UNIVERSITY OF SÃO PAULO
FFCLRP – DEPARTMENT OF PHYSICS

RAISSA RENATA DOS SANTOS WEBER

# Avaliação dos riscos para desenvolvimento de tumores secundários em pacientes com COVID-19 tratados com radioterapia

# Evaluation of the Development of Secondary Tumor Risks Using Radiotherapy Treatment in Patients with COVID-19

Ribeirão Preto - SP

2023

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Concentration area:

Physics Applied to Medicine and Biology.

Mentor:

Prof. Dr. Juliana Fernandes Pavoni

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*To my parents, Renata and Antônio, to my grandparents, Laurinda and Berseval, and to my sister, Laíza, for their love, dedication, care and encouragement.*

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*Aos meus pais, Renata e Antônio, aos meus avós, Laurinda e Berseval, e à minha irmã, Laíza, pelo amor, dedicação, carinho e incentivo.*

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*“Nothing in life is to be feared; it is only to be understood.”*

**Marie Curie**

# Abstract

WEBER, R. R. S. **Evaluation of the Development of Secondary Tumor Risks Using Radiotherapy Treatment in Patients with COVID-19.** 2023. 101 p. Dissertation (Master - Graduate Program in Physics Applied to Medicine and Biology) - Faculty of Philosophy, Sciences, and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto - SP, 2023.

SARS-CoV-2, most well-known as COVID-19, is an enveloped and single-stranded RNA virus larger than any RNA virus. Because it is highly contagious, there is no effective specific treatment for this disease, especially severe lung inflammation. In addition, there are limitations of medications, some of which are not recommended. Thus, clinical trials emerged with the premise of using low-dose radiation treatment to treat patients with pneumonia due to COVID-19. In this work, we investigated the risks of induced cancer and the effectiveness of low-dose radiation treatment in patients with pneumonia due to COVID-19. For this, mathematical models from epidemiological studies for ionizing radiation were used, and the clinical trial results were analyzed. Data were characterized by mathematical models from the mean doses collected using a virtual simulation for radiotherapy planning. The risks of induced cancer were estimated based on the doses used in clinical trials. A systematic review was performed regarding clinical trials. It was verified that each mathematical model has an individual characterization for estimating the risk of induced cancer and inferring that the risks are potential for incidence and mortality due to induced cancer exposure to ionizing radiation. The results of clinical trials were not favorable, as a significant number of patients succumbed even after treatment with low doses of ionizing radiation, showing the ineffectiveness of the practice. Therefore, considering the limitations of epidemiological studies in formulating mathematical models and the low sampling of data from clinical trials, treatment with low-dose ionizing radiation for patients with pneumonia due to COVID-19 is not justifiable.

**Keywords:** COVID-19, ionizing radiation, risk of induced-cancer, epidemiology

# Resumo

WEBER, R. R. S. A**valiação dos riscos para desenvolvimento de tumores secundários em pacientes com COVID-19 tratados com radioterapia.** 2023. 101 p. Dissertação (Mestrado - Programa de Pós-graduação em Física Aplicada à Medicina e Biologia) - Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto - SP, 2023.

SARS-CoV-2, mais conhecido como COVID-19, é um vírus envelopado e de uma fita simples de RNA, sendo maior que qualquer vírus de RNA. Por ser altamente contagioso, não há tratamento específico eficaz para a doença, principalmente para a inflamação pulmonar severa. Além disso, há limitações de medicamentos, sendo alguns não recomendados. Dessa forma, surgiram ensaios clínicos com a premissa de utilizar tratamento com radiação de baixa dose para tratar pacientes com pneumonia devido a COVID-19. Nesse trabalho foram investigados os riscos de indução de câncer e a eficácia do tratamento com radiação de baixa dose em pacientes com pneumonia devido a COVID-19. Para isso foram utilizados modelos matemáticos de estudos epidemiológicos para radiação ionizante e analisados os resultados dos ensaios clínicos. Utilizando uma simulação virtual para planejamento de radioterapia, os dados foram caracterizados pelos modelos matemáticos a partir das doses médias coletadas e os riscos de indução de câncer foram estimados com base nas doses utilizadas pelos ensaios clínicos. Uma revisão sistemática foi realizada em relação aos ensaios clínicos. Foi verificado que cada modelo matemático possui uma caracterização individual para estimativa de risco de indução de câncer, e inferindo que os riscos são potenciais, tanto para incidência quanto para mortalidade devido a indução de câncer por exposição à radiação ionizante. Os resultados dos ensaios clínicos não foram favoráveis, pois uma quantidade significativa de pacientes sucumbiu mesmo após o tratamento com baixa dose de radiação ionizante, mostrando a ineficácia da prática. Portanto, considerando as limitações dos estudos epidemiológicos na formulação de modelos matemáticos e, também da pouca amostragem dos dados dos ensaios clínicos, o tratamento com baixa dose de radiação ionizante para pacientes com pneumonia devido a COVID-19 não é justificável.

**Palavras-chave:** COVID-19, radiação ionizante, risco de indução de câncer, epidemiologia

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# ABBREVIATIONS

| | |
|---|---|
| **WHO** | World Health Organization |
| **CSG** | Coronavirus Study Group |
| **CDC** | Centers for Disease Control and Prevention |
| **CRS** | Cytokine Release Syndrome |
| **CT** | Computed Tomography |
| **NIH** | National Institutes of Health |
| **3DRT** | Tridimensional Conformal Radiation Therapy |
| **IMRT** | Intensity Modulation Radiation Therapy |
| **VMAT** | Volumetric Modulated Arc Therapy |
| **BEIR** | Biological Effects of Ionizing Radiation |
| **ICRP** | International Commission on Radiological Protection |
| **UNSCEAR** | United Nations Scientific Committee on the Effects of Atomic Radiation |
| **ELR** | Excess Lifetime Risk |
| **RER** | Relative Excess Risk |
| **REID** | Risk of Induced-Death |
| **LAR** | Lifetime Attributable Risk |
| **NRC** | National Research Council |
| **LSS** | Life Span Study |
| **ERR** | Excess Relative Risk |
| **EAR** | Excess Absolute Risk |
| **DDREF** | Dose-Rate Reduction Factor |

| | |
|---|---|
| **REIC** | Risk of Exposure-Induced Cancer |
| **LBR** | Lifetime Baseline Risks |
| **PTV** | Planning Target Volume |
| **OAR** | Organ at Risk |
| **RIC** | Risk of Induced-Cancer |
| **RT** | Radiation Therapy |
| **CI** | Confidence Interval |

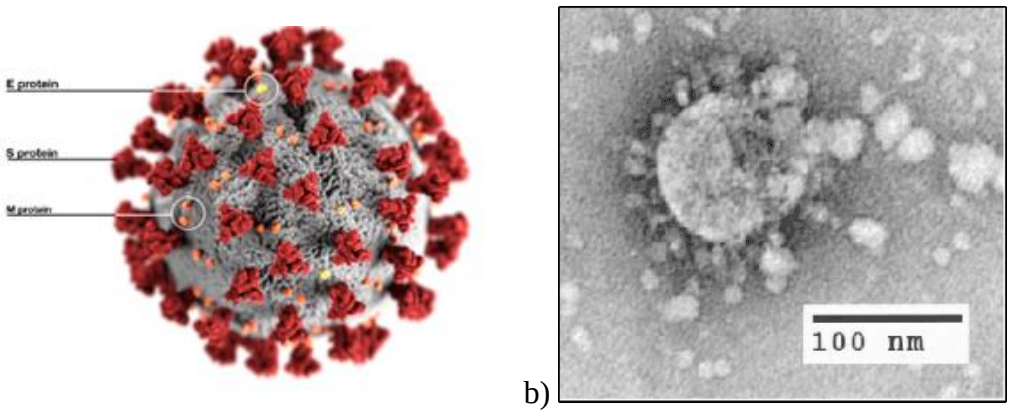
# Summary

# CHAPTER 1 - Introduction

## 1 COVID -19

COVID-19, the virus discovered in 2019 and named by the World Health Organization (WHO), called as well as “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG), is a highly contagious virus that can quickly develop severe pneumonia. There is no effective specific treatment for this disease, even if the development of a vaccine is highlighted, which can prevent the serious health complications caused by SARS-CoV-2. [1]

The SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus with a round, elliptic, or pleomorphic form, with a diameter between 60 and 140 mm, larger than any other RNA viruses (Figure 1.a and 1.b). The genome is enveloped and associated with membrane protein, spike protein, and envelope protein, and SARS-CoV-2 also contains the nucleocapsid protein. These fours proteins are called structural proteins. The other sixteen non-structural proteins are associated with RNA processing, replication, and transcription. And while the virus completes its life cycle in the host cell, the host’s immune system starts its action, regulating the expression of genes associated with the immune response or starting the chain of reactions for the immune response. [2,3]




a) b)

Figure 1. a) Illustration of structural morphology of SARS-CoV-2 showing the protein particles E, S, and M. b) SARS-CoV being showed in a negative stain electron microscopy. [Centers for Disease Control and Prevention (CDC) image library].

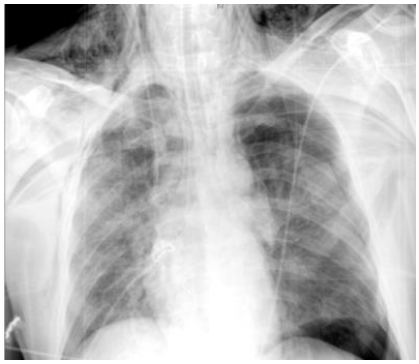
The virus can be spread through human-to-human transmission and indirect contact with contaminated air or objects. The transmission person-by-person is mainly via respiratory, like coughing, sneezing, and talking. The virus can be suspended in the air for hours, being contagious almost three meters away. Also, the person can be contaminated by the virus if he touches a surface contaminated with SARS-CoV-2 and brings the hands to the eyes, mouth, or nose. [1]

SARS-CoV-2 causes a chain of events in the immune system, which triggers an inflammatory response called Cytokine Release Syndrome (CRS). CRS is characterized by an increase in the inflammatory response, activating adaptive and spontaneous immune systems. In CRS, there is a large number of macrophages, which are associated with phagocytosis, making possible the liberation of cytokines. So, as macrophages participate in the activation and development of inflammatory events, if this activation is not controlled, macrophages can cause tissue damage. In summary, the chain of events after infection is rapid and can cause severe damage as the immune system tries to work against the virus. [2]

Symptoms of SARS-CoV-2 contamination vary according to the patient's degree of infection, but the first symptoms are usually fever, dry cough, and difficulty breathing. In some cases, the person may experience intestinal problems. Some symptoms that can also be developed are sneezing, nasal congestion, sore throat, and even dyspnea and conjunctivitis. Symptoms such as chest pain, confusion, nausea, and vomiting have been recorded in severe cases. [1]

Radiological images play a fundamental role in diagnosing COVID-19, mainly to assess the progress of the disease in the lungs (Figure 2.a and 2.b). The most used techniques are the X-ray and Computed Tomography (CT) scan. Chest X-ray detected lung consolidation, ground-glass and reticular opacities, pneumothorax, and pleural effusion. CT scan allows for detecting different pulmonary manifestations and establishing the stage of each one, as well as allows motoring the progression of the disease. With this imaging technique, it is possible to identify lung consolidation, ground-glass opacities, reticular pattern, bronchial wall thickening, pleural effusion, nodes, lymphadenopathies, and pericardial effusion. [4]

a)



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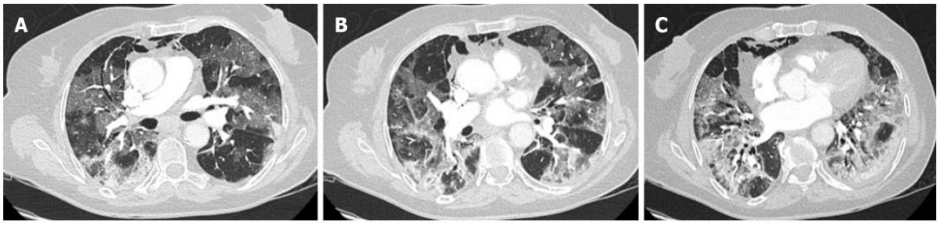



Figure 2. a) Chest X-ray of an 80-year-old man with COVID-19 pneumonia. b) Chest CT scan of a 45-year-old woman with COVID-19 pneumonia. [4]

Blood tests showed several changes with increasing components: white blood cell count, creatinine, urea, C-reactive protein, D-dimer level, erythrocyte sedimentation rate, and lactate dehydrogenase. And the drop in hemoglobin and lymphocyte count. [1]

With the rush to develop a vaccine, other treatments have been suggested, but some medications and treatments are not recommended. The case of Hydroxychloroquine and Azithromycin combination has the potential for toxicity, or protease inhibition, which has been shown to be ineffective in clinical trial results. The most used intervention in cases of COVID-19 pneumonia is mechanical ventilation, especially in severe cases, in patients with hypoxemia. [1]

As tests for medications and treatments can take time to obtain results and demonstrate their effectiveness, clinical trials for treating COVID-19 pneumonia using low-dose radiotherapy have been registered.

# 2 Low-dose radiotherapy for COVID-19 treatment

The primary purpose of the low-dose whole-lung radiotherapy clinical trials is to investigate the treatment's efficacy and reduce mortality. The currently registered clinical trials are listed in Table 1. Sixteen clinical trials are registered in ClinicalTrials.gov in the U.S. National Library of Medicine from the National Institutes of Health (NIH), one is registered in the Iranian

Registry of Clinical Trials, and one is registered in Ethics Committee Registration from the Government of India.

In an attempt to analyze the proposal to use radiotherapy to treat patients with COVID-19 pneumonia, some studies were published analyzing the benefits and harms of this practice, pointing out some suggestions for the treatment doses, and showing precautions and uncertainties.

Lara et al. (2020) suggested that a low-dose whole-lung of 0.5 Gy may be effective for anti-inflammatory and non-toxic treatment. Rodel et al. (2020) also proposed a single dose of 0.5 Gy in the lungs, demonstrating that such treatment requires monitoring to assess the evolution of the disease. As well as Chakrabarti and Verma (2020) suggested. [5]

Kefayat and Ghahremani (2020) demonstrated that the anti-inflammatory effects of low-dose radiotherapy might not be effective in controlling the called "cytokine storm" due to COVID-19 pneumonia and may delay the virus elimination. Kirsch et al. (2020) also concluded the potential risks of using low-dose radiotherapy for COVID-19 pneumonia treatment. [5]

Table 1. Clinical trials registered treatment of COVID-19 pneumonia using low-dose radiotherapy.

| Clinical Trial | ID | Dose (Gy) | Age (y) |
|---|---|---|---|
| COVID-19 Pneumonitis Low Dose Lung Radiotherapy | NCT 04377477 | 0.7 | ≥ 50 |
| Low Dose Whole Lung Radiation Therapy for Patients With COVID-19 and Respiratory Compromise | NCT 04427566 | 0.8 | ≥ 18 |
| Low Dose Radiotherapy for COVID-19 Pneumonitis | NCT 04420390 | ≤ 1 | ≥ 60 |
| Low Dose Radiotherapy in COVID-19 Pneumonia | NCT 04390412 | 0.5 | > 60 |

Table 1. (*continued*)

| Clinical Trial | ID | Dose (Gy) | Age (y) |
|---|---|---|---|
| Low-Dose Radiotherapy For Patients With SARS-COV-2 (COVID-19) Pneumonia | NCT 04466683 | 0.35<br>1 | ≥ 50 |
| Low Dose Radiation Therapy for Covid-19 Pneumonia | NCT 04394793 | 0.7 | ≥ 18 |
| Lung Irradiation for COVID-19 Pneumonia | NCT 04393948 | 1 | ≥ 40 |
| Low Dose Pulmonary Irradiation in Patients With COVID-19 Infection of Bad Prognosis | NCT 04414293 | 0.5<br>1 | ≥ 65 |
| Radiation Eliminates Storming Cytokines and Unchecked Edema as a 1-Day Treatment for COVID-19 | NCT 04366791 | ≤ 1 | ≥ 18 |
| Best Supportive Care With or Without Low Dose Whole Lung Radiation Therapy for the Treatment of COVID-19 | NCT 04433949 | ≤ 1 | ≥ 18 |
| Low Dose Anti-inflammatory Radiotherapy for the Treatment of Pneumonia by COVID-19 | NCT 04380818 | 0.5 | 18 - 99 |
| Ultra Low Doses of Therapy With Radiation Applicated to COVID-19 | NCT 04394182 | 0.8 | 18 - 120 |
| Low Dose Whole Lung Radiotherapy for Older Patients With COVID-19 Pneumonitis | NCT 04493294 | Not informed | ≥ 65 |
| Anti-inflammatory Effect of Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia | NCT 04534790 | ≤ 1 | ≥ 18 |
| Low Dose Lung Radiotherapy to Treat COVID-19 Pneumonia | NCT 04572412 | 0.5 | ≥ 50 |

Table 1. (*continued*)

| Clinical Trial | ID | Dose (Gy) | Age (y) |
|---|---|---|---|
| Low Dose Radiation Therapy for Severe-Acute-Respiratory-Syndrome-Coronavirus-2 (SARS-CoV-2) | NCT 04598581 | 1.0 | ≥ 40 |
| Low-dose whole-lung irradiation in severe COVID-19 pneumonia: a controlled clinical trial | IRCT20170211032494N3 | 1 | > 18 |
| Whole lung irradiation as a novel treatment for COVID-19 | ECR/926/Inst/TN/2017/RR-20 | 0.5 | ≥ 40 |

The clinical trials registered doses between 0.3 and 1.0 Gy to treat patients ≥ 18 years old. Some of them recruited patients ages ≥ 60 years old, as is the case of NCT 04420390, NCT 04390412, NCT 04414293, and NCT 04493294. But some others use doses > 0.5 Gy, about 13 clinical trials.

# 3 Previous Studies of low-dose radiotherapy as an anti-inflammatory treatment

After the discovery of X-rays in 1895, several studies with ionizing radiation started investigating the treatment of inflammatory and infectious diseases, such as gangrene, sinusitis, and arthritis. [6,7]

Sakamoto conducted a series of studies on mice in the early 1990s to understand the effects of X-rays on the immune system. He found that a low dose of radiation stimulates immunity. Radon therapies have also been proposed. One patient recovered from advanced rheumatoid arthritis after 15 months of low-dose ionizing radiation treatments. The patient's respiratory inflammation and pain throughout the body had almost disappeared. This success was followed by treating two patients with autoimmune diseases, showing improvement with the treatment. [6,7]

The first report using X-rays to treat patients with pneumonia was in 1905 by Musser and Edsall at the University of Pennsylvania. They believed that X-rays could be helpful in treating

patients with no chance of curing pneumonia. They hypothesized that X-ray treatment could accelerate immunity processes and improve metabolic conditioning. Based on this, Musser and Edsall selected five cases where the fever disappeared and showed clear signs of pulmonary improvement. In 1924, research by Heidenhain and Fried with 243 reported cases of lung infections showed that X-ray treatment not only blocked and reduced superficial inflammation, but other inflammation unrelated to the condition was also reduced. In 1943, Oppenheimer reported the application of radiotherapy in treating interstitial pneumonia, a fatal disease. He stated that he started using X-ray treatment on patients to help control cough in recovery from pneumonia. Since the results were positive, he extended its application into the acute stages. The author concluded that X-rays offer excellent potential as a treatment for interstitial pneumonia, especially when used in the early effects of the disease. [6,7]

Even with the publication of past studies, studies about the use of ionizing radiation for anti-inflammatory treatments are scarce and date from the last century, generating many uncertainties around this type of treatment. It is also worth mentioning that the treatment techniques with ionizing radiation are currently different from the past ones. They have been improved over time with the introduction of Tridimensional Conformal Radiation Therapy (3DRT), Intensity Modulation Radiation Therapy (IMRT), and Volumetric Modulated Arc Therapy (VMAT). Indeed, using these techniques can impact the analysis of the benefits and harms of this practice. Their results for estimating the risk of inducing cancer are potentially different from previous studies, mainly because they are used for other therapeutic purposes.

## Main purpose

The main purpose of this project is to estimate the risk of induced-cancer for COVID-19 patients treated with low-dose whole-lung based on a virtual simulation using mathematical models, as well as compare each mathematical model and evaluate the clinical results of clinical trials.

# CHAPTER 2 - Fundamentals

Over the past decades the need to study the risks involved with ionizing radiation has grown concomitantly with its use in several areas, as well as to deal with accidental or nuclear cases

at high-dose exposure. In this context, radiation epidemiological studies are important. Radiation epidemiology is the study that associates human disease and its effects with radiation exposure to populations. Even though the study with Japan atomic bomb survivors is the most largely on data, other studies with occupational workers are also recurrent.

Radiation epidemiology is important to guide how radiation affects the organism, how radiation exposure will reflect in the future, and how it may be possible to control it and increasingly decrease its effects so that it is used in the best way in treatments.

The study on low doses is one of, if not the most challenging, for radiation epidemiology. First, because the effects are intermittent, i.e., there is no dose threshold or limit for an effect to occur. Second, there is no time limit for manifestation after radiation exposure, and probably most manifestations occur after years. And due to these factors, low-dose has become essential in radiation epidemiological studies.

Whether low-dose ionizing radiation can cause cancer or other diseases, it is critical to understand how it works regarding radiation protection, particularly in cases where the justification for using radiotherapy is questionable, such as in patients with COVID-19 pneumonia.

Radiation epidemiological studies continue to develop, and here we highlight the studies we based on: Biological Effects of Ionizing Radiation (BEIR 2006) [11], International Commission on Radiological Protection (ICRP 103 - 2007) [12] and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2006) [14,15], as well the Excess Lifetime Risk (ELR) from Shuryak et al. (2009 and 2010) [8,9,10] and Risk of Exposure-Induced Death (REID) from Little et al. (2012) [16]. They provide guidelines to protect patients, workers, and the public, trying to understand the radiation risks.

# 1 Excess Lifetime Risk

ELR is a quantitative biological model of carcinogenesis that increments and emphasizes the induction of malignant cells (initiation) by ionizing radiation and the proliferation of cancer cells by ionizing radiation. This model tracks the quantitative procedure of malignant cells before, during, and after radiation exposure and presupposes that the cells can suffer an initial

process in a premalignant state, spontaneously or by radiation exposure. So it can presuppose that ionizing radiation can potentially increase the mean number of malignant cells. Therefore, it is possible to estimate the radiation-induced cancer risk by ionizing radiation. [8,9]

This model assumes that the organ cells reside in compartments called niches and can undergo initiation to a premalignant state spontaneously or by radiation. It considers the age at exposure and integrates, in a single formalism, the analysis of premalignant cell dynamics at different time scales: in the short term, during radiotherapy and recovery, in the long term, throughout the useful life before and after radiation exposure. [8,9]

The ELR model has three age-dependent parameters and three parameters that describe the induction modulations by ionizing radiation in the short- and long-term risks involved. The three parameters of radiation dependence characterize the initial (parameter X) and promotional processes (parameter Y) and the homeostatic regulation of the number of pre-existing malignant stem cells per group (parameter d). Thus, the X/Y ratio, although not an independent parameter, characterizes the relative yield of pre-existing radiation-induced malignant cells produced through initiation versus promotion processes. [8,9]

Based on the biological model described above, there are the expressions for cancer risk as a function of age reached (T) and for cancer risk related to radiation as a function of age at exposure (Tx) and time after exposure (Ty; such that T = Tx + Ty). [8,9]

$A_{bac}$ is the age-dependent expected mean number of fully malignant cells per individual per unit of time under background, without any radiation exposition. It is a function of the individual attained age (T), which is the sum of the age at exposure (Tx) and the time after exposure (Ty):

$$A_{bac}(T) = \left(\frac{a}{b}\right)(e^{bT} - 1)e^{-cT^2}$$

Equation 1

The age-dependent parameters *a*, *b*, and *c* describe spontaneous stem cell initiation and subsequent malignant transformation, premalignant niche replication, and effects of age on premalignant niches, respectively. [8,9]

The approximate risk expression for the radiation-related cancer risk after a brief single low-dose radiation is $A_{rad}$:

$$A_{rad}(Tx,Ty) = \frac{a}{b}\{\frac{(1+YD)[e^{bTx}-1=bXD]e^{bTy}}{1+YD(1-e^{-\delta Ty})} + e^{bTy} - 1\}e^{-c(Tx+Ty)^2}$$

Equation 2

where three parameters related to radiation are used: X characterizes the initiation dose dependence, Y describes the proliferation processes and δ describes the homeostatic regulation of the number premalignant stem cells per niche. [8,9]

Thus, the relative excess risk (RER) at a given age of Tx exposure and for a given time after exposure is given as:

$$RER = \frac{A_{rad}(Tx,Ty)}{A_{bac}(T)} - 1$$

Equation 3

Based on the equations above, the estimated lifetime risk of developing cancer (B) and the risk of developing cancer in individuals who have been irradiated (R) are:

$$B = \int_0^{T_x} A_{bac}(T_x = u\,, T_y = 0)\,du + \int_0^{\infty} \frac{A_{bac}(T_x, T_y = v)\,S(T_x + L + v)}{S(T_x + L)}\,dv$$

Equation 4

$$R = \int_0^{T_x} A_{bac}(T_x = u\,, T_y = 0)\,du + \int_0^{\infty} \frac{A_{raad}(T_x, T_y = v)\,S(T_x + L + v)}{S(T_x + L)}\,dv$$

Equation 5

where S(T) is the probability that an individual survives to age T. In the equations for B and R, the first integral refers to the time before exposure, and the second is the time since exposure. [10]. Therefore, the lifetime excess risks for radiation-induced cancer can be calculated as

$$ELR = R - B$$

Equation 6

# 2 Lifetime Attributable Risk

## 2.1 Biological Effects of Ionizing Radiation VII Phase 2 Report

The report is from National Research Council (NRC) and is a review to update the last BEIR report by adding new information from epidemiological and experimental research. The data has accumulated over 14 years and would help to characterize dose risks, which is directly related to the main objective of the study: to develop a risk estimate for exposure to low-dose that best fits the data and can predict risks associated with dose rates. [11]

BEIR VII Phase 2 Report has an extensive summary that brings background information about cellular responses to ionizing radiation; radiation-induced cancer, and the mechanisms; methods, and studies for epidemiologic data and risk assessment models and methods. After all, these topics are essential to estimate cancer risks and develop new models that can predict the estimations. [11]

## 2.2 Estimating Cancer Risk

BEIR VII model is developed from cancer incidence and mortality and is directly relatable to gender, age at exposure, time since exposure, and specific site. Estimates are given for all solid cancers and leukemia.

Life Span Study (LSS) cohort of survivors of the atomic bombings in Hiroshima and Nagasaki is the data evaluated by the committee. Several advantages made it chosen by the BEIR VII Phase 2 committee for developing risk estimations from exposure to ionizing radiation, mainly because it is one of the most important to calculate risks at low-dose radiation. The data has a large amount of information, including all ages, genders, a range of times of exposure-induced cancer, various doses, cancer cases in each body organ, and a massive number of cancer and mortality incidences over the years. Another point to highlight is that LSS cohort data is available to other researchers if they want to investigate it. The committee’s models using the LSS cohort were also evaluated to be compatible with different cohorts' data. Analyses of cancer incidence were based on cases diagnosed between 1958 and 1998, and cancer mortality studies were based on deaths from 1950 - 2000. [11]

The inclusion and exclusion criteria to estimate the lifetime risk of cancer (Figure 3) are based on public health impact. The primary interest is mortality and incidence of cancer because it is the most severe consequence of radiation exposure. Accompanying these risks, years of life lost or years of life per death is also important data because the time of cancer occurrence is of great

interest. The type of cancer is divided between leukemia and solid cancers because leukemia variables are very different from other types of cancers. The body's tissues receive different doses when exposed to radiation. Thus, the estimates of risks are calculated by specific sites. The development of risk models is quantified by variables such as dose, gender, age at exposure, and attained age. [11]

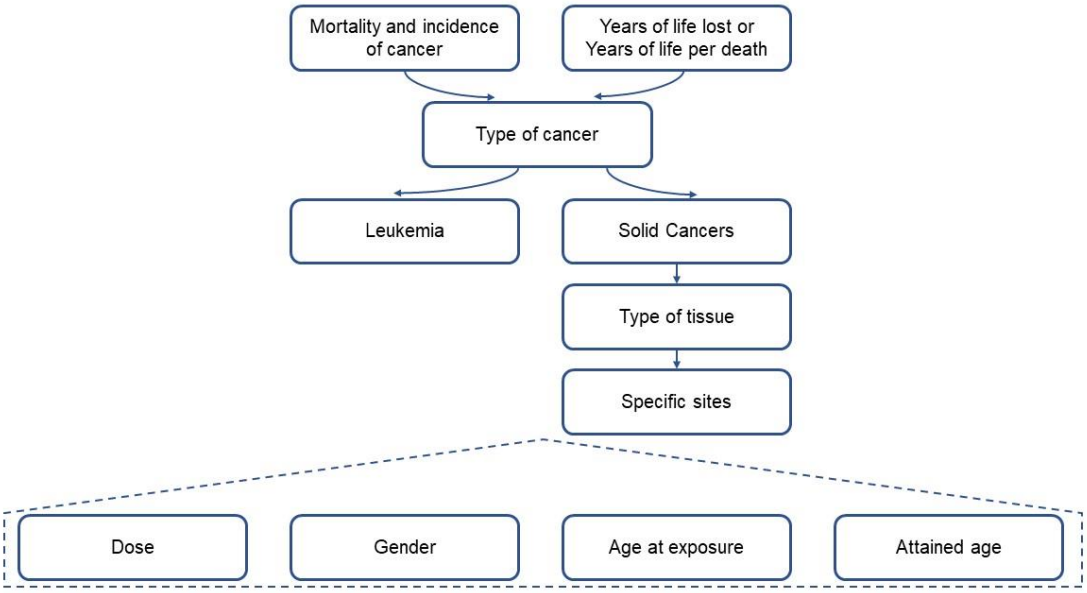



Figure 3. Inclusion and exclusion criteria to develop risk model by BEIR VII.

Considerations for selecting specific sites include statistically significant dose-response results, adjacent organs exposed to radiation in more common treatments, and organs affected by inhalation and/or ingestion exposures.

### 2.2.1 Models for Site Specific Solid Cancer and Breast

The DS02 system estimated the doses expressed in sievert (Sv). Such a system provides estimates for various doses in the body. Mathematical methods were based on Poisson regressions demonstrated by Pierce et al. (1996) and generated in software described by Preston et al. (1991). [11]

Models for estimating risk in specific sites were based on cancer incidence data, mainly because cancer incidence data are more detailed and accurate than cancer mortality data, and the number of cancer incidences is greater than the number of cancer deaths. The models preferred by the committee are based on Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) models

depending on the age at exposure for exposure ages under 30 years, and this dependence is constant for ages over 30 years. Then the BEIR VII model is described as follows:

$$ERR(e,a)\ or\ EAR(e,a) = \exp(\gamma e^{*})a^{\eta}$$

Equation 7

where *e* is the age at exposure (years), *e** is equal to *e - 30* when $e < 30$, and *e** is equal to zero when $e > 30$, and *a* is the attained age (years). Parameters were estimated from analyzes obtained from incidence data for all solid cancers, excluding thyroid cancer and non-melanoma skin cancer. [11]

For breast cancer estimates, the committee's preferred incidence and mortality models were developed by Preston et al. (2002), where there is a combination of other data and including data from the LSS cohort. Such models include differentiating factors for the age at exposure and attained age. The ERR model is described as follows:

$$\frac{ERR}{Sv} = \beta\left(\frac{a}{60}\right)^{-2}$$

Equation 8

where *a* is the attained age (years).

And the EAR model is described as follows:

$$EAR\ per\ 10^{4}\ woman - years\ per\ gray = 9.9\exp[-0.05(e-25)](a/50)^{\eta}$$

Equation 9

where *e* is the age at exposure (years), and *a* is the attained age (years).

### 2.2.2 Models for Risks to U.S. Population Estimated by the Committee

Some issues need to be investigated to estimate the risks for a population from models developed for another population because people differ from each other in different aspects, affecting the incidence rate. In this case, the risk models of Japanese atomic bomb survivors are being used for the population of the United States, and some issues must be added so that the risk model is correctly adapted for the population under study. Some of these issues are:

determining approximations for low-dose risk estimates, projecting risks over time, and transferring risks from one population to another. [11]

Usually, for low doses, linear models are used as a function of the dose. The dose-rate reduction factor (DDREF) is used to reduce the errors of other factors due to the estimation in a linear function. This factor has a value and is determined through the probability distribution of the estimate. The committee found values for DDREF between 1.1 and 2.3 when fitting linear models on the LSS cohort data. [11]

Another factor that may change the estimates is that the LSS cohort and other data change over the years as more cases of survivors who develop cancer after radiation exposure are added. The extrapolations related to risk estimates based on limitations to consecutive years have been one of the most significant sources of uncertainty. The committee uses risk models that assume dependence with attained age and assumes that the patterns found persist for the rest of the lives of younger survivors. [11]

The third issue is the risk transfer from one population to another, mostly related to specific sites. Baseline risks site-specific from one population to another are different, and therefore risk transfer models are used. For the breast, the committee relied on a combining analyses model including a Caucasian population. For other solid cancers, the committee calculated risks using relative risk and absolute risk models. [11]

### 2.2.3 Lifetime Attributable Risk

The BEIR VII committee model, uses to calculate lifetime risk is the Lifetime Attributable Risk (LAR). This model was already called risk of untimely death by Vaeth and Piercer (1990), and it is an approximation of the REID model. LAR and REID are distinguished by ELR, as the survival function of LAR does not include people dying from radiation-induced diseases. The LAR for a person exposed to dose *D* at an age at exposure *e* is written as follows:

$$LAR(D,e) = M(D,ea,)\left(\frac{S(a)}{S(e)}\right)$$

Equation 10

where *a* is attained age (years), *M(D,e,a)* is the EAR, *S(a)* is the probability of surviving until age *a*. There is a summation *a = e + L to 100*, where *L* is a latent period (a period between the exposure and the appearance of radiation-induced disease). [11]

The LAR estimation uncertainties provided by the linear models applied to the LSS cohort were derived from the delta method (Feinberg 1988). This method relies on log derivatives. The 95% confidence interval (CI) is also calculated using the log (LAR) and subsequently obtained by the antilogarithm of the maximum and minimum points. Then, the LAR estimate is obtained by combining the models based on ERR and EAR. [11]

LAR is used in this work to estimate risks of induced cancer regarding BEIR VII data and compare results with other models described by different committees.

# 3 Risk of Exposure-Induced Cancer

## 3.1 ICRP Publication 103: The 2007 Recommendation of the International Commission on Radiological Protection

The International Congress of Radiology established the ICRP to improve, reduce and control the risks of ionizing radiation to prevent possible effects on tissues.

The Commission's main objective is to contribute to ionizing radiation at a level where there is a balance between its use for treatments and protecting people and the environment.

## 3.2 Estimating Cancer Risk

One of the ICRP's main resolutions is to develop a more realistic cancer risk estimation model for low doses. For this, the Commission used, in addition to epidemiological data, biological data, such as dose-response dependence for genetic and chromosomal mutations and response cells to DNA damage. Figure 4 schematically demonstrates how the Radiation Exposure-Induced Cancer (REIC) model was developed.

The data to “feed” the construction of the REIC statistical model were collected from the Japanese LSS of the atomic bomb (A-bomb) survivors with follow-up from 1958 through to 1998. Estimates were derived from averages between Asian and Euro-American populations; survival functions were derived from these populations' mortality and incidence rates.

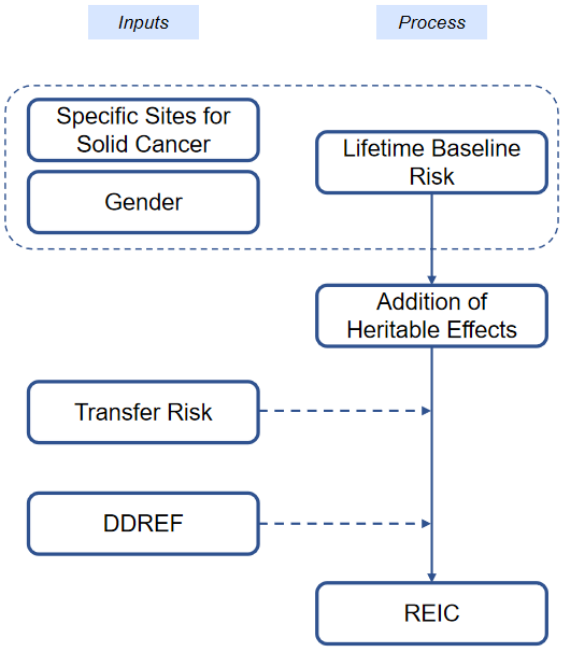



Figure 4. Scheme demonstrating the development of the REIC model by the ICRP

### 3.2.1 Lifetime Baseline Risks

The Lifetime Baseline Risks (LBR) corresponds to the cumulative risk of developing cancer in the absence and/or presence of radiation exposure. The LBR is calculated as follows:

$$\mathrm{LBR}\,(a_{min}, g) = \int_{a_{min}}^{a_{max}} m(a,g)S(a|a_{min}, g)da,$$

Equation 11

where g is the gender, $a_{min}$ is the age at the beginning of risk, $a_{max}$ is the maximum age included in the function (90 years), $m(a, g)$ is the age- and gender-specific cancer incidence rates, and $S(a|a_{min}, g)$ is the survival function. [12,13]

### 3.2.2 Models for Specific Sites for Solid Cancer

The ERR model and the EAR model are used for each cancer site. The general forms of these models are:

$$\lambda(g, a, e, d) = \lambda_0(g, a, e)[1 + \mathrm{ERR}(g, a, e, d)]$$

$$\lambda(g, a, e, d) = \lambda_0(g, a, e) + \mathrm{ERR}(g, a, e, d)$$

where $\mathrm{ER}(g,a,e,d) = \beta d \exp[\alpha_1((e-30)/10 + \alpha_2 \ln(a/70)]$ is an excess risk, e is the age at exposure (years), *a* is the attained age (years), *d* is the dose (Gy), and $\lambda_0$ is the baseline cancer rate. $\beta$ and $\alpha$ are parameters used for calculating nominal risks and are summarized in ICRP Publication 103. [12,13]

### 3.2.3 Heritable Effects and Transfer Risk Across Populations

Estimates of the risk of hereditable effects were derived from the UNSCEAR 2001 report. They were expressed as the number of predicted cases for each class of genetic disease per million live births per Gy for a population exposed to a low dose. As the assumptions for genetic radiation-induced effects are unrealistic, ICRP 103 proposed that the calculation for estimations cover future generations. [12,13]

As each population has different baseline rates, weighted averages of the ERR and EAR estimates were used for each cancer site. For the lung, the ERR model was used and received a weight of 0.3, and for the female breast, the EAR model was used without adding weight because in a previous study (Preston et al. 2007), there was evidence against the use of the ERR model. [12,13]

### 3.2.4 Dose and Dose Rate Effectiveness Factor

Applied to low dose, a DDREF of 2 was used in ICRP Publication 60, so also the same DDREF was applied in ICRP Publication 103 for each gender, using unique or fractional doses. [12,13]

### 3.2.5 Risk of Exposure-Induced Cancer

REIC is the cumulative number of cases of a given cancer type for an exposed population during a follow-up period. In ICRP 103, REIC was calculated for all solid cancers, except leukemia, and is given as follows:

$$\mathrm{REIC}(e,d) = \int_{a=e+L}^{90} [\mu(a|e,d) - \mu(a)] S(a|e,d) da,$$

Equation 12

where *e* is the age at exposure (years), *a* is the attained age (years), *d* is the dose (Gy), *L* is the latency period (years), $\mu$ is the annual risk of a type cancer incidence and $S(a|e,d)$ is the probability of the individual survive until age *a* without cancer given an exposure *d* at age *e*. [12,13]

# 4 Excess Relative Risk and Excess Absolute Risk

## 4.1 Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report

The Committee of UNSCEAR has undertaken extensive reviews of sources of ionizing radiation and its effects on human health and impacts on the environment. The committee analyzes the radiation sources and the resulting doses to evaluate the effects induced by ionizing radiation and understand by which mechanisms these effects can occur. [15,16]

The Report emphasizes the following topics: epidemiologic of radiation and cancer; non-cancerous diseases after radiation exposure; delayed effects of exposure to ionizing radiation; effects of ionizing radiation on the immune system; and assessment of the effects of radiation. [14,15]

## 4.2 Estimating Cancer Risk

The Committee uses a dosimetry system to develop risk estimates. The UNSCEAR cancer risk estimates are from the Japanese LSS of the atomic bomb (A-bomb) survivors' data by DS02 dosimetry. The DS02 dosimetry does not differ by 20% from the previous dosimetries, with no change in the dose-response pattern. Figure 5 shows a schematic of the process for calculating cancer risks by the dosimetry system.

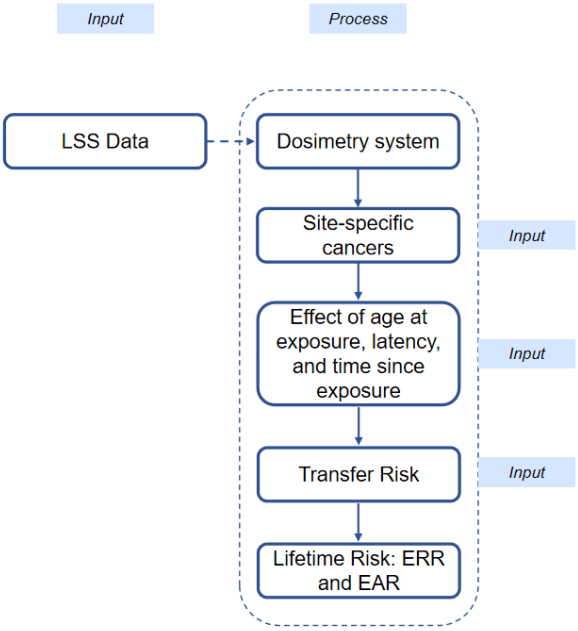



Figure 5. Scheme demonstrating the development of the Lifetime Risk for ERR and EAR by dosimetry system.

### 4.2.1 Lifetime Risks by Excess Relative Risk and Excess Absolute Risk

Cancer risk models fitted to the collected and analyzed data were described by models for risk rates or better-defined hazard functions. The hazard function is defined as the probability of dying in an interval divided by the probability of surviving to a given age, written as follows:

$$\mathrm{h(a)} = \lim_{\delta \to 0} (\mathrm{P}|[\text{time of death } \epsilon[\mathrm{a}, \mathrm{a}+\delta]]/(\delta \mathrm{P}[\text{time of death } \geq \mathrm{a}])$$

where h(a) is the hazard function for mortality at age *a* (years). [14,15]

The EAR is the difference between the instantaneous cancer death rate, the hazard function when exposure occurs, and the hazard function if there is no exposure, called the baseline hazard function. EAR is written as follows:

$$\mathrm{EAR}\ (\mathrm{a}, \mathrm{g}, \mathrm{D}, \mathrm{e}) \ = \ \mathrm{h}(\mathrm{a}, \mathrm{g}, \mathrm{D}, \mathrm{e}) - \mathrm{h}(\mathrm{a}, \mathrm{g}, 0, \mathrm{e})$$

Equation 13

where *a* is the age mortality (years), *g* the gender, *e* is the age at exposure (years), and *D* is the dose (Gy). Then the ERR is given by the EAR divided by the baseline rate, as follows:

$$\mathrm{ERR}\,(a, g, D, e) \;=\; \mathrm{EAR}(a, g, D, e) / \,h(a, g, 0, e)$$

Equation 14

# 5 Risk of Exposure-Induced Death

The REID is mainly calculated for the heart, estimating the risks of heart diseases and population mortality. Studies show that the risk of heart disease from exposure to ionizing radiation can be detected even at low doses, emphasizing the importance of assessing these risks. [16]

Little at el. (2012) model for REID was developed as shown in Figure 6. A meta-analysis was performed through a systematic review of heart disease studies that met the inclusion criteria.

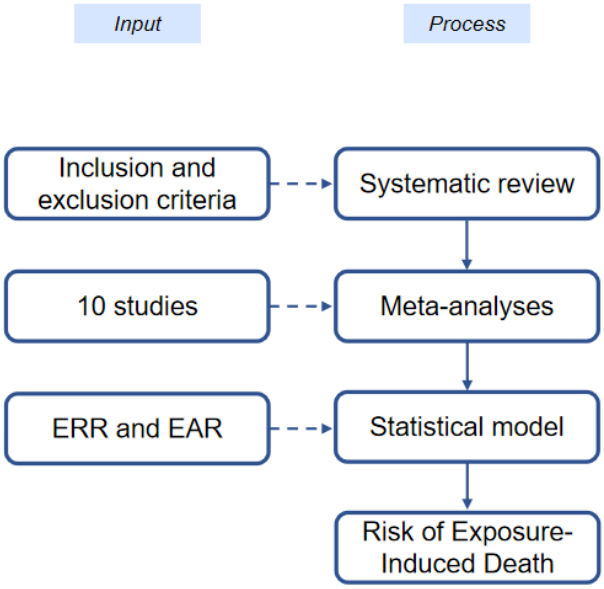



Figure 6. Process of development REID for heart diseases.

The ERR per sievert (Sv) was computed using data from the meta-analysis as:

$$\mathrm{ERR} \;=\; \Big(\sum_{i=1}^{N} \mathrm{ERR_i}/\mathrm{sd}(\mathrm{ERR_i})^2\Big) \;/\; \sum_{i=1}^{N} 1/\mathrm{sd}(\mathrm{ERR_i})^2\Big)$$

Equation 15

where $\mathrm{sd(ERR)} = 1/[\sum_{i=1}^{N} 1/\mathrm{sd}(\mathrm{ERR_i})^2)\ ]^{0.5}$. The ERR was derived from EAR estimates according to the mortality rates of each population. The minimum latency period was five years; the REID was estimated per sievert (Sv). [16]

# CHAPTER 3 - Methods

## 1 Choices for Evaluation Criteria

As previously presented, the biological effects of ionizing radiation vary depending on the tissue or organ, but effects differences between gender and age at exposure of the individual can be encompassed. Although the age at exposure has an impact on cancer incidence data among individuals who have been exposed to radiation at older ages, it is an essential factor of comparison, as it is possible to analyze how younger individuals respond to radiation exposure over the years and how radiation exposure has affected different generations. Comparison between genders is of interest because it presents a significant difference in cancer incidence and mortality, as well as the study by organ for each gender. These factors may be related to genetics and lifestyle. Among the other factors described, radiotherapy treatment techniques can also be compared. Each has a different dose distribution applied in the treatment, leading to different mean doses in each organ for each technique.

## 2 Treatment Planning Virtual Simulation

A whole lung radiotherapy planning was virtually simulated in a median female body computed tomography image with 20 cm of anterior-posterior and 30 cm of lateral-lateral distances. Eclipse (Varian Medical System, Palo Alto-CA, EUA) was the treatment planning system used.

Two treatment planning techniques were employed: a 3DRT plan, with two parallel opposed fields in the anterior-posterior directions, and an IMRT plan, with seven fields. A 1 Gy dose was planned for the PTV, and 95% of the planned dose covered 90% and 95% of the target volume in 3DRT and IMRT techniques, respectively. (Figure 7)

The planning target volume (PTV) is the two lungs, while the organs at risk (OARs) for both techniques are: the heart, esophagus, liver, and breast. Doses on the described organs were

evaluated and used to estimate the risks of radiation induced-cancer and other radiation-induced diseases.

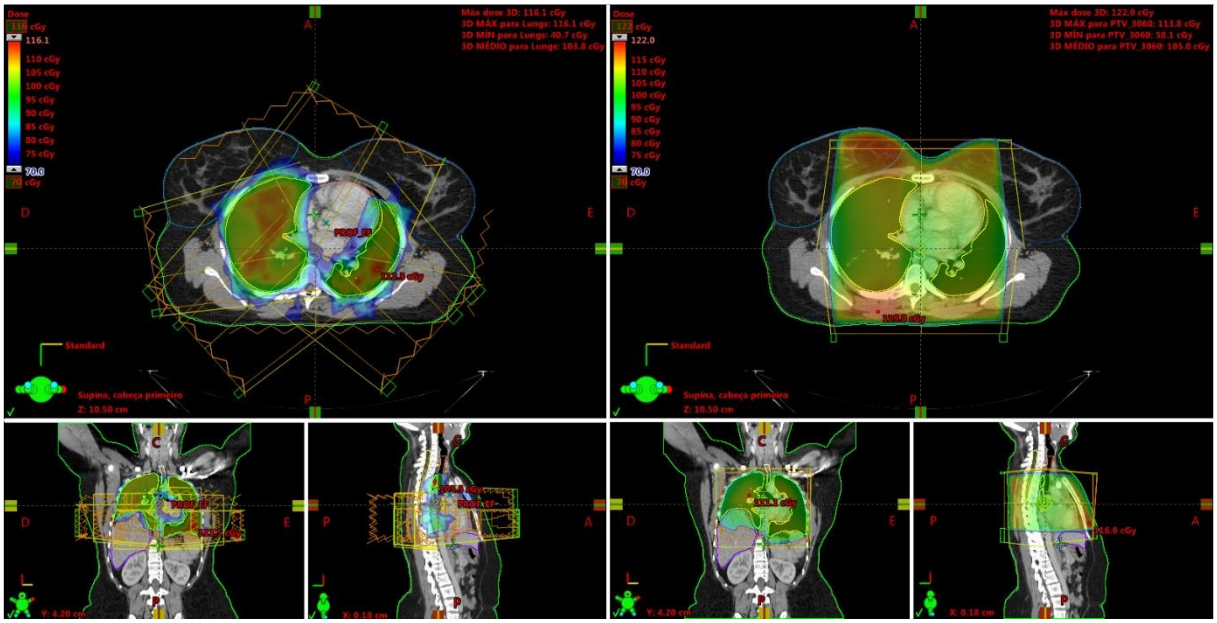


Figure 7. Dose distribution for the whole lung treatment with a dose of 1 Gy for the axial, sagittal, and coronal planes using IMRT (left) and 3DRT (right).

Based on clinical trials treatments [34 – 45] for patients with COVID-19, a choice of a median female body was proposed to be similar to patients' characteristics, but risks were also calculated for men, as estimates are also recorded for this gender. The choices of a dose of 1 Gy and the techniques 3DRT and IMRT also follow the same basis, in addition to facilitating the rescaling of the other doses used later to calculate the risk estimates of induced-cancer.

# 3 Excess Lifetime Risk

The lung ELR [8,9,10] was evaluated for the proposed dose range in the clinical trials for whole lung irradiation (0.3 – 1Gy). At the same time, for the breast, esophagus, and liver, the ELRs were estimated for the doses they received in the simulated treatment. ELR was estimated for age at exposure (years), dose (Gy), gender, and specific sites.

# 4 Lifetime Attributable Risk

Data from Table 12D-1 from the BEIR VII report (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation – National Research Council 2006) were used

as a basis to calculate the risk of induced-cancer (RIC) estimates applied to the results collected in the virtual simulation of treatment planning for lungs. [11]

First, a linear interpolation was performed to calculate the risk estimate as a function of the age at exposure, which ranges from 5 to 80 years, with five years intervals.

The reference dose in Table 12D-1 is 0.1 Gy, so to find the values of risk estimates as a function of the OAR and PTV mean doses from the virtual simulation, a weighting was performed on these mean doses, that is,

$$risk\ estimate = \frac{risk\ table\ x\ mean\ dose}{dose\ table}$$

Equation 16

The *risk estimate* is based on each organ's mean dose, the *risk table* is the risk from Table 12D-1, the *mean dose* is the mean dose of each organ found in the virtual planning, and the *dose table* is 0.1 Gy.

Then the LAR was performed for whole lung RT treatments using 0.5, 0.7, 1.0, and 1.5 Gy, calculated as follows:

$$LAR(0.5; 0.7; 1.0; 1.5\ Gy) = dose\ x\ risk\ estimate$$

Equation 17

The *dose* varied from 0.5 to 1.5 Gy; the LAR result is in cases / 100,000.

LAR was predicted for age at exposure (years), dose (Gy), gender, specific sites, and 3DRT and IMRT techniques. Results and discussion are based on analyzes for each characteristic described below.

# 5 Risk of Exposure-Induced Cancer

Data from Tables A.4.10 and A.4.11 from ICRP 103 [12] were collected to calculate REIC for COVID-19 treatment planning virtual simulation.

The reference dose in these tables is 0.1 Gy, so to find the values of risk estimates as a function of the mean doses of each OAR and PTV of the virtual simulation, a weighting was included as follows:

$$risk\ estimate = \frac{risk\ table\ x\ mean\ dose}{dose\ table}$$

Equation 18

where *risk estimate* is the estimated risk based on the mean dose of each organ, the *risk table* is the risk from Tables A.4.10 and A.4.11 from ICRP 103, the *mean dose* is the mean dose of each organ from the virtual simulation, and the *dose table* is 0.1 Gy.

The REIC was calculated for whole lung RT treatments using 0.5, 0.7, 1.0, and 1.5 Gy, as follows:

$$REIC(0.5; 0.7; 1.0; 1.5\ Gy) = dose\ x\ risk\ estimate$$

Equation 19

The dose varied from 0.5 to 1.5 Gy, and the REIC result is in cases / 100,000.

REIC was estimated for age at exposure (years), dose (Gy), gender, specific sites, and 3DRT and IMRT techniques.

# 6 Excess Relative Risk and Excess Absolute Risk

Data from Tables 21, 25, 27, and 33 from UNSCEAR 2006 Report [14] were used to calculate ERR and EAR to estimate the RIC for COVID-19 treatment based on the virtual simulation.

The weighting was included as follows:

$$risk\ estimate = \frac{risk\ table\ x\ mean\ dose}{dose\ table}$$

Equation 20

where *risk estimate* is the estimated risk based on the mean dose of each organ, the *risk table* is the risk from Tables 21, 25, 27, and 33 from UNSCEAR 2006 Report, the *mean dose* is the mean dose of each organ from the virtual simulation, and the *dose table* is 1.0 Gy.

The ERR and EAR were calculated for whole lung RT treatments using 0.5, 0.7, 1.0, and 1.5 Gy, as follows:

$$ERR(0.5; 0.7; 1.0; 1.5\ Gy) = dose\ x\ risk\ estimate$$

Equation 21

$$EAR(0.5; 0.7; 1.0; 1.5\ Gy) = dose\ x\ risk\ estimate$$

Equation 22

where the *dose* variable ranges from 0.5 to 1.5 Gy, ERR is cases /100,000, and EAR is 10,000 persons-year Sv.

ERR and EAR were estimated for age at exposure (years), dose (Gy), specific sites, and 3DRT and IMRT techniques.

# 7 Risk of Exposure-Induced Death

Data from Table 5 from Little et al. (2012) [15] were collected to calculate the REID to estimate the risk of induced heart diseases for a COVID-19 treatment based on a virtual simulation.

Data were calculated to absolute values, and weighting was applied for a reference dose of 0.01 Gy, as follows:

$$risk\ estimate = \frac{risk\ table\ x\ mean\ dose}{dose\ table}$$

Equation 23

where *risk estimate* is the estimated risk based on the mean dose of each organ, the *risk table* is the risk from Table 5 from Litte et al. (2012), the *mean dose* is the mean dose of each organ from the virtual simulation, and the *dose table* is 0.01 Gy.

Then the REID was calculated using 0.5, 0.7, 1.0, and 1.5 Gy, as follows:

$$REID(0.5; 0.7; 1.0; 1.5\ Gy) = dose\ x\ risk\ estimate$$

Equation 24

The dose varied from 0.5 to 1.5 Gy, and the REID result is in cases / 100,000.

REID was estimated for age at exposure (years), dose (Gy), and 3DRT and IMRT techniques.

# CHAPTER 4 - Results

## 1 Treatment Planning Virtual Simulation

The virtual simulation generated mean doses for PTV and OARs, shown in Table 2. For both techniques, the lung received the prescribed 1.0 Gy dose.

Table 2 – Mean Absolute doses (Gy) for the whole lung treatment with a dose of 1 Gy using IMT and 3DRT techniques.

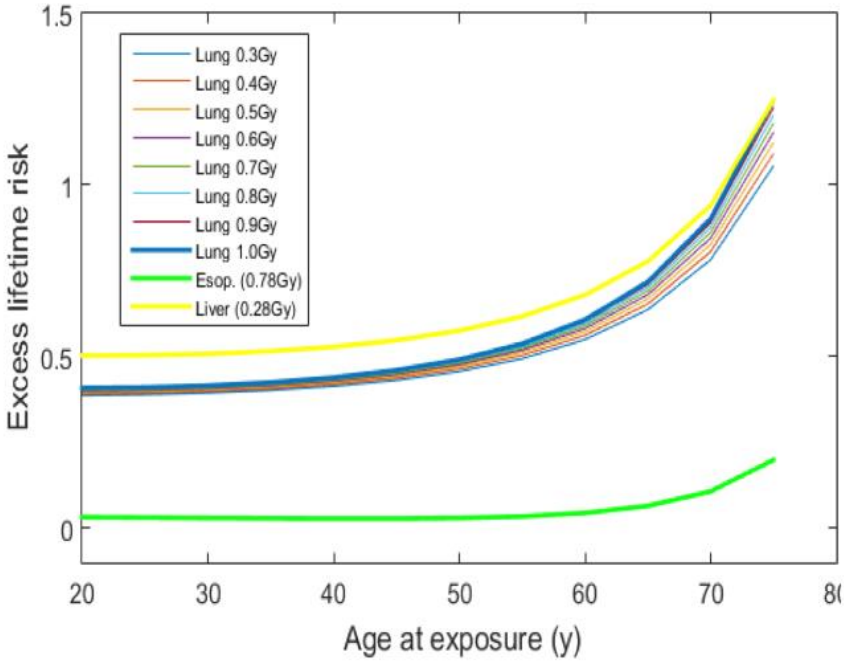
| Site | 3DRT | IMRT |
|---|---|---|
| Lung | 1.00 | 1.00 |
| Breast | 0.465 | 0.356 (-23%)* |
| Liver | 0.413 | 0.280 (-32%)* |
| Esophagus | 0.869 | 0.780 (-10%)* |

*IMRT percentage reduction compared to 3DRT treatment.

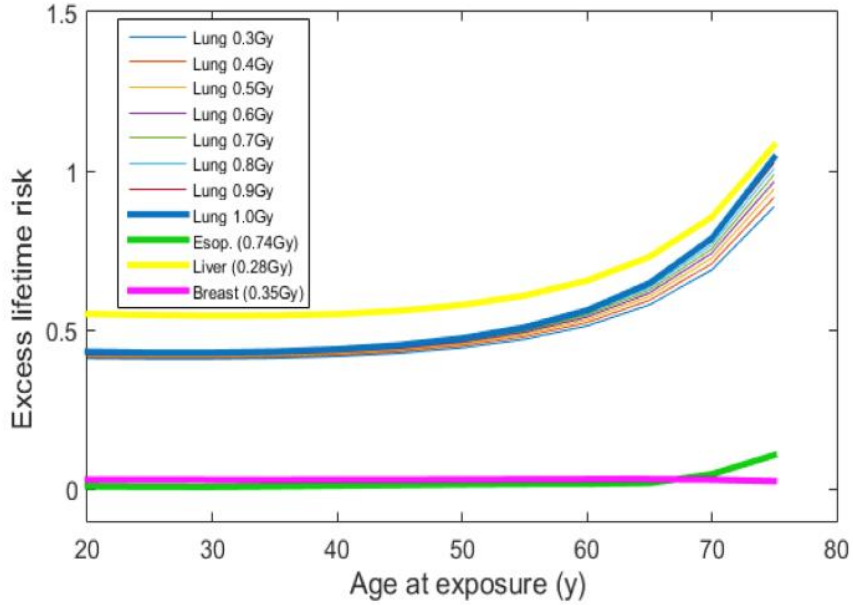
The most considerable difference in the OAR IMRT dose compared to the 3DRT one is for the liver and heart, with reductions of 32.20% and 37.60%, respectively.

## 2 Excess Lifetime Risk

The ELR versus age at exposure per 100,000 persons graphics were separated for men and women. ELR was estimated for doses between 0.3 and 1.0 Gy for the lung. For the breast, liver, and esophagus, the ELR was estimated using the doses generated by the planning virtual simulation rescaled by the prescription dose. Figure 8.a presents ELR as a function of age at exposure for men, and Figure 9.b for women.




a)




b)

Figure 8. ELR as a function of age at exposure a) for men, and b) for women.

The ELR increases as a function of age at exposure and increases rapidly since 50 years for the lung and liver. The ELR reached 1.3 cases / 100.000 after 70 years for the lung and liver, with the esophagus and breast remaining below 1 case/100.000 for all ages at exposure. The liver-relative increased risk was 6%, 7%, and 11% higher for the 20-45, 45-65, and 65-75 age at exposure ranges, respectively. Also, it was extremely low for the breast, as described in Figure 8 and ANNEX A.

The estimative of relative increased risk (%) by ELR for 0.5 Gy is 0.94 (CI 0.89 – 1.00) and 0.92 (CI 0.91 – 0.93) for women and men between 20 – 45 years, respectively. For ages 45 -65, the relative increased risk estimations are 1.12 (CI 0.46 – 1.78) and 1.19 (CI 1.03 – 1.35) for women and men, respectively. The RIC for the ELR model increases more rapidly for men than for women for the lungs.

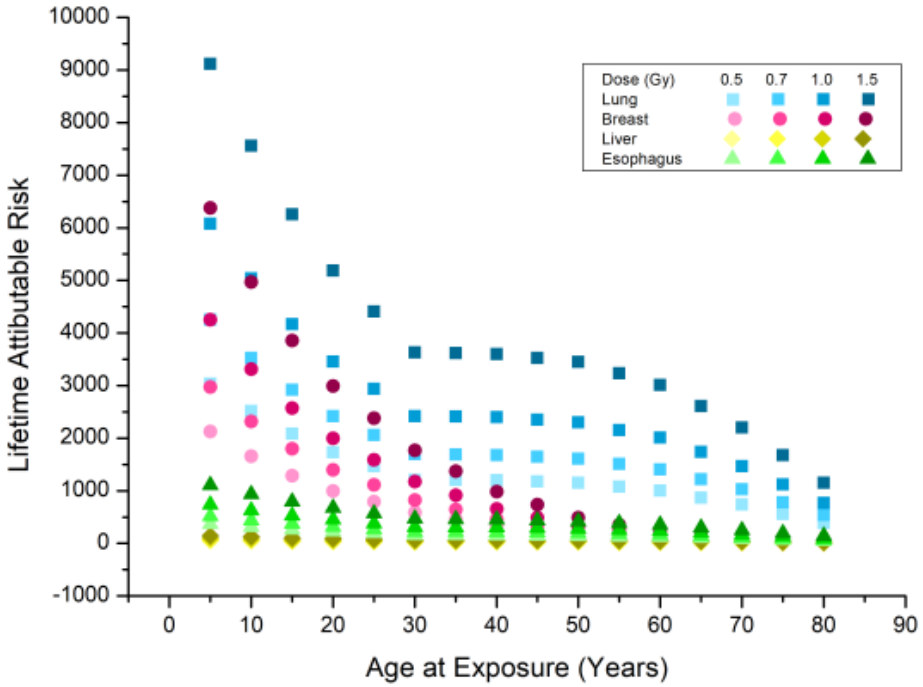
The RIC for the esophagus is higher for men than for women, approximately 70%. The RIC for the liver is higher for any gender. The relative increased risk estimative is 7.85 (CI 7.19 – 8.51) and 8.01 (CI 7.11 – 8.90) for women and men, respectively, for ages between 45 and 65 years.

# 3 Lifetime Attributable Risk

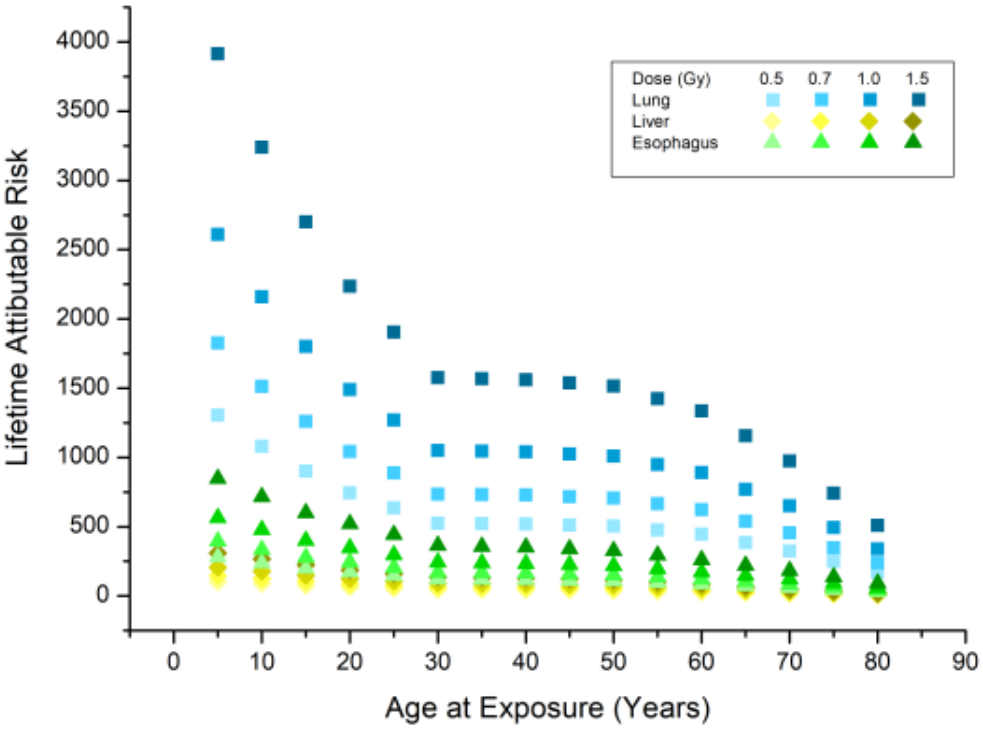
The graphs for LAR evaluation were stratified for gender and technique. All graphs are functions of the age at exposure and dose for each organ. They are distributed as follows: LAR as a function of age at exposure to RIC in women using the 3DRT technique (Figure 9.a), LAR as a function of age at exposure to RIC in men using the 3DRT technique (Figure 9.b), LAR as a function of age at exposure to RIC in women using IMRT technique (Figure 9.c), and LAR as a function of age at exposure to RIC in men using IMRT technique (Figure 9.d).

It is possible to see that LAR depends on gender. For females, it is between 0 and 10,000 cases / 100,000, and the range in the LAR distribution for males is between 0 and 4,000 cases / 100,00.

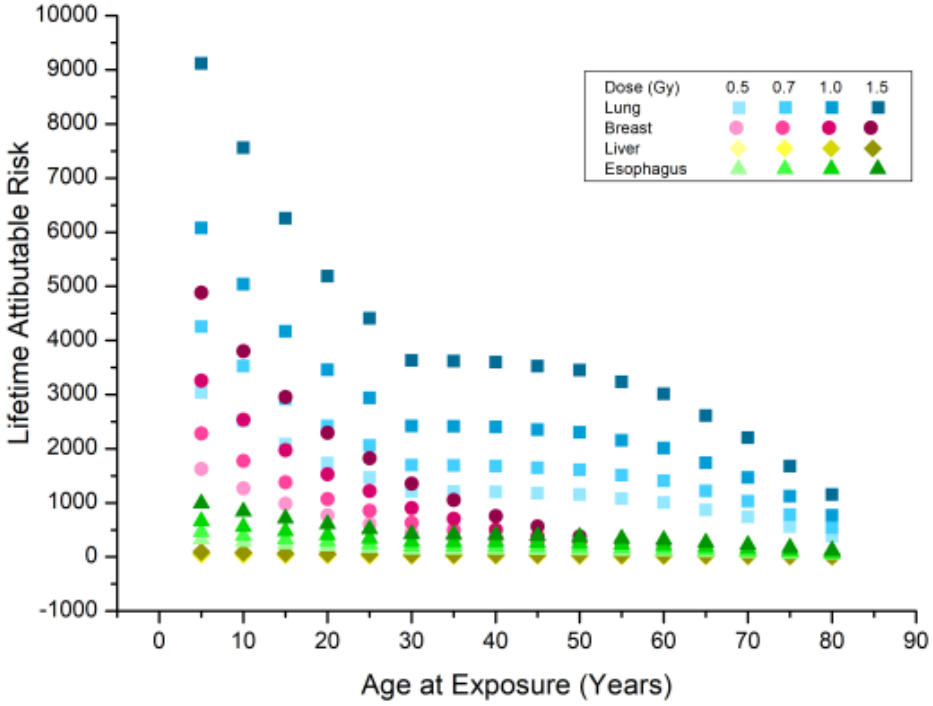
Tables showing RIC for each site and technique with a CI of 95% are in ANNEX B.


Dose (Gy) 0.5 0.7 1.0 1.5
Lung
Breast
Liver
Esophagus
Lifetime Attibutable Risk
Age at Exposure (Years)

a)


Dose (Gy) 0.5 0.7 1.0 1.5
Lung
Liver
Esophagus
Lifetime Attibutable Risk
Age at Exposure (Years)

b)

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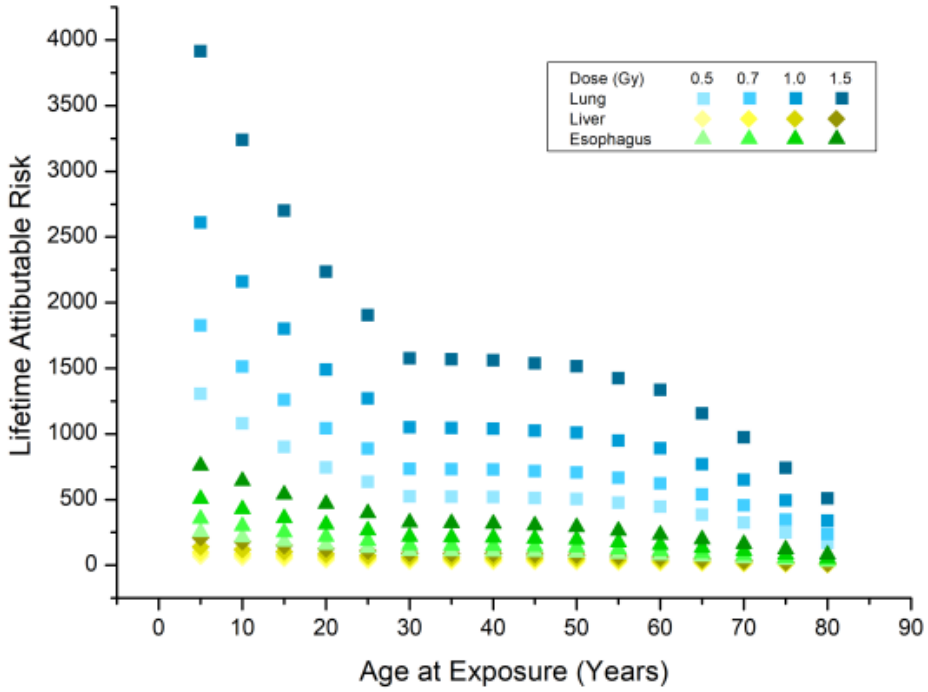



d)

Figure 9. LAR as a function of age at exposure to RIC in a) women using the 3DRT technique, b) men using the 3DRT technique, c) women using the IMRT technique, and d) men using the IMRT technique.

The RIC decreases as a function of the age at exposure in the LAR estimation, evidencing a high risk for ages < 35. For young women and radiotherapy techniques, LAR is above 1,500 cases / 100,000 for the breast and lungs and under 1,000 cases / 100,000 for the liver and esophagus. Also, for women, at ages above 60 years, the risk in organs such as the breast, liver, and esophagus are equal (below 250 cases / 100,000), while for lungs, the risk decreases slowly as a function of the age at exposure until 80 years old. For young men, LAR is below 1,000 cases / 100,000 for the liver and esophagus, and the function declines sharply with age at exposure for lungs, decreasing between ages 5 to 30 years for 3DRT and IMRT. For men over 40 years, the RIC as a function of age at exposure decreases less pronounced for all organs but still has a noticeable decrease for the lungs.

The lung RIC for women aged ≤ 30 has LAR < 1,200 cases / 100,000 for 0.5 Gy and LAR between 2,420 and 5,040 cases / 100,000 for 1.0 Gy. The lung RIC for 40-year-old women is 69.36% lower than for 20-year-old women; for 80-year-old women, the RIC is 32% lower than for 40-year-old women.

For 3DRT, the breast RIC for women aged ≤ 40 has LAR between 327.83 and 1,655.40 cases / 100,000 for 0.5 Gy, LAR, and LAR between 655.65 and 3,310.80 cases / 100,000 for 1.0 Gy. The breast RIC for 40-year-old women is 67.13% lower than for 20-year-old women, and for 60-year-women the RIC is 78.01% lower than for 40-year-old women.

The lungs LAR for 50-year-old men using 0.5 Gy in both techniques is 505.00 (CI 461.67 – 548.33) and 325 (CI 281.67 – 368.33) for 70-year-old men. For the 3DRT technique and dose of 0.5 Gy, the liver and esophagus RIC for 60-year-old men have LAR = 28.91 (CI 25.14 – 32.68) and LAR = 86.90 (CI 77.34 – 96.46), respectively. And for the IMRT technique, LAR = 19.60 (CI 17.04 – 22.16) and LAR = 78.00 (CI 69.41 – 86.59), respectively.

The lungs LAR for 50-year-old men using 1.0 Gy in both techniques is 1,010 (CI 923.34 – 1,096.66) and 650 (CI 563.34 – 736.66) for 70-year-old men. For the 3DRT technique and dose of 1.0 Gy, the liver and esophagus RIC for 60-year-old men have LAR = 57.82 (CI 50.28 – 65.36) and LAR = 173.80 (CI 154.67 – 192.93), respectively. And for the IMRT technique, LAR = 39.20 (CI 34.09 – 44.31) and LAR = 156.00 (CI 138.83 – 173.17), respectively.

The LAR estimation shows that RIC increases as a function of dose, evidencing that the risk is high for a dose of 1.5 Gy. For a dose of 1 Gy, precaution and criteria must be used to perform radiotherapy treatment. For 1 Gy, the LAR is > 1,000 cases / 100,000 for 3DRT and > 900 cases

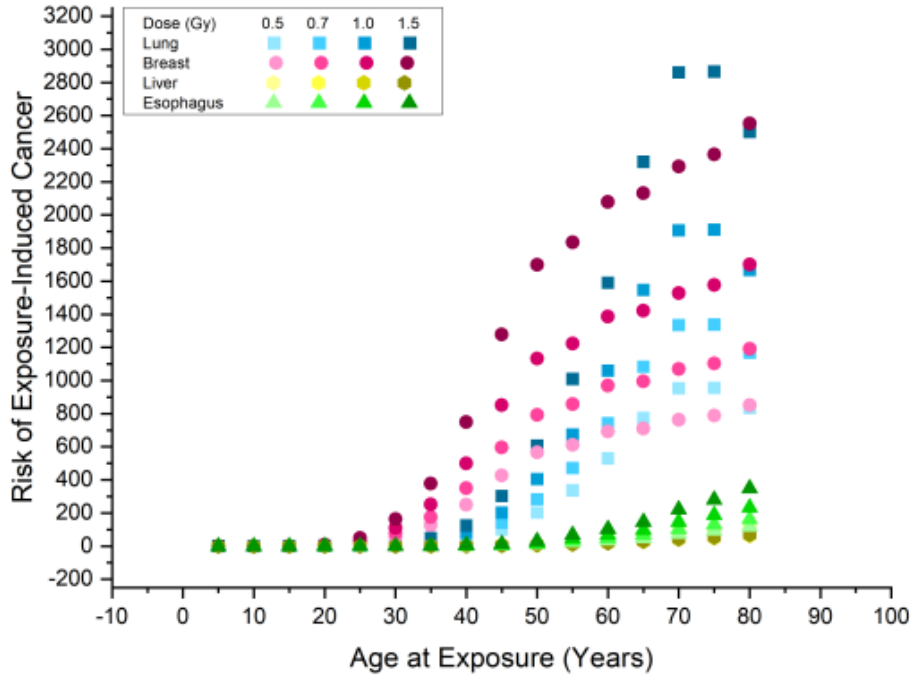
/ 100,000 for IMRT for breast in women at age ≤ 60, and > 800 cases / 100,000 in men at age ≤ 60 for both techniques. The LAR values have more significant variation between doses for the lung and breast for women and for the lung for men. The breast RIC for 1 Gy in women aged ≤ 50 has LAR > 300 cases / 100,000 and LAR > 240 cases / 100,000 for 3DRT and IMRT techniques, respectively.

The lungs and esophagus RIC in women is greater than in men, about 2.3 and 1.3 times, for the lungs and esophagus, respectively. The RIC for the liver is greater in men than in women, approximately 2.15 times. The RIC for women has an aggravating factor, the breast RIC, which has significant LAR values, especially at a young age. For both women and men, the LAR curves versus the age at exposure characteristic are the same, with a sharper drop up to 30 years.

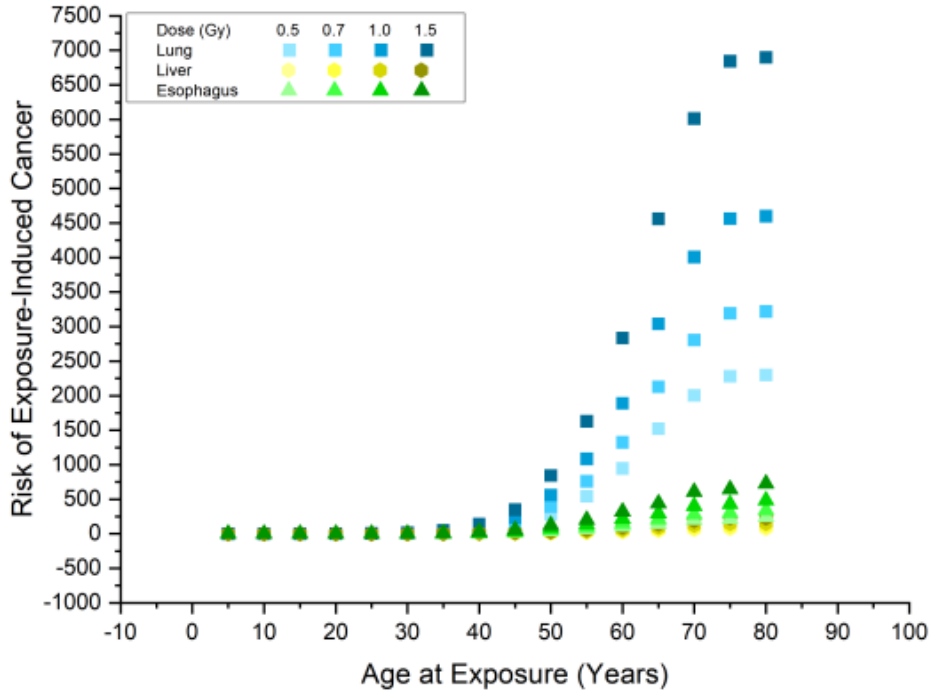
The RIC in organs increases with increasing dose and decreases with age at exposure. The lungs' RIC has LAR > 3,000 cases / 100,000, and the breast RIC has LAR > 3,800 cases / 100,000, the organs with the highest RIC for radiotherapy treatment, with a difference of approximately 50% between the risks for the 3DRT and IMRT techniques.

# 4 Risk of Exposure-Induced Cancer

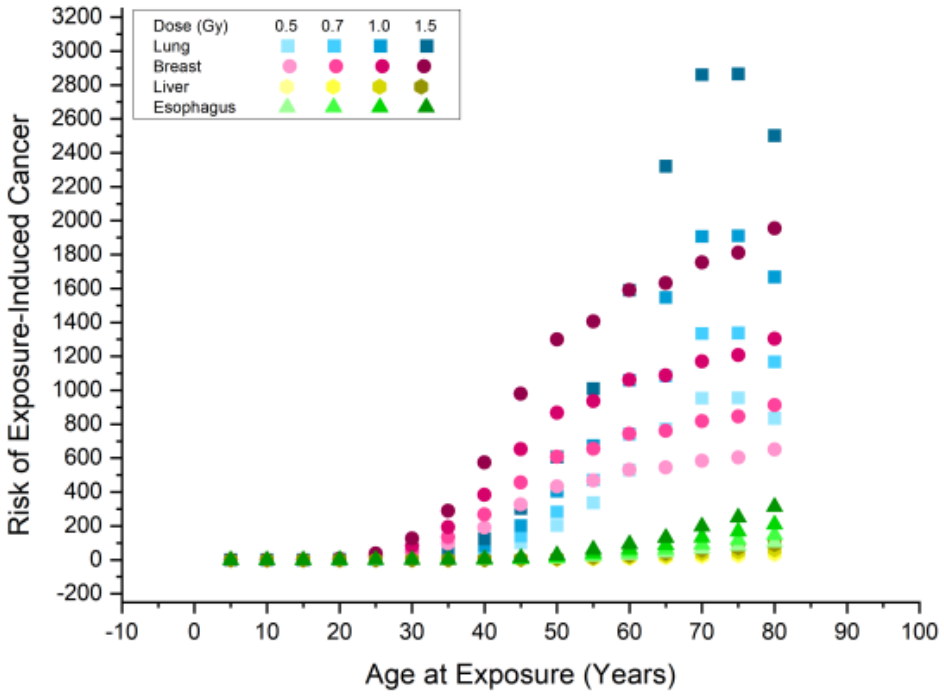
The graphs for REIC estimation were stratified for gender and technique. All graphs are functions of the age at exposure and dose for each organ. They are distributed as follows: REIC as a function of age at exposure in women using the 3DRT technique (Figure 10.a), REIC as a function of age at exposure in men using the 3DRT technique (Figure 10.b), REIC as a function of age at exposure in women using IMRT technique (Figure 10.c), and REIC as a function of age at exposure in men using IMRT technique (Figure 10.d). Tables showing REIC for each site, technique, gender, and dose, from 5 to 80 years with an interval of 5 years, are in ANNEX C. The CI is 95%.


Dose (Gy) 0.5 0.7 1.0 1.5
Lung
Breast
Liver
Esophagus
Risk of Exposure-Induced Cancer
Age at Exposure (Years)

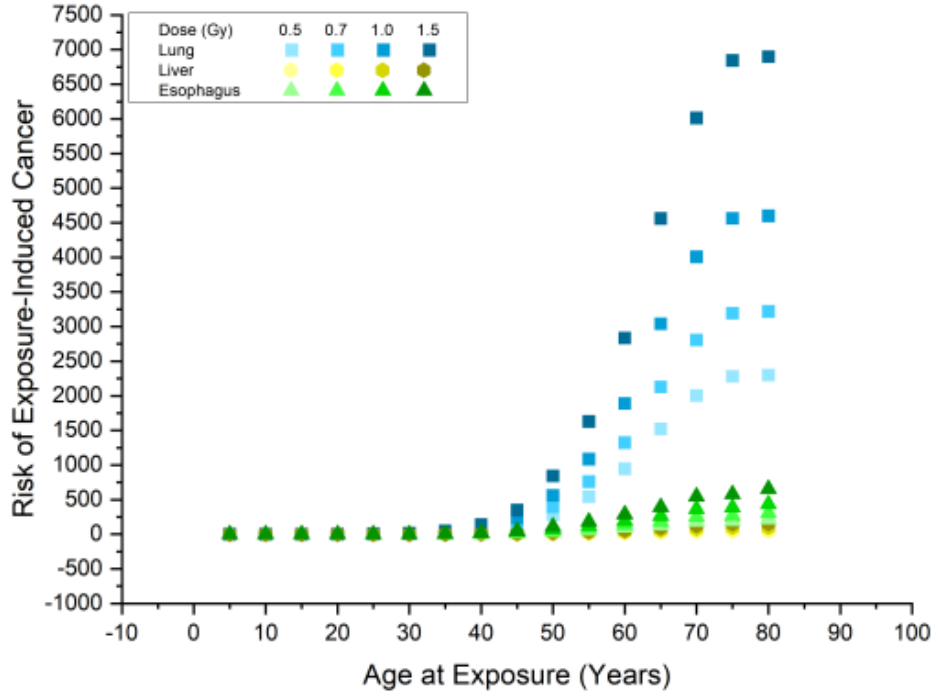
a)


Dose (Gy) 0.5 0.7 1.0 1.5
Lung
Liver
Esophagus
Risk of Exposure-Induced Cancer
Age at Exposure (Years)

b)




c)




d)

Figure 10. REIC as a function of age at exposure in a) women using the 3DRT technique, b) men using the 3DRT technique, c) women using the IMRT technique, and d) men using the IMRT technique.

For the REIC model, the RIC increases as a function of age at exposure, showing risks above 500 cases / 100,000 for ages > 50 years using a dose of 1.0 Gy or more. For women, the highest risk is for lungs and breast, where REIC is approximately 600 cases / 100,000 for ages ≥ 50 years for breast in any dose above 0.5 Gy.

Using the 3DRT technique, the REIC is higher for the breast than for the lung, approximately 700 cases / 100,000 and 500 cases / 100,000 for breast and lung, respectively, using a dose of 0.5 Gy at 60 years old in women. Using the IMRT technique, the risk is about the same at the same age. For men, the highest risk is for lung, being almost 1,000 cases / 100,000 at 60 years old using any of the techniques for 0.5 Gy. Liver and esophagus have RIC under 1,000 cases / 100,000 for any gender, age at exposure, dose, and technique, but the REIC is higher for men than for women for both organs, where for men the RIC is between 10 and 800 cases / 100,000 and for women is between 3 and 350 cases / 100,000.

The estimation calculated by the REIC model shows a RIC > 200 cases / 100,000 using a dose of 0.5 Gy and a RIC > 400 cases / 100,000 utilizing a dose of 1.0 Gy in women with ages ≥ 50 years. The RIC for lungs for 40-year-old women is 97.7% higher than for 20-year-old women and is 95% higher for 80-year-old women than for 40-year-old-women. The breast RIC for women 60 years old using 0.5 Gy is REIC = 698.01 (CI 651.91 – 734.11) using the 3DRT technique, and REIC = 530.56 (CI 499.10 – 562.02) using the IMRT technique, a risk reduction of 23.44% for IMRT technique.

The lungs REIC for 50-year-old men is 281.10 (IC 175.66 – 386.54) using 0.5 Gy in both techniques and 562.20 (CI 351.31 – 773.09) using 1.0 Gy in both techniques. The risk between 0.5 Gy and 1.0 Gy is 50% of the difference. The REIC for lung for 70-year-old men is 2003.90 (CI 1898.46 – 2109.34) and 4007.80 (CI 3796.91 – 4218.69) using 0.5 Gy and 1.0 Gy, respectively. Using a 1.0 Gy dose increases the RIC by 50% more than using a dose of 0.5 Gy for the REIC model.

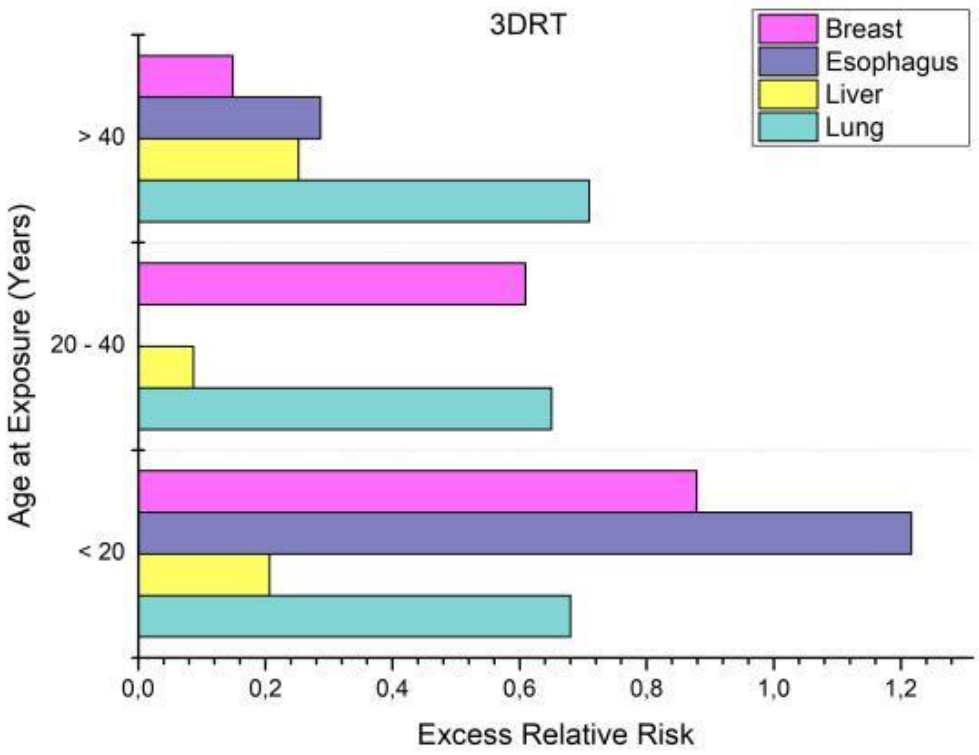
The lungs REIC in women is lower than man, about 1.78 times. For any dose and age at exposure, the organs RIC are higher in men than in women, except for the breast.

The RIC in organs increases with increasing dose and age at exposure. Lungs and breast have the highest REIC, with a difference of 23.44% between the risks for the 3DRT and IMRT techniques.

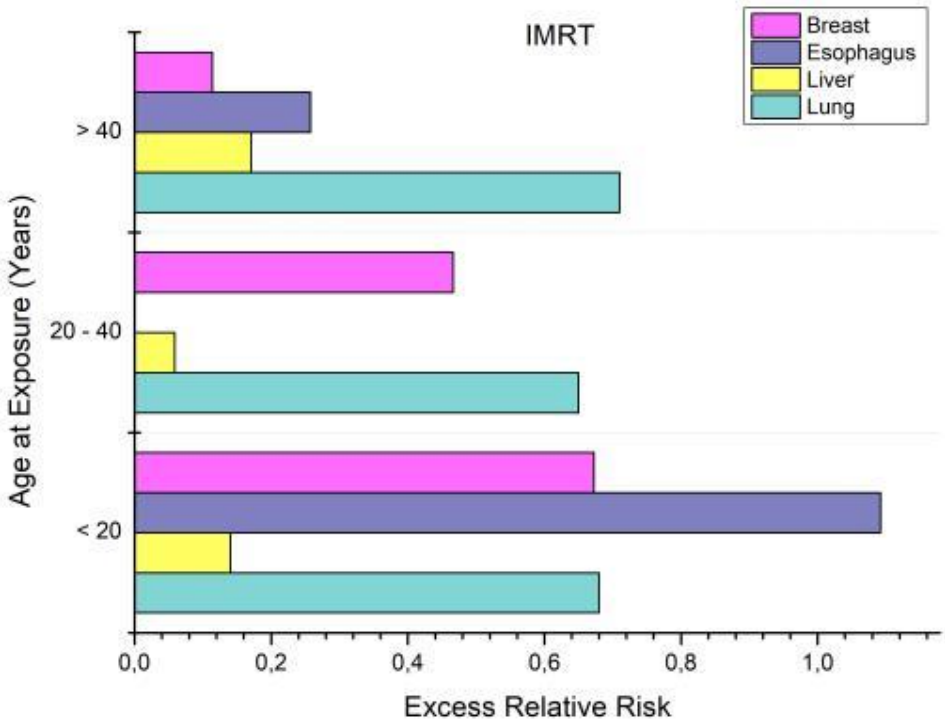
# 5 Excess Relative Risk and Excess Absolute Risk

The graphs are distributed as follows: ERR as a function of age at exposure using the 3DRT technique (Figure 11.a), ERR as a function of age at exposure using the IMRT technique (Figure 11.b), EAR as a function of age at exposure 3DRT technique (Figure 11.c), and EAR as a function of age at exposure using IMRT technique (Figure 11.d).

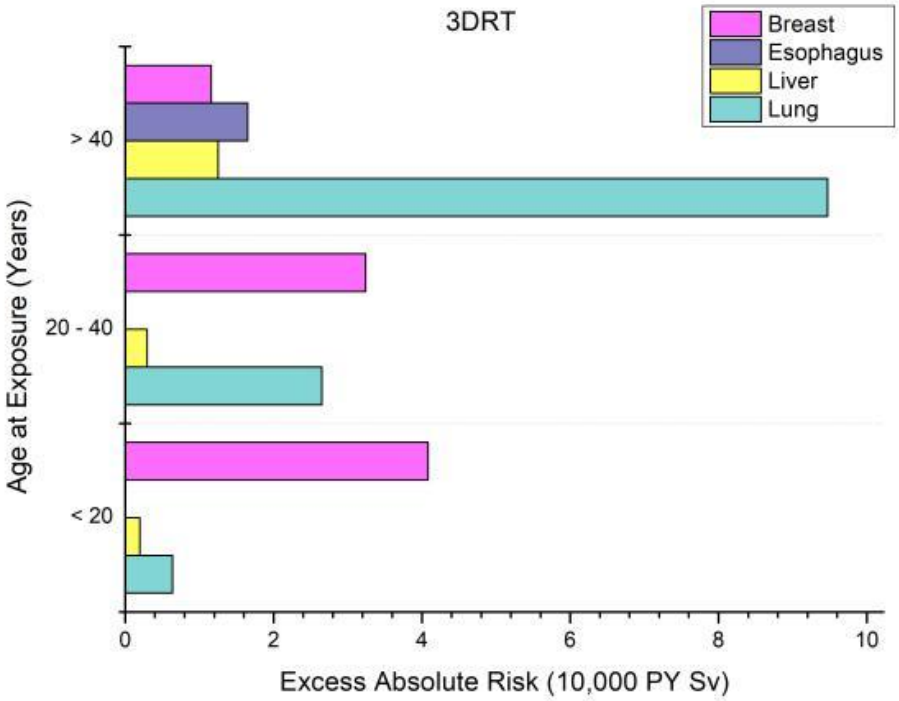
The ERR and EAR estimates were evaluated in a 20 years range group (20 years, between 20 and 40 years, and above 40 years). Tables showing ERR and EAR for each technique and site with a 95% of the CI are in ANNEX D.



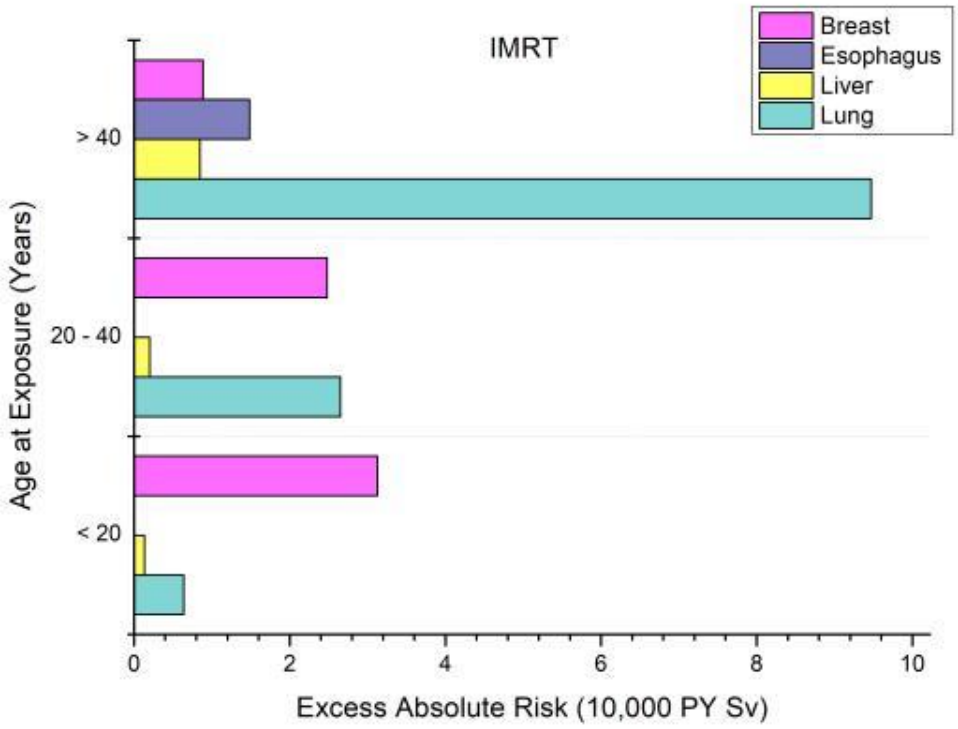

a)


IMRT
Breast
Esophagus
Liver
Lung
> 40
20 - 40
< 20
Age at Exposure (Years)
0,0
0,2
0,4
0,6
0,8
1,0
Excess Relative Risk

b)


3DRT
Breast
Esophagus
Liver
Lung
> 40
20 - 40
< 20
Age at Exposure (Years)
0
2
4
6
8
10
Excess Absolute Risk (10,000 PY Sv)

c)




d)

Figure 11. EAR and ERR as a function of age at exposure at 1 Gy for 3DRT and IMRT techniques. a) ERR for 3DRT, b) ERR for IMRT, c) EAR for 3DRT, and d) EAR for IMRT

For EAR estimates, a significant incidence of lung cancer is expected when increasing the age at exposure. The incidence of liver cancer is significant for ages > 40 years, while the incidence of breast cancer is significant at younger ages at exposure. The incidence of esophagus cancer is only notified for ages > 40 years. For ERR estimates, there are substantial incidences of lung and breast cancers, where the incidence of the lung is almost constantly over ages at exposure. The incidence of breast cancer decreases when the age at exposure increases.

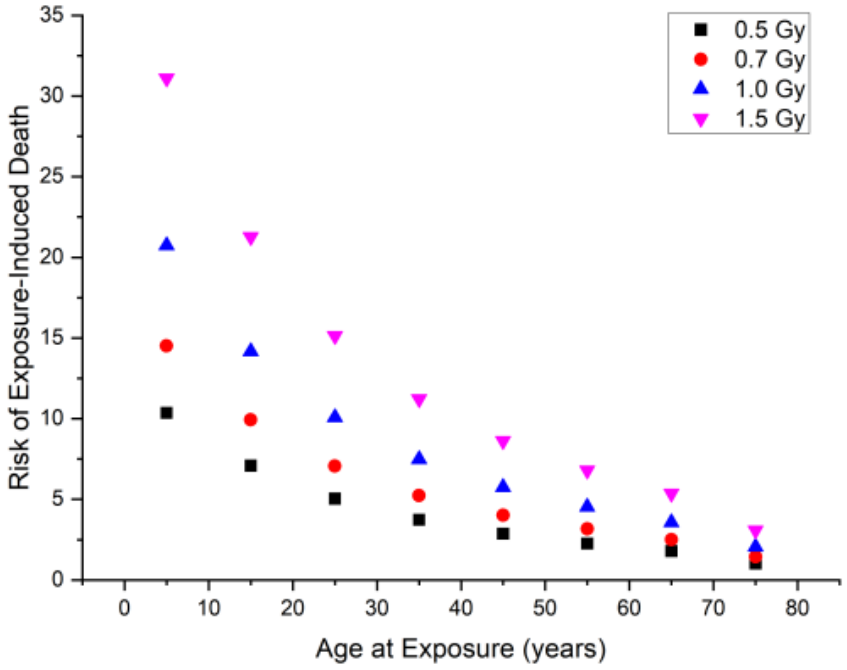
Irradiation of the lung with a 1.0 Gy dose prescription results in an EAR = 9.47 (CI 5.75 – 13.78) $10^4$ PY Sv for 3DRT for ages > 40 years, an ERR = 0.68 (CI 0.28 – 1.20) for ages < 20 years, and 0.78 (CI 0.40 – 1.09) for ages > 40 years. The breast highest risk induced cancer for the 3DRT technique is for ages at exposure until 40 years, with an EAR = 4.08 (CI 3.04 – 5.25) $10^4$ PY Sv and an ERR = 0.88 (CI 0.64 – 1.16) for ages < 20 years. Estimates of liver cancer for the 3DRT technique show an EAR < 2.00 $10^4$ PY Sv and an ERR = 0.25 (CI 0.06 – 0.51) for ages > 40 years. Incidences of esophagus cancer result in an EAR = 1.65 (CI 0.40 – 3.42) $10^4$ PY Sv for ages > 40 years and an ERR = 1.22 (CI 0.38 – 6.45) for ages < 20 years.

Irradiation of the lung for the IMRT technique with a 1.0 Gy dose prescription also results in an EAR = 9.47 (CI 5.75 – 13.78) and an ERR = 0.71 (CI 0.40 – 1.09) for ages > 40 years. For ages < 20 years, the EAR is 3.13 (CI 2.33 – 4.02) $10^4$ PY Sv, and the ERR is 0.67 (0.49 – 0.89) for the risk estimation of breast-induced cancer. The liver risk of induced cancer shows an EAR = 0.85 (CI 0.01 – 1.89) $10^4$ PY Sv and an ERR = 0.17 (CI 0.04 – 0.34) for ages > 40 years. An estimation of the esophagus risk-induced cancer results in an EAR = 1.48 (CI 0.36 – 3.07) $10^4$ PY Sv and an ERR = 1.09 (CI 0.34 – 2.20) for ages < 20 years.

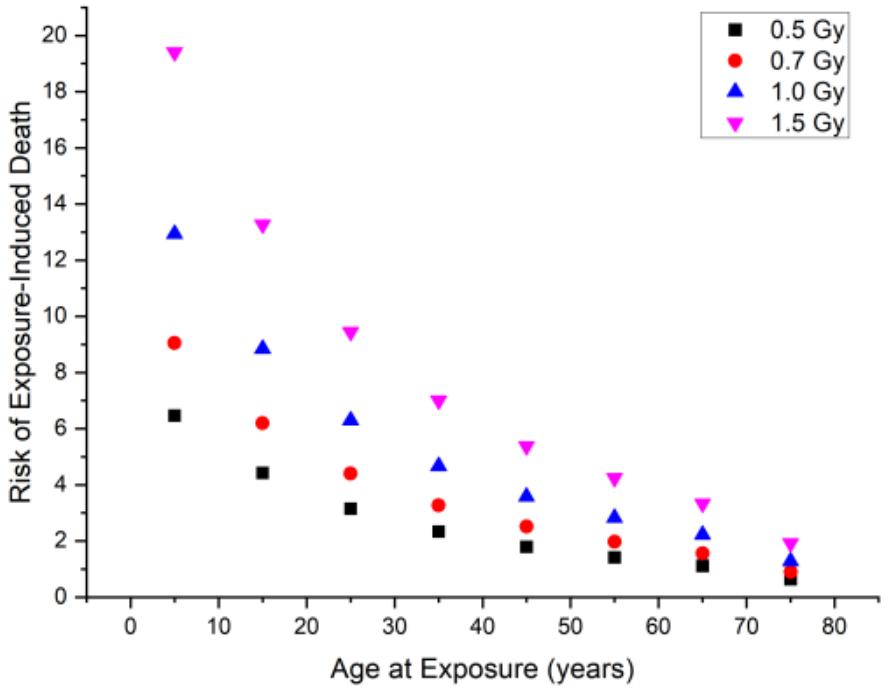
# 6 Risk of Exposure-Induced Death

The graphs for REID estimation were stratified for technique. All graphs are functions of the age at exposure and dose for each organ. They are distributed as follows: REID as a function of age at exposure using the 3DRT technique (Figure 12.a), and REID as a function of age at exposure using the IMRT technique (Figure 12.b). The REID estimates were evaluated for ages between 5 and 75 years. Tables showing REID for each technique with a CI of 95% are in ANNEX E.

Using the 3DRT technique, REID varies between 1 and 31 cases / 100,000, and using the IMRT technique, REID goes in a range between 0.6 and 20 cases / 100,000.




a)




b)

Figure 12. REID as a function of age at exposure a) using the 3DRT technique, and b) using the 3DRT technique.

The RIC in the REID model decreases as a function of the age at exposure and increases in the function of dose. For young people, REID is > 3 cases / 100,000 and > 6 cases / 100,000 for 0.5 Gy and 1.0 Gy, respectively. For a person with 65 years, REID is between 1 and 4 cases / 100,000 for the IMRT technique and between 1.5 and 6 cases / 100,000 for the 3DRT technique.

The REID for a 25-year-old person is 5.05 (CI 4.28 – 5.82) and 3.15 (CI 2.67 – 3.63) using a dose of 0.5 Gy for 3DRT and IMRT techniques, respectively. For a dose of 1.0 Gy, the REID is 10.09 (CI 8.56 – 11.62) and 6.30 (CI 5.34 – 7.26) for 3DRT and IMRT techniques, respectively. For 45-year-olds, the REID is 2.88 (CI 2.11 – 3.65) and 1.79 (CI 1.31 – 2.27), respectively, using a dose of 0.5 Gy for 3DRT and IMRT techniques. For a dose of 1.0 Gy, the REID is 5.75 (CI 4.22 – 7.28) and 3.59 (CI 2.63 – 4.55) for 3DRT and IMRT techniques, respectively.

The REID for 1.0 Gy is 49,9% higher than 0.5 Gy for the 3DRT technique, and the REID for 1.0 Gy is 50% higher than 0.5 Gy for the IMRT technique. The REID is above 1.75 times higher for a 25-year-old person than a 45-year-old person.

# CHAPTER 5 - Discussion

The chemical manifestations of ionizing radiation in the cell can cause several changes. In radiotherapy treatment, ionizing radiation is the key to damaging cancer cells and stopping their multiplication in the organism. On the other hand, damage can occur in healthy cells, which are repaired in the short or long term, and may or may not undergo genetic mutations. These structural changes in cells include hydrogen bond breaking, molecular breakdown or breakdown, and intermolecular and intramolecular crosslinking. [6,17]

For radiotherapy treatment, ionizing radiation strikes a DNA molecule, ionizing the contained water and producing a chain of reactions with oxygen. In addition to damaging DNA and other biomolecules, the chain of responses sends signals that affect systems in both irradiated and non-irradiated areas. Breaking the hydrogen bonds that unite base pairs in DNA can lead to irreversible alterations in the secondary and tertiary structure of the molecule that compromise genetic transcription and translation. A low dose of ionizing radiation creates a burst of circumstances, and the chain of reactions with oxygen is adequate to stimulate systems and produce observable health benefits. [6,17]

Over the past decades, data collected from animals and human cells have shown that the use of low-dose ionizing radiation (up to 0.3 Gy) stimulates every component of systems, antioxidants, enzyme repair, and immunological and apoptotic removal of the alteration of the organism. [6]

Potential cellular responses after radiation exposure are varied, such as DNA mutations, reproductive failure, genomic instability, damage to neighboring non-radiating cells, and adaptive responses. Ionizing radiation can cause damage whose expression is delayed for years or decades. The ability of ionizing radiation may increase the risk of cancer years after exposure, and as is well known, cancer is the most critical delayed somatic effect of radiation exposure. So, the importance of discussing the determinants of RIC. [17]

Although at high doses, the response of the biological effects as a function of the dose is better pre-established because these effects are faster and visible in a short period of time, for low doses, this determination is more complex.

Epidemiological studies show that the risks from exposure to low doses are small, but it is impossible to determine precisely how small they are. Data covering responses to low doses are

often insufficient, as it is very difficult to detect an increase in the cancer rate at low doses, and its latency period is long. [17] Therefore, using more extensive statistical data where a large population has been irradiated is necessary.

Currently, the population that best forms the basis of epidemiological investigation of the biological effects of ionizing radiation comes from the LSS cohort of survivors of the atomic bomb explosions in Hiroshima and Nagasaki.

The epidemiological studies addressed in this work differ in their responses to some parameters. However, it is worth mentioning that each study is based on a mathematical model and uses different factors to determine the data. As the main purpose is to investigate the RIC for COVID-19 patients treated with low-dose whole-lung based on a virtual simulation, we can use each study to analyze the risks and compare them.

Each organ has a different radiosensitivity, so it is important to individualize the estimate of the probability of risk of inducing cancer and other diseases due to exposure to each type of tissue. This data makes it possible to understand the toxicity of radiotherapy treatment and to try to save more healthy tissue as possible, particularly in the case of treating lung inflammation due to COVID-19, where the patient will receive a maximum of two fractions of radiation.

A priori, estimates were calculated only for doses being varied only in the PTV, so for the ELR method we do not have dose values varying for the OARs, only the average doses generated by the virtual simulation. The ELR (%) is higher for people ≥ 60 years old than for young people, that is, the percentage of developing cancer is higher for people ≥ 60 years old. In this case, the factors to be considered are biological. Biologically, radiation risks after exposure in younger individuals are dominated by initiating processes, while the promotion of pre-existing malignant cells influences the risks in middle age. [10] The mathematical models add that increasing age increases the probability of a person having cells predisposed to cancer induction, which increases the probability of cancer risk induced with increasing age.

ELR increases with increasing dose, which is to be expected, as the higher the dose, the more likely the cell will suffer some damage and possibly mutate the DNA. [18]

For lungs, the risk increases while increasing the dose, which is to be expected for any organ. The liver is more radiosensitive than other organs, which can be verified by its high ELR. [18,19]

The RIC has a higher LAR for young people ≤ 30 years old than for people aged ≥ 60 years old due to two factors to be considered: The first cause is that younger tissue undergoes biological effects from ionizing radiation in a more reparative than apoptotic way, i.e., when young tissue receives ionizing radiation, it is more likely to repair the damage than the cell undergoes apoptosis, thus increasing the likelihood of developing cancer. As Sadetzki et al. (2009) presented, children are more susceptible to developing induced cancer from ionizing radiation because their tissues are still developing. The studies from Shimizu et al. (1991) and Hall (2002) emphasize through data analysis that young people are more sensitive to ionizing radiation. The second cause, and more likely, is statistics since the follow-up of older people is shorter than that of younger people; that is if the follow-up is 10 years, a 20-year-old exposed person has more likely to be evaluated after this period than a 70-year-old person, who is of a certain advanced age and more likely not to live during this follow-up.

The LAR increases linearly with the increase in the dose. The parameter that characterizes the dose dependence decreases with the increase in the age of exposure, which shows us that the dose and the age of exposure, factors that multiply in the LAR function, are important endpoints for radiotherapy treatment for inflammation due to COVID-19. The younger the exposure age and the higher the dose, the higher the LAR value and, thus, the higher the RIC. But, the higher the exposure age and the lower dose, the lower the LAR value and thus, the lower the RIC. However, effects and damage can occur at low doses, regardless of the age of exposure, as described in Suzuki et al. (2012) and Mullenders et al. (2009).

The RIC has a higher LAR for women than for men due to a factor to be considered: statistics; since women are more careful with their health and undergo routine examinations more regularly than men, which end up having a greater number of diagnoses in women than in men [20,26,27,28]. The age of exposure in women has a mitigating factor due to exposure of the breast since the breast is a very sensitive organ, especially in growing women, ≤ 20 years, where the breast tissue is also developing. And studies show differences between both genders in response to ionizing radiation, reporting that women may be more radiosensitive than men. [20]

In the LAR method, both dose and age of exposure influence the RIC for the organs, with the RIC increasing about 1.5x with increasing dose and decreasing with age at exposure. For the treatment of pulmonary inflammation, the lung and breast are the organs with the highest RIC, and as for this treatment, the PTV is the total volume of the lungs, the lowest possible dose

should be used, and the breast volume should be saved as much as possible, especially in young people.

For the REIC model, the RIC increases as a function of age at exposure, which may have been determined by the committee´s detriment factor. [12] REIC increases with increasing doses, which is to be expected, as described in Mettler et al. (2012).

Using the 3DRT technique, the REIC is higher for the breast than for the lung, and using the IMRT technique, the risk is about the same at the same age. With the IMRT technique, it is possible to delimit the organs' dose better by concentrating it in the PTV, thus sparing the OAR. [29,30]

For any dose and age at exposure, the men's organs RIC are higher than for women, except for the breast. The breast is a potentially radiosensitive organ, but the high RIC for men contradicts what is expected in the literature. [20]

For EAR estimates, a significant incidence of lung cancer is expected when increasing age at exposure. The incidence of breast cancer is significant at the younger ages at exposure. For ERR estimates, there are significant incidences of lung and breast cancers, and the incidence of breast cancer decreases when increasing the age at exposure. [31,32,33]

For the REID model, the RIC decreases as a function of the age at exposure and increases with dose. The first finding is statistical since older people's follow-up is shorter than younger people. The second finding is as expected, as well known that cell damage increases with increasing dose, so the risk of developing cancer increases with increasing dose. [18]

The RIC in the REID model is higher using the 3DRT technique than in IMRT. As it is well known, the IMRT technique can delimit the organs, sparing the organs at risk. [29,30]

Comparing estimates for a prescribed dose of 1 Gy in the whole lung, the ELR, REIC, ERR, and EAR estimates increase with increasing age at exposure (Table 3), and LAR and REID decrease with age at exposure.

If we consider that 100,000 persons represent 100% of the sampling, then LAR estimates the highest number of cases per 100,000 persons, and REID estimates the lowest number per 100,000 persons aged 30 years. For age 60 years, REIC estimates the highest number of cases per 100,000 persons, and REID continues to estimate the lowest number per 100,000 persons.

Table 3. Comparison between estimates for a whole-lung prescribed dose of 1 Gy.

| Estimation | 30 years | 60 years |
|---|---|---|
| ELR (%) | 0.96 | 1.98 |
| LAR (cases / 100,000) | 1735 | 1450 |
| REIC (cases / 100,000) | 10.15 | 1475 |
| ERR (%) | 0.65 | 0.71 |
| EAR (10,000 PY Gy) | 2.65 | 9.47 |
| REID (cases / 100,000) | 7.48 | 3.57 |

In addition to the dose and type of tissue, which are factors whose characteristics are well known, the age of exposure is also a relevant factor that should be explored.

The time of manifestation of some effect or disease after exposure to low doses is also a factor that must be explored and not only added as a parameter to analyze the risks when calculating the risk estimation. Focusing on the follow-up can be a key to a better understanding on how the body responds to low-dose radiation.

A review was conducted in PubMed (U.S. National Library of Medicine, Washington, DC, USA), Scholar Google, and Clinical Research of National Institutes of Health (NIH), searching papers published between 2020 and 2022 to investigate the effects using low-dose radiotherapy as an anti-inflammatory treatment in patients with COVID-19 pneumonia.

Searches of the PubMed, Scholar Google, and Clinical Research of NIH database were conducted during the project development (2020 – 2022) using the terms “covid-19” AND “radiotherapy” AND “low-dose” AND “clinical trials” OR “clinical trials” AND “covid-19” AND “low-dose”, only papers published since 2020. One hundred thirteen articles were published in PubMed in these categories; 203 articles were published in Scholar Google; and 146 studies were registered in Clinical Research of NIH.

The exclusion criteria were: (1) Studies that didn’t describe the dose (Gy), age of the patients, and their health conditions, and (2) studies that didn’t publish results yet. A total of 17 studies

met the first criterion, and just 10 met the second criterion (Figure 13). Given the considerations, an investigation was conducted about the effects and results of using low-dose for anti-inflammatory treatment in patients with COVID-19.

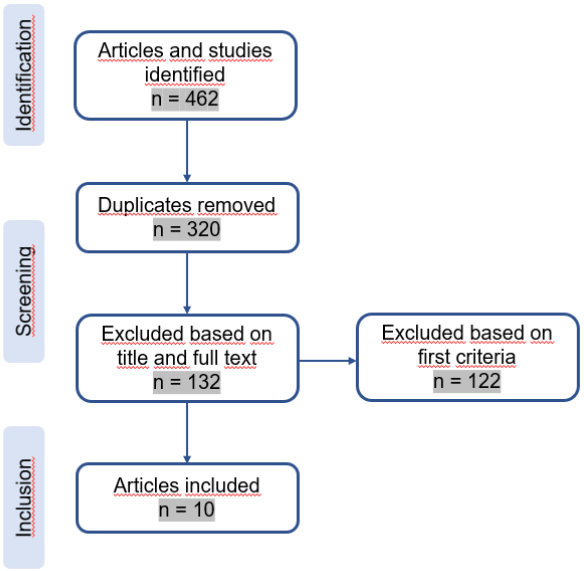



Figure 13. Development of the review.

The review's first step was to study each clinical trial's design, including the inclusion and exclusion criteria, the radiotherapy treatment technique, the dose (Gy), and outcome measures. The next step was to analyze the results of each clinical trial based on the number of deaths, follow-up, hospital discharge days after the treatment, improve of symptoms, and any adverse event post-treatment.

Tables F.1 and F.2 (ANNEX F) summarize the study design and clinical trials results. All clinical trials introduced evaluate the efficacy of low-dose whole-lung irradiation in patients with COVID-19 pneumonia as the main purpose, where 30% used a dose of 0.5 Gy, and 40% used a dose of 1.5 Gy, being a total of 50% using doses ≥ 1.0 Gy. 80% of clinical trials used 3DRT as the radiotherapy treatment. The chosen patients were those who, for the most part, were in a worse state of health and who had not improved with any other previous treatment. The outcome measures imperatively included $O_2$ saturation and CRP test for COVID-19.

Most results showed deaths after radiotherapy treatment, about 90% of clinical trials, with an average of 3.9 deaths per study. Table 4 shows the number of patients who were recruited and received low-dose radiation for the treatment of COVID-19 pneumonia, the number of deaths

after the intervention, and the percentage of deaths per number of recruited patients that received low-dose radiation.

Table 4. Percentage of deaths after low-dose radiation intervention

| Author | Recruited patients | Deaths | % Deaths per recruited patients |
|---|---|---|---|
| Papachristofilou et al. | 11 | 6 | 55 |
| Moreno-Olmedo et al. | 2 | 0 | 0 |
| Sharma et al. | 10 | 1 | 10 |
| Hess et al. | 10 | 1 | 10 |
| Sanmamed et al. | 9 | 2 | 22 |
| Ameri et al. (2020) | 5 | 1 | 20 |
| Arenas et al. (2021) | 36 | 8 | 22 |
| Darzikolaee et al. (2021) | 11 | 9 | 82 |
| Ganesan et al. (2021) | 25 | 3 | 12 |
| Ortiz et al. (2021) | 31 | 8 | 26 |
| TOTAL | 150 | 39 | 26 |

The median time to clinical recovery was three days in about 30% of clinical trials and 24 hours in about 30%. The average median follow-up was 39.4 days; about 80% did not observe any adverse event. However, one clinical trial observed acute gastrointestinal toxicity in one patient, and the other two patients developed lymphopenia in another trial.

This review aimed to investigate whether the doses used in clinical trials justified the practice through the numbers of clinical recovery, deaths, and recovery period.

Based on the results, it was concluded that the number of patients recruited demonstrates a low sample size. The number of deaths by patients treated with low-dose radiation shows that the treatment is ineffective, especially for patients with severe clinical conditions.

A potential portion of the clinical trials used doses above the recommended by the published studies that analyzed old studies with ionizing radiation [5] but recruited patients who had no clinical improvement with other treatments. If radiotherapy treatment had improved their health, it could be an option to treat patients with COVID-19 pneumonia. The results show clinical improvement, as recorded in Table F.2. As mentioned in Kolahdouzan et al. (2022) [44], for patients who presented clinical improvement, there was a significant reduction in the intubation period.

The conclusion between the published systematic reviews [44,45] and this work´s systematic review is unfavorable for using low-dose radiation to treat patients with COVID-19 pneumonia. While the publications focused on analyzing biological results, the focus of the systematic review of this work was to investigate whether the doses used in clinical trials justified the practice. The estimates calculated based on the doses of the clinical trials showed that the treatment is not justifiable.

Patients who recovered had a quick recovery time, with few instances of adverse events. However, the few results from clinical trials were unfavorable, as there were potential deaths even after low-dose radiotherapy treatment to the whole lung. This fact was also verified and concluded by Kolahdouzan et al. (2022) [44] and Mortazavi et al. (2022) [45].

# CHAPTER 6 - Conclusion

From the initial endpoint, patients treated with low-dose radiation for COVID-19 pneumonia may have a potential likelihood of RIC and a risk of developing heart disease. Epidemiologically, young people and women are more likely to have RIC due to exposure to ionizing radiation and risk of developing heart disease, as shown by the LAR and REID estimates, where the RIC decreases as a function of age at exposure and is approximately two times higher for women. On the other hand, including genetic and biological factors, elderly people also have potential RIC from exposure to ionizing radiation, as evidenced by the ELR and REIC estimates. The EAR and ERR estimate show significant RIC for exposure to ionizing radiation for the lung and breast, the organs with the highest potential risk for this practice. The treatment technique influences the RIC, so the contributing factor is the dose, whereas, in the IMRT technique, it can be better conformed, thus reducing the dose delivered to the OARs. However, treatment with the IMRT technique increases cost-effectiveness.

As investigated, many factors can contribute to formulating a mathematical model capable of calculating RIC estimates, which can directly or indirectly contribute to the results of estimates in epidemiological studies. Some models are based only on epidemiological data, while others use mathematical models covering biological and genetic factors. However, there is still a lack of data, such as epidemiological data on RIC from low-dose radiation exposure and the contribution of hereditary factors.

Considering the limitations (practical and inherent) to epidemiological investigation for RIC at low doses, factors such as the epidemiological data collected from high-dose exposures, differences between populations, and environmental and genetic factors influence and limit accurate conclusions. Clinical trials have not shown favorable results for using low-dose to treat patients with COVID-19 pneumonia. First, because there were many deaths after treatment, and second, the number of patients was potentially too low to consider a quality sample.

Therefore, considering the limitations of epidemiological studies in formulating mathematical models and the low sampling of data from clinical trials, treatment with low-dose ionizing radiation for patients with pneumonia due to COVID-19 is not justifiable.

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# ANNEX A

This annex contains the estimative of relative increased risk by ELR results as a function of age at exposure (years), stratified by dose (Gy), gender, and site.

Table A.1. Estimative of relative increased risk (%) of RIC by ELR for whole lung treatment dose of 0.5 Gy for both genders.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | 20 - 45 | 45 - 65 | 65 - 75 |
| **Female** | | | |
| **Lung** | 0.94 (0.89 – 1.00) | 1.12 (0.46 – 1.78) | 1.69 (0.00 – 3.70) |
| **Breast** | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) |
| **Liver** | 6.88 (6.83 – 6.94) | 7.85 (7.19 – 8.51) | 11.08 (9.06 – 13.10) |
| **Esophagus** | 0.22 (0.19 – 0.25) | 0.33 (0.17 – 0.49) | 1.59 (0.60 – 2.57) |
| **Male** | | | |
| **Lung** | 0.92 (0.91 – 0.93) | 1.19 (1.03 – 1.34) | 1.94 (1.21 – 2.67) |
| **Liver** | 6.48 (6.31 – 6.64) | 8.01 (7.11 – 8.90) | 12.32 (9.60 – 15.03) |
| **Esophagus** | 0.81 (0.80 – 0.82) | 1.15 (0.85 -1.45) | 3.18 (1.67 – 4.70) |

All values are followed by a parenthesis with the 95% confidence interval

Table A.2. Estimative of relative increased risk (%) of RIC by ELR for whole lung treatment dose of 0.7 Gy for both genders.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | 20 - 45 | 45 - 65 | 65 - 75 |
| **Female** | | | |
| **Lung** | 0.96 (0.90 – 1.01) | 1.15 (0.48 – 1.81) | 1.76 (0.00 – 3.79) |

| | | | |
|---|---|---|---|
| **Breast** | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) |
| **Liver** | 6.88 (6.83 – 6.94) | 7.84 (7.18 – 8.51) | 11.09 (9.06 – 13.12) |
| **Esophagus** | 0.21 (0.19 – 0.23) | 0.33 (0.21 – 0.45) | 1.53 (0.53 – 2.54) |
| **Male** | | | |
| **Lung** | 0.93 (0.92 – 0.94) | 1.22 (1.07– 1.37) | 2.03 (1.29 – 2.76) |
| **Liver** | 6.48 (6.31 – 6.64) | 8.00 (7.10 – 8.90) | 12.34 (9.61 – 15.07) |
| **Esophagus** | 0.78 (0.76 – 0.80) | 1.09 (0.79 -1.39) | 3.15 (1.60 – 4.69) |

All values are followed by a parenthesis with the 95% confidence interval

Table A.3. Estimative of relative increased risk (%) of RIC by ELR for whole lung treatment dose of 1.0 Gy for both genders.

| | **Age at Exposure (years)** | | |
|---|---|---|---|
| **Cancer site** | 20 - 45 | 45 - 65 | 65 - 75 |
| **Female** | | | |
| **Lung** | 0.97 (0.92 – 1.02) | 1.18 (0.51 – 1.84) | 1.84 (0.00 – 3.89) |
| **Breast** | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) | 0.02 (0.02 – 0.03) |
| **Liver** | 6.88 (6.83 – 6.94) | 7.83 (7.17 – 8.50) | 11.10 (9.05 – 13.15) |
| **Esophagus** | 0.23 (0.19 – 0.27) | 0.39 (0.33 – 0.44) | 1.46 (0.43 – 2.49) |
| **Male** | | | |
| **Lung** | 0.95 (0.94 – 0.96) | 1.25 (1.10 – 1.40) | 2.12 (1.29 – 2.76) |
| **Liver** | 6.47 (6.31 – 6.63) | 7.99 (7.09 – 8.89) | 12.36 (9.60 – 15.12) |
| **Esophagus** | 0.74 (0.71 – 0.76) | 1.00 (0.70 -1.30) | 3.09 (1.51 – 4.67) |

All values are followed by a parenthesis with the 95% confidence interval

# ANNEX B

This annex contains LAR results as a function of age at exposure (years), stratified by dose (Gy), technique, gender, and site.

Table B.1. Cancer risk estimated by LAR (cases / 100,000) for 3DRT whole lung treatment dose of 0.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 2520 (2418.07 - 2621.93) | 1730 (1628.07 - 1831.93) | 1210 (1108.07 - 1311.93) | 1200 (1098.07 - 1301.93) | 1150 (1048.07 - 1251.93) | 1005 (903.07 - 1106.93) | 735 (633.07 - 836.93) | 385 (283.07 - 486.93) |
| **Breast** | 1655.4 (1561.01 - 1749.79) | 997.43 (903.04 - 1091.82) | 588.23 (493.84 - 982.62) | 327.83 (233.44 - 422.22) | 162.75 (68.36 - 257.14) | 72.08 (-22.31 - 166.47) | 27.90 (-66.49 - 122.29) | 9.30 (-85.09 - 103.69) |
| **Liver** | 41.30 (39.64 - 42.96) | 28.91 (27.25 - 30.57) | 20.65 (18.99 - 22.31) | 20.65 (18.99 - 22.31) | 18.59 (16.93 - 20.25) | 14.46 (12.80 - 16.12) | 10.33 (8.67 - 11.99) | 4.13 (2.47 - 5.79) |
| **Esophagus** | 312.84 (300.34 - 325.34) | 225.94 (213.44 - 238.44) | 156.42 (143.9 - 168.92) | 152.08 (139.58 - 164.58) | 139.04 (126.9 - 151.54) | 117.32 (104.82 - 129.82) | 82.56 (70.06 - 95.06) | 47.80 (35.30 - 60.30) |
| **Male** | | | | | | | | |
| **Lung** | 1080 (1036.67 - 1123.33) | 745 (701.67 - 788.33) | 525 (481.67 - 568.33) | 520 (476.67 - 563.33) | 505 (461.67 - 548.33) | 445 (401.67 - 488.33) | 325 (281.67 - 368.33) | 170 (126.67 - 213.33) |
| **Liver** | 88.80 (85.03 - 92.57) | 61.95 (58.18 - 65.72) | 45.43 (41.66 - 49.20) | 43.37 (39.60 - 47.14) | 39.24 (35.47 - 43.01) | 28.91 (25.14 - 32.68) | 16.52 (12.75 - 20.29) | 6.20 (2.43 - 9.97) |
| **Esophagus** | 238.98 (229.42 - 248.54) | 173.80 (164.24 - 183.36) | 121.66 (112.10 - 131.22) | 117.32 (107.76 - 126.88) | 108.63 (99.07 - 118.19) | 86.90 (77.34 - 96.46) | 60.83 (51.27 - 70.39) | 30.42 (20.86 - 39.98) |

All values are followed by a parenthesis with the 95% confidence interval

Table B.2. Cancer risk estimated by LAR (cases / 100,000) for IMRT whole lung treatment dose of 0.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 2520 (2418.07 - 2621.93) | 1730 (1628.07 - 1831.93) | 1210 (1108.07 - 1311.93) | 1200 (1098.07 - 1301.93) | 1150 (1048.07 - 1251.93) | 1005 (903.07 - 1106.93) | 735 (633.07 - 836.93) | 385 (283.07 - 486.93) |
| **Breast** | 1267.36 (1195.09 - 1339.63) | 763.62 (691.35 - 835.89) | 450.34 (378.07 - 522.61) | 250.98 (178.71 - 323.25) | 124.60 (52.33 - 196.87) | 55.18 (-17.09 - 127.45) | 21.36 (-50.91 - 93.63) | 7.12 (-65.15 - 79.39) |
| **Liver** | 28.00 (26.87 - 29.13) | 19.60 (18.47 - 20.73) | 14.00 (12.87 - 15.13) | 14.00 (12.87 - 15.13) | 12.60 (11.47 - 13.73) | 9.80 (8.67-10.93) | 7.00 (5.87 - 8.13) | 2.80 (1.67 - 3.93) |
| **Esophagus** | 280.80 (269.58 - 292.02) | 202.80 (191.58 - 214.02) | 140.40 (129.18 - 151.62) | 136.50 (125.28 - 147.72) | 124.80 (113.58 - 136.02) | 105.30 (94.8 - 116.27) | 74.10 (62.88 - 85.32) | 42.90 (31.68 - 54.12) |
| **Male** | | | | | | | | |
| **Lung** | 1080 (1036.67 - 1123.33) | 745 (701.67 - 788.33) | 525 (481.67 - 568.33) | 520 (476.67 - 563.33) | 505 (461.67 - 548.33) | 445 (401.67 - 488.33) | 325 (281.67 - 368.33) | 170 (126.67 - 213.33) |
| **Liver** | 60.20 (57.64 - 62.76) | 42 (39.44 - 44.56) | 30.80 (28.24 - 33.36) | 29.40 (26.84 - 31.96) | 26.60 (24.04 - 29.16) | 19.60 (17.04 - 22.16) | 11.20 (8.64 - 13.76) | 4.20 (1.64 - 6.76) |
| **Esophagus** | 214.50 9205.91 - 223.09) | 156 (147.41 - 164.59) | 109.20 (100.61 - 117.79) | 105.30 (96.71 - 113.89) | 97.50 (88.91 - 106.09) | 78 (69.41 - 86.59) | 54.60 (54.60 - 63.19) | 27.30 (18.71 - 35.89) |

All values are followed by a parenthesis with the 95% confidence interval.

Table B.3. Cancer risk estimated by LAR (cases / 100,000) for 3DRT whole lung treatment dose of 0.7 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 3528 (3385.29 - 3670.71) | 2422 (2279.29 - 2564.71) | 1694 (1551.29 - 1836.71) | 1680 (1537.29 - 1822.71) | 1610 (1467.29 - 1752.71) | 1407 (1264.29 - 1549.71) | 1029 (886.29 - 1171.71) | 539 (396.29 - 681.71) |
| **Breast** | 2317.56 (2185.41 - 2449.15) | 1396.40 (1264.25 - 1528.15) | 823.52 (691.37 - 955.67) | 458.96 (326.81 - 591.11) | 227.85 (95.70 - 359.95) | 100.91 (-31.24 - 233.06) | 39.06 (-93.09 - 171.21) | 13.02 (-119.13 - 145.17) |
| **Liver** | 57.82 (55.49 - 60.15) | 40.47 (38.14 - 42.80) | 28.91 (26.58 - 31.24) | 28.91 (26.58 - 31.24) | 26.02 (23.69 - 28.35) | 20.24 (17.91 - 22.57) | 14.46 (12.13 - 16.79) | 5.78 (3.45 - 8.11) |
| **Esophagus** | 437.98 (420.49 - 455.47) | 316.32 (298.83 - 333.81) | 218.99 (201.50 - 236.48) | 212.91 (195.42 - 230.40) | 194.66 (177.17 - 212.15) | 164.24 (146.75 - 181.73) | 115.58 (98.09 - 133.07) | 66.91 (49.42 - 84.40) |
| **Male** | | | | | | | | |
| **Lung** | 1512 (1451.4 - 1572.66) | 1043 (982.34 - 1103.66) | 735 (674.34 - 795.66) | 728 (667.34 - 788.66) | 707 (646.34 - 767.66) | 623 (562.34 - 683.66) | 455 (394.34 - 515.66) | 238 (177.34 - 298.66) |
| **Liver** | 124.31 (119.03 - 129.59) | 86.73 (81.45 - 92.01) | 63.60 (58.32 - 68.88) | 60.71 (55.43 - 65.99) | 54.93 (49.65 - 60.21) | 40.47 (35.19 - 45.75) | 23.13 (17.85 - 28.41) | 8.67 (3.39 - 13.95) |
| **Esophagus** | 334.57 (321.18 - 347.96) | 243.32 (229.93 - 256.71) | 170.32 (156.93 - 183.71) | 164.24 (150.85 - 177.63) | 152.08 (138.69 - 165.47) | 121.66 (108.27 - 135.05) | 85.16 (71.77 - 98.55) | 42.58 (29.19 - 55.97) |

All values are followed by a parenthesis with the 95% confidence interval.

Table B.4. Cancer risk estimated by LAR (cases / 100,000) for IMRT whole lung treatment dose of 0.7 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 3528 (3385.29 - 3670.71) | 2422 (2279.29 - 2564.71) | 1694 (1551.29 - 1836.71) | 1680 (1537.29 - 1822.71) | 1610 (1467.29 - 1752.71) | 1407 (1264.29 - 1549.71) | 1029 (886.29 - 1171.71) | 539 (396.29 - 681.71) |
| **Breast** | 1774.30 (1673.13 - 1875.47) | 1069.07 (967.90 - 1170.24) | 630.48 (529.31 - 731.65) | 351.37 (250.20 - 452.54) | 174.44 (73.27 - 275.61) | 77.25 (-23.92 - 178.42) | 29.90 (-71.27 - 131.07) | 9.97 (-91.20 - 11.14) |
| **Liver** | 39.20 (37.92 - 40.78) | 27.44 (28.86 - 29.02) | 19.60 (18.02 - 21.18) | 19.60 (18.02 - 21.18) | 17.64 (16.06 - 19.22) | 13.72 (12.14 - 15.30) | 9.80 (8.22 - 11.38) | 3.92 (2.34 - 5.50) |
| **Esophagus** | 393.12 (377.42 - 408.82) | 283.92 (268.22 - 299.62) | 196.56 (180.86 - 212.26) | 191.10 (175.40 - 206.80) | 174.72 (159.02 - 190.42) | 147.42 (131.72 - 163.12) | 103.74 (88.04 - 119.44) | 60.06 (44.36 - 75.76) |
| **Male** | | | | | | | | |
| **Lung** | 1512 (1451.4 - 1572.66) | 1043 (982.34 - 1103.66) | 735 (674.34 - 795.66) | 728 (667.34 - 788.66) | 707 (646.34 - 767.66) | 623 (562.34 - 683.66) | 455 (394.34 - 515.66) | 238 (177.34 - 298.66) |
| **Liver** | 84.28 (80.70 - 87.86) | 58.80 (55.22 - 62.38) | 43.12 (39.54 - 46.70) | 41.16 (37.58 - 44.74) | 37.24 (33.66 - 40.82) | 27.44 (23.86 - 31.02) | 15.68 (12.10 - 19.26) | 5.88 (2.30 - 9.46) |
| **Esophagus** | 300.30 (288.28 - 312.32) | 218.40 (206.38 - 230.42) | 152.88 (140.86 - 164.90) | 147.42 (135.40 - 159.44) | 136.50 (124.48 - 148.52) | 109.20 (97.18 - 121.22) | 76.44 (64.42 - 88.46) | 38.22 (26.20 - 50.24) |

All values are followed by a parenthesis with a 95% confidence interval.

Table B.5. Cancer risk estimated by LAR (cases / 100,000) for 3DRT whole lung treatment dose of 1 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 5040 (4836.13 – 5243.87) | 3460 (3256.13 – 3663.87) | 2420 (2216.13 – 2623.87) | 2400 (2196.13 – 2603.87) | 2300 (2096.13 – 2503.87) | 2010 (1806.13 -– 2213.87) | 1470 (1266.13 – 1673.87) | 770 (566.13 - 973.87) |
| **Breast** | 3310.80 (3122.01 – 3499.59) | 1994.85 (1806.06 – 2183.64) | 1176.45 (987.66 - 1365.24) | 655.65 (466.86 - 844.44) | 325.50 (136.71 - 514.29) | 144.15 (- 44.64 - 332.94) | 55.80 (- 132.99 - 244.59) | 18.60 (- 170.19 - 207.39) |
| **Liver** | 82.60 (79.28 - 85.92) | 57.82 (54.50 - 61.14) | 41.30 (37.98 - 44.62) | 41.30 (37.98 - 44.62) | 37.17 (33.85 - 40.49) | 28.91 (25.59 - 32.23) | 20.65 (17.33 - 23.97) | 8.26 (4.94 - 11.58) |
| **Esophagus** | 625.68 (600.68 - 650.68) | 451.88 (426.88 - 476.88) | 312.84 (287.84 - 337.84) | 304.15 (279.15 - 329.15) | 278.08 (253.08 - 303.08) | 234.63 (209.63 - 259.63) | 165.11 (140.11 - 190.11) | 95.59 (70.59 - 120.59) |
| **Male** | | | | | | | | |
| **Lung** | 2160 (2073.34 - 2246.66) | 1490 (1403.34 - 1576.66) | 1050 (693.34 - 1136.66) | 1040 (953.34 - 1126.66) | 1010 (923.34 - 1096.66) | 890 (803.34 - 976.66) | 650 (563.34 - 736.66) | 340 (253.34 - 426.66) |
| **Liver** | 177.59 (170.05 - 185.13) | 123.90 (116.36 - 131.44) | 90.86 (83.32 - 98.40) | 86.73 (79.19 - 94.27) | 78.47 (70.93 - 86.01) | 57.82 (50.28 - 65.36) | 33.04 (25.50 - 40.58) | 12.39 (4.85 - 19.93) |
| **Esophagus** | 477.95 (458.82 - 497.08) | 347.60 (328.47 - 366.73) | 243.32 (224.19 - 262.45) | 234.63 (215.50 - 253.76) | 217.25 (198.12 - 236.38) | 173.80 (154.67 - 192.93) | 121.66 (102.53 - 140-79) | 60.83 (41.70 - 79.96) |

All values are followed by a parenthesis with a 95% confidence interval.

Table B.6. Cancer risk estimated by LAR (cases / 100,000) for IMRT whole lung treatment dose of 1 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 5040 (4836.13 – 5243.87) | 3460 (3256.13 – 3663.87) | 2420 (2216.13 – 2623.87) | 2400 (2196.13 – 2603.87) | 2300 (2096.13 – 2503.87) | 2010 (1806.13 -– 2213.87) | 1470 (1266.13 – 1673.87) | 770 (566.13 - 973.87) |
| **Breast** | 2534.72 (2390.18 - 2679.26) | 1527.24 (138.70 - 1671.78) | 900.68 (756.14 - 1045.22) | 501.96 (357.42 - 646.50) | 249.20 (104.66 - 393.74) | 110.36 (- 34.18 - 254.90) | 42.72 (- 101.82 - 187.26) | 14.24 (- 130.30 - 158.78) |
| **Liver** | 56.00 (53.75 - 58.25) | 39.20 (36.95 - 41.45) | 28.00 (25.75 - 30.25) | 28.00 (25.75 - 30.25) | 25.20 (22.95 - 27.45) | 19.60 (17.35 - 21.85) | 14.00 (11.75 - 16.25) | 5.60 (3.35 - 7.85) |
| **Esophagus** | 561.60 (539.17 - 584.03) | 405.60 (383.17 - 428.03) | 280.80 (258.37 - 303.23) | 273.00 (250.57 - 295.43) | 249.60 (227.17 - 272.03) | 210.60 (188.17 - 233.03) | 148.20 (125.77 - 170.63) | 85.80 (63.37 - 108.23) |
| **Male** | | | | | | | | |
| **Lung** | 2160 (2073.34 - 2246.66) | 1490 (1403.34 - 1576.66) | 1050 (693.34 - 1136.66) | 1040 (953.34 - 1126.66) | 1010 (923.34 - 1096.66) | 890 (803.34 - 976.66) | 650 (563.34 - 736.66) | 340 (253.34 - 426.66) |
| **Liver** | 120.40 (155.29 - 125.51) | 84 (78.89 - 89.11) | 61.60 (56.49 - 66.71) | 58.80 (53.69 - 63.91) | 53.20 (48.09 - 58.31) | 39.20 (34.09 - 44.31) | 22.40 (17.29 - 27.51) | 8.40 (3.29 - 13.51) |
| **Esophagus** | 429 (411.83 - 446.17) | 312 (294.83 - 329.17) | 218.40 (201.23 - 235.57) | 210.60 (193.43 - 227.77) | 195 (177.83 - 212.17) | 156 (138.83 - 173.17) | 109.20 (92.03 - 126.37) | 54.60 (37.43 - 71.77) |

All values are followed by a parenthesis with a 95% confidence interval.

Table B.7. Cancer risk estimated by LAR (cases / 100,000) for 3DRT whole lung treatment dose of 1.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 7560 (7254.20 - 7865.80) | 5190 (4884.20 - 5495.80) | 3630 (3324.20 - 3935.80) | 3600 (3294.20 - 3905.80) | 3450 (3144.20 - 3755.80) | 3015 (2709.20 - 3320.80) | 2205 (1899.20 - 2510.80) | 1155 (849.20 - 1460.80) |
| **Breast** | 4966.20 (4683.01 - 5249.39) | 2992.28 (2709.09 - 3275.47) | 1764.68 (1481.49 - 2047.87) | 983.48 (700.29 - 1266.67) | 488.25 (205.06 - 771.44) | 216.23 (- 66.97 - 499.42) | 83.70 (- 199.49 - 366.89) | 27.90 (- 255.29 - 311.09) |
| **Liver** | 123.90 (118.92 - 128.88) | 86.73 (81.75 - 91.71) | 61.95 (56.97 - 66.93) | 61.95 (56.97 - 66.93) | 55.76 (50.78 - 60.74) | 43.37 (38.39 - 48.35) | 30.98 (26.00 - 35.96) | 12.39 (7.41 - 17.37) |
| **Esophagus** | 938.52 (901.03 - 976.01) | 677.82 (640.33 - 715.31) | 469.26 (431.77 - 506.75) | 456.23 (418.74 - 493.72) | 417.12 (379.63 - 454.61) | 351.95 (314.46 - 389.44) | 247.67 (210.18 - 285.16) | 143.39 (105.90 - 180.88) |
| **Male** | | | | | | | | |
| **Lung** | 3240 (3110.01 - 3369.99) | 2235 (2105.01 - 2364.99) | 1575 (1445.01 - 1704.99) | 1560 (1430.01 - 1689.99) | 1515 (1385.01 - 1644.99) | 1335 (1201.01 - 1464.99) | 975 (845.01 - 1104.99) | 510 (380.01 - 639.99) |
| **Liver** | 266.39 (255.08 - 277.70) | 185.85 (174.54 - 197.16) | 136.29 (124.98 - 147.60) | 130.10 (118.79 - 141.41) | 117.71 (106.40 - 129.02) | 86.73 (75.42 - 98.04) | 49.56 (38.25 - 60.87) | 18.59 (7.28 - 29.90) |
| **Esophagus** | 716.93 (688.23 - 475.63) | 521.40 (492.70 - 550.10) | 364.98 (336.28 - 393.68) | 351.95 (323.25 - 380.65) | 325.88 (297.18 - 354.58) | 260.70 (232 - 289.40) | 182.49 (153.79 - 211.19) | 91.25 (62.55 - 119.95) |

All values are followed by a parenthesis with a 95% confidence interval.

Table B.8. Cancer risk estimated by LAR (cases / 100,000) for IMRT whole lung treatment dose of 1.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 7560 (7254.20 - 7865.80) | 5190 (4884.20 - 5495.80) | 3630 (3324.20 - 3935.80) | 3600 (3294.20 - 3905.80) | 3450 (3144.20 - 3755.80) | 3015 (2709.20 - 3320.80) | 2205 (1899.20 - 2510.80) | 1155 (849.20 - 1460.80) |
| **Breast** | 3802.08 (3585.28 - 4018.88) | 2290.86 (2074.06 - 2507.66) | 1351.02 (1134.22 - 1567.82) | 752.94 (536.14 - 969.74) | 373.80 (157.00 - 590.60) | 165.54 (-51.26 - 382.34) | 64.08 (-152.72 - 280.88) | 21.36 (-195.44 - 238.16) |
| **Liver** | 84.00 (80.62 - 87.38) | 58.80 (55.42 - 62.18) | 42.00 (38.62 - 45.38) | 42.00 (38.62 - 45.38) | 37.80 (34.42 - 41.18) | 29.40 (26.02 - 32.78) | 21.00 (17.62 - 24.38) | 8.40 (5.02 - 11.78) |
| **Esophagus** | 842.40 (808.75 - 876.05) | 608.40 (574.75 - 642.05) | 421.20 (387.55 - 454.85) | 409.50 (375.85 - 443.15) | 374.40 (340.75 - 408.05) | 315.90 (282.25 - 349.55) | 222.30 (188.65 - 255.95) | 128.70 (95.05 - 162.35) |
| **Male** | | | | | | | | |
| **Lung** | 3240 (3110.01 - 3369.99) | 2235 (2105.01 - 2364.99) | 1575 (1445.01 - 1704.99) | 1560 (1430.01 - 1689.99) | 1515 (1385.01 - 1644.99) | 1335 (1201.01 - 1464.99) | 975 (845.01 - 1104.99) | 510 (380.01 - 639.99) |
| **Liver** | 180.60 (172.93 - 188.27) | 126 (118.33 - 133.67) | 92.40 (84.73 - 100.07) | 88.20 (80.53 - 95.87) | 79.80 (72.13 - 87.47) | 58.80 (51.13 - 66.47) | 33.60 (25.93 - 41.27) | 12.60 (4.93 - 20.27) |
| **Esophagus** | 643.50 (617.74 - 669.26) | 468 (442.24 - 493.76) | 327.60 (301.84 - 353.36) | 315.90 (290.14 - 341.66) | 292.50 (266.74 - 318.26) | 234 (208.24 - 259.76) | 163.80 (138.04 - 189.56) | 81.90 (56.14 - 107.66) |

All values are followed by a parenthesis with a 95% confidence interval.

# ANNEX C

This annex contains REIC results as a function of age at exposure, stratified by dose, technique, gender, and site.

Table C.1. Cancer risk estimated by REIC (cases / 100,000) for 3DRT whole lung treatment dose of 0.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.10 (-41.68 - 41.88) | 0.95 (-40.83 - 42.73) | 5.20 (-36.58 - 46.98) | 41.45 (-0.33 - 83.23) | 202.20 (160.42 - 243.98) | 530.00 (488.22 - 571.78) | 953.70 (911.92 - 995.48) | 834.10 (792.32 - 875.88) |
| **Breast** | 0.02 (-41.08 - 41.12) | 2.77 (-38.33 - 43.87) | 54.71 (13.61 - 95.81) | 250.10 (209.00 - 291.20) | 566.30 (525.20 - 607.40) | 693.01 (651.91 - 734.11) | 764.02 (722.92 - 805.12) | 850.93 (809.83 - 892.03) |
| **Liver** | 0.08 (-1.84 - 2.00) | 0.19 (-1.73 - 2.11) | 0.50 (-1.42 - 2.42) | 1.32 (-0.60 - 3.24) | 5.02 (3.10 - 6.94) | 13.90 (11.98 - 15.82) | 29.14 (27.22 - 31.06) | 45.47 (43.55 - 47.36) |
| **Esophagus** | 0.00 (-5.58 - 5.58) | 0.09 (-5.49 - 5.67) | 0.43 (-5.15 - 6.01) | 2.17 (-3.41 - 7.75) | 10.51 (4.93 - 16.09) | 34.41 (28.83 - 39.99) | 73.69 (68.11 - 79.27) | 116.32 (110.74 - 121.90) |
| **Male** | | | | | | | | |
| **Lung** | 0.15 (-105.29 - 105.59) | 0.95 (-104.49 - 109.39) | 4.95 (-100.49 - 110.39) | 47.05 (-58.39 - 152.49) | 281.10 (175.66 - 386.54) | 945.00 (839.56 - 1050.44) | 2003.90 (1898.46 - 2109.34) | 2299.80 (2194.36 - 2405.24) |
| **Liver** | 0.10 (-3.64 - 3.84) | 0.31 (-3.43 - 4.05) | 0.66 (-3.08 - 4.40) | 4.25 (0.51 - 7.99) | 11.42 (7.68 - 15.16) | 30.98 (27.24 - 34.72) | 63.77 (60.03 - 67.51) | 76.32 (72.58 - 80.06) |
| **Esophagus** | 0.00 (-11.40 - 11.40) | 0.09 (-11.31 - 11.49) | 0.91 (-10.49 - 12.31) | 8.43 (-2.97 - 19.83) | 41.15 (29.75 - 52.55) | 107.71 (96.31 - 119.11) | 202.43 (191.03 - 213.83) | 242.80 (231.40 - 254.20) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.2. Cancer risk estimated by REIC (cases / 100,000) for IMRT whole lung treatment dose of 0.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.10 (-41.68 - 41.88) | 0.95 (-40.83 - 42.73) | 5.20 (-36.58 - 46.98) | 41.45 (-0.33 - 83.23) | 202.20 (160.42 - 243.98) | 530.00 (488.22 - 571.78) | 953.70 (911.92 - 995.48) | 834.10 (792.32 - 875.88) |
| **Breast** | 0.02 (-31.44 - 31.48) | 2.12 (-29.34 - 33.58) | 41.88 (10.42 - 73.34) | 191.47 (160.01 - 222.93) | 433.55 (402.09 - 465.01) | 530.56 (499.10 - 562.02) | 584.93 (553.47 - 616.39) | 651.46 (620.00 - 682.92) |
| **Liver** | 0.06 (-1.24 - 1.36) | 0.13 (-1.17 - 1.43) | 0.34 (-0.96 - 1.64) | 0.90 (-0.40 - 2.20) | 3.40 (2.10 - 4.70) | 9.42 (8.12 - 10.72) | 19.75 (18.45 - 21.05) | 30.83 (29.53 - 32.13) |
| **Esophagus** | 0.00 (-5.01 - 5.01) | 0.08 (-4.93 - 5.09) | 0.39 (-4.62 - 5.40) | 1.95 (-3.06 - 6.96) | 9.44 (4.43 - 14.45) | 30.89 (25.88 - 35.90) | 66.14 (61.13 - 71.15) | 104.40 (99.39 - 109.41) |
| **Male** | | | | | | | | |
| **Lung** | 0.15 (-105.29 - 105.59) | 0.95 (-104.49 - 109.39) | 4.95 (-100.49 - 110.39) | 47.05 (-58.39 - 152.49) | 281.10 (175.66 - 386.54) | 945.00 (839.56 - 1050.44) | 2003.90 (1898.46 - 2109.34) | 2299.80 (2194.36 - 2405.24) |
| **Liver** | 0.07 (-2.46 - 2.60) | 0.21 (-2.32 - 2.74) | 0.45 (-2.08 - 2.98) | 2.88 (0.35 - 5.41) | 7.74 (5.21 - 10.27) | 21.00 (18.47 - 23.53) | 43.23 (40.70 - 45.76) | 51.74 (49.21 - 54.27) |
| **Esophagus** | 0.00 (-10.23 - 10.23) | 0.08 (-10.15 - 10.31) | 0.82 (-9.41 - 11.05) | 7.57 (-2.66 - 17.80) | 36.93 (26.70 - 47.16) | 96.68 (86.45 - 106.91) | 181.70 (171.47 - 191.93) | 217.93 (207.70 - 228.16) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.3. Cancer risk estimated by REIC (cases / 100,000) for 3DRT whole lung treatment dose of 0.7 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.14 (-58.36 - 58.64) | 1.33 (-57.17 - 59.83) | 7.28 (-51.22 - 65.78) | 58.03 (-0.47 - 116.53) | 283.08 (224.58 - 341.58) | 742.00 (683.50 - 800.50) | 1335.18 (1276.68 - 1393.68) | 1167.74 (1109.24 - 1226.24) |
| **Breast** | 0.03 (-57.50 - 57.56) | 3.87 9-53.66 - 61.40) | 76.59 (19.06 - 134.120 | 350.14 (292.61 - 407.67) | 792.82 (735.29 - 850.35) | 970.22 (912.69 - 1027.16) | 1069.63 (1012.10 - 1127.16) | 1191.30 (1133.77 - 1248.83) |
| **Liver** | 0.12 (-2.56 - 2.80) | 0.26 (-2.42 - 2.94) | 0.69 (-1.99 - 3.37) | 1.85 (-0.83 - 4.53) | 7.03 (4.35 - 9.71) | 19.46 (16.78 - 22.14) | 40.79 (38.11 - 43.47) | 63.66 (60.98 - 66.34) |
| **Esophagus** | 0.00 (-7.81 - 7.81) | 0.12 (-7.69 - 7.93) | 0.61 (-7.20 - 8.42) | 3.04 (-4.77 - 10.85) | 14.72 (6.91 - 22.53) | 48.18 (40.37 - 55.99) | 103.17 (95.36 - 110.98) | 162.84 (155.03 - 170.65) |
| **Male** | | | | | | | | |
| **Lung** | 0.21 (-147.41 - 147.83) | 1.33 (-146.29 - 148.95) | 6.93 (-140.69 - 154.55) | 65.87 (-81.75 - 213.490 | 393.54 (245.92 - 541.16) | 1323.00 (1175.38 - 1470.62) | 2805.46 (2657.84 - 2953.08) | 3219.72 (3072.10 - 3367.34) |
| **Liver** | 0.14 (-5.09 - 5.370 | 0.43 (-4.80 - 5.66) | 0.93 (-4.30 - 6.16) | 5.96 (0.73 - 11.19) | 15.99 (10.76 - 21.22) | 43.37 (38.14 - 48.60) | 89.27 (84.04 - 94.50) | 106.85 (101.85 - 112.08) |
| **Esophagus** | 0.00 (-15.95 - 15.95) | 0.12 (-15.83 - 16.07) | 1.28 (-14.97 - 17.23) | 11.80 (-4.15 (27.75) | 57.61 (41.66 - 73.56) | 150.80 (134.85 - 166.75) | 283.41 (267.46 - 299.36) | 339.92 (323.97 - 355.87) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.4. Cancer risk estimated by REIC (cases / 100,000) for IMRT whole lung treatment dose of 0.7 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.14 (-58.36 - 58.64) | 1.33 (-57.17 - 59.83) | 7.28 (-51.22 - 65.78) | 58.03 (-0.47 - 116.53) | 283.08 (224.58 - 341.58) | 742.00 (683.50 - 800.50) | 1335.18 (1276.68 - 1393.68) | 1167.74 (1109.24 - 1226.24) |
| **Breast** | 0.02 (-44.03 - 44.07) | 2.97 (-41.08 - 4702) | 58.64 (14.59 - 102.69) | 268.06 (224.01 - 312.11) | 606.98 (562.93 - 651.03) | 742.79 (698.74 - 786.84) | 818.90 (774.85 - 862.95) | 912.05 (868.00 - 956.10) |
| **Liver** | 0.08 (-1.74 - 1.90) | 0.18 (-1.64 - 2.00) | 0.47 (-1.35 - 2.29) | 1.25 (-0.57 - 3.07) | 4.76 (2.94 - 6.58) | 13.19 (11.37 - 15.01) | 27.66 (25.84 - 29.48) | 43.16 (41.34 - 44.98) |
| **Esophagus** | 0.00 (-7.01 - 7.01) | 0.11 (-6.90 - 7.12) | 0.55 (-6.46 - 7.56) | 2.73 (-4.28 - 9.74) | 13.21 (6.20 - 20.22) | 43.24 (36.23 - 50.25) | 92.60 (85.59 - 99.61) | 146.16 (139.15 - 153.17) |
| **Male** | | | | | | | | |
| **Lung** | 0.21 (-147.41 - 147.83) | 1.33 (-146.29 - 148.95) | 6.93 (-140.69 - 154.55) | 65.87 (-81.75 - 213.490 | 393.54 (245.92 - 541.16) | 1323.00 (1175.38 - 1470.62) | 2805.46 (2657.84 - 2953.08) | 3219.72 (3072.10 - 3367.34) |
| **Liver** | 0.10 (-3.45 - 3.65) | 0.29 (-3.26 - 3.84) | 0.63 (-2.92 - 4.18) | 4.04 (0.49 - 7.59) | 10.84 (7.29 - 14.39) | 29.40 (25.85 - 32.95) | 60.52 (56.97 - 64.07) | 72.44 (68.89 - 75.99) |
| **Esophagus** | 0.00 (-14.32 - 14.32) | 0.11 (-14.21 - 14.43) | 1.15 (-13.17 - 15.47) | 10.59 (-3.73 - 24.91) | 51.71 (37.39 - 66.03) | 135.35 (121.03 - 149.67) | 254.38 (240.06 - 268.70) | 305.10 (290.78 - 319.42) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.5. Cancer risk estimated by REIC (cases / 100,000) for 3DRT whole lung treatment dose of 1 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.20 (-83.36 - 83.76) | 1.90 (-81.66 - 85.46) | 10.40 (-73.16 - 93.96) | 82.90 (-0.66 - 166.46) | 404.40 (320.84 - 487.96) | 1060.00 (976.44 - 1143.56) | 1907.40 (1823.84 - 1990.96) | 1668.20 (1584.64 - 1751.76) |
| **Breast** | 0.05 (-82.14-82.24) | 5.53 (-76.66 - 87.72) | 109.41 (27.22 - 191.60) | 500.20 (418.01 - 582.39) | 1132.60 (1050.41 - 1305.93) | 1386.03 (1303.84 - 1468.22) | 1528.04 (1445.85 - 1610.23) | 1701.85 (1619.66 - 1784.04) |
| **Liver** | 0.17 (-3.67 - 4.01) | 0.37 (-3.47 - 4.21) | 0.99 (-2.85 - 4.83) | 2.64 (-1.20 - 6.48) | 10.04 (6.20 - 13.88) | 27.79 (23.95 - 31.63) | 58.27 (54.43 - 62.11) | 90.94 (87.10 - 94.78) |
| **Esophagus** | 0.00 (-11.15 - 11.15) | 0.17 (-10.98 - 11.32) | 0.87 (-1028 - 12.02) | 4.35 (-6.81 - 15.50) | 21.03 (9.88 - 32.18) | 68.82 (57.67 - 79.97) | 147.38 (136.23 - 158.53) | 232.63 (221.48 0 243.78) |
| **Male** | | | | | | | | |
| **Lung** | 0.30 (-210.59 - 211.19) | 1.90 (-208.99 - 212.79) | 9.90 (-200.99 - 220.79) | 94.10 (-116.79 - 304.99) | 562.20 (351.31 - 773.09) | 1890.00 (1679.11 - 2100.89) | 4007.80 (3796.91 - 4218.69) | 4599.60 (4388.71 - 4810.49) |
| **Liver** | 0.21 (-7.26 - 7.68) | 0.62 (-6.85 - 8.09) | 1.32 (-6.15 - 8.79) | 8.51 (1.04 - 15.98) | 22.84 (15.37 - 30.31) | 61.95 (54.48 - 69.42) | 127.53 (120.06 - 135.00) | 152.64 (145.17 - 160.11) |
| **Esophagus** | 0.00 (-22.79 - 22.79) | 0.17 (-22.62 - 22.96) | 1.82 (-20.97 - 24.61) | 16.86 (-5.93 - 39.65) | 82.29 (59.50 - 105.08) | 215.43 (192.64 - 238.22) | 404.87 (382.08 - 427.66) | 485.60 (462.81 - 508.39) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.6. Cancer risk estimated by REIC (cases / 100,000) for IMRT whole lung treatment dose of 1 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.20 (-83.36 - 83.76) | 1.90 (-81.66 - 85.46) | 10.40 (-73.16 - 93.96) | 82.90 (-0.66 - 166.46) | 404.40 (320.84 - 487.96) | 1060.00 (976.44 - 1143.56) | 1907.40 (1823.84 - 1990.96) | 1668.20 (1584.64 - 1751.76) |
| **Breast** | 0.04 (-62.89 - 62.97) | 4.24 (-58.69 - 67.17) | 83.77 (20.84 - 146.70) | 382.95 (320.02 - 445.88) | 867.11 (804.18 - 930.04) | 1061.13 (998.20 - 1124.06) | 1169.85 (1106.92 - 1232.78) | 1302.92 (1239.99 - 1365.85) |
| **Liver** | 0.11 (-2.9 - 2.71) | 0.25 (-2.35 - 2.85) | 0.67 (-1.93 - 3.27) | 1.79 (-0.81 - 4.39) | 6.80 (4.20 - 9.40) | 18.48 (16.24 - 21.44) | 39.51 (36.91 - 42.11) | 61.66 (59.06 - 64.26) |
| **Esophagus** | 0.00 (-10.01 - 10.01) | 0.16 (-9.85 - 10.17) | 0.78 (-9.23 - 10.79) | 3.90 (-6.11 - 13.91) | 18.88 (8.87 - 28.89) | 61.78 (51.77 - 71.79) | 132.29 (122.28 - 142.30) | 208.81 (198.80 - 218.82) |
| **Male** | | | | | | | | |
| **Lung** | 0.30 (-210.59 - 211.19) | 1.90 (-208.99 - 212.79) | 9.90 (-200.99 - 220.79) | 94.10 (-116.79 - 304.99) | 562.20 (351.31 - 773.09) | 1890.00 (1679.11 - 2100.89) | 4007.80 (3796.91 - 4218.69) | 4599.60 (4388.71 - 4810.49) |
| **Liver** | 0.14 (-4.93 - 5.21) | 0.42 (-4.65 - 5.49) | 0.90 9-4.17 - 5.97) | 5.77 (0.70 - 10.84) | 15.48 (10.41 - 20.55) | 42.00 (36.93 - 47.07) | 86.46 (81.39 - 91.53) | 103.49 (98.42 - 108.56) |
| **Esophagus** | 0.00 (-20.46 - 20.46) | 0.16 (-20.30 - 20.62) | 1.64 (-18.82 - 22.10) | 15.13 (-5.33 - 35.59) | 73.87 (53.41 - 94.33) | 193.36 (172.90 - 213.82) | 363.40 (342.94 - 383.86) | 435.86 (415.40 - 456.32) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.7. Cancer risk estimated by REIC (cases / 100,000) for 3DRT whole lung treatment dose of 1.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.30 (-125.05 - 125.65) | 2.85 (-122.50 - 128.20) | 15.60 (-109.75 - 140.95) | 124.35 (-1.00 - 249.70) | 606.60 (481.25 - 731.95) | 1590.00 (1464.65 - 1715.35) | 2861.10 (2735.75 - 2986.45) | 2502.30 (2376.95 - 2627.65) |
| **Breast** | 0.07 (-123.22 - 123.36) | 8.30 (-114.99 - 131.59) | 164.12 (40.83 - 287.41) | 750.30 (627.01 - 873.59) | 1698.90 (1575.61 - 1822.19) | 2079.04 (1955.75 - 2202.33) | 2292.05 (2168.76 - 2415.34) | 2552.78 (2429.49 - 2676.07) |
| **Liver** | 0.25 (-5.50 - 6.00) | 0.56 (-5.19 - 6.31) | 1.49 (-4.26 - 7.24) | 3.96 (-1.79 - 9.71) | 15.05 (9.30 - 20.80) | 41.69 (35.94 - 47.44) | 87.41 (81.66 - 93.16) | 136.41 (130.66 - 142.16) |
| **Esophagus** | 0.00 (-16.73 - 16.73) | 0.26 (-16.47 - 16.99) | 1.30 (-15.43 - 18.03) | 6.52 (-10.21 - 23.25) | 31.54 (14.81 - 48.27) | 103.24 (86.51 - 119.97) | 221.07 (204.34 - 237.80) | 348.95 (332.22 - 365.68) |
| **Male** | | | | | | | | |
| **Lung** | 0.45 (-315.88 - 316.78) | 2.85 (-313.48 - 319.18) | 14.85 (-301.48 - 331.18) | 141.15 (-175.18 - 457.48) | 843.30 (526.97 - 1159.63) | 2835.00 (2518.67 - 3151.33) | 6011.70 (5695.37 - 6328.03) | 6899.40 (6583.07 - 7215.73) |
| **Liver** | 0.31 (-10.90 - 11.52) | 0.93 (-10.28 - 1214) | 1.98 (-9.23 - 13.19) | 12.76 (1.55 - 23.97) | 34.26 (23.05 - 45.47) | 92.93 (81.72 - 104.14) | 191.30 (180.09 - 202.51) | 228.97 (217.76 - 240.18) |
| **Esophagus** | 0.00 (-34.19 - 34.19) | 0.26 (-33.93 - 34.45) | 2.74 (-31.45 - 36.93) | 25.29 (-8.90 - 59.48) | 123.44 (89.25 - 157.63) | 323.14 (288.95 - 357.33) | 607.30 (573.11 - 641.49) | 728.40 (694.21 - 762.59) |

All values are followed by a parenthesis with a 95% confidence interval.

Table C.8. Cancer risk estimated by REIC (cases / 100,000) for IMRT whole lung treatment dose of 1.5 Gy for both genders.

| | Age at Exposure (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
| **Female** | | | | | | | | |
| **Lung** | 0.30 (-125.05 - 125.65) | 2.85 (-122.50 - 128.20) | 15.60 (-109.75 - 140.95) | 124.35 (-1.00 - 249.70) | 606.60 (481.25 - 731.95) | 1590.00 (1464.65 - 1715.35) | 2861.10 (2735.75 - 2986.45) | 2502.30 (2376.95 - 2627.65) |
| **Breast** | 0.05 (-94.34 - 94.44) | 6.35 (-88.04 - 100.74) | 125.65 (31.26 - 220.04) | 574.42 (480.03 - 668.81) | 1300.66 (1206.27 - 1395.05) | 1591.69 (1497.30 - 1686.08) | 1754.78 (1660.39 - 1846.17) | 1954.39 (1860.00 - 2048.78) |
| **Liver** | 0.17 (-3.73 - 4.07) | 0.38 (-3.52 - 4.28) | 1.01 (-2.89 - 4.91) | 2.69 (-1.21 - 6.59) | 10.21 (6.31 - 14.11) | 28.27 (24.37 - 32.17) | 59.26 (55.36 - 63.16) | 92.48 (88.58 - 96.38) |
| **Esophagus** | 0.00 (-15.02 - 15.02) | 0.23 (-14.79 - 15.25) | 1.17 (-13.85 - 16.19) | 5.85 (-9.17 - 20.87) | 28.31 (13.29 - 43.33) | 92.66 (77.64 - 107.68) | 198.43 (183.41 - 213.45) | 313.21 (298.19 - 328.23) |
| **Male** | | | | | | | | |
| **Lung** | 0.45 (-315.88 - 316.78) | 2.85 (-313.48 - 319.18) | 14.85 (-301.48 - 331.18) | 141.15 (-175.18 - 457.48) | 843.30 (526.97 - 1159.63) | 2835.00 (2518.67 - 3151.33) | 6011.70 (5695.37 - 6328.03) | 6899.40 (6583.07 - 7215.73) |
| **Liver** | 0.21 (-7.39 - 7.81) | 0.63 (-6.97 - 8.23) | 1.34 (-6.26 - 8.94) | 8.65 (1.05 - 16.25) | 23.23 (15.63 - 30.83) | 63.00 (55.40 - 70.60) | 129.70 (122.10 - 137.30) | 155.23 (147.63 - 162.83) |
| **Esophagus** | 0.00 (-30.69 - 30.69) | 0.23 (-30.46 - 30.92) | 2.46 (-28.23 - 33.15) | 22.70 (-7.99 - 53.39) | 110.80 (152.77 - 141.49) | 290.04 (259.35 - 320.73) | 542.10 (514.41 - 575.79) | 653.80 (623.11 - 684.49) |

All values are followed by a parenthesis with a 95% confidence interval.

# ANNEX D

This annex contains ERR, and EAR results as a function of age at exposure, stratified by technique and site.

Table D.1. Average ERR at 1 Gy for 3DRT technique for whole lung treatment.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | < 20 | 20 – 40 | > 40 |
| **Lung** | 0.68 (0.28 - 1.20) | 0.65 (0.35 - 1.00) | 0.71 (0.40 - 1.09) |
| **Breast** | 0.88 (0.64 - 1.16) | 0.61 (0.40 - 0.87) | 0.15 (0.02 - 0.70) |
| **Liver** | 0.21 (0.09 - 0.35) | 0.09 (<0.00 - 0.22) | 0.25 (0.06 - 0.51) |
| **Esophagus** | 1.22 (0.38 - 2.45) | 0.00 (<0.00 - 0.66) | 0.29 (<0.00 - 0.92) |

All values are followed by a parenthesis with a 95% confidence interval.

Table D.2. Average ERR at 1 Gy for IMRT technique for whole lung treatment.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | < 20 | 20 – 40 | > 40 |
| **Lung** | 0.68 (0.28 - 1.20) | 0.65 (0.35 - 1.00) | 0.71 (0.40 - 1.09) |
| **Breast** | 0.67 (0.49 - 0.89) | 0.47 (0.31 - 0.67) | 0.11 (0.01 - 0.54) |
| **Liver** | 0.14 (0.06 - 0.24) | 0.06 (<0.00 - 0.15) | 0.17 (0.04 - 0.34) |
| **Esophagus** | 1.09 (0.34 - 2.20) | 0.00 (<0.00 - 0.59) | 0.26 (<0.00 - 0.83) |

All values are followed by a parenthesis with a 95% confidence interval.

Table D.3. Estimative EAR ($10^4$ PY Gy) 3DRT technique for whole lung treatment.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | < 20 | 20 – 40 | > 40 |
| **Lung** | 0.64 (0.10 - 1.38) | 2.65 (1.04 - 4.60) | 9.47 (5.75 - 13.78) |
| **Breast** | 4.08 (3.04 - 5.25) | 3.24 (2.19 - 4.44) | 1.16 (0.01 - 2.71) |
| **Liver** | 0.20 (0.04 - 0.45) | 0.30 (<0.00 - 0.83) | 1.25 (0.01 - 2.79) |
| **Esophagus** | 0.00 (<0.00 - 227.74) | 0.00 (<0.00 - 435.66) | 1.65 (0.40 - 3.42) |

All values are followed by a parenthesis with a 95% confidence interval.

Table D.4. Estimative EAR ($10^4$ PY Gy) IMRT technique for whole lung treatment.

| | Age at Exposure (years) | | |
|---|---|---|---|
| **Cancer site** | < 20 | 20 – 40 | > 40 |
| **Lung** | 0.64 (0.10 - 1.38) | 2.65 (1.04 - 4.60) | 9.47 (5.75 - 13.78) |
| **Breast** | 3.13 (2.33 - 4.02) | 2.48 (1.68 - 3.40) | 0.89 (0.01 - 2.07) |
| **Liver** | 0.13 (0.03 - 0.30) | 0.20 (<0.00 - 0.57) | 11.08 (9.06 – 13.10) |
| **Esophagus** | 0.00 (<0.00 - 204.41) | 0.00 (<0.00 - 391.04) | 3.18 (1.67 – 4.70) |

All values are followed by a parenthesis with a 95% confidence interval.

# ANNEX E

This annex contains REID results as a function of age at exposure, stratified by technique and dose.

Table E.1. Cancer risk estimated by REID for heart diseases (cases / 100,000) for a whole lung treatment dose of 0.5 Gy.

| | Age at Exposure (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Technique** | 10 | 20 | 30 | 40 | 50 | 60 | 70 |
| **3DRT** | 7.09 (6.32 - 7.86) | 5.05 (4.28 - 5.82) | 3.74 (2.97 - 4.51) | 2.88 (2.11 - 3.65) | 2.27 (1.50 - 3.04) | 1.79 (1.02 - 2.56) | 1.03 (0.26 - 1.80) |
| **IMRT** | 4.42 (3.94 - 4.90) | 3.15 (2.67 - 3.63) | 2.33 (1.85 - 2.81) | 1.79 (1.31 - 2.27) | 1.41 (0.93 - 1.89) | 1.11 (0.63 - 1.59) | 0.64 (0.16 - 1.12) |

All values are followed by a parenthesis with a 95% confidence interval.

Table E.2. Cancer risk estimated by REID for heart diseases (cases / 100,000) for a whole lung treatment dose of 0.7 Gy.

| | Age at Exposure (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Technique** | 10 | 20 | 30 | 40 | 50 | 60 | 70 |
| **3DRT** | 9.93 (8.86 - 11.00) | 7.06 (5.99 - 8.13) | 5.24 (4.17 - 6.31) | 4.03 (2.96 - 5.10) | 3.17 (2.10 - 4.24) | 2.50 (1.43 - 3.57) | 1.44 (0.37 - 2.51) |
| **IMRT** | 6.19 (5.52 - 6.86) | 4.41 (3.74 - 5.08) | 3.27 (2.60 - 3.94) | 2.51 (1.84 - 3.18) | 1.98 (1.31 - 2.65) | 1.56 (0.89 - 2.23) | 0.90 (0.23 - 1.57) |

All values are followed by a parenthesis with a 95% confidence interval.

Table E.3. Cancer risk estimated by REID for heart diseases (cases / 100,000) for a whole lung treatment dose of 1.0 Gy.

| | Age at Exposure (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Technique** | 10 | 20 | 30 | 40 | 50 | 60 | 70 |
| **3DRT** | 14.18 (12.65 - 15.71) | 10.09 (8.56 - 11.62) | 7.48 (5.95 - 9.01) | 5.75 (4.22 - 7.28) | 4.53 (3.00 - 6.06) | 3.57 (2.04 - 5.10) | 2.05 (0.52 - 3.58) |
| **IMRT** | 8.85 (7.89 - 9.81) | 6.30 (5.34 - 7.26) | 4.67 (3.71 - 5.63) | 3.59 (2.63 - 4.55) | 2.83 (1.87 - 3.79) | 2.23 (1.27 - 3.19) | 1.28 (0.32 - 2.24) |

All values are followed by a parenthesis with a 95% confidence interval.

Table E.4. Cancer risk estimated by REID for heart diseases (cases / 100,000) for a whole lung treatment dose of 1.5 Gy.

| | Age at Exposure (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Technique** | 10 | 20 | 30 | 40 | 50 | 60 | 70 |
| **3DRT** | 21.27 (18.97 - 23.57) | 15.14 (12.84 - 17.44) | 11.22 (8.92 - 13.52) | 8.63 (6.33 - 10.93) | 6.80 (4.50 - 9.10) | 5.36 (3.06 - 7.66) | 3.08 (0.78 - 5.38) |
| **IMRT** | 13.27 (11.83 - 14.71) | 9.44 (8.00 - 10.88) | 7.00 (5.56 - 8.44) | 5.38 (3.94 - 6.82) | 4.24 (2.80 - 5.68) | 3.34 (1.90 - 4.78) | 1.92 (0.48 - 3.36) |

All values are followed by a parenthesis with a 95% confidence interval.

# ANNEX F

Table F.1. Study design of clinical trials developing radiotherapy treatment for patients with COVID-19 pneumonia.

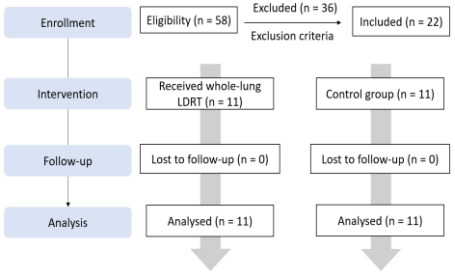
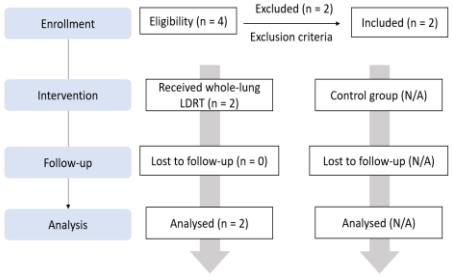
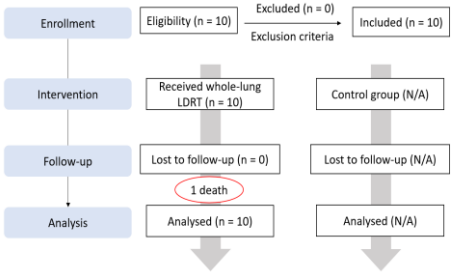
| Author and publication year | Study design | Inclusion and Exclusion criterias | Main purpose | Technique | Patients' age (Years) | Dose (Gy) | Outcome measures |
|---|---|---|---|---|---|---|---|
| Papachristofilou et al. (2021) |  | Inclusion:<br>- Patientes with COVID-19 related pneumonia requiring mechanical ventilation;<br>- Age: male ≥ 40 years, female ≥ 50 years.<br><br>Exclusion:<br>- Pregnants. | Study of whole-lung radiation therapy (LDRT) in patients with COVID-19 to reduce morbidity and mortality. | AP | 54 - 84 | 1 | CRP; Ferritin; Lymphocyte count; PaO2/FiO2; VFDs (ventilator-free days); Overall survival |
| Moreno-Olmedo et al. (2020) |  | Inclusion:<br>- Patientes diagnosed with COVID-19;<br>- PaO2/FiO2 <300 mmHg;<br>- Oxygen saturarion < 93%.<br>- Age: 18 - 120 years. | Establish the eficacy of LDRT, as an anti-inflammatory treatment in patients with COVID-19 pneumonia and with a poor response to medical treatment. | IMRT | 65<br>80 | 0.8 | PaO2/FiO2; Oxygen saturation; Lymphocyte count; IL-6; D-dimer; Ferritin; LDH; CRP; Fibrinogen; TSS (Radiological response) |
| Sharma et al. (2021) |  | Inclusion:<br>- Patientes with COVID-19 confirmed by RT-PCR;<br>- Moderate to severe illness (NEWS ≥ 5);<br>- Age: > 18 years;<br>- Respiratory rate of > 24 per minute;<br>- Oxygen saturation < 94%.<br><br>Exclusion:<br>- Patients requiring mechanical ventilatory support or having unstable hemodynamic status. | Study the feasibility and clinical efficacy of LDRT to lungs in management of patients with COVID-19. | AP/PA | 38 - 63 | 0.7 | The response assessment was done mainly on clinical parameters a per the NEWS (CRP; D-dimer; IL-6; Ferritin; etc) |

Table F.1. (*continued*)

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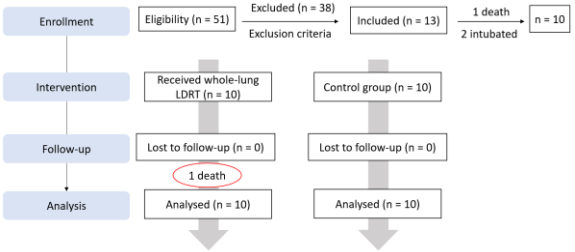
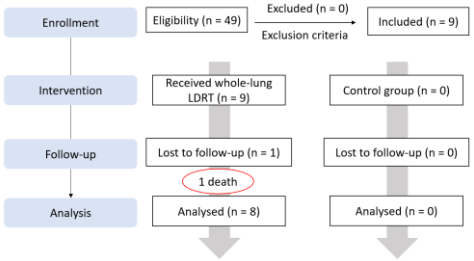
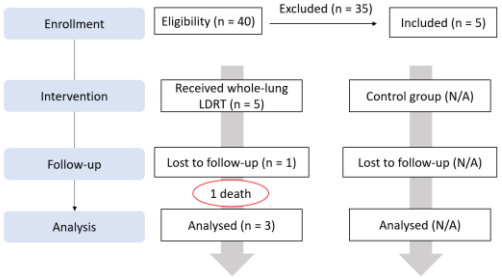
|---|---|---|---|---|---|---|
| Hess et al. (2021) |  | Inclusion:<br>- Patients tested positive for SARS-CoV-2;<br>- Patients with pneumonic consolidation on CXR or CT;<br>- Oxygen-dependent but non-intubated;<br>- Age: ≥ 18 years.<br><br>Exclusion:<br>- Pregnants;<br>- Administration of drugs therapies intended to treat COVID-19. | Establish low-dose, whole-lung radiation therapy (LD-RT) as a safe for patients with COVID-19 related pneumonia. | AP/PA | 40+<br>60+<br>65+<br>70+<br>80+<br>90+<br>100+ | 1.5 | Oxygen requirement; PaO2/FiO2; ARDS; CRP; LDH; Cardiac marker; Hepatic marker; Lymphocyte count; Renal biomarker; D-dimer; Myoglobin; Erytrocyte sedimentation rate; Ferritin; Fibrinogen; Procalcitonin; IL-6; TTCR (Time To Clinical Recovery); Chest radiograph changes; Radiotherapy toxicity (CTCAE) |
| Sanmamed et al. (2021) |  | Inclusion:<br>- Patients phase 2 (lung phase, develop a viral pneumonia, with cough, fever, and hypoxia PaO2/FiO2 < 300 mmHg);<br>- Patients phase 3 (hyperinflammatory phase, the disease manifests as an extrapulmonary systemic hyperinflammation syndrome);<br>- Age: ≥ 60 years.<br><br>Exclusion:<br>- Patients with severe comorbities that could hamper the radiation treatment<br>- Patients impossibility of holding a supine position. | Low-dose radiation therapy (LD-RT) as an anti inflammatory treatment in patients with COVID-19. | 3D-RT | 53<br>55<br>56<br>58<br>64<br>68<br>76<br>86<br>90 | 1 | SatO2/FiO2; Ferritin; Bood cell count; CRP; D-dimer; LDH; Radiotherapy toxicity (CTCAE); Radiologic response; Hospital discharge |
| Ameri et al. (2020) |  | Inclusion:<br>- Patientes who had clinical manifestations of COVID-19 with a positive polymerase chain reaction, antibody test, or radiographic pneumonic consolidations;<br>- Requiring oxygen supplmentation ≤ 93%;<br>- Age: > 60 years<br><br>Exclusion:<br>- Hemodynamic instability;<br>- Requiring mechanical ventilation;<br>- History of malignancy or heart failure;<br>- Contraindication for radiation therapy;<br>- Septic shock or end-organ failure;<br>- PaO2/FiO2 ≤ 100 mmHg. | Study to evaluate the clinical efficacy of low-dose whole-lung radiation therapy in patients with COVID-19 pneumonia. | AP/PA | 60<br>64<br>69<br>82<br>84 | 0.5 | O2 saturation; CRP; IL-6; P/F ratio; Temperature; Vital status; Performance status |

Table F.1. (*continued*)

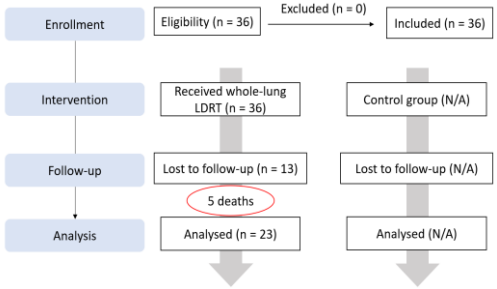
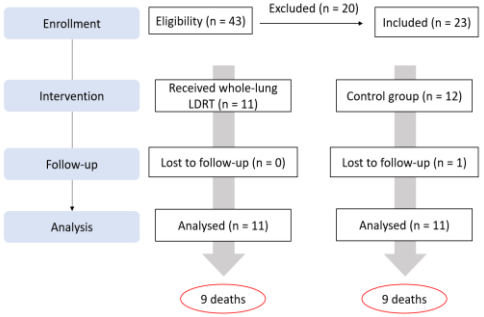
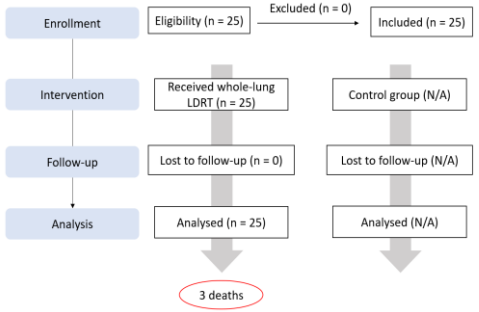
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Arenas et al. (2021) |  | Inclusion:<br>- Moderate or severe pneumonia;<br>- Not candidate for ICU;<br>- <8 days of sympton on-set;<br>- Age: > 18 years<br><br>Exclusion:<br>- Pregnancy;<br>- White cell count below 1000/ml | Evaluate the efficacy and safety of lung low-dose radiation therapy for pneumonia in patients with coronavirus disease 2019. | 2D | 50 - 100 | 0.5 | SpO2/FiO2; CRP; IL-6; Ferritin; D-dimer; LDH; PaO2/FiO2 |
| Darzikolaee et al. (2021) |  | Inclusion:<br>- Diagnosis of COVID-19 confirmed by PCR;<br>- Severe pneumonia due to COVID-19 with poor or no response to multiple lines of medical treatment;<br>- PaO2/FiO2 < 250 mmHg;<br>- Age: > 18 years<br><br>Exclusion:<br>- History of previous irradiation to the lung;<br>- Pregnancy | Assess whether low-dose whole-lung irradiation could provide any benefits for patients with refractory COVID-19 pneumonia. | AP/PA | 40 - 70 | 1 | O2 saturation; Overall survival; Mortality status; CXRS (Chest X-ray severity score) |
| Ganesan et al. (2021) |  | Inclusion:<br>- Diagnosis of COVID-19 confirmed by PCR;<br>- Fewer than 10 days of sympton;<br>- Moderate to severe dyspnea;<br>- Respiratory frequency ≥ 24/min<br>- SpO2 < 94%;<br>- SpO2/FiO2 ratio > 89 and < 357;<br>- Age: ≥ 40 years<br><br>Exclusion:<br>- Prior lobctomy or pneumonectomy;<br>- Actual or planned pregnancy;<br>- History of previous irradiation in a maximum lung dose of 100cGy;<br>- Prior chemotherapy and cancer immunotherapy;<br>- Severe pre-existing heart disease;<br>- History of bone narrow or solid organ transplantation | Evaluate this novel treatment option as an anti-inflammatory/immunomodulatory approach in moderate to severe diseased COVID-19 patients. | AP/PA | 40 - 59 (16 patients)<br>60 - 79 (8 patients)<br>> 80 (1 patient) | 0.5 | SpO2/FiO2; Lymphocyte count; Reduction in the need for oxygen supplementation; Time to clinical recovery; Time to hospital discharge |

Table F.1. (*continued*)

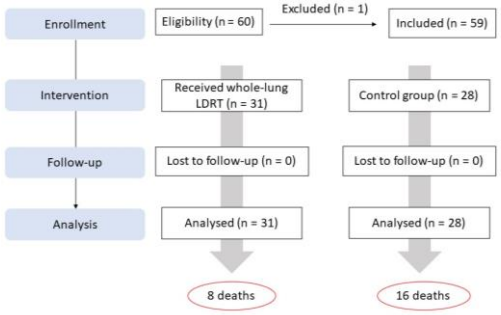
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ortiz et al. (2021) |  | Inclusion:<br>- PCR-confirmed COVID-19 pneumonia patients;<br>- Older than 18 years of age of both sexes;<br>- Moderate or severe acute distress respiratory syndrome (ADRS).<br><br>Exclusion:<br>- Patients with clinical findings of sepsis, haemodynamic instability, orotracheal intubation (OTI);<br>- Patients who did not agree to receive treatment with radiotherapy. | The primary objective of the study was to determine survival in patients treated with LD-WLI; the secondary objectives were to determine if there was a difference in orotracheal intubation, hypertension, diabetes, obesity and days of hospital stay. | AP/PA | 27 - 87 (Radiotherapy group)<br>36 - 87 (Control group) | 1 | SpO2/FiO2; Time to clinical recovery; Time to hospital discharge; requirement for orotracheal intubation (OTI); ARDS; |

Table F.2. Results of clinical trials using radiotherapy treatment for patients with COVID-19 pneumonia.

| Author | Follow-up | Deaths | Improvement of symptons | Adverse events |
|---|---|---|---|---|
| Papachristofilou et al. | Median follow-up was 45 days (range, 2-91) | 6 | Relative reductions in lymphocyte counts were more pronounced after LDRT. | No noticeable acute adverse events were observed |
| Moreno-Olmedo et al. | Median follow-up was 30 days | 0 | Both patients reported improvement of symptoms such as asthenia and dyspnea after 48h of treatment. In addition, the inflammatory parameters showed a decline, followed by some fluctuation and eventual stabilization. | No noticeable acute adverse events were observed, even after a 2-month follow-up period |
| Sharma et al. | Median follow-up was 15.7 days (range, 10-24) | 1 | Following NEWS status, improvement of symptons were noticed on day 3 | No noticeable acute adverse events were observed |

Table F.2. (*continued*)

| | | | | |
|---|---|---|---|---|
| Hess et al. | Median follow-up was 30 days | 1 patient died on hospital on day 16 after LDRT | Median time to clinical recovery was 3 days (range, 3 hours to 8.5 days) | One patient experienced Commom Terminology Criteria for Adverse Events grade 1 upper gastrointestinal acute toxicity within 24 hours follow LDRT delivery |
| Sanmamed et al. | Median time of hospitalization after LDRT was 13 days (range, 4-77) and overall was 59 days (range, 26-151) | One patient died 13 days after RT, and the other one, 34 days after RT | 72 hours after RT there was a significant improvent in 6 patients | 2 patients developed grade 2 lymphopenia 72 after RT, and 1 patient with baseline 3 worsened to grade 4 one week after RT |
| Ameri et al. (2020) | Median follow-up was 30 days | One patient died on the third day after irradiation | 4 patients showed initial improvement in O2 saturation and body temperature within 1 day after irradiation | During the observation, no acute skin, cardiac, pulmonary, or gastric toxicities were detected |
| Arenas et al. (2021) | Median follow-up was 30 days | 7 patients died in the first week and 1 patient died on day 11 following LDRT. 5 patients died from other causes during the follow-up. | 17 patients presented an improvement of SpO2/FiO2 24h after LDRT. At 1 week 4 patients did not present any improvement. After 1 month, none of 13 patients needed any supplemental oxygen | No noticeable acute adverse events were observed |

Table F.2. (*continued*)

| | | | | |
|---|---|---|---|---|
| Darzikolaee et al. (2021) | Median follow-up was 20 days (range, 7-104) | 9 | Mean O2 saturation in 8 out of 11 patients showed improvement in the first 24 h after RT. The final chest X-ray severity score was significantly lower | No noticeable acute adverse events were observed |
| Ganesan et al. (2021) | Median follow-up was 14 days post LDRT | 3 patients died after LDRT | Significant reduction in median lymphocyte count between pre-RT and day 7. Improvement in hypoxia with aa significant increase in SF ratio before and after LDRT. Median Time to Clinical Recovery was 3 days (range, 2-6) . | No noticeable acute adverse events were observed |
| Ortiz et al. (2021) | Median follow-up was 120 days | 8 (Radiotherapy group); 16 (Control group). | ARDS severity analyses: significantly better for the radiotherapy group compared with the control group. Regarding the requirement for orotracheal intubation (OTI), there was a tendency toward a decrease in patients treated with radiotherapy. | No noticeable acute adverse events were observed |