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Radiotherapy activity in the COVID 19 pandemic: Brazil's operational national-level study.

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Data Availability Statement for this Work:

Research data are stored and will be shared upon request to the corresponding author.

Abstract

Purpose: During the COVID-19 pandemic, patients with cancer are at increased risk of not having timely diagnosis and access to cancer treatment. The present study evaluated the COVID-19 pandemic impact on radiotherapy activity in Brazil.

Methods: A national-level study was performed to evaluate the RT utilization for prostate, breast, head & neck (HN), Gynecology (GYN), Gastrointestinal (GI), lung cancers, and bone/brain metastases. The data on the RT executed was extracted from the Brazilian Ministry of Health database. The NON-COVID period was considered the control group, and the comparison groups were COVID-2020 (without vaccine) and COVID-2021 (with vaccine).

Results: We collected the data of 238,355 procedures executed on three periods. Significant difference in the RT utilization between NON-COVID and COVID-2020 were observed for prostate cancer, bone and brain metastases (-12.3%, $p=0.02$, +24%, $p=0.02$ and +14%, $p=0.04$, respectively). Comparing 2 equivalent months from NON-COVID-2019 (ref), COVID-2020, and COVID-2021, a significant increase was identified for bone and brain metastases (2020 +21%, and 2021 +32%), and (2020 +20%, and 2021 +14%). A stable drop occurred for prostate cancer (2020 -11% and 2021 -10%), and a variation was observed for breast (2020 +8%, and 2021 -1%) and lung cancer (2020 +10%, and 2021 -3%). For other cancers, non-significant changes were observed when comparing 2020 and 2021.

Conclusion: The RT activity was heterogeneously affected with a substantial increase for bone and brain metastases and a meaningful decline for prostate cancer.

Policy summary: With a significant increase in the use of palliative radiotherapy for bone and brain metastases and a meaningful reduction in curative radiotherapy for prostate cancer, we hope these findings can help governments, RT services, medical communities, and other stakeholders develop strategies to mitigate the impact of the present and future pandemics. Finally, despite the changes imposed by the COVID pandemic, it is imperative to enhance screening, increase cancer diagnosis at an early stage, and improve access to all cancer treatments, including radiotherapy.

Introduction

Based on January of 2022 reports, Brazil was one the most profoundly affected countries globally by the COVID-19 pandemic, with around 22 million cases [1]. After the start of the pandemic (March 2020), the Brazilian Government, similar to other countries, implemented measures to provide COVID-19 patients adequate access to the hospitals with ventilatory support. The indirect COVID 19 pandemic impact on cancer patients is a concern because of the need for a timely diagnosis, multidisciplinary treatment, and symptom palliation.

During the pandemic, surgery units were closed, oncologists implemented risk-based guidelines to postpone systemic therapies in low-risk patients due to the potential infection during their cancer treatment and radiotherapy (RT) services were oriented to follow specific risk-based guidelines [2-4]. Moreover, RT has been used to replace or as a bridge to surgery or systemic therapy during the pandemic. In addition, Radiotherapy services were oriented to adopt treatment guidelines using short (hypofractionated) radiotherapy courses. However, with a recognized shortage of radiotherapy machines (LINAC) in Brazil, there are concerns about access to treatment [5-7].

Moreover, since the beginning of COVID19, the world has faced new waves of rising cases caused mainly by new mutation forms from the COVID 19 virus. Therefore, it is fundamental to understand what happened during this period to guide new actions and be prepared for future crises. In this aspect, currently, there is limited information about changes to radiotherapy practice from Latin America. As of now, most studies about the covid impact were based on surveys from RT services from high income countries [8-

12]. Low quality data (i.e., the absence of longitudinal information) are limitations with these studies. Therefore, it is fundamental to obtain high-quality data for adequate planning for future epidemics. In Brazil, the RT services monthly submit treatment data to the Public Health Database (DATA-SUS in Portuguese) [13]. In this study, DATA-SUS was queried and evaluated to investigate changes in RT treatments before and during the COVID-19 pandemic.

Methods:

We designed a national-population based study to evaluate the RT utilization for prostate, breast, head & neck (HN), Gynecology (GYN), Gastrointestinal (GI), lung cancers, and bone/brain metastases. This study evaluated the radiotherapy activity across all public Brazilian radiotherapy providers from August 2019 to September 2021. Ethical approval was not necessary for this work because it used public no-labeled data, being considered operational research. These same database sources and methods were previously used to evaluate the COVID-19 effect on dental health, cardiovascular diseases, and general surgical procedures [14-18].

Data were extracted from the national database (named DATASUS) to estimate the total of radiotherapy treatment performed for eight tumor sites (Prostate cancer, breast, head and neck, lung, gastrointestinal, gynecological, brain, and bone metastases). Cervix, endometrial, vulvar, and vagina cancer were grouped as gynecologic cancers. Esophageal, gastric, pancreatic, anal, and rectal cancer were classified as gastrointestinal cancers. We collected the data for specific tumors using the following codes: Prostate (0304010456), Breast (0304010413), HNC (0304010367), GYN

(0304010421), Lung (0304010383), GI (0304010375), bone metastases (0304010537), and brain metastases (0304010529). Data items from DATASUS used in this analysis were the radiotherapy numbers executed within the country and in the five regions (Southeast, South, Middle-west, Northeast, and North), independently the treatment intent. We divided the data into three periods (NON-COVID, COVID without vaccination and COVID with vaccination) to compare the percentage of changes in activity between the periods. The NON-COVID period (from August to December 2019) was compared with the COVID 2020 period without vaccination (from August to December 2020). The COVID 2020 (without vaccine) period was compared with COVID 2021 (with vaccine). The first case of COVID-19 in Brazil is dated from February 23, 2020, and in June 2020, Brazil achieved 1 million confirmed cases. The vaccination began in January 2021, with 50% of the population vaccinated on August 1, 2021.

Therefore, we compared the moving average using data from nine months from the COVID period without vaccination (march to December 2020) and nine months from the COVID period with vaccination (from January to September 2021). This approach was used to estimate tendencies and fluctuations in the radiotherapy activity previous and after vaccination. In Brazil, the vaccination began in January 2021, and we choose August and September to compare the three periods because in August 2020, Brazil had more than 1 million COVID cases, and in 2021 more than 50% of the population had been vaccinated. Therefore, using the same two-month period would give us one idea of the impact of COVID and, at the same time, the impact or not of the vaccination on the RT activity. The comparison between the two periods was made using the moving average calculated using the nine months of each period as bases. The

radiotherapy number activity between the periods was compared using the chi-square test for trends. The moving average was calculated and tested using T student. Statistical significance was defined as a p-value < 0.05. The statistical analysis was performed with Graph Prism software version 8.0 and Excel 2010.

Results

There was accurate data available on five months, 12 months and 9 months for NON-COVID 2019, COVID-2020 (without vaccine), and COVID-2021 (with vaccine) periods, respectively. During the NON-COVID 2019, COVID-2020 (without vaccine), and COVID-2021 (with vaccine) periods 45,148, 109,961, and 83,246 RT treatments were performed, respectively, **table-1**. The COVID-19 timeline in Brazil is illustrated in **figure 1**.

Matching five equivalent months of RT treatments between NON-COVID 2019 (45,148 RTT) and COVID-2020 (46,668 RTT), an increase of 1520 RT treatments (+3.4%) was observed. Considering the primary tumor site and all Brazilian regions, the RT activity showed an absolute increase of 497 RT treatments (+4%, p=0.286) for breast cancer, **figure 2a**. For prostate cancer we found a significant decline of -12.3% (-1020 cases, p=0.02), **figure 2b**. Head and neck cancer had stability with a no significant change of 70 (+1.3%, p=0.149); this pattern was seen in all Brazilian regions, **figure-2c**. Gynecology cancers had an increase of 112 procedures, corresponding to +2.2% with no significant difference across the Brazilian regions, **figure-2d**. Lung cancer increased 140 (+10%, p=0.08), without difference across the regions, **figure-2e**. GI cancer had an increase of 153 (+3%, p=0.411), with no significant difference across the regions,

figure-2f. In contrast, bone and brain metastases had a substantial increase of +24% (+1306, $p=0.02$) and 282 (+14%, $p=0.04$), **figure 2g-h.**

Comparing the moving average between 9 months from COVID 2020 (without vaccine) and COVID 2021 (with vaccine), a significant fall in the average from 2593 to 2344 (-249 RT procedures, -9.5%, $p=0.010$) was observed for breast cancer, **supplementary figure-1a.** A no significant increase in the moving average was detected for prostate cancer from 1433 to 1451 (+18 RT procedures, +1.2%, $p=0.644$, **supplementary figure-1b**), HN cancer from 1108 to 1110 (+2 RT procedures, +0.1%, $p=0.955$, **supplementary figure-1c**), Gyn cancer from 1025 to 1069 (+44 RT procedures, +4.2%, $p=0.150$, **supplementary figure-1d**), Lung cancer from 294 to 298 (+4 RT procedures, +1.3%, $p=0.742$, **supplementary figure-1e**) and GI cancer from 1082 to 11132 (+50 RT procedures, +4.6%, $p=0.09$, **supplementary figure-1f**). A substantial variation in the moving average was observed for Bone and brain metastases from 1265 to 1405 (+140 RT procedures, +11%, $p=0.03$, **supplementary figure-1g**) and from 443 to 482 (+38 RT procedures, +8.5%, $p=0.04$, **supplementary figure-1h**), respectively.

Finally, comparing 2 equivalent months from NON-COVID-2019 (ref), COVID-2020, and COVID-2021, a significant increase was identified for bone and brain metastases (2020 +21%, and 2021 +32%), and (2020 +20%, and 2021 +14%), **figure 3.** In contrast, a stable drop occurred for prostate cancer (2020 -11% and 2021 -10%), **figure 3.** Moreover, a variation was observed for breast (2020 +8%, and 2021 -1%) and lung cancer (2020 +10%, and 2021 -3%), **figure 3.** For other cancers, non-significant changes were observed when comparing 2020 and 2021.

Discussion

Our analysis shows that overall, the number of RT treatments during NON-COVID period in Brazil did not decrease significantly when compared to equivalent COVID periods (with and without vaccine). However, there was a significant increase in RT for bone and brain metastases and a significant decrease in RT treatment for prostate cancer. Our study was designed to assess the changes in the RT activity between 2019 and 2021, categorized in three distinctive periods; 2019 (NON-COVID, reference) and 2020 (COVID without vaccine), with 2021 (COVID with vaccine).

Considering all tumor sites, comparing the RT activity between 2020 and 2019, we noted a slight increase in the RT activity (+1540 RT procedures, +3.4%). Our results are divergent from the deep fall (~20%) observed in ESTRO, ASTRO, and the English NHS surveys on the impact of COVID-19 on the RT centers [8,9,18]. Besides, even after vaccination in 2021, RT treatments continued to be lower than NON-COVID for breast, prostate, and lung cancer, stable or slightly increased (<5%) for HN, Gyn, and GI cancer, and higher for bone and brain metastases independently of the period (with or not vaccination).

The reasons to explain the Brazilian findings comparing the periods are: first, the Brazilian RT accumulated patient demand due to the LINAC shortage [5-7]. Hence, even with the reduction in diagnosis and surgeries, the number RT treatments were maintained in 2020 for several tumor types. Second is the widespread adoption of hypofractionated schedules. The Brazilian radiotherapy society endorsed the international guidelines of hypofractionated treatment for prostate cancer, breast, rectal,

bone metastases, and, when possible, for other tumors [20-22]. Consequently, more patients were treated, absorbing the demand even with a LINAC shortage. The hypofractionation schedule associated with the high demand accumulated by the LINAC shortage possibly is the main reason for 8% of the increase in 2020 versus 2019 for breast cancer, **figure-3**. Third, RT replacing or delaying surgery for HN, Gyn, and lung cancers. On the contrary, RT for prostate cancer had a significant reduction in 2020. The fall of RT activity for prostate cancer might partially be explained by the decisions made by clinicians/patients to postpone treatment in low-risk prostate cancer and by using ADT with delayed RT for intermediate/high-risk patients. The contribution of adjuvant RT was expected on patients treated in 2019 but not in 2020 because of the suspension of elective surgeries as part of national policy for the pandemic.

In Brazil, the vaccination began in January 2021 (Covid timeline, **figure-1**), and we choose August and September to compare the three periods because in August 2020, Brazil had more than 1 million COVID cases, and in 2021 more than 50% of the population had been vaccinated. Therefore, using the same two-month period would give us one idea of the impact of COVID and, at the same time, the impact or not of the vaccination on the RT activity. The comparison between the two periods was made using the moving average calculated using the nine months of each period as bases.

The COVID period (with or without vaccine) analysis showed an increase for bone and brain metastases, a drop of the moving average for breast cancer, and stability for other tumors. We found that RT treatments for bone and brain metastases increased between the NON-COVID and COVID 2020 (+21% and +20%) and NON-COVID/COVID 2021

(+32% and +14%) and are of notable concern. It suggests that many patients did not have a timely diagnosis or access to treatment, resulting in late treatment and poor survival. Besides, the moving average from the last nine months of 2021 tends to maintain an increase for the following year. Our findings are significant and should support the return of cancer screening as fast as possible to mitigate further COVID impact on cancer. Currently, Brazil has more than 70% of the population vaccinated, with low COVID cases and mortality. However, even after vaccination, new virus mutations and waves can affect diagnosis, treatment access, and appropriate RT use. A recent meta-analysis reported an up to 8% increase in the chance of death for each 4-week treatment delay for several cancer types (bladder, breast, colon, rectum, lung, cervix, and head and neck) [23]. The reduced activity for prostate, breast, and lung in 2021 (with vaccine) is likely to be associated with this effect. Thus, understanding real world data is fundamental to mitigate pandemic impact on the oncological population.

Moreover, the same database and methods were formerly employed to evaluate the covid impact on cardiovascular diseases (CVD) care, surgical procedures, and dental health in the Brazilian Healthcare System [14-18]. Comparing March to May 2020 with the same period in 2019, Normando et al. described a 15% decrease in hospital admissions due to CVD diseases [15]. In addition, there was a 9% increase in the CVD in-hospital fatality rates, mainly for patients from 20-59 years old [15]. Luizeti et al., reported a 35% reduction in elective surgeries comparing 2020 with the previous four years [16]. In contrast, the decline was only 1.1 % for urgent surgical procedures [16]. The most affected surgical subgroups were endocrine gland, breast, oral-maxillofacial, upper airways, face, and head and neck surgery [16]. Moreover, Santos Filho et al.

specifically evaluated the COVID impact on elective surgeries [17]. Comparing 2020 with 2019, the number of elective surgeries declined 42% in the whole country and 31% in the Goias province [17]. Furthermore, dental procedures showed an overall 66% decrease comparing the first semester of 2019 with the same period in 2020 [14]. There were statistically significant differences for all the oral health procedures, i.e., preventive care, primary activities, endodontic procedures, and periodontal and oral surgeries [14].

Finally, it is essential to highlight that our study has some limitations. First, we did not evaluate the integration of RT with other treatments. Second, hypofractionated RT use was not assessed directly because of the database limitations. Third, the impact of palliative RT was assessed only for bone and brain metastases, which at least provided a partial idea of the impact on palliative care. Fourth, the impact of age, race and socioeconomic factors on RT utilization was not evaluated.

Conclusion

The RT treatments slightly increased during the pandemic in Brazil. However, the COVID-19 impact on RT activity was heterogeneous, with a substantial increase for bone and brain metastases and a decline for prostate cancer. The RT activity increased in the vaccinated period compared to the NON-COVID period for some tumor sites. Primary tumors depending on the screening, such as prostate, breast, and lung cancer, had a reduced RT activity even with vaccination, which indicates a slowing turn back to the normal for these tumors. These findings can help governments, RT services, medical communities, and other stakeholders to develop strategies to mitigate the pandemic impact.

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Contributors

All authors contributed to the conception, design, acquisition of data, analysis and interpretation of data, drafting of the Article, or critical revision of the Article for important intellectual content. GAV, FYM, and AGG verified the raw data and all authors had access to all the data in the study. All authors had final approval of the version to be published.

Declaration of interests

FYM received honoraria from AstraZeneca and International Association for the Study of Lung Cancer, grants or contracts from Clinical Teachers' Association of Queen's University, and consulting fees from Cancer em Foco, outside the submitted work. All other authors declare no competing interests.

Figure and tables legends



COVID-19 Timeline in Brazil

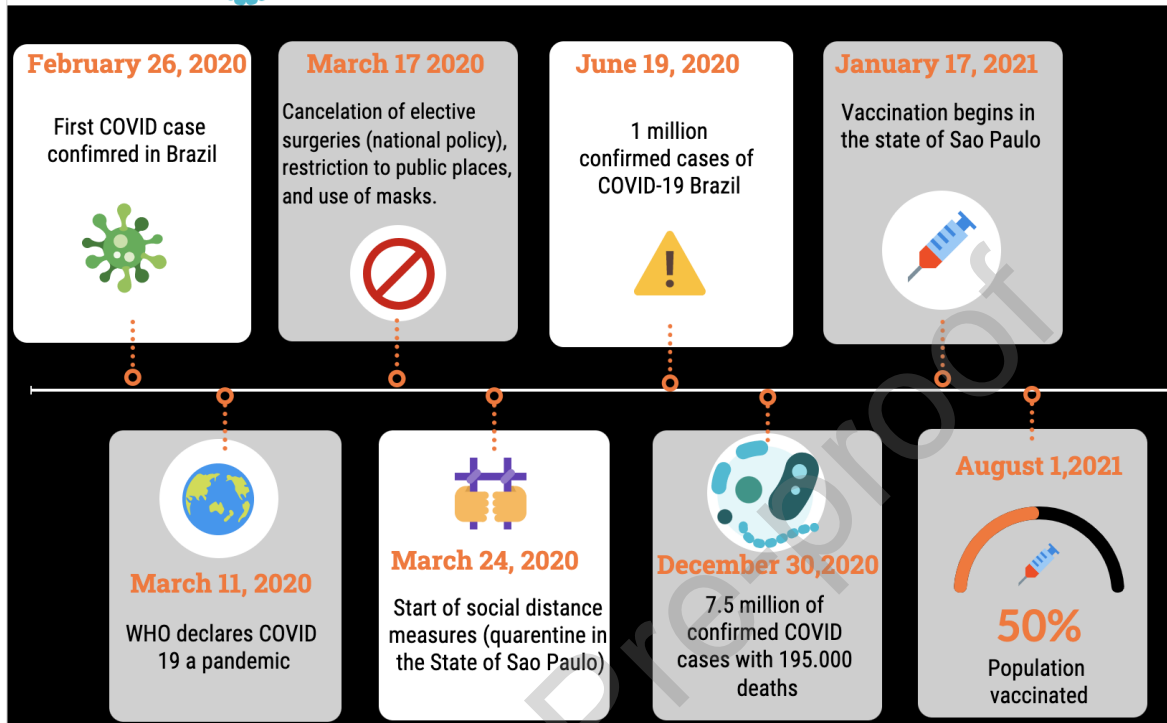


Figure 1 COVID -19 timeline in Brazil

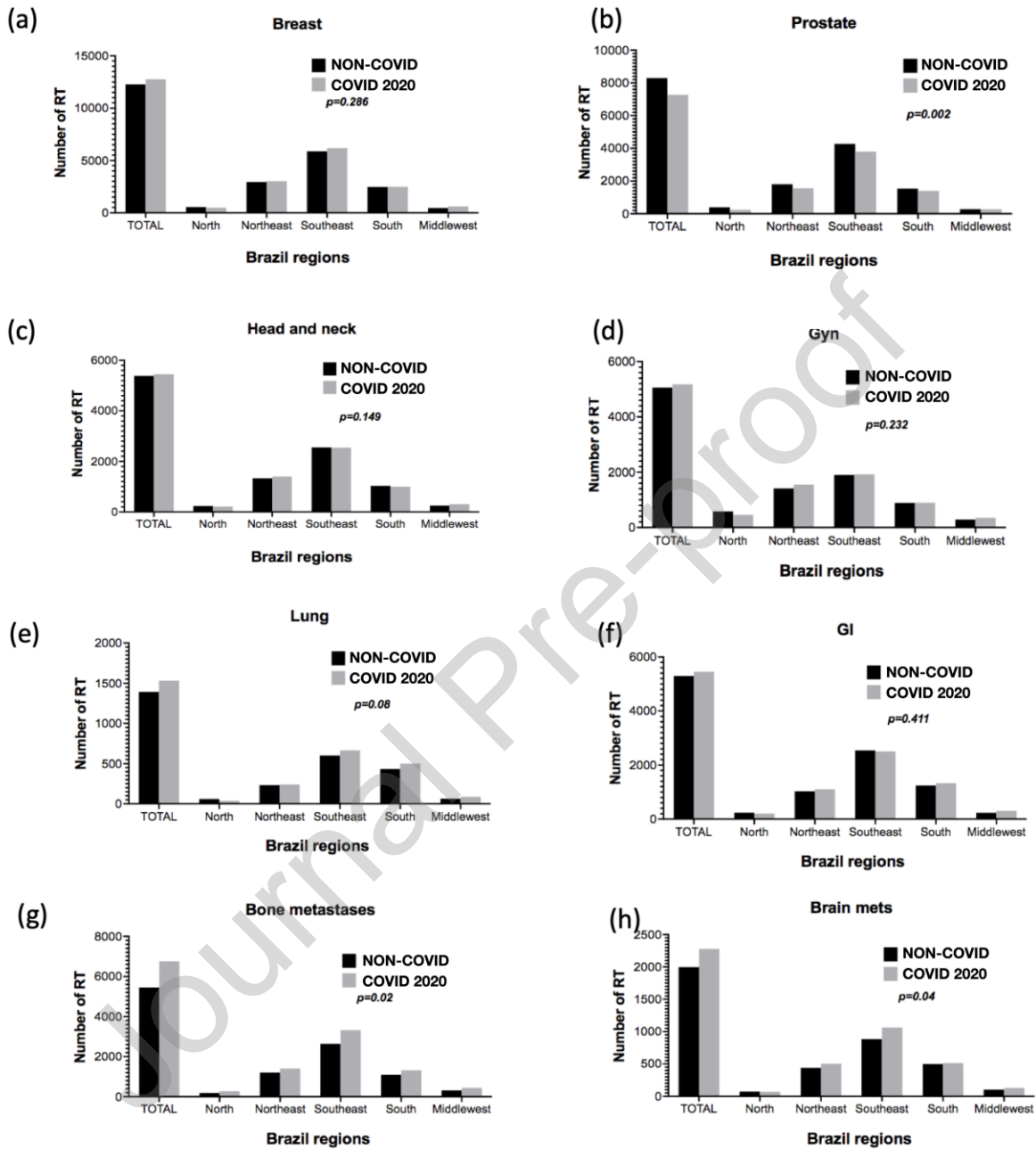


Figure 2 Overall and per region number of RT procedures for (a) breast cancer, (b) prostate cancer, (c) head and neck tumors, (d) Gynecological cancer, (e) Lung cancer, (f) Gastrointestinal tumors, (g) bone metastases, and (h) brain metastases for NON-COVID and COVID-2020 periods.

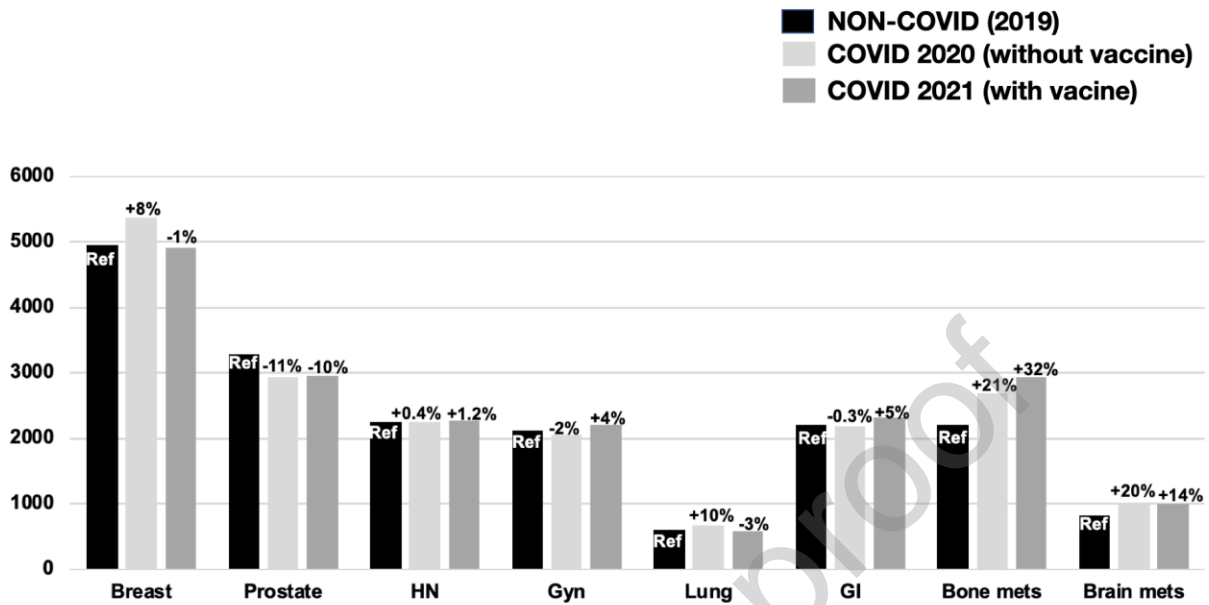


Figure 3 Comparison of equivalent two-month periods for NON-COVID, COVID-2020 (no vaccine), and COVID-2021 (vaccine) for multiple cancer types and presentation.

Table-1 Period analyzed containing the number of months, which months included, and the radiotherapy executed in each period.

Supplementary figure-1 Comparison of the moving average between COVID-2020 (no vaccine) and COVID 2021 (vaccine), for (a) breast cancer, (b) prostate cancer (b), (c) head and neck tumors, (d) Gynecological cancer, (e) Lung cancer, (f) Gastrointestinal tumors, (g) bone metastases, and (h) brain metastases.

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Highlights

- There was a significant difference in the radiotherapy utilization between NON-COVID and COVID-2020 periods in Brazil.
- The RT activity was heterogeneously affected with a substantial increase for bone and brain metastases and a meaningful decline for prostate cancer.
- These findings can support the development of strategies to mitigate the impact of the present and future pandemics.
- It is imperative to enhance screening, increase cancer diagnosis at an early stage, and improve access to all cancer treatments, including radiotherapy.