

Opinion Article

## Low Dose Whole Lung Radiotherapy for Covid-19 Pneumonia: What Is the Current Status? Opinion of The International Geriatric Radiotherapy Group

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Across the world, coronavirus disease 19 (COVID-19) causes a high mortality rate among older patients with multiple co-morbidities [1]. The virus induces a cytokine storm which results into multiple organ

damage, and frequently death from respiratory failure despite artificial ventilation for those individuals.

As an illustration, among patients who required artificial ventilation, only 5 out of 32 (15%) survived if they were over 70 years-old [2]. A review of autopsy studies for patients who died after viral infection reported severe lung damage characterized by consolidation, severe inflammation, diffuse hyaline membranes formation, and fibrosis [3]. Thus, by the time the patient requires mechanical ventilation, irreversible lung damage has occurred leading to respiratory failure, and ultimately death.

Low-dose-whole-lung-radiotherapy (LDWLRT) is an effective anti-inflammatory treatment which has been reported to improve pneumonia mortality rate before the introduction of antibiotics [4]. Preliminary results of LDWLRT are promising since older COVID-19 patients who required oxygen but were not on artificial ventilation improved clinically following a single application of radiation dose ranging from 50 to 150 cGy to both lungs [5-9]. A response rate up to 90% has been observed following irradiation [5]. Blood levels of cytokines were also reduced after treatment [6]. This potent anti-inflammatory response induced by radiation has been observed in patients who are not on steroid or other anti-inflammatory medication [7]. Hypoxemia improved significantly 24 hours after radiotherapy. Among patients who experienced worsening of their lung function despite anti-inflammatory and anti-viral medications, LDWLRT produced a significant improvement of their clinical condition associated with radiologic resolution of the lung infiltrates after hospital discharge [8]. Other studies also corroborated the safety and efficacy of LDWLRT through other criteria such as radiologic improvement of severity score and cytokines response after treatment [10,11]. As a result of those reports, many clinical trials are

being conducted to investigate the efficacy of LDWLRT for COVID-19 pneumonia.

However, a randomized study of 22 patients who required artificial ventilation for COVID-19 pneumonia did not report any survival benefit for those receiving LDRT (n=12) versus those with sham irradiation (n=11) [10]. Despite the small number of patients and the need for additional studies to corroborate this finding, the study raised doubt about the benefit of LDWLRT for COVID-19 pneumonia. How do we reconcile these apparent conflicting results?

For one thing, the LDWLRT randomized study elegantly illustrates that when severe end organ damage occurs, any pharmaceutical or radiotherapy intervention is likely to be ineffective [3]. A more judicious approach would be to start treatment early to prevent severe lung damage and to reduce the need for artificial ventilation.

As an international organization devoted to the care of older cancer patients (<http://www.igrg.org>), we propose to use LDWLRT as soon as the patient develop pneumonia to reduce the severity of the cytokine storm before irreversible lung damage occurs [13]. This strategy may be life-saving and cost effective because it may decrease the length of stay in the intensive care unit and/or the duration of hospitalization which is quite expensive. Radiotherapy is also readily available in developing countries which may not afford the cost of expensive medication such as remdesivir. We have designed a protocol to start LDWLRT within 24 hours of hospital admission for patients aged 65 or above who do not require artificial ventilation for their viral pneumonia

to test this hypothesis (Clinical Trial NCT04493294). Our study also incorporates the change in cytokines levels post irradiation with the patient recovery at long-term follow-up. Radiological findings may also be correlated with the cytokines response post irradiation. This is a phase I-II study which may pave the way for a randomized study if the study is conclusive about the benefit of radiotherapy. A grant application is underway. International patient recruitment will start following institutional review board approval of participating institutions.

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