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Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 (RESCUE 1-19): A Randomized Phase III Trial of Best Supportive Care versus Whole Lung Low-Dose Radiation Therapy in Hospitalized Patients with COVID-19

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1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 (RESCUE 1-19): A Randomized Phase III Trial of Best Supportive Care Plus Provider's Treatment Choice versus Best Supportive Care Plus Low-Dose, Whole-Lung Radiation in Hospitalized Patients with COVID-19
Study Description:	Hypothesis: Low-dose, whole-lung radiation therapy (LD-RT) improves clinical status in patients with COVID-19. This study investigates LD-RT as a anatomically-targeted, anti-inflammatory treatment to induce local suppression of pulmonary immuno-toxicity within viral pneumonia infiltrates in hospitalized patients with COVID-19.
Objectives:	To compare treatment of COVID-19 between best supportive care plus provider's treatment choice versus best supportive care plus low-dose, whole-lung radiation therapy.
Endpoints:	Primary Endpoint: Time to Clinical Recovery (TTCR). Secondary Endpoints: Time to Hospital Discharge, Radiographic Changes, Serological Biomarker Changes, Inflammatory Biomarker Changes, Freedom from Intubation, Freedom from ICU admission, Overall Survival, Toxicity.
Study Population:	Hospitalized COVID-19 patients with pulmonary infiltrates pre-inbutation who require supplemental oxygenation use.
Phase:	Phase III, preplanned analysis after first 8 patients treated on each arm at day 14.
Sites/Facilities Enrolling Participants:	Emory University Hospital, Clifton Road, Atlanta, GA Emory University Hospital Midtown, Peachtree Road, Atlanta, GA Emory St. Joseph's Hospital, Atlanta , GA
Description of Study Intervention:	Whole Lung Radiation to a dose of 1.5 Gy
Study Duration:	6 months
Participant Duration:	6 months

From ClinicalTrials.gov Protocol Data Element Definitions available at: https://prsinfo.clinicaltrials.gov/definitions.html.

1.2 Schedule of Activities (SoA)

Procedures	Screening Day -7 to -1	LD-RT Day 0	Follow-up day 1	Follow-up day 2	Follow-up day 3	Follow-up day 4	Follow-up day 5	Follow-up day 6	Follow-up day 7	Follow-up day 14
Informed consent	X									
Demographics*	X									
Medical history & Pregnancy test*	X									
Physical exam*	X	X								x
Vitals and O2 sat needs*	X	X	X	X	X	X	X	X	X	x
Performance status*	X	X			X				X	x
Hematology	X		X	X	X	X	X	X	X	x
Comorbidity Index*	X									
Serum chemistry *	X		X	X	X	X	X	X	X	x
Glasgow Coma Scale*	X	X	X	X	X	X	X	X	X	X
Blood gases *	X		X		X				X	x
Serologic immune markers*,##	X		X	X	X	X	X	X	X	X
Low-Dose Radiation Therapy*		X								
Chest Imaging (CT and/or CXR) *	X (Both)		X (chest xray)		X (chest xray)				X (both)	X (both)
Clinical Assessment*	X	X			X				X	x

All procedures are considered to follow standard of care procedures and timelines, and marked above with (*), unless otherwise noted with (##). The exact dates/timings of these may vary based evolving clinical circumstances and on patients' clinical course. These are only suggested timelines.

4 extra vials of 8 ml tubes will be extracted on days 0, 3, and 7 for additional correlative analysis (which may include CD 8 Tell, CD 4 T cells, cytokine analysis, and/or other immunological biomarkers, as well as any additional RNA/DNA sequencing on the blood samples). Day 14 are optional collections. All blood draws can be off by +/- 2 days for logistical reasons and to minimize extraneous blood draws for patients. Day 28 blood draw is optional;

*all day 14 activites listed in table are optional, especially if a patient is discharged from the hospital.
*A day 28 follow-up as inpatient or outpatient is encouraged, but at discretion of treating physicans. This would also be standard of care post RT check. A day 28 blood sample collection may also take place at discretion of the treating physician, but is not required. This is optional.

2. INTRODUCTION

2.1 Study Rationale

Main Points

- Mortality from cascading inflammatory lung injury for intubated COVID-19 patients is 50-80%.
- Immunomodulating LD-RT eliminates cytokine storms and cured past pneumonias.
- There is precedent to use RT to treat a wide breadth of benign or inflammatory conditions.
- COVID-19 injurious mechanisms resemble those of histiocytosis, which has response rates of >90% following LD-RT
- Radiation is routinely used in modern days to treat a histiocytosis disorder, especially the Langerhan's cell subtype. We suspect it may also help with the hemophagocytic lymphohistiocystosis (HLH)like syndrome that occurs in COVID-19 patients.

The novel coronavirus in 2019 (COVID-19) is associated with severe acute respiratory syndrome (SARS), intensive-care unit admission, and high mortality.[1,2] There is little awareness among modern investigators that low doses of ionizing radiation therapy (LD-RT) were successfully used to induce localized anti-inflammatory states as treatment of various types of infections during the first half of the 20th century, including pneumonia, sinus infection, and skin infection.[3-5] Anecdotally, RT reduced inflammation and reversed clinical decline at doses considerably lower than those currently used for oncologic purposes.[3] Abruptly in the early 1940's and for ensuing decades, the role of RT in treating pneumonia and other infections was eclipsed by the emergence of antibiotics.[3] In 2020, however, in an era of increasing antibiotic resistance,[6] a novel viral threat has emerged. The SARS from coronavirus in 2019 (SARS-COVID-19) pandemic has shut down the global economy.[7,8] COVID-19 is thought to induced a hyper-immune cytokine storm leading to pneumocyte injury and profound pulmonary edema. With mortality rates of 2-3% for all documented infected persons but around 50-80% for severe cases requiring ventilation support, bilateral patchy ground glass opacities have been reported in most patients with 97% diagnostic sensitivity.[8-11] Spread of the contagion has risen dramatically with a reproduction number of 2.2, and the global health care system has been further strained by dramatic shortages of critical medical supplies, most notably ventilators.[8] Given existing antiviral resistance, historical reports of success using LD-RT to treat pneumonia, the alarming mortality seen with COVID-19, and the need to preserve ventilator capacity, this study proposes to re-evaluate LD-RT as a localized anti-inflammatory treatment for COVID-19 pneumonia in critically ill patients following ICU admission.

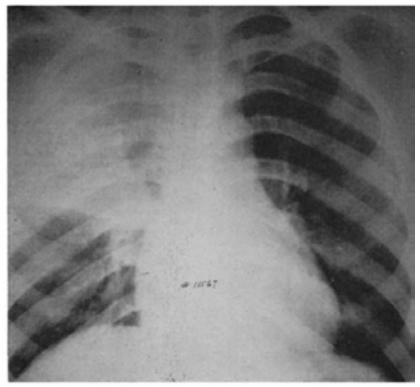
2.2 Background

Between 1905 and 1946, 700 pneumonia patients underwent LD-RT and subsequently experienced measurable clinical improvements in the hours and days following treatment. One to three treatments of LD-RT to cumulative doses of approximately 50 to 550 Roentgen (~44 to 482 cGy) yielded reduction in inflammatory markers, improved respiration, down-trending fever, resolution of radiographic consolidations, and reduction in mortality. At acute onset, observed success rates for lung irradiation were highest when RT

was delivered early in the disease process, with observed improvements after 5 days of pneumonia, and further still after 14 days, implying that the best responses were seen when RT was implemented early in the disease process.[3]

Table 1. X-ray therapy in the treatment of pneumonia.

Reference	Types of Pneumonia	Case Number	Cases Cured
Musser and Edsall [14]	Unresolved pneumonia	1	1
Edsall and Pemberton [37]	Unresolved pneumonia	2	2
Quimby and Quimby [15]	Unresolved pneumonia	12	11
Krost [20]	Unresolved pneumonia	12	11
Fried [72]	Post-operative pneumonia	40	32
Fried [73]	Post-operative pneumonia	57	N/A
Merritt and McPeak [22]	Unresolved pneumonia	7	6
Powell [3,28,33]	Lobar pneumonia and bronchopneumonia	231	215
Scott [24]	Lobar pneumonia	138	111
Solis-Cohen and Levine [25]	Lobar pneumonia	42	40
Settle [26]	Lobar pneumonia	34	32
Rousseau et al. [27]	Lobar pneumonia	104	98
Rousseau et al. [27]	Viral pneumonia	29	22
Correll and Cowan [34]	Acute atypical pneumonia (not pneumococcal)	23	22
Correll and Cowan, 1943	Unresolved pneumonia	9	7
Oppenheimer [32]	Interstital pneumonia (children)	36	33
Oppenheimer [35]	Virus pneumonia	56	45
Torbett, 1936 (see Abstract of Discussion in Powell [3])	N/A	30	29
Total		863	717



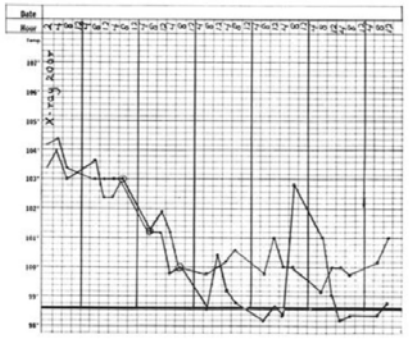


Fig. 1. Lobar pneumococcic pneumonia; 200 roentgens to anterior right chest immediately after admission. Prompt response to irradiation, with complete recovery, temperature, pulse, and respiration showing gradual decline to normal over three-day interval.

Table 1 (left). From Calabrese, et al. 2013.[3] Case series and case reports of observational data utilizing LD-RT for clinical pneumonia. These studies included a variety of control arm techniques including alternating treatment between patients, historical controls, and institutional cohort controls, but pre-dated wide implementation of modern clinical trial or randomization designs. Please see full publication for bracketed references.

Figure 1 (right). From Rousseau, et al. 1942.[12] "Lobar pneumococcic pneumonia; 200 roentgens to anterior right chest immediately after admission. Prompt response to irradiation, with complete recovery, temperature, pulse, and respiration showing gradual disease decline to normal of three-day interval."

The anecdotal reports from these studies are provocative:

> "A patient with a high fever, severe dyspnea, and cyanosis is irradiated. A few hours later, often within a period of six hours, he states that he can breathe more easily, and he takes some nourishment. After twelve to twenty-four hours the fever abates, in most cases by crisis, breathing is no longer painful, and dyspnea decreases or disappears entirely. In most of the cases reacting favorably, a normal condition is re-established in twenty-four to forty-eight hours. In some cases the fever does not resolve by crisis but falls in two long steps; in some there is a gradual decline to normal. In all these cases the decline of temperature, disappearance of dyspnea, general improvement, and indeed the whole course of the disease

> appear to have been definitely hastened by irradiation. And as this observation was made consistently, it would seem to be an established fact."[3] (Fried, et al 1941, cited in Calabrese, et al, 2013)

Another notable example among these studies was published in Radiology in 1942, which compared two sequential cohorts before and after the advent of antibiotics in 1939: LD-RT alone versus LD-RT following sulfonamides. At hospital admission for pneumonia with mean time from symptom onset of 2 days), patients received 200 R (~175 cGy) every 36 hours for 1, 2, or 3 treatments (as needed) while laying supine in bed using 2-D planning anterior-posterior and posterior-anterior (APPA) alternating fields (anterior beam for first treatment, posterior beam for second treatment). No other intervention was given. The investigators followed vital signs, white blood cell count, and chest x-ray imaging across time following administration of LD-RT. Of 104 patients treated, 98 recovered, and mortality was 5.7% against a backdrop of historical mortality rates of ~25-30%. The authors quoted, "X-ray therapy has been strikingly free from any toxic side-effects…Many theories have been advanced by various investigators, and sooner or later conclusive proof of how and why small doses of x-rays have a favorable influence on inflammatory processes will be established."

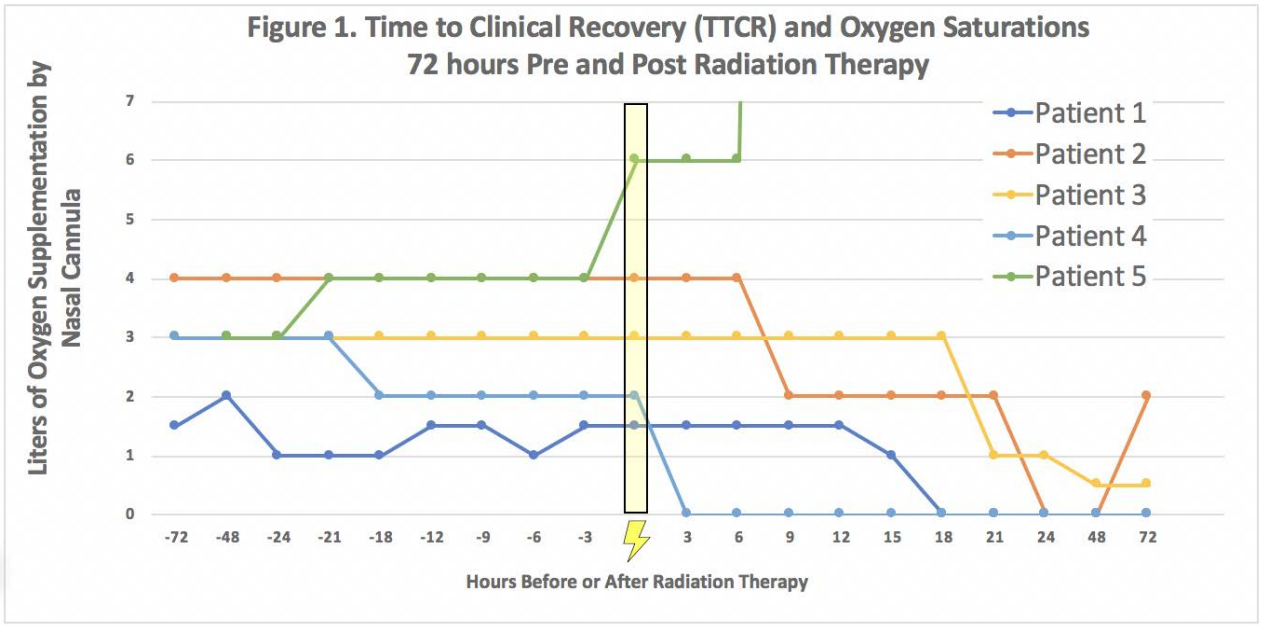
At the time, the mechanism by which LD-RT achieved these gains was not known. By the late 1940's, however, LD-RT disappeared as a treatment for infectious pneumonia as penicillin mass production marked the dawn of the modern antibiotic era. Since that time, few have even contemplated treating pneumonia with radiation, but discovery of the mechanisms and pathways of LD-RT's immune-modulating effects now elucidates how LD-RT may have helped treat pneumonia 80 years ago. Nearly a century later, 2020 has witnessed the rise of a novel pathogenic threat, the COVID-19 pandemic. Mortality rates hover near 50-80% for the most severe cases requiring ventilation support. The virus can induce an acute respiratory distress syndrome (ARDS) via macrophage activation of a cytokine storm that leads to immune-mediated and sometimes fatal organ damage. Anti-infectious agents are limited. Health care resources including intensive care units, personal protective equipment, and personnel are under unprecedented strain, highlighting the need for new strategies to reduce this burden. Faced with the prospect of overwhelmed health care systems, clinicians have a moral imperative to reassess readily-available treatment approaches that they may not have considered in non-pandemic times.

Preliminary Interim Analysis at day 7 from Phase I/II Trial (i.e. Cohort 1 @ day 7: Figure 1)

We are the first in the world (to our knowledge) to have conducted a small prospective IRB-approved pilot trial at Emory University. In this phase I/II single-arm trial, patients deemed to be clinically deteriorating and therefore in need of "rescue" were enrolled. We enrolled primarily elderly patients who were generally in their 90s with multiple co-morbidities, were COVID+ at time of admission, required supplemental oxygen, and had radiographic pulmonary infiltrates. The primary hospitalist team caring for these patients were asked to refer patients they felt were decompensating or refractory to non-invasive measures, and would therefore be good candidates for a novel intervention. The principal investigators and/or study coordinators informed hospitalists of eligibility criteria and were not involved in selecting candidates; this decision was ultimately decided by the primary hospitalist.

We treated five patients, ranging in age from 64 to 94, median 90 years. At enrollment, their Charlson comorbidity index ranged from 2-8 (average 5.6), and their Glasgow coma scale ranged from 9-15 (average 11.6). All underwent LD-RT. Within 24-48 hours, the average Glasgow coma scale had improved to 14.8, a 27.5% improvement. Four (80%) of the patients were weaned off supplemental oxygen within 72 hrs and were noted to have at least one level of ARDS improvement on their 24 hour chest x-ray. The oxygen saturations

within the 72 hours following LD-RT for all 5 patients are plotted in figure 2 below, along with a representative chest x-ray showing significant improvement within 24 hours. All patients had 50% or more of their serological biomarkers improve within 72 hrs. There was no increase in acute skin, GI, GU, pulmonary, or cardiovascular toxicity; as of day 7 post treatment, all patients were alive and four (80%) were anticipating discharge by the time of the preplanned day 7 interim analysis of the initial five patients (manuscript submitted for publication)



ID	Ordinal Scale for Clinical Improvement by Hospital Day																		TTCR
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Patient 1	5	5	5	5	4	4	4	4	3	3	3	3	3	3	3	3	-	-	**18 hours**
Patient 2	4	4	4	4	3	3	4	4	3	3	3	3	-	-	-	-	-	-	**24 hours**
Patient 3	5	5	5	4	4	4	4	4	4	4	3	-	-	-	-	-	-	-	**96 hours**
Patient 4	4	4	4	4	4	3	3	3	3	-	-	-	-	-	-	-	-	-	**3 hours**
Patient 5	4	5	5	5	5	5	-	-	-	-	-	-	-	-	-	-	-	-	Ongoing

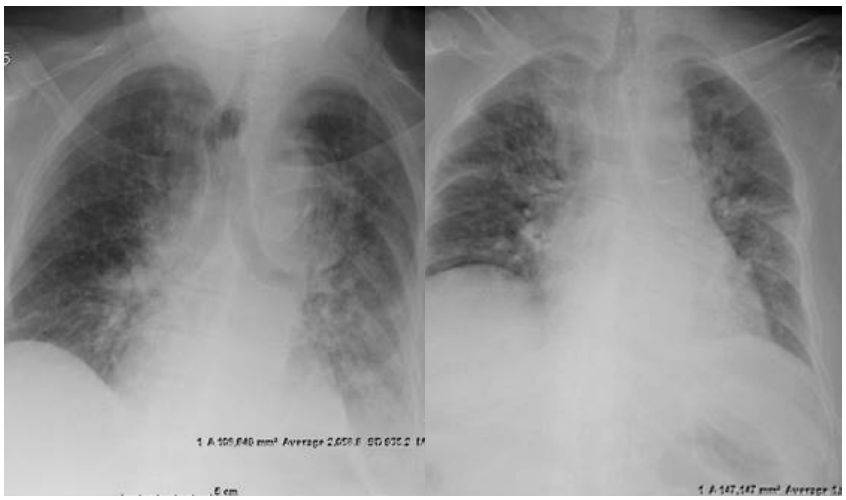


Figure 2: Oxygen Saturation and Chest X-ray Pre and Post Radiotherapy, within 72 hrs (lightning bold indicates radiation administration).

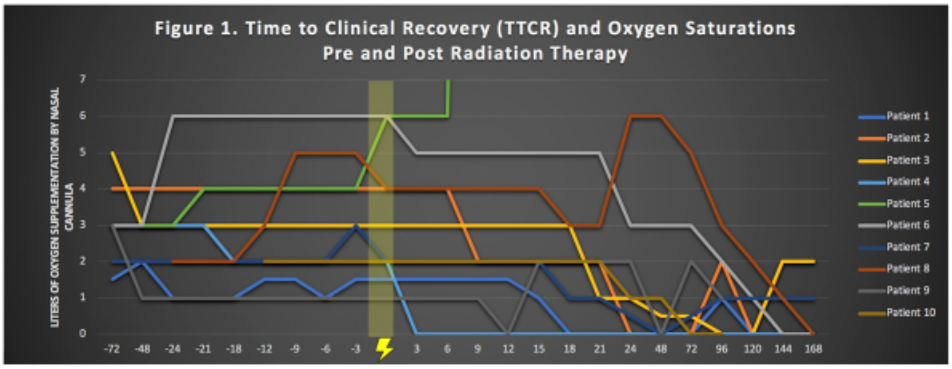
Full Pilot Data From Phase I/II Trial (see updated Figure 1 below with all 10 patients data plotted together);

As of May 28th, 2020, we have completed the Phase I/Phase 2 trial, and now request approval for phase 3. We have completed the treatments of Cohort 1 (5 patients) and Cohort 2 (5 patients), for a total of 10 patients. We found that low-dose radiation delivered prior to intubation may yield a clinical improvement time of just 3 days in a cohort of patients older, sicker, and more oxygen dependent (1-6L) at baseline with worse X-ray findings in the lungs compared to other recently published studies. Our mortality at Day 14 is 0%. [Of note, patient 5 died at Day 15]; This represents an overall survival of 90% as of May 28th, 2020 for all 10 patients treated on our pilot phase 1/2 Trial. Given the older age, severe COVID disease, oxygen dependency, and the multiple comorbidities of our patient cohorts, we are strongly encouraged by a 90% overall survival rate.

The mean time to discharge is 11 days. 83% of all biomarkers showed serologic recovery (safety endpoint) over 7 days. For patients age 65 and older (n=7), 100% percent of patients got off of oxygen within 96 hours, 100% percent of altered patients improved in mental status at 24 hours, 100% showed improvement in follow-up radiographs (day 3-28), 100% of patients recovered, despite large co-morbidity burden, older age, nursing home placement issues over COVID-19 immunity. The finding in our older patient is extremely encouraging. Certainly, much better than what was anticipated when we first conceptualized he trial.

For patients under age 65 (n=3), these patients appear to present with much higher burden of disease. We suspect that this may reflect pulmonary reserve, which allows these patients to develop extreme amount of disease before presenting to the hospital. All of these younger patients were treated at time of impending ICU admission or rapid clinical decline. Thus, we clinically expected them to be the worse actors, and enrolled them anyway on our pilot trial. Despite this, we note a 66% survival (2 out of 3) and rescue from impending ICU admission/intubation. Both patients were weaned off oxygen in a median time of 8 days. We noted signficiant evidence of infiltrate re-absorption at day 7 CT chest.

Full data on Oxygenation Improvement in all 10 patients:



ID (age)	Ordinal Scale for Clinical Improvement by Hospital Day																		Discharge (days after RT)	TTCR
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Patient 1 (90)	4	4	4	4	4	4	4	4	3	3	3	4	3	3	3	3	3	3	Day 23 (15)	18 hours
Patient 2 (69)	4	4	4	4	3	3	4	4	3	4	4	4	4	4	3	1	-	-	Day 16 (12)	24 hours
Patient 3 (94)	5	5	5	4	4	4	4	4	4	4	3	3	4	4	4	4	3	4	Day 21 (14)	96 hours
Patient 4 (93)	4	4	4	4	4	3	3	4	4	4	3	3	3	3	1	-	-	-	Day 15 (10)	3 hours
Patient 5 (64)	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	-	-	Died on Day 16 (15)	
Patient 6 (60)	4	4	4	4	4	4	4	4	4	4	3	4	1	-	-	-	-	-	Day 13 (9)	7 days
Patient 7 (81)	5	4	4	4	4	4	4	4	4	4	3	4	4	4	1	-	-	-	Day 15 (6)	48 hours
Patient 8 (43)	4	4	4	4	4	4	4	4	4	4	3								Pending	8.5 days
Patient 9 (74)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3	Pending	36 hours
Patient 10 (104)	4	4	4	3	3														Pending	60 hours
	1=not hospitalized. 2=hospitalized without need for oxygen or medical care. 3=hospitalized without need for oxygen. 4=hospitalized requiring low-flow supplemental oxygen. 5=hospitalized on high-flow oxygen. 6=hospitalized on mechanical ventilation 7=deceased.																			

Mean TTCR: **3 days** (73 hours) Mean time from RT to Discharge: **11 days** (3 pending)

Radiation Therapy for Benign Diseases, Including LCH and HLH

While most clinicians are familiar with the use of RT in the management of malignant neoplasms, curious practitioners of radiation medicine, based primarily in Europe, have broadened the applicability of RT to a variety of benign indications.

Low to modest doses of RT have proven efficacious in the treatment of immune-mediated inflammatory processes such as Graves orbitopathy. Multiple studies indicate that delivery of 10 to 30 Gy to the orbital tissue behind the eyes, typically via fractions of 1-2 Gy per day, leads to clinically significant improvements, both in subjective symptom scores and objective measurements including eye motility and oculomotor muscle size.[13-15] Long-term follow up of these patients up to and beyond 10 years indicates an acceptably low incidence of complications.[16,17] Randomized evidence comparing RT with systemic corticosteroids demonstrates that RT delivers comparable symptom relief with a lower toxicity burden, suggesting a steroid-sparing benefit with RT.[13]

Other proliferative disorders successfully managed with RT include Morbus Dupuytren, Morbus Ledderhose, and Peyronie's disease. For each of these entities, characterized by fibrotic contractures of the palm(s), sole(s) and penile shaft, respectively, focal RT delivered in 1.5-3 Gy fractions to a cumulative dose of 12-36 Gy has proven effective in reducing pain and in arresting or even reversing the fibrotic deformity in most treated patients.[18-23]

German investigators have explored multiple dose-fractionation schema to treat refractory pain from plantar fasciitis. Both older retrospective series and more recent randomized trials indicate that optimal analgesia occurs at a modest cumulative dose of 3-6 Gy with negligible acute or long-term toxicity.[24-26]

A benign application of RT familiar to radiation clinics on both sides of the Atlantic is the prevention of heterotopic ossification (HO). As a dysregulated inflammatory process supposedly mediates formation of this dystrophic bone,[27] investigators have explored multiple anti-inflammatory strategies to disrupt the process. As compared to systemic non-steroidal anti-inflammatory drugs, RT is equally, if not more efficacious in reducing the incidence of HO, especially when delivered at a moderate dose of 7 Gy in a single fraction.[28-30] As for Graves orbitopathy, RT for HO exerts a local immunomodulatory effect that avoids the undesirable non-local effects of systemic anti-inflammatory treatment.

It should be noted that the indications for RT in the aforementioned patient populations are far from life-threatening, but that RT nevertheless proved both effective in reducing symptoms and safe with a low toxicity burden. This favorable risk/benefit ratio in these low-acuity settings justifies the consideration of RT in patients suffering from higher-acuity disease processes, for whom the potential benefits are considerably higher and the risks are certainly no greater.

Pertinently, focal thoracic RT has been recently used by intrepid American investigators to treat patients suffering from ventricular tachycardia refractory to medical management. This approach, which entails the delivery of a single fraction of 25 Gy directly to an arrhythmogenic focus of the heart, dramatically reduced arrhythmia burden and improved quality of life while causing negligible toxicity in a prospective trial.[31,32]

Numerous mechanisms of action have been proposed to explain the observed anti-inflammatory and anti-fibrotic effects of LD-RT, including depletion through ionizing damage, exudative reduction, and wavelength vibrations causing immune and pathogenic cell disruptions.[3]

COVID-19 Infectious Pathway

The COVID-19 infectious mechanism of action is currently being investigated but is thought to be mediated by inhaled viral particles infecting airway alveolar type II pneumocytes using angiotensin-converting enzyme (ACE) receptor entry points, leading to iterative viral production and a cascading inflammatory event.[33] Macrophage- and monocyte-dominated local infiltration can lead to localized cytokine storms, pulmonary edema, exudative infiltrative inflammation, diffuse alveolar damage, and inflammatory-led myocardial injury.[34-37] It can lead to fatal acute lung injury from inflammatory response for which ACE-receptor modulators, and both steroidal and non-steroidal anti-inflammatories have been proposed.[34,38] Anti-inflammatory agents that are given systemically have to be carefully balanced with adverse unintended consequences (see discussion below about competing clinical trials). While these may be susceptible to systemic anti-inflammatory agents, based on the experience using glucocorticoids in the 2002 SARS epidemic, the World Health Organization (WHO) has advised caution and currently recommends avoidance of glucocorticoid treatments.[36,39]

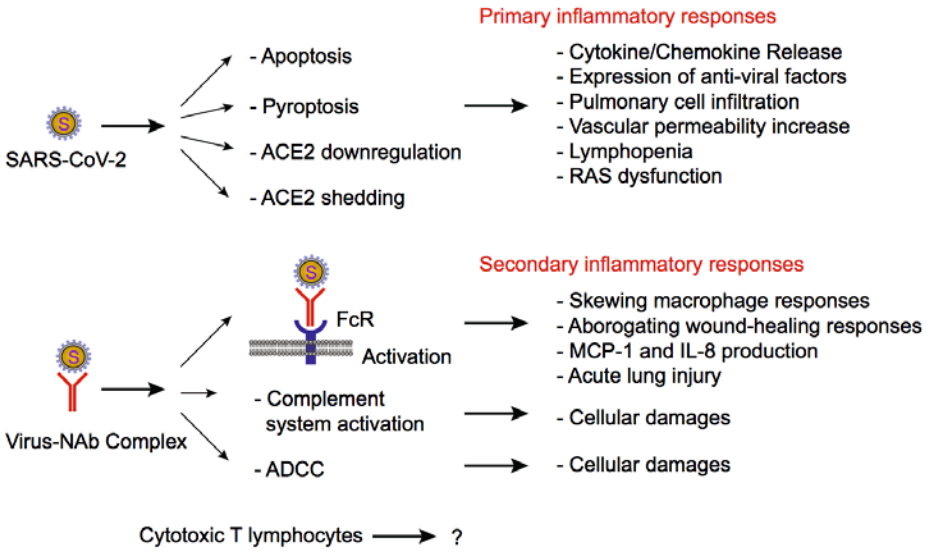


Fig. 1 Possible mechanisms of SARS-CoV-2-mediated inflammatory responses. Based on previous studies of SARS-CoV, we separate the inflammatory responses in SARS-CoV-2 infection into primary and secondary responses. Primary inflammatory responses occur early after viral infection, prior to the appearance of neutralizing antibodies (NAb). These responses are mainly driven by active viral replication, viral-mediated ACE2 downregulation and shedding, and host anti-viral responses. Secondary inflammatory responses begin with the generation of adaptive immunity and NAb. The virus-NAb complex can also trigger FcR-mediated inflammatory responses and acute lung injury.

Figure from Fu, et al.[34]

ARDS Pathways and Interventional Mechanisms

Acute respiratory distress syndrome (ARDS) in COVID-19 patients appears to be induced by a hyperinflammatory syndrome similar to secondary hemophagocytic lymphohistiocystosis (sHLH) or macrophage activation syndrome (MAS).[40] sHLH and MAS are cytokine storm-like syndromes most commonly associated with rheumatologic disorders;,[41,42] however, viral disease in both preclinical models and in the clinic have been shown to induce a similar phenomenon.[43,44] Pre-clinical data has shown CD8+ T-cell dysfunction is critical for sHLH development following a viral infection with CD8+ T-cell secreted IFN-gamma being an important mediator.[43] Mehta *et al.* noted that severe COVID-19 patients have a cytokine profile similar to sHLH characterized by increased IL-2, IL-6, and interferon-gamma.[40]

The data governing the role of induced immunosuppression in COVID-19 is currently mixed. There are on-going clinical trials evaluating blockade of IL-6 (ChiCTR2000029765). No current clinical evidence suggests a net benefit for ARDS mitigation with globally immunosuppressive corticosteroids in SARS-CoV, MERS-CoV or SARS-CoV2 infections,[45] although this may depend on the timing of steroid administration.[46] It is conceivable, however, that focal immunosuppression with local radiation to areas of immunopathology (i.e. the lung) may avoid globally immunosuppressing the systemic anti-viral response while mitigating the pulmonary inflammation.

Lymphocytes, a main mediator of sHLH, are exquisitely sensitive to ionizing radiation with a D_{90} (dose required to reduce the surviving lymphocyte population to 90% of initial values) of 0.5 Gy.[47] Additionally, fractionated radiotherapy can induce lymphopenia.[48] We and others have shown that fractionated radiation to a murine lymph node can deplete irradiated lymphatic tissue for up to one week and induce local immunosuppression with a decreased local anti-tumor CD8+ T-cell response (Buchwald et al., *Under Review*).[49] Interestingly, the data evaluating pulmonary irradiation and inflammatory infiltrates is highly dose- and timing- dependent. Paun et al. showed increased lymphocytic lung tissue infiltration at day 1 and 7 following 18 Gy to the whole thorax.[50] In contrast, Zheng et al. showed that 2.5 Gy TBI induces a delayed pulmonary inflammatory reconstitution with a CD8+ T-cell minima at 3 days post irradiation.[51] Importantly Zheng et al. did not show a rebound increase in lung T-cell infiltrates at later time points following RT. This suggests that a low radiation dose may be effective at inducing transient lympho-depletion within the lungs without inducing a subsequent pro-inflammatory rebound.

The probability that lymphoid-depleting LD-RT will have clinical effect in reducing the HLH-mediated cytokine storm in COVID-19 patients is arguably most well-informed by the published outcomes of patients irradiated for other histiocytic disorders. Among these, clinical experience with LD-RT for the treatment of Langerhan's-cell Histiocytosis (LCH) is most robust. Investigators report phenomenal response rates of over exceeding 90% of among patients with LCH. Complete responses range from 76%-93% with the majority of those remaining the remainder experiencing partial responses following LD-RT to doses typically ranging from 6 to 20 Gy.[52,53] Non-LCH histiocytoses are comparatively rare, with HLH being the next most common and clinically characterized by hyperactivation of ordinary macrophages and lymphocytes leading to the systemic hyper-inflammatory syndrome discussed previously.[54] We suspect that if the efficacy of radiotherapy is so effective in treating LCH, it should also help may also extend to mitigate the sHLH in COVID-19 patients.

In still further support of our mechanistic hypothesis, LD-RT has actually been used for the treatment of HLH itself in select case reports. Shinoda et al reported successfully treating a 5-year-old girl with HLH isolated to the central nervous system with complete resolution of the disease and improvement in neurological symptoms.[55] Fischer et al. reported described theon successful treatment of four patients with erythrophagocytic lymphohistiocytosis that were successfully treatment withusing a multifaceted treatment approach combination therapy that involved included cranial irradiation;[56] Hale et al reported on 5 children, 2 with LCH and 3 with HLH, who were successfully treated with LD-RT-based conditioning regimen, where total body irradiation (TBI) was the essential component of successful treatment.[57] Hege et al reported successful treatment using a reduced-intensity regiment based on 4 Gy TBI in a recurrent HLH patient who previously failed a non-TBI based conditioning regimen. Nishi et al reported on use of reduced intensity TBI-based conditioning regimen (using 2-4 Gy) to successfully treat 13 patients with familial hemophagocytic lymphohistocytosis (FHL) and no significant grade > 2 treatment related toxicity.[58]

Thus, it is plausible that radiotherapy may alter the course of the sHLH-mediated inflammatory storm observed in COVID-19 and therefore warrants further study.

Inflammatory hallmarks of COVID-19 (Table 2)

The clinical course of COVID-19 entails three phases;[59] the viremia phase; acute phase (viral pneumonia); and either a recovery phase or severe/critical phase. Given an appropriate immune response during the first two phases, there is a high likelihood that the patient will clear the virus and recover.

However, if the immune response is disproportional, a severe phase and criticality can occur, characterized by a hyperinflammatory state associated with mortality [60], [1], [61]. In this severe phase, a systemic inflammatory response develops that is characteristically the result of cytokine storm, in which there is excessive production and systemic release of the pro-inflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α [40] (see further table 2 below).

This state resembles that observed in other hyperinflammatory conditions, such as cytokine storm after CAR-T-cell therapy, thus, blocking of the IL-1 and/or the IL-6 receptor may be an effective treatment option in COVID-19 patients [62], [63]. We advocate that, these immunomodulatory drugs should be used cautiously, as they may prolong viral shedding and can be associated with infectious complications.

Anti-inflammatory effects of LD-RT (Table 2)

LD-RT is known to affect both immune and endothelial cells. In vitro, LD-RT results in apoptosis and decreased adhesion of leukocytes to endothelial cells (when administered at doses of 0.1 – 0.5 Gy) [64]. This decreased adhesion may be caused by a lower expression of E-selectin, an adhesion molecule expressed by endothelial cells (which has been shown to occur, after exposure to 0.3 – 0.5 Gy) [65]. In a mouse model of collagen-induced arthritis, an increase in regulatory T cells, which is capable of dampening immune responses, was observed after treatment with LD-RT [66].

Of interest, LD-RT has been shown to mitigate the proinflammatory effects of macrophages in murine studies. Prior to stimulation with lipopolysaccharide and interferon (IFN)-γ, LD-RT reduced the secretion of nitric oxide by macrophages [67]. Furthermore, proinflammatory cytokine production by macrophages in response to stimulation with lipopolysaccharide was shown to be suppressed by LD-RT [68]. Similarly, the secretion of reactive oxygen species by macrophages was depressed by LD-RT when administered at doses between 0.3 and 0.6 Gy [69].

Calabrese et al suggested that LD-RT induces polarization of M1-type macrophages to the anti-inflammatory M2-type [70]. This polarization distribution is probably not absolute, but rather represents a combinatory state of differing macrophage phenotypes. This M1- to M2- phenotypic conversion may be important to clinical outcomes of inflammatory disease, as the M2-type macrophage secrete anti-inflammatory cytokines, IL-10 and TGF-β1 and suppress IL-6.

Patients felled by critical COVID-19 illness (i.e.- hyperinflammation) have been shown to have high levels of cytokines, particularly IL-6 [60] as constituent to cytokine storm. In this light, we opine that LD-RT may be beneficial in reducing the pro-inflammatory effects and multi-organ manifestations of cytokine storm. Table 2 specifically addresses the pro-inflammatory cytokines LD-RT have shown to reduce, as compared to the inflammatory cytokines upregulated in COVID-19. We posit that low radiation doses of 1.5 Gy may suppress the inflammatory environment and mitigate or prevent the severe/critical phase of COVID-19, including ARDS.

Table 2
Pro-inflammatory Cytokines

Increased in COVID-19	Reduced with LD-RT
TNF-α [40,71[71]]	TNF-α [72[72]]
IL-1β [71[71],38*]	IL-1β [72[72]]
IL-2/R [71[71],38*]	IL-2 [73[73]]
IL-6 [71[71],38*]	IL-6 [74[74]]
IL-8 [71[71]]	IL-8 [75[75]]
INF-γ [71[71],42*]	INF-γ [76[76]]

References for Table 2 (need add to reference database);

[38] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393. https://doi.org/10.1016/j.clim.2020.108393.

[42] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. ACS Cent Sci 2020;6:315–31. https://doi.org/10.1021/acscentsci.0c00272.

The Landscape of Competing Trials

Since the December 2019 outbreak of COVID-19, the academic community has collectively responded to the virus' evolutionary evasion of immune defenses with its own iterative counter punches in the form of observational and therapeutic investigations and clinical trials. Agents currently under investigation include mechanism that act on the innate or adaptive immune response pathway (IL-6 blockade with Siltuximab, Tocilizumab), protease inhibition of viral replication (Oseltamivir, Favipiravir), pH modification for enzymatic lysosomal inhibition (anti-malarial drugs hydroxychloroquine and chloroquine), convalescent serum/plasma, angiotensin-converting enzyme (ACE) Inhibition and angiotensin-II type 1 receptor blockade (ARB), non-steroidal anti-inflammatory drugs (cautionary), steroidal anti-inflammatory drugs (cautionary) and vaccination development. Other efforts include but are not limited to phosphodiesterase enhancement (sildenafil), BCG vaccine, bevacizumab, and iron chelation with deferoxamine.[77]

Globally, as of May 2020, more than 3.3 million have been infected leading to over 240,000 deaths. Early data from Lopinavir-Ritonavir phase 3 randomized trial demonstrated a mean time to clincial improvement of 15 days, which was no different than than the observation arm of 16 days. The average age in this trial was 58 yrs old, and the 28 day mortality was 25% in the experimental arm vs 19.2% in the experimental arm. 23% of the patients died within 12 days after onset of symptoms. Only 6% in the experimental arm had improvements within 7 days in the experimental arm and only 2% in the observation arm.

Of note, patients in the lopinavir-ritonavir trial (NEJM, Cao et al. PMID 32187464) were only required to have less oxygen needs than our patients. The inclusion criteria was that if they were on room air, and if they saturated at or below 94%, the were allowed to go on the trial. Our patients, however, had to be dependend

on oxygen, and had to have bilateral xray findings. Despite our elderly patients (mean age 82), higher glasgow coma scale, higher Charleston comorbidities score, and higher requirements to be on our trial, the response rate of clinical improvement were much faster with low dose whole lung radiotherapy. Mean mean time for clinical improvement on he current Remdesevir trial was 11 days. We observed a mean time to clinical recovery of around 1.5 days in 80% of our patients. For statistical considerations, we will use a more conservative estitmate (see stats section).

No Current Standard Of Care Treatments Exist for COVID

As of June 2020, there are no standard of care treatment for hospitalized COVID patients. There has been no therapy that has shown any signficaint success in terms of increasing a patient's ability to get out of the hospital any faster, prevent them from going to the ICU, or extend their overall survival. The recently published randomized double blinded placebo controlled multicenter trial that tested remdesivr vs placebo conducted amongst 10 hospitals in China in 237 patients did not show any signficaint clinical benefit (Wang et al. Lancet. 2020. May. 395(10238):1694; Another trial from the United States (Biegel et al. NEJM. May 2020. DOI:10.1056/NEJMMoa2007764) changed its primary endpoint during the trial, and found that remdesivir was superior to placebo in shortenting time to recovery based on improvement in oxygen status in hospitalized CVOID-19 patients. However, there are several scientific criticisms regarding this trial, and many leading scientist have concluded that this still does not define the standard of care for COVID -19 patients (i.e. personal communication with Dr Aneesh Mehta, one of the co-authors on this paper). Furthermore, there was no benefit in the subgroup not receiving oxygen, and patients on high blow oxygen or were on non-invasive mechanical ventilation. Additionally, this minor improvement on oxygen dependency in a subgroup of patients did not translate into early hospital discharge, prevention of ICU admission, and/or extended survival in the patients that received Remdesivir. Thus, there is currently, no standard of care therapy for hospitalized COVID patients. Furthermore, there has been no vaccines or therapeutic prevention methods that have received FDA approval based on any phase 3 data. Thus, we believe that our phase 3 trial of best supportive care plus physician's choice vs best supportive care plus whole long LD-RT is reasonable.

Expected risks with radiotherapy:

Risk of radiotherapy are minimal in the near term. A single fraction of 1.5 Gy to the whole lung rarely causes any acute side effects. There is a small chance of mild fatigue and skin reaction. However, we did not observe this in our small cohort. On the contrary, most of our patients actually improved as their oxygen status improved. There is a hypothetical risk of worsening the cytokine storm in the short term. However, this was not noted in our patients, as more than 50% of biomarkers improved. In the long term, there is small risk for secondary cancer. However, radiotherapy is commonly used in many cancer and non-cancer indications with much lower mortality rates. And we accept the risk for secondary cancer in these indications. An example is a keloid patient, which have a very (nearly 100%) long term chance of surviving from their keloid. We use radiotherapy primarily for cosmetic reasons to provid local control, and we accept a very small risk of radiation induced cancer many years later. Furthermore, the radiotherapy uses for keloid patients is on a order 20-30 times higher than what we are using in our COVID cohort

Ventilator-dependence need for ICU admission, and mortality of the critically ill are extremely high in COVID-19 patients. Intubation rates are 70-75% of those admitted to the ICU, the mortality 50-70% and the extubation rate was only 20% at 3-4 weeks post ICU admission (including at EUH, personal communication).[78] Among those with cardiomyopathy, mortality rates in ICU patients have been reported at 70%.[79] Ventilator duration was estimated at 1-2 weeks for non-survivors and longer for survivors.[78] Thus, if we can improve and/or prevent hospitalized patients from becoming dependent on a ventilator by improving their oxygen needs earlier in the course of treatment, we would have provided significant medical value and the benefits of radiotherapy would outweigh the potential long risk of a secondary malignancy, in a population with very high early mortality rates.

2.3 Potential Risks and Benefits

EXACERBATION OF EXISTING COVID-19 SEQUELAE

Investigation into the safety of whole-lung low-dose radiation in critically-ill patients with SARS-COVID-19 requires prediction of potential interactions between low-dose ionization events and all previously-reported symptoms and adverse outcomes associated with SARS-COVID-19. Low-dose radiation therapy is a well-tolerated and well-studied treatment. 150cGy is unlikely to cause acute toxicity other than fatigue and transient cytopenia, and is much lower than what has been previously used in reduced intensity conditioning TBI-based regiments to treat HLH.

Symptoms

Fever, cough, myalgia, fatigue, sputum production, headache, hemoptysis, diarrhea, dyspnea have all been reported with COVID-19.[1] Radiation therapy to the whole lung at a dose of 150cGy is associated with very low rates of acute toxicity with symptom onset, with the possible exception of fatigue. Radiation may exacerbate the pre-existing fatigue of COVID-19 patients. Otherwise, few acute toxicities are anticipated with low dose lung radiotherapy.

Adverse Outcomes

To date, the virus has been associated with high mortality, as well as adverse sequelae including but not limited to lymphopenia, leukocytosis, leukopenia, hypoalbuminemia, pneumonia, abnormal chest CT, acute cardiac injury, acute respiratory distress syndrome, secondary infection, lung parenchyma destruction, diffuse alveolar damage, cardiomyopathy, brain injury, pleurisy, pericarditis, shock, and cytopenia.[1,80,81] Brain injury data is anecdotal and limited and will not be further discussed since at the time of protocol preparation, too little data has been published to inform discussed of the potential impact of LD-RT on neurologic injury -- likely negligible.

ARDS/Lung Parenchyma Destruction/Pulmonary Edema/ Pleurisy/Pneumothorax (45-80%)
Pneumocyte hyperplasia, focal Inflammation, and diffuse alveolar damage with exudates have been reported in COVID-19 patients, with predominantly lymphocytic, and multinucleated giant cells seen alongside large atypical pneumocytes.[80] Whole-lung irradiation is unlikely to contribute to this inflammatory damage because of the very low dose of 150 cGy per fraction. Pneumonitis constraints for lung radiation treatments limit the total lung volume receiving 5 Gy of radiation to be 60%or less (V5<60%). This is unquestionable achievable so long as no COVID-19 patient receives more than 3 fractions of 1.5 Gy (4.5 Gy total).[82]

Cardiomyopathy/Myositis/Heart Failure/Pericarditis (15-30%)
Patient with SARS-COVID-19 can develop cardiac injury diagnosed through elevated troponin levels.[1] Evidence of this injury has been strongly correlated with mortality in initial studies of early disease cohorts from Wuhan, China.[81] Mortality rates for those with underlying cardiovascular disease and elevated troponin levels is reported by numerous authors at 70%.[35,79] Proposed mechanisms include increase myocardial load, immune-cell disruption, dislodgement of existing atherosclerotic plaque, and even direct myocardial muscle invasion by viral pathogen.[79] Radiation therapy can induce late toxicity wherein the risks of accelerated atherosclerosis, but this is unlikely to occur in the acute phase of acute pulmonary infection and thus LD-RT is unlikely to exacerbating COVID-related cardiac morbidity.

Liver + Biliary Dysfunction (60%)
SARS-COV-2 shares 82% and 50% genetic homology to prior coronavirus infections SARS-COV and MERS, which each reported liver injury incidences of around 60%.[83] In 14-62% of COVID-19 patient, elevated AST and ALT were observed.[1,84] Radiation-induced liver injury (RILD) is a rare late radiation toxicity typically avoided by liver constraints that preserve portions the whole liver dose to 30 Gy.[84] Our proposed dose of 1.5 Gy may overlap with the upper portion or perhaps all of the liver, but our dose is 10-20 times lower than the published tolerance and thus unlikely to contribute significantly to COVID-related liver injury. Gamma-glutamyl transferase (GGT), a marker of cholangiocytic injury, as well a AST/ALT can monitor for liver/biliary injury in COVID-19 patients undergoing whole lung LD-RT.

Hypovolemic Shock//Cardiogenic Shock/Septic Shock (20-35% in ICU patients)
There is increasing data that COVID-19 infection can lead to shock through a variety of mechanisms including cardiac injury, superinfection, and superimposed hypovolemia.[85] Radiation therapy has little impact on the volume status or fluid balance and is unlikely to exacerbate this COVID sequelae.

Cytopenia/Lymphocytopenia/Splenic atrophy (80%)[86]
Radiation to the whole lungs has the potential to exacerbate cytopenia, since thoracic radiation alone is known to induce lymphocytopenia and could worsen this outcome in COVID-19 patients.[87]Decreased numbers of lymphocyte, cell degeneration and necrosis have been observed in the autopsy reports of spleens following lethal COVID-19 infection. The propensity for low-dose radiation therapy to focally deplete the immune system is both the mechanism objective of this protocol, but also could deplete the lymphocyte stores in the adjacent spleen – although likely transiently - which could hypothetically exacerbate splenic necrosis and further deplete lymphocytes outside of the intra-pulmonary cytokine storm,[36] but this is unlikely and has not previously been observed at such low doses.

Steroid-related Injury

Systemic anti-inflammatory medications have been deemed contra-indicated in SARS-COVID-19 by the World Health Organiztion.[39] Numerous reports have reported higher rates of adverse outcomes with the addition of systemic corticosteroids, including shock, acute kidney injury, high plasma viral load, prolonged viremia, and secondary infection.[1,2] These adverse events are particularly relevant to our investigation as adverse outcomes associated with anti-inflammatory interventions were somewhat surprising but sufficiently consistent to prompt the WHO to recommend against them. The current protocol proposes anti-inflammatory intervention but at the local level rather than systemic precisely to assess whether local anti-inflammatory effect and focal immune modulation can rapidly improve outcomes as it did in lobular, viral, and interstitial pneumonias the pre-antibiotic era.[3]

INHERENT RISKS OF LOW-DOSE RADIATION THERAPY ARE LOW

Whole Lung Dose

Lung irradiation is a well-studied treatment for both childhood and adult malignancies. Lung RT has well-established dosimetric threshold limits for the avoidance of toxicities such as radiation pneumonitis.[88,89] Children with metastatic cancer such as Wilm's tumor or Ewing sarcoma have been receiving whole-lung irradiation to doses of 15-18 Gy for decades, delivered in 1.5 Gy daily fractions over 10-13 treatments.[90] Total-body irradiation (TBI) for marrow ablation is common in the setting of stem cell transplant, utilizing doses around 12-14 Gy, but again typically delivered in smaller fractions of 1.5-2.5 Gy per day with lung blocks to

reduce pulmonary exposure.[91] Safety parameters for single-fraction radiation therapy has, more recently, been established for palliation of lung metastases at dose ranges of around 8 Gy per fraction or as high as 34 Gy per fraction for peripheral non-small lung cancers.[92,93] The proposed single-fraction dose (1.5 Gy in a single treatment) is considerably lower than any of these published lung toxicity thresholds. Even if multiple fractions were delivered, -dose volume constraints (V5<60%) would not be violated, and even these were not predictive of pneumonitis in a recent large trial.[82] Given this plethora of clinical experience, there is little risk of acute or late pulmonary toxicity following 150 cGy delivered in single fraction. Yet, this low dose of 1.5 Gy approximates an equivalence dose similar to the range of radiation doses reported as effective for various infections in the pre-antibiotic era (50-550 Roentgen).[3,88]

Risk Mitigation Strategies

Delivery of external radiotherapy to COVID-19 positive patients is within the standard operating procedures of the Winship Cancer Institute. However, there is risk of COVID-19 transmission to healthcare workers and contemporaneous COVID-19 negative patients. Risk mitigation strategies continue to evolve as new clinical data and best practice guidelines become available. Strict adherence to the most up to date intuitional guidelines for distancing, personal protective equipment, and disinfection is critical.

Mechanisms of transport

Patient transport to the department of Radiation Oncology will be at the discretion of the patient's primary intensivist. Adequate monitoring of patients during transportation and treatment in Radiation Oncology is required. Monitoring during transport guidelines will be established by the intensive care unit. In general, the patient's ICU nurse is recommended to travel with the patient and remain present throughout treatment and transport back to the ICU. EMS transportation may be required per ICU guidelines. Standard of care transport and monitoring guidelines will be followed.

The pathway through the department and into the designated treatment room will be clearly marked with signage. Radiation therapy staff will escort the patient from the doors of the department to the treatment room.

Pre-arrival strategy

This experimental radiotherapy will be delivered entirely outside of normal clinical hours. This will dramatically reduce the risk of transmission to COVID-19 negative patients and staff. Experimental treatments will be blocked together as much as feasible in order to minimize the total number of treatment sessions. A single treatment session is preferred.

All staff and providers are required to have completed all institutional PPE training. Prior to each treatment session, the radiotherapy treatment care team will meet to review PPE guidelines, including donning and doffing, clinical care plan, and post-treatment disinfection plan. At a minimum all staff and providers will wear N95 masks, approved face or eye shields, double gloves and gowns.

A single treatment machine will be designated for all treatments in the session. Clear plastic coverings will be placed over the radiation therapy treatment consoles, keyboards, and mouses and follow department standard operative procedures for COVID+ patients.

Using all available diagnostic imaging, a preliminary treatment plan will be generated by the treating radiation oncologist and dosimetry staff for each patient.

Strategy during RT delivery and planning
The clinical care plan will strive to minimize the time required to plan and deliver radiotherapy. The treating Radiation Oncologist will be available throughout the treatment session without other required clinical responsibilities. A medical physicist and dosimetrist will be available remotely as well.

Patients will be treated in the gurneys in which they are transported if at all possible, but moved onto the treatment table, if necessary, taking care to safely maintain the endotracheal tube and all lines. The ventilator will be positioned that such that the readout screen and vital signs are visible through the video monitoring system. During treatment planning, the patient will remain secured in his or her gurney on the treatment table. The radiation therapy staff will take special care to ensure no loose hanging materials (e.g. sheets, lines, etc.) come into contact with the linear accelerator during imaging or treatment. Radiation therapists will be instructed not to handle the in-room control wand to move the treatment couch or gantry.

Post-departure strategy
Once the patient has departed the Radiation Oncology area, the staff will change outer gloves but otherwise maintain all other PPE for the next scheduled patient. Standard cleaning procedures of the treatment room will be followed between patients. Staff and providers will be instructed to avoid entering any areas outside of the designated path and treatment area. Standard departmental procedures for COVID + patients will be followed.

At the conclusion of the treatment session, a deep cleaning procedure will be instituted that will include the treatment room, the treatment console area, and the entire pathway of transportation used during the session. Radiation Oncology staff will personally observe cleaning of these areas by environmental services. Approved cleaning materials will be used as referenced in the Emory Ambulatory Cleaning Protocol (http://www.ourehc.org/departments/communicable-diseases/ambulatory/cleaning-algorithm.pdf).

All high touch surfaces will be cleaned including but not limited to the following:

- Door knobs or door open/close buttons
- Treatment Table (including control wand)
- Cabinet handles
- Countertop
- All faucet handles
- All treatment keyboards, mouses, and control panels (following disposal of clear plastic coverings)
- All patient hand rails throughout the path from door to treatment room

The designated linear accelerator will not be used for any patient treatments for at least 12 hours after the last COVID-19 positive treatment patient. However, once the linear accelerator is cleaned per departmental protocols, the linear accelerator may be used thereafter.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
PHASE III	
To investigate clinical recovery, radiographic, and immune outcomes in critically-ill patients with COVID-19 pneumonia following best supportive care plus provider's treatment choice versus best supportive care plus low-dose whole-lung radiation therapy (LD-RT).	Clinical • time to clinical recovery* • freedom from intubation • temperature • heart rate • blood pressure • oxygen saturation • supplemental oxygenation need* • respiratory rate • Glasgow Comma Scale pre and post tx • performance status • time to hospital discharge • freedom from ICU admission • survival Radiographic • serial chest x-rays SARS scoring • Changes on CT scans pre and post RT Inflammatory and serologic markers • CRP/ESR/LDH/D-Dimer/ IL-6 • serum chemistry + CBC with differential • blood gases (when available) • albumin/ potassium • procalcitonin • AST/ALT/bilirubin • creatine kinase/ myoglobin • PT/PTT • troponin • lactate • NT-pBNP (cardiac injury) • Gamma-glutamyl transferase (GGT) • Triglycerides • Fibrinogen/Ferritin • may include CD 8 Tell, CD 4 T cells, cytokine analysis, other immunological biomarkers, RNA/DNA sequencing

* statistical analysis endpoint.

4. STUDY DESIGN

4.1 Overall Design

Phase III Clinical Trial

Primary Objective: Time to Clinical Recovery based on reducing the need of supplementary oxygenation in COVID 19 patients.
Secondary Objectives: To investigate (1) clinical, (2) radiographic, and (3) immune marker response to best supportive care plus whole-lung LD-RT compared to best supportive care plus provider's treatment choice. Will monitor improvement in chest xrays, changes in glasscow comma scale, time to hospital discharge, overall survival, freedom from intubation, freedom from ICU admission, and changes in biomarkers.

Intervention: LD-RT will be delivered to the bilateral whole lungs using a clinical set up to a dose of 150 cGy in one fraction. All patients be approached for enrollment within the 5 (+/- 2) days immediately preceding the designated treatment. Patients will be treated in subsequent 30 minute- time slots on the linear accelerator using a hand-calculation of dose and the required machine monitor units for their individual source-to-surface distance (SSD), field size, and soft tissue thickness. Hand calculations will be prepared prior to patient arrival to department and will be based on patient separation as determined from prior diagnostic CT scan, so as to expedite treatment delivery. Patients will be treated while laying flat or sitting upright at angle of optimal respiration.The gantry may be rotated perpendicular to this position and positioned at extended SSD so as not avoid transfer from gurney to treatment table, when needed. Treatment will be delivered with open fields with jaws set below the diaphragm and above the lung apices as seen by light fields or kV/mV imaging with lateral skin flash. Treatment will be delivered in anAPPA technique.

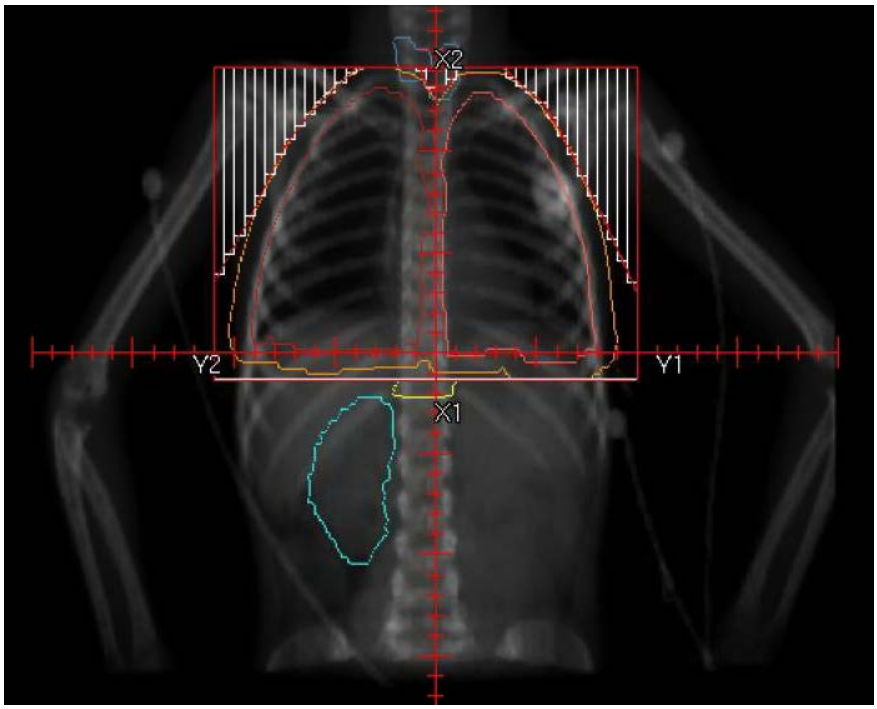


Figure 3. Representative Lung Fields.

Personnel present
- Qualified medical physicist (in person and/or remote)
- Faculty radiation oncologist x 1 (PPE protected)
- Radiation Therapists x 2 (PPE protected)

Equipment needed
- Megavoltage linear accelerator
- Shielded vault
- Computerized dosimetry

Patient positioning
- Supine or inclined at angle for optimal respiration in transport gurney with arms secure laterally at the patient's sides not overlapping the thorax.

Patient imaging
- Kilovoltage or megavoltage (kV/mV) on- board imaging

Manual calculation of dose
- As per TG-51 recommendations[94]

Population: The study population will be divided into two cohorts using central randomization approach once a patient has signed consent. The first cohort will undergo best supportive care plus provider's choice of available treatments (which would couldbe, azithromycin, remdesivr, etc. and/or whatever FDA approved treatment may be at that time). The second cohort will proceed with best supportive care plus low dose radiotherapy on this trial.

Stopping Rule: For the experimental arm, we would evaluate the first 8 patients treated on radiation arm for toxicity or worsening cytokine storm, and their outcomes will be compared with the first 8 patients treated on the provider's choice arm (i.e. remdesivir, etc). See stats section below.

Interim efficacy analysis:

1) We would do an interim anlysis after the first 8 patient treated on each arm to compare for primary and secondary endpoints at day 14. See stats section.

Intervention sites: Winship Cancer Institute, Emory University Hospital, and Emory University Hospital Midtown, Emory Saint Joseph's Hospital.

The investigational nature and objectives of the trial, the procedures involved, their attendant risks and discomforts will be carefully explained to the subject or the subject's parents or guardian if the subject is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

Patients and/or their legal surrogates will provide written informed consent/assent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam).

After signing the ICF, patients will be evaluated for entry criteria during the screening period. Rescreening after screen failure will be allowed. Documentation of the informed consent for screening will be maintained in the subject's research chart.

4.2 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure as shown in the Schedule of Activities (SoA), Section 1.2 OR if the trial has achieved superiority of one arm over another for the primary endpoint and/or secondary endpoints. If the primay endpoint is met, the trial may still continue to see if secondary endpoint differences also tend to occur or not. At this point, the trial may undergo an expansion and repowering for the secondary endpoint (but, only after IRB re-approval).

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

Patients are expected to be hospitalized, possibly incapacitated,sedated, or otherwise unable to provide informed consent for themselves. Next of kin or legal surrogate will be approached to screen for enrollment. Since no visitors are allowed in COVID ICU units, telephone-based or video-conference based consents will be obtained.

5.1 Inclusion Criteria

Inclusion criteria for the patients must

a. Be age 18 or over; Not pregnant (will undergo pregnancy testing if below age 50);

b. Have had a positive test confirming the diagnosis of COVID-19*

c. Have had clinical signs of severe acute respiratory syndrome or pneumonia (ie. dyspnea, cough, fever) that primary team feels like patient needs rescuing with treatments.**

d. Have visible consolidations/ground glass opacities on chest imaging.***

e. Requiring supplemental oxygen****

f. Willingness and ability of the subject to comply with scheduled visits, protocol-specified laboratory tests, other study procedures, and study restrictions.

g. Evidence of a signed informed consent/assent indicating that the subject is aware of the infectious nature of the disease and has been informed of the procedures to be followed, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

It is encouraged but not required that:
* patients have tested COVID positive within 72 hours of enrollment
** patients be enrolled and randomized within their first week (7 days) of hospital admission +/- 2 days.
*** patients have *bilateral* infiltrates or peripheral ground glass opacities.
**** patients undergo attempted weaning of supplemental oxygen prior to enrollment and demonstrate inability to tolerate room air for a 12-hour period wherein they consistently maintaining saturations >90%.

5.2 Exclusion Criteria

a. Use of disallowed medications prior to randomization, including remdesivir, hydroxycholooquine, glucocorticoid steroids or other COVID-directed therapies. This does not apply to azithromycin given its lack of published efficacy. Azithromycin must be discontinued at the time of enrollment but does not exclude a patient from study participation. After enrollment, patients randomized to receive best supportive care plus provider's choice of therapy may receive any COVID-directed therapy at provider discretion. However, administration of COVID-directed therapies is prohibited for patients randomized to the interventional arm of best supportive care plus radiation, with one exception. If a patient who has received radiation therapy experiences clinical decline after radiation delivery and requires intubation or mechanical ventillation, he or she may thereafter receive any COVID-directed therapy at providers' discresion.

b. Pregnant and/or planned to be pregnant within in next 6 months. (will undergo pregnancy testing)

6. REGISTRATION PROCEDURES

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

6.1 Local Winship Procedures

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

6.2 Study Enrollment

Enrolling a subject requires careful screening and determination of eligibility.
Subjects may be enrolled on the study once all eligibility requirements for the study have been met. Subjects who give informed consent for the protocol should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria.
Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.
When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off.
Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and “on study” status.
The date protocol procedures are projected to start must be no later than 14 calendar days after the date of study enrollment. Subjects must not receive any protocol blood draws prior to enrollment.
All clinical data required for determining eligibility of a subject enrolled on this trial must be available in the subject’s medical or research record which will serve as the source document for verification at the time of audit.

7. STUDY INTERVENTION

7.1 General Concomitant Medication and Supportive Care Guidelines

Best supportive care will be administered by direction of supervising internist or intensivist.

COVID-directed therapies (remdesivir for example, or other drugs) are allowed on the control arm receiving best supportive care plus provider-directed therapies. The use of COVID-directed therapies prior to enrollment is exclusionary and prohibited in patients randomized to the investigational arm with a severity exception (see section 5.2 above).

7.2 Duration of Follow Up

Patients will be followed until the patient's withdrawal of consent or loss to follow up, death, or study termination, planned for 14 days following first administration of LD-RT as listed on work flow table.
• All patients will be contacted during day 3 (+/- 2 days) of the first week following the last intervention, day 7 (+/-2 days), and at day 14 day (+/- 1 week). Blood draws will occur at baseline, before RT delivery, at days 3 (+/- 2 days) and 7 (+/- 2 days) following RT delivery, and one convalesce lab draw after disease recovery. Blood drays at day 14 is optional (but encouraged). Blood draws can be off by +/- 3 days due to logistical reasons.
• In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study procedures. If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

A participant will be considered lost to follow-up if one fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.3 Withdrawal from the Study

Participants, upon request, are free to withdraw or discontinue from participation in the study at any time, for any reason, and without prejudice to treatment.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

• Occurrence of a clinically significant AE found to be unacceptable or non-resolution of clinically significant AEs or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
• Symptomatic deterioration, disease progression which requires discontinuation of the study procedures.
• Significant noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of the Investigator.
• If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
• Continued participation is no longer in the patient's best interest in the opinion of the Investigator.
• Withdrawal of consent.

In the event of a patient's withdrawal, the Investigator will make every effort to complete the EOT procedures specified in the Schedule of Events.
The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).
Subjects who sign the informed consent form but do not proceed to the study procedures may be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Schedule of study procedures

Screening Phase

All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Prior anti-infectious medications for current COVID-19 course of disease
- Complete physical exam
- ECOG Performance Status,
- Glasgow Comma Scale assessment
- Use of any supplemental oxygen and O2 saturations.
- Vitals signs, weight and height
- Review of prior/concomitant medications
- Serologic studies
- Chest imaging

8.2 Description of study procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints,

extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs. A communication order will be placed in the chart of each enrolled patient to ensure proper measurement of fever, stating, "Clinical trial patient. No Tylenol."

Oxygenation

Both arms will follow identical standardized oxygenation weaning processes:

1. Oxygenation weaning will be attempted following enrollment for all patients with the exception of any patient whose oxygenation requirement or dyspnea has increased within the prior 12 hours. Patients with escalating symptoms are excempt from weaning until they have experienced stabilization of oxygen requirements for 12 hours.
2. For patients who have not required an increase in oxygenation in the immediately preceeding 12 hours, weaning will be attempted at least twice daily (at least one attempt per 12-hour nursing shift) over the 14-day trial.
3. To achieve this, a communication order will be placed into the chart requesting door signage that reads: "Clinical trial patient: attempt oxygen wean twice daily (at start of each nursing shift). Maintain sats above 90%."
4. Patients in both arms will be allowed to request additional weaning as tolerated.
5. Designation as having returned to room air will require that a patient remain on ambient air for 12 consecutive hours with no more than one documented transient drop below 90%. A second documented drop below 90% in the same 12-hour period will re-set the monitoring period. Any drop below 85% will reset the monitoring period. Worsening patient dyspnea or work of breathing that clinically merits a return to a higher oxygen level also resets the 12-hour monitoring period.
6. Patients who required chronic home oxygen supplementation at baseline and who were admitted with oxygenation requirements above baseline will be considered clinically recovered when their oxygen requirements return to their baseline use for a minimum of 12 consecutive hours.

Clinical laboratory tests

The following clinical laboratory tests may be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- COVID-19 testing.
- Viral testing using standard of care clinical procedures and timelines, which may include BAL, NP swaps, mouth swabs, etc to determine viral loads.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

Phase III investigation of efficacy of one-time low-dose radiation treatment for COVID-19 pneumonia. Our primary endpoint is the time to clinical improvement. We suspect that the mean time to wean off oxygen will be shorter in the experimental arm compared with the provider's choice arm. Secondary endpoints, such as clinical status (Glasgow coma scale, toxicity, radiographic, and immune biomarkers, time to discharge, freedome from ICU, freedome from intubation, time to hospital discharge, overall survival) will also be explored.

9.2 Sample Size/Accrual Rate

The required sample size is 16 patients for provider's choice arm, and an additional planned enrollment for 16 patients in experimental arm. We would also include another 20 patients for screen failure, for a total sample size of 52 . Patients will be randomized 1:1 to treatment arms using blocked randomization with a block size of 4.

In our pilot data, our mean time to clincial improvement was 4 days. Conservatively, we have assumed a mean time to clinical improvement of 7 days with a 4-day standard deviation. The provider's choice arm, driven by recent remdesivir data had a mean time of approval of 11 days (assuming all patients on the physician's choice arm may be receiving remedesivir and/or other FDA approved drugs at time of enrollment). Thus, with a sample size of 32, assuming a standard deviation of 4 days, we would have a 80% power to detect a statistically significant 4-day difference assuming a Type I error of 0.05. This calculation assumes one interim analysis for efficacy with the use of O'Brien-Fleming stopping boundaries.

9.3 Stratification Factors

There are no stratification factors.

9.4 Analysis of Endpoints

Primary endpoint: The primary endpoint is time to clinical improvement based on weaning from oxygen use and hospital discharge. Clinical improvement will be defined as meeting at least one of the following: 1) reduction in oxygen use back to baseline status prior to being hospitalized for COVID and/or [see section 8.2 above] 2) hospital discharge. Mean time to clinical improvement will be compared between the two treatment arms using a two-sample z-test, with a known population standard deviation of 4. If the test statistic is greater than 1.97, then we will reject the null hypothesis and conclude the experimental arm is superior using a two-sided Z-test. If Z-test assumptions are not valid, a Mann-Whitney U non-parametric test will be used. Difference in mean time to clinical improvement, and a 95% confidence interval will be reported.

Secondary endpoints: Secondary endpoints include toxicity, radiographic, immune biomarker, and overall survival endpoints. Point improvement on the Glasgow Coma scale, ARDS xray scale, and performance status. We would also analyze time to hospital discharge, freedom from ICU, and freedom from intubation, and changes on CT scans. All endpoints will be summarized descriptively, using mean, median, interquartile range, minimum/maximum, and standard deviation for continuous endpoints, and frequency and percentage for categorical endpoints. For time-to-event endpoints, we will use the Kaplan-Meier method to estimate survival.

9.5 Interim analysis

Stopping Rule for Efficacy: After 16 patients have been enrolled, treated, and evaluated, an interim look will be conducted to stop for efficacy of the experimental arm over the provider's choice arm. The boundary is determined using the O'Brien-Fleming group sequential method. If the critical value for a 2-sided Z-test is greater than 2.96, the primary endpoint will be considered completed and secondary endpoint will be pursued, including time to hospital discharge, etc. The study will acknowledge the efficacy of the experimental arm over the provider's choice arm in achieving clinical recovery, but will not be stopped. If at any point in the study, overall survival is found to be statistically superior, the study will be stopped. This analysis assumes a known population standard deviation of 4/group.

Analysis Populations:

The Efficacy and Safety populations include all subjects enrolled in the study and who receive best supportive care plus radiotherapy and best supportive care plus provider's treatment choice. The Efficacy Population will be used for analysis of the primary and secondary endpoints.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

10.2 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

10.3 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

10.4 Classification of an Adverse Event

10.4.1 **Severity of Event**

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
-

10.4.2 **Relationship to Study Intervention**

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

10.4.3 **Expectedness**

Investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

10.5 Adverse Event and Serious Adverse Event Reporting

10.5.1 **Adverse Event Reporting**

From the time of study entry through **14** days following last visit, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:
1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study intervention (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study intervention (none, temporarily interrupted, permanently discontinued, unknown, not applicable).
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 10.3

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.
Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion.

10.5.2 Serious Adverse Event Reporting

For the time period beginning at study intervention through **14** days following last visit, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, or FDA.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by regulatory authority and should be provided as soon as possible. The investigator will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the initial receipt of the information.

All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study intervention.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If Reported to FDA, all SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:
Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

10.5.3 **Definition of unanticipated problems (UP) and reporting requirements**

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

The Investigator will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

Study staff are responsible for submitting data and/or data forms in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.
Queries will be resolved by the research staff within the time frame specified by the protocol, not to exceed 2 weeks.

11.1.1 Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.
Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

Retention of Study Documents

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

11.2 Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical

practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

Study staff will get approval by the DSMC for opening the second cohort and provide an update on all relevant safety data of patients entered to cohort 1 when opening the of second cohort is planned.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

12. ETHICS AND PROTECTION OF HUMAN SUBJECTS

12.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, as well as the federal regulations pertaining to ICH E6.

12.2 Institutional review board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed consent/Assent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant (or their legal representative/next of kin/surrogate) and written documentation of informed consent is required prior to starting intervention/administering study product. Because intubated patients who would be eligible for this trial are not able to provide informed consent, legal representatives/next of kin/surrogate will be invited to the hospital to meet with investigators and provide consent in-person or they will be offer the option of electronic consent on behalf of patients. This process will require a video or telephone conference with the patient's surrogate to review the consent form in detail.

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing

to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 Participant and data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

12.5 Research use of stored samples, specimens, or data

Samples and data collected under this protocol may be used to study COVID-19. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX B GLASCOW COMA SCALE

https://www.cdc.gov/masstrauma/resources/gcs.pdf

Glasgow Coma Scale

Eye Opening Response

- Spontaneous--open with blinking at baseline **4 points**
- To verbal stimuli, command, speech **3 points**
- To pain only (not applied to face) **2 points**
- No response **1 point**

Verbal Response

- Oriented **5 points**
- Confused conversation, but able to answer questions **4 points**
- Inappropriate words **3 points**
- Incomprehensible speech **2 points**
- No response **1 point**

Motor Response

- Obeys commands for movement 6 points
- Purposeful movement to painful stimulus 5 points
- Withdraws in response to pain 4 points
- Flexion in response to pain (decorticate posturing) 3 points
- Extension response in response to pain (decerebrate posturing) 2 points
- No response 1 point

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APPENDIX C CHARLESON COMORDBITIY INFEX

https://www.rtog.org/LinkClick.aspx?fileticket=8o6FpyC8s9w%3D&tabid=290

Charlson Comorbidity Index
Scoring

Condition	Variable name	Points	Notes
Myocardial infarction	MI	1	
Congestive heart failure	CHF	1	
Peripheral vascular disease or bypass	PVD	1	
Cerebrovascular disease or transient ischemic disease	CVA	1	CVA only
Hemiplegia	PLEGIA	2	If hemiplegia, do not count CVA separately
Pulmonary disease/ asthma	COPD	1	
Diabetes	DM	1	DM only
Diabetes with end organ damage	DMENDORGAN	2	If end organ damage, do not count DM separately
Renal disease	RENAL	2	
Mild liver disease	MILDLIVER	2	
Severe liver disease	SEVERELIVER	3	
Gastric or peptic ulcer	ULCER	1	
Cancer (lymphoma, leukemia, solid tumor)	CANCER	2	Nonmetastatic cancer only
Metastatic solid tumor	METASTASES	6	If Metastatic, do not count cancer separately
Dementia or Alzheimer's	DEMENTIA	1	
Rheumatic or connective tissue disease	RHEUMATIC	1	
HIV or AIDS	HIV	6	
Hypertension	HBP	1	
Skin ulcers/ cellulitis	SKIN ULCER	2	
Depression	DEPRESSION	1	
Warfarin	WARFARIN	1	

Charlson Comorbidity Index
Chart review version

Components of classical Charlson Comorbidity Index[1]

1. Has the patient had a myocardial infarction? (MI)
   ___ No
   ___ Yes

Criteria: Myocardial infarction includes patients with one or more definite or probable myocardial infarction. These patients should have been hospitalized for chest pain or an equivalent clinical event and have had electrocardiographic and/ or enzyme changes. Patients with electrocardiographic changes alone who have no clinical history are not designated as having had an infarction.

2. Has the patient been hospitalized or treated for heart failure? (CHF)
   ___ No
   ___ Yes

Criteria: Congestive heart failure includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical examination) to digitalis, diuretics, or afterload reducing agents. It does not include patients who are on one of those medications but who have had no response and no evidence of improvement of physical signs with treatment.

3. Does the patient have peripheral vascular disease? (PVD)
   ___ No
   ___ Yes

Criteria: Peripheral vascular includes patients with intermittent claudication or those who had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm (6 cm or more).

4. Has the patient had a CVA or transient ischemic disease? (CVA)
   ___ No
   ___ Yes

Criteria: Cerebrovascular disease includes patients with a history of a cerebrovascular accident with minor or no residua, and patients who have had transient ischemic attacks. If the CVA resulted in hemiplegia, code only hemiplegia.

[1] Charlson, ME, Ales, KA, Pompei, P, MacKenzie, CR A new method of classification of prognostic comorbidity for longitudinal studies: development and validation J Chron Disease. 1987; 40(5): 373–383

5. Does the patient have hemiplegia? (PLEGIA)
   ___ No
   ___ Yes

Criteria: This includes patients with a hemiplegia or paraplegia, whether it occurred as a result of a cerebrovascular accident or other condition.

6. Does the patient have asthma, chronic lung disease, chronic bronchitis or emphysema? (COPD)
   ___ No
   ___ Yes

Criteria: Pulmonary disease includes patients with asthma, chronic bronchitis, emphysema, and other chronic lung disease who have ongoing symptoms such as dyspnea or cough, with mild or moderate activity. This includes patients who are dyspneic with slight activity, with or without treatment and those who are dyspneic with moderate activity despite treatment, as well as patients who are dyspneic at rest, despite treatment, those who require constant oxygen, those with CO_2 retention and those with a baseline PO_2 below 50 torr.

7. Does the patient have diabetes that requires treatment? (DM)
   ___ No
   ___ Yes

Criteria: Diabetes includes all patients with diabetes treated with insulin or oral hypoglycemic, but not diet alone. Diabetes during pregnancy alone is not counted.

7a. Does the patient have end organ damage from diabetes? (DMENDORGAN)
   ___ No
   ___ Yes

Criteria: This includes patients with retinopathy, neuropathy, or nephropathy attributable to diabetes.

8. Does the patient have moderate or severe renal disease? (RENAL)
   ___ No
   ___ Yes

Criteria: Moderate renal insufficiency includes patients with a serum creatinine >3 mg/dl. Severe renal disease includes patients on dialysis, those who had a transplant, and those with uremia.

9. Does the patient have a chronic liver disease? (MILDLIVER)
___ No
___ Yes

Criteria: Mild liver disease consists of chronic hepatitis (B or C) or cirrhosis without portal hypertension.

9a. Does the patient have moderate to severe liver disease? (SEVERELIVER)
___ No
___ Yes

Criteria: Moderate liver disease consists of cirrhosis with portal hypertension, but without bleeding. Severe liver disease consists of patients with ascites, chronic jaundice, portal hypertension or a history of variceal bleeding or those who have had liver transplant.

10. Has the patient had gastric or peptic ulcers? (ULCER)
___ No
___ Yes

Criteria: Peptic ulcer disease includes patients who have required treatment for ulcer disease, including those who have bled from ulcers.

11. Has the patient had cancer (other than basal cell skin cancer)? (CANCER)
___ No
___ Yes
If yes, which:
___ Lymphoma?
___ Leukemia?
___ Solid tumor (which?)_____

Criteria: Lymphoma includes patients with Hodgkins, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas. Leukemia includes patients with acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, and polycythemia vera. Solid tumor consists of patients with solid tumors without documented metastases, including breast, colon, lung, prostate, and a variety of other tumors.

11a. Has the patient had a metastatic solid tumor? (METASTASES)
___ Breast
___ Colon
___ Prostate
___ Lung
___ Melanoma
___ Other _____

Criteria: Metastatic cancer includes patients with metastatic solid tumors, including breast, lung, colon and other tumors

12. Does the patient have Alzheimer's, dementia from any etiology or any serious cognitive impairment? (DEMENTIA)
___ No
___ Yes

Criteria: Dementia includes patients with moderate to severe chronic cognitive deficit resulting in impaired function from any cause.

13. Does the patient have any rheumatic or connective tissue disease? (RHEUMATIC)
___ No
___ Yes

Criteria: Rheumatologic disease includes patients with systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyositis, polymyalgia rheumatica, vasculitis, sarcoidosis, Sjogrens syndrome or any other systemicvasculitis

14. Does the patient have HIV or AIDS? (HIV)
___ No
___ Yes

Criteria: Acquired immune deficiency syndrome includes patients with definite or probable AIDS, i.e. AIDS related complex, and those who are HIV positive and asymptomatic.

Additional components of Charlson Comorbidity Index adapted to predict cost[2]

15. Does the patient have hypertension? (HBP)
___ No
___ Yes

Criteria: Hypertension includes patients who have systolic pressures >140 mm Hg and/ or diastolic pressures >90 mm Hg if without diabetes or renal disease, as well as controlled hypertensives; or patients with diabetes or renal disease who have systolic pressures >140 mm Hg or diastolic pressures >80 mm Hg.

[2] Charlson, ME, Charlson RE, Briggs, W, Hollenberg, J Can disease management target patients most likely to generate high costs? The impact of comorbidity. J Gen Intern Med. 2007; 22(4): 464-469

16. Has the patient had decubitus ulcers, peripheral skin ulcers or repeated episodes of cellulitis? (SKINULCER)
    ___ No
    ___ Yes

Criteria: Partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.

17. Does the patient have depression? (DEPRESSION)
    ___ No
    ___ Yes

Criteria: Patients who are currently receiving treatment for depression, whether pharmacologic or psychotherapy, or cognitive behavioral therapy, or notes indicating that the patient has probable or definite depression.

18. Is the patient on warfarin or coumadin? (WARFARIN)
    ___ No
    ___ Yes

Conditions that are not assigned weights

- Angina includes patients with chronic exertional angina, those who had coronary artery bypass graft, and those initially admitted with unstable angina.
- Arrhythmia includes patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.
- Valvular disease includes patients with hemodynamically significant aortic stenosis and/or insufficiency, those with significant mitral stenosis and/or insufficiency, and those with prosthetic aortic or mitral valves, asymmetric septal hypertrophy requiring treatment, or tricuspid insufficiency.
- Other neurologic conditions includes patients with Parkinson's disease, uncontrolled seizures, or syncope without an identified cause or treatment.
- Other endocrine includes patients with hypopituitarism, adrenal insufficiency, and recurrent acidosis.
- Inflammatory bowel disease includes patients with ulcerative colitis or regional enteritis.
- Gastrointestinal bleeding includes those who have had bleeding requiring transfusions from causes other than ulcer disease.
- Coagulopathy includes patients with a circulating anticoagulant, or other coagulopathy.