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## Technical Note

# The clinical efficacy of low-dose whole-lung irradiation in moderate-to-severe COVID-19 pneumonia: RTMX-20 trial <sup>☆,☆☆</sup>



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## ABSTRACT

This is a paired prospective comparative cohort study with 58 patients, in order to analyze the clinical LD-WLI in patients with moderate or severe COVID19 pneumonia. The results of this study show that the Radiotherapy could be an option to improve the clinical response for patients with COVID-19.

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Infections caused by SARS-CoV-2 (COVID-19) have resulted in a pandemic and health emergency, with a global mortality rate between 5.6 and 15.2% [1].

The World Health Organization (WHO), in their care guidelines for the Clinical Management of Severe Acute Respiratory Infection in the event of suspected COVID-19, established acute respiratory distress syndrome (ARDS) that can be divided into mild, moderate or severe cases [2]. ARDS due to COVID-19 is characterized by the immune response against the virus and can result in a cytokine storm [3].

To date, multiple studies with antibiotics and monoclonal antibodies have been used; however, the studies have not been conclusive regarding the benefit to patients. Due to the current lack of effective pharmacological options, this situation has caused interest in reconsidering historical reports on the treatment of patients, such as with low-dose whole-lung irradiation (LD-WLI) [4].

In studies where radiation therapy (RT) was given for cases of lung infections between the 1930s and 1940s, the most important studies with the largest number of patients were the trials by Powel [5], Scott [6], Rosseasuy [7] and Openheimer [8]; together,

they treated 594 patients with viral and bacterial infections, obtaining clinical improvement in 524 patients, with an 88% chance of cure in an average of 7 days.

These results are similar to those obtained in one of the few studies of lung LD-WLI in patients with COVID-19, which was performed at Emory University Hospital in Atlanta. Five patients with COVID-19 associated with pneumonia required supplemental oxygen and received treatment with RT 1.5 Gy as a single dose. After 24 h, four of the patients quickly improved clinically, recovering in an average of 1.5 days (range 3–96 hours). Subsequent imaging and laboratory studies confirmed that low doses of RT are effective and safe in reducing the symptoms produced by COVID-19[9].

The study performed at Imam Hossein Hospital in Iran recruited 10 patients with [1–19] COVID-19 oxygen-dependent pneumonia and used a dose of 0.5–1.0 Gy radiotherapy. In this study, the 28-day mortality rate of 0.5 Gy whole-lung irradiation was less than that in the 1.0 Gy group (50% vs. 75%) [10].

Treatment with radiation therapy at low doses generates an anti-inflammatory effect, since it has been shown that doses lower than 1 Gy decrease selectins and nitric oxide (NO), increase NF-κB, and increase the expression of anti-inflammatory cytokines or inhibit the aggregation of leukocytes [11–16].

Additionally, recent studies have suggested that lung LD-WLI at 0.5 Gy is a cost-effective, evidence-based, nontoxic, anti-inflammatory treatment already available in most general

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hospitals. Furthermore, this treatment can potentially be used for the large number of patients in low- and middle-income countries that are suffering and will suffer from this disease and that would not otherwise receive specific anti-IL-6 treatments in intensive care units (ICUs) [17].

The present study was carried out with the objective of determining the clinical effect of low-dose whole-lung radiation therapy in patients with respiratory distress syndrome secondary to COVID-19 pneumonia.

## Methodology

### Study design

In this matched, prospective, comparative cohort study, patients were matched by age, sex and ARDS (moderate or severe). In both groups, there was an equal distribution among the patients. The primary objective of the study was to determine survival in patients treated with LD-WLI; the secondary objectives were to determine if there was a difference in orotracheal intubation, hypertension, diabetes, obesity and days of hospital stay. The control group received treatment based on the national protocol for COVID-19 pneumonia, and the intervention group additionally received low doses of radiotherapy to both lungs. The follow-up will be carried out 3 months after the last radiotherapy.

### Inclusion criteria

We included PCR-confirmed COVID-19 pneumonia patients older than 18 years of age of both sexes, with confirmed pneumonia by non-contrast chest-computed tomography by CO-RADS classification [18] or with high suspicion of COVID-19 pneumonia without laboratory confirmation. In all cases, patients had clinical findings of moderate ( $\text{PaO}_2/\text{FIO}_2$  ratio of 100–200) or severe ( $\text{PaO}_2/\text{FIO}_2$  ratio of 100 or less) acute distress respiratory syndrome (ARDS). Patients with clinical findings of sepsis, haemodynamic instability, orotracheal intubation (OTI) before radiotherapy or who did not agree to receive treatment with radiotherapy were excluded.

Patients were assigned to the treatment group according to the days previously assigned for treatment, from Friday night to Sunday, to continue oncologic attention without interruptions to avoid risk for oncologic patients and health workers of the oncology department. The control group was recruited during the week (from Monday to Thursday) and paired for sex, age and ARDS classification.

### Radiotherapy process

After signed informed consent was obtained, patients were treated with Varian iX LINAC with 6 MV AP/PA open fields in the supine or prone position. Physical planning was performed using diagnostic tomography upon admission to the hospital, considering the middle of the depth of the thorax as the isocentre. Treatment plans were manually calculated by a medical physicist with a single dose of 1 Gy to both lungs.

### Bioethics

The trial was authorized by the Research Ethics Committee and Research Committee of the National Committee for Scientific Research, IMSS; N° R-2020–785–107 and was registered at Clinical Trials with ID NCT04534790.

### Statistical analysis

For the statistical analysis, IBM SPSS Statistics V.25 and Graph-Pad Prism V.8 were used. The data obtained were captured in a database, descriptive statistics were carried out for each of the groups, and the different clinical and radiological parameters were analysed with Student's *t* and Pearson's correlation. Mortality was analysed by Kaplan–Meier and post hoc Mantel–Cox analyses. The central limit theorem was used to establish the statistical power. The sample size was 30; thus, the sampling distribution approximated the standard normal distribution.

## Results

The study was conducted from April 1st to August 30th, 2020. We included 60 patients; 31 were included in the treatment group, and 29 were included in the control group. One of the patients in the treatment group was excluded from the analysis because the severity of respiratory syndrome was mild. Finally, 59 patients were analysed. The characteristics of the patients are listed in Table 1.

Mortality among patients in the radiotherapy group was 27.5% compared with 58.6% in the control group ( $P$  0.05). When ARDS severity was analysed, survival among patients with moderate ARDS was significantly better for the radiotherapy group compared with the control group (100% vs. 40%, respectively ( $P$  0.01)). Furthermore, there was no difference in survival among patients with severe ARDS ( $P$  0.90), with 22% for the radiotherapy group and 0% for the control group (Fig. 1).

When comorbidities were analysed, we did not find any difference in survival between patients treated with radiotherapy and patients with hypertension ( $P$  0.8), diabetes ( $P$  1.09) or obesity ( $P$  0.6).

Regarding the requirement for orotracheal intubation (OTI), there was a tendency toward a decrease in patients treated with radiotherapy, with 33% intubated patients compared with 58% in the control group, although this difference was not statistically significant ( $P$  0.51). In the subgroup analysis according to ARDS severity, none of the moderate cases in the control group required OTI, while 45% of the control group required OTI ( $p$  < 0.001). In severe ARDS patients, there was no difference in the requirement of OTI between the radiotherapy and control group, with 100% vs. 89%, respectively ( $P$  0.47).

The average hospital length of stay was similar between the groups, with 11 days (range 3–43 days) in the radiotherapy group vs. 10 days (range 1–36 days) in the control group ( $P$  0.4).

## Discussion

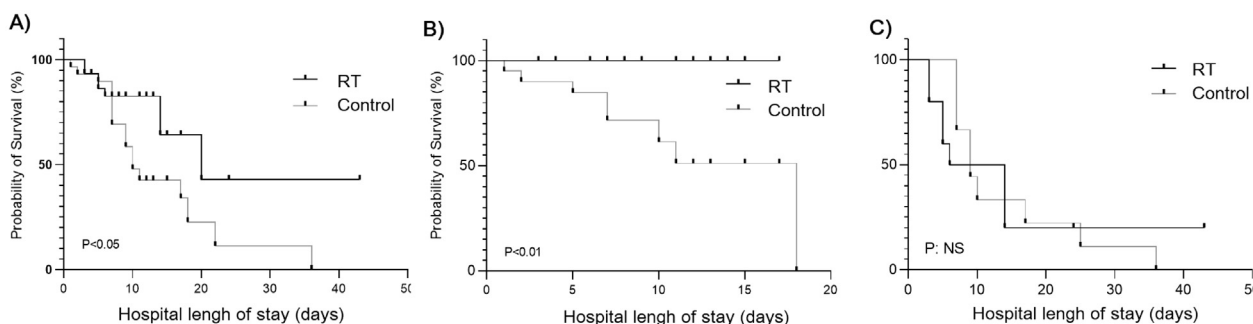
The results of this study with LD-WLI in patients with COVID-19 pneumonia show that it can help reduce mortality and decrease the probability of orotracheal intubation.

To date, there have been few published articles. One study with 5 patients showed that LD-WLI with 1.5 Gy as a single dose led to an 80% improvement of the patients. Additionally, in another study with 10 patients and two different doses (0.5 Gy and 1 Gy), the 28-day mortality rate of the 0.5 Gy whole-lung irradiation group was less than that of the 1.0 Gy group (50% vs. 75%). These results show that the 0.5 Gy dose could be a viable option for future studies [9,10]. In intubated patients, a study was carried out with 22 patients in two groups. One group was treated with radiotherapy at low doses (0.5–1.0 Gy, and the other was a control group. It was found that the overall survival at 28 days was identical in both groups, at 63.6%, showing that radiotherapy has no benefit in intubated patients [19].

**Table 1**  
Epidemiological characteristics of all the patients.

| Characteristics                 |                 | Radiotherapy group<br>N (%) | Control group<br>N (%) | P value |
|---------------------------------|-----------------|-----------------------------|------------------------|---------|
| Age (years)                     | Average (range) | 53 (27–87)                  | 57 (36–87)             | 0.8     |
| Gender                          | Female          | 8 (27.6)                    | 5 (17.2)               | 0.42    |
|                                 | Male            | 21 (72.4)                   | 24 (82.8)              |         |
| ARDS                            | Moderate        | 21 (72.4)                   | 21 (72.4)              | 0.6     |
|                                 | Severe          | 8 (27.6)                    | 8 (27.6)               |         |
| Hypertension                    | Yes             | 16 (55.2)                   | 15 (51.7)              | 0.7     |
|                                 | No              | 13 (44.8)                   | 14 (48.3)              |         |
| Diabetes                        | Yes             | 12 (41.4)                   | 11 (37.9)              | 0.7     |
|                                 | No              | 17 (58.6)                   | 18 (62.1)              |         |
| Obesity                         | Yes             | 4 (13.8)                    | 15 (51.7)              | 0.001   |
|                                 | No              | 25 (86.2)                   | 14 (48.3)              |         |
| Image classification by CO-RADS | Unsure          | 0                           | 1 (3.4)                | 0.005   |
|                                 | High            | 2 (6.9)                     | 8 (27.5)               |         |
|                                 | Very High       | 27 (93.1)                   | 20 (69.0)              |         |
| Mechanical Ventilation          | Yes             | 9 (10.3)                    | 17 (58.6)              | 0.7     |
|                                 | No              | 20 (89.6)                   | 12 (41.4)              |         |
| Remdesivir                      | Yes             | 0 (0)                       | 2 (6.8)                | 0.6     |

ARDS: Acute Respiratory Distress Syndrome.



**Fig. 1.** Survival analysis of patients with COVID-19 pneumonia treated with or without radiotherapy. (A) Moderate and severe ARDS patients. (B) Moderate ARDS patients. (C) Severe ARDS patients.

Our study shows that there was a decrease in mortality between the two groups of patients who received and did not receive radiotherapy treatment, at 27.5% vs. 58.6%, respectively ( $P 0.024$ ). In the subgroup analysis, low-dose pulmonary radiotherapy for patients with COVID-19 reduced mortality in the moderate group; the group that received radiotherapy treatment had a mortality of 0%, while it was 60% in the untreated group ( $P 0.002$ ). However, in the severe ARDS group, survival was 22% and 0% in the treated and untreated groups, respectively, with a nonsignificant difference ( $P 0.984$ ).

The requirement for orotracheal intubation in moderate ARDS was 45% less than that in the control group ( $P < 0.001$ ), and we could not detect a statistical difference in the severe group. These results are similar to other studies, showing a benefit in patients treated with LD-WLI; in this study, there was no benefit with LD-WLI in intubated patients, similar to the results reported in other articles [9,10,19].

During the subgroup analysis, the impact of the different comorbidities of the patients, including hypertension, diabetes and obesity, was evaluated, observing a tendency toward improved survival in patients treated with radiotherapy, although not statistically significant. A larger number of treated patients is likely required to determine the impact of comorbidities on the therapeutic response to radiation therapy.

Many limitations were found during the study, including logistics to treat patients in the radiotherapy department because it was located inside the oncology department, which lacked adequate physical barriers to manage COVID-19 patients. Thus, we were unable to treat patients during weekdays because of consultation and oncology treatments. Due to these limitations, we could not conduct a randomized study. The treatment group was not large enough to demonstrate significance in some values but clearly showed an important trend toward improve clinical outcomes in patients treated with radiotherapy, and these results could trigger randomized studies with a larger number of patients.

**Conclusion**

The results obtained in this study show that low doses of whole-lung radiotherapy could be an alternative to lessen the mortality of patients with moderate ARDS due to COVID-19 pneumonia. These results encourage future study of the clinical impacts of including radiotherapy where linear accelerators are available as an additional treatment for COVID-19 patients who do not interact with other treatments implemented by internal medicine departments or intensive care units. In addition, reducing the requirement of mechanical ventilation can impact the mortality of patients with moderate ARDS, particularly in low- and middle-

income countries that lack access to novel treatments, such as immunotherapy or antiviral drugs used in developed countries.

### Conflict of interest statement

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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Dedicated to Estefanía Olmos.

### References

- [1] Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis* 2020;20:773.
- [2] Organización Mundial de la salud. Manejo clínico de la infección respiratoria aguda grave (IRAG) en caso de sospecha de COVID-19. Última revisión 09/05/2020. Recuperado de: <https://apps.who.int/iris/bitstream/handle/10665/331660/WHO-2019-nCoV-clinical-2020.4-spa.pdf>.
- [3] Palacios Cruz M, Santos E, Velázquez Cervantes MA, León Juárez M. COVID-19, una emergencia de salud pública mundial. *RevClinEsp* 2021;221:55–61.
- [4] Rödel F, Arenas M, Ott OJ, Fournier C, Georgakilas AG, Tapio S, et al. Low-dose radiation therapy for COVID-19 pneumopathy: what is the evidence? *Strahlentheronkol* 2020;196:679–82.
- [5] Powell EV. Roentgen therapy of lobar pneumonia. *J Am Med Assoc* 1938;110:19–22.
- [6] Scott WR. X-ray therapy in the treatment of acute pneumonia: report covering the use of X-ray therapy in the treatment of pneumonia at the Niagara Falls Memorial Hospital, from Oct. 1, 1937, to Sept. 30, 1938. *Radiology* 1939;33:331–49.
- [7] Rousseau JP, Johnson WM, Harrell GT. The value of roentgen therapy in pneumonia which fails to respond to the sulfonamides. *Radiology* 1942;38:281–9.
- [8] Oppenheimer A. Roentgen therapy of interstitial pneumonia. *J Pediatr* 1943;23:534–8.
- [9] Clayton BH, Zachary SB, William S, et al. Low-dose whole-lung radiation for COVID-19 pneumonia: planned day-7 interim analysis of a registered clinical trial. medRxiv 2020.06.03.20116988.
- [10] Ameri A, Ameri P, Rahnama N, Mokhtari M, Sedaghat M, Hadavand F, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: final results of a pilot study. *Int J Radiat Oncol Biol Phys* 2021;109:859–66.
- [11] Rödel F, Keilholz L, Herrmann M, Sauer R, Hildebrandt G. Radiobiological mechanisms in inflammatory diseases of low dose radiation therapy. *Int J Radiat Biol* 2007;83:357–66.
- [12] Torres Royo L, Antelo Redondo G, Árquez Pianetta M, Arenas Prat M. Low-dose radiation therapy for benign pathologies. *Rep Pract Oncol Radiother* 2020;25:250–4.
- [13] Schae D, Jahns J, Hildebrandt G, Trott K-R. Radiation treatment of acute inflammation in mice. *Int J Radiat Biol* 2005;81:657–67.
- [14] Arenas M, Gil F, Gironella M, et al. Time course of anti-inflammatory effect of low-dose radiotherapy: Correlation with tgf-beta (1) expression. *Radiother Oncol* 2008;86:399–406.
- [15] Schröder S, Kriesen S, Paape D, Hildebrandt G, Manda K. Modulation of inflammatory reactions by low-dose ionizing radiation: cytokine release of murine endothelial cells is dependent on culture conditions. *J Immunol Res* 2018;2018:1–13.
- [16] Arenas M, Sabater S, Hernández V, et al. Anti-inflammatory effects of low-dose radiotherapy. Indications, dose, and radiobiological mechanisms involved. *Strahlenther Onkol* 2012;188:975–81.
- [17] Lara P, Burgos J, Macias D. Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment. *Clin Transl Radiat Oncol*. 2020;23 :27-29.
- [18] Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: A categorical CT assessment scheme for patients suspected of having COVID-19—definition and evaluation. *Radiology* 2020;296:E97–E104.
- [19] Papachristofilou A, Finazzi T, Blum A, et al Low-dose radiation therapy for severe COVID-19 pneumonia: A randomized double-blind study. *Int J Radiat Oncol Biol Phys*. 2021:S0360-3016(21)00239-X.