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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Effects of Radiotherapy in Coronary Artery Disease

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Abstract

Purpose of Review This review describes the effects of radiotherapy (RT) on coronary artery disease, its mechanisms, and clinical and laboratory evidence and discusses ways to minimize radiation-induced coronary atherosclerosis.

Recent Findings Radiation-induced cardiac toxicity is known in patients undergoing thoracic RT. One of the damages occurs in the coronary arteries, with accelerated atherosclerosis manifesting decades later. There is clinical and laboratory evidence of coronary damage in retrospective studies, systematic reviews, and meta-analyses. Clinical studies have shown that RT cardiotoxicity occurs decades after radiation, regardless of chemotherapy, and may occur earlier in patients with pre-existing risk factors or disease.

Summary The pathogenesis of radiation-induced coronary artery disease is complex and multifactorial, including endothelial dysfunction, altered vascular tone, hemostatic imbalance, and inflammatory activation. Some factors are responsible, such as mean heart dose, RT chest site, patient position, techniques, and breathing maneuvers. There are approaches to reduce radiation-induced cardiac toxicity. Among them, besides the mentioned factors, metformin and anti-inflammatory agents can minimize coronary damage, with impact on morbidity and mortality.

Keywords Radiotherapy · Radiation · Cancer · Cardiovascular disease · Heart toxicity

Introduction

Data from the International Cancer Research Agency show that lung cancer is the most commonly diagnosed cancer (11.6% of the total) in both sexes combined. It accounts for 18.4% of all deaths and is the leading cause of cancer death. Among women, breast cancer is the most common and leading cause of cancer death [1]. Due to preventive actions and treatment, the incidence of cancer remained stable in women and decreased in men by 2% in the last decade of data from the National Center for Health Statistics. This also reflected in the mortality rate, which decreased by 27% from 1991 to 2016 [2].

Radiation therapy (RT) is essential for the treatment of cancers and it is part of the treatment of at least 40% of cancer patients for its cure and symptom relief. The most commonly used modality is megavoltage photon therapy, which is a form of high-energy electromagnetic radiation reaching deeper internal body structures. New techniques have optimized treatment such as hypofractionation and highly targeted image-guided treatment with intensity-modulated RT to minimize its toxicity [3]. However, thoracic RT increases the risk of cardiovascular disease, such as myocardial infarction, myocarditis, heart failure, valvular heart disease, pericarditis, and conduction disorders, resulting in increased mortality [4]. With the increased survival of patients with cancer, there is an increase of their comorbidities. This increased survival and comorbidities associated with the late and permanent effects of RT imply knowledge of the mechanisms involved in increased cardiovascular risk, especially coronary atherosclerosis, and ways to minimize these effects.

Methodology

For review, the databases used were MEDLINE/PubMed, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. Search terms were combined in the search strategy using Boolean operators (cancer radiation

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therapy, OR radiation cancer, OR cancer radiotherapy, OR thoracic or mediastinal radiotherapy, AND coronary artery disease OR cardiotoxicity OR heart injury). English language articles published during the last 5 years have been included. Relevant articles from other years of publication were also included for this review.

Mechanisms of Radiation-Induced Atherosclerosis

In the 1940s, experimental studies demonstrated myocardial damage from radiation. Evidence in humans was documented in the mid-1960s in patients undergoing chest RT, especially in patients with Hodgkin's lymphoma [5]. This association between RT and atherosclerosis can occur in patients without risk factors for coronary artery disease (CAD) and even asymptomatic patients. Damage can occur at least 10 years after RT [6].

The pathogenesis of radiation-induced CAD is complex and multifactorial, resulting from direct damage by repeated exposure with endothelial dysfunction, altered vascular tone, hemostatic imbalance, and inflammatory activation (Fig. 1) [7•, 8].

Capillaries are more sensitive to RT because they are very thin blood vessels and without tunica media and adventitia. The effects of RT may be acute by endothelial cell apoptosis, or chronic, with deoxyribonucleic acid (DNA) damage, telomere shortening, and increased oncogenic expression. There are induction of mitochondrial dysfunction and endothelial senescence with accelerated atherosclerosis [8]. Exposure to ionizing radiation induces endothelial activation by triggering complex molecular mechanisms, such as activation of the genotoxic stress-induced nuclear factor pathway. This is the main cause of sterile inflammation. Other causes are DNA double-strand breaks, oxidative stress, and the release of damage-associated molecular patterns. This state triggers production and secretion of pro-inflammatory cytokines and a modified repertoire of adhesion molecules. Endothelial activation with prolonged and/or repeated exposure to RT causes depletion of endogenous anti-inflammatory protective effects resulting in endothelial dysfunction [7•]. Some examples of the pro-inflammatory state are interleukins IL-1, IL-6, IL-8, tumor necrosis factor, and C-reactive protein. Among the cell adhesion molecules are intercellular, vascular, and platelet endothelial cell adhesion molecules. They mediate acute and chronic inflammatory reactions and promote macrophage recruitment to endothelial cells [7•, 8].

Endothelial dysfunction and oxidative stress compromise vasomotor function. There is initial vasodilation within a few days of the onset of RT, followed by chronic vasoconstriction due to reduced availability of nitric oxide and vasodilating prostaglandins and increased endothelin, angiotensin, reactive oxygen species, and thromboxane [7•, 8]. These changes may depend on the dose and site of irradiation. Furthermore, long-term oxidative stress results in the release of calcium ions from intracellular reserves and increased proliferation of vascular smooth muscle cells, contributing to vasoconstriction [7•].

Endothelial integrity is also essential for protection against thrombosis and atherogenesis. Therefore, there is a procoagulant state due to decreased nitric oxide and prostaglandins. On the other hand, there is a prothrombotic state with increased von Willebrand factor, tissue factor and tissue plasminogen activator, and decreased fibrinolytic activity,

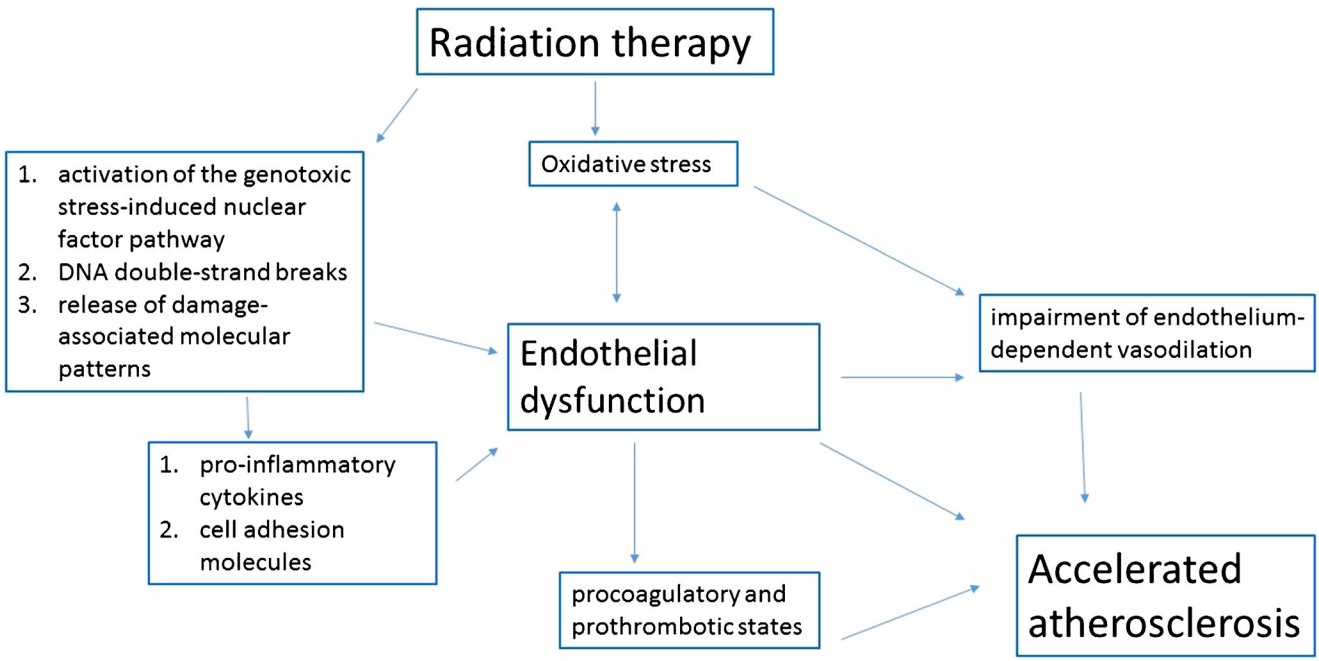

Fig. 1 Synthesis of the mechanisms of radiation-induced atherosclerosis

resulting in platelet aggregation and blood clot formation [7•, 8]. These interactions are dynamic (coronary endothelial dysfunction, arterial thromboembolism, and coronary vasospasm) and culminate in CAD. Nevertheless, precise biological and molecular mechanisms are not yet fully known given their complexity.

Another mechanism implicated in the pathogenesis of RT-related accelerated atherosclerosis is coronary artery calcification, especially in patients with risk factors for CAD [9].

Factors that Influence Coronary Damage by Radiotherapy

The dose of RT is one of the factors that influence the risk of coronary atherosclerosis. Population-based case-control study demonstrated that the risk of a major coronary event increased linearly with the mean heart dose of thoracic RT in women with breast cancer in the first 5 years after exposure and continued for at least 20 years [10]. This proportional increase in ischemic events was similar considering the absence or presence of risk factors for CAD before RT. A systematic review showed that this mean heart dose is variable in women with left breast cancer undergoing RT. Mean heart dose was 5.4 Grays (Gy), with lower means in the proton technique (2.6 Gy) and with tangential RT with breath control. On the other hand, the average dose was higher (9.2 Gy) when the internal mammary chain was included. In addition to the influence of doses and maneuvers, the mean heart dose differed if RT was performed for the right breast, with a mean dose of 3.3 Gy [11]. However, there was a decrease in the mean heart dose at RT for left breast cancer in the period 2012–2015, reaching 1.65 Gy, with the goal of greater cardiac preservation [12].

The chest site undergoing RT also influenced the incidence of CAD, the proportion of percutaneous coronary intervention, and survival. Among 29,102 women undergoing RT for breast cancer, the results were worse in those with a previous history of heart disease and undergoing RT for treatment of left breast cancer [13].

The radiation dose-response relationship and the risk of CAD were also linear among Hodgkin lymphoma survivors. There was a 2.5-fold increased risk for those undergoing a mean dose of 20 Gy of mediastinal RT in the case-control study of a cohort of 2617 survivors with a median interval of 19 years between lymphoma diagnosis and CAD detection [14]. Systematic literature review between 2008 and 2017 showed that the relative risk for CAD by thoracic RT increased approximately 10% per mean dose of Gy, with additional increase by age and risk factors [15]. High mean heart doses (70 to 90 Gy) were also independently associated with cardiovascular events, including myocardial infarction, in surviving patients with non-small-cell lung cancer undergoing RT with a mean follow-up of 8.8 years [16].

The technique may interfere with the radiation dose. Proton beam therapy resulted in lower radiation dose than intensity-modulated RT, which may decrease cardiovascular risks [11, 17–19].

Breathing and position are other interfering variables. Inspiratory deep breathing hold and prone positioning provided the lowest mean cardiac dose resulting from RT for treatment of left breast cancer [12, 20–22]. These resulted in less involvement of the anterior descending coronary artery, either by measuring dosimetric data or perfusion defect imaging. These findings are important since coronary involvement occurs mainly in the ostium or proximal segments of the coronary arteries, and the anterior descending artery was the most affected in women treated with RT for left breast cancer [23•].

As for the position, although some defend the prone position, others prefer the supine approach. In this last position, therapists have the ability to visually check the light field and the patient's positioning. Regional nodal treatment is more appropriate in the supine position, as well as for approaching very medial or lateralized lesions. On the other hand, the prone position may be indicated for patients with large pendulous breasts [24].

The image orientation schedule also interferes with dosimetric coverage and therefore possible damage. For left breast RT in prone position, using the technique of treatment of the source surface distance, the daily image orientation program is more appropriate, preventing high levels of radiation in the anterior descending artery. For the treatment of right breast irradiation, weekly image orientation seems to be the best choice [25].

Another approach is the improvement in linear accelerator technology with more personalized heart block for left breast RT, which allowed a significant reduction of heart doses [26]. A combination of techniques, such as 3-dimensional conformal hypo-fractionated, deep inspiratory breath-hold, and partial breast radiotherapy, can also reduce the mean heart dose of RT [27].

Table 1 lists the factors that interfere with coronary damage by RT.

Clinical and Laboratory Evidence of Coronary Damage by Radiotherapy

Cardiotoxicity due to RT occurs 1 to 3 decades after radiation, but may occur earlier in patients with risk factors or pre-existing disease, and depends on the RT technique [28, 29, 30••]. Among 20,871 women with breast cancer undergoing RT during the 1970s and 1980s, cardiovascular mortality exceeded 25% after 15 years in those with left breast cancer compared with those with right breast cancer [28]. The relationship between events or cardiac death is linear with the mean heart dose of RT. The risks are 3.1% per Gy for cardiac death and 7.4–10% per Gy for CAD [4, 10, 15].

Table 1 Factors interfering with radiotherapy-related coronary damage

Mean heart dose
Radiotherapy chest site
Techniques
1. Proton technique
2. Intensity-modulated therapy
3. Regional nodal radiation/target changes
4. Personalized heart block
5. Image orientation program
6. Radiotherapy regimes (hypo-fractionated, 3-dimensional conformal external beam radiotherapy)
Maneuver (deep inspiration breath-hold)
Patient position (prone position versus supine)

Another study of 115,165 women undergoing RT for breast cancer demonstrated increased cardiac mortality and also increased incidence of lung cancer among those treated until the early 1980s [31]. In addition, another study with 34,825 women treated with RT due to breast cancer showed no influence on tumor laterality or treatment period, either before or after 1990 [32]. However, recent systematic review including 289,109 patients from 13 observational studies showed higher cardiovascular mortality among those treated with RT for left breast cancer than for right breast cancer. The relative risk of death was 12% and more apparent after 15 years of radiation exposure [33].

A meta-analysis of 1,191,371 breast cancer patients showed that the absolute risk of RT was 76.4 for CAD and 125.5 for cardiac death per 100,000 person-years, with a relative risk of 1.30 and 1.38, respectively [34]. And there was an influence of smoking on the risk of cardiac death with mean heart dose of 4.4 Gy in randomized studies with breast cancer patients published during 2010 to 2015 [35].

There is a relationship between mean heart dose and location of CAD in women with breast cancer treated with RT which required a coronary intervention. The association was positive when comparing RT doses above 20 Gy and 0–1 Gy doses with the middle portion of the anterior descending artery and posterior coronary stenosis requiring intervention, with a statistically significant 5-fold increase in the odds ratio [36]. There was also an association between mediastinal RT dose in patients with Hodgkin lymphoma and coronary stenosis [37].

Increased mortality was observed in a retrospective cohort study of patients with breast cancer or Hodgkin lymphoma treated with RT for 18 years ago who underwent cardiac surgery, matched for sex and age [38].

The portion of coronary involvement related to RT depends on the radiation site. In the case of left breast cancer, the involvement is in the middle and distal segments of the anterior descending artery and distal segment of the diagonal branch. Patients undergoing RT for right breast cancer may present obstruction of the proximal segment of the right coronary artery. Childhood cancer survivors undergoing mediastinal RT may present ostial and proximal lesion of the left coronary artery and proximal segments of the left descending, diagonal, and right coronary arteries. There was usually no injury in the circumflex artery [39•].

In addition to the clinical presentation, there are biomarkers related to cardiac injury by chest radiation. High-sensitivity Troponin levels were increased in 21% of women with left breast cancer who underwent RT without chemotherapy. This increase was associated with higher heart radiation doses [40]. Evidence of left-chest RT-induced BNP (brain natriuretic peptide) and CAD increase is scarcer than that related to troponin and CK-MB [41–43]. In patients with lung cancer and mediastinal lymphoma, there was an increase in growth differentiation factor 15 levels after a median time of 20 days from the end of thoracic RT [43]. The usefulness of these markers in long-term risk stratification has yet to be determined.

Another biomarker, circulating microRNAs, may have prognostic value for patients with pre-existing heart disease undergoing RT for non-small cell lung cancer. Thus, this marker may be useful for radiation-specific dose selection [44].

Approaches to Reduce Radiation-Induced Coronary Artery Disease

The implementation of techniques that reduce cardiac damage caused by RT is of paramount importance for reducing short and long-term morbidity and mortality of patients. Thus, actions should be based on the factors that interfere with coronary damage by RT, follow-up of these patients, and control of risk factors for CAD. Among those factors are reduction in mean heart dose, patient position during RT, and techniques which result in less exposure of the heart to radiation [4, 15, 20–22, 26, 27, 30••, 45]. These factors were previously discussed in this article.

Metformin has been reported as an adjunct in cancer treatment by reducing cardiac toxicity due to its antioxidant, antifibrotic, and radioprotective properties [46–48]. Studies with a small population of up to 200 non-diabetic patients have been published to verify metformin action in women with breast cancer [48]. A recent study with a larger number of participants, with 6993 women who had early-stage left breast cancer, in which 2062 used metformin for at least 28 days after RT, showed a lower rate of cardiac events, including CAD, in this group than in the non-metformin group during follow-up of 5.14 years. Besides that, in the metformin group, the number of patients with more advanced age, hypertension, and ischemic heart disease was higher [46]. Metformin used in combination with RT reduces oxygen consumption and increases reactive oxygen species in the cell, with DNA damage,

resulting in cancer cell death [47]. Another action of metformin is synergistic with chemotherapeutic agents, reducing the development of resistance to these agents [48]. Therefore, it can minimize radiation damage to the heart or coronary artery [46].

For its anti-inflammatory effects, statin use has been studied in 5718 patients undergoing thoracic, neck, or head RT. 4166 patients were on statin and there was a 15% reduction in the composite endpoint of stroke, MI, or death caused by stroke or MI, although it was not significant [49]. Thus, statins may have a beneficial effect on reducing cardiovascular events after RT. It was also been hypothesized that colchicine is a prophylactic in the prevention of RT-induced CAD by its inhibitory effects on inflammation and platelet aggregation. However, there are still no clinical studies and this medication can have adverse effects [50].

Since inflammation is implicated in the pathophysiology of vascular injury by RT, an experimental study has recently been published to evaluate the preventive blocking effect of IL-1. This study demonstrated that anakinra, IL-1 receptor antagonist in clinical use for treatment of rheumatoid arthritis, improved sustained radiation-induced expression of inflammatory mediators in mice [51]. Further evidence of anti-inflammatory effect on cancer incidence was observed in the separate secondary CANTUS analysis. Randomized, double-blind, placebo-controlled study using canakinumab in 10,061 patients with previous myocardial infarction showed lower cancer incidence and lower total cancer mortality and lung cancer mortality after 3.7 years of follow-up [52••].

Experimental studies have been performed to evaluate the effect of pentoxifylline and sestrins on myocardial fibrosis, without mentioning its action on the coronary artery bed [53].

Despite several clinical studies to verify the protective effects of drugs or substances in cancer patients undergoing chemotherapy, especially breast cancer [54, 55], there are few clinical studies regarding therapy to prevent RT-related CAD. Table 2 shows the main clinical studies for prevention of coronary damage by RT.

The approach of patients should also include clinical assessment, control of risk factors, and complementary examinations. Among patients undergoing thoracic RT and with coronary damage, the presentation includes atypical chest pain in 30.3% (atypical because of the use of analgesics) and there is dyspnea in 44% of patients [39•]. About 5% of concurrent cancer patients have acute coronary syndrome. The management should be done as in other patients without cancer as recommended in the literature. There are particularities such as the presence of thrombocytopenia and risk of bleeding. Therefore, platelet transfusion may be required. Medical therapy is the first choice. For percutaneous coronary intervention, the preferred approach is radial access. However, it should be taken into account the possibility of obstruction of the subclavian artery due to RT. Triple therapy (dual anti-platelet therapy and an oral anticoagulant) may be given during the first month after percutaneous coronary intervention, followed by dual therapy over the next 11 months. Nevertheless, the use of only one antiplatelet agent may be considered in patients at risk of major bleeding [23•].

Gaps in Knowledge and Future Directions

There is a need for a multidisciplinary approach to the patient by oncologists, radiologists, and cardiologists since cancer survivors are increasing due to the growing arsenal of antitumor therapy. Therefore, cardio-oncology is a recent subspecialty with several knowledge gaps [55]. RT and chemotherapy have toxic effects on the heart. However, it is not known whether these effects are additive or synergistic [30••].

The effects of RT on coronary arteries are from retrospective, observational, or nonrandomized studies. Therefore, randomized clinical trials are required for refinements in the application of RT. There is a lack of data on the effects of other modalities on the possible induction of coronary atherosclerosis such as brachytherapy, a radiation therapy involving the deployment or placement of radioactive sources in close contact with the cancerous tumor [56]. Effects of metformin, statin, and other anti-inflammatory agents are still poorly understood.

Table 2 Main clinical studies for prevention of radiotherapy-induced coronary artery disease [46, 49, 52••]

Drugs	Author, year, study design	Number of patients	Cancer site	Outcome
Metformin	Yu et al. (2019); retrospective national cohort study	6993	Early-stage breast cancer	Reduction risk of major heart events (adjusted hazard ratio [aHR], 0.789; 95% confidence interval, 0.645–0.965
Statin	Boulet et al. (2019); retrospective cohort study	5718	Thorax and head or neck cancer	15% reduction in the composite outcome of cardiovascular and cerebrovascular events
Canakinumab	Ridker et al. (2017); randomized, double-blind, placebo-controlled trial	10,061	Without cancer	Incident lung cancer reduction, HR 0.33 [95% CI 0.18–0.59]*

* Subcutaneous dose of 300 mg every 3 months

The use of a standardized form of biomarkers for risk stratification and radiation dose selection can also assist in the management of cancer patients. Validation of cardiovascular risk prediction scores after breast cancer treatment, as reported recently derived in 60,294 women and validated on 29,810 women [57], may guide more rational follow-up and treatment.

Conclusions

RT results in coronary endothelial dysfunction with accelerated atherosclerosis, whose hypothetical pathogenesis is multifactorial. There are already known factors that influence this coronary damage with clinical and laboratory evidence. Therefore, RT protocols that include cumulative radiation dose lower, cardiac protection, 3D image–guided treatment planning, tangential fields, and deep inspiratory breath-hold should be used. Randomized, prospective, long-term studies are needed to validate the radioprotective effects of metformin and anti-inflammatory agents.

Compliance with Ethical Standards

Conflict of Interest Rose Mary Ferreira Lisboa da Silva declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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