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New therapeutic insights into radiation-induced myocardial fibrosis

Cheng-Xu Ma, Xin-Ke Zhao and Ying-Dong Li

***Abstract*:** Radiation therapy (RT) for the treatment of thoracic tumors causes radiation-induced heart disease (RIHD). Radiation-induced myocardial fibrosis (RIMF) is both an acute and chronic stage of RIHD, depending on the specific pathology, and is thought to be a major risk factor for adverse myocardial remodeling and vascular changes. With the use of more three-dimensional conformal radiation regimens and early screenings and diagnoses for RIMF, the incidence of RIHD is declining, but it still must be carefully investigated to minimize the mortality and morbidity of patients with thoracic malignancies after RT treatment. Effective methods for preventing RIMF involve a decrease in the direct radiation dose in the heart, and early screening and diagnosis. Medications remain as a useful adjunct for preventing or treating RIMF. This review mainly discusses the cellular and molecular mechanisms underlying RIMF, and new therapeutic drugs that can potentially be developed from this knowledge.

Keywords: miRNA, prevention and treatment of RIMF, radiation therapy, radiation-induced myocardial fibrosis (RIMF)

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Introduction

Radiation-induced heart disease (RIHD) is the leading cause of noncancer-related death, and may not present until several years after patients have undergone thoracic radiation therapy (RT). RIHD mainly manifests as asymptomatic myocardial ischemia, pericarditis (both acute and chronic forms), coronary artery disease (such as accelerated atherosclerosis), conduction abnormalities, valvulitis, myocarditis, and heart failure. With the use of more three-dimensional conformal radiation regimens, the heart toxicity that is associated with RT has declined, but must be carefully considered, in order to reduce the mortality and morbidity of patients with thoracic malignancies. In addition, RIHD is an important factor that restricts the radiation dose; thus, it can reduce the efficacy of the treatment of thoracic tumors.[1]

Radiation-induced myocardial fibrosis (RIMF) has both acute and chronic stages of RIHD, based on the specific pathology, and is thought to be a major risk factor for myocardial remodeling and vascular changes. Although patients may initially be asymptomatic, 10 years after RT, RIMF can subsequently result in restrictive or constrictive pericarditis and heart failure, which are lethal cardiovascular events. Thus, studies that include RIMF as an endpoint may contribute to the early prevention and diagnosis of radiation-induced heart toxicity.

RIMF is the result of a multifactorial interaction. Many studies have demonstrated that miRNAs, fibroblasts, transforming growth factor beta (TGF-β) and peroxisome proliferator-activated receptor (PPAR) alpha are implicated in the pathological processes of RIMF. At present, effective approaches for treating RIMF are limited, mainly because the pathogenesis has not been fully clarified. Therefore, it becomes pertinent to better understand the underlying pathophysiology of RIMF to develop optimal preventive and treatment strategies.

In fact, several existing drugs can reverse RIMF, at least partially. Recent research has shown that

Correspondence to:
Ying-Dong Li
Gansu University of Chinese Medicine, Lanzhou, 730000, PR China
lydj412@163.com

Cheng-Xu Ma
Gansu University of Chinese Medicine, Lanzhou, PR China

Xin-Ke Zhao
Department of Interventional Section, Affiliated Hospital of Gansu University of Chinese Medicine, Lanzhou, PR China

miRNAs may be a new therapeutic modality for RIHD, and new therapeutic approaches will be gradually discovered for the prevention and treatment of RIMF. The question of how to effectively prevent radiation myocardial injury after RT has become a topic of great research interest. In this paper, we will briefly review new advances in the pathophysiology of RIMF, and outline new therapeutic approaches to RIMF.

Epidemiology of RIMF

Radiotherapy is often used in patients with thoracic cancer. In some cases, the radiotherapy of tumors inevitably damages normal tissues, which results in an increased risk of cardiovascular disease, and may lead to structural and functional abnormalities in the coronary arteries, valves, pericardium, and myocardium. The incidence of major coronary events increases linearly with the mean cardiac radiation dose, leading to reported values of a 7.4% increase per Gy in breast cancer patients who received tangential fractionated breast irradiation,[2] a 33% increase per Gy in lung cancer patients after RT,[3] and an increase of more than 1.5–3 times in patients with risk factors after mediastinal RT.[4] Although breast cancer patients are usually considered to be fairly healthy, the RT of thoracic cancers may result in secondary heart events after several decades.

Risk factors for RIMF

Several studies have proposed that the first step in assessing patients with thoracic tumors after RT for a high incidence of RIMF is the assessment of the traditional risk factors of cardiovascular events.[5,6] These risk factors include current myocardial diseases (such as heart failure, coronary artery disease, left ventricular dysfunction, dilated cardiomyopathy, and restrictive cardiomyopathy), demographic risk factors of coronary artery disease (such as age, sex, family history of coronary artery disease, diabetes mellitus, arterial hypertension, and hypercholesterolemia), a history of RT of the chest or mediastinum, and lifestyle factors (such as smoking, drinking, sedentary habits, and risk factors for metabolic syndrome). In addition, primitive dosimetry techniques, extended RT fields, and high RT doses may be significant for the development of RIMF.[7] Even with the support of new RT technologies and regimens, such as image-guided radiotherapy and dimensional dosimetry, an association between RT and the incidence of cardiovascular mortality seems to exist.[8] The RT dose that is delivered to the heart should be reduced to prevent cardiac toxicity. Moreover, many chemotherapeutic agents have cardiotoxic effects, and the risk of cardiac toxicity may be increased when RT is combined with or more of these chemotherapeutic agents.[9] Tjessem reports that there is no evidence that low-to-moderate cardiac radiation doses contribute to the development of radiation-induced cardiovascular disease.[10] However, a recent report by Boaventura demonstrates that low-dose radiation exposure is also a risk factor for RIHD.[11] Moreover, Coleman demonstrates that low-dose radiation affects the molecular responses and gene expression levels in cardiomyocytes.[12] Finally, the number and severity of risk factors for RIMF should be identified for patients with thoracic tumors before the use of RT. If necessary, patients with high-risk factors should be assessed by experts in this field. In most cases, the presence of cardiovascular risk factors usually does not have an influence on the decision to use RT in thoracic tumors, except in cases of known, severely reduced cardiac function of any origin.

Pathology and pathophysiology of RIMF

RIMF is characterized by a nonspecific, diffuse interstitial fibrosis and develops through three phases of injury. The first phase is the onset of acute inflammation at approximately 6 h after radiation in small and medium-sized arteries, with a neutrophilic infiltrate in all layers of the heart.[13] In the first few minutes, the endothelial cells of myocardial capillaries that are exposed to radiation are activated with increased permeability, thus inducing early acute endothelial inflammation,[14] that may adversely transfer to the nonirradiated surrounding cells[15]; subsequently, neutrophils are recruited, and inflammatory cytokines, such as monocyte chemotactic factor, tumor necrosis factor (TNF), and interleukins (IL-1, IL-6, and IL-8), are released, which then leads to increased levels of neutrophil and lymphocyte infiltration.[16] After a few hours of irradiation, monocytes differentiate into the M2 subset of macrophages that secretes transforming growth factor β (TGF-β), which is responsible for the differentiation of fibroblasts into myofibroblasts.[17] In addition to the acute inflammatory responses,

there are immediate expressions of proto-oncogenes, including c-myc and c-jun, which may contribute to late fibrotic changes.[18] These prior studies in other organ systems suggest that similar changes may also occur in the irradiated heart.

The latent phase begins approximately 2 days after radiation and involves the mild progression of fibrosis with the progressive injury of endothelial cells in the myocardial capillaries of the healthy pericardium and myocardium, which then results in stenosis of the lumen, thrombosis formation, myocardial cell death, and fibrosis. In addition, the proinflammatory surroundings that are induced by radiation are powerful stimulators of fibrosis, wherein myocardial fibroblasts are recruited from the endocardium, epicardium, neural crest, and bone marrow. These changes eventually lead to collagen deposition and endothelial cell proliferation. The extracellular matrix deposition by fibroblasts results in the late pathologic dysfunctions of myocytes, vascular endothelial cells, and the pericardium.[19] On the other hand, ionizing radiation can induce the premature differentiation of fibroblasts. The premature differentiation cycles of fibroblasts that are exposed to ionizing radiation are shorter than that of naturally differentiated cells, thus resulting in an increase in postmitotic fibroblasts, which are five-to-eight times more active in secreting collagen and extracellular matrix than progenitor fibroblasts. The deposition of collagen and extracellular matrix components can produce a fibrotic scar that reduces the functionality of the affected tissue.

The late phase occurs approximately 70 days after radiation and involves extensive fibrosis in experimental animal models.[13] The chronic effects of radiation on tissues of the heart lead to RIMF, and, eventually, result in a decrease in elasticity and distensibility, thus leading to a reduction in ejection fraction and cardiac failure.[16]

Radiation-induced accelerated atherosclerosis is also a side effect of thoracic radiation therapy. In this situation, the exposure of macrophages to radiation produces inflammatory signals and induces the ingestion of lipids to transform into foam cells in the intima of the vessel wall. In the media, smooth muscle cells differentiate into myofibroblasts that secrete collagen and extracellular matrix, with these myofibroblasts subsequently entering the intima and leading to the formation of inflammatory plaques with high collagen and fibrin contents.[20] Moreover, plaque formation that is induced by radiation may be more prone to rupture and intraplaque hemorrhage, with notably increased levels of macrophages and granulocytes and without elevated levels of systemic inflammatory markers, in the intima of mice. Lipid cores have been observed to be larger in female mice and slightly smaller in male mice.[21] Moreover, the mid and distal left anterior descending arteries are primarily involved in RIMF.[22]

Early screening and diagnosis for RIMF

Early radiation-induced heart toxicity is usually asymptomatic, but pathological damage still progresses. The early screening and diagnosis of RIMF is crucial for patients with thoracic tumors after RT. Serum cardiac biomarkers, including both troponin I (TnI) and brain natriuretic peptide (BNP) (which are markers of other forms of injury in the heart, such as necrosis or myocardial cell death), may be useful for assessing radiation-induced cardiac damage, and seem to be superior to the use of echocardiography.[23]

BNP levels do not become significantly elevated until 1 month after radiation, and these levels begin to decrease at 12 months after radiation in breast cancer patients.[24,25] Furthermore, BNP levels have been observed to be associated with radiation-induced cardiac damage in 5-year breast cancer survivors after radiotherapy.[26] The levels of BNP/NT-proBNP (typically >100 pg/ml/>300 pg/ml) indicate the risk of adverse events in all patients who are at risk for heart disease.[27] Several studies have demonstrated that serum levels of TnI and BNP are correlated neither with cardiac radiation dose nor adverse cardiovascular events;[28] however, these controversial conclusions may be related to the differences in time in measuring serum markers and doses of radiation.

Multimodality cardiac imaging, which involves the use of echocardiography, computed tomography, cardiac magnetic resonance, and nuclear cardiology, is recommended for the early identification and monitoring of cardiovascular complications of radiotherapy.[29] The use of multimodality cardiac imaging depends on local expertise and availability, and the use of this method should adhere to the following principles:[5]

(1) The combination of the uses of echocardiography and cardiac MRI is a very attractive method in the assessment of clinical cardiotoxicity.
(2) Modalities with the best reproducibility are preferred.
(3) Imaging modalities that provide additional relevant clinical information are preferred (e.g. the evaluations of right ventricular dysfunction, pulmonary pressure, valvular function, and pericardial evaluation).
(4) High-quality, radiation-free imaging is preferred, if available.

Electrocardiogram and echocardiography are the preferred tools used for the assessment of the cardiovascular complications of radiation because of the ability of these tools to assess the left ventricular ejection fraction, to provide the strain and strain rate that are used to distinguish constrictive and restrictive forms of cardiomyopathy, and to evaluate myocardial ischemia, right ventricular dysfunction, and valvular heart disease. In addition, advanced cardiac magnetic resonance can assess simultaneous functional and structural data, with regards to myocardial inflammation, stress-rest perfusion defects, and fibrosis.[30] However, the uses of nuclear techniques and cardiac computed tomography are limited because of the radiation exposure to the heart. Cardiac catheterization can provide definitive data of the coronary artery anatomy and the pulmonary artery pressure with the risk of invasive instrumentation.[31]

Multiple types of DNA damage-associated biomarkers are induced by radiation, such as cytogenetic (e.g. micronuclei, translocations, and dicentrics), proteomic (e.g. γ-H2AX, pATM, and pP53), genomic (e.g. mRNA and SNPs), and epigenomic (e.g. miRNA and lncRNA) biomarkers.[32] These biomarkers are available for the monitoring of DNA damage and repair and can contribute to the early screening and diagnosis of RIMF. Recently, most of the fully automated and high-throughput analysis platforms available have been developed to detect and analyze the DNA damage-associated biomarkers for the evaluation of early radiation exposure. Although these markers have their own limitations for clinical applications, the changes in gene expression profiling upon radiation exposure occur in seconds to days, which may be potentially useful for the assessment of radiation exposure and the identification of radiosensitive patients.[33] DNA damage-associated biomarkers can help clinicians in designing tailored treatments for cancer patients.

Extracellular vesicles, including microparticles, apoptotic bodies, and exosomes, which contain proteins, nucleic acids, and chemicals, are derived from the original cells of myocardial capillaries that are exposed to radiation, and can interact with the recipient cells *via* membrane surface receptors to mediate cell-to-cell communication, microRNA transfer, and radiation-induced, non-targeted effects.[34] Different extracellular vesicles display characteristic expression profiles of mRNA and microRNA;[35] therefore, the identification of characteristic molecules in the vesicles can be potential biomarkers of radiation toxicity in the heart.

Novel drugs used to treat RIMF

The mechanism of RIMF has not yet been fully elucidated, but it is known that fibrosis can ultimately lead to congestive heart failure, malignant arrhythmia, and, eventually, sudden cardiac death. RIMF can also result in isolated right heart failure or left ventricular diastolic dysfunction. The endothelium of the vasculature is the initial target of radiation damage. Thus, pharmaceutical interventions for the maintenance of endothelial function and for the reversal of fibrosis are potential treatment strategies for RIMF.

Several potential drugs for RIMF are listed in Table 1. All of the potential drugs for preventing RIMF have been investigated in preclinical studies, and there are only a few reports available in humans.

Currently, the antioxidant amifostine is approved in the United States for reducing the toxicities of cancer treatment in certain types of cancer. However, amifostine has several side effects, such as nausea and vomiting; therefore, it may not be very commonly prescribed for cancer patients. The use of amifostine as a potential countermeasure for RIMF can inhibit oxidative stress and delay myocardial fibrosis to maintain the endothelium of the vasculature. Amifostine administration prior to irradiation has been demonstrated to significantly decrease the development of vasculitis in the heart, to improve coronary flow, aortic

Table 1. Several potential drugs for RIMF.

Substance	Effective for RIMF in theory	Target	Safety	Evidence
Amifostine	Yes[36]	Eliminate free oxygen radicals	Yes	Preclinical
ACE inhibitors	Yes[37]	Inhibit ACE Reverse adverse myocardial remodeling	Yes	Preclinical
Statins	Yes[38]	Inhibit hydroxy methylglutaryl coenzyme A reductase Promote DNA damage repair	Yes	Preclinical
Colchicine	Yes[39]	Inhibit mitosis Microtubule-disassembling agent Anti-inflammatory and anti-fibrotic activity	Yes	Preclinical
Sestrin2	Yes[40]	Regulate cardiomyopathy (such as myocardial fibrosis) after irradiation	–	Preclinical
IPW-5371	Yes[41]	Inhibit TGF-β receptor 1	–	Preclinical
RhNRG-1β	Yes[42]	Maintain mitochondrial integrity	–	Preclinical
miRNA-21 inhibitors	Yes[43]	Inhibit miRNA-21	–	Preclinical
Fibrates	$ [44]	PPAR-α agonist	–	Preclinical
Pentoxifylline	Yes[45]	Dimethylxanthine derivative	–	Preclinical
Alpha-tocopherol	–[45]	Eliminate free oxygen radicals	–	Preclinical
Tocotrienols	Acute phase: Yes Chronic phase: No[46]	Protect against oxidative stress	–	Preclinical
Molecular hydrogen	Yes[47]	Regulate miRNA-1, –15b, and –21	–	Preclinical
Black grape juice	Yes[48]	Protect against lipid peroxidation	Yes	Preclinical
Thalidomide	No[49]	Protect against inflammation and fibrosis	Yes	Preclinical

_No data or not indicated.
$Limited effects.
ACE, Angiotensin-converting-enzyme; PPAR, peroxisome proliferator-activated receptor; RIMF, Radiation-induced myocardial fibrosis; TGF-β, transforming growth factor beta.

flow, and cardiac output, and to reduce cardiac histological damage.[36,50] Other antioxidants, such as vitamin C and vitamin E, exhibit efficient cardioprotection in patients with malignancies at 3 weeks after RT.[51] Furthermore, two randomized trials suggest that antioxidant vitamin supplementations can reduce acute adverse effects in patients with head and neck cancer during RT; however, caution is advised because antioxidant vitamin administration has been demonstrated to compromise the effects of tumor control during RT.[52,53]

Angiotensin-converting-enzyme (ACE) inhibitors are known to be able to reverse adverse myocardial structural changes, and ACE inhibitors, such as captopril, can reduce radiation-related pleural and pericardial effusions to improve left

ventricular end-diastolic pressure in rats.[37] However, captopril cannot improve the progressive deterioration of cardiac function after irradiation.[54] There is no evidence to support the cardioprotective effects of ACE inhibitors with low-dose radiation. Similarly, based on the current preclinical data *in vitro* and *in vivo*, statins and hydroxy methylglutaryl coenzyme A reductase inhibitors can mitigate RIMF *via* the inhibition of the TGF-β/Smad3/RhoA/ROCK, PI3K/AKT signaling pathways and the expression of connexin-43 and miRNA-21 in rat heart,[43,55] as well as *via* the reduction in inflammation and the promotion of DNA damage repair that are induced by radiation.[38] In addition, the use of atorvastatin has also been observed to reverse left ventricular remodeling and to prevent decreases in left ventricular ejection fraction.[55] A retrospective analysis demonstrated that incidental statin use in patients with head and neck cancer during RT reduces the risk of cerebrovascular events,[56] but there is a lack of data on the efficacies of the statins against cardiac radiation injury. Existing data indicate that statins can prevent RIMF.

A clinical trial revealed that colchicine diminishes infarct sizes in patients with ST-segment elevation myocardial infarctions by increasing the expression of interleukin-10 (IL-10) and by inhibiting the expression of TGF-β.[57] Colchicine is a classic microtubule-disassembling agent that prevents antifibrotic effects and may be a new therapeutic alternative for the treatment of cardiovascular diseases.[39] Due to its anti-inflammatory and anticoagulant properties, colchicine has been hypothesized to be a promising agent in the treatment of radiation-induced coronary artery disease; however, the side effects of this drug limits its long-term or higher dose use.[58]

Fibrates, which are PPAR-α agonists, have a greater effect on decreasing serum lipoprotein levels than do statins.[59] A meta-analysis of clinical trials revealed that fenofibrate adversely affects cystatin C levels and has a limited effect on reducing cardiovascular events.[44] PPAR-α agonists demonstrate positive effects on both coronary heart disease and ischemic heart disease, but whether PPAR-α agonists are successful in treating RIHD remains to be determined. The anti-inflammatory effects of PPAR-α agonists are explicitly protective, whereas the promotion of systemic energy metabolism may be adverse because of the reduced cardiac lipid supply, which demonstrates a need to develop a tailor-made PPAR-α agonist treatment for RIMF.

A treatment combining pentoxifylline and alpha-tocopherol has previously been shown to reduce radiation fibrosis in the skin in clinical studies; therefore, these drugs have been selected for preclinical studies of radiation-induced heart disease.[60] A combination therapy using pentoxifylline and alpha-tocopherol for the treatment of RIMF has a positive effect of ameliorating left ventricular function by downregulating the expression of TGF-β, both when this therapy is given before and during radiation.[61] However, the withdrawal of the drugs after the 12th week of radiation can result in a rebound effect on the development of myocardial fibrosis.[62] Sridharan subsequently reported that the use of pentoxifylline alone, or in combination with tocopherol, from 3 months to 6 months after irradiation cannot rectify myocardial fibrosis and can change intracellular signals. Moreover, the use of pentoxifylline alone adversely affects the rhythm of the heart after irradiation. Whether or not tocopherol reduces the numbers of mast cells and promotes the expression of tissue factors, which contribute to the prophylaxis of RIMF, remains to be established.[45] These studies were performed in rat models of local heart irradiation.

New pharmacological drugs that inhibit radiation-induced heart toxicity after RT, such as sestrin2,[40] IPW-5371,[41] recombinant neuregulin-1 beta (rhNRG-1β),[42] and miRNA-21 inhibitors,[43] are being developed for the treatment of RIMF. Currently, these data are being collected from animal models.

Other interventions for the treatment of RIHD, including tocotrienols,[46] molecular hydrogen,[47] black grape juice,[48] and thalidomide,[49] have been tested (see Table 1).

Cell therapies for RIMF

National Institutes of Health/ National Institute of Allergy and Infectious Diseases (NIH/NIAID) and Institut de Radioprotection et de Sûreté Nucléaire (IRSN) workshops have reported that cell therapies have the potential ability to treat cardiomyocyte loss that is induced by RT.[63] Human-induced pluripotent stem cells that are exposed to a low, average, absorbed dose of less than 10 Gy differentiate into beating cardiac myocytes, but the differentiation ability of pluripotent stem cells

declines with increasing radiation doses.[64] A mesenchymal stem cell transplantation from the bone marrow ameliorates RIMF and reduces acute inflammatory reactions *via* DNA damage repair in a rat model.[65] Cardiac stem cells are currently recognized as being ideal stem cells that regenerate and repair lesions in the heart.[63] Under certain conditions, epithelial cells can transform into mesenchymal cells, in a process called epithelial to mesenchymal transition (EMT), and contribute to pulmonary fibrosis.[66] Pluripotent stem cells commonly acquire *TP53* mutations, which then increases the risk of cancer formation.[67] How to choose the best cell therapy for use in cases of large-scale, heavily irradiated patients will be determined in future studies.

Future prospects

Based on the above results, we conclude that decreasing the direct radiation doses in the heart, as well as early screenings and diagnoses, are crucial to preventing RIMF. Medications remain a useful adjunct to prevent or treat RIMF. miRNAs and cell therapies appear to be highly promising as novel therapeutic targets for the mitigation or prevention of RIMF, and clinical trials will be required to test the potential interventions for radiation-induced heart disease.

RIMF is the final pathological process of RIHD. The exploration of the potential genetic changes of the human body in radiation environments may further reveal the pathological mechanism of RIHD. The combination of transcriptomics, proteomics, and metabolomics is an enviable tactic for identifying potential biomarkers and therapeutic targets for RIHD. Our knowledge of the new pathophysiology and therapeutic approaches for RIMF may contribute to the prophylaxis and therapy of radiation-induced heart toxicity.

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ORCID iD

Cheng-Xu Ma https://orcid.org/0000-0001-6115-9806

References

1. Davis M and Witteles RM. Radiation-induced heart disease: an under-recognized entity? *Curr Treat Options Cardiovasc Med* 2014; 16: 317.
2. Darby SC, Ewertz M, McGale P, *et al*. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987–998.
3. Ming X, Feng Y, Yang C, *et al*. Radiation-induced heart disease in lung cancer radiotherapy: a dosimetric update. *Medicine (Baltimore)* 2016; 95: e5051.
4. Heidenreich PA, Schnittger I, Strauss HW, *et al*. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol* 2007; 25: 43–49.
5. Zamorano JL, Lancellotti P, Rodriguez Munoz D, *et al*. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 2768–2801.
6. Cuomo JR, Sharma GK, Conger PD, *et al*. Novel concepts in radiation-induced cardiovascular disease. *World J Cardiol* 2016; 8: 504–519.
7. Yusuf SW, Venkatesulu BP, Mahadevan LS, *et al*. Radiation-induced cardiovascular disease: a clinical perspective. *Front Cardiovasc Med* 2017; 4.
8. Al-Kindi SG and Oliveira GH. Incidence and trends of cardiovascular mortality after common cancers in young adults: analysis of surveillance, epidemiology and end-results program. *World J Cardiol* 2016; 8: 368–374.
9. Mege A, Zioueche A, Pourel N, *et al*. Radiation-related heart toxicity. *Cancer Radiother* 2011; 15: 495–503.
10. Tjessem KH, Bosse G, Fossa K, *et al*. Coronary calcium score in 12-year breast cancer survivors after adjuvant radiotherapy with low to moderate heart exposure – Relationship to cardiac radiation dose and cardiovascular risk factors. *Radiother Oncol* 2015; 114: 328–334.
11. Boaventura P, Duraes C, Mendes A, *et al*. Is low-dose radiation exposure a risk factor for

atherosclerotic disease? *Radiat Res* 2018; 189: 418–424.

12. Coleman MA, Sasi SP, Onufrak J, *et al.* Low-dose radiation affects cardiac physiology: gene networks and molecular signaling in cardiomyocytes. *Am J Physiol Heart Circ Physiol* 2015; 309: H1947–H1963.
13. Adams MJ, Hardenbergh PH, Constine LS, *et al.* Radiation-associated cardiovascular disease. *Crit Rev Oncol Hematol* 2003; 45: 55–75.
14. Liu LK, Ouyang W, Zhao X, *et al.* Pathogenesis and prevention of radiation-induced myocardial fibrosis. *Asian Pac J Cancer Prev* 2017; 18: 583–587.
15. Philipp J and Azimzadeh O. Radiation-induced endothelial inflammation is transferred via the secretome to recipient cells in a STAT-mediated process. *J Proteome Res* 2017; 16: 3903–3916.
16. Madan R, Benson R, Sharma DN, *et al.* Radiation induced heart disease: pathogenesis, management and review literature. *J Egypt Natl Canc Inst* 2015; 27: 187–193.
17. Yarnold J and Brotons MC. Pathogenetic mechanisms in radiation fibrosis. *Radiother Oncol* 2010; 97: 149–161.
18. Sherman ML, Datta R, Hallahan DE, *et al.* Ionizing radiation regulates expression of the c-jun protooncogene. *Proc Natl Acad Sci U S A* 1990; 87: 5663–5666.
19. Taunk NK, Haffty BG, Kostis J B, *et al.* Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. *Front Oncol* 2015; 5.
20. Cuomo JR, Javaheri SP, Sharma GK, *et al.* How to prevent and manage radiation-induced coronary artery disease. *Heart* 2018; 104: 1647–1653.
21. Stewart FA, Heeneman S, Te Poele J, *et al.* Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006; 168: 649–658.
22. Nilsson G, Holmberg L, Garmo H, *et al.* Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012; 30: 380–386.
23. Nellessen U, Zingel M, Hecker H, *et al.* Effects of radiation therapy on myocardial cell integrity and pump function: which role for cardiac biomarkers? *Chemotherapy* 2010; 56: 147–152.
24. Palumbo I, Palumbo B, Fravolini ML, *et al.* Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: a prospective study. *Breast* 2016; 25.
25. Demissei BG, Freedman G, Feigenberg SJ, *et al.* Early changes in cardiovascular biomarkers with contemporary thoracic radiation therapy for breast cancer, lung cancer, and lymphoma. *Int J Radiat Oncol* 2019; 103: 851–860.
26. Portaluri M, Petruzzelli MF, Tramacere F, *et al.* B-type natriuretic peptide plasma level in 5-year breast cancer survivors after radiotherapy. *Int J Radiat Biol* 2019; 95: 201–206.
27. Wayne Causey M and Singh N. Clinical implications of B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide in the care of the vascular surgery patient. *Semin Vasc Surg* 2014; 27: 143–147.
28. Kuo AH, Ancukiewicz M, Kozak KR, *et al.* Cardiac and inflammatory biomarkers do not correlate with volume of heart or lung receiving radiation. *Radiat Oncol* 2015; 10.
29. Lancellotti P, Nkomo VT, Badano LP, *et al.* Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013; 14: 721–740.
30. Desai MY, Jellis CL, Kotecha R, *et al.* Radiation-associated cardiac disease: a practical approach to diagnosis and management. *JACC Cardiovasc Imaging* 2018; 11: 1132–1149.
31. Mavrogeni S, Koutsogeorgopoulou L, Dimitroulas T, *et al.* Complementary role of cardiovascular imaging and laboratory indices in early detection of cardiovascular disease in systemic lupus erythematosus. *Lupus* 2017; 26: 227–236.
32. Lee WH, Nguyen PK, Fleischmann D, *et al.* DNA damage-associated biomarkers in studying individual sensitivity to low-dose radiation from cardiovascular imaging. *Eur Heart J* 2016; 37: 3075–3080.
33. Manning G and Rothkamm K. Deoxyribonucleic acid damage-associated biomarkers of ionising radiation: current status and future relevance for radiology and radiotherapy. *Br J Radiol* 2013; 86: 20130173.
34. Flamant S and Tamarat R. Extracellular vesicles and vascular injury: new insights for radiation exposure. *Radiat Res* 2016; 186: 203–218.

35. Crescitelli R, Lasser C, Szabo TG, *et al*. Distinct RNA profiles in subpopulations of extracellular vesicles: apoptotic bodies, microvesicles and exosomes. *J Extracell Vesicles* 2013; 2.
36. Gurses I, Ozeren M, Serin M, *et al*. Histopathological efficiency of amifostine in radiationinduced heart disease in rats. *Bratisl Lek Listy* 2018; 119: 54–59.
37. Van Der Veen SJ, Ghobadi G, De Boer RA, *et al*. ACE inhibition attenuates radiation-induced cardiopulmonary damage. *Radiother Oncol* 2015; 114: 96–103.
38. Fritz G, Henninger C and Huelsenbeck J. Potential use of HMG-CoA reductase inhibitors (statins) as radioprotective agents. *Brit Med Bull* 2011; 97.
39. Chaldakov GN. Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases. *Cell Biol Int* 2018; 42: 1079–1084.
40. Zeng YC, Chi F, Xing R, *et al*. Sestrin2 protects the myocardium against radiation-induced damage. *Radiat Environ Biophys* 2016; 55: 195–202.
41. Rabender C, Mezzaroma E, Mauro A G, *et al*. IPW-5371 proves effective as a radiation countermeasure by mitigating radiation-induced late effects. *Radiat Res* 2016; 186: 478–488.
42. Gu A, Jie Y, Sun L, *et al*. RhNRG-1beta protects the myocardium against irradiation-induced damage via the ErbB2-ERK-SIRT1 signaling pathway. *PLoS*.2015; 10.
43. Viczenczova C, Kura B, Egan Benova T, *et al*. Irradiation-induced cardiac connexin-43 and miR-21 responses are hampered by treatment with atorvastatin and aspirin. *Int J Mol Sci* 2018; 19.
44. Sahebkar A, Simental-Mendia LE, Pirro M, *et al*. Impact of fibrates on circulating cystatin C levels: a systematic review and meta-analysis of clinical trials. *Ann Med* 2018; 1–22.
45. Sridharan V, Tripathi P, Sharma S, *et al*. Effects of late administration of pentoxifylline and tocotrienols in an image-guided rat model of localized heart irradiation. *PLoS*.2013; 8.
46. Sridharan V, Tripathi P, Aykin-Burns N, *et al*. A tocotrienol-enriched formulation protects against radiation-induced changes in cardiac mitochondria without modifying late cardiac function or structure. *Radiat Res* 2015; 183: 357–366.
47. Kura B, Kalocayova B, Lebaron TW, *et al*. Regulation of microRNAs by molecular hydrogen contributes to the prevention of radiation-induced damage in the rat myocardium. *Mol Cell Biochem* 2019; 457: 61–72.
48. De Freitas RB, Boligon AA, Rovani BT, *et al*. Effect of black grape juice against heart damage from acute gamma TBI in rats. *Molecules* 2013; 18: 12154–12167.
49. Hoving S, Seemann I, Visser NL, *et al*. Thalidomide is not able to inhibit radiation-induced heart disease. *Int J Radiat Bio* 2013; 89: 685–691.
50. Kruse JJ, Strootman EG and Wondergem J. Effects of amifostine on radiation-induced cardiac damage. *Acta oncologica (Stockholm, Sweden)* 2003; 42: 4–9.
51. Wagdi P, Rouvinez G, Fluri M, *et al*. Cardioprotection in chemo- and radiotherapy for malignant diseases – an echocardiographic pilot study. *Praxis* 1995; 84: 1220–1223.
52. Bairati I, Meyer F, Gelinas M, *et al*. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. *J Clin Oncol* 2005; 23: 5805–5813.
53. Meyer F, Bairati I, Fortin A, *et al*. Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: a randomized trial among head and neck cancer patients. *Int J Cancer* 2008; 122: 1679–1683.
54. Yarom R, Harper IS, Wynchank S, *et al*. Effect of captopril on changes in rats' hearts induced by long-term irradiation. *Radiat Res* 1993; 133: 187–197.
55. Zhang K, He X, Zhou Y, *et al*. Atorvastatin ameliorates radiation-induced cardiac fibrosis in rats. *Radiat Res* 2015; 184: 611–620.
56. Addison D, Lawler PR, Emami H, *et al*. Incidental statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer. *J Stroke* 2018; 20: 71–79.
57. Bakhta O, Blanchard S, Guihot AL, *et al*. Cardioprotective role of colchicine against inflammatory injury in a rat model of acute myocardial infarction. *J Cardiovasc Pharmacol Ther* 2018; 23: 446–455.
58. O'Herron T and Lafferty J. Prophylactic use of colchicine in preventing radiation induced coronary artery disease. *Med Hypotheses* 2018; 111.

59. Sahebkar A, Simental-Mendia LE, Watts G F, *et al*. Comparison of the effects of fibrates versus statins on plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of head-to-head randomized controlled trials. *BMC Med* 2017; 15.

60. Delanian S, Porcher R, Rudant J, *et al*. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; 23: 8570–8579.

61. Boerma M, Roberto KA and Hauer-Jensen M. Prevention and treatment of functional and structural radiation injury in the rat heart by pentoxifylline and alpha-tocopherol. *Int J Radiat Oncol Biol Phys* 2008; 72: 170–177.

62. Liu H, Xiong M, Xia YF, *et al*. Studies on pentoxifylline and tocopherol combination for radiation-induced heart disease in rats. *Int J Radiat Oncol Biol Phys* 2009; 73: 1552–1559.

63. Dicarlo AL, Tamarat R, Rios CI, *et al*. Cellular therapies for treatment of radiation injury: report from a NIH/NIAID and IRSN workshop. *Radiat Res* 2017; 188: e54–e75.

64. Baljinnyam E, Venkatesh S, Gordan R, *et al*. Effect of densely ionizing radiation on cardiomyocyte differentiation from human-induced pluripotent stem cells. *Physiol Rep* 2017; 5.

65. Gao S, Zhao Z, Wu R, *et al*. Bone marrow mesenchymal stem cell transplantation improves radiation-induced heart injury through DNA damage repair in rat model. *Radiat Environ Biophys* 2017; 56: 63–77.

66. Gomperts BN and Strieter RM. Stem cells and chronic lung disease. *Annu Rev Virol* 2007; 58.

67. Merkle FT, Ghosh S, Kamitaki N, *et al*. Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations. *Nature* 2017; 545: 229–233.