

# Low-dose radiation therapy for coronavirus disease-2019 pneumonia: Is it time to look beyond apprehensions?

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**Abstract:**

Coronavirus disease-2019 (COVID-19) has become a global health crisis. Mortality associated with COVID-19 is characterized mainly by acute respiratory distress syndrome (ARDS), sepsis, pneumonia, and respiratory failure. The pathogenesis of the disease is known to be associated with pro-inflammatory processes after virus infection. Hence, various therapeutic strategies are being developed to control the inflammation and cytokine storm in COVID-19 patients. Recently, low-dose radiation therapy (LDRT) has been suggested for the treatment of pneumonia/ARDS in COVID-19 patients through irradiation of lungs by gamma/X-ray. In this direction, a few clinical trials have also been initiated. However, a few recent publications have raised some concerns regarding LDRT, especially about possibilities of activation/aggressiveness of virus (severe acute respiratory syndrome coronavirus 2 in case of COVID-19), lung injury and risk of second cancer after low-dose therapy. The present manuscript is an attempt to analyze these apprehensions based on cited references and other available literature, including some from our laboratory. At this point, LDRT may be not the first line of therapy. However, based on existing anti-inflammatory evidence of LDRT, it needs encouragement as an adjuvant therapy and for more multi-centric clinical trials. In addition, it would be worth combining LDRT with other anti-inflammatory therapies, which would open avenues for multi-modal therapy of pneumonia/ARDS in COVID-19 patients. The mode of irradiation (local lung irradiation or whole-body irradiation) and the window period after infection of the virus, need to be optimized using suitable animal studies for effective clinical outcomes of LDRT. However, considering ample evidence, it is time to look beyond the apprehensions if a low dose of radiation could be exploited for better management of COVID-19 patients.

**Keywords:**

Corona virus disease-2019, cytokine storm, low-dose radiation therapy, pneumonia

U Till now (August 12, 2020), coronavirus disease-2019 (COVID-19) has taken more than 732 thousands of lives around the world spread over in >200 countries.<sup>[1]</sup> It resulted in a very serious global health crisis, especially for developing countries like India. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the pandemic, poses serious clinical challenges due to its action on

multiple sites, especially infecting the upper respiratory tract as well as lungs.<sup>[2,3]</sup> When SARS-CoV-2 infects the target organs, its active replication and subsequent release of the viruses results in the host cell to release damage-associated molecular patterns (like ATP, nucleic acids). These molecules get recognized by surrounding epithelial cells, endothelial cells and alveolar macrophages, triggering the generation of pro-inflammatory cytokines/chemokines (such as IP-10, interleukin-6 [IL-6]). Monocytes, macrophages and T-cells attracted to the site of infection, promote further inflammation, and thus the

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excessive release of these cytokines/chemokines, also known as “cytokine storm”. It ultimately results in damage of the lung cells, reduced diffusion capacity, and small airways obstruction.<sup>[3]</sup> Mortality associated with COVID-19 is mainly characterized by acute respiratory distress syndrome (ARDS), sepsis, pneumonia, and respiratory failure.<sup>[3]</sup> Various strategies are being explored, and clinical trials have been initiated to prevent infection at one side and treatment of infected patients on the other side, which have been reviewed recently.<sup>[3]</sup> These therapeutic strategies are aimed to repair the infected/damaged airways, prevention of infectivity, and minimizing the effects of inflammatory processes. To control the pathogenesis associated with inflammation, the efficacy of anti-inflammatory agents (like corticosteroids, fingolimod and thalidomide in combination with methylprednisolone) is being evaluated in COVID-19 patients. A few antagonists against cytokines like IL-6, Granulocyte-macrophage colony-stimulating factor are also being assessed to mitigate the harmful effects of these elevated cytokines. To control the cytokine storm, an approach is also being studied to pass the patient’s blood through a column to trap the pro-inflammatory cytokines, which can be again administered back to the patients.

In this direction, recently a few publications appeared suggesting the application of low-dose radiation therapy (LDRT) for treatment of pneumonia/ARDS in COVID-19 patients through gamma/X-ray irradiation of lungs in the range of 30–100 cGy<sup>[4]</sup> or 30–50 cGy<sup>[5]</sup> or 10–25 cGy.<sup>[6]</sup> Ghadimi-Moghadam *et al.*<sup>[6]</sup> also suggested treatment of patients with a single adaptive low dose (a few mGy of X-ray) before another dose of 10, 18, or 25 cGy X-ray. The proposed LDRT is based on the induction of the immune system and anti-inflammatory response (to control the cytokine storm) by a low dose of radiation. The LDRT for treatment of pneumonia/ARDS in COVID-19 patients is based on animal studies showing activation of the immune system after low dose of radiation<sup>[7-11]</sup> and the evidence generated in the early twentieth century from the application of low dose radiation for the treatment of pneumonia.<sup>[12-14]</sup> Cytokines released in response to virus by macrophages, other immune cells, endothelial cells, and fibroblasts govern the progression of pulmonary fibrosis. LDRT through its anti-inflammatory processes, could control the cytokine storm induced by virus infection and thus prevent the damage caused to lung tissue leading to pneumonia/ARDS in COVID-19 patients.<sup>[4,5]</sup> In this direction, researchers/clinicians around the world also initiated a few clinical trials for the application of low dose radiation to the lung for the treatment of pneumonia/ARDS [Table 1].<sup>[15]</sup> Many of the studies are aimed for diagnostically/clinically confirmed COVID-19 elderly patients (>50 years) patients with arterial oxygen partial pressure (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen

ratio <300 and elevated inflammatory markers (like IL-6). Out of these clinical trials, two are proposing to use dose of 70 or 100 cGy, and others tend to use 70–80 cGy in a single fraction [Table 1]. One of the trials is proposed with a single dose of 50 cGy and based on the clinical outcome, the patient will receive another dose of 50 cGy (to a maximum of 100 cGy in two fractions with the interval of at least 72 h). However, a few publications also appeared with apprehensions (mainly in terms of virus activation, lung injury, and radiation risk) for the use and success of the proposed LDRT in COVID-19 patients.<sup>[16-18]</sup>

### Low Dose Radiation Therapy and Virus Activation

Activation of latent viruses after radiation treatment is one of the concerns raised against LDRT. It is based on a few publications,<sup>[19-24]</sup> which were reviewed in the context of LDRT. In one of the cited papers, reactivation of Latent Epstein-Barr Virus (EBV) was studied in Akata cells (with a latent EBV episome) after exposure (0.1–2 Gy) to Cs-137 gamma radiation.<sup>[20]</sup> The activation was evaluated at the RNA level of two key EBV lytic genes [BZLF1 (an immediate-early gene that codes for ZEBRA or Zta, an important trans-activator critical for reactivation) and BLLF1 (a late gene that codes for the envelope glycoprotein gp350)]. In this paper, 0.1 Gy gamma irradiation did not significantly change the transcription of BZLF1 but caused a significant increase in BLLF1. However, these are *in vitro* results and derived from a transformed cell line. In another study, treatment of T cells and monocytes at the therapeutic dose of radiation (5 Gy) led to an increase of HIV-1 transcription, which was also validated in HIV-1 infected humanized mice.<sup>[23]</sup> In a similar study, activation of herpes simplex virus was observed at a dose range of 5–10 Gy.<sup>[21]</sup> Spread of an apathogenic rabies virus was studied in the mouse brain after cranial irradiation (2–6 Gy). At the doses of 4 and 6 Gy, an increase in the viral spread was observed but not at 2 Gy.<sup>[19]</sup> An increase in antibody was observed in influenza A virus-infected juvenile pups after 5 Gy whole-body-irradiation but not in mice internally injected with 50 µCi soluble <sup>137</sup>Cs that delivered 2.5–2.7 Gy over 50 days (0.05 Gy/day). In fact, the viral load is similar in irradiated (externally and internally) and nonirradiated groups.<sup>[24]</sup> An increased susceptibility to death was observed in influenza virus-infected mice after lung irradiation but in the dose range of 10–15 Gy.<sup>[22]</sup> Based on these publications, virus activation occurring at low doses could not be well established. In fact, activation of latent viruses was reported at relatively higher doses (more than 4 Gy), which may not be appropriate to be linked with low doses. Moreover, due to lack of immune system, the observations at

**Table 1: Details of low-dose radiation therapy clinical trials for coronavirus 19 disease patients Source: US National Library of Medicine, ClinicalTrail.gov.<sup>[15]</sup>**

Clinical trial number; title of the study	Institute/hospital, country	Dose of radiation/ frequency	Major inclusion criteria	Major exclusion criteria	Phase of the study
NCT04394793; Low Dose Radiation Therapy for Covid-19 Pneumonia: A Pilot Study	All India Institute of Medical Sciences, New Delhi, India	Single 70 cGy to lungs	COVID-19 positive, patients with National Early Warning Score $\geq 5$ . Age >18 years	Patients on mechanical ventilatory support, hemodynamically unstable	Not applicable
NCT04366791; The RESCUE 1-19 Trial: Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19	Emory University Hospital Midtown/ Winship Cancer Institute, Atlanta, Georgia, United States	Single fraction of whole lung low-dose radiation therapy*	COVID-19 positive; clinical signs of severe acute respiratory syndrome or pneumonia; visible consolidations/ ground glass opacities on chest X-ray or computed tomography; received pre-intubation respiratory support or undergone endotracheal intubation and have been on ventilator support for no >5 days; age >18 years	Pregnant and/or planned to be pregnant within in next 6 months	1 and 2
NCT04433949; RESCUE 1-19: A Randomized Phase III of Best Supportive Care $\pm$ Whole Lung Low-Dose Radiation Therapy in Hospitalized Patients	Emory University Hospital/Winship Cancer Institute, Atlanta, Georgia, United States	LDRT (whole lung)*	COVID-19 positive; clinical signs of severe acute respiratory syndrome or pneumonia; visible consolidations/ ground glass opacities on chest imaging; requiring supplemental oxygen; age >18 years	No use of disallowed medications prior to randomization (remdesivir or approved drug treat COVID); pregnant and/ or planned to be pregnant within in next 6 months	3
NCT04427566; 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	Arthur G. James Cancer Hospital and Solove Research Institute at Ohio State University Medical Center, Columbus, Ohio, United States	Single dose of 80 cGy to the bilateral lungs	COVID-19 positive based on reverse transcriptase PCR; CT findings typical of COVID-19 pneumonia; receiving ICU-based mechanical ventilation; life expectancy $\geq 24$ h; hypoxemia defined as Pa/FiO <sub>2</sub> ratio <300 or SpO <sub>2</sub> /FiO <sub>2</sub> <315; age >18 years	Expected survival <30 days due to chronic illness present prior to COVID-19 infection; immune suppressing medications in last 30 days; chronic hypoxemia requiring supplemental oxygen at baseline; active connective tissue disease (scleroderma) or idiopathic pulmonary fibrosis; history of prior radiation therapy resulting in $\geq$ grade 2 radiation pneumonitis within 365 days; active or history of prior radiation to the thorax completed within 180 days; known active uncontrolled bacterial or fungal infections of the lung; active cytotoxic chemotherapy; females who are pregnant or have a positive pregnancy test, breast feeding	2

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Table 1: Contd...

Clinical trial number; title of the study	Institute/hospital, country	Dose of radiation/ frequency	Major inclusion criteria	Major exclusion criteria	Phase of the study
NCT04414293; Phase II Study of Low Dose Pulmonary Irradiation in Patients With COVID-19 Infection of Bad Prognosis	Hospital Provincial de Castellon, Castellón De La Plana, Castellon, Spain	Low-dose lung radiation (0.5-1.0 Gy)	COVID-19 positive with severe disease (presence of unilateral or bilateral pulmonary infiltrates in chest X-ray or computed tomography; acute respiratory failure P/F <300; lymphopenia $\leq 0.8 \times 10^9/L$ ; patients within $\leq 8$ days from the onset of symptoms; age >65 years	Patient not consent to participate	Not applicable
NCT04466683; Phase II Protocol of Low-Dose Whole Thorax Megavoltage Radiotherapy for Patients With SARS-COV-2 Pneumonia	Ohio State University Comprehensive Cancer Center, United States	Low radiation arm: A single dose of 35 cGy to whole thorax; high radiation arm: A single dose of 100 cGy to whole thorax; selection of best radiotherapy dose-arm after 20 patients	COVID-19 positive with pneumonia; hospitalized with COVID-19; at least one of the following risk factors for significant pulmonary compromise: fever $> 102^\circ F$ , respiratory rate of $\geq 26/min$ within 24 h of screening; $SpO_2 \leq 95\%$ ; ratio of P/F <320; age: 50 years and older	Patients on mechanical ventilation; prior thoracic radiotherapy (exception breast or postmastectomy chest wall radiation; thoracic skin radiation therapy); hereditary syndrome with increased sensitivity to radiotherapy; known prior systemic use of the drugs; history of or current diagnosis of lung disorders, malignancy receiving any cytotoxic chemotherapy or immunotherapy within the past 6 months and bone marrow transplantation; females who are pregnant or breast feeding	2
NCT04393948; Pilot Study of Low-Dose Single or Bilateral Whole Lung Irradiation for SARS-CoV-2 Pneumonia	Brigham and Women's Hospital, Boston, Massachusetts, United States	100 cGy single lung radiation; 100 cGy bilateral lung radiation	COVID positive $\leq 3$ days or progressive disease $\leq 14$ days; age $\geq 40$ years; may receive antiviral medication and/or convalescent plasma	Prior or planned treatment with interleukin inhibitors or TNF- $\alpha$ inhibitors; prior lobectomy or pneumonectomy, thoracic radiotherapy, chemotherapy or other systemic therapy or immunotherapy; history of bone marrow or solid organ transplantation, autoimmune collagen vascular disease, hereditary syndrome with increased sensitivity to ionizing radiation; pregnancy	Not applicable
NCT04493294; Low Dose Whole Lung Radiotherapy for Older Patients With COVID-19 Pneumonitis: Practical Protocol by the International Geriatric Radiotherapy Group	Institute of Radiation Oncology, Cantonal hospital Graubunden, Chur, Switzerland	Low dose whole lung radiotherapy*	Age $\geq 65$ years with proven COVID-19 pneumonitis who may or may not require oxygen	Require artificial ventilation or hemodynamically unstable	1 and 2

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Table 1: Contd...

Clinical trial number; title of the study	Institute/hospital, country	Dose of radiation/ frequency	Major inclusion criteria	Major exclusion criteria	Phase of the study
NCT04377477; Pilot Study on the Feasibility of Low Dose Radiotherapy for SARS-Cov-2 Pneumonitis (COLOR 19)	Radiation Oncology Department, ASST Spedali Civili, Brescia, Brescia, Italy	Single fraction whole lung radiotherapy of 0.7 Gy	Age $\geq$ 50 years; Covid positive ; patient with Brescia Covid Respiratory Severity Scale score 2-3; interstitial pneumonia on chest X-ray and/or chest CT); At least 3 of the following laboratory criteria (PCR >5 times the maximum limit of the normal value; ferritin >500 ng/ml; LDH >2 times the maximum limit of the normal value; D-dimer >3 times the maximum limit of the normal value; AST>2 times the maximum limit of the normal value; total lymphocytes <1000/ml; negative pregnancy test	Patients undergoing invasive mechanical ventilation; patients with active autoimmune systemic diseases	Not applicable
NCT04390412; Assessment of Adding Low Dose Pulmonary Radiotherapy to the National Protocol of COVID-19 Management: A Pilot Trial	Imam Hossein Hospital Tehran, Iran, Islamic Republic of Iran	0.5 Gy radiation to both lungs; may be another fraction of 0.5 Gy (maximum 1 Gy in two fractions at least 72 h apart)	COVID-19 positive; presence of pulmonary involvement; less than 3 days since the onset of ARDS; age >60 years; $\uparrow$ IL-6; $\uparrow$ CRP	Hemodynamic instability; septic shock and organ dysfunction; severe ARDS P/F ratio $\leq$ 100 mmHg; history of cardiac failure; contraindications to radiation	1 and 2
NCT04420390; Low Dose Radiotherapy as Anti-inflammatory Treatment for COVID-19 Pneumonitis	Servicio de Oncología Radioterápica. Hospital Clínico San Carlos Madrid, Spain	Low-dose radiotherapy*	Age $\geq$ 60 years; COVID-19 positive; Phase II or lung phase without any improvement with pharmacological treatment; Phase III or hyper-inflammatory phase without any improvement with pharmacological treatment; poor clinical and functional respiratory evolution (>30 breaths/min, SpO <sub>2</sub> <93%, P/F<300, D-dimer>1000 ng/mL or rising, ferritin >1000 ng/mL, PCR >10 mg/dL or double than before)	Severe comorbidities that could hamper the radiation treatment	Not applicable
NCT04380818; Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19: Multi-central Prospective Study	Hospital Sant Joan de Reus, Tarragona, Spain, Hospital Del Mar, Barcelona, Spain, Hospital Universitario, Madrid, Sanchinarro Madrid, Spain	Bilateral low-dose lung irradiation: 0.5 Gy in a single fraction. Optionally, additional 0.5 Gy fraction 48 h later	Age $\geq$ 18-99 years; moderate-to-severe COVID-19 pneumonia; Pa/FIO <sub>2</sub> <300 mmHg; one of the following conditions: IL-6 >40 or PCR >100 mg/L, D-dimer greater than 1500 ng/ml, suspected cytokine release syndrome	Leukopenia <1000; pregnancy	Not applicable

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**Table 1: Contd...**

Clinical trial number; title of the study	Institute/hospital, country	Dose of radiation/ frequency	Major inclusion criteria	Major exclusion criteria	Phase of the study
NCT04394182; Low Doses of Lung Radiation Therapy in Cases of COVID-19 Pneumonia: Prospective Multicentric Study in Radiation Oncology Centers	Hospital La Milagrosa, GenesisCare, Madrid, Spain, Hospital Vithas Valencia Consuelo, Valencia, Spain	Single 0.8 Gy including both whole-lungs extended 1 cm isometric in all directions	Age >18-122 years; pneumonia due to COVID-19; Charlson Comorbidity Index <6; poor or no response to standard medical treatment, based on: % SPO2<93%, P/F <300 mmHg; 1 or more inflammatory and immunological analytical parameters (lymphocytes, IL-6, D-dimer, ferritin, LDH, CRP and fibrinogen) more than normal range except lymphocytes; life expectancy >1 month; no previous thoracic radiotherapy or chemotherapy	Any uncontrolled intercurrent illness that would put the patient at greater risk or limit compliance with study	Not applicable

See addendum for full form of abbreviations

individual cell level under *in vitro* conditions may be difficult to get extrapolated up to complex *in vivo* systems. In the contrary, the curative effect of split low dose total-body irradiation (150 cGy) on mice infected with the Friend Virus Complex was reported involving interferon-gamma and IL-2.<sup>[25,26]</sup> Inflammation and associated DNA damage are known to be governed by cellular mitochondrial activity. In this context, in our publications, the enhanced mitochondrial protein import<sup>[27]</sup> and DNA damage repair<sup>[28]</sup> shown in human normal cells after low dose radiation (10 cGy) may contribute in overall survival/recovery of virus-infected cells, which, however, need further investigation.

### Lung Injury and Radiation Risk in Low Dose Radiation Therapy

Another apprehension of LDRT in COVID-19 patients is lung injury and radiation pneumonitis (RP).<sup>[29-31]</sup> These studies were based on lung fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake (a surrogate marker of inflammation) to predict the susceptibility of radiation-induced lung toxicity/RP. Lung cancer patients with high FDG uptake reported prior to radiotherapy (mean lung dose 5–30 Gy) were found more likely to develop symptomatic RP.<sup>[30]</sup> Based on lung FDG-PET uptake, other studies showed increased susceptibility to radiation-induced lung toxicity/RP in cancer patients with mean lung dose >5.8 Gy<sup>[31]</sup> and 2–5 Gy.<sup>[29]</sup> RP, observed during cancer radiotherapy, occurs in high-risk patients (~40% incidence) with mean lung dose >20 Gy.<sup>[32]</sup> Data from ninety-seven studies of stereotactic body radiation therapy were analyzed for radiation-induced lung toxicity including

RP and pulmonary fibrosis. Most studies showed safe treatment with a rate of symptomatic lung toxicity of <10%-15% at a mean lung dose of the combined lungs ≤8 Gy (in 3–5 fractions) and the percent of total lung volume receiving more than 20 Gy <10%–15%.<sup>[33]</sup> In another study with ~600 breast cancer patients undergone radiotherapy, the prevalence of pneumonitis was 1.8% with potential risk at mean radiation dose to ipsilateral lung >7 Gy.<sup>[34]</sup> To investigate radiation-induced edema,<sup>[35]</sup> effect of low dose radiation (<200 cGy) was studied in terms of the cell-cell integrity in pulmonary microvascular endothelial cells. In this study, evaluation of lung edema after a low dose of radiation is based on the measurement of lung weight of control and irradiated animals. In this regard, it may be worth citing a publication, in which pulmonary response after low doses (2-200 mGy) and 4 Gy whole-body irradiation was studied in the rat model. Lung injury was assessed via multiple cellular and functional parameters such as respiratory mechanics, pulmonary edema, cellular, and proteinaceous fluid infiltrate, and oxidative stress markers. These measured lung parameters did not differ from sham-irradiated animals except for an increase in catalase after high dose (4 Gy) exposure.<sup>[36]</sup> The apprehension about lung radiation-induced lung toxicity/RP is based on either *in vitro* observation<sup>[35]</sup> or at high radiation doses<sup>[29-31]</sup> not matching with dose range during LDRT. On the other hand, the studies supporting the use of LDRT for the treatment of pneumonia<sup>[12-14,37]</sup> may be old<sup>[16]</sup> but derived from patients providing superior clinical information than the *in vitro* observations. The risk of genetic abnormalities and secondary malignancies in the case of LDRT of COVID-19 patients<sup>[18]</sup> have been raised, which is supported in the literature.<sup>[38,39]</sup> On the other

side, counter-arguments negate such risk advocating the hermetic effects at low dose of radiation.<sup>[40,41]</sup> However beyond the debate, in a health crisis scenario with average global fatality ~3.5% (as on August 12, 2020<sup>[1]</sup>) and without effective treatment available, LDRT needs better consideration for long-term risk versus immediate benefit if can be used to save human lives especially in geriatric patients with lower risk of second cancer due to short life expectancy.<sup>[42,43]</sup> While raising the above concerns, some publications are not mentioned with the dose/dose rate and the experimental model used. The absence of such basic information may result in incomplete and/or wrong first level information to the readers. Hence, the author opines that to avoid any such ambiguity, radiation biology publications should be included with information like dose/dose rate/type of radiation and experimental models used in the study.

### Immune Activation in Low Dose Radiation Therapy

Low dose of radiation has been shown to activate the immune system in various experimental models<sup>[7-11]</sup> which however been not well considered while raising the concerns about LDRT. Like any viral infection, in the case of SARS-CoV-2 also, activation of T- and B-cell responses will play a crucial role in pathogenesis and control of the disease. Activation of CD8+ T and dendritic cells are known at the lower doses of radiation,<sup>[9-11,25]</sup> which will facilitate to attack and eliminate the virus-infected cells. Low level of radiation stimulates the immune system acting at cellular and molecular levels of immune and other cells. Low dose of radiation (<1 Gy) is known to polarize the M2 phenotype of macrophages involved in anti-inflammatory and tissue repair processes. These activated immune cells (like IL10-producing lung macrophages), in turn, would facilitate to control the cytokine storm caused due to infection of virus.<sup>[5,44]</sup> Mechanistic insights of LDRT at clinical level could be also gained from the anti-inflammatory effect of radiation to control the pain in nonmalignant degenerative diseases, especially when the option for nonsteroid anti-inflammatory drugs or corticosteroids is not available. LDRT is known to activate endothelial cells and reduced leukocyte adhesion, which results in decreased expression of selectins and the production of anti-inflammatory cytokines. Moreover, LDRT is known to impair the oxidative stress<sup>[45,46]</sup> and nitric oxide<sup>[47,48]</sup> pathways, which would ultimately act behind the anti-inflammatory role of LDRT. Overall, LDRT, through its anti-inflammatory processes would likely to prevent the damage caused through pro-inflammatory cytokines/chemokines released after virus infection and mitigate the associated clinical symptoms of pneumonia/ARDS in COVID-19 patients.<sup>[4,5]</sup>

### Optimizing Low-Dose Radiation Therapy Parameters

Infection of SARS Cov-2 virus initially activates the host's immune system; however, weak/suppressed immune system subsequently facilitates the progression of the disease. At the pro-inflammatory phase of the disease, LDRT will be more beneficial where anti-inflammatory treatments such as steroids and other cytokine inhibitors are employed. Hence, likely synergy of LDRT in such window period of the disease would be effective for control of pneumonia/ARDS in COVID-19 patients. Local lung irradiation and low dose whole-body irradiation (LDWBI) are the options available for LDRT application in COVID-19 patients. Most of the recent literature and clinical trials related to LDRT for control of pneumonia/ARDS in COVID-19 patients are aimed for lung irradiation. LDWBI has been employed for the treatment of cancer<sup>[49-51]</sup> as it would cause systemic activation of the immune system. Due to this reason, LDWBI is thought to have higher efficacy than lung irradiation.<sup>[16]</sup> The target of the SARS-Cov-2 virus is not limited to the lungs, but it infects/affects other critical organs like the heart and kidney. Hence, activation of systemic immune response after LDWBI would likely to have better control of the viruses than local lung irradiation. However, these two modalities of irradiation need a better comparison in terms of complications, risk, and therapeutic gain.

### Conclusions

Due to a lack of direct pre-clinical/clinical evidence using SARS-Cov-2 models, at this point, LDRT may be not the first line of therapy. However, based on existing anti-inflammatory evidence of LDRT at non-COVID animal/patient levels, it needs encouragement as an adjuvant therapy and for more multi-centric clinical trials. In addition, it would be worth combining LDRT with other therapies like convalescent plasma therapy<sup>[6]</sup> and other anti-inflammatory strategies (like cytokine inhibitors, steroids), which would open more avenues for multi-modal therapy of pneumonia/ARDS in COVID-19 patients. For effective clinical outcomes of LDRT, various parameters (like window period, dose, frequency, and mode of irradiation) need to be optimized using suitable immuno-competent animal models (rodents or primates). However, considering ample existing evidence, it is time to look beyond the apprehensions if a low dose of radiation could be exploited for better management of COVID-19 patients.

### Addendum

**Low-dose radiation therapy clinical trials for coronavirus 19**

Search criteria: COVID-19 (disease) + LDRT (other term). \*Dose not mentioned. PaO<sub>2</sub> (in mmHg)=Arterial oxygen partial pressure, FiO<sub>2</sub>=Fractional inspired oxygen, LDRT=Low dose radiation therapy, RESCUE 1-19=Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19, COVID-19=Coronavirus 19 disease, COLOR-19=COVID-19 Pneumonitis Low-Dose Lung Radiotherapy, LDH=Lactate dehydrogenase, AST=Aspartate aminotransferase, CRP=C-reactive protein, SPO<sub>2</sub>=Oxygen saturation, PCR=Polymerase chain reaction, IL-6=Interleukin-6, P/F=PaO<sub>2</sub>/FiO<sub>2</sub>, ARDS=Acute respiratory distress syndrome, CT=Computed tomography, TNF=Tumor necrosis factor, ICU=Intensive care unit.

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### Conflicts of interest

There are no conflicts of interest.

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