RESEARCH ARTICLE

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Treatment Delay during Radiotherapy of Cancer Patients due to COVID-19 Pandemic

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Abstract

Purpose: To analyze the impact of treatment delay caused by COVID-19 infection on patients scheduled for radiotherapy treatment. **Methods and Materials:** In this descriptive study, we analyzed all patients who were COVID-19 positive during the scheduled radiotherapy course, those who had an infection while on neoadjuvant treatment period, or during surgery before the start of radiation. The study period was from June 2020 to May 2021. A treatment delay was defined as a delay in starting the radiation treatment, a gap during their scheduled radiation treatment, or treatment discontinuation. All patients who had a treatment delay were followed-up till November 2021. **Results:** The median follow-up time of the study was 13 months. Ninety-four patients were selected for the study who met the inclusion criteria. Seventy-seven patients had a mild COVID-19 infection, while 17 had a moderate to severe illness. Of the entire cohort, 83 patients had a treatment delay. The median treatment delay (MTD) in days was 18 (6 to 47). Amongst those who had a treatment delay, 66 patients were treated with curative intent, of which 51 patients are on follow-up – 34 patients are disease-free (MTD – 18.5, 10 to 43), seven had either a residual disease or locoregional recurrence (MTD – 22, 10 to 32), seven had distant metastasis (MTD – 18, 15 to 47), and three patients died (MTD – 20, 8 to 27). Of three patients who died, only one died of COVID-19-related causes. **Conclusions:** Even though the mortality due to COVID-19 infection among those who underwent radiotherapy was low, a treatment delay might have caused adverse treatment outcomes. Longer follow-up of these patients is required to further establish this. It will remain debatable whether it was worth delaying radiotherapy for mild to moderate COVID-19 infection for a significant time to cause a potential cancer treatment failure.

Keywords: Treatment delay- radiotherapy- cancer patients- COVID 19- pandemic

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Introduction

The COVID-19 pandemic had a significant impact on health care systems worldwide. However, the brunt of this impact was on the cancer patients getting treatment in specialized oncology hospitals (Bhandoria et al., 2020; Mallick et al., 2021; Sekhon et al., 2021). This could be due to the immunocompromised state of cancer patients, caused partly by cancer itself and partly by treatments such as radiation and chemotherapy. The effect of the pandemic was not only on the patients but also on the staff who came in close contact with infected patients such as nurses and radiation technologists (Chetia et al., 2020; Haresh et al., 2020).

The COVID-19 pandemic has affected oncology patients at many levels. Apart from the psychological stress caused by a cancer diagnosis and COVID-19 infection, the pandemic has caused a delay in oncology treatments (Mallick et al., 2021). However, to overcome treatment delays and provide well-balanced cancer care to their patients, many institutes used pragmatic solutions such as zoning, triaging, hypofractionated radiotherapy regimens, and telemedicine facilities, to name a few (Dewi et al., 2020; Haresh et al., 2020).

A treatment delay negatively impacts the outcome and survival of cancer patients. According to a study from India, a delay in cancer treatment due to the pandemic caused progressive disease in 50% of cancer patients (Ghosh et al., 2021). Moreover, the treatment delay, especially during radiotherapy, could be critical, as any gap during treatment could lead to accelerated repopulation of cancer cells (González Ferreira et al., 2015; Nagar and Formenti, 2020). The delay during radiation treatment was a major concern even during the

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pre-pandemic time (Razmjoo et al., 2020).

In this study, we have retrospectively analyzed the data of radiotherapy patients who were COVID-19 positive during the first and second waves of the COVID-19 pandemic in India.

Materials and Methods

Patients

This is a descriptive study. All patients who were tested positive for COVID-19 infection (except hospital staff) either by Reverse Transcription–Polymerase Chain Reaction (RT-PCR) or by Cartridge Based Nucleic Acid Amplification Test (CBNAAT), reported to the Indian Council for Medical Research (ICMR) from our institute, between 1st June 2020 and 31st May 2021, are considered for the analysis. The inclusion criteria are as follows – all patients who were positive during the scheduled radiotherapy course, those who had an infection during the neoadjuvant treatment, or during surgery, before the start of radiation. All patients who were positive for COVID-19 after radiation treatment were excluded from the analysis. For all COVID-19 positive patients, radiotherapy was withheld for 10 to 14 days, or until they were negative by RT-PCR test. However, in certain exceptional cases, on a case-to-case basis, radiotherapy was continued.

COVID-19 departmental protocol

The departmental policy was not to routinely test all asymptomatic patients throughout the pandemic. However, all patients were asked to fill in a questionnaire regarding their contact and travel history. In addition, daily temperature checks of all patients were done. If any patient had a positive contact history or raised temperature, they were tested for COVID-19 infection. Furthermore, the institution's infection control team tested random radiotherapy patients for COVID-19 infection as part of surveillance. All patients undergoing invasive procedures such as feeding tube insertion and direct laryngoscopy were routinely tested before the procedure. While treating the patients, the radiotherapy technologist and other staff wore an N95 mask with or without a visor. In addition, a disposable gown and gloves were provided to the treating staff. After each radiotherapy session, the couch top was disinfected, and a new couch roll paper was secured.

However, while treating a COVID-19 positive patient, the extra measures taken in the department to contain the infection are given in Table 1.

Follow-up

All patients were followed-up till 30th November 2021. The follow-up data of patients were gathered from the electronic files. In addition, those patients who were lost to follow-up were contacted through telephone.

Statistical analysis

The descriptive statistics for quantitative variables are depicted using the median (with range). While categorical variables are presented in frequencies and respective percentages. Statistical Package for the Social Sciences version (SPSS) 20.0 (IBM Corporation, Armonk, NY, USA) was used to carry out all statistical computations.

Results

From June 2020 to May 2021, 1782 patients were positive for COVID-19 infection. Amongst these 1782 patients, 94 patients, who met the selection criteria, were included in the analysis. Of these 94 patients, 83 patients had a delay in radiation treatment, and 11 patients had no delay. (Figure 1) Seventy-seven patients had a mild COVID-19 infection, while 17 had a moderate to severe infection. The severity of the COVID-19 infection has been classified according to the ICMR definition (MoHFW, 2021). All patients were treated with the standard radiotherapy fractionation schedules, as they were treated during the pre-infection era.

Treatment delay

A treatment delay was defined as a delay in starting the radiation treatment, a gap during their scheduled radiation treatment, or treatment discontinuation. According to this definition, 83 (88.30%) out of 94 patients had a treatment delay. Of these 83 patients, 80 (96.39%) patients had treatment delays during external beam radiotherapy (EBRT) and three during brachytherapy. The median treatment delay (MTD) in days was 18 (6 to 47). The tumor, COVID-19 infection, and patient characteristics are given in Table 2.

Eleven (11.70%) of the 94 patients had no treatment delay for two reasons. The first reason is that four (36.36%) out of these 11 patients were COVID-19 positive after surgery while waiting to start adjuvant radiation, which means they were COVID-19 positive between 0 to 6 weeks after surgery. The second reason is that, for seven of these 11 patients, treatment continued despite COVID-19 infection without delay. The reasons why treatment was continued in these patients were the following. Four of these patients were palliative patients, and radiation was given for bone pain or symptomatic brain metastases. The rest three patients had an aggressive brain tumor (glioblastoma). All seven patients were asymptomatic for COVID-19 infections and had turned positive for COVID-19 infection either during infection surveillance by the hospital's infection control team or during a routine test done before an invasive procedure.

Out of the 83 patients with treatment delay, 8 (9.64%) discontinued radiation treatment after a positive COVID-19 diagnosis. Six (75.0%) of these eight patients were asymptomatic and were sent home for home isolation, but they were lost to follow-up. Two (25.0%) of these eight patients were symptomatic of COVID-19 infection and were hospitalized. Both of them were sent home for convalescence. However, both these patients did not return to attend further radiation. Of these two patients, one head and neck cancer patient returned after two months with local recurrence.

Follow-up

The median follow-up time of the study was 13 months. Among the 83 patients who had treatment delays, 66 (79.52%) patients were treated with curative intent, and

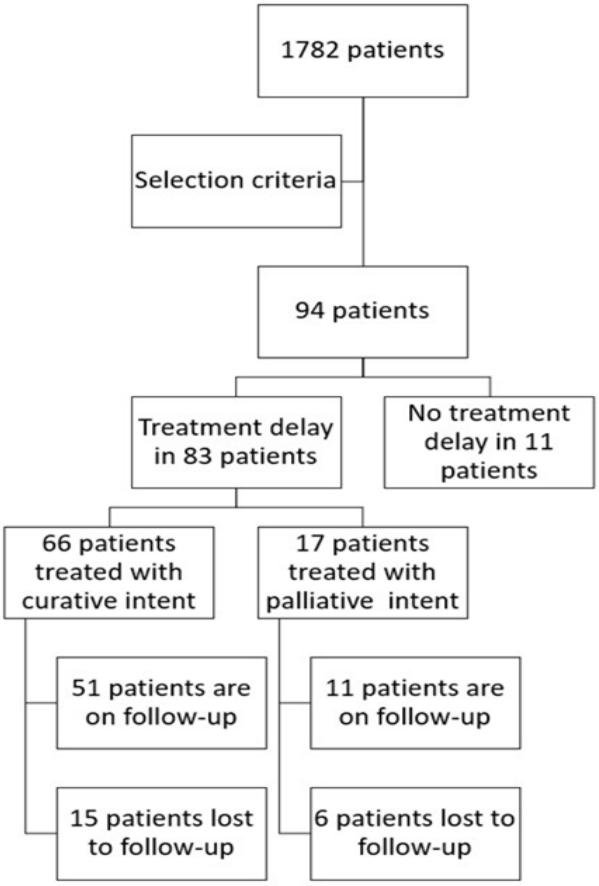

Figure 1. Flowchart Showing the Schema of the Study.

17 (20.48%) patients with palliative intent. Out of these 66 patients, 51 patients are on follow-up – 34 patients are disease-free (MTD – 18.5, 10 to 43), seven had either a residual disease or locoregional recurrence (MTD – 22, 10 to 32), seven had distant metastasis (MTD – 18, 15 to 47), and three patients died (MTD – 20, 8 to 27). Of the three patients who died during the study, one died of COVID-19 infection during the radiation course, and two died due to septicemic shock, not directly related to COVID-19 infection. The stages of the seven patients who had a residual disease or locoregional recurrences were as follows: 2 patients of stage II, 3 of stage III, and

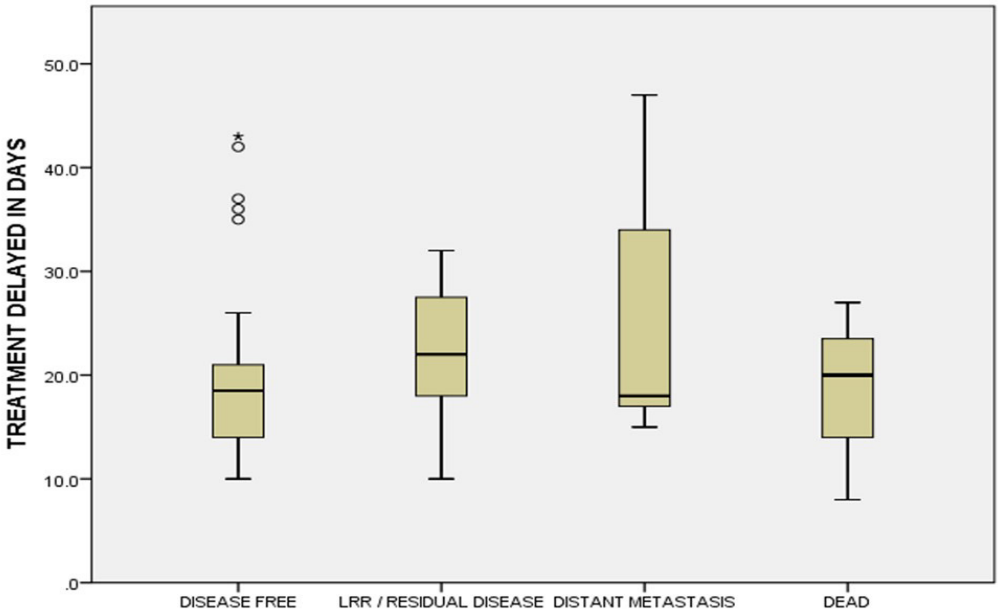

Figure 2. The Box and Whisker Graph Depicts the Median Treatment Delay in Days, and their respective interquartile percentiles, of those patients who are under follow-up in the following categories: disease-free, LRR or residual disease, distant metastasis, and dead. Abbreviation: LRR, locoregional recurrence.

Table 1. Departmental Protocol to Treat Asymptomatic COVID-19 Positive Patients

All staff should wear PPE* kits while treating these patients. (Doctor, technologist, and nursing orderly).
All COVID-19 positive patients were treated on a designated EBRT machine at a specific time as the last patient of the day. After that, the machine was disinfected.
The holding area of a COVID-19 positive patient was separate.
The corridor used by the patient for their transfer was disinfected as per institutional protocol.

Abbreviation: PPE, Personal Protective Equipment

Table 2. Tumor, COVID-19 Infection, and Patient Characteristics

Number of patients	Parameters N = 94 (%)
52 years (2-76)	Age {median (range)}
Sex	
Male	53 (56.38)
Female	41 (43.62)
Diagnosis	
Head and neck cancer	47 (50.00)
Breast cancer	13 (13.83)
Gastrointestinal malignancies	10 (10.64)
Gynecological malignancies	8 (8.51)
Lung cancer	4 (4.26)
Brain cancer	3 (3.19)
Genitourinary malignancies	2 (2.13)
Hematological malignancies	2 (2.13)
MUO*	2 (2.13)
Rhabdomyosarcoma	1 (1.06)
Soft tissue sarcoma	1 (1.06)
Multiple myeloma	1 (1.06)
Stage	
I	0 (0)
II	14 (14.90)
III	26 (27.66)
IV	48 (51.06)
Unknown / not applicable	6 (6.38)
The intent of radiation treatment	
Curative	73 (77.66)
Palliative	21 (22.34)
Comorbidities	
Yes	46 (48.90)
No	48 (51.10)
COVID-19 diagnosed by	
RT-PCR †	68 (72.34)
CBNAAT‡	26 (27.66)
At the time of the COVID-19 test, covid symptoms	
Yes	27 (28.72)
No	67 (71.28)
COVID-19 management	
Home	77 (81.91)
Hospital	17 (18.09)

Abbreviations: * MUO, Metastasis of Unknown Origin; †RT-PCR, Reverse Transcription–Polymerase Chain Reaction; ‡ CBNAAT, Cartridge Based Nucleic Acid Amplification Test.

2 of stage IV.

Of the 48 patients who were treated with curative intent, 24 (50%) patients were of head and neck cancer, three (6.25%) cervical cancer, eight (16.67%) breast cancer, six (12.50%) esophageal cancer, two (4.18%) rectal cancer, one (2.08%) patient each of lung cancer, glioblastoma, diffuse large B cell lymphoma (DLBCL), rhabdomyosarcoma, and metastasis of unknown origin (MUO). The number of patients who have no disease, residual disease / locoregional recurrence, distant metastasis, and those who are dead in each cancer subsites, along with MTD in days, are given in Table 3.

Lost to follow-up patients

A high number of patients in the study, 21 (25.30%) out of 83 patients who had treatment delay, are lost to follow-up. These patients were contacted through telephone calls. All these patients recovered from COVID-19 infection without any sequelae. A majority of these patients (14 / 21, 66.67%) are lost to follow-up due to lockdown restrictions in India from time to time. A few patients (3 / 21, 14.29%) followed alternative medications. The rest of the patients (4 / of 21, 19.04%) are palliative patients who are on best supportive care under the care of a general physician in their respective hometowns.

Discussion

Delay in radiation treatment results in poor treatment outcomes (Bese et al., 2007; Graboyes et al., 2019). Unplanned treatment interruptions have resulted in poor local control in many cancer subsites including, head and neck, cervix, urinary bladder, lung, and breast (Maciejewski and Majewski, 1991; Chen et al., 2000; Bese et al., 2005; Bese et al., 2007). Among all subsites, the most robust evidence is in head and neck cancers. A treatment delay of one day could decrease the local control rate by approximately 1.4% (Maciejewski et al., 1983; Vikram et al., 1985; Maciejewski et al., 1989; Barton et al., 1992; Fowler and Lindstrom, 1992). In our analysis, the median treatment delay was 18 days.

In order to compensate for the treatment delay, different approaches have been described in the literature (Bese et al., 2007; RCR, 2020). The first method is to maintain the overall treatment time (OTT) by accelerated radiotherapy (treating the patients on weekends) and by hyperfractionation (giving multiple fractions a day with 6 hours gap between fractions). However, this method will be difficult to implement when the OTT is increased due to a gap near the end schedule of radiotherapy because there would not be many weekends left to compensate

Table 3. The Number of Patients, who were Treated with Curative Intent and are under Follow-up, with no Disease, residual disease / locoregional recurrence, distant metastasis, and those patients who are dead in each cancer subsite

Cancer sites (number of patients)	Disease free (MTD*)	Residual disease / locoregional recurrence (MTD*)	Distant metastasis (MTD*)	Dead (MTD*)
Head and neck cancer (24)	20 (17.8)	2 (19)	2 (21)	3 (20)
Cervical cancer (3)	2 (19.5)	1 (28)	-	-
Breast cancer (8)	7 (15)	-	1 (47)	-
Esophageal cancer (6)	2 (16.5)	1 (27)	3 (16.25)	-
Rectal cancer (2)	2 (35.5)	-	-	-
Lung cancer (1)	-	1 (32)	-	-
Glioblastoma (1)	-	1 (10)	-	-
Diffuse large B cell lymphoma (DLBCL) (1)	1 (26)	-	-	-
Rhabdomyosarcoma (1)	-	1 (20)	-	-
Metastasis of unknown origin (MUO) (1)	-	-	1 (43)	-

Abbreviation: MTD, Median Treatment Delay

for the delay in OTT (Bese et al., 2007). The second method is hypofractionated radiotherapy for the rest of the fractions after the gap. The hypofractionated dose is calculated according to the equivalent dose at 2Gy per fraction – EQD2 (Bese et al., 2007; RCR, 2020). Both first and second methods are logical approaches and maintain the OTT; but, both techniques are not validated in studies as methods of gap correction.

The third rational approach is to add a few extra fractions of radiotherapy to compensate for the treatment delay at the end of the scheduled radiotherapy course (RCR, 2020). All the patients who had treatment delays in our department were compensated using this third technique.

Out of the 83 patients who had treatment delays, 66 patients were treated with curative intent. Amongst these patients, seven patients, who are on follow-up, had either a residual disease or locoregional recurrence. A strong reason for this could be treatment delays. The MTD for those with residual disease or locoregional recurrence was 22 days (range – 10 to 32 days). This is higher than the MTD of patients in complete remission (19 days; range – 14 to 35.5 days). (Figure 2)

According to one study, death due to COVID-19 infection in cancer patients was 24% (Russell et al., 2021). The death rate was significantly higher in hematological malignancies than in solid organ malignancies (32% vs. 19%) (Russell et al., 2021). The case fatality rate (CFR) due to COVID-19 infection among cancer patients reported by Mehta et al., (2021) from a tertiary care oncology center was 14.52% during the first wave of the pandemic (Mehta et al., 2021). However, in our study, the CFR was very low for those who underwent radiotherapy. Only one patient in the study died due to the infection while undergoing radiotherapy. The reasons for this are not known.

To our knowledge, this is the first study that analyzed the oncology outcomes because of treatment delay due to COVID-19 infection. However, the study's median follow-up time is very short to draw any conclusions. Moreover, the results could be skewed due to the high number of lost to follow-up cases in the study.

In conclusion, COVID-19 positivity during the scheduled radiotherapy treatment course has caused treatment delays. Even though compensated using the gap correction technique, this treatment delay could potentially cause adverse oncological outcomes. Of note, most patients had only mild or asymptomatic COVID-19 infection. At the same time, CFR due to the infection was significantly low. Therefore, it will remain debatable whether it was worth delaying radiotherapy for a significant time to cause a potential cancer treatment failure.

Author Contribution Statement

Idea and concept design by S Mitra and DK Simson; medical writing by DK Simson, H Khurana, and P Ahlawat; statistics by DK Simson, H. Khurana, and S Tandon; provision of study materials by S Barik, N Bansal, M Gairola, JS Sethi, and KS Chufal.

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Ethical and scientific committee approval

As this was a descriptive retrospective analysis, approval was not sought.

Data availability statement for this work

Research data are stored in an institutional repository and will be shared upon request with the corresponding author.

Conflict of Interest

Nil.

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