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Editorial
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Radiotherapy Management during COVID Pandemic: From Evidence-Based Medicine (EBM) to Emergency-Based Medicine (EMBM)

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Editorial

The outbreak of Coronavirus disease (COVID-SARS 2) in December 2019 has been declared a public health emergency and pandemic by World Health Organization (WHO). Today the pandemic is spread all over the planet, causing major problems for health systems worldwide. Regretfully, the numbers of contagion are constantly evolving on the rise, making it difficult to accurately estimate its real impact in daily life [1]. Furthermore, the time length of the pandemic is unknown and it could still last several months or years. Considering this convulsive situation, a reorganization of the health resources becomes mandatory, on side to avoid excessive exposure to infectious risk; on the other to prevent that life-saving treatments could not correctly perform, including cancer treatment delay. Some modeling studies predict that even a four-week delay of cancer treatment is associated with increased mortality [2]. Another important observation is that from data collected in recent months, many patients arrive at the cancer diagnosis at a more advanced stage of disease compared to the past, mainly because of the fear of infection. It is also increasingly difficult to guarantee surgery in the appropriate time and manner, due to the reorganization of health resources. In fact, many hospitals are currently limited in non-COVID activities and spaces, while intensive care is overloaded by COVID-patients. In the management of the healthcare staff to face the emergency and to increase intensive and sub-intensive care beds, anesthesiologists and especially anesthesia nurses are no longer available for surgery sessions and the scheduling of oncological surgery is delayed. In most countries of the world the situation has apparently improved with the implementation of an extensive vaccination campaign, but, due to the possible mutations of the virus, at the gates of the new winter the current scenario is extremely uncertain. In this complex emergency puzzle, the Radiation Treatment (RT) finds its place with the need to prioritize essential therapies. Approximately 50% of all cancer patients will receive RT during their illness (around 40% with curative aim) and based on the projected cancer distributions in 2025, a 16% expected increase in the number of RT treatment courses was estimated [3]. Unfortunately, RT requires long times between the clinical valuation, the planning and the completion of treatment, with multiple accesses to the Radiation Oncology Department, increasing the risk of contagion. Recently several papers have been published regarding the radiation management of cancer patients during COVID era [4]. During the first wave, with the hypothesis that the problem would last a few months, the most frequently recommended behaviors in RT were:

- Do not treat COVID-positive patients;
- Postpone non-urgent treatments (within 6 months);
- Apply hypo fractionated treatment schedules;
- Modify some therapeutic indications that in the pre-COVID era were considered the standard;
- Omit RT, in more than some clinical situations.

Unfortunately, the trend of the pandemic has made it clear that it is not possible to postpone treatment times excessively in cancer diseases, even with a lower profile of aggression. Furthermore, it must be considered that about 1/3 of COVID-positive patients are currently asymptomatic or oligosymptomatic [5]. After a further 6 months of waiting and the worldwide spread of the pandemic,

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it is necessary to review the whole organization of the therapies and some previously given indications. In the current time, the health system organization should be completely restructured, switching "from Evidence-Based Medicine (EBM) to Emergency-Based Medicine (EMBM)", optimizing the resources. In this perspective, a review of the role of RT in the management of the cancer patient is absolutely mandatory, with emphasis on even stronger customization of each decision for an individual patient, however still in accordance with standard of care guidelines. Some of the measures used in the first wave have been confirmed as valid, others less.

In this enlarged context, the following approaches should be taken into account:

- Consider the possibility of treating COVID-positive patients in selected cases (i.e. little symptomatic or asymptomatic COVID cases, highly symptomatic for cancer, with priority to oncological emergencies like spinal cord compression, mediastinal syndrome, hemorrhages, worsening pain not controlled by drugs etc.);
- Prioritize treatments based on the biological aggressiveness of the cancer (i.e. H&N cancer, anal canal, central nervous system);
- Preferably use hypofractionated schedules and highly favor stereotactic RT treatments when clinically indicated;
- Consider the possibility that, in selected clinical situations, RT with a radical purpose could replace/assist the surgical approach.

In this scenario, a paradigmatic example could be the management of Breast Cancer (BC). It is an extremely heterogeneous disease, which requires careful therapeutic planning to achieve the best possible cure. BC is the oncological condition with the highest incidence in women and also the first cause of cancer death, in which RT halves the overall recurrence rate and reduces mortality by about one-sixth. Various factors influence the therapeutic choices such as age, stage, biology, the presence of other co-morbidities, and, last but not least, the individual predisposition of the adequately informed patient on the benefits and risks of the treatments. Considering the already mentioned contingencies, new issues of growing importance in this emergency situation are the surgical management of BC as much as to find new roles for RT. One of the questions could be: "Having few available resources that need to be maximized, can radiosurgery replace the knife for management of breast cancer in selected cases?" In some situations, RT could also be performed as a real substitute of resection. It would be necessary to clearly define in which cases. The second question concerns the feasibility of the neoadjuvant radiation treatment associated or not with systemic therapy for locally advanced BC, based on clinical and disease characteristics [5], to reach downsizing and down staging, which leads patients to be eligible for lumpectomy. This strategy could improve the results to be pursued in this era, favoring shorter surgical times (day-surgery) and less risk of complications. Even in field of preoperative RT, recently, radiosurgery in early stage and low risk BC is arising [6]. In addition, when shortcomings of anesthesiologic resources endanger timely surgery, neoadjuvant approaches are best suited for bridging the gap. Third point, Intraoperative Radiotherapy (IORT) is a logical approach for reducing or – in low risk situations - even omitting subsequent repeated hospital contacts for adjuvant radiotherapy [7]. In particular IORT with electrons (IOERT) as boost has proven to substantially reduce in-breast failure rates in any risk situation, not least due to suppression of tumor cell repopulation until adjuvant RT might start [8]. This fact could give more space delaying the onset of RT until an epidemiological situation reaches acceptable levels. Finally, extreme hypofractionated schedules could be used in the treatment of early-stage breast cancer. Recently, the phase 3 FAST-Forward study [9], using 26 and 27 Gy in 5 fractions in 1 week, showed the non-inferiority of this approach in terms of local tumor control and confirmed the safety of the treatment. Considering that patients affected by pT1–3/pN0–1/M0 were enrolled and the median age was 61 years, these results suggest that most of the patients with breast cancer could receive this treatment, avoiding longer radiotherapy schedules. In a world where scientific progress made possible to obtain treatment results that were unimaginable up to 20 years ago for the most of cancers, and in this BC is at the top, we cannot witness inert to its regression just for fear. Moreover, professionally and ethically we have clear duties towards our patients: For this reason, it is mandatory to contain the infection spread with the respect of the rules promoted by WHO; on the other hand, we must find quick solutions that can allow the patients to receive adequate care. During the pandemic, making a fair balance of all the factors involved is very hard. However, it must always be kept in mind that COVID as cause of death is by far ruled out by cancer. The technical and technological advances achieved in RT, supported by scientific evidences, but mainly based on results observed in decades of practice, made it possible to modulate and organize treatments in a highly personalized way. If the term "personalized medicine" has conquered the scientific community with increasing interest, it now takes on an even more significant meaning. In fact in this delicate time some of the therapeutic solutions listed above for BC RT might serve as example of personalized medicine and become a therapeutic standard even without long-term hard evidence, due to the emergency condition. The present short editorial would like to provide a concrete idea on BC RT management during COVID-19 pandemic that can be practicable and useful in all RT Cancer Centers of the World, to ensure patients continuity of care, with an impact on local health policies compatible with the current emergency. Combining future worldwide observational data and results will allow us to discover that sometimes we learn much more from the daily experience than what years of study could have suggested us to be "feasible and effective".

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