Low Dose Radiotherapy As A Treatment For COVID-19 Pneumonias (IRAS 285167)

Hadjiyiannakis P, Vyas A, Mannion P, Ingham W, Robinson A, McGlynn J, McGurk L, Howells J, Eastlake L, Tripathi L, Patel I, Bidmead M, Banks C, Chalmers A, Shentall G, Clarkson G, Clements H, Bennett K, Dimitroyannis D.

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References

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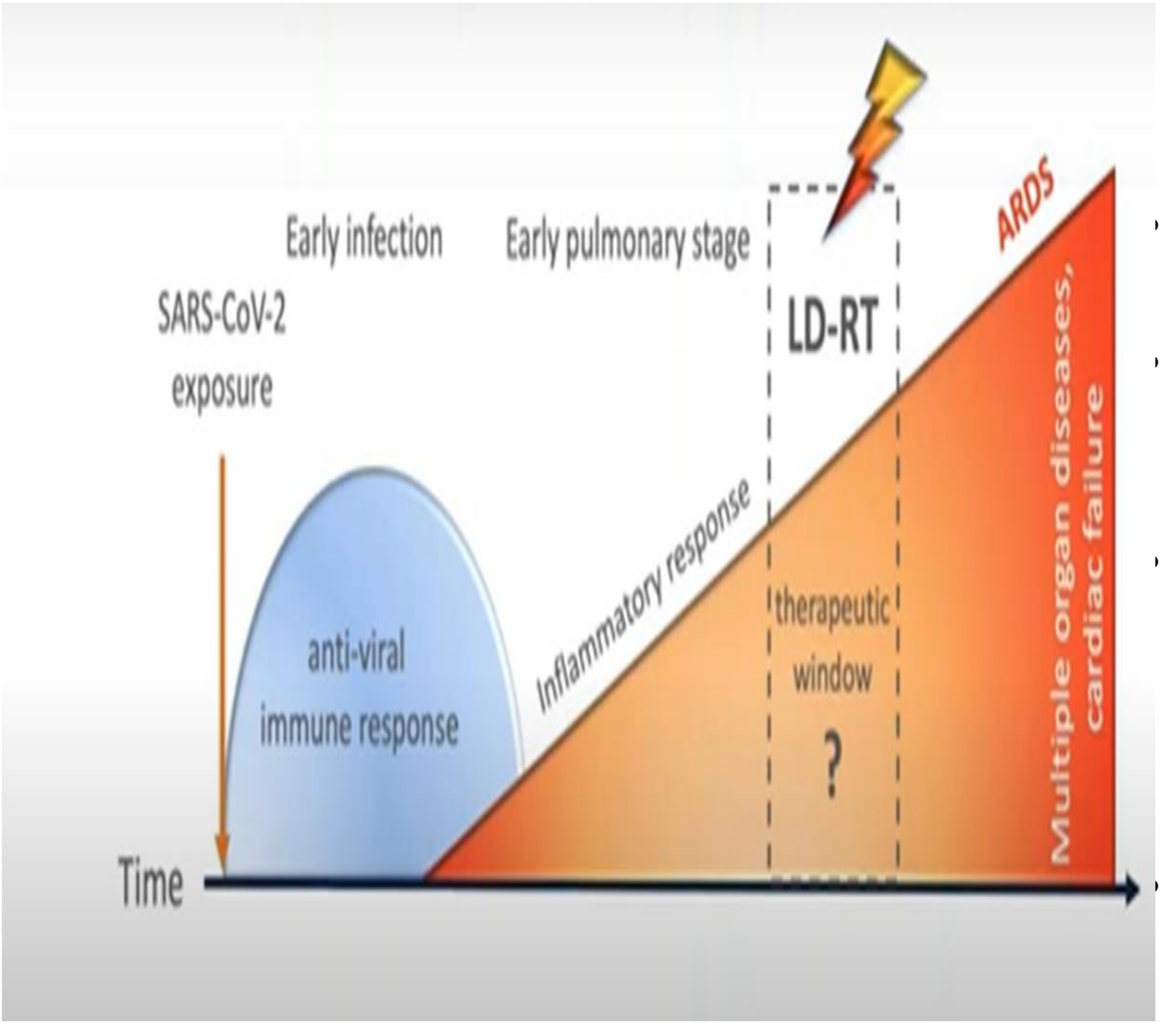
- Lara PC, Burgos J, Macias D. Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment. Clinical and Translational Radiation Oncology 2020;23:27-29
- Hadjiyiannakis D, Dimitroyannis D, Eastlake L, et al. Personal View: Low-Dose Lung Radiotherapy Should be Evaluated as a Treatment for Severe COVID-19 Lung Disease. *Clin Oncol (R Coll Radiol)*. 2021;33(1):e64-e68.

The COVID-19 pandemic to date has caused over 4.5 million deaths, with a global fatality rate of 3.5%.

The excessive release of cytokines/chemokines results in damage of lung cells. Death is mainly due to Acute Respiratory Distress Syndrome (ARDS), sepsis, pneumonia, and respiratory failure.



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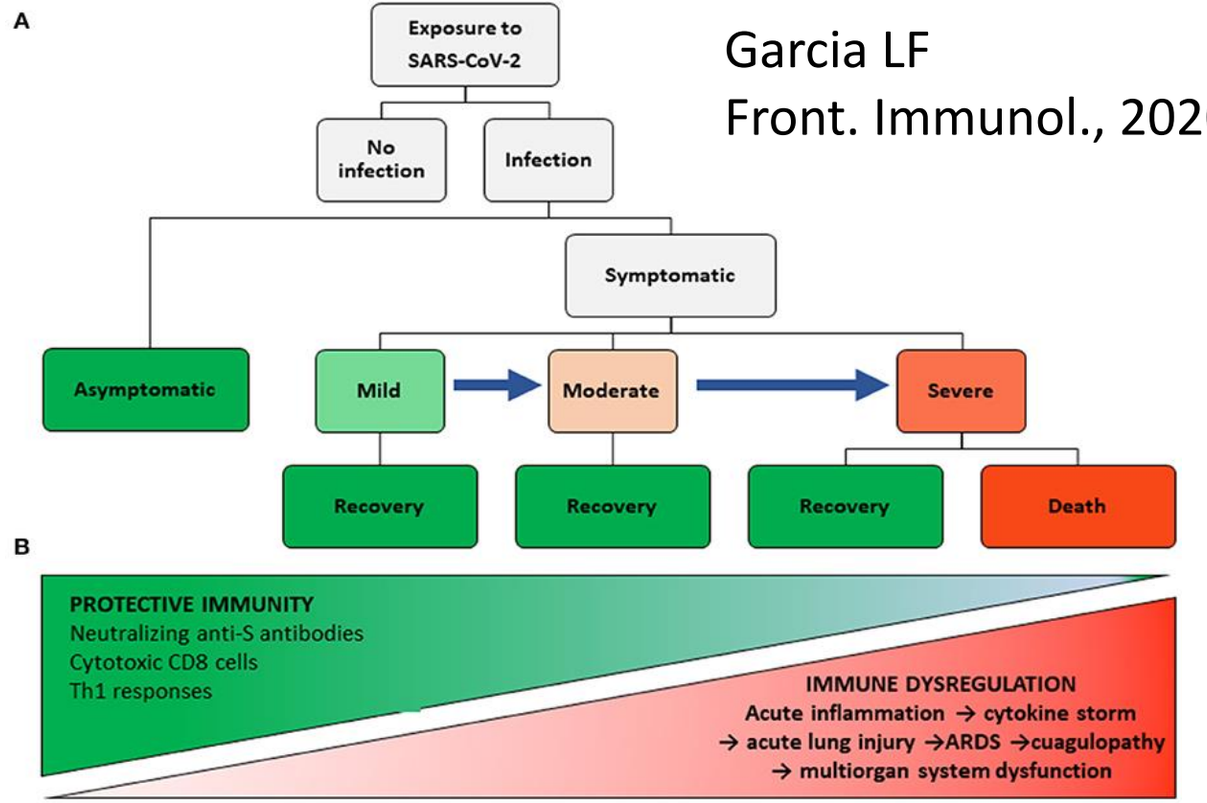


Garcia LF
Front. Immunol., 2020

What is the rationale for LDRT?

- Animal studies showed modulation of the immune system after low dose of radiation.
- LDRT for influenza virus in animals models demonstrated the efficacy of such treatment in almost half of the experimental cases
- Openheimmer treated 56 patients with life-threatening progressive interstitial pneumonia at doses of 0,5 Gy. Patients treated in the first 14 days responds successfully to the therapy but after 14 days responses were around 50%.
- LDRT through its anti-inflammatory processes, could control the cytokine storm induced by virus infection

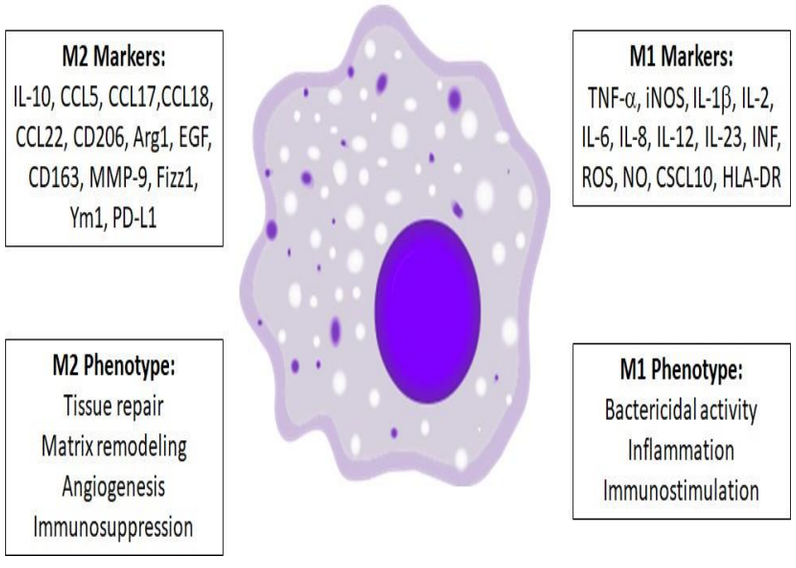
The Protocol

- Single fraction of 0.5 Gy with the aim to cover the entire bilateral lung volume with 0.5Gy.
- inhomogeneity corrections for tissue composition and density differences via CT planning / dosimetry
- Minimum lung dose must be over 0.4Gy.
- Utilise standard Linear Accelerator output rate at approximately 600Mu/minute using large flattened fields.

The hypothesis

Low Dose (< 1 Gy) ⟶ High Dose (> 1 Gy)

LDRT, through its anti-inflammatory processes would prevent the damage caused through pro-inflammatory cytokines/chemokines released after virus infection and mitigate the associated clinical symptoms of pneumonia/ ADRS in COVID-19 patients



Effects of radiation dose on macrophage polarization (adapted from Calabrese et al.2019

UK Submission

Single treatment arm Phase 1 feasibility and tolerability study at LTHTr, sponsored by LTHTr.

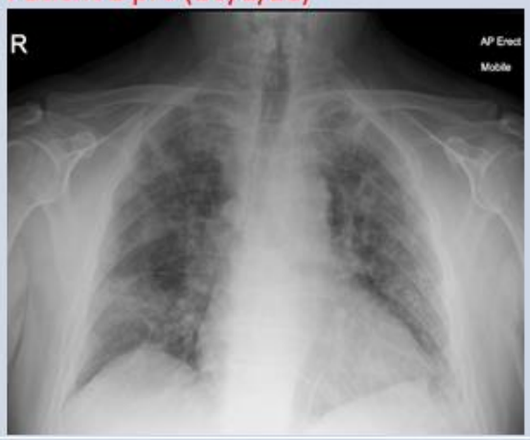
<u>Primary Outcomes</u>

- Feasibility to recruit to the study.
- Proportion of patients with no decline in PaO2/FiO2 Ratio (P/F Ratio) at 48 hours after each fraction of radiotherapy.
- The study will recruit 13 patients with the first, sentinel patient being treated and followed up for 7 days after last fraction of radiotherapy. Study to progress based on DMC recommendation.
- Radiotherapy to start within 48 hours of enrolment
- 0.5Gy single fraction whole lung radiotherapy, repeated before 96 hours if appropriate
- Minimum improvement of 20% in P/F ratio is a pre-requisite to allow second fraction of radiotherapy to proceed

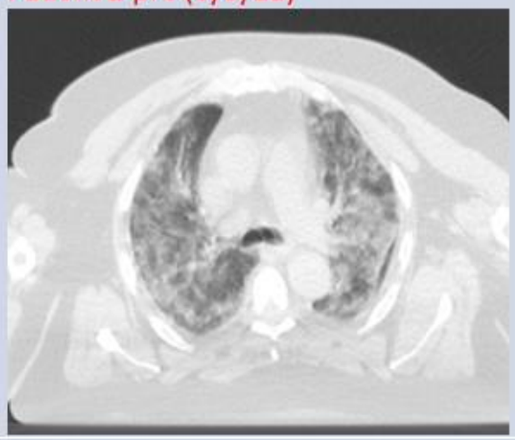
Results

Value	Patient 1 Pre-treatment	Patient 1 48-96 hours post treatment	Patient 2 Pre-treatment	Patient 2 48-96 hours post treatment
P/F Ratio	140	238	225	304
FiO2	40	21	40	21
BNP	473	80	1187	439

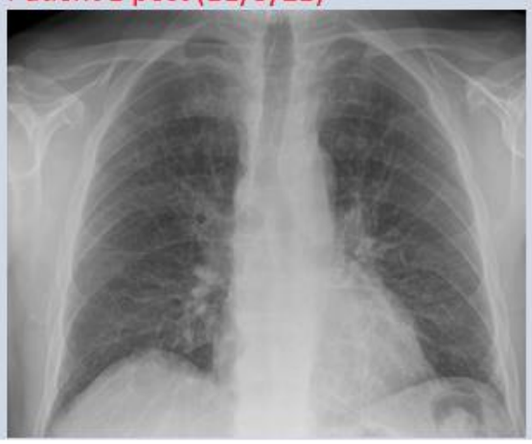
Patient 1 pre (16/1/21)



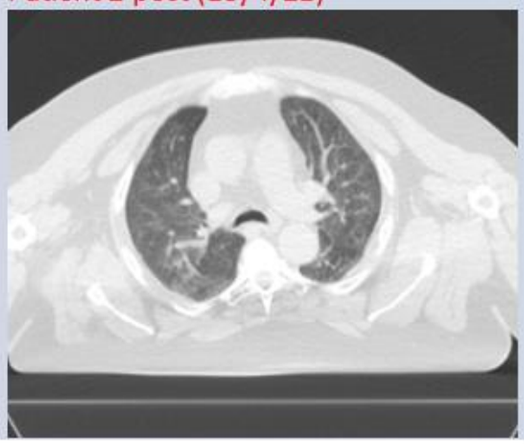
Patient 2 pre (3/3/21)



Patient 1 post (11/3/21)



Patient 2 post (15/4/21)



Carcinogenicity

Cautious estimates suggest excess lifetime risks to be well below 1- 2%.

Clinical results in favour of LD-RT (Rodel F. September 2021)

Author	Patients	Dose	Effects
Govindaraj (2021)	25 Men age 57 years	Single dose of 0.5 Gy within 10 days of symptom onset and 5 days of hospital admission	88% patients attained clinical recovery within 10 days, median time to hospital discharge was 6 days
Ameri (2021)	10 Age > 60 years	Single dose of 0.5 Gy, single dose of 1 Gy	Clinical improvement of four patients in the first few days after irradiation
Arenas (2020)	36 Mean age 84 years	Single dose of 0.5 Gy, optionally second 05. Gy dose	In survivors: a significant improvement was observed in the percentage of lung involvement in the CT scan at 1 week after LD-RT
Sharma (2020)	10 Range 39-63 years	Single dose of 0.7 Gy	Nine patients completed LD-RT, mostly within a period ranging from 3 to 7 days with 90% response date
Mousavi Darzikolaee (2021)	11 Mean age 55 years	Single dose of 1 Gy	Chest X-ray severity score was significantly lower in the irradiated group; overall survival after 28 days was 32% in the irradiated group and 11% in the control group
Sanmamed (2021)	9 > 50 years	Single dose of 1 Gy	Sat02/FiO2 index significantly improved 3 days after LD-RT, lung inflammation decreased 1 week after LDRT. 7 patients recovered
Hess (2021)	5/10 Age > 60 years	Single dose of 1.5 Gy	Benefit of LD-RT. Median time to clinical recovery, median time to hospital discharge and intubation rates were 3 vs. 12 days, 12 days vs. 20 days, 10% vs. 40%. Statistically significant reduction of hematologic, cardiac, hepatic, and inflammatory markers with LD-RT.

Clinical results not in favour of LD-RT

(This trial was in patients not expected to benefit from LD-RT, due to wrong time window)

Author	Patients	Dose	Effects
Papachristofilou (2021)	11 irrad, 11 sham irrad. Median age 75, mechanical ventilation	Single dose of 1 Gy	After 15 day follow-up, survival was estimated 72.7% and 63.6% for LD-RT group and sham-RT group, but after 4 weeks, survival was estimated equal (63.6%)

Conclusions

- Our two patients have benefitted clinically, biochemically and radiologically from LD-RT
- The clinical trials reported so far indicate an effectiveness of LD-RT in treating COVID-19 up to 90% (if treated at the appropriate time point).
- LD-RT should continue to be explored as a feasible treatment in clinical trials for pneumonia.