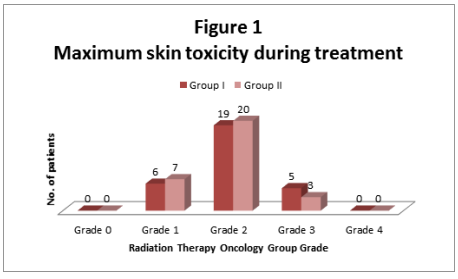
Table 1: Patient Characteristics

Patient characteristic		Group I n (%)	Group I n (%)	p value
Age	<40	3(10%)	7(23%)	0.555
	41-50	8(27%)	6(20%)	
	51-60	11(36%)	9(30%)	
	>60	8(27%)	8(27%)	

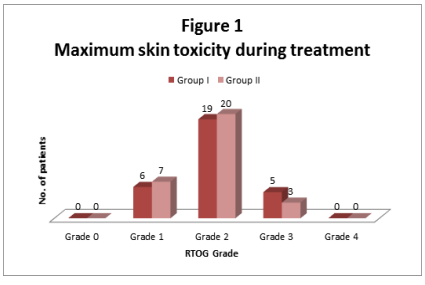
Rural Urban	22 (73%) 8 (27%)	24(80%) 6(20%)	0.542
KPS 70 80 90	3 (10%) 17 (57%) 10 (33%)	1 (3%) 16 (54%) 13 (43%)	0.491
Stage IIA IIB IIIA IIIB	2(7%) 20(67%) 1(3%) 7(23%)	2(7%) 20(67%) 0(0%) 8(26%)	0.795
Parity 1-3 >3	14 (47%) 16 (53%)	11 (37%) 19 (63%)	0.432
Histopathology WDSCC MDSCC PDSCC SCC- Not specified Adenocarcinoma	1(3%) 21(70%) 2(7%) 4(13%) 2(7%)	0(0) 22(73%) 5(17%) 2(7%) 1(3%)	0.508

Table 2: Acute toxicities during External Beam Radiation Therapy Treatment

	Maximum Grade	Group I (%)	Group II (%)	p value
Hematologic	Grade 3	0	3%	0.494
Renal	Grade 2	0	7%	0.206
Metabolic	Grade 1	0	3%	1.000
skin	Grade 3	17%	10%	0.740
mucosal	Grade 3	20%	13%	0.670
Upper gastrointestinal	Grade 3	0	3%	0.503
Lower gastrointestinal	Grade 3	27%	20%	0.369
Genitourinary	Grade 2	7%	10%	0.717



Locoregional control after the completion of treatment in group I and group II was as follows: Complete response at the end of treatment was observed in 67% of patients in group I and 77% of patients in group II. Overall at six months of follow up, 77% of patients in group I and in 80% patients in group II respectively had no evidence of disease. Progressive disease was seen in 23% of patients of group I and in 20% of patients of group II at six months of follow up.



DISCUSSION:

A Cochrane metanalysis done on concurrent chemoradiotherapy revealed 6% absolute survival benefit and also a 8% disease free survival benefit at 5 years in patients with carcinoma cervix.8 Concurrent chemoradiation is currently the standard treatment regimen in patients with locally advanced cervical cancer.2 The rationale for accelerating radiation schedules is predicated on tumour cells undergoing accelerated repopulation during the treatment course after a lag time. By shortening the overall treatment time, less of the total dose of radiation will be wasted in compensating for accelerated tumour cell repopulation during the treatment course. Approximately 40-60cGy per day is required to correct for accelerated repopulation. Accelerating the treatment course will also result in an increase in normal tissue toxicity, especially mucositis.

Many studies have been done in head and neck cancers employing the accelerated radiation schedules, one of which is The Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 trial six fractions of radiotherapy per week was compared with five fractions per week of radiotherapy, the results of this trial was an improvement in the locoregional control rates at 5 years which was 70% for the study group and 60% for the control group.9 Similar studies on done on lung and bladder cancer showed improvement in local control and survival.10,11 In a randomised trial conducted 106 patients with cancer cervix, hematological toxicity and metabolic toxicity were seen more in the chemoradiation arm while cutaneous toxicity was seen more in the accelerated radiotherapy arm. At 6 months 84% patients in the control group and 65% patients in the study group showed complete response. Overall survival at 3 years was 62% in the control group and 61% in study group.[12]

In the present study, the acute toxicities i.e haematological, renal, metabolic, upper gastrointestinal and genitourinary was observed less in group I than group II except acute skin reactions, acute mucosal reactions and acute lower gastrointestinal toxicities which was observed more in group I than group II, though the observations were not statistically significant. The tumour response at the end of treatment and at six months of treatment was similar in both the groups and the observations were not statistically significant.

CONCLUSION:

The six fractions per week accelerated fractionation regimen in cervix may be a treatment option in selected patients of locally advanced carcinoma cervix who are not suitable for standard chemoradiation which is five fractions per week conventional RT with weekly concomitant cisplatin, especially in patients with deranged renal function tests, deranged liver function tests and in patients who refuse chemotherapy. Further randomised trials are needed to explore data on long term survival benefits of accelerated fractionation in locally advanced carcinoma cervix.

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