

Low-dose radiation therapy: a treatment for pneumonia resulting from COVID-19

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Introduction

Lung is the primary organ which the COVID-19 virus affects and leads to pneumonia, an acute respiratory distress syndrome (ARDS). COVID-19 infects the lower respiratory system, and the lung's response to this infection is recruiting macrophages and monocytes leading to inflammation, this response causes widespread damage to the lung's airways. Activating cytokines leads to the migration of macrophages and monocytes to parts of lung infected with the COVID-19 virus.

After irradiating these cells with low radiation doses (0.01–2 Gy), the monocyte adhesion is significantly enhanced, and the mechanism of this phenomenon activates tumor necrosis factor- α after irradiation. For mammalian cells, hyper-radiosensitivity and induced radioresistance are determined below 0.3 Gy and in the dose range of 0.3 Gy to 0.6 Gy,

Materials

In this paper, we review the available literature on the use of low-dose radiation in improving inflammation and pneumonia. Hence, in vivo and in vitro studies evaluating the anti-inflammatory effects of low-dose radiation on different cell lines and animals, as well as twelve recent clinical studies, in which the effects of low-dose radiotherapy in the treatment of patients with coronavirus disease has been evaluated. The results of most of these clinical studies have not yet been published.

Published paper for this literature review were identified by searching PubMed database from 1940 onwards with the following Medical Subject Heading terms 'pneumonia', 'COVID-19', 'coronavirus', 'inflammation', 'low dose Radiotherapy'. Articles in English language were reviewed.

Humans studies of using LDRT to treat COVID-19

A clinical study was recently carried out on five patients with COVID-19 in the age range of 64–96 years, in which the patients' lungs were exposed to 1.5 Gy of radiation in one fraction for 10–15 minutes. In four patients in the first 24 hours of exposure, their respiratory condition was quickly improved. The results of blood tests and imaging also confirmed the positive effect of low-dose radiation on COVID-19 treatment.

Another study of five patients with COVID-19 aged over 60 years who underwent national COVID-19 therapy protocols showed that using 0.5 Gy of radiation in one fraction led to the improvement of four patients in the first few days after exposure.

Table 1 summarizes 12 different groups throughout the

world are applying low doses in the treatment of COVID-19 in humans.

One of the controversies surrounding the use of low-dose radiation therapy in the treatment COVID-19 is the incidence of cancers such as lung, esophagus and breast cancer.

Using BEIR VII model to estimate the risk of lung cancer at 0.5Gy for patients with coronavirus disease aged 25, 45, 65 years and treated by low-dose radiation, the incidence of lung cancer can increase by 2.1%, 2.09% and 1.68%, respectively, for men, or almost three times for women.

According to this model, with an increase in the dose received by the lungs, the risk of lung cancer increases linearly.

Table 1. Studies are applying low doses in the treatment of COVID-19 in humans (*Severe Acute Respiratory Syndrome)

Title	Location	Dose	Participations	Conditions	Interventions	Estimated Study Completion Date
Low Dose Radiotherapy for COVID-19 Pneumonitis (LOWRAD-Cov19)	Madrid, Spain	≤ 1 Gy	41	COVID-19	Low-dose radiation	8 September 2020
COVID-19 Pneumonitis Low Dose Lung Radiotherapy (COLOR-19)	Brescia, Italy	0.7 Gy	30	COVID-19	Low-dose radiation	23 July 2022
Low Dose Pulmonary Irradiation in Patients With COVID-19 Infection of Bad Prognosis (COVRTE-19)	Castellon, Spain	0.5–1 Gy	41	COVID-19 PneumoniaViral	Low-dose radiation	31 March 2021
Ultra Low Doses of Therapy With Radiation Applied to COVID-19	Valencia, Spain	0.8 Gy	15	Pneumonia, Viral Cytokine Storm	Low-dose radiation + drug	21 April 2021
Best Supportive Care With or Without Low Dose Whole Lung Radiation Therapy for the Treatment of COVID-19 (RESCUE1-19)	Georgia, United States	–	52	Pneumonia SARS* COVID-19 Infection	Low-dose radiation	30 May 2022
Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19	Tarragona, Barcelona Madrid, Spain	0.5 Gy additional 0.5 Gy fraction 48 h later	106	Pneumonia, Viral	Low-dose radiotherapy + Drug	1 July 2021
Low Dose Whole Lung Radiation Therapy for Patients With COVID-19 and Respiratory Compromise (VENTED)	Ohio, USA	0.8 Gy	24	COVID-19	Low-dose radiation	31 December 2021
Low Dose Radiation Therapy for Covid-19 Pneumonia	New Delhi, India	0.7 Gy	10	COVID Pneumonia	Low-dose radiation	July 2020
Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 (RESCUE 1-19)	Clayton Hess, Emory University	—	10	SARS COVID Pneumonia	Low-dose radiation	23 October 2020
Lung Irradiation for COVID-19 Pneumonia	Boston, USA	1 Gy	48	SARS-COVID-Pneumonia	Low-dose radiation	October 2020

In vivo and In vitro Studies

The anti-inflammatory effect of radiation on the lungs is through modulation of cytokine and adhesion molecule expression on activated endothelial cells and leukocytes and on nitric oxide (NO) production and oxidative burst in activated macrophages and native granulocytes. The highest efficiency was reported at doses of 0.3–0.7 Gy.

In addition, the in vitro studies suggest that low-dose radiation therapy (LD-RT) has a potent anti-inflammatory effect, inhibiting leukocyte–endothelium interactions at doses <0.7 Gy. In contrast, inflammatory and degenerative bone diseases in humans are treated with doses ranging from 0.3 to 1.5 Gy. Thus, using lower doses in the range 0.1–0.3 Gy could maximise anti-inflammatory effects and minimise toxicity.

In vivo studies indicated that the effects of LD-RT on decreasing inflammation are realised by the effects of these radiations on endothelial cells, mononuclear cells and macrophages. The doses used in these studies were in the range of 0.3–1 Gy. Studies on animals whose lungs have been directly affected by bacterial and viral pneumonia have indicated that low-dose application has been able to significantly decrease mortality in animals that received low doses in one fraction in comparison to those which did not receive the dose

Conclusion

A review of in vitro and in vivo studies showed that the use of low doses up to 1.5 Gy eliminates tissue inflammation and pneumonia by stimulating macrophages. Although completed clinical studies on the use of low doses in the treatment of COVID-19 are limited, the results of these studies have indicated that low-dose lung irradiation up to 80% has been effective in treating inflammation and pneumonia caused by COVID-19.

Calculations indicated that within the recommended dose range in clinical studies (up to 1 Gy), the risk of lung cancer did not remarkably increase. It is hoped that ongoing clinical studies using this method will be completed as soon as possible, and their results will be positive in COVID-19 treatment.