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Original Article

Whole-lung low-dose radiation therapy (LD-RT) for non-intubated oxygen-dependent patients with COVID-19-related pneumonia receiving dexamethasone and/or remdesivir



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ABSTRACT

Background: Low-dose radiotherapy (LD-RT) has produced anti-inflammatory effects in both animal models and early human trials of COVID-19-related pneumonia. The role of whole-lung LD-RT within existing treatment paradigms merits further study.

Methods: A phase II prospective trial studied the addition of LD-RT to standard drug treatments. Hospitalized and oxygen-dependent patients receiving dexamethasone and/or remdesivir were treated with 1.5 Gy whole-lung LD-RT and compared to a blindly-matched contemporaneous control cohort.

Results: Of 40 patients evaluated, 20 received drug therapy combined with whole-lung LD-RT and 20 without LD-RT. Intubation rates were 14% with LD-RT compared to 32% without ($p = 0.09$). Intubation-free survival was 77% vs. 68% ($p = 0.17$). Biomarkers of inflammation (C-reactive protein, $p = 0.02$) and cardiac injury (creatinine kinase, $p < 0.01$) declined following LD-RT compared to controls. Mean time febrile was 1.4 vs 3.3 days, respectively ($p = 0.14$). Significant differences in clinical recovery (7.5 vs. 7 days, $p = 0.37$) and radiographic improvement ($p = 0.72$) were not detected. On subset analysis, CRP decline following LD-RT was predictive of recovery without intubation compared to controls (0% vs. 31%, $p = 0.04$), freedom from prolonged hospitalizations (21+ days) (0% vs. 31%, $p = 0.04$), and decline in oxygenation burden (56% reduction, $p = 0.06$). CRP decline following 1st drug therapy was not similarly predictive of outcome in controls ($p = 0.36$).

Conclusions: Adding LD-RT to standard drug treatments reduced biomarkers of inflammation and cardiac injury in COVID-19 patients and may have reduced intubation. Durable CRP decline following LD-RT predicted especially favorable recovery, freedom from intubation, reduction in prolonged hospitalization, and reduced oxygenation burden. A confirmatory randomized trial is now ongoing.

Clinical Trial Registration: NCT04366791.

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The severe-acute-respiratory-syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) have caused unprecedented death and disruption. Mediated by a cascading, hyperinflammatory, macrophage-activating event in

the lungs [1], patients can face mortality rates of 30–50% once dependent on mechanical ventilation [2–4]. The anti-inflammatory effects of low-dose, ionizing radiation therapy (LD-RT) are well-established for multiple hyper-inflammatory conditions [5–12]. LD-RT has reduced inflammatory opacities in the lung, pro-inflammatory markers interleukin-6 and interferon-gamma, and increased anti-inflammatory marker interleukin-10 in murine models of acute lung injury using intra-tracheal administration of lipopolysaccharide (LPS) [13]. LD-RT directed at the lungs may dampen COVID-19's cytokine hyperactivity through similar immunomodulatory pathways [14–16]. Initial reports of LD-RT for COVID-19 demonstrated safety, reduced intubation

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; CT, chest tomography; CXR, chest X-ray; LD-RT, low-dose radiation therapy; OS, overall survival; PCR, polymerase chain reaction; P:F ratio, ratio of arterial pressure (mmHg) of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) [P:F ratio]; TTCR, time to clinical recovery.

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rates, declined inflammatory markers, and hastened recovery in non-intubated patients [17–19]. A recent but small randomized trial studied LD-RT in 11 intubated patients and detected no benefit compared to 11 intubated controls [20]. Further study of LD-RT combined with current standard treatments in non-intubated patients is warranted.

Materials and methods

Trial design

The Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-day Treatment for COVID-19 (RESCUE 1–19) trial is an investigator-initiated, single-institution combined phase I/II trial. One trial cohort studied 1.5 Gy whole-lung LD-RT with concurrent dexamethasone and/or remdesivir. All participants gave written informed consent prior to study procedures, which included risk of second cancer and accelerated cardiovascular disease. Clinical Trial Registration Number was NCT04366791. The research protocol was approved by the Emory University Institutional Review Board.

Patients

Eligible LD-RT patients tested positive for SARS-CoV-2 using PCR, were hospitalized, had pneumonic consolidation on either chest radiograph (CXR) or computed tomography (CT), required oxygen supplementation, and failed a trial of oxygen weaning. Exclusion criteria included disease severity that was too mild (weanable to room air) or too severe (intubated). Patients who required oxygen levels beyond 15 L/min were transport ineligible. Anti-pyretic medications were suspended at enrollment. Following LD-RT, oxygen weaning followed standards of care. Patients underwent clinical assessment at the time of enrollment and on post-RT days 1, 3, 7, and 28, as well as optional assessment on days 14 and 21. Charlson Comorbidity Index (CCI) [21] was used to assess comorbidity burden. Radiographs were permitted at any time as clinically indicated, but obtained at least within 1 day prior to radiation, 24 hours following radiation, and at the timepoints mentioned above. Evaluation of serum inflammatory, renal, cardiac, chemistry, clotting, and hematologic markers were encouraged daily, but obtained at least at baseline and at the timepoints mentioned above. Following trial completion, a prospective cohort of 20 contemporaneous controls was retroactively and blindly matched by age, comorbidity burden, and disease severity for comparative outcome analysis. Controls were selected from among SARS-CoV-2-positive patients who had enrolled on a separate, non-therapeutic, prospective institutional trial. Study investigators were blinded to the selection and outcomes of control patients. Controls were permitted but not required to be co-enrolled on any therapeutic trial of COVID-19-directed drugs, including the Adaptive COVID-19 Treatment Trial (ACTT-1, Clinical Trial NCT04280705). To match disease severity, eligible controls were required to have received supplemental oxygen during hospitalization and were excluded if they experienced rapid clinical decline requiring intubation on the day of admission. No oxygen wean attempt prior to enrollment was feasible for controls.

Intervention

All enrolled patients received best supportive care plus dexamethasone and/or remdesivir prior to LD-RT delivery. A single treatment of 1.5 Gy was delivered to the bilateral whole lungs with 15 megavoltage photons on a linear accelerator, utilizing a 2-dimensional technique, an anterior-posterior beam configuration, and standard dose rates (600 MU/min). Patients in the control

cohort received best supportive care and standard of care drug therapies for COVID-19 (i.e., glucocorticosteroids, remdesivir, etc.) per physician discretion or therapeutic protocol without LD-RT.

Outcome measures

Primary objectives were (1) safety and (2) efficacy of LD-RT delivered concurrently with dexamethasone and/or remdesivir [17]. Efficacy was explored by comparing intubation rates and time to clinical recovery (TTCR). TTCR was defined equivalently as it was in the ACTT-1 trial, as time from first COVID-19 intervention to the first day on which a subject satisfied one of three categories: (1) Not hospitalized, no limitations on activities; (2) Not hospitalized, limitation on activities and/or requiring home oxygen; or (3) Hospitalized, not requiring supplemental oxygen. A full 24-hour calendar day free of oxygen supplementation was required to trigger the binary classification of a patient as recovered. Additional secondary outcomes explored clinical course, radiographic changes, and clinical lab results. Clinical course was evaluated by overall survival (OS), total hospital duration, time from admission to clinical recovery, freedom from intubation, intubation-free survival, duration of intubation, and cumulative oxygen supplementation requirement. Intubation-free survival was defined as the proportion of patients who were both alive and had not required intubation or mechanical ventilation during hospitalization. Disease severity was assessed at baseline by oxygen requirement (L/min) and arterial blood gas using a ratio of arterial pressure (mmHg) of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) [P:F ratio]. Radiographic changes were evaluated by serial imaging. Chest radiographs were categorized as improved (I), stable (S), or worse (W) by comparing to the immediately preceding study by a blinded board-certified diagnostic radiologist (BW) and also blindly assigned an ordinal 1–5 score, using an acute respiratory distress syndrome (ARDS) scoring scale [22]. Radiological blinding allowed knowledge of radiograph sequencing but ensured no knowledge of cohort designation, intervention received, or timing thereof. Chest computed tomography studies obtained at baseline and day 7 were subjectively assessed and visually compared without a standardized scoring system. Serological course was measured by serial laboratory evaluations of hematologic, renal, cardiac, chemistry, clotting, and inflammatory markers. Start time to clinical recovery was defined as it was in prior cohorts [17], as the time from LD-RT delivery (in the radiation cohort), as the first day of administration of COVID-19 therapy (in control patients, if received [$n = 18$]), or as the first full-day of hospitalization (in control patients who received best supportive care alone [$n = 2$]). To control for lead-time bias from this definition, hospital duration and time from hospital admission to clinical recovery were also evaluated. Days febrile and oxygenation duration and burden were tracked.

CRP response

During trial enrollment, durable declines in C-reactive protein (CRP) were observed following LD-RT in most recovering patients, while CRP rise occurred prior to poor outcomes. A subset analysis was planned mid-trial, defining a predictive variable “CRP response.” Patients who did and did not experience consistent decline in CRP over 3 days following LD-RT were categorized as *responders* and *non-responders*, respectively. CRP *non-responders* were defined as experiencing both of the following: (1) elevated CRP level (>10 mg/dL) the morning prior to LD-RT (baseline), and (2) two sequential rises in CRP above baseline among the first three daily measurements immediately following LD-RT. To control for lab variability, rise in CRP level was defined as an increase of

≥2% above the immediately preceding result. Daily labs were drawn approximately 24 hours apart so that duplicate or rapidly repeated lab rises did not overestimate sequential CRP rise. Evaluation was permitted to span 4 days following LD-RT in the event of missing labs.

Statistical analysis

Wilcoxon rank sum tests, Fisher’s exact tests, and log-rank tests were used for continuous, categorical, and time-to-event endpoints, respectively. Cumulative incidence of recovery and discharge, overall survival, freedom from intubation, and intubation-free survival were estimated and/or graphed using the Kaplan-Meier method. Deceased patients were censored at time of death. Univariate Cox proportional hazards models were fit and hazard ratios reported. Serial imaging ARDS scores were carried forward from Day 7 to 14 to 21, if missing. CXR outcomes were reported as mean ARDS scale scores for sequential time periods. Median and interquartile range was calculated for laboratory values at clustered time points: hospital days 0–2, 3–5, 6–8, 9–11, and 12–14. Univariate ANOVA (within clustered days) and multivariate repeated values ANOVA (between clustered days) were used to compare changes in repeated laboratory measures. Clinical outcomes were stratified in subset analysis by binary classification of CRP responders vs. non-responders. Within this analysis, t-tests were used for continuous endpoints rather than Wilcoxon rank sum tests because of observations of effect on outlier data points likely to alter means rather than medians. Means were reported wherever medians did not explain cohort differences. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary,

NC), and statistical significance was two-sided and assessed at the 0.05 level. To evaluate the predictive value of CRP decline following drug interventions alone, the same definition of CRP response and stratified analysis was applied to controls.

Results

From June 11, 2020 to December 7, 2020, 65 patients were screened for eligibility, and twenty-five were enrolled. Of these, the first twenty were treated with LD-RT and 5 were reserved as future controls for immunologic profiling. None required more than 15 L/min of supplemental oxygen, making all patients eligible for transport. Of the 40 patients screened but not enrolled, 21 had disease too mild to meet severity criteria, 5 declined to participate, 5 were young and likely to spontaneously recover, 5 had no documented rationale for non-enrollment, 3 had disease too severe to meet severity criteria and were intubated before written consent, and 1 did not ultimately meet SARS-CoV-2 eligibility criteria (Fig. 1). Following trial completion, 20 control patients hospitalized between March 6, 2020 and November 19, 2020 and enrolled on a separate collaborating non-therapeutic trial were blindly matched for comparison against the LD-RT group. One control rapidly intubated on the day of admission and later died and was excluded and blindly replaced to ensure matching of disease severity at admission between cohorts.

Table 1 outlines patient demographics at the time of hospital admission and administered COVID-19 drug therapies. Median age was 63 (49–88). Fifty-three percent of patients were African-American, 38% were female, and 12% were residents of assisted living centers. None experienced altered mentation at

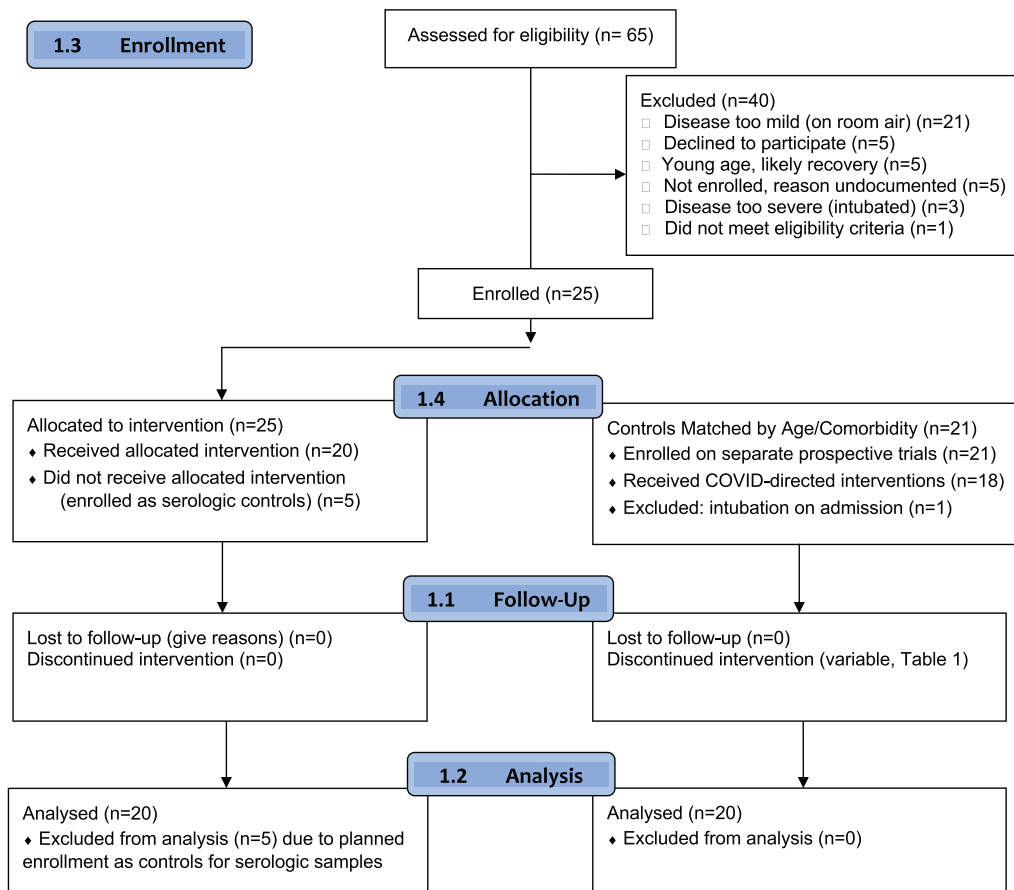


Fig. 1. CONSORT flow diagram.

Table 1
Patient demographics.

	LD-RT Cohort (n = 20)	Matched Controls (n = 20)	Total (n = 40)	p-Value*
Median age in years (range)	64.5 (53–85)	63 (49–88)	63 (49–88)	0.54
Age 65 and over	10	8	18 (45%)	0.75
Age 64 and under	10	12	22 (55%)	
Race/Ethnicity				1.0
Black/Non-Hispanic	11	10	21 (53%)	
Non-Black/Other	9	10	19 (47%)	
White/Non-Hispanic	5	8	13 (33%)	–
Asian	0	1	1 (3%)	
White/Hispanic	2	1	3 (8%)	
Not disclosed	2	0	2 (5%)	
Gender				0.51
Female	6	9	15 (38%)	
Male	14	11	25 (62%)	
Residence				1.0
Independent/With Family	17	18	35 (88%)	
Caregiver/Assisted Living/Nursing Home	3	2	5 (12%)	
Median Comorbidity Index (CCI) (Range)	3 (1–10)	3 (1–12)	3 (1–12)	0.74
Chronic Home Oxygen Supplementation	1	0	0 (0%)	–
Median duration of symptoms: days prior to admission (range)	10 (1–15)	7 (2–14)	7 (1–15)	0.10
Positive SARS-CoV-2 test prior to admission	8	6	14 (35%)	0.74
Mean time (in days) between prior positive SARS-CoV-2 test and admission (range)	3.3 (0.13)	1.7 (0–12)	2.5 (0–13)	0.32
Median O ₂ (L/min) at admission (range)	3.0 (0–15) [Mean 4.4]	3.0 (0–15) [Mean 3.3]	3.0 (0–15) [Mean 3.8]	0.51
Median P:F Ratio: Ratio of Arterial Pressure (mmHg) of Oxygen (PaO ₂) to Fraction of Inspired Oxygen (FiO ₂) (range)**	169 (122–325)	183 (94–314)	176 (94–325)	0.84
COVID therapy				–
Hydroxychloroquine	0	2	2 (5%)	
Remdesivir	14	15	29 (72%)	
Dexamethasone	19	10	29 (72%)	
Anti-coagulants				–
Enoxaparin	14	17	31 (78%)	
Aspirin	5	1	6 (15%)	
Heparin	6	2	8 (20%)	
Rivaroxaban	1	0	1 (3%)	
Apixaban	2	1	3 (8%)	
Warfarin	0	1	1 (3%)	
Single-agent	11	15	26 (65%)	
Multi-agent	9	5	14 (35%)	
None	0	0	0%	
Median days of COVID drugs (range)	7.5 (1–11)	7.5 (0–16)	7.5 (0–16)	0.87
Median start day of RT (range) ^{§§}	3 (1–8)	–	3 (1–8)	–
Median start day of COVID drugs (range) ^{§§}	1 (1–5)	2.5 (1–6)	1 (1–6)	0.02

* The non-parametric p-value is calculated by a Wilcoxon rank sum test for numerical covariates and Fisher's exact test for 2-level categorical covariates.

** P:F ratio normal range in ARDS: 300 to 200 is mild, 200 to 100 is moderate and less than 100 is severe.

enrollment. Median CCI comorbidity scores were: 3 (range 1–12). Median duration of symptoms prior to admission was 10 (range 1–15) and 7 (2–14) days following LD-RT and for controls, respectively ($p = 0.10$). Median oxygen supplementation requirement at the time of admission was 3 liters (range 0–15) for both cohorts ($p = 0.51$). Disease severity, as assessed by median ratio of arterial pressure (mmHg) of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) [P:F ratio] was not statistically different between the cohorts: 169 (range 122–325) compared to 183 (range 94–314), respectively ($p = 0.84$). Patients in both the LD-RT and control cohorts received COVID-directed drug therapy for a median of 7.5 days ($p = 0.87$). LD-RT was administered at median hospital day 3 (range 1–8). Patients in the LD-RT cohort received COVID-directed therapy (dexamethasone and/or remdesivir, etc.) at a median start time of hospital day 1 (range 1–5), compared to 2.5 (range 1–6) in controls ($p = 0.02$).

LD-RT was delivered safely with dexamethasone and/or remdesivir without acute toxicity or reflex clinical, radiographic, or serologic worsening of pneumonia. Intubation rates reduced by 56% following LD-RT compared to controls (14% vs. 32% in controls), translating to freedom from intubation at day 28 (Fig. 2) of

86% following LD-RT compared to 68% in controls, which approached statistical significance ($p = 0.09$). Intubation-free survival was 77% compared to 68%, respectively ($p = 0.17$). Statistical differences in median time to clinical recovery (TTCR) and time from admission to clinical recovery between the cohorts were not detectable ($p = 0.37$, Table 2). Median hospital duration was 10.5 days (range 5–33) in the LD-RT cohort compared to 11.5 days (range 3–42) in controls ($p = 0.61$). Additional treatment outcomes for the entire cohort are reported in Table 2.

Radiographic improvement was not detectable between the LD-RT and control cohorts ($p = 0.72$, Fig. 4). Representative CT images from patients with high burden of pulmonary consolidations associated with COVID-19 that radiographically worsened following LD-RT, as well as an example of radiographic improvement, are shown in Fig. 5.

Hematologic, renal, cardiac, chemistry, clotting, and inflammatory markers were tracked from the first day of hospitalization. Plotted medians and inter-quartile ranges of serologic biomarkers for both LD-RT and control patients are shown in Fig. 6. Decline of inflammatory biomarker C-reactive protein (CRP) was statistically superior in the LD-RT cohort compared with controls

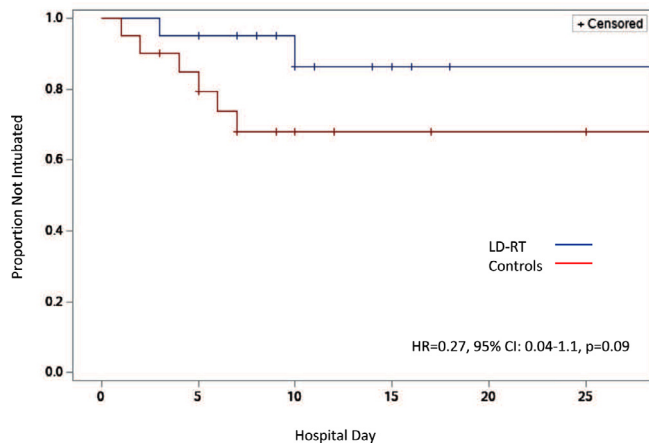


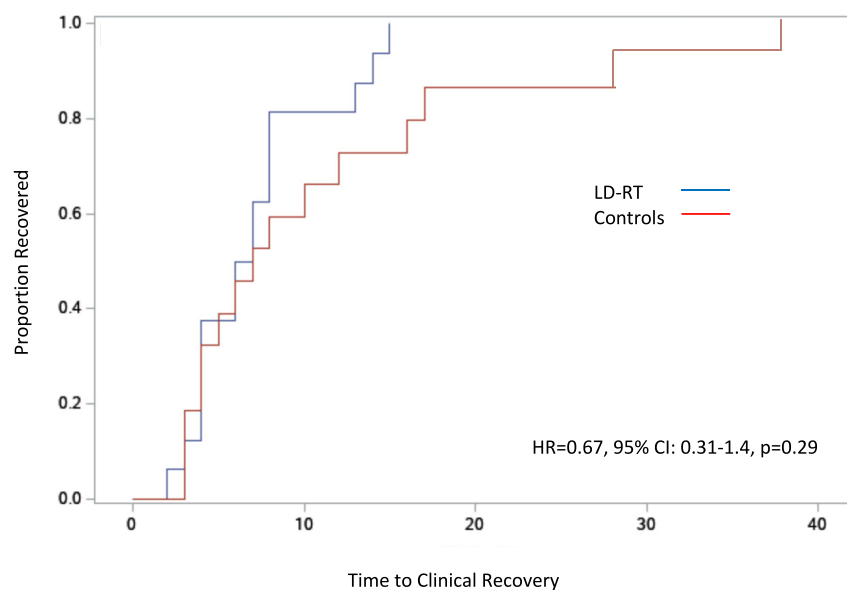
Fig. 2. Freedom from intubation for the entire LD-RT cohort vs. matched controls.

($p = 0.02$). Cardiac marker, creatine kinase, started higher in LD-RT patients, but was also significantly reduced over controls ($p < 0.01$). Lower troponin-1 levels in the LD-RT were not statistically detectable ($p = 0.29$). Liver function remained normal following LD-RT, while transaminitis occurred in some controls, but did not reach significance (AST $p = 0.35$; ALT $p = 0.60$). Neutrophil-to-lymphocyte ratio trended higher following LD-RT ($p = 0.12$). There were no detectable reductions ($p = 0.80$) in white blood cell count. No neutropenia was observed. Renal biomarker creatinine was not significantly affected ($p = 0.75$). Myoglobin, erythrocyte sedimentation rate, lactate dehydrogenase, monocyte count, ferritin, fibrinogen, procalcitonin, and interleukin-6 trended downward after LD-RT but did not reach significance or control comparisons were not different or not available (Fig. 6).

Sixteen of 20 irradiated patients (80%) experienced durable decline in CRP levels over 3 days following LD-RT and were classified as *CRP responders*. The remaining four (20%) experienced sequential rises in CRP above elevated baseline levels and were

classified as *non-responders* (Fig. 6, bottom right pane. Supplemental Fig. 1). Outcomes for these 16 LD-RT responders compared with their 16 matched controls are shown in Fig. 3 and Table 3 ($n = 32$). Freedom from intubation was 100% for LD-RT responders compared to 66% for matched controls ($p = 0.01$, Table 3, Fig. 3d), translating to a reduction in intubation from 34% to 0%. As a categorical variable, none of the LD-RT responders died or required intubation, compared to 5 of 16 matched controls ($p = 0.04$, Table 3). Median duration of time intubated was 0 days for LD-RT responders vs. 10 days in those matched controls who required intubation. Median time to clinical recovery was 7.5 days (range 2–15) in LD-RT responders and 7 days (range 3–38) in controls but maximum recovery time was reduced (15 vs 38 days), shown as upper curve separation ($p = 0.29$, Fig. 3a). Median time from admission to clinical recovery was 9.5 days (range 1–17) following LD-RT compared to 9 days (range 1–41) in controls, with reduction in maximum recovery time (17 vs. 41 days) and upper curve separation ($p = 0.26$, Fig. 3b). Median hospital duration was 10 days (range 5–18) for LD-RT responders compared to 10 days (range 3–42) for controls, with reduced maximum hospitalization (18 vs 42 days) and upper curve separation ($p = 0.22$, Fig. 3c). The proportion of patients requiring prolonged hospitalization of 3 weeks or longer fell from 30% to 10% with the addition of LD-RT ($p = 0.24$). Of the 4 patients who were CRP non-responders in the LD-RT cohort, 2 required intubation, 3 died by day 28 (1 refused intubation), and the 4th died on day 33.

CRP decline over 3 days was observed in 18 of 20 controls (90%) but was not predictive of outcome. Six of 18 CRP responder-controls (33%) required intubation despite post-drug CRP decline and both of the non-responders recovered without intubation ($p = 0.36$). Mean total time requiring oxygen supplementation prior to recovery was 10.5 days (range 4–18) in LD-RT responders compared to 14.3 days (range 3–42) in controls ($p = 0.24$). Average daily oxygen maximums per patient were 32% lower at 7.6 L/min (mean) in LD-RT responders compared to 24 L/min in controls ($p = 0.03$, Table 3). Mean aggregated amount of oxygen supplementation (maximum daily L/min \times total days oxygenated per patient)



*Defined from LD-RT (top) or first day of COVID drug in controls (bottom)

Fig. 3a. Time to clinical recovery for LD-RT responders vs. controls.

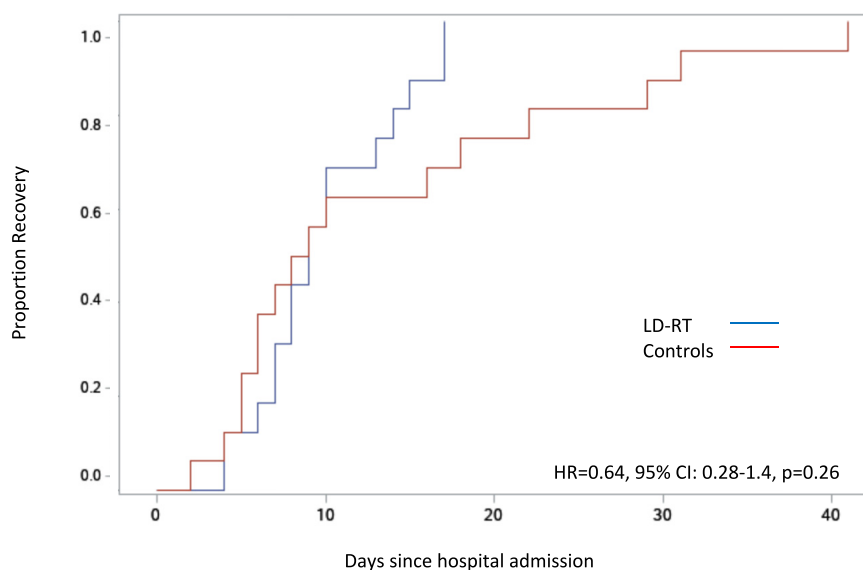


Fig. 3b. Time from admission to clinical recovery for LD-RT responders vs. controls.

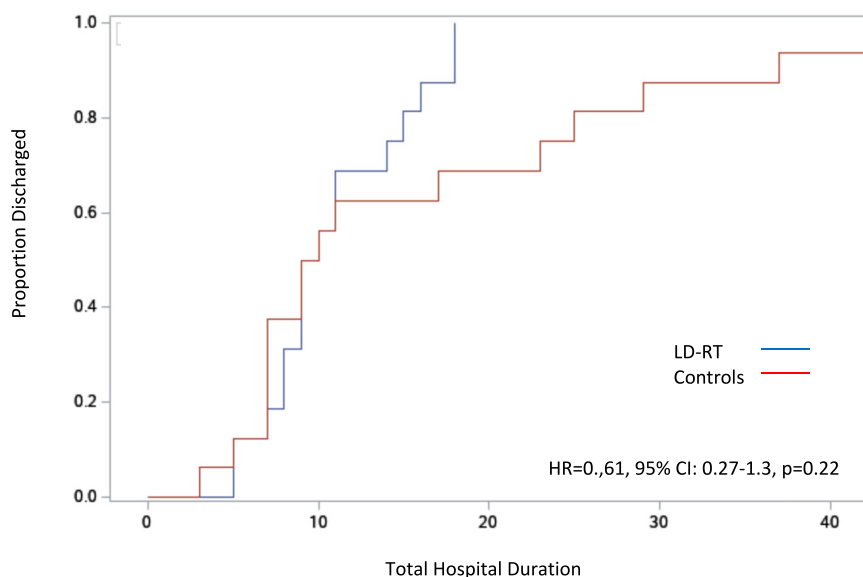


Fig. 3c. Total hospital duration for LD-RT responders vs. controls.

was 56% lower at 46.2 vs. 104.5 L/min * days, respectively ($p = 0.06$). Average number of days febrile (any fever) was 1.4 days (range 0–9) vs. 3.3 days (range 0–12), respectively ($p = 0.14$, [Table 3](#)), in favor of LD-RT responders. Rates of prolonged hospitalizations of 21+ days fell from 31% to 0% among CRP responders compared to matched controls ($p = 0.04$). Additional treatment outcomes for LD-RT responders are reported in [Table 3](#).

There were no recorded acute toxicities. The 3 deaths (15%) observed at day 28 in the LD-RT cohort are described in [Table 2](#). Two patients had COVID-19 symptoms escalate despite LD-RT; both went on to intubation and could not be weaned. The third was a patient with a large brain meningioma who died after family removed opted to remove supportive high-flow oxygen. Contrary to published mortality rates, none of the 20 blindly selected con-

trols died. No other toxicity, airway emergencies, or adverse events were observed following LD-RT.

Discussion

This report describes 28-day outcomes of an exploratory phase II trial of whole-lung, low-dose radiation therapy (LD-RT) given concurrently with standard drug treatments for COVID-19-related pneumonia. Intubation rates declined 56% following LD-RT compared to controls, from 32% to 14%, which approached significance despite a sample size of only 40 patients ($p = 0.09$, [Fig. 2](#)). This reproduces findings from prior reports, where intubation fell from 40% to 10% following LD-RT [17]. Among CRP responders, intubation was not required in any patient, compared to 31% of

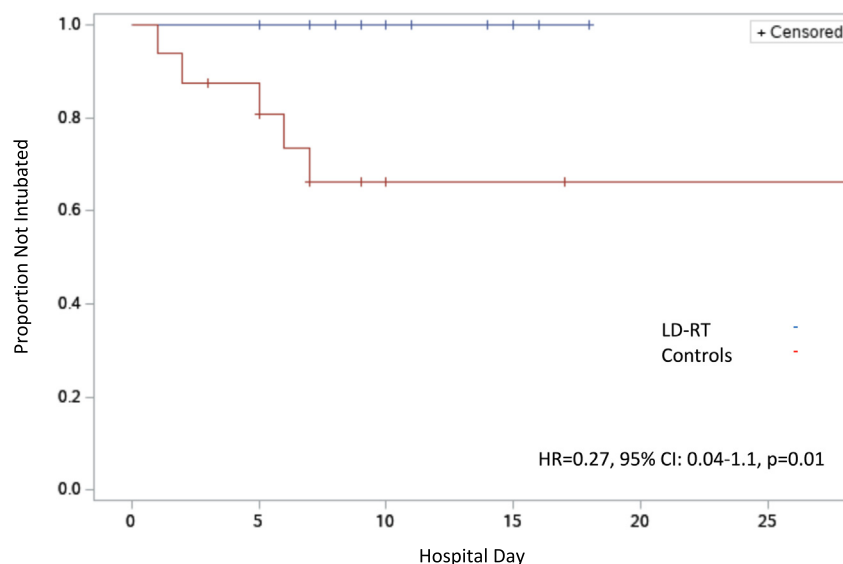


Fig. 3d. Intubation-free survival for LD-RT responders vs. controls.

Table 2

Day 28 outcomes for the entire LD-RT cohort vs. matched controls (n = 40).

Variables	LD-RT Cohort (N = 20)		Control Cohort (N = 20)		p-value*					
Categorical	Outcome	Yes	No	Yes	No					
	Clinically Recovered	16 (80%)	4 (20%)	17 (85%)	3 (15%)	1.0				
	Mechanically Ventilated	2 (10%)	18 (90%)	6 (30%)	14 (70%)	0.24				
	Deceased**	3 (15%)	17 (85%)	0	20 (100%)	0.23				
Continuous	Hospital Duration 21+ days	2 (10%)	18 (90%)	6 (30%)	14 (70%)	0.24				
	Hospital Duration (days)	Median	10.5	Range	5–33	Median	11.5	Range	3–42	0.61
		Mean	12.5			Mean	15.8			
	Duration of Oxygen Supplementation (days)	10.5		4–33		9.5		3–42		0.72
		Mean	12.1			Mean	13.9			
	Duration of Ventilation, if intubated (days)	9.5		5–14		9.5		1–34		0.87
		Mean	9.5			Mean	13			
	Average Daily Maximum Oxygen Need (L/min)	6.7		1.5–81.5		4.0		1.5–86		0.91
		Mean	15.3			Mean	23.1			
	Cumulative Cohort Oxygenation Need (max daily L/min * days oxygenated)	48.3		6–1591		60.3		7.5–3636		0.73
Mean		210			Mean	530				
Days Febrile	1.0		0–9		1.0		0–12		0.91	
	Mean	2.0			Mean	3.0				
Time-to-Event	Median		Range		Median		Range			
	Time to Clinical Recovery [TTCR] (days)	7.5		2–30		7		2–38	0.37	
	Time from Admission to Clinical Recovery (days)	10		4–33		9		2–41	0.37	
	Freedom from Intubation at day 28 (percent, 95% CI)	Not reached		86 (54–97)		Not reached		68 (42–84)	0.09	
Intubation-free Survival at day 28 (percent, 95% CI)	Not reached		77 (42–92)		Not reached		68 (42–84)	0.17		

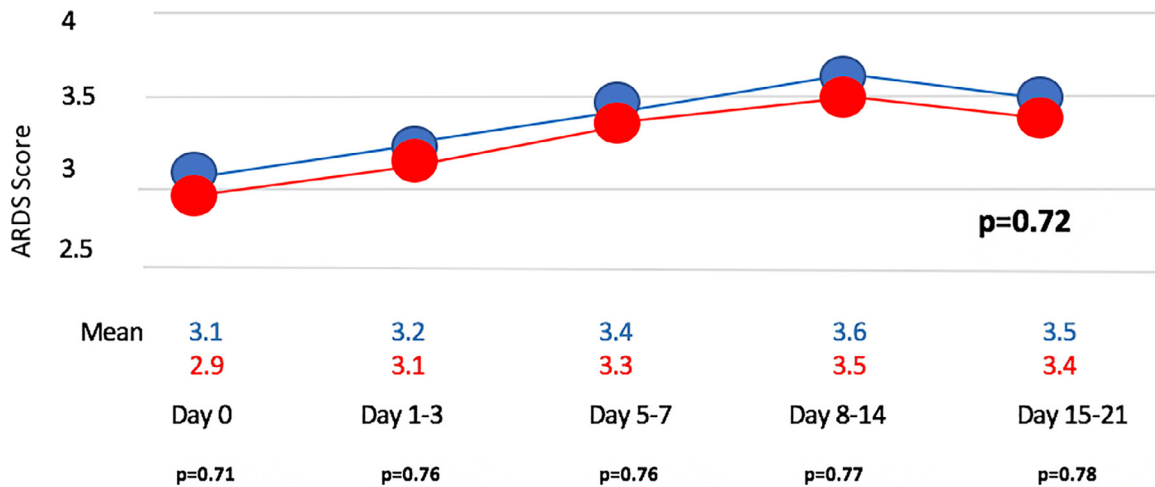
* The non-parametric p-value is calculated by a Wilcoxon rank sum test for numerical covariates, Fisher's exact test for 2-level categorical covariates, and log-rank test for time-to-event covariates with medians reported from Kaplan-Meier curves.

** (1) Patient around 80–85 years old with do-not-resuscitate orders, whose family refused intubation, de-escalated care, and pursued comfort measures. Died hospital day 11, hypoxic after refusing high-flow oxygen support. (2) Patient around 55–60 years old who received dexamethasone and LD-RT before intubation. Died on hospital day 8 despite aggressive care. (3) Patient around age 70–75 who received dexamethasone and LD-RT before intubation. Died on hospital day 25 despite aggressive care.

matched controls. An ongoing phase III trial has been powered based on these findings. A sample size of 150 randomized patients will be used to determine LD-RT's effect on intubation rates and intubation-free survival.

TTCR and hospital duration were improved following LD-RT without drug therapies in a prior report (n = 20) [17]. In this study, TTCR and prolonged hospitalizations were improved among CRP responders, but not in the total cohort despite a larger sample size

(n = 40, Table 2). Outcomes may have been confounded by an unusually favorable control population. Controls were not able to undergo oxygen weaning trials prior to enrollment, were not all ill enough to prioritize enrollment on therapeutic trials, and were specifically excluded if they experienced rapid clinical decline on admission. These factors may have introduced a favorable selection bias among controls, corroborated by the surprising observation that no deaths were observed among controls.



ARDS Scale Scores- Radiation Cohort						ARDS Scale Scores- Control Cohort						
ID	Day 0	Day 1-3	Day 4-7	Day 8-14	Day 15-21	ID	Day 0	Day 1-3	Day 4-7	Day 8-14	Day 15- 21	
1	5	NA (5)	5	4 (day 8)	NA (4)	1	2	NA (2)	2	NA (2)	NA (2)	
2	2	NA (2)	2	4 (day 9)	NA (4)	2	4	NA (4)	NA (4)	NA (4)	NA (4)	
3	1	NA (1)	1	NA (1)	NA (1)	3	3	4 (day 3)	5	4.3*	4.4*	
4	2	2	2	NA (2)	NA (2)	4	2	2	3 (day 5)	NA (3)	NA (3)	
5	2	NA (2)	2	2	NA (2)	5	2	NA (2)	NA (2)	NA (2)	NA (2)	
6	4	NA (4)	4	NA (4)	NA (4)	6	2	NA (2)	4 (day 5)	NA (4)	3 (day 15)	
7	5	5	4.8*	NA (4)	NA (4)	7	2	4.5*	4 (day 2)	NA (4)	NA (4)	
8	5	NA (5)	4 (day 5)	5 (day 9)	5	8	4	4	2 (day 6)	NA (2)	NA (2)	
9	4	5 (day 3)	5	2 (day 8)	NA (2)	9	4	2 (day 1)	4 (day 6)	4	4	
10	2	NA (2)	4 (day 6)	NA (4)	NA (4)	10	4	NA (4)	NA (4)	NA (4)	NA (4)	
11	4	NA (4)	3 (day 7)	NA (3)	NA (3)	11	2	NA (2)	NA (2)	NA (2)	NA (2)	
12	1	NA (1)	1	4.6*	3.8*	12	4	NA (4)	NA (4)	5 (day 12)	5	
13	3	NA (3)	4 (day 5)	4	NA (4)	13	2	2	NA (2)	NA (2)	NA (2)	
14	4	NA (4)	4	NA (4)	NA (4)	14	2	NA (2)	2.5*	3	2.5*	
15	2	NA (2)	5 (day 4)	4*	NA (4)	15	5	5	4 (day 5)	4	NA (4)	
16	3	NA (3)	3	4.7*	4 (day 13)	16	2	NA (2)	NA (2)	NA (2)	NA (2)	
17	4	NA (4)	NA (4)	NA (4)	NA (4)	17	1	NA (1)	2 (day 4)	NA (2)	NA (2)	
18	3	4 (day 2)	3 (day 5)	4	NA (4)	18	3	4 (day 3)	4	5	NA (5)	
19	4	NA (4)	NA (4)	4	4	19	5	5	5	5	NA (5)	
20	2	NA (2)	3 (day 6)	NA (3)	NA (3)	20	4	NA (4)	NA (4)	NA (4)	NA (4)	
Mean	3.1	4 (3.2)	3.3 (3.4)	3.8 (3.6)	4.2 (3.5)	Mean	2.9	3.6 (3.1)	3.5 (3.3)	4.1 (3.5)	3.9 (3.4)	
LD-RT: 9 of 19 any radiographic improvement (47%)						Controls: 7 of 14 any radiographic improvement (50%)						p=0.88
LD-RT: 10 of 19 any radiographic decline (53%)						Controls: 9 of 14 any radiographic decline (64%)						p=0.50
Median Time to First Improvement (n=9): 8 days (IQR 6-13.5)						Median time to first improvement (n=7): 6 days (IQR 2-15)						

RED= first radiographic worsening. BLUE=first radiographic improvement.

*Mean ARDS score over the date range specified.

-LD-RT patient #7: day 4 (5), 5 (5), 6, (5), 7 (4).

-LD-RT patient #12: day 8 (4), 10 (5), 12 (5), 16 (5), 17 (4), 18 (4), 20 (2).

-LD-RT patient #15: day 10 (5), 14 (3).

-LD-RT patient #16: day 9 (5), 11 (5), 13 (4).

-Control patient#3: day 8 (5), 10 (4), 12 (4), 15 (4), 16 (4), 18 (5), 20 (5), 21 (4).

-Control patient #7: day 1 (5), 2 (4), 3 (4).

-Control patient #14: day 3 (5), 3 (11, 12, 13, 14, 18), 2 (20).

Statistical significance testing for categorical (percent improved per cohort) and continuous variables (mean ARDS scale) performed using chi-square test and t-test, respectively. Day 0: first day of COVID-19 intervention, defined as the date of LD-RT delivery (in the radiation cohort), as the first day of administration of COVID-19 therapy (in control patients). Gray= Control patients (#2, 5, 10, 11, 16, 20) and LD-RT patient #17 with insufficient x-rays for comparison (<2). NA=not available. Parentheses = data carried forward.

Fig. 4. ARDS X-ray scale scores by hospital day.

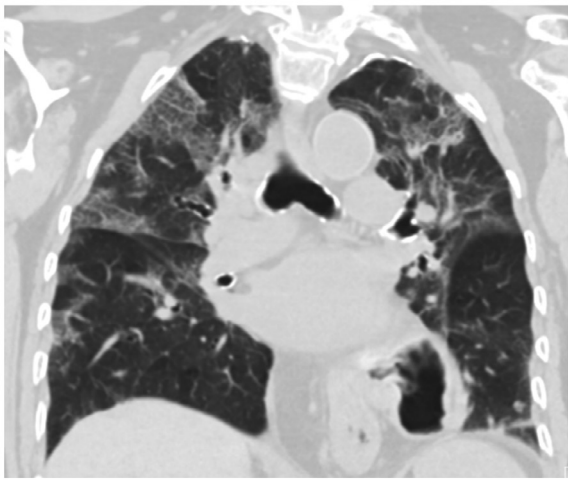
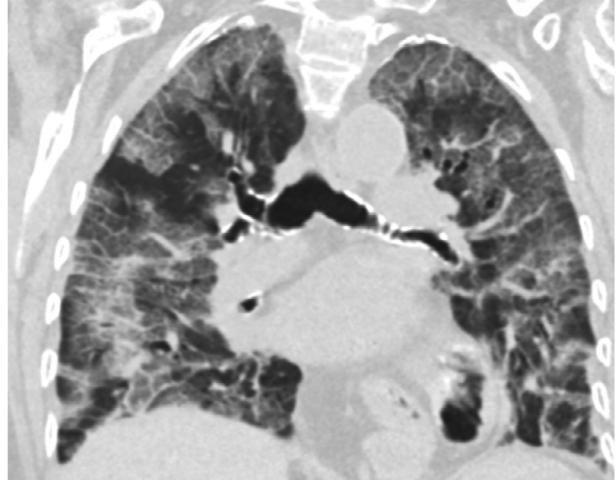
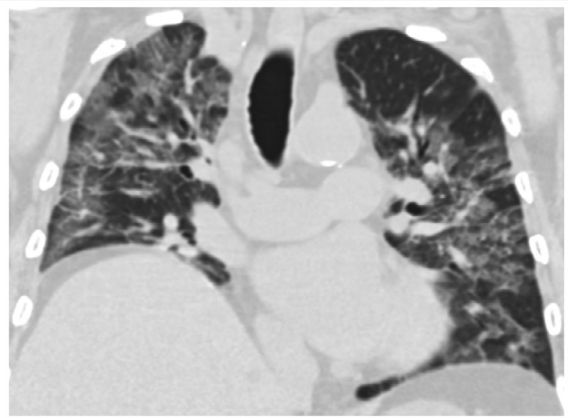
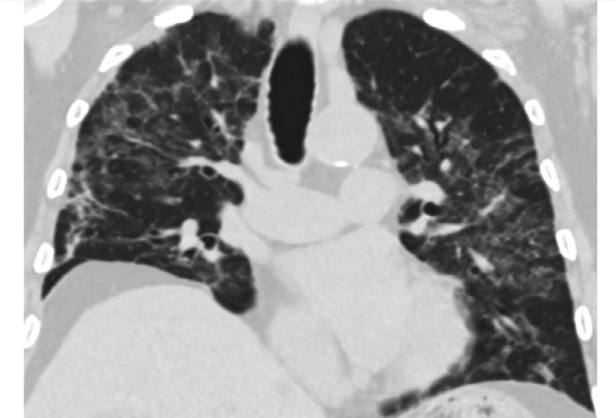
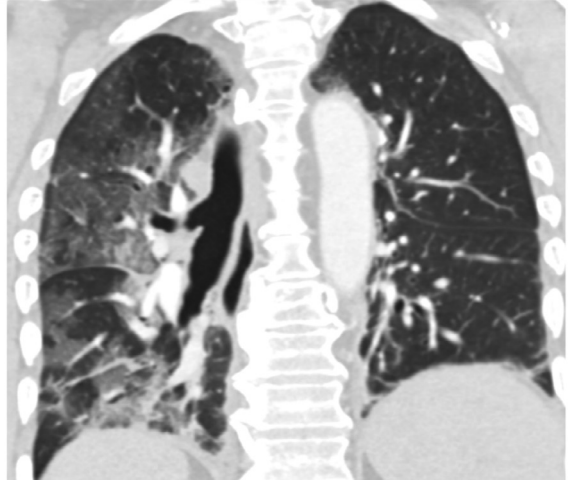
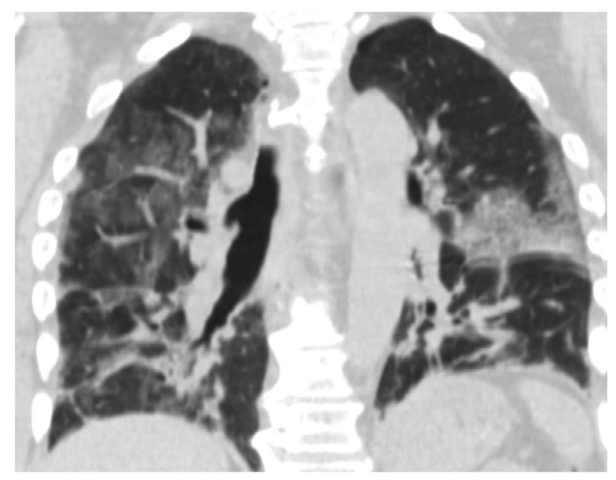
	Day 3	Day 10 (not improved)
LD-RT Patient Example 1		
	Day 9	Day 14 (improved)
LD-RT Patient Example 2		
	Day 1	Day 9 (not improved)
LD-RT Patient Example 3		
	Patients who did and did not demonstrate radiographic improvements following LD-RT	

Fig. 5. Radiographic changes after low-dose whole-lung radiotherapy (LD-RT).

A recent randomized trial of 11 intubated patients with advanced COVID-19 evaluated LD-RT and observed no clinical benefit [20]. This study was small and lacked prior knowledge of effect size to inform its power analysis but is the only published

randomized trial to date. We also observed little improvement in CRP non-responders. Both CRP rise following LD-RT and intubation may be indicative of disseminated or more severe COVID-19. Mechanistically, LD-RT may be utilized best as an extinguisher of

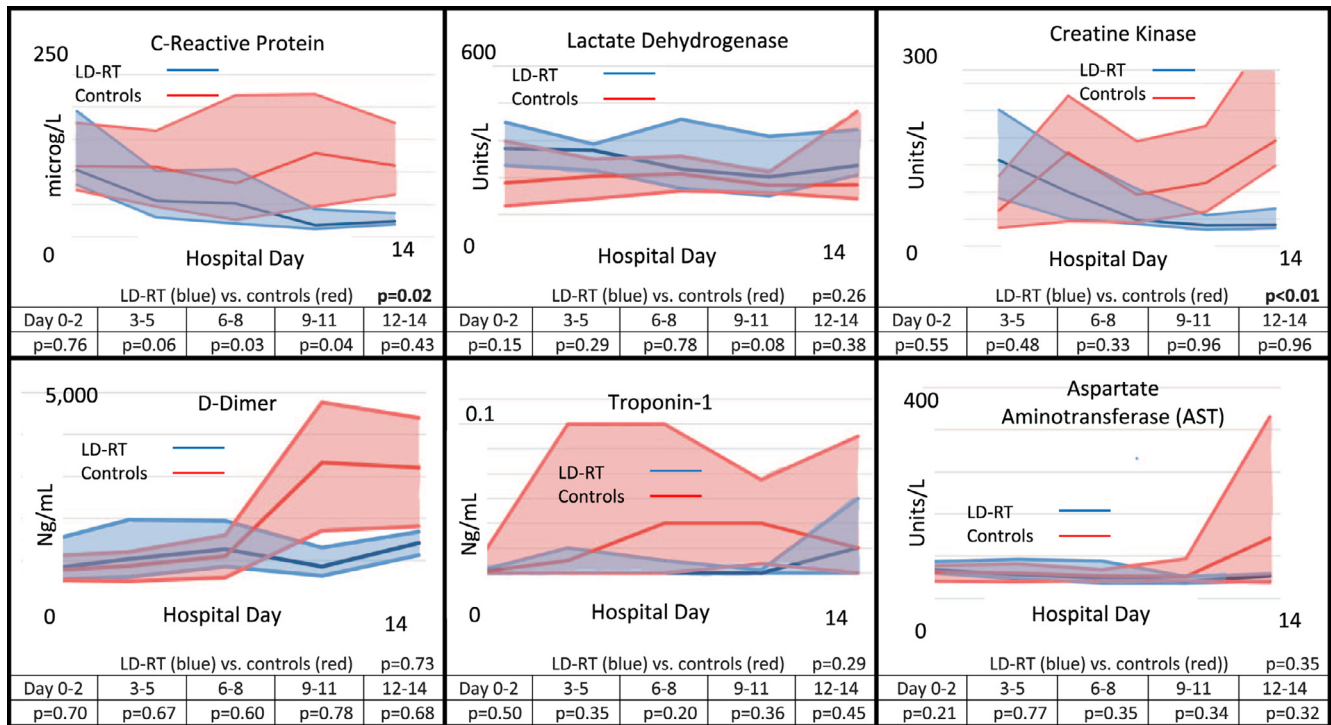


Fig. 6. Serologic median and interquartile ranges after low-dose whole-lung radiation therapy with concurrent dexamethasone and/or remdesivir.

Table 3
Day 28 outcomes for LD-RT responders vs. matched controls (n = 32).

Variables	LD-RT Responders (N = 16)		Control Cohort (N = 16)		p-value*	
Categorical	Outcome	Yes	No	Yes	No	
	Clinically Recovered	16 (100%)	0	13 (81%)	3 (19%)	0.23
	Mechanically Ventilated	0	16 (100%)	5 (31%)	11 (69%)	0.04
	Deceased	0	16 (100%)	0	16	1.0
	Hospital Duration 21+ days	0 (0%)	16 (100%)	5 (31%)	11 (69%)	0.04
Continuous	Median	Range	Median	Range		
	Hospital Duration (days)	9.5	5–18	9.5	3–42	0.15
	Duration of Oxygen Supplementation (days)	Mean 10.8		Mean 15.5		
		9.5	4–18	9.5	3–42	0.24
	Duration of Ventilation, if intubated (days)	Mean 10.5		Mean 14.3		
		0	NA	10	1–34	-
		Mean 14.2		Mean 14.2		
	Average Daily Maximum Oxygen Need (L/min)	4.8	1.5–30	7.1	1.5–86	0.03
		Mean 7.6		Mean 24.0		32% lower
	Cumulative Cohort Oxygenation Need (max daily L/min * days oxygenated)	46.2	6–454	104.5	8–3636	0.06
	Mean 94.2		Mean 593		56% lower	
Days Febrile	1.0	0–9	1.0	0–12	0.14	
	Mean 1.4		Mean 3.3			
Time-to-Event	Median	Range	Median	Range		
	Time to Clinical Recovery (days)	7	2–15	7	3–38	0.29
	Time from Admission to Clinical Recovery (days)	9.5	4–17	9	2–41	0.26
	Freedom from Intubation at day 28 (percent, 95% CI)	Not reached	100%	Not reached	66 (36–84)	0.01
	Intubation-free Survival at day 28 (percent, 95% CI)	Not reached	100%	Not reached	66 (36–84)	0.01
Intubation-free Survival at day 28 (percent, 95% CI)	Not reached	100%	Not reached	66 (36–84)	0.01	

local cascading hyperimmunity prior to dissemination and severe organ damage. The RECOVERY trial evaluated dexamethasone with a sample size was over 6000, where 1500 deaths had to be observed to detect a survival benefit for steroids [23]. The small sample size (n = 22) in the aforementioned randomized trial represents less than 1% of the power needed to detect a benefit equal to that of dexamethasone [23].

Our results complement recent preclinical data reporting reduced inflammatory cytokines IL-6 and INF-gamma, and increased anti-inflammatory cytokine IL-10 in C57BL/6 mice with induce ARDS. We report serologic reductions following LD-RT compared to controls: C-reactive protein (p = 0.02) and creatine kinase (p < 0.01), as well as cardiac marker troponin-1, liver function, and coagulopathies (Fig. 6), suggesting LD-RT may prevent “long-

COVID" sequelae and may be detectable with larger sample sizes. LD-RT did not exacerbate but rather decreased inflammation and did not promote but rather reduced biomarkers of cardiac injury. As of July 2021, more than 186 million people globally are confirmed as infected with SARS-CoV-2, leading to over 4 million known COVID-19-related deaths. The worldwide accessibility of LD-RT as a rapid and inexpensive potential treatment merits further study, especially in countries with limited access to drugs or vaccines.

Our study has numerous limitations: a blindly-matched but non-randomized design, exploratory intent, small patient numbers, differing control treatments, differing laboratory and imaging schedules between the LD-RT and control cohorts, variable times of symptom onset, limited imaging (Fig. 5) and serological (Fig. 6) studies in the control cohort before intervention and beyond 7 days, and lack of detailed viral load evaluations. Future work with LD-RT will include a phase III design, lower dose ranges, detailed CD-8 and CD-4T-cell activation studies, changes in B-cell profiles, antibody formation, cytokine analysis, and neutralization tests.

Conclusion

A cohort of hospitalized patients with COVID-19 safely received LD-RT concurrently with dexamethasone and/or remdesivir, required fewer intubations ($p = 0.09$), and showed reductions in inflammatory and cardiac biomarkers. Patients whose CRP declined over 3 days following LD-RT had 100% survival without intubation, fewer prolonged hospitalizations, and lower burden of oxygen requirements. Early intervention with LD-RT after oxygen dependency but prior to intubation may be an optimal therapeutic timeline. Further clinical trials are justified.

[Clinical Trial Registration: NCT04433949].

Authors contributions

Clayton Hess: conceptualization, design, data acquisition, data analysis, data interpretation, manuscript drafting/revision and final draft review. Tony Eng: data acquisition, manuscript drafting/revision and final draft review. Tahseen Nasti: conceptualization, design, data acquisition, data analysis, data interpretation, manuscript drafting/revision and final draft review. Vishal Dhere: data acquisition, manuscript drafting/revision and final draft review. Troy Kleber: data acquisition, manuscript drafting/revision and final draft review. Jeff Switchenko: design, data analysis, manuscript drafting/revision and final draft review. Brent Weinberg: data acquisition, data analysis, manuscript drafting/revision and final draft review. Nadine Roupheal: design, data acquisition, data analysis, data interpretation, manuscript drafting/revision and final draft review. Sibio Tian: data acquisition, manuscript drafting/revision and final draft review. Soumon Rudra: data acquisition, manuscript drafting/revision and final draft review. Luisa Taverna: data acquisition, manuscript drafting/revision and final draft review. Alvaro Perez: data acquisition, manuscript drafting/revision and final draft review. Rafi Ahmed: conceptualization, design, data interpretation, manuscript drafting/revision and final draft review. Mohammad Khan: conceptualization, design, data acquisition, data interpretation, manuscript drafting/revision and final draft review.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.10.003>.

References

- [1] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
- [2] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- [3] Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med* 2020;382:2012–22.
- [4] Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020.
- [5] Calabrese EJ. X-Ray treatment of carbuncles and furuncles (boils): a historical assessment. *Hum Exp Toxicol* 2013;32:817–27.
- [6] Calabrese EJ, Dhawan G. How radiotherapy was historically used to treat pneumonia: could it be useful today? *Yale J Biol Med* 2013;86:555–70.
- [7] Calabrese EJ, Dhawan G. The historical use of radiotherapy in the treatment of sinus infections. *Dose Response* 2013;11:469–79.
- [8] Calabrese EJ, Dhawan G, Kapoor R, Kozumbo WJ. Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose. *Hum Exp Toxicol* 2019;38:888–98.
- [9] Fischer A, Virelizier JL, Arenzana-Seisdedos F, et al. Treatment of four patients with erythrophagocytic lymphohistiocytosis by a combination of epipodophyllotoxin, steroids, intrathecal methotrexate, and cranial irradiation. *Pediatrics* 1985;76:263–8.
- [10] Kienapfel H, Koller M, Wüst A, et al. Prevention of heterotopic bone formation after total hip arthroplasty: a prospective randomised study comparing postoperative radiation therapy with indomethacin medication. *Arch Orthop Trauma Surg* 1999;119:296–302.
- [11] Olschewski T, Seegenschmiedt MH. Radiotherapy for bony manifestations of Langerhans cell histiocytosis. Review and proposal for an international registry. *Strahlenther Onkol* 2006;182:72–9.
- [12] Schuster J, Saraiya S, Tennyson N, et al. Patient-reported outcomes after electron radiation treatment for early-stage palmar and plantar fibromatosis. *Pract Radiat Oncol* 2015;5:e651–8.
- [13] Mezziani L, Robert C, Classe M, et al. Low doses of radiation increase the immunosuppressive profile of lung macrophages during viral infection and pneumonia. *Int J Radiat Biol* 2021;110:1283–94.
- [14] Salomaa S, Cardis E, Bouffler SD, et al. Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence? *Int J Radiat Biol* 2020;96:1224–7.
- [15] Lara PC, 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;23:27–9.
- [16] Prasanna PG, Woloschak GE, DiCarlo AL, et al. Low-Dose Radiation Therapy (LDRT) for COVID-19: Benefits or Risks? *Radiat Res* 2020;194:452–64.
- [17] Hess CB, Buchwald ZS, Stokes WA, et al. Immunomodulatory low-dose whole-lung radiation for patients with COVID-19-related pneumonia. *Int J Radiat Oncol Biol Phys* 2020;108:1401.
- [18] Hess CB, Buchwald ZS, Stokes W, et al. Low-dose whole-lung radiation for COVID-19 pneumonia: Planned day 7 interim analysis of a registered clinical trial. *Cancer* 2020;126:5109–13.

- [19] Ameri A, Rahnama N, Bozorgmehr R, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: short course results. *Int J Radiat Oncol Biol Phys* 2020.
- [20] 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.
- [21] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- [22] Taylor E, Haven K, Reed P, et al. A chest radiograph scoring system in patients with severe acute respiratory infection: a validation study. *BMC Med Imaging* 2015;15:61.
- [23] Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021;384:693–704.