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Low dose radiation therapy for severe COVID-19 pneumonia: a randomized double-blind study

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**Low dose radiation therapy for severe COVID-19 pneumonia:  
a randomized double-blind study**

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Running title: LDRT for severe COVID-19 pneumonia

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## Abstract

### Purpose

The morbidity and mortality of patients requiring mechanical ventilation for coronavirus disease 2019 (COVID-19) pneumonia is considerable. We studied the use of whole-lung low dose radiation therapy (LDRT) in this patient cohort.

### Methods and Materials

Patients admitted to the intensive care unit (ICU) and requiring mechanical ventilation for COVID-19 pneumonia were included in this randomized double-blind study. Patients were randomized to 1 Gy whole-lung LDRT or sham irradiation (sham-RT). Treatment group allocation was concealed from patients and ICU clinicians, who treated patients according to the current standard of care. Patients were followed for the primary endpoint of ventilator-free days (VFDs) at day 15 post-intervention. Secondary endpoints included overall survival, as well as changes in oxygenation and inflammatory markers.

### Results

Twenty-two patients were randomized to either whole-lung LDRT or sham-RT between November and December 2020. Patients were generally elderly and comorbid, with a median age of 75 years in both arms. No difference in 15-day VFDs was observed between groups ( $p = 1.00$ ), with a median of 0 days (range, 0-9) in the LDRT arm, and 0 days (range, 0-13) in the sham-RT arm. Overall survival at 28 days was identical at 63.6% (95%CI, 40.7-99.5%) in both arms ( $p = 0.69$ ). Apart from a more pronounced reduction in lymphocyte counts following LDRT ( $p < 0.01$ ), analyses of secondary endpoints revealed no significant differences between the groups.

### Conclusions

Whole-lung LDRT failed to improve clinical outcomes in critically ill patients requiring mechanical ventilation for COVID-19 pneumonia.

### **Introduction**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the viral cause of the coronavirus disease 2019 (COVID-19) pandemic. Although symptoms of COVID-19 are mild to moderate in the vast majority of cases, some patients present with severe illness, which may quickly deteriorate to acute respiratory distress syndrome (ARDS) or end-organ failure (1, 2). The mortality of critically ill patients requiring intensive care unit (ICU) admission remains considerable, with global ICU mortality rates of 30-40% in most geographical regions (3).

Respiratory failure from ARDS is the leading cause of mortality in patients with COVID-19 (4). Viral pneumonia can induce a hyperinflammatory syndrome characterized by a cascade of cytokine activation, overwhelming systemic inflammation, and multiorgan failure (5). In addition to direct viral damage, this excessive host immune response is thought to play a key role in the pathophysiology of lung injury in COVID-19, characterized by diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis (6, 7). Evidence of hyperinflammation has led to the use of glucocorticoids in patients with severe COVID-19, an approach supported by findings of the randomized RECOVERY trial, which demonstrated that dexamethasone reduces mortality in patients requiring supplemental oxygen or invasive mechanical ventilation (7). Remdesivir, an antiviral agent, has also been shown to shorten the time to recovery in hospitalized patients with COVID-19 pneumonia (8). However, since remdesivir and other repurposed antiviral drugs appear to have little or no effect on overall mortality, the World Health Organization

has recommended against their use based on results of the multinational Solidarity trial (9). Therefore, despite improvements in survival seen in ICU patients (10), the clinical management of COVID-19 remains largely supportive, and additional improvements remain desirable for critically ill patients requiring intensive care.

One novel approach which has been suggested is the use of whole-lung low dose radiation therapy (LDRT) to treat COVID-19 pneumonia. This unconventional use of ionizing radiation is based on its anti-inflammatory and immunomodulatory effects, which have been well established in preclinical models. These effects are the likely mechanism by which low doses of x-rays were historically effective in treating various forms of pneumonia in the first half of the 20<sup>th</sup> century (11). Due to the limited treatment options for COVID-19 pneumonia, several clinical trials of LDRT have been initiated, using radiation doses in the range of 0.3 – 1.5 Gy (12). Initial experiences have suggested that LDRT is a feasible and well-tolerated treatment, which appeared to be associated with a reduction of inflammation and possibly bearing signs of clinical improvement in these small single-arm studies (13–16). However, due to the lack of prospective controls, the efficacy of LDRT in the treatment of COVID-19 remains unknown. We therefore performed a randomized double-blind study of whole-lung LDRT in patients with severe COVID-19 pneumonia requiring mechanical ventilation.

## **Methods and Materials**

### Study design and participants

XXXXXXXXXXXX (NCTXXXXXXXX) was a randomized double-blind phase II trial conducted at the XXXXXXXXXXX XXXXXXXX of XXXXX in XXXXX, XXXXXXXXXXXXX.

Patients with COVID-19 related pneumonia requiring mechanical ventilation were included. The lower age limit for male and female patients was 40 and 50 years, respectively, with exclusion of pregnancy required in women of childbearing potential. No other exclusion criteria were applied. The trial was approved by the Ethics Committee of XXXXXXXXXXXX XXX XXXXXXXX XXXXXXXXXXXX.

Patients with a confirmed SARS-CoV-2 infection requiring intensive care were screened for eligibility by three sub-investigators present on the ICU. The presence of COVID-19 related pneumonia was identified based on clinical and radiological findings, including ground glass opacities and other typical characteristics observed in thoracic computed tomography (CT) imaging (1, 17). All patients were dependent on mechanical ventilation, applied using an endotracheal tube following endotracheal intubation (ETI), or using face masks for continuous or intermittent non-invasive ventilation (NIV). Informed consent was granted by the legal representatives of the patients prior to trial inclusion, and deferred consent was later obtained from recovering patients. The aim was to carry out the study intervention within 72 hours after onset of mechanical ventilation.

#### Randomization and masking

Patients were randomly assigned with a 1:1 ratio to either whole-lung LDRT or sham irradiation (sham-RT). No stratification criteria were applied. Randomization was performed on the Castor EDC platform (Castor, Hoboken, USA), using variable block sizes of 4, 6 and 8 patients. The two principal investigators (PIs) in the radiation oncology department, who carried out the randomization, as well as one medical physicist, responsible for quality assurance, were aware of the group allocation. All other investigators remained blinded for the duration of the study. This included the

entire ICU treatment team, who continued to treat patients in accordance with local standards, without any involvement by the two study PIs.

### Procedures

The study procedure was performed in compliance with hospital-wide measures for infection prevention, including use of personal protective equipment, dedicated access ways, and decontamination measures. Patients were transported from the ICU to the radiation oncology department under continuous surveillance by one ICU physician and one ICU nurse. Treatments were performed after the regular daily program, using two beam-matched Elekta Synergy (Elekta, Sweden) linear accelerators (Linacs).

Two radiation oncologists, including one of the PIs, carried out the patient positioning inside the Linac vault with assistance of a radiation therapy technologist (RTT). Patients remained in their hospital beds and were positioned under the Linac gantry, with the treatment couch rotated away from the isocenter. The gantry angle was set at  $0^\circ$  (perpendicular to the patient), and all beam blocking leaves of the multileaf collimator (MLC) were left open, corresponding to a maximum treatment field size of 40 cm x 40 cm at the isocenter. Using the field light as guidance, the position of the patients' beds was adjusted so that the projected field covered the entire thorax at a source-to-skin distance (SSD) of 110 cm (*Figure 1*). Treatment was performed in supine position for patients on NIV, and in supine or prone position (depending on ICU preference) for intubated patients. Following patient setup, one of the in-room cameras was directed at the ICU monitor for remote patient surveillance, and all personnel exited the treatment vault. The medical physicist, aware of the group allocation, authorized treatment with MLC leaves fully open (whole-lung LDRT) or

closed (sham-RT). The RTT then initiated the approximately 60 seconds of beam-on time. Treatment group allocation remained invisible to the blinded personnel, for whom both interventions were completely indistinguishable.

Treatment was delivered using a single 10 megavoltage (MV) photon beam with a tissue phantom ratio ( $TPR_{20,10}$ ) of 0.728 and a dose maximum depth at 2.1 cm. The prescribed dose was 1 Gy at the reference point, which was set to the depth of dose maximum. Pre-study treatment planning was performed using a collapsed cone algorithm in Monaco (v.5.51.02; Elekta, Sweden), taking into account the estimated anterior-posterior electron density configuration of an average thorax. The mean lung dose was estimated at 0.8 Gy, with a predicted lung dose range of 0.5 – 1.0 Gy based on phantom simulations. For illustration, an estimated dose distribution (calculated retrospectively using a diagnostic CT scan of an average-sized study patient) is shown in *Supplementary Figure E1*. A set of SSD-specific monitor unit calculations was prepared, although all patients were ultimately treated using the pre-specified SSD of 110 cm, which appeared adequate in all cases. We performed no patient-specific simulation, dosimetry, or image-guidance, thereby limiting the unattended in-vault time to 1-2 minutes. After treatment, patients were transported back to the ICU, completing the study procedure within a total out-of-ICU time of less than 20 minutes.

### Outcomes and statistical methods

The primary endpoint was the number of ventilator-free days (VFD) at day 15, calculated from the day of intervention (day 0). VFDs were defined as the number of days a patient was alive and free of mechanical ventilation. Patients who died before day 28 were assigned zero VFDs (18). VFDs at 15 days were assumed at 3.93 days

with standard of care, based on unpublished in-house data of COVID-19 patients admitted to the ICU in spring 2020. We hypothesized that LDRT would increase VFDs to 10 days, which required randomization of 22 patients to detect superiority of LDRT with a power of 90%, a significance level of 5%, and a standard deviation of 4.36 days (based on in-house data). Exploratory secondary endpoints, based on routinely conducted measurements, included: changes in PaO<sub>2</sub>/FiO<sub>2</sub> ratio (Horowitz index), measured from baseline (day 0) compared to the lowest observations within 24 hours (day 1) and on subsequent days; overall survival at day 15, 28; and levels of inflammatory markers up to day 15. Baseline comorbidity assessment was performed using the Charlson comorbidity index (CCI), based on pre-existing conditions prior to SARS-CoV-2 infection (19). The Simplified Acute Physiology Score (SAPS II), a predictor of hospital mortality, was calculated within 24 hours after ICU admission (20). ARDS severity was defined according to Berlin criteria based on the lowest PaO<sub>2</sub>/FiO<sub>2</sub> ratio measured on treatment day (prior to the intervention) (21). Continuous and categorical data were compared using two-tailed Wilcoxon rank sum test and Fisher's exact test, respectively. A p-value <0.05 was considered statistically significant. Overall survival was calculated using the Kaplan-Meier method, calculated from the day of intervention. All statistical analyses were performed using RStudio (v.1.3.1093; Boston, USA).

## Results

### Recruitment and patient characteristics

A total of 58 SARS-CoV-2 positive patients admitted to the ICU were screened for trial inclusion in November and December 2020 (*Figure 2*). Reasons for non-inclusion were the lack of consent given by a legal representative (n = 14),

respiratory improvement with expected weaning within 24-48 hours (n = 8), prolonged ventilation (>7 days) prior to screening (n = 7), and hemodynamic instability or death (n = 7).

Twenty-two patients were enrolled, randomized and treated per protocol. The characteristics of these patients are summarized in *Table 1*. Patients were a median of 75 years (range, 54-84) old, and had a median comorbidity index of 5 (CCI; range, 1-11) prior to SARS-CoV-2 infection. Most patients were male (77%), and two-thirds (64%) had a body mass index (BMI) of over 25 kg/m<sup>2</sup>, with a median of 26.9 kg/m<sup>2</sup> for the entire cohort. Smoking history was common (59%), although only one patient was a current smoker. Patients were diagnosed with SARS-CoV-2 a median of 7 days (range, 0-16) prior to ICU admission, which occurred after a median hospitalization duration of 1 day (range, 0-10).

The patterns of COVID-19 treatment were overall similar between groups (*Table 1*). All patients (100%) received standard of care with dexamethasone, which was initiated a median of 3.5 days (range, 1-12) prior to the study intervention, and given for a median of 10 days (range, 5-11) total. Remdesivir was given to 50% of patients for a median of 5 days (range, 5-6), and three patients (14%) received experimental drugs (canakinumab, conestat alfa) as part of ongoing clinical trials. At the time of study intervention, patients had been mechanically ventilated for a median of 2 days (range, 0-2) by way of ETI (59%) or NIV (41%). The proportion of patients managed with ETI was 73% in the LDRT group, and 45% in the sham-RT group. SAPS II scores were a median of 52 and 43, respectively, in the LDRT and sham-RT arms.

### Outcomes

The study intervention occurred after a median of 0 days (range, 0-3) following patient enrollment, with most patients being treated in supine position (86%). The procedure was executed without incident in all cases, and no noticeable adverse events were observed in the hours and days following the intervention.

Individual outcomes for the primary endpoint are visualized in *Figure 3*. Median VFDs at 15 days were 0 days (range, 0-9) in the LDRT group, and 0 days (range, 0-13) in the sham-RT group. No significant difference in VFDs at 15 days was observed between the groups (LDRT vs. sham-RT: difference 0 days, 95%CI [-4.0, +2.0];  $p = 1.00$ ). Tracheostomy was performed in 6 patients with prolonged intubation. During the first 15 days, a total of 9 (41%) patients were weaned from mechanical ventilation for  $\geq 1$  day, and 8 (36%) of these patients subsequently remained ventilator-free. In contrast, zero VFDs were observed in 13 patients (59%) during the first 28 days, and only 3 (14%) of these patients were ultimately discharged to rehabilitation after prolonged hospitalization periods.

Kaplan-Meier plots of overall survival are shown in *Figure 4*. Median follow-up was 45 days (range, 2-91). The estimate of survival at 15 days was 72.7% (95%CI, 50.6-100%) in the LDRT group, and 63.6% (95%CI, 40.7-99.5%) in the sham-RT group. Estimates of 28-day survival were identical at 63.6% (95%CI, 40.7-99.5%) in both arms. No difference in survival was observed between the groups ( $p = 0.69$ ). At the time of writing, a total of 11 patients (6 in the LDRT group, and 5 in the sham-RT group) had died, with most deaths occurring within the first 2 weeks after study inclusion. The primary cause of death was ARDS due to COVID-19 in all but one patient, who died of infectious complications secondary to malignant disease.

Measurements of secondary outcome parameters are summarized in *Table 2*, with post-intervention changes in inflammatory markers visualized in *Supplementary Figures E2-E4*. Measurements of secondary endpoints revealed overall similar results in both groups. Relative reductions in lymphocyte counts (baseline vs. lowest measurement up to 15 days or death) were more pronounced after LDRT compared to sham-RT ( $p < 0.01$ ), although most patients had a largely stable lymphopenia (*Supplementary Figure E4*). The statistical difference remained when two patients in the LDRT group, who had marked lymphocytosis at baseline due to known chronic lymphocytic leukemia, were excluded from the analysis ( $p < 0.01$ ). Otherwise, no significant difference in the reduction of inflammatory markers was observed between groups. Similarly, no significant differences were seen in oxygenation changes within 24 hours (LDRT vs. sham-RT: median PaO<sub>2</sub>/FiO<sub>2</sub> change +5 vs. +9,  $p = 0.49$ ), nor in serial longitudinal measurements, which were limited due to the low number of (alive) patients still on ventilator (data not shown).

## Discussion

Despite global efforts to improve outcomes in patients hospitalized with COVID-19, the mortality rates remain high in patients requiring mechanical ventilation. We now report on, to the best of our knowledge, the first randomized investigation of whole-lung LDRT in this patient population. In our study, whole-lung LDRT failed to improve VFDs compared to sham-RT, suggesting a lack of clinical benefit in critically ill patients requiring mechanical ventilation for COVID-19 pneumonia.

We used a primary endpoint of VFDs, a composite outcome measure commonly reported in ARDS trials (18), and based our statistical power calculation on ICU data

gathered during the early phase of the COVID-19 pandemic. The observed outcomes were worse than predicted, which is likely a consequence of patient selection for our study, which enrolled elderly and comorbid patients with poor or uncertain prognosis. In addition, changes in ICU admission practice likely increased the average case severity, as non-critical patients are now routinely treated in the dedicated COVID-19 ward. We acknowledge that our initial hypothesis was optimistic in regards to the magnitude of improvement with whole-lung LDRT. However, we were looking for a clear clinical benefit, which would justify potential risks for patients and staff related to the procedure, and which would reflect the rapid symptom reversal described in historical series of x-ray therapy for pneumonia (11), and in some early experiences of LDRT use for COVID-19 pneumonia (13–16). Our study was not powered to detect small differences in outcomes, which would require a larger sample size. However, as we failed to detect any meaningful signal in primary and secondary endpoints, it appears questionable whether larger studies in similar cohorts are warranted unless more robust (preclinical) data become available.

We chose a simple approach to deliver whole-lung LDRT due to the clinical priorities in these critically ill patients. In particular, we did not perform patient-specific (CT-based) treatment planning, and we decided against using more sophisticated radiotherapy techniques, which could be used to achieve a more favorable dose distribution (22). Rather, we optimized our workflow to minimize the risk of unexpected events while outside the ICU (23, 24). This included treating patients in their hospital beds to eliminate the need for patient transfer, and using simple setup and delivery techniques to reduce treatment times. Since we used only one photon beam, the prescribed dose of 1 Gy was not delivered homogeneously to the lungs. Rather, the lungs were irradiated with a spectrum of anti-inflammatory doses in the

range of approximately 0.5 – 1.0 Gy, which is comparable to other ongoing studies (12, 25). Since we did not perform serial CT imaging, we were unable to quantify radiological responses in different areas of the lung, and correlate changes to the dose distribution. Furthermore, due to the simple technique used, LDRT was also delivered to parts of the liver and spleen, as well as axillary, supraclavicular and upper abdominal lymph nodes. The impact of irradiating these regions in the context of systemic hyperinflammation remains unknown.

The doses used in clinical trials of LDRT are highly unlikely to cause any deterministic side effects, such as radiation pneumonitis or fibrosis. However, there is a risk of radiation-induced cardiac disease and a stochastic risk of cancer induction (26–28), which led us to introduce a lower age limit in our study. The long-term risks appeared to be of little concern in our patients, considering their age and risk of early mortality from COVID-19 pneumonia. However, the ratio of risk to potential benefit appears less favorable in younger patients, as well as in less critical patients in earlier phases of SARS-CoV-2 infection. Based on historical data, LDRT may be most effective in treating interstitial pneumonia when delivered early (29), and similar assumptions could be made for COVID-19 pneumonia based on the pathogenesis of ARDS (12). Although we enrolled patients as soon as possible after onset of mechanical ventilation, the lack of effect could therefore be attributed to the advanced stage of COVID-19 pneumonia in our cohort. In addition, the use of dexamethasone as a standard of care could have masked anti-inflammatory effects of LDRT in our patients, most of whom already had lymphopenia at study entry, reflecting a severe clinical course (30, 31). The latter can be further complicated by an array of extrapulmonary manifestations of COVID-19 (32), which are unlikely to be affected by LDRT, and which add another dimension of complexity to these patients.

Despite these complicating factors, the possible lack of a clinical effect of LDRT for any stage of SARS-CoV-2 infection has to be considered in the absence of randomized evidence.

Our results are in contrast to the initial experiences reported from small single-arm studies, which observed signs of clinical and radiographic improvement following LDRT for COVID-19 pneumonia (13–16). These studies used LDRT doses in the range of 0.5 - 1.5 Gy, and treated non-intubated patients receiving supplemental oxygen via nasal cannula or face mask. Due to the lack of prospective control groups, and the small sample size of 2-10 patients per report, no conclusions can be drawn regarding the efficacy of LDRT based on these studies. Furthermore, since these studies were conducted during an earlier phase of the COVID-19 pandemic, patients generally did not receive either remdesivir or dexamethasone, the latter of which remains the only agent shown to reduce mortality in patients hospitalized with COVID-19 (7). In our study, where all patients received dexamethasone as a standard of care, we were unable to reproduce anecdotal evidence of rapid clinical improvement after LDRT. This included secondary outcome measures, such as improvements in PaO<sub>2</sub>/FiO<sub>2</sub> ratio after 24 hours, which were not different between the groups. Whether a different outcome would have been observed in patients not requiring mechanical ventilation remains unclear, as results of ongoing clinical trials are pending (12).

The main strengths of our study are its randomized and double-blind design, the swift accrual period of 2 months, and the patient-centered clinical endpoint. Main weaknesses are the small sample size, and possibly the inclusion of only patients requiring mechanical ventilation. The latter was a consequence of our decision to

focus on critically ill patients, for whom the ratio of risk to potential benefit appeared most favorable, which is relevant considering the experimental nature of our study. Although the baseline characteristics were overall similar in both groups, the impact of random differences has to be considered when interpreting our results. This includes a higher proportion of patients managed with ETI, and a numerically higher rate of comorbidities, in the LDRT group. The influence of these and other factors, such as the number of ventilator days prior to the intervention, could not be studied due to the small sample size. However, since these small imbalances would not have changed the overall outcome of our study, we believe that future efforts would need to explore a different approach than reported here. This could, at least in theory, involve the use of a different LDRT regime and technique, or application in earlier clinical stages of COVID-19 pneumonia.

In conclusion, whole-lung LDRT failed to improve clinical outcomes in critically ill patients requiring mechanical ventilation for COVID-19 pneumonia. While results of ongoing studies are awaited, there is currently no role for the routine use of LDRT in this setting.

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### Figure captions

Figure 1: Whole-lung low dose radiation therapy was delivered using a linear accelerator, with patients remaining in their hospital bed under continued intensive care surveillance (left image). Using the field light (green) as guidance, the position of the patients' beds was adjusted so that the projected field covered the entire thorax up to the supraclavicular fossae (middle and right image; reenactment using a clinician). Patients were treated at a central source-to-skin distance of 110 cm, which was verified using an optical distance indicator (red).

Figure 2: Enrollment, randomization, and inclusion in the primary analysis. Twenty-two patients were enrolled and randomized to either whole-lung low dose radiation therapy (LDRT) or sham irradiation (sham-RT).

Figure 3: Visualization of individual patient outcomes following either whole-lung low dose radiation therapy (LDRT) or sham irradiation (sham-RT). Patients receiving mechanical ventilation by way of either endotracheal intubation (ETI; red) or non-invasive ventilation (NIV; orange) were eligible for inclusion. No difference in ventilator-free days (VFD; green) at day 15 was observed. Eleven deaths (indicated by 'x') were observed during follow-up, most of which occurred within the first 2 weeks.

Figure 4: Kaplan-Meier plot of overall survival following the study intervention (day 0).

No difference in survival was observed between patients who underwent whole-lung low dose radiation therapy (LDRT) or sham irradiation (sham-RT).

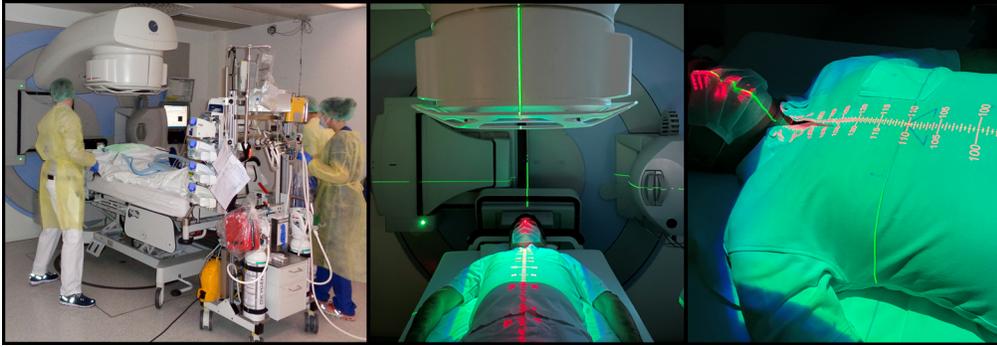
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		Whole-lung LDRT (n = 11)	Sham-RT (n = 11)
<b>Age, median (range)</b>		75 (54-84)	75 (69-82)
<b>Sex</b>			
	Male	10 (91%)	7 (64%)
	Female	1 (9%)	4 (36%)
<b>BMI (kg/m<sup>2</sup>), median (range)</b>		24.8 (19.1-37.0)	28.0 (23.5-31.1)
<b>Medical history (prior to COVID-19)</b>			
	Smoking history	6 (55%)	7 (64%)
	Cardiovascular disease	6 (55%)	3 (27%)
	Diabetes	6 (55%)	6 (55%)
	Pulmonary disease	4 (36%)	1 (9%)
	Malignancy	3 (27%)	1 (9%)
	CCI, median (range)	5 (1-11)	4 (3-7)
<b>SAPS II, median (range)</b>		52 (29-67)	43 (29-64)
<b>ARDS severity (Berlin definition)</b>			
	Mild	1 (9%)	0 (0%)
	Moderate	5 (45%)	7 (64%)
	Severe	5 (45%)	4 (36%)
<b>Type of ventilation</b>			
	Endotracheal intubation	8 (73%)	5 (45%)
	Non-invasive ventilation	3 (27%)	6 (55%)
<b>Ventilator days prior to intervention, median (range)</b>		2 (0-7)	2 (1-5)
<b>COVID-19 drug treatment</b>			
	Dexamethasone	11 (100%)	11 (100%)
	Remdesivir	4 (36%)	7 (64%)
	Experimental drug	1 (9%)	2 (18%)

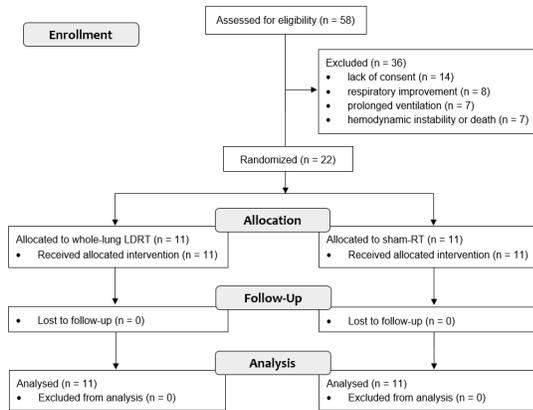
**Table 1:** Characteristics of 22 patients randomized to either whole-lung LDRT or sham irradiation. Data are presented as number (percentage) of patients unless indicated otherwise. *Abbreviations: ARDS, acute respiratory distress syndrome. BMI, body mass index. CCI, Charlson comorbidity index. COVID-19, coronavirus disease 2019. LDRT, low dose radiation therapy. SAPS II, Simplified Acute Physiology Score II. Sham-RT, sham irradiation.*

	Whole-lung low dose radiation therapy				Sham irradiation				Δ
	Day 0	Day 5	Day 10	Nadir (15d)	Day 0	Day 5	Day 10	Nadir (15d)	
CRP (mg/l), median (range)	103.6 (13.0-329.3)	73.9 (27.2-249.4)	132.8 (12.2-225.8)	36.4 (12.2-111.2)	108.9 (4.1-184.6)	74.6 (16.9-337.6)	162.0 (64.4-292.6)	32.8 (2.4-112.6)	
<i>CRP reduction (baseline to nadir)</i>	<i>Median -60% (range, [-90%, -6%])</i>				<i>Median -61% (range, [-96%, -11%])</i>				<i>p = 0.85</i>
Ferritin (µg/l), median (range)	1733 (489-3846)	1557 (653-3980)	2048 (673-4739)	1045 (602-2864)	1067 (431-7251)	926 (496-3712)	1052 (541-1449)	854 (419-3712)	
<i>Ferritin reduction (baseline to nadir)</i>	<i>Median -24% (range, [-66%, +29%])</i>				<i>Median -17% (range, [-49%, 0%])</i>				<i>p = 0.59</i>
Lymphocytes (10 <sup>9</sup> /l), median (range)	0.6 (0.4-23.0)	0.6 (0.2-11.3)	0.6 (0.2-1.4)	0.4 (1.0-2.5)	0.5 (0.3-1.3)	0.6 (0.3-1.5)	0.7 (0.3-1.7)	0.3 (0.2-1.0)	
<i>Lymphocyte reduction (baseline to nadir)</i>	<i>Median -66% (range, [-97%, -30%])</i>				<i>Median -10% (range, [-59%, 0%])</i>				<i>p &lt; 0.01</i>
	Day 0	Day 1 (24h)	Day 5		Day 0	Day 1 (24h)	Day 5		
PaO <sub>2</sub> / FiO <sub>2</sub> ratio, median (range)	101 (69-238)	113 (102-182)	107 (80-123)		108 (56-173)	92 (78-182)	133 (56-217)		
<i>PaO<sub>2</sub> / FiO<sub>2</sub> ratio, change within first 24h</i>	<i>Median +5 (range, [-68, +102])</i>				<i>Median +9 (range, [-57, +34])</i>				<i>p = 0.49</i>

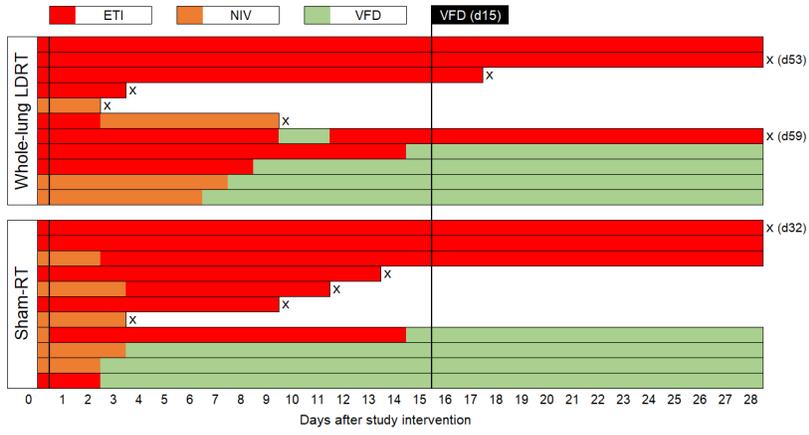
**Table 2:** Summary of changes in inflammatory markers and pulmonary function (PaO<sub>2</sub> / FiO<sub>2</sub> ratio) after whole-lung low dose radiation therapy (LDRT) and sham irradiation (sham-RT). Median values are based on alive patients for whom observations were available. Reductions in inflammatory markers were measured as relative reduction from baseline to the lowest value observed until 15 days or death. With the exception of a more pronounced relative reduction in lymphocyte counts after LDRT, analyses of secondary outcome parameters did not reveal significant differences between the groups.



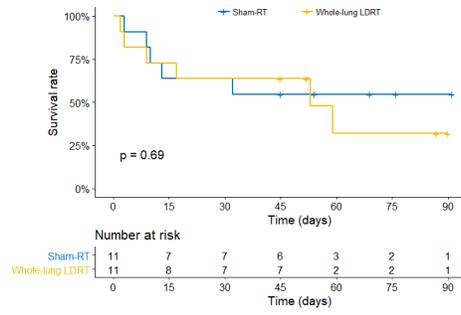
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