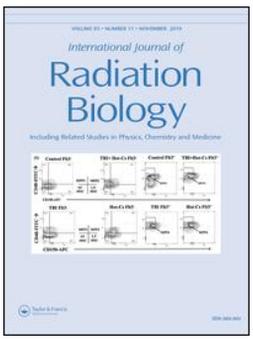

International Journal of Radiation Biology

2020/I-028

ISSN: 0955-3002 (Print) 1362-3095 (Online) Journal homepage: https://www.tandfonline.com/loi/irab20

Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence?

Sisko Salomaa, Elisabeth Cardis, Simon D. Bouffler, Michael J. Atkinson & Nobuyuki Hamada

To cite this article: Sisko Salomaa, Elisabeth Cardis, Simon D. Bouffler, Michael J. Atkinson & Nobuyuki Hamada (2020): Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence?, International Journal of Radiation Biology, DOI: 10.1080/09553002.2020.1762020

To link to this article: https://doi.org/10.1080/09553002.2020.1762020

COMMENTARY

Low dose radiation therapy for COVID-19 pneumonia: is there any supportive evidence?

Sisko Salomaa[a,b], Elisabeth Cardis[c,d,e], Simon D. Bouffler[f], Michael J. Atkinson[g], Nobuyuki Hamada[h]

[a]Department of Environmental and Biological Sciences, University of Eastern Finland, Yliopistonranta 1, 70210, Kuopio, Finland; [b]STUK-Radiation and Nuclear Safety Authority, P.O. Box 14, 00811 Helsinki, Finland; [c]Barcelona Institute for Global Health (ISGlobal), Campus Mar, Barcelona Biomedical Research Park (PRBB), Dr Aiguader 88, 08003, Barcelona, Spain; [d]University Pompeu Fabra, Dr Aiguader 88, 08003, Barcelona, Spain; [e]Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP), Carlos III Institute of Health, C/Sinesio Delgado, 4, 28029, Madrid, Spain; [f]Public Health England Centre for Radiation, Chemical and Environmental Hazards, Chilton, Didcot, Oxon OX11 0RQ, UK; [g]Institute of Radiation Biology, Helmholtz-Center Munich, National Research Centre for Health and Environment, Ingolstädter Landstrasse 1, D-85764, Neuherberg, Germany; [h]Radiation Safety Research Center, Nuclear Technology Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), 2-11-1 Iwado-kita, Komae, Tokyo 201-8511, Japan

CONTACT
Nobuyuki Hamada, RT, Ph.D
E-mail: hamada-n@criepi.denken.or.jp
Address: Radiation Safety Research Center, Nuclear Technology Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), 2-11-1 Iwado-kita, Komae, Tokyo 201-8511, Japan

Running title
Low dose radiotherapy for COVID-19 pneumonia

Keywords
COVID-19; pneumonia; low dose radiation therapy; lung cancer; circulatory disease

Over the last two decades, humans have encountered three substantial outbreaks of new coronavirus (CoV) epidemics. The first, in the early 2000s, was caused by the severe acute respiratory syndrome (SARS)-CoV (Poon et al. 2004). The second, in the 2010s, was caused by the Middle East respiratory syndrome (MERS)-CoV (Zumla et al. 2015). Lastly, the ongoing outbreak is caused by the SARS-CoV-2 (now termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO)) emerged in China in December 2019, resulting in more than 150,000 deaths as of 19 April 2020 (WHO 2020a). The lungs represent one of the organs most affected by COVID-19, and some patients develop life-threatening viral pneumonia and sepsis. There is also growing evidence for associations between multiple cardiovascular complications and COVID-19 (Driggin et al. 2020). Currently there are few clinical management options available for COVID-19 patients with pneumonia, beyond the supply of oxygen and administration of antibiotics to avoid co-infection, and possibly, though not recommended, administration of corticosteroids (WHO 2020b). Interestingly there is ongoing discussion of the potential use of diagnostic X-rays, most notably by computerized tomography (CT) scanning for COVID-19 related lung pathology (Chua et al. 2020; Hope et al. 2020; Huang et al. 2020). Clinical studies on several potential therapeutic agents are being conducted, such as favipiravir, lopinavir and remdesivir (Dong et al. 2020; Lu et al. 2020; UKCDR 2020).

In the first half of 20th century, uncoordinated individual attempts were made to treat various non-cancer diseases with ionizing radiation, including viral or bacterial pneumonia. In 2013, Calabrese and Dhawan (2013) reviewed 19 papers, mostly case reports, describing outcomes from low dose radiotherapy with X-rays (LDRT) for pneumonia, among them 3 papers published in 1905–1916 and 16 published between 1925–1943. Their review identified a total of 863 cases, among which 717 showed good clinical response within three days of treatment (Calabrese and Dhawan 2013). However, the human data reviewed were limited to case series, many based on small numbers of subjects, with in some instances comparisons to differently defined control groups, with various doses used (determined by treatment for other diseases), making the results difficult to interpret. There were three radiobiological studies assessed in the review, all from experiments done in the 1940s, namely Fried (1941) using a guinea pig model, Lieberman et al. (1941) using a canine model and Dubin et al. (1946) using a murine model, the first two of these for bacterially-induced pneumonia and the last for virally-induced pneumonia. The evidence for any effect of radiation post-inoculation is weak in the studies of Fried (1941) and Dubin et al. (1946) Only in the study of Lieberman et al. (1941) on bacterial pneumonia is there a conventionally statistically significant beneficial effect of radiotherapy; however, this effect is confined to a single treatment group, the third of three groups. Moreover, in the third group, most recovered animals received irradiation at 3 days after bacterial inoculation, which exceeded the

average lifetime of 2.1 days in control (infected but not irradiated) animals: this suggests an experimental selection bias. Importantly, only one study was performed using a highly pathogenic viral trigger for the pneumonia, that of Dubin et al. (1946) Based on this review, Kirkby and Mackenzie (2020) recently suggested that LDRT with a single acutely delivered dose to the lungs of 0.3–1 Gy of low-linear energy transfer (LET) radiation could be used to treat COVID-19 pneumonia with very low risk and with normal tissue toxicities avoided. Similarly, but with a slightly lower dose of low-LET radiation, Ghadimi-Moghadam et al. (2020) have also suggested that a priming dose with a few mGy followed by a single dose of 0.1, 0.18 or 0.25 Gy could be used to treat COVID-19 pneumonia (0.25 Gy was selected because it is lower than the maximum dose of ~0.26 Gy/year from natural background radiation in Ramsar, Iran). Both of these papers suggest clinical trials of LDRT for COVID-19 pneumonia (Ghadimi-Moghadam et al. 2020; Kirkby and Mackenzie 2020). However, the body of evidence for a proposed beneficial effect of low dose radiation on viral pneumonia is clearly extremely slight.

Set against these possible beneficial effects, there is abundant evidence that radiation causes lung cancer in both sexes, with higher risk in females and smokers than males and non-smokers, respectively. According to risk factors evaluated by the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR 2008) based on the Japanese atomic bomb survivor data, the acutely delivered lung doses of 0.3–1 Gy proposed by Kirkby and Mackenzie (2020) would nominally induce 0.6–4.4 excess lung cancers in a hundred persons exposed. There is also accumulating evidence of association between moderate and low dose ionizing radiation and most types of circulatory disease (Little et al. 2012, 2016). Taken at face value a single 0.3–1 Gy lung dose (which the heart and aorta would also receive) would be associated with 0.8–7.6 extra deaths from circulatory disease in a hundred persons exposed (Little et al. 2012). It is vital that a risk-benefit and ethical evaluation of an exposure of the lungs of critically ill individuals with COVID-19 to a putatively therapeutic lung irradiation be conducted before a clinical trial could be recommended.

Use of radiotherapy (RT) for non-malignant diseases, in particular mild tissue inflammation, is common in some countries. Every year about 50,000 patients in Germany are treated for non-malignant disorders, mainly those with painful degenerative joint disorders by using ionizing radiation applied in more than 300 RT facilities, as reviewed by Seegenschmiedt et al. (2015). Patients treated for non-malignant indications represent about 10–30% of all patients treated with RT in most academic, public and private radiotherapy facilities in Germany, which is an exceptionally high rate compared to many other countries. However, there have been no studies on use of RT for pneumonia, and sensitive tissues are typically avoided in therapy planning. Importantly, Seegenschmiedt *et al.* address the possible placebo effect

in the studies reviewed: “In previously published double-blinded studies from the 1970s, which did not fulfil current quality criteria of prospective clinical trials, a variety of different degenerative skeletal diseases were treated with LDRT. In contrast to the reported data from all studies above, these studies could not prove a significantly higher response for the RT group in comparison to the placebo group” (Seegenschmiedt et al. 2015).

At extremely high dose (≥10 kGy), low-LET radiation has been reported to inactivate MERS-CoV and SARS-CoV (Kumar et al. 2015; Feldmann et al. 2019). On the other hand, at much lower dose, viral reactivation may occur as reported for various viruses, such as Epstein-Barr virus (EBV, e.g., at ≥0.1 Gy of gamma-rays (Mehta et al. 2018)), hepatitis B/C virus (HBV/HCV), and human immunodeficiency virus (HIV), although the impact on CoV remains unknown.

Unlike the sites treated by LDRT for benign inflammatory conditions, the lung is radiosensitive. In radiotherapy for pulmonary neoplasms, breast carcinoma, esophageal carcinoma or Hodgkin’s disease, the risk of complications to the normal pulmonary tissues is a major limitation in the prescription of the therapeutic dose (Jain and Berman 2018). Radiation-induced edema, pneumonitis and fibrosis are well-documented complications in such radiotherapy patients. Early reactions develop within days or weeks, whereas late reactions require months or years. The clinical presentation of radiation-induced lung damage principally depends on the lung volume irradiated, the radiation dose and the pre-existing lung disease. There is some evidence that pretreatment inflammation in the lung would make pulmonary tissue more susceptible to radiation induced lung injury (Petit et al. 2011; Castillo et al. 2014; Chaudhuri et al. 2016; Jain and Berman 2018). Pulmonary inflammation manifests as enhanced uptake of [^{18}F]fluorodeoxyglucose (FDG), hence allowing for quantitative assessment. Petit et al. (2011) performed a retrospective study of 101 patients with non-small cell lung cancer (NSCLC) and evaluated the correlation between radiation-induced symptomatic lung toxicities (RILT) and pre-RT FDG positron emission tomography (PET) evidence of pulmonary inflammation. They demonstrated that the 95th percentile of the standard uptake value (SUV_{95}) within the lungs was predictive of RILT on multivariate analysis (p = 0.016), suggesting that SUV_{95} can be used to predict the risk of RILT during thoracic RT treatment planning. However, there is currently no knowledge on the response of COVID-19-infected lung tissue to low dose exposures or whether the low doses increase the risk of pulmonary complications. A viral infection taking place after the radiation exposure may also increase mortality, as shown for the influenza A virus (Manning et al. 2013; Misra et al. 2015).

There is a substantial body of radiobiological data which suggests that certain cytokines and adhesion molecules related to endothelial function and modulating immunological responses are differentially up- or downregulated with a boundary

around 0.5 Gy, as reviewed elsewhere (Little et al. 2008; Averbeck et al. 2018). In a recent study, Schröder et al. (2019) investigated the immune modulatory properties of low doses of ionizing radiation on endothelial cells with respect to an early response to inflammatory stimuli solely and in combination with low dose radiation. They measured the levels of a total of 27 inflammatory cytokines. While the test panel also included anti-inflammatory markers, only pro-inflammatory cytokines were detected, after doses as low as 10 and 50 mGy (Schröder et al. 2019). Overall, the evidence on anti-inflammatory *vs* pro-inflammatory effects at very low doses is not clear-cut but rather a balance between the two types of effect. There is radiobiological evidence that low dose irradiation induces pro-inflammatory responses due to spatiotemporal propagation of damage signals caused by nontargeted effects of low dose radiation exposure (Hamada et al. 2011). Examination of the totality of cytokine data suggests that the overall anti-inflammatory response at low doses is, at best, modest and unlikely to reach therapeutic levels against the cytokine storm typical for the COVID-19 pneumonia.

Onoda et al. (1999) reported that low dose radiation (0.5–2 Gy) produces significant changes in the morphology and microfilament organization of pulmonary microvascular endothelial cells (PMEC) characterized by retraction and the resulting loss of close contact between individual cells within the monolayer. They used the radiation dose levels and time course for PMEC retraction *in vitro* to design studies to determine radiation-induced acute edema in a murine *in vivo* model and demonstrated that low dose thoracic radiation induces pulmonary edema characterized by increased lung wet weight. The incidence of increased weight was radiation dose-dependent up to 2 Gy and was coincident with the time course for radiation-induced endothelial retraction *in vitro*. They determined that pretreatment of animals with 25 μM nordihydroguaiaretic acid (NDGA, a non-specific lipoxygenase inhibitor), 15 min prior to radiation exposure inhibited radiation induced edema. These observations were consonant with their *in vitro* studies. Therefore, the PMEC model system may prove useful for the screening of compounds and physical agents that may prove clinically useful for the prevention of acute and late radiation injuries to the lungs and other normal tissues.

In conclusion, there is very little, if any, supportive evidence that LDRT will be a curative or palliative treatment for COVID-19 pneumonia or be superior to any of potential therapeutic agents currently under clinical trials. It would appear to us to be difficult to justify an immediate initiation of clinical trials at this point, based on inadequate data from clinical and experimental studies on viral pneumonia, dose levels and timing of the irradiation. The prudent course would appear to be further (and perhaps better) experimental studies, for example those using the PMEC system (Onoda et al. 1999). However, even if some supportive evidence becomes available, irradiating

COVID-19 patients will be impractical without significant medical justification, given the logistical concerns for safety and patient care needs.

Acknowledgements
The authors would like to thank Drs Mark P. Little (NCI, USA) and Dörthe Schaue (UCLA, USA) for helpful discussion. ISGlobal acknowledges support from the Spanish Ministry of Science, Innovation and Universities through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.

Funding details
The authors receive no specific funding for this work.

Disclosure statement
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. The views expressed in this paper represent collective opinions of the authors, and are not necessarily those of their professional affiliations.

Biographical notes on contributors

Sisko Salomaa, Ph.D, is Professor of radiobiology in University of Eastern Finland and Coordinator of National Radiation Safety Research Program in STUK. As part of setting up the European low dose program (MELODI), she coordinated DoReMi Network of Excellence 2010–2015. She is representative of Finland to UNSCEAR and a member of ICRP C1.

Elisabeth Cardis, Ph.D, is Research Professor in Radiation Epidemiology at ISGlobal. Before moving to CREAL (now ISGlobal Campus MAR) in 2008, she was the head of the Radiation Group at IARC in Lyon, where she coordinated studies of ionizing and non-ionizing radiation for over 20 years. She was a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, Japan, in 1981–1982 and received a PhD in Biostatistics from the School of Public Health of the University of Washington in Seattle, in 1985.

Simon D. Bouffler, Ph.D, leads the Radiation Effects Department at Public Health England. He is involved in several European research initiatives and is currently Chair of the MELODI Strategic Research Agenda working group. He leads the UK delegation to UNSCEAR and is a Main Commission member of ICRP.

Michael J. Atkinson, Ph.D, is Professor of Radiation Biology at the Medical Faculty of the Technical University of Munich, Director of the Institute of Radiation Biology at the Helmholtz Zentrum München, and a member of the Federal Radiation Protection Commission in Germany.

Nobuyuki Hamada, RT, Ph.D, is Research Scientist at CRIEPI Radiation Research Center and Visiting Professor at Hiroshima University Research Institute for Radiation Biology and Medicine. He serves on ICRP Task Groups 102 and 111, NCRP PAC 1, and IRPA Phase 3 Task Group on the implementation of the eye lens dose limits. He has published >115 papers in peer reviewed international journals.

References

Averbeck D, Salomaa S, Bouffler S, Ottolenghi A, Smyth V, Sabatier L. 2018. Progress in low dose health risk research: Novel effects and new concepts in low dose radiobiology. Mutat Res. 776:46–69. doi: 10.1016/j.mrrev.2018.04.001.

Calabrese EJ, Dhawan G. 2013. How radiotherapy was historically used to treat pneumonia: Could it be useful today? Yale J Biol Med. 86:555–570. doi: unavailable. PMCID: PMC3848110.

Castillo R, Pham N, Ansari S, Meshkov D, Castillo S, Li M, Olanrewaju A, Hobbs B, Castillo E, Guerrero T. 2014. Pre-radiotherapy FDG PET predicts radiation pneumonitis in lung cancer. Radiat Oncol. 9:74. doi: 10.1186/1748-717X-9-74.

Chaudhuri AA, Binkley MS, Rigdon J, Carter JN, Aggarwal S, Dudley SA, Qian Y, Kumar KA, Hara WY, Gensheimer M, et al. 2016. Pre-treatment non-target lung FDG-PET uptake predicts symptomatic radiation pneumonitis following stereotactic ablative radiotherapy (SABR). Radiother Oncol. 119:454–460. doi: 10.1016/j.radonc.2016.05.007.

Chua F, Armstrong-James D, Desai SR, Barnett J, Kouranos V, Kon OM, José R, Vancheeswaran R, Loebinger MR, Wong J, et al. 2020. The role of CT in case ascertainment and management of COVID-19 pneumonia in the UK: insights from high-incidence regions. Lancet Respir Med. in press. doi: 10.1016/S2213-2600(20)30132-6.

Dong L, Hu S, Gao J. 2020. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 14:58–60. doi: 10.5582/ddt.2020.01012.

Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, Brown TS, Nigoghossian C, Zidar DA, Haythe J, et al. 2020. Cardiovascular considerations for patients, health care workers, and health systems during the Coronavirus Disease 2019 (COVID-19) pandemic. J Am Coll Cardiol. in press. doi: 10.1016/j.jacc.2020.03.031.

Dubin IN, Baylin GJ, Gobble WG, Jr. 1946. The effect of roentgen therapy on experimental virus pneumonia; on pneumonia produced in white mice by swine

influenza virus. Am J Roentgenol. 55:478–481.
Feldmann F, Shupert WL, Haddock E, Twardoski B, Feldmann H. 2019. Gamma irradiation as an effective method for inactivation of emerging viral pathogens. Am J Trop Med Hyg. 100:1275–1277. doi: 10.4269/ajtmh.18-0937.
Fried C. 1941. The roentgen treatment of experimental pneumonia in the guinea-pig. Radiology. 37:197–202. doi: unavailable.
Ghadimi-Moghadam A, Haghani M, Bevelacqua JJ, Jafarzadeh A, Kaveh-Ahangar A, Mortazavi SMJ, Ghadimi-Moghadam A, Mortazavi SAR. 2020. COVID-19 tragic pandemic: Concerns over unintentional "directed accelerated evolution" of novel coronavirus (SARS-CoV-2) and introducing a modified treatment method for ARDS. J Biomed Phys Eng. 10:241–246. doi: 10.31661/jbpe.v0i0.2003-1085.
Hamada N, Maeda M, Otsuka K, Tomita M. 2011. Signaling pathways underpinning the manifestations of ionizing radiation-induced bystander effects. Curr Mol Pharmacol. 4:79–95. doi: 10.2174/1874467211104020079.
Hope MD, Raptis CA, Shah A, et al. 2020. A role for CT in COVID-19? What data really tell us so far. Lancet. 395:1189–1190. doi: 10.1016/S0140-6736(20)30728-5.
Huang Y, Cheng W, Zhao N, Qu H, Tian J. CT screening for early diagnosis of SARS-CoV-2 infection. Lancet Infect Dis. in press. doi: 10.1016/S1473-3099(20)30241-3.
Jain V, Berman AT. 2018. Radiation pneumonitis: Old problem, new tricks. Cancers. 10:E222. doi: 10.3390/cancers10070222.
Kirkby C, Mackenzie M. 2020. Is low dose radiation therapy a potential treatment for COVID-19 pneumonia? Radiother Oncol in press. doi: 10.1016/j.radonc.2020.04.004.
Kumar M, Mazur S, Ork BL, Postnikova E, Hensley LE, Jahrling PB, Johnson R, Holbrook MR. 2015. Inactivation and safety testing of middle east respiratory syndrome coronavirus. J Virol Methods. 223:13–18. doi: 10.1016/j.jviromet.2015.07.002.
Lieberman LM, Hodes PJ, Leopold SS. 1941. Roentgen therapy of experimental lobar pneumonia in dogs. Am J Med Sci. 291:92–100.
Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P. 2008. A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. Radiat Res. 169:99–109. doi: 10.1667/RR1070.1.
Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, et al. 2012. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect. 120:1503–1511. doi: 10.1289/ehp.1204982.
Little MP. 2016. Radiation and circulatory disease. Mutat Res. 770:299–318. doi: 10.1016/j.mrrev.2016.07.008.

Lu CC, Chen MY, Chang YL. 2020. Potential therapeutic agents against COVID-19: What we know so far. J Chin Med Assoc. in press. doi: 10.1097/JCMA.0000000000000318.

Manning CM, Johnston CJ, Reed CK, Lawrence BP, Williams JP, Finkelstein JN. 2013. Lung irradiation increases mortality after influenza A virus challenge occurring late after exposure. Int J Radiat Oncol Biol Phys. 86:128–135. doi: 10.1016/j.ijrobp.2012.10.019.

Mehta SK, Bloom DC, Plante I, Stowe R, Feiveson AH, Renner A, Dhummakupt A, Markan D, Zhang Y, Wu H, et al. 2018. Reactivation of latent Epstein-Barr virus: A comparison after exposure to gamma, proton, carbon, and iron radiation. Int J Mol Sci. 19:E2961. doi: 10.3390/ijms19102961.

Misra RS, Johnston CJ, Groves AM, DeDiego ML, St Martin J, Reed C, Hernady E, Miller JN, Love T, Finkelstein JN, et al. 2015. Examining the effects of external or internal radiation exposure of juvenile mice on late morbidity after infection with influenza A. Radiat Res. 184:3–13. doi: 10.1667/RR13917.1.

Onoda JM, Kantak SS, Diglio CA. 1999. Radiation induced endothelial cell retraction in vitro: Correlation with acute pulmonary edema. Pathol Oncol Res. 5:49–55. doi: 10.1053/paor.1999.0049.

Petit SF, van Elmpt WJC, Oberije CJG, Vegt E, Dingemans AM, Lambin P, Dekker AL, De Ruysscher D. 2011. [^{18}F]fluorodeoxyglucose uptake patterns in lung before radiotherapy identify areas more susceptible to radiation-induced lung toxicity in non-small-cell lung cancer patients. Int J Radiat Oncol Biol Phys. 81:698-705. doi: 10.1016/j.ijrobp.2010.06.016.

Poon LL, Guan Y, Nicholls JM, Yuen KY, Peiris JS. 2004. The aetiology, origins, and diagnosis of severe acute respiratory syndrome. Lancet Infect Dis. 4:663–671. doi: 10.1016/S1473-3099(04)01172-7.

Schröder S, Juerß D, Kriesen S, Manda K, Hildebrandt G. 2019. Immunomodulatory properties of low-dose ionizing radiation on human endothelial cells. Int J Radiat Biol. 95:23–32. doi: 10.1080/09553002.2018.1486515.

Seegenschmiedt MH, Micke O, Muecke R, German Cooperative Group on Radiotherapy for Non-malignant Diseases (GCG-BD). 2015. Radiotherapy for non-malignant disorders: State of the art and update of the evidence-based practice guidelines. Br J Radiol. 88:20150080. doi: 10.1259/bjr.20159003.

UKCDR. 2020. COVID-19 Research Project Tracker. Available at https://docs.google.com/spreadsheets/d/1zMGzEJqAYHT4k1HkbmQDPvaaINrBgFRq1X5G6QptiKE/edit#gid=788682229 (accessed 20 April 2020).

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). 2008. UNSCEAR 2006 Report. Annex A. Epidemiological studies of radiation and cancer. United Nations, 2008.

World Health Organization (WHO). 2020a. Coronavirus disease (COVID-2019) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed 20 April 2020).

World Health Organization (WHO). 2020b. Clinical management of severe acute respiratory infection (sari) when covid-19 disease is suspected. Interim guidance 13 March 2020. https://www.Who.Int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.Pdf (accessed 20 April 2020).

Zumla A, Hui DS, Perlman S. 2015. Middle East respiratory syndrome. Lancet. 386:995–1007. doi: 10.1016/S0140-6736(15)60454-8.