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Comparison of Local Disease Control and Toxicities in Two High Dose Rate Intracavitatory Brachytherapy Dose Fractionation Regimens (7Gy/3# v/s 9Gy/2#) in the Radical Treatment of Carcinoma Cervix: a Prospective Randomized Trial in Sub-Himalayan Region

Era Sankhyayan

Abstract: ***Background: Cervical carcinoma is the most prevalent gynecological cancer. Majority of patients in sub-himalayan region presents in locally advanced stage in which chemoradiotherapy followed by intracavitatory brachytherapy is the main line of treatment. ICBT plays an integral part of the treatment but there is no consensus guideline about an optimal fractionation regimen. In a resource limited setting with increased patient load, there is a need to reduce ICBT sessions with simultaneous increase in dose per fraction. We performed a RCT comparing local disease control and toxicities between two different dose regimens of ICBT i.e., 7Gy per fraction in 3# and 9Gy per fraction in 2# in sub-himalayan region. Methods: The prospective study was undertaken in 59 patients of ca cervix from stage IB3 to IVA from May 2020 to May 2021 at Department of Radiotherapy and Oncology, Tertiary Cancer Centre, Indira Gandhi Medical College Shimla (H.P.). All patients were treated initially with external beam radiotherapy of 50Gy/25# by four field technique combined with weekly injection cisplatin (dose 40mg/m2). Study group had 28 patients who received 2 fractions of ICBT of 9Gy each whereas 31 patients in control group received 3 fractions of ICBT of 7Gy each. Local response and rectal as well as genitourinary toxicities were assessed after 4 months of treatment completion. Results: Patients in both the arms had equivalent local response with 60% complete response in study arm and 83.9% complete response in control arm. The difference in local response was not statistically significant (p=0.08). Similarly, GIT and GUT toxicities were comparable in both the arms with only 1 patient in control arm developing grade III GIT toxicity. None of the patients developed grade IV GIT/GUT toxicities. Conclusion: The results show that 9Gy/2# ICBT schedule is as effective and safe option as 7Gy/3# with similar local control and manageable GIT and GUT toxicities, making it a practical alternative in a resource-limited setting.***

Keywords: Carcinoma cervix, ICBT dose regimen, 9Gy/2# v/s 7Gy/3#, GIT/ GUT toxicities

1. Introduction

Carcinoma cervix is the most common gynecological malignancy. As per GLOBOCAN 2020 data, there were 19.3 million newly diagnosed cancer cases throughout the world with 10 million deaths in 2020.[1] In females, it is 4th most common malignancy and 4th leading cause of cancer death with annual incidence of disease 6 lakh in the year 2020 and 3,42,000 deaths.[1] In India, carcinoma cervix is 3rd most common malignancy with 1,23,907 new cases in 2020 accounting for 9.4% of all malignancies[2].

In sub-himalayan region, majority of patients presents with locally advanced stage in which chemoradiotherapy followed by intracavitatory brachytherapy is the main line of treatment. ICBT is an integral component in the treatment of carcinoma cervix. The American Brachytherapy society has recommended an individual fraction size of < 7.5Gy in 4 to 8 fractions but has also issued a caution stating that the recommendation has not been thoroughly tested. At present there are no consensus guidelines about an optimal fractionation schedule.

Himachal Pradesh is a hilly state with wide geographical variation, adverse climatic conditions, limited public transport and majority of patients coming from far flung rural areas for their treatment. It poses a great challenge for successful completion of long treatment which includes 5 weeks of EBRT and multiple sessions of ICBT.

The present study was aimed to evaluate local response and toxicities in two high dose rate intracavitary brachytherapy dose fractionation regimens (7Gy/3# v/s 9Gy/2#) in the radical treatment of carcinoma cervix.

2. Methods

The prospective study was conducted in the patients with cervical cancer from stage IB3 to IVA who were treated with curative intent in the Department of Radiotherapy and Oncology, Tertiary Cancer Centre, Indira Gandhi Medical College, Shimla (H.P.) during the period May 2020 to May 2021. At our institute in the last 10 years, 1896 patients of carcinoma cervix were registered. So, on an average 180-190 patients are registered every year of all stages of carcinoma cervix. Hence, we enrolled 82 patients in the study after approval by the institutional ethics committee, as per inclusion/exclusion criteria.

Inclusion criteria included age ≤70 years, histological confirmation by biopsy: squamous, adenocarcinoma, Adenosquamous, KPS ≥70, Stage IB3–IVA (FIGO 2018), Hb≥10 gm%, complete blood picture, renal function test, and liver function test results within normal limits, No previous pelvic irradiation. Exclusion criteria included age

>70 years, KPS<70, Stage IA, IB1, IB2, IVB, previous pelvic irradiation, and patients not fit for concurrent chemotherapy.

External beam radiotherapy in the dose of 50Gy/25# for 5 weeks was given to all patients in both the arms by four field box technique along with weekly injection of cisplatin (40mg/m2).Patients were assessed for brachy therapy after 2 weeks of completion of treatment. Due to defaulter patients and inability to perform ICBT on some patients, the study was conducted only on 59 patients and these were randomized into two groups using sealed opaque envelopes which contained computer generated random numbers. There were 31 patients in control arm of 7Gy in 3# and 28 patients in study arm of 9Gy in two fractions.

Data analysis

Date was entered in Microsoft® Excel workbook 2019 and exported into SPSS v21.0 for statistical analysis. Categorical data were presented as frequency, percentage, and compared using Chi square test. P<0.05 was considered statistically significant.

3. Results

Baseline Characteristics

Table 1 shows baseline characteristics of the study subjects. Majority of patients in both the groups (75% in study and 74% in control) were having baseline hemoglobin levels of more than 11gm/dl.There was only one patient in control group that was having pretreatment hemoglobin level of less than 7.5 gm/dl..

Comparison of local disease response between study and control group.

Local disease control and genitourinary and gastrointestinal toxicities were assessed 4 months after treatment completion. Table 3 shows that, 60.7% patients of study group and 83.9% patients of control group had complete response. The difference in response was not statistically significant (p=0.08)

Comparison of Gastrointestinal toxicities between study and control group.

There was only one patient (3.2%) in control arm that developed grade III toxicity. There was no grade IV toxicity in either arm. 3.6% patients of study arm and 6.5% patients in control arm developed grade II toxicity at 2nd follow up. The difference between toxicities was not statistically significant (Table 4).

Comparison of Genitourinary toxicities between study and control group.

Table 5 shows that the 1 patient developed grade I toxicity in control arm. There was no grade II, III, IV genitourinary toxicity at 2nd follow up in either group.

4. Discussion

The median age of patients enrolled in the study group was 49.5 years and that of control group was 52 years. Majority of the patients (57%) in study group were in stage IIIB and IIIC1 whereas maximum number patients (40%) were of stage IIB in control group. Also, there was only one patient enrolled in stage IIIA and stage IB3 in study arm. Similarly, only 1 patient was enrolled in stage IIA and no patient in stage IIIA in control group. The data of stage wise distribution of patients. Majority of the patients in both the arms had parametrial involvement i.e., 85% of patients in study group and 87% in control group had parametrium involvement. Most patients had an ulcer proliferative growth in both the groups i.e., 82% in study group and 70% in control group. While infiltrative growth pattern was seen in least number of patients. Most common histology was squamous cell carcinoma in both arms. The demographic and tumor characteristics are outlined in table1.

In our study we compared two brachytherapy schedules in locally advanced ca cervix patients in terms of local tumor control and radiation toxicities.

In a study by **Sharma et al**,[3]on locally advanced ca cervix patients, ICBT dose of 10Gy was delivered in two fractions 1 week apart and recurrence free survival was 67%, 34%,20% for stage IIB, IIIB,IV respectively and was associated with manageable toxicities.

A study by **S. Ghosh et al,**[4] regarding ICBT fractionation dose schedule, concluded that 9Gy in two fractions is as effective regimen in terms of local control, disease free survival and overall survival, although toxicties were increased in this schedule but were manageable.

Similarly a study by **S. Gangopadhyay et al**[5], compared dosimetery and efficacy between 9Gy/2# and 7Gy/3# using same applicator and concluded 9Gy/2# to be an effective and safe alternative.

Likewise, the results of our study are in concordance with these studies showing similar local response rates and comparable genitourinary and gastrointestinal toxicities in between the two regimens.The difference in response and toxicities between two arms was not statistically significant, thereby, indicating 9Gy/2# regimen , a feasible option in a region like sub Himalayas where treatment compliance is challenging.

5. Conclusion

The findings suggest that ICBT schedule of 9Gy/2# is as effective and safe treatment option as 7Gy/3# with similar local control and manageable GIT and GUT toxicities, hence making it a feasible option in a resource limited setting.

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Table 1: Baseline Characteristics

Baseline Characteristics	Study Group (n=28)	Control Group (n=31)
Age (Years)		
20-30	1 (3.57%)	0 (%)
31-40	7(7.14%)	4 (14.3%)
41-50	14(50.00%)	7 (25.0%)
51-60	6(21.43%)	12 (42.9%)
>60	5(17.86%)	8 (28.6%)
Stage		
IB3	1(3.57%)	3 (10.7%)
IIA	3(10.71%)	1 (3.6%)
IIB	7(25.00%)	15 (53.6%)
IIIA	1(3.57%)	0.0
IIIB	8(28.57%)	5 (17.9%)
IIIC1	8(28.57%)	7 (25.0%)
Parametrium involvement		
Yes	24 (85.71%)	27(96.4%)
No	4(14.29%)	4(14.3%)
Type of Growth		
Ulcero proliferative	23(82.14%)	22(78.6%)
Infiltrative	2(7.14%)	3(10.7%)
Nodular	3(10.71%)	6(21.4%)
Type of Histology		
Squamous cell	24(85.71%)	28(100.0%)
Adenocarcinoma	3(10.71%)	3(10.7%)
Adeno-squamous carcinoma	1(3.57%)	0.0
Histological grading		
Well differentiated	3(10.71%)	4(14.3%)
Moderately differentiated	18(64.29%)	21(75.0%)
Poorly differentiated	2(7.14%)	4(14.3%)
Not graded	5(17.86%)	2(7.1%)
Parity		
≤3	16(57.14%)	17(60.7%)
>3	12(42.86%)	14(50.0%)
Smoking		
Smoker	2(7.14%	3(10.7%)
Non-smoker	26(92.86%)	28(100.0%)

Table 2: GIT and GUT Toxicity (Control and Study Group)

	GIT Toxicity		GUT Toxicity	
	Grade 1	Grade 2	Grade 1	Grade 2
Week 1	0 (0.00%)	0 (0.00%)	(0.00%)	(0.00%)
Week 2	0 (0.00%)	1 (3.57%)	(14.29%)	0 (0.00%)
Week 3	11 (39.29%)	1 (3.57%)	(35.71%)	0(0.00%)
Week 4	10 (35.71%)	0 (0.00%)	(28.57%)	0 (7.14%)
Week 5	18 (64.29%)	1 (3.57%)	(46.43%)	2 (0.00%)

Table 3: Comparison of Response between study and control group

Local Response	Group				Total	
	Study		Control			
	n	%	n	%	n	%
Complete response	17	60.7	26	83.9	43	72.9
Partial response	9	32.1	5	16.1	14	23.7
Stable disease	2	7.1	0	0.0	2	3.4
Total	28	100.0	31	100.0	59	100.0
Chi-square value = 4.887 P value = 0.087 Not significant						

Table 4: Comparison of Gastrointestinal toxicities between study and control group

GIT Toxicities	Group				Total	
	Study		Control			
	n	%	n	%	n	%
Grade 0	27	96.4	27	87.1	54	91.5
Grade I	0	0.0	1	3.2	1	1.7
Grade II	1	3.6	2	6.5	3	5.1
Grade III	0	0.0	1	3.2	1	1.7
Grade IV	0	0.0	0	0.0	0	0.0
Total	28	100.0	31	100.0	59	100.0
Chi-square value = 2.186 P value = 0.535 Not significant						

Table 5: Comparison of Genitourinary Toxicities between study and control group

GUT Toxicities	Group				Total	
	Study		Control			
	n	%	N	%	n	%
Grade 0	28	100.0	30	96.8	58	98.3
Grade 1	0	0.0	1	3.2	1	1.7
Grade 2	0	0.0	0	0.0	0	0.0
Grade 3	0	0.0	0	0.0	0	0.0
Grade 4	0	0.0	0	0.0	0	0.0
Total	28	100.0	31	100.0	59	100.0
Chi-square value = 0.919, P value = 0.338 Not significant						