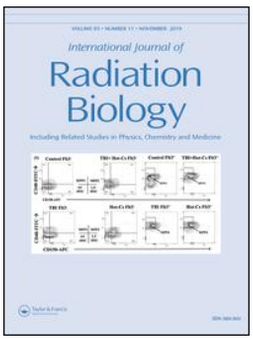

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REVIEW

Is there any supportive evidence for low dose radiotherapy for COVID-19 pneumonia?

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Running title
Low dose radiotherapy for COVID-19 pneumonia

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COVID-19; pneumonia; low dose radiotherapy; clinical trials; adaptive response

Abstract

Since early April 2020, there has been intense debate over proposed clinical use of ionizing radiation to treat life-threatening pneumonia in Coronavirus Disease 2019 (COVID-19) patients. At least twelve relevant papers appeared by 20 May 2020. The radiation dose proposed for clinical trials are a single dose (0.1–1 Gy) or two doses (a few mGy followed by 0.1–0.25 Gy involving a putative adaptive response, or 1–1.5 Gy in two fractions 2–3 days apart). The scientific rationale for such proposed so-called low dose radiotherapy (LDRT) is twofold (note that only doses below 0.1 Gy are considered as low doses in the field of radiation protection, but here we follow the term as conventionally used in the field of radiation oncology). Firstly, the potentially positive observations in human case series and biological studies in rodent models on viral or bacterial pneumonia that were conducted in the pre-antibiotic era. Secondly, the potential anti-inflammatory properties of LDRT, which have been seen when LDRT is applied locally to subacute degenerative joint diseases, mainly in Germany. However, the human and animal studies cited as supportive evidence have significant limitations, and whether LDRT produces anti-inflammatory effects in the inflamed lung or exacerbates ongoing COVID-19 damage remains unclear. Therefore, we conclude that the available scientific evidence does not justify clinical trials of LDRT for COVID-19 pneumonia, with unknown benefit and known mortality risks from radiogenic cancer and circulatory disease. Despite the significant uncertainties in these proposals, some clinical trials are ongoing and planned. This paper gives an overview of current situations surrounding LDRT for COVID-19 pneumonia.

Introduction

The ongoing pandemic of Coronavirus Disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in late 2019, leading to >4,700,000 cases and >310,000 deaths as of 20 May 2020 (WHO 2020a). Currently, few clinical management options are available for the severe COVID-19 pneumonia or acute respiratory distress syndrome (ARDS) requiring intensive care, although there are ongoing clinical studies on remdesivir and other several potential therapeutic agents (Cao et al. 2020; UKCDR 2020; WHO 2020b).

In early April 2020, two papers appeared that proposed clinical trials of low dose radiotherapy (LDRT) for COVID-19 pneumonia using low-linear energy transfer (LET) radiation exposure. This treatment was claimed to pose very low risk to patient health and avoid normal tissue toxicities (Ghadimi-Moghadam et al. 2020; Kirkby and Mackenzie 2020a). On one hand, Ghadimi-Moghadam et al. (2020) suggested use of a priming dose of radiation to the lungs of a few milligrays (mGy), e.g., 2 mGy, followed by a single dose of 0.1, 0.18 or 0.25 Gy. On the other hand, Kirkby and Mackenzie (2020a) suggested use of a single acute lung dose of 0.3–1 Gy. These suggestions were based on an earlier review of 19 papers published between 1905 and 1943, describing outcomes from LDRT for viral or bacterial pneumonia conducted in the pre-antibiotic era (Calabrese and Dhawan 2013). In our previous commentary, however, we pointed out the limitations both in the human data (limited to case reports) and in the biological data (only three studies) reviewed in Calabrese and Dhawan (2013); thus, the body of evidence for a proposed beneficial effect of LDRT on viral pneumonia is clearly extremely slight (Salomaa et al. 2020). Moreover, accounting for the associated risks of radiogenic cancer and circulatory disease, we concluded that there is very little, if any, supportive evidence that LDRT could be a curative or palliative treatment for COVID-19 pneumonia or could be superior to any of the potential therapeutic agents currently under clinical trials (Salomaa et al. 2020), or the existing anti-inflammatory drugs. Our previous commentary (Salomaa et al. 2020) was written based on information available before 20 April 2020, and we now provide an update on this rapidly evolving topic.

An update since mid-April 2020: relevant new papers and ongoing clinical trials

From 20 April through 20 May 2020, ten papers on LDRT for COVID-19 pneumonia appeared (Kefayat and Ghahremani 2020; Kirkby and Mackenzie 2020b; Lara et al. 2020; Trott et al. 2020; Dhawan et al. 2020; Rödel et al. 2020; Chakrabarti and Verma 2020; Kirsch et al. 2020; Schaue and McBride 2020; Salomaa et al. 2020).

Consistent with the arguments made in Salomaa et al. (2020), Kefayat and Ghahremani (2020) demonstrated that the case reports and biological studies reviewed in Calabrese and Dhawan (2013) have limitations, and that anti-inflammatory effects of LDRT may not be very effective in controlling "cytokine storm" due to COVID-19 pneumonia; rather, radiation-induced disruption of the immune system may delay virus elimination. Kefayat and Ghahremani (2020) added, however, that the lungs with a high viral load should not serve as the target organ, so total body LDRT may be more effective for COVID-19 pneumonia than lung LDRT. The paper of Kefayat and Ghahremani (2020) was prepared in response to Kirkby and Mackenzie (2020a). In a reply to Kefayat and Ghahremani (2020), Kirkby and Mackenzie (2020b) considered that the risk of LDRT for COVID-19 pneumonia would be very low, but the risk they considered was limited only to radiogenic pneumonitis. Kirkby and Mackenzie (2020b) further wrote that "there are no indications that multiple imaging doses exacerbate COVID-19 symptoms", which rather implies that multiple low doses given by medical imaging does not alter or alleviate COVID-19 symptoms.

Lara et al. (2020) suggested that lung LDRT at 0.5 Gy is a cost-effective, evidence-based, non-toxic, anti-inflammatory treatment already available in most general hospitals in some countries. They considered that the cytokine storm triggered by interleukin 6 (IL-6) and other inflammatory cytokines in COVID-19 pneumonia resembles LDRT-treatable rheumatic arthritis, and suggested that lung LDRT will serve as an anti-IL-6 treatment.

Again, consistent with Salomaa et al. (2020), Kirsch et al. (2020) concluded that the potential risks of clinical trials of LDRT for COVID-19 pneumonia outweigh the potential benefits, and that clinical trials of LDRT for COVID-19 should only be started after robust results in preclinical models demonstrating efficacy. Kirsch et al. (2020) pointed out the limitations in the two historical animal studies on viral pneumonia that were carried out in the same research group, i.e., Dubin et al. (1946) on swine influenza virus pneumonia in a murine model, and Baylin et al. (1946) on feline virus pneumonia in a feline model.

Both Kirsch et al. (2020) and Trott et al. (2020) cited the case series of Oppenheimer (1943) as evidence that LDRT may be useful if it is given at the early phase of the development of severe clinical symptoms, but not at later stages (e.g., once

hypoxia or ARDS develops in COVID-19 patients). Likewise, Schaue and McBride (2020) also considered that the chances of LDRT being effective in counteracting even a minor cytokine release storm in advanced stage disease would seem slim at best. Trott et al. (2020) considered biological studies in vitro that concentrate on specific pathways in the complex network of molecular signaling leading from trigger to overt disease to be most relevant, as we previously proposed the use of pulmonary microvascular endothelial cells (PMEC) to this end (Salomaa et al. 2020).

Dhawan et al. (2020) suggested the use of a single dose of 0.3–0.5 Gy to the chest for LDRT for COVID-19 pneumonia, and concluded that there is evidence for an anti-inflammatory property of LDRT that can potentially afford benefit to COVID-19 patients. This conclusion was derived from Calabrese and Dhawan (2013), who reviewed literature on anecdotal studies on LDRT for viral or bacterial pneumonia and bronchial asthma, and that on the experimental studies on anti-inflammatory effects of LDRT. Historically, LDRT was used for various non-malignant diseases in the pre-antibiotic era (Trott 1994). Since then, LDRT has been increasingly restricted to painful degenerative joint diseases (e.g., osteoarthritis) in the elderly where non-steroidal anti-inflammatory drugs or corticosteroids are not an option (Schaue and McBride 2020). However, a number of double-blinded studies on painful degenerative skeletal disorders have not shown a significantly higher response for the LDRT group compared with the placebo group (Seegenschmiedt et al. 2015). Trott et al. (2020) pointed out a selective quoting of experimental studies in Dhawan et al. (2020), and considered that pathogenesis, disease progression and treatment response in animal models of painful degenerative joint diseases are not necessarily good models for the per-acute interstitial inflammation observed in severe COVID-19 ARDS (Trott et al. 2020). It should also be noted that Calabrese and Dhawan (2013) did not cite many relevant papers relevant to effects of pre- or post-inoculation irradiation (Murphy and Sturm 1925; Tanner and McConchie 1949: Hale and Stoner 1954; Quilligan et al. 1963; Berlin 1964; Berlin and Cochran 1967; Lundgren et al. 1973).

Dhawan et al. (2020) as well as Calabrese and Dhawan (2013) took into account both studies with viral pneumonia and those with bacterial pneumonia equally as the supportive evidence. However, we note that pathogenesis of viral pneumonia and bacterial pneumonia is very different, providing little supportive evidence specifically relevant to viral pneumonia. In this regard, the most relevant models for preclinical studies on LDRT for COVID-19 pneumonia will be animals infected with SARS-CoV-2.

Rödel et al. (2020) concluded that LDRT with a single dose of 0.5 Gy to the entire lungs warrants clinical investigation, while acknowledging the need for strict monitoring and disease phase-adapted treatment based on lung function tests and

clinical markers (e.g., IL-6 and D-dimer in serum). They considered that LDRT may stimulate anti-viral immunity in the early to mid stages of SARS-CoV-2 infection, rather than the chronic stage of COVID-19 disease.

Chakrabarti and Verma (2020) considered LDRT for COVID-19 pneumonia with a single dose to be both cost and time effective. The supportive evidence for their suggestion was again based on Calabrese and Dhawan (2013). The suggested underlying mechanism for a beneficial effect was enhanced apoptosis, but enhanced apoptosis of normal cells should in fact culminate in increased normal tissue toxicity. However, as noted by Kirsch et al. (2020) and Schaue and McBride (2020), the consequences of a potential infection of staff and equipment in a repurposed radiation oncology unit were not taken into account.

Schaue and McBride (2020) cautioned that it is premature to suggest that LDRT would be superior to any of the drugs currently under trials, and until information from drug trials is available, it may be unethical to proceed with human trials given the potential adverse health effects consequent to radiation exposure. Schaue and McBride (2020) have posed six groups of important questions to guide relevant discussion, among which we here quote only one group of questions to define radiotherapy parameters: “In what patients should LDRT be used? When should it be started, with what dose, how often and at what volume/field size? Should there be a control arm and what should it be?”.

Trott et al. (2020) considered that there can be no supportive evidence specifically relating to COVID-19 as it is a new disease: this is undoubtedly true, but we rather consider that there is very little, if any, supportive evidence for LDRT being an effective treatment for viral pneumonia more broadly (Salomaa et al. 2020). Trott et al. (2020) considered that doses, timings and endpoints for treating COVID-19 pneumopathy cannot be generalized from German experience using LDRT for subacute painful degenerative joint diseases, but concluded that extensive clinical experience with the use of single local doses around 0.5 Gy to the target volume in the early acute phase, together with the comprehensive experimental work on the underlying mechanisms, would justify compassionate use in COVID-19 patients eligible for intubation and mechanical ventilation, but under close supervision and centralized documentation. We add that current experience of LDRT for treatment of inflammation in elderly patients does not include sufficient evaluation of long-term consequences in critical organs such as the lung, the heart and the breast.

Kirsch et al. (2020) estimated the potential risks for lung, esophageal and breast cancer and circulatory disease posed by thoracic irradiation with 0.5 or 1 Gy. We also previously discussed that the lung irradiation with a single dose of 0.3–1 Gy proposed by Kirkby and Mackenzie (2020a) would nominally induce 0.6–4.4 excess lung cancers

and potentially 0.8–7.6 extra circulatory disease deaths in a hundred persons exposed (Salomaa et al. 2020), the risk being highest at younger age at exposure. However, Chakrabarti and Verma (2020) considered that LDRT for COVID-19 pneumonia with a single dose causes no significant long-term sequelae, by ignoring potential mortality risk from cancer and circulatory diseases. On the other hand, there is no available evidence to compare the benefits of a curative effect with the projected risk for LDRT for COVID-19 pneumonia, and to this end, long follow up after LDRT will be needed. In this regard, it is noteworthy that in the 1910s to 1960s, patients with tuberculosis received on the order of 100 chest X-ray fluoroscopies of the chest over several years. These tuberculosis patients showed increased risk for breast cancer and circulatory disease, but not for lung cancer, although the mean protracted lung dose (about 1 Gy to the lungs, although protracted, similar to the level of acute dose for proposed LDRT treatment of COVID-19 pneumonia) was higher than in the atomic bomb survivor epidemiological studies, and the number of patients was similar to these atomic bomb survivor studies (reviewed in NCRP 2018). It remains unclear whether lungs and different tissues (e.g., breasts and the circulatory system) respond differently to fractionated/protracted dose (e.g., inverse dose fractionation effect suggested for the risk of circulatory disease in tuberculosis patients (Zablotska et al. 2014)), and whether healthy lungs and lungs affected with tuberculosis, COVID-19 pneumonia or other non-cancer disease differ in radiosensitivity.

Recent observations on the course of COVID-19 infection raise additional concerns regarding the use of radiation in infected patients. Reports are now showing significant comorbidities associated with COVID-19 infection, involving the nervous (Hess et al. 2020) and cardiovascular systems (Long et al. 2020). It has been suggested that viral entry into endothelial cells via the angiotensin-converting enzyme 2 (ACE2) receptor (Hamming et al. 2004) leads to apoptotic cell death and inflammatory reactions (Varga et al. 2020). Whilst low dose irradiation may alleviate inflammation, radiation exposures of 0.5 Gy are sufficient to damage endothelial cells in vitro (Azimzadeh et al. 2017a) and in vivo (Onoda et al. 1999). Consequently, a detrimental interaction between radiation and COVID-19 infection on endothelial cell function cannot be excluded. Such interactions could precipitate comorbidities of greater severity involving the microvasculature within a lung irradiation field.

Use of putative adaptive response to treat COVID-19 pneumonia?

In response to our previous commentary (Salomaa et al. 2020), Bevelacqua et al. (2020) submitted a letter to the Editor in early May 2020. The letter was written by three out of eight authors of the Ghadimi-Moghadam et al. (2020) paper, and we take this

opportunity to thank Bevelacqua et al. for their comments.

In the letter, Bevelacqua et al. (2020) emphasized the usefulness of the so-called "(radio-)adaptive response" in the LDRT scheme proposed in Ghadimi-Moghadam et al. (2020). Conceptually, this suggested that the application of a dose of only a few mGy (e.g., 2 mGy) to the chest or a whole body would serve as a priming (also called "adapting" or "conditioning") dose prior to the delivery of the single therapeutic (also called "challenge") dose of 0.1, 0.18 or 0.25 Gy to the lungs. Bevelacqua et al. (2020) considered that such priming irradiation would stimulate the immune system and enhance mitigation and repair mechanisms prior to the delivery of the therapeutic dose. However, there is little if any evidence for the existence of such an adaptive response in humans, nor is there scientific evidence to support a consensus on the timing and doses of either the priming or therapeutic doses, and there is as yet no mechanistic basis for the adaptive response phenomena (UNSCEAR 2012). This situation is further complicated by recent studies that have failed to observe the adaptive response (e.g., Bannister et al. 2015, 2016) or have documented considerable variability in experimental observations (Schwartz 2007). Further, it is possible that, were the effect to exist, patients are already adapted by exposure to natural background radiation and previous medical exposures (e.g., for diagnostic imaging). As the lungs with COVID-19 pneumonia are already subject to excessive immune response, one may ask if a priming irradiation to stimulate the immune system would provide any benefit.

Bevelacqua et al. (2020) added the hypothesis that "LDRT would reduce or prevent the blood clotting (observed in COVID-19 cases) through reducing oxidative stress", which was not described in the original paper of Ghadimi-Moghadam et al. (2020). In fact, low dose radiation has actually been reported to provoke a prolonged increase in oxidative stress in both mice and humans (Azimzadeh et al. 2017b; Barjaktarovic et al. 2019). Moreover, conventional high dose radiotherapy may promote blood clotting (Ouerhani et al. 2019). Conversely, LDRT may help reduce or prevent blood clotting via dilated blood vessels and capillaries. The resulting enhanced circulation in turn would cause edema in the lungs through facilitated leakage of fluids through endothelium (Onoda et al. 1999). As such, LDRT may further exacerbate COVID-19 pneumonia.

Bevelacqua et al. (2020) also wrote "The cardinal basis for the claims of Saloma et al. is linear no-threshold (LNT) hypothesis". Likewise, Lara et al. (2020) cautioned that an LNT model may overestimate the risks by one order of magnitude. However, the dose range suggested in all papers proposing LDRT of COVID-19 pneumonia, involves an acute dose above 0.1 Gy. So, linear extrapolation is neither necessary nor relevant for estimating risks, as the LNT model is applied when extrapolating the risk for exposures at doses around or below about 0.1 Gy. This is because there is direct evidence for cancer risk above that dose level (Little et al. 2009; NCRP 2018), although an issue

relating to the possibility of model misspecification remains in that there is a difference between accurately quantifying a risk around 0.1 Gy and being able to detect it.

Ongoing clinical trials

Eight clinical trials are apparently ongoing in the US, Spain, Iran, Italy, Finland and India, irrespective of all of the aforementioned reservations, both in terms of the efficacy of the treatment and the known adverse effects of radiation in the dose-range considered for LDRT. These studies include patients of various ages.

First, the Winship Cancer Institute of Emory University in the US initiated a single-arm Phase I/II clinical trial of LDRT for COVID-19 pneumonia, named "RESCUE 1–19" (Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19) in late April 2020 (NLM 2020a). In the first cohort, five patients would receive a single dose to the whole lung (information on the administered doses unavailable) with follow up for 28 days. A second cohort of five patients would follow (WCIEU 2020).

Second, the Fundacion GenesisCare in Spain initiated a single-arm, multicenter study of LDRT for COVID-19 pneumonia, named "ULTRA-COVID" (Ultra Low Doses of Therapy With Radiation Applicated to COVID-19) in late April 2020 (NLM 2020b). The study will enroll 15 patients at the age of ≥18 years who will receive a single session of 0.8 Gy to the whole lungs. Patients may also receive various drugs (lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperacillin/tazobactam, low molecular weight heparin, corticosteroids, and tocilizumab). Blood tests will be performed at days 2, 5 and 7, including measurement of the level of IL-6. Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) and Radiation Therapy Oncology Group (RTOG) scales will be used to evaluate acute toxicities at months 1 and 3 post-LDRT.

Third, the Grupo de Investigación Clínica en Oncología Radioterapia (GICOR) in Spain initiated a multicenter study on LDRT for COVID-19 pneumonia in early May 2020 (NLM 2020c). This study consists of two phases and involves patients at age ≥18 years. The first exploratory, single-arm phase intends to enroll 10 patients who will receive a single dose of 0.5 Gy to both lungs. If an improvement in clinical condition of >30% is achieved, then a second comparative, two-arm phase is anticipated. The second phase plans to enroll 96 patients (64 in the LDRT group and 32 in the control group). The LDRT group will receive a single dose of 0.5 Gy to both lungs, but a second additional dose of 0.5 Gy may be given at 48 h later. Both LDRT and control groups may receive various drugs (hydroxychloroquine sulfate, ritonavir/lopinavir, tocilizumab, azithromycin, corticosteroids, and low molecular weight heparin). The levels of various

pro-inflammatory cytokines (IL-1, IL-2, IL-8, IL-6, IL-10, TGF-beta, TNF-alpha), expression of L-, E- and P-selectin, cell adhesion molecules ICAM-1 and VCAM and an oxidative marker PON-1 will be measured at days 1, 4 and 7 post-LDRT. CTCAE v5.0 will be used to evaluate lung toxicities at days 30 and 90 post-LDRT.

Fourth, Shahid Beheshti University of Medical Sciences in Iran initiated a single-arm pilot study on LDRT for COVID-19 pneumonia in early May 2020 (NLM 2020d). The study intends to enroll 5 patients aged ≥60 years who receive a single dose of 0.5 Gy to both lungs with follow up for 28 days, but a second dose of 0.5–1 Gy may be subsequently delivered at ≥72 h later. Patients will receive additional doses from chest CT examinations at days 1, 7, 14 and 28. The level of IL-6 in the serum will also be evaluated at days 1, 4, 7 and 14 post-LDRT.

Fifth, the Azienda Socio Sanitaria Territoriale (ASST) degli Spedali Civili di Brescia in Italy initiated a single-arm pilot study on LDRT for COVID-19 pneumonitis, named "COLOR-19" (COVID-19 Pneumonitis Low Dose Lung Radiotherapy" as of mid-May 2020 (NLM 2020e). The study will enroll 30 patients aged ≥50 years who will receive a single dose of 0.7 Gy to both lungs. Up to 6 months post-irradiation, normal tissue toxicities will be evaluated according to CTCAE v5.0. This phase I study is expected to be followed by a phase II study.

Sixth, Helsinki University Hospital Comprehensive Cancer Center in Finland initiated a pilot study on LDRT for COVID-19 pneumonia in mid-May 2020 to examine whether a small dose of radiation to the lungs can reduce the severity of COVID-19 (YLE 2020). The study will first enroll 5 patients aged >50 years who will receive radiation to a limited volume of the lung, then may enroll more patients depending on the initial result. Information on dose and follow-up is unavailable. The investigators of this study consider that LDRT with undefine dose will be effective in immunosuppression as it is used in treating graft-versus-host disease after bone marrow transplantation.

Seventh, Brigham and Women's Hospital in the US will initiate a pilot study on LDRT for COVID-19 pneumonia in late May 2020 (NLM 2020f). The study will enroll 36 patients aged ≥40 years who will receive a single dose of 0.1 Gy of 6 MV photons to a single (right-sided) lung or to both lungs, and will be followed up for 30 days.

Finally, the All India Institute of Medical Sciences in India will initiate a pilot, single-arm study on LDRT for COVID-19 pneumonia in June 2020 (NLM 2020g). The study will enroll 10 patients aged ≥18 years who will receive a single dose of 0.7 Gy. The outcome will be evaluated with the National Early Warning Score (NEWS) at baseline and days 3, 7 and 14 post-LDRT.

The irradiation schedules in these trials (NLM 2020a, 2020b, 2020c, 2020d, 2020e, 2020g) follow those proposed in Kirkby and Mackenzie (2020a), except for NLM

(2020c, 2020d) that may choose to deliver a second dose of 0.5–1 Gy and NLM (2020f) that delivers 0.1 Gy. Also, in NLM (2020c), both LDRT and control groups include administration of a single or two doses of tocilizumab as an anti-IL-6 agent (an IL-6 receptor agonist): this also applies to NLM (2020b). If the major mechanisms by which LDRT dampens inflammation are through reduction of IL-6 as proposed in Lara et al. (2020), tocilizumab administration may mask the effect of LDRT.

In addition, several clinical trials (NLM 2020b, 2020c, NLM 2020f, 2020g) will enroll young and middle-aged patients aged 18–50 years who have more time to develop radiogenic health effects and may have higher radiosensitivity than elderly patients. In this regard, there is evidence that ERR/Gy decreases with increasing age at exposure for stroke and all circulatory disease in the Life Span Study (LSS) of the Japanese atomic bomb survivors (Little et al. 2012). According to such model (Little et al. 2012), a single 1 Gy lung dose (which the heart and aorta would also receive) would be associated with 8.5 extra deaths from circulatory disease in a hundred persons exposed when all age at exposure was considered, and 14.2, 10.1, 7.5, 5.8, 4.5 and 3.6 extra deaths at age at exposure 10–19, 20–29, 30–39, 40–49, 50–59 and 60–69 years, respectively. However, such trend was not apparent for heart disease in the LSS (Takahashi et al. 2017), and the opposite trend was suggested by the meta-analysis for circulatory disease (Little 2016). In addition, there is evidence that ERR/Gy increases with increasing age at exposure for lung cancer in the LSS (Cahoon et al. 2017), and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) considers that children are less sensitive to radiogenic lung cancer than adults (UNSCEAR 2013). Therefore, it remains unclear whether younger patients are more sensitive to lung irradiation. For sex which also affects radiation detriment (Zhang et al. 2020), females exhibit higher risk for radiogenic lung cancer and breast cancer, but lower mortality risk following COVID-19 (Parohan et al. 2020), compared with males. So, females may have less opportunity to receive LDRT, but once received, radiation risk may be higher. Openly available programs (e.g., STUK 2015; Ulanowski et al. 2019; NCI 2020) will be useful to estimate risks in advance of medical use of radiation (including discussion on the need of clinical trials and its dose levels).

There are possibly other similar clinical trials ongoing or in planning elsewhere, although there is no open information available on the web or in the literature to the best of our knowledge.

Conclusions

For LDRT for COVID-19 pneumonia using low-LET radiation, a number of empirical irradiation schemes have been proposed namely, a single dose of 0.1 Gy to a single lung or both lungs (NLM 2020f), a single dose of 0.3–0.5 Gy to the chest (Dhawan et al. 2020), a single dose of 0.3–1 Gy to the lungs (Kirkby and Mackenzie 2020a), a single dose of 0.5 Gy to the lungs (Lara et al. 2020; Rödel et al. 2020), a single dose of 0.7 Gy (target organ unspecified) (NLM 2020g), a single session of 0.8 Gy to the whole lungs (NLM 2020b), total body irradiation with a single dose (dose unspecified) (Kefayat and Ghahremani 2020), an initial dose of a few mGy to the chest or whole body followed by a single dose of 0.1–0.25 Gy to the lungs (Ghadimi-Moghadam et al. 2020; Bevelacqua et al. 2020), 1 Gy in two equal fractions separated by 2 days (NLM 2020c) or 1–1.5 Gy in two fractions (0.5 Gy followed by 0.5–1 Gy) ≥3 days apart (NLM 2020d).

Despite the fact that there is very little, if any, supportive scientific evidence to justify these treatments, and despite the very predictable deleterious effects of the intended radiation doses, several clinical trials are ongoing, the results of which may be reported in the next several weeks or months. When considering the value of proposals for clinical trials in this area, we would encourage Institutional Review Boards (ethical review committees) to bear in mind the justification principle that is consistently applied in radiation protection, including all clinical settings. This principle requires that the beneficence/non-maleficence of a proposed use of radiation is considered, in other words the balancing of ‘doing good’ and ‘avoiding harm’ (ICRP 2018; NCRP 2020). Individual patients should be able to give informed consent about individual risk versus benefit depending on age, co-morbidities etc. Acute mortality in COVID-19 patients admitted to the intensive care unit is high (Bhatraju et al. 2020; Richardson et al. 2020), but if LDRT can be a life-saving treatment in such severe cases, then some patients may manifest with edema, cancer and circulatory disease later. In our view the available evidence upon which the proposed and ongoing trails is based is inadequate to provide sufficient confidence for justification. It is imperative that no further studies are initiated until the evidence of these preliminary studies is carefully evaluated to determine if there is any beneficial effect of LDRT for COVID-19 pneumonia. The investigators of ongoing clinical studies should be strongly encouraged to collaborate and pool their data to increase statistical power of analyses, and to follow up their patients for several years.

We hope that our comments, together with those from others (Kirsch et al. 2020; Schaue and McBride 2020), may be used to support scientific, ethical and legislative bodies in their decision-making regarding the approval of further clinical trials.

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