INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
https://doi.org/10.1080/09553002.2021.1846818

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RAPID COMMUNICATION

The risk of induced cancer and ischemic heart disease following low dose lung irradiation for COVID-19: estimation based on a virtual case

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ABSTRACT

Background: Recently, low dose radiotherapy delivered to the whole lung has been proposed as treatment for the pneumonia due to COVID-19. Although there is biological plausibility for its use, the evidence supporting its effectiveness is scarce, and the risks associated with it may be significant. Thus, based on a virtual case simulation, we estimated the risks of radiation-induced cancer (RIC) and cardiac disease.

Methods: Lifetime attributable risks (LAR) of RIC were calculated for the lung, liver, esophagus, and breast of female patients. The cardiovascular risk of exposure-induced death (REID) due to ischemic heart disease was also calculated. The doses received by the organs involved in the treatment were obtained from a simulation of conformal radiotherapy (RT) treatment, delivering a dose of 0.5 Gy–1.5 Gy to the lungs. We considered a LAR and REID <1% as acceptable, 1–2% cautionary, and >2% unacceptable.

Results: The lung was at the highest risk for RIC (absolute LAR below 5200 cases/100,000 and 2250 cases/100,000 for women and men, respectively). For women, the breast had the second-highest LAR, especially for young women. The liver and esophagus had LARs below 700/100,000 for both sexes, with a higher incidence of esophageal cancer in women and liver cancer in men. Regarding the LAR cutoff, we observed an unacceptable or cautionary LAR for lung cancer in all women and men <60 years with an RT dose >1 Gy. LAR for lung cancer with an RT dose of 1 Gy was cautionary for women >60 years of age and men <40 years of age. No LAR estimation was unacceptable for the RT dose ≤0.7 Gy in all groups irrespective of sex or age at exposure. Only 0.5 Gy had an acceptable REID.

Conclusions: A RT dose ≤0.5 Gy provides an acceptable LAR estimate (≤1%) for RIC and REID, irrespective of sex and age. The current ongoing trials should initially use doses ≤0.5 Gy to maintain the risks at an acceptable level and include only patients who fail or do not have any other treatment option.

ARTICLE HISTORY
Received 1 June 2020
Revised 27 October 2020
Accepted 28 October 2020

KEYWORDS
COVID-19; radiotherapy; cancer induction; whole lung irradiation

Introduction

Coronavirus disease 2019 (COVID-19), which is now a pandemic, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Some symptomatic patients with COVID −19 have pneumonia, which may progress to a life-threatening clinical condition (Zhou et al. 2020).

Pneumonia is an inflammatory immune response to infection. The pulmonary alveoli become inflamed, secreted fluid increases, and this compromises pulmonary function (Chen and Li 2020). In COVID-19, the immune cells are stimulated by the viruses to synthesize cytokines and chemokines, producing an immune response. This leads to pneumonia (Chen and Li 2020). There are currently limited clinical options for treating COVID-19 patients with pneumonia (Cascella et al. 2020). Therefore, some authors have suggested that radiotherapy (RT), with a total dose to the whole thorax ranging between 0.35 and 1.5 Gy, could be effective in reducing the inflammatory response. Moreover, a moderate dose will at the same time not appreciably increase the risk of radiation-induced cancer (RIC) for the patients being treated (Rödel et al. 2012; Yang et al. 2014; Dhawan et al. 2020; Kirkby and Mackenzie 2020; Kirsch et al. 2020; Salomaa, Cardis, et al. 2020).

Although there is a biological plausibility to the use of low dose RT to restrict the immune response caused by SARS-CoV-2, the evidence supporting its effectiveness is scarce and of low quality (Kirsch et al. 2020; Salomaa, Bouffler, et al. 2020; Salomaa, Cardis, et al. 2020). There are currently fifteen prospective studies being carried out to assess the role of low dose RT in COVID-19 patients. The first results of two trials have just been published and have shown promising results (Ameri et al. 2020; Hess et al.

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2020). However, a careful interpretation is required as they are based on very small participant numbers ($n = 5$, $n = 5$), are non-randomized, and have no control groups. It is also clear that many patients additionally received other drug treatments such as remdesivir and dexamethasone, which could as well account for the clinical improvement observed. Kirsch et al. presented a letter indicating that the potential risks of such trials outweigh their potential benefits (Kirsch et al. 2020).

In this scenario, we designed a study using data collected from a simulated patient who received whole lung irradiation to treat COVID-19 pneumonia by conformal RT (3DRT) and intensity-modulated radiation therapy (IMRT) techniques with a dose ranging between 0.5 and 1.5 Gy. The lifetime attributable risk (LAR) of developing RIC and the risk of exposure-induced death (REID) by cardiovascular disease were evaluated.

Methods

Whole lung treatment was simulated in a median female body (20 cm of anterior-posterior distance and 30 cm of lateral-lateral distance) at the treatment planning system. A 3DRT plan with two parallel opposed fields in the anterior-posterior directions and an IMRT plan with seven fields were prepared. A dose of 1 Gy was initially planned for the PTV, and 95% of the planned dose covered 90% and 95% of the target volume for the 3DRT and IMRT techniques, respectively (Figure 1). The breast, liver, heart, and esophagus doses were evaluated and used to simulate the risks of the exposures.

All the RIC estimates after RT treatment were based on LAR values provided by the Biological Effects of Ionizing Radiation (BEIR) VII report (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation – National Research Council 2006). The relationship between LAR and age at exposure was studied since it can help in developing clinical protocols for patient selection. Cardiovascular risks of ischemic heart disease (IHD) due to radiation exposition were also estimated based on REID, following the systematic review and meta-analysis performed by Little et al. (2012). These estimations were performed for whole lung RT treatments using 0.5, 0.7, 1.0, and 1.5 Gy, by only changing the simulated planned dose, without any other alteration in the plans. We considered a LAR and REID <1% as acceptable, 1–2% cautionary (i.e. used if necessary), and >2% unacceptable.

Results

Simulation of whole lung treatment with 1 Gy resulted in the following mean doses for the lung, liver, esophagus, heart, and breast: 1.0 Gy, 0.413 Gy, 0.869 Gy, 1.0 Gy, and 0.465 Gy for 3DRT, and 1.0 Gy, 0.280 Gy, 0.780 Gy, 0.624 Gy, and 0.356 Gy for IMRT, respectively.

The LAR results for men and women were evaluated as a function of the age at exposure (Figure 2(a,b)). For both sexes, the exposure of young persons may lead to a higher incidence of cancer, and the highest risk of cancer incidence was for lung cancer. Irradiation of the lung with doses ranging between 0.5 Gy and 1.5 Gy presents an absolute LAR below 5200 cases/100,000 for women and 2250 cases/100,000 for men. For women, the breast presents the second-highest LAR, especially for exposures of young women. The liver and esophagus presented LARs below 700/100,000 for both sexes, with a higher incidence of esophageal RIC for women and liver RIC for men. These values were also stratified in groups related to age at exposure (Figure 2(c,d)) and evaluated in a percentage form (Table 1). Regarding the LAR cutoff, we observed an unacceptable and cautionary LAR for

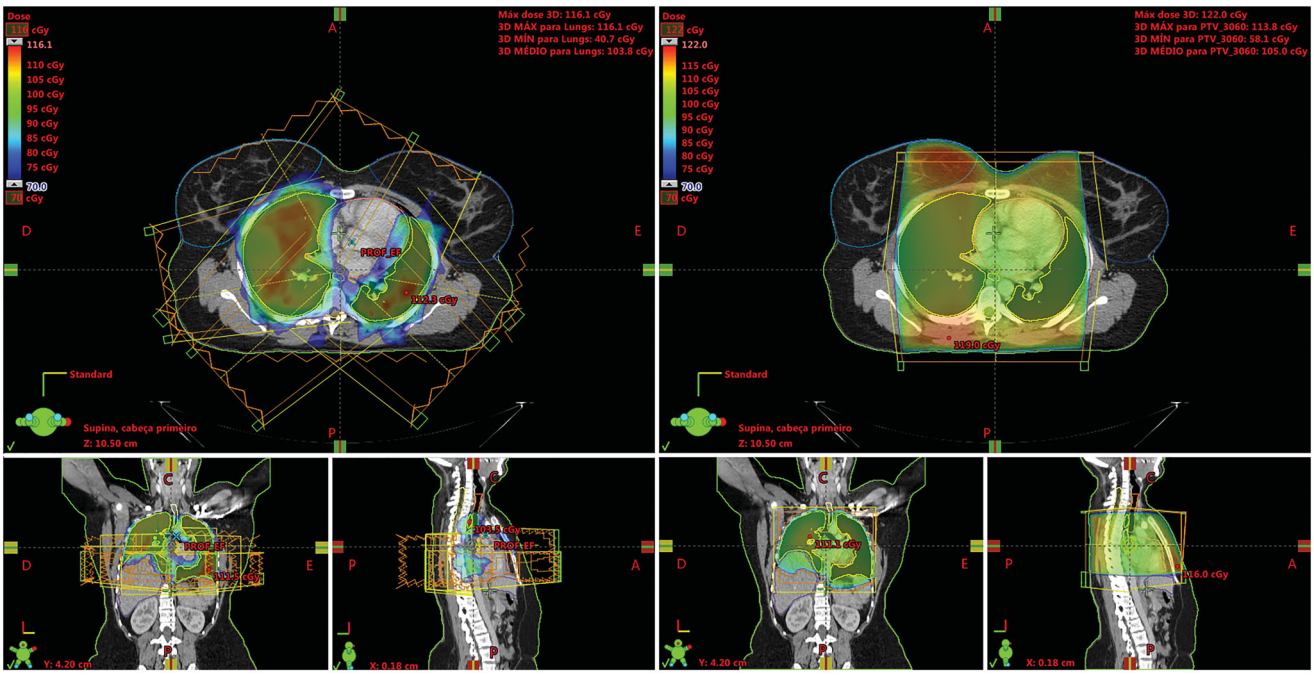

Figure 1. Dose distribution for the whole lung treatment with a dose of 1 Gy for the axial, sagittal, and coronal planes using IMRT (left) and 3DRT (right).

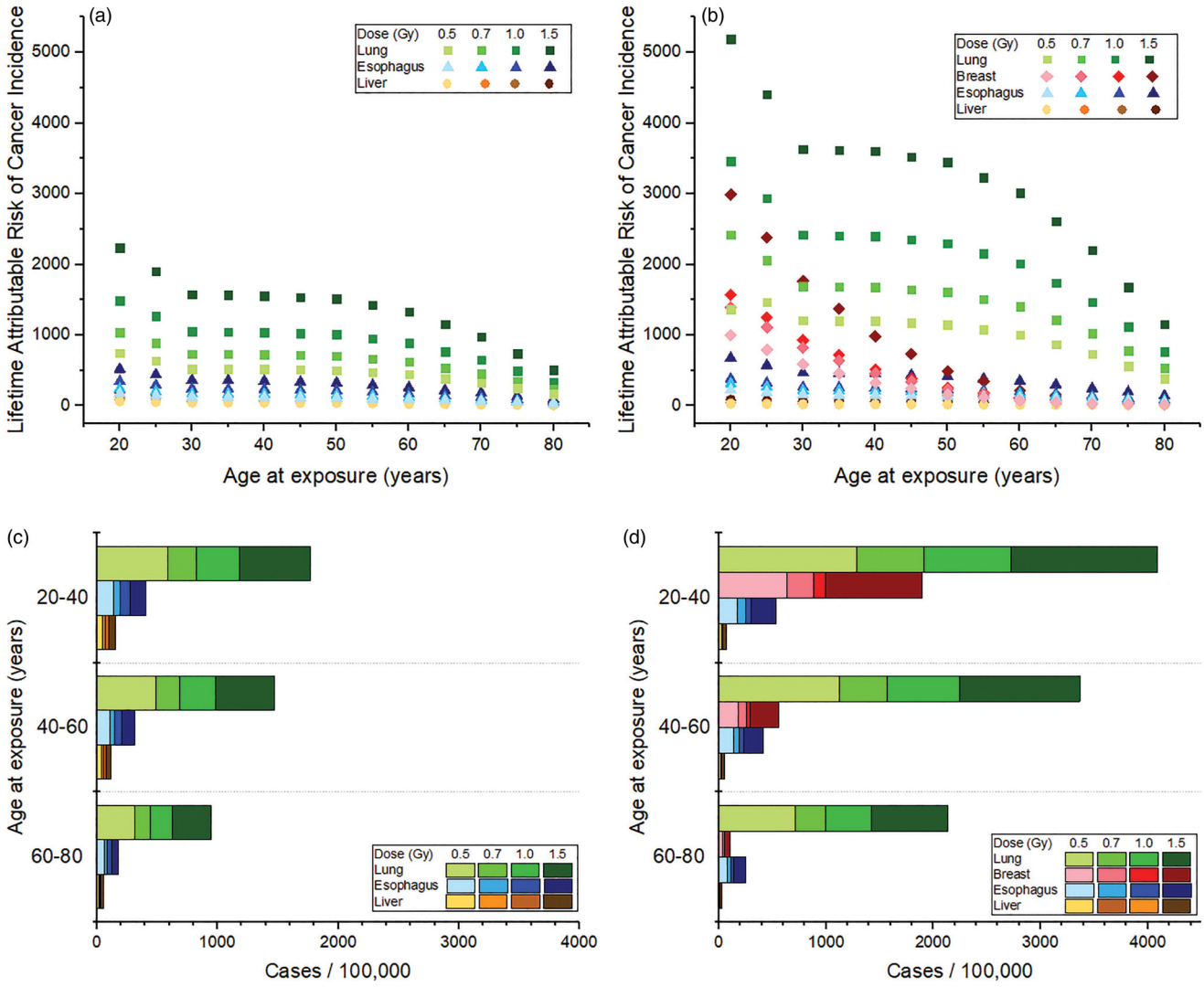

Figure 2. LAR as a function of the age at exposure per 100,000 persons and age-stratified for men (a,c) and women (b,d). LAR Lung was simulated as receiving doses form 0.5–1.5 Gy, while the other organs were simulated as receiving the 3D planning evaluated doses.

lung cancer in all women and men between 20–60 years of age, with RT dose >1 Gy (Table 1). LAR for lung cancer with an RT dose of 1 Gy was cautionary for women aged >60 years and men aged <40 years. No LAR estimation was unacceptable for the RT dose below <0.7 Gy in all groups irrespective of sex or age at exposure (Table 1). The REID for 1.5, 1.0, 0.7, and 0.5 Gy was 2.5% (CI95% 1.1–3.9%), 1.6% (CI95% 0.7–2.6%), 1.1% (CI95% 0.5–1.8%), and 0.8% (CI95% 0.3–1.3%), Table 1.

Discussion

Our main objective was to estimate the risks involved in using low dose RT for the treatment of COVID-19 patients, based on a virtual lung irradiation simulation.

The interest in using lung irradiation to treat pneumonia came between 1905 and 1946. Historical reports of patients with severe pneumonia (bacterial or viral) treated with low doses of kilovoltage X-rays showed a good clinical response. Similar results are being reported in published clinical trial results using low dose RT to treat COVID-19 patients (Ameri et al. 2020; Hess et al. 2020). However, these studies are limited, present a low-level of evidence, involve a small sample of patients, and have no appropriate control group. The reanalysis of historical radiobiological data also does not provide support for reductions in morbidity or mortality associated with post-infection radiation exposure (Little et al. 2020). Therefore, the possible potential harm and the extent to which benefits may exceed risks from low-dose lung irradiation remains unclear (Kirsch et al. 2020; Little et al. 2020; Salomaa, Bouffler, et al. 2020; Salomaa, Cardis, et al. 2020). This caution may be kept in mind when evaluating the present results.

Currently, we have fifteen clinical trials registered, and are recruiting patients around the world, including patients of different ages and disease severities, as well as using different radiation doses (Table 2). In these trials, a single lung dose ranges between 0.35 and 1.5 Gy, and patients from 18 to 65 years of age are included. Age is a critical component of these trials' inclusion criteria since the RIC directly relates to the age of the patient at radiation exposure. Regarding this point, for seven (50%) of the trials, the age cutoff for one to be enrolled in the study was higher than 18 years.

Table 1. Cancer risk estimated by the mean percentage LAR achieved after the age stratification for all organs with whole lung treatment doses of 0.5–1.5 Gy for both sexes.

Dose to Lung (Gy)	Age at exposure (years)	CANCER RISK – LAR (%)*							CARDIOVASCULAR RISK – REID (%)**
		FEMALE				MALE			
		Lung	Liver	Esophagus	Breast	Lung	Liver	Esophagus	
1.5	20–40	4.09 (3.53–4.64)	0.07 (0.06–0.08)	0.53 (0.45–0.60)	1.90 (1.27–2.52)	1.76 (1.53–2.00)	0.15 (0.13–0.17)	0.41 (0.35–0.46)	2.51 (1.12–3.90)
	40–60	3.36 (3.18–3.55)	0.05 (0.05–0.06)	0.41 (0.38–0.44)	0.55 (0.31–0.79)	1.47 (1.40–1.55)	0.11 (0.09–0.13)	0.31 (0.28–0.34)	
	60–80	2.13 (1.55–2.71)	0.03 (0.02–0.04)	0.24 (0.18–0.31)	0.11 (0.05–0.17)	0.94 (0.69–1.20)	0.05 (0.03–0.07)	0.18 (0.12–0.23)	
1.0	20–40	2.73 (2.36–3.09)	0.05 (0.04–0.05)	0.35 (0.30–0.40)	1.27 (0.85–1.68)	1.18 (1.02–1.34)	0.10 (0.09–0.11)	0.27 (0.23–0.31)	1.68 (0.75–2.60)
	40–60	2.24 (2.12–2.37)	0.04 (0.03–0.04)	0.27 (0.25–0.29)	0.37 (0.21–0.53)	0.98 (0.93–1.03)	0.07 (0.07–0.08)	0.21 (0.19–0.23)	
	60–80	1.42 (1.04–1.81)	0.02 (0.01–0.03)	0.17 (0.12–0.21)	0.07 (0.03–0.11)	0.63 (0.46–0.80)	0.03 (0.02–0.05)	0.12 (0.08–0.15)	
0.7	20–40	1.91 (1.65–2.17)	0.03 (0.03–0.04)	0.25 (0.21–0.28)	0.89 (0.59–1.18)	0.83 (0.72–0.93)	0.07 (0.06–0.08)	0.19 (0.16–0.22)	1.17 (0.52–1.82)
	40–60	1.57 (1.48–1.66)	0.03 (0.02–0.03)	0.19 (0.18–0.21)	0.26 (0.15–0.37)	0.69 (0.65–0.72)	0.05 (0.05–0.06)	0.15 (0.13–0.16)	
	60–80	1.00 (0.73–1.27)	0.01 (0.01–0.02)	0.12 (0.09–0.15)	0.89 (0.02–0.08)	0.44 (0.32–0.56)	0.02 (0.01–0.03)	0.08 (0.06–0.11)	
0.5	20–40	1.36 (1.18–1.55)	0.02 (0.02–0.03)	0.18 (0.15–0.20)	0.63 (0.42–0.84)	0.59 (0.51–0.67)	0.05 (0.04–0.06)	0.14 (0.12–0.16)	0.84 (0.37–1.30)
	40–60	1.12 (1.06–1.18)	0.02 (0.02–0.02)	0.14 (0.13–0.15)	0.19 (0.10–0.27)	0.49 (0.47–0.52)	0.04 (0.03–0.04)	0.10 (0.10–0.11)	
	60–80	0.71 (0.52–0.90)	0.01 (0.01–0.01)	0.08 (0.06–0.10)	0.04 (0.02–0.06)	0.31 (0.23–0.40)	0.02 (0.01–0.02)	0.06 (0.04–0.08)	

*LAR values extracted from BEIR VII document and considering a dose and dose rate effective factor (DDREF) of 1.5 Gy.
**REID values extracted from Little et al. (2012) from the IHD disease data and correspond to a mean value of several countries, independent of sex and of the age at exposure.
Cardiovascular risks estimated by the mean percentage REID without stratification by age and sex. All values are followed by a parenthesis with the 95% confidence interval value found in the group.

Table 2. Registered clinical trials for COVID-19 RT with the planned doses and patients age.

Clinical trial	Dose (Gy)	Age (years)
NCT04377477	0.7	≥50
NCT04427566	0.8	≥18
NCT04420390	≤1	≥60
NCT04390412	0.5	>60
NCT04466683	0.35	≥50
	1	
NCT04394793	0.7	≥18
NCT04393948	1	≥40
NCT04414293	0.5	≥65
	1	
NCT04366791	1.5	≥18
NCT04433949	≤1	≥18
NCT04380818	0.5	18–99
NCT04394182	0.8	18–120
NCT04493294	Not informed	≥65
NCT 04534790	≤1	≥18
NCT 04572412	0.5	≥50

Thus, our study evaluates the risks of the treatment for the involved organs, stratifying the lung radiation treatment doses and the age at exposure per sex (Table 1). Lung irradiation with doses ≥1 Gy crossed the unacceptable limit for lung RIC estimation for populations of ages lower than 40 years, especially females. These outcomes call for attention once several trials are enrolling younger patients to be submitted to a dose of 1 Gy or 1.5 Gy. Considering the dose of 1.5 Gy, the LAR in females crossed the unacceptable limit for all ages, reaching 4.09% for ages between 20 and 40 years (Table 1). Using our criteria, the RIC would be acceptable for patients aged >40 years, delivering a radiation dose of 0.7 Gy for both sexes, and would still be better if the studies enrolled elderly patients of >60 years of age, irrespective of the sex. Regarding the cardiac risks, the REID analyses for whole-lung irradiation with 1.5 Gy, 0.7–1.0 Gy, and 0.5 Gy resulted respectively in an excessive, a cautionary (i.e. used if necessary), and an acceptable risk irrespective of age.

The lung was observed as the primary organ at risk for RIC after the treatment of COVID-19 pneumonia with RT, with a higher incidence in women than men. This sex difference can be explained by the difference in background cancer incidences between the sexes. The background male incidence is almost three times higher than that for females. This is due to the higher prevalence of smoking in men than in women since cigarette smoking is the most important cause of lung cancer. Its effects, combined with radiation exposure, lead to higher rates of lung cancer incidence (Furukawa et al. 2010).

Our work significantly differs from the paper recently published by Kirsch et al. (Kirsch et al. 2020). We used data from a simulated patient, and we collected the dose received by the involved organs to run the estimations. From our analysis, it is possible to observe that even for organs with a relatively low LAR (Table 1), the absolute risk is high (Figure 2(a,b)). For example, the mean LAR for the lungs of females aged 20–40 years using 1 Gy was 2.73%, but the absolute number of the new attributable cases reached almost 3500/100,000 for exposures at the age of 20. The absolute number is an essential component from a public

health/epidemiological perspective when deciding on an intervention like radiation to treat a massive number of patients in the COVID-19 pandemic. In countries like Brazil, or the USA, with more than five million cases, estimating that 10% receive lung radiation with a dose of 1 Gy, by our data, about 17,500 new lung cancer cases due to the intervention would be expected in the next few years.

Due to these outcomes, we also evaluated if the treatment technique would reduce the risks of radiation exposure. Comparing the 3DRT to the IMRT technique, the impact of both on the LAR of RIC was insignificant. For the cardiac risks, IMRT can reduce the heart doses and consequently reduce the involved cardiac risks. However, IMRT is an expensive and more time-consuming technique; it needs more treatment fields, making the patients' time in the machine longer.

It is essential to highlight that our study has limitations inherent to the risk estimates. The LAR for RIC estimates were extracted from table 12D-1 of the BEIR VII report published in 2006. The main reason for using it was the straightforward availability of parameters for specific organs, sex, and age at exposure, which is directly related and aligned with the inclusion criteria of the trials investigating the role of radiation in treating COVID-19 patients. LAR estimates include high uncertainties due to estimate variability from the life span study (LSS) data, the risk transportation from the Japanese atomic bomb survivor to other populations, and the appropriate dose and dose rate effectiveness factor. LAR is a linear approximation of the radiation exposure induced cancer (REIC) or REID. Its estimates are approximately the same for doses smaller than 0.4 Gy, but as the dose increases, the LAR estimates become higher than the REIC/REID ones, reaching +2% at 1 Gy (Zhang et al. 2020). Therefore, the presented LAR estimates for doses up to 1 Gy may be within this difference from the REIC estimates, but a higher difference may occur for the 1.5 Gy estimates. However, all data were extracted from a simulated case using strict criteria for admission, provided the lung irradiation is safe for COVID-19 patients.

Conclusion

By evaluating the lung irradiation with the doses used in the ongoing clinical trials to treat COVID −19 patients, our data shows that a radiation dose $\leq$0.5 Gy provides an acceptable RIC risk estimate (LAR $\leq$1%), irrespective of sex and age at exposure, while also maintaining the cardiac risks at acceptable levels. It is important to note that even with favorable initial clinical outcomes from lung RT, it is still unknown if the benefit is derived directly from the intervention or from the combination with other treatments. Therefore, due to the potential shorter latency period in elderly patients and the high risk of pneumonia induced with doses >1 Gy, trials should initially test doses $\leq$0.5 Gy to maintain an acceptable threshold of the RIC/REID risks. Only patients who fail or do not have any other clinical treatments for SARS-CoV-2 should be included in the trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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