James S. Welsh, MS, MD
Department of Radiation Oncology
Stritch School of Medicine
Loyola University
Chicago, Illinois
Department of Radiation Oncology
Edward Hines, Jr. VA Hospital
Hines, Illinois

Joe Bevelacqua, PhD
Bevelacqua Resources
Richland, Washington

S.M.J. Mortazavi, PhD
Medical Physics and Engineering Department
School of Medicine
Shiraz University of Medical Sciences
Shiraz, Iran

Bill Sacks, MD, PhD
FDA (retired medical officer)
Gaithersburg, Maryland

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References

1. Shuryak I, Kachnic LA, Brenner DJ. Lung cancer and heart disease risks associated with low-dose pulmonary radiotherapy to COVID-19 patients with different background risks. *Int J Radiat Oncol Biol Phys*. 2021; S0360-3016(21)00379-5. https://doi.org/10.1016/j.ijrobp.2021.04.018.
2. Arruda GV, Weber RRDS, Bruno AC, Pavoni JF. The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: Estimation based on a virtual case. *Int J Radiat Biol* 2021;97:120–125.
3. Bevelacqua JJ, Welsh JS, Regarding Mortazavi S. The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: Estimation based on a virtual case. *Int J Radiat Biol* 2020;1–4.
4. Arruda GV, dos Santos Weber RR, Bruno AC, Pavoni JF. Reply to: Regarding: "The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: Estimation based on a virtual case. *Int J Radiat Biol* 2020;1–7.
5. Ghadimi-Moghadam A, Haghani M, Bevelacqua J, et al. 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* 2020;10:241.
6. Hess CB, Nasti TH, Dhere VR, et al. Immunomodulatory low-dose whole-lung radiation for patients with coronavirus disease 2019-related pneumonia. *Int J Radiat Oncol Biol Phys* 2021;109:867–879.
7. Ameri A, Rahnama N, Bozorgmehr R, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: Short course results. *Int J Radiat Oncol Biol Phys* 2020;108:1134–1139.
8. Ameri A, Ameri P, Rahnama N, et al. Low-dose whole-lung irradiation for COVID-19 pneumonia: Final results of a pilot study. *Int J Radiat Oncol Biol Phys* 2021;109:859–866.
9. Sanmamed N, Alcantara P, Cerezo E, et al. Low-dose radiation therapy in the management of coronavirus disease 2019 (COVID-19) pneumonia (LOWRAD-Cov19): Preliminary report. *Int J Radiat Oncol Biol Phys* 2021;109:880–885.
10. Sharma DN, Guleria R, Wig N, et al. Low dose radiation therapy for COVID-19 pneumonia: A pilot study. *medRxiv* 2020.
11. ICRP, The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. ICRP publication 103. *Ann ICRP* 2007;37:2–4.
12. Stewart FA, Akleyev, AV, Hauer-Jensen M, et al. ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs–threshold doses for tissue reactions in a radiation protection context. *Ann ICRP* 2012;41:1–322.
13. Niwa O, Barcellos-Hoff MH, Globus RK, et al. ICRP, 2015. Stem Cell Biology with Respect to Carcinogenesis Aspects of Radiological Protection. ICRP Publication 131. *Ann ICRP* 2015;44(3/4).
14. Huff J, Carnell L, Blattnig S, et al. *Evidence report: Risk of radiation carcinogenesis*; April 7, 2016. Available at; *https://humanresearchroadmap.nasa.gov/evidence/reports/cancer.pdf*. Accessed May 26, 2021 .
15. Kefayat A, Ghahremani F. Low dose radiation therapy for COVID-19 pneumonia: A double-edged sword. *Radiother Oncol* 2020;147:224–225.
16. Kefayat A, Ghahremani F. Low dose radiation therapy for COVID-19 pneumonia: A double-edged sword. *Radiother Oncol* 2020.

In Reply to Welsh et al.

To the Editor: We appreciate the comments[1] regarding our article "Lung Cancer and Heart Disease Risks Associated with Low-Dose Pulmonary Radiotherapy to COVID-19 Patients With Different Background Risks."[2] It is indeed true that the effects of very low radiation doses are uncertain, and epidemiologic evidence at these very low doses is limited. However, the pulmonary and cardiac doses relevant to pulmonary radiation therapy for patients with COVID-19 are not in that "very low" dose range. Specifically, the pulmonary and cardiac doses are very similar to the prescription dose, typically in the range from 0.5 to 1.5 Gy[2]—and we summarize here evidence that these values are in the organ dose range where we have significant epidemiologic data.

Considering first radiation-induced cancer, at very low doses it is true that potential risks remain uncertain. The dose above which there is clear epidemiologic evidence of increased risk is often termed the "minimal significant dose" (MSD).[3] Among atomic bomb survivors, the estimated MSD, both for cancer incidence and for cancer mortality, is 0.15 Gy.[3] Of course, there are uncertainties associated with risk estimates derived from atomic bomb survivors, but the fact that the risk estimates for both radiation-induced cancer incidence and radiation-induced cancer mortality—which derive from entirely different databases—are very similar suggests that these MSD estimates are realistic. Recent data from a large study (N = 259,350) of nuclear workers also yields a similar estimated MSD of ~0.2 Gy for radiation-induced cancer.[4]

Turning to radiation-induced circulatory disease, as recently summarized,[5] there has long been statistically significant evidence for increased risks in the 0.5 to 1.5 Gy (and

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greater) organ dose range (eg, among atomic bomb survivors,[6] nuclear workers,[7] and Chernobyl emergency workers[8]). In fact, a large combined study (N = 77,275) of patients from the Massachusetts and Canadian fluoroscopy cohorts provides clear evidence of increased radiation-induced circulatory disease mortality, even at doses less than 0.5 Gy.[9]

In summary, our motivation was to enable realistic benefit-risk analyses for low-dose pulmonary radiation therapy for patients with COVID-19. Our overall conclusion was that the balance is generally favorable, but attention should be paid to high-risk groups such as smokers and individuals with high baseline risks of circulatory disease. The dose range of interest here is considerably greater than the MSDs for both radiation-induced cancer and radiation-induced circulatory disease, so we are able to rely on epidemiologic data without needing to speculate about mechanisms.

Igor Shuryak, MD, PhD
Lisa A. Kachnic, MD, PhD
David J. Brenner, PhD, DSc
Department of Radiation Oncology
Center for Radiological Research
Columbia University Irving Medical Center
New York, New York

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References

1. Welsh JS, Bevelacqua J, Mortazavi SMJ, et al. In regard to Shuryak et al. *Int J Radiat Oncol Biol Phys* 2021;111:574–576.
2. Shuryak I, Kachnic LA, Brenner DJ. Lung cancer and heart disease risks associated with low-dose pulmonary radiotherapy to COVID-19 patients with different background risks [e-pub ahead of print]. *Int J Radiat Oncol Biol Phys* 2021. https://doi.org/10.1016/j.ijrobp.2021.04.018, accessed June 23, 2021.
3. Cologne J, Preston DL, Grant EJ, et al. Effect of follow-up period on minimal-significant dose in the atomic-bomb survivor studies. *Radiat Environ Biophys* 2018;57:83–88.
4. Leuraud K, Richardson DB, Cardis E, et al. Risk of cancer associated with low-dose radiation exposure: Comparison of results between the INWORKS nuclear workers study and the A-bomb survivors study. *Radiat Environ Biophys* 2021;60:23–39.
5. Little MP, Azizova TV, Hamada N. Low- and moderate-dose non-cancer effects of ionizing radiation in directly exposed individuals, especially circulatory and ocular diseases: A review of the epidemiology. *Int J Radiat Biol* 2021;97:782–803.
6. Shimizu Y, Kodama K, Nishi N, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *BMJ* 2010;340:193.
7. Gillies M, Richardson DB, Cardis E, et al. Mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom and the United States (inworks). *Radiat Res* 2017;188:276–290.
8. Kashcheev VV, Chekin SY, Karpenko SV, et al. Radiation risk of cardiovascular diseases in the cohort of Russian emergency workers of the Chernobyl accident. *Health Phys* 2017;113:23–29.
9. Tran V, Zablotska LB, Brenner AV, et al. Radiation-associated circulatory disease mortality in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts. *Sci Rep* 2017;7:744147.

Barriers to Psychological Support for Cancer Patients

In Regard to Small et al.

To the Editor: I read the article by Small et al,[1] and the authors are to be commended for addressing the barriers of psychological treatment. However, this study might not be reflective of the many barriers to treatment, and the results need to be taken with a grain of salt.

Psychological distress is a byproduct of cancer diagnosis and treatment. To mitigate its effect on patients with cancer, it must be identified, measured, and managed appropriately. Although Radiation Therapy Oncology Group study 0841 addresses the issue of identifying psychological distress using validated questionnaires, it is important to note that the identification of distressed patients remains an important barrier that was highlighted previously. Health care professionals might not have a systematic approach to identifying psychological distress,[2] and patients might not bring it up with their radiation oncologist.[3]

Small et al.[1] did a secondary analysis of results of the Structured Clinical Interview for DSM-IV (SCID) mood disorder modules of patients accrued on the trial; some were identified to be distressed, and their level of distress was measured. Interestingly, only 79 out of 150 patients selected for SCID completed the interview, and those patients had significantly more comorbidities and psychotropic drug utilization compared with patients who did not complete the SCID. Furthermore, out of the 79 patients who completed the SCID, 43 screened positive for a mood disorder and only 16 met the criteria for depression/mood disorder.[4] The population analyzed was mostly women, and a significant proportion had breast cancer and nonmetastatic disease; such distribution differs from an average radiation oncology department distribution and also might affect the barriers identified due to gender, cancer type, and stage differences.[5,6]

The most common barriers reported were cost, daily responsibilities, and physical symptoms. However, those barriers are not mutually exclusive (eg, a patient who indicated cost was a barrier might also have daily responsibilities, as they need to work to pay for medical bills, including medications for other comorbidities). It would have been helpful to show the overlap between these barriers because this might provide more insight in understanding patients' preferences. Lastly, the study accrual completed in 2011, and the dynamics of delivering care might have changed, especially with the advancements in telehealth and the increased utilization of social media over the past 10 years, so patient preferences might be different today.

Disclosures: None