Volume 22, No 2 | International Journal of Radiation Research, April 2024

The non-targeted effect increases the risk of the radiation-induced myocardial injury

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► ***Original article***

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Received: March 2023
Final revised: June 2023
Accepted: August 2023

Int. J. Radiat. Res., April 2024; 22(2): 289-295

DOI: 10.61186/ijrr.22.2.289

Keywords: *Ionizing radiation, abscopal effect, lipid peroxidation, oxidative stress, cytokines.*

ABSTRACT

Background: Radiotherapy is an important and effective modality in treating cancer patients. Radiation-induced cardiovascular injury is one of the consequences of radiotherapy due to undesired exposure of the heart. The non-targeted effects of radiation add to the risk of cardiovascular injury following radiotherapy. Accordingly, we investigated the abscopal effect of radiation in the myocardium of partially irradiated rats and compared the abscopal effect with the effect induced in the myocardium following either direct or sham irradiation. ***Materials and Methods:*** Twenty male rats divided into four groups; sham, 2Gy whole-body, 2Gy cranially- and 2Gy lower-limb irradiated, were used. Myocardium samples were collected and examined for MDA, p53, caspase 3, and glutathione reduced expression. Additionally, TGF-β and NF-κB expression levels were investigated. ***Results:*** Our data revealed elevated levels of lipid peroxidation in abscopal myocardium following cranial- /lower-limb irradiation with 2 Gy γ-radiation, as compared with the sham or whole-body irradiated groups. Similar behavior was noticed with p53 and caspase3 expression, suggesting apoptosis induction in the abscopal cardiomyocytes. The rise in lipid peroxidation and apoptosis markers in the abscopal myocardium was associated with an increase in glutathione reduced. The data propose oxidative stress induction in the myocardium following distant irradiation, which was further confirmed by the elevation in TGF-β and nuclear NF-κB expression. ***Conclusion:*** Abscopal effect was induced in the myocardium of partially-irradiated rats, suggesting increased risk of myocardial injury following localized radiotherapy.

INTRODUCTION

For decades, the biological effects of radiation have drawn the attention of the scientific community, especially with wide-ranging applications of radiation in various daily life activities. The medical uses of ionizing radiation represent the highest source of artificial exposure to ionizing radiation [1]. It has long been considered that only the irradiated cells exhibit the effects of radiation. However, in the 90s of the twentieth century, this concept was challenged by the data obtained by Nagasawa and Little [2] suggesting that not only the irradiated cells respond to irradiation but also non-irradiated cells neighboring the irradiated cells. These data gave rise to the concept of radiation-induced bystander effect. This concept has been expanded to encompass both the longer-lasting abscopal effects in entire organisms as well as effects connected to the synthesis of clastogenic components [3]. Abscopal effects, the in vivo form of bystander effects, refer to the response of tissues distant from the irradiated regions [4, 5]. According to the abscopal effect concept, direct or close irradiation is not necessary for the implementation of the radiation effects [5]. This notion includes both the effects on distant tumor metastasis [6-9] and normal tissues [10-14]. Despite the fact that the precise mechanism causing the abscopal effect is not yet clear, the abscopal effect is evident through numerous endpoints including apoptosis induction [10, 11], p53 overexpression, lipid damage [12], and protein damage [15].

Exposure to ionizing radiation results in generation of myriad of reactive oxygen/nitrogen species (ROS/RNS) [16], which mediate most of the biological effects of radiation either in the directly irradiated cells or in the distant cells in case of bystander and abscopal effects [17-20]. The reactive species, ROS and RNS disrupt various cellular processes and induce damage in the biological macromolecules [17, 18, 21, 22]. To maintain their redox balance, cells have various biochemical mechanisms including antioxidants and enzymes that neutralize the reactive species, such as glutathione (GSH), superoxide dismutase (SOD) and catalase. Despite these defense mechanisms, the radiation-induced excessive generation of ROS/RNS outperforms the capability of these mechanisms and results in the induction of oxidative stress (OS). The term "oxidative stress (OS)" describes a situation in which

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[DOI: 10.61186/ijrr.22.2.289]

the generation of reactive species overweighs the antioxidants. This leads to damage in the biological macromolecules. Therefore, OS has always been posited as a profound effect of exposure to ionizing radiation.

Advantaging from the detrimental effects of ionizing radiation, radiotherapy has been developed based on inducing the maximum damaging effect in tumor cells while sparing normal cells. However, the unmeant exposure of normal cells to radiation can introduce challenges to physicians and patients. In this regard, there has been an increase in awareness of the damage that radiotherapy can cause to the heart when exposed to radiation during the radiotherapy course. Cardiovascular diseases (CVD) are known side effects of radiotherapy and can develop immediately or years later [23]. Although modern radiotherapy techniques are designed to spare the organs at risk close to tumors, there is still a remarkable chance that the heart receives significant radiation doses while treating breast or lung cancers. Therefore, increasing the risk of CVDs. Recently, an increase in cardiovascular deaths by 2 fold in patients who experienced radiotherapy was reported [24]. Comparing this increase with a 7.2-fold increase in cardiovascular deaths in patients who experienced radiotherapy before the 1970s [25]. Despite the obvious improvement in mortality rates as a result of cardiovascular injuries following radiotherapy, a 2-fold increase in cardiovascular deaths is still a considerable challenge that needs to be considered.

Available data highlight the importance of inflammation and OS in radiation-induced CVD and demonstrate that majority of chemotherapeutic medications and irradiation can increase OS. There are burgeoning indications linking OS to cardiovascular disease incidence following radiotherapy. Oxidative degradation of the biological macromolecules such as proteins and lipids can result in cardiotoxicity since OS has long been recognized as a significant pathophysiological mediator of CVD. The high abundance of polyunsaturated fatty acids (PUFA) in the membrane of cardiomyocyte makes the myocardium more vulnerable to oxidative damage [26, 27]. The interaction of ROS/RNS with PUFA leads to lipid peroxidation and consequently damage to the cell membrane and cell apoptosis [11, 28]. Overproduction of ROS/RNS under pathophysiological conditions contributes significantly to the development of CVD. Clinical data have shown that patients receiving radiotherapy for left breast cancer have considerable risk of cardiovascular problems than those who received treatment for right breast cancer [29]. Tissue remodeling as a result of ROS/RNS attacks involves various correlated mediators of the inflammatory response, including transforming growth factor-beta (TGF-β) [30], tumor necrosis factor-alpha (TNF-α) [31], and nuclear factor kappa B (NF-κB) [32]. Myocardial cell inflammation and fibrosis cause restrictive cardiomyopathy [24].

In addition to the cardiovascular injury following direct irradiation, the emergence of the concept of abscopal effect adds to the risk of radiation-induced cardiac damage [33]. Based on the concept of the abscopal effect, every organ can be at risk following localized radiotherapy.

This study was designed to examine cardiac damage induced following abscopal irradiation. We investigated the abscopal effect induced in the myocardium of animals received cranial/lower-limb irradiation, in which the heart of the animals did not receive direct irradiation. The Lipid damage, alteration in endogenous antioxidant capacity, apoptosis induction, and inflammatory cytokines expression were investigated as markers of abscopal effect induction.

MATERIALS AND METHODS

Experimental animals

Twenty Sprague-dawley rat males (~3.5 months old) divided into four groups were used in this study. The first group is the sham group, in which the rats were not irradiated. The second group is the whole-body irradiated group, in which the rats were whole-body irradiated with 2Gy ϒ-radiation. The third group is the cranially-irradiated group, in which the rats were irradiated at the head only. The fourth group is the lower-limb irradiated group, in which only the right thigh of the rats was irradiated. Throughout the experiment, the rats were maintained at laboratory conditions of 20-24˚C and 12h light/dark cycle under a balanced diet with free access to food and water.

The rats were euthanized 24h post-irradiation, and samples from the myocardium of rats from the different groups were collected and preserved in a -80˚C freezer until use.

Experimental rats were purchased from the breeding facility at the National Research Centre animal house in Egypt.

Biochemical investigations

Lipid peroxidation was investigated by colorimetric quantification of malondialdehyde (MDA) using MDA detection kits (MD 2529, Bio-diagnostic, Egypt) following the manufacturer's protocol. The glutathione reduced concentration was measured by colorimetric method using the glutathione detection kit (GR 2511, Bio-diagnostic, Egypt), following the manufacturers protocol.

Enzyme-linked Immunosorbent Assay (ELISA) investigations

p53 detection

The levels of p53 were measured in samples from

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the animals of the different groups using a rat p53 Elisa kit (NBP2-75359, Novus Biologicals, USA) according to the manufacturer's protocol.

Caspase 3 detection

The levels of *caspase 3*, were measured in samples from the animals of the different groups using a highly sensitive enzyme-linked immunosorbent assay kit (HEA626Ra, Cloud-Clone Corp., USA) according to the manufacturer's protocol.

TGF-β detection

The levels of TGF-β were measured in samples from the animals of the different groups using an ELISA kit for transforming growth factor beta 1 (SEA124Ra, Cloud-Clone Corp., USA) according to the manufacturer's protocol.

NF-κB detection

The levels of NF-κB were measured in samples from the animals of the different groups using a rat nuclear factor-kappa B Elisa kit (CSB-E13148r, CUSABIO, USA) according to the manufacturer's protocol.

Irradiation

The experimental animals were irradiated with 2 Gy 1.25 MeV γ-radiation using ^{60}Co γ-radiator Theratron Gammabeam 100-80 (Best Theratronics Ltd, Canada) at a dose rate of 0.5 Gy/min. For each experimental group, different radiation fields were used to accommodate the designated target region with the five rats being irradiated at once. For whole-body irradiation, a field size of 30x30 cm was used to accommodate the whole body of the five rats. In the cranially-irradiated group, a field size of 30x3 cm was used to accommodate the heads of the five rats only while sparing the rest of their bodies. In the lower-limb irradiated group, the field size was adjusted to accommodate only the right thighs of the rats. To ensure uniformity of the radiation dose, we prevented the mobility of the animals during irradiation by anesthetizing the rats prior to irradiation using intraperitoneal injections of Ketamine and Xylazine cocktail (75 mg/kg and 5 mg/Kg, respectively). In addition, the rats in the sham-irradiated group were anesthetized too for adequate control comparisons.

Statistical analysis

Results are presented as the mean ± standard deviation (SD). Statistical analysis was performed using a student's t-test with data considered significant if the p-value ≤0.05 or less.

RESULTS

To examine the effect of abscopal irradiation on the myocardium, lipid damage, expression of apoptosis markers, and inflammatory cytokines were investigated. In both cases of abscopal irradiation, the myocardium was out of the irradiation field, hence did not receive direct irradiation.

Lipid peroxidation

Lipid peroxidation was investigated by quantifying the MDA levels in all of the groups. Our data in figure 1 show the percentage increase in MDA level in all irradiated groups relative to the sham group. The data show significantly elevated levels of MDA in all of the irradiated groups above the control level. The highest effect is reported in the cranially-irradiated group (~50%), while comparable levels were recorded in the whole-body (~24%) and lower-limb (~21%) irradiated groups.

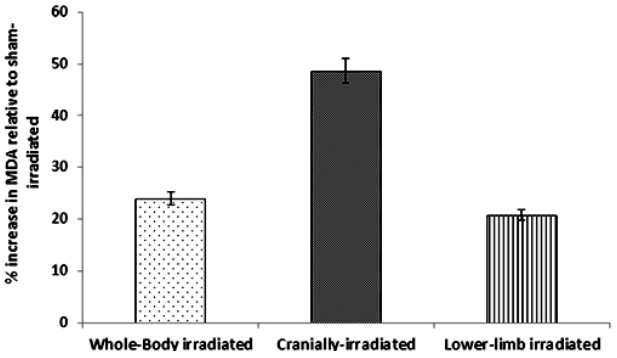

Figure 1. Percentage increase in the expression of lipid peroxidation product malondialdehyde (MDA) in the myocardium of whole-body, cranially-, and lower-limb irradiated groups relative to sham-irradiated group. The MDA measurements were performed for the different groups 24h post irradiation/sham-irradiation. Data presented as the mean ±SD.

Expression levels of p53 and caspase 3

The expression levels of two major apoptotic cell death signaling proteins; p53 and caspase3 were then investigated. Figure 2 shows the expression level of p53 protein in the myocardium of the four groups. The data show a significant increase (~2.5-fold) in the p53 concentration in all of the irradiated groups. The levels of p53 in both cranially- and lower-limb irradiated groups were comparable and slightly higher than that of the whole-body irradiated group.

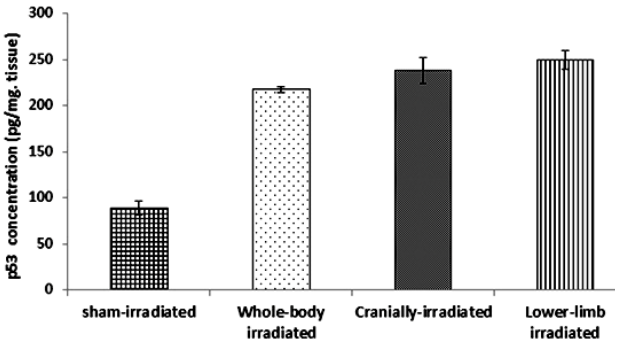

Figure 2. Expression level of p53 (pg/mg tissue) in the myocardium of sham-, whole-body, cranially-, and lower-limb irradiated groups. ELISA technique was used to measure the p53 level in the different groups 24h post irradiation/sham-irradiation. Data present as the mean ±SD.

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Similar to p53 data, caspase 3 data in figure 3 show significant increase in the caspase 3 levels in all of the irradiated groups. Compared to sham group, whole-body and cranially-irradiated groups reported ~3-fold increase. Nonetheless, lower-limb irradiated group recorded ~2 folds increase.

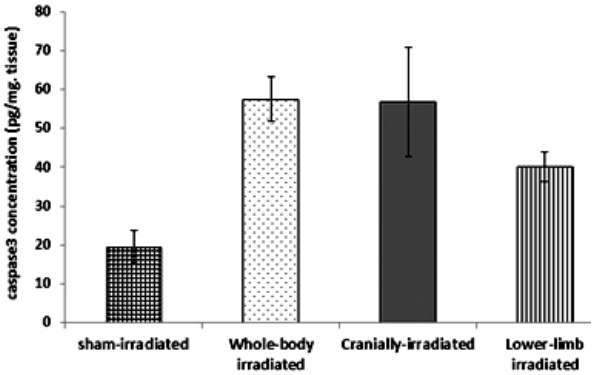


Figure 3. The expression level of caspase3 (pg/mg tissue) in the myocardium of sham-, whole-body, cranially-, and lower-limb irradiated groups. ELISA technique was used to measure the caspase3 level in the different groups 24h post irradiation/ sham-irradiation. Data presented as the mean ±SD.

Endogenous GSH antioxidant investigation

Figure 4 represents the percentage increase in GSH expression in the myocardium of whole-body, cranially-, and lower-limb groups relative to the sham-irradiated group. The data show significant increase in GSH expression in all irradiated groups. Percentage increase in the GSH levels in whole-body, cranially- and lower-limb irradiated groups were 135, 210, and 125%, respectively.

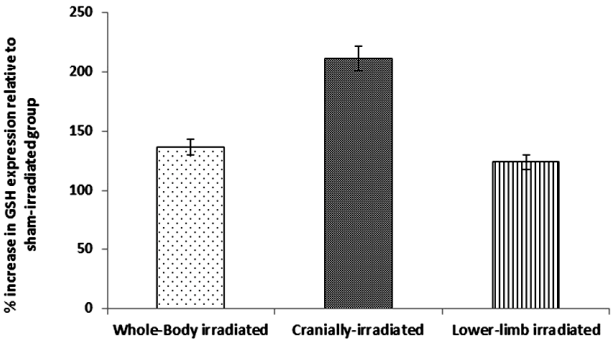


Figure 4. The percentage increase in GSH expression in the myocardium of whole-body, cranially- and lower-limb irradiated groups relative to the sham-irradiated group. GSH was measured in the different groups 24h post irradiation/ sham-irradiation using colorimetric technique. Data presented as the mean ±SD.

TGF-β expression

The expression level of TGF-β in myocardium was investigated. Figure 5 shows significant increase in TGF-β level in the whole-body (85 pg/mg.tissue), cranially- (125 pg/mg.tissue), and lower-limb (110 pg/mg.tissue) irradiated groups in comparison with sham-irradiated group (26 pg/mg.tissue). As it appears from the data, TGF-β levels the abscopal groups were higher than that of whole-body irradiated group.

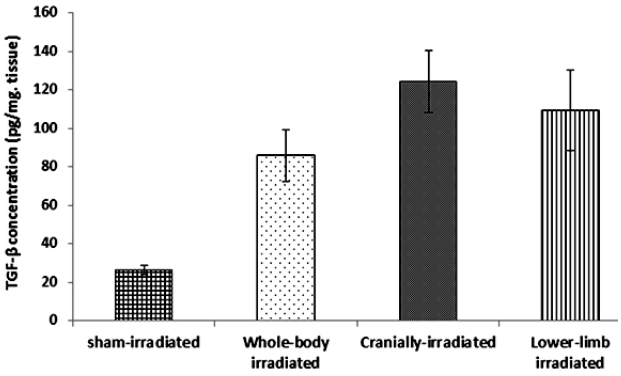
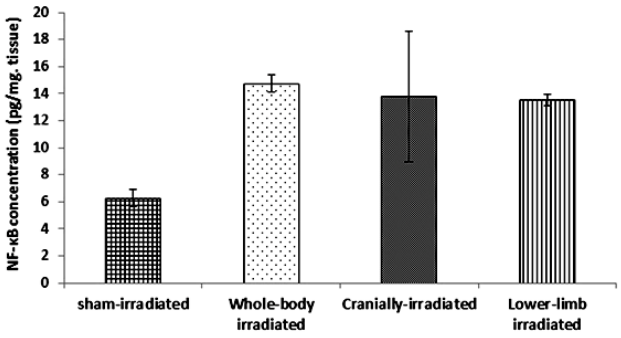


Figure 5. The concentration of Transforming Growth Factor β (TGF-β) (pg/mg.tissue) in the myocardium of sham-, whole-body, cranially-, and lower-limb irradiated groups. ELISA technique was used to measure the TGF-β concentration in the different groups 24h post irradiation/sham-irradiation. Data presented as the mean ±SD.

NF-κB expression

Figure 6 represents the concentration of NF-κB (pg/mg.tissue) recorded in the myocardium of the different groups. The figure shows comparable significant increase in the NF-κB expression in the whole-body (15 pg/mg.tissue), cranially- (14 pg/ mg.tissue), and lower-limb (14 pg/mg.tissue) irradiated groups as compared with the sham-irradiated group (6 pg/mg.tissue).



DISCUSSION

In this study, we investigate the effect of abscopal irradiation on the myocardium in the form of lipid damage, expression of apoptosis markers, and inflammatory cytokines. In abscopal irradiation, cranial or lower-limb irradiation, the myocardium was out of the irradiation field, hence did not receive direct irradiation. We first examined the lipid peroxidation in the myocardium of the sham-, whole-body, cranially-, and lower-limb irradiated groups. Our data in figure 1 shows an elevated level of MDA in all of the whole-body, cranially-, and lower-limb irradiated groups. However, the highest effect is detected in the cranially-irradiated group. Lipid peroxidation is one of the major causes of apoptotic cell death [34, 35]. Lipid peroxidation products can activate caspases, which activate DNA degrading enzymes leading to apoptosis induction [36]. Our data in figures 2 and 3 show that elevated levels of MDA in

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the whole or partial-body irradiated groups are associated with a significant increase in the expression of p53 and caspase3, two major signaling proteins in apoptotic cell death [37-39]. These data suggest the induction of p53-dependent apoptosis in the myocardium of whole-body, cranially-irradiated, and lower-limb irradiated groups. These data are concomitant with previously published data reporting an increase in the MDA level in abscopal splenocytes, which was also associated with an increase in the levels of p53 and caspase 3, indicating apoptosis induction [12, 14]. Ataxia telangiectasia-mutated (ATM) gene and DNA-dependent protein kinase are activated as a result of radiation-induced DNA damage, which phosphorylates p53 and causes cell cycle arrest. Cells will either repair DNA damage or begin apoptotic cell death via the tumour necrosis factor (TNF) death receptor route or the cytochrome c-mediated mitochondrial pathway [40].

Apoptotic cell death is activated by caspase3 and caspase7. Caspase3 is activated via both intrinsic and extrinsic apoptosis pathways [37]. Intrinsically, caspase3 is activated downstream of caspase9 activation following the mitochondrial outer membrane permeabilization of caspase activators into the cytoplasm. Extrinsically, caspase3 is activated downstream of TNF signaling, which recruits procaspase8 and cleaves caspase3.

The data in figure 4 shows that the increase in the MDA levels in the cardoimyocytes is also accompanied by an increase in the levels of glutathione reduced (GSH). GSH reduces the oxidative stress-induced peroxides in the cells and is reported to be crucial in controlling both cell growth and cell death [41]. GSH increase in three irradiated groups compared with the non-irradiated control is concomitant with the increase in the MDA levels in the same groups, in which the highest level was recorded in the cranially irradiated group with the whole-body and lower-limb irradiated groups showing comparable levels. Our results are in concomitant with previously published data [14] reporting overexpression of antioxidants in response to *in vivo* radiation-induced damage in a defense attempt to neutralize the overproduction of reactive species.

In addition to contributing to various signaling mechanisms, ROS can activate TGF-β in a positive feedback loop [42-44]. TGF-β is a cytokine with pleiotropic functions including controlling cell growth and differentiation [45], tumorigenesis [46], apoptosis [17, 18], and fibrosis induction [47]. The data in figure 5 show that, in comparison with the sham-irradiated group, all irradiated groups reported remarkable increase TGF-β expression. However, the cranially- and lower-limb irradiated groups reported higher levels of TGF-β than that of the whole-body irradiated group. These data suggest the induction of prolonged myocardial damage since active TGF-β plays key roles in radiation-induced fibrosis by initiating the upregulation of collagen and Smad-dependent pathways leading to myocardial infarction and heart failure [48]. Our data in figures 2,3 and 5 showing the association of TGF-β increase in the irradiated groups with an increase in the p53 and caspase 3 levels are in agreement with previous reports linking the activation of TGF-β to the activation of procaspase-3 and procaspase-7 [49-52].

Active TGF-β signaling through binding to TGFβR1 or TGFβR2 leads to stimulation of pro-apoptosis Bax through Smad2/3 (small mother against decapentaplegic 2/3) pathway [49]. Radiation stimulation of p53 leads to activation of initiator caspase3 [50, 51]. Initiator caspase-8 activation leads again to activation of procaspase-3 and procaspase-7 [52].

TGF-β activation also mediates NF-κB activation [53, 54], which is evident in our data by the overexpression of NF-κB in all of the irradiated groups (figure 6). NF-κB is a member of a group of transcription factors that can be activated in response to inflammatory cytokines signaling including TGF-β, TNF-α, interleukin-1, interleukin-4, and interleukin 13 [55]. NF-κB controls a variety of biological functions, such as the immune system, inflammation, cell growth, and apoptosis [56]. NF-κB is also activated by the overproduction of intracellular ROS. Activated NF-κB stimulates the production of intracellular ROS by increasing the expression of COX -2 and 5-LPO [57]. So, NF-κB is activated in a positive feedback mechanism by the radiation-induced intracellular ROS. Active NF-κB targets many pro-inflammatory genes, which in turn increases the risk of myocardium fibrosis and myocardium injury following irradiation. Our observations illustrated in figure 6 are in concordance with previous data, where gamma-irradiated rats showed an increase in cardiac NF-κB content [58] and the radiation-stimulation of NF-κB DNA binding activity in the non-targeted heart [59].

Our data show an evident abscopal effect in the myocardium in the form of lipid damage, antioxidant, and pro-inflammatory cytokine expression. The effects reported in this study show that the abscopal effect was in most cases greater than the effect of direct irradiation (in the whole-body irradiated group). Moreover, despite the differential response between the cranial and lower-limb irradiation results, the abscopal effect was still imminent. These data highlight the radiation risk to myocardium following direct irradiation and abscopal irradiation. So, the myocardium could be at risk of radiation injury even if it was not directly irradiated, which means magnification of the cardiac injury risk. However evident, the abscopal effect is still unpredictable and the signaling pathways responsible for it are yet known. Even though, the possibility of cardiac injury following exposure to

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ionizing radiation for example in radiotherapy should be considered.

CONCLUSIONS

Our data provide clear evidence of the abscopal effect induced in the myocardium of partially-irradiated rats, either cranially- or lower-limb irradiated rats highlighting a substantial possibility of heart injury following radiotherapy even when the heart was not directly irradiated. Hence, comprehensive follow-up is advised for cancer patients following radiotherapy treatment.

ACKNOWLEDGMENTS

The authors would like to acknowledge Prof. Gamal El-Bahy, NRC, Egypt, for study-related discussions.

***Funding*:** This work was partially supported by National Research Centre, Cairo (grant number 12020305) to cover the cost of experimental animals, assay kits, and analyses.

***Conflicts of interests*:** The authors declare no conflict of interest.

***Ethical consideration*:** All experimental procedures were approved by the Animal Care and Ethics Committee at the National Research Centre, Cairo, Egypt (approval no:17-018).

Author contribution: L.R. contributed to the investigations, data analysis, and manuscript preparation. A.A. designed the study, performed the irradiation, contributed to the investigations, performed data analysis, and prepared the manuscript.

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