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.

physician payment data, is possible to assess whether there is an association between physician payments and treatment selection; such data were not used for our study.[3]

To continue this conversation about impacts of financial payments to physicians, here we provide a summary of Open Payments data on inflation-adjusted[4] general and research payments[5] made to radiation oncologists and teaching hospitals for proton therapy equipment from 2014 to 2019. Of known proton equipment manufacturers, ProTom International and Hitachi did not report to Open Payments. Varian Medical Systems paid $426,158 in general payments to physicians, as well as $527,482 in general payments and $960,874 in research payments to teaching hospitals. Ion Beam Applications paid $169,290 to physicians and $19,800 to teaching hospitals as general payments. Finally, Mevion Medical Systems paid $76,797 in general payments to physicians and $6360 in research payments to teaching hospitals. A substantial limitation of these data is that names of the associated products or research studies are often nonspecific. Therefore, these numbers likely underestimate the extent of relationships. Specifically, Varian payments exclude general payments ($1,436,332) and research payments (eg, Master Research Agreements; Total: $14,757,058) that did not identify the product or research project.

Halperin's inquiry as to whether Open Payments can confirm data demonstrating lower likelihood of physician-industry interactions among Veterans Health Administration (VHA) physicians is important when considering effectiveness of system policies. The VHA obliges physicians to follow Federal and Executive Branch laws, which include prohibiting use of one's position for private gain. Because Open Payments is regulated by the Centers for Medicare & Medicaid Services[6] and the VHA does not accept Medicare reimbursement, Open Payments does not statutorily include VHA physicians or hospitals. To address this question, assessment of journal or professional society data on reported financial conflicts of interest and author affiliation may provide additional, potentially confirmatory insight into associations of reported financial conflicts of interest and VHA policies.

I look forward to continued dialogue on this important topic.

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Risks of Low-Dose Pulmonary Radiotherapy for COVID-19

In Regard to Shuryak et al.

To the Editor: This commentary expresses our concerns regarding the article titled "Lung Cancer and Heart Disease Risks Associated With Low-Dose Pulmonary Radiotherapy to COVID-19 Patients With Different Background Risks," by Shuryak et al., published in the *International Journal of Radiation Oncology, Biology, Physics*.[1] The authors aim to evaluate the benefit−risk balance of low-dose radiation therapy (LDRT) for COVID-19. To do so, they estimated the lifetime risk of radiation-induced lung cancer and heart disease for patients with different background risks (e.g., sex, age, and the existence of other risk factors such as smoking and heart disease) by using what the authors call "state-of-the-art radiation risk models" for lung cancer and heart disease. Shuryak et al. suggest that in such evaluations, the background risk factors, and in particular cigarette smoking, should be precisely considered, and they conclude that the predicted risks are lowest in older nonsmoking patients and those with lower cardiac risk factors. Despite some strengths, their report has some major shortcomings, as follows:

1. The model of risk estimation used by Shuryak et al. is flawed because they have ignored substantial data that support hormetic responses. It is worth noting that Arruda et al. recently reported that only radiation therapy at doses ≤0.5 Gy may provide an acceptable lifetime estimate of attributable risks (≤1%) for radiation-induced cancer and cardiovascular risk of exposure-induced death, regardless of sex and age.[2] In a response to our comments,[3] Arruda et al. stated that they ignored the hormetic responses because the leading international authorities on radiation protection do not accept hormetic models.[4] Shuryak et al. apparently have the same troubling opinion.

Disclosures: none.

2. Although Shuryak et al. have cited Arruda et al.,[2] they have not paid enough attention to their very low risk estimates for LDRT at doses ≤0.5 Gy. In March 2020, when LDRT was first proposed for pneumonia associated with COVID-19,[5] the initial suggested radiation doses were not higher than 250 mGy (0.25 Gy). Given this consideration, the dose of 0.5 Gy that is considered as the minimal radiation dose for LDRT can be decreased to lower doses (a few hundred mGy). Unfortunately, after this first publication, different researchers around the globe, in competition, tried to investigate the effects of much higher radiation doses. For example, Hess et al. in the United States used 1.5 Gy,[6] and Ameri et al. first tried 0.5 Gy[7] but later exposed their patients to 1.0 Gy.[8] In Spain and India, Sanmamed et al[9] and Sharma et al[10] used 1.0 Gy and 0.7 Gy, respectively. To ensure a safety margin, radiation doses can be ≤0.5 Gy to show the maximum anti-inflammatory and immune-system-optimizing responses. However, current data are not sufficient to draw firm conclusions, and we need more data on lower doses.
3. Shuryak et al have not paid enough attention to the role of adaptive response in reducing the radiation risk. In the first report on LDRT for pneumonia associated with COVID-19,[5] pre-exposure to a few mGy of gamma radiation was suggested to use the advantages of adaptive response in reducing the risk of exposure to higher subsequent doses. It should be noted that International Commission on Radiological Protection (ICRP) publications 103 (2007),[11] 118 (2012),[12] and 131 (2015)[13] have addressed the increased resistance of cells or tissues to radiation after a priming dose. However, these ICRP publications are based on the linear no-threshold (LNT) hypothesis, which fails to account for the immune system and the body's effective repair mechanisms at low doses. The LNT approach also significantly overestimates the radiation risks of these doses and discounts the possibility of hormesis. Moreover, the National Aeronautics and Space Administration, in a report published in 2016, supported the protective role of adaptive response against cancer.[14]
4. Shuryak et al are fully aware of the life-threatening outcomes of COVID-19, such as the "cytokine storm" and thrombosis and state that

   > Current evidence suggests that the most serious symptoms and death from COVID-19 result from an ineffective immune response in some patients, where a proinflammatory feedback loop is created.[15] This process leads to accumulation of immune cells in the lungs and the overproduction of proinflammatory cytokines ("cytokine storm") which damages the lungs and multiple other organs.[15,16]

However, they ignore the cardinal advantages of LDRT regarding inhibition of cytokine storm and thrombosis and reducing the risk of adaptive mutations as a response to selective pressure-exerting treatments such as antiviral drugs or steroids (Fig. 1).

Given these considerations, in contrast with what is claimed by Shuryak et al, the effectiveness of LDRT for COVID-19 is not limited to older patients with low baseline risk factors, and more realistic evidence-based risk estimates are needed.

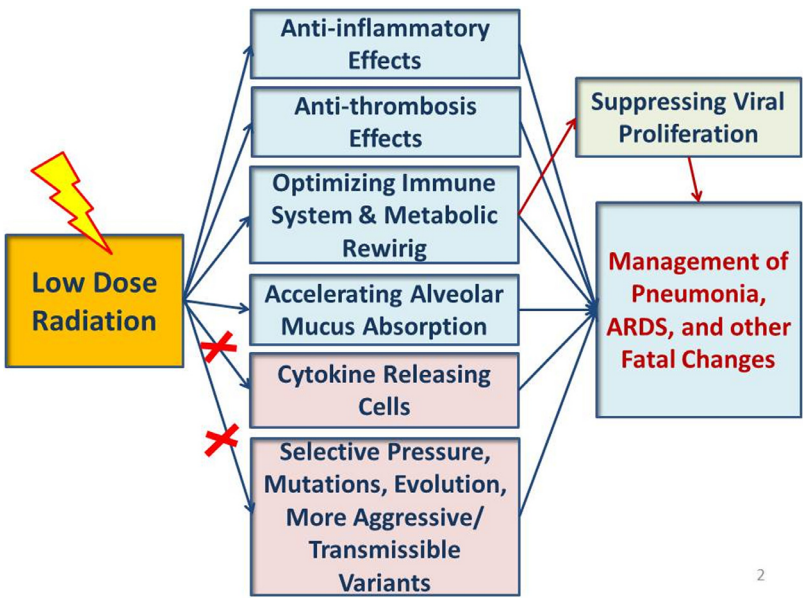

Fig. 1. Low-dose radiation therapy for COVID-19 is based on some key properties of low-dose radiation, such as anti-inflammatory and antithrombosis effects, optimization of the immune system and inhibition of cytokine storm, and reducing the risk of viral mutations that can lead to the emergence of new variants with higher transmissibility and virulence.

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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

Disclosures: none.