

Single-arm Cohort Study on the Effects of the COVID-19 Pandemic on the Radiation Treatment of Cancer Patients Referred to the Radiation Oncology Division of a Tertiary Hospital

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ABSTRACT

Objective. This study aimed to identify the effects of COVID-19 pandemic on radiation treatment delays, interruptions, and cancer outcomes if any, in a Philippine tertiary hospital.

Methods. A retrospective observational cohort study was conducted among patients living with cancer who were referred for radiation therapy from March to July 2020. Data on treatment delays, treatment interruptions, and average treatment times were collected and analyzed. An association between radiation treatment interruption and disease failure rate was also evaluated.

Results. The study found the mean radiation treatment time ranged from 50.3 days to 140.6 days from the start of radiation treatment to the end of radiation treatment, and 181.7 days to 217.3 days from the date of CT simulation to the end of radiation treatment. These radiation treatment times and treatment interruptions are beyond any published recommendations for external beam radiation therapy, thus potentially leading to worse oncologic outcomes. However, no association between treatment interruption and disease failure rate was noted. This may be due to limitations of the study such as small sample size and heterogeneous patient characteristics such as different cancer pathologies and different disease stages.

Conclusion. This study showed that the COVID-19 pandemic had a significant impact on radiation treatment interruptions and delays, potentially leading to worse oncologic outcomes. The lack of association between treatment interruption and disease failure rate needs further investigation with a larger sample size, more homogeneous patient characteristics, and longer follow-up. The findings highlight the importance of maintaining cancer care services during pandemics and implementing measures to minimize treatment interruptions and delays to improve cancer outcomes.

Keywords: recurrence, radiotherapy, outcomes, COVID-19, disease recurrence, Philippines



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INTRODUCTION

In February 2020, the World Health Organization (WHO) declared the novel coronavirus a pandemic leading to several degrees of community quarantines and travel restrictions in Metro Manila and eventually the entire country. The COVID-19 pandemic affected healthcare services in many dimensions, particularly in oncologic practice.¹ As a precautionary approach, specific protective measures were implemented such as reducing the number of patients in outpatient radiation therapy facilities and clinics, reducing unnecessary or elective procedures, and reducing patient screening.

Patients living with cancer are vulnerable and susceptible to life-threatening infections, including the lethal COVID-19 infection. Many of them struggled to receive treatment for their cancers because of cancelled hospital appointments and delayed treatment procedures including radiotherapy. The strain of the pandemic on the local healthcare system, aggravated by travel restrictions, stay-at-home directives, shortage of healthcare providers, limited access to hospital care, and the fear of contracting COVID-19 resulted in radiation treatment interruptions and delays.²⁻⁷ This was particularly alarming for tumors where total treatment time significantly affected outcomes.

The Philippine General Hospital (PGH), the national university hospital, serves a large number of cancer patients including those requiring radiation therapy. PGH was designated one of the country's COVID-19 Referral Centers during the pandemic. Logistical challenges arose for patients needing radiation therapy in PGH because of the implementation of extra protective measures within the hospital leading to interruption of patient flow to the clinics and limited access to radiotherapy services, particularly those from the provinces.

In this study, we identified the effects of the COVID-19 pandemic on the radiation treatment of patients who were referred to the Philippine General Hospital - Division of Radiation Oncology from March to July 2020.

METHODS

Research Design and Patients

This was a single-institution, retrospective, observational study in a cohort of adult and pediatric patients with pathologically confirmed diagnoses of cancer who underwent CT simulation and planning, and/or external beam radiation therapy under the charity service of the Division of Radiation Oncology of the Philippine General Hospital from March to July 2020. Only charity service cases were included in the study due to difficulty in accessing records and consent of private patients. Also, the experiences of service patients during the pandemic may be different from those of private patients because of more socioeconomic disadvantages faced by service patients.

Patients who were unable to provide informed consent, those who had benign disease, those treated with palliative intent, and those with metastatic disease were excluded from the study. The exclusion of patients treated with palliative intent from the study was due to their unique situation, in which they were prioritized and given prompt access to radiation therapy, often in hypofractionated regimens, differing significantly from patients treated with curative intent, most of whom underwent radiotherapy using standard fractionation schedules, oftentimes experiencing delays or treatment interruptions due to clinic closures or lockdowns.

Data Collection

Eligible patients were identified from the service patient census from March to July 2020. Patients who underwent CT simulation, treatment planning, as well as those currently undergoing radiation therapy were selected.

After the identification of patients from the census, their medical records were retrieved by the authors to identify the patients' demographics, such as age, sex, primary cancer site, and TNM staging based on the American Joint Committee on Cancer 2017 (8th edition) manual. All patients were then scheduled for follow-up as part of their regular medical surveillance for two years. In-person follow-up check-ups were advised at the start of the recruitment but as the hospital changed institutional protocols due to the COVID-19 pandemic, the shift to telemedicine check-ups (phone calls, video calls) as a form of follow-up was done. All patient information were anonymized and kept confidential.

Overall treatment time (elapsed calendar days between the first and last fractions of external beam radiotherapy), duration of interruption or delay, and fractionation were recorded. Data on locoregional failure, distant failure, and mortality were likewise recorded. Patient death due to any cause was recorded as mortality. Tumor recurrence limited to the primary site and/or draining lymph nodes was recorded as local failure, and progression to distant metastasis was recorded as distant failure.

No formal sample size calculation was performed for this study because all eligible patients referred for radiation therapy within the observation period were included. Inclusion of all eligible patients within the period of observation was done to ensure the representativeness of the sample and reduce the possibility of selection bias.

Data Analysis

Demographical data of the participants were summarized through descriptive statistics: frequency and proportion for categorical variables, and mean for continuous variables. Chi-square test analysis was done to determine the relationship of variables. Statistical significance was set at p -value <0.05 .

Ethical Consideration

This research complied with the declaration of Helsinki's ethical principles for medical research involving human subjects. The study was approved by the Ethics Review Board of University of the Philippines Manila (UPMREB 2020-0650-01).

RESULTS

There were 101 patients who were included in the study. Of this, 76.2% (77) were females and 23.8% (24) were males. The study population had a mean age of 48.32 years. The study population consisted mostly of older adults greater than 50 years old (54.46%), followed by middle-aged adults aged 31-50 years old (29.7%), those less than 18 years old (10.89%),

Table 1. Demographic Information of the Participants

	Frequency	Percentage (%)
Sex		
Female	77	76.20
Male	24	23.80
Total	101	
Age		
Mean		48.32
Range		1-82
<18	11	10.89
18-30	4	3.96
31-50	30	29.70
>50	55	54.46
Organ system		
Gynecologic	41	40.60
Head and Neck	22	21.80
Breast	14	13.90
GI/GU	12	11.90
Others	7	6.90
Primary Brain	5	5.00
Disease Stage		
Unknown	20	19.80
I	2	2.00
II	18	17.80
III	48	47.50
IV	13	12.90

and young adults aged 18-30 years old (3.96%). Most of the patients were diagnosed with gynecologic malignancies (40.6%), followed by head and neck cancers (21.8%), breast cancers (13.9%), genitourinary/gastrointestinal malignancies (11.9%), other organs not specified (6.9%), and primary brain cancers (5%). Most of the patients were diagnosed with Stage III cancer (47.5%), followed by unknown or un-staged disease (19.8%), Stage II cancer (17.8%), non-metastatic Stage IV (12.9%), and Stage I disease (2%) (Table 1).

Figure 1 shows the distribution of participants whether they received external beam radiation therapy (EBRT) and whether they were able to complete their EBRT course in relation to the lockdown in Metro Manila in March 2020 (pre-lockdown vs post-lockdown). Out of the 101 participants, 44 (43.6%) underwent CT simulation but did not proceed with the prescribed radiation therapy treatment, and 57 (56.4%) underwent EBRT. Among those who had EBRT, 33 patients were able to complete their EBRT course, seven of whom started before the lockdown in March 2020 with a mean treatment duration of 140.6 days from the start of treatment and 181.7 days from the day of CT simulation. The other 26 patients who completed their EBRT started after the lockdown, with a mean of 50.3 days from the start of treatment and 217.3 days from the day of CT simulation. Twenty-four patients did not complete their EBRT, 17 of whom started before the lockdown, and seven started after the lockdown.

Out of the 101 participants initially included in the study, 52 patients were lost to follow-up so data on mortality and failures were obtained from 49 patients (48.5%) who were able to follow-up for 2 years. Figure 2 details the distribution of patients who were able to follow-up in relation to the status of their external beam radiotherapy treatment.

Deaths and failures were recorded at different follow-up time points. Patients without recorded failure proceeded to have follow-up until the completion of the study period.

At 3 months follow-up, there were two reported deaths and three distant failures; at 6 months - two deaths, two local failures, and three distant failures; at 12 months four deaths; at 18 months - six deaths, two local failures, one distant failure; and at 24 months - two local failures and two distant failures. At the end of the study, there were 20 patients with no tumor progression (Table 2).

Figure 3 shows patients with no/incomplete external beam radiation therapy (EBRT) had a higher incidence of

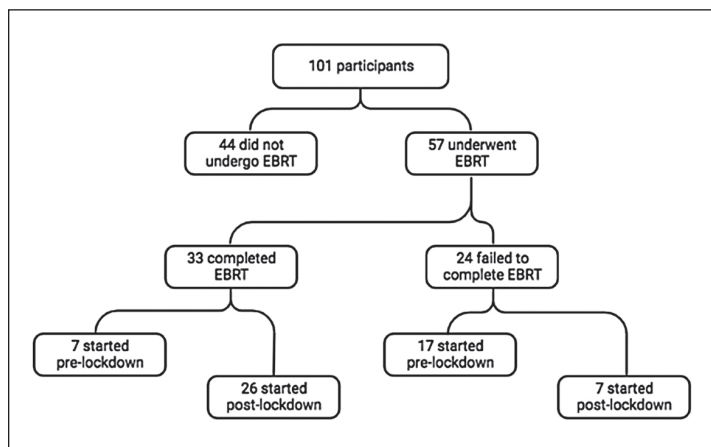


Figure 1. Distribution of patients who started and completed their EBRT course in relation to the March 2020 lockdown in Metro Manila.

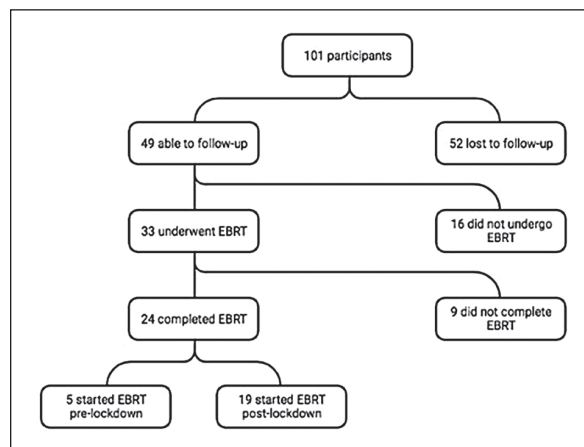


Figure 2. Distribution of patient follow-up and respective EBRT status.

Table 2. Incidence on Mortality and Failure

Follow-up Period	Mortality	Locoregional Failure	Distant Failure	No Failure
3 Months	2	0	3	44
6 Months	2	2	3	37
12 Months	4	0	0	33
18 Months	6	2	1	24
24 Months	0	2	2	20 (40.8%)
Total	14 (28.5%)	6 (12.5%)	9 (18.75%)	

failures (10) compared to those who completed EBRT (5). In Stage II disease, distant metastasis was the sole failure observed in the no/incomplete RT group; for the completed RT group, one patient died at 18 months follow-up and another had distant metastasis at 24 months follow-up.

Stage III patients exhibited the highest number of failures and deaths for both groups with no/incomplete EBRT and with completed EBRT. For patients with no/incomplete EBRT, mean time to local failure was 18 months and mean time to distant failure was 5 months. For patients with completed EBRT, mean time to local failure was 14 months. No incidence for distant metastasis was noted in this group. Although mortalities were more frequent in the completed RT group, more failures were recorded in the no/incomplete RT group. Distant failures were exclusive to the no/incomplete RT group, occurring within 3-6 months of follow-up. Loco-regional failures were equally distributed relative to RT completion, but those who completed RT experienced earlier onset of loco-regional failure.

In Stage IV patients, one distant metastasis occurred at 18 months in the no/incomplete RT group and at 3 months in the completed RT group. Two patients over 50 years old

died at 12- and 18-month follow-up in the no/incomplete RT group, while one patient within the 31 to 50-year age group who completed EBRT died at 18 months.

The distribution of patients without failure showed that 9 patients were in the no/incomplete EBRT group, while 11 were in the completed EBRT group. This suggests that the completion of EBRT has a positive impact on disease outcomes, as more patients with Stage II and IV who completed RT had no failure. However, in Stage III disease, 7 patients with no/incomplete RT had no failure compared to 6 patients in the completed RT group, suggesting the heterogeneity in disease biology in the Stage III cohort.

Chi-square test analysis did not show a correlation between radiation treatment interruption and treatment failure (Table 3).

DISCUSSION

The COVID-19 pandemic caused a shock worldwide and its effects on healthcare services has been far-reaching. While protocols to address the demands of the pandemic were being developed, mobility of people became limited thus timely delivery of cancer treatments and services became difficult in many cancer centers around the world including the Philippines. Initiatives for early detection, screening, and prevention were suspended during the March 2020 lockdown.⁸ The Philippine General Hospital (PGH) became one of the COVID-19 referral centers in Metro Manila. COVID-19 measures including social distancing, limited hospital visits, and border lockdowns, significantly disrupted cancer screening, diagnosis, surgery, radiotherapy, and chemotherapy services within PGH. A survey by the European Society for Radiotherapy and Oncology found

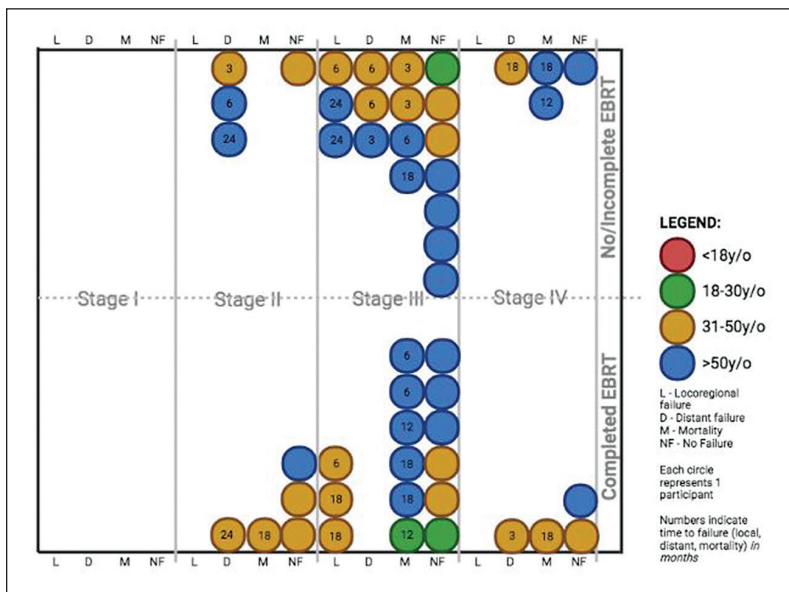


Figure 3. Characteristics of patients who were able to follow-up.

Table 3. Treatment Interruption and Treatment Failure Association

	Patients with failure	Patients without failure
Patients with treatment interruption	9	5
Patients without treatment interruption	20	15
Chi-square	0.211207	
p-value	0.6458	

that 58% of radiation oncology departments delayed therapies for new patients, and 60% reported a reduction in the number of patients, highlighting the impact of COVID-19 on cancer patient management.⁹

Older patients, who comprised the largest proportion of the study population, faced challenges in accessing timely cancer care due to limited mobility caused by the lockdown, cancelled hospital appointments, delayed surgeries or other treatment procedures, such as chemotherapy, and fear of contracting the deadly COVID-19 disease. These could have potentially resulted in delays in cancer diagnosis and treatment, affecting their overall outcomes. Similarly, the pediatric patients, although comprising a very small proportion of the sample, may have encountered similar difficulties in accessing necessary cancer-related healthcare services.

The three most common cancer sites in this study were gynecologic, head and neck, and breast cancers. Most of the patient presented with Stage III disease, followed by Stage II, and Stage IV. These disease stages represent locally aggressive tumor and as a part of their treatment must receive radiation therapy. Fourteen (28.5%) of the patients died throughout the 24-month follow-up period. This high mortality rate can be due to the higher percentage of patients having locally advanced disease stage upon CT simulation. Locally advanced cancer is likewise known to progress rapidly without timely treatment, although the possibility of mortality due to COVID-19 was not investigated and is outside the scope of this study.

The mean treatment time in the study cohort ranged from 50.3 days to 140.6 days from the start of radiation treatment to end of treatment, and 181.7 days to 217.3 days from the day of CT simulation to end of treatment. Several studies have shown the detrimental effects of prolonged treatment times for certain cancer types. In the case of cervical cancer, Song, et al. showed >56 days treatment time is detrimental to pelvic control.¹⁰ For breast cancer, Nagar and Formenti observed that postponing the start of adjuvant radiotherapy for more than eight weeks after surgery increases the risk of local recurrence by two-fold. They also showed that patients with newly diagnosed glioblastoma experience a decline in survival by approximately seven months when the initiation of radiotherapy is delayed for more than 48 days after surgery. Analysis of head and neck patients revealed detriment in overall survival with longer interval from surgery to post-operative RT >43 days.¹¹ The treatment durations observed in our study are beyond any recommended total treatment times of cancer management for any organ system potentially leading to poor local control and decrease in survival.

Crisostomo et al.¹² found that treatment delays and interruptions were significantly associated with increased re-simulation rates in head and neck cancer patients in the same institution. Sixty-eight out of 101 participants (67%) did not comply with their planned radiation therapy course, with 44 not undergoing EBRT and 24 not completing

EBRT. This decline in compliance with radiation therapy is supported by Chauhan et al.,¹³ who observed a 10% decrease in the number of patients receiving treatment during the COVID-19 lockdown. Additionally, 20 of the 49 (40.8%) patients in our study completed the follow-up period without disease failure, but nine patients (18.4%) did not finish their radiation treatment and remain at risk.

Treatment completion plays a critical role in tumor control, prevention of disease progression, and potential improvement of survival outcomes. In our study, patients with no/incomplete RT had a higher incidence of local and distant failures compared to those who completed treatment. The higher number of failures in Stage III patients, particularly among those over 50 years old, may be influenced by the lockdown and reduced mobility leading to delayed access to healthcare. Mortality rates were higher in the completed RT group, but more failures were observed in the no/incomplete RT group. Distant failures occurred exclusively in the no/incomplete RT group, indicating poor disease control. The earlier onset of loco-regional failure in patients who completed RT may be due to more frequent surveillance. Among Stage IV patients over 50 years old, incomplete RT and limited mobility further impact treatment outcomes and survival. The distribution of patients without failure revealed a higher proportion of no failure in stage II and IV patients who completed RT, supporting the impact of treatment completion on disease outcomes. However, in stage III disease, there was a subset of patients with no/incomplete RT who also had no failure, suggesting potential disease biology heterogeneity.

The study did not find an association between treatment interruption and treatment failure. Several factors contribute to this lack of association, including the small sample size, heterogeneity of the cohort, diverse cancer pathologies, and different disease stages. The impact of the COVID-19 pandemic on healthcare-seeking behavior is evident on the limited patient follow-up and high number of drop-outs. Movement restrictions during the initial lockdown period hindered patient access to healthcare, leading to a shift towards telemedicine for consultation and follow-up. However, some patients were unreachable or not attended to due to outdated or unavailable contact information.

Delays and interruptions in cancer treatment have been linked to adverse outcomes. Untreated advanced cancers can quickly lead to mortality or significant clinical progression. These patients often cannot afford to wait for the COVID-19 surge to pass and reduce healthcare burden.¹⁴ The need for uninterrupted cancer treatment is supported by the analysis of Nogueira et al.¹⁵ on the impact of a hurricane disaster where worse survival was correlated with longer radiation therapy treatment duration (66.9 vs. 46.2 days; $P < 0.001$).

This pandemic is expected to indirectly increase cancer-related mortality due to disruptions in healthcare, including financial constraints and fragmented healthcare systems.¹⁶ The vulnerabilities of the Philippine healthcare system have

been exposed, adding pressure to the already strained system in the country.¹⁷

CONCLUSION

This study showed that the Covid-19 pandemic significantly prolonged radiation treatment interruptions and delays, potentially leading to worse oncologic outcomes. There was a lack of association between treatment interruption and treatment failure due to the March 2020 lockdown. This may be due to inherent limitations of the study such as small sample size and heterogeneous patient characteristics, including different cancer pathologies and different disease stages. Numerous recommendations on radiation therapeutic management of cancer patients during the time of pandemic are published and radiation oncologists should be knowledgeable of these for optimal management and clinical outcomes of patients. There is also a need to develop sustainable strategies and systems to ensure continuous access to cancer care during pandemics.

Recommendations

Based on the findings of this study, the authors recommend increasing the number of participants and including data from more radiotherapy centers throughout the country to draw more reliable conclusions. Other sociodemographic factors such as place of residence (NCR vs. other region), educational level, and family income can also be included to give more context to the study. Future researchers may also want to focus on only one specific type of cancer in determining the correlation between treatment interruption and failure.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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