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Low dose radiotherapy for COVID pneumonia: Irradiate to Eradicate – Will it be possible?

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To The Editor,

The novel corona virus (SARS-CoV-2) which emerged in Wuhan, China continues to create havoc throughout the world. The management of Covid-19 is rapidly evolving. No cure has been found till now, although several avenues are being explored. If we look back into the 20th century, low dose radiotherapy (LDRT) was used to treat a variety of infections like gas gangrene, carbuncles, furuncles, inner ear infections, sinusitis, and pneumonia. Desperate time calls for desperate measure and hence the safety and efficacy of this therapy for COVID-19 pneumonia is currently being explored.

There are many ways via which radiation therapy has been postulated to work in pneumonia. First is by exerting an anti-inflammatory effect, second by inducing metabolic rewiring of the host cells, and third by virtue of inducing the "abscopal effect". Phenotypically, macrophages are of two types – M1 and M2. M1 macrophages promote Th1 polarization of CD4 cells while M2 macrophages exert an anti-inflammatory effect by inducing production of anti-inflammatory mediators such as IL-4, IL-10, and TGF-β (1). The pathogenesis of SARS-CoV-2 involves uncontrolled inflammation secondary to the cytokine storm. Low dose radiotherapy polarizes the macrophages to a M2 "anti-inflammatory" phenotype and thus will help in controlling the hyperinflammatory state in COVID- 19. Viruses are known to hijack the host cell machinery and utilise glucose and glutamine for replication (2). Low dose radiotherapy increases the oxygen metabolism of cells, thus increasing metabolic competition and limiting viral replication. Klug et al showed that low dose radiation mobilises macrophages and T-cells into the irradiated area, thus orchestrating effective immune response against the virus (3).

LDRT has been used historically for the treatment of bacterial and viral pneumonia. In a review of 15 papers with total 863 patients of bacterial and viral pneumonia, Calabrese et al showed that low dose radiotherapy was associated with promising results (4). However, most of the papers were case series, case reports and studies with no control arm, resulting in a very low-quality evidence. Till date, there are no randomised controlled trials on the use of LDRT in SARS-CoV-2 pneumonia. We found twelve clinical trials registered on clinical trials.gov and WHO International Registry of Clinical Trials Platform (IRCTP) which will study the safety and efficacy of radiotherapy in COVID-19. They are summarised in table 1. The patients recruited will be moderate to severe cases of COVID-19 and the dose used will be 0.5-1 Gy in a single fraction to both the lungs. The results of an interim analysis of a clinical trial NCT04366791 are available on a preprint server (5). Five oxygen dependent, lab confirmed cases of COVID-19 with bilateral pneumonia received single fraction of low dose radiation to both the lungs. Mean age of the patients was 90 years (range 64-94 years). Mean time to clinical recovery was 35 hours post radiation. Four patients showed radiological improvement within 24 hours. Three patients could be weaned off supplemental oxygen within 24 hours while one patient could be weaned off after 96 hours. However, the results are not yet peer reviewed.

Sr. No	Clinical trial identifier	Country	Study title	Study design	Patient group	Intervention	Primary outcome studied
1.	NCT04377477	Italy	Pilot Study on the Feasibility of Low Dose Radiotherapy for SARS-Cov-2 Pneumonitis (COVID-19 Low Dose Radiotherapy - COLOR 19)	Single center, single-arm, clinical trial	Lab confirmed COVID-19 cases more than 50 years old with Brescia Covid Respiratory Severity Scale (BCRSS) score 2-3.	Bilateral lung radiation – single fraction of 0.7 Gy	Length of hospital stay (days) Number of Intensive Care Unit admissions
2.	NCT04420390	Spain	Low Dose Radiotherapy as Antinflammatory Treatment for COVID-19 Pneumonitis	Single-arm, clinical trial	Lab confirmed COVID-19 cases more than 60 years old with lung involvement with > 30 breaths / minute, SpO2 <93%, PaO2 / FiO2 <300 and D-dimer> 1000 ng / mL or rising ferritin> 1000 ng / mL, doubling CRP> 10 mg / dL.	Dose not mentioned	Radiological response 3 days and 7 days after low dose radiation.
3.	NCT04427566	United States	Vented COVID: A Phase II Study Of The Use Of Ultra Low-Dose Bilateral Whole Lung Radiation Therapy in the Treatment Of Critically Ill Patients With COVID-19 Respiratory Compromise	Single-arm, clinical trial	Lab confirmed COVID-19 cases in ICU receiving mechanical ventilation with Pa/ FIO2 ratio < 300 or SpO2/FiO2 < 315.	Bilateral lung radiation – single fraction of 0.8 Gy	Mortality rate up to 28 days post radiation delivery.
4.	NCT04390412	Iran	Assessment of Adding Low Dose Pulmonary Radiotherapy to the National Protocol of COVID-19 Management: A Pilot Trial	Single-arm, clinical trial	Lab confirmed COVID-19 cases more than 60 years old within 3 days of ARDS onset and with rising CRP and IL-6	Bilateral lung radiation – single fraction of 0.5 Gy	Change in PaO2 / FiO2 from baseline at 28 days, Number of Hospital stay days, Number of ICU stay days, Number of intubation events
5.	NCT04414293	Spain	Phase II Study of Low Dose Pulmonary Irradiation in Patients With COVID-19 Infection of Bad Prognosis	Single-arm, clinical trial	Lab confirmed COVID-19 cases more than 65 years old within 8 days of symptom onset with presence of unilateral or bilateral pulmonary infiltrates in chest X-ray or computed tomography (CT), acute respiratory failure expressed by PaO2 / FIO2 <300, lymphopenia ≤ 800 lymphocytes / ml.	Dose not mentioned	Radiological improvement and improvement in blood oxygenation level at 48 hours after radiation treatment
6.	NCT04393948	United States	Pilot Study of Low-Dose Single or Bilateral Whole Lung Irradiation for SARS-CoV-2 Pneumonia	Randomised controlled trial	Lab confirmed COVID-19 cases more than 40 years old with SpO2 on room air <94%	No radiation vs 1 Gy single lung irradiation vs 1 Gy bilateral lung irradiation.	Phase 1: Feasibility and safety of treating hospitalized patients with SARS-CoV-2 pneumonia with single or bilateral whole lung irradiation Phase 2: Proportion with clinical improvement on a 7-point ordinal scale on day 4 after randomization

7.	NCT04394793	India	Low Dose Radiation Therapy for Covid-19 Pneumonia: A Pilot Study	Single-arm, clinical trial	Lab confirmed COVID-19 cases more than 18 years old with NEWS ≥5	Bilateral lung radiation – single fraction of 0.7 Gy	Improvement in NEWS at days 3, 7, 14. Length of hospital stay. Number of ICU admissions or deaths.
8.	NCT04366791	United States	The RESCUE 1-19 Trial: Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19	Single-arm, clinical trial	Lab confirmed COVID-19 cases with ARDS/ pneumonia with preintubation respiratory support or mechanical ventilation	Single fraction, dose not mentioned	Rate of extubation upto 28 days after radiotherapy
9.	NCT04433949	United States	Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 (RESCUE 1-19): A Randomized Phase III of Best Supportive Care +/- Whole Lung Low-Dose Radiation Therapy in Hospitalized Patients	Randomised, Parallel group, open label	Lab confirmed COVID-19 cases with ARDS/ pneumonia	Low dose radiotherapy - Dose not mentioned vs standard therapy	Time to clinical recovery which will be measured by improvements in oxygenation need prior to intervention compared with after intervention and/or hospital discharge
10.	NCT04380818	United States	Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19: Multi-central Prospective Study	Prospective multicenter study in 2 phases: Exploratory phase and Comparative phase	Age ≥18 years old with moderate to severe COVID-19 pneumonia within 8 days of symptom onset and PAO2/FIO2 of less than 300 mmHg or SaO2/FI02 <315 mmHg with either IL-6 > 40, CRP >100 mg/l or d-dimer > 1500 ng/ml or suspected cytokine release syndrome. Patients who are not candidates for admission to the intensive care unit due to age, concomitant diseases or general condition with suspected cytokine release syndrome	Comparative phase - Bilateral lung radiation – single fraction of 0.5 Gy in addition to pharmacological therapy vs only pharmacological therapy	Efficacy of low-dose pulmonary irradiation assessed by change in PAO2/FIO2 at 48 hours after treatment.
11.	NCT04394182	Spain	Low Doses of Lung Radiation Therapy in Cases of COVID-19 Pneumonia: Prospective Multicentric Study in Radiation Oncology Centers	Single-arm, clinical trial	Lab confirmed COVID-19 cases with ARDS/ pneumonia, age more than 18 years, Charles comorbidity index less than 6, poor or no response to medical therapy, not requiring invasive mechanical ventilation	Bilateral lung radiation – single fraction of 0.8 Gy	Status of oxygen therapy and oxygen saturation at day 2 after radiotherapy
12.	IRCT20170211 032494N3	Iran	Evaluation of low dose whole lung irradiation for treatment of resistant COVID-19 pneumonia	Single arm	Lab confirmed COVID-19 cases more than 60 years old with pneumonia or ARDS	Single fraction, low dose whole lung irradiation of 1 Gy	Pulse rate, VP, oxygen saturation, temperature after every 6 hours after intervention; CT score 5 days after intervention, length of hospital stay, death.

Based on invitro, in vivo and human data, a single dose of 0.1-0.5 Gy has been advocated for use in COVID pneumonia (6). While COVID-19 itself is associated with coagulopathy, there is a potential concern that radiotherapy may worsen it. Radiation induced coagulopathy superimposed on COVID induced coagulopathy can have disastrous consequences. However, it is unlikely to occur at a single low dose which will be administered to patients of COVID-19. Lymphocytes are one of the most radiosensitive mammalian cells. Radiation therapy can deplete lymphocytes resulting in exacerbation of already existing lymphocytopenia in these patients. As only low dose is used, the possibility of long-term adverse effects like cancer is minimal.

LDRT can be considered a promising option as it seems to confer a modest theoretical benefit due to its varied mechanisms. Whether these theoretical benefits will translate into better clinical outcomes is still to be known. At present, there is paucity of evidence regarding its safety and efficacy. Therefore, it is advised to await the results of various trials and refinement of the existing evidence before incorporating this therapy in the management of Covid-19 pneumonia.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Atri C, Guerfali FZ, Laouini D. Role of Human Macrophage Polarization in Inflammation during Infectious Diseases. Int J Mol Sci. 2018;19(6):1801.
2. Thaker SK, Ch'ng J, Christofk HR. Viral hijacking of cellular metabolism. BMC Biol. 2019;17(1):59.
3. Klug F, Prakash H, Huber PE, et al. Low-dose irradiation programs macrophage differentiation to an iNOS$^+$/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell. 2013;24(5):589-602.
4. Calabrese EJ, Dhawan G. How radiotherapy was historically used to treat pneumonia: could it be useful today? Yale J Biol Med 2013; 86: 555-570.
5. Hess CB, Buchwald ZS, Stokes W et al. Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia: Planned Day-7 Interim Analysis of a Registered Clinical Trial. medRxiv 2020.06.03.2011698.
6. Dhawan G, Kapoor R, Dhawan R, et al. Low dose radiation therapy as a potential life-saving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS). Radiother Oncol. 2020; 147: 212-216.

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