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Short review

Low dose lung radiotherapy for COVID-19 pneumonia: A potential treatment

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ABSTRACT

The covid-19 pandemic has been affecting many countries across the world and lost precious lives. Most patients suffer from respiratory disease which progresses to the severe acute respiratory syndrome, termed as SARS-CoV-2 pneumonia. A systemic inflammatory response occurs in SARS-CoV-2 pneumonia severely ill patients, The inflammation process if uncontrolled has a detrimental effect, and the release of cytokines play an important role leading to lung fibrosis. Radiation therapy used in low doses has an anti-inflammatory and immunomodulatory effect. Its low cost, wider availability, and decreased risk of acute side effects can reduce the burden on the health care system.

1. Introduction

The 2019-novel coronavirus (2019-nCoV) has led to a pandemic which has affected almost all the countries globally. Most patients suffer from respiratory disease which progresses to the severe acute respiratory syndrome, termed as SARS-CoV-2 pneumonia, which leads to lethal consequences for patients. There is approximately 5 days incubation period before the development of symptoms of COVID-19. The utmost common being fever, cough, fatigue, sputum, headache, hemoptysis, diarrhea, and shortness of breath. Patients having comorbidities, such as chronic renal disease, diabetes, and/or chronic pulmonary disease have a higher risk of complications leading to mortality from respiratory viral infections such as COVID-19.

2. Pathogenesis of COVID pneumonia

COVID-19 pneumonia is a respiratory disease caused by a coronavirus. The presentation may vary from mild to severe illness. In SARS-CoV-2 pneumonia, a systemic inflammatory response occurs in severely ill patients and Cytokine Release Syndrome (CRS) is developed, in which there is a rapid increase in numerous pro-inflammatory cytokines, comprising of TNF- α , IL-1 and IL-6 [1]. Macrophages play an important role in this cytokine storm syndrome and are considered to be a vital constituent of this CRS syndrome. The proinflammatory M1 subclass of macrophage is triggered by lipopolysaccharides of infectious

and cytokines (interferon- γ) and initiate inflammatory events, through IL-1 β , IL-6, and TNF- α , the inflammatory cytokines. This uncontrolled expansion of the inflammatory cascade is responsible for tissue damage. On the other hand, M2 macrophages play an anti-inflammatory role and they respond to Th2 (T-helper type 2)-related cytokines such as IL-4 and IL-10, leading to expression of high levels of anti-inflammatory cytokines. It has been suggested that disproportion of pro-inflammatory M1 and anti-inflammatory M2 is the likely pathogenetic mechanism in the SARS-CoV-2 IL-6 related pneumonia. This inflammatory process if uncontrolled has a detrimental effect and the release of cytokines plays an important role in leading to lung fibrosis. It has been clinically observed that in patients with the weakened immune response the virus spreads and leads to lung damage. There are three stages of this disease manifestation. In the first stage, there is benefit from drug therapy, in the second stage patients develop viral pneumonia and radiological imaging shows changes and systemic inflammation markers may not be markedly elevated. Anti-inflammatory therapy may be beneficial at this stage. Few patients progress to stage three in which there is extra-pulmonary systemic inflammation and inflammatory markers are also raised. Therefore, management strategies are directed towards mitigation of the inflammatory factors and decrease the severity of this dreadful disease.

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Table 1
Studies conducted to assess efficacy of low dose radiation in covid pneumonia.

S No	Study title	Treated/total Number of patients	Dose	Primary endpoint	Outcome	Limitations
1.	Ameri et al.	10	0.5 Gy	Improvement in Spo ₂	RR and CR were 63.6% and 55.5%	Small sample size. Only >60 years patients were enrolled. Hence results cannot be applied to whole population.
2.	Sharma et al.	10	0.7 Gy	Clinical parameters using NEWS	90% response rate	Small sample size.
3.	Moreno-Olmedo et al. (a) (ULTRA-COVID study)[23]	2	0.8 Gy	Improvement in Spo ₂ and decreased oxygen demand, improvement in blood parameters	Improvement in symptoms after 48 h in both patients	Small sample size. Lead time bias as patients given radiation were in different phases of disease.
4.	Hess et al.	5/9	1.5Gy	Safety	60% improvement in SPO2 levels, 4 (80%) radiological improvement	Small sample size. Mainly included old aged patients Compared to other studies dose of Radiation was a bit on higher side which can be associated with more risk of secondary malignancy.
5.	Castillo	1	1Gy	Improvement of ventilatory function and decrease in serum inflammatory markers and oxygen support needs	Recovered	Case report of one patient. Result based on one patient cannot be implied to general population.
6.	Sanmamed et al.[24]	9	1 Gy	Radiologic response using severity and extension score	7 patients recovered	Small sample size Non-randomized study Short follow up Heterogeneity of previous medical treatments received by the patients

3. Role of radiation in COVID pneumonia

3.1. Mechanism

Role of low dose radiation therapy (LDRT) has been studied to treat pneumonia as early as the 1900s. Fifteen studies that involved 863 patients of various etiologies were treated with a success rate of 80–85% and reduction in mortality from 30% to 10%. of pneumonia [2].

The postulated mechanism for LDRT is its anti-inflammatory property of reduction in levels of pro-inflammatory cells such as cytokines and macrophages and polarization towards an anti-inflammatory M2-like phenotype [3]. LD-RT helps in modulating the function of inflammatory cells like endothelial cells, polymorphonuclear cells, and macrophages. In vitro studies have suggested that doses ≤ 0.7 Gy modulate the expression of adhesion molecules and the production of cytokines, which leads to a decrease in leukocyte adherence to endothelial cells. Also LD-RT leads to induction of apoptosis in the cells compromising the inflammatory infiltrate, decrease in expression of adhesion molecules (P-, L-, E-selectins, ICAM, VCAM), decrease in iNOS leading to decrease in NO and ROS, increase in activation of nuclear factor-kappa B (NF- κ B), increase in expression of anti-inflammatory cytokines (IL-10, TGF- β 1) [4–7]. Thus in covid pneumonia, the LDRT may reduce the inflammatory response, cytokine storm and thus decrease the need for ventilators, associated morbidity, and fatal events like death.

3.2. Dose of LDRT

Calabrese et al., in 2019 reported that hundreds of studies had been conducted on 37,000 patients and it has been shown that low dose radiation was effective in various inflammatory conditions [8]. Therapeutic responses occurred with 0.3 to-1.0Gy radiation dose and the mechanism being decreased inflammation by radiation due to polarization of macrophages to M2 type.

Ameri et al. conducted a study on five covid pneumonia patients and a single dose of 0.5Gy was given to both lungs. Four out five patients responded to this dose of treatment without any acute radiation toxicity [9].

Hess et al. treated 5 patients with covid pneumonia with LDRT with dose prescription of 1.5 Gy to both lungs and four patients had good clinical improvement without any acute side effects.10 Similarly, a pilot study conducted by Sharma et al. recruited [10] patients of covid

pneumonia for LDRT. The dose prescribed was single 0.7 Gy to the whole lung and 90% of patients had clinical recovery post treatment [11]. Castillo et al. reported a case study of 64 years males with covid pneumonia, in which they adopted volumetric modulated arc therapy and prescribed a dose of 1.0 Gy to the whole lung. The use of CT-based contouring and planning is debatable for such small doses [12]. Doses more than 2 Gy can have a pro-inflammatory effect of radiation therapy, leading to radiation toxicity [13]. Table 1 shows the list of studies conducted so far worldwide to assess the effectiveness of LDRT in covid pneumonia.

The timing of LDRT administration is also challenging. Usually, as per the mechanism of anti-inflammatory action of radiation, it should be a pro-inflammatory phase, similar to the other treatments such as steroids and tocilizumab [14]. In 1943, Oppenheimer reported that if effectiveness of radiation was better if delivered in the first week of the disease phase (100%) cure rates, as compared to 50% when radiation was given after 2 weeks [15].

3.3. Patient selection for LDRT

Most of the studies have selected patients with mild to moderate covid pneumonia illness for LDRT and patients who were on a mechanical ventilator or aerosol-generating devices were excluded, the reason being shifting of such unstable patients to treatment room was a difficult task.

3.4. Advantages of LDRT

- Low dose radiation therapy is available in many parts of the world and is administered on standard Radiation machines (LINACS).
- The LDRT treatment is cost-effective, without associated toxicities.
- It can decrease the need for hospitalization, hospital stay, and need for ICU
- If a dedicated radiation unit is used, one single-fraction at very low doses is required and whole lung volume for this low does not require sophisticated planning technique and so it would be have the potential to treat a huge number of patients.

3.5. Concerns regarding LDRT

Lack of efficacy possess a major concern for LD-RT. In a human,

lymphocytes are required for immune response against COVID-19. However, if there is excess inactivation of these cells, it can lead to inability to counteract against this virus and can lead to early mortality. Although the degree of lymphocytic inactivation depends on the dose and volume of LD-RT, but currently there are no validated measures for radiation-induced lymphopenia. Further, there may be a risk of radiation-induced mutations of the viral genome which can induce selection pressure, which further lead to undesirable evolutionary changes during viral replication. Another disadvantage of LDRT is logistical aspects of RT delivery. Transportation of a COVID-19 patient to radiotherapy department, computed tomography simulation and RT delivery possess a risk of developing infection for staff involved in handling of Covid patient. Also, the time required to sterilize RT equipment adequately between patients limits the ability to treat other patients in a given time frame. Due to these reasons, LDRT for COVID-19 is logistically, mechanistically, and ethically challenging and warrants careful consideration of the pros and cons of using LD-RT [16].

Hanna et al. conducted semi-structured interviews to identify the barriers among clinicians regarding LDRT in clinical practice [17]. The barriers assessed were.

- LDRT could worsen the inflammatory state and which might not be predictable, the possible mechanism being idiosyncratic and not dose-dependent.
- Also, the concern raised was the challenge in designing a clinical trial, sample size, and primary endpoint determination. It was further mentioned the recruiter in covid cases might be a pulmonologist or intensivist with a radiation oncologist taking care of treatment delivery, and this was considered an unusual situation in a clinical trial. Concerns were raised regarding optimal patient selection for a trial.
- Logistic issues were also considered to be a barrier. Patient shifting from medical ward to radiotherapy machine and then back to ward, other staff, personnel, and patients risk in many regions with limited resources.

4. Risk of radiation-induced cancer

Radiation is a non-toxic, cost-effective management strategy for covid pneumonia, but the concern is the occurrence of radiation-induced cancer later on. Various studies have shown probability of incurring cancer at doses about 100 mSv or less [18]. It is not yet clear whether cancer risk has a threshold or not. However, in radiation protection linear no-threshold (LNT) model of cancer risk is accepted, which implies that there is no safe dose of ionizing radiation [19]. It has been seen that such low doses given in benign diseases did not pose any such risk [20]. In contrast, Kirsch et al. have raised the concerns regarding late occurring toxicities due to radiation based on dose limits defined on the basis of occupational radiation exposure models [21]. It has been predicted that organs such as lung and breast may have high risk of developing secondary malignancy post LDRT. Garcia et al. reported that LDRT in COVID-19 results in a very low dose to organs outside the treatment field and therefore there is very low risk of cancer induction (lower than 0.06 cases per 10,000). However, there are many organs which are within the large fields employed, and contribute to increase the total risk (with doses between 1 and 10 mSv/cGy). Lung and breast, among the most radiosensitive organs, are within this highest dose region. Hence, non-negligible stochastic effects of cancer induction were estimated for LDRT treatment in their study [22]. However seeing such a rapid deterioration in the general condition of patients, patients with comorbidities at high risk of covid and risk of cancer has a long dormancy of occurrence, this concern carries a less of relevance as opposed to the benefit achieved by radiation. But at the same time, patients being treated by LDRT should be followed longitudinally to assess long-term outcomes.

Table 2
Ongoing Clinical Trials of Low dose lung Radiotherapy in COVID pneumonia (ClinicalTrials.gov).

S No	Title	Status	Dose	Country
1.	Anti-inflammatory Effect of Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia	Completed	1 Gy whole lung	Guanajuato, Mexico
2.	Lung Irradiation for COVID-19 Pneumonia	Recruiting	Arm A: No Radiation Arm B: 1 Gy Single Lung Arm C: 1 Gy Whole Lung	Massachusetts, United States
3.	Low Dose Lung Radiotherapy to Treat COVID-19 Pneumonia	Recruiting	0.5 Gy whole lung ±0.5 Gy upto 96 h apart	Preston, United Kingdom
4.	Ultra Low Doses of Therapy With Radiation Applied to COVID-19	Recruiting	0.8 Gy Whole lung	Valencia, Spain
5.	Low Dose Radiotherapy in COVID-19 Pneumonia	Active, not recruiting	0.5 Gy whole lung	Iran, Islamic Republic of
6.	Low Dose Pulmonary Irradiation in Patients With COVID-19 Infection of Bad Prognosis (COVRTE-19)	Recruiting	–	Castellon, Spain
7.	Low-Dose Radiotherapy For Patients With SARS-COV-2 (COVID-19) Pneumonia	Recruiting	Low dose radiation 0.35Gy High dose radiation 1 Gy	Florida, United States Florida, United States Loyola University Chicago, Illinois, United States Indiana, United States Massachusetts, United States Michigan, United States Ohio, United States Bogotá, Colombia Brescia, Italy
8.	COVID-19 Pneumonitis Low Dose Lung Radiotherapy (COLOR-19)	Recruiting	0.7 Gy Whole lung	
9.	Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19	Recruiting	0.5 Gy whole lung additional 0.5 Gy fraction 48 h later	Madrid, Spain
10.	Low Dose Radiotherapy for COVID-19 Pneumonitis	Recruiting		Madrid Spain
11.	Best Supportive Care With or Without Low Dose Whole Lung Radiation Therapy for the Treatment of COVID-19	Recruiting	–	United States

5. Future directions

LDRT is a viable treatment option for covid pneumonia but with barriers as mentioned, further research should be conducted keeping them in cognizance and these hurdles should be addressed in a very preemptive way to provide the benefit of LDRT in covid pneumonia. Table 2 shows ongoing clinical trials worldwide of LDRT in covid pneumonia.

6. Conclusion

Radiotherapy may be considered as a hopeful treatment option for COVID-19 pneumonia management. Its low cost, wider availability, and decreased risk of acute side effects can reduce the burden on the health care system. Based on the encouraging results of recently published institutional studies, large, multicentric, randomized controlled trials should be done to establish the clinical efficacy of LDRT to reduce COVID-19 mortality. On the basis results of these trials guidelines can also be developed.

Authorship statement

Sweety Gupta: the conception and design of the study, formatting of final draft; Rachit Ahuja: review of literature; critical review; Nidhi Sharma: review of literature and collection of data; Pragya Singh: review of literature and data collection; Swati Verma: collection of data and critical review; Manoj Gupta: drafting the article and final approval.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] R. Channappanavar, S. Perlman, Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology, *Semin. Immunopathol.* 39 (5) (2017 Jul) 529–539.
- [2] A. Montero, M. Arenas, M. Algara, Low-dose radiation therapy: could it be a game-changer for COVID-19? *Clin. Transl. Oncol.* 23 (1) (2021 Jan) 1–4.
- [3] M. Arenas, F. Gil, M. Gironella, V. Hernández, A. Biete, J.M. Piqué, et al., Time course of anti-inflammatory effect of low-dose radiotherapy: correlation with TGF-beta(1) expression, *Radiother. Oncol.* 86 (3) (2008 Mar) 399–406.
- [4] P.M. Kern, L. Keilholz, C. Forster, et al., Low-dose radiotherapy selectively reduces adhesion of peripheral blood mononuclear cells to endothelium in vitro, *Radiother. Oncol.* 54 (2000) 273–282, 32.
- [5] P. Kern, L. Keilholz, C. Forster, et al., In vitro apoptosis in peripheral blood mononuclear cells induced by low-dose radiotherapy displays a discontinuous dose-dependence, *Int. J. Radiat. Biol.* 75 (1999) 995–1003.
- [6] F. Rodel, F. Kamprad, R. Sauer, G. Hildebrandt, Functional and molecular aspects of anti-inflammatory effects of low-dose radiotherapy, *Strahlenther. Onkol.* 178 (2002) 1–9.
- [7] F. Rodel, N. Kley, H.U. Beuscher, et al., Anti-inflammatory effect of low-dose X-irradiation and the involvement of a TGF-beta1-induced downregulation of leukocyte/endothelial cell adhesion, *Int. J. Radiat. Biol.* 78 (2002) 711–719.
- [8] E.J. Calabrese, G. Dhawan, How radiotherapy was historically used to treat pneumonia: could it be useful today? *Yale J. Biol. Med.* 86 (4) (2013 Dec 13) 555–570.
- [9] A. Ameri, N. Rahnama, R. Bozorgmehr, et al., Low-dose whole-lung irradiation for COVID-19 pneumonia: short course results, *Int. J. Radiat. Oncol. Biol. Phys.* 108 (5) (2020 Dec 1) 1134–1139.
- [10] C.B. Hess, Z.S. Buchwald, W. Stokes, et al., Low-dose whole-lung radiation for COVID-19 pneumonia: planned day 7 interim analysis of a registered clinical trial, *Cancer* 126 (23) (2020 Dec 1) 5109–5113.
- [11] D.N. Sharma, R. Guleria, N. Wig, A. Mohan, G.K. Rath, V. Subramani, et al., Low Dose Radiation Therapy for COVID-19 Pneumonia: a Pilot Study, *medRxiv*, 2020.
- [12] R. Del Castillo, D. Martinez, G.J. Sarria, et al., Low-dose radiotherapy for COVID-19 pneumonia treatment: case report, procedure, and literature review, *Strahlenther. Onkol.* 196 (12) (2020 Dec) 1086–1093.
- [13] R. Mahajan, S. Marcus, Low-dose radiation therapy for COVID-19 pneumonia, *Clin Cancer Invest J* 10 (2021) 1–4.
- [14] P. Conti, G. Ronconi, A. Caraffa, et al., Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies, *J. Biol. Regul. Homeost. Agents* 34 (2) (2020) 327–331. March–April.
- [15] A. Oppenheimer, Roentgen therapy of interstitial pneumonia, *J. Pediatr.* 41 (1943) 404–414.
- [16] Bhanu P. Venkatesulu, Lester Scott, Cheng-En Hsieh, Vivek Verma, Elad Sharon, Mansoor Ahmed, et al., Low-dose radiation therapy for COVID-19: promises and pitfalls, *JNCI Cancer Spectr.* 5 (2021 Feb) 103.
- [17] C.R. Hanna, K.A. Robb, K.G. Blyth, et al., Clinician attitudes to using low-dose radiation therapy to treat COVID-19 lung disease, *Int. J. Radiat. Oncol. Biol. Phys.* 109 (4) (2021 Mar 15) 886–890.
- [18] Thomas Mulliez, Kurt Barbé, Mark de Ridder, Estimating lung cancer and cardiovascular mortality in female breast cancer patients receiving radiotherapy, *Radiother. Oncol.* 152 (2020 Nov) 111–116.
- [19] Monty Charles, Sources and effects of ionizing radiation: UNSCEAR Report 2000, *J. Radiol. Prot.* 21 (2001) 83–85.
- [20] K.R. Trott, F. Kamprad, Estimation of cancer risks from radiotherapy of benign diseases, *Strahlenther. Onkol.* 182 (8) (2006 Aug) 431–436.
- [21] D.G. Kirsch, M. Diehn, F.A. Cucinotta, et al., Lack of supporting data make the risks of a clinical trial of radiation therapy as a treatment for COVID-19 pneumonia unacceptable, *Radiother. Oncol.* 147 (2020 Jun) 217–220.
- [22] T. García-Hernández, M. Romero-Expósito, B. Sánchez-Nieto, Low dose radiation therapy for COVID-19: effective dose and estimation of cancer risk, *Radiother. Oncol.* 153 (2020 Dec) 289–295.
- [23] E. Moreno-Olmedo, V. Suárez-Gironzini, M. Pérez, T. Filigheddu, et al., COVID-19 pneumonia treated with ultra-low doses of radiotherapy (ULTRA-COVID study): a single institution report of two cases, *Strahlenther. Onkol.* 197 (5) (2021 May) 429–437.
- [24] N. Sanmamed, P. Alcántara, E. Cerezo, et al., Low-dose radiation therapy in the management of coronavirus disease 2019 (COVID-19) pneumonia (LOWRAD-Cov 19): preliminary report, *Int. J. Radiat. Oncol. Biol. Phys.* 109 (4) (2021 Mar 15) 880–885.