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COMPARISON OF ACCELERATED RADIATION AND CHEMO - RADIATION IN LOCALLY ADVANCED CARCINOMA CERVIX: A PROSPECTIVE RANDOMIZED, CONTROLLED STUDY.

Oncology

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ABSTRACT

Standard of care in locally advanced carcinoma cervix is Cisplatin based chemo - radiotherapy (CRT). Effectiveness of this modality in locally advanced cervical cancer patients was unclear. In this randomized, prospective, controlled study, 60 patients were randomized to either accelerated radiotherapy (ART) alone or CRT followed by high dose rate intracavitary brachytherapy (HDR - ICBT). The tumour response, Overall treatment time (OTT) and toxicities were recorded 6 weeks after HDR - ICBT. Complete response (CR) was observed in 84.61% patients in ART and 86.2% of patients in CRT groups. Median OTT in ART group was 55.5 days and in the CRT group was 64 days. Overall toxicities were higher in the CRT group. ART decreased the overall treatment time compared to CRT, which has a proven benefit of improving survival. Both the modalities were equally effective in reducing the tumour size.

KEYWORDS

Chemo- radiation, Overall treatment time, Carcinoma cervix.

Introduction

The cancer cervix is one of the leading cancers and is the 4th most common cancer in women. Poverty, ignorance and lack of proper screening facilities at the primary care level are the root causes for the initial presentation of locally advanced stages [1, 2]. According to National Cancer Institute (NCI) - USA, the worldwide standard of care in locally advanced carcinoma cervix is concurrent Cisplatin based chemo - radiotherapy (CRT) [3]. However the question remains unanswered as to whether certain sub - groups/stages of locally advanced cervical cancer patients had greater benefit and the rest had more risk of toxicity than benefit from CRT [4-6].

Cochrane meta-analysis published in the Cochrane library 2005, on concomitant CRT for cancer of the cervix has reviewed 24 randomized controlled trials with 4921 patients and concluded that chemo-radiation improved overall survival (OS) by 10% and progression free survival (PFS) by 13%, whether or not platinum compound was used. However, they found a statistical heterogeneity in these outcomes as there was some evidence that the effect of CRT on OS and PFS was greater in trials including a high proportion of stage I and stage II patients. Acute haematological and gastro-intestinal toxicity was higher in the CRT group. Long term effect of treatment could not be determined due to inadequate reporting [7]. CRT tended to prolong the treatment time due to increased acute toxicities and related treatment breaks, especially in more advanced stages.

Over the years, many studies have shown that prolongation of overall treatment time (OTT) had detrimental effects on tumour control in carcinoma cervix [8-12]. Yoon et.al[14] evaluated six versus five fractions of External Beam Radiotherapy (EBRT) followed by intracavitary brachytherapy (ICBT) in a phase I/ II study in cancer cervix patients. They reported that 6 versus 5 per week EBRT is an effective treatment for patients of carcinoma cervix and can be used as a possible alternative to concomitant chemo-radiation in elderly patients or patients with co-morbidities (renal involvement, poor physical condition).

Based on the above literature, the present study was conducted in locally advanced carcinoma cervix in south Indian patients, to evaluate the feasibility and compare the efficacy of 6 fractions per week of accelerated EBRT (with conventional fraction size), with standard CRT followed by ICBT. In this study, the primary strategy was delivering EBRT by decreasing the OTT, by halving the weekend gap with same dose per fraction, rather than addition of CRT. The main focus of this study is to test if pure accelerated radiotherapy (ART) is a potential alternative to concurrent chemo - radiotherapy in locally advanced carcinoma cervix by comparing the tumour responses and treatment related toxicities of both the modalities, banking on the proven radiobiological benefit of reducing the OTT by pure ART.

Materials and Methods:

The present study was conducted in the department of Radiation Oncology, in a tertiary care cancer centre. This prospective randomized, controlled study was conducted from February 2015 to August 2016. Study was started after Institutional ethics committee approval. Sixty eligible patients were included in the study after obtaining written informed consent. Inclusion criteria were Patients aged between 30 - 65 years, Treatment naive patients with biopsy proven squamous cell carcinoma of the cervix of stages IB_2 to IV A, ECOG performance status 0 - 2. Exclusion criteria were clinical or radiological evidence of metastasis, Stages IA_1, IA2, IB_1 and IVB, other than squamous cell carcinoma of cervix and cancers of other organs, Hemoglobin < 10g%, WBC count < 4000/mm^3, Platelets < 1, 00, 000/mm^3, pregnant patients, patients with impaired liver, heart and renal functions, any co morbid condition or infection where treatment is contra-indicated and Participation in any other clinical trial. Complete history, Physical examination, laboratory investigations (CBP, renal and liver function tests, Chest x-ray, ultrasound abdomen and pelvis) and Punch biopsy were done. MRI pelvis was done if parametrium cannot be assessed adequately on clinical examination. Staging was decided by physical examination and FIGO staging.

Eligible patients were randomized to either ART or CRT. In this study a score was given to parametrial involvement. It was divided into medial 1/3, middle 1/3 and lateral 1/3. Score of 1 was given for involvement of each 1/3 on one side. Minimum score was 1 and maximum score was 6 (3 + 3 bilateral parametrium involvement up to pelvic walls). Parametrial involvement index was similar in both groups.

All patients were examined once weekly during the treatment. Hydration, protein and caloric intake and hygiene were adequately maintained for all the patients during the study. The regression of primary tumour and toxic effects were assessed weekly. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy was done. Patients, who completed entire schedule of radiotherapy irrespective of the delay and receiving chemotherapy were evaluated for response and assessed for ICBT feasibility.

In ART group, the patient was given RT of 2 Gy per day for 6 fractions a week, to a total dose of 50 Gy in 25 fractions for a span of 4 week 3 days. First fraction of high dose rate (HDR) ICBT was started with 7 Gy per fraction, for a total of 3 fractions, after completion of EBRT, with an interval of one week between each fraction. The 3 fractions

achieved a dose equivalent to 85 Gy to point A. Patients not fit for HDR-ICBT due to central residue were boosted by lateral portals up to 66Gy and those of them with parametrial residue were boosted to 60Gy with midline block.

In the CRT group the patient was given RT of 2 Gy per day for 5 fractions a week to a total dose of 50 Gy in 25 fractions for a span of 5 weeks 3 days with simultaneous infusions of cisplatin, 3 per week, for the entire course of EBRT. Injection cisplatin 50 mg was started intravenously on the 2nd day of EBRT and it was ensured that EBRT was given 4 hours after cisplatin infusion. Patient was given tablet Ondensetron 8 mg thrice a day for 3 days as routine anti emetic therapy after cisplatin. Three fractions of HDR ICBT in doses of 700 cGy were started on the next day of completion of EBRT with an interval of 1 week between them. The 3 fractions achieved a dose equivalent to 85 Gy to point A.

Response was assessed 6 weeks after the last fraction of HDR - ICBT according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1).

Assessment of toxicity: The acute toxicity was assessed weekly during treatment, at 6 weeks after completion of the treatment, using RTOG acute toxicity criteria. Chemotherapy induced toxicity like nausea, vomiting, haematological and other toxicities were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis:
All the data was presented as mean ± SEM or median and percentages. Data was analysed by using Graph pad prism software. The clinical response, toxicities and radiation treatment time between the control and study groups were compared by two tailed Mann - Witney test. Confidence intervals were kept at 95%. P value < 0.05 was considered as significant.

Results

A total of 60 patients were included in the study. Thirty patients in ART group (study group) and 30 patients in CRT (control group) were included. Demographic data and stages of disease were presented in table - 1. Majority of the patients were of stage IIIB in both the groups and all the stages were equally distributed between the groups (Table - 1). Majority patients had parametrial disease up to the pelvic wall in both the groups.

Table - 1 Mean age and staging in the study groups

	ART (n= 30)	CRT (n= 30)
Mean age (yrs)	51.6 ± 2.08	49.9 ± 1.7
FIGO Stage		
I B_2	2	1
II A	3	5
IIB	7	6
III A	0	1
III B	18	17
IIB	7	6
III A	0	1
III B	18	17
Parametrial involvement Index		
0	5	6
1	0	1
2	2	2
3	3	1
4	5	5
5	3	2
6	12	13

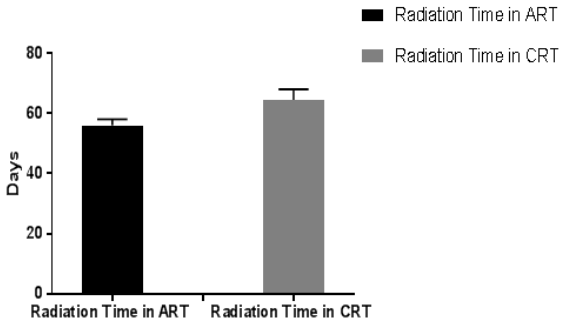
In ART group, out of 30 patients, 26 patients completed the treatment and 4 patients had incomplete treatment. In CRT group out of 30 patients, 29 patients completed the treatment and 1 patient had incomplete treatment. The response rates between ART and CRT groups showed no statistically significant change (table - 2). This shows that both treatment modalities were equally effective in treating cancer cervix to get a complete response.

Table - 2 Treatment responses between study groups

Response	ART (n= 30)	CRT (n= 30)	P value
Complete Response	22 (84.61%)	26 (86.2%)	0. 999
Partial Response	4 (15.39%)	4 (13.8%)	
Incomplete Treatment	4	1	

The median OTT in ART group was 55.5 (41-70) days and in CRT group was 64 (53-75) days. The median EBRT time in ART arm was 32 (28-36) days and in the CRT arm was 39 (35 - 44) days. Median time gap between EBRT and 1st fraction of ICBT in both the arms was 4 (1 - 8) days. In ART group the OTT required was less (55 days) when compared to CRT group (64 days). When compared between ART and CRT, there was a highly significant ($p < 0.0001$) difference in OTT. CRT group required more radiation treatment days than ART group (Figure - 1).

Figure - 1 Overall radiation treatment time in study groups



A total of 108 toxicities were observed in 60 patients. Out of which 39 toxicities occurred in ART group and 69 occurred in CRT group. Toxicities were more in CRT group compared to ART group. The most common toxicities in ART group were nausea, diarrhoea and vaginal discharge/ mucositis where as in CRT group nausea, haematological toxicity and vaginal discharge/ mucositis were observed (Table - 4). There was a highly significant ($P < 0.01$) increase in toxicity in CRT group. Haematological toxicity showed very high significant occurrence ($P < 0.001$) in CRT group than in ART group. There was a significant increase ($P < 0.05$) in Vomiting in ART group compared to CRT group. Nausea, diarrhoea, dermatological side effects, fever, vaginal discharge/ mucositis and bladder irritation showed no statistically significant difference in either ART or CRT groups.

Majority of toxicities observed in both the treatment groups were of Grade 1 toxicity. In ART group grade 1 toxicities were (72.48%) where as in CRT group (64%). Grade 2 toxicities constituted 33% in ART group and 23.1% in CRT group. Grade 3 toxicities were none in ART group and in CRT group they were 2.9%. Grade 4 toxicities were 2.56% in ART group and 1.44% in CRT group (Table - 3). Both the treatments were well tolerated in majority of patients.

Table - 3 showing toxicity profile in study groups

S No	Toxicity Grade	ART (n = 30)					CRT (n = 30)				
		G1	G2	G3	G4	Total	G1	G2	G3	G4	Total
1	Nausea	6	1	-	-	7	11	2	-	-	13
2	Vomiting	1	2	-	-	3	9	2	-	-	11
3	Diarrhoea	4	3	-	-	7	5	2	-	-	7
4	Haematological	-	-	-	1	1	6	4	2	1	13
5	Dermatological	1	3	-	-	4	2	4	-	-	6
6	Fever	5	-	-	-	5	5	1	-	-	6
7	Vaginal discharge/ Mucositis	5	2	-	-	7	7	1	-	-	8
8	Bladder irritation	3	2	-	-	5	5	-	-	-	5
	Total	25	13	0	1	**39**	50	16	2	1	**69**

Discussion

The recent Cochrane review (2010) on concurrent chemo-radiotherapy shows 6% absolute survival benefit and 8% Disease Free Survival (DFS) benefit at 5 years in carcinoma cervix [1]. Moreover, there is a trend of decreasing relative effect of chemo-radiotherapy on survival with increasing tumour stage, with estimated absolute survival benefit of 7% for stage IIB and 3% for stage IIIA-IVA at 5 years. The treatment failure in carcinoma cervix still remains primarily

loco regional and improvisation of local therapy needs to be made to improve treatment results.

In our study, 84.61% patients showed complete response (CR) and 15.39% showed partial response (PR) in ART group. In the CRT group, 86.2% patients showed CR and 13.8% patients showed partial PR. Our results were consistent with the previous studies. In a study by Yoon et.al CR was 79.1% and PR was 18.6% [13]. In the study by Chhaya Roy et.al [14] the ART arm showed CR of 82.14% and PR of 7.14%. In the CRT arm, 74.07% patients showed CR and 3.70% PR. All the responses in this study were given after a median follow up of 15 months.

The response rates in our study were comparable to the response rates of previous studies. In the trials on pure accelerated radiotherapy versus concurrent chemo-radiation conducted in other centres of India, the immediate post treatment response rates, 3 year local control rates and disease free survival rates (DFS) were similar between the ART and CRT arm suggesting that pure accelerated radiation is an effective alternative to concurrent chemo-radiation in Indian patients. Other forms of altered fractionation like hyper fractionation, hypo fractionation and combined hyper and accelerated radiotherapy (CHART) were also tried in several trials [15, 16, 17] in locally advanced carcinoma cervix. These modalities were successful in decreasing the OTT to around 30-40 days but were heterogeneous in their respective inclusion criteria and the responses also differed accordingly. Though responses were comparable to pure accelerated radiotherapy and conventional chemo radiation but they were not superior to ART or CRT.

In our study median OTT in the accelerated radiotherapy arm was 55.5 days and in the CRT arm was 64 days. Our results were similar to the previous studies results. Yoon et .al [13] reported that the median OTT in the ART arm was 51 days. Chhaya Roy et al [14] showed that the median OTT in ART arm was 56.54 days and in CRT arm was 62.59 days. In a study by Petereit DG et.al [8] 5 years survival rates in stage III disease with OTT of less than 55 days was 52% and OTT more than 55 days was 42%, Pelvic control rates were 76% in OTT of less than 55 days group and 55% in OTT more than 55 days group. Girinsky et.al [10], Lanciano et.al [11], Fyles A et.al [18], Perez et.al [19] have also concluded from their respective studies that prolongation of treatment time was an independent prognostic factor in loco regional control and overall survival of carcinoma cervix.

In our study a total of 108 toxicities were observed in both the arms put together of which 39 (36%) occurred in the ART arm and 69 (64%) occurred in the CRT arm. Overall toxicities were higher in the CRT group compared to ART group ($P < 0.01$). Haematological toxicity was significantly high in the CRT group compared to ART group ($P < 0.001$). A meta-analysis showed increased overall acute toxicity and specifically haematological and gastro intestinal toxicity with chemo-radiation which was evident in our study too. Late toxicities were similar in chemo-radiation and radiation only arm from the 12 trials which provided information on late toxicity [20].

In our study, we have included more number of stage III patients in whom benefit of chemo-radiotherapy was not proven conclusively and reduction of OTT was the most important consideration and inclusion of an entity called the parametrial involvement index to overcome the gaps in FIGO staging to avoid bias. Our study was one of the very few studies on altered fractionation in carcinoma cervix done on a linear accelerator with 3D conformal planning.

Limitation of this study was less sample size (55 completed patients), exclusion of other pathologies of cancer cervix and non-stratification of well and poorly differentiated cancers and no availability of long term follow up data. In conclusion, Pure accelerated radiotherapy decreased the overall treatment time compared to chemo-radiotherapy, which has proven benefit of improving survival. Both the modalities were equally effective in locally advanced carcinoma cervix to get a complete response. Toxicities were more in the concurrent chemo-radiotherapy arm, especially haematological toxicity. However, RCTs with more number of patients with documented improvement in long term disease free survival and overall survival and comparison of long term toxicities is necessary to prove ART, as an alternative to CRT, which is a standard of care.

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