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ORIGINAL RESEARCH

Cardiac Substructure Radiation Dose and Associations With Tachyarrhythmia and Bradyarrhythmia After Lung Cancer Radiotherapy

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ABSTRACT

BACKGROUND Arrhythmias are common following radiotherapy for non–small cell lung cancer.

OBJECTIVES The aim of this study was to analyze the association of distinct arrhythmia classes with cardiac substructure radiotherapy dose.

METHODS A retrospective analysis was conducted of 748 patients with locally advanced non–small cell lung cancer treated with radiotherapy. Cardiac substructure dose parameters were calculated. Receiver-operating characteristic curve analyses for predictors of Common Terminology Criteria for Adverse Events grade ≥3 atrial fibrillation (AF), atrial flutter, non-AF and non–atrial flutter supraventricular tachyarrhythmia (SVT), bradyarrhythmia, and ventricular tachyarrhythmia (VT) or asystole were calculated. Fine-Gray regression models were performed (with noncardiac death as a competing risk).

RESULTS Of 748 patients, 128 (17.1%) experienced at least 1 grade ≥3 arrhythmia, with a median time to first arrhythmia of 2.0 years (Q1-Q3: 0.9-4.2 years). The 2-year cumulative incidences of each arrhythmia group were 8.0% for AF, 2.7% for atrial flutter, 1.8% for other SVT, 1.4% for bradyarrhythmia, and 1.1% for VT or asystole. Adjusting for baseline cardiovascular risk, pulmonary vein (PV) volume receiving 5 Gy was associated with AF (subdistribution HR [sHR]: 1.04/mL; 95% CI: 1.01-1.08; $P = 0.016$), left circumflex coronary artery volume receiving 35 Gy with atrial flutter (sHR: 1.10/mL; 95% CI: 1.01-1.19; $P = 0.028$), PV volume receiving 55 Gy with SVT (sHR: 1.03 per 1%; 95% CI: 1.02-1.05; $P < 0.001$), right coronary artery volume receiving 25 Gy with bradyarrhythmia (sHR: 1.14/mL; 95% CI: 1.00-1.30; $P = 0.042$), and left main coronary artery volume receiving 5 Gy with VT or asystole (sHR: 2.45/mL; 95% CI: 1.21-4.97; $P = 0.013$).

CONCLUSIONS This study revealed pathophysiologically distinct arrhythmia classes associated with radiotherapy dose to discrete cardiac substructures, including PV dose with AF and SVT, left circumflex coronary artery dose with atrial flutter, right coronary artery dose with bradyarrhythmia, and left main coronary artery dose with VT or asystole, guiding potential risk mitigation approaches. (JACC CardioOncol 2024;6:544-556) © 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/).

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Although the prognosis for patients with non-small cell lung cancer (NSCLC) has historically been poor, recent advances in treatment approaches have translated to significant improvements in median survival,[1,2] underscoring the importance of balancing treatment-associated toxicities with tumor control. Radiotherapy-associated cardiac events have been observed to occur frequently in patients with locally advanced NSCLC, often with a median interval to events of <2 years and associated with baseline cardiovascular risk.[3-5] Although initial data described the association between whole-heart radiotherapy dose and major adverse cardiac events (MACE) and mortality,[3] subsequent analyses characterized the association between radiotherapy dose to cardiac substructures, specifically the left anterior descending coronary artery (LAD) with MACE and mortality,[6] sinoatrial and atrial doses with atrial fibrillation (AF) and mortality,[7,8] as well as areas of the base of the heart (which encompasses the coronary origins and sinoatrial node [SAN]) with mortality.[9,10]

Although the magnitude of impact of MACE (eg, cardiovascular death, myocardial infarction, heart failure, unstable angina, coronary revascularization) is well recognized, these endpoints do not capture the full spectrum of symptomatic cardiac events following radiotherapy. Indeed, arrhythmias are commonly reported, with rates of 5% to 17% following radiotherapy in lung cancer.[3,7,11] Most arrhythmias are supraventricular tachyarrhythmias (SVTs), including AF (61%), supraventricular tachycardia (12%), atrial flutter (11%), and are more common in patients with histories of preexisting coronary heart disease.[3] Furthermore, recent lung cancer data have revealed an association between SAN and atrial dose with AF and mortality in lung cancer[7] and pulmonary vein (PV) dose with AF in lung cancer,[12] highlighting the importance of considering cardiac pathophysiological mechanisms of disease for specific cardiac endpoints when mapping cardiac substructure dose limits.

However, data comprehensively detailing distinct classes of arrhythmias with specific pathophysiology and associated cardiac substructure dose-volume predictors remain limited. In particular, given the distinct pathophysiology and anatomical origins of the major arrhythmias, including bradyarrhythmia (heart rate <60 beats/minute caused by atrioventricular node [AVN] or SAN or conduction system disorders), SVT (heart rate >100 beats/min with a narrow QRS complex and origins at or above the AVN in the atria, PVs, and/or supraventricular conduction pathways), and ventricular tachyarrhythmias (VTs) (heart rate >100 beats/min with a wide QRS complex and origins below the AVN and in the ventricle), we hypothesized that the specific putative cardiac substructures at risk and dose thresholds might differ for each arrhythmia subtype. Therefore, we sought to comprehensively characterize the cumulative incidence of distinct classes of arrhythmias following radiotherapy and evaluate the associations with specific radiotherapy dose-volume parameters and baseline cardiovascular risk in patients with locally advanced NSCLC.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AVN = atrioventricular node
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
LMCA = left main coronary artery
MACE = major adverse cardiac event(s)
NSCLC = non-small cell lung cancer
PV = pulmonary vein
RCA = right coronary artery
SAN = sinoatrial node
SVT = supraventricular tachyarrhythmia
VT = ventricular tachyarrhythmia

METHODS

PATIENTS AND TREATMENT. We performed a retrospective cohort analysis of 748 consecutive patients with locally advanced NSCLC treated with thoracic radiotherapy between 1998 and 2014 at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Dana-Farber Cancer Institute/Brigham and Women's Hospital at Milford Regional Medical Center. Eligible patients included those with 2010 American Joint Commission on Cancer clinical stage II (surgically inoperable or unresectable) or stage III NSCLC. Patients were treated with 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy techniques, and we excluded those treated with stereotactic body radiotherapy. Cardiac chambers (left atrium and right atrium, left ventricle and right ventricle) and coronary arteries (left main coronary artery [LMCA], LAD, left circumflex coronary artery [LCx], right coronary artery [RCA], and posterior descending artery) were manually segmented,[6] with all contours manually verified (R.H.M., A.N.). PV and left ventricle myocardium (excluding blood pool) were segmented using open-source deep learning-based algorithms (TotalSegmentator[13]) and manually verified (M.B., R.P.M.).

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.

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The AVN and SAN were segmented according to the criteria of Loap et al[14] in a subset of patients (n = 46) from an independent NSCLC data set (Cedars-Sinai Medical Center),[15] and these segmentations were then used to train a deep learning model. Patients were divided randomly into training (n = 36), validation (n = 5), and testing (n = 5) sets. PyTorch framework version 1.13.0 and NVIDIA RTX A6000 GPU with CUDAToolkit 11.7 were used. All networks used nnU-Net version 2.0, a deep learning-based segmentation platform featuring self-configuration of preprocessing, network architecture selection and training, and postprocessing for the given training data.[16] For training, all volumes were resampled to 256 × 256 × 128 voxels, with minimum and maximum voxel values rescaled to 0 and 1, respectively. Separate deep learning models were trained for AVN and SAN detection over 1,000 epochs using a combination of Dice and cross-entropy loss functions and manual segmentations as ground truth labels. Each artificial intelligence-generated output was resized into a sphere centered around the volume's center of mass with a 1-cm radius to match the criteria of Loap et al[14] and was manually verified (K.M.A., R.P.M.). For all structures, dose-volume histogram parameters (mean, maximum, and volume [V] as a percentage and in milliliters receiving *x* Gy [in 5-Gy increments to 60 Gy]) were calculated. This study was approved by the Dana-Farber/Harvard Cancer Center and Cedars-Sinai Medical Center Institutional Review Boards under a data-use agreement and a waiver of the requirement to obtain informed consent because of minimal risk.

ASSESSMENT OF CARDIOVASCULAR RISK AND ARRHYTHMIAS. Detailed manual electronic medical record review was performed.[3] Pre-existing coronary heart disease included anyone with a history of coronary artery disease (including extensive coronary artery calcifications), congestive heart failure (ischemic etiology), or a coronary heart disease risk equivalent such as peripheral vascular disease or ischemic stroke. Grade ≥3 Common Terminology Criteria for Adverse Events arrhythmia types (version 4.0) were assessed by detailed manual electronic medical record review, including electrocardiographic reports (obtained as standard of care) and cardiology notes, and grouped into the following categories: 1) AF; 2) atrial flutter; 3) other SVT (supraventricular tachycardia, symptomatic sinus tachycardia, and atrial arrhythmia not otherwise specified); 4) bradyarrhythmia (atrioventricular block [first degree, second degree, complete], sick sinus syndrome, and symptomatic sinus bradycardia); and 5) VT or asystole (ventricular fibrillation, ventricular tachycardia, ventricular arrhythmia not otherwise specified, and asystole). MACE (cardiovascular death, unstable angina, heart failure, myocardial infarction, and coronary revascularization) were collected as previously described.[17] Moderate and heavy alcohol use levels were defined according to National Institute on Alcohol Abuse and Alcoholism criteria.[18]

STATISTICAL ANALYSIS. Follow-up was calculated from the start of RT using the reverse Kaplan-Meier method. Continuous data are presented as median (Q1-Q3), while categorical data are presented as count (percentage). Continuous variables were compared using a Wilcoxon rank sum test and categorical variables using the chi-square test (or Fisher exact test when an expected cell count was <5). Areas under the receiver-operating characteristic curve were estimated and cutpoint analysis performed according to the Liu method.[19] Arrhythmia cumulative incidence estimates with 95% CIs were calculated for the following groups: grade ≥3 AF, atrial flutter, non-AF and non-atrial flutter SVT (other SVT), bradyarrhythmia, and VT or asystole, adjusting for noncardiac death as a competing risk and compared using Gray's test. Fine-Gray regression models were performed, accounting for noncardiac death as a competing risk, and model results are presented as subdistribution HRs with 95% CIs. For dosimetric variables, to avoid collinearity, those with the top 10 C indexes on analysis of areas under the curve were selected for univariable analysis, and only the dosimetric variable with the lowest *P* value[20] was included in the multivariable model. In this methodology, we did not explore the adjusted association of all top-ranked (by area under the curve) dosimetric parameters (to limit multiple testing), so additional dosimetric parameters might also hold significant prognostic value. In general, multivariable models included variables with *P* values ≤0.05 on univariable analysis[21] and a priori defined clinically pertinent variables. As only analyses of area under the curve (without hypothesis testing) were performed in the discovery phase, multiple testing correction was not determined to be strictly necessary. All analyses were performed using Stata/SE version 17.0 (StataCorp).

RESULTS

BASELINE CHARACTERISTICS. Baseline clinical and treatment characteristics are summarized in **Table 1**. The median age was 65 years (Q1-Q3: 57-73 years), and 49.2% (n = 368) were women. A sizable subset of patients, 13.8% (n = 103), had pre-existing arrhythmia

TABLE 1 Clinical Characteristics of the NSCLC Cohort

Age, y	65 (57-73)
Sex	
Female	368 (49.2)
Male	380 (50.8)
ECOG PS	
0 or 1	660 (88.2)
2	69 (9.2)
3 or 4	19 (2.5)
Weight loss	237 (31.7)
Tobacco	
Never	60 (8.0)
Current	298 (39.8)
Former	390 (52.1)
Pack-years	43 (30-60)
NIAAA alcohol use level	
None	297 (39.7)
Moderate	372 (49.7)
Heavy	71 (9.5)
Unknown	8 (1.1)
Medical history	
Hypertension	375 (50.1)
Hyperlipidemia	359 (48.0)
Diabetes mellitus	105 (14.0)
DVT/PE	34 (4.6)
Arrhythmia	103 (13.8)
Valvular disease	42 (5.6)
PAD	61 (8.2)
Stroke	14 (1.9)
CAD	216 (28.9)
Prior MI	86 (11.5)
HF	61 (8.2)
Any CHD	268 (35.8)
Framingham risk, %	14.8 (8.4-26.1)
Low (<10%)	134 (17.9)
Moderate (10%-20%)	120 (16.0)
High (>20%)	226 (30.2)
NSCLC clinical stage	
II	79 (10.6)
IIIA	418 (55.9)
IIIB	251 (33.6)
Tumor laterality	
Right	417 (55.8)
Left	281 (37.6)
NSCLC histology	
Adenocarcinoma	331 (44.3)
SCC	234 (31.3)
Large cell carcinoma	133 (17.8)
Other	50 (6.7)
Chemotherapy	
Timing	
Induction	158 (21.1)
Concurrent	641 (85.7)
Adjuvant	247 (33.0)
Type	
Platinum plus etoposide	284 (38.0)
Platinum plus taxane	373 (49.9)
Pemetrexed based	39 (5.2)
Other	65 (8.7)
RT/surgery sequence	
Definitive CRT	433 (57.9)
Any surgery	259 (34.6)
Neoadjuvant RT/CRT	171 (22.9)
Adjuvant RT/CRT	88 (11.8)
RT alone	56 (7.5)
RT technique	
3D-CRT	584 (78.1)
IMRT	164 (21.9)
RT year	
Before 2008	273 (36.5)
2008 or later	475 (63.5)
Prescribed RT dose, Gy	64.0 (54.9-66.0)
Dose, Gy (n = 701[a])	
Heart mean	12.3 (5.9-19.0)
Esophagus mean	23.7 (17.1-30.6)
Lung mean	14.9 (11.6-17.2)
Lung V5, %	42.9 (32.8-52.1)
Lung V20, %	25.2 (19.2-29.6)

Values are median (Q1-Q3) or n (%). [a]Based on patients with radiotherapy dose plan information available.

3D-CRT = 3-dimensional conformal radiation therapy; CAD = coronary artery disease; CHD = coronary heart disease; CRT = chemoradiotherapy; DVT = deep venous thrombosis; ECOG = Eastern Cooperative Oncology Group; HF = heart failure; IMRT = intensity-modulated radiation therapy; MI = myocardial infarction; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NSCLC = non-small cell lung cancer; PAD = peripheral artery disease; PE = pulmonary embolism; PS = performance status; RT = radiation therapy; SCC = squamous cell carcinoma; V*x* = volume receiving *x* Gy.

Continued in the next column

diagnoses prior to radiotherapy, and other common cardiac comorbidities included hypertension in 50.1% (n = 375), hyperlipidemia in 48.0% (n = 359), any coronary heart disease in 35.8% (n = 268), valvular disease in 5.6% (n = 42), and prior stroke in 1.9% (n = 14). Most patients (57.9% [n = 433]) were treated using definitive chemoradiotherapy, with 34.7% (n = 259) receiving radiotherapy in combination with surgery.

ARRHYTHMIA EVENTS. The median follow-up duration was 5.5 years (Q1-Q3: 3.4-8.1 years). Of 748 patients, 128 (17.1%) experienced at least 1 grade ≥3 arrhythmia, with a 2-year overall cumulative incidence of 11.9% (95% CI: 9.7%-14.4%) and a median time to first arrhythmia of 2.0 years (Q1-Q3: 0.9-4.2 years).

There were 78 AF events, with a 2-year cumulative incidence of 8.0% (95% CI: 6.2%-10.1%) and a median time to event of 2.0 years (Q1-Q3: 0.9-4.2 years); 14 atrial flutter events, with a 2-year cumulative incidence of 2.7% (95% CI: 1.7%-4.1%) and a median time to event of 1.7 years (Q1-Q3: 0.8-3.8 years); 20 other SVT events, with a 2-year cumulative incidence of 1.8% (95% CI: 1.0%-2.9%) and a median time to event of 1.7 years (Q1-Q3: 0.7-3.8 years); 19 bradyarrhythmia events, with a 2-year cumulative incidence of 1.4% (95% CI: 0.7%-2.5%) and a median time to event of 1.7

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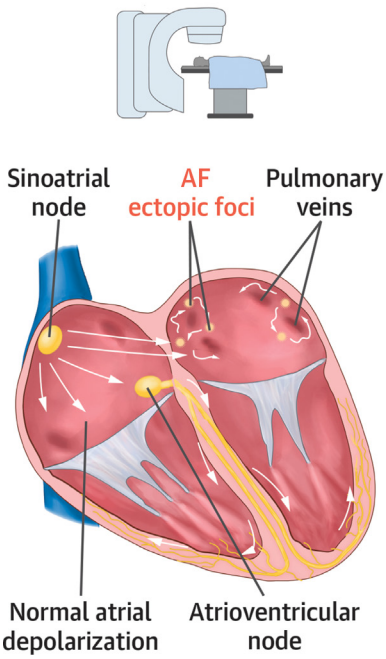
CENTRAL ILLUSTRATION **Radiotherapy Dose Exposure to Cardiac Substructures Is Associated With Distinct Arrhythmia Subgroups**



	2-y Incidence of Grade ≥3	Dose Predictor	Baseline Risk Factors
Atrial Fibrillation	8%	Pulmonary veins	CHD, arrhythmia
Atrial Flutter	3%	Left circumflex CA	None
Other Supraventricular Tachycardia	2%	Pulmonary veins	None
Bradyarrhythmia	1%	Right CA	CHD
Ventricular Tachyarrhythmia/ Asystole	1%	Left main CA	CHD

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(Left) Cartoon depicting normal conduction from sinoatrial node (white arrows) vs the ectopic foci of atrial fibrillation (AF) (yellow stars, wavy white arrows) from the pulmonary veins. CA = coronary artery; CHD = coronary heart disease.

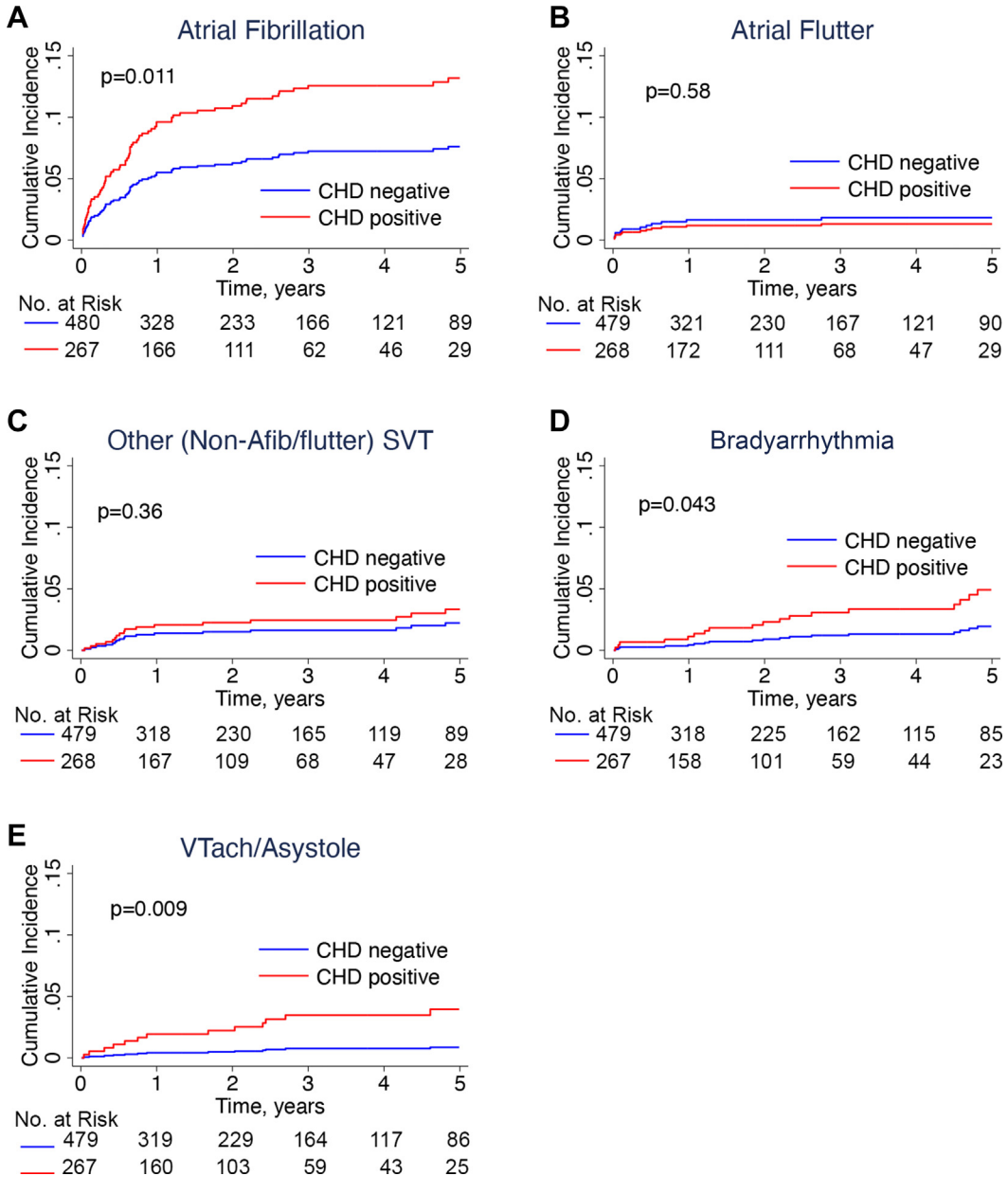
TABLE 2 **Grade ≥3 Common Terminology Criteria for Adverse Events Arrhythmia by Pre-Existing Cardiovascular Risk**

		By Pre-Existing CHD			By Pre-Existing Arrhythmia		
Grade ≥3 Arrhythmia Type	Total Population (N = 748)	No CHD (n = 480)	Prior CHD (n = 268)	*P* Value	No Arrhythmia (n = 645)	Prior Arrhythmia (n = 103)	*P* Value
Any arrhythmia, total	128 (17.1)	64 (13.3)	64 (23.9)	<0.001	99 (15.4)	29 (28.2)	0.001
Supraventricular arrhythmia, total	102 (13.6)	54 (11.0)	49 (18.3)	0.006	77 (11.9)	25 (24.3)	0.001
AF	78 (10.4)	39 (8.1)	39 (14.6)	0.006	56 (8.7)	22 (21.4)	<0.001
Non-AF SVT	32 (4.3)	20 (4.2)	12 (4.5)	0.84	26 (4.0)	6 (5.8)	0.40
Atrial flutter	14 (1.9)	10 (2.1)	4 (1.5)	0.78	10 (1.6)	4 (3.9)	0.11
Supraventricular tachycardia	15 (2.0)	10 (2.1)	5 (1.9)	>0.99	14 (2.2)	1 (1.0)	0.71
Sinus tachycardia	3 (0.4)	1 (0.2)	2 (0.8)	0.29	2 (0.3)	1 (1.0)	0.36
Atrial arrhythmia NOS	2 (0.3)	0	2 (0.8)	0.13	2 (0.3)	0	>0.99
Bradyarrhythmia, total	19 (2.5)	8 (1.7)	11 (4.1)	0.042	15 (2.3)	4 (3.9)	0.35
Bradycardia	12 (1.6)	5 (1.0)	7 (2.6)	0.101	9 (1.4)	3 (2.9)	0.26
AV block (complete)	5 (0.7)	4 (0.8)	1 (0.4)	0.66	5 (0.8)	0	>0.99
Sick sinus syndrome	3 (0.4)	0	3 (1.1)	0.046	2 (0.3)	1 (1.0)	0.36
VT/asystole, total	14 (1.9)	4 (0.8)	10 (3.7)	0.009	10 (1.6)	4 (3.9)	0.11
Ventricular tachycardia	6 (0.8)	1 (0.2)	5 (1.9)	0.024	4 (0.6)	2 (1.9)	0.20
Ventricular fibrillation	2 (0.3)	1 (0.2)	1 (0.4)	>0.99	1 (0.2)	1 (1.0)	0.26
Ventricular arrhythmia NOS	1 (0.1)	0	1 (0.4)	0.36	1 (0.2)	0	>0.99
Asystole	7 (0.9)	2 (0.4)	5 (1.9)	0.11	5 (0.8)	2 (1.9)	0.25

Values are n (%).

AF = atrial fibrillation; AV = atrioventricular; CHD = coronary heart disease; NOS = not otherwise specified; SVT = supraventricular tachycardia; VT = ventricular tachyarrhythmia.

FIGURE 1 **Cumulative Incidence of Arrhythmia Groups by CHD Status**



Cumulative incidence estimates stratified by coronary heart disease (CHD) status for (A) atrial fibrillation (Afib), (B) atrial flutter (Aflutter), (C) other supraventricular tachyarrhythmia (SVT), (D) bradyarrhythmia, and (D) ventricular tachyarrhythmia (VTach) or asystole. Estimates were compared using Gray's test for competing risks.

years (Q1-Q3: 0.7-3.7 years); and 14 VT or asystole events, with a 2-year cumulative incidence of 1.1% (95% CI: 0.5%-2.1%) and a median time to event of 1.7 years (Q1-Q3: 0.7-3.7 years) (**Central Illustration**).

Patients who developed grade ≥3 AF were more likely to have a history of coronary heart disease (14.6% vs 8.1%; $P = 0.008$) or baseline arrhythmia (21.4% vs 8.7%; $P < 0.001$), but development of atrial flutter or other SVT was not associated with baseline cardiovascular risk (**Table 2**, **Figure 1**). Bradyarrhythmia and VT or asystole were more likely in patients with histories of coronary heart disease (4.1% vs 1.7% [$P = 0.042$] and 3.7% vs 0.8% [$P = 0.009$], respectively) but not in those with pre-existing

TABLE 3 C Indexes of the Top 10 Dose Volume Parameters for Cardiac Substructures Predictive of Each Arrhythmia Endpoint

Atrial Fibrillation		Atrial Flutter		Other SVT		Bradyarrhythmia		VT/Asystole	
Predictors	C Index	Predictors	C Index	Predictors	C Index	Predictors	C Index	Predictors	C Index
PVs V5, mL	0.66	LCx V40, mL	0.65	RA D_{max}	0.76	AVN V5, mL	0.60	LMCA V25, %	0.66
PVs V10, mL	0.65	LCx V40, %	0.65	PVs V55, %	0.75	RV V25, mL	0.60	LMCA V25, mL	0.65
PVs V15, mL	0.64	LCx V35, mL	0.65	PVs V55, mL	0.75	AVN V5, %	0.60	LMCA V30, %	0.65
LA V5, mL	0.64	LMCA V50, mL	0.65	PVs mean	0.74	RV V20, mL	0.59	LMCA V45, %	0.65
PVs V20, mL	0.64	LCx V35, %	0.64	PVs V60, mL	0.74	RV V30, mL	0.59	LMCA V20, %	0.65
PVs V25, mL	0.63	LMCA V50, %	0.64	PVs V50, %	0.73	RV V25, %	0.59	LMCA V45, mL	0.65
LA V25, mL	0.63	LCx V30, mL	0.64	LA V55, %	0.73	RV V20, %	0.59	LMCA V35, %	0.64
PVs V30, mL	0.62	LAD V50, mL	0.64	PVs V60, %	0.73	RCA V25, %	0.59	LMCA V50, mL	0.64
LA V20, mL	0.62	LCx V30, %	0.64	PVs V40, %	0.73	RCA V25, mL	0.59	LAD V25, %	0.64
PVs V55, mL	0.62	LV-myo V45, mL	0.64	RA V60, %	0.73	RV V30, %	0.59	LAD V25, mL	0.64

AVN = atrioventricular node; LA = left atrium; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; LV = left ventricle; myo = myocardium; PV = pulmonary vein; RA = right atrium; RCA = right coronary artery; RV = right ventricle; SAN = sinoatrial node; other abbreviations as in Tables 1 and 2.

arrhythmias ($P > 0.05$). There was no significant difference in arrhythmia subtype incidence in patients who did or did not undergo surgery ($P > 0.05$). Nearly one-third of patients who experienced arrhythmia also experienced MACE (31.3% [40 of 128]). MACE were most common among those who developed VT or asystole (12 of 14 [85.7%]) and bradyarrhythmia (9 of 19 [47.4%]) and less common among those with AF (21 of 78 [26.9%]), atrial flutter (3 of 14 [21.3%]), or other SVT (3 of 20 [15.0%]). Among the 12 patients who experienced MACE and VT or asystole, 1 experienced myocardial infarction or heart failure 2 years after radiotherapy and developed a nonfatal VT 2 years later, 1 experienced unstable angina or coronary revascularization 1 year after radiotherapy and fatal asystole 1 year later, and 9 ultimately experienced cardiac death.

DOSE PREDICTORS OF DISTINCT ARRHYTHMIA GROUPS. The top 10 dose-volume histogram predictors by area under the curve for each arrhythmia group are shown in Table 3, and observations include an association between AF with low to intermediate dose exposure to the PVs and left atrium; atrial flutter with moderate to high LMCA dose exposure; other SVT with high dose exposure to the right atrium and left atrium (PV); bradyarrhythmia with low to intermediate dose to the AVN, right ventricle, and RCA; and VT or asystole with moderate to high LMCA dose. The areas under the curve for all dose-volume histogram parameters and substructures are detailed in Supplemental Table 1.

On competing risk regression, adjusting for age, sex, smoking, alcohol use, baseline arrhythmia or coronary heart disease, surgery, chemotherapy type, and radiotherapy technique, PV V5 was associated with an increased risk for AF (subdistribution HR: 1.04/mL; 95% CI: 1.01-1.08; $P = 0.016$) (Table 4). Adjusting for alcohol use, pre-existing arrhythmia, coronary heart disease, and surgery, LCx V35 was associated with an increased risk for atrial flutter (subdistribution HR: 1.10/mL; 95% CI: 1.01-1.19; $P = 0.028$). Adjusting for pre-existing arrhythmia, coronary heart disease, and taxane chemotherapy use, PV V55 was associated with an increased risk for other SVT (subdistribution HR: 1.03/mL; 95% CI: 1.02-1.05; $P < 0.001$). Adjusting for pre-existing arrhythmia and coronary heart disease, RCA V25 was associated with an increased risk for bradyarrhythmia (subdistribution HR: 1.14/mL; 95% CI: 1.00-1.30; $P = 0.042$), and LMCA V50 was associated with an increased risk for VT or asystole (subdistribution HR: 2.45/mL; 95% CI: 1.21-4.97; $P = 0.013$) (Table 5, Supplemental Tables 2 to 5). There was no significant interaction between pre-existing coronary heart disease or baseline arrhythmia and any of the dosimetric variables ($P > 0.05$ for all). Given collinearity and limited event numbers, only the adjusted association of a single top-ranked (by area under the curve) dosimetric parameter was tested per multivariable model, and the prognostic potential of the other top-ranked dosimetric parameters was not explored.

To assess candidate dose thresholds, cutpoint analysis was performed for the top dose-volume histogram variable as follows: AF (PV V5 15 mL; 0.62), atrial flutter (LCx V35 1.8 mL; 0.67), other SVT (PV V55 31%; 0.77), bradyarrhythmia (RCA V25, 1.9 mL; 0.61), and VT or asystole (LMCA V50, 0.5 mL; 0.69). Stratified by cutpoint, the 2-year cumulative incidence of each arrhythmia type was as follows: for AF, in those with PV V5 ≥15 mL vs <15 mL, 13.1% (95% CI: 9.2%-17.7%) vs 4.7% (95% CI: 3.1%-7.0%) ($P < 0.001$); for atrial flutter, in those with LCx V35 ≥1.8 mL vs <1.8 mL, 3.3% (95% CI: 1.3%-7.1%) vs 0.6% (95% CI:

0.2%-1.5%) ($P = 0.012$); for other SVT, in those with PV V55 ≥31% vs <31%, 3.3% (95% CI: 1.6%-5.9%) vs 0.3% (95% CI: 0.0%-1.3%; $P = 0.003$); for bradyarrhythmia, in those with RCA V25 ≥ 1.9 mL vs <1.9 mL, 3.0% (95% CI: 1.1%-6.5%) vs 1.0% (95% CI: 0.4%-2.2%) ($P = 0.024$); and for VT or asystole, in those with LMCA V50 ≥0.5 mL vs <0.5 mL, 2.4% (95% CI: 0.8%-5.6%) vs 0.8% (95% CI: 0.3%-1.9%) ($P = 0.006$) (Figure 2).

DISCUSSION

We observed that symptomatic arrhythmic events are common after lung cancer radiotherapy, occurring within 2 years, and have differential associations with baseline cardiovascular risk and pre-existing arrhythmia status. AF was most common, with a 2-year incidence of 8%, and was more likely in patients with histories of coronary heart disease or prior arrhythmia. atrial flutter and other SVT were not associated with baseline cardiovascular risk, although bradyarrhythmia and VT or asystole were more likely in patients with histories of coronary heart disease (but not prior arrhythmia). We report that radiotherapy dose to discrete cardiac substructures is associated with distinct arrhythmia classes and correlates with potential pathophysiological mechanisms. Specifically, low to intermediate dose exposure to the PV and left atrium (V5-V30) was associated with an increased risk for AF. Moderate to high LCx dose exposure was associated with atrial flutter, which might be related to its pathway along the left atrium in proximity to the coronary sinus. In comparison, other SVTs were associated with high-dose atrial exposure (left atrium [PV]/right atrium V50-V60), suggesting a distinct pathophysiological mechanism even among arrhythmias originating in the atria. Furthermore, low to intermediate dose exposure to the RCA, AVN, and right ventricle was associated with bradyarrhythmia (RCA/right ventricle V20-V30, AVN V5), which pathophysiologically might correlate with injury either directly to the AVN or to the blood supply to the AVN from the atrioventricular nodal branch of the sinoatrial nodal artery (which originates from the RCA in 90%). Last, VT and asystole were associated with moderate to high LMCA dose (V25-V50), which fits with the potential pathway of coronary injury leading to myocardial infarction and the creation of left ventricle scar-based re-entry loops. Indeed, our observation that several arrhythmia events occurred in the context of recent or prior MACE, particularly in those with VT or asystole and bradyarrhythmia, is suggestive that a subset of postradiotherapy arrhythmias might be secondary to MACE and represent a clustering of cardiac event types. Together, these data highlight that low vs high radiotherapy dose might confer distinct injury patterns and arrhythmogenicity risk according to cardiac location and inform a biological framework to better understand and potentially mitigate cardiac toxicities following radiotherapy.

Data describing arrhythmia events after lung cancer radiotherapy show event rates ranging from 5% to 17%.[3,5,7,11,12] Yegya-Raman et al[11] reported that 21 of

TABLE 4 Competing Risk Regression Model for Atrial Fibrillation

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
Age	1.02 (1.00-1.04)	0.039	1.01 (0.98-1.04)	0.53
Sex				
Female	1.00 (Reference)		1.00 (Reference)	
Male	1.85 (1.16-2.95)	0.010	1.38 (0.78-2.42)	0.27
Smoking				
Never	1.00 (Reference)		1.00 (Reference)	
Ever	6.99 (0.98-50.02)	0.053	6.57 (0.83-51.10)	0.075
Alcohol intake level				
None	1.00 (Reference)		1.00 (Reference)	
Moderate	0.84 (0.53-1.34)	0.47	0.77 (0.47-1.25)	0.29
Heavy	0.59 (0.23-1.52)	0.27	0.44 (0.15-1.34)	0.15
Hypertension	1.49 (0.95-2.35)	0.085	1.13 (0.68-1.87)	0.64
Hyperlipidemia	1.01 (0.65-1.58)	0.97		
Statin use	1.38 (0.88-2.15)	0.16	0.93 (0.53-1.49)	0.77
Diabetes	1.25 (0.69-2.27)	0.46		
Valvular disease	1.84 (0.83-4.11)	0.13		
Baseline arrhythmia	2.67 (1.64-4.36)	<0.001	2.31 (1.30-4.11)	0.004
Any CHD	1.79 (1.14-2.79)	0.011	1.18 (0.71-1.96)	0.52
Clinical stage				
I or II	1.00 (Reference)			
III	1.19 (0.55-2.59)	0.66		
Chemotherapy				
Platinum plus etoposide	1.14 (0.72-1.79)	0.58		
Platinum plus taxane	0.95 (0.61-1.49)	0.83	0.74 (0.44-1.24)	0.25
Pemetrexed based	0.52 (0.13-2.11)	0.36		
Other	0.66 (0.26-1.63)	0.37		
Surgery	0.66 (0.40-1.09)	0.11	0.72 (0.39-1.32)	0.29
RT technique				
3D-CRT	1.00 (Reference)		1.00 (Reference)	
IMRT	1.56 (0.95-2.57)	0.077	1.32 (0.78-2.23)	0.30
Post-RT locoregional relapse	1.29 (0.82-2.02)	0.27	1.56 (0.97-2.49)	0.066
RT dose				
PV V5, mL	1.07 (1.04-1.10)	<0.0001	1.04/cc (1.01-1.08)	0.016
PV V10, mL	1.06 (1.03-1.10)	<0.0001		
PV V15, mL	1.07 (1.03-1.10)	<0.0001		
LA V5, mL	1.01 (1.00-1.01)	0.0003		
PV V20, mL	1.07 (1.03-1.10)	0.0001		
PV V25, mL	1.07 (1.03-1.10)	<0.0001		
LA V25, mL	1.01 (1.00-1.02)	0.0004		
PV V30, mL	1.07 (1.03-1.10)	0.0002		
LA V20, mL	1.01 (1.00-1.01)	0.0004		
PV V55, mL	1.08 (1.04-1.12)	0.0002		

sHR = subdistribution HR; other abbreviations as in Tables 1 to 3.

TABLE 5 Top Substructure Dose Variables From Multivariable Competing Risk Regression Models for All Arrhythmia Outcomes

	Top Substructure Variable	Multivariable Model[a]	
		sHR (95% CI)	*P* Value
Atrial fibrillation	PV V5, mL	1.04/mL (1.01-1.08)	0.016
Atrial flutter	LCx V35, mL	1.10/mL (1.01-1.19)	0.028
Other SVT	PV V55, %	1.03/1% (1.02-1.05)	<0.001
Bradyarrhythmia	RCA V25, mL	1.14/mL (1.00-1.30)	0.042
VT/asystole	LMCA V50, mL	2.45/mL (1.21-4.97)	0.013

[a]Each individual multivariable model was adjusted for baseline cardiovascular and prognostic factors; see Table 4 and Supplemental Tables 2 to 5 for full models for each arrhythmia outcome.

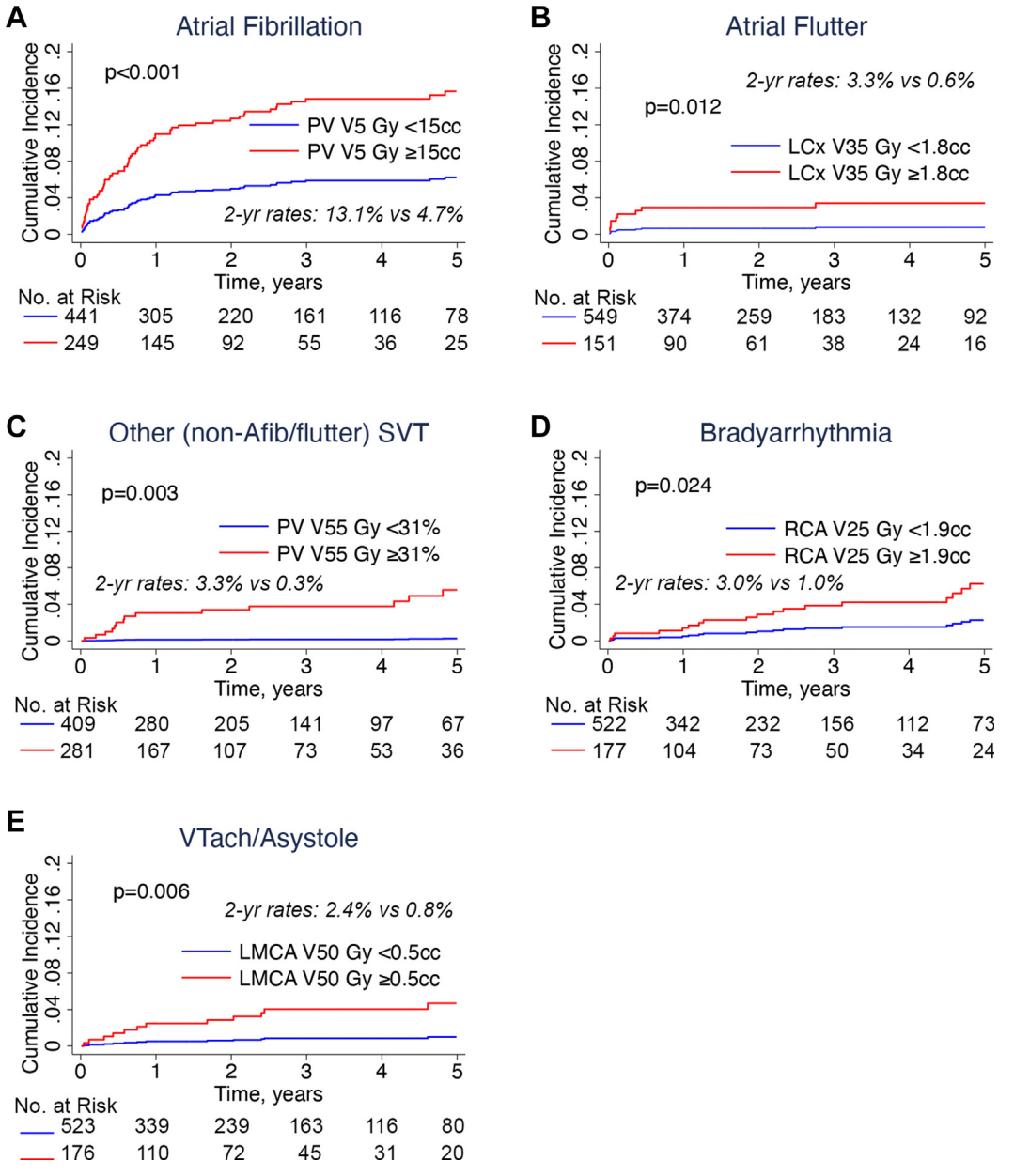
Abbreviations as in Tables 2 to 4.

148 patients experienced supraventricular arrhythmic events (mostly AF) after lung cancer radiotherapy, with no association with dose to the heart or atria, likely because of limited patient sample size. Kim et al[7] used a larger cohort but observed lower rates after thoracic radiotherapy, with only 5% of patients with NSCLC reported to develop AF, potentially related to the lower reported baseline rate of cardiovascular disease in this Korean cohort (15%-18%) compared with Western cohorts (30%-40%).[3,22] Similarly, Miller et al[8] recently reported a 1-year cumulative incidence of AF of 20% in patients with esophageal cancer treated with thoracic radiotherapy and observed that increasing radiotherapy dose to the left atrium was associated with mortality. Most recently, Walls et al[12] analyzed a cohort of 420 patients with NSCLC, identifying 26 cases of new AF (6%), with PV dose exposure associated with increased risk for AF, though event numbers were limited. Notably, each of these studies, including the present study, is subject to the limitations of retrospective review and potential underreporting or inadequate capture of post-treatment events.

There is a growing body of data demonstrating strong associations between radiation dose exposure to cardiac substructures and specific cardiac events and/or mortality following thoracic radiotherapy. Notably, the LAD has been observed to be robustly associated with MACE and mortality.[6,15,23-26] In addition, the base of the heart, which anatomically encompasses the SAN and proximal coronary vessels, has been associated with mortality[9,10] and more recently the composite endpoint of AF, heart failure, and acute coronary syndrome.[27] Although initial data from the base of the heart mapped the dose associated with survival to an area centered around the right atrium,[9] later data identified the important region of the base of the heart to be centered around the left atrium.[10] Of note, cardiac anatomy typically defines the base of the heart as the posterior surface of the left atrium and to a lesser degree the right atrium.[28] In the only study to link dose to the base of the heart to a cardiac event outcome (vs survival), Walls et al[27] defined the base of the heart as a composite structure including the right atrium, superior vena cava, aortic root, LMCA, proximal LAD, and proximal RCA. The multitude of cardiac substructures in this region and data linking several of these substructures to distinct cardiac event endpoints raise the possibility that dose exposure to the base of the heart might act through multiple pathophysiological pathways of injury to several distinct cardiac substructures and/or be a surrogate for significant generalized cardiac dose exposure. These types of associations highlight the need for radiation oncologists to further collaborate with cardiology and cardio-oncology experts to better understand the pathophysiology and plausible mechanisms of injury.

Kim et al manually segmented the SAN and AVN[14] in a cohort of patients with lung cancer (n = 321 with NSCLC and n = 239 with small cell lung cancer) and observed that the maximum dose to the SAN (and to a lesser extent the right and left atria) was most predictive of AF and associated with mortality.[7] Walls et al[12] performed manual segmentation of the PVs and observed that PVs (but not the left atrium or SAN) were associated with increased risk for AF. We similarly observed that PV dose was significantly associated with an increased risk for AF and SVT, as well LCx dose with atrial flutter, RCA dose with bradyarrhythmia, and LMCA dose with VT or asystole. Together, these data underscore the importance of understanding cardiac anatomy and AF electrophysiology to contextualize the findings. To start, the SAN is the physiological pacemaker, located in the right atrium at the junction of the crista terminalis and superior vena cava. Conversely, most (80%-94%) of the rapid, uncoordinated atrial activity of AF is due to ectopic beats originating from the left atrial cardiac muscle within the myocardial sleeves of the proximal PVs.[29,30] By comparison, only a minority of AF ectopic foci (3%-15%) originate near the SAN.[29,30] This distinction is critical, as the PVs were not specifically delineated by Kim et al[7] (who evaluated the association of SAN dose with AF) and the PVs are the most common site of ectopic foci generation. Thus, although Kim et al[7] observed that SAN as well as right and left atrial doses were associated with AF and mortality, we hypothesize that this might be due to the proximity of these structures to the PVs and their behaving as a surrogate (ie, the SAN is approximately 2-4 cm from the right and left PVs, respectively) rather than direct injury to the SAN itself. Moreover,

FIGURE 2 **Cumulative Incidence of Arrhythmia Groups by Radiotherapy Dose Predictor Cutpoint**



Cumulative incidence estimates stratified by cutpoint of radiotherapy dose predictors for (A) Afib, (B) Aflutter, (C) other SVT, (D) bradyarrhythmia, and (D) ventricular VTach or asystole. Estimates were compared using Gray's test for competing risks. Abbreviations as in Figure 1.

at the time of Kim et al's[7] study, there was no contouring atlas available to guide PV delineation for radiotherapy planning. Several resources are now available to aid future dosimetric analyses for arrhythmia endpoints, including a PV contouring atlas,[31] a conduction atlas,[14] and a magnetic resonance-based cardiac atlas (including conduction pathway delineation),[32] each of which will contribute to better informing future arrhythmia-based radiotherapy dosimetric analyses.

The biology driving radiotherapy-associated changes is complex, and further research is needed to better elucidate the pathways connecting radiation exposure and cardiac events to specific cardiac structures, tissues, and cell types, as evidenced by recent data exploring electrical conduction reprogramming

in the context of radiotherapy-associated termination of ventricular arrhythmias in patients with refractory VT.[33,34] Furthermore, as we continue to gain substantial knowledge in cardiac substructure dosimetric predictors and mechanisms of injury, we can leverage the capabilities of modern radiotherapy techniques to intentionally prioritize sparing of critical cardiac regions during radiotherapy planning, thereby continuing to transform cardiac radiotherapy dose into a modifiable cardiac risk factor. Additionally, although cardio-oncology consensus guidelines and expert panels continue to develop recommendations for post-treatment surveillance (eg, screening transthoracic echocardiography and cardiac magnetic resonance imaging)[35-37] on the basis of emerging data, there is no guidance or recommendations to screen for occult arrhythmias. The present study, together with recent studies, will help inform evolving surveillance and screening recommendations in these high cardiovascular risk patients.

STUDY LIMITATIONS. First, this study's retrospective nature might have resulted in inadequate capture of baseline cardiovascular risk and/or cardiac events endpoints. Second, the Common Terminology Criteria for Adverse Events arrhythmia classes might not fully capture the spectrum of heart rate and rhythm abnormalities, as they currently lack categories for autonomic dysfunction or significant electrocardiographic changes, which are difficult to capture in a retrospective fashion. Similarly, the pre-immunotherapy treatment era might underestimate conduction abnormalities given the additive impact of immunotherapy on interval prolongation changes.[38]

This study also included a lower rate of intensity-modulated radiotherapy compared with a more modern treatment era, though we believe that the key findings are still applicable, as we would not expect the radiation dosimetric associations and thresholds to change but rather a potential difference in event rate given generally higher and more homogenous cardiac exposures in 3-dimensional conformal vs intensity-modulated radiotherapy treatments. Moreover, while we used state-of-the-art cardiac contouring techniques, we acknowledge that there need to be continued efforts in advancing contouring algorithms.

Last, as the adjusted association of only a single top-ranked (by area under the curve) dosimetric parameter was tested in each multivariable model (to limit collinearity and multiple testing), the present results do not necessarily establish that the selected parameter is "best," and the prognostic potential of the other top-ranked dosimetric parameters in comparison was not explored. Future studies should consider a penalized regression approach to explore whether a combination of dosimetric parameters might provide additional predictive value.

CONCLUSIONS

This work shows that radiotherapy dose to discrete cardiac substructures was associated with distinct arrhythmia classes, including PV dose with AF and SVT, LCx dose with atrial flutter, RCA dose with bradyarrhythmia, and LMCA dose with VT or asystole. These observations support continued fine mapping of cardiac substructure dose limits by considering cardiac physiological and pathophysiological mechanisms of disease. Last, given the high baseline cardiovascular risk of this population,[22] known suboptimal treatment with guidelines-based cardiovascular medical therapy,[22,39] and the cumulative excess cardiovascular risk from multimodality treatment (ie, radiotherapy, chemotherapy, immunotherapy, and/or targeted molecular drugs) that is not captured by standard cardiovascular risk assessment tools, oncologists should more frequently refer these patients to cardiology (or cardio-oncology) for optimizing risk factor treatment[40] and post-treatment surveillance.[35-37]

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Dr Atkins has received honoraria from OncLive. Dr Mak is a consultant for AstraZeneca, ViewRay, Novartis, Sio Capital Management, and Varian Medical Systems; is an advisory board member for ViewRay and AstraZeneca; and has received grant funding from AstraZeneca and ViewRay. Dr Nohria has received research support from Bristol Myers Squibb; and has received consulting fees from Altathera Pharmaceuticals, AstraZeneca, Bantam Pharmaceuticals, Regeneron Pharmaceuticals, and Takeda Oncology. 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: In patients treated for lung cancer with radiotherapy, radiation dose exposure to specific cardiac substructures is associated with distinct arrhythmia subgroups.

TRANSLATIONAL OUTLOOK: Further research in radiation therapy is needed to optimize approaches to cardiovascular risk mitigation and identify markers of early cardiovascular injury for intensified surveillance.

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KEY WORDS **atrial fibrillation, arrhythmia, bradyarrhythmia, cardiac toxicity, lung cancer, radiotherapy**

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