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COVID-19 Scientific Communication

Immunomodulatory Low-Dose Whole-Lung Radiation for Patients with Coronavirus Disease 2019-Related Pneumonia

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Purpose: Phase 1 clinical trials have established low-dose, whole-lung radiation therapy (LD-RT) as safe for patients with coronavirus disease 2019 (COVID-19)-related pneumonia. By focally dampening cytokine hyperactivation, LD-RT may improve disease outcomes through immunomodulation.

Methods and Materials: Patients with COVID-19-related pneumonia were treated with 1.5 Gy whole-lung LD-RT, followed for 28 days or until hospital discharge, and compared with age- and comorbidity-matched controls meeting identical disease severity criteria. Eligible patients were hospitalized, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) positive, had radiographic consolidations, and required supplemental oxygen but had not rapidly declined on admission or before drug therapy or LD-RT. Efficacy endpoints were time to clinical recovery, radiographic improvement, and biomarker response.

Results: Ten patients received whole-lung LD-RT between April 24 and May 24, 2020 and were compared with 10 control patients blindly matched by age and comorbidity. Six controls received COVID-19 drug therapies. Median time to clinical recovery was 12 days in the control cohort compared with 3 days in the LD-RT cohort (hazard ratio 2.9, $P = .05$). Median

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Data Sharing Statement: Data analyzed included clinical datapoints as described in the methods section for primary and secondary outcomes. Select de-identified raw data for each patient have been made available in the supplemental materials while aggregated cohort data are available for reuse upon request after case-by-case consideration and with data-use agreement.

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time to hospital discharge (20 vs 12 days, $P = .19$) and intubation rates (40% vs 10%, $P = .12$) in the control and LD-RT cohorts were compared. Median time from admission to recovery was 10 versus 13 days ($P = .13$). Hospital duration average was 19 versus 22.6 days ($P = .53$). Average hospital days on supplemental oxygen of any duration was 13.1 versus 14.7 days ($P = .69$). Average days with a documented fever was 1 versus 4.3 days ($P = .12$). Twenty-eight−day overall survival was 90% for both cohorts. The LD-RT cohort trended toward superior rates of improved radiographs ($P = .12$) and delirium ($P < .01$). Statistically significant reductions were observed in numerous hematologic, cardiac, hepatic, and inflammatory markers. **Conclusions:** A prospective cohort of predominantly elderly hospitalized patients with COVID-19-related pneumonia were recovered to room air quicker than age- and comorbidity-matched controls, with trending or significant improvements in delirium, radiographs, and biomarkers, and no significant acute toxicity. Low-dose, whole-lung radiation for patients with COVID-19-related pneumonia appears safe and may be an effective immunomodulatory treatment. Larger prospective randomized trials are needed to define the efficacy of LD-RT for COVID-19.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its novel viral syndrome, the coronavirus disease 2019 (COVID-19), have brought unprecedented global death and disruption. Although most infected patients exhibit an indolent course, those with advanced age or comorbidities face higher risk of respiratory failure, mediated by a cascading, hyperinflammatory, macrophage activation event in the lungs,[1] and can face mortality rates of 30% to 80% once dependent on mechanical ventillation.[2-4] Cytokine-mediated injurious mechanisms have been described previously,[5] leading to damage of both lungs and extrapulmonary organs.[6-8] Numerous prior articles have described the mechanistic pathways whereby low-dose radiation therapy (LD-RT) could provide a therapeutic advantage.[9-16] The first exploration into this intervention, a 7-day interim safety analysis of 5 initial patients treated on a phase 1 trial, investigated safety of LD-RT using a dose of 1.5 Gy and detected no acute toxicity or reflex exacerbation of the cytokine storm.[17] Pre-print publication of this safety data was first released on June 8, 2020.[18] Thereafter investigators from Tehran, Iran, reported outcomes of 5 patients treated with 0.5 Gy also reporting safety.[19] A national workshop was recently convened and published a consensus report that neither refuted or endorsed LD-RT as a treatment, but came out in favor of allowing further exploration of LD-RT for COVID-19 in both human clinical trials and animal studies.[20] Twenty-eight-day outcomes of 10 initial patients treated on the first modern prospective trial of LD-RT for SARS-CoV-2 pneumonia are presented herein, compared with a control cohort meeting the same disease severity criteria and matched for age and comorbidities

Methods

Trial design

The RESCUE 1-19 trial is an investigator-initiated, single-institution combined phase 1 and 2 trial aimed to determine safety and to explore preliminary efficacy of single-fraction, whole-lung LD-RT for hospitalized and oxygen-dependent patients with SARS-CoV-2 pneumonia. Clinical Trial Registration Number NCT04366791. The research protocol was approved by the Emory University institutional review board. All participants gave written informed consent before any study procedures. Informed consent regarding potential late toxicities, risk of second cancer, and accelerated cardiovascular disease, was individualized to age and COVID-19-related mortality risk.[20,21] The study protocol and approved addenda permitted treatment of an initial phase-I cohort of 5 oxygen-dependent but non-intubated patients with a pre-planned, 7-day interim analysis and built-in safety stopping rule to evaluate acute toxicity and reflex cytokine storm exacerbation. After evaluating safety, a predetermined stopping rule was not triggered, and an institutional data safety monitoring committee permitted investigators to proceed with 5 additional treatments to explore efficacy.[17] In total, 10 oxygen-dependent but non-intubated patients received LD-RT and were followed for a minimum of 28 days or until discharge. Thereafter, a cohort of matched controls meeting equivalent disease severity criteria was blindly and retroactively selected for comparative outcome analysis. Controls were selected from among SARS-CoV-2-positive patients who had previously enrolled on a separate, prospective, non-therapeutic institutional trial and matched by age and comorbidity burden. 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).

Patients

Eligible LD-RT patients tested positive for SARS-CoV-2 by nasopharyngeal swab using polymerase chase reaction-based testing, were hospitalized, had pneumonic consolidation on either chest radiograph (CXR) or computed tomographic (CT) imaging, required oxygen supplementation, and were assessed by physician providers as clinically declining (delirium due to physiological condition,

increasing oxygen demands, or oxygen weaning intolerance). Exclusion criteria included actual or planned pregnancy or administration of drug therapies intended to treat COVID-19 within 1 day before radiation therapy delivery through post-LD-RT day 3. According to institutional policy at the time of trial enrollment (April to May 2020), patients requiring more than 6 L/min of supplemental oxygen immediately before planned LD-RT were deemed ineligible for safe transport and were not treated. Eligible controls were also floor-status patients on supplemental oxygen at the time of first supportive care or drug therapy (if received). Potential controls who clinically declined or were intubated on the day of admission or before the delivery of COVID-19-directed drug therapy (if received) were deemed to have non-matching disease severity and were ineligible to act as matched controls. Antipyretic medications were suspended at enrollment for enrolled patients but not controls. Oxygen weaning was recommended at no less than 12-hour intervals in non-declining patients to maintain oxygen saturations above 90%, in line with hospital nursing standard practices and subject to primary team and respiratory therapy recommendations. Patients were preplanned for clinical assessment at the time of enrollment and on post-RT days 1, 3, and 7, and 28, as well as optional assessment on days 14 and 21. The Glasgow Coma Scale (GCS)[22] was not included in the initial analysis plan but after observation of improved delirium at trial onset, GCS was added by amendment to rapidly assess delirium rather than lengthier scales validated for delirium and related disorders in the critically ill. Charlson Comorbidity Index[23] was used to assess comorbidity burden. Radiographs were permitted at any time as clinically indicated but obtained per-protocol at least 12 hours before radiation, 24 hours after radiation, and on post-RT days 3, 7, 28, and optionally at day 14 and 21. Evaluation of serum inflammatory, renal, cardiac, chemistry, clotting, and hematologic markers were encouraged daily, but obtained at least at baseline and also on post-RT days 3, 7, and 28, and optionally on days 14 and 21. Age as a binary variable was added to the analysis plan to evaluate time to clinical recovery in patients age 65 and older compared with patients age 64 and younger based on observations made during the trial.

Intervention

Enrolled patients received best supportive care plus LD-RT to a dose of 1.5 Gy to the bilateral whole lungs, delivered in a single fraction, using a 2-dimensional therapeutic radiation technique, an anterior-posterior, opposed, 2-beam configuration, and standard dose rates. Treatment planning called for a 75 cGy prescription to midplane for each beam. Calculation of monitor units was based on anatomic dimensions obtained from diagnostic x-rays and thoracic widths obtained by caliper measurement or CT-based imaging, when available. No CT-based simulations or heterogeneity corrections were performed. Patients were treated with open fields without blocking or multi-leaf collimators to the whole thorax with 15 megavoltage (MV) beams and MV-based image guidance to confirm a central location of the bilateral lungs within the treatment fields. Small shifts were applied when needed to center the lungs. Median treatment time from hospital room to treatment and back to hospital room was 30 minutes. Patients were present in the radiation therapy vault for a median of 10 minutes for set-up and treatment delivery. Beam-on time at standard dose rates was consistently less than 30 seconds.

Patients in the control cohort received best supportive care with or without drug therapies for COVID-19 (ie, remdesevir, hydroxychloroquine, glucocorticosteroids, or azithromycin) per protocol or physician discretion. Convalescent plasma was not available for use.

Outcome measures

The trial's initial endpoint was to broadly explore "clinical improvement." This endpoint was refined to specifically evaluate time to clinical recovery (TTCR) in mimicry of the ACTT-1 trial, adopting the trial's initial Feburary 2020 definition using an ordinal scale of recovery (below). This definition was tightened to require that patients remain off of supplemental oxygen for at least 12 consecutive hours to trigger classification as "not requiring supplemental oxygen". This primary objective was reported previously as safety data for the first 5 patients who received LD-RT.[18] Efficacy was explored by comparing TTCR between the LD-RT cohort and controls. TTCR was define as the time from first COVID-19 intervention to the first day on which a subject satisfied 1 of 3 categories from an ordinal scale: (1) not hospitalized, no limitations on activities; (2) not hospitalized, limitation on activities or requiring home oxygen; or (3) hospitalized, not requiring supplemental oxygen. Initially and throughout all published trial revisions on www.clinicaltrials.gov, the ACTT-1 trial defined recovery using this scale, assessing freedom from supplemental oxygen on the first assessment of a given hospital day. However, at final publication (November 2020), a revision of this initial definition of TTCR was revealed, which instead, required that patients remain off supplemental oxygen for at least 24 consecutive hours to meet the definition of recovery. Therefore, the defintion of recovery used in the present trial (that required patients to remain off 12 hours off oxygen), while an intentionally tightening of the initially ACTT-1 definition, did not require 24 consecutive hours off oxygen. The first day of COVID-19 intervention was 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, if received [n = 6]), or as the first full-day of hospitalization (in control patients who received best supportive care alone [n = 4]). Controls were selected from enrollees on a nontherapeutic trial that did not enroll most patients until the midpoint or

end of hospitalization for a venipuncture sample. Thus, use of "time of enrollment" as a starting measurement date to time recovery was not possible in controls. To inform lead-time bias based on variable start-time definitions in recovery start times, time from admission to clinical recovery was added as a secondary endpoint in post hoc analysis.

Additional exploratory secondary outcomes broadly explored clinical course, radiographic changes, and serologic response without prespecified units or planned statistical comparison. After study closure, units of secondary endpoints were selected as data was explored for hypothesis generation. Clinical course was evaluated by total hospital duration, intubation events, duration of intubation, oxygenation requirements, days febrile, and vital status. Disease severity was assessed at baseline by oxygen requirement (L/min) and arterial blood gas using a ratio of arterial pressure (mm Hg) 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 comparison to an immediately preceding study film, performed by a blinded board-certified diagnostic radiologist (B.W.). Images were also blindly assigned an ordinal 1 to 5 score, using an acute respiratory distress syndrome (ARDS) scoring scale.[24] Radiologic blinding allowed knowledge of study sequencing but ensured no knowledge of cohort designation, intervention received, or timing thereof. Unlike CXR, chest CT images obtained at baseline and day 7 were subjectively assessed and visually compared without a scoring system. Serologic course was measured by serial laboratory evaluations of hematologic, renal, cardiac, chemistry, clotting, and inflammatory markers.

Statistical analysis

Two-sample t tests and χ^2 tests were used for continuous and categorical endpoints, respectively. Recovery and hospital discharge were plotted using the cumulative incidence function curves while intubation was plotted using the Kaplan-Meier method. Competing event analysis was not required since data were uncensored, discharge defined recovery, and neither patent who died (n = 2) did so without first being intubated. Deceased patients were censored at time of death. Univariate Cox proportional hazards models were fit, and hazard ratios with 95% confidence intervals were reported. Serial imaging SARS scores were carried forward from day 7 to 14 to 21 if missing. CXR outcomes were reported both as mean ARDS scale scores for sequential periods, and as a binary assessment of whether any CXR ever improved or failed to improve over a 21-day follow-up period. Median and interquartile range was calculated for laboratory values at clustered time points: 3 days before RT through the day of intervention, and at days 1 to 3, 4 to 7, and 8 to 14 post-RT, when available. Paired and unpaired t tests were used to compared changes in repeated laboratory measures in single individuals and between cohorts, respectively.

Results

Patients

From April 23 to May 24, 2020, 51 patients were screened for eligibility, and 13 were enrolled to the LD-RT cohort. Three patients became ineligible for transport due to worsening COVID-19-related symptoms and clinical decline while awaiting LD-RT delivery (2 died and 1 was intubated and later recovered). The remaining 10 patients were treated with LD-RT (Fig. 1). Most patients who were screened but not enrolled also failed to meet disease severity criteria by either not requiring supplemental oxygen or rapidly declining (n = 33; Fig. 1). Ten separate patients were admitted between March 27 and May 12, 2020, enrolled onto a separate institutional prospective trial, and later blindly and retroactively selected as controls for comparative analysis after meeting the same disease severity criteria and after being blindly matched by age and comorbidities with those that received LD-RT.

Table 1 outlines patient demographic at the time of hospital admission and administered COVID-19 drug therapies. Median age was 78 (range, 43-104) and 75 (44-99) for the LD-RT and control cohorts, respectively (P = .71). Seventy-five percent were black, 55% were female, and 40% were residents of nursing homes that experienced COVID-19 infection outbreaks. Median Charlson Comorbidity Index comorbidity scores were 6.5 (range, 0-10) and 5.5 (0-8), respectively (P = .49). Median duration of symptoms before admission was 7.5 (range, 1-30) and 5.5 (0-21) days, respectively (P = .38). One control patient was admitted for a prior SARS-CoV-2 positive test and had no COVID-19 symptoms on admission, but developed symptoms soon thereafter. Another control who received best supportive care alone had very mild disease and required oxygen for only 5 hours at admission. Median GCS scores were 15 (range, 8-15) and 15 (14-15) on admission, which were categorically mild (range, 13-15) in 80% and 90% of the LD-RT and control cohorts, respectively (P = .53). Median oxygen supplementation requirement at the time of admission were 3 L (range, 2-15) and 2 L (0-40), respectively (P = .26). The sole control patient who was admitted on 40 L/min of oxygen improved to 2 L/min on hospital day 3 with best supportive care alone. Maximum oxygen support on admission for other controls was 15 L/min, similar to the LD-RT cohort. Disease severity, as assessed by median ratio of arterial pressure (mm Hg) of oxygen (PaO2) to fraction of inspired oxygen (FiO2) [P:F ratio] was 138 (range, 79-281) and 194 (range, 100-452) in the LD-RT and control cohorts, respectively (P = .25). Faster median time to rise of highest oxygen supplementation level was not significant (P = .26) in the LD-RT cohort (1.5 days) compared with

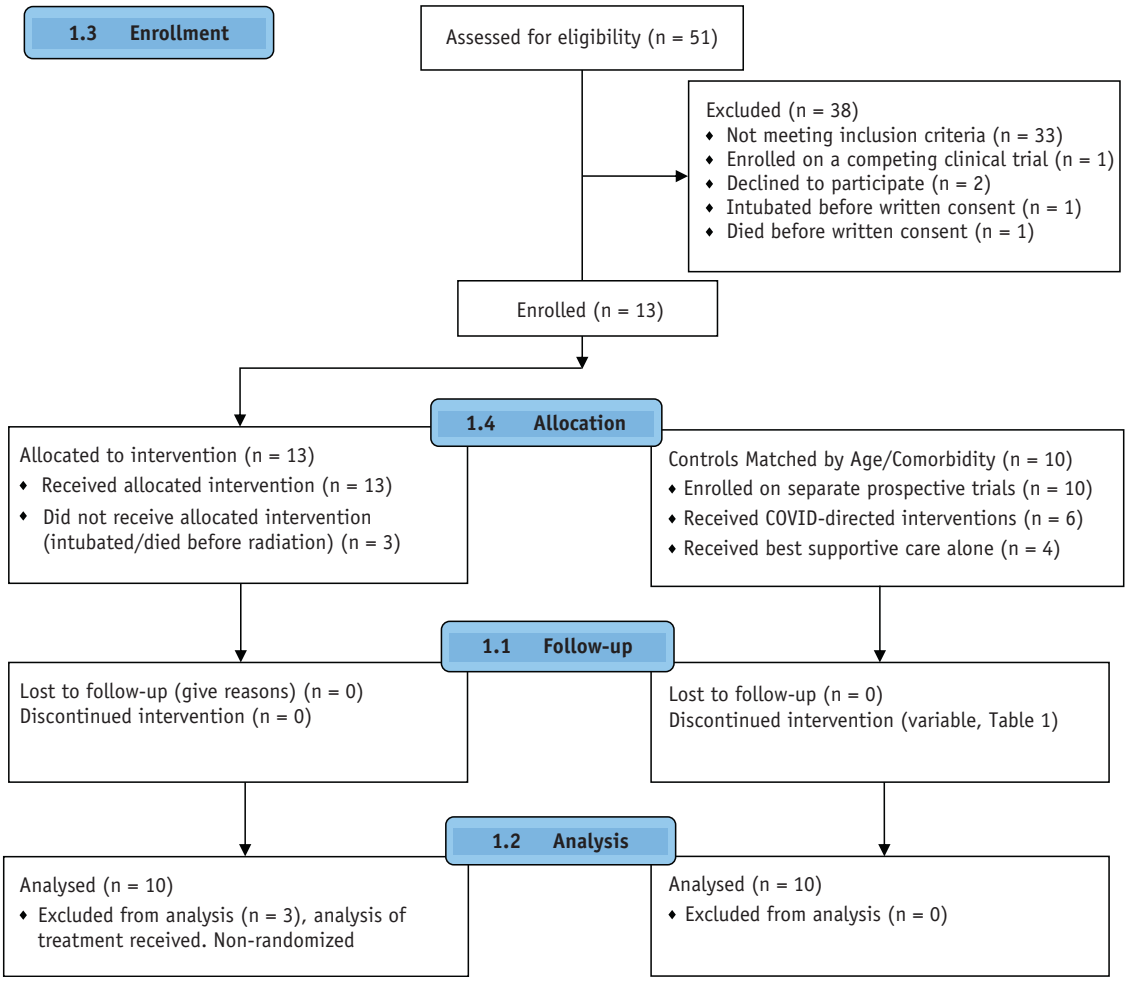

Fig. 1. CONSORT flow diagram.

controls (4 days). Common presenting symptoms for the whole cohort were dyspnea or cough (65%); fever or chills (45%); dizziness, confusion, delirium, or altered mentation (40%); and body aches, myalgias, or weakness (25%). Patients received LD-RT later in their hospital stay (median day 4.5; range, 1-18) than controls received COVID-19-directed intervention (n = 6) or best supportive care alone (n = 4; median day 2.0; range, 1-4; $P = .02$). Patients age 65 and over had less severe oxygen dependence (median 3 L/min) at the time of COVID-19 intervention compared with younger patients (6 L/min, $P = .05$), suggesting that older patients may have presented with milder disease. Median documented follow-up was 22 days in the LD-RT cohort compared with 46 days in the control cohort.

Clinical outcomes

Median time to clinical recovery was 3 days (range, 3 hours to 8.5 days) in the LD-RT cohort compared with 12 days (range, 19 hours to 32 days) in the control cohort (hazard ratio [HR] 2.9; 95% confidence interval [CI], 1.01%-8.39%; $P = .048$; Fig. 2a). Median time from first COVID-19 intervention to hospital discharge was 12 days (range, 7-25) compared with 20 days (5-45 days), respectively (HR 2.13; 95% CI, 0.68%-6.66%; $P = .19$; Fig. 2b). Median time from admission to clinical recovery was 10 versus 13 days, respectively (HR 2.3; 95% CI 0.8%-6.9%; $P = .13$; Fig. 2c). Freedom from intubation was 90% and 60%, respectively (HR 4.9; 95% CI, 0.72%-100%; $P = .16$; Fig. 2c). Twenty-eight-day overall survival was 90% in both cohorts and median survival time was not reached. Additional treatment outcomes are reported in Table 2. Average time from admission to hospital discharge was 19 days (range, 13-43) compared with 22.6 days (7-48), in the LD-RT and control cohorts, respectively ($P = .53$). Average duration of intubation in each cohort was 1 and 4.3 day(s) per patient, respectively ($P = .12$). Average number of hospital days with a documented fever of 100.4°F or higher was 1.9 in the LD-RT cohort compared with 4.6

Table 1 Patient demographics

	Radiation cohort (n = 10)	Matched controls (n = 10)	Total (n = 20)	*P* value*
Median age, y (range)	78 (43-104)	75 (44-99)	76 (43-104)	.71
Age ≥65	7	7	14 (70%)	1.0
Age ≤64	3	3	6 (30%)	
Race/ethnicity non-Hispanic black	7	8	15 (75%)	.66
Non-Hispanic white	3	2	5 (25%)	
Female	6	5	11 (55%)	.65
Residence				
Independent/with family/caregiver	6	7	13 (65%)	.64
Assisted living/nursing home	4	3	7 (35%)	
Median CCI (range)	6.5 (0-10)	5.5 (0-8)	5.5 (0-10)	.49
Comorbidities none	1	1	2 (10%)	-
Hypertension	6	8	14 (70%)	
Dementia	2	3	5 (25%)	
CVA/TIA	1	3	4 (20%)	
Diabetes	3	3	6 (30%)	
PE/DVT	3	1	4 (20%)	
COPD/asthma	1	2	3 (15%)	
Aspiration risk/prior pneumonia	2	1	3 (15%)	
CAD/valvular/PVD/CHF/MI/arrythmia	4	1	5 (25%)	
Previous cancer	1	3	4 (20%)	
Renal disease/dialysis	3	0	3 (15%)	
Chronic home oxygen dependence	0	1	1 (5%)	-
Median GCS				
At hospital admission (range)	15 (8-15)	15 (14-15)	15 (8-15)	.83
Proportion mild (13-15)	8	9	17 (85%)	.53
Proportion moderate (9-12)/severe (3-8)	2	1	3 (15%)	
At time of intervention (range)	13.5 (8-15)	15 (11-15)	14 (8-15)	.26
Proportion mild (13-15)	5	9	14 (70%	.05
Proportion moderate (9-12)/severe (3-8)	5	1	6 (30%)	
Chest radiograph consolidation				
Bilateral	9	6	16 (80%)	.30
Unilateral	1	3	3 (15%)	
Median duration of symptoms: days before admission (range)	7.5 (1-30)	5.5 (0-21)	6.5 (0-30)	.38
Positive SARS-CoV-2 test before admission	7	4	11 (55%)	.32
Median time (in days) between prior positive SARS-CoV-2 test and admission (range)	2 (0-25)	0 (0-36)	1 (0-36)	.26
Presenting symptoms hypoxia	2	2	4 (20%)	-
Headache	1	3	4 (20%)	
Diarrhea/anorexia	3	1	4 (20%)	
Body aches/myalgias/weakness	2	3	5 (25%)	
Dizzy/confusion/altered mental status	3	5	8(40%)	
Fever/chills	3	6	9 (45%)	
Dyspnea/cough	7	6	13 (65%)	
Median O2 (L/min) at admission (range)	3 (2-15)	2 (0-40)	2.5 (0-40)	.26
Median O2 (L/min) at time of intervention	3 (2-6)	5 (2-40)	3.5 (2-40)	.37
Median days from admission to highest oxygen requirement (range)	1.5 (1-37)	4.0 (1-17)	3 (1-17)	.26
Median days from symptom onset to highest oxygen requirement (range)	10 (2-67)	11 (3-24)	11 (2-43)	.79
Median P:F ratio: ratio of arterial pressure (mm Hg) of oxygen (PaO2) to fraction of inspired oxygen (FiO2) (range)	138 (79-281)	194 (100-452)	171 (79-452)	.25

(*continued on next page*)

Table 1 (*continued*)

	Radiation cohort (n = 10)	Matched controls (n = 10)	Total (n = 20)	*P* value*
COVID-19-directed therapy (combined d)				-
BSC	10 (entire stay)	10 (entire stay)	20 (100%)	
BSC without COVID-19 drug therapy	6 (entire stay)	4 (entire stay)	10 (50%)	
BSC + ACTT-1 trial (Remdesevir vs placebo)†	0	4 (24 days)	4 (20%)	
BSC + hydroxychloroquine‡	0	2 (10 days)	2 (10%)	
BSC + azithromycin§	4 (11 days)	6 (19 days)	10 (50%)	
BSC + systemic steroids‖	1 (day 11-14 postRT)	3 (13 days)	4 (20%)	
BSC + combination COVID-19 therapy¶	1	5	6 (30%)	
Low-dose whole-lung irradiation	10	0	10 (50%)	
Median COVID-19 therapy start day (range)#	4.5 (1-18)	2 (1-4)	3 (1-16)	.02

Abbreviation: BSC = best supportive care; CAD = coronary artery disease; CCI = Charlson Comorbidity Index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; CVA = cerebral vascular accident; DBP = diastolic blood pressure; DD = developmental delay; DM = diabetes mellitus; DVT = deep venous thrombosis; GCS = Glasgow Coma Score (E-eyes, V-verbal, M-motor); HR = heart rate; HTN = hypertension; MDD = major depressive disorder; MI = myocardial infraction; PE = pulmonary embolus; PVD = peripheral vascular disease; RT = radiation therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SBP = systolic blood pressure; TIA = transient ischemic attack.

* The parametric *P* value is calculated by a Wilcoxon rank-sum test for numerical covariates, χ^2 test for 2-level categorical covariates, and Bowker test of symmetry for categorical covariates with more than 2 levels.

† Four patients in the control cohort were co-enrolled on the ACTT-1 trial and received 4, 5, 5, and 10 days of the trial drug versus placebo (blinded administration), respectively. Combinations below.¶

‡ Two patients in the control cohort each received 5 days of hydroxychloroquine. Combinations below.¶

§ Four patients in the radiation cohort received azithromycin before enrollment, which was discontinued no later than 24 hours before RT delivery. These received 5, 3, 2, and 1 day(s) of azithromycin, respectively. Six patients in the control cohort received 6,5, 3, 2, 2, and 1 day(s) of azithromycin, respectively. Combinations below.¶

‖ One patient in the radiation cohort received 4 daily doses of intravenous hydrocortisone after clinical decline and intubation on days 11 through 14 post-RT. Three patients in the control arm received systemic steroids: (1) 7 sequential administrations of oral prednisone (20 mg bid) over 4 days; (2) 2 days of oral prednisone (30 mg daily); (3) 12 days of intravenous dexamethasone. Combinations below.¶

¶ COVID-19-directed drug combinations:
Radiation patient 5 received both 1 day of azithromycin (pre-RT) and 4 days of once-daily IV hydrocortisone (post-RT days 11-14).
Control patient 2 received both 2 days of azithromycin and 10 of 10 planned days of remdesevir/placebo enrolled on the ACTT-1 trial.
Control patient 5 received both 6 days of azithromycin, 5 days of hydroxychloroquine, and 4 days of twice-daily oral prednisone.
Control patient 6 received both 2 days of azithromycin and 5 of 10 planned days of remdesevir/placebo enrolled on the ACTT-1 trial.
Control patient 7 received 1 day of azithromycin, 4 of 10 planned days of remdesevir/placebo enrolled on the ACTT-1 trial, and 12 days of once-daily IV dexamethasone.
Control patient 9 received 5 days of azithromycin, 5 days of hydroxychloroquine, and 2 days of once-daily oral prednisone.

First day of COVID-19 intervention for the radiation and control cohorts was defined as the day of radiation delivery or first day of either remdesevir/placebo/hydroxychloroquine administration, respectively. For patients on the control arm who received best supportive care alone, the first day of intervention was defined as the first day of hospitalization.

days in controls ($P = .16$). Average total time requiring oxygen supplementation during hospitalization was 13.1 days (range, 4-31) in LD-RT cohort compared with 14.7 days (range, 1-33) in the control cohort ($P = .69$). Age 65 and over was associated with a lower oxygen requirement at the time of intervention and shorter time to clinical recovery in the LD-RT cohort ($P = .01$) but not the control cohort ($P = .40$).

Mentation

Five patients in the LD-RT cohort compared with 1 in controls had severe delirium due to their physiological condition at the time of first COVID-19 intervention (median GCS 13.5 vs 15, $P = .26$). The LD-RT cohort had more patients with moderate or severe delirium (a GCS score of 12 or lower, 50% compared with 10%, $P = .05$). Within 24 hours of first COVID-19 intervention, change in median GCS was 2.5 points higher (range, 0-5) in the LD-RT cohort compared with controls ($P < .01$), whose GCS was stable (n = 9) or worse (n = 1).

Radiographic response

Any radiographic improvement by day 21 occurred in 90% versus 57% of patients in the LD-RT versus control cohorts ($P = .12$, Table 2), while any radiographic worsening through day 21 occurred in 40% versus 43% ($P = .91$). Clinical vignettes of patients with high burden of pulmonary consolidations associated with COVID-19 and corresponding 3-dimensional radiographic responses to LD-RT on chest CT are shown in Fig. 3. Average daily ARDS scale scores for serial radiographs from all patients, mean change in radiographic ARDS scale between baseline and last available radiograph at days 7 and 21, and comparison statistics of the LD-RT to control cohorts ($P = .17$) are shown in Fig. E1.

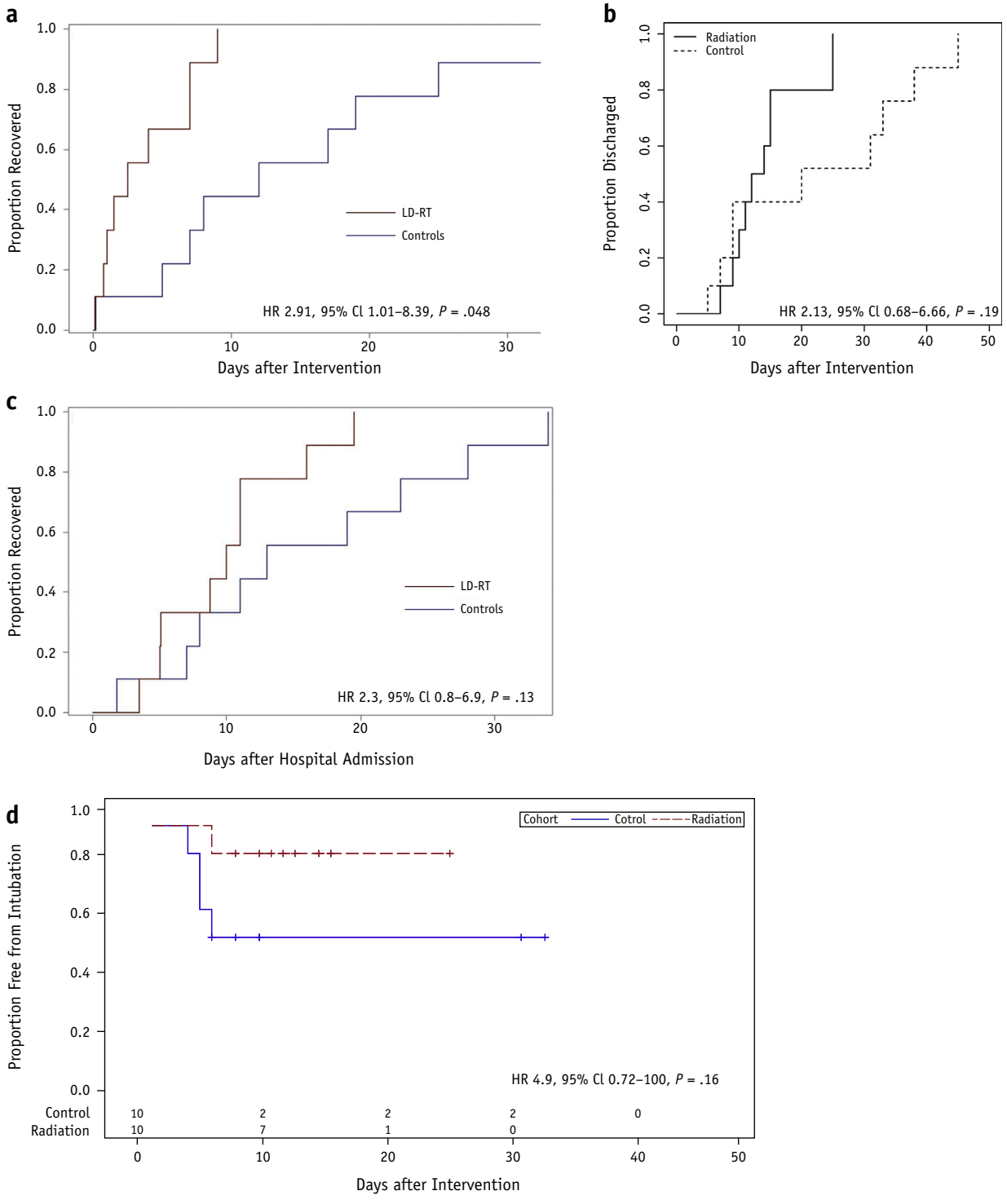

Fig. 2. (a) Time from first COVID-19 intervention to clinical recovery. (b) Time from first COVID-19 intervention to hospital discharge. (c) Time from admission to clinical recovery. (d) Freedom from intubation. *Abbreviations*: CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; LD-RT = low-dose whole-lung radiotherapy.

Serologic response

Safety of hematologic, renal, cardiac, chemistry, clotting, and inflammatory markers within 7 days after LD-RT was reported previously.[18] Plotted medians and interquartile ranges of serologic biomarkers for both LD-RT and control patients are shown in Fig. E2. Inflammatory biomarkers C-reactive protein ($P < .01$) and lactate dehydrogenase (LDH, $P = .03$) were significantly reduced with improved daily changes compared with before LD-RT ($P = .01$ and 0.07,

Table 2 Treatment outcomes

Variable	LD-RT cohort (n = 10) Yes	LD-RT cohort (n = 10) No	Control cohort (n = 10) Yes	Control cohort (n = 10) No	*P* value*
Categorical					
Clinical recovery	9	1	9	1	1.0
Intubated after intervention	1	9	4	6	.12
Death	1	9	1	9	1.0
Any radiographic improvement after intervention	9	1	4	3	**.12**
Any radiographic worsening after intervention	4	6	3	4	.91
	Mean	Range	Mean	Range	
Continuous					
Hospital days febrile (admission to discharge)	1.9	0-6	4.6	0-17	.16
Days of hospitalization (admission to discharge)	19	13-43	22.6	7-48	.53
Total days of oxygen supplementation (admission to discharge)	13.1	4-31	14.7	1-33	.69

Abbreviation: CCI = Charlson Comorbidity Index; LD-RT = low-dose whole-lung radiotherapy.

* The parametric *P* value is calculated by a *t* test for numerical covariates, and χ^2 test for 2-level categorical covariates.

respectively). For 7 days before LD-RT, C-reactive protein values rose at a median rate of 22% per day but fell more rapidly after LD-RT than in controls ($P = .01$), at a median rate of 11% per day for 7 days. Cardiac marker, creatine kinase, was also significantly reduced ($P < .01$) and trended toward superiority over controls ($P = .08$). Liver function remained normal after LD-RT, while transaminitis occurred in controls (AST $P = .07$; ALT $P = .04$), suggesting that hepatic biomarker elevation may be prevented by LD-RT. Immune cell modulation was confirmed by transient reductions ($P = .04$) in white blood cell count and lack of leukocytosis compared with controls ($P < .01$). Modulated reductions of monocytes ($P = .02$) and neutrophil-to-lymphocyte ratios ($P = .04$) were observed after LD-RT with trending superiority over controls ($P = .08$ and .09, respectively). No neutropenia was observed. Renal biomarker creatinine was not significantly affected ($P = .94$). D-dimer did not change after LD-RT ($P = .68$) and a visual rise in controls not seen after LD-RT suggested coagulopathy prevention, but was not statistically significant ($P = .49$, Fig. E2). Myoglobin, erythrocyte sedimentation rate, ferritin, fibrinogen, procalcitonin, and interleukin-6 trended downward after LD-RT but did not reach significance. Control comparisons were not available (Fig. E2).

Adverse events

One patient (10%) experienced Common Terminology Criteria for Adverse Events grade 1 upper gastrointestinal acute toxicity within 24 hours follow LD-RT delivery (nausea without alteration in eating habits). No LD-RT

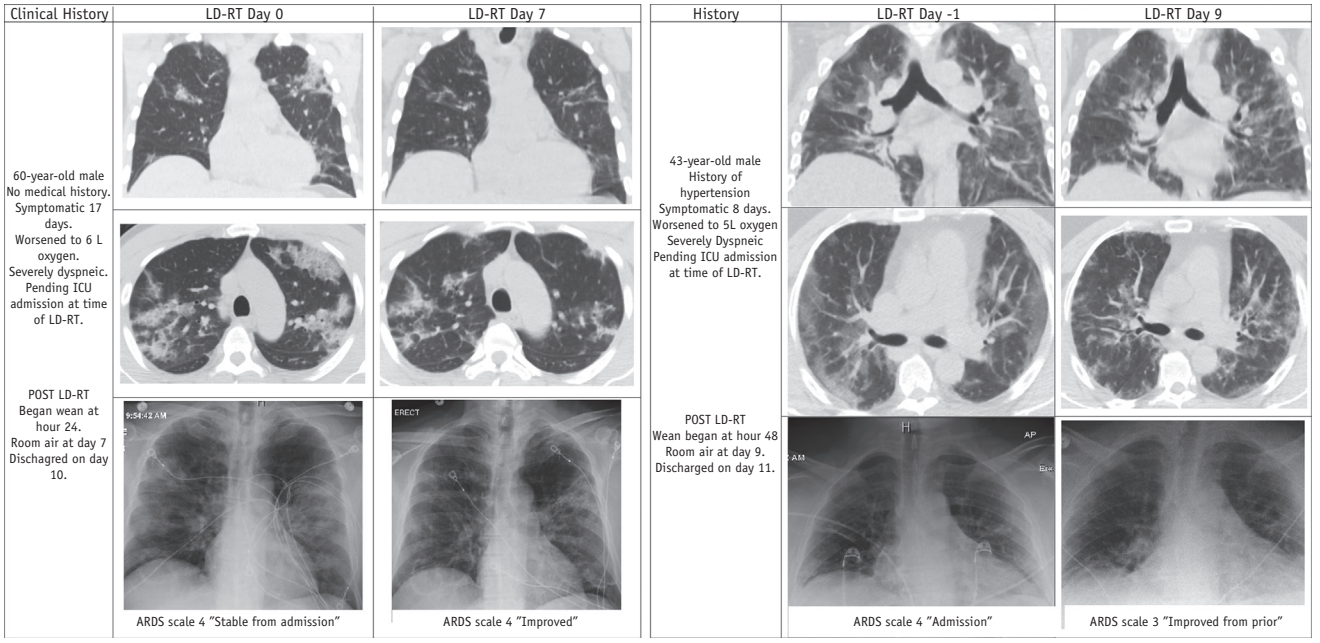

Fig. 3. Radiographic improvements after low-dose whole-lung radiotherapy (LD-RT).

Table 3 Raw data table for the LD-RT cohorts (1 and 2) versus matched controls

Cohorts 1 and 2												
Patient	1	2	3	4	5	6	7	8	9	10	AVG	SEM
Age	90 +	65 +	90 +	90 +	60 +	60 +	80 +	40 +	70 +	100 +	77.2	±5.9
CCI	7	8	7	5	2	2	9	0	7	10	5.7	±1.1
Highest 02 (L/min)	2	4	15	3	100 (INT)	6	15	6	4	2	15.7	±9.5
Symptom onset (preadmission)	−1	−2	−2	−8	−7	−17	−5	−8	−30	−15	−9.5	±2.8
Bilateral infiltrate	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	80%	-
Hospital intervention	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	LD-RT	-	-
Intervention day	8	4	6	5	2	4	9	2	18	1	5.9	±1.6
Admission to recovery (d)	9	5	10	6	.	11	16	11	20	4	10.2	±1.7
Intervention to recovery (d)	1	1	4	1	.	7	7	9	2	3	3.9	±1.0
Symptom to recovery (d)	10	7	12	14	.	28	14	19	50	19	19.2	±4.4
Hospital O2 days	9	11	16	9	16	13	15	13	31	4	13.7	±2.3
Hospital duration (d)	23	16	19	14	16	14	16	13	43	16	19.0	±2.8
Days with fever	2	1	1	0	6	6	0	2	1	0	1.9	±0.7
Matched controls												
Patient	1	2	3	4	5	6	7	8	9	10	AVG	SEM
Age	85+	65+	90+	80+	60+	60+	75+	40+	70+	95+	74.1	±5.1
CCI	6	3	8	6	3	2	5	0	7	6	4.6	±0.8
Highest 02 (L/min)	3	100/INT	15	4	2	100/INT	100/INT	15	100/INT	60	49.9	±14.6
Symptom onset (preadmission)	−2	−9	0	−21	−5	−7	−3	−7	−6	−1	-6.1	±1.9
Bilateral infiltrate	N	Y	N	Y	N	Y	Y	Y	Y	N	60%	-
Hospital intervention	Supportive	Remdesevir chlorouine	Supportive	ACTT-1	Remdesevir chloroquine steroids	ACTT-1	ACTT-1	Supportive	Chloroquine steroids	Supportive	-	-
Intervention day	1	4	1	3	2	4	3	1	5	1	2.5	±0.5
Admission to recovery (d)	2	22	33	11	7	.	27	8	19	13	15.8	±3.4
Intervention to recovery (d)	1	19	33	8	5	.	24	8	15	13	14	±3.4
Symptom to recovery (d)	4	31	33	32	12	.	30	15	25	14	21.8	±3.6
Hospital O2 days	1 (3h)	22	33	9	7	12	26	7	17	13	14.7	±3.1
Hospital duration (d)	8	26	33	11	7	12	41	9	48	31	22.6	±4.8
Days with fever	0	0	0	6	3	8	8	3	17	1	4.6	±1.7

Abbreviations: AVG = average; CCI = Charlson Comorbidity Index; INT = intubated; LD-RT = low-dose whole-lung radiotherapy; SEM = standard error of the mean.

patients experienced rapid reflex worsening of symptoms, radiographs, or serologies. The patient who died in the LD-RT cohort was less than age 65, had minimal past medical history, presented with rapidly rising pre-RT oxygen requirement, and diffuse bilateral disease on x-ray. Oxygen supplementation trajectory increased from 2 to 6 L/min within 36 hours of admission and 24 hours of enrollment. LD-RT was delivered amid clinical deterioration at the end of full hospital day 2. Oxygen requirement continued to rise for 3 hours after LD-RT from 6 L/min low-flow to 50 L/min high-flow but plateaued thereafter for 5 days, suggesting an abrupt slowing of disease trajectory. During this time, the

patient defervesced and inflammatory, cardiac, immune, and hepatic laboratory results fell for 3 to 5 consecutive days after LD-RT, consistent with serologic responses observed in other patients. However, on post-LD-RT day 5, a cardiac event occurred after pronation with bathing with abrupt rise in troponin, D-dimer, creatinine, and inflammatory markers, requiring intubation. The patient remained intubated for 9 days with coagulopathies and died on hospital day 16. Whether LD-RT contributed to the plateauing of his clinical course before global decline cannot be confirmed nor excluded. No other toxicity, airway emergencies, or other adverse events were observed after LD-RT.

Given the potential importance of this unique data set to inform subsequent randomized trials of LD-RT for COVID-19, a summary table of the individual patient data are provided (Table 3) and comprehensive data for each patient is included in Appendix E1.

Discussion

This report describes 28-day outcomes of the first phase 2 trial exploring efficacy of immunomodulatory, single-fraction, low-dose, whole-lung radiation for patients with SARS-CoV-2 hyperinflammatory pneumonia. In a cohort of 10 patients and 10 matched controls, LD-RT was delivered safely and without acute toxicity or reflex clinical, radiographic, or serologic worsening. LD-RT was associated with a shorter time to clinical recovery of 3 versus 12 days (HR 2.9, $P = .05$). Shorter median time from intervention to hospital discharge was 12 days after LD-RT versus 20 days in the control group but did not reach significance ($P = .19$). Shorter time from admission to clinical recovery trended toward significance (Fig. 2c), suggesting that a larger cohort may detect this difference and that any benefit attributable to LD-RT was not confounded by lead-time bias from inherent differences in the measurement start of time to recovery. Intubation rates were lower at 10% versus 40%, and total intensive care unit duration in each cohort was shorter at 10 versus 43 days, with statistical trends meriting further evaluation in larger cohorts. Although these outcomes appear promising, and although potential efficacy mechanisms are well delineated for COVID-19, these findings remain preliminary and require confirmation through randomized trials.[9-16] Additional immunologic analyses of these and other cytokines and immune markers was performed and will be forthcoming.

Although our findings support additional randomized testing of LD-RT, they suggest that LD-RT may complement existing COVID-19 therapies due to lack of observed acute toxicity in the elderly. It is notable that whole-lung LD-RT did not induce posttreatment pancytopenia, or immunosuppression, such as glucocorticoids. Therefore, LD-RT may be unlikely to worsen whole-body immunity or slow viral clearance. In contrast, dexamethasone can induce global immunosuppression, which can slow viral clearance in murine models and remains a concern. In addition, steroids can induce hyperglycemia, insulin requirements, and superimposed bacterial infections or even sepsis during COVID-19 hospitalization, complicating recovery.[25,26] Thus, it is reasonable to explore LD-RT as a focal anti-inflammatory option that minimizes acute effects, as observed in this study. Furthermore, in patients who required oxygen but who were not intubated, 10-days of steroid administration prevented death in only 1 of 25 treated patients, a considerably smaller benefit compared with intubated patients.[27,28] It could be that LD-RT has additive effect with steroids and may further improve upon survival rates. LD-RT may also act to short-circuit the hyper-activation cascade in its early stages and prevent hyper-inflammatory damage, as suggested in this study wherein later rise in AST, ALT, and NLR may have been prevented compared with controls (Fig. E2). One-time LD-RT can be rapidly administered. From department arrival to departure, the end-to-end workflow for set-up and treatment delivery was approximately 10 minutes, requiring less than 30 seconds of beam-on time.

Dose selection

Rationale for the selection of 1.5 Gy as an exploratory dose included: (1) computational equivalence of prior orthovoltage treatments using 200 Roengten (~175 cGy)[29]; (2) known therapeutic dose ranges for histiocytosis above 0.5 Gy (~7-11 Gy), total body irradiation (2-8 Gy), and low-grade lymphoma (2 Gy x 2); (3) historical precedent and safety of delivering 1.5 Gy whole lung radiation in children with Ewing sarcoma; (4) knowledge that in vitro animal model doses may not reliably translate to clinical response in humans to quench diffuse and potentially lethal pulmonary histiocytosis; and (5) foresight of the critical role of the first trial of LD-RT as either a barrier or catalyst to subsequent trials. Our objective was to simply repeat exactly what was done historically and attempt to reproduce the reported signal without deviation in dose, lest we fail to observe the reported benefit only for failure to repeat reported methods. Thus, we opted for 1.5 Gy and left it to investigators who follow thereafter to explore de-escalated dose, which pursuit would only be possible if the inaugural trial reproduced the therapeutic signal of LD-RT for infectious pneumonia first reported in the 1940s.

Clinical trial design

The findings of this small phase 2 trial have been tested in a larger cohort of patients receiving concurrent remdesevir and dexamethasone with outcomes pending additional follow-up and analysis. Together with the current article, the effect size after LD-RT compared with controls has informed the statistical design and power analysis of an

ongoing phase 3 clinical trial randomizing patients between LD-RT and physician's choice of COVID-directed drug therapy. Of the multiple endpoints with trending or statistical significance reported herein, we anticipate incremental increases in sample size required to detect difference in intubation rates, clinical recovery, and hospital duration.

Potential effect

As of December 2020, more than 80 million people globally are confirmed as infected with SARS-CoV-2, leading to more than 2,000,000 known COVID-19-related deaths. This report suggests that outcomes of COVID-19 patients might be improved with a one-time treatment with LD-RT that carries minimal acute toxicity and is well-tolerated even in the elderly and fragile patients. However, randomized trials to define the efficacy of LD-RT for COVID-19 are needed. The worldwide implications of such a rapid, inexpensive, and globally available treatment, if effective, are hard to overstate, especially for elderly patients in whom hyperinflammatory pneumonia could be treated early without risk of acute toxicities. Linear accelerators capable of delivering LD-RT for COVID-19 are already operational at hospitals globally with trained staff and comparatively few barriers to access.

Limitations

Limitations to this study include its nonrandomized approach, exploratory intent, small patient numbers, differing control treatments, different laboratory and imaging schedules between the LD-RT and control cohorts, inherent subjectivity of recovery definitions, noncontemporaneous controls, LD-RT transport ineligibility requirements, differences in disease severity and time of symptom onset, limited imaging (Fig. E1) and serologic (Fig. E2) studies in the control cohort before intervention and beyond 7 days, and lack of detailed viral load evaluations in the LD-RT and control cohorts. Outcomes after LD-RT may not be generalizable to patients who experience rapid clinical decline because such patients were excluded from analysis in both the LD-RT and control cohorts. Future work with LD-RT will include randomized trials testing efficacy, detailed CD-8 T-cell activation studies, CD-4 T cell activation, changes in B-cell profiles, antibody formation, cytokine analysis, and neutralization tests. These further immunologic analyses will provide insight regarding the role of LD-RT to not only improve clinical outcomes, but perhaps aid viral clearance and reregulate hyper-activated immune responses.

Conclusion

A prospective cohort of predominantly elderly hospitalized patients with SARS-CoV-2 pneumonia and oxygen dependence, visible pneumonic consolidations, and clinical decline were recovered to room air at a median time of 3 days and discharged at a median time of 12 days. Delirium improved by hour 24 and radiographs by day 7 to 21. Multiple inflammatory, cardiac, hepatic, and immune biomarkers were confirmed to have responded to LD-RT in support of observed clinical improvements. There was no significant acute toxicity. Exploration of efficacy against age- and comorbidity-matched controls suggested improvements but require further testing in a randomized controlled trial. Low dose whole-lung radiation in hospitalized and oxygen-dependent patients with COVID-19-related pneumonia was safe and further clinical trials are justified Clinical Trial Registration NCT04366791.

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