Review Article

The risk of cardiovascular toxicity caused by cancer radiotherapy—a narrative review

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Background and Objective: Radiotherapy is an efficient treatment for cancer. However, some cancer survivors who receive thoracic radiotherapy experience radiation-induced cardiovascular toxicity, leading to long-term impact on cardiovascular health. This review summarizes the current literature regarding the basic pathogenic mechanisms, development, and prevention of radiation-induced cardiovascular toxicity.

Methods: A literature search was performed on PubMed to find reported histological observations and studies on acute and late cardiovascular toxicity in cancer patients treated with radiotherapy. A systematized review of articles on the present topic published between May 1967 and April 2021 was carried out.

Key Content and Findings: Since 1967, heart disease following cancer radiotherapy was increasingly being reported. The development of cardiovascular toxicity among cancer survivors receiving mediastinal radiation correlates primarily with the total dose of mediastinal radiation received, total heart dose, and the dose of radiation per fraction. Modern radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) in the respiratory-gated radiotherapy in deep-inspiration breath-hold (DIBH) position achieve a considerable dose sparing to the heart and reduce mean heart dose. Modern irradiation techniques in combination with cardio-oncology will help to optimize the care of patients with cancer.

Conclusions: Improvements in radiotherapy planning have reduced the volume of the heart and major coronary vessels to be exposed to high doses. Reducing the risk of cardiovascular toxicity caused by cancer radiotherapy is urgent because it is an important cause of morbidity and mortality in survivors.

Keywords: Cancer; radiotherapy (RT); cardiovascular toxicity

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Introduction

Radiotherapy (RT), also known as radiation therapy, is an important component of anticancer treatment currently administered to about half of the patients with cancer worldwide (1). The modality has led to a significant improvement in the chances of surviving a diagnosis of cancer. On the other hand, during the course of therapeutic radiation, noncancerous normal tissues might be affected either by direct radiation exposure or by radiation-induced bystander effect, resulting in radiation-induced toxicity which sometimes become clinically evident years or decades after completion of therapy (2,3).

It has long been known that high doses of radiation like those given during mediastinal RT may damage cardiovascular health (4,5). A potential short- or long-term complication of cancer RT involving the heart and circulation is so-called radiation-induced cardiovascular toxicity. A range of cardiovascular complications have been recognized as cardiovascular toxicity caused by cancer RT, including pericarditis, valvular disease, arrhythmias, ischemic heart disease, coronary artery diseases, cardiomyopathy and heart failure (6-8). In fact, complications can be seen with any dose. The number of cancer survivors who diagnosed with premature heart disease is increasing despite the patients with no preexisting cardiovascular disease or presence of other cardiac risk factors such as hypertension, dyslipidemia, and diabetes mellitus (9).

Nowadays, despite an awareness of the potential cardiotoxicity of irradiation, leading to the application of improved RT techniques and modalities that reduce the volume of normal tissue to be exposed to high doses of radiation compared with conventional therapies, the risk of subsequent heart disease remains an issue among cancer survivors (10-12). Because the biological mechanisms of harm are very complex and only partially understood, radiation oncologists face the challenge of treating patients with the best strategies without adversely impacting cardiovascular health. This review summarizes the current literature regarding the basic pathogenic mechanisms, development and prevention of radiation-induced cardiovascular toxicity. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-21-34/rc).

Methods

We performed a literature search on PubMed to find reported histological observations and studies on acute and late cardiovascular toxicity in cancer patients treated with RT (*Table 1*). A systematized review of articles on the present topic published between May 1967 and April 2021 was carried out.

We included literature data on case studies of cardiovascular toxicity after cancer RT, mainly from survivors of breast cancer and Hodgkin's lymphoma, risk factors, pathogenesis, development of cardiovascular toxicity after RT, and modern RT techniques utilized to reduce cardiac radiation dose. Included studies were limited to publish in English or German languages.

The search strategy used on PubMed included the following terms: 'radiation', 'cancer', 'cardiac', 'heart', 'cardiovascular toxicity', 'heart disease', 'breast cancer', 'lung cancer', 'Hodgkin's lymphoma', 'radiotherapy', 'modern radiotherapy technique', 'cardiac toxicity', 'echocardiography', 'radiation therapy', 'cardiotoxicity'.

Risk factors

Risk factors of radiation induced cardiovascular toxicity have been investigated. A major risk factor for subsequent development of cardiovascular toxicity is the total dose of mediastinal radiation received (13). The dose of radiation per fraction, the volume of heart irradiated, and the extent to which the coronary arteries are exposed in the radiation field are also critical risk factors for development of cardiovascular toxicity (9,14,15). Generally, radiation doses are fractionated into smaller daily doses of <2 Gy because it has been suggested that fractions of >3 Gy are implicated in a greater risk of developing cardiotoxicity, particularly pericardial effusions (15). In addition, concomitant use of cardiotoxic chemotherapy agents, typically 5-fluorouracil, trastuzumab, and anthracyclines further increase the risk of heart disease (16). Other risk factors include younger age at the time of radiation treatment, preexisting cardiovascular disease, presence of cardiac risk factors (hypertension, dyslipidemia, diabetes, smoking and obesity) and genetic susceptibility (6).

Radiation associated cardiotoxicity appears to be delayed—usually 10 to 40 years following treatment, but acute cardiac inflammation can occur at the time of RT or shortly afterwards, resulting in myocarditis or pericarditis (17). Establishment of models for early risk stratification may help to identify high-risk patients. Modification of RT and administration of preventive treatment will be needed for high-risk patients to reduce the risk of cardiovascular toxicity

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	28 April 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	The search strategy used on PubMed included the following terms: 'radiation', 'cancer', 'cardiac', 'heart', 'cardiovascular toxicity', 'heart disease', 'breast cancer', 'lung cancer', 'Hodgkin's lymphoma', 'radiotherapy', 'modern radiotherapy technique', 'cardiac toxicity', 'echocardiography', 'radiation therapy', 'cardiotoxicity'
Timeframe	May 1967 to April 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion: publish in English or German languages
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Dai-Wei Liu, Yen-Rong Fu, Shu-Hsin Liu conducted the selection independently and performed data analysis and interpretation. All authors discussed to reach a consensus
Any additional considerations, if applicable	None

caused by cancer RT.

Case studies of cardiovascular toxicity after cancer RT

In 1967, the first comprehensive series of heart disease following radiation was reported by Cohn *et al.* (18). Since then cardiac involvement after mediastinal radiation therapy has been increasingly described. *Table 2* listed a summary of the selected histological observations and studies of cancer RT reported in the first century. The literature on the late cardiovascular toxicity of RT comes mainly from survivors of breast cancer and Hodgkin's lymphoma, diseases in which RT is a common modality of the initial management and in which survival is often prolonged. Similar cardiovascular toxic effects may be present in patients with lung cancer, head and neck cancer and esophageal cancer who receive thoracic RT while data are more limited (24-26).

Studying the risk of the radiation-induced cardiovascular toxicity after RT for lung cancer are more complex than others for several reasons. First, patients with lung cancer are old at diagnosis (average 71-year-old) and most have multiple comorbidities including cardiovascular diseases, chronic obstructive pulmonary diseases, diabetes and other malignancies (27-29). Second, the prognosis of patients with lung cancer is poor. The 5-year survival rate for all patients with lung cancer worldwide is 10% to 20% (30). Third, patients with lung cancer have shown a high prevalence of concomitant cardiac disease (approximately 25% to 30%) (27). Preexisting cardiovascular comorbidities have been involved in increased incidence of cardiovascular events and mortality. Sometimes a proportion of lung cancer patients can be treated curatively due to advances in RT, but the dose to the heart in curative-intent lung RT is usually larger than that for lymphoma or breast cancer; some patients received high-dose conformal RT with concurrent chemotherapy (31). Despite a non-negligible risk of complications- the relatively higher heart dose exposure for lung cancer leading to the earlier onset of cardiovascular toxicity, the benefits of application of radiation outweigh its risks in selected cases. Therefore, much work remains to further refine the strategies of cancer RT, and it is suggested that future research with the evidence around cardiovascular toxicity of lung cancer RT can be separated from previous evidence from other cancer sites (27).

Recent thirty years a number of research groups conducted prospective cohort studies to assess the risk of cardiovascular toxicity caused by cancer RT, with a large study population that make it possible to estimate relative and absolute risk of radiation-related heart disease. Selected key studies are described as followed.

Breast cancer

Early studies with RT in breast cancer patients uncovered the correlation of incidental radiation to the heart with an increase in the frequency of cardiovascular disease. Darby SC and colleagues conducted a population-based case-control study of major coronary events in 2,168 women in Sweden and Denmark who underwent RT for breast

Table 2 Descriptions of cardiac signs and symptoms caused by irradiation: the first century of radiation

Year	Neoplasm	Treatment	Description	Ref.
1984	Hodgkin's disease	3,000 rad or more to the mediastinum	A significant increase in the incidence of pericarditis with an increased dose of radiation at 2 cm, 5 cm and midplane depths and also with the presence of a large intrathoracic tumor	(19)
1987	Hodgkin's disease Lymphoma Breast carcinoma Cystic hygroma	42±7 Gy	CAD developed in 15 patients at a mean of 16 years (range, 3–29 years) after chest irradiation. At least 50% diameter narrowing of the left main coronary artery and severe ostial stenosis of the right coronary artery were observed in some cases by coronary angiography. Valvular heart disease, pericardial disease and complete heart block were found in some cases. Severe mediastinal and pericardial fibrosis were presented in 3 patients	(20)
1989	Breast carcinoma	Immediate post-operative radiotherapy (radiated group) or delayed radiotherapy on recurrence (watched group)	There was a significantly increased mortality in the radiated group. After 15 years. The relative risk after 15 years for the radiated group relative to the watched group was 1.43 with a 95% confidence interval of 1.13 to 1.81. This increased mortality was correlated to deaths from cardiovascular disease	(21)
1991	Hodgkin's disease	25 MV photons from a linear accelerator	Of the 499 patients, 35 pericarditis (10-year cumulative incidence rate of 9.5%) and 13 myocardial infarctions (10-year cumulative incidence rate of 3.9%). The pericarditis risk was significantly increased with total dose greater than or equal to 41 Gy and with dose per fraction greater than or equal to 3.0 Gy	(22)
1993	Hodgkin's disease Lymphoma Breast Cancer Seminoma	40–122 Gy	Onset of clinical signs from 3 to 28 years (mean 12), including aortic stenosis, pericardial effusion, constrictive pericarditis, mitral/tricuspid regurgitation, myocardial infraction, mitral regurgitation, or mitral stenosis/regurgitation. The effect of chest irradiation could be a reason leading the young patients who free from risk factors to development of CAD	(23)

CAD, coronary artery disease.

cancer between 1958 and 2001. They found that incidental exposure of the heart to radiation treatment for breast cancer elevated the rate of major coronary events (i.e., coronary revascularization, myocardial infarction, or death from ischemic heart disease) by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart (13). Moreover, in the study, women with and women without preexisting cardiac risk factors have a similar proportional increase in the rate of major coronary events per gray (13).

The potential damage to the heart is correlated to the heart-absorbed dose and differs between left- and right-breast radiation therapies. The mean cardiac dose from irradiation of a left-sided breast cancer can be 2 or 3 times that for a right-sided breast cancer (32). As a consequence, long-term mortality from heart disease is increased among women with left-sided breast tumors compared with women with right-sided breast tumors. A prospective cohort study reported by Darby *et al.* have shown that, in women recorded in the US Surveillance Epidemiology and End Results (SEER) cancer registries as having been diagnosed with breast cancer during 1973–1982 and received radiation, the cardiac mortality ratio, left versus right tumor laterality, was during the periods 10–14 years (1.42) and 15 years or more (1.58) after diagnosis, significantly greater than 1.00 (33).

As described above, accumulated studies and clinical evidence indicated that cardiac mortality and morbidity of breast cancer survivors treated with conventional RT was increased, and thus, for chronic cardiac events in breast cancer patients treated until the 1990s, RT was referred as a risk factor (34). However, improved modern techniques minimize heart doses and reduce radiation exposure of the heart. Merzenich and colleagues investigated cardiac mortality and morbidity of breast cancer survivors treated with contemporary RT in Germany (34). A total of 11,982 breast cancer patients treated between 1998 and 2008 were included in the retrospective cohort study. They found that, after a median follow-up time of 11.1 years, there was no significant correlation between tumor laterality and cardiac mortality in irradiated patients and tumor laterality was not a strong risk factor for cardiac morbidity. However, longer

follow-up is needed for assessment of clinically manifest late cardiac effects of cancer RT (34).

Hodgkin's lymphoma (HL)

HL survivors are at relative high risk of cardiovascular diseases and serve as a model for radiation-induced heart diseases because higher radiation doses to the mediastinum are utilized for HL treatment compared to other cancers (7). A retrospective study of 2,232 patients with HL who received mediastinal irradiation from 1960 through 1991 reported that, in comparison with a matched general population, total doses of >30 Gy led to a 3.5-fold higher risk for cardiac death (35). The study further assessed the risk factors of death from heart disease after Hodgkin's disease therapy by comparing treated patients with a matched general population. The results indicated that high mediastinal doses, young age at irradiation, lack of protective cardiac blocking, and the increased length of follow-up time were the risk factors of subsequent death from heart disease (35).

In 2015, van Nimwegen FA and colleagues conducted a retrospective cohort study to examine relative and absolute excess risk up to 40 years since HL treatment compared with cardiovascular disease incidence in the general population (36). The study included 2,524 Dutch patients who received treatment for HL, including prescribed mediastinal RT dose and anthracycline dose, at younger than 51 years from 1965 through 1995. They found that after 35 years or more, patients still had a 4- to 6-fold increased standardized incidence ratio of coronary heart disease (CHD) or congestive heart failure (HF) compared with the general population. Moreover, patients who received mediastinal RT had a 40-year cumulative incidence of any cardiovascular disease of 54.6% compared with 24.7% in patients not treated with mediastinal RT or anthracyclines (36).

Pathogenesis

RT is the use of ionizing radiation (IR) to eradicate a tumor. Principally, high-energy radiation is deposited on the tumor site to damage the genome of cancer cell and destroy their ability to divide and grow. When living cells are exposed to IR, a burst of excess reactive oxygen species (ROS) is immediately produced and targets molecules such as DNA, proteins, and lipids. This can induce DNA damage and thereafter cell death (37). Ideally, doses are delivered only to the targeted cancer cells, but the physical nature of radiation beams as well as current techniques make this impossible. Therefore, normal tissues are usually exposed or affected by RT, followed by induction of DNA damage, inflammatory responses and oxidative stress, leading to toxicity. This accounts for acute and long-term adverse effects seen with radiation treatment (4,38,39).

The absorption of IR by normal tissue can disrupt DNA structures and produce DNA breaks that activates DNA repair protein ATM. Meanwhile, a sharp increase in ROS through radiolysis of water results in oxidative stress and initiation of a series of molecular and biological signaling events that may repair the damage or injury as well as culminate in permanent physiological changes or cell death (40). Both of activation of ATM and oxidative stress trigger the nuclear factor-kappa B (NF-κB) signaling pathway and inflammatory responses (41,42). Many genes related to the NF-κB signaling pathway were found to be dysregulated even years after radiation (43). NF-κB activation led to sustained inflammation in irradiated human arteries that can explain cardiovascular disease years after radiation exposure (43).

The persistent increase of inflammation markers ICAM-1 and VCAM-1 was observed when comparing time kinetics of radiation-induced changes of inflammatory markers (PECAM-1, ICAM-1, ICAM-2, VCAM-1) in heart microvascular endothelial cells (ECs) (44). When mice received local thorax irradiation with a single dose of 8 Gy, ICAM-1 and VCAM-1 remained up-regulated 20 weeks after irradiation in heart ECs. The late inflammatory responses in heart ECs implied the predisposition for the development of atherosclerotic plaques in heart ECs at later time points (44).

Numerous processes occur, including activation of DNA repair and signaling mechanism, expression of radiation response genes, increased proliferation, and initiation and perpetuation of inflammation, in response to DNA damage to recover the damaged cell, tissue, or organism after radiation exposure. However, these pathways may also play a role in the development of toxicity. The progeny of the irradiated cells may express a high frequency of gene mutations, chromosomal aberrations and cell death. These effects are collectively known as radiation-induced genomic instability (45). Another effect which is proved to be existed outside of radiation field, in non-irradiated cells, is called radiation-induced bystander effect (3). After radiation exposure, free radicals, immune system molecules, expression changes of some genes involved in inflammation and epigenetic factors are produced in irradiated area and may affect nearby non-irradiated cells. Subsequently, process of gene expression, translation, cell proliferation, apoptosis and cells death in nearby non-irradiated cells may be

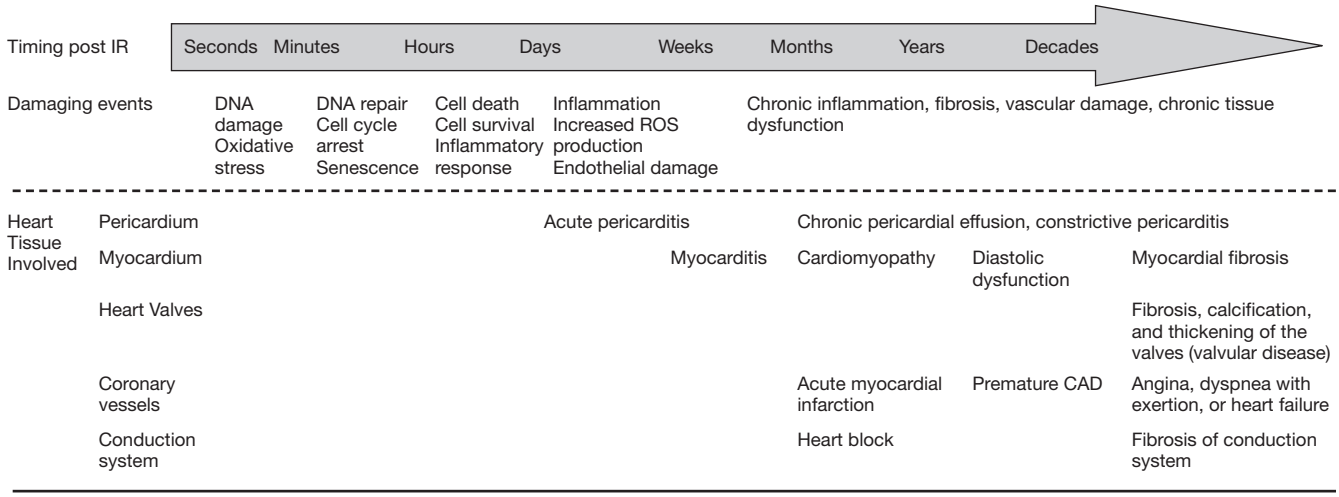

Figure 1 Sequence of events and cardiovascular structures being affected after RT. Radiation-induced damaging effects on the heart tissue occur within seconds to decades after ionizing radiation (IR), causing acute or chronic cardiac diseases (18,28,30,31,42,49-53). A selection of the damaging effects and diagnosed cardiovascular toxicity are presented to the bottom of the timeline. CAD, coronary artery disease.

changed. These changes are demonstrated by results of some *in vivo* studies (46-48). The induction of bystander effects and instabilities may cause a non-specific inflammatory-type response and injury and be implicated in various pathological consequences of radiation exposures (45).

Development of cardiovascular toxicity after RT

The symptoms of radiation-induced cardiovascular toxicity usually require a long incubation period to manifest (18,20,22,23,42,49-53) (*Figure 1*). It is believed that endothelial cell senescence results from DNA damage and oxidative stress caused by radiation is an initial key pathophysiologic step for development of radiation-induced cardiovascular toxicity (6). After exposure to IR, the damaged cells with double-stranded DNA breaks (DSBs) may continue to divide a limited number of times before undergoing mitotic or apoptotic cell death. Remarkably, malignant transformation and subsequent malignancies may occur years or decades after RT due to some DSBs-affected tumor suppressor genes and cell cycle signaling pathways (2,54).

In addition, in response to cellular stress, insulin-like growth factor 1 receptor (IGF-1R) signaling cascade is activated and promotes accelerated senescence in irradiated endothelial cells (55). A decrease in nitric oxide bioavailability, premature senescence and mitochondrial dysfunction in endothelial cells resulted from oxidative stress lead to endothelial dysfunction and inflammatory changes in the radiation field (10).

Senescent endothelial cells with chromosomal aberrations and rearrangements release proteins and proinflammatory cytokines (49,55,56). Elevated levels of IL-1, IL-6, IL-8, and TNF-α as well as ROS (superoxide and peroxynitrite) have all been involved as mediators of the subsequent processes, explaining the latency of acute side effects (2,42,57). Senescent endothelial cells with altered morphology do not proliferate but they stay metabolically active such as oxidative metabolism. This may linked to prolonged oxidative stress (58). Importantly, oxidative changes may continue to arise for days and months after the initial exposure not only in the irradiated cells but also in their progeny (58).

Accumulated evidence suggests that radiation-induced cardiovascular toxicity is a result of various mechanisms interacting with each other through multiple complex signaling pathways (4,38,39). Radiobiology research reveals that normal tissue injury is a dynamic and progressive process (59). As a consequence, chronic inflammation occurs and subsequent fibrosis develops that contribute to structural changes of the heart, such as pericardial inflammation (pericarditis), fibrosis of conduction system, chronic development of fibrosis in the myocardium, endothelial damage in the coronary vessels, and valvular heart diseases (5,51,60,61). A short-term complication of RT, acute pericarditis, is rare but may occur during or days to weeks after irradiation while chronic pericardial effusion or constrictive pericarditis may develop months or years

later (62,63). Radiation-related myocardial fibrosis can occur asymptomatically for over 10 years before becoming clinically apparent. The diagnosis of radiation-induced coronary artery disease (CAD) often extends to decades, between radiation exposure and development of obstructive coronary disease (20,23). The majority of patients present with angina, dyspnea with exertion, or heart failure which are traditional symptoms of coronary obstruction. Fibrosis of conduction system is one of the main reasons for developing arrhythmias in later life. Valvular disease is a late complication. Fibrosis, calcification, and thickening of the valves is often asymptomatic but can be diagnosed late, at least 15 years after the original treatment (6). Intimal thickening, lipid deposition, and adventitial fibrosis were observed within the vascular system after irradiation in patients as well as animal studies (64). These changes also follow external irradiation to other parts of the body. All these changes, seen in atherosclerosis and with the normal aging process, accelerate the damage to the vascular endothelium. Atherosclerosis is also worsened by IR (64).

The microvasculature of the myocardium are damaged by presently-used doses of radiation (65). The main cause is inflammatory changes in the microvasculature in response to radiation damage to the myocardium, leading to microthrombi and occlusion of vessels, reduced vascular density, perfusion defects and focal ischemia (53). Subsequently, progressive myocardial cell death and fibrosis can occur. Moreover, capillary network damage is appeared to be irreversible, though endothelial cells can regenerate (38). Biologically, cardiac capillary endothelial cells exposure to radiation can result in their proliferation, swelling and degeneration, injury, and dramatically reduce the number of capillaries (66). This may lead to reduction of the blood supply of myocardium. In addition, the myocardium is particularly vulnerable to oxidative activity of free radicals produced by IR due to the low antioxidant capacity (5).

The primary and fundamental cause of myocardial injury is thought to be radiation-induced endothelial cell injury (38). The thresholds for injury are not fully elucidated. The extent of structural damage to a tissue depends on cell radiosensitivity. Mammalian cardiomyocytes are thought to be relatively resistant to radiation because most of them lose the capacity to undergo cell division shortly after birth (67). However, because of, at least partly, the quite limited proliferative capacity, once tissues in cardiomyocyte are damaged, loss is hardly reconstituted and is irreversible. This frequently results in diminished cardiac function and severe heart failure (67). In addition, cardiomyocyte membrane is rich in phospholipids which are particularly sensitive to oxidative stress. Lipid peroxidation in cardiomyocyte membrane can also lead to functional and structural injury (5).

As mentioned above, radiation-induced cardiovascular toxicity can lead to long-term adverse outcomes, with the median time to diagnosis of radiation-related heart disease being approximately 19 years (65). Besides, damage mechanisms in heart irradiation are affected in a dose-dependent manner. Post-radiation-induced mortality is significantly increase with higher radiation doses, particularly dose >40 Gy. In addition, damaging effects can also be observed even after applying doses as low as 2 Gy (65).

Detection of cardiac toxicity

Echocardiography is a type of ultrasound scan wildly used in the evaluation of cardiac toxicity during and after RT (68-70). It is a noninvasive method of examining the structure and function of the heart and nearby blood vessels (71). Left ventricular ejection fraction (LV-EF) obtained using 2D echocardiography or 3D echocardiography and global longitudinal strain (GLS) measurement based on 2D speckle-tracking echocardiography have been used to evaluate radiation-induced cardiac toxicity (69,71-73). Reduction in LVEF and/or GLS reduction >10% have been considered clinically relevant and referred to subclinical LV dysfunction (69,73,74). Doppler echocardiography is also widely used to monitor cardiotoxicity and identify the main forms of cardiac complications, such as left ventricular (systolic and diastolic) dysfunction, pericarditis and pericardial effusion, valve heart disease, carotid artery lesions, of cancer therapy (70). Use of myocardial strain imaging by echocardiography is critical for the early detection of cardiovascular toxicity in patients during and after cancer RT. Another common noninvasive method chosen for evaluation and management in patients with known or suspected cardiac complications, especially coronary artery disease, is nuclear myocardial perfusion imaging (MPI) with single-photon emission tomography (SPECT) or positron emission tomography (PET) (61,75,76). A controlled clinical head-to-head comparative study showed that PET exhibited higher accuracy and higher sensitivity for diagnosis of myocardial ischemia compared with that of SPECT, whereas SPECT revealed better specificity than PET (75).

Protection against radiation-induced cardiovascular toxicity

Patients with thoracic cancers receiving radiation treatment

Table 3 Effects of modern radiotherapy techniques

Cancer type	Number of patients	Treatment type	Outcome	Ref.
Left-sided breast cancer	15	t-IMRT- deep-DIBH; VMAT-DIBH; t-IMRT- FB; VMAT-FB	MHD was 5±2.4 Gy, 5.7±1.4 Gy, 9.7±3.3 Gy and 8.1±2.0 Gy for t-IMRT-DIBH, VMAT-DIBH, IMRT-FB and VMAT-FB respectively. On average, there was no significant difference in MHD between VMAT-DIBH and t-IMRT-DIBH. However, VMAT-DIBH was found to benefit a select group of patients	(83)
Left-sided breast cancer		3D-CRT or VMAT, in FB or DIBH	3D-CRT plans in DIBH pose the lowest risk for major coronary events	(84)
Left-sided breast cancer	25	IMRT- DIBH; VMAT-DIBH; IMRT- FB; VMAT-FB	Both IMRT and VMAT techniques in the DIBH position achieved a considerable dose sparing to the heart and LADCA. Additionally, in comparison with VMAT, both IMRT plans produced a significantly lower mean heart dose	(85)
Left-sided breast cancer	20	DIBH-t-IMRT and DIBH-t-VMAT plans	T-IMRT showed a significant reduction in mean cardiac dose of 26%, in mean dose to LADCA of 20%, in normal tissue integral dose of 19% and the V5% of total body of 24% compared to t-VMAT. EAR for the induction of secondary tumors was significantly lower in the contralateral lung and breast following t-IMRT than t-VMAT. However, t-VMAT achieved better homogeneity and conformity	(82)
Early-stage, mediastinal HL	27	Chemotherapy and INRT delivered as 3D-CRT, VMAT, or PT, compared with the extensive MF	3D-CRT, VMAT or PT significantly lower the dose to the heart, lungs and breasts and provide lower risk estimates compared with MF, but with substantial patient variability. The risk of cardiovascular disease is not significantly different for 3D-CRT versus VMAT	(86)
Lower mediastinal lymphoma	21	FB-IMRT, DIBH-IMRT, FB-PT, and DIBH-PT plans	Both PT plans produced a significantly lower mean dose to the lung, heart, left ventricle, esophagus, and nontarget body than DIBH-IMRT. DIBH-PT reduced the median MHD by 4.2 Gy (P<0.0001); left ventricle dose by 5.1 Gy (P<0.0001); and lung V5 by 26% (P<0.0001) versus DIBH-IMRT. The 2 PT plans were comparable, with DIBH-PT reducing mean lung dose (7.0 *vs.* 7.7 Gy; P=0.063) and with no difference in MHD (10.3 *vs.* 9.5 Gy; P=0.992)	(87)

INRT, involved node radiotherapy; 3D-CRT, 3D conformal radiotherapy; VMAT, volumetric modulated arc therapy; PT, proton therapy; MF, Mantle Field; t-IMRT, tangential intensity-modulated radiotherapy; DIBH, deep-inspiration breath-hold; FB, free-breathing; MHD, mean heart dose; EAR, excess absolute risk; LADCA, left anterior descending coronary artery.

often involve some incidental exposure of the heart to IR, leading to a late cardiovascular toxic effect which negatively affects quality of life. Unfortunately, prospective studies in the modern era hardly determine their long-term impact on cardiovascular health and therefore no precise program is available for effective eradication of the onset and subsequent development of radiation-induced cardiovascular toxicity. Currently, reducing heart exposed range and minimizing the radiation dose given have become a recognized primary strategy. Improvements in RT planning have reduced the volume of the heart and major coronary vessels to be exposed to high doses. Advanced RT delivery modalities include prior computed tomography (CT)-guided field planning, three-dimensional conformal radiotherapy (3D-CRT) intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), proton therapy, and respiratory-gated radiotherapy in deep-inspiration breath-hold (DIBH) (77-79). In order to minimize heart doses over a course of RT, DIBH were developed for a more favorable position of the heart during inspiration (80). The patient is either instructed to hold his or her breath at certain points in the breathing cycle, or use devices named as active breathing control (ABC) to hold their breath to maintain the volume. DIBH serving a tool for cardiac sparing during irradiation can produce a significantly lower mean heart dose (80-82). A number of studies have investigated the effects of modern RT techniques (*Table 3*). The studies suggest that tangential intensity-modulated radiotherapy (t-IMRT) and proton therapy (PT)-DIBH plans showed a significant reduction in mean cardiac dose than VMAT-DIBH whereas as VMAT-DIBH found to

benefit a select group of patients (82-87).

Attention to reducing the risk of cardiovascular disease should be a priority for the long-term care of patients, especially children, adolescents, and young adults, following the diagnosis and treatment of thoracic cancer.

Conclusions

RT has been used to treat carcinomas for over a century. Cancer survivors who receive thoracic RT in the initial treatment carry a higher risk of developing cardiovascular toxicity (6). Reduction of total heart dose (mean/median) is critical as it is importantly correlated with late cardiac toxicity. Mean heart dose (MHD) over 10 Gy can significantly increase the risk of cardiovascular toxicity after radiation therapy (88). Thus, RT delivery modalities have advanced and additional heart shielding techniques are used. Several different clinical conditions such as pericarditis, cardiomyopathy, coronary syndrome, conduction abnormalities, heart failure, and valvular disease can result from radiation-induced cardiovascular toxicity. None of these conditions is restricted to radiation exposure, but it seems that the pathogenesis of these symptoms is accelerated significantly by irradiation. The exact detail and pathophysiology of radiation-induced cardiovascular toxicity are largely unknown. However, modern irradiation techniques in combination with cardio-oncology have to develop to reduce the risk of cardiac toxicities and optimize the care of patients with cancer.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-21-34/coif). The series "Cardio-Oncology" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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