

Unethical not to Investigate Radiotherapy for COVID-19

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Abstract

The *primum non nocere* letter by Boon et al. urged caution and careful examination of the evidence and logistics of low-dose radiotherapy in COVID-19 patients. This is exactly what was requested in March and what has occurred since late April 2020 when the first phase I/II clinical trial was approved at the Winship Cancer Institute, Emory University Hospital. The preprint of day-7 interim results by the investigators concluded, “In a small pilot trial of 5 oxygen-dependent patients with COVID-19 pneumonia, low-dose whole-lung radiation led to rapid improvement in clinical status, encephalopathy, and radiographic infiltrates without acute toxicity or worsening the cytokine storm. Low-dose whole-lung radiation appears to be safe, shows early promise of efficacy, and warrants larger prospective trials.” Preliminary results from another clinical trial gave similar results. In conclusion, the authors believe it would be unethical not to investigate radiotherapy as a potential remedy against COVID-19 induced pneumonia

Keywords

low dose radiation, lung radiotherapy, COVID-19, pneumonia

The COVID-19 Rapid Letter by Boon et al. urged caution and careful examination of the evidence and logistics of low-dose radiotherapy in COVID-19 patients.¹ This is exactly what was requested in the March 20, 2020, Cuttler to Hahn letter to the FDA² and what has occurred since late April 2020 when the first phase I/II clinical trial was approved at the Winship Cancer Institute, Emory University Hospital.³ The preprint of day-7 interim results by the investigators concluded, “In a small pilot trial of 5 oxygen-dependent patients with COVID-19 pneumonia, low-dose whole-lung radiation led to rapid improvement in clinical status, encephalopathy, and radiographic infiltrates without acute toxicity or worsening the cytokine storm. Low-dose whole-lung radiation appears to be safe, shows early promise of efficacy, and warrants larger prospective trials.”⁴ Preliminary results from another clinical trial gave similar results.⁵

More than 10 clinical trials have been approved by institutional review boards after reviewing the potential benefits of this radiotherapy and the risk of radiogenic cancer.⁶ The optimal radiation dose will be determined in the trials; however, the investigators are using a single dose in the range from 0.3 to about 1 Gy. Considering the typical radiotherapy for lung cancer, a daily fraction of 2 Gy for 6 weeks (60 Gy), we question the fearful concerns raised in the *primum non nocere* letter by Boon et al.¹ regarding this radiotherapy for severe COVID-19 disease.

Overall, around 5%-10% of patients who are treated in a hospital setting die from pneumonia. Calabrese and Dhawan pointed out 7 years ago that an X-ray treatment was effective in the 1940s and suggested a focused clinical research program to assess the use of X-ray therapy as an adjunct treatment for high-risk patients.⁷ This recommendation was ignored, likely because radiotherapy is accepted only to cause biological damage, such as killing cancer cells. Would the availability of radiotherapy against acute respiratory distress syndrome have avoided many of the 685,000 deaths to date⁸ and eliminated most of the extreme precautionary measures that have been adopted worldwide during this pandemic?

A recent review of medical therapies using low doses of radiation discusses the evidence and mechanism by which radiation upregulates adaptive protection systems against many diseases.⁹ It identifies high dose thresholds for the onset of harmful effects.

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Nasal radium irradiation (NRI), widely used from 1940 through 1970 to treat adenoid inflammation or ear dysfunction, was stopped because of concerns about potential adverse effects. Children are considered most vulnerable to radiation-related cancers; however, the studies did not confirm a definite link between NRI and any disease.^{10,11} Hence, any concerns about children being particularly sensitive to radiation are unwarranted.

Biological dosimetry determined the exposures received by 106 Chernobyl workers, who recovered from acute radiation syndrome. Twenty-two of them died during the next 19 years, a mortality rate of 1.1% per year, lower than the 1.4% average mortality rate in Russia in 2000. Thirty years after the accident, 26 had died, a mortality rate of 0.82% per year. Their cancer mortality was 27%, which is about the same as the fraction of cancer deaths among all mortality causes for Central Europe.⁹ A 29-year follow-up study by Tubiana et al. on a cohort of 5,000 survivors of childhood cancer¹² suggested a lower than normal cancer incidence for an exposure dose below several Gy. This human evidence contradicts the concerns raised by Boon et al. about delayed health effects.¹ In conclusion, we believe it would be unethical not to investigate radiotherapy as a potential remedy against COVID-19 induced pneumonia.

Authors' Note

J.J.B. and S.M.J.M. have contributed to this work.

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