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.

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Editorial

Radiation therapy for COVID-19 pneumopathy ☆

Klaus Rüdiger Trott [a,*], Sebastian Zschaeck [b,c], Marcus Beck [b]

[a] Department of Radiation Oncology, Technical University of Munich; [b] Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Radiation Oncology; and [c] Berlin Institute of Health (BIH), Berlin, Germany

The COVID-19 pandemic has a dramatic impact on global healthcare. In lack of effective SARS-CoV-2 directed therapeutics, several treatment approaches are currently being re-purposed. In this regard, Kirkby and Mackenzie drew the radiotherapy community's attention to the historical use of low-dose lung radiotherapy for bacterial and viral pneumonia in the pre-penicillin-era [1].

The two papers which are being published in this issue of Radiotherapy and Oncology present the extreme alternative positions in the current discussion about the potential value of using radiotherapy to treat acute respiratory distress syndrome (ARDS). Both make their point very clear, yet the interested reader will still find it difficult to arrive at practical, clinically useful conclusions [2,3].

Kirsch et al. convincingly argue that there is no clinical evidence that is compatible with the criteria that are required to provide evidence in current evidence-based medicine [2]. This, however, is a futile point since there can be no such evidence as COVID-19 is a new disease that has never been treated before. Moreover, the last clinical study on treating inflammatory lung diseases using radiotherapy is more than 50 years old, long before modern criteria of evidence-based medicine were developed. One has to keep in mind that all medical knowledge has to be interpreted within its historical context.

The criticism expressed by Kirsch et al. of the two experimental in-vivo studies is valid. They really do not meet criteria of good experimental practice in radiation biology. The overall experimental design is flawed and the endpoints are poorly defined. Moreover, animal studies should rather be designed to provide quantitative insights into mechanisms of particular radiation effects.

The paper by Dhawan tries to do exactly this, arguing from the point of mechanisms of radiation action in inflammatory diseases [3]. Yet, this paper also has some weaknesses attributable to a rather selective quoting of experimental work, most of which has been going on in Germany since the mid 1980s. Most of those in-vivo experiments were performed using animal models of painful degenerative joint diseases. Such a model was also used in the one experimental study described in Dhawan's paper. Yet, pathogenesis, disease progression and treatment response of these popular models are not necessarily good models for the per-acute interstitial inflammation observed in severe COVID-19 acute respiratory syndrome. The in-vitro studies may be more relevant as most of them concentrate on specific pathways in the complex network of molecular signaling, leading from trigger to overt disease. A consistent finding in these experiments was a bi-phasic dose response relationship with anti-inflammatory effects at doses <1 Gy (maximum 0.5 Gy) and pro-inflammatory effects at doses >1 Gy (progressing with dose). A review of results of these studies is currently being published in Strahlentherapie und Onkologie in English by Roedel et al. [7].

A major problem of both papers is based on the fact that the majority of clinical applications of low-dose radiotherapy for acute and sub-acute inflammatory diseases were performed in the 1930s to 1970s in Germany, and mostly reported in German. The standard textbook on anti-inflammatory radiotherapy is written in German by Glauner with the title "Entzündungsbestrahlung" [4]. Seegenschmidt et al. found out that even as late as in the 1980s, more than 50,000 patients per year were treated in Germany using low-dose radiotherapy for non-malignant diseases [5]. Yet, doses, timings and endpoints for treating COVID-19 pneumopathy cannot be generalised from these reports on sub-acute painful degenerative joint diseases. Information on mechanisms, dose dependence, time dependence of effectiveness and on endpoints are probably best derived from studies on acute, severe inflammatory conditions, such as abscess and post-partum mastitis. Herrmann reported results of a large series of low dose (average 0.5 Gy) single exposure for mastitis [8]. Most important for the current discussion is the observation that 90% of the patients were cured within a few days if radiotherapy was given within 24 h of the development of severe clinical symptoms. However, if radiotherapy was delayed for a few days or up to one week the cure rate dropped to 50% (as reported in Roedel et al.). This was a consistent observation reported by the old radiotherapists, also by Oppenheimer as quoted by Kirsch. The authors of this editorial conclude that the extensive clinical experience with single local radiation doses

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* Corresponding author at: Department of Radiation Oncology, Technical University of Munich, Klinikum rechts der Isar, 81675 Munich, Germany.

E-mail address: klaustrott@yahoo.it (K.R. Trott).

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around 0.5 Gy to the target volume in the early acute phase together with the comprehensive experimental work on the underlying mechanisms would justify compassionate use in those patients who are so ill that they are eligible for intubation and mechanical ventilation (which has an acute mortality of 20–50%), but under close supervision and centralized documentation.

Both papers also address the issue of side effects. At this dose of 0.5 Gy, no acute, early normal tissue damage needs to be considered, yet Kirsch at al. discuss at length potential very late occurring normal tissue damage, in particular the induction of lung cancer in advanced age and late heart failure. They use, for their risk estimation, models and concepts developed in radiation protection for setting dose limits in occupational radiation exposure. The tabulated mortality risk estimations should be seen in the context of the recommendation of the International Commission for Radiological Protection (ICRP) not to use such risk estimations in medical exposure situations and in individuals. Dhawan et al. do not provide any numbers, only making a more cursory statement of the risk being low. It goes without saying that for none of the potentially effective pharmacological agents can any reliable estimates about life-time risks be made. Even taking the tabulated risk estimations from Kirsch et al., into account, the overall life time risk from this potentially life-saving treatment is 1–2% with a lower confidence limit of 0.

Last but not least one has to keep in mind that experimental drugs used in COVID-19 patients can have serious side effects, including cardiac toxicity for Chloroquin [6]. We think that the two papers published in this issue point out, that careful selection of COVID-19 patients is a pivotal issue. Radiotherapy should probably be restricted to elderly patients progressing into critical illness.

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