

# COVID-19 and radiotherapy: potential new strategies for patients management with hypofractionation and telemedicine

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**Abstract.** COVID-19 disease is one of the biggest public health challenges in Italy and global healthcare facilities, including radiotherapy departments, faced an unprecedented emergency.

Cancer patients are at higher risk of COVID-19 infection because of their immunosuppressive state caused by both tumor itself and anticancer therapy adopted. In this setting, the radiation therapy clinical decision-making process has been partly reconsidered; thus, to reduce treatment duration and minimize infection risk during a pandemic, hypofractionated regimens have been revised. Moreover, telemedicine shows its helpfulness in the radiotherapy field, and patients get the supportive care they need minimizing their access to hospitals.

This review aims to point out the importance of hypofractionated RT and telemedicine in cancer patient management in the COVID-19 era.

#### Key Words:

Radiotherapy, Coronavirus disease, Cancer treatment, Hypofractionation, Telemedicine.

## Introduction

Cancer patients are more susceptible to COVID-19 infections because of their often-compromised immune system resulting from systemic therapies or radiation therapy. They have an increased risk of developing serious events during COVID-19 disease.

Cancer patients are vulnerable population members. According to the most remarkable Italian cancer societies, AIOM (Italian Association Clinical Oncology), SIE (Italian Association of Hematolo-

gy), AIRO (Italian Association of Radiotherapy and Clinical Oncology), life-saving treatments for oncological patients, as radiotherapy, must be guaranteed during COVID-19 outbreak.

Radiotherapy is the cornerstone of cancer treatment for several types of malignant tumors and is estimated that about 50-60% of cancer cases will require radiation therapy as part of their treatment protocols<sup>1</sup>.

Radiation therapy as a neoadjuvant treatment before surgery and adjuvant therapy after primary cancer treatment plays an important role in oncological treatments related to other therapies for synergistic effects and exclusive treatment. In all these cases, the omission of radiation therapy may negatively affect oncological patients local control (LC) and overall survival (OS). Moreover, in metastatic patients, with bone or brain metastases, cord compression and mediastinal disorders, palliative radiotherapy significantly improves pain control and quality of life.

During the COVID-19 outbreak, radiotherapy departments could represent a site of exposure for both patients and care-providers given that radiotherapy usually involves daily treatment delivered over days to weeks in closed environment (many radiotherapy centers are placed in basements).

One of the main critical issues was to manage patients' flow and their caregivers who needed to access radiotherapy facilities. Thus, it was necessary to develop specific protocols and protective measures to prevent the spread of COVID-19 and reduce overcrowding in hospital facilities to mitigate the infection risk among frail and vulnerable patients and staff.

In this review, we discuss how radiation therapy facilities faced up to the COVID-19 crisis focusing on the hypofractionated protocols and telemedicine.

### Radiotherapy Treatments During the COVID-19 Pandemic

During the challenging time of the COVID-19 outbreak, each radiotherapy center had to implement specific policies and procedures to reduce the infection risk. Radiation oncologists had to redefine and adapt the current treatment protocols: treating patients in the COVID-19 era could be more dangerous than overlooking radiation therapy<sup>2</sup>.

Every radiation oncologist during the COVID-19 pandemic definitely prioritized radiotherapy treatments and postponed non-essential procedures and/or appointments.

Radiation oncology departments adjusted management protocols in order to keep deliver optimal care to all patients<sup>3</sup>, for patients undergoing or planned for radiotherapy.

The most widely applied strategies included hypofractionated schedules since a shorter course of radiation therapy decreases the need for prolonged daily carriage and exposure to infection. Telemedicine played a great role in the pre-clinical evaluation and follow-up management.

Several authors<sup>2,4</sup> summarized radiation oncologists' opinions and highlighted that radiation treatments, considered a gold standard, could be reconsidered in a pandemic context. Important scientific societies, such as ASTRO, ESTRO, and GEMO released recommendations in this regard<sup>5-7</sup>.

Different approaches have been pointed out: radiotherapy omission, treatment delay, or use of hypofractionation in not-deferrable treatments. About radiotherapy delay, Simcock et al<sup>2</sup> summarized radiation oncologists' opinions from 17 countries and 6 continents that contributed to make appropriate treatment decisions, balancing between risks and benefits.

General criteria for omission might include more time-sensitive need for treatment decision-making and availability of non-emergency/urgency, lower-risk alternatives.

The additional risk of treating the patient during the pandemic could be greater than the risk of omitting radiation therapy, taking into account different alternatives. Whenever feasible (assuming it does not represent an emergency), the delay of radiation treatment should be as short

as possible and triaged based on the additional risks related to the pandemic. An observation period may be arranged for these patients, especially for *benign tumors*, or in cases of hormone therapy like in *breast cancer (T1-2 N0, luminal A + B)*, or when neoadjuvant Androgen Deprivation Therapy (ADT) (6-7 months) for *prostate cancer* was indicated.

For non-deferrable interventions (such as symptomatic treatments) and for radical treatments, hypofractionated schedules facilitated the access to treatment for oncological patients while reducing the risk of exposure to infection. We made a literature review about the use of hypofractionated treatments in the COVID era.

Table I shows the most common hypofractionation schedules used for breast cancer, prostate cancer, brain metastasis, and bone metastasis<sup>8-13</sup>. Hypofractionation has a radiobiological rationale based on the linear-quadratic model; a larger dose per fraction applied to tumors with a lower  $\alpha/\beta$  ratio should result in better tumor control.

Hypofractionation represents a great resource for radiation oncologists, not only for the radiobiology of tumors, but also for logistical and management reasons. It can be a valuable aid in critical times, such as a pandemic.

### Telemedicine Service in Radiation Oncology

In the last ten years, several authors<sup>14-24</sup> depicted the development of telemedicine applications in oncology to share knowledge, opinions, and experiences.

Virtual meeting platforms turned into a standard practice for multidisciplinary meetings, sharing test results (radiology, pathological analyzes) and treatment planning (radiotherapy, chemotherapy) in order to improve patient care.

Video consultations are specific forms of telemedicine to provide a real-time visual and audio patient evaluation. Allen and Hayes<sup>25,26</sup> first described the use of video consultations for clinical evaluation in cancer patients in 1994.

Telemedicine should be seen as a remote support to patients to reduce in-person hospital access during the COVID-19 outbreak. Moreover, the use of telemedicine improve access to medical care and decrease health care costs. For cancer patients, telemedicine can be used for remote chemotherapy supervision, symptoms management, survivorship care, palliative care, and clinical trials<sup>27</sup>.

**Table I.** Hypofractionation schemes used during COVID-pandemia. Authors, Hypofractionation schemes with dose (Gy/fz) (Gray/fraction), technique (SIB = Simultaneous Integrated Boost; PBI = Partial Breast Irradiation; WBRT = Whole Breast Radiation Therapy; SBRT = Stereotactic Body Radiation Therapy; SRS = Stereotactic RadioSurgery; IORT = IntraOperative Radiation Therapy; BID = bis in die) and Trials.

Type of cancer	Author	Hypofractionation schemes	Group/trial
Breast	Lancia et al, 20208	- 28-30 Gy/weekly - 26 Gy five daily fz	FAST FAST FORWARD
	Braunstein et al, 2020 <sup>9</sup>	- partial breast: 30 Gy/5fz every other day (preferred) or daily (acceptable) 40 Gy/10fz daily - whole breast: 26 Gy/5fz daily ± 5.2 Gy x 1fz boost 45Gy/15fz daily 42.4Gy/16fz daily - postmastectomy: 42.56 Gy/16fz - breast and RNI: 42.56 Gy/16fz with SIB to tumor bed 48 Gy/16fz (3 Gy/fz) - 40 Gy/15fz with SIB to tumor bed 48 Gy/15fz (3.2 Gy/fz)	Florence PBI trial; MSK prospective  UK-FAST FORWARD  RTCHARM (NCT03414970) UK START B and extrapolation from RTOG 1005  SIB: EQD2 57Gy for a/b 3
	Simcock et al, 2020 <sup>2</sup>	- PBI-early stage: 30 Gy/5fzf or 38.5 Gy/10fz (BID) - PBI-early stage (IORT): 20 Gy/1fz - WBRT, N0-early stage: 28.5 Gy/5fz - WBRT, with or without LN-early stage: 26 Gy/5fz - WBRT plus LNs: 40.05 Gy/15fz - chest wall: 40.05 Gy/15fz or 43.5 Gy/15fz - whole breast/chest wall (>70y): 30-37.5 Gy/6fz (weekly)	University of Florence, RTOG 0413 TARGIT, UK FAST, FAST FORWARD FAST FORWARD, NCRI/ICR Beijing PMRT (Phase III) Beijing PMRT (Phase III) Hospital del Mar Parc de Salut Mar Barcelona
	Coles et al, 2020 <sup>10</sup>	- WBRT, node negative: 28-30 Gy/5fz (weekly) or 26 Gy/5fz (daily) - WBRT, node positive: 40.05 Gy/15fz - PBI: 28.5-6 Gy/5fz (over 1-2 weeks)	FAST and FAST Forward trials, respectively START trial Livi 2015; PAPBI trial 2015
	Combs et al, 2020 <sup>11</sup>	- DCIS: 40.05 Gy/15fz (omit RT in case of low risk) - invasive: 40.05 Gy/15fz or 26 Gy/5fz (omit RT in case of low risk) N+: 40.05 Gy/15fz - postmastectomy (Hypofractionation if not implant): 40.05 Gy/15fz or 43.5 Gy/15fz - ASTRO PBI criteria: PBI: 38.5 Gy/10fz (BID) or 30 Gy/5fz or 28.5 Gy/5fz (weekly) or 26 Gy/5fz (daily); PBI (IORT): 20 Gy/1fz	Nilsson et al, Radiother Oncol 2015 Haviland et al, Lancet Oncol 2013 AST Forward Trial Wang et al. 2019  Correa et al, 2017 Livi et al, Eur J Cancer 2015 Brunt et al, FAST Forward Trial 2016 Vaidya et al, Lancet 2014 Veronesi et al, Lancet Oncol 2014

*Continued*

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Type of cancer	Author	Hypofractionation schemes	Group/trial
Prostate	Lancia et al, 2020 <sup>8</sup>	- 60Gy in 20 fz or even 5-6 fractions in total)	NCCN
	Zaorsky et al, 2020 <sup>12</sup>	- IR/HR localized: 5 to 7fz (SBRT) or 60-62 Gy/20fz - post-prostatectomy: 52.5 Gy/20fz - oligometastatic: 1 or 3 fz (SBRT) - low volume M1: 3-5 fz (SBRT) or 36 Gy/6fz	(2020 NCCN guidelines)  (STAMPEDE)
	Simcock et al, 2020 <sup>2</sup>	- any risk: 60 Gy/20fz - IR-HR, prostate only: 42.7 Gy/7fz - LR-IR, prostate only: 36.25-40 Gy/5fz (SBRT) - HR or M1 (>75y or 70y with comorbidities): 36 Gy/6fz - post-prostatectomy, fossa only: 52.4 Gy/20fz or 62.5 Gy/25fz	CHHiP PROFIT HYPO-RT-PC MSKCC NRG GU005 (Phase III), ongoing STAMPEDE Christie TADICALS ; NRG GU003-trial ongoing
	Combs et al, 2020 <sup>11</sup>	- IR/HR: 60 Gy/20fz - IR/HR <75y: 42.7 Gy/7fz - adjuvant/salvatage: 52.5 Gy/20fz	CHHIP Dearnaley et al, 2016 and 2017 HYPO-RT-PC, Widmark et al Chin et al, RED Journal 2020
Brain metastasis	Yerramilli et al, 2020 <sup>13</sup>	- 4 Gy x 5 fz daily - steroids alone for patients with poor performance status	Rades et al, QUARTZ
	Simcock et al, 2020 <sup>2</sup>	- brain metastases (SRS) 15-20 Gy/1fz - palliative WBRT: 20 Gy/5fz - palliative WBRT (poor prognosis): 12 Gy/2fz	RTOG QUARTZ
	Combs et al, 2020 <sup>11</sup>	- 1-10 mts: good KPS: 18-20 Gy/1fz (SRS)	Kocher et al, JCO 2011
	Yamamoto et al, Lancet Oncol 2017	- post op: 35 Gy/7fz or SRS  - life expectancy >3 months: 20 Gy/5fz (WBRT)	Brown et al, Lancet Oncol 2017 Mahajan et al, 2017 Sahgal et al, 2017 RTOG QUARTZ
Bone Metastasis	Yerramilli et al, 2020 <sup>13</sup>	- 8 Gy x 1 fz daily - cord compression: 8 Gy x 1 fz daily	RTOG 9714 Maranzano et al, SCORAD III, ICORG 05-03
	Simcock et al, 2020 <sup>2</sup>	- painful bone metastases (no fracture) ± spinal cord compression: 6-10 Gy/1fz - bone metastases (fracture/surgery): 20 Gy/5fz	TROG 96.05; SCORAD III, ICORG 05-03  RTOG QUARTZ
	Combs et al, 2020 <sup>11</sup>	- bone mets: 8 or 10 Gy/1fz or 20 Gy/5fz or 21 Gy/3fz - oligometastatic: SBRT (1-5fz)	Chow et al, JCO 2007 Otake et al, Cancers 2019
	Thureau et al, 2020 <sup>7</sup>	- retreatment of painful bone metastasis: 8Gy/1fz - SBRT for retreatment of symptomatic MESCC: (16 to 24Gy)  - metastatic epidural spinal cord compression (MESCC): 8Gy/1fz - painful bone metastasis: 8Gy/1fz	Van Derlinden, 2004 Husain, 2017 Hashmi, 2016 Rades, 2018 SCORAD trial, 2019 Willeumier, 2016

Patients who were not currently receiving active therapy may be suitable for telemedicine follow-up.

Follow-up visits deferment or reduction can be considered to minimize exposure to the risk of infection. A rescheduled planned is needed in order to avoid patients being lost to follow up<sup>28</sup>.

Furthermore, telemedicine facilitates decentralized radiotherapy services by allowing remote treatment planning and quality assurance of treatment delivery<sup>29</sup>.

During the era of the COVID-19, virtual assistance technology enables greater collaboration between specialties through interdisciplinary virtual consultations<sup>30</sup>.

### ***An Institutional Experience of Radiation Treatment Management in Covid-19 Emergency***

During the COVID-19 emergency, our radiotherapy department implemented several measures and strategies in order to mitigate risks of infection and ensure continuity of treatments. According to Institute's COVID-19 control guidelines, a triage point has been established at the hospital's main entrance. Every patient and their caregivers are examined for suspect symptoms (cough, dyspnea, fever) or to verify possible contact with COVID-19 positive patients. Radiotherapy workflow modifications have been implemented to reduce patient's access to the department. The result is avoiding overcrowding, ensuring social distancing in the waiting rooms and treatment areas, re-scheduling patient treatment appointments, redistributing them among all available machines and restricting access to one visitor per patient, only if necessary. During the COVID-19 pandemic, in order to reduce overall treatment time, hypofractionated regimens have been preferred.

In prostate cancer treatment, we applied moderate hypofractionated schedules with 62 Gy in 20 fractions with VMAT-SIB technique with unfavorable intermediate risk, and extreme hypofractionation with 30-36.25 Gy in 5 fractions every other day with VMAT and IGRT Clarity.

The clarity system due to intrafraction monitoring can improve accuracy through the application of in-treatment motion correction. In case of low and intermediate favorable risk, Cyberknife system that provides non-isocentric non-coplanar arcs, can produce the most compliant isodoses and can use fiducial markers to verify the target position and real-time monitoring during the delivery.

In breast cancer, we used moderate hypofractionation with 50 Gy doses in 20 fractions in patients < 70 years; 42.56 Gy in 16 fractions in patients > 70 years; 28.5 Gy in 5 fractions once a week in patients > 80 years.

We used a single fraction (8 Gy) or 20 Gy in 5 fractions for palliative radiotherapy to treat bone metastasis.

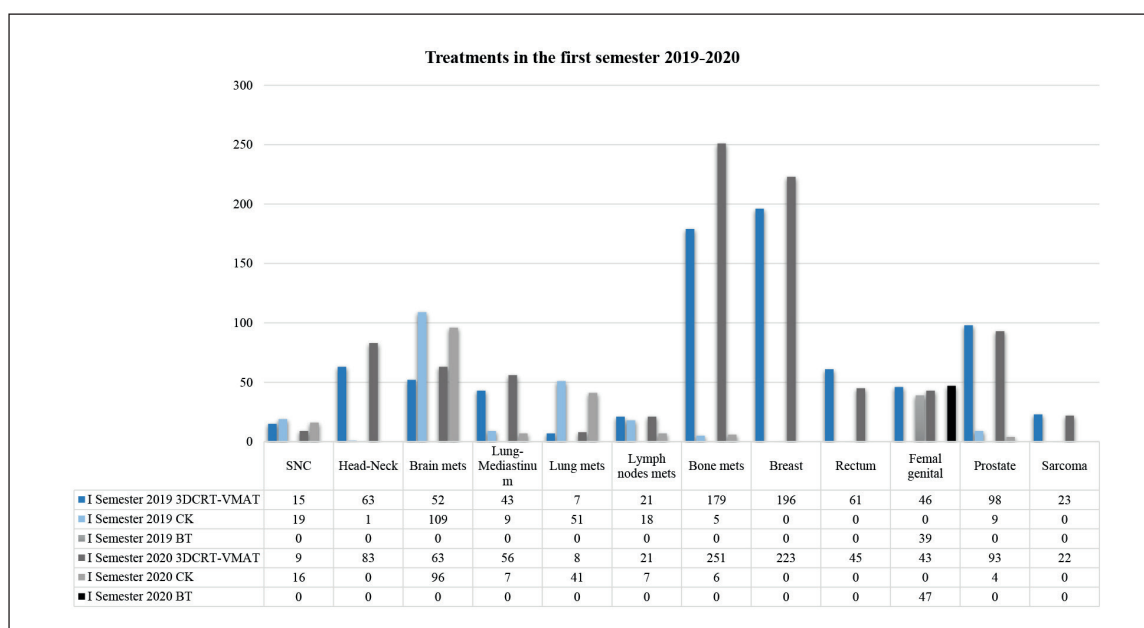
In brain metastases, up to a number of 4, Stereotactic RadioSurgery (SRS) were preferred, with a dose of 15 Gy for lesion > 3 cm < 4 cm, 18 Gy for lesion > 2 cm < 3 cm, 21 Gy for lesion < 2 cm; 24 Gy for lesion < 2 cm according to RTOG 9508<sup>31</sup>. For patients with 4-9 brain metastases the standard of care remains WBRT, but in cases where the lesions' size were small, we used SRS or SRT.

About the use of telemedicine, during the COVID-19 outbreak, the first clinical evaluation was guaranteed for all patients. Hence, multidisciplinary evaluations have been discussed in a teleconference.

All the clinical activities, including CT-simulation, were re-scheduled in order to reduce the risk of contagion for both patients and staff. During phase 1 of emergency, medical doctor, medical physicists and administrative staff, had to work divided in two shifts with rotations assignments and all activities that did not require presence *in situ* (as telephone calls with patients and planning for medical physics) were carried out *via* telemedicine. Staff meetings were not performed anymore and staff workstations were placed in different areas, allowing social distancing. The adequate interval time between CT-simulation and start of the radiation therapy was guaranteed with no further delay or extended radiotherapy interruption. As a result of our strategies, there was no reduction in terms of number of patients treated during the COVID-19 outbreak, but there was a reduction in treatment waiting list. Comparing radiation therapy treatments performed in the first semester of 2019 vs. 2020 were recorded 1121 and 1206 treatments, respectively.

Figure 1 demonstrates the number of treatments delivered in the first semester of two years (2019 and 2020) divided according to the pathology. Hypofractionated regimens and collaboration with Ascalesi Hospital in Naples allow the treatment of a greater number of patients with an increased number of breast cancer and bone metastasis treated in 2020 compared to 2019.

In general, treatments including neoadjuvant hormonal therapy have been postponed, whereas

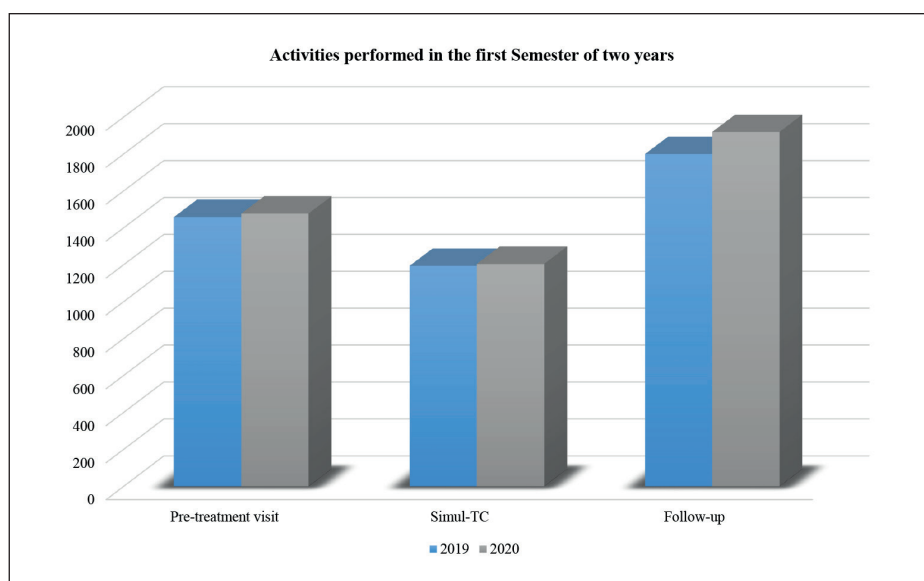


**Figure 1.** Number of patients treated with brachytherapy (BT), cyberknife (CK), three-dimensional conformal radiation therapy (3DCRT) and volumetric modulated arc therapy (VMAT) in the first semester of 2019 and 2020.

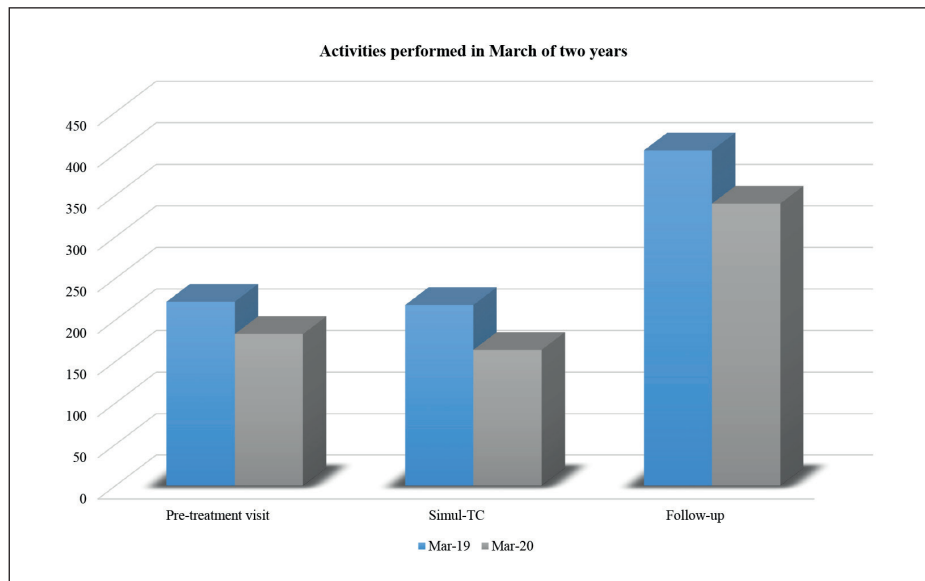
radiation therapy was ensured for patients with on-site cancer and for candidates for adjuvant or concomitant radiation therapy.

Figures 2 and 3 compare the activities carried out in the first six months of 2019 and 2020 and in March 2019 and 2020. As observed in Figure 2, there was a slight reduction of pre-treatment visits in the first semester of 2020 compared to 2019.

This was due to the postponement of radiotherapy access for patients eligible to neoadjuvant systemic treatment. Instead, thanks to the collaboration with Ascalesi Hospital, each non-postponable patient candidate to radiation treatment had been treated. Figure 3 shows as radiation oncologists, using telemedicine (telephone calls, app and emails), carried out about 340 follow-up visits in March 2020.



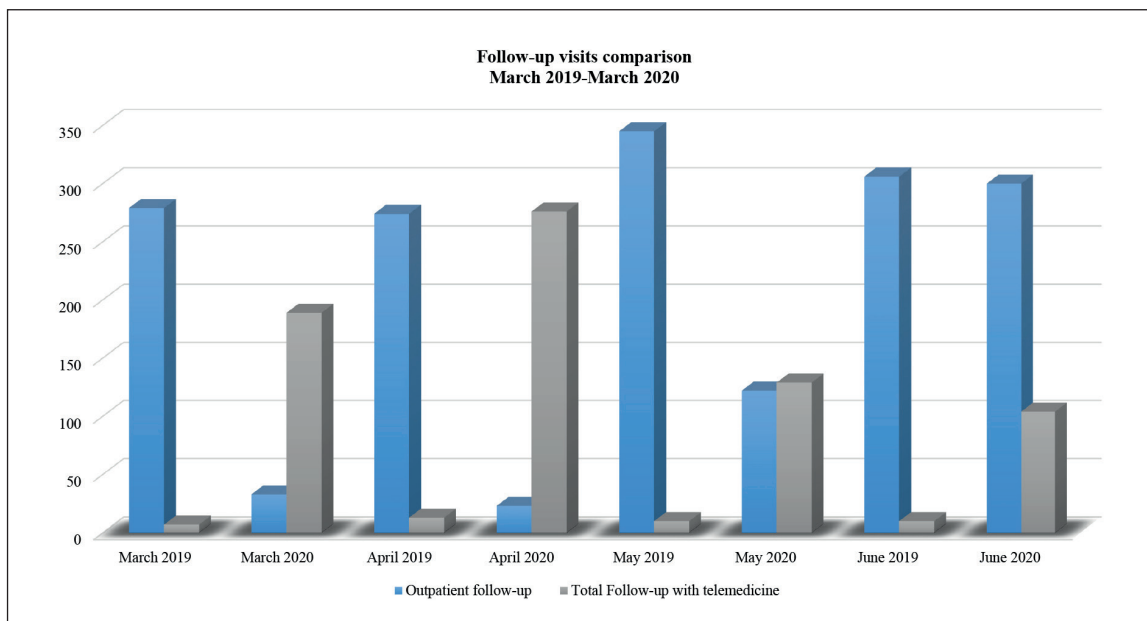
**Figure 2.** Number of activities of pre-treatment visit, simul-TC and follow-up performed in the first semester of 2019 and 2020.



**Figure 3.** Number of activities pre-treatment visit, simul-TC and follow-up performed in March 2019 and 2020.

Figure 4 compares the follow-up modalities in March 2019 and March 2020. In the first week of March 2020, 33 outpatient visits were performed; then, after government lockdown law, every patient was asked to share diagnostic tests with the radiation oncologists, with telemedicine. The majority of patients with prostate cancer were performed by our PRT-App (ProstateRadioTherapy-App), which was used as routine clinical practice for sev-

eral years. The app collects biochemical control, genitourinary and gastrointestinal toxicity, sexual function and quality of life questionnaire score that prostate cancer patients entered into the database. Thanks to the app, the staff is able to follow more than 100 patients, and during the COVID-19 emergency, it has proved to be an important tool for the management of prostate cancer patients. Therefore, from an analysis of the follow-up data, in March



**Figure 4.** Types of follow-up carried out from March to June 2020 compared same period of 2019.

2019, there were 279 accesses in the department compared to 286 follow-ups carried out (98%), while in March 2020, the accesses were 33 compared to a total 222 follow-up (15%). These data show that the use of telemedicine applied in 85% of cases has allowed a drastic decrease in patient access in the facility.

Of note, some patients were unable to perform clinical exams because of the Covid-19 emergency. As a consequence, it was recorded a reduction of about 16% of total follow-up visits in March 2020 compared to March 2019 (Figure 4). The priority use of telemedicine has been confirmed even during April for 92% of follow-up, compared with 4.5% in 2019. Of course, in May and June the percentage of accesses in the department for follow-up visits increased again, but a fair share of telemedicine checks has been preserved. In the so-called “phase 2” that started at the end of the lockdown, the medical staff was scheduled into two 8-hour working shift, with approximately 3 hours used for telemedicine activities; in this way, all activities had been guaranteed for 12 hours a day in relation to the social distancing.

### Conclusions and Future Perspectives

The COVID-19 outbreak had a significant impact on cancer treatments and overall health care. Radiation therapy is a life-saving treatment and must be guaranteed to all patients with cancer for whom it is indicated<sup>32-34</sup>.

Certainly, prioritizing radiotherapy treatments and postponing non-essential procedures and/or visits is crucial for any radiation oncologist to deal with the COVID-19 pandemic.

In the radiotherapy departments, there is a turnover of patients from different territorial areas, which increases the risk of infection between patients and health professionals and treatments are delivered in a closed environment.

The indication for hypofractionated treatment is a recommendation to be adopted in emergency health conditions for many cancers, including prostate cancer, breast cancer, bone metastasis and brain metastasis. Telemedicine is an essential tool among patient evaluation equipment, both in the first collegial clinical evaluation and in follow-up visits and, as highlighted in our experience, it represents an excellent tool to reduce the number of accesses to radiotherapy departments. The development of apps dedicated to different

oncological pathologies can make a great contribution to follow up cancer patients and about clinical studies management. Moreover, telemedicine modalities using the evaluation of patients by videoconference can help to safeguard the important relationship doctor-patient, respecting emergency measures. The strategies for risk mitigation have promoted new dimensions of patient care; it is almost certain that many of these adaptations will permanently transform cancer care. The virtual care has become an acceptable alternative to the in-person visits for many patients and providers.

Another aspect to consider is probably the health services value carried out in telemedicine mode. In addition, it will probably be necessary for legislators to evaluate this new approach to patients and adapt health services because regional and national healthcare structures will be pushed in this direction by the management of COVID-19 emergency.

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### Conflict of Interests

The Authors declare that they have no conflict of interests.

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