CHAPTER 3

Radiotherapy challenges in COVID era

Camil Ciprian Mireștean[1,2], Maricel Agop[3], Călin Gheorghe Buzea[4,5], Marius Mihai Cazacu[3], Marius Prelipceanu[6], Roxana Irina Iancu[7,8] and Dragos Teodor Iancu[7,9]

[1]University of Medicine and Pharmacy Craiova, Craiova, Romania
[2]CF Clinical Hospital, Iasi, Romania
[3]Department of Physics, Gheorghe Asachi Technical University of Iasi, Iasi, Romania
[4]National Institute of Research and Development for Technical Physics, Iasi, Romania
[5]Emergency Clinical Hospital "Prof. Dr. Nicolae Oblu", Iasi, Romania
[6]Department of Computers, Electronics and Automation, Stefan cel Mare University of Suceava, Suceava, Romania
[7]"Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[8]"St. Spiridon" Clinical Emergency Hospital, Iaşi, Romania
[9]Regional Institute of Oncology, Iasi, Romania

3.1 Introduction

The pandemic caused by the new coronavirus (SARS-CoV-2) associated with a disease named COVID-19 by the World Health Organization (WHO) that began in late 2019 in Wuhan city (the residence of Hubei province in China) has become a global public health problem. Only 2 months later, the new virus affected most countries of the world; Italy became the epicenter of the pandemic outbreak in Europe, followed soon by Spain, France, the United Kingdom, but also the United States of America and Brazil, where a large number of cases and deaths were reported. In less than a month, Russia and Latin America, were affected, the consequence being an overload of health systems, especially intensive care units (ICU). Considered a category of patients at high risk of developing severe forms of the disease, cancer patients can develop a severe form of the disease, complicated by acute respiratory distress syndrome (ARDS) that requires mechanical ventilation.

The emergence in almost all countries with a large number of cancer patients affected by the new coronavirus SARS-CoV-2 and the subsequent coronavirus disease 2019 (COVID-19), generated a pandemic that affected the delivery of curative and palliative treatments. The introduction of the multidisciplinary concept of tumor board has led to an integrated approach for oncological disease, in the context of increasing diagnostic and therapeutic resources. Radiation therapy, as a locoregional treatment, is part of the multimodal treatment for approximately 70% of cancer patients, of which 45% are treatments with curative intent. Reduced death rates and increased life expectancy associated with most oncological diseases are the result of the implementation of a set of evidence-based measures for the treatment of asthma. Determining the timing,

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dose, and therapeutic sequence is also essential in the case of radiotherapy. Historically, the standard fractionation (dose fractions 1.8–2 Gy/day) has been accepted as ideal and has been adopted as a therapeutic standard in guidelines in most countries. However, the development of the linear quadratic model and the understanding of radiobiological mechanisms provided theoretical support for the clinical application of "altered fractionation regimens" in order to improve the therapeutic ratio. Hypofractionated radiotherapy gains, in pandemic settings, a new reason for being included in the general regulations of social distancing and limiting the patient's visits in the radiotherapy department.

Radiotherapy, as a treatment included in the multidisciplinary management of cancer for both curative and palliative purposes, is also affected by the COVID-19 pandemic. In this particular context for a treatment that can only be delivered in a hospital, it is necessary to establish regulations that allow limiting the risk of contact with COVID-19 disease both by patients and by the staff of the radiotherapy department. Another challenge is the triage of patients in order to ensure the continuity of treatment in cases where a postponement or omission of radiotherapy significantly increases the risk of recurrence or progression of the disease. COVID-19-positive or -suspected patients are a special category for which the decision to postpone treatment should be made based on the particularities of tumor biology and the radiobiological effect of a gap in radiation fractions delivery. In the case of locally advanced lung cancer, moderate hypofractionation may be used in combination with sequential chemotherapy and patients should benefit from multimodal treatment. Hypofractionated radiotherapy is the preferred option for two types of cancers with increased incidence worldwide (breast and prostate). Similar to each other from a radiobiological point of view, this is a strong argument for implementation as a standard of hypofractionated radiotherapy in a pandemic scenario for breast and prostate cancers. For low-risk cases eligible for hormone, active surveillance, and postponement of radiation therapy for up to 6 months is an option. Taking account the limitation of the number of beds in clinical departments and in ICU, palliative treatments are not considered a priority, the recommendation being to deliver the treatment in oral drugs form at home, in order to reduce patients contact with medical staff. Emergencies, including spinal cord compressions, tumor bleeding, brain metastases not responsive to corticosteroid treatment, should be considered a priority but the palliative treatment should be limited from one single fraction to a maximum five fractions for spinal cord compression and whole brain radiotherapy. Radiotherapy for brain metastases does not bring a benefit in terms of overall survival (OS) for patients with life expectancy of days or weeks and Dexamethasone treatment is the correct choice in this situation. In all settings, the approach of radiotherapy treatment must be adapted for both scenarios of an outbreak pandemic, when general measures of social distancing and protection with specific equipment of patients and radiotherapy staff are a priority, but also for a long period of coexistence with the virus in possible new "pandemic waves." In this context, radiotherapy centers must be prepared for an emergency situation with limited resources and staff, but also for a new long-term strategy.

Practical recommendations regarding the management of radiotherapy departments in COVID-19 pandemic outbreaks were made by experts from the pandemic epicenters in Wuhan (China) and the Lombardy region of northern Italy, in order to share the experience of the most affected worldwide "Red Zones." The recommendations are a basic guide including important aspects of ensuring the continuity of radiotherapy treatments for cancer patients, a category at high risk for developing severe forms of disease. The protection of the radiotherapy team members and the provision of a priority treatment according to the correct evaluation of the risk/benefit ratio as well as the main concepts related to the use of hypofractionated radiotherapy regimens and the concepts of delay the radiotherapy palliative and curative treatments are discussed. An approach based on level 3 protective equipment used in Wuhan radiotherapy center for contact with COVID-19-positive or -suspected patients can be adopted as a standard considering the final ratio of 0% contamination among the center's staff at the end of pandemic outbreak.

Coronaviruses are pathogens that cause animal and human viral infections. At the end of 2019, a new coronavirus was identified, being associated with cases of pneumonia in Wuhan, a city of Hubei Province in China. The increase in the number of cases resulted in an epidemic throughout China, followed by an increasing number of cases in other countries around the world. In February 2020, the WHO designated COVID-19 disease, the name being the association of the class of virus that produces it (an enveloped RNA betacoronavirus2) and 2019, the year in which the first cases were identified. A particularity of this disease is severe acute respiratory syndrome called SARS-CoV-2 which is associated with the severity of the disease. Soon, Europe became the most affected continent. At the end of February and in the first weeks of March 2020 an explosion of cases was identified in Lombardy, a region of northern Italy. Pope Giovanni XXIII Bergamo Hospital became the European epicenter of the fight against COVID-19. From February to April 2020, Spain, the United Kingdom, and France report worrying deaths on the European continent, but the same phenomenon is found in the United States of America. Social distancing measures have been imposed in most states to flatten the severe case curve, with most health systems becoming overworked and caught unprepared due to the large number of patients requiring admission to ICU and needing mechanical ventilation (Buoro et al., 2020; Sohrabi et al., 2020; World Health Organization, 2020; Zheng, 2020).

With the onset of serious cases and deaths, a pattern of patients with the potential to develop severe forms has been identified. Thus elderly patients or those with chronic cardiovascular, respiratory, and metabolic diseases have the highest death and ARDS rates.

The treatment of oncological diseases in this situation is difficult, considering the risks of death caused by cancer and due to the complications of oncological treatments versus death or serious complications associated with SARS-CoV-2 infection. Also hypotheses about the high death rate in immune-suppressed patients associated with COVID-19 justify the high rate of cancer patients developing severe ARDS forms. One unsolved problem for cancer patients is the timing or delay of surgery or other medical procedures including chemotherapy and radiation therapy, especially for cancers with healing potential, for which delaying the intervention may affect the disease prognostic. In these cases there are dilemmas in the therapeutic approach for patients who have not contacted COVID-19 and have curable cancers that require timely implementation of surgery, chemotherapy, or radiation therapy. In these cases oncological treatment exposes them to the risk of contracting COVID-19. Thus the risk of disease and the potential for serious evolution with SARS-CoV-2 may outweigh the benefits of cancer treatment (Dai et al., 2020; Sidaway, 2020; Yu, Ouyang, Chua, & Xie, 2020; Zheng, 2020; World Health Organization, 2020). Multiple reasons may limit patient access to radiotherapy in these situations, especially in countries with limited resources in terms of the number of linear accelerators or cobalt machines. A major challenge is the possibility of providing separation of epidemiological circuits for COVID-19 positive patients, the possibility of adequate protection for staff and patients in radiotherapy departments but also the transport of patients over long distances for those who live far away from radiotherapy department. Detailed aspects regarding the epidemiological triage and the organization of a radiotherapy department in the context of the COVID-19 pandemic are not the subject of the current article, the recommendations obtained from the experience of some centers that were confronted with pandemic outbreaks in the vicinity being summarized in several general ideas. Also, the prioritization of irradiation treatments according to each oncological disease individual risk of recurrence/mortality, must take account the risk of contact COVID-19 disease but also of developing a severe ARDS with possible risk of death.

Another reality in the current epidemiological context is represented by the cancelation of some treatments or the delay of the surgical procedures in some hospitals. One of the reasons is the need to maintain reserves of hospital beds, especially in ICU for patients with severe SARS-CoV-2 ARDS. The nonurgent surgical procedures for oncological disease lead to the occupation of a bed and mechanical ventilators in ICU. Also, the impossibility of providing protection to patients and staff in some units is another cause of treatments delayed.

It is initially thought that approximately 1%–2% of all SARS-CoV-2 infections occur in cancer patients, but data on factors associated with the severity of the disease in cancer patients are extremely limited and more clinical trials are needed. Initial data from Wuhan, China are optimistic compared to Lombardy, Italy, where 8% of patients admitted to the ICU for COVID-19 are reported as having active cancers or a history of malignancy, about 20% of deaths in Italy are reported as active cancer patients (De Felice, Polimeni, & Tombolini, 2020; Sidaway, 2020; World Health Organization, 2020).

A group of radiotherapy departments in Northern Italy that are located inside or very close to the "Red Zone" have transmitted their own experience of being the first European radiotherapy centers that treated patients during a state of emergency generated by the pandemic outbreak. The premise from which it started was that the continuity of radiotherapy services must exist in order to provide the necessary treatment for cancer patients. A priority in the recommendations is to ensure patient triage at the hospital level in order to avoid the exposure of the radiotherapy staff, thus risking the closure of a department and/or the accidental contamination of cancer patients from a possible COVID-19-positive staff member. Taking into account the incubation period which can reach up to 14 days and the fact that patients may be asymptomatic virus carriers, the teams recommend the implementation of measures such as the use of a hydroalcoholic solution for disinfecting the hands at the entrance to the radiotherapy center and wearing surgical masks according to WHO recommendations. In cases where the patients being treated present respiratory symptoms the use of sterile overalls and FFP2 masks is mandatory. Regarding the management of suspected or positive COVID-19 patients, recommendations include continuing treatment if the patient has a cough, fever, or dyspnea due to other preexisting diseases but the patient will continue treatment wearing a protective mask. COVID-19-positive patients did not start the treatment but for symptomatic ones, COVID-19 tested, it is preferred to wait and stop the treatment until a negative result for COVID-19 is proven. The team also recommends stopping treatment for COVID-19-positive patients, even if they are asymptomatic. Treatment should be continued with caution if the patient is declared cured, but precautions are required depending on his clinical condition. If it is still decided to treat positive COVID-19 patients, they should be treated at the end of the daily schedule and previously suspected patients or those awaiting a test result should be treated. Subsequent intensive desinfection is required for the waiting rooms, treatment bunker, and all devices including Linac, treatment table, and contention devices.

Staff protection is a priority both for maintaining the continuity of the department and for not transforming the radiotherapy technicians into sources of COVID-19 infection due to their close contact with treated patients. For this purpose, it is necessary to change the management of cases to avoid direct contact of the team members; the communication will be made mostly by electronic devices (phone, internet), and group meetings such as for multidisciplinary teams should be converted into online sessions. In the context of the lack of qualified personnel and of the technical difficulties that require a special training that involves the administration of radiotherapy by modern techniques with complex linear accelerators, the staff COVID-19 illness may have serious negative consequences. The separation of the treatment teams, so that one team does not come into contact with the other, the evaluation of the availability of the retired staff members, and the collaboration with other centers are part of the continuity assurance strategies. Where COVID-19 occurs in a department involving one or more staff members, the collaboration with other centers in the region ensures the continuity of the treatment in the cases that do not allow the interruptions of the radiotherapy administration for radiobiological and rapid proliferation of disease reasons.

Perhaps the most difficult mission is to reduce patient access to treatment facilities without affecting their prognosis and disease progression. The last few years have provided indisputable evidence of the use of hypofractionated regimens, especially in the case of slow-growing tumors, breast cancer, and prostate cancer, that have already benefited from solid scientific evidence in this regard. The use of hypofractionated regimens is recommended when possible in this epidemiological context. Periodic posttreatment evaluation should be limited to telephone or video calls and, if strictly necessary, evaluation by the closest department to the patient's home will be recommended to avoid long-distance travel. Palliative treatments with radiotherapy can be delayed if the control of symptoms can be obtained by drug treatment and the use of short irradiation palliative protocols even with a single fraction is indicated during this pandemic outbreak period. Also in the case of nonurgent radiotherapy treatments for patients in whom the timing of radiotherapy does not severely affect the prognosis, a treatment delay is recommended. Also mentioned should be adjuvant radiotherapy for breast cancer patients with a favorable biology or even definitive radiotherapy for prostate cancer patients included in low risk disease categories. In this case the best choice is the hormonal treatment delivered until an epidemiologically safe start of the radiotherapy. A last recommendation of the team from the northern region of Italy is represented by the administration of radiotherapy for benign and functional diseases that are not considered a priority (Filippi, Russi, Magrini, & Corvò, 2020; World Health Organization, 2020).

Useful information and recommendations regarding the management of oncological treatments are provided by Cheng Chen and collaborators who treated 153 patients at Zhongnan Hospital, Wuhan, from January 28, 2020 to March 10, 2020 without becoming contaminated with COVID-19. An experience of a radiotherapy stuff having negative SARS-Cov-2 real-time polymerase chain reaction tests or by chemoiluminescenta immunoassay IgM and IgG tests for SARS-Cov-2 can be a reference along with the experience of the teams from the "Red Zone" in northern Italy. The first preventive attitude in this center was based on informing patients about the risk of infection, preventive behavior regarding the risk of infection and scheduling telephone treatment in order to reduce congestion in waiting rooms and to ensure social distancing. In this case, a triage based on history and symptoms in the "isolation zone" outside the radiotherapy center was used. Also, all staff and patients benefited from daily temperature checking with a digital thermoscanner. In addition to a complete level 2 safety equipment dressed by staff members, all keyboards of phones and control units were disinfected at least three times a day. An adequate ventilation system is necessary for avoiding aerosol contamination. Staff members in contact with positive or possibly contaminated patients were equipped with complete level 3 protection equipment including N95 masks and eye shield protection.

The patients' approach was different depending on the presence or absence of COVID-19 infection and the presence of symptoms with no confirmed infection. Depending on these criteria, three patient categories were identified. Different hours were chosen for treatment administration, decontamination followed each patient of the treatment table, the liniar accelerator, the contentions systems, and the route of the patient traveled in the radiotherapy department. Hand hygiene was mandatory for patients and staff according to the WHO recommended protocol (20 seconds), the alternative being the use of sanitizers containing 60%–95% alcohol. The face mask was also used by all patients during their presence in the radiotherapy center. During irradiation, patients who required the use of a thermoplastic mask used a face mask during treatment but a window was cut out of the thermoplastic material to avoid breathing difficulties. All patients were evaluated regarding the presence of COVID-19 symptoms for 14 days from the last presence in the radiotherapy center in order to detect a possible COVID-19 infection. During the presence in the waiting room which was reduced to a minimum time the distance between patients of at least 1.5 m was maintained. For surfaces desinfection, the Wuhan team recommends 75% alcohol solutions for control interfaces surfaces and the treatment machine and table mass with all contentions systems. UV irradiation is recommended for air sterilization and ensuring a minimum of six air exchange cycles in any room into which entered a patient contaminated with COVID-19. Chlorine-based detergent was used for daily disinfection of the department's floor and walls (Wu et al., 2020).

These recommendations are based on experience in the management of cancer patients in radiotherapy departments at the peak of the pandemic outbreaks in the most affected regions of Italy and China. The use of level 3 protective equipment in case of contact with positive or possibly contaminated COVID-19 patients has been shown to be effective, noting the absence of positive COVID-19 cases in all 35 evaluated team members. Also the use of air disinfection with UV radiation and the use of air exchanges provided by the ventilation systems of the department can contribute to the reduction of aerosol transmission risk for patients and for staff members who use masks with a lower level of protection than N95 type masks. Prioritizing treatment according to the risk of recurrence of the disease and assessing in each case the risk–benefit balance is a decision of the clinician but must be based on recommendations specific to each neoplastic type and stage offered by professional societies. For the future, in the context of the forecasts of "coexistence with the virus," a development of the telemedicine system is needed to avoid unnecessary follow-up visits in the department. Hypofractionated radiotherapy could be implemented on a large scale using modern techniques that reduce the risks of late toxicity related with higher doses per fraction. By implementing high epidemiological protection strategies and by informing staff and patients of the risks to contact the COVID-19 disease, the continuity of radiotherapy treatment can be ensured in the case of development of a local or regional pandemic outbreak.

3.2 Clinical, radiobiological, and therapeutic considerations in the decision of palliative whole brain irradiation in the COVID-19 pandemic outbreak

Among the palliative treatments using radiotherapy, whole brain irradiation (WBRT) has been considered a standard in the treatment of brain metastases since 1954. In the context of the current pandemic caused by the new coronavirus, limiting access to radiotherapy services and technical difficulties created by treating patients with low life expectancy (days or weeks), establishing an algorithm for patient' traige for brain irradiation is a priority. This situation brings into the foreground the establishment of priorities in WBRT treatment. In most radiotherapy departments, it is recommended to avoid and postpone palliative radiotherapy if possible and provide to patients an option based on drug treatment, preferably at home, in order to reduce the risk of COVID-19 disease contamination during the visit to the palliative medicine or radiotherapy department. The unpredictable evolution of the COVID-19 pandemic with possible "waves" creates the need for measures to reduce the spread of infection among patients and among department staff. There is also a need for planning to create the ability to deliver and continue essential treatments, even in the conditions of limited technical and human resources available (Borasio, Gamondi, Obrist, & Jox, 2020; Ali, 2020).

The basic treatment with a total dose of 20 Gy/5 fractions is the most feasible option considering the possible limitation of the treatment resources and the need to protect the department staff and cancer patients from a possible COVID-19 infection. In the case of metastases with driver mutations that respond to molecular treatment, delaying radiotherapy as long as there is local control under treatment with tyrosine kinase inhibitors (TKI) or other active oncological drugs that cross the blood—brain barrier may be an option. A dose escalation or stereotactic radiotherapy (SRT) should be reserved for oligometastatic disease and only if there is clearly a benefit that outweighs the risk of overloading the department's resources. Given the risks of prolonging treatment and increasing the number of patient visits in the radiotherapy department, the SIB technique must be chosen because it does not have the consequence of increasing the number of treatment fractions. For patients with a life expectancy of days or months, radiation therapy should be omitted in this epidemiological context and replaced with dexamethasone and best supportive care options. The use of prognostic estimation models can help the clinician in the decision and the Karnofsky performance score is one of the most suggested tools for this purpose. Brain metastases are the most common brain tumors in adults, being diagnosed in 20%–40% of patients with advanced cancers. Among the most common cancers that metastasize to the brain we mention lung cancer, breast, malignant melanoma, and clear renal cell carcinoma. For patients with symptomatic brain metastases, corticosteroids are the preferred drug treatment but in the case of severe symptoms or when associated with significant vasogenic edema and *midline*-shift (MLS) or associated with the brain herniation, a neurosurgical approach is essential. The first-line treatment is neurosurgical in the case of bulky, unique metastases, but resection can also be considered for cytoreduction or decompression purposes. If neurosurgery is not applicable, corticosteroid treatment and radiation therapy should be a preferred option. Radiotherapy treatments for brain metastases have evolved from the "German Helmet" technique to state-of-the-art image guided radiotherapy (IGRT) and evolved later to the use of boost for dose escalation to target volumes of metastases or to the technique with "hippocampal sparing." SRT requires rigorous treatment planning, advanced technical resources, and qualified human resources, taking into account the risks posed by the administration of high doses per fraction that can cause irreversible damage to healthy brain tissue with possible fatal consequences for the patient if the spatial accuracy of dose delivery is not ensured. In the context of limited resources due to the COVID-19 pandemic outbreak, the decision to offer a treatment with maximum potential benefit on the oncological disease symptoms must raise the risk of COVID-19 contamination of this group of patients considered at high risk to develop a severe form of this new infectious disease. Treatments that may be complicated by the need for intensive inpatient care (ICU), which in this context may be difficult to access, should also be avoided. One of the controversies is related to the benefits of WBRT for patients with poor prognosis.

Initially, stereotactic radiosurgery (SRS) was used for a limited number of lesions (1–3) but later this method was tested in clinical trials for irradiation of much larger number of lesions (up to 10), Yamamoto and colleagues recommend this approach in carefully selected cases. The use of SRS, whether or not followed by WBRT, was evaluated for 1–4 lesions and did not bring a benefit in OS, but the addition of WBRT to a total dose of 30 Gy in 10 fractions improved local control. Chang et al. mentioned cognitive impairment for the arm of a study in which SRT was associated with WBRT, the risk being higher 4 months after treatment. Deterioration in life quality (QoL) and asthenia, are also mentioned by Soffietti et al., if WBRT is associated to the radiosurgery. The authors note that adjuvant WBRT after surgery or SRT can lead to impaired QoL and propose careful monitoring by MRI imaging as an alternative option. A randomized multicenter trial proposed by the Radiation Therapy Oncology Group (RTOG) included two arms of patients who received WBRT + SRT boost or only WBRT. Patients who received both treatments had improved Karnofsky Performance Status (KPS) 6 months after treatment, but OS was improved only for patients with one unresectable metastasis. One of the most conclusive evidence regarding the benefit of SRT association after WBRT is provided by the results of a study published 11 years ago in which Kondzikola et al. demonstrated a benefit in OS of 3.5 months in the group in which SRT was administered after WBRT, results that led to the premature closure of the study (Andrews et al., 2004; Chang et al., 2009; Kondziolka, Patel, Lunsford, Kassam, & Flickinger, 1999; Nishioka, Abo, & Aoyama, 2009; Soffietti, Kocher, & Abacioglu, 2013).

Yerramilli and colleagues propose a simple decision algorithm in the event of a pandemic outbreak for the triage and prioritization of patients with brain metastases. The decision tree is based on the clinical benefit and the possibility of radiotherapy to relieve symptoms. For life expectancy limited to days or weeks, the authors recommend best supportive care approach. The highest numbers of brain metastases are associated with advanced lung cancer. Improving survival due to advances in cancer treatments has inevitably led to an increase in the percentage of patients who will develop brain metastases during the course of the disease. Mulvenna and colleagues demonstrate an improvement in intracranial control without an increase in OS and a significant improvement in QoL for patients with poor prognosis. Thus this phase III study (QUARTZ) supports the omission of WBRT in this category of patients. For the WBRT arm, median survival was 49 days versus 51 days in the arm that received only symptomatic treatment. However, the QUARTZ study has some limitations among which are that it is lacking in phase II studies and the patient's or clinician's preferences for one of the two treatment options. Also, the study provided valid results only for brain metastases with a lung primary tumor origin. It is also necessary to evaluate the prognosis as accurately as possible, and for this purpose the recursive partitioning analysis (RPA) algorithm was used. RPA and DS-GPA (Diagnosis Specific Graded Prognosis), are models based on clinical data such as age, presence of extracranial disease, Karnofsky' performance index, number of metastases and primary tumor evolution. The Quartz trial demonstrated the futility of WBRT in the RPA 3 prognostic class but the results should be viewed with caution. In general, Karnofsky performance index of at least 70, age under 60 years, and a well-controlled primary tumor are factors associated with a favorable prognosis (Agarwal et al., 2018; Mulvenna et al., 2016; Yerramilli et al., 2020).

In the case of surgically treated brain metastases from lung cancer that received adjuvant WBRT, Enders et al. identified in 114 cases of nonsmall cell carcinoma (NSCLC) complete resection and a preoperative KPS of $>80\%$ as factors being associated with a favorable prognosis. The presence of infratentorial metastases is associated with an unfavorable prognosis. Rades-SCLC and DS-GPA scores can most accurately predict the survival of patients with brain metastasis with small cell lung carcinoma (SCLC) with a cut-off value of 6 months (Filippi, Russi, Magrini, & Corvò, 2020; Wu, Zheng, & Liu, 2020).

A systematic review and metaanalysis that included 4373 NSCLC cases in 18 studies demonstrated the prognostic value of the EGFR mutation in the evolution of brain metastases and treatment with TKI. Thus the EGFR mutation is an important predictive factor in OS that must be taken into account in assessing the timing of radiotherapy (Borasio, Gamondi, Obrist, & Jox, 2020).

For ALK-positive lung cancer patients, survival is considerably longer after WBRT than for those with KRAS, EGFR, or wild-type mutations. Thus a study that included 172 cases of genotyped brain metastases revealed a median OS of 13.6 months for patients with EGFR mutations. Patients with ALK mutations had a median OS of 26.3, and those with KRAS mutations only 5.7 months. The lowest survivals were recorded for "wild-type" cases, only 5.5 months. The data analysis also showed improved survival for patients who received target therapy and WBRT.

In the case of breast cancer, the molecular subtypes have also a prognostic value. Thus brain metastases from triple-negative breast cancer (TNBC) treated with WBRT have the lowest mean OS, of about 2 months, when the ECOG performance status is 3 or 4, the median survival of these patients is about a month by Frisk et al. on a group of 241 breast cancer patients treated with WBRT (20 Gy in 5 fractions) (Ali, 2020; Nishioka et al., 2009).

Although before the age of molecular biology the data showed that, even if metastases have the same starting point but with different histologies, the prognosis is different. Radiotherapy regimens do not take into account the variation radiosensitivity of different histological types and due to different molecular subtypes for the same histological type. Thus analyzing the data obtained in a single institution from 1292 patients, the authors identified different prognostic factors regarding the evolution of brain metastases treated with WBRT. These prognostic factors may be particular depending on the primary tumor (age for lung cancer) but also the histological type. The response to corticosteroids and serum lactate dehydrogenases but also the interval between the diagnosis of the primary tumor and the appearance of brain metastases are general prognostic factors valid for brain metastases with different histological origins (Chang et al., 2009).

A series of retrospective studies have demonstrated different results in terms of local control after WBRT depending on histology, thus proving that radioresistance determined by the histological type of the primary tumor plays an important role in the treatment response. Most radioresistant brain metastases are clear cell kidney cancer and malignant melanoma. A model developed and validated on different histological types based on the radiosensitivity index (RSI) is considered directly proportional to radioresistance. Ahmen and collaborators tried to validate this model on brain metastases. Data extracted from 277 brain metastases were analyzed, identifying the molecular profile and subsequently calculating RSI based on the validated algorithm for other types of metastatic lesions, considering that a high value of RSI is associated with radioresistance. The median RSI was 0.46 and the values did not indicate significant differences between different histological types. Even if they did not notice large variations in radiosensitivity between histological types, all brain metastases proved to be radioresistant and there were large variations of RSI between metastases with the same histological type. Starting from the radioresistance evidence of most brain metastases, the authors recommend the use of SRS to adapt the treatment to the concept of radioresistance, highlighting the potential benefit of higher doses per fraction (Andrews et al., 2004; Kondziolka, Patel, Lunsford, Kassam, & Flickinger, 1999; Soffietti, Kocher, & Abacioglu, 2013).

The hypothesis of long-term survival for patients with brain metastases with driver mutations such as EGFR, ALK, HER2neu, BRAF in lung cancer, breast cancer, and melanoma has brought to the fore the problem of cognitive impairment due to high-dose irradiation of the hippocampus. The phase II study RTOG 0933 aims to explore the hypothesis that sparing of the hippocampus in WBRT can reduce radiation-induced nervous system toxicity, thus reducing cognitive decline. The hypothesis from which it starts is that of stem cells in the region of the hippocampus whose destruction is associated with impaired cognitive function. Using modern technologies of intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) or helical tomotherapy, treatment plans can be obtained in order to reduce the dose received by the hippocampus region. This strategy is useful for patients with potential for long-term survival and low risk of late decline in cognitive function which can severely affect quality of life. The hypothesis of long-term survival for patients with brain metastases with driver mutations such as EGFR, ALK, HER2neu, BRAF in lung cancer, breast cancer, and melanoma has brought attention to the problem of cognitive impairment due to high-dose irradiation of the hippocampus. The phase II study RTOG 0933 aims to explore the hypothesis that sparing of the hippocampus in WBRT can reduce radiation-induced brain tissue toxicity, thus reducing cognitive decline in this category of patients. The hypothesis is that stem cells in the hippocampus region affected by irradiation are the cause of cognitive function impairment. Using modern technologies of IMRT, VMAT or helical tomotherapy, more conformed treatment plans can be obtained, with reduced dose received by the hippocampus region. This strategy is useful for patients who have potential for long-term survival, patients considered at a high risk of late decline in cognitive function can severely affect quality of life. The evolution of cognitive function after WBRT has a biphasic evolution, the second stage being highlighted with the progress that has prolonged the survival of patients with brain metastases, but generally the signs of decline in cognitive function can be seen 4 months after irradiation (Agarwal et al., 2018; Yerramilli et al., 2020).

IMRT and VMAT radiotherapy techniques have also opened new horizons in terms of simultaneous irradiation with different doses of different volumes. Thus if SRT is not technically available, with the help of these advanced techniques an escalated dose of 6—10 Gy per gross tumor volume (GTV) of metastases can be administered in the case of oligometastatic disease (1—3 lesions). Jiang and colleagues propose an even 50 Gy escalation in 10 fractions on GTV of metastases simultaneously with hippocampal avoidance using the VMAT technique. Ferro et al. demonstrate the feasibility of a treatment plan with irradiation of eight brain metastases using the technique simultaneous integrated boost (SIB)-VMAT. Although technically feasible there is a tendency to increase the number of metastases that can be irradiated by the SIB-IMRT or SIB-VMAT technique, the benefit in OS and local control as well as the effect on quality of life is not yet evaluated (Enders et al., 2016; Mulvenna et al., 2016; Rades, Hansen, Janssen, & Schild, 2019).

In a COVID-19 pandemic outbreak scenario, palliative radiation therapy of symptomatic brain metastases for patients with life expectancy of months or years must remain a priority. The treatment scheme of a 20 Gy in five fractions is the most feasible option considering the possible limitation of the treatment resources and the need to protect staff and patients from a possible COVID-19 infection. In the case of metastases with driver mutations that respond to molecular systemic therapy, delaying radiotherapy as long as can be obtained a local control only with a TKI or other active treatment that cross the blood—brain barrier may be an option. A dose escalation with conventional radiation therapy or with SRT should be reserved for oligometastatic disease and is recommended only if there is clearly benefit that outweighs the risk of overloading the department's resources. Given the risks of prolonging treatment and increasing the number of patient visits, the SIB technique must be chosen because of the advantage so as not to increase the number of fractions. For patients with a life expectancy of days or months, radiotherapy should be omitted in this epidemiological context and replaced with corticoids and best supportive care. The use of prognostic estimation models can help the clinician in the decision and the Karnofsky performance index is a suggestive tool for this purpose.

3.3 New perspectives for hypofractionated radiotherapy in breast cancer—recommendations during the COVID-19 pandemic

In most clinical situations, adherence to the timing of radiation therapy is essential in ensuring control of the cancer disease. Radiation therapy should also be available during the COVID-19 pandemic. Given that radiotherapy resources are not theoretically related to the mandatory need, for each patient, for a bed in the ICU, radiotherapy should be seen as an alternative to surgery in cases where intervention is not possible due to technical reasons or justified by the need of ICU resources. Also, the immunosuppressive effect of radiotherapy is in most cases lower than that of cytotoxic chemotherapy. Based on these premises, the adoption of hypofractionation schemes is now entering a state of accelerated clinical validation with the need to reduce the risk of contamination of patients and staff in radiotherapy departments. Proper adoption of personal protective equipment (PPE) has been shown to allow safety in the activity of the radiotherapy centers even in case of contact with asymptomatic carrier patients of SARS-CoV-2. This attitude is justified by evidence that suboptimal delivery of radiation therapy compromised local control and negatively affects the survival of patients.

Implications of suboptimal administration of adjuvant radiotherapy in breast cancer may result in a doubling of the risk of loco-regional recurrence if adjuvant radiotherapy is delayed by more than 8 weeks. Flores-Balcázar et al. demonstrate, by analyzing a lot of medical data obtained from 1000 patients treated for locally advanced breast cancer, a reduction in disease-specific survival if patients receive adjuvant radiotherapy with a delay of maximum 60 weeks. If the adjuvant treatment protocol includes chemotherapy the results are different. To assess the impact of delayed initiation of adjuvant therapy (chemotherapy and/or radiotherapy) on tumor control and survival of breast cancer patients, Abdel-Rahman analyzed medical data from 3390 breast cancer patients using a treatment delay cutoff value of 6 weeks for comparative evaluation of results. The results showed that a postponement of radiotherapy more than 6 weeks after surgery does not bring a negative effect on survival without recurrence if during this time the patient receives chemotherapy. The negative impact of delaying the start of adjuvant treatment was more associated with patients with negative hormone receptors (Abdel-Rahman, 2018; Flores-Balcázar, Flores-Luna, Villarreal-Garza, Mota-García, & Bargalló-Rocha, 2018; Nagar & Formenti, 2020).

To evaluate the effect of delayed adjuvant radiotherapy in women with breast cancer surgically treated by partial mastectomy, 34 publications were included in a meta-analysis that included clinical data from 79,616 patients. With a relative risk of local recurrence per month of delay of 1.08 and with a relative risk of death per month of delay of 0.99 the study concluded that delay in postlumpectomy radiotherapy is a factor that increases the risk of local recurrence (Gupta, King, Korzeniowski, Wallace, & Mackillop, 2016).

The American Society of Radiation Oncology has proposed a guide that recommends the use of hypofractionated radiotherapy regimens for all cancer patients regardless of their age, whether they have received chemotherapy or not. The decision of the expert task force was supported by the results of trials that assessed the feasibility of implementing hypofractionation regimes in clinical practice. Theoretically, it is considered that hypofractionated regimens are likely to produce more severe late effects, starting from the calculation of the dose equivalent to the dose of 50 Gy/25 fractions (5 weeks) considered standard regimen. Evidence from the historical START-A and START-B trials proves similar rates of late toxicity (subcutaneous fibrosis and breast hardness). Although different fractionation schemes were used including 41.6 Gy, 39 Gy, 42.56 Gy with fractions of 3.2 Gy, 3 Gy, and 2.66 Gy/fraction, respectively, the authors did not report high rates of toxicity in the group that benefited from hypofractionation compared to the control group treated with standard 50 Gy/25 fractions. In the case of early breast cancer, Curigliano and colleagues recommend postponing of radiotherapy start by a maximum of 3 months for groups of high-risk patients and by a maximum of 6 months for low-risk patients. There is no evidence that for these groups of patients the concept of starting "as soon as possible" after surgery brings a benefit in survival, the recommendations of maximum 3 and 6 months respectively of radiation treatment delay having as reasoning the concept of balance benefit risk. Moderate hypofraction protocol (40 Gy/15 fraction) can be adopted and should be used for all cases (whole breast or chest wall) even if irradiation of the lymph nodes is required. In the context created by the COVID-19 pandemic, the authors recommend the use of moderate hypofractionation even after reconstructive surgery. Even if we do not have yet 5 years mature follow-up for cases included in the FAST Forward trial, in order to reduce the risk by limiting the presence of patients in radiotherapy departments, the accelerated implementation of this protocol proposed can be considered. In conclusion, the delivery of treatment for patients with breast cancer that has no indication of nodal irradiation and does not require a "boost" can be performed in a single week, in five fractions. The total recommended dose may be 28 Gy or 30 Gy in a weekly fraction or 26 Gy/5 fractions daily, for 1 week according to data from clinical trials FAST and Fast Forward. In order to reduce the number of patients' visits in the radiotherapy department, it is recommended to avoid using the boost with a cutoff age of 40 years, above this age the irradiation boost being recommended only for patients with risk factors for a local relapse. The benefit of the boost is considered an improved local control by 10% at 72 months in patients below 40 years. In case of relapse, hypofraction is recommended also. Such a case is considered for patients with positive margins where surgical reintervention is not possible, or patients aged <60 years with high grade tumors, after irradiation of the entire breast and also for patients with invasive disease. In the case of "low-risk" patients, the authors propose the use of partial accelerated breast irradiation (APBI) condensing the "Florence" protocol (30 Gy/5 fractions over 2 weeks) which can be delivered in a single week. Omission of RT may be considered in elderly patients with higher risk of developing severe forms of COVID-19 disease. However, this decision must also take into account the risk of individual recurrence, but the authors recommend reconsidering the therapeutic attitude every 4 weeks, weighing the benefit of omitting RT with the risk of contact COVID-19 disease. Low-risk ductal carcinoma in situ (DCIS) may also be a candidate for omission of RT (Nahum, 2015; Omlin et al., 2006; Smith et al., 2018; Yarnold et al., 2005; Youssef & Stanford, 2018).

International efforts to formulate therapeutic decision recommendations for radiotherapy in various clinical settings of breast cancers have resulted in a guide written by 17 experts from radiotherapy university centers around the world. The five formulated recommendations bring in addition to what we mentioned before, the recommendation to omit RT for patients with invasive breast cancer over 65 years or even younger but who have significant comorbidities, specifying the limit of up to 30 mm clear margins, and for luminal subtypes A and B which are proposed for hormone therapy. If there is an indication for boost administration and the administration is chosen sequentially, the authors propose the scheme 12 Gy/4 fraction over 4 days. As a criterion for omitting nodal irradiation, the guide proposes postmenopausal women who require irradiation of the entire breast and who have benefited from sentinel node or surgery for T1 tumors, Lumial A and B subtypes, G1-G2 tumors with 1–2 macro-metastases (Bloomfield, 2017; Coles, Aristei, & Bliss, 2020; Murray Brunt et al., 2018; Smith, Bellon, & Blitzblau, 2018).

The theoretical premises that supported the theory that fewer fractions with high dose per fraction increase the risk of late toxicity are based on the approximation of toxicity risk by calculating the biologically equivalent dose (BED) considering α/β values of 3 Gy for late effects and α/β of 10 Gy for acute responding tissues. Thus for standard fractionation (50 Gy/25 fractions) BED for late effects was estimated at 83.3 Gy and in hypofractionation schemes BED values for late responding tissues were framed between 78–83 Gy. Other late toxicities associated with hypofractionation regimens in clinical trials were brachial plexopathy, breast hardening, and cosmetic changes. However, most authors do not report higher rates of late toxicity when using regimens with >2 Gy/fraction compared to conventional regimens (50 Gy/25 fractions). Haviland reports an increased rate of late effects, especially shoulder stiffness in the branch protocol that received a 13 fractions with 3.3 Gy per fraction. In the therapeutic decision that includes radiotherapy, the general principles regarding the epidemiologic risk must be taken into account. Breast cancer patients should be approached starting from premises related to the risk group in the context of the current crisis caused by COVID-19. The first group includes newly diagnosed or suspected breast cancer patients, followed by a second level risk group, that of patients receiving active treatment, and a third group includes patients in follow-up for breast cancers or who receive only hormone therapy as adjuvant monotherapy. In these three categories, the risk is modulated by additional factors, including cardiovascular and respiratory diseases, smoking, and sex. In this context, the general recommendations for the prevention of infection of patients with patients with SARS-CoV-2 should be applied in the case of the decision of radiotherapy treatment in patients with breast cancer, but these measures are not the subject of current work. According to the risk level assessed from the available data, Braunstein et al. considers as level I priority inflammatory breast cancer, node positivity after neo-adjuvant chemotherapy, recur recurrently, more than

4 positive lymph nodes (N2) TNBC with positive nodes and extensive lymphovascular invasion (LVI). Estrogen receptor positive with 1–3 positive nodes (N1a), TNBC without nodal disease, a pathological complete response after NAC and LVI are considered factors that place patients in a level II priority category for radiation treatment. DCIS and estrogen receptor positive early stage breast cancer are considered low priority cases. The implementation of hypofractionate regimes under pandemic pressure must take into account the need to limit the risks of toxicity. Most breast cancer hypofractionation clinical trials accept the use of IMRT and VMAT inverse planning techniques as an alternative to the 3D-CRT technique. Data regarding the late toxicities when using the VMAT technique are relatively limited due to the novelty of the method. Even if in terms of dose conformity and homogeneity as well as organs at risk (OARs) protection there is a demonstrated superiority over the 3D-conformal technique (3D-CRT), the increased values of V5 (volume in an organ receiving a dose higher or equal to 5 Gy) may expose the lung to an increased risk of radiation pneumonitis, and the risk of second radio-induced cancer is still poorly quantified for long-term breast cancer survivors. However, the major advantage of the possibility of irradiating different volumes with different doses per fraction, with consequences in reducing an additional number of fractions is of major interest in the context of measures to reduce any factor causing patient exposure to possible COVID-19 contamination (Haviland et al., 2018)(Liang et al., 2020).

Recent radiobiology studies have reevaluated the α/β value, the (Liang et al., 2020) values being considered framed between 3–4 Gy for both tumoricidal and toxic effects in the case of breast tissue, these studies are used as pleading for the potential radiobiological advantage of hypofractionated treatments. On a batch of 44 patients using scales and questionnaires that assessed acute toxicity as well as quality of life assessment (QOL) questionnaires, Pall et al. demonstrated the clinical viability with lower rate of acute toxicities and satisfactory results in terms of QOL 6 months after VMAT technique treatment. The implementation of moderate hypofractionation must take into account certain dosimetry recommendations validated in clinical trials. Thus for ipsi-lateral lung a V10Gy <20% and for contralateral lung a V5Gy <10% it is recommended in the case of a 30 Gy/5 fractions protocol, where V_x is the volume in the anatomical structure that receives a dose at least equal to xGy. For a 26 Gy in five fractions regimen a V8Gy <15% is recommended for the lungs, considering <17% as an acceptable value A V7Gy < 5% and V1.5 Gy < 30% is recommended for the heart. In case of moderate hypofractionation (42.16 Gy/16 fractions), V18Gy <35% for lungs is recommended but a value less than 40% is acceptable. For the heart it is preferred to obtain a mean dose of maximum 3 Gy but 5 Gy dose is also accepted. If a left breast is treated, a V22.5 Gy <10% is accepted and for right breast radiotherapy a V22.5 Gy <2% is recommended for the heart. It is important to keep in mind that the dosimetry constraints used in most departments are based on data published mainly in the guidelines formulated by Emami et al. and in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations, which propose the dose—volume parameters evaluated for standard fractionation protocols. If these guidelines are considered, the iso-effect formulas derived from the quadratic linear model and the calculation of EQD2 for a dose delivered in 2 Gy/fraction biologically equivalent, a total dose in another fractionation regimen, can be done by allocating the α/β value of 4 Gy.

$$SF(D) = e^{-\alpha \cdot D - \beta \cdot D2} \tag{3.1}$$

where SF is cell surviving fraction, D is total dose, α and β are parameters of cell radiosensitivity, and α/β is index of fractionation cell sensitivity.

$$(\mathrm{BED}) = n \cdot d\left(1 + \frac{d}{\alpha/\beta}\right) \tag{3.2}$$

where N is number of fractions, and D is dose per fractions (Table 3.1).

$$(\mathrm{EQD2}) = D\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)} \tag{3.3}$$

Contouring the heart cavities and coronary arteries according to the guidelines, evaluating the dose received by the contralateral breast and also by the remaining volume at risk (RVR) is necessary especially in case of using inverse planning techniques (IMRT and VMAT). The unpredictable doses distribution can lead to the irradiation of anatomical structures not considered as OARs in the 3D-CRT era. The biological effect of small doses scattered in large volumes of tissue is still less known. Lisbon and collaborators mention for dose of <100 mGy multiple changes that are involved in the short- and long-term pathophysiological changes with less known consequences. The induction of some genes, the triggering of mechanisms of activation of proteins, bystander effect, and hypersensitivity are just some of these effects (Bentzen et al., 2010; Braunstein et al., 2020; Emami, Lyman, & Brown, 1991;

Table 3.1 Biologically equivalent dose and EQD2 for hypofractionation protocols considering $\alpha/\beta = 4$ (breast tissue).

Fractionation scheme	30 Gy/5fr	26 Gy/5fr	40 Gy/15fr	42.4 Gy/16	42.56/16	48 Gy/16fr (SIB)	48 Gy/15 (SIB)
Biologically equivalent dose (Gy)	75	59.8	66.6	70.67	70.86	84	86.4
EQD2 (Gy)	50	39.87	44.4	47.11	47.24	56	57.6

SIM, simultaneous integrated boost.

Journy et al., 2019; Lisbona et al., 2010; Pallath et al., 2019; Yarnold et al., 2005; Youssef & Stanford, 2018).

Hypofractionated radiotherapy is one of the current indications mentioned in breast cancer management recommendations during the COVID-19 pandemic. The effect will be an accelerated adoption of these protocols under the pressure of increased risk generated by the exposure of patients and radiotherapy departments' staff. Although there is currently controversy over the risk of increased late toxicity, the benefit of reducing the number of visits at risk of contact COVID-19 disease is a priority. A "double check" system using dosimetry recommendations from clinical trials and the isoequivalence formula for the calculation of EQD2 for late toxicities risk assessment is a safer protocol for prevention of these toxicities. According to current data α/β value of 4 Gy seems to correspond to the radiosensitivity of the mammary gland tissue. The implementation of IMRT/VMAT techniques should take into account the effect of low doses with unknown effect regarding lung gas exchange in the case of COVID-19 infection during treatment. It is worth noting the advantage of integrated boost delivery, an obvious benefit of these modern irradiation techniques in the current epidemiological context.

3.4 Prostate cancer radiotherapy in the COVID-19 pandemic outbreak

The concept of RADS—"remote visits, avoid, defer, and shorten or reduce radiation therapy"—was created to provide a special set of recommendations for prostate cancer during the COVID-19 pandemic. The recommendations took into account the scenario that the pandemic will have several waves over several months, even up to a year or more, and will put health systems under a prolonged stress that will deflect in all sectors, including health services provided to cancer patients.

The main purpose of the concept refers to the minimization of the direct patient−physician contact by implementing telemedicine services. Avoiding radiation therapy can be done when the evidence is questionable and the "active surveillance" option becomes the best choice in this context.

If there is an indication and postponement of treatment, it is recommended to shorten the treatment so as to avoid exposing the patient and staff of the radiotherapy department to the risk of COVID-19 disease, but the treatment schedule must be adapted to each case so as not to jeopardize the prognosis, taking into account the progression risk of oncological disease (Moujaess, Kourie, & Ghosn, 2020).

With the introduction of radiotherapy techniques based on better target volume coverage and superior protection of radiosensitive organs, the concept of IGRT has become a standard, requiring a reproducibility of the treatment plans, in order to avoid geographic-miss errors in radiation dose delivery. The introduction of multiple imaging techniques that allow the delineation of target volumes with high accuracy, including multiparametric magnetic resonance imaging (MRI), but also hybrid imaging like positron emission tomography (PET-CT) that uses specific radiotracers, creating the possibility of identifying hypoxic subvolumes in order to escalate the radiation doses, and have as a consequence a more precise delimitation of target volumes with a supposed benefit in the therapeutic ratio. The introduction of fiducial markers in the prostate volume increased the accuracy of prostate target volume tracking during each treatment session in order to reduce the margins of uncertainties between clinical target volume (CTV) and planning target volume (PTV). Another technique, the insertion of aerogel spacers between the rectum and the prostate has the same final goal, the dose escalation in the prostate target volume and reduction of the dose received by the rectum. Being considered the highest organ at risk (OAR), the rectum is sensitive to high doses of irradiation, which are correlated with the risk of rectal bleedings. All these "state-of-the-art" innovations and developments in diagnostics and in radiotherapy planning increase the number of patient visits and the need to use special protective conditions, the need for anesthesia, and the use of a higher security level PPE—fiducial markers insertion for example. The risk of exposing the patient and staff to SARS-CoV-2 contamination is also increased by the number of treatment fractions, generally between 37 and 39 for a curative treatment for locally advanced prostate cancer in standard fractionation regimen. A steep dose gradient, produced by intensity modulated radiation therapy (IMRT) and VMAT radiotherapy techniques, may lead to an underdosage in the target volumes or worse, a delivery of the prescribed dose in healthy tissue regions. For doses escalated up to 81 Gy as are those proposed by Zelefsky et al. and Huang et al., IGRT is essential to prevent the risk of late rectal toxicity (Huang et al., 2019; Zelefsky et al., 2006).

The approach to the urgency of initiating radiotherapy treatment in prostate cancer must take into account the biology of the tumor, which is different from other forms of cancer. Thus the recommendation is to postpone by 1–6 months the consultation and visits to the radiotherapy department, if possible depending on the stage and degree of risk of the disease in each case, but the final decision belongs to the clinician. In the case of very low and low risk cases, treatment can be avoided by choosing active surveillance or it can be postponed until the infection risk caused by the pandemic will be considered minimal. Another particularity of prostate cancer is that even in intermediate and high-risk cases, androgen deprivation therapy (ADT) can be used to delay treatment in a possible pandemic outbreak scenario until 4–6 months. Given these data in patients positive for the SARS-CoV-2 virus, the attitude of delaying treatment until the cure of COVID-19 is the most appropriate attitude. In the case of an emergency or a rapidly progressive disease, the clinician may consider the advantage of radiotherapy versus the risk of COVID-19 disease complications. There is a consensus among experts on shortening treatment to a minimum number of presentations tailored to deliver safe treatment for each patient. Regarding pelvic prophylactic irradiation (WPRT), the recommendation to avoid is based on unpublished data from the RTOG 9413 trial that reports elevated rates of grade IV lymphopenia. These data are also supported by the study of Chad et al. which reports a correlation between pelvic nodal irradiation (PNI) and radiation-related lymphopenia (RRL). The National Comprehensive Cancer Network (NCCN) also recommends the use if possible of ultrahypofractionated regimens, and radiotherapy to be delivered in 5–7 fractions.

Based on the RADS framework, Zaorsky and collaborators proposed a more detailed set of recommendations that complement the NCCN recommendations for the management of prostate cancer by radiotherapy during the COVID-19 crisis. Recommendations started from the premises that it is possible that following the scenario according to which the pandemic will last several months with evolution in waves, the radiotherapy resources could be limited by possible quarantine/illness of the staff or even the closure of radiotherapy services. This effect can be generated by stress induced by several mechanisms on health services. Regarding remote visits, the recommendations are in line with the general trend to avoid as much as possible the presence of the patient in the radiotherapy department, the evaluation of prostate specific antigen (PSA) being recommended to be postponed ≥ 3 months. Patients with intermediate or high risk after prostatectomy or with oligometastatic disease (low metastatic volume), need a more vigilant attitude based on periodic consultations through telemedicine services. The authors also indicate the reasons why the benefits and risks of initiate radiotherapy for the intermediate-high risk prostate cancers should be reevaluated in cases where ADT is not recommended (doubling PSA ≤ 3 months, unacceptable toxicities, patient' refusal). If in the "battle" adjuvant versus early salvage a winner was not yet decided, most studies considering both feasible and equivalent options, the COVID-19 pandemic gave a clear cause for early salvage, the beginning of the salvage radiotherapy treatment being recommended at PSA levels <0.3 ng/mL (Falchook & Chen, 2015; Schad, Dutta, Wijesooriya, & Showalter, 2019; Vogel & Kerstin, 2019; Zaorsky, Yu, & McBride, 2020; Care of Prostate Cancer Patients During the COVID-19 Pandemic).

Regarding the possibilities of reducing the treatment time, the authors encourage the shortest fractionation regimen, mentioning as in the NCCN recommendations 5–7 fractions for localized prostate cancer with intermediate and higher risk, the preferred option being in this case stereotactic body radiation therapy (SBRT) or ultrahypofractionation. The use of cone beam computer tomography (CBCT) and/or the use of fiducial markers for imaging guided dose delivery are also mentioned. If IGRT cannot be provided according to the recommendation, a hypofractionation regimen (for example 60 Gy/20fractions), and a moderate hypofractionation (52.5 Gy/20fractions) in the post-prostatectomy settings is agreed as an alternative. It is also noteworthy that the recommendation to use the conformal 3D technique (3D-CRT) and the suggestion to reduce the CTV-PTV margins to 7 mm, as well as the possibility to omit rectal spacers and fiducial markers if "extreme or ultra" fractionation regimes are not chosen. CT simulation and the use of IGRT based on the use of kilovoltage on-board imaging (kV-OBI) is considered a minimum standard in quality assurance (QA) of prostate radiotherapy; any other techniques to improve dose delivery ballistics including the use of prostate MRI become optional in this epidemiological context. All of these procedures increase the patient's time spent in the department, and the number of patient contacts with radiotherapy staff and are considered to bring an additional risk of contact with COVID-19 disease. In the case of low-volume oligometastatic disease in which the new trend is the curative treatment option, SBRT or a dose of 36 Gy/6 fractions over 6 weeks regimen are preferred. With a late side effect rate of approximately 5% of grade 3 or worse according to the Common Terminology Criteria for Adverse Events (CTCAE), Parker et al. demonstrates that this scheme used in the STAMPEDE phase-3 trial is a safe option.

If there is a recommendation for palliative radiotherapy, the authors do not make special mentions, the concept of trying to control the symptoms by systemic treatment administered at home remains valid. If there is an indication with obvious benefit of radiotherapy, it recommends for spinal cord compression a dose of 8 Gy in a single fraction according to the SCORAD III trial. Even if the criteria of noninferiority to the 40 Gy/20fraction treatment regimen were not met, acceptable results recommend this treatment option by significantly limiting the risk of patient exposure to COVID-19 infection. Another aspect is that of the possibility of retreatment by SBRT technique considering the spinal cord tolerance to reirradiation after an 8 Gy single fraction first in the first treatment sequence. For uncontrollable bleeding, the use of a 20 Gy/5 fraction scheme is an alternative to the Quad Shot protocol, consisting of 3.7 Gy/4 fractions twice daily, with the recommendation to repeat every 3 weeks in three sequences. These schemes were adopted taking into account the severe digestive toxicity associated with the 10 Gy in one single fraction scheme, proposed by the RTOG 8502 trial which led to the premature close of the study.

The authors conclude the recommendations with a schematic representation from which we note that in the case of an ultrahypofractionated regime it is necessary to respect the dosimetric constraints based on radiobiological adapted calculations to a dose/fraction between 7.25 and 8 Gy. To avoid frequent entries in the treatment room of the staff to ensure the position corrections in order to assure a quality in the delivery of treatment based on image guidance and thus limit the time spent by the radiotherapy technician in the proximity of the patient, a protocol for filling the bladder to the level of comfortable fullness for the patient and emptying the rectum is necessary. It is recommended that the patient understand the importance of following this protocol and all details related to these rules can be provided by telephone or in print detailed paper. To avoid late rectal toxicity a V40Gy < 1cc, a V36 < 2cc and a V24 <50% of rectal circumference are recommended. In the case of the bladder of a V40 <2cc, V37 <10cc, and V18.1 <40%, maximum accepted doses are considered. To preserve the sexual function of bulbs a mean dose <16 Gy and a D2% <28.5 Gy are recommended. V_x is the volume of OAR that receives at least xGy and D_x% is the minimum dose that receives at least x% of the volume of OAR. If a fractionation protocol "twice a week," "every other day," or "once a week" is preferred, a radiobiological correction introducing the time factor is necessary for a precise equivalent dose to the dose to be delivered in a standard fractionation (1.8−2 Gy/fraction) (EQD2) calculation. If another hypofractionation scheme used and validated in the clinical trials PROFIT, RTOG 0415, Dutch HYPRO, CHHiP, and Italian Trail is chosen, it is recommended to respect the dose constraints proposed by the authors of each trial to avoid difficulties in equivalence and comparative evaluation (Hoskin et al., 2019; Care of Prostate Cancer Patients During the COVID-19 Pandemic; Rades et al., 2018; Spanos et al., 1994; Spyropoulou & Kardamakis, 2012; Yerramilli et al., 2020; Yu et al., 2016; Zaorsky et al., 2020).

In the current epidemiological context, RADS measures include several management directions in radiotherapy services, some general to all types of cancers, in terms of reducing visits and the physical presence of the patient in the radiotherapy department, avoiding or postponing treatment for patients at low risk of recurrence of the disease and ensuring regulations to limit to the minimum the patient's visits in the department. Hypofractionation as the preferred treatment method is also a recommendation in accordance with all malignant disease management guidelines in radiotherapy departments. Notable are the recommendation of ultrahypofractionation and SBRT for localized disease, the option for "early salvage" versus "adjuvant" and especially the recommendation to give up "state-of-the-art" investigations and treatments such as MRI and PET-CT or daily CBCT and fiducial markers, even the delivery of radiotherapy through the old 3D-CRT technique, both in case of palliative or with curative intent definitive irradiation, with a minimum of IGRT if the risk of contamination and the adverse effects on the patient of a possible COVID-19 disease outweigh the benefits. The results published in the metaanalysis of Ting Yu and collaborators regarding the benefit of IMRT versus 3D-CRT technique demonstrated from data from 924 patients that 3D-CRT technique is not inferior in terms of OS although the IMRT technique is superior in the reduction of gastrointestinal (GI) toxicities, so any reasoning to reduce the risk of exposing the patient to a potentially fatal COVID-19 infection is warranted (Care of Prostate Cancer Patients During the COVID-19 Pandemic; Spyropoulou & Kardamakis, 2012; Yu et al., 2016; Zaorsky et al., 2020).

3.5 Radiation therapy for locally advanced NSCLC during COVID-19 pandemic—challenges and risks beyond clinical guidelines

Since the beginning of the global pandemic caused by SARS-CoV-2 coronavirus infection, which started in Wuhan (Hubei province, China) in early December 2019, the disease named COVID-19 by the WHO has become a public health problem. The rapid spread of the infection has caused concern in the scientific community, with unprecedented efforts being made to speed up the development of a treatment and a possible vaccine. The severity of possible respiratory complications, the increased mortality rate compared with seasonal flu and the highest potential for contagion have generated an unprecedented series of social distancing measures worldwide declaring a state of health emergency. In his work "COVID-19 is not just a flu. Learn from Italy and act now," Andrea De Giorgio mentions the need not to underestimate the small "opponents" who cannot be seen. With an incubation period ranging in most cases between 3.6 and 6.4 days but reaching up to 14 days, the disease that in the most severe forms is associated with respiratory failure, ARDS has a potential increased severity in the elderly with comorbidities. Italy became the epicenter of the pandemic and soon countries like France, Spain, and the United Kingdom reported worrying figures of cases and deaths. The United States reported a record number of cases (over 1 million cases and over 67,000 deaths) as of May 3, 2020 (De Giorgio, 2020; de la Viña, Ortega Granados, & Alcázar-Navarrete, 2020; https://www.worldometers.info/coronavirus/country/us/).

In many cases, patients with respiratory diseases, including lung cancer patients, have a potentially severe evolution in the case of coinfection with SARS-CoV-2. It is estimated that cancer patients are three times more likely than the general population to develop forms of the disease that require hospitalization in ICUs and have a higher risk of death. The pathological mechanisms are not elucidated, but the effect of oncological therapies is added to the decrease of the immune response of the patient, with a potential synergic effect. In lung cancers, the coexistence of cardiovascular and respiratory comorbidities, such as *chronic obstructive pulmonary disease* (COPD) or pulmonary fibrosis, increases the risk of death and the difficulties of managing mechanical ventilation in the case of severe ARDS. According to data obtained from China and Italy, countries where the incidence of COVID-19 was very high, a large proportion of patients were asymptomatic but of those diagnosed positive with SARS-CoV-2, 14%–24% developed pneumonia that required hospitalization or administration of oxygen. The rate of patients who developed ARDS was 5%, with higher death rates being reported in patients aged $>$70 years in Italy (Sohrabi et al., 2020; World Health Organization, 2020).

Given these data, most specialists consider as mandatory the need for oncological guidelines that include both clinical aspects and patient management recommendations during the crisis created by the COVID-19 pandemic, as well as recommendations for the protection of staff and patients in cancer centers to become a priority. In order not to exceed the limited capacity supported by the health services, social distancing strategies and rigorous rules for the prevention of infections in order to "flatten" the SARS-CoV-2 infection curve are necessary. At the level of units that offer health services, strategies have been developed to reduce visits and implement telemedicine services, and limit the length of stay of patients in waiting rooms. The use of minimum level-2 protection equipment in departments and level-3 protection equipment in the case of contact with positive or possibly infected COVID-19 patients as well as periodic surface sanitation are also necessary to prevent infection of patients and staff.

Strategies to reduce the severity of the pandemic must be rigorously applied in oncology and radiotherapy services, given the possibility that these patients may develop severe forms of disease with the potential risk of death. Cases of locally advanced, nonmetastaticNSCLC, according to the guidelines, treated with definitive radiochemotherapy treatment are included in a very high risk category, especially in the case of concurrent SARS-CoV-2 infection. Under these conditions, it is necessary for the radiation oncologist to carefully evaluate whether the application of the guidelines cannot be detrimental for patient prognosis, increasing the risk of mortality by associating lung cancer with COVID-19 disease.

The more recent approach to the problem of radiotherapy services during the pandemic brings into question a problem initially neglected, in the first stage of the pandemic, that of management in a second stage of "virus cohabitation" that could last for long periods. There are two potential scenarios that can occur, as mentioned by a group of experts who issued an ESTRO-ASTRO consensus statement regarding the management of NSCLC in radiotherapy services. The first scenario refers to the moment of limiting the risk of pandemic outbreaks in which the priority is to ensure as far as possible the oncological treatment but without neglecting all the steps to prevent a pandemic outbreak. At this stage, any effort to limit the spread of the virus is promoted, including limiting patients' long-distance travel. This decision must take into account the urgency of the cancer treatment and the individual patient's risk of contracting the disease, given the increased potential for it to develop a severe ARDS during treatment.

The second scenario is that in which mode the radiotherapy center is affected by a pandemic outbreak that could have as a consequence the limitation of radiotherapy resources by possible illness or quarantine of the staff or technical problems. At this stage, the priority would be to manage resources in such a way as to ensure the continuity of treatment centers and provide alternatives to patients, so as not to jeopardize the chance of cure and ensure that the risk that patient and staff contact with COVID-19 disease is limited as much as possible. At this stage, the choice of cases for which the treatment will not be postponed must include as decisive factors the risk of compromising the chance of cure, the high tumor proliferation rate being a factor in favor of prioritizing the treatment (Guckenberger et al., 2020; Passaro et al., 2020; Troost, Nestle, Putora, & Bussink, 2020).

Locally advanced NSCLC represents around 30% of all newly diagnosed lung cancers. Unresectable bulky N2 disease is a therapeutic challenge, due to the essential role of systemic treatment with loco-regional radiotherapy, for obtaining a tumor control and a long overall survival (OS). Concomitant radiochemotherapy is the standard treatment, and recently immunotherapy is taking place in the therapeutic spectra with the potential to modulate a long-term therapeutic response. With the introduction of Durvalumab immunotherapy in maintenance after a favorable response from curative chemoradiotherapy, the risk of pneumonitis also increased, requiring a reassessment of currently accepted dose−volume constraints in order to reduce the risk of this complication. A panel of 32 lung cancer radiotherapy experts proposed conduct in various cases of lung cancer, including a locally advanced NSCLC case scenario. It was considered a threshold of ≥66% for agreement and ≥80% for strong consensus. Regarding the time of onset of radiotherapy treatment a strong consensus was against a delay of 4−6 weeks in this case (Fukui et al., 2020; Troost, Nestle, Putora, & Bussink, 2020).

Regarding the preferred treatment scheme, there were different opinions in choosing the fractionation and the total dose depending on the administration of radiotherapy as a unique method of treatment or in combination with chemotherapy (concomitant or sequential). In the case of using hypofractionation, there was a consensus in the administration of this regimen only in cases where concomitant radiochemotherapy is not chosen, the proposed dose varying between 50−66 Gy delivered in 25−33 fractions. If hypofractionation was chosen, the option was for daily doses between 2.2−2.75 Gy/fraction. Despite most choosing standard treatment (concomitant chemoradiotherapy), one-third of experts are against deescalating the treatment for patients eligible for concurrent radiochemotherapy. Without consensus, the most agreed upon chemotherapy regimen was Carboplatin−Paclitaxel or Carboplatin monotherapy and there is no consensus for combination of target therapies (EGFR or ALK inhibitors) or immunotherapy with chemotherapy. In the case of COVID-19-positive patients, there was a consensus to discontinue and delay treatment if it was not started, and different opinions if SARS-CoV-2 infection occurs after the start of radiotherapy. Factors that influenced the decision to discontinue or continue radiotherapy were considered symptoms associated with COVID-19 or cancer and nearing the end of radiotherapy at the time of COVID-19 infection. In the case of a COVID-19 pandemic outbreak scenario, locally advanced NSCLC with curable potential was considered to be a top priority even in case of treatment resource limitations, moderate hypofractionation (55−60 Gy in 20 fractions being the preferred treatment scheme) (Guckenberger et al., 2020; Troost, Nestle, Putora, & Bussink, 2020).

From the experience of the centers that were in the world's epicenters of the pandemic outbreaks produced by the new coronavirus we can apply measures that have proved useful in the uninterrupted operation of radiotherapy centers in the Lombardy Region of Northern Italy and radiotherapy center in Zhongnan Hospital (Wuhan

City, Hubei Province, China). The authors report overcoming the critical moment of the pandemic and the state of emergency without having any contaminated staff members. We are facing successful "recipes" offered by colleagues from these centers, proving that the application of basic rules in the prevention of infectious diseases based on patient triage, wearing high-level equipment in the vicinity of patients, hand sanitization, and face masks by all the patients. First of all a priority was considered to be the importance of the understanding by each patient of the necessity of social distancing, avoiding the agglomeration of the department by limiting the visits, and compliance with the scheduled treatment hours for each patient, associated with the sanitation measures for all departments and treatment devices. It is essential to consider patients with locally advanced NSCLC as likely to be the highest risk group for severe COVID-19 associated ARDS. We mention smoking, one of the ethological factors of lung cancer. A severity of symptoms 1.4 times higher and a risk of hospitalization in ICU with potential death 2.4 times higher than for a nonsmoker to which is added to the risk of infections caused by bronchiolar inflammation and fibrosis. The detrimental effect restrictive and/or obstructive phenomenon caused by cancer makes a COVID-19 patient with locally advanced NSCLC a candidate for a severe form and at very high risk of death from ARDS requiring mechanical ventilation. The effect of the COVID-19-associated "cytokine storm" is amplified by the proinflammatory potential of curative radiation therapy. The prothrombotic effect of radiotherapy but also the paraneoplastic syndromes, that associate with states of hypercoagulability, partially explain the high death rates associated with COVID-19. Trousseau's syndrome, disseminated intravascular coagulation, and venous thromboembolism are associated with lung cancer, demonstrated by autopsy results for about 50% of patients who die with a history of oncological hypercoagulability disorders (Filippi, Russi, Magrini, & Corvò, 2020; Lee, Lim, & Kim, 2014; Wu, Zheng, & Liu, 2020).

There are no data available on the use of modern radiotherapy techniques such as Intensity Modulated Radiation Therapy (IMRT) and VMAT characterized by a steeper gradient dose with the potential for dose reduction to organs at risk (OARs) during the COVID-19 pandemic. Increasing low doses spread in large volumes of lung parenchyma may increase the risk of radioinduced pneumonitis, with a V5 (volume in the lungs receiving a dose of at least 5 Gy) $>50\%$ being considered a significant predictor of toxicity risk. The risk of long-term inflammation associated with Paclitaxel-based chemotherapy or myelo-suppression secondary to both components of the platinum doublet (Carboplatin—Paclitaxel), recommended by ASTRO-ESTRO experts, cannot be overlooked. A sensitive topic is the use of TKI in combination with radiation therapy in the treatment of cancer, which are associated with short-term respiratory distress. The bilateral appearance of ground-glass opacities observed on CT images associated with TKI treatment may lead to a false positive diagnosis of COVID-19. And in terms of COVID-19 infection in patients treated with TKI inhibitors, data are limited. Leonetti et al. presented two cases of SARS-CoV-2 infection in patients treated with TKI, in both cases being moderate forms of the disease without requiring ICU admission (Leonetti, Facchinetti, Zielli, Brianti, & Tiseo, 2020; Li, Wang, & Tan, 2018; Liu, Zhong, & Cao, 2015).

Mechanical ventilation, performance status (IP) Eastern Cooperative Oncology Group (ECOG) ≥2 and acute respiratory failure are mentioned as factors that associate with an unfavorable prognosis. The use of corticosteroids often used in these patients for the treatment of chemotherapy-induced ARDS may mask the symptoms of a possible SARS-CoV-2 coinfection, increasing the risk of late diagnosis with serious epidemiological consequences. The use of cone beam-CT used daily during the delivery of radiotherapy has proven the ability to identify specific COVID-19 lesions. Suplli et al. presents the experience of the team from Copenhagen University Hospital "Rigshospitalet" in the retrospective identification in CBCT imaging of the specific changes for a patient treated by curative visa radiotherapy for an advanced NSCLC premises. Imaging revealed the presence of specific lesions 2 days before the patient developed specific COVID-19 clinical symptoms. The authors thus recommend careful analysis of daily images obtained from CBCT or kV in order to identify new patchy infiltrates, with the potential to identify the early presence of COVID-19 disease in patients treated with radiotherapy for lung cancer.

Locally advanced NSCLC is considered a priority in treatment even during a COVID-19 pandemic outbreak. The use of competing chemoradiotherapy supported by experts increases the risk of complications that require hospitalization and in the case of a COVID-19 infection creates the premise for an unfavorable evolution. Moderate hypofractionate regimens appear to be a feasible option when choosing sequential induction chemotherapy. Given the very high risk of death in the development of ARDS that requires mechanical ventilation of these patients, the therapeutic decision must take into account all factors that expose the patient to a possible SARS-CoV-2 infection during treatment. The risk of developing ARDS secondary to concomitant treatment, the proinflammatory effect of radiation therapy, the need to use corticosteroids, prothrombotic conditions, smoking as a mediator of inflammation, and the cause of COPD, increase the risk of death and create difficulties in managing mechanical ventilation of these patients. Daily CBCT or kV imaging analysis may be useful in identifying specific lesions prior to symptoms during radiotherapy treatment.

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