

## POINT/COUNTERPOINT

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### Low-dose radiation as a treatment for COVID-19 pneumonia: A threat or real opportunity?

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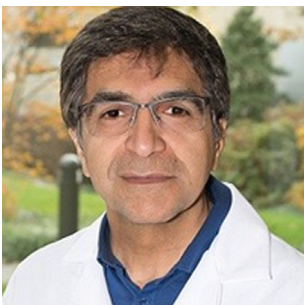
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#### OVERVIEW

Low-dose radiation is known to induce anti-inflammatory responses and has been historically used for treating infectious diseases such as pneumonia. As the outbreak of COVID-19 continues globally and effective treatment methods are lacking, low-dose radiation has drawn increasing attention recently. While some are optimistic about the clinical adoption of low-dose radiation for the treatment of COVID-19, others have significant concerns about its effectiveness and safety. This is the premise debated in this month's Point/Counterpoint.

Arguing for the Proposition is SMJ Mortazavi, Ph.D. Dr. Mortazavi serves as Professor of Medical Physics at School of Medicine, Shiraz University of Medical Sciences. His background is in medical physics, with specific training and expertise in the biological effects of ionizing and non-ionizing radiation. He was awarded the Young Scientist Award at the 11th International Congress of Radiation Research, Dublin, Ireland. After completing a postdoc awarded by the Japan Society for Promotion of Science (JSPS) at the Kyoto University of Education, he joined the faculty of RUMS, Rafsanjan, and served as Assistant/associate professor until 2008. Then he moved to SUMS, Shiraz where he served as associate/full professor. He was also, a visiting scientist at Fox Chase Cancer Center, Philadelphia (2017–2018) and University



of Wisconsin-Milwaukee, Milwaukee (2018). He has authored more than 250 papers in peer-reviewed journals. Some of his papers/letters have been published in prestigious journals such as *Circulation*, *PNAS*, *British Journal of Cancer*, and *Environmental Research*. He has also published papers on the future role of radioadaptation in the long-term stay of humans in space. He is also a member of editorial boards of some well-known journals such as *International Journal of Low Radiation (IJLR)*, *Radiology of Infectious Diseases* and *International Journal of Radiation Research (IJRR)*.

Arguing against the proposition is Amirhosein Kefayat, M.D. He received his M.D. degree from the Isfahan University of Medical Sciences, Iran. His research encompasses many different aspects of cancer diagnosis and treatment. His major research interest is design and assessment of novel nanomaterials and nanostructures for enhancement of cancer treatment efficacy. He has published more than 30 peer-reviewed papers.

P.S. This article was written before the publication of Emory University Hospital on the phase I/II trial evaluating the safety and efficacy of single-fraction, low-dose, whole-lung radiation for COVID-19 pneumonia.<sup>1</sup> The authors were unaware of the findings of the Emory study during their writings of this article. The topic of this debate is still actively developing. According to *ClinicalTrials.gov* website, about ten trials have been registered by 25 June 2020 to investigate the use of low-dose radiation for



COVID-19 treatment, and most of them are currently recruiting patients. Hopefully, results from these clinical trials will be available soon for further and more informative discussions.

## FOR THE PROPOSITION: SMJ MORTAZAVI, PH.D

### Opening Statement

It has long been known that low-dose radiation can induce anti-inflammatory responses due to its potential for inducing polarization of both M1 and M2 macrophage phenotypes.<sup>2</sup> Historically, low-dose radiation was successfully used for treatment of infectious diseases such as pneumonia.<sup>3</sup> The concept of using low-dose radiation therapy (LDRT) for COVID-19 pneumonia was first introduced by a group of Iranian and American scientists in March 2020.<sup>4</sup> Subsequently, Canadian, Spanish, American, German and more recently French scientists also confirmed the potential efficacy of LDRT for COVID-19 pneumonia. These reports have mainly focused on the anti-inflammatory and immunomodulatory effects of LDRT and suggested that lung doses ranging 100–1000 mGy could be beneficial for treatment of severe pneumonia in COVID-19 patients.

In less than a month, the report by Ghadimi-Moghadam et al.<sup>4</sup> received attention not only for introducing LDRT as a treatment method for pneumonia in COVID-19 patients but also for noting the key disadvantages of other treatment methods such as using antiviral drugs. Rödel et al.<sup>5</sup> in their paper published recently state *SARS-CoV-2 is an RNA virus with an expected moderate to high mutation rate . . .*<sup>6</sup> *In addition, as discussed in a recent manuscript,<sup>4</sup> any antiviral drug treatment against SARS-CoV-2 would probably result in a more intense selective pressure on the virus.* Moreover Dilucca et al.<sup>7</sup> in their paper published recently in the Viruses Journal highlight the importance of LDRT and address the potential problems associated with the widespread use of different antiviral drugs *as discussed in a recent paper,<sup>4</sup> any antiviral drug against SARS-CoV-2 would exert an intense selective pressure on the virus. This may result in highly adaptive and treatment-resistant virus types with enhanced pathogenicity.*

Furthermore, low doses of ionizing radiation can combat the cytokine storm in severe pneumonia associated with COVID-19 pulmonary damage. The rapid responses of pneumonia patients to LDRT suggest that apoptosis of cytokine-producing infiltrating cells might be a substantial component as symptoms started to improve within hours. In addition, autopsies have revealed hundreds of micro thrombi in the lungs of infected people. When the blood clots grow larger in size they can embolize to the brain or heart, causing a stroke or heart attack.<sup>8</sup> Thus, scientists hypothesized that severe hematological alterations can be involved in some of these abnormalities.<sup>8</sup> As oxidative stress plays a key role in the clotting cascade through multiple pathways including enhanced formation of isoprostanes,<sup>9</sup> it might be hypothesized that LDRT would also reduce or prevent the blood clotting by reducing oxidative stress.

## AGAINST THE PROPOSITION: AMIRHOSEIN KEFAYAT, M.D

### Opening Statement

Recently, the potential of different therapeutic approaches for COVID-19 pneumonia treatment has been discussed. Some researchers have suggested LDRT for COVID-19 treatment. They mostly relied on previous studies that reported positive effects of radiation beams on the different types of pneumonia. However, these publications belong to the early 20th century and a significant lack of satisfactory scientific reliability is apparent in them. For instance, most of these studies on pneumonia patients had case report format and modern randomization of subjects, and blinded investigation principles were not used in their methods. Also, their animal experiments contained evident limitations and pitfalls.<sup>10</sup> Thus, these observations which support the effectiveness of LDRT for pneumonia treatment are not reliable and need re-assessment with the latest scientific principles.

Many researchers believe that the anti-inflammatory effect of LDRT is the main mechanism of action by which LDRT treats pneumonia. Although LDRT exhibits anti-inflammatory effects, it is currently used just for controlling local and limited inflammations.<sup>11</sup> However, the main reason for COVID-19 patients' death is cytokine storm which is an extensive systemic inflammatory response.<sup>12</sup> Therefore, the anti-inflammatory effect of LDRT may not be strong enough for inhibiting the SARS-CoV-2-induced cytokine storm. The current knowledge about the LDRT effect on the cytokine storm is extremely limited and there is no report about controlling systemic inflammations by LDRT. On the other hand, one of the most important concerns about utilizing anti-inflammatory approaches in infectious diseases is the suppression of immune responses against the invading pathogen which are necessary for fighting and eliminating the pathogen. To date, numerous numbers of anti-inflammatory drugs and approaches have been investigated for cytokine storm management in infectious diseases. However, none has been proved to be effective, and some have even worsened outcome.<sup>13</sup>

Some studies have reported a significant increase in uptake, activation, transcription, and spread of some viruses after irradiation *in vitro* and *in vivo*. Moreover, apoptosis induction by ionizing radiation beams to the virus-infected cells as the reservoirs of millions of virus particles, might accelerate the spreading of the virus and consequently disease progression.<sup>14–17</sup> Therefore, due to the lack of knowledge about radiation beams' effects on SARS-CoV-2 and its infected cells, it is even possible that radiotherapy worsens the progression of the COVID-19 disease.

Altogether, it seems necessary to comprehensively assess the different aspects of utilizing LDRT for COVID-19 treatment including LDRT effect on SARS-CoV-2 virus and the infected cells, the ability of LDRT to control cytokine storm of COVID-19 and its effect on the immune system fighting against SARS-CoV-2. Paying attention to these fundamental

points may significantly enhance the efficacy and outcomes of further clinical trials for the treatment of COVID-19 patients with LDRT.

### Rebuttal: SMJ Mortazavi, Ph.D

My PCP colleague has raised concerns about the efficiency of LDRT for treatment of COVID-19-associated pneumonia. He, particularly believes that the early studies were mostly case reports, without randomization and blinding. The accidental discovery of penicillin by Alexander Fleming (1928) that changed the course of medicine started with a mold that developed on a staphylococcus culture plate. Previous studies clearly show that LDRT can potentially afford therapeutic benefit against respiratory complications of COVID-19. Given this consideration, researchers have suggested clinical trials of LDRT for COVID-19 pneumonia; *we consider low-dose irradiation to be worth investigating in the clinical setting.*<sup>5</sup> It is worth noting that my research team is getting ready to start a randomized, blinded, sham-controlled trial that fully investigates the effects of LDRT on COVID-19-associated pneumonia.

My PCP colleague claims that *the anti-inflammatory effect of LDRT may not be strong enough for inhibiting the SARS-CoV-2-induced cytokine storm.* We addressed this challenging issue in our paper.<sup>4</sup> Other researchers also believe that considering the available data and the mechanism proposed for LDRT, a single dose of 0.3–0.5 Gy would be beneficial for COVID-19 patients with severe symptoms who experience the cytokine storm.<sup>18</sup>

He also believes that the anti-inflammatory effects of LDRT may lead to suppression of immune responses against the invading pathogen. Substantial evidence indicates that LDRT does not cause either suppression or over-activation of the immune system but plays a critical role in both maintaining and optimizing the immune system. Optimizing the immune system by LDRT can help protect against COVID-19 and mitigates acute respiratory distress syndrome (ARDS).

Moreover, he claims that LDRT can lead to increase in uptake, activation, transcription, and spread of some viruses. Since there are no data about SARS-CoV-2, this claim is thoroughly based on speculations and presumptions. Regarding other viruses, radiotherapy has been proposed as a cost-effective treatment for patients infected with the Ebola virus.<sup>19</sup> In addition, some studies have introduced radioimmunotherapy (RIT) as the most promising backbone strategy for eradication of human immunodeficiency virus (HIV).<sup>20</sup>

My PCP colleague also claims that apoptosis by LDRT might accelerate the spread of the virus. Although apoptosis by low-dose radiation is reported in some cancer cells, accelerating the spread of a virus by this phenomenon is just a speculation. In normal tissues, low-dose radiation can lead to beneficial effects; *Low-dose radiation induces apoptosis of tumor cells and has numerous beneficial effects on normal tissues, including radiation homeostasis and adaptive response.*<sup>21</sup>

### Rebuttal: Amirhosein Kefayat, M.D

Dr. Mortazavi mentioned the history of using LDRT for pneumonia treatment and suggested using this therapeutic method for COVID-19 patients. Also, he mentioned the anti-inflammatory effects of LDRT as a key factor for treating COVID-19 cytokine storm. I have explained my ideas about both these subjects in my opening statement in detail.

Moreover, Dr. Mortazavi mentioned the increased risk of thrombosis formation in COVID-19 patients and suggested that LDRT may reduce or prevent blood clotting in these patients by reducing oxidative stress. However, several studies have demonstrated the promoting effects of LDRT on oxidative stress by increasing free radical production.<sup>22,23</sup> On the other hand, there are some supporting findings about the procoagulant changes after irradiation with different radiation qualities and doses for instance, induction of endothelial cells death and loss of their integrity which separates blood clotting factors from exposure to subendothelial prothrombotic extracellular matrix components.<sup>24</sup> Taking together, it seems LDRT may not only decrease the risk of coagulopathy in COVID-19 patients but also may promote clot formation.

Numerous studies on developing vaccines and antiviral drugs for COVID-19 prevention and treatment are ongoing. It is somehow apparent that using antiviral drugs and vaccines for COVID-19 treatment would be more acceptable for patients in comparison with ionizing radiations even in low-dose form. Therefore, further achievements in these fields like approving Remdesivir for COVID-19 treatment<sup>25</sup> may bury the subject of employing LDRT for COVID-19 treatment.

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### CONFLICT OF INTEREST

There is no conflict of interest to declare.

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