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The impact of heart irradiation dose on cardiac injury and survival in lung cancer patients after radiotherapy

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Thoracic radiotherapy is a primary treatment modality for lung cancer, with approximately two-thirds of patients receiving it. The association between heart dose and post-radiotherapy survival and cardiac injury represents a critical area of contemporary radiotherapy research, yet understanding of radiation-induced heart disease (RIHD) in lung cancer remains incomplete. This review synthesizes literature on the effects of heart dose on survival and substructure-specific cardiac injury in lung cancer patients, evaluating thresholds for reversible and irreversible damage to cardiac substructures. We further summarize key mechanisms underlying RIHD.

KEYWORDS

lung cancer, radiotherapy, heart irradiation dose, survival, RIHD

1 Introduction

Lung cancer is a prevalent type of cancer with a increasing incidence and mortality. According to statistical analysis of data from the American Society of Clinical Oncology (ASCO), in 2020, lung cancer was the second most commonly diagnosed cancer in both men and women in the United States, but it was the leading cause of cancer-related deaths among both genders, with a mortality rate of 23% in men and 22% in women (1). Early-stage lung cancer is often asymptomatic, and approximately one-third of patients have already progressed to the locally advanced stage by the time they present with symptoms, which can result in the loss of the opportunity for surgical treatment (2). Radical surgery may not be a viable option for some early-stage patients due to poor general health or other reasons. For the past 30 years, radical concurrent chemoradiotherapy has been the standard treatment for locally advanced unresectable non-small cell lung cancer (3). However, the time to disease progression after chemoradiotherapy is only approximately 8 months, with a 5-year survival rate of less than 15% (2, 4). The Radiation Therapy Oncology Group (RTOG) 7301 study established that a radiation dose of 60–63 Gy (single dose of 1.8–2.0 Gy) used to treat non-small cell lung cancer (5). Subsequently, studies have attempted to increase the radiation dose to improve survival outcomes (6–10). Published in 2015, RTOG

0617 is a phase III randomized controlled clinical trial that employed a dose-escalating radiotherapy design for the treatment of stage III unresectable lung cancer (11). The study demonstrated that contrary to mainstream review, increasing the radiation dose did not result in improved survival benefits (11). The secondary analysis of RTOG 0617 revealed that the survival of patients with locally advanced non-small cell lung cancer is associated with the radiation dose received by the heart (12).

2 Methods

2.1 Search strategy

PubMed, Embase, Cochrane Library, and Web of Science databases were searched. The time range of the literature was from 2010 to 2025 in each database, and the language was limited. The medical subject terms used were as follows: lung cancer, NSCLC, radiotherapy, radiation therapy, cardiac toxicity, heart dose, RIHD.

2.2 Inclusion criteria

(1) Subjects: patients with pathologically confirmed lung cancer (NSCLC or SCLC); (2) Interventions: radiotherapy; (3) Study types: retrospective/prospective; (4) Outcome indicators: overall survival (OS), progression-free survival (PFS), pericarditis, myocardial infarction, heart failure, arrhythmia, etc.

2.3 Exclusion criteria

Articles with the following conditions will be excluded: (1) animal or cell experiments, case reports, scientific experiment plans, reviews, letters, editorials, conference papers, etc.; (2) articles with missing data or serious errors; (3) repeated publications; (4) no data on survival or cardiac events were reported; (5) The full text was not found.

2.4 Data extraction

The retrieved literature was imported into Zotero, and the title and abstract of the literature were screened independently by two researchers according to the inclusion and exclusion criteria, and then the full text was read for a second screening. Conflicting studies were re-evaluated by discussion or by seeking the advice of a third researcher. Two researchers independently extracted the data information of the final included literature using Excel 2016. Two researchers used Excel 2016 to independently extract the data information of the final included literature, including Study, Study type, Enrollment, Stage, Dose(Gy), Radiotherapy technique, Heart substructures, Cut-off value, Conclusion.

3 The correlation between heart dose and survival

The term RIHD was originally first described in the cardiac complications that arose in patients with breast cancer or lymphoma who received thoracic radiotherapy (13, 14). Radiation oncologists have long held the belief that RIHD was a delayed effect that primarily affected those who survived cancer for an extended period. However, this notion overlooked the significant impact that RIHD could have on patients with cancers that had a shorter survival rate, such as lung cancer, which has a 5-year survival rate of approximately 10%-20% (15). Following the RTOG 0617 study, an increasing number of researchers have turned their attention to the relationship between heart dose and survival in lung cancer patients receiving thoracic radiotherapy. On the one hand, lung cancer patients are typically diagnosed at an older age than breast cancer patients and tend to have more comorbidities, including cardiac complications. On the other hand, lung cancer patients receive higher radiation doses than breast cancer patients, which makes them less tolerant of heart irradiation, leading to earlier onset of cardiac adverse events. Thus, it is crucial to consider the radiation dose received by the heart during radiotherapy for lung cancer patients. Table 1 provides a summary of the relevant studies published to date that investigate the relationship between radiation dose received by the whole heart and survival.

Existing studies indicate a potential association between cardiac radiation dose and overall survival (OS) in lung cancer patients receiving radiotherapy, yet the conclusions remain inconsistent. Such variability largely reflects differences in patient population characteristics, the evolution of treatment techniques, and variations in follow-up duration. In early clinical cohorts, the high tumor-related mortality of lung cancer often obscured the long-term impact of radiation-induced cardiac injury, making it difficult to detect a significant correlation between cardiac dose and prognosis (16, 17). With the refinement of radiotherapy and chemotherapy, as well as the widespread adoption of consolidation immunotherapy, median OS has been markedly prolonged; consequently, the detrimental effect of cardiac irradiation on long-term survival has gradually become more evident, a phenomenon confirmed by large-scale studies in recent years (18).

Meanwhile, advances in radiotherapy are reshaping the relationship between cardiac dose and survival. During the 3D-CRT era, extensive irradiation field increased the volume of low-dose exposure, and as a result, low-dose and intermediate-dose parameters (V5, V30, V50) showed a trend toward correlation with OS in some studies—for example, Speirs et al. (19) reported a significant association between V50 and OS. With the widespread implementation of IMRT, however, greater conformity has led to the concentration of high-dose exposure in specific cardiac regions or substructures, such as the left anterior descending artery (LAD) and the left atrium. In this setting, high-dose parameters pertaining to these substructures appear to carry stronger prognostic value. Notably, Atkins et al. (20) reported that LAD V15 $\geq$ 10% was

TABLE 1 Study on the correlation between heart dose and survival.

Study	Study type	Enrollment	Stage	Dose(gy)	Radiotherapy technique	Conclusion
Schytte et al. (16)	retrospective	328	I-III	60/66/80	3DCRT	MHD not associated with OS
Bradley et al. (11)	prospective	554	III	74 vs. 60	3DCRT/ IMRT/	V5, V30 associated with OS
Tucker et al. (21)	retrospective	468	IIIA/IIIB	63(60-76)	3DCRT/ IMRT/ PROTON	V5, MHD not associated with OS
Guberina et al. (17)	prospective	161	IIIA/IIIB	45 vs. 45+(20-26)	3DCRT	V5 not associated with survival
Dess et al. (22)	prospective	125	II/III	70(45-88)	IMRT/ 3DCRT	V5, V30, V50, MHD not associated with OS
Wang et al. (23)	prospective	127	III	74(70-90)	3DCRT	V5, V30, MHD not associated with OS
McWilliam et al. (24)	retrospective	1101	–	55	IMRT/ 3DCRT	V5, V30, MHD not associated with OS
Ning et al. (25)	prospective	201	I-IV	74(60-74)	PROTON/ IMRT	MHD not associated with OS
Chun et al. (12)	prospective	482	IIIA/IIIB	74 vs. 60	IMRT/ 3DCRT	V40 associated with OS
Vivekanandn et al. (26)	prospective	78	IIB-III	67.6(63-73)	3DCRT/ VMAT	V63–69 associated with OS
Ma et al. (27)	retrospective	141	III	66(60-76)	IMRT/ 3DCRT	V30, V35, V40, V45 not associated with OS
Stam et al. (28)	retrospective	469	IIA-IIIB	66	IMRT	V2 associated with OS
Speirs et al. (19)	retrospective	416	II-III	(50-84.9)	3D-CRT/ IMRT	V50 associated with OS
Contreras et al. (29)	retrospective	400	II-III	66(50-77.25)	3DCRT/ IMRT/ PROTON	V50 associated with OS
Yegya-Ramn et al. (30)	retrospective	140	IIA-IV	61.2(50.4-70.2)	3DCRT/ IMRT	MHD associated with OS; MHD not associated with V5, V30, V50
Xue et al. (31)	prospective	94	I-III	70(45–85.5)	3DCRT	V5, V30, V55, MHD not associated with OS
Atkins et al. (18)	retrospective	748	IIIB	64.0(54.9-66.0)	3DCRT/ IMRT	MHD associated with all-cause mortality

3DCRT, three dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy; PROTON, proton radiotherapy; MHD, mean heart dose; OS, overall survival.

associated with a significantly increased risk of major adverse cardiac events and death (HR 1.58, 95% CI 1.09-2.29). The development of proton therapy has substantially reduced exposure to mean heart dose (MHD). Nevertheless, results may be subject to bias due to stringent patient selection criteria. For instance, Tucker et al. (21) often selected high-risk cases with tumors situated close to the heart, a factor that may have contributed to an overestimation of the relationship between MHD and OS. Furthermore, the biological interpretations of different dosimetric parameters are not entirely consistent: MHD reflects only the global average and may underestimate the impact of focal high-risk exposure; intermediate and high-dose volume fractions (V30–V50) provide a better indication of risks such as cardiac fibrosis or large-vessel injury; and low-dose volume (V5) has been linked to systemic inflammatory responses or immunosuppression. It should also be emphasized that in the era

of immunotherapy, prolonged survival has made delayed cardiotoxicity increasingly relevant, and accumulating evidence suggests that focal irradiation of critical substructures such as the LAD or atrium is associated with increased mortality risk (20).

4 The correlation between substructure heart dose and survival

According to some researchers, limiting the radiation dose to the heart as a whole organ is a crude method. As a result, scholars have divided the heart into several substructures to assess the radiation dose more accurately. Table 2 provides a summary of relevant studies that explore the correlation between cardiac substructures dose and survival. In some studies, the

substructures of the heart are defined based on its inherent basic structure, including the left and right atria, left and right ventricles, pericardium, coronary system, valves, and major blood vessels. Other studies have examined the correlation between self-defined special structures or regions and survival. In a retrospective study, McWilliam demonstrated that the radiation dose received by the bottom region of the heart was correlated with the survival of lung cancer patients undergoing radiotherapy (24). In another retrospective study, the same author defined a special region of the heart that included the right atrium, right coronary artery, and ascending aorta (32). The study revealed that patients with an equivalent dose in 2-Gy fractions (EQD2) greater than 23 Gy in this region had significantly shorter overall survival (OS) than those with an EQD2 of less than 23 Gy (EQD2 >23 Gy: 12 months, 95% CI: 10–14 months; EQD2 <23 Gy: 21 months, 95% CI: 17–23 months, $P = 0.008$) (32). However, recent studies have attempted to explore the correlation between established substructures of the heart and survival. For instance, Thor et al. utilized the RTOG 0617 database to establish a multifactorial survival prediction model (33). Cox multivariate analysis revealed that both the left atrium D45% (the minimum dose received by 45% of the volume) and the ventricular MOH5% (the average dose received by 5% of the volume) were independent prognostic factors for survival (33). In a study of 701 non-small cell lung cancer patients, Atkins et al. discovered that a coronary left anterior descending artery V15 $\geq 10\%$ significantly increased the mortality of lung cancer patients (HR = 1.58, 95% CI: 1.09–2.29, $P = 0.02$) [33]. However, manually or automatically segmenting and delineating substructures of the heart

remains a challenging and time-consuming task in routine radiotherapy planning (34–36). Therefore, the delineation of substructures of the heart has not yet been widely implemented in clinical practice.

Table 2 shows that several studies have reported associations between radiation dose to specific cardiac substructures (such as the left anterior descending artery (LAD), left atrium, heart base, and pulmonary artery—and OS) whereas the MHD often failed to demonstrate statistical significance. This suggests that the effect of small, high risk cardiac substructures may be “diluted” when assessed using the MHD. At present, however, substantial heterogeneity exists among studies, including differing definitions and delineation methods for substructures, limited sample sizes, and variable results. For instance, McWilliam et al. (32) reported that the dose to the heart base was associated with OS, whereas certain chamber-based parameter (such as the mean dose to the right ventricle) did not demonstrate prognostic value, indicating that clinical significance may depend on both structural function and its spatial relationship to tumor location. Overall, when tumors are located in the left upper lobe or in the mediastinum adjacent to major vessels, particular attention should be paid to the coronary arteries and left atrium. Conversely, when the target volume is close to the pulmonary artery or heart base, limiting intermediate-dose to high-dose exposure in these regions becomes essential. In the future, the integration of automated segmentation and multicenter validation may enable the development of standardized substructure dose–survival models, which are expected to provide greater guidance than reliance on MHD alone.

TABLE 2 Study on the correlation between heart substructures dose and survival.

Study	Stage	Heart substructures	Cut-off value	HR (95%CI)	OS difference (months)
Xue et al. (31)	I–III	Pericardium V30	29%	1.019 (1.004–1.033)	13.3 vs. 35.8
		Pericardium V55	21%	1.030 (1.006–1.054)	13.3 vs. 30.0
McWilliam et al. (32)	–	Specific area (including right atrium, right coronary artery, ascending aorta) Dmax	19.5 Gy	1.010 (1.010–1.020)	12.0 vs. 21.0
McWilliam et al. (24)	–	Specific area (cardiac base) Specific doses	8.5Gy	1.250 (1.01–1.56)	NA
Ma et al. (27)	–	Pulmonary artery V40	80%	2.113 (1.014–4.936)	14.0 vs. 27.8
		Pulmonary artery V45	68%	2.660 (1.089–5.717)	13.5 vs. 37.9
		Pulmonary artery V50	45%	1.203 (0.062–2.056)	14.2 vs. 32.7
		Pulmonary artery V55	32%	1.489 (0.098–2.096)	10.9 vs. 41.8
Vivekanandan et al. (26)	IIB/III	Left atrial wall V63	2.2%	1.520 (1.070–2.170)	39.2 vs. 27.9
Thor et al. (33)	III	Atrium cordis D45%	44/30Gy	NA	NA
		Pericardium MOH55%	51/39Gy	NA	NA
		Ventricle MOH5%	56/41Gy	NA	NA
Atkins et al. (20)	II–III	Left anterior descending coronary artery V15	10%	1.580 (1.090–2.290)	NA
Olive et al. (37)	–	Ventricle Dmax	NA	1.020 (1.000–1.040)	NA
Stam et al. (38)	–	Left atrium D0%	NA	1.006 (NA)	NA
		Superior vena cava D90%	NA	1.025 (NA)	NA

5 Mechanisms of cardiac fibrosis in RIHD

The development of fibrosis is the primary damage caused by radiotherapy to the heart. Radiotherapy generates reactive oxygen species (ROS) by ionizing water molecules and damaging the mitochondrial respiratory chain, leading to ROS accumulation. The activation of enzymes such as NADPH oxidase and cyclooxygenase can also accelerate ROS accumulation. Meanwhile, radiation suppresses antioxidant enzymes, which impairs the ability of antioxidants to clear accumulated ROS, exacerbating oxidative stress and resulting in various chemical reactions in the body (39). Oxidative stress is closely associated with myocardial fibrosis. The release of proinflammatory factors, such as TNF- α , IL-1, and IL-11, as well as adhesion molecules, increases the number of fibroblasts (40). This leads to the formation of microthrombi and vascular occlusion, resulting in perfusion defects and focal ischemia, which exacerbate cardiomyocyte death and fibrosis (40). Myocardial fibrosis is primarily identified by the accumulation of collagen in the heart, which eventually replaces cardiomyocytes (41). Moreover, ROS and lipid peroxidation products can deactivate membrane-bound receptors and enzymes, resulting in increased tissue permeability, protein inactivation, and ultimately the destruction of cardiomyocyte membranes (41). Studies have shown that ROS and protein oxidation may impact the function of receptors, enzymes, and transport proteins (41). For instance, ROS can overactivate Ca²⁺-calmodulin-dependent protein kinase II, resulting in irregular excitation-contraction coupling, heart failure, and arrhythmia (42). Radiation-induced microvascular damage can cause elevated capillary permeability and the swift emergence and progression of protein-rich exudates, ultimately resulting in radiation-induced pericarditis (43). The accumulation of collagen in the interstitium and apex of the pericardium can also result in pericardial fibrosis.

The DNA double-strand breaks (DSBs) which is caused by the radiation and the ROS can activate I- κ B kinase, which mediates I- κ B degradation and releases NF- κ B into the nucleus (44). NF- κ B binds to the promoter regions of target genes, promoting the expression of NADPH oxidase and cyclooxygenase in target genes to result in further elevation of ROS levels (45). These ROS, in turn, continue to affect NF- κ B, forming a positive feedback loop that speeds up the cardiac fibrosis. In addition, NF- κ B also induces some pro-inflammatory factors such as TNF- α to increase the number of presenting cells.

Radiation-induced cardiac fibrosis frequently demonstrates overexpression of TGF- β , indicating that an elevated level of transforming growth factor may worsen RACD. Ionizing radiation damage can activate TGF β through various pathways, including ROS generation, excessive inflammation activation, microvascular damage, platelet activation, and cellular aging and apoptosis (46). TGF- β can induce fibrosis through both the canonical and noncanonical signaling pathways. In the canonical pathway, TGF- β activates target genes, including type I collagen, type III collagen, CTGF, and α -smooth muscle actin, via Smad

transcription factors (47). TGF- β can also exert its effects through non-Smad pathways, such as Rho/ROCK, which further enhance fibrosis. Simultaneously, TGF- β can strengthen the profibrotic signals mentioned earlier through ROS, resulting in the formation and accumulation of myofibroblasts and extracellular matrix and accelerating the onset and progression of fibrosis (48). The platelet-derived growth factor (PDGF) family of factors is another critical mediator of myocardial fibrosis. Research has revealed that the overexpression of cardiac PDGF-C and PDGF-D through transgenic technology leads to extensive cardiac fibrosis (49, 50).

6 Mechanisms of cardiac cell injury and death in RIHD

Radiation can cause various types of DNA damage, among which DNA double-strand breaks (DSBs) are the most severe. ROS and DSBs activate I- κ B kinase, which mediates I- κ B degradation and releases NF- κ B into the nucleus (44). NF- κ B binds to the promoter regions of target genes, inducing the expression of proinflammatory factors such as TNF- α , IL-1, IL-6, and IL-8, thereby regulating the inflammatory response (44). Simultaneously, NF- κ B can enhance the adhesion ability of leukocytes by inducing the secretion of adhesion molecules (41). The infiltration of neutrophils can result in the additional release of various proinflammatory factors, worsening endothelial cell damage (41). Infiltrating monocytes can differentiate into activated macrophages, which struggle to degrade low-density lipoprotein oxidized by ROS, progressively transforming into foam cells, a process closely linked to the development of atherosclerosis (41). Furthermore, NF- κ B promotes the expression of NADPH oxidase and cyclooxygenase in target genes, resulting in further elevation of ROS levels (45). These ROS, in turn, continue to affect NF- κ B, forming a positive feedback loop that speeds up the progression of coronary artery disease and vascular damage (45).

Research has demonstrated that in the initial phases of radiotherapy, ROS and DNA damage repair (DDR) can boost NO by phosphorylating serine 1177 on endothelial nitric oxide synthase (eNOS) in human endothelial cells (51, 52). However, the interaction between ROS and NO results in reactive nitrogen species, which decreases the bioavailability of NO (53). Simultaneously, ROS stimulate the production of vasoconstrictive substances such as prostaglandins, which hinder vascular relaxation and eventually result in vascular stenosis (53). Moreover, radiotherapy can cause a reduction in myocardial capillaries, and increase the expression of von Willebrand factor in endothelial cells, leading to platelet adhesion and thrombus formation in blood vessels, worsening ischemia and hypoxia (54, 55). ROS and DNA damage signals trigger cell apoptosis through the Bcl-2/Bax protein family and the p53 protein, respectively (45, 54). The Bcl-2/Bax protein family can also cause cell apoptosis by changing mitochondrial permeability (56). Furthermore, radiotherapy can enhance the release of Ca²⁺ from the endoplasmic reticulum, resulting in an elevation of mitochondrial Ca²⁺ uptake (57). Calcium overload can ultimately lead to cell membrane swelling

and the release of apoptotic factors (57).

7 The expression mechanism of micro-RNAs provides ideas for RIHD prediction

Several studies have suggested that micro-RNAs (miRNAs) are involved in the pathogenesis and progression of RIHD (58–60). Therefore, we believe that miRNAs can be used as an early molecular marker to predict heart damage. To begin with, exposure to ionizing radiation and other oxidative stress-inducing factors can lead to alterations in miRNA expression (58). Numerous investigations have demonstrated that miRNAs are implicated in the pathological processes related to cardiac radiation damage, such as oxidative stress, inflammation, endothelial dysfunction, hypertrophy, fibrosis, and subsequent heart failure (59, 60). Recently, miRNAs have also been found to be involved in the regulation of radiation-induced DNA damage (61). For instance, miRNA-21 has been shown to promote cell proliferation and anti-apoptosis (62). Csilla et al. reported that the expression of miRNA-21 in the myocardium was significantly increased following radiation, particularly in the left ventricle (63). On the other hand, miRNA-1 expression was down-regulated in irradiated animal models, consistent with changes in cardiac hypertrophy and heart failure, and altered in various cardiovascular diseases (59). Furthermore, changes in miRNA-34a expression have also been associated with heart injury, and a study has indicated that miRNA-34a expression was up-regulated after radiation exposure (64).

The above-described mechanisms are depicted in Figure 1.

8 Strategies for prevention and management of RIHD

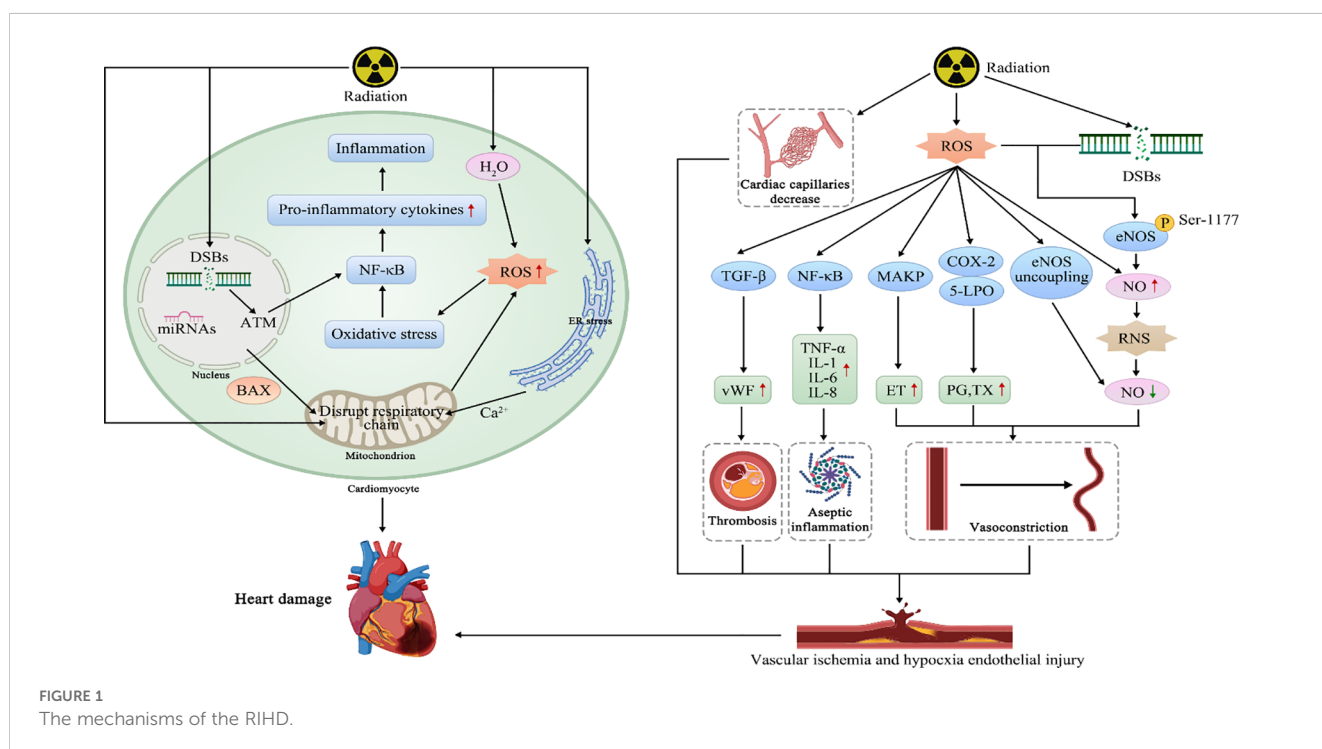
8.1 Cardiac-sparing radiotherapy techniques

Preventive strategies mainly focus on reducing the cardiac irradiation dose. With conventional 3D conformal radiotherapy (3DCRT), considerable incidental exposure of the heart is common. Modern photon techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) provide more conformal dose distributions and significantly reduce heart volumes receiving intermediate to high doses (12).

Proton therapy has demonstrated superiority in reducing mean heart dose (MHD) and left anterior descending artery (LAD) exposure when compared to photon IMRT, as shown by randomized and dosimetric studies (65). Robust optimization and spread-out Bragg peak characteristics eliminate exit dose, leading to improved sparing of cardiac substructures.

Motion management techniques, including deep inspiration breath hold (DIBH), expiration breath hold, respiratory gating, and tumor tracking, have emerged as pivotal strategies to increase the distance between the tumor and critical cardiac structures (66). DIBH is widely adopted for left breast and mediastinal targets, and increasingly used in locally advanced lung cancer to reduce MHD.

Adaptive radiotherapy and MRI-guided RT enable daily plan adaptation and improved visualization of heart substructures. At the same time, AI-based automatic substructure delineation provides standardization and efficiency, overcoming the steep learning curve of manual segmentation (32, 67).



Collectively, these strategies highlight a paradigm shift from whole-heart dose limitation to substructure-specific constraints (eg, LAD V15 < 10% or pericardium V30 < 30%) with the aim of better predicting RIHD and survival outcomes (20, 66).

8.2 Management of established RIHD events

Once RIHD occurs, management resembles standard cardiology approaches. Arrhythmias may be treated with antiarrhythmic agents or pacemaker/ICD implantation. Heart failure is managed with beta-blockers, ACEIs/ARBs, diuretics, and guideline-directed therapy. Pericarditis responds to anti-inflammatory drugs and colchicine, while constrictive disease may require pericardiectomy. Coronary disease can be managed with percutaneous intervention or bypass grafts, and valvular damage may necessitate surgery (43, 55). In patients receiving immune checkpoint inhibitors, immune-related myocarditis requires corticosteroids and sometimes additional immunosuppressants (68). These treatments control symptoms and prevent progression, but do not reverse structural fibrotic changes induced by radiation.

8.3 Lifestyle and risk factor modification

Risk factor control is essential. Smoking cessation, strict management of hypertension, diabetes, and dyslipidemia, and the use of statins or aspirin in selected patients may reduce the burden of RIHD (69). Multidisciplinary “cardio-oncology” programs are increasingly important for high-risk patients undergoing thoracic RT (70).

9 Conclusion

Radiation-induced heart disease (RIHD) is an emerging determinant of survival in lung cancer patients receiving thoracic radiotherapy. Current evidence indicates that whole-heart mean dose alone is inadequate to describe clinically relevant risk, as the prognostic impact often arises from focal exposure of critical substructures such as the left anterior descending artery, left atrium, pulmonary artery, and heart base. This underscores the need to move from global dose metrics toward substructure-specific evaluation.

Recent advances (including IMRT, proton therapy, motion management, and adaptive radiotherapy) facilitate selective cardiac sparing, but heterogeneous delineation methods and limited prospective validation hinder the establishment of universal

constraints. Future research should prioritize standardized segmentation, multicenter collaboration, and prospective dose-response modeling.

In the immunotherapy era, where patient survival is improving, refinement of cardiac-sparing strategies is essential to balance tumor control with long-term cardiovascular safety, ultimately optimizing both overall survival and quality of life in lung cancer patients.

Author contributions

BL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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