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.

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Whole-Lung Low-Dose Radiation Therapy for Severe COVID Pneumonia

In Regard to Papachristofilou et al

To the Editor: This comment is regarding the paper by Papachristofilou et al.[1] To study the morbidity and mortality of patients with COVID-19 who needed mechanical ventilation, the authors investigated the use of whole-lung low-dose (1 Gy) radiation therapy (LDRT). Their randomized trial showed that whole-lung LDRT did not improve clinical outcomes in critically ill COVID-19 patients.[1] These results contradict the findings of earlier clinical trials. To identify the source of the descrepancy, it should be noted that substantial evidence shows that 1 Gy, at least for a proportion of the COVID-19 patients, may be beyond the range of therapeutically effective doses. In March 2020, LDRT was proposed for COVID-19 using doses up to 250 mGy.[2] However, later different researchers around the world, in competition, increased the radiation doses. Emory University Hospital used 1.5 Gy[3] and Ameri et al tried both 0.5 Gy[4] and 1.0 Gy.[5] Sanmamed et al also used 1.0 Gy.[6] Interestingly, a paper[7] published recently clearly indicates that although doses <1 Gy have anti-inflammatory effects, doses >1 Gy have proinflammatory effects and cause fibrosis. Thus, the doses used in the clinical trials such by Papachristofilou et al were possibly unjustified as the doses were not within the optimal window of dose. We believe that this is 1 reason that Papachristofilou et al failed to find any therapeutic effects of LDRT for COVID-19.[1] Addtionally, there is probably a window of opportunity during which LDRT can effectively address the pulmonary symnptoms of COVID-19 or other viral pneumonias. This concept is akin to the window of opportunity during which external beam radiation therapy is effective for spinal cord compression. In the case of COVID pneumonia, the window of opportunity is likely before the patient becomes so ill that mechanical ventilation is required. In addition, the concept of a "therapeutic window" clearly explains why Ameri et al concluded that in their trial, 0.5 Gy was more effective than 1.0 Gy.[5]

Using doses <1 Gy (in particular, doses <0.5 Gy) not only increases the therapeutic effects of low-dose radiation therapy but also reduces the cancer risk to an acceptable level. Arruda et al have recently reported that regardless of the sex, enrolling patients older than 40 years, particularly elderly patients older than 60 years, can provide acceptable lifetime attributable risks of radiation-induced cancer for a radiation dose of 0.7 Gy.[8] It is of crucial importance to note that using doses ≤0.5 Gy not only increases the thrapeutic effects of LDRT and maintains the risks at an acceptable level but also prevents potential deterministic effects such as transient bone marrow damage. Studies conducted in patients with acute radiation sickness in Chernobyl show that even a modest dose of 0.5 to 0.7 Gy may compromise marrow function.[9]

In summary, both the timing and delivered dose are important considerations in LDRT studies. These factors are important considerations in developing an effective LDRT approach to treating patients with COVID-19.

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In Reply to Bevelacqua et al

We thank Bevelacqua et al for their comments[1] 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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