

## Low dose lung radiotherapy – an alternative route to treat pneumonia linked to COVID-19

COVID-19 is caused by coronavirus 2 (SARS-CoV-2) which causes severe acute respiratory syndrome. The UN WHO declared it as a global public health emergency on 30 January 2020. SARS-CoV-2 has R naught (basic reproductive number of a virus) of about 2 similar to that of H1N1 (Jacob John, T., *Curr. Sci.*, 2020, **118**, 855–856); but its generation time on an average is 10 days, much longer than that of H1N1, which is 2 days. Yet, in the USA, while H1N1 pandemic registered a fatality rate of just 0.02%, SARS-CoV-2 has so far registered death rate of 6.0%. The death rate is about 3.2% in India, 14.0% in Italy and 11.9% in Spain. The average global death rate for COVID-19 is about 6.7%. It is this high death rate that makes COVID-19 pandemic dreadful, without a parallel in recent times. Increased incidence of death has to do with the severity of infection. The spectrum of clinical symptoms of the patients with SARS-CoV-2 is broad and encompasses asymptomatic infection, mild and moderate to severe illnesses of the upper respiratory tract, severe pneumonia, acute respiratory distress syndrome (ARDS) and respiratory failure leading to death.

COVID-19 originated in Wuhan in the Hubei province of China. So far as its effective treatment is concerned, words of wisdom of the Chinese philosopher Confucius are relevant today. Confucius stated, 'Study the past if you would define the future'. The treatment of severe pneumonia over one hundred years ago involved low dose radiation therapy to the lungs. During the past three months, scores of papers have been published on the rationale of low LET (linear energy transfer radiation like X-rays and gamma rays), on low dose radiotherapy (LDRT) to save critically ill COVID-19 patients with lungs affected by 'cytokine storm' which fills the alveolar cells with fluid and induces inflammation that leads to breathlessness, lack of oxygen and eventual death; it is the uncontrolled systemic inflammatory response of the body immune system resulting from the release of large amounts of pro-inflammatory cytokines.

Historically, treatment of pneumonia with small doses of X-rays is known since 1905 (Musser, J. H. and Edsall,

D. L., *Tr. Assoc. Am. Phys.*, 1905, **105**(20), 294–321). During the first half of the 20th century, approximately 700 cases of bacterial (lobar and bronchopneumonia), sulphanilamide-resistant interstitial and atypical pneumonia were effectively treated by X-rays (for historical details of pneumonia treatment with low dose X-rays see Calabrese, E. J. and Dhawan, G., *Yale J. Biol. Med.*, 2013, **86**(4), 555–570). Since the early 1940s, until about 2010, there have been no reports of use of LDRT for non-malignant diseases. A paper on Roentgen therapy of interstitial pneumonia (Oppenheimer, A., *J. Pediatr.*, 1943, **41**, 404–414) describes the impressive success of saving lives of children. And that appears to be amongst the very last few reports on LDRT for life-threatening serious respiratory diseases during the 20th century. The logical question is, 'why the sudden demise of LDRT'? There are three most plausible reasons: (i) World War II, (ii) emergence of the anti-biotic era and (iii) H. J. Muller's statement in his Nobel lecture 'no escape from the conclusion that there is no threshold' for induction of genetic changes (i.e. mutations). With the background of atom-bomb detonations over Hiroshima and Nagasaki in August 1945, detailed studies initiated by the Atomic Bomb Casualty Commission (ABCC), and then Muller's role in the United Nation's Scientific Committee on the Effects of Atomic Radiations (UNSCEAR), anchored the 'linear, no-threshold (LNT)' hypothesis firmly. The nuclear safety and regulatory agencies adopted the LNT model and this in turn accentuated 'radiation phobia' among the people of the world. Yet, a few scientists stood up firmly against the LNT fallacy and are still fighting to restore the truth, that even for genetic effects, there is indeed a threshold dose (Luckey, T. D., *Radiat. Hormesis*, CRC Press, Boca Raton, 1991, p. 239; Calabrese, E. J., *Arch. Toxicol.*, 2011, **85**, 1495–1498; Kesavan, P. C., *Curr. Sci.*, 2014, **107**, 46–53; Kesavan, P. C., *Radiat. Protec. Environ.*, 2017, **40**, 51–59). Presently, a group of international scientists referred to as 'Scientists for Accurate Radiation Information' (SARI) based in the USA is harnessing science-based knowledge to dismiss the LNT model and bring to humankind the benefits of LDRT.

Already, in Germany patients are being treated with LDRT for several non-malignant ailments including arthritis.

The question is how can LDRT be effective in saving the lives of critically ill patients with respiratory failures caused by various pathogenic organisms including COVID-19. The answer in one sentence is that, LDRT can effectively remove the inflammation of the lungs. The LDRT does so by countering the ‘cytokine storm’ leading to Cytokine Release Syndrome (CRS). Basically, the cytokine storm involves a sudden and sharp increase in the pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF-alpha by activated macrophage of M2 type. Low dose ionizing radiation reduces the inflammation through several pathways such as (i) induction of apoptosis in immune cells, (ii) activates the genes for anti-inflammatory reaction, and (iii) accelerates the destruction of lymphocytes. It is known that lymphocytes are highly radio-sensitive than most other tissues and organs in the human body. So, with the low dose radiation-induced immuno-suppression, the highly fatal pulmonary ‘cytokine storm’ can be quenched.

As of today, dozens of hospitals across the USA (e.g. Emory University Medical Centre) and Germany are using LDRT to treat and save the lives of seriously ill COVID-19 patients. LDRT is quite cost-effective and, more importantly, proven in the fight against the killer ‘cytokine storm’. Having become extremely desperate, several countries are now resorting to using the malarial drug hydroxychloroquine, despite its known undesirable side-effects. There are also vigorous endeavours to use plasma therapy, antibiotics, vaccines, etc. Many of these systemic therapies can also exert selection pressure to accelerate the mutations in the COVID-19 RNA virus that has already shown a very high mutation rate. Therefore LDRT in the range of 0.3 to 1.0 Gy could be tried as an alternative approach in treating lung infections due to

COVID-19. The apprehension about LDRT-inducing cancers after latencies of >10 years in adjacent organs is unwarranted as it is quite negligible (<1% of spontaneous occurrence) (Trot, K. R. and Kamprad, F., *Strahlenther Onkol*, 2006, **182**(8), 431–436).

As this editorial was being finalized, a message was received from Dr Mohan Doss, Medical Physicist, Fox Chase Cancer Center, Philadelphia, USA, that seven clinical trials of LDRT for COVID-19 patients seriously ill with pneumonia are presently listed in ClinicalTrials.gov website (<https://clinicaltrials.gov/ct2/results?cond=COVID&term=lowdose+radiotherapy&cntry=&state=&city=&dist=>). It is heartening to note that the All India Institute of Medical Sciences (AIIMS), New Delhi is one among the seven centres for Clinical Trial. As of now Iran, Italy, Spain and USA are the other countries involved in the Clinical Trials. If LDRT (which is cost-effective) proves successful, two things can be possibly avoided: (i) use of systemic drugs which will increase the mutation rates of the virus, (ii) prolonged lockdown which has adverse economic implications. India with its highly capable scientific staff in nuclear sciences and outstanding medical experts in viral diseases and their treatment would be able to contain COVID-19 which is rapidly becoming pan-endemic.

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