Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Oncology 32 (2020) 497–500

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Personal View: Low-dose Lung Radiotherapy for COVID-19 Pneumonia – The Atypical Science and the Unknown Collateral Consequence

H. Tharmalingam [*], P. Díez [†], Y. Tsang [*], A. Hawksley [‡], J. Conibear [§], N. Thiruthaneeswaran [¶||]

[*] Department of Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK
[†] Department of Radiotherapy Physics, Mount Vernon Cancer Centre, Northwood, UK
[‡] Department of Acute Medicine, University Hospital Lewisham, London, UK
[§] Department of Clinical Oncology, St Bartholomew's Hospital, London, UK
[¶] Division of Cancer Sciences, The University of Manchester, Manchester, UK
[||] Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

Received 16 May 2020; accepted 4 June 2020

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a devastating impact, with the number of deaths worldwide by June 2020 over 400 000 [1]. There are currently no proven, effective treatments, so there is an urgent need for clinical trials to test new therapeutic interventions that may be of benefit.

The lungs represent one of the organs most commonly affected by COVID-19. The vast majority of patients present with a respiratory illness that can in some progress to a life-threatening acute respiratory distress syndrome (ARDS) associated with a systemic inflammatory response characterised by a sudden increase in the release of a number of pro-inflammatory cytokines, such as interleukin-1, interleukin-6 and tumour necrosis factor-α [2].

During the first half of the 20th century, efforts were made to use low-dose radiotherapy (LDRT) in the form of X-rays to treat pneumonia. Fifteen studies reported on around 700 cases of predominantly bacterial pneumonia that responded clinically to LDRT [3]. The proposed molecular mechanism is thought to be the propensity of LDRT to mediate a host of anti-inflammatory effects, including reduced functioning of macrophages, decreased levels of pro-inflammatory cytokines and apoptotic induction in immune cells [4]. Thus, it is hypothesised that LDRT of $<$100 cGy to the lungs of patients with COVID-19 pneumonia may reduce the life-threatening inflammation and improve mortality. On this basis, early phase studies have been initiated to explore this further [5–7].

Pathogenesis of COVID-19 Pneumonia – Not a Typical ARDS

Although it can meet the Berlin criteria for ARDS [8], evolving evidence suggests that COVID-19 pneumonia is a unique disease with a novel pathophysiology and an atypical phenotype not previously seen with other respiratory viruses [9]. Conventionally, ARDS is characterised by extensive alveolar inflammation and non-cardiogenic pulmonary oedema. The reduced aerated lung space results in poor lung compliance and an increased work of breathing, resulting in dyspnoea [10]. In marked contrast, early on in the disease time course, patients with COVID-19 pneumonia often have severe hypoxaemia but, remarkably, maintain relatively good lung compliance [11,12]. Many are therefore not overtly dyspnoeic despite very low oxygen saturations ('happy hypoxics'). Inflammatory infiltrates are often minimal and characterised on computed tomography by ground-glass opacities signifying interstitial as opposed to alveolar oedema. This initial hypoxaemia is therefore thought to be due to a perfusion defect not a ventilation defect, attributable to viral-induced endothelial dysfunction initiated in the pre-symptomatic phase [13]. The consequent dysregulation of pulmonary blood flow, vasoplegia and micro-thromboses in the lung result in a significant ventilation/perfusion (V/Q) mismatch and type 1 respiratory failure. For some patients, the disease may stabilise at this time point with appropriate immune clearance of the

Author for correspondence: H. Tharmalingam, Department of Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK.
E-mail address: hannah.tharmalingam@nhs.net (H. Tharmalingam).

https://doi.org/10.1016/j.clon.2020.06.002

virus. In others, however, a deterioration to a clinical picture more typical of ARDS may occur, either because of unchecked viral disease inciting excess inflammation or suboptimal ventilatory management contributing to patient self-induced and/or ventilator-induced lung injury [13].

Underlying these observations is the paradigm that COVID-19 is not a simple pneumonia caused by a typical respiratory virus as initially thought. Instead it is also a complex, multisystem disease targeting the vascular endothelium mediated in part by viral entry through ACE-2 receptors, of which this tissue is enriched [14,15]. A highly activated coagulation cascade secondary to endothelial dysfunction with widespread micro- and macro-thromboses in multiple organs is well reported [14–18] and elevated D-dimer levels are increasingly being recognised as a very poor prognostic factor [19,20]. If the lung disease in COVID-19 is not managed taking into consideration the key vasocentric components of this novel illness, as well as the differing respiratory phenotypes throughout its time course, the propensity to cause harm is high.

Timing of LDRT and the Therapeutic Tightrope

With the differing temporal pathophysiologies and phenotypes of COVID-19 pneumonia, the timing of delivery of LDRT is critical and this does not appear consistent among the early phase trial protocols established [5–7]. Some propose LDRT delivery early in the disease [5,6] at a time where vascular phenomena, not excess alveolar inflammation, appear to underlie hypoxaemia. Such early deployment does not seem logical, especially when spontaneous recovery can often occur here upon effective clearance of the virus. As oxygen requirements increase, preventing disease progression using LDRT at an interim time point has sounder biological rationale. However, the specific effects of LDRT on endothelial function and, in particular, the coagulation cascade are unclear. Worryingly, animal studies have shown exposure to 1 Gy proton irradiation to lead to deranged levels of clotting factors, increased bleeding times and higher plasma concentrations of soluble fibrin, resulting in thromboses in the lungs, liver and kidneys [21,22]. Although more evidence is required, there is concern over the potential for LDRT to exacerbate the pathological coagulopathy active in COVID-19 patients.

At this early stage, disease stabilisation is dependent on an appropriate host immune response and clearance of the virus. Lymphopenia is consistently reported to be a poor prognostic factor in COVID-19; patients with low lymphocyte counts develop more severe disease with higher rates of mortality [23–25]. Radiotherapy is known to deplete peripheral lymphocytes as a result of their high sensitivity to radiation-induced apoptosis. Studies suggest that the absolute risk of lymphopenia is related to the pre-treatment lymphocyte count and the extent of the irradiated volume [26]. In the context of LDRT to the whole lung, although the prescribed dose is low, the integral body dose is high owing to the considerable volume being irradiated, increasing the risk of inducing severe post-treatment lymphopenia [27]. The mechanisms underlying lymphopenia in COVID-19 are unclear, but its negative effect in the presence of a systemic viral infection is not surprising. Exacerbation of this effect with LDRT at the very time when an adequate cellular immune response is needed to clear the pathogen could have potentially grave consequences.

An alternative approach [7] is to deliver LDRT later on in the disease process when excess inflammation and cytokine release underlie the severe respiratory failure characterised by ARDS. However, by this point, patients are critically unwell and may be intubated. Some will have developed systemic manifestations of the disease, with severe renal complications occurring in 20–35% of cases in intensive care units in the UK [28]. Although the anti-inflammatory response of LDRT has been shown to be effective in benign conditions [29], its ability to achieve the therapeutic levels needed at this time point to abate the extensive cytokine storm mediated by a systemic virus affecting the entire vasculature, not solely the lungs, is questionable.

It is clear that the delivery of LDRT on the premise of mediating a safe and effective anti-inflammatory response would need to take place within a very narrow time window (Figure 1). The varying presentation of patients at different time points of disease and the unpredictable nature of its progression make this highly challenging. Patients with COVID-19 may deteriorate very rapidly and not all acute medical units are co-located with radiotherapy centres, posing the added complication of inter-hospital transfer in these cases. Where the high throughput of palliative patients completing the radiotherapy workflow pathway in a matter of hours is alluded to [30], there is failure to acknowledge the extent of morbidity of COVID-19 patients who are acutely unwell with high oxygen requirements and often in intensive care units. Outwith the narrow therapeutic window, subjecting these patients to the radiotherapy delivery process may in itself trigger a deleterious clinical deterioration beyond any caused by LDRT *per se,* further questioning the feasibility of safely delivering this intervention on a broad scale.

Cancer Services, Cancer Patients and Unintended Harm

Beyond safety and feasibility, in order to provide strong evidence of modest effects on survival derived from LDRT for COVID-19 pneumonia, substantial numbers of patients would need to be recruited on to a large, multi-centre trial. As we move towards an era of endemic COVID-19, the ongoing safe delivery of radiotherapy services for cancer patients already poses significant challenges. Following the peak of the pandemic, the recovery phase will see the demand for radiotherapy increase considerably to account for known deferrals, altered referral pathways and diagnostic backlogs. Staffing levels may continue to fluctuate and required infection control and social distancing measures will limit throughput and capacity. An extensive scale-up of LDRT for the treatment of COVID-19 would put undoubted

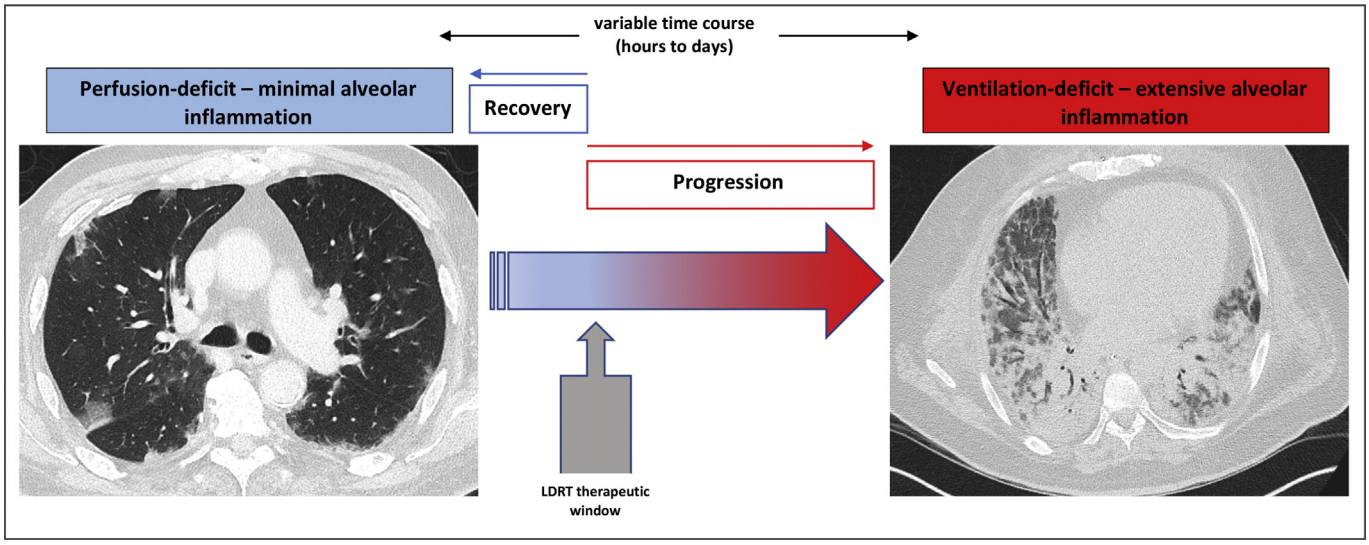

Fig 1. Respiratory failure in novel coronavirus disease 2019 (COVID-19) pneumonia. Severe early hypoxia mediated by a perfusion deficit secondary to viral-induced endothelial dysfunction (left panel). Patients may either recover with effective viral clearance or progress to critical acute respiratory distress syndrome (ARDS; right panel) due to unchecked viral disease, patient self-induced and/or ventilator-associated lung injury. The time course is unpredictable and the therapeutic window for low-dose radiotherapy is very narrow.

strain on an already over-stretched radiotherapy resource designated for cancer patients and presents an added infection risk to frontline staff. Furthermore, cancer patients are a vulnerable group at higher risk of severe morbidity and mortality from COVID-19 [31]. The safety of these patients when attending hospital for their treatments is paramount. A key feature of the recovery and restoration of radiotherapy services in the coming months will be their delivery in COVID-19 protected sites. The transfer of numerous acutely unwell, symptomatic COVID-19 patients into the department for the planning and delivery of experimental LDRT does not align with this philosophy and the potential for harm, although impossible to quantify, is unlikely to be negligible.

The use of LDRT to treat COVID-19 pneumonia represents an interesting but controversial strategy. Arguments with respect to the strength of the supporting clinical and preclinical evidence and the risk of radiation-induced cancer have been eloquently versed and debated elsewhere [30,32–35]. As our understanding of the unique biology of SARS-CoV-2 now begins to unfold, we advise additional caution and consideration given the highly atypical pathogenesis of this novel virus and the negative collateral impact large clinical trials may have on cancer patients and the safe delivery of cancer services.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgements

Images were provided courtesy of Dr A. Beale, Consultant Radiologist, Great Western Hospitals NHS Foundation Trust, and Dr S. Harden, Consultant Radiologist, Southampton University Hospital NHS Foundation Trust.

References

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports; 2020. [Accessed 10 June 2020].
[2] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395(10229):1033–1034.
[3] Calabrese EJ, Dhawan G. How radiotherapy was historically used to treat pneumonia: could it be useful today? *Yale J Biol Med* 2013;86:555–570.
[4] Arenas M, Sabater S, Hernández V, Rovirosa A, Lara PC, Biete A, *et al.* Anti-inflammatory effects of low-dose radiotherapy. Indications, dose and radiobiological mechanisms involved. *Strahlenther Onkol* 2015;191(1):1–6.
[5] https://clinicaltrials.gov/ct2/show/NCT04380818.
[6] https://clinicaltrials.gov/ct2/show/NCT04377477.
[7] https://clinicaltrials.gov/ct2/show/NCT04366791.
[8] Force TADT. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307(23):2526.
[9] Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not. *Crit Care* 2020;24(1):154.
[10] Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L. The 'baby lung' can become an adult. *Intensive Care Med* 2016;42(5):663–673.
[11] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323(16):1574–1581.
[12] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020;323(16):1612–1614.
[13] Marini J, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* 2020;323(22):2329–2330.

[14] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med* 2020; 9:1417.
[15] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395(10234):1417–1418.
[16] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, *et al*. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382(17):e38.
[17] Klok F, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–147.
[18] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(6):1421–1424.
[19] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–847.
[20] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395: 1054–1062.
[21] Krigsfeld G, Sanzari JK, Kennedy AR. The effects of proton radiation on the prothrombin and partial thromboplastin times of irradiated ferrets. *Int J Radiat Biol* 2013;88:327–334.
[22] Krigsfeld G, Kennedy A. Is disseminated intravascular coagulation the major cause of mortality from radiation at relatively low whole body doses. *Radiat Res* 2013;180:231–234.
[23] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46(5): 846–848.
[24] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H. Clinical course and outcomes of critically ill patients with SARSCoV2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475–481.
[25] Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y, *et al*. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Sig Transduct Target Ther* 2020;5:33.
[26] Joseph N, McWilliam A, Kennedy J, Haslett K, Mahil J, Gavarraju A, *et al*. Post-treatment lymphocytopaenia integral body dose and overall survival in lung cancer patients treated with radical radiotherapy. *Radiother Oncol* 2019;135:115–119.
[27] Joseph N, Choudhury A. Lymphocytopenia and radiotherapy treatment volumes in the time of COVID-19. *Clin Oncol (R Coll Radiol)* 2020;32(7):420–422.
[28] https://uclpartners.com/work/sharing-real-world-insights-on-covid-19-in-intensive-care; 2020. [Accessed 10 June 2020].
[29] Seegenschmiedt MH, Micke O, Muecke R. German Cooperative Group on Radiotherapy for Non-malignant Diseases (GCG-BD). Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. *Br J Radiol* 2015;88:20150080.
[30] Kirkby C, Mackenzie M. Is low dose radiation therapy a potential treatment for COVID-19 pneumonia? *Radiother Oncol* 2020. https://doi.org/10.1016/j.radonc.2020.04.004.
[31] Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, *et al*. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. *Cancer Discov* 2020. https://doi.org/10.1158/2159-8290.CD-20-0422.
[32] Kefayat A, Ghahremani F. Low dose radiation therapy for COVID-19 pneumonia: a double-edged sword. *Radiother Oncol* 2020. https://doi.org/10.1016/j.radonc.2020.04.026.
[33] Lara PC, Burgos J, Macias D. Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment. *Clin Transl Radiat Oncol* 2020;23: 27–29.
[34] Salomaa S, Cardis E, Bouffler SD, Atkinson MJ, Hamada N. Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence? *Int J Radiat Biol* 2020. https://doi.org/10.1080/09553002.2020.1762020.
[35] Kirsch D, Diehn M, Cucinoata FA, Weichselbaum R. Lack of supporting data make the risks of a clinical trial of radiation therapy as a treatment for COVID-19 pneumonia unacceptable. *Radiother Oncol* 2020. https://doi.org/10.1016/j.radonc.2020.04.060.