



## Time Reveals the Truth! What Treatments for COVID-19 Were Quickly Abandoned, and Which Methods, Contrary to Popular Belief, Are Still Flourishing?

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### ABSTRACT

During the early days of the COVID-19 pandemic, low dose radiation therapy (LDRT) was proposed as a potentially effective treatment method. To minimize potential toxicity, the initial treatment approach involved a few mGy of adapting radiation followed by a single 250 mGy whole lung challenging dose. However, antiviral drugs were also introduced as a promising treatment option, which were thought to have the potential to revolutionize the management of the crisis. Despite early warnings, many physicians did not fully consider the key point that, in contrast with LDRT, antiviral drug treatments can result in strong selective pressure on the virus. This can lead to the emergence of new SARS-CoV-2 variants, a phenomenon that can have serious global consequences. After more than two years, the truth has been revealed: the WHO Guideline Development Group has advised against the use of remdesivir, a widely used antiviral medication, for COVID-19. Meanwhile, a growing body of evidence suggests that LDRT can be a promising, low-risk approach for avoiding or delaying invasive respiratory support in COVID-19 patients. Although there is substantial supporting documentation, more high-quality, controlled, and randomized double-blind clinical trials are needed to further investigate the efficacy and potential therapeutic mechanisms of LDRT for COVID-19.

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### Keywords

COVID-19; SARS-CoV-2; Pneumonia; Low Dose Radiation; Remdesivir

### Introduction

At the early days of the pandemic, there was no consistent suggestion of possible SARS-CoV-2 mutations and the emergence of new variants. At that time, our team warned the medical community that the widespread and unjustified use of ineffective antiviral drugs could exert selective pressure on the SARS-CoV-2, and eventually lead to the evolution of the virus and the emergence of new variants. In addition, that article proposed the use of low doses of ionizing radiation as an effective treatment approach for COVID-19-associated pneumonia [1].

At the time, the idea was so unorthodox that the medical community refused to accept its validity. Some radiotherapists claimed that treating

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of COVID-19 using antiviral medications as well as vaccination was obviously more acceptable to patients than ionizing radiation, even at very low doses.

*“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 may bury the subject of employing LDRT for COVID-19 treatment”* [2].

Now, after 2 years, the outcome of treatment with Remdesivir and LDRT have been elucidated. While the World Health Organization Guidance Development Group recommends not using Remdesivir for COVID-19: *“WHO Guideline Development Group advises against use of remdesivir for covid-19”* [3].

Moreover, Rodriguez-Thomas et al. in their study indicate that whole lung irradiation at doses of 0.5-1.5 Gy can significantly improve clinical and radiological status without acute toxicity *“Several groups, including our own, have shown that whole-lung radiation at doses of 0.5–1.5 Gy can accelerate the recovery in clinical and radiographic status without acute toxicity”* [4]. In addition, Piras et al. [5] in their systematic review state *“Forty-three studies investigated treatment of Covid-19 pneumonia with RT”*. They also note that *“Whole-lung LDRT seems to be a promising approach for avoiding or delaying invasive respiratory support with a low risk of toxicity”*.

Since the early days of the pandemic, our team was actively involved in studies on COVID-19 [6-23]. Table 1 summarizes some of the citations from our 1st paper published on April 2020, to clarify the impact of our contribution to global COVID-19 management. The authors, their affiliations, the journal and its impact factor, publication date and the type of contribution to the field (e.g., controlling the virus mutations and its evolution, and justification of LDRT for COVID-19)

that is cited by the authors are summarized in Table 1.

## Conclusion

Low dose radiation therapy (LDRT) was proposed as a potential treatment for COVID-19, involving a small amount of adapting radiation followed by a single 250 mGy whole lung dose. However, antiviral drugs were also introduced, which can result in the emergence of new SARS-CoV-2 variants. The WHO advised against using remdesivir, a widely used antiviral medication, for COVID-19. LDRT is showing promise as a low-risk approach to avoid invasive respiratory support in COVID-19 patients, but more controlled and randomized clinical trials are needed to investigate its efficacy and potential therapeutic mechanisms. In summary, after two years, the efficacy of LDRT for COVID-19-associated pneumonia has become increasingly clear despite initial controversies. However, to better understand the multi-potential mechanisms of LDRT, further high-quality, controlled, and randomized double-blind clinical trials are needed.

## Authors' Contribution

SAR. Mortazavi, JJ. Bevelacqua, AK. Ghadimi-Moghadam and M. Haghani conceived the idea. The draft was prepared by JJ. Bevelacqua, SAR. Mortazavi and M. Haghani. All the authors read, revised, and approved the final version of the manuscript.

## Conflict of Interest

None

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**Table 1:** The citations of our first paper on LDRT for COVID-19. The authors, their affiliations, the journal and its impact factor, publication date, the type of contribution to the field (e.g., controlling the virus mutations and its evolution, and justification of LDRT for COVID-19) are summarized.

Author(s)	Affiliations of 1 <sup>st</sup> and corresponding authors	Journal (Impact factor)	Publication date	Highlighted Contribution	Contribution of the article published on April 2020 to our knowledge about COVID-19 [1].
Little et al. [24]	National Cancer Institute, National Institute of Health (NIH), (United States)	Int J Radiat Oncol Biol Phys (7.038)	March 15, 2021	Proposing a treatment method	"Low dose radiotherapy (LDRT) for Coronavirus Disease 2019 (COVID-19) pneumonia was proposed in early April 2020. At least 15 clinical studies are currently ongoing in 9 countries."
Chrysostomou [25]	University of Cyprus, Aglantzia, Nicosia 2109, (Cyprus)	Viruses (5.818)	Jan 2023	Controlling the virus mutations and its evolution	"As a result of high transmission and replication rates, along with other evolutionary pressures, such as the host's immune system, SARS-CoV-2 has been accumulating mutations over the course of the pandemic."
Hussien [26]	Egyptian Atomic Energy Authority, Cairo (Egypt)	European Journal of Medical Research (2.175)	Feb 2023	Proposing a treatment method	"Ghadimi-Moghadam et al. propose that COVID-19 pneumonia be treated with a few mGy priming doses followed by a single 0.25 Gy dose. ... Clinical LD-RT investigations are recommended for COVID-19 pneumonia by both Ghadimi-Moghadam et al. and Kirkby and Mackenzie."
Chalka et al. [27]	National and Kapodistrian University of Athens (Greece)	Cells (4.829)	Feb 2022	Justification of LDRT for COVID-19	"In the struggle to manage the continuously incoming patients on healthcare systems, scientists have suggested Low Dose Radiation Therapy (LDRT) as a possible therapy for COVID-19 patients. With a total dose to the whole thorax ranging between 35 and 150 cGy, LDRT could be effective in reducing the inflammatory response."
Little et al. [28]	National Cancer Institute, NIH, (United States)	International Journal of Radiation Biology (2.649)	2022	Proposing a treatment method	"In part because of these early clinical and experimental data, use of LDRT for treatment of COVID-19-associated pneumonia was proposed in early April 2020 (Ghadimi-Moghadam, Haghani et al. 2020, Kirkby and Mackenzie 2020)."
Wen et al. [29]	Beijing Key Laboratory for Radiobiology (China)	International Journal of Radiation Biology (2.649)	2022	Proposing a treatment method	"In the COVID-19 pandemic, Ghadimi-Moghadam et al. used an improved therapy with a single dose of 100, 180, or 250 mSv X-ray radiation to treat COVID-19 patients (Ghadimi-Moghadam et al. 2020)."
Oksengendler [30]	Ion-plasma and Laser Technologies Institute after U. Arifov, (Uzbekistan)	Nuclear Inst. and Methods in Physics Research, B (1.377)	Feb 2022	Proposing a treatment method	"Indeed, in the first half of the 20 <sup>th</sup> century, such attempts of radiation exposure to pneumonia (both bacterial and viral) sometimes led to encouraging successes, but these results were not systematic and were rejected even after the creation of antibiotics. After the onset of the SARS-CoV-2 and COVID-19 problem, these attempts have resumed on a more systematic basis in evidence-based medicine."

Author(s)	Affiliations of 1 <sup>st</sup> and corresponding authors	Journal (Impact factor)	Publication date	Highlighted Contribution	Contribution of the article published on April 2020 to our knowledge about COVID-19 [1].
Rodel et al. [31]	Department of Radiotherapy and Oncology, Universitätsklinikum Frankfurt am Main, Goethe-University, Theodor-Stern-Kai, (Germany)	Strahlentherapie und Onkologie (3.621)	May 2020	Controlling the virus mutations and its evolution	SARS-CoV-2 is an RNA virus with an expected moderate to high mutation rate similar to other SARS RNA viruses and usually higher than the corresponding rate of the human host cells <sup>5</sup> . In addition, as discussed in a recent manuscript <sup>3</sup> , any antiviral drug treatment against SARS-CoV-2 would probably result in a more intense selective pressure on the virus <sup>5</sup> .
Nestle and Krause [32]	Klinik für Strahlenheilkunde, Universitätsklinikum Freiburg, and German Cancer Consortium (DKTK) partner site Freiburg and German Cancer Research Center (DKFZ) (Germany)	Strahlentherapie und Onkologie (3.621)	Nov 2020	Proposing a treatment method	"Which summarizes experiences with irradiation of viral and bacterial pneumonia from the first half of the 20 <sup>th</sup> century, this concept was taken up very early in coronavirus-plagued Iran and also discussed, e.g., in Canada."
Sharma et al. [33]	Department of Radiation Oncology, All India Institute of Medical Sciences (India)	The British Journal of Radiology (3.30)	Sep 2021	Controlling the virus mutations and its evolution	"Therefore, LDRT may also be capable of reducing bacterial co-infections in patients with COVID-19. Additionally, LDRT might prevent accelerated viral drug-related mutation thus potentially improving the immune response by means of the enhanced RNA damage compared to antiviral therapy."
Dilucca et al. [34]	Physics Department, Sapienza University of Rome (Italy)	Viruses (5.048)	May 2020	Controlling the virus mutations and its evolution	"SARS-CoV-2 is an RNA virus with an expected mutation rate similar to other RNA viruses, as discussed above. This mutation rate is usually much higher than the corresponding one of any human host. Therefore, as discussed in a recent paper <sup>3</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."
Yu et al. [35]	Radiobiology and Health, Isotopes, Radiobiology & Environment Directorate (IRED), Canadian Nuclear Laboratories (CNL) (Canada)	Cells (4.28)	Sep 2021	Controlling the virus mutations and its evolution	"3. Low-dose radiotherapy is less likely to induce drug-resistant mutation in the virus compared to anti-viral drugs."
Chrysostomou et al. [36]	Department of Biological Sciences, University of Cyprus (Cyprus)	Viruses (5.048)	June 2021	Controlling the virus mutations and its evolution	"Furthermore, this virus has a global distribution, infecting populations of different genetic backgrounds, ages and health statuses, and it is subjected to evolutionary and selection pressures imposed by the host's immune system, as well as by antiviral drugs."
Gao et al. [37]	Institute for Hepatology, National Clinical Research Center for Infectious Disease, Shenzhen Third People's Hospital, the Second Affiliated Hospital, School of Medicine, Southern University of Science and Technology (China)	Virulence (5.542)	May 2021	Controlling the virus mutations and its evolution	"... and other selective pressures, for instance, the widespread use of vaccines, X-ray radiation therapy, and public health intervention strategies. Moreover, such variations contribute significantly to the design of effective strategies for disease control and prevention."



Author(s)	Affiliations of 1 <sup>st</sup> and corresponding authors	Journal (Impact factor)	Publication date	Highlighted Contribution	Contribution of the article published on April 2020 to our knowledge about COVID-19 [1].
Mahallawi and Aljerais [38]	Department of Medical Laboratory Technology, College of Applied Medical Sciences, Taibah University, (Saudi Arabia)	Saudi Journal of Biological Sciences (4.219)	April 2021	Identifying effective therapeutics to treat COVID-19	"Numerous institutions and public research organizations have focused their efforts on identifying effective therapeutics to treat COVID-19 (A et al., 2020)."
Dunlap et al. [39]	Department of Radiation Oncology, University of Louisville School of Medicine (USA)	Radiation Medicine and Protection (0.878)	Dec 2021	Controlling the virus mutations and its evolution	"As suggested in by Ghadimi-Moghadam et al., 2 COVID-19 patients may receive a single dose of 100, 180 or 250 mGy X-rays, .... In contrast with antiviral drugs, a single dose of either 100, 180 or 250 mSv of low LET X-rays may not exert a significant selective pressure on the SARS-CoV-2 and hence does not lead to directed accelerated evolution of these viruses."
Jahani-Sherafat et al. [40]	Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences (Iran) and the Canadian Optic and Laser Center, Training Institute, Victoria, BC, (Canada)	Journal of Lasers in Medical Sciences (1.61)	2020	Proposing a treatment method	"Since many mortality rates in most cases are due to ARDS and cytokine storm, all suggested methods help patients balance the immune responses. Recently, PBMT and the use of X-ray radiation that is less than the maximum annual radiation dose have been suggested for the treatment of pneumonia associated with SARS-COV2."
Sharma et al. [41]	Department of Pharmacology and Pharmaceutical Chemistry, School of Pharmaceutical Sciences (India)	Pharmacologyonline	2021	Proposing a treatment method	"Scientists from America and Iran during March 2020 introduced the use of low-dose radiation therapy (LD-RT) for COVID-19 pneumonia patients. Afterward, Canadian, Spanish, French, and German scientists also started following this approach. The suggested dose ranges between 100–1000 mGy for lungs, thus could be a helpful therapeutic option for chronic pneumonia in COVID-19 patients."
Abdelwahed [42]	King Fahad Specialist Hospital Buraydah (Saudi Arabia)	Journal of MAR Case Reports	Jan 2022	Proposing a treatment method	"Some researchers introduced the concept of LDRT and recommended doses were as low as 100 mGy. Moreover, to reduce any potential risk, in their model patients receives a conditioning dose of 2 mGy. This dose not only maximizes the anti-inflammatory effects of the main dose (100/180/250 mGy), but reduces the risk of cancer and any potential circulatory disease."

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