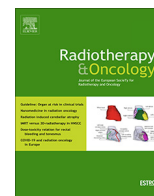




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## COVID-19 Rapid Letter

**Letter to the editor regarding “Lack of supporting data make the risks of a clinical trial of radiation therapy as a treatment for COVID-19 pneumonia unacceptable”<sup>☆</sup>**



## To the Editor

We read with great interest the paper by Kirsch et al. entitled “Lack of supporting data make the risks of a clinical trial of radiation therapy as a treatment for COVID-19 pneumonia unacceptable”. The authors make valid points that merit serious consideration, but in the setting of an ongoing pandemic without effective therapies, the recommendation against carefully designed clinical trials is understandable but not the only valid point of view.

Because of the almost complete lack of pre-existing immunity to COVID-19, the pandemic overcame most of the health systems facing it and causing the rapid saturation of the available intensive care units beds (ICU) in many countries [1]. Early published series show high mortality among patients admitted to the ICU and in older hospitalized patients [2,3]. Almost all of the current therapies in clinical trials other investigators selected because of possible preclinical or clinical efficacy in diseases other than COVID-19 in the hopes something might work [4].

Many of us in the global radiation oncology community independently raised the possibility of using low doses of thoracic radiation therapy based upon historical data suggesting benefit in pneumonia and its ongoing use in the treatment of non-neoplastic disease [5,6]. COVID-mediated hyper-inflammatory response arises typically in the lungs, due to the difficulty of the immune system in eradicating the virus, as it happens in primary hemophagocytic lymphohistiocytosis [7]. Is it possible that older data from the pre-antibiotic era might be worth reviving, given the possibility that a local treatment may work for other types of pneumonia?

The authors minimize the past clinical observations published in well-respected peer-reviewed journals, focusing heavily on cautious interpretations by the authors rather than the data. By today's standards, these papers are Level III evidence, the “weakest form of study design, but they may be the only available or practical information in support of a therapeutic strategy, especially

in the case of rare diseases or *when the evolution of the therapy pre-dates the common use of randomized study designs in medical practice.*” [8].

We agree with the authors that it is essential to conduct rigorous preclinical testing of low dose radiation therapy. We hope they agree that this research as a critical priority given the ongoing pandemic. Most preclinical data for pharmacologic strategies come from non-COVID-19 data. With old but relevant clinical data and research suggesting anti-inflammatory effects of radiation at very low doses that may affect key inflammatory cells involved in the hyper-inflammatory host response to COVID-19 [9], we do not agree that preclinical studies are require for radiation therapy and should be treated differently than the other therapies being tested.

The authors correctly raise concerns about cardiac disease and second malignancy as a late effect of radiation therapy. The very low doses (35–100 cGy) being considered for clinical trials fall in an unknown area for quantifying risk. Assuming whole body radiation exposure risks from atomic bombs or space exploration equate to risk from a single very low dose is a cognitive leap, particularly when the validity of the LNT hypothesis at very low doses is uncertain with modern techniques [10]. With thorough informed consent, it is a reasonable late risk for older patients balanced against a potential reduction in COVID-19 related morbidity or mortality within weeks. If we routinely offer many cancer patients treatment to lower recurrence rates without a survival benefit with a higher risk of late effects, it should be reasonable to offer to patients on protocol.

## References

- [1] Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet* 2020;395:1225–8. [https://doi.org/10.1016/S0140-6736\(20\)30627-9](https://doi.org/10.1016/S0140-6736(20)30627-9).
- [2] Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically ill patients in the Seattle region – case series [published online ahead of print, 2020 Mar 30]. *N Engl J Med* 2020;NEJMoa2004500. doi:10.1056/NEJMoa2004500.
- [3] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area [published online ahead of print, 2020 Apr 22]. *JAMA*. 2020;e206775. doi:10.1001/jama.2020.6775.
- [4] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review [published online ahead of print, 2020 Apr 13]. *JAMA*. 2020;10.1001/jama.2020.6019. doi:10.1001/jama.2020.6019.
- [5] Calabrese EJ, Dhawan G. How radiotherapy was historically used to treat pneumonia: could it be useful today?. *Yale J Biol Med*. 2013;86:555-570. Published 2013 Dec 13.
- [6] Calabrese EJ, Dhawan G, Kapoor R, Kozumbo WJ. Radiotherapy treatment of human inflammatory diseases and conditions: optimal dose. *Hum Exp Toxicol* 2019;38:888–98. <https://doi.org/10.1177/0960327119846925>.
- [7] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19. 102537. <https://doi.org/10.1016/j.autrev.2020.102537>.

<sup>☆</sup> The Editors of the Journal, the Publisher and the European Society for Radiotherapy and Oncology (ESTRO) cannot take responsibility for the statements or opinions expressed by the authors of these articles. Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. For more information see the editorial “Radiotherapy & Oncology during the COVID-19 pandemic”, Vol. 146, 2020.

- [8] Levels of evidence for adult and pediatric cancer treatment studies (PDQ®)-Health Professional Version, accessed May 14, at <https://www.cancer.gov/publications/pdq/levels-evidence/treatment>.
- [9] Arenas M, Sabater S, Hernández V, et al. Anti-inflammatory effects of low-dose radiotherapy. indications, dose, and radiobiological mechanisms involved. *Strahlenther Onkol* 2012;188:975–81. <https://doi.org/10.1007/s00066-012-0170-8>.
- [10] Tharmalingama Sujeenthara, Sreetharanb Shayenthiran, Brooks Antone L, Borehama Douglas R. Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies. *Chem Biol Interact* 2019;301:54–67.

Stefano Maria Magrini <sup>a</sup>  
Matthew S. Katz <sup>b</sup>  
Davide Tomasini <sup>a,\*</sup>  
Giuseppe Sasso <sup>c,d</sup>  
Luca Triggiani <sup>a</sup>  
Michela Buglione di Monale e Bastia <sup>a</sup>  
Luigi Spiazzi <sup>e</sup>

<sup>a</sup> Radiation Oncology Department, ASST Spedali Civili di Brescia - Brescia University, Italy

<sup>b</sup> Department of Radiation Medicine, Lowell General Hospital, Lowell, USA

<sup>c</sup> Radiation Oncology Department, Auckland City Hospital

<sup>d</sup> Faculty of Medical and Health Sciences, University of Auckland, New Zealand

<sup>e</sup> Medical Physics Department, Spedali Civili Hospital, Brescia, Italy

\* Corresponding author at: Radiation Oncology Department, Brescia University, Piazzale Spedali Civili 1, 25123 Brescia, Italy.  
E-mail address: [tomad88@libero.it](mailto:tomad88@libero.it) (D. Tomasini)

Received 19 May 2020

Accepted 20 June 2020

Available online 1 July 2020