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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COVID-19 Rapid Letter

Response Letter: Radiation therapy for COVID-19 pneumopathy ☆

To the Editor

Trott and colleagues wrote an editorial [1] on our manuscript in which we argue that in the absence of supportive pre-clinical or clinical data for using radiation therapy for viral pneumonia, the risks of low dose thoracic radiotherapy make clinical trials testing radiation therapy as a treatment for COVID-19 pneumonia unacceptable [2]. Trott et al. concur with our interpretation of the available pre-clinical data testing low dose radiotherapy in animal models of viral pneumonia: "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." It is deeply troubling that some [3] have pointed to a review of these same pre-clinical data of radiation therapy for viral pneumonia as evidence to support a clinical trial of radiotherapy for COVID-19. Remarkably, these authors erroneously cited one of the pre-clinical studies as support for the concept of low dose radiotherapy for COVID-19, when in fact this study demonstrated that radiation therapy delivered to mice after inoculation of swine influenza virus had no effect on mortality [4].

Trott et al. also agree that we "convincingly argue that there is no clinical evidence" to support the use of radiotherapy for COVID-19 pneumonia "that is compatible with the criteria that are required to provide evidence in current evidence-based medicine." However, they mischaracterize our argument by stating that this "is a futile point since there can be no such evidence as COVID-19 is a new disease that has never been treated before." Our point is not that there is no clinical evidence for treating COVID-19 patients with radiotherapy. Instead, we argue that the anecdotal clinical literature describing radiotherapy for any viral pneumonia shows no reliable evidence of benefit. Had any of these studies provided robust evidence to support the use of thoracic radiotherapy for any related viral pneumonia, then we would support a clinical trial of radiotherapy for COVID-19 pneumonia. This is not the case.

We also disagree with Trott et al. in their characterization of our risk estimates as appropriate for radiation protection rather than "medical exposure situations." The radiation risks are real to the individual patient receiving these kinds of medical exposures and must be weighed against an experimental therapy that has no convincing pre-clinical or clinical evidence of likely benefit. Indeed, others have recently made independent calculations of the risks of thoracic radiotherapy for COVID-19 pneumonia [5]. In addition to the cogent radiobiological arguments that low dose radiotherapy could in fact exacerbate viral infection and worsen outcomes from COVID-19, Salomaa et al. estimate that 0.3 Gy–1 Gy of thoracic radiation to 100 patients would induce 0.6–4.4 excess lung cancers and 0.8–7.6 extra cardiovascular deaths [5]. We agree with Salomaa and colleagues that these risks cannot be justified in a clinical trial of COVID-19 patients in the absence of either reliable pre-clinical or clinical data with any viral pneumonia to suggest benefit in the setting of COVID-19 pneumonia.

Finally, we disagree with Trott et al. that "the interested reader will still find it difficult to arrive at practical, clinically useful conclusions." For clinicians considering using thoracic radiotherapy for COVID-19 pneumonia, rather than relying on misleading reviews and unsupported conjecture [3], they should read the primary literature of the two pre-clinical studies of using radiation therapy for viral pneumonia performed in the 1940's [4,6]. Those leading clinical trials of thoracic radiotherapy for COVID-19 pneumonia and members of Institutional Review Boards and other bodies that determine whether these trials are ethical should read the anecdotal reports of using thoracic radiotherapy for viral pneumonia [7] and reconsider whether the risks to patients of such clinical trials can be justified by the available scientific evidence. Instead of proceeding with exposing patients with COVID-19 to thoracic radiation therapy, proponents of such clinical trials should work with scientists to test low dose thoracic radiotherapy in pre-clinical experiments of SARS-CoV-2 infection in relevant models, such as transgenic mice expressing the human angiotensin converting enzyme 2 (ACE-2) [8] or non-human primates [9]. These pre-clinical studies are needed to generate efficacy data that could support exposing patients with COVID-19 to the risks of thoracic radiotherapy in ongoing and planned clinical trials.

Conflict of interest

DGK is on the scientific advisory board and owns stock in Lumicell, Inc which is developing intraoperative imaging technology. DGK is a co-founder of X-RAD Therapeutics, which is developing radiosensitizers. DGK reports research support from Merck, Bristol Myers Squibb, and X-RAD Therapeutics. MD reports research funding from Varian Medical Systems and Illumina, ownership interest in CiberMed, patent filings related to cancer biomarkers, paid consultancy from Roche, AstraZeneca, Illumina, RefleXion, and BioNTech. RW has stock and other ownership interests with Boost Therapeutics Inc., Coordination Pharmaceuticals Inc., ImmunoVir LLC, Magi Therapeutics, Oncosenescence, and Reflexion Pharmaceuticals. RD has served in a consulting or advisory role for Aettis Inc., Astrazeneca, Coordination Pharmaceuticals, Genus, Immuno-

☆ The Editors of the Journal, the Publisher and the European Society for Radiotherapy and Oncology (ESTRO) cannot take responsibility for the statements or opinions expressed by the authors of these articles. Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. For more information see the editorial "Radiotherapy & Oncology during the COVID-19 pandemic", Vol. 146, 2020.

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Vir LLC, Merck Serono S.A., Nano proteagen, NKMax America Inc, Reflexion Pharmaceuticals, Shuttle Pharmaceuticals. RW has research grants from Varian and Regeneron, and has a patent pending entitled "Methods and Kits for Diagnosis and Triage of Patients With Colorectal Liver Metastases." RW has received compensation including travel, accommodations, or expense reimbursement from Astrazeneca, Boehringer Ingelheim LTD and Merck Serono S.A. None of these interests present a conflict with the content in this manuscript.

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