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8. Arruda GV, Dos Santos Weber RR, Bruno AC, et al. The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: Estimation based on a virtual case. *Int J Radiat Biol* 2021;97:120–125.
9. Barabanova A, Bushmanov A, Kotenko K. *Encyclopedia of Environmental Health*; 2011:1–8. Available at: <https://www.elsevier.com/books/encyclopedia-of-environmental-health/nriagu/978-0-444-52273-3>. Accessed 17 March 2021.

In Reply to Bevelacqua et al



We thank Bevelacqua et al for their comments¹ on our study of whole-lung low-dose radiation therapy (LDRT) for severe COVID-19 pneumonia.² In their letter, Bevelacqua et al suggest that suboptimal dosing and timing of LDRT may explain the negative outcome.

Bevelacqua et al cite “substantial evidence” showing that 1 Gy may be beyond the range of effective doses for COVID-19 patients. Unfortunately, they did not provide references that adequately support this statement. In addition, our patients did not receive the prescribed dose of 1 Gy to the whole lungs. Rather, as described in the manuscript, the lungs received anti-inflammatory doses in the range of 0.5 to 1.0 Gy, which appears adequate based on recent preclinical research.^{3,4}

It is essential to acknowledge the uncertainty surrounding the “ideal” LDRT dose. Bevelacqua et al cite the Iranian study and declare that their concept “clearly explains why Ameri et al concluded that 0.5 Gy was more effective than 1.0 Gy.” This was not a conclusion of the study’s authors, who address important limitations in their paper.⁵ We cannot exclude that a different outcome would have been observed in our study with use of a lower radiation dose. However, such assumptions are speculative, if not disconnected from the clinical reality of these patients, for whom LDRT failed to produce any meaningful effect.

Our study focused on ventilated patients, for whom the presumed risk-benefit ratio of LDRT appeared most favorable. Although an earlier application could be more effective, the long-term risks may outweigh potential benefits in less critically ill patients. Moreover, the timing of immunomodulatory treatments is complex. RECOVERY showed large benefits of dexamethasone in ventilated patients, but only small improvements in patients on oxygen.⁶ Tocilizumab, an interleukin-6 receptor antibody, may further reduce mortality in these patients.⁷ Even if LDRT were to improve on these results, it would likely require large-scale randomized trials to show a potential benefit.

Our trial was borne out of a clinical need, and we chose a randomized double-blind design to reduce any potential bias. The availability of prospective controls

is the crucial difference between our study and earlier reports,^{5,8,9} a difference that Bevelacqua et al unfortunately did not consider as a source of discrepancy between results. Although vaccines now provide a light at the end of the COVID-19 tunnel, the discussion of anti-inflammatory LDRT will go on. We should continue to separate evidence from opinion and work together to investigate what is best for our patients both during and after the COVID-19 pandemic.

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References

1. Bevelacqua JJ, Welsh JS, Mortazavi SMJ. In Reply to Papachristofilou et al. *Int J Radiat Oncol Biol Phys* 2021;110:1549–1550.
2. Papachristofilou A, Finazzi T, Blum A, et al. Low-dose radiation therapy for severe COVID-19 pneumonia: A randomized double-blind study [e-pub ahead of print]. *Int J Radiat Oncol*. doi:10.1016/j.ijrobp.2021.02.054, accessed May 1, 2021.
3. Meziani L, Robert C, Classe M, et al. Low doses of radiation increase the immunosuppressive profile of lung macrophages during viral infection and pneumonia [e-pub ahead of print]. *Int J Radiat Oncol Biol Phys*. doi:10.1016/j.ijrobp.2021.03.022, accessed May 1, 2021.
4. Jackson MR, Stevenson K, Chahal SK, et al. Low-dose lung radiotherapy for COVID-19 lung disease: A pre-clinical efficacy study in a bleomycin model of pneumonitis. *BioRxiv*. Available at: <https://doi.org/10.1101/2021.03.03.433704>. Accessed May 4, 2021.
5. Ameri A, Ameri P, Rahnama N, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: Final results of a pilot study. *Int J Radiat Oncol Biol Phys* 2021;109:859–866.
6. Horby P, Lim WS, Emberson JR, et al. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
7. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): Preliminary results of a randomised, controlled, open-label, platform trial. *MedRxiv*. Available at: <https://doi.org/10.1101/2021.02.11.21249258>. Accessed May 4, 2021.
8. Hess CB, Nasti TH, Dhere V, et al. Immunomodulatory low-dose whole-lung radiation for patients with COVID-19-related pneumonia. *Int J Radiat Oncol Biol Phys* 2021;109:867–879.
9. Sanmamed N, Alcantara P, Cerezo E, et al. Low-dose radiotherapy in the management of coronavirus disease 2019 (COVID-19) pneumonia (LOWRAD-Cov19): Preliminary report. *Int J Radiat Oncol Biol Phys* 2021;109:880–885.