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A comparative study to assess the disease outcome in cervical carcinoma in patients treated with EBRT and concurrent Cisplatin and sequential brachytherapy versus treatment with interdigitated brachytherapy.

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ABSTRACT: Aims and Objectives: To study the disease outcome in patients of carcinoma cervix treated with External beam radiotherapy (EBRT) with concurrent Cisplatin based chemotherapy followed by Intracavitary brachytherapy (ICBT) (3# of 7Gy each) orEBRT with concurrent cisplatin-based chemotherapy, interdigitated with Intracavitary brachytherapy.

Materials and methods: 23 histo-pathologically proven cervical cancer patients,fulfilling the inclusion criteria were chosen for this study over a period of two years. All patients received 50 Gy in 25 fractions to the pelvis. Depending on the geometry, patients either received sequential brachytherapy (Control arm) with 7 Gy in 3 fractions to point A or interdigitated brachytherapy (Study arm). In the study arm, depending on the number of EBRT fractions received, they were assigned to receive 4.5 Gy/fraction if taken after 20 Gy, 5 fractions/ 5.0 Gy each if taken after 30 Gy and 4 fractions/6 Gy each if taken after 40 Gy exposure to point A.

Results: Out of the 23 patients, 14 patients were assigned to the control arm and 9 patients to the study arm. All patients completed treatment within 8 weeks from the time of diagnosis except for 3 patients who exceeded the overall treatment time (OTT) due to personal reasons. Median follow up time was 6-18 months. We lost 4 patients to follow-up, 3 in the control arm and 1 in the study arm.

Assessment of Tumour response was done as per RECIST criteria (version 1.1). 11 patients (78.57%)in the control arm and 8 patients (88.8%) in the study arm showed complete response at 6 weeks.

At the time of the last follow up for this study, 1 patient from each group had progressive disease.

There was no statistically significant difference noted in terms of OTT and outcome.

Acute toxicities were assessed using CTCAE criteria and no statistically significant difference between the 2 arms was seen.

Late toxicities were seen in 2 patients in the study arm, of which1 patient developed Grade I cystitis (11.1%) and 1 patient developed Grade II proctitis (11.1%).

Conclusion: Owing to the ongoing COVID-19 pandemic, the sample size accrued was much lower than anticipated. Hence no conclusive correlation could be made. However, we hope future studies will help consolidate findings of the existing data.

Keywords: Cervical cancer, Brachytherapy, Interdigitated Brachytherapy, Overall treatment time

I. INTRODUCTION:

Cancer of the Cervix Uteri or Cervical cancer is a major public health concern especially in lower resourced countries with lower- and middle-income countries.

Globally speaking, cervical cancer accounts for 3.1% of all diagnosed cases and accounts for 3.4% of all cancer related deaths according to Globocan 2020[1].There is a staggering disparity in rates between transitioning and transitioned countries (18.8 vs 11.3 per 100,000 for incidence; 12.4 vs 5.2 per 100,000 for mortality)[1].

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As per Globocan 2020[1], India has a higher incidence and mortality rate, with 123,907 new cases diagnosed and 283,842 deaths were recorded making cervical cancer the 2nd most frequent cancer in females (only behind breast) accounting for 18.3% of all the cancers recorded. Overall, in both the genders, It's the 3rd most frequently seen cancer (9.4%); with Breast carcinoma ranking first (13.5%) followed by Lip and Oral cavity cancers at the 2nd rank (10.3%).

India also has a higher Age- standardized incidence rate (ASIR) at 14.7/100,000 and Age-standardized mortality rate of 9.2/100,000[2] compared to developed nations which necessitates the need for early diagnosis and treatment.

The primary treatment in early-stage cervical cancer can be either surgery or RT. Surgery is usually reserved for early-stage disease, fertility preservation and smaller lesions like IA, IB1, IB2 and selective IIA stage. Since both surgery and RT are viable options, attention must also be paid to try and avoiding surgery in cases with risk factors necessitating adjuvant RT. This allows us to avoid morbidities resulting from multimodal therapy.

It is generally agreed that concurrent chemoradation (CRT) with Brachytherapy (BT) is the standard of care for Stages IB3-IVA[3].

When combined with external beam radiation therapy (EBRT), BT is usually started in the latter part of the treatment (Generally starting no earlier than week 3 of treatment), once sufficient primary tumour regression has occurred which increases the distance between the tumour and the organs at risk (OAR), to allow proper brachytherapy apparatus geometry.

BT can be either interdigitated with EBRT or given sequentially following EBRT. The main rationale behind delivering interdigitated brachytherapy is to decrease the overall treatment time (OTT). It is recommended that radiation therapy should be delivered in the shortest period of time for best results. Conventional radiation protocol with sequential brachytherapy takes about 9 weeks for completion. With interdigitated brachytherapy, the treatment duration can be decreased. From a radiobiological perspective, this helps us achieve better local control and thus can be assumed to be more effective. All efforts must be taken to ensure that all patients receive BT. If not possible, a boost can be planned either as a Simultaneous integrated boost or with IMRT[4].

The main objective of this study was to compare the two modalities in terms of response to treatment, acute and long-term toxicities, and disease-free interval.

II. MATERIALS AND METHODS.

This is a descriptive longitudinal study conducted in the Department of Radiation Oncology in a hospital located in rural Maharashtra after obtaining the approval from the Institutional Ethics committee. All female cervical carcinoma patients, presenting in the Oncology OPD at Pravara Rural Hospital between October 2019 and September 2021, fulfilling the inclusion criteria (Biopsy proven Squamous cell carcinoma of cervix, FIGO stages IB to IVA, ECOG status up to 2, normal hemogram, liver and renal function tests, and those who consented to be a part of the study) were taken in the study.

Treatment planning and treatment:

All 23 patients received EBRT to the Pelvis (50 Gy, 25 fractions at 2Gy fractions 5 days a week) with either parallel opposed Anterior-Posterior fields or a box technique using 6 MV photons energy on the LINAC machine. They also received weekly concurrent chemotherapy with Inj. Cisplatin (40 mg/m2).

Patients were assessed weekly for treatment response, acute toxicities and the geometry for brachytherapy application.

Patients were then assigned to either the sequential or the interdigitated brachytherapy group depending on the treatment response, geometry and general condition.

Arm A: In this arm, 14patients were treated with 50 Gy/25#s of EBRT over 5 weeks with weeklyInj.Cisplatin 40mg/m2, followed by HDR-ICBT using Ir192 started within 1 week of completion of EBRT and was given in 3 weekly fractions (7Gy each to point A).

Arm B: If during the course of EBRT, the patient was considered fit for brachytherapy, they were assigned to Arm B. Depending on the number of fractions of EBRT delivered, 9 patients were assigned to receive HDR-Brachytherapy using Ir192; 6 fractions, 4.5 Gy/fraction if taken after 20 Gy exposure from EBRT, 5 fractions/ 5.0 Gy each if taken after 30 Gy exposure from EBRT and 4 fractions/6 Gy each if taken after 40 Gy exposure from EBRT to point A.

All patients were monitored during the entire treatment duration. The nutrition status, local hygiene and hydration was adequately maintained for all the patients. During treatment, patients were assessed weekly for treatment response, toxicities as per CTCAE criteria, and all routine investigations were done prior to each chemotherapy cycle. Even with the COVID-19 pandemic, all the patients successfully completed the treatment with or without gap correction.

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Follow up:

On treatment completion, both disease response and toxicities were assessed and documented.

Post treatment, patients were asked to follow up at 1.5 months, 3 monthly thereafter for 1 year and 6 monthly after that.

On each follow up, patients were assessed with history, clinical examination, blood investigations, radiological investigations with chest x-ray and ultrasonography of the abdomen and pelvis. CECT was done only if warranted.

The treatment outcome was then graded according to the RECIST 1.1 criteria and toxicities were graded according to the CTCAE 5.0 criteria.

Local failure was determined clinically and with a biopsy proven report.

Distant failure was determined as any lesion in the extra-pelvic region, diagnosis of which needed to be confirmed radiologically and if possible, with a confirmed biopsy report.

III. RESULTS:

The most common age of presentation was between 61 and 70 years. The most common presenting symptom was bleeding per vaginum (BPV) followed by white discharge per vaginum (WPV).The most common histological grade was Grade 2 (moderately differentiated)and the most common stage atpresentation FIGO Stage III B. Most of our patients belonged to the lower middle socioeconomic status. The pre-treatment hemoglobin levels were assessed, 20 patients had levels less than 12 gm/dl. The parameters have been tabulated in Table 1.

Table 1: General parameters

Parameter	Patients (n=23)
Age in years	
<40	2 (8.7%)
41-50	7 (30.4%)
51-60	6 (26.1%)
61-70	8 (34.7%)
Socio-economic status:	
Upper Middle	2 (8.7%)
Middle	7 (30.4%)
Lower Middle	13 (56.52%)
Lower	1 (4.3%)
Presenting symptom:	
BPV	13 (56.52%)
WPV	11 (47.82%)
Lower Abdominal pain (LAP)	3 (13.04%)
Post-coital Bleed (PCB)	5 (21.73%)
Stage:	
IIA	3 (13.04%)
IIB	1 (4.3%)
IIIB	15 (65.21%)
IIIC	2 (8.6%)
IVA	2 (8.6%)
Histological Grade:	
1	4 (17.39%)
2	17 (73.91%)
3	2 (8.6%)
Pre-treatment Hemoglobin (g/dl)	
7.5-9.0	1 (4.3%)
9.1-10.5	9 (39.13%)
10.6-12.0	10 (43.47%)
>12	3(13.04%)

Toxicities:

Acute and Late toxicities were assessed using CTCAE 5.0 criteria. The skin, genito-urinary (GU) and Gastrointestinal toxicities have been described in Table 2.

Acute Skin toxicity: In this study, both the groups had comparable skin toxicities. 57.14% in group A

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and 55.5% patients in group B showed Grade I toxicity. The rest had no toxicity.

Acute GU toxicity: In this study, 3 patients in Group B had Grade I GU symptoms whereas only 1 patient in the control arm had grade I GU toxicity. The rest had no GU toxicity.

Acute GI toxicity: Only 1 patient in the control arm developed Grade I GI toxicity. No patient in the control arm had any GI toxicity.

Table 2: Acute toxicities

Acute Toxicities	Control arm	Study arm
Skin toxicities		
None	6 (42.8%)	4 (44.4%)
Grade I	8 (57.14%)	5 (55.5%)
GU toxicities		
None	13 (92.8%)	6 (66.3%)
Grade I	1 (7.14%)	3 (33.3%)
GI toxicities		
None	13 (92.8%)	9 (100%)
Grade I	1 (7.14%)	0

Late toxicities:

No patient in the Control arm developed any Late toxicities. 1 patient developed Grade I cystitis and 1 patient developed Grade II proctitis in the study arm. Both were conservatively managed.

Local Response Criteria:

- This was evaluated using the Revised RECIST (Response Evaluation Criteria in Solid Tumours) criteria (version 1.1). They were categorized as those with Complete Response (CR), Partial Response (PR), Progressive disease (PD) and Stable Disease (SD).
- Response was assessed at 6 weeks post completion and 3 monthly thereafter with a median follow-up period of 6-18 months.

1. **Response at 1st follow-up (6 weeks):** At the time of the 1st follow-up, all our patients in both the group who presented for follow-up showed a complete response. We lost 4 patients totally to follow up. A Fisher's Exact test showed no statistically significant difference in the outcome between the 2 groups (p=1.00), details of which are described in Table 3:

Table 3: Response at first follow-up (6 weeks)

Response	Group A (Control)	Group B (Study)
CR	11 (78.57%)	8 (88.8%)
PR	0	0
SD	0	0
PD	0	0
Loss to follow-up	3 (21.42%)	1 (1.1%)

2. **Response at the last follow up (6-18 months):** At the time of the last follow-up, with a median range of 6-18 months, a total of 17 patients had complete response. 1 patient in each group had progressive disease, and 4 patients were lost to follow up. We applied a Chi-square test which showed no significant difference in the outcomes between the 2 groups (p=0.46). The details have been tabulated below in Table 4.

Table 4: Response at last follow-up (6-18 months)

Response	Group A (Control)	Group B (Study)
CR	10 (71.4%)	7 (77.7%)
PR	0	0
SD	0	0
PD	1 (7.14%)	1 (11.1%)
Loss to follow-up	3 (21.42%)	1 (1.1%)

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Overall treatment time: (OTT): The OTT was comparable in both the groups. Most of our patients completed treatment within 56 days. By applying a Mann Whitney U test, we saw no difference in the probability of outcomes between both the groups (p=0.64). The details have been described in Table 5a and 5b.

Table 5a: Overall treatment time (OTT)

OTT (days)	Group A (Control)	Group B (Study)
≤56	8	6
>56	6	3

Table 5b: Mean treatment time distribution

Mean treatment time distribution of treatment groups			
	Treatment groups		**Mann Whitney U test**
	CG	**SG**	
Mean age ± SD	61.07 ± 18.71	54.66 ± 4.71	**P: 0.64**
Median	55.5	55.5	
Min-Max	46-120	48-63	

IV. DISCUSSION:

Survival in cervical cancer is dictated by the depth of stromal invasion, tumour size, parametrial and pelvic node metastasis.Perez et al[5] in a review of 1499 cervical cancer of Stage IA-IVA treated with EBRT and 2 fractions of ICBT, reported a close correlation between tumour size, extent and pelvic tumour control, incidence of distant metastasis and DFS in all stages.

Since ours is a rural center, most of our patients present in the advanced stages which can be contributed to a lack of awareness and hesitancy in seeking early medical attention[6 7]. We also observed that most of our patients in the control arm belonged to stage IIIB, and they were not considered fit for ICBT prior to 50 Gy exposure to EBRT. However, it is difficult to definitely correlate the stage with the DFS owing to the small sample size and short duration of follow-up.

Brachytherapy is an integral component of cervical cancer treatment.HDR-Brachytherapy has virtually replaced LDR-Brachytherapy worldwide. This is mainly due to the shorter treatment duration and hence better compliance, improved patient comfort and increased cost-effectiveness. Multiple studies proved that both were equivalent in terms of local control and survival[8 9].

In our study, we compared 2 groups, with patients in Group A receiving 7 Gy/ 3 fractions and Group B receiving Interdigitated BT with either 6 Gy/ 4 fractions, 5 Gy/ 5 fractions or 4.5 Gy/ 6 fractions. However, no patient was fit to receive 6 fractions.

In the control arm Group-A, we treated 14 patients with 50 Gy EBRT along with concurrent chemotherapy with Cisplatin followed by sequential ICBT; 7 Gy/ 3 # to point A

In the study arm Group-B, we treated 9 patients with interdigitated brachytherapy, 5 of whom received 6 Gy/4# and 4 patients received 5Gy/ 5# to point A.

Prolongation of treatment beyond 6 weeks, results in a higher total dose required to achieve a given probability of tumor control[10 11]. Dose has to be increased by 0.6 Gy for each day of prolongation, to control the accelerative repopulation of the cells, i.e., 1 % loss of tumor control, and to avoid increased treatment delays and drop outs due to the prolonged gap between EBRT and intracavitary brachytherapy (ICBT)[12].

In our study, the overall treatment time was equivalent in both the arms with the maximum number of patients completing their treatment under 2 months. In 3 patients, the treatment time extended beyond 60 days due to the patient's personal reasons.

Updated ABS guidelines published in 2012[13] approved of multiple fractionation schedules for brachytherapy with an EQD2 of ≥80 Gy in case of complete response or a partial response with residual disease <4 cm or the EQD2 can be escalated up to 85-90 Gy in case of bulkier lesions. Ultimately, the fractionation schedule is left to the discretion of the treating radiation oncologist and the institutional protocols.

A study done by Maruthavanan et al[14], comparing sequential (6Gy/ 3 fractions) and interdigitated ICBT (5.5GY/ 4 fractions after 40 Gy EBRT) in 20 patients with Stage III B cervical cancer, showed 85% local control rate, 10% with Stable disease and 5% with progressive disease at 1

year. They also reported low rates of acute toxicities.

Ghosh P et al[15] analysed 2 different fractionation schedules; 9 Gy/ 2 fractions and 7 Gy/ 3 fractions in 124 patients following EBRT. They concluded that both fractionations were equally effective in terms of local control, DFS and OS.

We found that at the time of completion of treatment, all the patients in the study arm showed a clinical complete response compared to 78.57% of the patients in the control arm. The remaining 21.42% in the control arm showed a partial response at the time of completion of treatment. But in the subsequent follow-ups, the disease had regressed completely. In our study, patients received different fractionations in the interdigitated arm depending on the time of starting ICRT. We found equivalent response in terms of local control irrespective of the fractionation schedule.

Although, we lost 1 patient in study arm and 3 patients in the control arm to follow, until the last follow-up (range from 6-18 months), the response was marginally better in the study arm compared to the control arm. The disease-free survival rate at one year was 71.4% in the control arm and 77.7% in the study arm. However, owing to the small sample size, the difference is not statistically significant.

Treatment failure was seen in both the groups. One patient in the control arm developed liver metastasis while one patient developed local recurrence in the study arm which is under control with chemotherapy.

Interdigitated HDR-BT also raised concerns about increased acute toxicities due to higher dose delivery.

Basu et al[16] studied the effects of different dose schedules in ICBT. They delivered sequential ICBT using two different fractionation schedules. In one arm, patients received 7Gy/3# while in the other arm they received 9 Gy/ 2#. They reported similar outcomes between the two arms in terms of local control (80% vs 63%) and 1-year DFS (60% vs 53%). They also reported an increase in acute and late vaginal toxicities but were statistically insignificant.

In our study, no patient in either arm developed Grade 3 toxicities. 1 patient in the control arm and 3 patients in the study arm developed Grade 1 GU toxicity. Only symptomatic care was given and there was no interruption in the treatment schedule.

V. CONCLUSION:

Despite the ongoing COVID-19 pandemic, all 23 patients completed their entire treatment, most of whom completed it within 56 days. However, given this is a rural centre and a majority of our patients come from remote areas, the pandemic and the multiple lockdowns thus enforced, has not only resulted in women delaying seeing a practitioner for a diagnosis but have also delayed seeking treatment post diagnosis. This has severely restricted the sample size and hence no statistically significant conclusion could be drawn. However, we hope that future studies offer us clarity and help draw a conclusion.

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