Review Article

Ionizing Radiation-Induced Non-Cancer Diseases

Kharman A. Faraj
Department of Physics, College of Science, University of Sulaimani, Kurdistan Region, Iraq

Abstract

People are exposed to both natural and artificial sources of ionizing radiation. The effects of high doses of radiation are known; however, the effects of low doses are still controversial. Several cohorts of epidemiological studies showed that high and low doses of ionizing radiation can induce noncancerous diseases in humans such as cardiovascular disease, brain injury, and liver disease. These diseases are classified as specific tissue reactions determined by threshold dose. In this article, the author reviews the role of radiation to induce the above nonmalignant diseases and outlines the relationship between exposure to ionizing radiation and diseases. At the end of the review evidence of the association between cardiovascular disease, brain injury, and liver disease and exposure to low and high doses of ionizing radiation was found through the presentation of several studies. Most epidemiological studies and authors have indicated an elevated risk of diseases upon exposure to low and high doses of the radiation

Keywords: Exposure, high dose, ionizing radiation, low dose, non-cancer diseases

Introduction

People are exposed to both natural and artificial sources of ionizing radiation. Exposure from natural sources includes mainly cosmic radiation, earthly sources, food, and water. Artificial sources involve nuclear decay in nuclear reactors, X-ray machines, cyclotrons, and radioactive waste management in the nuclear industry, but most sources are from diagnostic X-rays, nuclear medicine, and treatment.[1] Ionizing radiation is recognized as carcinogenic. Due to a lack of human evidence, its effects at doses below 100 mSv are still controversial.[2] Various factors such as the type of radiation, dose, dose rate, age, sex, and type of target have the main rules on increasing or decreasing the effects of the radiation. The reaction of the radiation may be with the critical target of human cells such as DNA or with the water inside the cell causing water radiolysis and then producing free radicals,[3] in both cases the results could be dangerous. Following the finding out of X-rays by Wilhelm Roentgen in 1895, the first biological damage related to ionizing radiation was discovered. The effect of radiation was based on the experience of early radiologists and mine workers.[4,5] The International Commission on Radiation Protection (ICRP) has categorized harmful ionizing radiation into stochastic and deterministic effects. Deterministic effects occur due to cell death or delayed cell division if a large number of cell deaths affect the function of the tissue or organ. In stochastic effects, cells do not die but change in some way leading to late effects such as carcinogenesis and genetic effects.[1,6] It is known that there are some diseases associated with exposure to ionizing radiation. The effects of the high dose of radiation are known but the characteristics of cancers and noncanine diseases are not clear or difficult. Focus on non-cancer diseases and studies are needed to record information about this point recommended by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 2008.[7]

In response to low and moderate doses, the risk of non-cancerous diseases such as heart disease, liver disease, etc. increases. Identifying risks is important to protect people and radiation protection systems. The idea for this review came after I conducted several surveys at different hospitals to detect the effect of low X-ray doses on the technicians, sometimes the technicians complain about heart disease, so the aim of this review was to discuss and

Access this article online

Quick Response Code:

Website: www.medjbabylon.org

DOI: 10.4103/MJBL.MJBL_238_22

Address for correspondence: Prof. Kharman A. Faraj, Department of Physics, College of Science, University of Sulaimani, Kurdistan Region, Iraq.
E-mail: kharman.faraj@univsul.edu.iq

Submission: 08-Oct-2022 **Accepted:** 13-Nov-2022 **Published:** 02-Aug-2023

How to cite this article: Faraj KA. Ionizing radiation-induced non-cancer diseases. Med J Babylon 2023;20:228-35.

overview some of these diseases (non-cancer diseases), presented the roles of low and high doses to induce such diseases, and what conditions should be obeyed by the people in order to protect themselves.

Ionizing radiation-induced heart diseases

The harmful effects of ionizing radiation on the cardiovascular system probably have a significant public health impact. Epidemiological studies have shown that very low radiation doses [≤1 gray (Gy)] typical of occupational, medical, or environmental exposures increase the hazard of cardiovascular disease (CVD) along time after exposure.[8-11] On the contrary, some studies have shown that there is no relation between a low dose of ionizing radiation and an elevated risk of CVD, which remains controversial.[12-15]

Heart disease associated with ionizing radiation has been conducted in several cohorts and epidemiological studies. One such study showed that a significant increase was observed between ischemic heart disease (IHD) and exposure to external doses of gamma rays ranging from below 100 mGy to more than 5 Gy of workers working at the Mike Plutonium Enrichment Plant.[16-19] In another study, Azimzadeh *et al*. suggested that exogenous radiation to gamma rays of workers increases the risk for IHD by preventing peroxisome proliferator-activated receptor (PPAR) alpha and altering the expression of cardiac mitochondrial, structural, and antioxidant components.[20] IHD and cerebrovascular diseases are more commonly caused by atherosclerosis and may lead to acute myocardial infarction and stroke.[21] A study of radiation workers on 61,017 Chornobyl rescue workers receiving an average cumulative dose of 0.109Gy resulted in a statistically significant dose risk of IHD and provided confirmation for the presence of a high dose risk of essential hypertension and essential cerebrovascular disease.[22] The results of a large cohort study showed that no significant, circulatory disease mortality was observed in 275,000 industrial workers who received an average dose of 20.7 mSv, from 15 countries.[23] McGeoghegan *et al.* found an association between mortality circulatory system disease and external exposure to ionizing radiation in their study of 42,426 radiation workers.[24] A study of 206,620 radiation workers in the industrial and medical fields was conducted by Ashmore *et al.* noted increased CVD mortality (male and female) and accidents (male only).[25] Stroke mortality increased but not significantly between 90,957 radiologic technologists performing fluoroscopically guided interventional procedures.[26] A meta-analysis of epidemiological data for low and intermediate doses was done by the Ionizing Radiation Advisory Group in 2010 which included different studies; they noted that there is a lot of heterogeneity in risk estimates between studies.[27] Little *et al.* extended analyze of the previous group and estimated the additional risk of four subgroups of circulatory diseases: HD, non-IHD, cerebrovascular disease, and all other diseases related to the circulatory system. A significant heterogeneous effect was observed between different studies for cerebrovascular disease and other circulatory diseases, but for IHD and IH was not recorded.[28] In general, from previous studies and others not reported here, it can be concluded that there is a significantly elevated risk of CVD for doses >0.5 Gy.[27,29]

Although there are functional differences between mouse and human hearts mouse models are frequently used in cardiology studies,[30] one of these studies was performed by Barjaktarovic *et al*., they exposed mice to local irradiation with the doses 0.2 Gy or 2 Gy their results showed that mitochondrial oxidative metabolism and mitochondria-associated cytoskeleton changed at this range of doses, they proposed that these first pathological changes lead to an increase of CVD after exposure to radiation.[31] Studies on some animals have been also performed, it has been observed acute pericarditis in rabbits, rats, and dogs after irradiation of their hearts to a single dose of 16–20 Gy.[32-34] For other studies and information on the association between ionizing radiation and CDV in mice, the readers can benefit from the references.[35-38]

Radiotherapy (RT) is now frequently used to treat cancer. More than half a percent of patients with cancer treated with RT are evaluated. Late cardiovascular effects are often seen in cancer survivors.[39] In the late 1960s, the association of CVD with high doses of ionizing radiation is recognized.[40] A number of studies have shown that one of the most popular side effects after RT of patients is CVD. Associations between therapeutic doses of chest radiation and elevated risk of CVD have been documented by several epidemiological studies. Experimental studies show that the expression of inflammatory and thrombotic molecules in endothelial cells is induced after exposure to doses >2 Gy, this leads to progressive capillary loss and ultimately leads to hypoperfusion and cardiomyocyte and fibroblast cell death in the heart. In large arteries, doses of >8Gy, combined with hypercholesterolemia, atherosclerosis predisposes to the production of inflammatory and unstable lesions, which are caused rupture and may lead to fatal heart attack or stroke.[41] The Early Breast Cancer Trialists Collaborative Group performed a meta-analysis of mortality data for more than 30,000 breast cancer patients after 15 years of treatment and observed a 27% increase in cardiac death in patients treated with both surgery and RT compared to patients treated with surgery alone.[42] Cardiac radiation doses are smaller in RT patients with right breast cancer than in RT patients with left breast cancer.[43] In Denmark and Sweden, a study was done in the period 1976 to 2006 on 72,134 women diagnosed with breast cancer observed an elevated risk of IHD, pericarditis, and valvular disease in women with left-sided tumors irradiation (mean cardiac dose 6.3 Gy) compared to women with right-sided tumors irradiation (mean cardiac dose 2.7 Gy).[44] Epidemiological investigations in

very large cohorts of patients who received postoperative RT for breast cancer show that radiation exposure to the heart with a single median equivalent dose of about 2 Gy significantly increased the risk of IHD after more than 10 years of radiation exposure.[45]

It has been shown that after irradiation of the human heart to treat Hodgkin's lymphoma vascular disease develops; the first case was reported and published in 1924. Among patients with irradiated Hodgkin lymphoma, the most common causes of death were cardiomyopathies and coronary artery disease, heart valvular disease, congestive heart failure, pericardial disease, and sudden death.[46-48] The heart may be exposed to radiation during RT of breast cancer; in a study of 2168 women with breast cancer treated by RT during 1958–2001 done by Darby *et al.* they showed that during RT of breast cancer cardiac exposure to radiation increased the rate of IHD. The rate increases with increasing the mean cardiac dose beginning within a few years after exposure and persisting for at least 20 years.[49]

Brain injury after exposure to ionizing radiation

It has been shown that radiation can be harmful to the brain. Most of the effects of radiation on the brain are found in the hippocampus.[50,51] Irradiation of the brain to high doses induces apoptosis and dysfunction of different cells associated with the hippocampal network and this leads to changes in synaptic protein levels, dendritic complexity, morphology, and changes in spine density.[52] It is recognized that increasing the dose (>2 to 45 Gy) can cause the inhibition of neurogenesis due to the radiosensitive of a population of neural stem cells and progenitors residing in the sub-granular region of the brainstem gyrus,[53] and this leads to neuroinflammation.[54,55] Central nervous system function can be altered by means of oxidative stress, mitochondrial dysfunction, and protein breakdown, this leads to programmed cell death and ultimately neurodegenerative disease after the brain is exposed to different doses, this process is shown in Figure 1.[56]

The brain may be exposed to radiation for both therapeutic and diagnostic medical interventions. For treating different types of brain tumors and head and neck cancers RT is a good choice. A dose in a medium range of 50–70 Gy is delivered in several fractions to the entire or a specific area of the brain. One of the goals of RT is to avoid exposure to healthy tissues but sometimes, it will occur according to some factors such as the radio sensitivity of the patients.[57] Brain injury is frequently observed when partial or whole brain irradiation is given during RT. Brain injury induction by ionizing radiation is classified into two types; acute injuries, early and late delay according to the time of clinical expression [Figure 2]. Symptoms of acute injury rarely occur with modern RT

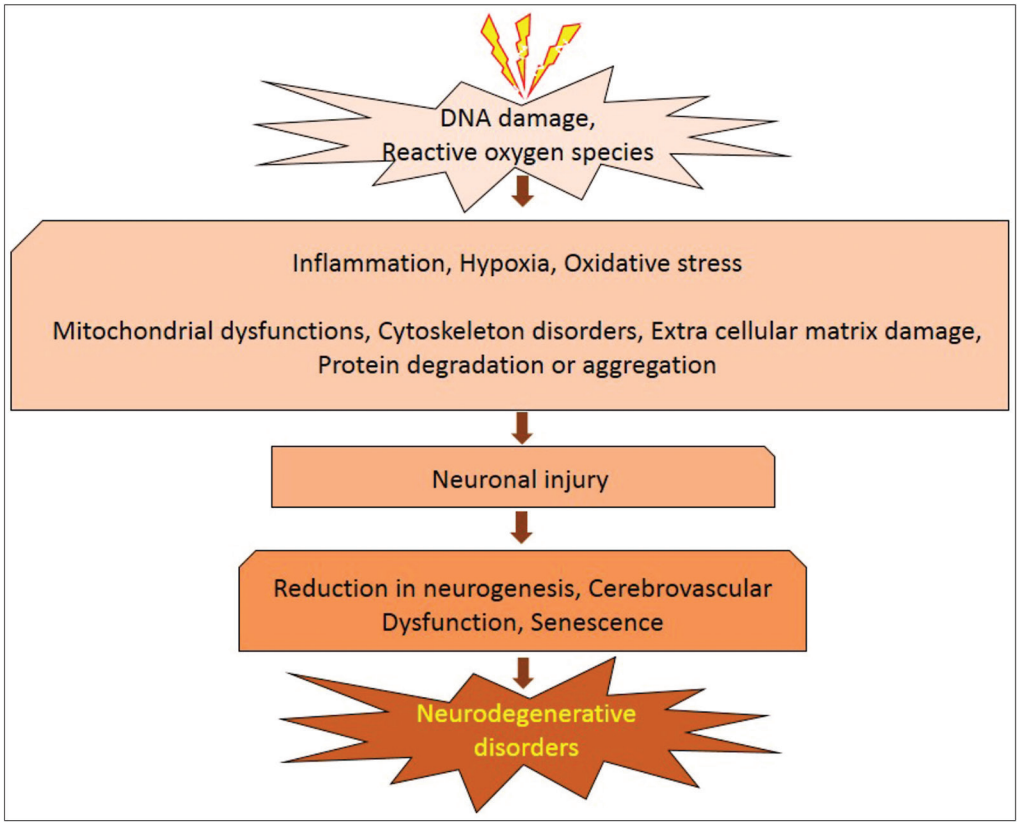

Figure 1: Neurodegenerative diseases induction after exposure to ionizing radiation[56]

techniques but sometimes appear hours to days after radiation, and are reversible. Symptoms of early brain injury include transient demyelination with drowsiness appearing one to six months after irradiation. Late brain injury develops after six months of irradiation and it is often irreversible and persistent, injury includes vascular abnormalities, demyelination, gliosis, and in severe cases white matter necrosis.[57,58]

During the treatment of different types of head and neck tumors using radiation, the brain may receive doses of ionizing radiation. It has been shown that congestive impairment increases in those patients.[59] The cognitive achievement of patients who irradiated their paranasal sinus was studied by Meyers *et al.*, and the delivered dose 60 Gy in fractions 1.8–2 Gy was used. They found memory weakness in 80%, learning difficulties in more than 50%, and difficulty with optical motor speed, executive functions of the frontal lobe, and fine motor coordination in more than 30% of the patients.[60] Paulino *et al.* reported severe cognitive deficit in children treated with RT for head and neck rhabdomyosarcoma and the symptoms appeared after 10 years of the treatment.[61] Patients with lung cancer are also at peril of growing late cognitive changes when their prophylactic brain is irradiated to decrease the rate of brain metastasis.[62,63] At the Hospital of Children in Philadelphia at the beginning of the 80s, a study on children was done, they received 24 Gy cranial irradiation for prophylactic purposes the result showed that a significant decrease in the total IQ score for the majority of children was observed, younger patients were more affected and those whom they did not have decreasing in IQ yet had learning deficits and no cognitive deficits in children treated with intrathecal chemotherapy alone.[64] One study found that 18Gy cranial irradiation could not be directly related to cognitive deficit due to low doses.[65] These studies explained that cognitive impairment arises from high-dose brain irradiation and its severity depends on certain factors such as patients' age and the irradiated brain region.[66] Several animal experiments and clinical studies have shown that hippocampal sensitivity is stabilized by stem cells of neurons, also confirmed by the most general neuronal changes hippocampus associated with memory deficits.[67-72]

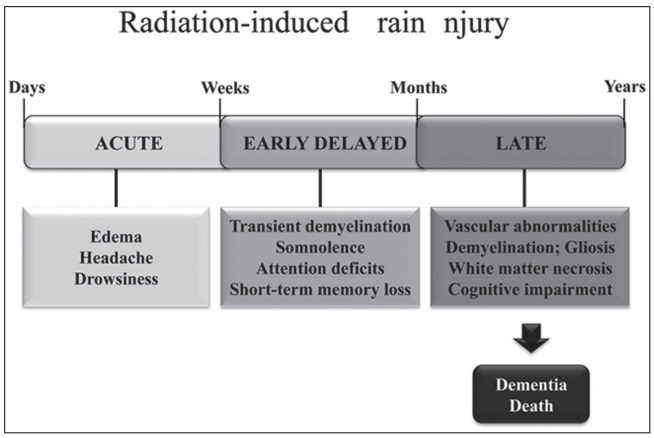

Figure 2: Types of ionizing injuries[59]

Due to diagnostic purposes, most of the population's brain is exposed to doses of below 100mGy. Some epidemiological studies have shown brain tumor risk increased in children during head computed tomography (CT) scan.[73-75] In another study, elevated brain cancer risks have been observed among technicians who performed fluoroscopically guided interventional procedures.[76] Increasing cognitive damage by head exposure to low doses of radiation has been investigated in several animal

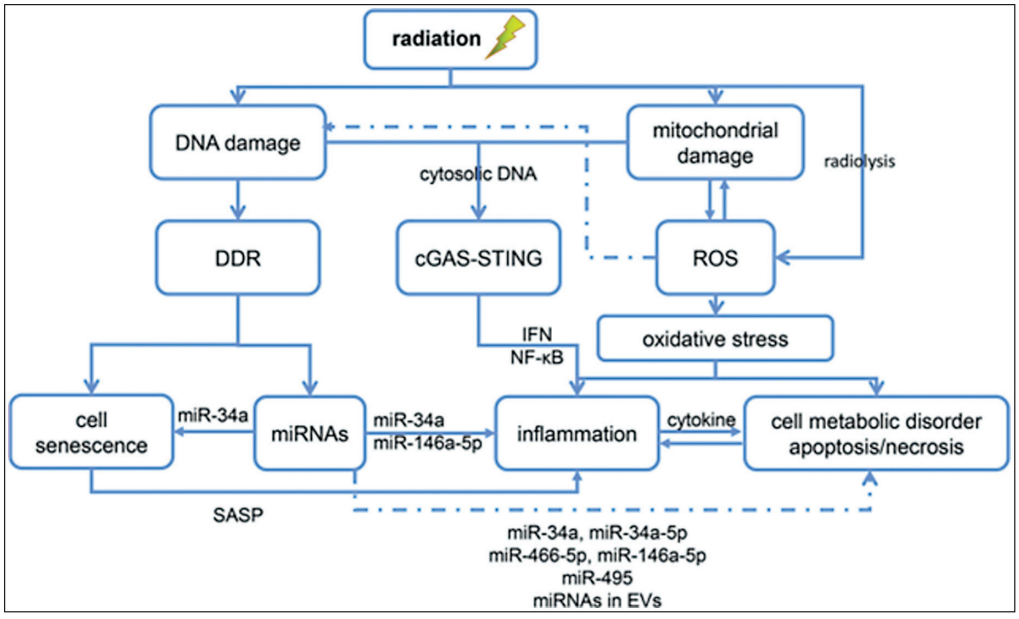

Figure 3: Different biological processes in radiation-induced injury[86]

experiments. Buratovic *et al.* established adult spontaneous behavioral alterations and impaired habituation capacity in very young mice exposed to doses (500 mGy), indicating high sensitivity of the young brain to radiation.[77]

Astronomers when flying into deep space exposed to different types of intense ionic radiation called cosmic rays. They interact directly with the critical target of a cell; the effects are mostly harmful and irreversible. It was supposed that exposure to heavy ions at a dose as low as 0.5Gy could induce paired neurogenesis with very poor or no recovery.[78] Lee *et al.* showed that energetic charged particles at low vacuum-relevant doses induce a surprising selective long-term plasticity in synaptic microcircuits in the hippocampus.[79] It was observed that whole-body irradiation to a low dose of protons could alter neurogenesis in the hippocampus.[80] Baulch *et al.* showed that radiation-induced changes in the redox state may render the brain more susceptible to the development of neurocognitive deficits that could affect an astronaut's ability to perform complex tasks during extended missions in deep space.[81]

Ionizing radiation-induced liver injury

The liver was considered to be a radiosensitive organ.[82] Oxidative stress caused by ionizing radiation can cause liver injury and this can lead to liver diseases.[83] It has been shown that liver function tests can be used to diagnose liver damage after radiation exposure.[84] It has been shown that perivascular fibrosis, sinus congestion, damage to Kupffer cells (KCs), and hepatocyte injuries are induced in humans after exposure to ionizing radiation.[85] The process of radiation-induced liver injury is shown in Figure 3.

A study belonging to the author observed that prolonged exposure to doses of X-rays from a traditional X-ray machine may significantly change the values of alanine transaminase (ALT), aspartate transaminase (AST), serum ferritin (s. ferritin), malondialdehyde (MDA), total protein, albumin, globulin, and glutathione (GSH) in technicians who received overdose at the workplace.[87] Shahid *et al.* concluded that radiation-induced injuries could occur in medical radiologists and therapists from low doses. Therefore, there is a need to check the liver function of humans exposed to radiation regularly.[88]

Nwokocha *et al.* found that upon total body irradiation of mice to 1.27 Gy/min for 5 days, ALT and AST levels significantly increased and bilirubin levels were different but not significant.[89] Several studies have reported decreased serum total protein and albumin levels following radiation exposure.[89-92] Barshishat-Kupper *et al.* reported a hepatic metabolic alteration with 8.5Gy radiations, leading to radiation-related carbonylation of hepatic enzymes.[93] In a study by Farid, I, and Conibear SA. showed the metabolic levels of AST, ALT, and bilirubin were highly associated with radiothorium exposure in occupational workers.[94] Elevated levels of AST, ALT, bilirubin, and albumin in female workers were highly associated with alpha emissions (50μCi) from the radium industry.[95]

Radiation may cause liver injury during RT. Different factors have rules of thumb to induce injury during radiotherapies such as baseline liver function, background liver cirrhosis, and liver volume in the planning target volume (PTV), dose per fraction, and type of modalities.[96] Dawson *et al.* studied 203 patients treated with conformal hepatic radiation therapy and concomitant hepatic artery chemotherapy and found that radiation-induced liver disease was not observed when the mean liver dose was below 31Gy in partial liver radiation.[97] Cao *et al.* reported radiation-caused hepatopathy in patients with intrahepatic carcinoma who received a radiation dose of (45-84) Gy.[98]

Liver parenchymal cell subunits have parallel structures that enable each subunit to function separately. This let high-dose therapy for small liver volumes as long as the mean normal liver dose remains within tolerable limits.[99]

Radiation protection systems should be used to minimize nonmalignant diseases. In radiation therapy, modern radiographic techniques have the rule of thumb to eliminate diseases. A systematic evaluation of these nonmalignant diseases is needed for radiologists who may be exposed to overdose in their workplace.

Radiation protection to avoid or reduce non-cancer diseases

Educating medical professionals about radiation protection and radiation safety issues may be an ongoing problem, mostly in developing countries. Despite the rules of radiation protection, there are mistakes and unexpected events that were not anticipated. Radiation protection procedures and policies are developed around an existing kit base and assuming a specific technology. As the number of procedures in diagnosis and higher-quality RT increases, radiation protection measures for both patients and staff members must evolve to continue the use of this modality in medical practice. There is an inexorable need to review and update all radiation protection policies and procedures as new equipment is adopted for clinical use. Insistence and verification to apply the principles that have all been called diagnosis and RT departments in hospitals are needed, especially in developing countries, to avoid unnecessary exposure to patients as well as staff. Education, knowledge of radiological results, and training of medical staff involved in diagnostic and treatment procedures are essential to the protection of patients and medical personnel.

Conclusions

This study is likely to enhance understanding in terms of the hazard of nonmalignant diseases after exposure to low or high doses of radiation. At the end of the review evidence of the association between CVD, brain injury, and liver diseases and exposure to different doses of ionizing radiation was found through the presentation of several studies. Most epidemiological studies and authors have indicated an elevated risk of diseases upon exposure to low and high doses of radiation. Although new radiological techniques in RT and diagnosis have decreased the incidence of disease, more research and studies are needed to formulate prevention and management guidelines. Ongoing epidemiological studies are required to affirm the results of the studies presented in the present review.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bohm EL, Hendry JF, Hill JR, Heron JM, Trott KL, Wondergem JC. Radiation Biology: A Handbook for Teachers and Students. Vienna: International Atomic Energy Agency; 2010. p. 94-8.
2. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of Ionizing Radiation, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2006 Report, Volume I: Report to the General Assembly, Scientific Annexes A and B. United Nations; 2008.
3. Cember H. Introduction to Health Physics. New York: The McGraw-Hill Companies; 2009.
4. Kassis AI. Therapeutic radionuclides: Biophysical and radiobiologic principles. Semin Nucl Med 2008;38:358-66.
5. Michal F, Nnunziata LA. Radioactivity Introduction and History. 1st ed. London : Elsevier Science; 2007.
6. Yan Y, Moros EG. In: Podgorsak EB, editors. Radiation Oncology Physics: A Handbook for Teachers and Students. Vienna: International Atomic Energy Association; 2005. 657 p.
7. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008 Report, Volume I: Report to the General Assembly, with Scientific Annexes A and B-Sources. United Nations; 2010.
8. Howe GR, Zablotska LB, Fix JJ, Egel J, Buchanan J. Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Radiat Res 2004;162:517-26.
9. Ivanov VK. Late cancer and noncancer risks among Chernobyl emergency workers of Russia. Health Phys 2007;93:470-9.
10. McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. The non-cancer mortality experience of male workers at British Nuclear Fuels Plc, 1946-2005. Int J Epidemiol 2008;37:506-18.
11. Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL, *et al*. Mortality and cancer incidence following occupational radiation exposure: Third analysis of the national registry for radiation workers. Br J Cancer 2009;100:206-12.
12. Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: Follow-up 1946-2003. Radiat Environ Biophys 2010;49:177-85.
13. Kreuzer M, Kreisheimer M, Kandel M, Schnelzer M, Tschense A, Grosche B. Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946-1998. Radiat Environ Biophys 2006;45:159-66.
14. Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987;55:179-90.
15. Davis FG, Boice JD, Jr., Hrubec Z, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer Res 1989;49:6130–6.
16. Azizova TV, Grigorieva ES, Hunter N, Pikulina MV, Moseeva MB. Risk of mortality from circulatory diseases in Mayak workers cohort following occupational radiation exposure. J Radiol Prot 2015;35:517.
17. Azizova TV, Muirhead CR, Druzhinina MB, Grigoryeva ES, Vlasenko EV, Sumina MV, *et al*. Cardiovascular diseases in the cohort of workers first employed at Mayak PA in 1948–1958. Radiat Res 2010;174:155-168. [CrossRef] [PubMed]
18. Azizova TV, Muirhead CR, Moseeva MB, Grigoryeva ES, Vlasenko EV, Hunter N, *et al*. Ischemic heart disease in nuclear workers first employed at the Mayak PA in 1948–1972. Health Phys 2012;103:3-14. [CrossRef] [PubMed]
19. Azizova TV, Grigoryeva ES, Haylock RG, Pikulina MV, Moseeva MB. Ischaemic heart disease incidence and mortality in an extended cohort of Mayak workers first employed in 1948–1982. Br J Radiol 2015;88:20150169. [CrossRef] [PubMed].
20. Azimzadeh O, Azizova T, Merl-Pham J, Subramanian V, Bakshi MV, Moseeva M, *et al*. A dose-dependent perturbation in cardiac energy metabolism is linked to radiation-induced ischemic heart disease in Mayak nuclear workers. Oncotarget 2017;8:9067-78. https://www.oncotarget.com/article/10424/text/.
21. Tapio S, Little MP, Kaiser JC, Impens N, Hamada N, Georgakilas AG, *et al*. Ionizing radiation-induced circulatory and metabolic diseases. Env J Int 2021;146:106235.
22. Breckenridge R. Heart failure and mouse models. Dis Model Mech 2010;3:138-43.
23. Barjaktarovic Z, Schmaltz D, Shyla A, Azimzadeh O, Schulz S, Haagen J, *et al*. Radiation–induced signaling results in mitochondrial impairment in mouse heart at 4 weeks after exposure to X-rays. PLoS One 2011;6:e27811. https://doi.org/10.1371/journal.pone.0027811.
24. McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946–2005. InJ Epidemiol 2008;37:506-18.
25. Ashmore JP, Krewski D, Zielinski JM, Jiang H, Semenciw R, Band PR. First analysis of mortality and occupational radiation exposure based on the national dose registry of Canada. Am J Epidemiol 1998;148:564-74.
26. Rajaraman P, Doody MM, Yu CL, Preston DL, Miller JS, Sigurdson AJ, *et al*. Incidence and mortality risks for circulatory diseases in US radiologic technologists who worked with fluoroscopically guided interventional procedures, 1994-2008. Occup Environ Med 2016;73:21-7.
27. McMillan TJ, Bennett MR, Bridges BA, Hendry J, Jones B, Kanthou C, *et al*. Circulatory Disease Risk. Report of the independent Advisory Group on Ionising Radiation.
28. Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis E, Chekin S, *et al*. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect 2012;120:1503-11.
29. Working Party on Research Implications on Health and Safety SotAGoE: Emerging evidence for radiation induced circulatory diseases. Radiation Protection No. 158. EU Scientific Seminar 2008, Luxembourg, November 25, 2008.
30. Ivanov VK, Maksioutov MA, Chekin SY, Petrov AV, Biryukov AP, Kruglova ZG, *et al*. The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. Health Phys 2006;90:199-207.

31. Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae JM, Engels H, *et al*. Mortality from diseases other than cancer following low doses of ionizing radiation: Results from the 15-Country Study of nuclear industry workers. Int J Epidemiol 2007;36:1126-35.
32. Fajardo LF, Stewart JR. Experimental radiation-induced heart disease. I. Light microscopic studies. Am J Pathol 1970;59:299-316.
33. Gavin PR, Gillette EL. Radiation response of the canine cardiovascular system. Radiat Res 1982;90:489-500.
34. Lauk S, Kiszel Z, Buschmann J, Trott KR. Radiation-induced heart disease in rats. Int J Radiat Oncol Biol Phys 1985;11:801-808.
35. Mitchel RE, Hasu M, Bugden M, Wyatt H, Hildebrandt G, Chen YX, *et al*. Low-dose radiation exposure and protection against atherosclerosis in ApoE(-/-) mice: The influence of P53 heterozygosity. Radiat Res 2013;179:190-9.
36. Mitchel RE, Hasu M, Bugden M, Wyatt H, Little MP, Gola A, *et al*. Low-dose radiation exposure and atherosclerosis in ApoE-/- mice. Radiat Res 2011;175:665-76.
37. Mancuso M, Pasquali E, Braga-Tanaka I III, *et al*. Acceleration of atherogenesis in ApoE-/- mice exposed to acute or low-dose-rate ionizing radiation. Oncotarget 2015;6:31263-71.
38. Le Gallic C, Phalente Y, Manens L, Dublineau I, Benderitter M, Gueguen Y, *et al*. Chronic internal exposure to low dose 137Cs induces positive impact on thestability of atherosclerotic plaques by reducing inflammation in ApoE-/- mice. PLoS One 2015;10:e0128539.
39. Yusuf SW, Sami S, Daher IN. Radiation-induced heart disease: A clinical update. Cardiol Res Pract 2011;2011.
40. Stewart JR, Fajardo LF. Radiation-induced heart disease. Clinical and experimental aspects. Radiol Clin North Am 1071;9:511-31.
41. Stewart FA. Mechanisms and dose-response relationships for radiation-induced cardiovascular disease. Ann ICRP 2012;41:72-9.
42. Clarke M. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. Lancet 2005;365:1687-717.
43. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005;6:557-65.
44. McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, *et al*. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011;100:167-75.
45. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys 2007;67:10-8.
46. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-termcause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431-9.
47. Hoppe RT. Hodgkin's disease: Complications of therapy and excess mortality. Ann Oncol 1997;8(Suppl 1):115-8.
48. Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, *et al*. Myocardial infarction mortality risk after treatment for Hodgkin disease: A collaborative British cohort study. J Natl Cancer Inst 2007;99:206-14.
49. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, *et al*. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987-98.
50. Harada KH, Niisoe T, Imanaka M, Takahashi T, Amako K, Fujii Y, *et al*. Radiation dose rates now and in the future for residents neighboring restricted areas of the Fukushima Daiichi Nuclear Power Plant. Proc Natl Acad Sci 2014;111:E914-23.
51. Pospisil P, Kazda T, Bulik M, Dobiaskova M, Burkon P, Hynkova L, *et al*. Hippocampal proton MR spectroscopy as a novel approach in the assessment of radiation injury and the correlation to neurocognitive function impairment: Initial experiences. Radiat Oncol 2015;10:1-8.
52. Parihar VK, Limoli CL. Cranial irradiation compromises neuronal architecture in the hippocampus. Proc Natl Acad Sci 2013;110:12822-7.
53. Acharya MM, Patel NH, Craver BM, Tran KK, Giedzinski E, Tseng BP, *et al*. Consequences of low dose ionizing radiation exposure on the hippocampal microenvironment. PLoS One 2015;10:e0128316.
54. Belarbi K, Jopson T, Arellano C, Fike JR, Rosi S. CCR2 deficiency prevents neuronal dysfunction and cognitive impairments induced by cranial irradiation. Cancer Res. 73, 1201-10.doi: 10.1158/0008-5472.CAN-12-2989
55. Greene-Schloesser D, Moore E, Robbins ME. Molecular pathways: Radiation-induced cognitive impairment. Clin Cancer Res 2013;19:2294-300.
56. Sharma NK, Sharma R, Mathur D, Sharad S, Minhas G, Bhatia K, *et al*. Role of ionizing radiation in neurodegenerative diseases. Front Aging Neurosci 2018;10:134.
57. Lumniczky K, Szatmári T, Sáfrány G. Ionizing radiation-induced immune and inflammatory reactions in the brain. Front Immunol 2017;8:517.
58. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol 2012;2:73.
59. Tang Y, Luo D, Rong X, Shi X, Peng Y. Psychological disorders, cognitive dysfunction and quality of life in nasopharyngeal carcinoma patients with radiation-induced brain injury. PloS One 2012;7:e36529.
60. Meyers CA, Geara F, Wong PF, Morrison WH. Neurocognitive effects of therapeutic irradiation for base of skull tumors. Int J Radiat Oncol Biol Phys 2000;46:51-5.
61. Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2000;48: 1489-95.
62. Cull A, Gregor A, Hopwood P, Macbeth F, Karnicka-Mlodkowska H, Thatcher N, *et al*. Neurological and cognitive impairment in long-term survivors of small cell lung cancer. Eur J Cancer 1994;30:1067-74.
63. Gondi V, Paulus R, Bruner DW, Meyers CA, Gore EM, Wolfson A, *et al*. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: Pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys 2013;86:656-64.
64. Meadows A, Massari D, Fergusson J, Gordon J, Littman P, Moss K. Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. Lancet 1981;318:1015-8.
65. Waber DP, Tarbell NJ, Fairclough D, Atmore K, Castro R, Isquith P, *et al*. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: Cranial radiation requires an accomplice. J Clin Oncol 1995;13:2490-6.
66. Lumniczky K, Szatmári T, Sáfrány G. Ionizing radiation-induced immune and inflammatory reactions in the brain. Front Immunol 2017;8:517.
67. Casciati A, Dobos K, Antonelli F, Benedek A, Kempf SJ, Bellés M, *et al*. Age-related effects of X-ray irradiation on mouse hippocampus. Oncotarget 2016;7:28040.
68. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, *et al*. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. J Clin Oncol 2014;32:3810.
69. Nageswara Rao AA, Ye H, Decker PA, Howe CL, Wetmore C. Therapeutic doses of cranial irradiation induce hippocampus-dependent cognitive deficits in young mice. J Neurooncol 2011;105:191-8.
70. Tomé WA, Gökhan Ş, Brodin NP, Gulinello ME, Heard J, Mehler MF, *et al*. A mouse model replicating hippocampal sparing cranial irradiation in humans: A tool for identifying new strategies to limit neurocognitive decline. Sci Rep 2015;5:1-1.
71. Pereira Dias G, Hollywood R, Bevilaqua MC, da Silveira da Luz AC, Hindges R, Nardi AE, *et al*. Consequences of cancer treatments on adult hippocampal neurogenesis: Implications for cognitive function and depressive symptoms. Neurooncology 2014;16:476-92.

72. Pinkham MB, Bertrand KC, Olson S, Zarate D, Oram J, Pullar A, *et al*. Hippocampal-sparing radiotherapy: The new standard of care for World Health Organization grade II and III gliomas? J Clin Neurosci 2014;21:86-90.
73. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, *et al*. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: Data linkage study of 11 million Australians. BMJ 2013;346.
74. Orbach DB, Stamoulis C, Strauss KJ, Manchester J, Smith ER, Scott RM, *et al*. Neurointerventions in children: Radiation exposure and its import. Am J Neuroradiol 2014;35:650-6.
75. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, *et al*. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. Lancet 2012;380:499-505.
76. Rajaraman P, Doody MM, Yu CL, Preston DL, Miller JS, Sigurdson AJ, *et al*. Journal club: Cancer risks in US radiologic technologists working with fluoroscopically guided interventional procedures, 1994-2008. Am J Roentgenol 2016;206:1101-9.
77. Buratovic S, Stenerlöw B, Fredriksson A, Sundell-Bergman S, Eriksson P. Developmental effects of fractionated low-dose exposure to gamma radiation on behaviour and susceptibility of the cholinergic system in mice. Int J Radiat Biol 2016;92:371-9.
78. Cacao E, Cucinotta FA. Modeling heavy-ion impairment of hippocampal neurogenesis after acute and fractionated irradiation. Radiat Res 2016;186:624-37.
79. Lee SH, Dudok B, Parihar VK, Jung KM, Zöldi M, Kang YJ, *et al*. Neurophysiology of space travel: energetic solar particles cause cell type-specific plasticity of neurotransmission. Brain Struct Funct 2017;222:2345-57.
80. Sweet TB, Panda N, Hein AM, Das SL, Hurley SD, Olschowka JA, *et al*. Central nervous system effects of whole-body proton irradiation. Radiat Res 2014;182:18-34.
81. Baulch JE, Craver BM, Tran KK, Yu L, Chmielewski N, Allen BD, *et al*. Persistent oxidative stress in human neural stem cells exposed to low fluences of charged particles. Redox Biol 2015;5:24-32.
82. Kłuciński P, Mazur BO, Kaufman JO, Hrycek A, Cieślik PA, Martirosian G. Assessment of blood serum immunoglobulin and C-reactive protein concentrations in workers of x-ray diagnostics units. Int J Occup Med Environ Health 2005;18:327-30. PMID: 16617848.
83. Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, *et al*. The role of oxidative stress and antioxidants in liver diseases. Int J Mol Sci 2015;16:26087-124.
84. Nwokocha CR, Nwokocha M, Mounmbegna P, Orhue J, Onyezuligbo O, Olu-Osifo EH, *et al*. Proteins and liver function changes in rats following cumulative total body irradiations. West Indian Med J 2012;61:773-7. PMID: 23757896.
85. Nwokocha CR, Nwokocha M, Mounmbegna P, Orhue J, Onyezuligbo O, Olu-Osifo EH, *et al*. Pathology and images of radiation-induced hepatitis: A review article. Jpn J Radiol 2018;36:241-56.
86. Zhu W, Zhang X, Yu M, Lin B, Yu C. Radiation-induced liver injury and hepatocyte senescence. Cell Death Discov 2021;7:244.
87. Kharman F. Occupational exposure of diagnostic technicians to X-ray may change some liver functions and proteins. Iran J Med Phys 2021;18:111-6. 10.22038/ijmp.2019.43559.1660.
88. Shahid S, Khalid M, Khan AW. Prediction of impacts on liver enzymes from the exposure of low-dose medical radiations through artificial intelligence algorithms. Revista da Associação Médica Brasileira 2021;67:248-59.
89. Nwokocha CR, Nwokocha M, Mounmbegna P, Orhue J, Onyezuligbo O, Olu-Osifo EH, *et al*. Proteins and liver function changes in rats following cumulative total body irradiations. West Indian Med J 2012;61:773-7. PMID: 23757896.
90. Holten I, Christiansen C. Unchanged parathyroid function following irradiation for malignancies of the head and neck. Cancer 1984;53:874-7.
91. Moulder JE, Fish BL, Cohen EP. Impact of angiotensin II type 2 receptor blockade on experimental radiation nephropathy. Radiat Res 2004;161:312-7.
92. Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: Causes, consequences, and treatment. Am J Kidney Dis 1994;23:331-46.
93. Barshishat-Kupper M, Tipton AJ, McCart EA, McCue J, Mueller GP, Day RM. Effect of ionizing radiation on liver protein oxidation and metabolic function in C57BL/6J mice. Int J Radiat Biol 2014;90:1169-78.
94. Farid I, Conibear SA. Hepatic function in previously exposed thorium refinery workers as compared to normal controls from the health and nutrition survey. Health Phys 1983;44:221-30.
95. Polednak AP. Long-term effects of radium exposure in female dial workers: Liver function and liver disease. Env Res 1979;18:454-65.
96. Cheng JC, Wu JK, Huang CM, Liu HS, Huang DY, Cheng SH, *et al*. Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: Dosimetric analysis and implication. Int J Radiat Oncol Biol Phys 2002;54:156-62.
97. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53:810–21, Erratum in: Int J Radiat Oncol Biol Phys 2002;53:1422.
98. Cao Y, Pan C, Balter JM, Platt JF, Francis IR, Knol JA, *et al*. Liver function after irradiation based on computed tomographic portal vein perfusion imaging. Int J Radiat Oncol Biol Phys 2008;70:154-60.
99. Benson R, Madan R, Kilambi R, Chander S. Radiation induced liver disease: A clinical update. J Egypt Natl Cancer Inst 2016;28:7-11.