Ultra- Low-Dose Thoracic Radiation for COVID-19 Patients

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ASTRO ANNUAL MEETING 2020

VENTED TRIAL: NCT04427566

A PHASE II STUDY OF THE USE OF ULTRA LOW-DOSE BILATERAL WHOLE LUNG RADIATION THERAPY IN THE TREATMENT OF CRITICALLY ILL PATIENTS WITH COVID-19 RESPIRATORY COMPROMISE

Co-enrollment in other COVID-19 clinical studies will be permitted

Vented Study Schema

Screening/Registration:
Baseline evaluations, repeat CT chest if none within 5 days of enrollment.

< 2 days

Day 0, Treatment :
Transport to BSH-G LINAC, Treatment 80 cGy AP/PA

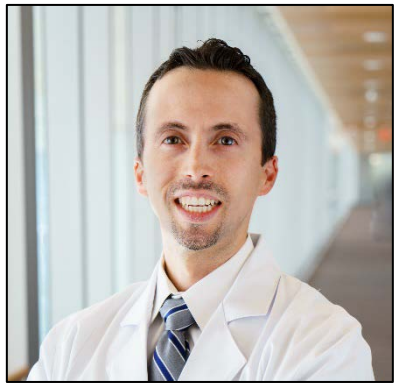
Day 1-18 mos.

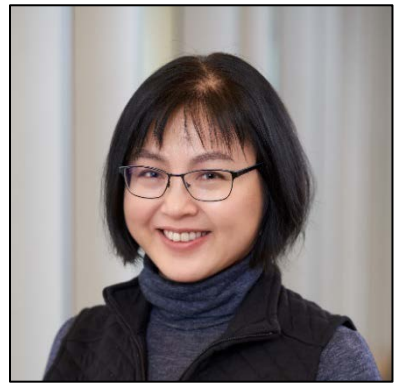
Follow-up Evaluations:
HP, KPS, CT, CBC/Chem/CRT, Mortality, ICU stay, Vent/O2 status, OI/OSI, Correlative blood and urine samples.

Day 3-10:
Evaluate for OPTIONAL 2nd 80-cGy ULD-WLRT


Karl Haglund MD, PhD


Jeremy Brownstein MD


Terence M. Williams, MD, PhD


Meng X. Welliver, MD

Hypothesis

Low-dose thoracic radiation by conventional linear accelerators will result in decreased mortality in patients who are critically ill requiring ventilatory support for COVID-19 pulmonary disease.

Patient Selection

****Co-enrollment in other COVID-19 clinical studies will be permitted****
Male and female patients ≥ 18 years of age with documented COVID-19 respiratory compromise requiring mechanical ventilation.

Inclusion Criteria	Exclusion Criteria
-Patient age ≥18 years of age. -COVID-19 test within 14 days of enrollment. -CT findings typical of COVID-19 pneumonia within 5 days of enrollment. -Receiving ICU-based mechanical ventilation. -Life expectancy ≥ 24 hours, as judged by investigator. -Hypoxemia defined as a Pa/FIO2 ratio < 300 or SpO2/FiO2 < 315. -Signed informed consent by patient or legal/authorized representatives. -Concurrent, prior, or planned future therapy with passive convalescent immune serum administration is allowed.	-Moribund with survival expected < 24 hours. -Expected survival < 30 days due to chronic illness present prior to COVID infection. -Patient or legal representative not committed to full disease specific therapy i.e. comfort care (DNRCCA is allowed). -Treatment with immune suppressing medications in last 30 days (steroids for ARDS or septic shock allowed). -Presumed COVID-associated illness greater than 14-days. -Inpatient admission greater than 14-days. -Patient deemed unsafe for travel for radiation therapy. -Chronic hypoxemia requiring supplemental oxygen at baseline. -Documented active connective tissue disease (scleroderma) or idiopathic pulmonary fibrosis. -Active or history of prior radiation therapy resulting in ≥ grade 2 radiation pneumonitis within 365 days of enrollment. -Active or history of prior radiation to the thorax completed within 180 days of enrollment (skin or surface only skin treatments are acceptable). -Known active uncontrolled bacterial or fungal infections of the lung. -Active cytotoxic chemotherapy. -Pregnancy -Breast feeding

Study Objectives

Primary Objectives:

- To evaluate 30-day mortality rate after ULD-WLRT.

Secondary Objectives:

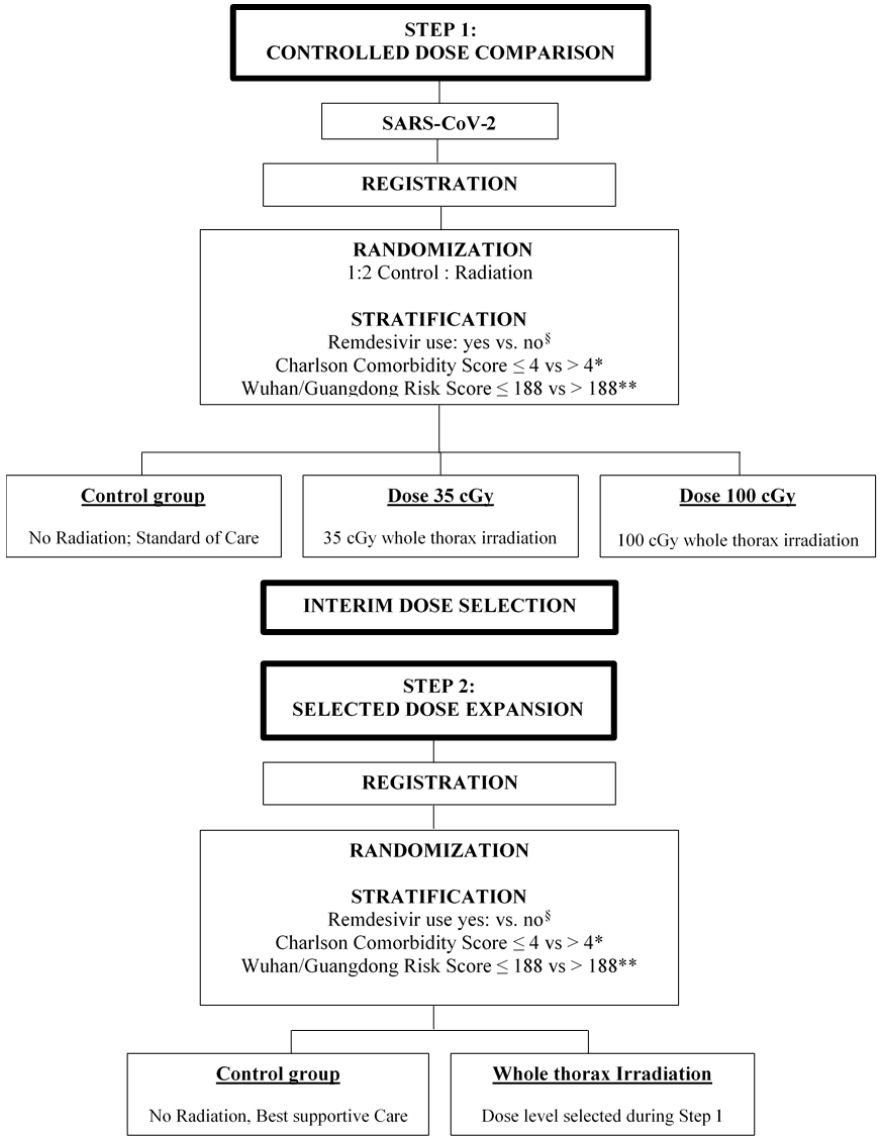
- To evaluate overall survival after ULD-WLRT.
- To evaluate total and post-LDRT ICU length of stay.
- To evaluate total and post-LDRT length of hospital stay.
- To evaluate total and post-LDRT requirement for mechanical ventilation (ventilator-free days).
- To evaluate total and post-LDRT requirement for supplemental oxygen therapy (days).
- To evaluate oxygenation index for 14 days post treatment or until extubated.
- To quantitate post-LDRT differences between baseline and Day 7, 14, and 28 CT chest finding (number of involved lung segments, size of GGO, lung infiltrate/opacification percentage).
- To evaluate SARS-CoV2 viral titers at baseline and post-LDRT at Day 7, 14, and 28.
- To establish feasibility, safety, and tolerability of this regimen.
- To establish KPS changes post-LDRT at baseline and Day 7, 14, and 28.

PRE-VENT TRIAL: NCT04466683

PHASE II PROTOCOL OF LOW-DOSE WHOLE THORAX MEGAVOLTAGE RADIOTHERAPY FOR PATIENTS WITH SARS-COV-2 PNEUMONIA

Co-enrollment in other COVID-19 clinical studies will be permitted

Pre-Vent Study Schema



Minesh Mehta, MD

Jim Fontanesi, MD

Matthew Katz, MD

Karl Haglund MD, PhD

Kimberly Mahler, MS

Hypothesis

Low-dose thoracic radiation will be an effective anti-inflammatory adjunctive therapy to reduce the host inflammatory response associated with SARS-CoV-2 pneumonia and to objectively improve clinical outcomes.

Patient Selection

****Co-enrollment in other COVID-19 clinical studies will be permitted****

Inclusion Criteria	Exclusion Criteria
-Laboratory-confirmed diagnosis of SARS-CoV-2 pneumonia. -Currently hospitalized with COVID-19 -Age ≥ 50 years -Symptomatic fever, cough and/or dyspnea for < 9 days -Patient or his or her legal/authorized representatives can understand and sign the study informed consent document. -Able to be positioned on a linear-accelerator couch for RT delivery AND at least one of the following risk factors for significant pulmonary compromise: a. Fever > 102 degrees Fahrenheit during index admission b. Respiratory rate of ≥ 26 / minute within 24 hours of screening c. SpO2 ≤ 95% on room air within 24 hours of screening d. Any patient requiring 4 L/min oxygen therapy to maintain SpO2 >93% within 24 hours of screening e. Ratio of partial pressure of arterial oxygen to fraction of inspired air < 320. -Patients may be enrolled on this trial while concurrently enrolled on other COVID-19 clinical trials.	-Currently requiring mechanical ventilation. -Prior thoracic radiotherapy, with the exception of the following: a. Breast or post-mastectomy chest wall radiation (without regional nodal irradiation) may be included at the discretion of the site primary investigator, an b. thoracic skin radiation therapy (without regional nodal irradiation) is allowed. -Known hereditary syndrome with increased sensitivity to radiotherapy, including ataxia-telangiectasia, xeroderma pigmentosum, and Nijmegen Breakage Syndrome -Known prior systemic use of the following drugs: Bleomycin, Carmustine, Methotrexate, Busulfan, Cyclophosphamide, or Amiodarone -History of or current diagnosis of pulmonary fibrosis, or an alternative pulmonary condition responsible for significant lung compromise at the discretion of the site primary investigator. -History of lung lobectomy or pneumonectomy. -Known history of pulmonary sarcoidosis, Wegener's granulomatosis, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, Sjögren's syndrome, mixed connective tissue disease, Churg-Strauss syndrome, Goodpasture's syndrome, or ankylosing spondylitis. -Symptomatic congestive heart failure within the past 6 months including during current hospitalization -History of recent or current malignancy receiving any cytotoxic chemotherapy or immunotherapy within the past 6 months. -History of bone marrow transplantation. -History of any solid organ transplant (renal, cardiac, liver, lung) requiring immunosuppressive therapy. -Females who are pregnant or breast feeding. -Inability to undergo radiotherapy for any other medical or cognitive issues.

Study Objectives

Primary Objectives:

- Determine which of the 2 dose levels appears most efficacious.
- Determine whether low-dose thoracic radiotherapy at a dose determined in Step 1 above produces clinical benefit (CB) in COVID-19 pneumonia patients.

Secondary Objectives:

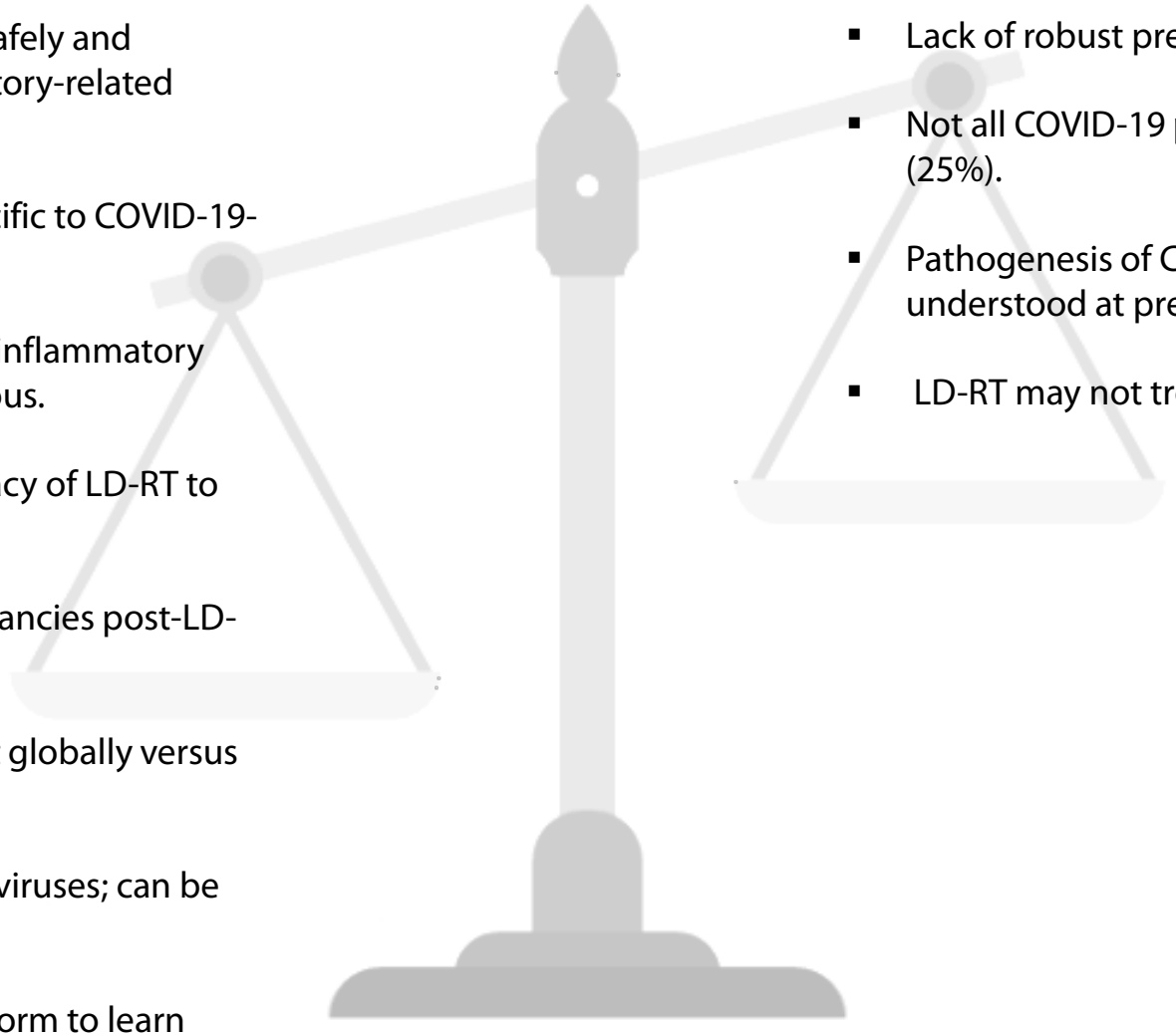
- Compute and compare the total episodic cost of care for the control vs the low-dose radiation therapy arm through collection of billing codes for COVID-19 hospitalization.
- Assess differences in pre-enrollment vs. post-enrollment pulmonary function between control and LD-RT arms. For pre-treatment pulmonary function tests (PFTs), any available within a 6-month time period before enrollment will be acceptable (as these reflect the pre-existing baseline), and for post-treatment, any PFTs available between 1 to 3 months post-discharge will be acceptable.

PRE-VENT Participating Clinical Sites

Contact	Institution	Location
Jim Fontanessi	Beaumont Hospital	Detroit, MI
Ramesh Rengan	University of Washington	Seattle, WA
Minesh Mehta	Baptist Health	Miami, FL
Mike Kasper	Lynn Cancer Institute	Boca Raton, FL
Arnab Chakravarti	Ohio State University	Columbus, OH
Leland Rogers	Dignity Health	Phoenix, AZ
Charles Thomas	Oregon Health & Science University	Portland, OR
Matthew Katz	Lowell General Hospital	Lowell, MA
Paul Anthony	Indiana University	Bloomington, IN
Dodul Mondal	Apollo Hospital	New Delhi, India
Gary Kantor and Prof. Cotton	University of Cape Town	Cape Town, South Africa
Joost Verhoeff	Utrecht Medical Center	Netherlands
Michael Malabanan	Asian Hospital and Medical Center	Manila, Philippines
Juan Galvis	Hospital San Ignacio	Bogotá, Colombia

Do the Potential Benefits of LD-RT Outweigh the Risks?

- LD-RT historically has been used to safely and effectively treat numerous inflammatory-related diseases.
- Biological mechanisms of LD-RT specific to COVID-19-related response.
- Drug trials have shown that treating inflammatory state in COVID-19 patients is efficacious.
- Emory trial indicates safety and efficacy of LD-RT to treat COVID-19.
- Risk of developing secondary malignancies post-LD-RT appears to be low.
- LD-RT is a readily available treatment globally versus many newly-engineered drugs
- LD-RT does not discriminate against viruses; can be used in future pandemics.
- COVID-19 LD-RT trials provide a platform to learn about the effects of treatment on virus in a systematic way.



- Lack of robust pre-clinical data for LD-RT on COVID-19.
- Not all COVID-19 patients have severe immune response (25%).
- Pathogenesis of COVID-19 remains poorly and incompletely understood at present.
- LD-RT may not treat thrombotic issues.