Research Article

iMedPub Journals
www.imedpub.com

Journal of Medical Physics and Applied Sciences
ISSN 2574-285X

2021
Vol.6 No.5:6344

Low dose radiation therapy for covid-19 pneumonia: the pros and cons

*Ode Samuel Omenka

Department of Physics, Benue State University, Nigeria.

***Corresponding author:** Ode Samuel Omenka Department of Physics, Benue State University, Nigeria Tel: 07061097868; E-mail: ediaemugo@gmail.com

Received date: October 8, 2020 ; Accepted date: August 23, 2021**; Published date:** September 3, 2021

Citation: Ode Samuel Omenka (2021) Low dose radiation therapy for covid-19 pneumonia: the pros and cons. Insights Med Phys Vol.6 No.4.

Abstract

In evaluating the efficacy and detrimental impact of low-dose lung irradiation as an adjunctive treatment in interstitial pneumonia in patients with COVID-19, by improving the PAO2/FIO2 ratio (Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen), an in-depth review is imperative to satisfy the global health safety as the whole world is in a raging fight against Covid-19. Some medical X-rays like extremity, chest and dental radiographs, involve effective doses of just a few micro sieverts. However, organ doses and effective doses can be tens of millisieverts for extensive fluoroscopic or CT examinations. This work reviews studies on the impacts of the use of LDRT for covid-19 patient, both the LNT (Linear No Threshold) hypothesis and hormesis to avert cytokine storm during radiotherapeutic process while reducing inflammation and explains why the general scientific consensus is currently in check of the LNT model as the most appropriate dose–response relationship for radiation protection purposes at low doses considering the pros and the cons for appropriate medications.

Background

Sometime in December 2019, a cluster of severe pneumonia cases of unknown cause was reported in Wuhan, Hubei province, China. The initial cluster was epidemiologically linked to a seafood wholesale market in Wuhan, although many of the initial 41 cases were later reported to have no known exposure to the market (WHO,2019). A novel strain of coronavirus belonging to the same family of viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), as well as the 4 human coronaviruses associated with the common cold, was subsequently isolated from lower respiratory tract samples of 4 cases on 7 January 2020. Infection with the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be asymptomatic or can result in mild to severe symptomatic disease (coronavirus disease 2019 (COVID-19)).

On 30 January 2020, the World Health Organization declared that the SARS-CoV-2 outbreak constituted a Public Health Emergency of International Concern, and more than 80 000 confirmed cases had been reported worldwide as of 28 February 2020. On 31 January 2020, the U.S. Centers for Disease Control and Prevention announced that all citizens returning from Hubei province, China, would be subject to mandatory quarantine for up to 14 days.

From the time of the outbreak in Wuhan, Chinese researchers have made it known base on their experience with COVID-19 and have highlighted high-risk groups, including, the elderly and patients with comorbidities, including cancer. In one of the largest series reported from Wuhan, elderly patients were at a higher risk for disease severity with an 8.0% case fatality rate in those aged 70 to 79 years, and 14.8% in those aged 80 years and older.

The novel disease (COVID-19) has caused a devastating impact globally, with the number of deaths worldwide by June 2020 over 500 000 (WHO, 2020). There are currently no proven, effective treatments, this call for an urgent need for clinical trials to test new therapeutic interventions that may be of benefit globally.

The lung has been known to represent one of the organs most affected by COVID-19, and some patients develop life-threatening viral pneumonia and sepsis. There is also growing evidence for associations between multiple cardiovascular complications and COVID-19.

The vast majority of patients present with a respiratory illness that can in some progress to a life-threatening acute respiratory distress syndrome (ARDS) associated with a systemic inflammatory response characterized by a sudden increase in the release of a number of pro-inflammatory cytokines, such as interleukin-1, interleukin-6 and tumor necrosis factor-α.

Before Deal

Research shows that during the first half of the 20th century, efforts were made to use low-dose radiotherapy (LDRT) in the form of X-rays to treat pneumonia. Fifteen studies reported on around 700 cases of predominantly bacterial pneumonia that responded clinically to LDRT (Calabrese and Dhawan, 2013). The proposed molecular mechanism is thought to be the propensity of LDRT to mediate a host of anti-inflammatory effects, including reduced functioning of macrophages, decreased levels of pro-inflammatory cytokines and apoptotic induction in immune cells. Thus, it is hypothesized that LDRT of less than 100 cGy to the lungs of patients with COVID-19 pneumonia may reduce the life-threatening inflammation and improve mortality. On this

basis, early phase studies have been initiated to explore this further.

For so long, anti-inflammatory effects of low-dose radiotherapy (LD-RT) have been known. Nevertheless, LD-RT in benign conditions is often only used as a last resort because of the possibility of delayed toxicities observed with much higher doses of radiotherapy. In Germany, LD-RT is used extensively, whereas the use of radiotherapy for these conditions remains infrequent in other countries. The explanations for the limited use of radiotherapy for treating benign diseases include the potential for radiation carcinogenesis and a lack of controlled studies investigating this application. However, the evidence of cancer risk comes from disparate sources using outdated radiotherapy techniques or data from Hiroshima and Nagasaki where radiation exposure was evenly distributed throughout the body. In a review of radiotherapy for benign disease, it was concluded that the risks of cancer after radiotherapy for benign disease for currently advised protocols are low, especially in older patients.

Two-thirds of over 37,000 patients are treated for inflammatory or degenerative osteoarticular diseases in Germany, degenerative joint disorders or the prevention of heterotopic ossification. The German Working Group on Radiotherapy of Benign Diseases in 2002 published a consensus on possible indications and guidelines for treatment. The consensus was that low doses should be administered for acute and chronic inflammatory diseases and painful acute and chronic degenerative joint disease. The mechanism of low-dose radiation in these inflammatory diseases is finely regulated by sequential leukocyte-endothelial cell interactions and by the action of inflammatory mediator and adhesion molecules secreted by a variety of peripheral blood cells including leukocytes, neutrophils and macrophages.

In recent times, the use of radiation to treat inflammatory diseases was reviewed. The review summarized the data from over 37,000 patients with 13 different ailments. Despite the ailments differing from each other extensively in terms of etiology, symptomatology and conventional therapy, all 13 ailments were resolved using radiotherapy, with response rates of 70–90%. This impressive and consistent success of radiotherapy was achieved at a relatively narrow dose range of between 30 roentgen (r) and 150 r (0.3–1.5 Gy).

The only commonality of these ailments was that inflammation was a central feature of each, and that radiotherapy counteracted the inflammatory process, affording protection and enabling tissue repair. Therefore, the authors concluded that it was not unreasonable to deduce that radiotherapy at the right dose can act as a potent anti-inflammatory agent (Calabrese et al, 2019). Studies review also that the early part of the last century when technology was more primitive and dosing was based on the skin erythema (i.e., skin reddening) dose (SED), which was used as an upper bound exposure point of reference, and in the estimation and selection of most doses for all end points. The SED estimate could be affected by X-ray filtration techniques and multiple patient characteristics, such as age, gender, degree of skin pigmentation and vascularization, among others, and thus carries a significant degree of uncertainty and inaccuracy. However, the more recent German consensus study using modern technology and contemporary data recommends single doses of 0.5–1.0 Gy, total doses of 3.0–6.0 Gy and two or three fractions per week with orthovoltage or megavoltage techniques for inflammatory diseases.

Low radiation doses produce anti-inflammatory effects, which may be useful in the treatment of respiratory complications of COVID-19. This type of treatment is non-invasive and therefore, a priori, it can be used in all types of patients. Radiotherapy is known to deplete peripheral lymphocytes as a result of their high sensitivity to radiation-induced apoptosis. Studies suggest that the absolute risk of lymphopenia is related to the pre-treatment lymphocyte count and the extent of the irradiated volume. In the context of LDRT to the whole lung, although the prescribed dose is low, the integral body dose is high owing to the considerable volume being irradiated, increasing the risk of inducing severe post-treatment lymphopenia. The mechanisms underlying lymphopenia in COVID-19 are unclear, but its negative effect in the presence of a systemic viral infection is not surprising. Exacerbation of this effect with LDRT at the very time when an adequate cellular immune response is needed to clear the pathogen could have potentially grave consequences. Low dose radiotherapy of about 0.5 Gy is an evidence-based anti-inflammatory treatment that could modify the immune landscape in the lung affected of SARS-CoV-2 pneumonia, through macrophages polarization to alternatively activated Macrophages (M2 phenotype). Radiation-induced cancer risk could be assumed due to the very low dose used, the advanced age of the patients and the life-threatening condition of SARS-Cov2 pneumonia. LDRT is a cost-effective non-toxic treatment already available in most hospitals.

Radiotherapy is known to deplete peripheral lymphocytes as a result of their high sensitivity to radiation-induced apoptosis. Studies suggest that the absolute risk of lymphopenia is related to the pre-treatment lymphocyte count and the extent of the irradiated volume (Joseph N. et al, 2019). In the context of LDRT to the whole lung, although the prescribed dose is low, the integral body dose is high owing to the considerable volume being irradiated, increasing the risk of inducing severe post-treatment lymphopenia. The mechanisms underlying lymphopenia in COVID-19 are unclear, but its negative effect in the presence of a systemic viral infection is not surprising. Exacerbation of this effect with LDRT at the very time when an adequate cellular immune response is needed to clear the pathogen could have potentially grave consequences.

An alternative approach is to deliver LDRT later on in the disease process when excess inflammation and cytokine release underlie the severe respiratory failure characterised by ARDS. However, by this point, patients are critically unwell and may be intubated.

To achieve the expected safe outcome, critical safety procedures must be put in place and first, a preliminary test of pneumonia visible on chest x-ray has to be conducted, intubated patients has to be deemed unstable for transport and not treated. Patients will be required to receive a single-fraction radiation dose of 1- 1.5 Gy to the bilateral lungs or whole-lung

radiation, delivered via an anterior posterior beam configuration. The primary endpoint was safety as assessed by clinical, radiographic, and inflammatory marker response. The following criteria's for patients inclusion must be met:

- Must have had a positive test confirming the diagnosis of COVID-19
- Must be 18 years and above
- Have had clinical signs of severe acute respiratory syndrome or pneumonia (dyspnea, cough, require oxygen supplementation at the time of enrollment), have radiographic pneumonic consolidations and be clinically deteriorating (i.e. mentation, oxygenation, dyspnea).
- Have visible consolidations/ground glass opacities on chest x-ray or computed tomography
- Have received pre-intubation respiratory support or undergone endotracheal intubation and have been on ventilator support for no longer than 5 (five) calendar days prior to the schedule date of delivery of low-dose radiation therapy.
- Willingness and ability of the subject to comply with scheduled visits, protocol-specified laboratory tests, other study procedures, and study restrictions
- Evidence of a signed informed consent/assent indicating that the subject is aware of the infectious nature of the disease and has been informed of the procedures to be followed, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation

Criteria for Exception

No use of disallowed medications one day prior to delivery of LDRT: Azithromycin, chloroquine, hydrochloroquine, COVID-targeted antiviral medications.

Importantly, it is conceivable that focal immunosuppression with LD-RT may reduce pulmonary inflammation associated with COVID-19 pneumonia and thereby alter the clinical course of infected patients.

A turn against these possible beneficial effects, there are also numerous evidences that radiation causes lung cancer in both sexes, with higher risk in females and smokers than males and nonsmokers, respectively. According to risk factors evaluated by the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR 2008) based on the Japanese atomic bomb survivor data, the acutely delivered lung doses of 0.3–1 Gy proposed by Kirkby and Mackenzie would nominally induce 0.6–4.4 excess lung cancers in a hundred persons exposed. Also there exist an accumulating evidence of association between moderate and low dose ionizing radiation and most types of circulatory disease. A look at face value a single 0.3–1 Gy lung dose (which the heart and aorta would also receive) would be associated with about 0.8–7.6 extra deaths from circulatory disease in a hundred persons exposed It is vital that a risk-benefit and ethical evaluation of an exposure of the lungs of critically ill individuals with COVID-19 to a putatively therapeutic lung irradiation be conducted before a clinical trial could be recommended.

After Deal

Effects like deterministic and stochastic associated with high-dose ionizing radiation (x-ray) exposure have been known for almost as long as ionizing radiation itself. At lower doses, radiation risks are primarily stochastic effects, in particular, somatic effects (cancer) rather than the deterministic effects characteristic of higher-dose exposure. In contrast to deterministic effects, for stochastic effects, scientific committees generally assume that at sufficiently low doses there is a positive linear component to the dose response—that is, that there is no threshold.

Studies shows that the most direct evidence on radiation risks comes from epidemiological studies of increased levels of cancer in exposed human populations. However, these epidemiological studies inevitably suffer from problems of insufficient statistical power at low doses. When these limitations are fully recognized, epidemiological studies are generally unable to provide clear evidence of the effects of protracted low doses of radiation of less than about 50–100 mSv.

Today, the magnitude of the risks from low doses of radiation is one of the central questions in radiological protection. It is particularly relevant when discussing the justification and optimization of diagnostic medical exposures. Medical X-rays can undoubtedly confer substantial benefits in the healthcare of patients, but not without exposing them to effective doses ranging from a few microsieverts to a few tens of millisieverts. Do we have any evidence that these levels of exposure result in significant health risks to patients? The current consensus held by national and international radiological protection organizations is that, for these comparatively low doses, the most appropriate risk model is one in which the risk of radiation-induced cancer and hereditary disease is assumed to increase linearly with increasing radiation dose, with no threshold (the so-called linear no threshold (LNT) model).

Radiation risks are reviewed by international and national organizations, such as the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the UK's Radiation Protection Division of the Health Protection Agency (formerly the National Radiological Protection Board, NRPB) and the National Council on Radiation Protection and Measurement (NCRP) in the USA. It is an important function of these bodies to continually assess and review publications from all over the world on the effects of exposure to ionizing radiation on human health and to reach a balanced view of the risks involved.

One of the important effects of low-dose radiation worthy of note is, it appears to alter the phenotype of the more radioresistant alveolar macrophages with a change in their polarization from an M1 pro-inflammatory phenotype to an anti-inflammatory or M2 phenotype. This phenotype results in decreases in nitric oxide levels, iNOS and ROS, with increases in heme oxygenase, suppression of TNF-α and IL-1β and TGF-β. Importantly, low-dose radiation does not affect the phagocytic function or viability of these cells, since alveolar macrophages play pivotal roles in the clearance of dying and damaged cells.

Furthermore, there is radiobiological evidence that low dose irradiation induces proinflammatory responses due to spatiotemporal propagation of damage signals caused by nontargeted effects of low dose radiation exposure (Hamada et al. 2011). Examination of the totality of cytokine data suggests that the overall anti-inflammatory response at low doses is, at best, modest and unlikely to reach therapeutic levels against the cytokine storm typical for the COVID-19 pneumonia.

In a work, Onoda et al. (1999) reported that low dose radiation (0.5–2 Gy) produces significant changes in the morphology and microfilament organization of pulmonary microvascular endothelial cells (PMEC) characterized by retraction and the resulting loss of close contact between individual cells within the monolayer. They used the radiation dose levels and time course for PMEC retraction in vitro to design studies to determine radiation-induced acute edema in a murine in vivo model and demonstrated that low dose thoracic radiation induces pulmonary edema characterized by increased lung wet weight. The incidence of increased weight was radiation dose-dependent up to 2 Gy and was coincident with the time course for radiation-induced endothelial retraction in vitro. They determined that pretreatment of animals with 25 lM nordihydroguaiaretic acid (NDGA, a nonspecific lipoxygenase inhibitor), 15 min prior to radiation exposure inhibited radiation induced edema. These observations were consonant with their in vitro studies. Therefore, the PMEC model system may prove useful for the screening of compounds and physical agents that may prove clinically useful for the prevention of acute and late radiation injuries to the lungs and other normal tissues. In conclusion, there is very little, if any, supportive evidence that LDRT will be a curative or palliative treatment for COVID-19 pneumonia or be superior to any of potential therapeutic agents currently under clinical trials. It would appear to us to be difficult to justify an immediate initiation of clinical trials at this point, based on inadequate data from clinical and experimental studies on viral pneumonia, dose levels and timing of the irradiation. The prudent course would appear to be further (and perhaps better) experimental studies, for example those using the PMEC system. However, even if some supportive evidence becomes available, irradiating COVID-19 patients will be impractical without significant medical justification, given the logistical concerns for safety and patient care needs.

Conclusion

Consider the application of low-dose whole-lung irradiation, which has a long forgotten and well-established history of use for pneumonias in the pre-antibiotic era, with overall success rates of approximately 80% and minimal reported side effects. Owing to the fact that this LDRT approach is an intervention not a cure, yet it must be placed in the relevant medical warehouse for appropriate use time.

At the moment, it appears to be a limited knowledge about the interaction of LDRT and viruses. Some investigations have reported the significant increase of uptake, activation, transcription and spread of some viruses after radiation therapy. Therefore, the use of lungs as the target organ for radiation therapy due to high virus concentration won't be the best and safe way. Additional investigations to assess the relative risks and benefits are highly recommended.

Reference

1. Arenas M, Sabater S, Hernaez V, Rovirosa A, Lara PC, Biete A et al (2012) Anti-inflammatory effects of low-dose radiotherapy. Indications, dose, and radiobiological mechanisms involved. Strahlenther Onkol; 188 : 975-981.
2. B.F. Wall, G. M Kendall, A A Edwards, S Bouffler, C R Muirhead And J.R Meara et al (2006). What are the risks from medical X-rays and other low dose radiation? The British Journal of Radiology, 79: 285–294. Health Protection Agency, Radiation Protection Division, Centre for Radiation, Chemical and Environmental Hazards, Chilton, Didcot, Oxon. OX11 0RQ, UK.
3. Calabrese E.J., Dhawan G (2013). How radiotherapy was historically used to treat pneumonia: could it be useful today? Yale J Biol Med; 86:555–570.
4. Calabrese E. J, Dhawan G, Kapoor R, Kozumbo W. J (2019). Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose. Hum Exp Toxicol;38 : 888 – 898.
5. Clayton B. Hess, Zachary S. Buchwald, William Stokes, Jeffrey M. Switchenko, Tahseen H. Nasti, Brent D. Weinberg, James P. Steinberg, Karen D. Godette, David Murphy, Rafi Ahmed, Walter J. Curran Jr, Mohammad K. Khan et al (2020). Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia: Planned Day-7 Interim Analysis of an Ongoing Clinical Trial. Emory University Hospital 1365 Clifton Road NE Atlanta GA 30345. A publication from the ongoing clinical trial on Covid-19.
6. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, Brown TS, Nigoghossian C, Zidar DA, Haythe J, et al. 2020. Cardiovascular considerations for patients, health care workers, and international journal of radiation biology 3 health systems during the coronavirus disease 2019 (covid-19) pandemic. j am coll cardiol.
7. George D. Wilson; Minesh P. Mehta; James S. Welsh; Arnab Chakravarti; C. Leland Rogers; James Fontanesi (2020). Investigating Low-Dose Thoracic Radiation as a Treatment for Covi-19 patients to prevent respiratory failure. Journal of radiation research, volume 194, issue 1, 2020. Radiat Res (2020) 194: 1–8.
8. Joseph N., McWilliam A., Kennedy J., Haslett K., Mahil J., Gavarraju A (2019). Post-treatment lymphocytopaenia integral body dose and overall survival in lung cancer patients treated with radical radiotherapy. Radiother Oncol;135:115–119.
9. Joseph N., Choudhury A (2020). Lymphocytopenia and radiotherapy treatment volumes in the time of COVID-19. Clin Oncol (R Coll Radiol); 32:420–422.
10. Lara, P. C., Burgos, J., & Macias, D. (2020). Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment. Clinical and translational radiation oncology, 23: 27–29.
11. Lauer SA, Grantz KH, Bi Q, et al. (2020) The Incubation Period of Coronavirus Disease 2019 (COVID-19) From

Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med.

12. Little M. P, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, et al. 2012. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect. 120:1503–1511.
13. Little, M. P., Wakeford, R., Tawn, E. J., Bouffler, S. D. and Berrington de Gonzalez. A. (2009). Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology, 251: 6–12.
14. McKeown SR, Hatfield P, Prestwich R J, Shaffer R E, Taylor R E (2015). Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. British Journal of Radiotherapy; 88 : 20150405.
15. Mehta P., McAuley D.F., Brown M., Sanchez E., Tattersall R.S., Manson J.J. (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. ;395: 1033–1034.
16. Micke O, Seegenschmiedt M.H (2002). German Working Group on Radiotherapy in G . Consensus guidelines for radiation therapy of benign diseases: a multicenter approach in Germany. Int J Radiat Oncol Biol Phys; 52 : 496 – 513.
17. Rodel F, Keilholz L, Herrmann M, Sauer R, Hildebrandt G (2007). Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. International Journal of Radiation and Biology, 83: 357 – 66.
18. Sisko Salomaa, Elisabeth Cardis, Simon D. Bouffler, Michael J. Atkinson & Nobuyuki Hamada (2020): Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence?, International Journal of Radiation Biology,
19. Tan H.Y, Wang N, Li. S, Hong. M, Wang. X, Feng. Y (2016). The reactive oxygen species in macrophage polarization: Reflecting its dual role in progression and treatment of human diseases. Oxid Med Cell Longev; 2016 : 2795090
20. Tharmalingam, H., Díez, P., Tsang, Y., Hawksley, A., Conibear, J., & Thiruthaneeswaran, N.(2020). Personal View: Low-dose Lung Radiotherapy for COVID-19 Pneumonia - The Atypical Science and the Unknown Collateral Consequence. Clinical oncology (Royal College of Radiologists (Great Britain)), S0936-6555(20)30236-3.
21. U.S National Library of Medicine (2020). Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 (RESCUE 1-19). Clayton Hess, Emory University publication 2020.
22. U.S National Library of Medicine (2020). Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19. Clayton Hess, Emory University publication 2020.
23. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008. UNSCEAR 2006 Report. Annex A. Epidemiological studies of radiation and cancer. United Nations.
24. World Health Organization. Coronavirus disease (COVID-19) outbreak.
25. World Health Organization (WHO) 2020. Emergencies disease novel corona virus situation.
26. Wu Z, Mc Googan JM (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Centre for Disease Control and Prevention. JAMA.