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Cardiac Substructure Analysis of Radiation-associated Cardiac Disease in Thoracic Malignancy Patients

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Abstract

Radiation-associated cardiac disease frequently affects cancer patients when radiation fields overlap the heart, but relationships between cardiac substructure dose and specific cardiac events remain poorly understood. This study examined associations between radiation dose to cardiac substructures and adverse cardiac events in thoracic malignancy patients. We retrospectively analyzed 94 patients with lung, esophageal and breast cancers who received radiation therapy. Radiation-induced adverse cardiac events included pericardial disease, atrial fibrillation/flutter, heart failure and valve disease. We evaluated associations between cardiac substructure radiation doses and adverse event types. Results showed that increasing radiation doses to the pericardium, left atrium and whole heart were associated with higher odds of pericardial disease. Median onset times varied: 7 months for pericardial disease, 10 months for atrial fibrillation/flutter and 16 months for heart failure. Clear associations emerged between specific cardiac substructure radiation doses and corresponding adverse event types. Sex-specific differences in cardiac substructure radiation dose were also identified. These findings demonstrate important relationships between cardiac substructure radiation exposure and specific adverse events in patients receiving thoracic radiation therapy. The results underscore the critical importance of considering both cardiac substructure dose distributions and patient sex when developing strategies to mitigate treatment-related cardiac risks in cancer patients.

Keywords: Ionizing radiation • Cardiac toxicity • Thoracic malignancies

Introduction

Ionizing radiation treatment is associated with an increased risk of cardiovascular disease in cancer patients when radiation fields overlap with the heart [1,2]. Early studies performed in Hodgkin lymphoma and breast cancer patients reported that radiation therapy placed patients at an elevated risk for developing various types of cardiovascular disease, including coronary artery disease, valvular heart disease and heart failure [3-7]. Ionizing radiation-associated events typically occurs years to decades post treatment and were initially considered less relevant in lung and esophageal cancer patients due to poor prognoses and limited survival, which made adverse cardiac events less likely to manifest. However, recent trials have demonstrated that therapeutic ionizing radiation increases the risk of adverse cardiac events in these patients [8-10]. Unlike patients with breast cancer and Hodgkin lymphoma, patients with lung and esophageal cancer tend to be older and exhibit higher rates of cardiovascular risk factors such as smoking, hypertension and dyslipidemia [7,8,11]. Furthermore, patients with lung and esophageal cancer typically receive higher heart radiation doses compared to breast cancer and Hodgkin lymphoma patients. Consequently, they remain at elevated risk of radiation-associated cardiac disease despite their generally poor prognosis and higher risk factor rates [12,13].

Several organizations have created guidelines that aim to minimize the risk for development of radiation-associated cardiac disease [14-16]. Initial guidelines focused on mean heart radiation dose [3]. Since different types of cardiac disease are believed to arise from distinct areas of the heart, we hypothesized that the specific type of cardiac disease that emerges after radiation therapy may be determined by which cardiac substructures receive higher doses of radiation. Although a limited number of studies have explored this hypothesis, the results remain inconsistent and no definitive relationships have emerged [17-22]. Some recent studies have indicated that dose to cardiac substructure may be more predictive of cardiac outcomes than mean heart dose [8,11,21,23]. For example, dosimetric studies in patients with breast cancer found that radiation doses to the left ventricle and left anterior descending artery may predict cardiac toxicity [24,25]. Similarly, radiation dose the right atrium is associated with non-cancer associated survival and overall survival [26]. Pre-clinical studies further suggest that male and female hearts differ in their sensitivity to ionizing radiation [27], potentially due to differences in oxidative stress metabolism [28,29].

An improved understanding of the relationships between cardiac substructure radiation dose and specific types of adverse cardiac events could enable the identification of patients at high risk for particular cardiac conditions. This knowledge could facilitate tailoring of radiation fields to avoid or minimize doses to substructures linked with adverse cardiac side effects. Cardiac monitoring strategies, including modalities and intervals, could be individualized based on the specific cardiac substructures receiving higher doses of radiation. Our study aimed to investigate the relationship between dose to cardiac substructure and adverse cardiac events for thoracic cancers.

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Methods

The study was approved by the University of Iowa Institutional Review Board (IRB-01; biomedical). We conducted a retrospective study of 94 patients with stages I-IV thoracic malignancies who received radiation therapy between October 2003 and December 2021 and had an adverse cardiac event following the onset of radiation. Patients with a prior history of each cardiac event were excluded from the respective analysis. TriNetX was used to find relevant patient records of thoracic malignancy patients who were treated with radiation therapy. Patient charts were reviewed to identify patients with radiation fields involving the heart and those who developed adverse cardiac events following radiation therapy. Cardiac substructure radiation doses of patients who had a particular adverse cardiac event were compared to patients who did not have that specific adverse cardiac event. Radiation delivery techniques included external beam radiation therapy, intensity-modulated radiation therapy, stereotactic body radiation therapy and volumetric modulated arc radiotherapy. Radiation therapy dosing and fractionation depended on the radiation indication and patient characteristics. Standard dose constraints for normal tissues were observed.

Cardiac substructures including the pericardium, left and right atria and whole heart were contoured using radiation therapy Pinnacle Software, allowing radiation dose (total radiation dose, maximum radiation dose point) to each substructure to be determined in each patient. Pinnacle is a manual contouring package that does not use artificial intelligence. The pericardium was a rim of tissue on the outer heart. The contours were performed by or reviewed by American Board of Radiology certified radiation oncologists.

Demographic data including patient age, sex and Karnofsky Performance Status scale were collected. Information on baseline cardiac risk factors including hypertension, dyslipidemia, diabetes and smoking history was gathered. Cancer type and treatment information including histology, stage, chemotherapy and radiation types were obtained. New cardiac events identified after the administration of radiation therapy included pericardial effusions, atrial fibrillation, atrial flutter, aortic valve stenosis and regurgitation, mitral valve stenosis and regurgitation and heart failure. These newly diagnosed cardiac issues were distinguished from pre-existing conditions through thorough chart reviews. The follow-up period extended until either the conclusion of the data collection period (March 31, 2022) or the patient's date of death, whichever came first.

Patients requiring multiple radiation treatments for recurrence or progression were excluded given the complexities of consolidating dosimetry into a single effective dose. Given the radiobiological processes of cell and tissue damage, adverse cardiac events occurring shortly after radiation therapy were deemed unlikely to be radiation related. To mitigate these concerns, the study excluded patients with cardiac events occurring within 14 days of initiating radiation therapy. Due to sample size limitations, a multivariable analysis focusing on the impact of cardiotoxic chemotherapy could not be conducted.

Instead, radiation doses delivered to cardiac substructures were analyzed and compared between patients who did and did not experience specific types of cardiac events. Wilcoxon rank sum tests were employed to examine sex differences in cumulative radiation exposure. The effects of radiation dose on specific types of cardiac disease were estimated using logistic regression. Estimated covariate effects are reported as Odds Ratios (OR) with 95% Confidence Intervals (CI). All statistical tests were two-sided and evaluated for significance at the 5% level using SAS v9.4 software (SAS Institute, Cary, NC).

Results

The review included 94 patients with an average age of 61 years (range 37–92), 57% of whom were male (n=54). The average Karnofsky Performance Status score was 80 (excluding two missing values). Patient demographics, cardiac risk factors and cancer diagnoses are outlined in Table 1. Various radiation therapy modalities were utilized, including external beam radiation therapy, intensity modulated radiation therapy, stereotactic body radiation therapy and volumetric modulated arc radiotherapy.

Table 1. Patient demographics.

		n (%) (N=94)
Sex	Male	41
	Female	53
Cardiac Risk Factors	HTN	48 (51.1)
	HLD	31 (33.0)
	DM	17 (18.1)
	Smoking	81 (86.2)
	Lung Cancer	61 (64.9)
	Non-small cell, adenocarcinoma	24 (39.3)
	Non-small cell, squamous	21 (34.4)
	Small cell	5 (8.2)
	Other	11 (18.0)
	Esophageal Cancer	16 (17.0)
	Adenocarcinoma	12 (75.0)
	Squamous	4 (25.0)
	Breast Cancer	12 (12.8)
	Infiltrating ductal carcinoma	9 (75.0)
	Infiltrating lobular carcinoma	2 (16.7)
	DCIS	1 (8.3)
	Head and Neck Cancer	2 (2.1)
	Renal Cancer	1 (1.1)
	Other	2 (2.1)
Cancer Stage	I	9 (9.6)
	II	8 (8.5)
	III	41 (43.6)
	IV	30 (31.9)
	Limited	3 (3.2)
	Extensive	2 (2.1)
	Localized	1 (1.1)

The average follow-up was 1,231 days (ranging from 17 days to 4,896 days). Forty-two patients developed pericardial disease, the majority of which (48%) were small pericardial effusions; however, 19% of the patients with effusions had cardiac tamponade (Table 2). Thirty patients developed atrial fibrillation or flutter and 25 experienced heart failure after radiation, with 60% showing preserved ejection fraction and 40% reduced ejection fraction. Aortic valve disease was identified in 14 patients, while 22 patients developed mitral valve disease, all of which presented as mitral regurgitation. Among these, 82% had mild severity. Pericardial disease manifested at a median of 218 days after completing radiation treatment, while heart failure occurred at a median of 492 days after completing radiation (Table 3). Atrial fibrillation/flutter, aortic valve disease and mitral valve disease occurred at median intervals of 319, 335 and 450 days, respectively, following radiation therapy (Table 3).

Significant gender-based differences were observed in radiation doses to cardiac substructures (Table 4). Men received significantly higher maximum radiation doses to the left and right atrium (p=0.02 and p=0.05, respectively).

Statistically significant associations were identified between maximum radiation doses to pericardium, left atrium and whole heart for pericardial disease (Table 5). Radiation doses to the pericardium, left atria and whole heart all correlated with an increased odds of pericardial disease. Patients with breast cancer were at lower odds of pericardial disease compared to those with lung cancer (OR 0.16; CI 0.04–0.66; p=0.04) (Table 6).

Gender was also linked to the odds of heart failure post-radiation therapy, with men experiencing significantly lower odds of heart failure compared to women (OR 0.31; CI 0.12–0.85; p=0.02) (Table 7).

There was a statistically significant association between maximum radiation dose to the left atrium and mitral valve disease with increasing cumulative left atrium maximum radiation dose being associated with decreased odds of mitral valve disease (OR 0.97; CI 0.95-0.99; p<0.01) (Table 8). Significant associations with decreased odds of mitral valve disease were observed for maximum radiation doses to the right atrium, pericardium and whole heart. Breast cancer patients were at increased odds of developing mitral valve disease compared to lung cancer patients (OR 6.30; CI 1.49–26.61; p=0.04) (Table 8). Insufficient patient data prevented detailed analysis of aortic valve disease.

Table 2. Cardiac events.

	n (%) (N=94)
Pericardial Disease	42
Trivial	7 (16.7)
Small	20 (47.6)
Moderate	6 (14.3)
Large	1 (2.4)
Tamponade	8 (19.0)
Atrial Fibrillation/Flutter	30
Atrial fibrillation	22 (73.3)
Atrial flutter	8 (26.7)
Heart Failure (HF)	25
HFrEF	10 (40.0)
HFpEF	15 (60.0)
Mitral Valve Disease	22
Mitral regurgitation	22 (100)
Mitral stenosis	0 (0.0)
Trace	3 (13.6)
Mild	18 (81.8)
Moderate	1 (4.5)
Severe	0 (0)
Aortic Valve Disease	14

Table 3. Radiation doses to cardiac substructure and time to cardiac events.

Variable	N	Missing	Minimum	Maximum	Median	Mean	Standard Deviation
Cumulative Pericardium Mean/Gy	94	0	0.1	37.9	12.1	13.6	10.5
Cumulative Pericardium Max/Gy	94	0	0.5	78.0	52.2	45.3	20.9
Cumulative L Atrium Mean/Gy	94	0	0.1	53.7	16.3	19.5	16.2
Cumulative L Atrium Max/Gy	94	0	0.2	77.6	37.4	36.2	23.0
Cumulative R Atrium Mean/Gy	94	0	0.1	64.3	12.7	15.8	14.8
Cumulative R Atrium Max/Gy	94	0	0.2	72.8	31.2	31.0	20.9
Cumulative Heart mean/Gy	94	0	0.1	41.7	12.4	13.4	10.8
Cumulative Heart max/Gy	94	0	0.4	77.8	50.3	44.3	21.2
Time to Pericardial Disease (days)	42	0	20.0	3592.0	217.5	464.5	659.0
Time to Afib (days)	30	0	52.0	2513.0	318.5	666.1	759.4
Time to Heart Failure (days)	25	0	51.0	2832.0	492.0	845.3	824.6
Time to Aortic Valve Disease (days)	14	0	51.0	2832.0	334.5	693.4	818.4
Time to Mitral Valve Disease (days)	22	0	51.0	2832.0	450.0	870.9	898.5

Table 4. Radiation doses to cardiac substructure in males *vs*. females.

		Sex		
		Female	Male	
Covariate	Statistics	N=41	N=53	P-value
Cumulative Pericardium Mean/Gy	Median	10.2	12.3	0.41
	Min	0.1	0.4	
	Max	37.8	37.9	
Cumulative Pericardium Max/Gy	Median	48.1	53.8	0.17
	Min	0.5	2.0	
	Max	70.9	78.0	
Cumulative L Atrium Mean/Gy	Median	16.3	16.9	0.26
	Min	0.1	0.2	
	Max	53.7	52.3	
Cumulative L Atrium Max/Gy	Median	30.9	49.7	0.02
	Min	0.2	0.4	
	Max	70.5	77.6	
Cumulative R Atrium Mean/Gy	Median	9.4	13.7	0.35
	Min	0.1	0.1	
	Max	55.3	64.3	
Cumulative R Atrium Max/Gy	Median	29.0	34.2	0.05
	Min	0.2	0.2	
	Max	66.3	72.8	
Cumulative Heart mean/Gy	Median	12.0	12.5	0.46
	Min	0.1	0.2	
	Max	40.8	41.7	
Cumulative Heart max/Gy	Median	43.5	53.4	0.15
	Min	0.4	1.6	
	Max	70.9	77.8	

Table 5. Odds ratios of pericardial disease by radiation dose to cardiac substructures.

		Pericardial Disease				
Covariate	Level	N	Odds Ratio	95%	CI	P-value
Sex	M	38	1.92	0.75	4.90	0.17
	F	36	Ref	-	-	
Disease	Breast	12	0.16	0.04	0.66	0.04
	Other	18	0.58	0.19	1.80	
	Lung	44	Ref	-	-	
Cumulative Pericardium Mean/Gy	Units=1	74	1.03	0.99	1.08	0.15
Cumulative Pericardium Max/Gy	Units=1	74	1.04	1.01	1.07	<.01
Cumulative L Atrium Mean/Gy	Units=1	74	1.02	0.99	1.05	0.20
Cumulative L Atrium Max/Gy	Units=1	74	1.03	1.01	1.05	<.01
Cumulative R Atrium Mean/Gy	Units=1	74	1.02	0.99	1.06	0.15
Cumulative R Atrium Max/Gy	Units=1	74	1.02	1.00	1.04	0.10
Cumulative Heart mean/Gy	Units=1	74	1.03	0.99	1.08	0.12
Cumulative Heart max/Gy	Units=1	74	1.04	1.01	1.07	<.01

	Pericardial Disease				
Covariate	Level	Odds Ratio	95%	CI	P-value
Cumulative Pericardium Mean/Gy	Units=1	1.03	0.97	1.09	0.30
Cumulative Pericardium Max/Gy	Units=1	1.04	1.01	1.06	<.01
Cumulative L Atrium Mean/Gy	Units=1	1.01	0.98	1.05	0.49
Cumulative L Atrium Max/Gy	Units=1	1.02	1.00	1.05	0.08
Cumulative R Atrium Mean/Gy	Units=1	1.02	0.98	1.06	0.36
Cumulative R Atrium Max/Gy	Units=1	1.01	0.98	1.04	0.41
Cumulative Heart mean/Gy	Units=1	1.03	0.98	1.09	0.25
Cumulative Heart max/Gy	Units=1	1.03	1.01	1.06	0.01

*Estimates are for each covariate separately adjusted for disease.

Table 6. Odds ratios of atrial fibrillation/flutter by radiation dose to cardiac substructures.

Afib/flutter						
Covariate	**Level**	**N**	**Odds Ratio**	**95%**	**CI**	**P-value**
Sex	M	43	1.06	0.42	2.66	0.91
	F	34	Ref	-	-	
Disease	Breast	10	2.07	0.52	8.25	0.38
	Other	21	1.88	0.65	5.40	
	Lung	46	Ref	-	-	
Cumulative Pericardium Mean/Gy	Units=1	77	1.01	0.97	1.06	0.60
Cumulative Pericardium Max/Gy	Units=1	77	1.02	0.99	1.04	0.24
Cumulative L Atrium Mean/Gy	Units=1	77	1.00	0.97	1.03	0.94
Cumulative L Atrium Max/Gy	Units=1	77	1.00	0.98	1.02	0.80
Cumulative R Atrium Mean/Gy	Units=1	77	1.00	0.97	1.04	0.82
Cumulative R Atrium Max/Gy	Units=1	77	1.00	0.98	1.02	0.93
Cumulative Heart mean/Gy	Units=1	77	1.00	0.95	1.04	0.86
Cumulative Heart max/Gy	Units=1	77	1.01	0.99	1.04	0.28

Table 7. Odd ratios of heart failure by radiation dose to cardiac substructures.

Heart Failure						
Covariate	**Level**	**N**	**Odds Ratio**	**95%**	**CI**	**P-value**
Sex	M	43	0.31	0.12	0.85	0.02
	F	35	Ref	-	-	
Disease	Breast	11	2.91	0.76	11.13	0.24
	Other	19	0.87	0.26	2.87	
	Lung	48	Ref	-	-	
Cumulative Pericardium Mean/Gy	Units=1	78	1.01	0.96	1.05	0.84
Cumulative Pericardium Max/Gy	Units=1	78	1.00	0.97	1.02	0.80
Cumulative L Atrium Mean/Gy	Units=1	78	1.01	0.98	1.04	0.68
Cumulative L Atrium Max/Gy	Units=1	78	1.00	0.98	1.02	0.98
Cumulative R Atrium Mean/Gy	Units=1	78	1.02	0.99	1.05	0.32
Cumulative R Atrium Max/Gy	Units=1	78	0.99	0.97	1.02	0.48
Cumulative Heart mean/Gy	Units=1	78	1.01	0.97	1.06	0.55
Cumulative Heart max/Gy	Units=1	78	1.00	0.98	1.02	0.88

Table 8. Odds ratios for mitral valve disease by radiation dose to cardiac substructures.

Mitral Valve Disease						
Covariate	**Level**	**N**	**Odds Ratio**	**95%**	**CI**	**P-value**
Sex	M	45	0.44	0.16	1.20	0.11
	F	36	Ref	-	-	
Disease	Breast	10	6.30	1.49	26.61	0.04
	Other	19	1.94	0.59	6.36	
	Lung	52	Ref	-	-	
Cumulative Pericardium Mean/Gy	Units=1	81	0.96	0.91	1.01	0.09
Cumulative Pericardium Max/Gy	Units=1	81	0.98	0.95	1.00	0.05
Cumulative L Atrium Mean/Gy	Units=1	81	0.97	0.94	1.01	0.10
Cumulative L Atrium Max/Gy	Units=1	81	0.97	0.95	0.99	<.01
Cumulative R Atrium Mean/Gy	Units=1	81	0.97	0.93	1.01	0.10
Cumulative R Atrium Max/Gy	Units=1	81	0.96	0.93	0.99	<.01
Cumulative Heart mean/Gy	Units=1	81	0.97	0.92	1.02	0.17
Cumulative Heart max/Gy	Units=1	81	0.98	0.95	1.00	0.04

Discussion

Increased cardiovascular side effects have been described after radiation therapy in patients with advanced thoracic malignancies [1,2]. However, the relationship between ionizing radiation dose, specific cardiac substructures and type of adverse cardiac events remains unclear. Our retrospective study, conducted on 94 patients treated at a single academic medical center, explored the association between radiation doses to cardiac substructures and the occurrence of specific cardiac events. The focus was placed on the atria and pericardium in relation to adverse outcomes such as pericardial disease and heart failure. Key findings included that pericardial disease was significantly associated with radiation dose to several substructures, including the pericardium. Conversely, no significant association was found between atrial fibrillation/flutter and radiation doses to the left or right atria. The timing of cardiac events varied, with clinically apparent pericardial disease occurring at a median of approximately 7 months post-radiation, atrial fibrillation/flutter at 10 months and heart failure at 16 months. Additionally, men received higher radiation doses to the left and right atria compared to women.

Wang K, et al. [21] reported that pericardial events correlated with right atrium, left atrium and whole heart radiation doses in 112 patients with stage III non-small cell lung cancer treated with dose-escalated radiation therapy (median 74 Gy). Mean heart dose of 12.3 Gy was similar to that in our study (12.7 Gy). The median time to asymptomatic pericardial events was longer than in our study, at 28 months. Moreover, 27% of patients had asymptomatic pericardial effusions at a median of 11 months after radiation treatment. Associations between pericardial events and ionizing radiation dose to the left and right atria and whole heart were similar to our study; however, our study included patients with esophageal and breast cancers as well as stage I through IV lung cancers. Tamari K, et al. reported that in 69 patients with stage I esophageal cancer, ionizing radiation dose to the pericardium was a significant predictor of developing a pericardium effusion at a median follow-up of 37 months [30]. Mean time to the onset of pericardial effusions was approximately six months after radiation treatment.

Our study found no significant association between atrial fibrillation and flutter with radiation dose to the left or right atria. These arrhythmias were observed at a median of approximately ten months post-radiation treatment. Wang K, et al. previously reported "borderline significant" associations of arrhythmic events with left and right atrial radiation dose (p=0.082 and 0.076, respectively), using a broader definition of arrhythmias that included both tachy- and brady-arrhythmias [21]. By contrast, our analysis focused exclusively on atrial fibrillation and flutter. Yegya-Raman N, et al. [22] demonstrated that in 140 patients with inoperable non-small cell lung cancer treated with concurrent chemoradiation, ionizing radiation dose to the atria was not associated with arrhythmias at a median follow-up of 47 months. Their findings, with a median follow-up of 47 months, encompassed all types of supraventricular arrhythmias.

Men in our study received higher maximum radiation doses to the left and right atria compared to women. One potential explanation is that a larger proportion of the breast cancer patients included in our research were women. Since breast cancer is outside of the chest wall, low dose limits to the heart can be achieved, as opposed to lung or esophageal cancer, where the treated area may be adjacent to the heart itself. Darby SC, et al. found a mean heart dose of around 6.6 Gy for left-sided breast cancer patients treated without modern radiation planning techniques [3]. With more modern techniques, including the use of the deep inspiratory breath hold technique, much lower cardiac doses can be achieved.

In contrast, with lung and esophageal cancer patients, tumors can be located adjacent to the heart and thus achieving lower dose limits to the heart is more difficult. Additionally, women generally have smaller hearts than men, which could contribute to differences in radiation distribution. On average, female hearts weigh 245 grams, while male hearts weigh 331 grams, potentially offering a smaller surface area for radiation exposure [31,32]. Finally, our study found that left atrium radiation dose was associated with decreased odds of mitral valve regurgitation. However, a pathophysiologic explanation for this result is unclear and it may be a chance finding.

A strength of our study is that we considered pericardial disease, atrial fibrillation/flutter, heart failure and mitral valve disease as stand-alone adverse cardiac event endpoints, rather than a composite endpoint. However, we did not include coronary events, such as myocardial infarction and revascularization, nor did we include coronary arteries as one of the cardiac substructures evaluated. Three recent studies have investigated the relationship between ionizing radiation dose to the coronary arteries and the development of coronary events. Atkins KM, et al. [17] evaluated 701 patients with locally advanced non-small cell lung cancer at a median follow-up of 20.4 months. They found an elevated radiation dose to the left anterior descending coronary artery was associated with increased risk of major adverse cardiac events. Wang X, et al. [33] analyzed 355 patients with esophageal cancer at a median follow-up of 67 months.

They observed that radiation dose to the left anterior descending coronary artery was significantly associated with the incidence of major coronary events. Zureick AH, et al. [23] evaluated 375 patients who received left-sided breast or chest wall radiation therapy with a median follow-up of 48 months. They found that the mean and max dose to the left anterior descending artery was significantly associated with the incidence of major coronary events [23]. The findings from these three studies suggest that surveillance of the radiation dose to the left anterior descending coronary artery may be of greater significance than radiation dose to the atria or whole heart in patients receiving radiation treatment for thoracic cancers. Coronary events may also be more relevant than arrhythmias or valve disease in a cardiac substructure cardiotoxicity analysis.

Our study has several limitations. Due to the retrospective nature, some cardiac events may have been overlooked, as patients did not undergo routine cardiac surveillance at regular intervals. In addition, the duration of cardiac surveillance is unknown and could not be accounted for in the analysis. Our sample size is relatively small and contains a heterogeneous patient population with a wide diversity of cancer types and stages and chemotherapy and radiation types. Different populations have disparate cardiovascular risk profiles and survival periods and different treatment modalities have a range of cardiac risk associations. Thus, associations between radiation dose to cardiac substructures and the type of adverse cardiac events may be limited to more specific populations.

Most of the cardiac events recorded in our study were mild in severity, potentially raising questions about their clinical significance. However, these findings may gain greater importance as advancements in cancer treatment extend patient survival, allowing cardiac issues to progress in severity over time. It is worth noting that some cardiac events occurred shortly after radiation treatment, casting doubt on whether they were directly attributable to radiation exposure. Finally, we did not include radiation dose to heart valves or ventricles as cardiac substructures in our analysis. On a pathophysiologic and anatomic basis, cardiac diseases such as aortic stenosis and regurgitation, mitral stenosis and regurgitation and heart failure may be more closely related to these structures than those we assessed.

Conclusion

The current study provides key insights into radiation-associated cardiac disease by analyzing 94 patients receiving various radiation modalities. A distinct temporal progression of cardiac complications was identified, with pericardial disease appearing first (465 days post-radiation), followed by arrhythmias (666 days) and later valvular abnormalities (693–871 days). These patterns suggest a pathophysiological cascade that could inform surveillance practices and preventive strategies.

A dose-response relationship was observed, with high radiation doses to the pericardium, left atrium and whole heart significantly predicting pericardial disease. Intriguingly, an inverse correlation between left atrial radiation and mitral valve disease was noted, warranting further investigation into potential compensatory mechanisms.

Sex-based differences were identified, as men, despite receiving higher doses to both atria, had a 69% lower risk of heart failure compared to women, pointing to potential gender-specific cardiac radiosensitivity. Additionally, cancer type influenced cardiac outcomes, with breast cancer patients showing a notably lower odds of pericardial disease (OR 0.16) but higher odds of mitral valve disease compared to lung cancer patients. Atrial radiation doses were not significantly linked with atrial fibrillation/flutter or heart failure.

The findings emphasize the importance of substructure-specific dosimetry in treatment planning and individualized cardiac risk stratification. These results pave the way for personalized strategies to minimize cardiac morbidity, including targeted dosimetry, demographic considerations and post-treatment monitoring.

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Criteria for Author Inclusion

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Conflict of Interest

None.

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