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RADIOTHERAPY AGAINST SARS-COV-2: RISK OR BENEFIT

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ABSTRACT: The noble coronavirus SARS-CoV-2 results in a devastating, multisystem disease among which COVID-19 pneumonia creates serious complications and most of COVID-19 related deaths. COVID-19 patients develop a systemic inflammatory response through interleukin (IL) and tumor necrosis factors. In COVID-19 patients, cytokine storm controlling is the key step for treatment because cytokine attacks own body cells instead of fighting with the virus. We reviewed several literatures to summarize the safety and efficacy of LD-RT in COVID-19 patients. Low dose chest radiation may reduce the inflammation in the lungs in severely ill patients. The radiation offset an immune system called AS a cytokine storm. Several randomized/non-randomized, single/multi-centered, open/close clinical trials are underway in U.S, India, Iran and around the globe. Early studies showed LD-RT reduces the inflammatory cytokines, time of hospitalization, duration of ventilation, and a number of deaths. However, some researchers warned for radiation-induced cancer (lung, breast, and esophageal) and cardiovascular diseases. So, further extensive preclinical studies should be conducted to identify the risk-benefit ratio in COVID-19 patients.

INTRODUCTION: A novel coronavirus was outbroken in Wuhan, China [1, 2]. Later the World Health Organization (WHO) named as Coronavirus Disease 2019 (COVID-19) [3] and declared a pandemic on 11th March. As of now, COVID-19 affected all the countries around the globe [4]. The high rate of transmission and rapid escalation in several COVID-19 cases resulted in an unpredictable strain in the healthcare system worldwide [5, 6]. Currently, there are no proven effective treatments, so; there is an urgent need against clinical trials to test new therapeutic interventions [7, 8].

Acute respiratory distress syndrome (ARDS), sepsis, pneumonia and respiratory failure are distinguished as severe COVID-19 9 and the lungs are the vital organ commonly affected by COVID-

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19 [10]. The majority of patients with a respiratory illness can, in some, progress to a life-threatening acute respiratory distress syndrome (ARDS) [11] associated with a systemic inflammatory response govern by the rapid escalation in the release of pro-inflammatory cytokines [12], such as interleukin-1, interleukin-6 and tumor necrosis factor-α. Radiotherapy is a commonly used modality for the treatment of cancers either for curative or palliative purposes [13]. Radiation damage tumor as well as normal cells by generating free radicals [14, 15]. To obtain better results from the high dose of radiotherapy, the surrounding normal tissues should be protected against radiation [16]. Thus, the radio-protective agents are very important in clinical radiotherapy [14]. These free radicals are resulting from the aqueous hydrolysis of water present in cells. Thus, formed free radicals react with cellular macromolecules such as DNA, RNA, Protein, *etc.*, leading to cell damage and cellular death [14]. In the 20th century lobular pneumonia caused a serious risk of mortality. In the 1930s, radiotherapy was discovered as an alternative to serum therapy for pneumonia patients because of its wide range of success in different inflammatory and infectious diseases such as sinusitis, arthritis, gas gangrene, carbuncles. Radiotherapy was also broadly accepted by the radiological community due to its wide success in different areas [17].

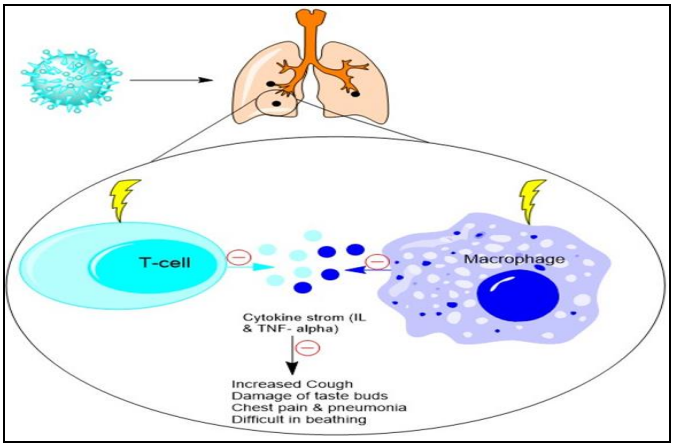

FIG. 1: PATHOPHYSIOLOGY OF CORONAVIRUS IN LUNG CELLS AND PROBABLE MECHANISM OF ACTION OF LOW DOSE RADIOTHERAPY (LD-RT) ON COVID-19 PATIENTS.

COVID-19 pneumonia critically ill patients, develop a systemic inflammatory response with a cytokine release syndrome (CRS) [18, 19]. Low dose radiotherapy (LD-RT) can cause apoptosis and decrease the adhesion of leukocytes to endothelial cells, relieve pro-inflammatory effects associated with macrophages through depletion of nitric oxide secretion and reactivation of oxygen species [20]. LD-RT also reduces the COVID-19 inflammatory cytokines, namely, IL-1β, IL-2, IL-6, IL-8 and TNF-ϒ [21]. COVID-19 activates both innate and adaptive immunity systems [23] so, reducing the inflammatory response in COVID-19. The patient's is the important step in reducing mortality of disease [22, 24]. The probable mechanism of action and pathophysiology is elucidated in **Fig. 1.** To reduce the inflammatory response, different medications such as steroids, monoclonal antibodies and IL-6 inhibitors were found to some effective. In contrast, toxicity-related steroids and lesser effectiveness of other medication driven us to approach a new treatment strategy, *i.e.*, radiotherapy. LD-RT may reduce the lung's hyper-activation and relief of the COVID-19 symptoms in hospitalized patients [25].

COVID-19 Induced Immune Responses: COVID-19 patients develop a Cytokine Release Syndrome (CRS), marked by a sudden increase in pro-inflammatory cytokines, namely IL-1, IL-6, and TNF-α [26]. Those cytokines were also observed in SARS-CoV, MERS CoV, and COVID-19 pneumonia [27]. COVID-19 activates both innate and adaptive immunity. Macrophages seem to be a key component of CRS syndrome, phagocytic activity of macrophages was through the donger-associated molecular patterns (DAMPS) activated by Troll-like receptors (TLR). COVID-19 is activated by TLRs, which subsequently trigger the release of cytokines from macrophages. The activated macrophages manage and repair the inactive tissue-destructive M 1 responses [28]. They also activate immune regulatory proteins such as IL-10, resistin-like molecules-α (RELMα), chitinase-like proteins, and arginase 1 (ARG1). The initiation and resolution of immune responses critically depend on inflammatory (M1) and suppressive (M2) macrophages [18]. Thus, the neutralization of inflammatory cytokines in COVID-19 pneumonia will be of great value in treating severe patients [39]. However, the regulation and activation of macrophages in COVID-19 were not completely clear.

Management of Immune Responses in COVID-19 Patients: Several pro-inflammatory cytokines,

such as leukotrienes and tumor necrosis factor-α, develop cytokines release syndrome (CRS) [30]. Different off-label medications have shown effectiveness for controlling inflammatory cytokines namely, Tocilizumab, Convalescent plasma, Dexamethasone, and vitamin D. Tocilizumab is a humanized monoclonal antibody that works against interleukin-6 (IL-6) receptors [31, 32]. IL-6 is one of the key inflammatory cytokines present in COVID-19. Convalescent plasma is a passive polyclonal antibody that provides immediate immunity to patients with COVID-19 pneumonia [33] while Dexamethasone is the first-line corticosteroid against chemotherapy-induced nausea and vomiting [34]. Dexamethasone is likely to depletion of B and T cells, which cause immune suppression [35]. A higher dose of corticosteroids may increase the risk of secondary infections [36]. Meanwhile, there is no FDA-approved medication present for COVID-19 [37] so, researchers and scientists are working deliberately to find the medication and vaccine. In the earlier 20th century, radiotherapy was used as a control measure of pneumonia and shown some effectiveness. LD-RT reduces the time of clinical improvement by 3 fold compared to patients receiving COVID-19 directed therapy for COVID-19 pneumonia and also decreases pro-inflammatory effects associated with macrophages. Researches are going on to evaluate the effectiveness of radiotherapy on COVID-19 pneumonia [38].

Low Dose of Radiotherapy for COVID-19 Patients: Radiotherapy has been widely used since the early 20th century in the treatment of pneumonia [39]. Low-dose radiotherapy (LD-RT) has emerged as an evidence-based beneficial alternative to patients who are progressing to or unfit for common anti-inflammatory treatments. Ionizing radiation is able to lower inflammation via various mechanisms, including apoptosis in the immune cells [40] reducing the function of macrophages and secretion of anti-inflammatory factors [41]. Focusing on the use of low-dose radiotherapy in SARS-CoV-2 IL-6-related pneumonia, radiotherapy's role in modifying the monocyte-macrophage axis would be very relevant [42]. According to recent studies, LDRT has the ability to polarize macrophages towards an M2-like phenotype in a rheumatoid arthritis model [43]. In the study, LDRT gave at a single dose of of O.5 Gy influenced M1/M2 balance towards M2 anti-inflammatory phenotype when bone marrow-derived macrophages and fibroblasts like synoviocytes were co-cultured in an experimental model of RA, which suggest that LDRT could play a relevant role in those situations that hyper inflammation resembles RA, through reduction of IL-1 and TNF-alfa target cells producing IL-6. Therefore, a very dose of localized radiotherapy would modify the inflammatory environment in the lung of SARS-CoV-2 IL-6 related pneumonia patients [18, 44]. Radiotherapy doses > 200 cGy tend to show pro-inflammatory effects, which may trigger common toxicities. However, the lower doses (<100 cGy) incite anti-inflammatory properties such as a decrease in the levels of pro-inflammatory cytokines [45] like IL-1 β, or inhibition of leukocyte recruitment.

A single fraction of 30-100 cGy treatment can be given easily on a conventional megavoltage radiation therapy unit [46]. According to the proof of principle simulations, POP treatment with a megavoltage beam could easily ensure 99% of the whole lung volume received between 90% and 120% of the prescribed dose of 70 cGy [44]. However, on a routine basis, much higher single fraction doses can be delivered in a palliative context with fast-tracked patients going through the full workflow process of scanning, planning, and treatment in a matter of hours. Due to the low dose, the common radiotherapy toxicities would be avoided [18].

Researchers at Emory University's Win ship Cancer institute, Georgia was conducted the experiment between 23 to 28 April where five patients of 64-94 years old were treated with low dose radiation therapy. All these patients had pneumonia visible on their chest X-rays, required supplemental oxygen and had declining health. A single dose of radiation (1.5 Gray) was delivered to patient's lungs for 10-15 min. The preliminary studies showed that within 24 h of the therapy, four patients showed rapid improvement in breathing and started to recover at an average of 1.5 days and Were Were discharged on day 14. Blood tests and repeat imaging further confirmed that the therapy showed no toxicities, radiation-related dermatitis or cytopenia. No signs of Increased cytokine storm were observed [47].

TABLE 1: SUMMARY OF DIFFERENT REGISTERED CLINICAL TRIALS OF LOW DOSE RADIOTHERAPY AGAINST COVID-19 AROUND THE GLOBE

S. no.	Clinical trial identifier	Name of trial	Location	Participants	Study start Date	Study completion Date	Study Design
1.	NCT04420390	Low Dose Radiotherapy for COVID-19 Pneumonitis	Madrid, Spain	41	May 1, 2020	September 8, 2020	Single-centered, Open-label
2.	NCT04377477	COVID-19 Pneumonitis Low Dose Lung Radiotherapy (COLOR-19)	Bresica, Italy	30	May 10, 2020	August 30, 2022	Single-centered, Open-label
3.	NCT04534790	Anti-inflammatory Effects of Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia	Leon, Guanajuato, Mexico	30	July 24, 2020	January 8, 2021	Randomized, Open-label trial
3.	NCT04390412	Low Dose Radiotherapy in COVID-19 Pneumonia.	Tehran, Iran	5	May 4, 2020	December 2020	Single-center, Open-label
4.	NCT04414293	Low Dose Pulmonary Irradiation in Patients with COVID-19 Infection of Bad Prognosis	Castellon, Spain	41	October 1, 2020	December 31, 2021	Single-centered, Open-label
5.	NCT04394182	Ultra-Low Doses of Therapy With Radiation Applicated to COVID-19	Madrid, Valencia, Spain	15	April 21, 2020	April 21, 2021	Single-centered, Open-label
6.	NCT04433949	Best supportive care with or without Low Dose Whole Lung Radiation Therapy for the treatment of COVID-19	Georgia, USA	52	June 12, 2020	May 30, 2022	Randomized, multi-centered
7.	NCT04380818	Low Dose Anti-inflammatory Radiotherapy for the treatment of pneumonia by COVID-19	Tarragona, Barcelona, Madrid, Spain	106	June 5, 2020	July 1, 2021	Nonrandomized, Parallel control and Open-label
8.	NCT04427566	Low Dose Lung Radiation Therapy for patients with COVID-19 and respiratory compromise (VENTED)	Ohio, USA	24	July 23, 2021	December 31, 2021	Single-centered, Open-label
9.	NCT04394793	Low Dose Radiation Therapy for COVID-19 Pneumonia	Delhi, India	10	June 13, 2020	September 2020	Single-centered, Open-label
10.	NCT04366791	Radiation eliminates storming cytokines and unchecked Edema as a 1-Day treatment for COVID-19 (RESCUE 1-19)	Atlanta, USA	10	April 24, 2020	March 16, 2022	Single-centered, Open label

A recent study was conducted in Imam Hossein Educational Hospital, Iran from 21 May -24 June 2020. Individuals with positive polymerase chain reaction Tests, antibody tests and patients which require oxygen supplementation who enrolled. 5 out of 40 eligible patients (4 males and 1 female) Ageing 60-84 years (mean: 71.8 years) were approached for the clinical trials. All patients were allowed to receive a single fraction of O.5 Gy to the whole lungs. All these participants were planned with AP/PA photon fields with a 3-dimensional conformal technique with the help of The ISO gray treatment planning system. Tympanic membrane thermometry was used to assess core body temperature. Performance status, Blood oxygenation, CRP, Vital signs, and IL-6 were assessed at baseline. 4 out of 5 patients (80%) recovered from oxygen saturation on day one. Therefore, with a single fraction of of O.5 Gy had encouraging results in oxygen-dependent patients [48]. 10 patients with COVID-19 pneumonia were treated with lung radiation by the doctors at Emory University in Atlanta, the USA in a randomized controlled trial and compared them with 10 patients of the similar age group who received usual normal treatment apart from radiation. The patients with radiotherapy treatment showed significant improvement in 3 days, whereas the controlled group patients took 10 days to show any significant improvement. The other benefits of LDRT shown by this study are the shorter average time to hospital discharge (*i.e.* 12 days with radiation whereas 20 days with usual treatment) and also the lower risk of mechanical ventilation (only 10%

with radiation) than usual treatment (40%) [47]. Throughout the world, trials of low-dose radiation therapy are being carried out, including the countries like Spain, U.S., Italy, India, Iran and so on. These studies are participating around 5 to 106 volunteers with covid-19 pneumonia in which half of the patients are at least 40 years of age.

Ohio State Radiation and Oncology department is dividing LDRT trials into two groups, the first trial being PREVENT, which 100 oxygen-dependent patients will be selected at 20 different hospitals around U.S. and the second trial named VENTED, unlike the previous is limited only in to Ohio State, where only 24 critically ill patients requiring ventilated support will be enrolled. Apart from this, VENTED is not restricted to older patients like PREVENT and is open to participants of and above 18 years old. Ohio State University Comprehensive Cancer Centre is conducting a randomized Phase II Clinical trial for low dose whole thorax megavoltage radiotherapy with 100 participants from July 1, 2020. The participants will be randomized 2:1 to receive radiation therapy of 2 different doses, (35 cGy and 100 cGy doses) or control (with no radiation). Doctors are planning to find out the best dose for radiation therapy. The sixty patients will be selected to 3 arms (low dose, high dose, and control arm) and best dose will be chosen. After this, randomization of an additional [40] participants will be performed in 2:1 to find out the best suited dose versus control with no radiation [49].

The clinical trial conducted in AIIMS, India to study the effects of one-time low dose radiation therapy to treat COVID-19 symptoms. The Pilot study was conducted from June to August 2020, nine out of 10 patients recovered within 3-7 days. One patient having hypertension showed clinical deterioration and died after 24 days. Less than 1 Gray was used for the study and trial carried out in those patients who needing oxygen support or mechanical support [50].

Risk of Radiation-Induced Cancer in COVID-19 Patients: There is no FDA-approved COVID-19 medications; some researchers have experimented 0.5-1 Gy of whole thorax radiation therapy would decrease risk to COVID-19 patients in a clinical trials. It can be believed that LD-RT could revamp inflammation and benefit COVID-19 patients. However, radiotherapy will kill B and T cells necessary to fight SARS-CoV-2, which ultimately increases the risk of mortality from COVID-19. Although the risk generated by 0.5-1 Gy radiation can be evaluated, the risk of radiation exposure to cancer, and cancer mortality was different in males lung and esophagus and in the female lung, breast, and esophagus at different doses. The risk of radiation induces lung and breast cancer for 25 years, old women with 1 Gy radiation dose was higher than 5.9% and 5.5%. For same-age males risk of radiation-induced esophageal cancer was higher than 0.32%. The risk of radiation-induced cancer decline sharply with age at exposure for breast cancer and a small degree for lung and esophageal cancer. Different researches showed exposure to radiotherapy also generates lifetime risks of circulatory diseases. The major proof of radiation-induced cancer comes from the accidental exposure of the general population to radiation [51, 52]. Cancer, a long-term radiation-induced disease, is the major limitation of radiotherapy [53, 54]. However, cancer-induced risks with radiotherapy treatment of benign diseases based on various epidemiology data showed no increased risk of cancer at a very low dose of radiation [55]. The major issue about the cancer-induced risk is age [56]. The risk of inducing cancer is even lesser in patients over 40 years of age due to the expected long latency of tumor development [57].

The available weak clinical anecdotes and preclinical animal models data showed the potential risk of trial exceeds the potential benefits [58]. Furthermore, the preclinical trial should be conducted to investigate the safety profile of radiotherapy before conducting the clinical trial in COVID-19 patients. Unlike the other sites treated by LDRT for inflammatory conditions, the human lung is very radiosensitive. Radiation-induced edema, fibrosis is the complications seen in patients in radiotherapy treatment for pulmonary neoplasms, Hodgkin's disease, or esophageal carcinoma [59]. Early reactions may develop within days or weeks; however, the late reactions may be seen after months or years after the treatment [60, 61]. Radiation-induced lung damage is principally based on the lung volume irradiated, pre-existing lung disease and the dose administered [62].

The pre-treatment inflammation in the lung could make pulmonary tissue much more susceptible to radiation-induced lung injury. The risk associated with radiation therapy in COVID-19 patients is elucidated in **Fig. 2.**

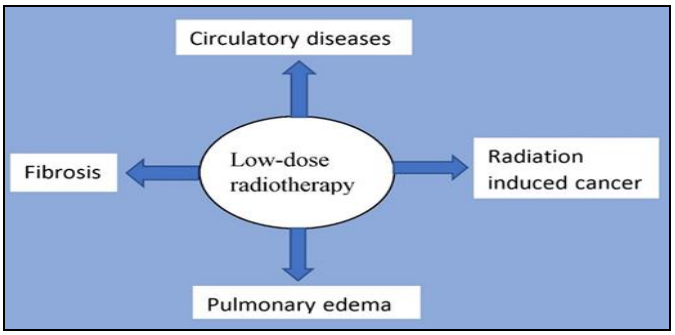

FIG. 2: SUMMARY OF RISK FACTORS ASSOCIATED WITH LOW-DOSE RADIOTHERAPY.

Low radiation (0.5-2 Gy) causes a significant change in the microfilament organization as well as the morphology of pulmonary vascular endothelial cells (PEMC) [63, 64]. It is characterized by loss of close contact and retraction within the individual cells in the monolayer [65]. *In-vitro* studies using radiation dose levels and time course for PMEC retraction demonstrated that low dose thoracic radiation induces pulmonary edema characterized by increased lung wet weight [66].

The incidence of increased weight is radiation dose-dependent up to 2 Gy and found to be coincident with the time course for radiation-induced endothelial retraction [67]. PEMC model system may be beneficial for screening different compounds and physical agents, which could be useful clinically in the prevention of acute and late lung and other tissue injuries due to radiation [68]. The selection of the right time to administer LD-RT in COVID-19 patients is very challenging [69]. It is at the beginning of the pro-inflammatory phase where LDRT to both lungs would be effective in acting against the cascade of pro-inflammatory cytokines [70].

LDRT treatment from 30 to 100 cGy to the lungs of COVID-19 pneumonia patients could reduce inflammation but may alleviate the symptoms that are life-threatening [71, 72]. However, viral reactivation may be a problem at a very low dose as reported in other viruses such as hepatitis B/C virus (HBC/HCV) [73] and human immunodeficiency virus (HIV), although the impact on CoV is unknown [74].

CONCLUSION: The COVID-19 pandemic has created unprecedented challenges to our world. Researchers are working tirelessly to discovered medication and vaccines. Based on available evidence of LD-RT to treat several non-malignant inflammatory conditions, the researcher summarizes that LD-RT can control the inflammatory response to COVID-19 in the lungs. LD-RT is believed to counteract against cytokine storm that was created by SARS-CoV-2. But the dose-related radiation-induced cancer was the major concern after radiotherapy so, further preclinical studies should be conducted in animal models to evaluate safety, efficacy, and risk-benefit ratio.

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