Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions

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ABSTRACT

The impact of radiotherapy on the heart has become an area of interest in recent years. Many different cardiac dose-volume constraints have been associated with cardiac toxicity and survival; however, no consistent constraint has been found. Many patients undergoing treatment for lung cancer have risk factors for cardiovascular disease or known cardiac comorbidities; however, there is little evidence on the effects of radiotherapy on the heart in these patients. We aim to provide a summary of the existing literature on cardiac toxicity of lung cancer radiotherapy, propose strategies to avoid and manage cardiac toxicity, and suggest avenues for future research.

Keywords: Lung cancer; Radiotherapy; Cardiac toxicity; Cardio-oncology; Dose-volume

Introduction

Lung cancer and heart disease are the two major causes of death owing to noncommunicable diseases worldwide.[1] These conditions share common etiologies in terms of cigarette smoking, increasing age, and socioeconomic deprivation, and approximately a quarter of people diagnosed with having lung cancer have known concomitant cardiac disease.[2-4]

The prognosis of patients with lung cancer is poor compared with patients with other cancers. The 5-year survival rate for all patients with lung cancer worldwide is 10% to 20%[5]; therefore, the priority has been disease control rather than reducing late effects. A seminal phase 3 trial of radiotherapy dose-escalation in stage III lung cancer (RTOG 0617) reported that the median survival for patients in the higher dose arm (74 Gy) was worse than that in the standard dose arm (60

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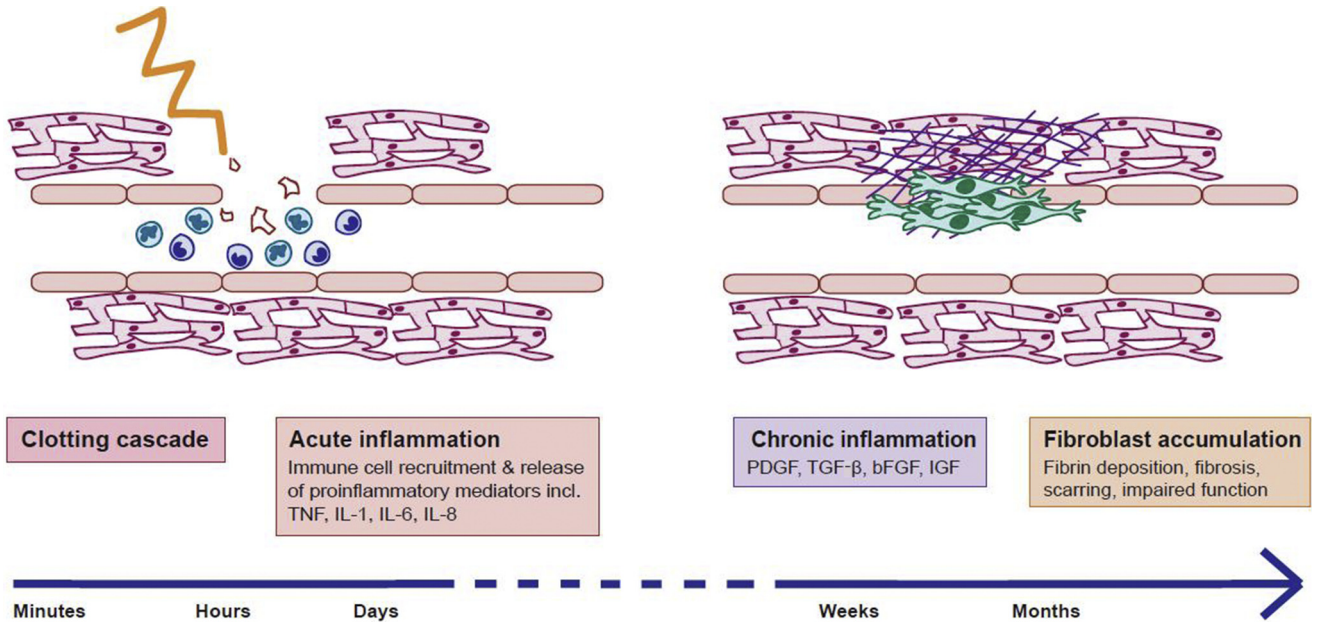

Figure 1. Cardiac endothelial damage caused by radiation resulting in fibrosis. bFGF, basic fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

Gy) (20.3 mo versus 28.7 mo, respectively).[6] The dose delivered to the heart has emerged as one contributing factor to the surprising result of RTOG 0617 as higher heart dose was associated with increased risk of death on multivariable analysis.[6]

Thoracic radiotherapy in patients with breast cancer or lymphoma is known to cause radiation-induced heart disease (RIHD) many years later. Patients with lung cancer are older at diagnosis than patients with breast cancer (71 y versus 62 y[7]) and most have multiple comorbidities. Furthermore, the dose to the heart in curative-intent lung radiotherapy is often larger than that for breast cancer or lymphoma, especially in patients treated for stage III disease. Recent targeted lung cancer screening programs have revealed lung cancer incidence rates between 1% and 1.5%[8,9]; most of whom are diagnosed with having early stage disease and proceed to curative-intent surgery. Nevertheless, in one lung cancer screening program, 31% of patients received curative radiotherapy.[9] It is therefore time to consider the evidence around cardiac toxicity of lung cancer radiotherapy separately from previous evidence from other cancer sites.

This review has been written by a multidisciplinary team comprising of scientists, cardiologists, physicists, and radiation oncologists. We summarize the existing literature on the biology, pathophysiology, management, and prevention of RIHD. We review existing cardiac dose constraints derived from other patient populations with cancer and how these apply to patients with lung cancer treated with radiotherapy. Finally, we discuss the limitations of the literature on RIHD, propose strategies to reduce the effects of radiotherapy on the heart, and suggest future research directions.

Pathophysiology of RIHD

In the past four decades, research has enhanced our understanding of the pathophysiological, cellular, and molecular processes governing RIHD. These processes are complex and involve crosstalk between the various cellular types, alteration of wound healing, and proinflammatory signaling pathways.[10,11] The classical hallmarks of RIHD include the following: fibrosis and calcification of the aortic root and the aortomitral curtain that can lead to progressive stenosis of the aortic and mitral valves; ostial coronary stenosis; myocardial atrophy and widespread pericardial adhesions and thickening ultimately leading to intractable and inoperable pericardial constriction.

The hallmarks of RIHD are a result of radiation-induced activation of acute inflammatory pathways (Fig. 1) causing a chronic pathogenic cascade. The process starts with the disruption of the endothelial barrier integrity and albumin leakage leading to up-regulation of inflammatory signals and platelet aggregation. In parallel, radiation-induced decrease of the microvascular density causes tissue ischemia and oxidative stress inside cardiomyocytes causing their death. Reactive oxygen species lead to the up-regulation of NF-κB. This

protein complex is involved in the regulation of DNA transcription, and its activation increases the expression of cellular adhesion molecules and cytokine secretion.[12] Oxidative stress and chronic inflammation in coronary arteries cause accelerated atherosclerosis.[13] Damaged and dying cells are removed by macrophages and replaced by amyloid and fibrin, contributing to scar formation. This transmural infiltration of extracellular matrix, associated with pathologic accumulation of immune cells (macrophages, mastocytes) and the alteration of calcium flux in the cardiomyocytes, causes systolic and diastolic dysfunction and affects cardiac conduction systems.[10]

Preclinical Models of Cardiac Toxicity

Radiation-induced congestive heart failure, myocardial infarction (MI), and valvular pathology have been reproduced in rodents.[14] Until recently, the protocols of irradiation used in rodents were mainly high-dose single fractions, which does not reflect standard clinical radiotherapy regimens delivered in a number of weeks. The implementation of image-guided radiotherapy for small animals has allowed clinically relevant treatment planning to be applied to mice, rats, and rabbits in combination with various chemotherapeutic drugs and biotherapies. The zebrafish is an exotic animal model that is emerging for use in cardiovascular and RIHD research. These preclinical models allowed full characterization of the pathophysiology of acute, subacute, and delayed RIHD, leading to the identification of potential therapeutic targets at the cellular and molecular levels.

Treating the Patient With Complex Lung Cancer With Radiotherapy

Animal models provide biological information on the effect of radiotherapy on the heart; however, their use is limited as these animals do not adequately model the comorbidities affecting the patient population with lung cancer. The prevalence of cardiac comorbidities in patients with lung cancer is approximately 25% to 30% and is often associated with smoking.[3,4] The commonest cardiac comorbidities are ischemic heart disease (IHD) and cardiac arrhythmia.[15] Preexisting cardiac comorbidities have been associated with increased incidence of cardiac events and mortality in patients after chemoradiotherapy.[15-17]

A retrospective analysis of 748 patients with locally advanced NSCLC who received radiotherapy found that patients with underlying cardiovascular disease (CVD) had a 2-year cumulative incidence estimate of major adverse cardiac events (MACEs) of 11.7%.[18] The mean heart dose (MHD) did not affect MACE rate in patients with a history of underlying CVD; however, in those with no history of CVD, a MHD $\geq$ 10 Gy substantially increased the MACE rate (2-y cumulative incidence estimate 3.5% versus 1.1%).[18] These results indicate that preexisting CVD is a risk factor for future MACE independent of cardiac dose. Cardiac dose may be more relevant in younger patients without CVD as radiation exerts its negative effects in a time-dependent manner.

At least a quarter of patients treated for lung cancer have CVD; others have known risk factors for CVD such as hyperlipidemia (40%), hypertension (12%–60%), and diabetes mellitus (7%–11%).[2,3,15] The WHO/International Society of Hypertension (ISH) risk score predicts the 10-year risk of MI or stroke.[19] Wang et al.[20] paired WHO/ISH risk score with dose parameters and found that, on multivariable analysis, patients with a high WHO/ISH risk score and higher MHD had a significantly higher incidence of cardiac events after radiotherapy for lung cancer (HR, 1.04, $p = 0.001$). WHO/ISH risk score and other cardiovascular risk predictors such as Q-risk[21] are not validated for use in patients with a history of cardiovascular events and tend to overestimate the risk of CVD.[22]

Cardiac imaging, especially cross-sectional imaging in the form of cardiac computed tomography, and cardiac magnetic resonance imaging (CMR) are highly sensitive and specific respectively for the identification of IHD in general and oncology patients. CMR offers a multiparametric approach that allows the assessment of cardiac anatomy, function, and perfusion. CMR can simultaneously perform detailed tissue characterization and assessment of specific myocardial injury types including edema and fibrosis.[23]

Cardiac computed tomography can be used to identify coronary artery stenosis and calculate coronary artery calcification scores (CACSs) and soft plaque burden; high CACS is associated with increased rates of MACE and death.[24,25] A high CACS, calculated on radiotherapy planning scan before adjuvant breast radiotherapy, has been associated with subsequent cardiac events.[26] A small study of CACS in patients who received thoracic radiotherapy found that diabetes and radiation dose to coronary arteries were associated with higher CACS after radiotherapy.[27] A larger study of cardiac calcifications in patients having curative radiotherapy for lung cancer found a relationship between survival and increased dose to calcifications; however, this study did not use CACS.[28] Both Q-risk score[21] and CACS have been found to be raised in a cohort of patients undergoing lung cancer screening compared with the general population,[29] revealing the increased risk of cardiac events in this population which could be further increased by cardiac irradiation.

Limiting Heart Dose: Lessons From Other Cancers

Existing cardiac dose constraints are based on the Qualitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)[30] and are mainly derived from studies of radiotherapy in patients with esophageal cancer and lymphoma. QUANTEC recommended that the volume of heart receiving greater than or equal to 30 Gy (V30) should be kept below 46% and MHD less than 15 Gy. It should be noted that the QUANTEC recommendations for cardiac dose did not include any studies of radiotherapy in patients with lung cancer. Furthermore, challenges in contouring heart substructures, competing patient and treatment risk factors, lack of quantitative dose and volume dependence for cardiac toxicity were acknowledged.

In contrast to the QUANTEC recommendation suggesting that MHD less than 15 Gy is safe, Darby et al.[31] reported for the first time that the risk of MACE (defined as MI, coronary revascularization, or death from IHD) in breast cancer survivors increases in a linear relationship to cardiac radiation dose, even at low-dose levels. The rate of MACE increased by 7.4% per one gray increase in MHD in this cohort of patients. Radiation dose to the heart was also associated with heart failure[32] and valvular heart disease[33] in Hodgkin's lymphoma (HL) survivors. In these patient groups, RIHD can occur up to several decades after treatment.[34] Patients with breast cancer and HL tend to have a low initial comorbidity burden, and, until recently, RIHD was considered a "late effect" affecting only long-term survivors. Nevertheless, these studies revealed that the risk of cardiac events after chest radiotherapy is even higher in patients with preexisting IHD and in those with other cardiac risk factors such as smoking, hypertension, diabetes mellitus, and obesity.[31,32,34]

Although there are important learning points from the breast and lymphoma literature, a number of limitations of these studies should be considered when applied to patients having radiotherapy for lung cancer. First, outdated radiotherapy techniques, delivering a higher dose to larger volumes of the heart compared with modern radiotherapy techniques, were used in these studies.[35,36] Second, the cardiovascular risk from systemic agents (e.g., anthracyclines) was not always included. Third, these dose-response relationships are based on rough estimates of the average radiation dose received by the whole heart. More recent studies suggest that the dose to the left ventricle or coronary arteries might be more relevant[37,38] for patients with breast cancer. Finally, the effect of dose to the heart in lung cancer may occur earlier than in patients with breast cancer or lymphoma.

Limiting Heart Dose: Applications to Lung Cancer

RTOG 0617 was the first study that highlighted the issue of cardiac dose in lung cancer radiotherapy. The original article revealed that the volume of heart receiving greater than or equal to 5 Gy (V5) or greater than or equal to 30 Gy (V30) was associated with worse overall survival.[6] A secondary analysis of RTOG 0617 published 2 years later reported that heart volume of heart receiving greater than or equal to 40 Gy was the dose parameter most strongly associated with survival.[39] Table 1 reveals the results of post hoc analysis of prospective studies that evaluate cardiac toxicity of lung radiotherapy.

After the initial results of RTOG 0617, a number of studies have been published investigating the relationship between cardiac dose, cardiac events, and mortality in patients with lung cancer. Zhang et al.[40] performed a systematic review of studies published before January 2018. They included 18 studies of patients with NSCLC treated with concurrent chemoradiotherapy and four studies of patients with early stage disease treated with stereotactic ablative body radiotherapy. Most of the studies evaluated were retrospective, from single institutions, and had different test populations and differing end point definitions. A total of 96 different cardiac dose parameters were examined; 20 dose parameters were found to be significantly associated with either overall survival or cardiac events on multivariable analysis. The most often studied parameters were MHD, heart V5, and V30. Most cardiac dose parameters were only significant in one study. Heart V30 was associated with decreased overall survival in two studies and MHD was associated with postradiotherapy cardiac events in two studies.[20,41] These results reveal how testing multiple dose parameters can lead to overfitting the statistical model thus increasing the likelihood of a type 1 error. The analysis could not derive reliable dose constraints for the heart.

Zhang et al.[40] excluded articles that did not report cardiac dose parameters, and therefore, a large retrospective study of residual set-up error in 780 patients with NSCLC treated with radical radiotherapy was not included. This study reported that patients with a small, uncorrected set-up error in the direction of the mediastinum (and therefore the heart) had significantly poorer survival (hazard ratio = 1.1).[42] A similar, retrospective study in 136 patients who had stereotactic ablative body radiotherapy to lung lesions outside the "no fly zone" found that the hazard ratio for death was 1.262 per 1 mm shift toward the heart.[43] These results suggest a very steep dose-response curve for cardiac dose.

Table 1. Cardiac Outcomes of Post hoc Analysis of Prospective Studies of Lung Cancer RT Trials

Trial	Data Source	End Point	No. of Patients and Stage	Median Follow-Up	Median Age, y	RT Dose and Technique	Median Tumor Volume, cm^3	CEs	Conclusions Dose Constraints
Wang et al.2017[20]	6 Phase 1 and 2 radiotherapy dose-escalation trials	Symptomatic CE	112 Stage III	8.8 y for surviving patients	58	74 Gy in 37 fractions 3D conformal	GTV = 46.6	29 Events in 26 patients (23%) 7 Ischemia 1 CHF 9 Pericardial 12 Arrythmia	MHD, V5, V30, LV V5 sig associated with CEs in patients with IHD or high WHO/ISH risk scores. MHD ≥ 20 Gy higher rate of CE No association between OS and heart dose
Dess et al.2017[41]	Radiotherapy Dose-escalation trials	CE ≥ grade 3 CE ≥ grade 2 OS	16 stage II 109 stage III	23 mo	66	Median EQD2 dose 70 Gy 121 3D-CRT 4 IMRT	Not stated	28 Grades 1-2 (22%) 13 ≥Grade 3 (10%)	Preexisting cardiac disease and higher MHDassociated with higher CE on MVA
Vivekanandan et al.2017[53]	IDEAL-RT Phase 1 trial of dose escalated, accelerated radiotherapy	OS	6 Stage II 72 Stage III	Not stated	66	Isotoxic 63-73 Gy Median 67.6 Gy 3D-CRT and VMAT	PTV = 400	20/53 (38%) had ECG changes	Higher death rate in patients with ECG changes at 6 mo and left atrium dose > 64 Gy
Guberina et al.2017[73]	ESPATUE Phase 3 trial of surgery vs. chemoradiotherapy	OS in patients in	155 Stage III	72 mo	58	45 Gy in 30 fractions over 3 wk. Inoperable patients had further 20-26 Gy in 2 Gy per fraction 3D-CRT	PTV = 784	Not stated	Heart V5 is not associated with OS
Ning et al.2017[74]	Phase 2 trial of IMRT vs. protons	Grade ≥ 2 PCE	15 Stage I/II 174 Stage III/IV	24 mo	Not stated	74 Gy in 37 fractions 126 IMRT 75 Protons	Not stated	81 (43%) Grade 2 PCE 5 (3%) Grade 3 PCE	Heart V35 > 10%, adjuvant chemotherapy and preexisting cardiac disease associated with ≥ grade 2 PCE
Chun et al.2017[39]	RTOG 0617 Phase 3 radiotherapy dose-escalation trial	2 y OS Toxicity ≥ grade 3	482 Stage III	21.3 mo	64	60 Gy in 30 fractions 74 Gy in 37 fractions IMRT and 3D-CRT	PTV = 426.7 for 3D-CRT PTV = 486.2 for IMRT	32 grade ≥ 3 cardiac toxicity	Lower heart doses with IMRT Heart V40 associated with OS
Xue et al.2019[54]	Prospective imaging and phase 1/2 dose-escalation trials	Grade ≥ 2 PCE OS	11 Stage I 7 Stage II 76 Stage III	58 mo for surviving patients	66	60-85.5 Gy in 2-3.8 Gy fractions 3D-CRT	GTV = 129.6	38 (40%) grade ≥ 2 PCE	Prescription dose, hypertension, MHD, cardiac V5 and V55, pericardial mean, V5, V30, and V55 associated with PCE Pericardial V30 > 29% and pericardial V50 > 21% associated with worse OS

(continued)

Table 1. Continued

Trial	Data Source	End Point	No. of Patients and Stage	Median Follow-Up	Median Age, y	RT Dose and Technique	Median Tumor Volume, cm^3	CEs	Conclusions Dose Constraints
Thor et al.2020[44]	RTOG 0617 Phase 3 radiotherapy dose-escalation trial	OS	437 Stage III	24 mo	64	60 Gy in 30 fractions 74 Gy in 37 fractions 3D-CRT and VMAT	GTV = 93	Not stated	A model combining atria D45%, mean lung dose, minimum dose to hottest 55% of pericardium, and minimum dose to the hottest 5% of both ventricles predicted OS

3D, three dimensional; CE, cardiac event; CHF, congestive heart failure; CRT, conformal radiotherapy; D45%, dose to 45% of the volume; ECG, electrocardiogram; EQD2, equivalent dose in 2 Gy fractions; GTV, gross tumor volume; IHD, ischemic heart disease; IMRT, intensity modulated radiotherapy; ISH, International Society of Hypertension; LV, left ventricular; MHD, mean heart dose; MVA, mitral valve area; OS, overall survival; PCE, pericardial effusion; PTV, planning target volume; RT, radiotherapy; sig, significantly; VMAT, volumetric-modulated arc therapy; VxGy, volume of organ (%) receiving greater than or equal to XGy.

Since the publication of this systematic review, Thor et al.[44] published a modeling study on the basis of the RTOG0617 data set revealing that the primary drivers for differential mortality were dose-volume loads on multiple cardiopulmonary structures. This suggests a potential negative effect of the irradiation of blood-carrying structures on the immune system, which needs to be elucidated in further studies.[45]

Limiting Dose to Cardiac Substructures

The lack of a definite dose constraint for the whole heart and effect on survival of small residual set-up errors toward the heart could indicate that dose to cardiac substructures is more important than whole heart dose. Moreover, studies of HL survivors have highlighted that different heart diseases exhibit dose-response relationship with varied shapes and slopes, for example, linear for IHD[32] and nonlinear for valvular heart disease.[33]

The heart is comprised substructures with unique physiological functions. Figure 2 reveals the different cardiac substructures that have been found to be significantly associated with cardiac events or mortality in patients having radical radiotherapy for lung cancer.[20,46-54] A number of studies point to dose received by cardiac substructures at the base of the heart as being associated with reduced survival or cardiac events. The base of the heart is defined anatomically as posterior to the sternum, at the level of the third costal cartilage. Posteriorly, it is formed by the left atrium and connecting upper pulmonary veins, and anteriorly, it includes the right ventricular outflow tract, aortic root, and origin of the coronary arteries. The base of the heart also includes the junction of the superior vena cava and right atrium, which is the location of the sino-atrial node, the origin of the electrical impulse that stimulates cardiac contraction.[55]

One hypothesis for increased cardiac events after lung radiotherapy is that the conduction system may be damaged directly by radiation or indirectly through inflammation, fibrosis, or ischemia. Dose to both the superior vena cava and left atrium has been associated with electrocardiogram changes.[52,53] Novel applications of stereotactic radiation therapy to treat refractory cardiac arrhythmias reveal that the cardiac conduction system can be considered a serial structure. Although the biological mechanisms underlying the use of radiotherapy in the treatment of refractory ventricular tachycardia are unknown, proof-of-concept and clinical studies have revealed some benefit in reducing the number of episodes.[56,57]

Cardiac Contouring

The heart is now a recognized organ at risk in lung cancer radiotherapy and is routinely contoured. Current

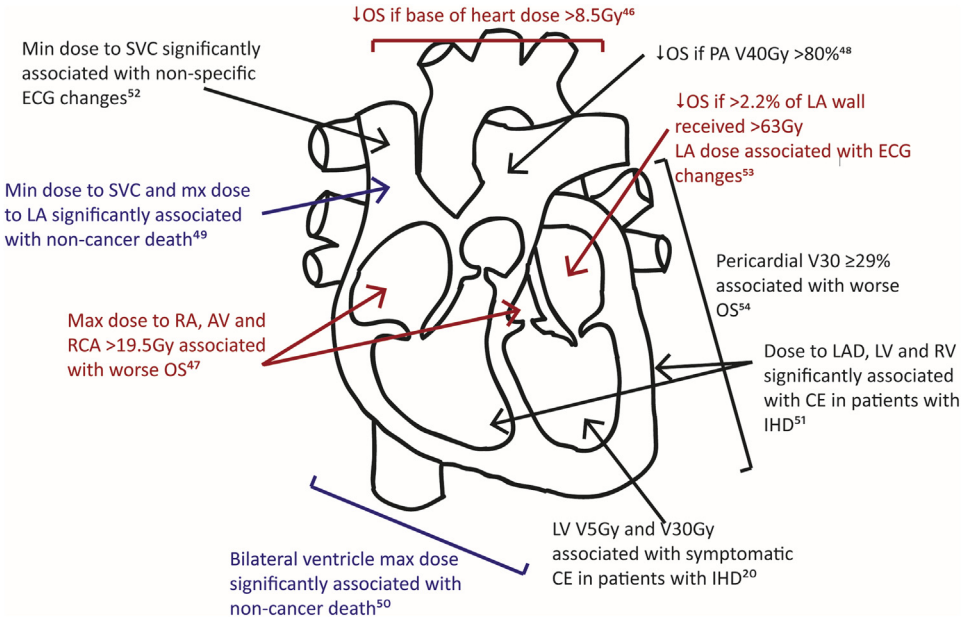

Figure 2. Cardiac substructures found to be significantly associated with cardiac events or overall survival in prospective and retrospectives studies. Labels in black reveal studies using standard fractionation, those in red reveal studies using hypofractionated radiotherapy, and those in blue reveal studies using SABR. AV, aortic valve; CE, cardiac events; ECG, electrocardiogram; IHD, ischemic heart disease; LA, left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; OS, overall survival; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RV, right ventricle; SABR, stereotactic ablative body radiotherapy; SVC, superior vena cava; V30, volume of heart receiving greater than or equal to 30 Gy; V40, volume of heart receiving greater than or equal to 40 Gy; V5, volume of heart receiving greater than or equal to 5 Gy.

guidelines recommend limiting dose to the whole heart or pericardium[58]; however, it is still not known whether we should limit the radiation dose to the whole heart or to the substructures. Several heart contouring atlases have been developed[59-61] with the aim of consistent dose reporting in clinical practice and clinical trials. Key differences exist between atlases with different substructures being highlighted. Two atlases were developed in patients undergoing breast cancer radiotherapy. The atlas by Duane et al.[59] subdivides the left ventricle into five sections and describes the anatomy of 10 coronary artery segments and is meant only for research use, not for clinical practice. The atlas by Feng et al.[60] includes the four cardiac chambers, in addition to heart valves and the atrioventricular node. In contrast, the atlas by Kong et al.[61] was developed in the context of lung radiotherapy and only includes the four cardiac chambers. Most studies of cardiac dosimetry use either the Feng or Kong atlases. The effect of contouring differences on dose parameters (MHD or volumetric parameters) should not be underestimated, and comparison between patients and between institutions depends on clinicians after strictly standardized guidelines. When interpreting the literature on radiotherapy-induced cardiac toxicity, it is important to understand the important differences between contouring atlases because these will affect dose reporting and comparison of outcomes.

The limitations described in delineating cardiac substructures can be overcome by employing analysis techniques that do not require any cardiac delineation. Studies by Stam et al.[49] and McWilliam et al.[46] used a reference anatomy and nonrigidly registered each patient. Stam et al.[49] evaluated the dose to individual cardiac substructures contoured on the reference anatomy, whereas McWilliam et al.[46] used a voxel-based approach to find a region associated with worse patient outcomes. The later technique does not use any segmentations removing any need for previous assumptions on the important anatomy.

Identification and Management of Cardiac Toxicity

Radiation results in a variety of toxicity depending on the affected substructure. Table 2 reveals the diseases that can occur after thoracic radiotherapy and the possible treatment options for these conditions. The treatment of RIHD is similar to the treatment of heart failure, pericardial, valve, and IHD in the general cardiac setting; however, patients previously exposed to radiotherapy may have worse outcomes. A case-control study of cardiac revascularization in patients who had previous thoracic radiotherapy found that they were at significantly increased risk of death up to 5 years after coronary artery stenting (hazard ratio = 4.2, 95%

Table 2. Manifestations of RIHD and Potential Treatments

Disease	Symptoms and Signs	Investigation	Management
Pericardium			
Acute pericarditis	Fever, chest pain, pericardial rub	Echo, CMR	Symptomatic pain relief with anti-inflammatory medications (e.g., NSAIDs or aspirin) Colchicine
Pericardial effusion	Dyspnea, cardiac tamponade, quiet heart sounds	Serial echo	Pericardiocentesis if patient acutely unwell secondary to cardiac constriction/tamponade
Constrictive pericarditis	Dyspnea, edema, fatigue, pericardial rub	Echo, CMR, CCT to identify calcification	Diuretics if heart failure present Surgery in intractable cases
Myocardium			
Cardiomyopathy and heart failure	Dyspnea, edema, fatigue, cough	Blood NT-proBNP Echo CMR	Diuretics, B-blockers, ACE inhibitors, angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors
Coronary arteries			
IHD	Chest pain	Blood troponin levels ECG Echo CCT Angiography	Cardiac risk factor optimization and secondary prevention with statins and aspirin B-blockers, Ca-channel blockers Antianginals, for example, nitroglycerine, ivadrabine, ranolazine, nicorandil Revascularization if high symptom burden or significant stenosis of left main stem/proximal left anterior descending
Valves			
Regurgitation and stenosis	Dyspnea, edema, fatigue, cough, chest pain, cardiac murmur	Echo CMR CCT	Diuretics, anticoagulation, blood pressure control Valve replacement with surgery or TAVI
Conduction system			
Arrythmia	Palpitations, dizziness, dyspnea, chest pain	ECG (ambulatory) Echo CMR	Antiarrhythmics Pacemaker Cardiac resynchronization

ACE, angiotensin-converting enzyme; Ca, calcium; CCT, cardiac computed tomography; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; Echo, echocardiogram; IHD, ischemic heart disease; NSAID, nonsteroidal anti-inflammatory drug; NT-proBNP, N-terminal fragment B-type natriuretic peptide; RIHD, radiation-induced heart disease; TAVI, transcatheter aortic valve implantation.

confidence interval: 1.8–9.5).[62] The pathophysiology of RIHD is different to that of standard heart disease, and therefore, further research is required to improve its management.

Preclinical research on signal transduction pathways has helped to identify potential therapeutic targets for RIHD, some of which have been transferred into the clinic in small studies. Antioxidant drugs such as amifostine and vitamins C and E reduce reactive oxygen species and delay myocardial fibrosis.[63] Statins target the activation of the Rho/ROCK pathway whereas angiotensin-converting enzyme inhibitors prevent adverse cardiac remodeling to preserve and improve left ventricular function.[64]

If patients are suspected of having cardiac complications after radiotherapy, assessment should include current symptoms, risk factors for cardiac disease, and treatment history (including radiotherapy treatment information and previous/current systemic therapy). Cisplatin is often used concurrently with radiotherapy in stage III lung cancer, in the adjuvant setting after surgery, and to treat metastatic disease. The drug is not directly cardiotoxic; however, it can cause endothelial dysfunction and platelet activation leading to ischemia and thrombosis.[65] Checkpoint inhibitors are used both after concurrent chemoradiotherapy in stage III NSCLC and in patients with metastatic disease. These drugs can cause myocarditis and cardiac arrhythmias; however, the incidence of these events is low.[66] Patients with cardiotoxicity from cancer treatment should be referred to a cardiologist, ideally one with experience of the cardiac complications of cancer treatment.

Preventing Cardiac Toxicity

As previous CVD predicts cardiac events after lung radiotherapy, risk factor modification has an important role in these patients before and after thoracic radiotherapy. Risk factor modification includes smoking cessation, blood sugar control, and lowering blood pressure and cholesterol.

Radiation dose to the heart is another potentially modifiable risk factor. As discussed previously, there is emerging evidence that dose-volume statistics for the

whole heart are suboptimal; therefore, clinical benefit could be found with defined heart avoidance regions and tolerance doses combined with improved image-guided radiotherapy. A daily on-treatment imaging strategy with smaller action threshold levels has been found to improve patient survival.[42] A number of advanced radiotherapy technologies can be considered to further reduce the radiation dose to the heart. For example, deep inspiratory breath hold can increase lung capacity and reduce tumor motion. This technique has been reported to be tolerable[67] and to reduce MHD and hospitalizations at 3 months in cohorts of patients with lung cancer.[68] MR-guided radiotherapy strategies may allow reduced planning target volume margins and reduced heart dose.[69] In the setting of locally advanced lung cancer, proton beam therapy (PBT) can reduce MHD and spare more heart volume at all dose levels compared with intensity modulated radiotherapy, particularly at low-dose levels.[70] Another advantage of PBT is that it may decrease the integral dose and reduce the risk of lymphopenia, which can cause severe opportunistic infection and excess mortality.[71] Despite promising results, there is to date little evidence that the use of protons reduces cardiac toxicity or mortality so studies are ongoing or in set-up worldwide (Clinicaltrials.gov NCT 01993810). Furthermore, PBT is extremely sensitive to uncertainties related to tumor motion and lung tissue density, which may limit its use as a heart-sparing strategy in patients with lung cancer.

Conclusions and Future Directions

Thoracic radiotherapy is known to cause a variety of cardiac damage through the inflammatory pathways. Patients with lung cancer, who typically have multiple comorbidities, are at higher risk of cardiac events and early mortality after thoracic radiotherapy. To make progress in our understanding of radiation-induced cardiac toxicity, a number of issues should be addressed.

First, prospective and sufficiently powered studies in patients with lung cancer using an agreed cardiac atlas and robust quality assurance are required. A key limitation of the existing literature on cardiac toxicity is that most published work consists of small, retrospective, mostly single-centre studies with varying end points. Furthermore, large variations in preexisting cardiac disease, comorbidities, radiotherapy technique, and use of chemotherapy in test populations contribute to different outcomes. In addition, data pooling between centers would allow the creation of applicable models with improved power to identify heart dose constraints and factors that predict for cardiac toxicity.[72]

Second, there is a need to develop a better understanding of the impact of radiation dose on cardiac substructures. Such effects are challenging to evaluate as echocardiography, electrophysiological, or cardiac perfusion studies are currently not part of the routine assessment of patients with lung cancer. There is therefore a requirement to perform prospective studies in collaboration with cardiologists, to prospectively investigate and correlate blood and cardiac imaging biomarkers with outcome. Prospective studies are ongoing (NCT04305613, NCT03978377, and NCT03645317).

Finally, there is a need for high-quality prospective research to investigate advanced radiotherapy technologies such as MR-guided radiotherapy and PBT. Such studies should include cardiac end points and biomarkers to understand the effect of the cardiac-sparing strategy on the outcome of patients with lung cancer treated with thoracic radiotherapy.

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