JACC: CARDIOONCOLOGY VOL. 6, NO. 6, 2024

MINI-FOCUS ISSUE: HEART DISEASE IN WOMEN

ORIGINAL RESEARCH

Predictors of Atrial Fibrillation After Thoracic Radiotherapy

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) has been associated with thoracic radiotherapy, but the specific risk with irradiating different cardiac substructures remains unknown.

OBJECTIVES This study sought to examine the relationship between irradiation of cardiac substructures and the risk of clinically significant (grade ≥3) AF.

METHODS We analyzed data from patients who underwent definitive radiotherapy for localized cancers (non–small cell lung, breast, Hodgkin lymphoma, or esophageal) at our institution between 2004 and 2022. The 2-Gy fraction equivalent dose was calculated for cardiac substructures, including the pulmonary veins (PVs), left atrium, sinoatrial node, and left coronary arteries (the left main, left anterior descending, and left circumflex arteries). Competing risk models (subdistribution HRs [sHRs]) for AF incidence were adjusted for the Mayo AF risk score (MAFRS).

RESULTS Among 539 patients, the median follow-up was 58.8 months. The 5-year cumulative incidence of AF was 11.1% for non–small cell lung cancer, 8.3% for esophageal cancer, 1.3% for breast cancer, and 0.8% for Hodgkin lymphoma. Increased AF risk was associated with a higher PV maximum dose (d_{max}) (sHR: 1.22; $P < 0.001$), larger left atrial volume (sHR: 1.01; $P = 0.002$), greater smoking history in pack-years (sHR: 1.01; $P = 0.010$), and higher MAFRS (sHR: 1.16; $P < 0.001$). PV d_{max} remained a significant predictor of AF across different MAFRS subgroups ($P_{interaction} = 0.11$), and a PV d_{max} >39.7 Gy was linked to a higher AF risk, even when stratified by MAFRS.

CONCLUSIONS PV d_{max} is a significant predictor of grade ≥3 AF regardless of underlying risk factors. These findings highlight the importance of cardiac substructures in radiation toxicity and suggest that various PV dose metrics should be further validated in clinical settings. (JACC CardioOncol. 2024;6:935-945) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Thoracic radiotherapy (RT) has been associated with several potential late cardiac effects, including arrhythmias and conduction system abnormalities.[1,2] Specifically, studies have demonstrated an increased incidence of atrial fibrillation (AF) in patients who have undergone thoracic RT,[3-7] with the highest rates observed in those with lung and esophageal cancers. This increased

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 5, 2024; revised manuscript received August 23, 2024, accepted August 27, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.08.007

JACC: CARDIOONCOLOGY, VOL. 6, NO. 6, 2024
DECEMBER 2024:935–945

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CAC = coronary artery calcium

CTCAE = Common Terminology Criteria for Adverse Events

d_{max} = maximum dose

HL = Hodgkin lymphoma

LA = left atrium

LCA_{tot} = left coronary arteries

MAFRS = Mayo atrial fibrillation risk score

NSCLC = non-small cell lung cancer

PV = pulmonary vein

ROC = receiver-operating characteristic

RT = radiotherapy

SAN = sinoatrial node

V15 = volume of structure receiving ≥15 Gy

incidence is partly because of a higher prevalence of pre-existing AF risk factors within these patient populations.[8-10]

Pathophysiologically, AF is classically thought to originate from arrhythmogenic ectopic foci located in damaged myocardial tissue within the pulmonary veins (PVs).[11,12] The PVs anatomically function to transport reoxygenated blood from the lungs to the left atrium (LA) of the heart. The myocardial sleeve, an extension of the atrial myocardium, covers the proximal portion of the PVs as the veins enter the LA.[13] Consequently, the goal of PV isolation through AF catheter ablation is to mechanically disrupt and block abnormal electrical conduction between the myocardial sleeves and the normal left atrial myocardium.[12,14]

Based on these mechanisms, it is plausible that radiation-induced fibrosis of the PVs,[15] resulting in structural remodeling and electrical conduction heterogeneity,[11,16] could contribute to the development of AF as a late effect of RT, as recent data have demonstrated.[17] However, this relationship is still being explored, and it remains unclear whether the maximum radiation dose to the PVs is a clinically relevant metric or if this relationship persists when considering doses to other nearby cardiac substructures that may also influence AF risk. This study aimed to further investigate and validate the relationship between PV dose and the development of AF using a diverse patient cohort across multiple cancer types. Additionally, we sought to determine whether specific PV dose constraints could predict clinically relevant AF.

METHODS

STUDY COHORT. A total of 539 serial patients who underwent definitive thoracic RT for primary locoregional cancers (ie, non-small cell lung cancer [NSCLC], breast cancer, Hodgkin lymphoma [HL], and esophageal cancer) between 2004 and 2022 were retrospectively identified from a single-institutional database. Seventy-two patients lacked RT dose data in Digital Imaging and Communications in Medicine format within our institutional software but were included in nondosimetric analyses because relevant clinical data were available for assessing other AF risk factors. This study was approved by the Institutional Review Board of the Stanford Research Compliance Office.

Clinical patient data were collected through a comprehensive chart review, which included patient demographics, physician hospital and clinic notes, diagnostic imaging, and reports from diagnostic testing (such as radiology, pathology, and cardiology). All patients had electronic medical record sharing enabled, allowing us to capture and code data from external medical systems if they were also managed for AF elsewhere. For each patient, we calculated the Mayo AF risk score (MAFRS), a validated score based on 7 clinical risk factors: age, coronary artery disease, diabetes mellitus, sex, heart failure, hypertension, and cardiac valvular disease. The MAFRS ranges from 0 to 12, with higher scores indicating a greater risk of AF.[18] Coronary artery disease in this context was defined as the presence of atherosclerotic plaque in the coronary arteries detected through imaging (eg, computed tomography angiography) or cardiac stress testing.[19]

For this study, the MAFRS was dichotomized into 2 categories (0-1 vs ≥2) based on results from the initial MAFRS study, which identified a score of 2 or greater as indicating a high risk for AF development.[18] We also documented any prior history of grade ≥3 cardiac events before RT. These events were defined as a history of heart failure, coronary artery disease, unstable angina, myocardial infarction, constrictive pericarditis or myocarditis, severe or symptomatic valvular disease, second- or third-degree heart block or conduction abnormalities requiring a permanent pacemaker, new atrial fibrillation, or new-onset ventricular arrhythmias requiring interventions.

Lastly, quantitative coronary artery calcium (CAC) scores were also calculated for each patient, with a higher score indicating a higher calcium content. These scores were determined through visual analysis of individual coronary vessels using the modified Chiles method in accordance with previously published methods because this metric is recognized as a significant risk factor for grade ≥3 cardiac events.[20,21]

DOSIMETRIC ANALYSIS. Cumulative doses to organs at risk were evaluated using MIM version 7.3.3 (MIM Software Inc). All doses were converted to equivalent doses in 2-Gy fractions with an alpha/beta ratio of 3. We calculated the mean and maximum (d_{max}) RT doses for each cardiac substructure of interest, including the PVs, LA, and sinoatrial node (SAN).

For the PV and LA dose analysis, we primarily focused on maximum dose metrics rather than mean or volumetric dose metrics. This focus was because of the physiological potential for these structures to behave as a serial organ in the pathogenesis of AF. Clinically, it is plausible that a single point of maximum dose could trigger sufficient paracrine-induced myocyte fibrogenesis, leading to aberrant

electrical foci and subsequent AF arrhythmogenesis.[11,15-17]

Additionally, we calculated the absolute volume in cubic centimeters receiving ≥15 Gy for the combined left coronary arteries (LCA_{tot} [the left main, left anterior descending, and left circumflex]). This metric has also been identified as a significant risk factor for grade ≥3 cardiac events.[20]

For the PV cardiac substructure, 4 separate PVs (ie, the right superior, right inferior, left superior, and left inferior PVs) were contoured following published contouring atlas guidelines for RT planning.[22] Additionally, a fifth PV (ie, the supernumerary right middle lobe PV) was contoured if this anatomical variant was present in an individual patient. For the primary analysis, all PVs were combined into a total PV structure (hereafter referred to as PV). PVs were also analyzed individually and in smaller anatomical subgroups as recommended by the contouring atlas.[22] The right middle lobe PV was not analyzed separately because of a high percentage of missing data given that this structure is not anatomically present in most patients. The SAN and LCA_{tot} were also contoured in accordance with their respective published contouring guidelines.[23-25]

Contours were manually created in MIM version 7.3.3 by 2 physicians who were blinded to clinical outcomes (S.B. and H.N.). A random representative sample of contours, comprising 5% of the total cohort, was audited for review by M.S.B. A consensus among the research group was reached to ensure that these contours were accurate and precise in accordance with the published guidelines.[23-25]

CARDIAC ENDPOINTS. The primary endpoint of interest was the development of grade ≥3 AF as defined as follows by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0: "symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset."[26] For this study, "new-onset" AF was considered necessary but not sufficient for diagnosing a grade ≥3 AF event. We chose this more stringent definition of grade ≥3 AF, excluding new-onset asymptomatic AF events, to ensure events were adequately captured in this retrospective analysis in which continuous rhythm monitoring to detect new-onset asymptomatic AF events was not feasible.

Patients were classified as having grade ≥3 AF if any single criterion from the CTCAE definition was met at any time after completing RT. This included cases in which a patient experienced symptomatic AF with urgent intervention indicated or when urgent intervention was deemed necessary because of clinical suspicion of impending symptoms from severe AF regardless of the presence of active symptoms. It also included situations in which a device was implanted for AF-related treatment or if the patient underwent cardiac ablation for AF.

AF events were identified through chart review conducted by investigators (S.B. and H.N.) under the supervision of a fellowship-trained cardiologist (D.E.C.) as previously described. The time to AF was defined as the interval between the completion of RT and the occurrence of a qualifying event for grade ≥3 AF. The chart review confirmed that no patients had planned cardiac ablations before undergoing RT; all patients who received cardiac ablation (and were thus classified as grade ≥3) were referred for the procedure because of AF after completing RT. Grade ≥3 AF was specifically chosen as the endpoint because it was considered more clinically significant for medical management and patient quality of life. This contrasts with grade 1 to 2 AF, which, according to CTCAE standards, is classified as either "asymptomatic" ("intervention not indicated") or managed with pharmaceutical treatment in an outpatient setting ("nonurgent medical intervention indicated").[26]

Moreover, grade ≥3 AF events provide a reliable endpoint for retrospective detection because of their severity, making them unlikely to be undiagnosed or inaccurately recorded in electronic medical records. In contrast, grade 1 to 2 AF events are more susceptible to detection bias; certain patient populations may be more likely to be diagnosed, whether incidentally or otherwise, because of increased interactions with the health care system, the presence of other comorbidities, indications for electrocardiogram or heart rhythm monitoring, or other unknown confounders. Therefore, the grade ≥3 endpoint was ultimately chosen to minimize potential confounders and statistical biases.

STATISTICAL ANALYSIS. Baseline characteristics. Continuous variables are presented as median values with their respective ranges, whereas categoric variables are presented as counts and percentages. The median follow-up was measured using the reverse Kaplan-Meier method. Cohort characteristics were compared across different cancer types using chi-square tests for categoric variables and Kruskal-Wallis tests for continuous variables. Missing data for smoking pack-years were addressed using nearest neighbor imputation based on age and cancer type.

Survival outcomes. Overall survival was measured using Kaplan-Meier analysis and stratified by cancer type subgroups. The comparisons between groups were made using the log-rank test, with incidence rates reported as Kaplan-Meier estimates and 95%

CIs. Survival time was defined as the time from the completion of RT until death from any cause.

AF outcomes. Cumulative incidence rates of AF were calculated using a nonparametric competing risks probability function modeling, adjusting for the competing risk of death. Groups were compared using Gray's test. Time to event was defined as the period from the completion of RT until either a diagnosis of AF or death from any cause before AF, considered a competing event. Patients were censored either at the last follow-up or, for those who underwent subsequent repeat courses of thoracic/chest RT, at the start of reirradiation (n = 54). This approach was chosen because repeat treatment would inherently alter the effect of the initial radiation dose, making further time-to-event analysis uninterpretable. Consequently, any time-to-event analysis investigating the relationship between reirradiation and AF risk would need to be performed separately, starting after the completion of reirradiation. Our cohort was not powered for such a secondary analysis because of the relatively few cases of reirradiation observed.

Subdistribution HRs (sHRs) for AF incidence with 95% CIs were calculated for variables of clinical interest using Fine-Gray competing risk regression analysis clustered by cancer type (similar to a stratified Cox regression accounting for histology type)[27,28] and adjusted for the competing risk of death. A multivariable analysis was performed to calculate adjusted sHRs for AF; noncollinear variables with a P value <0.05 in univariable analyses were included in the multivariable model, whereas colinear variables (Pearson correlation coefficient >0.4) were excluded based on clinical judgment. Patients with a prior history of grade ≥3 AF (n = 19) were excluded from these regression analyses, resulting in a cohort of 520 patients for analysis.

A subgroup analysis was conducted by excluding breast cancer patients from the cohort, and the multivariable analysis was repeated using Fine-Gray competing risk regression, again clustered by cancer type. This approach was used to confirm the robustness of the initial multivariable model results given that breast cancer patients typically receive minimal radiation doses to the heart compared with those with other thoracic cancers. A second subgroup analysis excluded patients with unknown dosimetric data followed by a repeat multivariable analysis.

Next, a spline analysis was performed to identify potential dosimetric cutoff points for the PV d_{max}, determined by visualizing local maxima on the spline analysis matrix. Lastly, to evaluate the performance of various potential prediction models for AF, a time-dependent receiver-operating characteristic (ROC) analysis was conducted, and the area under the curve (AUC) values were compared at the 60-month time point across prediction models. Patients with a prior history of AF (n = 19) were excluded from both the spline and ROC analyses. All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing), with a 2-sided P value < 0.05 considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. We identified 539 patients with a median follow-up time of 58.8 months (range 0.1-120.0 months). The cohort included 230 patients (42.7%) with NSCLC, 174 (32.3%) with breast cancer, 119 (22.1%) with HL, and 16 (3.0%) with esophageal cancer. The median age across the cohort was 58 years (range 19-91 years); 39.9% were male, 51.5% were never smokers, 58.8% had a MAFRS of 0 to 1, and 16.0% had a history of a prior grade ≥3 cardiac event. The most common prescription doses were 66 Gy in 30 fractions for NSCLC, 50 Gy in 25 fractions for breast cancer, 30 Gy in 20 fractions for HL, and 50 Gy in 25 fractions for esophageal cancer. The median PV d_{max}, measured in 2-Gy equivalent doses across the entire cohort, was 36.2 Gy (range 0.2-103.9 Gy). When stratified by cancer type, the median PV d_{max} was 73.1 Gy for NSCLC (range 0.4-103.9 Gy), 52.5 Gy for esophageal cancer (range 1.0-60.2 Gy), 20.1 Gy for HL (range 0.2-39.4 Gy), and 2.2 Gy for breast cancer (range 0.4-58.3 Gy) expressed as equivalent doses in 2-Gy fractions with an alpha/beta ratio of 3. Complete baseline characteristics are summarized in **Table 1** and Supplemental Table 1.

SURVIVAL OUTCOMES. The median follow-up time was 58.8 months (range 0.1-120). Across the entire cohort, there were 163 deaths (30.2%). Stratified by cancer type, the 5-year overall survival rates were 41.1% (95% CI: 34.5-48.8) for NSCLC, 35.9% (95% CI: 17.2-74.8) for esophageal cancer, 84.5% (95% CI: 79.1-90.3) for breast cancer, and 98.2% (95% CI: 95.7-100) for HL (**Figure 1A**). A higher risk of AF (MAFRS ≥2 vs 0-1) was not associated with a change in overall survival after multivariable adjustment (sHR: 1.05; 95% CI: 0.99-1.10; P = 0.11).

AF OUTCOMES. A total of 35 patients experienced grade ≥3 AF, with 32 of these cases occurring in patients without a prior history of AF. The median time to AF was 22.9 months (range 0.3-120 months). The overall 5-year cumulative incidence of AF was 5.2% (95% CI: 4.9%-5.4%) (**Figure 1B**). When stratified by cancer type, the 5-year cumulative incidence was 11.1% for NSCLC (95% CI: 10.4%-11.8%), 8.3% for esophageal cancer (95% CI: 5.9%-11.2%), 1.3% for

TABLE 1 Baseline Characteristics of Cohort Who Underwent Definitive Thoracic Radiotherapy Stratified by Cancer Type

	Overall (N = 539)	Breast Cancer (n = 174)	Esophageal Cancer (n = 16)	Hodgkin Lymphoma (n = 119)	NSCLC (n = 230)	Missing
Median age, y	58.0 (19.2-91.9)	47.1 (23.7-74.7)	76.3 (37.6-91.9)	31.6 (19.2-82.8)	68.2 (35.2-90.9)	0
Male	215 (39.9)	0 (0.0)	12 (75.0)	62 (52.1)	141 (61.3)	0
Race						1 (0.2)
Asian	102 (19.0)	43 (24.7)	2 (12.5)	12 (10.2)	45 (19.6)	
Native Hawaiian or Pacific Islander	8 (1.5)	3 (1.7)	0 (0.0)	3 (2.5)	2 (0.9)	
Black	25 (4.6)	12 (6.9)	0 (0.0)	0 (0.0)	13 (5.7)	
White	311 (57.8)	84 (48.3)	11 (68.8)	72 (61.0)	144 (62.6)	
Other race	92 (17.1)	32 (18.4)	3 (18.8)	31 (26.3)	26 (11.3)	
Smoking status						1 (0.2)
Former smoker	220 (40.9)	32 (18.4)	9 (56.2)	22 (18.6)	157 (68.3)	
Never smoker	277 (51.5)	137 (78.7)	5 (31.2)	92 (78.0)	43 (18.7)	
Current smoker	41 (7.6)	5 (2.9)	2 (12.5)	4 (3.4)	30 (13.0)	
Median pack-years	5.0 (0.0- 160.0)	0.0 (0.0- 90.0)	5.0 (0.0- 55.0)	5.0 (1.0- 90.0)	30.0 (0.0- 160.0)	0.0
Hypertension	185 (35.0)	35 (20.5)	10 (62.5)	22 (19.6)	118 (51.3)	10 (1.9)
Diabetes	76 (14.2)	14 (8.2)	3 (18.8)	7 (5.9)	52 (22.6)	3 (0.6)
Statin medication	136 (26.4)	18 (10.5)	0 (0.0)	27 (23.7)	91 (39.6)	24 (4.5)
Prior ≥G3 cardiac event[a]	86 (16.0)	6 (3.4)	5 (31.2)	6 (5.0)	69 (30.0)	0.0
Prior AF event	19 (3.5)	0 (0.0)	4 (25.0)	1 (0.8)	14 (6.1)	0.0
Concurrent chemotherapy	252 (46.8)	12 (6.9)	16 (100.0)	0 (0.0)	224 (97.4)	0.0

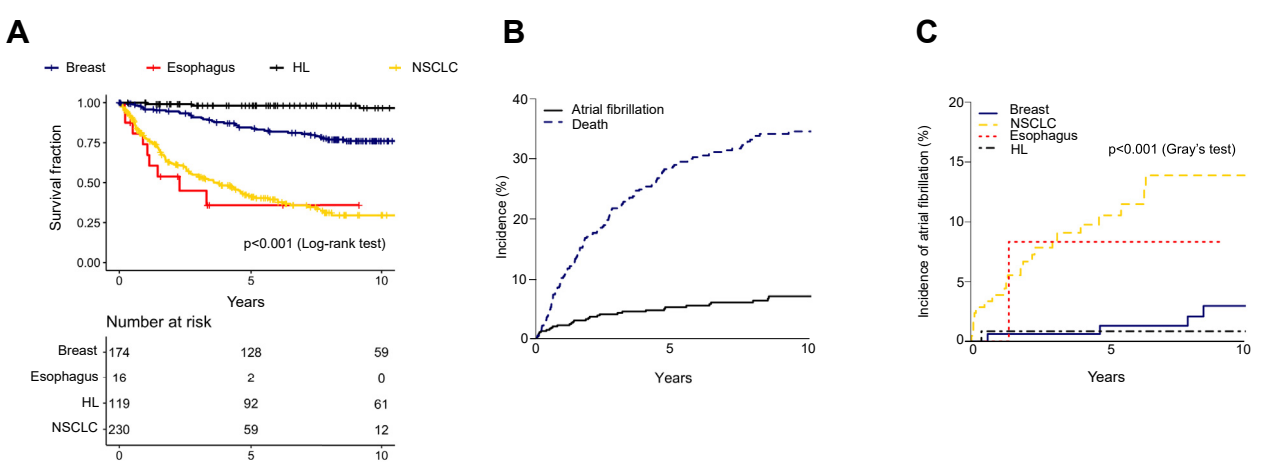
Values are median (Q1-Q3) or n (%). Baseline characteristics stratified by cancer type among 539 patients who underwent definitive thoracic radiotherapy for primary locoregional cancer including NSCLC, breast cancer, Hodgkin lymphoma, and esophageal cancer. [a]Prior grade ≥3 cardiac events included heart failure, coronary artery disease, unstable angina, myocardial infarction, constrictive pericarditis or myocarditis, valvular disease, second- or third-degree heart block or conduction abnormalities requiring permanent pacemaker, new-onset atrial fibrillation, or new-onset ventricular arrhythmias requiring interventions.

AF = atrial fibrillation; G3 = grade 3; NSCLC = non-small cell lung cancer.

breast cancer (95% CI: 0.2%-4.1%), and 0.8% for HL (95% CI: 0.1%-4.2%) (Figure 1C).

Higher SAN d_{max}, LCA_{tot} volume of structure receiving ≥15 Gy, and CAC scores were not associated with an increased risk of AF on univariable analysis ($P > 0.05$) (Table 2). In contrast, there was a greater risk of grade ≥3 AF associated with a higher d_{max} for all individual PVs (the right superior, right inferior,

FIGURE 1 Clinical Outcomes After Thoracic Radiotherapy



The cohort comprised 539 patients who underwent definitive thoracic radiotherapy for primary locoregional cancers, including non-small cell lung cancer (NSCLC), breast cancer, Hodgkin lymphoma (HL), or esophageal cancer. (A) Overall survival curves are shown across cancer subtypes. (B) The incidence of grade ≥3 atrial fibrillation and the competing risk of death are depicted for the total cohort. (C) The incidence of grade ≥3 atrial fibrillation is presented across various cancer subtypes.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 6, 2024
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TABLE 2 Univariable and Multivariable Fine-Gray Regression Analyses for Incident Grade ≥3 Atrial Fibrillation[a]

	Univariable Analysis			Multivariable Analysis			Multivariable Analysis Excluding Missing Dosimetry Data[b]			Multivariable Analysis Excluding Breast Cohort[c]		
	HR	95% CI	*P* Value	sHR	95% CI	*P* Value	sHR	95% CI	*P* Value	sHR	95% CI	*P* Value
Age, y	1.04	1.03-1.06	<0.001									
MAFRS, points	1.37	1.23-1.53	<0.001	1.16	1.11-1.21	<0.001	1.37	1.20-1.56	<0.001	1.18	1.14-1.23	<0.001
Male	2.23	1.08-4.60	0.31									
Smoking, pack-years	1.01	1.01-1.02	0.002	1.01	1.00-1.01	0.010	1.01	1.00-1.02	0.006	1.01	1.00-1.01	0.020
Hypertension	1.85	1.16-2.95	0.010									
Diabetes	2.77	2.33-3.30	<0.001									
Statin medication	2.42	1.76-3.31	<0.001									
Any prior ≥G3 cardiac event[d]	1.51	0.94-2.43	0.090									
Concurrent chemotherapy	1.27	0.73-2.22	0.40									
Mean heart dose, Gy	1.01	1.00-1.02	0.17									
CAC score, points	0.99	0.99-1.00	0.070									
LA volume, mL	1.02	1.01-1.03	0.006	1.01	1.00-1.02	0.002	1.02	1.01-1.03	0.006	1.01	1.01-1.01	<0.001
LA d_{max}, Gy	1.02	1.01-1.03	<0.001	0.99	0.99-1.00	0.21	0.99	0.99-1.00	0.21	0.99	0.99-1.00	0.51
LA mean dose, Gy	1.01	0.99-1.04	0.30									
PV_{combo} d_{max}, per 10 Gy	1.02	1.02-1.03	<0.001	1.22	1.14-1.31	<0.001	1.22	1.14-1.31	<0.001	1.24	1.07-1.45	0.006
PV_{combo} d_{max} >39.7 Gy	5.61	3.60-8.74	<0.001									
PV_{combo} mean dose, Gy	1.03	1.01-1.04	0.002									
SAN d_{max}, per 10 Gy	1.01	0.99-1.03	0.37									
SAN mean dose, Gy	1.01	0.98-1.03	0.60									
SAN V20, Gy	1.00	0.99-1.01	0.98									
SAN V20, mL	1.01	0.83-1.22	0.94									
LAD V15, mL	1.19	0.79-1.80	0.42									
LCA_{tot} V15, mL	1.02	0.93-1.13	0.65									

The cohort included a total of 520 patients who underwent definitive thoracic radiotherapy for primary locoregional cancers (non-small cell lung cancer, breast cancer, Hodgkin lymphoma, and esophageal cancer) and did not have a prior history of ≥G3 atrial fibrillation. All radiation doses calculated in 2-Gy fraction equivalents. [a]Adjusted for the competing risk of death. [b]Subgroup analyses on multivariable regression excluding patients missing dosimetric data (n = 72). [c]Subgroup analyses on multivariable regression excluding patients with breast cancer (n = 174). [d]Prior grade ≥3 cardiac events included heart failure, coronary artery disease, unstable angina, myocardial infarction, constrictive pericarditis or myocarditis, valvular disease, second/third-degree heart block or conduction abnormalities requiring permanent pacemaker, new-onset atrial fibrillation, or new-onset ventricular arrhythmias requiring interventions.

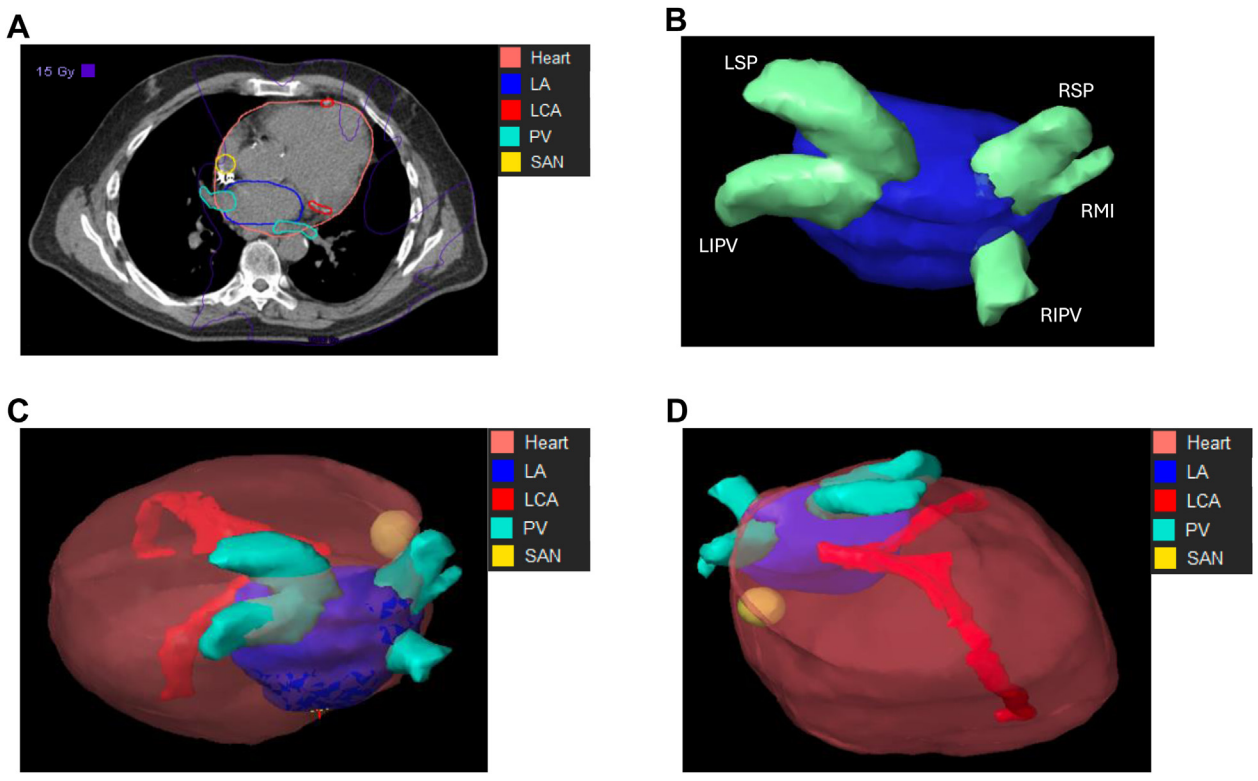
CAC = coronary artery calcium score (higher score indicates higher calcium content); d_{max} = maximum radiation dose to structure; G3 = grade 3; LA = left atrium; LCA_{tot} = combined left coronary arteries (left main, left anterior descending, and left circumflex arteries); MAFRS = Mayo AF risk score (range 0-12; higher scores indicate greater baseline AF risk); PV_{combo} = combined pulmonary veins; SAN = sinoatrial node; sHR = subdistribution HR; V15 = absolute volume receiving ≥15 Gy; V20 = absolute volume receiving ≥ 20 Gy.

left superior, and left inferior PVs; $P < 0.01$ for all) as well as for the combined PV structure ($P < 0.001$) (representative structure contours depicted in Figure 2). Given that the combined PV structure was statistically significant and had a greater HR compared with any individual vein and because tumors may be located medially or closer to 1 side of the heart, this combined PV variable was chosen to represent the PV structures in the multivariable analysis. Complete univariable regression analyses are presented in Table 2, and details of AF events and management are provided in Supplemental Table 2.

Using multivariable analysis clustered by cancer type, the risk of AF was higher among patients with a higher PV d_{max} (per 10 Gy; sHR: 1.22; 95% CI: 1.14-1.31; $P < 0.001$), larger LA volume (per mL; sHR: 1.01; 95% CI: 1.00-1.02; $P = 0.002$), higher MAFRS (per point; sHR: 1.16; 95% CI: 1.11-1.21; $P < 0.001$), and greater smoking history in pack-years (per year; sHR: 1.01; 95% CI: 1.00-1.01; $P = 0.010$) (Table 2). However, a higher LA d_{max} was not associated with a significant difference in AF risk (per Gy; sHR: 0.99; 95% CI: 0.99-1.00; $P = 0.21$) (Table 2). The HR for PV d_{max} remained consistently significant across baseline MAFRS groups ($P_{interaction} = 0.11$); similarly, there were no statistically significant interactions between PV dose and other cardiac substructure variables in our multivariable analysis model ($P_{interaction} > 0.05$ for all).

In spline analysis, patients with a PV d_{max} >39.7 Gy compared with those with a PV d_{max} ≤39.7 Gy (among several potential local maxima identified) had a significantly higher risk of AF (9.1% [95% CI: 8.6%-9.6%] vs 1.0% [95% CI: 0.8%-1.2%], respectively; $P = 0.001$), even when stratified by baseline MAFRS (Supplemental Figure 1). For example, among patients with a low baseline AF risk (MAFRS 0-1), the 5-year incidence rate of AF was 4.3% (95% CI: 2.9%-6.0%) for those with a PV d_{max} >39.7 Gy vs 1.2% (95% CI: 0.9%-1.4%) for those with a PV d_{max} ≤39.7 Gy ($P = 0.036$) (Figure 3). In comparison, among those

FIGURE 2 Representative Example and Cardiac Substructures



(A) A representative axial image from a 4-dimensional computed tomography planning scan of a patient treated for non–small cell lung cancer showing normal tissue contours and treatment plan isodose lines. All radiation doses were calculated in 2-Gy fraction equivalents. (B) A 3-dimensional reconstruction of the pulmonary vein contours. (C) A posterior view of relevant cardiac substructure contours. (D) An anterior view of relevant cardiac substructure contours. LA = left atrium; LCA = left coronary arteries (combined left main, left anterior descending, and left circumflex arteries); LIPV = left inferior pulmonary vein; LSP = left superior pulmonary; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RMI = right middle inferior; RSP = right superior pulmonary vein; SAN = sinoatrial node.

with a high baseline AF risk (MAFRS ≥2), the 5-year incidence rate of AF was 12.3% (95% CI: 11.3%-13.3%) for patients with a PV d_{max} >39.7 Gy compared with 0% for those with a PV d_{max} ≤39.7 Gy ($P = 0.026$) (Figure 3).

Lastly, in the ROC analysis, PV dosing had the highest AUC of 0.77 (95% CI: 0.70-0.85) among all variables in our prediction model. Adding all other predictive variables from the multivariable analysis into the ROC curve model resulted in a minimal increase in the AUC value (AUC: 0.79; 95% CI: 0.74-0.85) (Supplemental Figure 2).

SUBGROUP ANALYSES. After excluding patients with breast cancer, repeat multivariable regression yielded similar results across all variables of interest (Table 2), including a greater risk of AF with higher PV d_{max} (per 10 Gy; sHR: 1.24; 95% CI: 1.07-1.45; $P = 0.006$). Additionally, interaction between PV d_{max} and MAFRS remained nonsignificant on multivariable analysis ($P_{interaction} = 0.15$). Similarly, after excluding patients with unknown dosimetric data, multivariable regression analyses remained unchanged (Table 2).

DISCUSSION

In this study, we investigated risk factors for grade ≥3 atrial fibrillation after definitive RT for localized thoracic cancers (NSCLC, breast cancer, HL, and esophageal cancer) (Central Illustration). Our cohort included a diverse range of ages, cancer types, and smoking history. We found that the maximum RT dose to the combined PVs (PV d_{max}) was strongly associated with AF development. Specifically, our model showed a 22% relative increase in AF risk for every 10-Gy increase in PV d_{max}, even after adjusting for other relevant clinical and dosimetric variables. Consequently, the 5-year incidence of AF was highest among patients with NSCLC (11.1%) and esophageal cancer (8.3%), who also had the highest median PV d_{max} of 73.1 Gy and 52.5 Gy,

JACC: CARDIOONCOLOGY, VOL. 6, NO. 6, 2024
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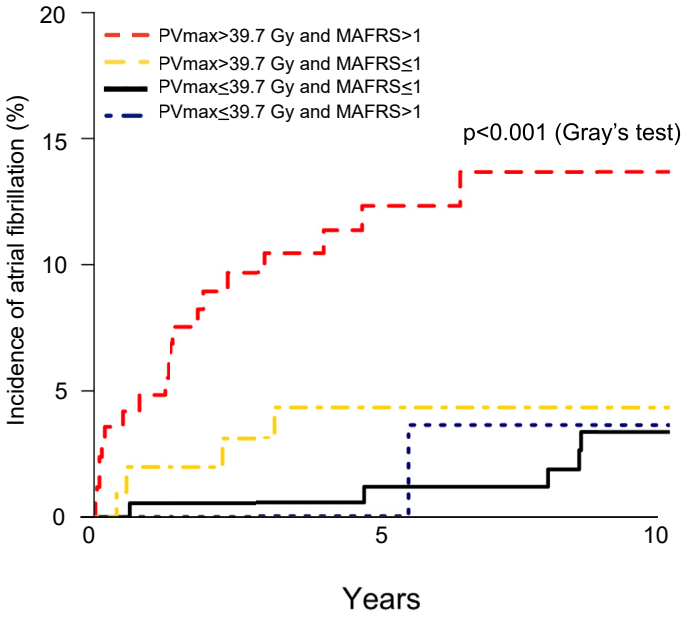
FIGURE 3 Cumulative Incidence of Grade ≥3 AF Across Baseline Risk and Pulmonary Vein Maximum Dose Subgroups



The cohort comprised 539 patients who underwent definitive thoracic radiotherapy for primary locoregional cancers, including non-small cell lung cancer, breast cancer, Hodgkin lymphoma, and esophageal cancer. A comparison of all subgroups showed a significantly higher incidence of grade ≥3 atrial fibrillation (AF) ($P < 0.001$), including patients with a Mayo AF risk score (MAFRS) of 0 to 1 ($P = 0.036$) and MAFRS ≥2 ($P = 0.026$). Baseline AF risk was determined by MAFRS, and all radiation doses were calculated in 2-Gy fraction equivalents.

respectively. In contrast, the 5-year AF rate was notably low in patients with breast cancer (1.3%), which correlated with a similarly low median PV d_{max} (2.2 Gy). Lastly, our ROC curve data demonstrated that PV dose had the highest predictive value for AF in the univariable model (AUC: 0.77), with minimal improvement after including other variables in the multivariable model.

Several studies have investigated the risk of AF after radiation exposure to cardiac substructures. Notably, our results align with those reported by Walls et al,[17] which demonstrated an association between left PV volume of structure receiving ≥55 Gy and right PV volume of structure receiving ≥10 Gy and the incidence of new AF, although not with pulmonary veins mean dose. Although comparing performance across cohorts is challenging, our ROC analysis showed that the predictive value of PV d_{max} (AUC: 0.77) was numerically higher than the PV volume of structure receiving ≥55 Gy and PV volume of structure receiving ≥10 Gy values reported in Walls et al[17] (AUC: 0.61-0.64). Additionally, their analysis did not adjust for left atrial volume or maximum dose, both of which have been associated with AF in prior studies.[29-32] Although Walls et al[17] included a volumetric left atrial cutoff (volume of structure receiving ≥20 Gy), this did not reach significance in their univariable regression analysis for AF.

Our findings also align with a recent study showing high predictive performance for the PV volume receiving 40 Gy or higher, with an AUC of 0.61.[33] Interestingly, in our cohort, SAN d_{max} was not associated with AF incidence, even on univariable analysis. This outcome is in agreement with Walls et al[17] but contrasts with the findings of Kim et al[34] despite both studies using the same contouring guidelines for SAN delineation.[23] The reasons for these differences have been theorized;[35,36] however, because the SAN is not typically involved in the classic pathophysiology of AF, it might serve as a dosimetric proxy for the nearby right superior PV.

Lastly, surprisingly, neither the LCA_{tot} dose nor CAC scores were associated with AF risk in our cohort. However, there was a nonsignificant increased AF risk among those with prior grade ≥3 cardiac events ($P = 0.09$). This finding contrasts with earlier preclinical evidence showing that cardiac ischemia and infarction are significant triggers for cardiac fibrotic remodeling, which can lead to arrhythmias such as AF.[37-39] Recent findings by Cai et al[40] also demonstrated an association between the dose to the 2 major branches of the left coronary artery (the left anterior descending and left circumflex arteries) and grade ≥3 AF. Altogether these differences emphasize the need for additional studies to validate and establish best practices for cardiac substructure dose metrics in future clinical settings.

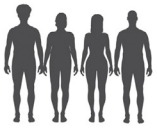
As the importance of PV in RT planning increases, it is worth noting that the contouring of this cardiac substructure can be challenging because of its anatomy. For example, a supernumerary right middle lobe vein variant is observed in 9% to 26% of patients, with variable branching patterns. Additionally, the shape and size of PV can change with varying pressures throughout the cardiac cycle.[13]

The PV acts as a proxy for contouring the true organ at risk—the myocardial sleeve, which is not visible by computed tomography and also has variable anatomy.[13,22] The myocardial sleeve is typically thickest at the venoatrial junction and thins as it extends into the PV, usually measuring between 2 and 2.5 cm in length. However, superior PVs are typically longer than inferior PVs,[13] and PV anatomy can also vary by sex and body mass index.[41] These structural variations in PV and myocardial sleeve structure are clinically significant because they introduce

CENTRAL ILLUSTRATION **Predictors of Grade ≥3 Atrial Fibrillation After Thoracic Radiotherapy**

Patient Cohort

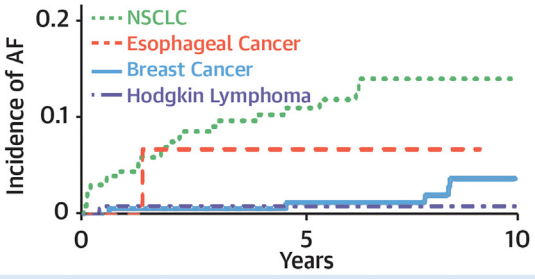
539 patients treated with definitive thoracic external beam radiotherapy



NSCLC, N = 230
Breast Cancer, N = 174
Hodgkin Lymphoma, N = 119
Esophageal Cancer, N = 16

- Median follow-up: 58.8 (range, 0.1-120 months)
- Low baseline AF risk (Mayo risk score) in 59%
- Median pulmonary vein (PV) d_{max}: 36.2 Gy (range, 0.2-103.9 Gy)

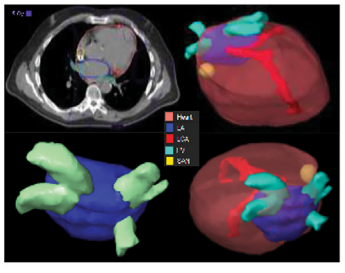
Atrial Fibrillation (AF) Incidence



5-year AF Incidence: 5.2% overall

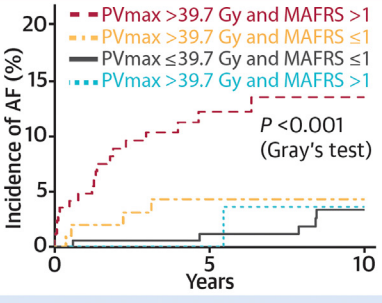
- NSCLC: 11.1%
- Esophageal Cancer: 8.3%
- Breast Cancer: 1.3%
- Hodgkin Lymphoma: 0.8%

Normal Tissue Dose & Imaging



Variable / OAR Dose	AF Risk
↑ • PV d_{max} • Left atrial volume • Pack-years • Mayo AF risk score (MAFRS)	↑
↑ • Sinoatrial node dose • Left coronary artery, left atrium dose	↔

Dose Cutoff Model



- PV d_{max} limit: >39.7 Gy → AF risk ↑
- Low baseline AF risk (MAFRS 0-1):
  5 year AF 4.3% for PV d_{max} >39.7 Gy vs 1.2% for PV d_{max} ≤39.7 Gy
- High baseline AF risk (MAFRS ≥2):
  5-year AF 12.3% for PVd_{max} >39.7 Gy vs 0% for PV d_{max} ≤39.7 Gy
  P interaction = 0.11

Butler S, et al. JACC CardioOncol. 2024;6(6):935-945.

This figure describes the patient cohort, atrial fibrillation (AF) incidence across cancer subtype, associations of AF with normal tissue dose, a representative example of cardiac substructures, and a dose cutoff model for pulmonary veins (PVs). All radiation doses were calculated in 2-Gy fraction equivalents. The images were created with the assistance of DALL-E 3 software. d_{max} = maximum dose; MAFRS = Mayo AF risk score; NSCLC = non-small cell lung cancer; OAR = organs at risk.

considerable complexity when contouring these structures in different patients.[22]

Finally, regarding clinically applicable dose metric cutoffs, we found that patients with a PV d_{max} >39.7 Gy had a significantly higher risk of AF compared with those with a PV d_{max} <39.7 Gy, even when stratified by AF risk score. Although there appeared to be a greater relative increase in AF risk among patients with higher baseline AF risk scores (MAFRS ≥2 vs MAFRS <2), there was no statistically significant interaction between these 2 variables ($P = 0.11$). This finding highlights that PV dose metrics may serve as a useful clinical tool across all patients regardless of comorbidities. However, it is possible that our cohort lacked the power to detect a significant interaction in subgroup analyses, necessitating further studies to explore this potential relationship.

Additionally, spline analysis revealed several other potential local maxima, suggesting that multiple optimal cutoffs may exist and that this specific cutoff point may not be fully generalizable to other patient populations. While awaiting further research and consensus on optimal cutoffs, our study's data strongly support the clinical practice of contouring PVs to limit significant dose exposure (>39.7 Gy) whenever possible.

STUDY LIMITATIONS. First, the retrospective nature of this study makes it susceptible to issues related to unmeasured confounding. Second, the data were derived from a single institution, which may limit the generalizability of the findings. Third, there was a lack of available data on patient alcohol intake, an established risk factor for AF.[42] Lastly, the modest number of AF events limited the power to compare results on multivariable analysis. However, by using a validated AF risk score as a single variable in our regression model, we were still able to adjust for multiple cardiac substructure variables without overfitting the model despite the low event rate. Taken together, these limitations highlight the need for further research to validate our findings in larger, more diverse cohorts, particularly in determining clinically optimal dose metric cutoffs.

CONCLUSIONS

PV d_{max} appears to be a significant predictor of grade ≥3 AF independent of other underlying risk factors and even after adjusting for dose to nearby cardiac substructures relevant to AF. These findings support and extend beyond recent evidence on the clinical relevance of cardiac substructures concerning radiation toxicity, suggesting that various PV dose metrics may warrant further investigation for potential clinical use.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr No has received materials/services from Limbus AI and Coreline Soft; has received payment/honoraria from AAMD; and has received grants from RSNA and ACRO. Dr Loo is a lecturer for Mevion; is a consultant for Beigene; holds equity in TibaRay; and is an advisor for NCCN. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients receiving definitive thoracic radiotherapy, the dose to the PVs is associated with an increased risk of grade ≥3 AF, with an incidence of 5.2% at 5 years in our patient cohort of 539 patients.

TRANSLATIONAL OUTLOOK: Future studies should investigate these specific cardiac substructures to determine optimal clinical dose limits for individualized radiation treatment planning and to better characterize the mechanistic pathways by which radiation exposure leads to AF from a pathophysiologic perspective.

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KEY WORDS **breast cancer, esophageal cancer, Hodgkin lymphoma, left coronary arteries, myocardial sleeves, non–small cell lung cancer, pulmonary veins, radiation toxicity**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**