COVID-19 & Radiation Oncology
Initial Impact and Operational Response of Radiation Oncology Practices to the COVID-19 Pandemic in the United States, Europe, and Latin America

Daniel V. Wakefield, MD
University of Tennessee Health Science Center, Harvard T.H. Chan School of Public Health
Disclosures

• PGY-5 Resident Physician, Radiation Oncology, University of Tennessee Health Science Center
• MPH student, Harvard T.H. Chan School of Public Health
• I have no conflicts of interest to disclose.

• **Full author list for LBA-11**: D. V. Wakefield¹,², T. Sanders³, E. Wilson³, A. Hubler², T. L. DeWeese⁴, B. D. Smith⁵, T. J. Eichler⁶, B. J. Slotman⁷, Y. Lievens⁸, P. Poortmans⁹, V. Cremades¹⁰, U. Ricardi¹¹, D. A. Martinez Perez¹², G. R. Sarria¹³,¹⁴, C. Flores¹⁵, S. H. Malhotra¹⁶, B. Li¹⁶,¹⁷, M. Ehmann¹⁸, G. J. Sarria¹⁹, and D. L. Schwartz²,²⁰; ¹Harvard T.H. Chan School of Public Health, Boston, MA, ²University of Tennessee Health Science Center, Department of Radiation Oncology, Memphis, TN, ³American Society for Radiation Oncology, Arlington, VA, ⁴Johns Hopkins University School of Medicine, Department of Radiation Oncology and Molecular Radiation Sciences, Baltimore, MD, ⁵The University of Texas MD Anderson Cancer Center, Houston, TX, ⁶VCU Health, Massey Cancer Center, Richmond, VA, ⁷Amsterdam University Medical Centers, Department of Radiation Oncology, Amsterdam, Netherlands, ⁸Ghent University Hospital and Ghent University, Department of Radiation Oncology, Ghent, Belgium, ⁹Iridium Kankernetwerk, Department of Radiation Oncology, Antwerp, Belgium, ¹⁰European SociëTy of Radiation Oncology, Brussels, Belgium, ¹¹University of Turin, Turin, Italy, ¹²Radioncologìa - Oncosalud / AUNA, Lima, Lima, Peru, ¹³Department of Radiation Oncology, Oncosalud-AUNA, Lima, Peru, ¹⁴Instituto Nacional De Enfermedades Neoplásicas, Lima, Lima, Peru, ¹⁵Department of Statistics and Translational Investigation, Oncosalud-AUNA, Lima, Peru, ¹⁶Rayos Contra Cancer, Nashville, TN, ¹⁷University of California San Francisco, Department of Radiation Oncology, San Francisco, CA, ¹⁸Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany, ¹⁹Radiotherapy Department, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru, ²⁰University of Texas MD Anderson Cancer, Department of Radiation Oncology, Houston, TN
Background & Method

• The COVID-19 pandemic has profoundly changed practice patterns in medicine around the world. The full impact on radiation oncology is unknown.

• We surveyed radiation oncology practice leaders from the United States, Europe and Latin America to gauge initial impact and immediate operational responses to the pandemic.

• Surveys were administered April 16 - May 30, 2020 by the American Society for Radiation Oncology (ASTRO; US survey), the European SocieTy for Radiotherapy and Oncology (ESTRO; European survey), and Rayos Contra Cancer (Latin American survey)

• 474 of 1,246 practice leaders responded → 38% response rate
45 nations represented
USA

222/517 (43%) practices
43 states
Europe

139/500 (28%) practices
29 nations
Latin America

115/229 (50%) practices
15 nations
Clinics Stayed Open

- Nearly all radiation therapy practices reported uninterrupted operation in the early months of the pandemic.

100% 100% 97%
Patient Volumes Dropped

Average treatment volumes were reduced from pre-pandemic levels by varying degrees.

- 68% ↓ 32%
- 75% ↓ 25%
- 59% ↓ 41%
Treatment Postponed for Low-Risk Disease

Postponement of radiation therapy for **low-risk patients** was widely adopted across centers.

92% 65% 60%
Practice Revenues Fell

Many practices estimated reductions in revenue *greater than 20%* due to the pandemic.
Widespread Adoption of Safety Protocols

Nearly all practices implemented new formal safety procedures to protect patients and staff from infections.

98% 95% 97%
Practices Experienced Staffing Shortages

Staffing shortages were reported across centers:

- 70%
- 57%
- 52%
Practices Experienced PPE Shortages

PPE shortages were reported across centers:

- 69%
- 48%
- 51%
Practices Adopted Telemedicine

First-time adoption of telemedicine programs was widespread:

- 89% in the United States
- 76% in Europe
- 64% in South America
Conclusions

• Surveyed impact of the early COVID-19 pandemic on radiation oncology practices across the US, Europe, and Latin America was substantial.

• Despite staffing shortfalls, safety supply deficits, and financial instability, practices across these regions demonstrated resilience, quickly adopting safety recommendations and leveraging new telemedicine programs to facilitate prioritized treatment continuity.

• Treatment access policies reflected rapidly published international guidelines to delay treatment for low-risk diagnoses.

• Patients with higher risk disease continued to receive uninterrupted access to cancer care.
Publications

Effect of COVID-19 pandemic on practice in European radiation oncology centers

Berend J. Slotman, Yolande Lievens, Philip Poortmans, Valerie Cremades, Thomas Eichler, Daniel Victor Wakefield, Umberto Ricardi

COVID-19 Rapid Letter

OPERATIONS AND ECONOMICS IN A PANDEMIC

Initial Impact and Operational Responses to the COVID-19 Pandemic by American Radiation Oncology Practices

Daniel V. Wakefield, MD, Tim Sanders, BS, Emily Wilson, BS, Adam Hubler, BS, Theodore DeWeese, MD, Benjamin D. Smith, MD, Berend J. Slotman, MD, PhD, Gustavo R. Sarria, MD, Thomas Eichler, MD, and David L. Schwartz, MD, FACS

OPERATIONS AND ECONOMICS IN A PANDEMIC

COVID’s Impact on Radiation Oncology: A Latin American Survey Study

David Martinez, MD, Gustavo J. Sarria, MD, Daniel Wakefield, MD, Claudio Flores, MSc, Sameeksha Malhotra, BA, Benjamin Li, MD, MBA, Michael Ehrmann, MD, David L. Schwartz, MD, and Gustavo R. Sarria, MD

2020 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING
ASTRO COVID-19 Practice Response Survey: Updated Results from Three Waves of Data Collection

David Schwartz, MD
University of Tennessee Health Science Center
Disclosures

• Employer: University of Tennessee Health Science Center, Department of Radiation Oncology

• I have no relevant conflicts of interest to disclose.

• Data reported on behalf of the American Society of Radiation Oncology (ASTRO) in collaboration with the University of Tennessee Health Science Center (UTHSC)
Study Design

• Web-based survey of leaders from academic and community practices.
• To our knowledge, this is only longitudinal U.S. specialty COVID-19 practice survey.

Longitudinal Design (3 Timepoints)

Timepoint 1
April 16-30
222 responses (43%)

Timepoint 2
April 30-May 14
156 responses (30%)

Timepoint 3
June 11-25
159 responses (31%)
The Good News

- 100% of radiation oncology networks/departments remained open during the pandemic.
- Only 6% closed a satellite clinic to centralize services.
- Nearly all practices (97%) increased and implemented measures to reduce transmission risk for patients and staff.

### Infection Control Practices

<table>
<thead>
<tr>
<th>Practice</th>
<th>Timepoint 1</th>
<th>Timepoint 2</th>
<th>Timepoint 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff wear masks</td>
<td>99%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Social distancing in clinic</td>
<td>98%</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>Extra cleaning of equipment</td>
<td>91%</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>
Infection Control

• Patients did their part—adoption of masking grew briskly across time.
Patient Visits

• The vast majority of sites experienced delays in referrals (76%) and/or patient treatment (92%) in April, in keeping with lock-down events and guidelines.

• Scheduling of new patients resumed over time, consistent with national re-opening, though not to pre-pandemic levels.
Treatment Delays

• In line with expert guidelines, most common treatment delays were for early-stage, lower-risk disease. These delays decreased with each survey.
The Challenges

- 80% sites reported shortages of COVID-19 resources; this continued through June.
  - PPE (masks, gowns, gloves)
  - Medical-grade hand sanitizer
  - COVID-19 test swabs

![Practices Experiencing Resource Shortages](chart.png)
Fewer Patient Visits

- More than 8 in 10 U.S. radiation oncology practices experienced declines in patient volume due to the pandemic.

- Roughly half of the practices also reported staffing shortages due to reduced patient volume.

Has the COVID-19 pandemic led to a decline in patient volume at your practice?

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=222)</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>2 (n=156)</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>3 (n=159)</td>
<td>83%</td>
<td>17%</td>
</tr>
</tbody>
</table>
Financial Hardship

- Over 2/3 practices reported at least 10-30% revenue loss.
- About 10% practices reported high-threat losses.

**Estimated Practice Revenue Loss Due to the COVID-19 Pandemic**

<table>
<thead>
<tr>
<th>Percentage Range</th>
<th>Timepoint 1 (n=189)</th>
<th>Timepoint 2 (n=133)</th>
<th>Timepoint 3 (n=131)</th>
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<tr>
<td>1-10%</td>
<td>5%</td>
<td>5%</td>
<td>2%</td>
<td>0%</td>
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<tr>
<td>11-20%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>21-30%</td>
<td>24%</td>
<td>31%</td>
<td>43%</td>
<td>0%</td>
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<tr>
<td>31-40%</td>
<td>24%</td>
<td>25%</td>
<td>34%</td>
<td>0%</td>
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<td>41-50%</td>
<td>5%</td>
<td>9%</td>
<td>8%</td>
<td>0%</td>
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<tr>
<td>More 51%</td>
<td>12%</td>
<td>11%</td>
<td>7%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Conclusions

• Patient access to radiation treatment was fully sustained.

• Practice responses were rapid, flexible, and data-driven. These were maintained and refined despite financial headwinds.

• Pandemic supply chain shortfalls were broadly felt.

• The current “3rd U.S. surge” lends a unique opportunity for our field to lead the way towards studying long-term pandemic impact and health system responses.
Low-Dose Radiation Therapy and Severe COVID-19-Related Pneumonia

Mohammad K. Khan, MD, PhD
Winship Cancer Institute of Emory University
Associate Professor of Radiation Oncology
Disclosure

- Employment Disclosure: Emory University

- Founder of CureRaysTM, a start-up manufacturer of commercial products to offer COVID-19 treatments with low-dose radiation therapy
RESCUE 1-19 (First LD-RT Trial in the World)

- **Eligible patients** were SARS-CoV-2 positive, hospitalized, bilateral radiographic consolidations & required supplemental oxygen (i.e., severe ARDS)
- **Intervention**: 1.5 Gy whole-lung LD-RT
- **Primary & Secondary Endpoints**: Safety (Phase 1) and Efficacy (Phase 2)
  - Phase 1 included outcomes in first 5 patients with preplanned interim 7-day analysis (PMID: 32986274)
  - Phase 2 included outcomes in all 10 patients @ day 28 compared with age- and comorbidity-matched controls.
- **Efficacy endpoints**: time to clinical recovery (TTCR), radiographic improvement on serial x-rays, and biomarkers response
- Two-sample t-tests, chi-square tests, univariate Cox proportional hazard models, cumulative incidences, and hazard ratios were reported.
Results

- Ten patients received whole-lung LD-RT between April 24 and May 24, 2020 and compared with ten matched controls treated with best supportive care and COVID-directed therapies

- **Primary endpoint:** 7 Day interim

- **Secondary Endpoints:** Median TTCR was 12 days in controls compared to 3 days in the LD-RT cohort (HR 2.9, p=0.05)

- Median time to hospital discharge was 20 versus 12 days in LD-RT (p=0.19)

- Intubation rates were 40% versus 10%, in favor of LD-RT (p=0.12)

- 28-day overall survival was 90% for both cohorts

- Age ≥65 was associated with lower oxygen requirement and shorter TTCR in the LD-RT cohort (p=0.01) but not the control cohort (p=0.40)

- Inflammatory, cardiac, hepatic biomarkers, and serial radiographs also were favored of LD-RT

LD-RT was safe (PMID: 32986274)
Observed clinical improvements following LD-RT

- **Time to Clinical Recovery**: $P=0.048$
- **Time to Hospital Discharge**: $P=0.19$
- **Intubation Free Rates**: $P=0.12$
Observed laboratory improvements following LD-RT

**Inflammation**

- C-Reactive Protein
- Lactate Dehydrogenase

**Cardiac Injury**

- Creatine Kinase

**Hepatic Injury**

- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-zero change detected</th>
<th>p-value</th>
<th>Change superior to pre-LDRT levels</th>
<th>p-value</th>
<th>Change superior to controls (red)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Non-zero change detected</td>
<td>p&lt;0.01</td>
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<td>Non-zero change detected</td>
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<td>Change superior to controls (red)</td>
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</tbody>
</table>
Earlier radiographic improvement following LD-RT

### ARDS Scale Scores - Control Cohort

<table>
<thead>
<tr>
<th>ID</th>
<th>Day 0</th>
<th>Day 1-3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NA (2)</td>
<td>NA (2)</td>
<td>NA (2)</td>
<td>NA (2)</td>
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<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>NA (3)</td>
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<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>4</td>
<td>2</td>
<td>NA (2)</td>
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<tr>
<td>6</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>NA (4)</td>
<td>NA (4)</td>
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<td>7</td>
<td>2</td>
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<td>8</td>
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<td>4</td>
<td>4</td>
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<td>NA (4)</td>
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<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Mean</td>
<td>3.1</td>
<td>3.9 (3.6)</td>
<td>3.3 (3.2)</td>
<td>3.7 (3.4)</td>
<td>3.3 (3.3)</td>
</tr>
</tbody>
</table>

Controls: 4 of 7 radiographically improved (57%)  
*p = 0.04*

- First blinded ARDS score decline
- Insufficient radiographs (≤ 1)

### ARDS Scale Scores - Radiation Cohort

<table>
<thead>
<tr>
<th>ID</th>
<th>Day 0</th>
<th>Day 1-3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
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<tbody>
<tr>
<td>1</td>
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<td>2</td>
<td>3</td>
<td>2</td>
<td>NA (2)</td>
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</tr>
<tr>
<td>Mean</td>
<td>3.8</td>
<td>3.5</td>
<td>3.3</td>
<td>2.7 (3.1)</td>
<td>2.3 (2.8)</td>
</tr>
</tbody>
</table>

LD-RT: 9 of 10 radiographically improved (90%)
Conclusion/Summary

• LD-RT for COVID-19 appears to be safe
• LD-RT seems to improve oxygen status, delirium, radiographs, and biomarkers when compared against age and comorbidity matched cohorts
• Confirmatory trials are needed.
• Clinical Trial Registration: NCT04366791

PrePrints and Pubmed References:
https://www.medrxiv.org/content/10.1101/2020.06.03.20116988v1
https://www.medrxiv.org/content/10.1101/2020.07.11.20147793v1
Ultra-Low-Dose Thoracic Radiation for COVID-19 Patients

Arnab Chakravarti, MD
The Ohio State University Comprehensive Cancer Center
Professor and Chair of Radiation Oncology
Klotz Family Chair of Cancer Research
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**
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.

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

### Inclusion 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.

### Exclusion Criteria

- 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, orankylosing 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

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

- 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.
Low-Dose Whole Lung Radiotherapy for Immunomodulation in COVID-19-Related Pneumonia

Ramesh Rengan, MD, PhD, FASTRO
Professor and Chair, Department of Radiation Oncology
University of Washington School of Medicine
Disclosures

• No financial conflicts relevant to this presentation

• Honoraria/Incidental Expenses: MDACC, AACR, IBA, Novocure

• Consultant: AstraZeneca
Does radiation therapy have value in the short-term clinical management of severe pulmonary inflammation caused by COVID-19?
Does radiation therapy have value in the short-term clinical management of severe pulmonary inflammation caused by COVID-19?

- This is a reasonable question to test in clinical trials
  - Inflammatory cells are very sensitive to radiation
  - Low-dose radiotherapy can act as an immunosuppressant and has been used effectively in inflammatory conditions such as arthritis, etc.
  - Early data suggest potential value of LD-RT in this setting
Does radiation therapy have value in the short-term clinical management of severe pulmonary inflammation caused by COVID-19?

• There are important caveats to consider, however
  • Questions about the magnitude of potential harm relative to benefit
  • Lack of clarity about what dose of radiation will be sufficient but also safe
  • Treatment may suppress immediate inflammation but also make patients potentially more vulnerable to secondary lung inflammation
  • Practical concerns bringing COVID-19+ patients into cancer clinics, where patients are particularly vulnerable to infection
Take Home Points

• Important early data suggesting potential value of LD-RT in this setting

• Need larger patient numbers and longer-term follow-up (3-6 months)
  • This is 10 patients of ~57,000 hospitalized with COVID-19 in US
  • Comparator data should be interpreted with caution as this was not randomized
  • Unclear whether LD-RT will provide additional benefit over better established therapies (convalescent plasma, mAB therapy, steroids)

• 15 ongoing multi-institutional prospective (some randomized) trials of LD-RT should provide guidance

• These trials will also provide important data on
  • Long-term impact of LD-RT in high-risk population
  • Radiotherapy workforce protection
  • Cancer patient exposure mitigation
Low-dose Radiation Therapy and Severe COVID-19-Related Pneumonia

Deborah E. Citrin, MD
National Cancer Institute
Senior Investigator, Radiation Oncology Branch
Deputy Director, Center for Cancer Research
Disclosures

• I have no conflicts of interest to disclose
Biologic Rationale: COVID-19 pneumonia

• Accumulation of macrophages in the alveolus, lymphocytes in the interstitium, and a diffuse alveolar damage

• Cytokine storm is the result of activated immune cells producing large amounts of cytokines that in turn leads to hyperinflammation
  • Macrophage activation implicated as a key component of cytokine storm
  • Immune suppression (dexamethasone) has proven useful in severe COVID-19

Why might this work?

• Cells of different types have varying sensitivity to radiation
  • Immune cells – relatively sensitive
  • Other lung cells - relatively resistant
• Low dose radiation (< 1 Gy)
  • can reduce the oxidative burst and NO· production from macrophages¹,²
  • can cause fibrocytes to differentiate, reducing proliferation and eventual fibrosis³
  • may reduce leukocyte adhesion to endothelial cells

Cytokines/Correlatives

- **Inflammation**
  - IL-6
  - **CRP**
  - LDH
  - Ferritin
  - ESR

- **Kidney injury**
  - Creatinine

- **Liver injury**
  - AST
  - ALT

- **Neurologic**
  - Headaches
  - Dizziness
  - Encephalopathy
  - Guillain-Barré
  - Agenesis
  - Myelitis
  - Anosmia
  - Stroke

- **Renal**
  - Acute kidney injury
  - Proteinuria
  - Hematuria

- **Hepatic**
  - Elevated aminotransferases
  - Elevated bilirubin

- **Gastrointestinal**
  - Diarrhea
  - Nausea/vomiting
  - Abdominal pain
  - Anorexia

- **Thromboembolism**
  - Deep vein thrombosis
  - Pulmonary embolism
  - Catheter-related thrombosis

- **Cardiac**
  - Takotsubo cardiomyopathy
  - Myocardial injury/myocarditis
  - Cardiac arrhythmias
  - Cardiogenic shock
  - Myocardial ischemia
  - Acute cor pulmonale

- **Endocrine**
  - Hyperglycemia
  - Diabetic ketoacidosis

- **Dermatological**
  - Petechiae
  - Livedo reticularis
  - Erythematous rash
  - Urticaria
  - Vesicles
  - Pernio-like lesions

- **Clotting**
  - D-Dimer

- **Cardiac injury**
  - Creatine Kinase
  - Troponin-1
  - Myoglobin

- **Immune cells**
  - **White blood count**
  - Neutrophil/WBC ratio
  - Monocyte count

**Bold:** p<0.05; **italics:** trend

What are some concerns?

• Risk of long-term toxicity
  • Risk of cancer or cardiac damage is well documented from similar radiation doses in long term atomic bomb survivors

• Reducing long term toxicity
  • Determining whether there is a benefit that outweighs risks
  • Treating patients at lower risk of cancers (shorter overall life expectancy)
  • The lowest dose that achieves successful outcomes will reduce long term risks
  • Fractionated versus single dose (safety of patients and caregivers)

• Low dose is variably defined

• Lymphocytes more sensitive than macrophages – can this impact immunity or clearance?