Adjuvant Therapeutic Role of Low Dose Ionizing Radiation in Patients with Respiratory Viruses (COVID-19)

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ABSTRACT

In the current dismal situation of the COVID-19 pandemic, effective management of patients with pneumonia and acute respiratory distress syndrome is of vital importance. Due to the current lack of effective pharmacological concepts, this situation has caused interest in (re)considering historical reports on the treatment of patients with low-dose radiation treatment for pneumonia. Kirkby, Mackenzie and Mohmmad K. Khan[21] indicate effectiveness in the dose range between 0.3 to 1.5Gy (Gray), similar to more recent dose concepts in the treatment of acute and chronic inflammatory/degenerative benign diseases with, e.g., a single dose per fraction of 0.5Gy. This low dose radiation treatment can be possible to given by using diagnostic tools CT scan, because diagnostic CT scan will be easily available, low cost, within the hospital setting, accessible and affordable[26]. This concise review aims to critically review the evidence for low-dose radiation treatment of COVID-19 pneumopathy and discuss whether it is worth investigating in the present clinical situation.

Keywords: SARS-CoV-2, Low-dose radiation therapy, Pneumonia, COVID-19, Consolidation, Anti-inflammatory

INTRODUCTION

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spectrum of clinical symptoms of patients with SARS-CoV-2 infection is broad and encompasses asymptomatic infection mild and moderate to severe illness of the upper respiratory tract, severe pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, and death. Severe courses are often associated with comorbidities such as hypertension[1] and a severe respiratory symptomatic stage goes along with a high viral load occurring during the early phase of disease.[2,3] High viral load could be the result of low immune responses against the virus, but also due to high expression of the cell entry receptor for SARS-CoV-2 (the angiotensin-converting enzyme 2 [ACE2] receptor).[4] Although a multitude of pharmacological studies are underway, no effective treatment (except supportive oxygen breathing and mechanical ventilation systems) appears to be available and intensive care units which provide these options are severely limited. This situation has caused interest in (re)considering the historical treatment of patients with low-dose radiation treatment for pneumonia.

Historically, LR and antiserum treatment were the only two choices for the control of bacteria- and virus induced pneumonia. In fact, X-ray was used to treat pertussis/whooping cough from 1923 to 1936 in North America and Europe. Surprisingly, LR was reported to reduce the pneumonia mortality to a similar rate as treated by immune serum and sulfonamide. In 2013, Calabrese and Dhawan published a milestone review on this historic period regarding control of different types of pneumonia by radiation. Among a total of 863 pneumonia patients treated by X-ray therapy, including 85 virus-induced pneumonia and 36 interstitial pneumonia cases, the reported total cure rate was 83.1% (717 out of 863 cases), including 67 of 85 (78.8%) cases of virus-induced pneumonia and 22 of 29 (75.9%) cases of interstitial pneumonia. In addition, animal model using feline-virus-induced cat pneumonia, which mimicked the human atypical pneumonia, showed that the incidence of pneumonia was reduced by 50% and 25%, respectively by radiation delivered 24 h and 48 h after the virus infection. Impressively, the same group also demonstrated the survival advantage of LR in a mouse pneumonia model induced with high-risk swine influenza virus. It is remarkable that the radiation-mediated pneumonia control was believed by then to be linked to the number and responsiveness of immune cells.[5] Similar protocols of radiation therapy are currently prescribed in Germany for benign painful chronic inflammatory degenerative disorders such as peri arthritis of the shoulder.[6] In addition, low-dose low dose ionizing radiation has been reported to be effective in acute inflammation. In a cohort of 130 patients treated for postpartum mastitis with single doses of 0.2–0.5 Gy up to a total dose of 1–1.5 Gy, Herrmann reported on a cure rate of over 90% if given within the first 24 h of the first signs of inflammation, but a decline to 50% if given at full blown inflammation.[7] The biological mechanisms underlying the effectiveness of these doses have been subjected to intensive research during the past 30 years. Indeed, experimental in vitro and in vivo studies have revealed a multilevel interrelationship between low-dose ionizing radiation and inflammatory cascades. These include, among others, modulation of the inflammatory properties of leukocytes, macrophages, fibroblasts, and endothelial cells, as well as of the secretion of cytokines/chemokines and

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growth factors (reviewed in[8,9]). In addition, the mechanisms explored so far display common dose–effect relationships, with a pronounced effect in the range between 0.3 to 0.7 Gy, as empirically identified to be the most effective in the clinical situation, including in historical treatment of pneumonia. Although no experimental or preclinical data on testing low dose low dose ionizing radiation in COVID-19 patients suffering from respiratory distress are available at present, in analogy to the evidence mentioned above, a single dose of 0.5 Gy to the entire lung may be recommended based on radiobiological and clinical considerations.

Recently, in a 2020 publication, Dhawan et al. propose a total dose of 0.3–0.5 Gy in the thoracic region for patients with COVID-19 in the acute phase of the disease, when cytokines increase, and for those who present a moderate or severe clinical situation (‘‘cytokine storm”). According to those authors, the theoretical basis that would justify the use of LD-RT in patients with COVID-19 rests on the fact that inflammation mediators triggered by COVID-19 initiate the cascade that leads to a hyper inflammatory state, the so-called ‘‘cytokine storm”, ultimately responsible for the rapid and extensive damage to the lungs and other organs.[4] The well-known anti-inflammatory phenotype induced by LD-RT is expected to decrease the intensity and severity of COVID-19 pneumonia.

In contrast to most pharmacological approaches which have a major systemic effect on the organism, radiation mainly covers a local treatment area, with a direct impact on the organ affected by inflammatory stress, i.e., lung tissue. Radiation doses required for effective treatment are very low (<1% of doses used for anti-cancer low dose ionizing radiation) and do not exceed the tolerance doses of the critical organs in the irradiated volume such as heart, thyroid, stomach, or kidneys. Upon a 0.5 Gy exposure, radiation doses are considered to not increase cardiac disease[10], although other studies report an increased risk for circulatory disease.[11] Nevertheless, saving lives in the present situation is the most important factor and may justify treatment by irradiation. Furthermore, the risk of late and very late radiation damage in adjacent organs from such low-dose radiation treatment which needs to be considered is induction of cancer after latencies of >10 years. Cautious estimates suggest risks to be well below 1%.[12]

If considering a clinical study, however, a major obstacle is the appropriate timing of irradiation. In general, early control of viral replication by, particularly, type I interferons (IFNs-I), limits viral spread within the host during the early phases of disease. IFNs-I increase the expression of interferon stimulated genes, which results in stimulation of effectors functions of cells of the innate and adaptive immune system. However, sustained expression of IFNs-I might also result in viral persistence.[13] This highlights the complexity and time dependence of immune responses against SARS-CoV2. Severe cases of SARS have further been reported to be associated with high serum levels of pro-inflammatory cytokines and increased accumulation of innate immune cells in the lung, finally resulting in extensive lung damage.[14] Recent analyses have confirmed that severe cases of COVID-19 are associated with increased interleukin6 (IL-6) levels in the serum. Low dose irradiation does not decrease the viability of virus directly, yet it may increase the effectiveness of anti-viral immune responses. An additional prominent risk factor for severe disease progression is D-dimer >1 µg/ml in the serum.[1] In the early to medium stages of SARS-CoV2 infection, treatment with low-dose ionizing radiation of the lungs might be beneficial to ameliorate the establishing inflammation and to slow down its chronicity. In addition, low-dose irradiation is reported to stimulate anti-viral immune parameters
including natural killer cell activity and IFN production.[15] At chronic stages of disease characterized by cytokine release syndrome (CRS, cytokine storm), low-dose irradiation might not be as efficient as in the early progressive stage, as also reported in historical publications. However, one has to consider that in the recovery phase of COVID-19 patients, particularly activated CD38- and HLA-DR-expressing CD4+ and CD8+ T cells are increased in the patients alongside IgM and IgG SARS-CoV-2-binding antibodies.[16] This stresses the point that timing of irradiation has to be carefully chosen to avoid attenuation of disease-resolving immune response, e.g., by stimulating INFs-I. The indication for low-dose ionizing radiation should be based on lung function, i.e., progression of respiratory distress.

Another point to consider is that low doses of irradiation in the infected lungs, even at doses up to 0.5 Gy, are expected to induce a low number of RNA damage events and mutations in the virus and be of a low selective pressure. For a dose of 0.5 Gy in an approximately 30 kb single-stranded virus genome, about 0.005 single-strand breaks (SSBs)/virus are expected (assuming ~1000 SSBs per ~3 Gb genome) and up to 5–6 times more base damage.[17,18] SARS-COV2 is an RNA virus with an expected moderate to high mutation rate similar to other SARS RNA viruses and usually higher than the corresponding rate of the human host cells.[19] In addition, as discussed in a recent manuscript[20], any antiviral drug treatment against SARS-CoV2 would probably result in a more intense selective pressure on the virus.

Adverse effect of radiation with the dose

Exposure to radioactivity released during nuclear disasters (1986 accident at the Chernobyl power plant in Russia or the 2011 nuclear disaster in Fukushima, Japan) has been associated with an increased risk of developing thyroid cancer, particularly in exposed children, and thyroid cancers can be seen in exposed individuals as many as 40 years after exposure.[24]

Thyroid cancer was many times more common than normal in children who lived near Chernobyl, the site of a 1986 nuclear plant accident that exposed millions of people to higher dose radioactivity. Adults involved with the cleanup after the accident and those who lived near the plant have also had higher rates of thyroid cancer.[24]

Some radioactive fallout occurred over certain regions of the United States after nuclear weapons were tested in western

Recent trials					
1: Details of low-dose radiation therapy clinical trials for coronavirus 19 disease patients Source: US National Library of Medicine, ClinicalTrail.gov.					
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≥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 ± 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

states during the 1950s. This exposure was much, much lower than that around Chernobyl. A higher risk of thyroid cancer has not been proven at low exposure levels.[24]

Being exposed to radiation an adult carries much less risk of thyroid cancer.

Whenever RT is employed for benign conditions, concerns are expressed about risk of radiation induced carcinogenesis. It is often ignored that even without radiation exposure; a healthy human being does carry a certain amount of life-time risk of developing cancer. The excess absolute risk (EAR) induced by radiation exposure is determined by the below formula proposed by Preston considering the $\beta = 10$, $\theta = -0.05$ and $\gamma = 1$.[22]

EAR per 10000 person years = $\beta De^{\theta(agex-25)}(age/50)\gamma$

According to this formula, the increase in EAR is about 0.4% for 0.5 Gy and 1.2% for 1.5 Gy over a 20 year period. The LDRT involves only thoracic organs as OAR rather than whole body exposure thus further minimizing the risk. This EAR is negligible considering the potential benefit of LDRT in the current pandemic.

DISCUSSION

There are major concerns regarding the current status of global pandemic of corona virus disease 2019 (COVID-19). COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spectrum of clinical symptoms of patients with SARS-CoV-2 infection is broad and encompasses asymptomatic infection mild and moderate to severe illness of the upper respiratory tract, severe pneumonia, acute respiratory distress syndrome

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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≥24 h; hypoxemia defined as Pa/ FIO_2 ratio <300 or SpO_2/ FiO_2<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≥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
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 ≤0.8×10^9/L; patients within ≤8 days from the onset of symptoms; age>65 years	Patient not consent to participate	

Recent trials					
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Clinical trial number; title of the study	**Institute/hospital, country**	**Dose of radiation/ frequency**	**Major inclusion criteria**	**Major exclusion criteria**	**Phase of the study**
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°F, respiratory rate of ≥26/min within 24 h of screening; SpO_2≤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	
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

Recent trials					
1: Details of low-dose radiation therapy clinical trials for coronavirus 19 disease patients Source: US National Library of Medicine, ClinicalTrail.gov.					
Clinical trial number; title of the study	**Institute/hospital, country**	**Dose of radiation/ frequency**	**Major inclusion criteria**	**Major exclusion criteria**	**Phase of the study**
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≤3 days or progressive disease≤14 days; age≥40 years; may receive antiviral medication and/or convalescent plasma	Prior or planned treatment with interleukin inhibitors or TNF-α 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 Graubuenden, Chur, Switzerland	Low dose whole lung radiotherapy*	Age≥65 years with proven COVID-19 pneumonitis who may or may not require oxygen	Require artificial ventilation or hemodynamically unstable	1 and 2

(ARDS), respiratory failure, and death. Severe courses are often associated with co morbidities such as hypertension and a severe respiratory symptomatic stage goes along with a high viral load occurring during the early phase of disease. High viral load could be the result of low immune responses against the virus, but also due to high expression of the cell-entry receptor for SARS-CoV-2 (the angiotensin-converting enzyme 2 [ACE2] receptor). Although a multitude of pharmacological studies are underway, no effective treatment (except supportive oxygen breathing and mechanical ventilation systems) appears to be available and intensive care units which provide these options are severely limited. This situation has caused interest in (re)considering the historical treatment of patients with low-dose radiation treatment for pneumonia.

Since the weakness of the immune system is one of the major contributing factors for the occurrence of pneumonia, and inflammation contributes to increased mortality rates of pneumonia patients, interventions that improve the immune response and/or reduce inflammation may reduce the pneumonia incidence and mortality in COVID-19 patients. There are indeed a large number of interventions that improve the immune response and/or reduce inflammation. However, all the interventions would not be applicable or acceptable to everyone and so the interventions would need to be individualized based on individual circumstances and preferences. This approach, known as "Individualized Interventions to Improve the Immune Response", or the I4R approach needs to be tested in pilot clinical trials for the treatment of COVID-19 patients.(Mohan Doss)[46] If the pilot clinical trials demonstrate that it is effective in reducing the incidence and mortality due to pneumonia, widespread adoption of the I4R approach for treating COVID-19 patients may reduce their morbidity and mortality, reducing the concerns regarding the coronavirus.

Radiotherapy is a one of the treatments for cancer patients, it usually involves daily treatment deliveries over days to weeks. It has wide variety of treatment techniques which

Computed Tomography	Diagnostic Reference level
Adult head	75 mGyCTDIvol
Adult abdomen-pelvis	25 mGyCTDIvol
Adult chest	21 mGyCTDIvol
*Taken from ACR-AAPM Practice Guideline Parameter for Diagnostic Reference Levels and Achievable Doses in Medical X-Ray Imaging - Revised 2013 (Res. 47)	

Table-1:

Radiation dose	Radiation effect
<5 rad	No immediate observable effect
~ 5 rad to 50 rad	Slight blood changes may be detected by medical evaluation
~ 50 rad to 150 rad	Slight blood changes will be noted and symptoms of nausea, fatigue, vomiting, etc. likely.
~ 150 rad to 1100 rad	Severe blood changes will be noted, and symptoms appear immediately.
~ 1100 rad to 2000 rad	The probability of death increase to 100% within one to two weeks
>2000 rad	Death is certainly
This data is derived from The national council on radiation protection and measurement, reactor concept manual.	

Table-2:

Tissue	Total acute threshold (Gy)	dose
Lens of Eye		
Detectable opacities	0.5–2.0	
Cataract formation	5.0	
Skin		
Skin reddening	3–6.0	
Temporary hair loss	4.0	
Skin death and scarring	5-10	
Testes		
Permanent sterility	3.5–6.0	
Ovaries		
Permanent sterility	2.5–6.0	
Gastrointestinal		
Mucosa lining loss	6.0	
Bone Marrow		
Reduction of blood cell production	0.5	
Lung[24]		
Radiation induced pulmonary fibrosis	Above 30	
Thyroid[24]		
Thyroid cancer	10-30	
Urinary bladder[24]		
Radiation cystitis	Above 40	
* incidence level based on ICRP publication 103 (2007)		

Table-3:

offers quality of life for the patients. In the same way use of radiation in the present scenario for the treatment of corona virus is a provoking idea to manage the disease outbreak. Radiation may play a major role increasing the overall survival of the patients and to control the disease. As we know radiation can control the growth malignant tumor to a greater extent by cell killing mechanism.[27] Our idea is to implement the radiation for de-activating the COVID-19 cells[44] in terms of delivering some minimum dose (in terms of Gray) to the patient.

Pathogenesis of COVID-19

In asymptomatic stage (initial 1-2 days of infection) the inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV2 and SARS-CoV.[30] There is local propagation of the virus beta limited innate immune response. At this stage the virus can be detected by nasal swabs.

Next few days, the virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. At this time, the disease COVID-19 is clinically manifest. The level of CXCL10 (or some other innate response cytokine) may be predictive of the subsequent clinical course.[7] CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza.[28] CXCL10 has also been reported tobe useful as disease marker in SARS. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells.[29] SARS-CoV propagates within type II cells, large number of viral particles are released /and the cells undergo apoptosis and die. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells in adjacent units. I suspect areas of the lung will likely lose most of their type II cells, and secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. This postulated sequence of events has been shown in the murine model of influenza pneumonia.[35] The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. (Gu J, Korteweg C.)

Role of CD4 cells: SARS-CoV-2 infection induced a cytotoxic response of CD8_T cells, but not CD4_ T cells, characterized by the simultaneous production of granzyme A and B as well as perforin within different effector CD8_ T cell subsets. Cytotoxic T cells are responsible for the elimination of infected cells and are key players in the control of viruses. CD8_ T cells with an effector phenotype express cytotoxic molecules and are able to perform target cell killing. COVID-19 patients with a mild disease course were analyzed for the differentiation status and cytotoxic profile of CD8_ T cells. SARS-CoV-2 infection induced a vigorous cytotoxic CD8_ T cell response.

Depletion of CD4+ T cells, CD8+ T cells, and B cells, among other immune cells, reportedly occurs.[33,34] Although there is so far limited understanding of the mechanisms of lymphopenia in COVID-19, many patients with severe

disease have reduced T cell numbers in particular, and perhaps specifically CD8+ T cells.[32]

A particularly high frequency of CD4+ T cell responses specific to virus spike protein has been observed in patients who have recovered from COVID-19, which is similar to what has been reported for influenza virus infections.[31]

The pro- inflammatory roles of IFN- I are well described in a mouse model of SARS.[36] In SARS- CoVinfected BALB/c mice, a delayed but considerable IFN- I response induces the accumulation of monocytes and macrophages and the production of pro- inflammatory cytokines, resulting in lethal pneumonia, vascular leakage and insufficient T cell responses.

Lacassagne, Levaditi, and Galloway (1927) irradiated Rous sarcoma virus with X-rays, and they confirmed that weak doses, although they could control the formation of tumors, were unable to affect filtrates containing the virus. In 1934, Knorr and Ruff showed that cathode rays can affect bacteriophage, though to a much lesser extent. Although their inactivation figures are not quantitative, the effect produced by 1.5ma. for 3 sec. at 65 kv. is of the right order of magnitude to agree with modern observations of 2-Mev. electron action on T1 cell bacteriophage.[47]

The first observation of radiation action on a plant virus appears to be that **of** Gowen and Price (1936), who noted the loss of activity of preparations of tobacco mosaic virus after bombardment by X-rays. The first quantitative analysis of radiation action applied to virus inactivation is that of Holweck (1938).

As with any other research agent, the action of the radiation must be understood at least in part before it can be used satisfactorily. This understanding can certainly be obtained for the materials in a virus, though it is not so certain that it can be reached soon for the much richer content of a host cell. A great deal of the work described here depends on the limited understanding of the inactivating effect of a localized energy release in a specialized biological molecule, and is largely based on the twofold feature of strong local inactivation and random distribution of energy release. The work of Latarjet, for example, rests on this. However, cases are now being discovered in which this energy release does not act unless of more than a limiting energy, and the energy requirement can be laid bare ex post fucto by studies of the response to different rates of energy release. As soon as understanding of the reason for such energy requirement progresses, it can be turned to advantage in analysis of the internal structure of viruses.[48]

Radiotherapy has been used for more than a century in the treatment of pneumonia, especially interstitial and atypical. Over the last two decades, humans have encountered three Substantial outbreaks of new corona virus (CoV) epidemics. The lungs represent one of the organs most affected by COVID-19, and some patients develop life-threatening viral pneumonia and sepsis. There is also growing evidence for associations between multiple cardiovascular complications and COVID-19.[37] Currently there are few clinical management options available for COVID-19 patients with pneumonia, beyond the supply of oxygen and administration of antibiotics to avoid co-infection, and possibly, though not recommended, administration of corticosteroids.[38]

Interestingly there is ongoing discussion of the potential use of computerized tomography(CT) scanning for COVID-19 related lung pathology.[13]

Based on Kirkby and Mackenzie[21] (2020) recently suggested that LDRT with a single acutely delivered dose to the lungs of0.3–1Gy of low-linear energy transfer (LET) radiation could be used to treat COVID-19 pneumonia with very low risk and with normal tissue toxicities avoided. Similarly, but witha slightly lower dose of low-LET radiation, Ghadimi-Moghadam et al.[20] (2020) have also suggested that a priming dose with a few mGy followed by a single dose of 0.1, 0.18or 0.25 Gy could be used to treat COVID-19 pneumonia (0.25 Gy was selected because it is lower than the maximum dose of _0.26 Gy/year from natural background radiation in Ramsar, Iran).

There is a substantial body of radiobiological data which suggests that certain cytokines and adhesion molecules related to endothelial function and modulating immunological responses are differentially up- or down regulated with a boundary around 0.5 Gy, as reviewed elsewhere.[41] In a recent study, Schr€oder et al. (2019) investigated the immune modulatory properties of low doses of ionizing radiation on endothelial cells with respect to an early response to inflammatory stimuli solely and in combination with low dose radiation. They measured the levels of a total of 27 inflammatory cytokines. While the test panel also included anti-inflammatory markers, only pro-inflammatory cytokines were detected, after doses as low as 10 and 50 mGy.[16]

There is radiobiological evidence that low dose irradiation induces pro-inflammatory responses due to spatiotemporal propagation of damage signals caused by non targeted effects of low dose radiation exposure.[43] Examination of the totality of cytokine data suggests that the overall anti-inflammatory response at low doses is, at best, modest and unlikely to reach therapeutic levels against the cytokine storm typical for the COVID-19 pneumonia.

Another study started Dr. Daya Nand Sharma, All India Institute of Medical Sciences, New Delhi of “Low Dose Radiation for COVID pneumonia”.[45]

Patient treated with a dose of 70 cGy in one fraction radiation therapy in addition to standard therapy. They also recorded primary outcomes (clinicaltrial.gov/ct2/show / NCT04394793)

From June to August 2020, they enrolled 10 patients with COVID-19 having moderate to severe risk disease [National Early warning Score (NEWS) of >=5]. Patients were treated as per the standard COVID-19 management guidelines along with LDRT to both lungs with a dose of 70cGy in single fraction. Response asseement was done based on the clinical parameters using the NEWS. All patients completed the prescribed treatment. 9 patients had complete clinical recovery mostly within a period ranging from 3 to 7 days. 1 patient, who was known hypertensive, showed clinical deterioration and died 24 days after LDRT.

No patient showed signs of acute radiation toxicity.[45]

Results of study (90% response rate) suggest the feasibility and clinical effectiveness of LDRT in COVID-19 patients having moderate to severe risk disease. This mandate a randomized controlled trial to establish the clinical efficacy of LDRT in COVID-19 pneumonia. Dr D. N. Sharma study on 10 patients treated with LDRT to both lungs with dose of 70 cGy in one fraction. No patients showed signs of acute radiation toxicity as per Dr D. N. Sharma study as mentioned above.[45]

An additional advantage of this treatment would be that, unlike vaccines and pharmacological treatments that depend on the stock, radiotherapy devices are always available for the treatment of patients without being subject to fluctuations according to higher demand.[45]

Studies into the safety of LD-RT for the treatment of benign non-tumour pathology have all concluded that the risk of presenting complications attributable to irradiation is extremely low at the doses suggested in the present study.

In conclusion, there is a broad metabolic and immunological basis that would justify the use of LD-RT in COVID-19 patients, mainly in the most advanced stages of the disease when it could be effective by acting as a powerful anti-inflammatory agent against the cascade of pro inflammatory cytokines, and together with its low acute and late toxicity profile, it is an option that could be considered for patients with COVID-19 pneumonia.

It in moving step towards clinical radiology but more clinical trials are required.

CONCULSION

Novelty/Innovation: Since the COVID-19 emerged in human world various treatment methods have been employed, but till now not any successful definitive treatment established. If the concept of radiation treatment achieves expected result. This may show new vision to world in COVID-19 pneumonia treatment.

If radiation treatment will show positive outcome than in future we can carried out this study in geriatrics population an also patient with severe symptoms and associated morbidities can be included. To know better outcome in most vulnerable population.

Application of ionizing radiation will give the opportunity to eliminate viruses, besides other technologies, or a combined treatment of radiation, however at present the research in this field is limited. Research activities in this field should be increased and supported, because the future prospect of using radiation to eliminate those viruses are very promising.

ABBREVIATIONS

COVID 19: Corona virus disease of 2019, HLA: Human leucocyte antigen, HRCT: High resolution computed tomography, NEWS: National early warning score, NS: Nasal swab, NPS: Nasopharyngeal swab, RNA: ribonucleic acid, RTPCR: Reverse transcription polymerase chain reaction, SARSCoV-2: Severe acute respiratory syndrome corona virus 2.

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