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COMMENTARY

Low-Dose Radiation Therapy (LDRT) for COVID-19: Benefits or Risks?

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The limited impact of treatments for COVID-19 has stimulated several phase 1 clinical trials of whole-lung low-dose radiation therapy (LDRT; 0.3–1.5 Gy) that are now progressing to phase 2 randomized trials worldwide. This novel but unconventional use of radiation to treat COVID-19 prompted the National Cancer Institute, National Council on Radiation Protection and Measurements and National Institute of Allergy and Infectious Diseases to convene a workshop involving a diverse group of experts in radiation oncology, radiobiology, virology, immunology, radiation protection and public health policy. The workshop was held to discuss the mechanistic underpinnings, rationale, and preclinical and emerging clinical studies, and to develop a general framework for use in clinical studies. Without refuting or endorsing LDRT as a treatment for COVID-19, the purpose of the workshop and this review is to provide guidance to clinicians and researchers who plan to conduct preclinical and clinical studies, given the limited available evidence on its safety and efficacy. **© 2020 by Radiation Research Society**

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INTRODUCTION

To improve clinical outcomes for COVID-19 patients, a variety of experimental treatments are undergoing clinical trial evaluation, including whole-lung low-dose radiation therapy (LDRT) (*1, 2*), *defined here* as 0.3–1.5 Gy delivered in a single fraction, which is lower than doses used in clinical radiotherapy and higher than the 50 mSv/year occupational exposure limit and 1 mSv/year limit to the general public (https://bit.ly/3ctWAAz).

Clinical trials currently testing whole-lung LDRT for COVID-19 are listed in Table 1. Most of these trials are open-label, single-institution, non-randomized studies, but some randomized trials are also emerging. Among several hospital centers worldwide, enrollment of 982 patients is planned to date. To address the uniqueness and accompanying scientific controversy of this unconventional treatment (*3, 4*), the National Cancer Institute (NCI), National Council on Radiation Protection and Measurements (NCRP) and National Institute of Allergy and Infectious Diseases (NIAID) convened a virtual workshop on July 23, 2020 to discuss available data concerning potential risks/benefits of LDRT. One main goal of the workshop was to establish a set of suggested guidelines for future clinical trials by developing components for inclusion in clinical studies, taking into consideration pros and cons of several parameters that would address the pathogenesis and underlying mechanisms of COVID-19.

The workshop brought together a diverse group of scientific experts in radiation oncology, pulmonary virology, immunology, vascular- and radiation-biology, radiation protection, and public health policy. There were three sessions: 1. Clinical trials/trial design; 2. Preclinical studies;

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TABLE 1
Completed and Ongoing Clinical Trials on Whole-Lung LDRT for COVID-19 Registered at *ClinicalTrials.gov*

Trial name	Status	Conditions	Locations	Interventions	Estimated enrollment	ClinicalTrials.gov ID no.
Low dose whole lung radiotherapy for older patients with COVID-19 pneumonitis	NYR	Covid-19 pneumonitis	International Geriatric Radiotherapy Group, Institute of Radiation Oncology, Cantonal Hospital Graubuenden, Chur, Switzerland	Radiation: Whole-lung LDRT for older patients with COVID-19 pneumonitis	500	NCT04493294
Radiation eliminates storming cytokines and unchecked edema as 1-day treatment for COVID-19 (RESCUE 1-19)	R	Pneumonia| COVID-19| SARS pneumonia	Emory University Hospital, Winship Cancer Institute, Atlanta, GA	Radiation: LDRT	10	NCT04366791
COVID-19 pneumonitis low dose lung RT (COLOR-19)	R	COVID-19	ASST SpedaliCivili, Brescia, Italy	Radiation: Single-fraction whole-lung radiotherapy	30	NCT04377477
Low dose anti-inflammatory RT for the treatment of pneumonia by COVID-19	R	Pneumonia, viral	Hospital Sant Joan de Reus, Reus, Tarragona, Spain	Radiation: LDRT| Drug: Hydroxychloroquine sulfate| Drug: Ritonavir/lopinavir| Drug: Tocilizumab injection [Actemra]| Drug: Azithromycin| Drug: Corticosteroid| Drug: Low-molecular-weight heparin| Device: Oxygen supply	106	NCT04380818
LDRT in COVID-19 pneumonia	R	COVID|SARS	Imam Hossein Hospital, Tehran, Iran	Radiation: LDRT	5	NCT04390412
Lung irradiation for COVID-19 pneumonia	R	SARS-CoV 2	Brigham and Women's Hospital, Boston, MA	Radiation: Phase 1| Radiation: Phase 2	48	NCT04393948
Ultra-low doses of therapy with radiation applicated to COVID-19	R	Pneumonia, viral| Cytokine storm	Hospital La Milagrosa, GenesisCare, Madrid, Spain	Radiation: Ultra-low-dose RT| Device: Ventilatory support with oxygen therapy| Drug: Lopinavir/ritonavir| Drug: Hydroxychloroquine| Drug: Azithromycin| Drug: Piperacillin/tazobactam| Drug: Low-molecular-weight heparin| Drug: Corticosteroid injection| Drug: Tocilizumab	15	NCT04394182
LDRT for COVID-19 pneumonia: a pilot study	R	COVID-19| Pneumonia	All India Institute of Medical Sciences, New Delhi, India	Radiation: LDRT	10	NCT04394793
Low dose pulmonary irradiation in patients with COVID-19 infection of bad prognosis	NYR	COVID| Pneumonia, viral	Hospital Provincial de Castellon, Castellón De La Plana, Castellon, Spain	Radiation: lung LDRT	41	NCT04414293
LDRT for COVID-19 pneumonitis	R	COVID-19	Servicio de Oncología Radioterápica. Hospital Clínico San Carlos, Madrid, Spain	Radiation: RT	41	NCT04420390
Low dose whole lung RT for patients with COVID-19 and respiratory compromise	R	COVID-19	Arthur G. James Cancer Hospital and Solove Research Institute at Ohio State University Medical Center, Columbus, OH	Radiation: RT	24	NCT04427566
Best supportive care with or without low dose whole lung RT for the treatment of COVID-19	R	Pneumonia| Severe acute respiratory syndrome| Symptomatic COVID-19 infection laboratory-confirmed	Emory University Hospital, Winship Cancer Institute, Atlanta, GA	Other: Best practice| Radiation: LDRT	52	NCT04433949
LDRT for patients with SARS-COV-2 (COVID-19) pneumonia	NYR	Covid-19|Sars-CoV2| Pneumonia	Ohio State University Medical Center, Columbus, OH	Radiation: Low-dose radiation 35 cGy| Radiation: high-dose radiation 100 cGy	100	NCT04466683

Note. R = recruiting; NYR = not yet recruiting.

and 3. Radiobiological/immunological mechanisms of LDRT. The available results of clinical trials conducted to date, including those just accruing patients and those being implemented and in the final planning phase, served as a key focal point of debate about the need for preclinical data prior to initiating trials and the protocol design and methodology. Issues discussed included those related to COVID-19 biology, low-dose radiation biology, radiation lung injury and how these complex mechanisms might interact. Given the use of ionizing radiation for a purpose other than treating cancer, potential life-time radiation risks and regulatory aspects of the use of radiation for LDRT were discussed. Without supporting or refuting LDRT for COVID-19 as a treatment, this review is intended to provide

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guidance to clinicians and researchers who plan to conduct preclinical and clinical studies, given the limited evidence on its safety and efficacy. Also, we recognize the need for novel treatments for patients in a dire clinical condition; however, it is essential that any use of LDRT for COVID-19 be on a clinical trial with Institutional Review Board (IRB) oversight, and investigators must provide complete details of trials, including patient selection, tracking those who were eligible, consented and received LDRT, and report both short- and long-term results.

CLINICAL TRIALS AND TRIAL DESIGN

The workshop participants recognized the dire need for effective treatments as well as scientific consensus from the NCRP (https://bit.ly/3mS0AQ5), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR; https://bit.ly/3hZVg9L) and others, that radiation doses > 0.1 Gy carry long-term risks, which include cancer and cardiovascular events, modulated by several factors such as age at time of exposure and sex (*3, 5, 6*).

The impetus for LDRT comes from case studies of patients treated with thoracic irradiation for pneumonia between 1905 and 1943, which suggest clinical improvement (*7, 8*). As the studies lacked a randomized control arm without radiation exposure, it is difficult to establish whether treatment influenced the course of the disease. Given the paucity of preclinical data and limited interpretability of the historical data, some workshop participants insisted on the need to establish the efficacy of LDRT in animal models of SARS-CoV-2 before testing in human clinical trials, opining that LDRT is not indicated (*9*). Others argued for continuation of IRB-approved clinical trials based on the need to investigate treatments that aim to reduce COVID-19 morbidity and mortality and on initial phase I trial observations. While several other COVID-19 therapies are being evaluated, to date, only two drugs have shown improved outcomes: the steroid dexamethasone lowers the odds of death (*10*), and the antiviral remdesivir shortens oxygen dependency and recovery time but does not improve survival (*11*). Ultimately, management of this pandemic will be modified by improved understanding of pathogenesis of tissue injury, immunological/inflammatory response, the availability of preventive and therapeutic vaccines, and continually updated clinical guidance (https://bit.ly/3kO4I1M).

The risk/benefit considerations for LDRT include the possibility of short-term worsening of the disease course (to be determined by phase 1 and 2 clinical trials) and long-term population-based radiation risks should a large number of patients live many years/decades vs. the potential benefit of reduced mortality and morbidity in the most severely ill patients in the immediate term (days/weeks). While speculative, it is conceivable that whole-lung LDRT could exacerbate SARS-CoV-2 infection. Autopsies of patients who died from COVID-19 show infection of endothelial cells with associated endothelial inflammation, vasculopathy and microangiopathy (*12, 13*). In general, a >2 Gy dose is likely to induce endothelial activation (*14*). Endothelial molecules, ICAM-1 (*15*) and E-selectin (*16*), are upregulated in a dose- and time-dependent manner, in part due to NF-κB activation (*17*), in preclinical studies. Because the endothelial cells in small vessel capillaries in the lung can potentially be damaged by ionizing radiation (*14*), it is conceivable that LDRT might promote endothelial cell injury and coagulopathy in the COVID lungs due to combined injury. Furthermore, there might be differences in the dynamics of response of endothelial cells between preclinical models and humans to a given dose of radiation. Therefore, characterization of dose-effect and time-course responses of endothelial cells to radiation are essential to fully understand the adverse effects of LDRT.

The general rationale for LDRT is that it could inhibit the cytokine storm that promotes the virus-induced pulmonary dysfunction contributing to the development of acute respiratory distress syndrome (ARDS). It is also likely that the potential anti-viral effect of LDRT could be due to the activation of immune and endothelial cells and inhibition of subsequent viral loading. However, preclinical data are necessary to support or refute this notion. LDRT as a treatment for COVID-19 patients to prevent respiratory failure, based on its role in treating inflammatory and degenerative diseases, has been reviewed elsewhere (*18*). Use of LDRT requires meticulous planning to overcome the challenges, including: 1. Determining the optimum time, if any, during disease progression to treat COVID-19 with LDRT, considering its safety and efficacy; 2. Safety of healthcare personnel during patient transport to the radiation therapy facility; 3. Rapid deterioration of eligible and enrolled patient's medical condition; and 4. Availability of radiation therapy facilities only on certain days (in many centers), potentially causing a delay between obtaining informed consent and the actual treatment delivery. Patients who deteriorate during this delay and fail to receive LDRT influence the interpretation of the existing preliminary phase 1 data.

The first published peer-reviewed results from the U.S. are from a safety trial of 1.5 Gy LDRT in elderly patients (median age 90 years), with bilateral pulmonary infiltrates, oxygen dependence without mechanical ventilation, and high comorbidity burdens, factors known to predispose patients to a worse outcome (*2*). A pre-specified interim safety analysis on day 7 was the primary end point: seven patients were enrolled (however, one was transferred to the ICU and one expired prior to LDRT); thus, five received radiation treatment. No acute worsening of the cytokine storm nor acute events were noted in four patients whose clinical status improved over 3 to 96 h post-LDRT. The trial met the primary safety end point with day 7 survival in the five LDRT-treated patients.

In Iran, five patients with COVID-19 on supplemental oxygen received 0.5 Gy whole-lung radiotherapy: one

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patient died, one withdrew consent and three showed clinical improvement so that they could be discharged, with one patient discharged with oxygen support at home (*1*). As these patients were not treated with dexamethasone, the death of one of four evaluable patients from COVID-19 is consistent with the expected mortality of 25% for hospitalized patients on supplemental oxygen (*19*). The authors reported a response rate of 4 out of 5 initially enrolled patients, based on an initial improvement in oxygen saturation and body temperature within one day after LDRT. Collectively, these studies established the feasibility of 0.5 to 1.5 Gy whole-lung irradiation in COVID-19 patients on supplemental oxygen.

Two trials underway that were discussed are: 1. A phase 2, single-arm study of 30-day mortality for patients requiring mechanical ventilation (NCT04427566) to receive 0.8 Gy LDRT and possibly other investigational treatments; and 2. A randomized, multi-institutional study for patients requiring hospitalization for hypoxemia, fever, or pulmonary compromise, but not mechanical ventilation (NCT04466683). In addition to experimental drugs, initial randomization is to LDRT 0.35 Gy or 1 Gy; after interim pre-specified evaluation, randomization will be to standard of care (SOC) or SOC plus the more efficacious/safer LDRT dose.

PRECLINICAL TRANSLATIONAL APPROACHES

While the U.S. Food and Drug Administration (FDA) has informed that radiotherapy devices are cleared for certain indications, such as tumor treatment in adults and children, their use has not been cleared for treating COVID-19 or modulating the inflammatory response in patients with COVID-19 indications. Other regulatory pathways available include emergency use authorization (EUA) (https://bit.ly/2G5chSy) and investigational device exemptions (IDEs) (https://bit.ly/2G9n66c). EUAs are in effect only during a public health emergency; no radiotherapy devices currently have an EUA for COVID-19. A physician may choose to use radiation therapy to treat a patient for COVID-19-associated pathologies as part of the practice of medicine; however, treating clinicians should be well informed about the treatment and base their decision on solid scientific and medical evidence. IRB oversight and informed consent may be required by the physician's institution before treatment. The practice of medicine does not include use of a device in clinical trials.

The importance of considering correlative, preclinical work in the design and conduct of LDRT clinical studies was discussed using a schema of the clinical and pathological evolution of COVID-19 infection. Figure 1 shows the chronology of events that leads to the cytokine storm in SARS-CoV-2 infection, causing a dysfunctional immune response and ultimately ARDS (*20*).

The pathological evolution toward severe ailment does not always depend on viral load and culminates in a

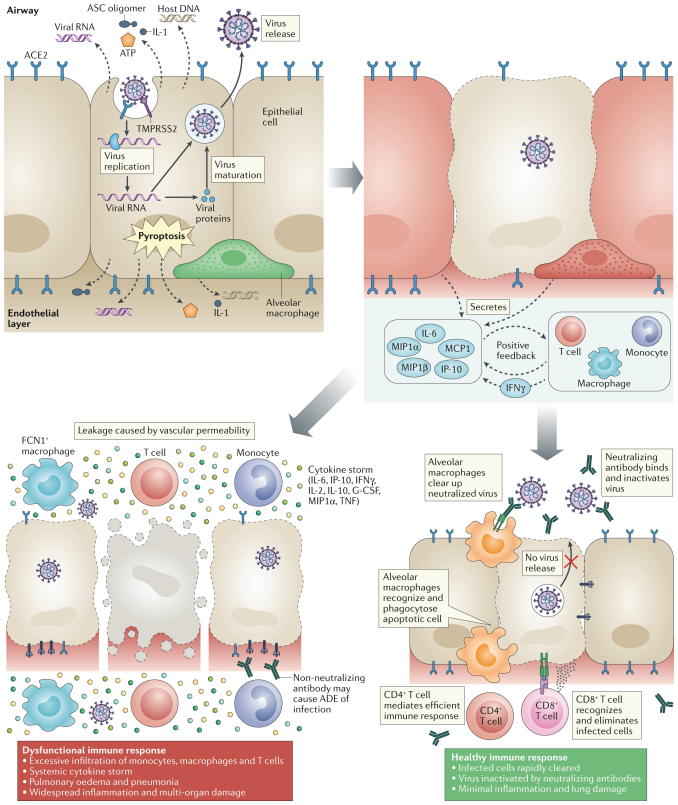


FIG. 1. Chronology of events leading to the cytokine storm in SARS-CoV-2 infection causing dysfunctional immune response and ultimately ARDS. Published and modified, with permission, Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20:363–74.

combination of symptoms. These include lymphopenia, with a relative abundance of abnormally functioning or exhausted $CD8^+$ T cells, high neutrophil-to-lymphocyte ratio, increased antibody-secreting B cells, and monocytopenia with a relative increase in inflammatory $CD14^+$ and $CD16^+$ monocytes. Also observed are increases in multiple cytokines (e.g., IL-2, IL-6, IL-7, IL-10) and chemokines responsible for recruiting neutrophils to the lung. The evidence for some effectiveness of anti-viral therapy during the moderate phase and steroid therapy during the severe phase was also presented. Based on the discussions, suggested correlative studies for clinical trials are provided in Table 2.

A re-analysis of several animal datasets from experiments performed decades ago testing radiation treatment for bacterial and viral pneumonia reveal that results are heterogeneous, but collectively indicate lack of efficacy of radiation after infection (*71*). Animal models of SARS-CoV-2 infection (while not identical to human COVID-19) include non-human primates, hamsters, and transgenic mice expressing the human ACE2 receptor. However, no studies of LDRT in these models are available (*3*), and some workshop participants called for such preclinical experi-

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TABLE 2
Suggested correlative studies in the clinic (*21, 22*)

Peripheral blood mononuclear cells (PBMC) – flow cytometry, CyTOF®
Plasma: Cytokines, miRNA, exosomes, proteins/metabolites, neutralizing antibodies, hypoxia markers
Radiation pneumonitis markers (TGF-β, KL-6, surfactants, IL-1ra, IL-6, sTNF, C3, C4b-binding protein-α)
Endothelial/cardiac injury markers (hscTnT, CKMB, NT-proBNP, ANP)
Systemic inflammation markers (CRP, LDH, ferritin, D-dimer, IL-6)
Bronchial secretions (BAL fluid) – viral load, flow cytometry
Pulmonary function tests, oxygen requirements, ventilator settings, radiographic imaging, dosimetry
Stool: Viral load
Co-morbidities: Concurrent medications, prior treatments, quality-of-life

ments before continued testing of LDRT in COVID-19 patients.

RADIOBIOLOGICAL AND IMMUNOLOGICAL MECHANISMS

Using X rays to treat non-malignant disorders, including pneumonia (*23*), was more common in the U.S. until the 1950s, although LDRT is used in Germany, mainly for degenerative, hyperproliferative or inflammatory diseases (*24*), where single doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy are delivered to patients >40 years old (*24*). Rapid decreases in pain and edema are commonly reported. The relevance to LDRT for COVID-19 can be questioned; however, efficacy suggests an anti-inflammatory action, supported by preclinical studies (*25*).

Our understanding of the biology of SARS-CoV-2 is constantly evolving and studies on the effects of radiation on COVID-19 are limited and challenging. This complex biology adds to the debate about the essential need for preclinical data and clinical trials, to include carefully specified indications, exclusions, treatment regimens, biomarkers and clinical outcomes, and the importance of a randomized study comparing radiation therapy vs. drug therapy or drug therapy ± LDRT. Selecting radiation dose may be from a randomization (noted in the study above) or by the investigators' choice.

SARS-CoV-2 in the lung targets primarily bronchial and alveolar epithelial cells, but other targets are likely, including immune cells. Pathogen-associated molecular patterns are sensed by innate pattern recognition receptors (PRR) on resident immune and non-immune cells, leading to the production of chemokines and cytokines. These molecules activate leukocyte-endothelial interactions to allow an influx of immune cells into the inflammatory site. The PRRs that sense the presence of SARS-CoV-2 have yet to be fully identified, but are likely important for the outcome of infection and could explain why this virus stimulates a vigorous hyperinflammatory response (*26*). Radiation is known to modulate Toll-like receptor (TLR) expression, which could alter early innate immune response (*27*), although it is unknown whether LDRT can do this. Immune cells, especially the myeloid subsets, are activated to phagocytose debris in the inflammatory site while dendritic cells (DC) present antigens to stimulate adaptive immunity in primary lymphoid tissues. Myeloid cells, however, appear to be dysregulated (further discussed below), and conventional DCs and pDCs are decreased in COVID-19 patients (*28*), but whether the generation of antiviral immunity is affected is, as yet, unclear.

Inflammation is a multistep process involving many cell types and mediators such as reactive oxygen species (ROS), nitric oxide, prostaglandins, and pro-inflammatory chemokines and cytokines, especially interleukin (IL)-1, tumor necrosis factor-α (TNF-α), IL-6, IL-8, and IL-12. Pro-inflammatory cytokines also tie into coagulation pathways and fibrin deposition, which is important in the later stages of COVID-19 pathogenesis. Vascular endothelial cells play a central role in responding to and producing cytokines that further drive cytokine production and lead to a coagulation response, mainly through the extrinsic pathway involving tissue factor and factor VIIa. Such inflammatory, pro-coagulation events can overwhelm host defenses, leading to disseminated intravascular coagulation and multiple organ failure. Coagulopathy is frequently associated with excessive systemic inflammation and is a distinct feature of advanced COVID-19 (*29*). The ability of single high doses of radiation to induce inflammation and trigger clotting has been known for decades (*30*). In contrast, little is known as to how LDRT might affect the coagulation process, particularly in ARDS. The effects of LDRT on ongoing inflammatory processes have been investigated in other model systems. However, detailed dose-response and time-course studies are essential to deciphering the pro-survival immune-modulatory response vs. cytotoxic effects of LDRT on lung vascular endothelial cells. Since endothelial cells are relatively radiosensitive, LDRT-mediated benefit may be linked to an inhibitory effect on coagulopathy, which needs to be verified. The effects of LDRT on many inflammatory processes have been investigated, but data are not consistent with respect to dose and time of response. However, a general picture has emerged of anti-inflammatory actions of doses in the range 0.1–1.0 Gy with notably reduced immune cell/endothelial cell adhesion and production of inflammatory mediators such as ROS, nitric oxide, and cytokines *in vitro* that translated *in vivo* to LDRT efficacy on experimental collagen-induced arthritis (*31, 32*), experimental autoimmune encephalomyelitis (*33*), TNF-induced polyarthritis (*34*), and decreased neuroinflammation in mouse models of Alzheimer's disease (*35, 36*). Although these LDRT studies were performed in the context of inflammatory conditions, it should be noted that LDRT was often delivered just before or after a challenge. There is a paucity of data on the effects of LDRT in preclinical animal models in the context of viral infection.

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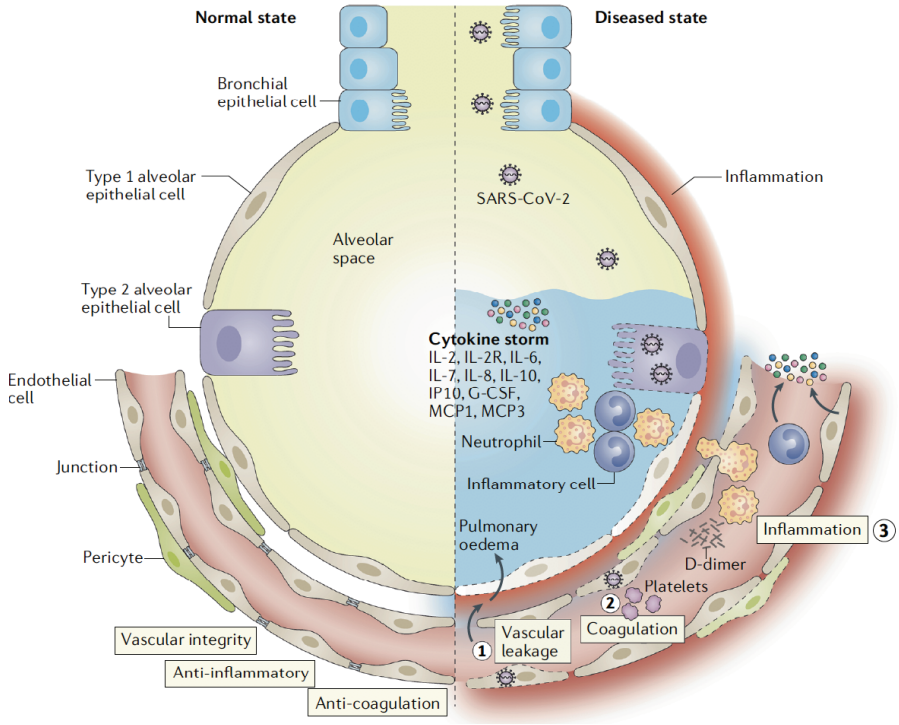


FIG. 2. Pathophysiological changes in vessel-lung interface due to SARS-CoV-2 infection leading to the loss of vascular integrity, activation of the coagulation pathway, and inflammation. Published and modified, with permission, Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol. 2020; 20:389–91.

Many factors, including IL-6 (*37*), affect radiation responses, and the use of an appropriate animal model is crucial as a preexisting inflammation can dramatically alter the response to radiation, especially if it is hyperinflammatory.

Pathophysiological changes in vessel-lung interface due to SARS-CoV-2 infection leading to the loss of vascular integrity, activation of the coagulation pathway, and inflammation have been recently reported (*38*) (Fig. 2). In its worst form, COVID-19 is a complex pathophysiological disease state, which includes severe pneumonia, ARDS, septic shock syndrome, disseminated intravascular coagulation, and multiorgan failure (*39, 40*). In patients, IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, G-CSF, IP10/CXCL10, MCP1/CCL2, MIP1A, CCL3 and TNF-α are frequently elevated (*41*). High levels of a subset of these pro-inflammatory chemokines and cytokines, especially IL-6, correlate directly with disease severity and could be responsible for at least some of the disease's pathological features (*42*). Given these findings, it is not surprising that attempts are being made to target inflammation in COVID-19 (*43*), including IL-6 blocking antibodies, IL-1R agonists, NADPH oxidase (NOX) inhibitors, dexamethasone, JAK1 inhibitors, and now LDRT.

Figure 3 illustrates the timeline of dynamic changes in lungs resulting from SARS-CoV-2 exposure, causing antiviral immune response and inflammatory response, leading to ARDS and multiorgan failure due to hyperinflammation. This mechanistic understanding of pathophysiological processes, resulting from early infection and pulmonary phase to the development of ARDS due to hyperinflammation, provides a ''hypothetical window of opportunity'' to intervene in the disease progression with LDRT; however, this concept needs to be tested and confirmed with biomarkers of immune and inflammatory responses (see Tables 2 and 3) alongside tissue oxygenation status.

In considering the cytokine profile of COVID-19, the lack of type 1 interferon (IFN) production in response to SARS-CoV-2 infection is striking. Other coronaviruses are known to interfere with IFN synthesis (*44*), and SARS-CoV-2 may have similar attributes. Since type 1 IFNs are important for antigen presentation, viral impairment of IFN production could have profound effects on development of adaptive anti-viral immunity and allow unrestricted viral replication. Recently, IFN-α has shown promise, either alone or with HIV-specific protease inhibitors, in treating coronavirus infections, including COVID-19 (*45*).

Myeloid cells appear to be dysregulated in COVID-19 and, although reports are inconsistent, increases in pro-inflammatory monocytes that produce high levels of IL-6 and other cytokines and have low MHC class-II expression may be related to dysfunctional innate and adaptive immunity and disease status (*46*). Dysfunction of alveolar macrophage by SARS-CoV-2 has also been proposed as a driver of the cytokine storm (*47*). Other features of the disease that correlate with its severity are T- and NK-cell depletion and exhaustion (*48*). Along with increases in

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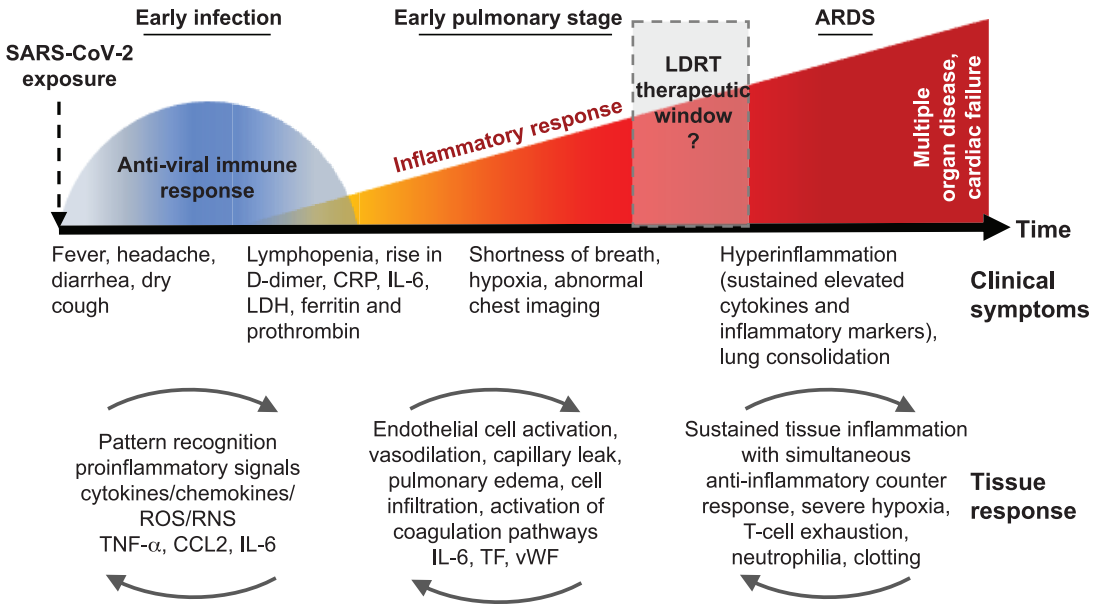


FIG. 3. Timeline of the dynamic changes resulting from SARS-CoV-2 exposure. The current understanding of the pathophysiological processes from the early anti-viral immune response to the development of ARDS and multi-organ failure due to hyperinflammation, opens a ''hypothetical window of opportunity'' for intervention with LDRT. However, this is a concept that needs to be tested and confirmed with biomarkers of immune and inflammatory response (see Tables 2 and 3 for potential biomarkers) alongside tissue oxygenation status. The LDRT window of opportunity will likely follow the principle of *as early as possible and as late as necessary* but the suggestion is that LDRT will be most effective during the early stages of inflammation, with the caveat of potential adverse effects of lung irradiation and combined injury.

myeloid suppressor cells (*49*), these outcomes contribute to a high neutrophil-to-lymphocyte ratio (*41*).

SARS-CoV2 infection evolves rapidly, as will the microenvironment within the tissue receiving the LDRT. Understanding the time-dose dependency of LDRT effects will be very challenging but crucial for dissecting therapeutic potential of LDRT, if any. Therefore, many questions remain about the anti-inflammatory action of LDRT in infectious diseases, and appropriate animal models of COVID-19 are urgently needed.

RISKS

Previously published studies with mouse models using combined radiation and influenza A exposure led to the hypothesis that prior lung irradiation might increase severity/susceptibility to SARS-CoV-2 and elevate the risk of pulmonary fibrosis (*50*). Prior SARS-CoV-2 exposure and recovery may also promote sensitivity and susceptibility to radiation-mediated lung injury and fibrosis in cancer patients. Notably, increased morbidity and mortality from SARS-CoV-2 infection was reported among lung cancer or lung metastasis patients in a multicenter study, while cancer patients without lung metastasis had no statistically significant differences compared to COVID-19 patients without cancer (*51*). COVID-19 patients with a history of lung radiotherapy had a poor prognosis and higher mortality risk, with a mathematical survival model having a nearly linear relationship between mortality risk after COVID-19 diagnosis and mean lung radiation dose (*52*).

LDRT includes exposure of whole lungs to radiation. Data from survivors of the atomic-bombings in Japan, who had average organ doses of approximately 0.2 Gy, indicate that the lifetime risk of lung cancer is higher in females than in males, the excess risk at 1 Sv for acute exposures being 2.6–6.7% vs. 1.3–2.0%, respectively (*6*). These ranges reflect differences in age at exposure for adults, statistical and dosimetry errors and the use of absolute vs. relative risk projection/transfer models.

Other published epidemiological studies provide similar estimates (*6*). The risk of fatal cancer and circulatory diseases after 1 Gy acute radiation exposure is estimated by modeling at approximately 2 to 6% (*3, 53, 54*), with morbidity risk about twofold higher. Smoking has a major effect on risk, as does inflammation. Overall COVID-19 mortality is $<5\%$, with a higher loss of life expectancy than death from radiation-induced cancer or circulatory disease. However, persons above age 70 years may have a risk that is much higher than 5%. Risk estimates for adverse events from LDRT should be weighed against other treatment approaches.

OVERALL PERSPECTIVES

While there was a general consensus that LDRT for COVID-19 should be utilized only within a framework of rigorous and well-designed clinical studies, there was no agreement on whether safety data are sufficient and whether there is adequate rationale to proceed with clinical trials. Placing the role of LDRT in the context of safe and effective

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TABLE 3
Suggested Parameters for the Study Protocol, if LDRT is Planned to be Tested for COVID-19

Section	Protocol content/stipulation	Comments/concerns to address
Background	Rationale for the use of LDRT for COVID-19.	Biology of disease and radiation. Specific biological rationale for use and timing of LDRT.
Objectives of LDRT		
Primary	Presumably anti-inflammatory or this can be immunomodulatory (therapeutic effect of vaccine).	Address anti-inflammatory effect(s).
Secondary	Development of biomarker panels in the context of LDRT use, to aid in acute clinical management and in the analysis of late clinical trajectories of COVID-19 (*55–66*).	Address any anti-viral effect(s) as well as potential immune enhancement of disease. Address coagulopathy effect(s).
Patient selection		
Eligibility	Clinical condition and measurable parameters.	Stratification much like the PREVENT trial likely useful to match controls better. Examples are the Charlson Comorbidity Index (*67*) and the Wuhan/Guangdong Risk Score (*68*).
	Specify clinical criteria in terms of respiratory status, overall performance status, and laboratory parameters of immune and inflammatory status.	Assess both rate of clinical decline in addition to net scores.
	Adapt criteria with IRB approval as natural history and other treatments of COVID19 evolve.	Randomize patients to LDRT or control arm a few hours prior to availability of linear accelerator to deliver radiation. This will reduce number of patients randomized to LDRT that deteriorate without receiving the experimental LDRT.
	Carefully track number of eligible patients consented to the study receiving treatment. Intent-to-treat analysis essential.	
Exclusion	Criteria should be clearly specified. Some discussants felt that trials of LDRT are currently not indicated, due to lack of data on mechanism and shifting standard care (e.g., Dexamethasone use making value of immune markers potentially challenging).	Ethical review- Institutional Review Board or another similar panel necessary.
Gender and minority inclusion	Inclusion particularly relevant with the epidemiology of infection. Data should be collected regarding social and economic status, living conditions, co-morbidities and patient geography (e.g., pollution and lung disease correlations, etc.).	Underlying disparities in genetics or biology may impact outcome.
Trial type and projected number of patients, duration of study		
Phase 1	Generally, this is a specified phase 1 trial or a run-in part of a phase 2.	Intent-to-treat analysis is essential.
Phase 2, single arm or randomized	Run-in and randomization favored.	Phase 2 run-in favored when there are Phase 1 safety data available.
Phase 3	Felt to be insufficient evidence at present for a phase 3 trial.	
Treatment		
Radiation, target, dose and schedule	Dose range of 0.35–1.5 Gy (or up to 2 Gy); Single dose due to complex logistics.	Megavoltage recommended.
	Need to standardize definition of low, ultra-low, etc.	Needs better biological assessment of intention of chosen dose because different doses may affect different subsets of the COVID-19 immune response and may vary from person to person.
Concomitant drugs required as part of treatment	Critical to include data on corticosteroids; other antivirals, and other inflammatory agents.	Describe/examine course of drugs in relation to LDRT because the relative timing of interventions could theoretically cause different therapeutic maneuvers to block each other.
	Consider anticoagulants, oxygen use and status, cardiac inotropes, history of prior and current use of ACE inhibitors, diabetes. Complex geographic and environmental interactions linked to lung disease in addition to smoking and mining (*69*). Remdesivir (*70*) and dexamethasone (*10*) are baseline for all patients currently.	This may vary by economic situation (e.g., low to middle income country).

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TABLE 3
Continued.

Section	Protocol content/stipulation	Comments/concerns to address
Other drugs	Details of prior/current medications.	Timing of course in relation to LDRT.
Excluded	In this early phase it was felt that recruitment of pediatric/juvenile/middle-age and pregnant patients be avoided.	No formal age cut-off was selected. Risk for secondary cancers made most feel age consideration to be reasonable.
Drug, if randomized	Radiation was felt to be the primary agent to randomize (e.g., comparing different radiation doses or ''standard of care'' ± radiation).	Radiation (dose) ± steroids vs. steroids without radiation.
	Steroid dose could be added if necessary (or frequency of its use).	More than one radiation dose could be tested vs. arm without radiation.
Drug no. 1	One participant mentioned concomitant use of antibodies to reduce selected cell populations and minimize cytokine storm as a possible treatment.	No specific recommendation by workshop.
Response criteria		
Circulating blood counts	Include granulocytes and lymphocytes, with a focus on subtyping via flow cytometry to evaluate subtypes (exhaustion, etc.).	Neutrophil/lymphocyte ratio may be a helpful biomarker.
	Mast cell populations are also of interest.	Dexamethasone may reset current trial designs in this context.
	T cell lymphopenia and exhaustion, N:L ratio, HLA-DR + monocytes, CD14+:CD16+ monocytes, TF+ monocytes.	
Immunological, general	Pre- and post-treatment evaluation.	Involvement with appropriate expertise. Dexamethasone may reset the current trial designs in this context.
	Fibrosis biology felt to be important for both control and treatment patient cohorts.	
	Evidence of (pros): Anti-fibrotic effect. Normalization: IL-6, ratio of IL-10: TNF-α, CRP, IL-10/23, IL-1β, IFN-type I, IL-2, fibrinogen, TPA, PAI-1, ferritin, albumin, D-dimer, LDH, prothrombin, C3/C5 complement.	
	Evidence of (cons): No anti-fibrotic effect. Further rise in systemic proinflammatory markers, coagulopathy and immune paralysis.	
Immunological- SARS-CoV-2 related (see Table 2)	As above, other factors to be collected from the same samples as allowed (complement, IL-6, other IL factors, TNF factors, etc.)	As above, appropriate expertise.
	Evidence of (pros): Improvement of viral disease. Normalization: IFN-α (or IP-10), Ab titers, S-protein tetramers.	
	Evidence of (cons): No improvement. Rising angiotensin II (viral load and lung injury).	
Chemistry	AST, ALT and others per routine care.	
Imaging		
Chest (CT, X ray)	Chest X ray, unilateral or bilateral changes or 3D ultrasound if no X ray available.	Lung infiltration may impact radiation lung dose.
	CT scans likely difficult due to logistics involving movement of patients, possible contamination of equipment and staff exposures.	
Other organs	Liver, mediastinal content, scatter dose to the thyroid, stomach, colon, the great vessels, the bones of the chest including their marrow, and potentially other organs.	Not known if LDRT would be equally effective if blocking at the diaphragm is used rather than at the true inferior limit of the lungs.
Symptomatic response		
System	Subjective and objective measures.	Some felt symptomatic relief useful but not a sufficient end point.
Patient outcomes		
ICU-care required, or no longer required	Outcome measurements that are validated for the acute phase of therapy.	Hospital costs and outcomes related to ICU admission timing will vary situationally.
		Acute medical management phase measurements like more rapid ICU discharge need to be used cautiously as it is unknown how these may correlate with severe late effects; i.e., early ''benefits'' that alter hospital management may not predict late functional outcome which may be more important.

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TABLE 3
Continued.

Section	Protocol content/stipulation	Comments/concerns to address
Duration in ICU (pre- and post-LDRT)	Important parameter to consider as a primary trial efficacy end point	Changing acute management with LDRT might not correlate with ultimate pulmonary function.
Alive, duration	Long-term data should be sought.	
Death, when post-LDRT	Possible co-primary end point with ICU duration.	
Long-term survivors	For survivors, evaluation of the long-term symptoms from viral infection, treatment, and the neutralizing capacity of antibodies.	Can LDRT degrade development and maintenance of long-term immunity for survivors? Research subjects should be followed for the development of cancer and cardiovascular disease.

vaccines as well as improved anti-viral and anti-inflammatory strategies is essential.

Although the workshop did not reach consensus on whether or not clinical trials of LDRT for COVID-19 are appropriate, based on biological knowledge and clinical experience to date with the pandemic and LDRT to treat COVID-19, one major goal of the workshop was to suggest guidelines to consider for a well-designed clinical study. Taking into consideration the pros and cons of many parameters, a possible framework for a protocol was developed (Table 3). However, this framework is not a blueprint; rather, it provides guidance for those who are committed to testing LDRT as a treatment option for the COVID-19 public health crisis.

CONCLUSIONS

It is clear that more preclinical data, ideally derived from a robust model reflective of SARS-CoV-2 pathophysiology, are needed, and that little data exist regarding the pathophysiological effects of treating a lung with LDRT in the midst of a viral vasculopathy and pneumonia. However, the efforts of radiation biologists to reveal the potential mechanistic interplay between radiobiologic response and virus-induced cytokine response in a target organ was recognized. Without supporting or refuting LDRT for COVID-19 as a treatment, this review intends to assist clinicians and researchers who plan to conduct preclinical and clinical studies, given the limited evidence on the safety and efficacy of LDRT for COVID-19. Recognizing that improved treatments for severely ill patients with COVID19 are necessary, any trial that is performed must be done cautiously, with full appropriate IRB oversight and ongoing awareness of rapid changes in the biological understanding of the phases of the illness and the standard of care in this patient cohort. Also, the workshop participants recognize the potential of these novel trials to enhance understanding of the effects of radiation in modulating host immunity and anti-inflammatory response; this supports the essential inclusion of biomarkers in all studies. While the opinions of workshop participants spanned the entire arc, from ''for'' to ''agnostic/neutral'' to ''against'' the clinical application of LDRT, there was general agreement that collaborative preclinical research and rapid reporting of results from any clinical trials are necessary.

Search Strategy and Selection Criteria

Two authors independently searched *clinicaltrials.gov* for currently registered clinical trials using ''low dose radiation therapy'' and PubMed using MeSH terms, ''arthritis/radiotherapy; inflammation/radiotherapy; ionizing radiation/anti-inflammatory effects; pneumonia/radiotherapy; Germany/radiotherapy; radiotherapy dosage; radiation injury/blood; oxidative stress/radiotherapy; COVID-19/SARS-CoV-2/lung innate immunity; coronavirus infection/blood; betacoronavirus/blood coagulation; coronavirus infection/pathology; cytokine release syndrome; encephalomyelitis, autoimmune, experimental/gamma rays; Alzheimer's disease/radiation; interleukin-6/radiation; cytokines/low-dose radiation; Nrf-2/radiation; myeloid cells/low-dose radiation'', for published literature from 1999–2020 for this review, prepared as the Workshop Report on LDRT for COVID-19.

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Provisional pending. Dr. Kirsch reports other support from Lumicell, Xrad Therapeutics, grants from Merck, grants from Eli Lilly, grants from Bristol Myers Squibb, grants from Varian Medical Systems, outside the submitted work. In addition, Dr. Kirsch has a patent Radiosensitizer, issued to XRad Therapuetics, a patent Imaging device, licensed to Lumicell, and a patent Imaging agent with royalties paid to Lumicell. Dr. Mehta reports personal fees from Abbvie, Celgene, Blue Earth Diagnostics, Astra Zeneca, Tocagen, Karyopharm, Mevion and Oncoceutics, outside the submitted work. Dr. Weichselbaum reports grants from Varian Medical Systems and Regeneron during the conduct of the study; and others from Boost Therapeutics, Coordination Pharmaceuticals Inc., ImmunoVir LLC, Magi Therapeutics, Oncosenescence, RefleXion Pharmaceuticals, AstraZeneca, Coordination Pharmaceuticals, Genus, Merck Serono S.A., Nano Proteagen, and NK Max America Inc., and personal fees from Boehringer Ingelheim, Astrazeneca, and Merck Serono S.A., outside the submitted work. In addition, Dr. Weichselbaum has a patent, Methods and Kits for Diagnosis and Triage of Patients with Colorectal Liver Metastases, pending.

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