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RESEARCH ARTICLE

A Low Dose Whole Lung Radiotherapy for Covid-19 Pneumonia: What have we Learned? Opinion of the International Geriatric Radiotherapy Group.

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ABSTRACT

Background: Coronavirus disease 19 carry a high mortality rate among older patients and minorities such as ethnic Africans and Latinos through the induction of a cytokines storm. Many pharmacologic interventions were proposed to improve the mortality rate from normal organ damage such as pneumonia. Low dose whole lung radiotherapy has been used in the past to treat pneumonia and may improve survival through modulation of the inflammatory cytokines. However, there is a lot of controversy about the efficacy and safety of this treatment modality. Thus, a review of the clinical studies using irradiation for COVID-19 pneumonia is needed to answer those questions

Methods: A literature search of PubMed and Google Scholar was conducted. Reported studies were analyzed to assess safety, efficacy, and inflammatory biomarkers response following low dose whole lung radiotherapy

Results: Patients who required artificial ventilation for COVID-19 did not benefit from low dose whole lung radiotherapy, most likely due to severe lung damage. The inflammatory response may be attenuated after irradiation but it is unclear whether it is independent of the steroid effect.

Conclusion: Randomized studies are required to assess the effect low dose whole lung radiotherapy for COVID-19 pneumonia and its anti-inflammatory property. Such studies are needed for emerging countries with limited resources as radiotherapy may be cost-effective to reduce hospital admission and intensive care unit monitoring.

Keywords: COVID-19, low dose radiotherapy, pneumonia, cytokines.

INTRODUCTION:

Coronavirus Disease 19 (COVID 19) is a pandemic of unprecedented epic proportion. Even though mortality rate is multifactorial, one of the main causes of death is virus-induced pneumonitis causing respiratory failure despite artificial ventilation[1]. Countries with limited resources experience a higher hospital mortality rate for COVID pneumonia[2]. The introduction of effective antiviral vaccines has reduced significantly the mortality rate of vaccinated people who are previously vulnerable to the virus because of their age and/or pre-existing morbidity such as obesity or malignancy[3,4]. Thus, it is clear, for public health purposes, COVID vaccine should be available and administered to adults across the world[5]. However, in many emerging countries, vaccination rates remain low because of limited resources. This is a vicious circle as the high infection rates in those countries may also lead to a high mortality rate because of the poor health care infrastructure and limited number of intensive care unit beds[2,6].

Antiviral medications such as remdesivir (Veklury), molnupiravir (Lagevrio) and combination of nirmatrelvir and ritonavir (Paxlovid) are expensive and may not be available in those countries. Paxlovid must be taken within five days of symptom onset and it can reduce development of severe illness and death by 89%. In addition, remdesivir reduced the length of hospitalization but mortality was not significantly improved compared to a placebo[7]. Another medication, dexamethasone may reduce mortality rates among patients who required artificial ventilation for their pneumonitis but not for those requiring oxygen[8].

Low dose whole lung irradiation (LDWLRT) was introduced as a potential treatment for COVID pneumonia as it was effective in the past to treat pneumonia before the introduction of antibiotics[9]. In the early 20th century, low-dose X-ray had been used to treat pneumonia and reviews showed reduction in mortality from 30% to 10% range with some showing relief of symptoms within hours[10]. Radiotherapy at low dose, may reduce inflammation, and has been reported to decrease inflammatory cytokine levels such as Interleukin 6 (IL-6)[11]. Thus, during the early phase of the pandemic, among many pharmacologic interventions that were proposed to reduce the severity of the systemic inflammation, LDWLRT were advocated by many radiation oncologists to treat COVID pneumonia. On the other hand, radiotherapy to the lungs and heart may expose the patient to lung damage, cardiac dysfunction, and cancer development in the long-term[12]. As a result, there were controversies among radiation oncologists whether radiotherapy may be safe and/or effective in the treatment of this new disease in the absence of data[13]

Given the lack of clarity and controversy surrounding irradiation for COVID pneumonia, we would like to review all the published clinical data that may shed some light on the safety and efficacy of this treatment modality. As an international research organization with many institutions in low-income countries, the International Geriatric Radiotherapy Group (IGRG) (http://www.igrg.org) would like to make recommendations about LDWLRT as this modality may be cost-effective for those countries [14,15].

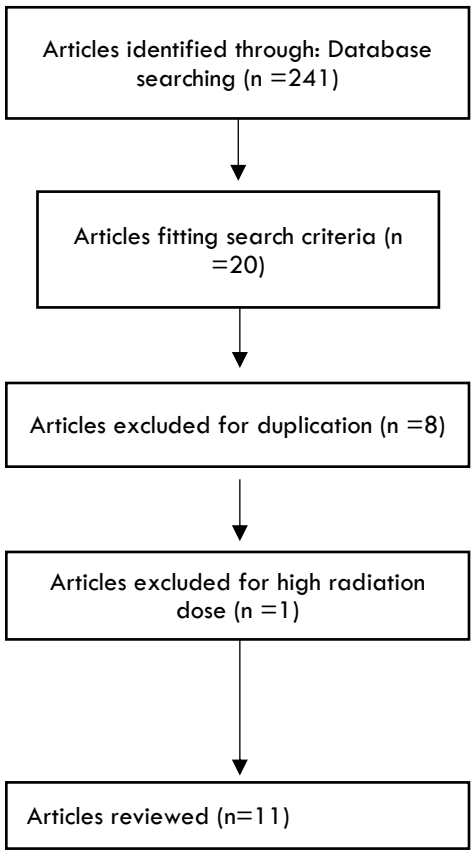
MATERIALS AND METHODS

A search was conducted based on the PubMed electronic database and Google Scholar. The following terms were explored and used for each database search: COVID-19, pneumonia, whole lung radiation, and low dose. A reference list of relevant papers was then searched for additional articles. The following criteria were analyzed in each articles: side effects and complications, survival, biomarkers for inflammation, mortality, and follow-up. Only studies reported in English were included. Duplicate studies, animal studies and review articles were excluded.

RESULTS

A total of 241 articles were screened. 20 articles fitting the criteria for the search were reviewed. One was excluded due to high radiation dose. Another eight were excluded due to duplication. A total 11 articles were reviewed and analyzed. Only eight articles contained information about inflammatory biomarkers change following radiotherapy. All patients had proven COVID pneumonia. Figure 1 summarizes the data review process.

Figure 1. Flow chart for data search



Overall, most studies had small number of patients ranging from 1 to 51 (median: 22) with a short follow-up ranging from 7 to 112 days (median: 28 days). Only two studies were randomized between LDWLRT and control (no radiotherapy). The other ones were prospective non-randomized. Three studies included patients on artificial ventilation. Radiation dose ranged from 50 to 150 cGy (median: 100 cGy) to the whole lung in a single fraction. Only six studies reported inflammatory cytokine change following LDWLRT

Radiotherapy was well tolerated. The most common side effect was mild lymphopenia. Patients who were on artificial ventilation did not benefit from LDWLRT. Survival following LDWLRT for those not on artificial ventilation ranged from 50% to 100% (median: 73%). Table 1 summarizes efficacy and safety of LDWLRT.

Table 1. Summary of clinical studies on safety and efficacy of whole lung low dose radiotherapy for Covid 19 pneumonia

Study	Type	Patient No	Artificial ventilation	Efficacy	Safety	FU (D)
Sanmamed et al[25]	PNR	9	No	7/9 (77%)	1 grade 3 lymphopenia	112
Papachristofilou et al[28]	PR	22 11 LDWLRT 11 Control	Yes	No survival benefit	lymphopenia	45
Ortiz et al[30]	PNR	58 31 LDWLRT 27 Control	Yes 9 (LDWLRT) 20 Control	73% (LDWLRT) 41% (Control) No survival benefit	NS	NS
Darzikolaee et al[31]	PNR	22 11 LDWLRT	Yes 9 (LDWLRT)	2/11 (LDWLRT) 2/11 (Control) If intubated	NS	20
Ganesan et al[36]	PR	51 34 LDWLRT 17 Control	No	85.3% (LDRT 76.5% (Control) No survival benefit	No difference in lymphopenia	
Hess et al[37]	PNR	40 20 DWLRT 20 Control	No	Intubation free survival 77% LDRT, 68% Control No difference	No side effects	28
Arenas et al[38]	PNR	36	No	23/36 (63%)	NS	30
Sharma et al[39]	PNR	10	No	9/10 (90%)	No side effects	30
Ameri et al[40]	PNR	10	No	6/10 (60%)	No side effects	28
Moreno-Olmedo et al[41]	PNR	2	No	2/2 (100%)	No side effects	60
Del Castillo et al[42]	CR	1	No	1/1 (100%)	No side effects	7

D: days; PNR: prospective non-randomized; PR: prospective randomized; LDWLRT: low dose whole lung radiotherapy; NS: not specified

Except for one study, inflammatory cytokines decreased following LDWLRT. C-reactive protein (CRP) was the most common cytokine studied, followed by ferritin and Interleukin-6 (IL6). However, except for one study, all patients also received steroids. Thus, it remains unclear whether the decreased cytokine levels reflect the effect of LDWLRT, steroid effects or both. Table 2 summarizes the biomarkers levels change following DLWLRT.

Table 2. Inflammatory biomarkers change after low-dose whole lung radiotherapy for COVID-19 pneumonia

Study	RT dose	Biomarkers	Steroids	Change after RT	Timing
Sanmamed et al[25]	100 cGy	CRP, LDH, ferritin	Yes	Decreased (88%)	7 days
Ganesan et al[36]	50 cGy	CRP, IL-6, Ferritin D-dimer	Yes	No difference between Control and RT groups	28 days
Hess et al[37]	150 cGy	CRP D-dimer	Yes	Decreased in RT group	14 days
Arenas et al[38]	50 cGy	CRP, ferritin, IL-6	Yes	Decreased in survivors	30 days
Ameri et al[40]	50 cGy 100 cGy	CRP, IL-6	Yes	CRP decreased in 4 IL-6 decreased in 4	7 days
Moreno-Olmedo et al[41]	80 cGy	CRP, IL-6, ferritin LDH, fibrinogen	Yes	Decreased (100%)	30 days
Del Castillo et al[42]	100 cGy	Ferritin, Il-6, CRP, D-dimer	No	CRP, LDH decreased IL-6, D-dimer increased	8 days

RT: radiotherapy; cGy: centigray; CRP: C-reactive protein; IL-6: interleukin-6

DISCUSSION

It is believed that cytokine storms play an essential role in acute respiratory distress syndrome (ARDS) and are responsible for deaths in patients with COVID-19[16]. Interleukins, tumor necrosis factor (TNF)-α and interferons are the most frequent cytokines released by immune cells in response to inflammatory events. Immune cells, particularly lymphocytes are the most radiosensitive cells in humans[17].

Thus, long before radiotherapy was used as an effective modality to treat cancer, its anti-inflammatory effect at low dose has been used to treat a variety of diseases characterized by excessive inflammation[18]. Indeed, various animal experiments demonstrated that production of inflammatory cytokines such as IL6, TNF-1α, IL1-β was reduced following administration of low dose radiotherapy (LD-RT)[10,18,19].

The anti-inflammatory effect of LD-RT was advocated by clinicians to treat pneumonia and bronchopneumonia due to the high mortality rate (up to 24%) before the introduction of antibiotics[20]. A single dose ranging from 20 cGy to 200 cGy to the whole lungs was reported to be an effective cure for pneumonia[21-24]. Randomized studies comparing LDWLRT to sham radiation were not conducted during that time as it was considered unethical due to the high survival rate up to 95% with LDWLRT[22]. Patient fever and respiratory distress were reduced within 24 hours after radiation.

Thus, it is not surprising during the early days of COVID-19 pneumonia, LDWLRT was advocated as a potential treatment of the viral infection due to its anti-inflammatory effect and the clinical experience reported during the early 20th century[9,25]. Planning systems were tested for potential treatment of COVID 19 pneumonia and later on for the viral mutants[26,27]. The lack of effective treatment and the high mortality rates observed prompted many institutions across the world to conduct prospective studies on LDWLRT for COVID-19 pneumonia. However, there was a lot of criticism among clinicians who were concerned with radiotherapy toxicity on the heart, lungs, and potential of carcinogenesis in the long-term[13]. In addition, there was skepticism about LDWLRT efficacy which prompted us to conduct this review.

The acute toxicity of LDWLRT was low. Only two studies reported transient lymphopenia during treatment[25,28]. This is not surprising as lymphocytes are very sensitive to radiation-induced apoptosis. Indeed, radiation-induced lymphocyte apoptosis has been proposed as an assay to evaluate radiation toxicity[29]. There was no lung or cardiac toxicity reported. However, because of the short term follow-up, no conclusion can be made regarding long-term toxicity. There was no benefit to LDWLRT when the patient was already on artificial ventilation. In a randomized study involving 22 patients who were on mechanical ventilation due to respiratory failure, there was no difference in survival between the patients who received LDWLRT and sham radiotherapy[28]. Two other studies also corroborated the poor survival rates of patients who were on ventilators despite LDWLRT[30,31]. Indeed, among patients who were admitted to the intensity care unit (ICU) for COVID-19 pneumonia, mortality rate was highest among the ones who required artificial ventilation[32]. Causes of death were multifactorial with multiple organ dysfunction, secondary infection, and pulmonary fibrosis accounting as leading causes[33]. Those patients may have already developed severe lung injury from the viral infection and would likely not benefit from any pharmacological intervention. Autopsy reports from patients who died from COVID-19 support this hypothesis. There were diffuse alveolar damage and widespread thromboembolic disease in the lungs which prevented effective oxygenation[34,35]. Thus, to be effective, LDWLRT needs to be initiated early before respiratory failure.

Among patients who did not require artificial ventilation, LDWLRT may be effective with survival ranging from 60 to 100%. However, only two studies included a control group who did not receive radiotherapy[36,37]. There are also other limitations as the study group and the control group are not comparable. Ortiz et al[30] reported a significant increase in survival among patients who had moderate respiratory distress (defined as a ratio of partial pressure of oxygen (Pa02) and fraction of inspired oxygen (FI02) between 100 and 200) when they received LDWLRT. Survival rates were 100% and 40% for LDWLRT and control, respectively. Interestingly, for those who had moderate respiratory distress, radiotherapy also decreased the need for artificial ventilation. The risk of artificial ventilation was 45% and 0% for the control group and the LDWLRT, respectively. For patients who had severe respiratory distress (defined as Pa02/FI02 ratio of 100 or less), there was no difference in survival or intubation rate with the addition of radiotherapy. Thus, this study highlights the need for early LDWLRT before respiratory failure developed. Ganesan et al[36] also corroborated the improved oxygenation rate which increased with time following LDWLRT. However,

there was no significant improvement in survival rates after irradiation which may be attributed to the higher co-morbidity rates in the experimental arm. The percentage of patients with co-morbidities was 85% and 59% for the LDWLRT group and control group, respectively.

Another study reported a reduced need for artificial ventilation for those who received LDWLRT which was not statistically significant, likely due to the small number of patients (20 in each group)[37]. Other studies also corroborated the improvement of oxygenation rate following LDWLRT in patients with mild to moderate lung disease but they are limited because of a lack of control group and/or the small number of patients treated[38-42]. Taking together, those studies suggested that LDWLRT may be effective if administered early before severe lung damaged developed. The next question is how effective is LDWLRT as a pharmacologic agent to modulate the inflammatory response following viral infection?

The lone study by del Castillo et al[42] offered evidence that LDWLRT may be effective to reduce the inflammatory response following COVID-19 pneumonia. A 64-year old patient with rapidly deteriorating respiratory function refractory to oxygen due to COVID-19 pneumonia, was treated with 100 cGy to the whole lung on an emergency basis. Inflammatory cytokines such as C-reactive protein (CRP), IL6, and ferritin level was recorded before radiotherapy. The patient experienced a fast and dramatic response to the treatment which paralleled a significant reduction of the cytokine level. To date, this is the only reported case where antiviral agents and steroids were not used during the treatment.

Other studies also corroborated the decreased inflammatory response following LDWLRT for COVID-19 pneumonia. However, the patients in those studies also received dexamethasone which is known for its anti-inflammatory effect and survival improvement for patients on oxygen for their COVID-19 pneumonia[8]. Thus, an independent effect of LDWLRT on the inflammatory response following viral infection cannot be assessed. Nevertheless, those studies suggested that LDWLRT may be used with dexamethasone to enhance its anti-inflammatory effect. For instance, Arenas et al[38] reported the effect of LDWLRT and dexamethasone on 36 patients who developed moderate to severe COVID-19 pneumonia not requiring endotracheal intubation. All patients received 50 cGy to the whole lung. A significant improvement in patient oxygenation was reported among patients who had reduction of IL-6, ferritin, and CRP, 24 hours following LDWLRT. Those who did not have IL-6 reduction, did not improve, and died afterward either directly from COVID-19 (22%) or other complications (13.8%). Ferritin and CRP levels decreased in patients who died. Thus, the study highlighted the importance of cytokines reduction for the improvement of the ventilation parameters. Hess et al[37] also corroborated relationship between the inflammatory response and improvement of oxygenation. Among 16 patients who had significant reduction in CRP levels following 150 cGy whole lung radiotherapy and steroid, no patient required intubation. In contrast, 34% of a matched control group who experienced a steady rise of CRP level required intubation. Other studies also reported a significant decrease in inflammatory cytokines following LDWLRT and steroid combination[25,37,40].

In summary, LDWLRT combined with steroid may be effective to decrease the inflammatory response and improve oxygenation rate in patients with mild to moderate respiratory distress secondary to COVID-19 pneumonia. However, this hypothesis needs to be tested in randomized studies comparing dexamethasone alone to dexamethasone combined with LDWLR for COVID-19 pneumonia. This is particularly important for low-income countries (LIC) because of the lack of intensive care units and ventilators. A systemic review of 15 low-income countries reported a severe shortage of ICU beds which are mostly located in large referral hospitals in major cities, thus preventing the population access to critical care[6]. There are between 0.1 and 2.5 ICU beds per 100,000 people in LIC compared to 5 and 30 ICU beds per 100,000 people in high income countries[43]. As an illustration, the number of ICU beds in Sri Lanka is 0.3/100,000 compared to 20/100,000 in the United States[44]. In addition, the cost of operating an ICU bed is prohibitive if the patient requires artificial ventilation[45]. Low-income countries also have a low COVID-19 vaccination rate compared to high income countries[46]. Thus, a cost-effective treatment should be investigated for patients who developed COVID-19 pneumonia to prevent respiratory failure and the need for ICU monitoring for LIC. Low-dose whole lung radiotherapy may provide a potential solution which needs to be investigated in future prospective randomized studies. As an international research organization dedicated to older cancer patients with many members in emerging countries, the IGRG strongly supports such a study[14,15,47].

CONCLUSION:

Low-dose whole lung radiotherapy may be effective to improve oxygenation through the modulation of inflammatory cytokines in patients with mild to moderate COVID-19 pneumonia. The combination of dexamethasone and LDWLRT may prevent respiratory failure and the need for artificial ventilation but needs to be tested in future prospective randomized studies to assess its efficacy and long-term complications.

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