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# Aftereffects of delayed intracavitary brachytherapy in cancer cervix patients during COVID-19 lockdown — a tertiary care centre review

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## ABSTRACT

**Introduction:** To evaluate the impact of the COVID outbreak on the extension of overall treatment time (OTT) in diagnosed cases of non-metastatic Carcinoma Cervix patients.

**Material and methods:** A retro-prospective analysis of all patients with non-metastatic biopsy-confirmed Carcinoma Cervix who received radical radiotherapy including intracavitary brachytherapy (ICBT) between 20th March 2020 to 1st June 2020 and 1st April 2021 to 1st June 2021 respectively. All patients were re-staged prior to 1st fraction brachytherapy with clinical examination supplemented with MRI pelvis for patients with a treatment gap of more than 30 days. Follow-up was done with clinical examination at 3-month intervals post-completion of treatment for 2 years. Imaging was done annually in the form of an MRI abdomen and pelvis.

**Results:** A total of 51 patients were reviewed by the Department of Radiation Oncology during the aforementioned period out of which 41 patients completed their treatment. The median age of the patient was 52 years. The median time interval between completion of external beam radiotherapy (EBRT) and 1st fraction ICBT was 22 days (range: 7–52 days). The median time interval between two consecutive fractions of ICBT was 11 days (range 7 days to 25 days). The median OTT defined from the start of EBRT to the completion of brachytherapy was 82 days. The median follow-up interval was 15 months (range 6–24 months). There was a statistically significant relationship between the time interval between EBRT and ICBT and disease outcome (p-value = 0.002). Also, patients with longer OTT had poorer outcomes (p-value = 0.003), as did patients with poor response to EBRT (p-value = 0.001)

**Conclusions:** In the era of COVID-19, long treatment gaps, extended OTT and poor response to external beam treatment have significantly altered the outcome of treatment in cancer cervix patients. Longer follow-up is required to understand the long-standing implications of the same in the Indian setting.

**Keywords:** COVID-19, EBRT, ICBT, cancer cervix

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## Introduction

The COVID-19 pandemic has affected virtually every sector of the country including the economic, agricultural, telecommunication, transportation, and health-care systems. The cancer care delivery system is one of the worst affected health sectors, especially in developing countries such as India, where 95% of cancer centres are situated in urban areas, while 70% of the population lives in rural areas [1].

To curb the rising incidence and rapid spread of COVID, nationwide lockdowns were imposed which further led to disruption in cancer care delivery services, leading to delays in diagnosis or treatment initiation and treatment interruptions and rescheduling, aggravated by a complete halt in transportation, resulting in the progression of the disease and poor survival outcomes [2].

The above scenario has severely impacted the management of Cancer patients, including Cancer Cervix, which is the third most common cancer in the

country, and second most common among females, accounting for about 123,907 incidence of new patients every year [3].

The standard Treatment of Carcinoma cervix in the pre-COVID era includes, whole pelvic RT or extended field RT can be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m$^2$). This is followed by brachytherapy to achieve a tumoricidal dose of > 85 Gy to the tumour, with a goal to limit the total treatment time to ≤ 7 to 8 weeks. The overall treatment time (OTT) has prognostic implications on disease outcomes and should be completed in 55 days for best treatment outcomes [4, 5].

## Material and methods

An audit of all patients with biopsy-confirmed carcinoma cervix FIGO stage (I-IVA) who were planned for/treated with radical radiotherapy including patients who received external radiotherapy in other hospitals and were planned for intracavitary brachytherapy (ICBT) in the hospital between 20$^{th}$ March 2020 to 1st July 2020 and 1$^{st}$ April 2021 to 1$^{st}$ July 2021 respectively. Patients with initial staging II to IVA, underwent radical concurrent chemoradiotherapy with a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40 mg/m$^2$). Following whole pelvic RT or extended field RT, all the patients either outside treated or in-patient treated were taken for ICBT, using dose fractionation of 9Gy for 2 fractions(#), 7Gy for 3# or 7GY for 4#. All patients were screened for COVID-19 with RT-PCR prior to the first fraction of external beam radiotherapy (EBRT) followed by a repeat RT-PCR prior to the first fraction ICBT. Additionally, patients who developed symptoms at any given time during treatment underwent interim repeat RT-PCR testing. All patients were restaged prior to 1$^{st}$ fraction brachytherapy with clinical examination along with an MRI pelvis for patients with a treatment gap of more than 30 days. Only patients re-staged IIB and below post-EBRT were treated with ICBT. Overall treatment time was calculated from the first day of EBRT to the completion of the last fraction of ICBT. Follow-up was done with clinical examination on a 3-month basis after treatment completion, till 2 years. CEMRI abdomen-pelvis was done once a year.

### Statistical analysis

Data was described in terms of range, mean and ± standard deviation, frequencies and relative frequencies or percentages as appropriate. A Kolmogorov-Smirnov test was used to determine the normal distribution of data. Comparison of quantitative variables between study groups was done using the Mann-Whitney test for non-parametric data. For comparing categorical data, the Chi-square test was performed and the Fisher exact test was used when the expected frequency was less than 5. A probability (*p*) value of less than 0.05 was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Science (SPSS) version 21 (SPSS Inc., Chicago, IL, USA) program for Microsoft Windows.

### Observations

51 patients were reviewed in the Department of Radiation Oncology during the time frame, 7 in 2020 and the remaining 44 in 2021. The median age of the patient was 52 (Range 32–67 years). 34/51 received EBRT in other hospitals and were referred for ICBT. 10 patients tested COVID positive during the treatment course. 7 patients were asymptomatic positives out of which treatment was delayed by 15 days in 5/7 patients. 2/7 patients defaulted. 3 patients were symptomatic positive. 1 patient developed severe pneumonia requiring ICU care and ventilatory support and passed away due to COVID-related complications. 2 patients developed mild Upper respiratory infection during external radiation. EBRT was delayed in both the patients until complete recovery. Both patients tested negative on the 15$^{th}$ day of testing positive and resumed treatment on the 16$^{th}$ day. 1 patient withdrew consent for treatment midway through EBRT.

6/47 patients were restaged III and above on clinical examination and/or MRI and were ineligible for ICBT. The remaining 41 patients were planned for ICBT.

The ICRT schedule of 41 patients was as follows in Table 1.

## Results

41 patients completed the entire course of treatment. EBRT dose ranged from 45–50.4 Gy/25–28 fractions

**Table 1. Different dose fractionation for ICRT**

| N | Remarks | Dose schedule |
|---|---|---|
| 14 | Time interval > 21 days post-EBRT and no residual disease post-EBRT | 2 fractions, 9 Gy/fraction |
| 7 | Residual disease ≥ 2 cm on clinical examination post-EBRT, ± bleeding | 4 fractions, 7 Gy/fraction |
| 20 | All remaining | 3 fractions, 7 Gy/fraction |

**Table 2.** Disease outcome of n = 39 patients with 1-year follow-up

| | Disease outcome (n = 39) | Disease free (n = 32) | | Nodal recurrence (n = 2) | | Residual (n = 5) | | Total | Chi-square value | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | Percentage | No. of cases | Percentage | No. of cases | Percentage | | | |
| FIGO stage | IIA | 8 | 25.0% | 0 | 0.0% | 0 | 0.0% | 8 | 14.53 | 0.150 |
| | IIB | 8 | 25.0% | 0 | 0.0% | 1 | 20.0% | 9 | | |
| | IIIA | 5 | 15.6% | 0 | 0.0% | 0 | 0.0% | 5 | | |
| | IIIB | 5 | 15.6% | 0 | 0.0% | 1 | 20.0% | 6 | | |
| | IIIC | 2 | 6.3% | 1 | 50.0% | 0 | 0.0% | 3 | | |
| | IVA | 4 | 12.5% | 1 | 50.0% | 3 | 60.0% | 8 | | |
| Histology | Adenocarcinoma | 1 | 3.1% | 0 | 0.0% | 2 | 40.0% | 3 | 8.457 | 0.150 |
| | Squamous | 31 | 96.9% | 2 | 100.0% | 3 | 60.0% | 36 | | |
| EBRT dose | 45 Gy/25# | 3 | 9.4% | 0 | 0.0% | 0 | 0.0% | 3 | 1.836 | 0.766 |
| | 50.4 Gy/28# | 7 | 21.9% | 1 | 50.0% | 2 | 40.0% | 10 | | |
| | 50 Gy/25# | 22 | 68.8% | 1 | 50.0% | 3 | 60.0% | 26 | | |
| Residual after EBRT | Residual | 19 | 59.4% | 2 | 100.0% | 5 | 100.0% | 1 | 37.121 | 0.001 |
| | No residual | 13 | 40.6% | 0 | 0.0% | 0 | 0.0% | 8 | | |
| ICRT dose | 7 Gy/3# | 18 | 56.3% | 1 | 50.0% | 1 | 20.0% | 18 | 22.384 | 0.10 |
| | 7 Gy/4# | 1 | 3.1% | 1 | 50.0% | 4 | 80.0% | 6 | | |
| | 9 Gy/2# | 13 | 40.6% | 0 | 0.0% | 0 | 0.0% | 14 | | |

over 5–6 weeks. The mean time interval between Completion of EBRT and 1st fraction ICBT was 22 days (Range 7–52 days). The mean time interval between two consecutive fractions of ICBT was 11 days (Range 7–25 days). The mean OTT was 82 days (Range 60–122 days).

Due to travel restrictions, the first follow-up was recorded 3 months post-completion of treatment, and 3 months thereafter until 2 years post-completion of treatment. The disease-free interval was calculated from the last day of treatment until 2 years post-treatment. 2 patients were lost to follow-up. The median follow-up interval was 15 months (6–24 months). The results of 39 patients have been reported in Table 2.

32 patients remained disease-free until 2 years of follow-up. 5 patients had persistent residual disease and were started on palliative chemotherapy, out of which 1underwent salvage surgery and remained disease-free till the last follow-up. Pelvic lymph nodal recurrence was reported in 2 patients who were started on palliative chemotherapy. Metastasis was not reported in any patient until the end of the prescribed follow-up. Table 3 describes result that is mentioned above.

## Discussion

COVID-19 arrived in the Indian subcontinent in the state of Kerala in early January, following which a steady increase in the number of cases was observed. The first nationwide lockdown in the country began uniformly with effect from 25th March 2020 and ended on 31st May 2020 with complete restrictions on all forms of travel. The second and largest COVID wave was witnessed from March to May 2021 and resulted in state-wide lockdowns and night curfews.

Owing to travel restrictions and the COVID-19 case burden, cancer treatment suffered tremendously. According to a cohort study by Ranganathan et al. [2], a 54% reduction in new cancer registration was observed, while a 23% reduction was reported in patients accessing radiotherapy services. A higher reduction in oncology provisions was reported among centres in Tier 1 cities as compared to Tier 2 and 3 cities.

Cancer cervix is the second most common gynaecological cancer in India [3] and multimodality treatment in the form of radiotherapy, and concurrent chemotherapy now forms the basis of treatment. The time taken to

**Table 3.** Correlation of age, time between external beam radiotherapy and intracavitary brachytherapy, intra-fraction time, and overall treatment time with disease outcome

| | Disease free (n = 32) | | Nodal recurrence (n = 2) | | Residual (n = 5) | | F | P-value |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | | |
| Age | 52.47 | 8.83 | 62.50 | 7.78 | 54.40 | 6.66 | 1.34 | 0.275 |
| Time b/w EBRT and ICBT | 22.13 | 10.44 | 50.00 | 2.83 | 21.60 | 3.36 | 7.77 | 0.002 |
| Time b/w ICBT fractions | 11.16 | 3.80 | 16.00 | 8.49 | 10.60 | 0.89 | 1.62 | 0.211 |
| OTT | 82.56 | 14.69 | 119.50 | 3.54 | 89.40 | 4.28 | 7.07 | 0.003 |

EBRT — external beam radiotherapy; ICBT —intracavitary brachytherapy; OTT — overall treatment time

complete treatment constitutes an important prognostic factor in determining the disease-specific outcomes [4–6]. Petereit et al. [6] in their study, illustrated significantly improved 5-year survival [(65 and 54%, (p = 0.03)] and pelvic control [87% *vs.* 72% (p = 0.006)] in patients with treatment times < 55 days *vs.* ≥ 55 days respectively.

In the Indian setting, a 17-questions-based survey conducted by Chatterjee et al. [5] across 116 centres in India revealed that more than 90% of patients completed treatment within 56 days and 10% exceeded OTT in the pre-COVID era. There is, however, a paucity of similar literature in COVID setting.

At the Institute, none of the patients could complete treatment within 56 days. 80.4% of patients could complete treatment in its entirety and 8/41 (19.5%) patients exceeded OTT beyond 100 days.

Also, in this study, 34% (14/41) of patients with no residual disease post-EBRT received a BT dose of 9Gy in 2 fractions. 1 patient was lost to follow-up. The remaining 13 patients (92.9%) remained disease-free until the last follow-up. These findings were like most studies in literature wherein a brachytherapy schedule of 9 Gy in 2 fractions produced equivocal results while simultaneously reducing the OTT [7, 8].

A local recurrence of 10–30% has been reported in several studies [9–11]. A local recurrence rate of 34.7% within a 24-month interval was reported by Bandyopadhyay within the Indian setting [12]. In the same study, OTT, the gap between EBRT and ICBT, and mean EQD2 to point A was associated with 2yr DFS, whereas stage, histology and treatment gap was associated with improved survival.

In the current study, a statistically significant association was found between disease outcome and the time interval between EBRT and ICBT (p-value = 0.004) as well as OTT (p-value = 0.033) (Tab. 3). Also, patients with residual disease post-EBRT and before ICBT had significantly poorer outcomes when compared to patients having no residual disease post-external treatment (p-value = 0.001).

## Conclusion

In the era of COVID-19, long treatment gaps, extended OTT and poor response to external beam treatment have significantly altered the outcome of treatment in cancer cervix patients. Longer follow-up is required to understand the long-standing implications of the same in the Indian setting. Limitation of this study includes a shorter duration of follow-up and paucity of more data to compare, that can be continued further.

## Article information

**Data availability statement:** *All data supporting the findings of this study are available in the paper and table.*

**Ethics statement:** *II subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and treatment was done using standard treatment protocol.*

**Author contributions:** *concepts — NA, APS, DDL, AC; design — NA, APS, DDL, AC; definition of intellectual content — NA, APS; literature search — NA, APS, AC; clinical studies — NA, APS, DDL; experimental studies — NA, APS, AC; data acquisition — NA, APS, DDL; data analysis — NA, APS, AC; statistical analysis — NA, APS, DDL, AC; manuscript preparation — NA, APS, DDL, AC; manuscript editing — NA, APS, AC; manuscript review — NA, APS, DDL, AC; guarantor — NA, APS, DDL, AC.*

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