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ORIGINAL RESEARCH

Baseline Cardiac Parameters as Biomarkers of Radiation Cardiotoxicity in Lung Cancer

An NI-HEART Analysis

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ABSTRACT

BACKGROUND Radiation-induced cardiotoxicity poses a significant challenge in lung cancer management because of the close anatomical proximity of the heart to the lungs, compounded by a high prevalence of cardiovascular risk factors among patients.

OBJECTIVES The aim of this study was to assess the predictive value of routinely available clinical and imaging-based cardiac parameters in identifying "high risk" patients for major adverse cardiac events (MACE) and mortality following radiation therapy (RT).

METHODS The medical records of patients who underwent definitive RT for non-small cell lung cancer using modern planning techniques at a single center between 2015 and 2020 were retrospectively reviewed. Cardiac events were verified by cardiologists, and mortality data were confirmed with the national registry. Cardiac substructures were autosegmented on RT planning scans for retrospective structure and dose analysis, and their correlation with clinical factors was examined. Fine-Gray models were used to analyze relationships while considering the competing risk for death.

RESULTS Among 478 patients included in the study, 77 (16%) developed 88 MACE, with a median time to event of 16.3 months. A higher burden of pre-existing cardiac diseases was associated with an increased cumulative incidence of MACE (55% [95% CI: 12%-20%] vs 16% [95% CI: 35%-71%]; $P < 0.001$). Left atrial and left ventricular enlargement on RT planning scans was associated with cumulative incidence of atrial arrhythmia (14% [95% CI: 9%-20%] vs 4% [95% CI: 2%-8%]; $P = 0.001$) and heart failure (13% [95% CI: 8%-18%] vs 6% [95% CI: 3%-10%]; $P = 0.007$) at 5 years, respectively. However, myocardial infarction was not associated with the presence of coronary calcium (4.2% [95% CI: 2%-7%] vs 0% [95% CI: 0%-0%]; $P = 0.094$). No cardiac imaging metrics were found to be both clinically and statistically associated with survival.

CONCLUSIONS The present findings suggest that cardiac history and RT planning scan parameters may offer potential utility in prospectively evaluating cardiotoxicity risk following RT for patients with lung cancer. (JACC CardioOncol 2024;6:529-540) © 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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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

CT = computed tomography

CVRF = cardiovascular risk factor

LA = left atrial/atrium

LAD = left anterior descending coronary artery

LV = left ventricle/ventricular

MACE = major adverse cardiac event(s)

NSCLC = non-small cell lung cancer

OS = overall survival

RT = radiation therapy

Radiation-induced cardiotoxicity presents a complex challenge in the context of radiation therapy (RT) for non-small cell lung cancer (NSCLC), primarily because of the close anatomical proximity of the heart to the lung field. This proximity exposes the heart to incidental irradiation during treatment for NSCLC, leading to a spectrum of acute cardiac events and potential reductions in survival.[1] Unlike the historically recognized late effects seen with breast cancer RT,[2] symptomatic radiation cardiotoxicity can manifest within months to a few years following treatment for NSCLC.[3,4] This accelerated pattern of toxicity is attributed to higher doses of radiation received by the heart during treatment for NSCLC and the greater prevalence of baseline cardiovascular risk factors (CVRFs) among patients with NSCLC. The resulting cardiac damage encompasses muscle, connective tissue, vascular, and immune system pathology within the heart.

A recent guideline from the European Society of Cardiology's cardio-oncology committee[5] recommends comprehensive pretreatment evaluation of cardiac health status for all patients undergoing thoracic RT, including calculation of the 10-year cardiovascular risk score, to facilitate optimization of CVRFs.[5] Additionally, baseline transthoracic echocardiography is advised for patients scheduled for thoracic RT if the heart lies within the radiation dose distribution and there is a history of established cardiac disease.[6]

To optimize cardiovascular health and incorporate it into treatment planning, it is crucial to identify patients with lung cancer who are at risk for cardiac events. Targeting these strategies toward patients predisposed to future cardiac disease would be judicious, informing resource allocation priorities and minimizing the burden of unnecessary cardiac investigations during cancer diagnosis. In this study, we investigate established clinical cardiac parameters and computed tomography (CT)-based cardiac metrics for their association with the incidence of post-RT major adverse cardiac events (MACE) and mortality after RT for NSCLC.

Patients with lung cancer routinely undergo CT for diagnostic and staging purposes, as well as for RT planning. This provides an opportunity to evaluate baseline cardiovascular status using cross-sectional imaging features. Notably, coronary calcification has emerged as a prognostic factor following RT for NSCLC, whether assessed quantitatively or qualitatively.[6] Although cardiac geometry has demonstrated clinical implications in cardiology research, quantitative measures of cardiac dimensions have not been investigated within the context of RT.

Identifying patients at high risk for cardiac events prior to RT and incorporating this information into treatment planning could improve patient outcomes and inform personalized care strategies. The aim of this study was to assess the utility of routinely available clinical and imaging-based cardiac parameters in predicting MACE and mortality after RT in patients with NSCLC.

METHODS

PATIENTS AND TREATMENT. We conducted a retrospective analysis of 478 consecutive patients diagnosed with NSCLC who underwent curative-intent (chemo)radiation at the Cancer Centre Belfast City Hospital between January 1, 2015, and December 31, 2020. Clinical records were reviewed to gather baseline patient, tumor, and cardiovascular status details, as well as cardiovascular outcomes from the initiation of RT until death or last follow-up. Comprehensive details regarding the NI-HEART (Northern Ireland Cardiovascular Health Events After Radiation Therapy) study have been previously published[7] and are briefly outlined in the following discussion. Ethical approval was waived by the Belfast Health & Social Care Trust, and governance approvals were obtained for the study.

CARDIOVASCULAR BASELINE RISK AND MACE. CVRFs were defined as hypertension, dyslipidemia, diabetes mellitus, and smoking. Established cardiac disease encompassed a history of coronary artery disease, arrhythmia, or heart failure. We used the QRISK3 risk estimator to calculate scores for eligible patients, including those without histories of coronary heart disease (including angina or heart attack) or stroke or transient ischemic attack. QRISK3 is a predictive tool developed and validated using the UK population to estimate the 10-year risk for cardiovascular events, similar to the Framingham score.[8]

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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Post-RT MACE were graded according to the Common Terminology Criteria for Adverse Events version 5 scale and were verified by cardiology subspecialists (M.H., C.M., P.M.). MACE were defined as events exhibiting increases in grade compared with the 6 months preceding RT in patients with histories of the disease. Our analysis of post-RT MACE was focused specifically on atrial arrhythmia, acute heart failure, and myocardial infarction, as pericardial and valve-related outcomes were infrequently and inconsistently included in echocardiography reports.

RT PLANNING SCAN CARDIAC CHARACTERISTICS. The outer aspect of the cardiac chambers and great vessels were autosegmented on RT planning scans using Eclipse (Varian Medical Systems) with a validated deep learning-based tool,[9] following the Feng atlas method.[10] Manual delineation of all other structures was performed by a clinical oncologist (G.M.W.). A composite cardiac base structure was created, including the right atrium, superior vena cava, aortic root, and proximal left anterior descending coronary artery (LAD) and right coronary artery,[11] as dose to this subregion has been consistently shown to relate to prognosis in this patient population.

A limited number of chamber volumes, both isolated and in combination,[12-15] were extracted from RT planning scans for analysis. These volumes were selected on the basis of their unadjusted predictive capacity to minimize multiple testing. Coronary artery calcification (CAC) was graded according as none, mild, moderate, or severe by 1 of 4 observers (G.M.W., N.H., B.K., M.M.), following an international grading system.[16] Additionally, 5% of CAC assessments were independently verified by an interventional cardiologist (P.M.). If the RT planning scan was contrast enhanced, staging positron emission tomography/CT was used instead.

STATISTICAL ANALYSIS. Patient characteristics were summarized using descriptive statistics, including the median with 25th and 75th percentiles (Q1-Q3) or counts and percentages. The cumulative incidence of cardiac events at 5 years was analyzed using Gray's test[17] to account for the competing risk for death in univariable analysis. Additionally, the Fine-Gray model[18] was used to adjust for relevant cardiovascular covariates, including cardiac structure characteristic, dose metrics, CVRFs, and established cardiac diseases.

CVRFs and established cardiac disease were categorized as 0 to 2 vs 3 or 4 and as 0 or 1 vs 2 or 3. This categorization reflects the grouping of patients according to the number of CVRFs and early cardiac diseases. Patients were followed until the date of the first cardiac event, death, or last known follow-up, whichever occurred first. Results are presented as the cause-specific HR with 95% CI.[17,18]

For atrial arrhythmia and heart failure outcomes, the selection of cardiac structures taken forward was based on the highest ranking Harrell's C index at maximum available follow-up to identify the most appropriate structural feature among physiologically relevant options. To account for radiation dose, established metrics were used, including left atrial (LA) maximum dose,[19] left ventricular (LV) mean dose,[20] and the volume receiving ≥15 Gy for the LAD.[21]

In addition to age and sex, known risk factors for inclusion were coronary artery disease, alcohol consumption, antiarrhythmic drug use, and a history of heart failure and use of angiotensin-axis medications for heart failure. Kaplan-Meier analysis was used to assess the effect of cardiac parameters on overall survival (OS), using the time between the RT start date and the date of death or last follow-up.

These analyses were conducted for all patients and stratified by whether the LAD volume receiving ≥15 Gy was >10% or <10%[21] and whether the heart base maximum dose was >19.5 or <19.5 Gy (McWilliam et al., personal communication). Cardiac chamber volumes were dichotomized at the median, and CAC grades were grouped into CAC positive (mild, moderate, or severe) and CAC negative (none).

All statistical analyses were performed using Prism version 9 (GraphPad) or R Studio (R Core Team).

RESULTS

PATIENT CHARACTERISTICS. Of the 535 patients treated during this period, 478 were eligible for inclusion in the study, with a median follow-up duration of 47.7 months (Q1-Q3: 43.6-51.6 months). The median age of the cohort was 70 years (Q1-Q3: 64-76 years) (**Table 1**), and the majority of patients received curative-intent RT alone (326 [58%]), planned using intensity-modulated or volumetric arc techniques (339 [71%]). The median mean heart dose was 7.0 Gy (Q1-Q3: 3.0-12.4 Gy).

Table 1 illustrates the prevalence of CVRFs and established cardiac diseases among the study population. Among eligible patients (n = 277), the median QRISK3 score was 19% (Q1-Q3: 12%-27%). Serum lipid analysis was conducted in 403 patients (84%) at a median of 9.5 months (Q1-Q3: 4.5-19.5 months) prior to RT. Glycated hemoglobin testing was performed in 98 patients (95%) with diabetes mellitus at a median of 4.4 months (Q1-Q3: 2.6-8.5 months) prior to RT.

Various medications were regularly prescribed in this cohort, including statins (283 [59%]),

TABLE 1 Patient Characteristics

Patient/tumor factors	
Patients	478
Age, y	70 (64-76)
Sex	
Female	224 (47)
Male	254 (53)
Performance status	
0	45 (9)
1	234 (49)
2	176 (37)
3	23 (5)
CCI	5.0 (5.0-6.0)
T stage	
0	20 (4)
1	117 (24)
2	134 (28)
3	101 (21)
4	106 (22)
N stage	
0	152 (32)
1	78 (16)
2	210 (44)
3	38 (8)
Subtype	
Squamous cell carcinoma	223 (43)
Adenocarcinoma	153 (32)
Clinical	66 (14)
Other	36 (8)
Dose fractionation	
52-55 Gy/19-20#	461 (96)
60-66 Gy/30-33#	14 (3)
72-79 Gy/40-44#	3 (1)
Chemotherapy	
No	325 (68)
Concurrent	50 (10)
Neoadjuvant	100 (21)
Neoadjuvant concurrent	3 (1)
Adjuvant durvalumab	5 (1)

Continued in the next column

TABLE 1 Continued

Cardiac status	
Patients	478
Hypertension	242 (51)
Dyslipidemia	272 (57)
Diabetes mellitus	
No	375 (78)
Type 1	6 (1)
Type 2	94 (20)
Prediabetes	3 (1)
Smoking	
Never	29 (6)
Previous	308 (64)
Current	152 (32)
Pack-years	40.0 (30.0-50.0)
QRISK3 score[a]	18.7 (11.9-27.2)
Coronary artery disease[b]	
No	403 (84)
Stable angina	57 (12)
Acute coronary syndrome	66 (14)
Any	109 (23)
Arrhythmia[b]	
No	426 (89)
Atrial fibrillation	36 (8)
Ventricular arrhythmia	5 (1)
Other	13 (3)
Any	52 (11)
Heart failure	41 (9)
Cerebrovascular disease[b]	
No	411 (86)
Ischemic	33 (7)
Hemorrhagic	3 (1)
Transient ischemic attack	30 (6)
Amaurosis fugax	1 (<1)
Any	62 (13)

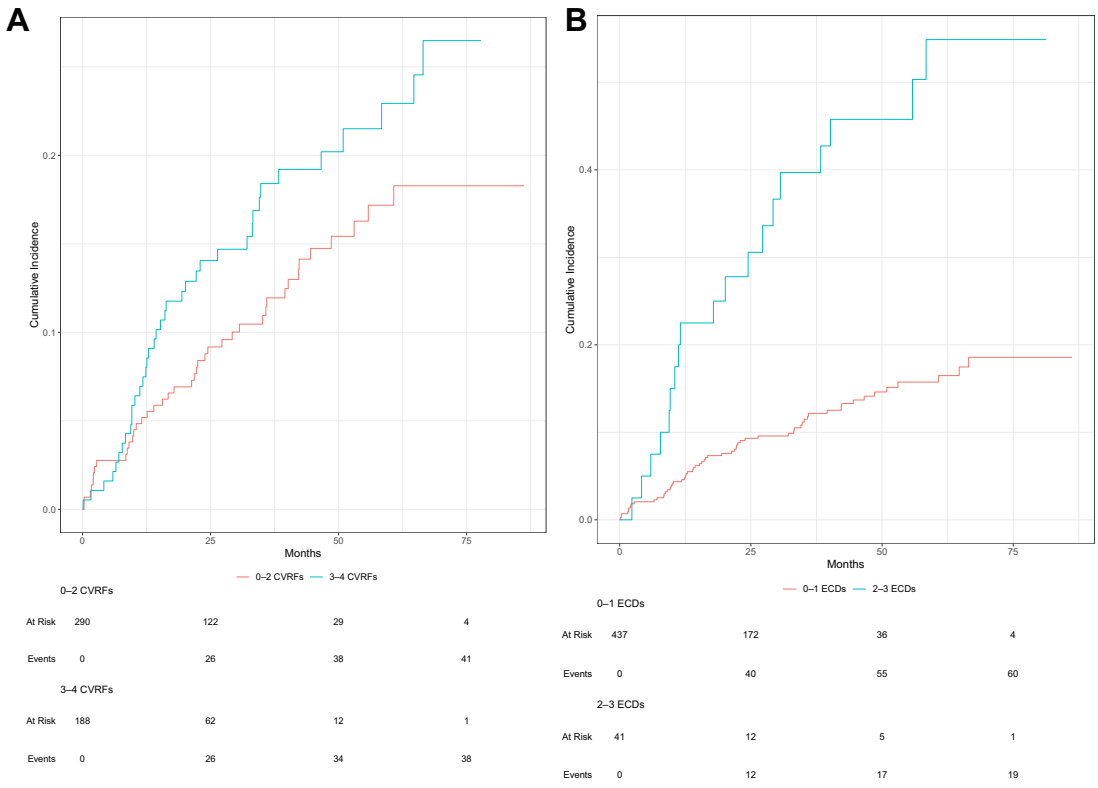
Values are n, median (Q1-Q3), or n (%). Patient characteristics at baseline are listed, including details of tumor location and cardiac features. [a]Available for 277 patients only. [b]More than 1 response per patient was possible.
CCI = Charlson comorbidity index.

antithrombotic agents (223 [46%]), angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors (160 [33%]), beta-blockers (128 [27%]), and oral nitrates (36 [8%]). Some patients received or were under the care of a cardiologist prior to RT (102 [21%]). The median OS for the cohort was 23.0 months (Q1-Q3: 10.7-34.9 months).

MACE. Among the cohort, 77 patients (16%) experienced 88 MACE, with a median time to event of 16.3 months (Q1-Q3: 9.5-33.9 months) and a median grade of 3 (Q1-Q3: 3.0-3.5). Specifically, atrial arrhythmia, heart failure, and myocardial infarction were observed in 38, 34, and 16 patients, respectively. Of these MACE, 15 cases of heart failure and 1 case of myocardial infarction were observed in patients with histories of the same event at a lower grade, while all other events represented initial diagnoses. Notably, 9 patients experienced 2 events, and 1 patient experienced 3 events.

BASELINE CLINICAL RISK AND ASSOCIATIONS WITH MACE. The cumulative incidence of MACE was higher for patients with greater numbers of established cardiac diseases (55% [95% CI: 35%-71%] for 2-3 cardiac diseases vs 16% [95% CI: 12%-20%] for 1-2, $P < 0.001$). However this was not the case for CVRFs (23% [95% CI: 16%-30%] for 3-4 risk factors vs 17% [95% CI: 12%-23%] for 0-2, $P = 0.077$) (Figures 1A and 1B). Neither CVRFs nor established cardiac diseases was significantly associated with OS in Kaplan-Meier analysis. The HRs for CVRFs and established cardiac diseases were 0.89 (95% CI: 0.71-1.11; $P = 0.29$) and 1.14 (95% CI: 0.79-1.64; $P = 0.51$), respectively. The C index of QRISK3 scores for MACE was 0.62 (95% CI: 0.53-0.71)

FIGURE 1 Baseline Cardiovascular Factors and Risk for Cardiac Events and Death



The cumulative incidence of post-radiation therapy cardiac events by (A) cardiovascular risk factors (CVRFs) (0-2 vs 3 or 4) and (B) established cardiac diseases (ECDs) (0 or 1 vs 2 or 3) after adjustment for the competing risk for death. Gray tests were performed for the 60-month time point.

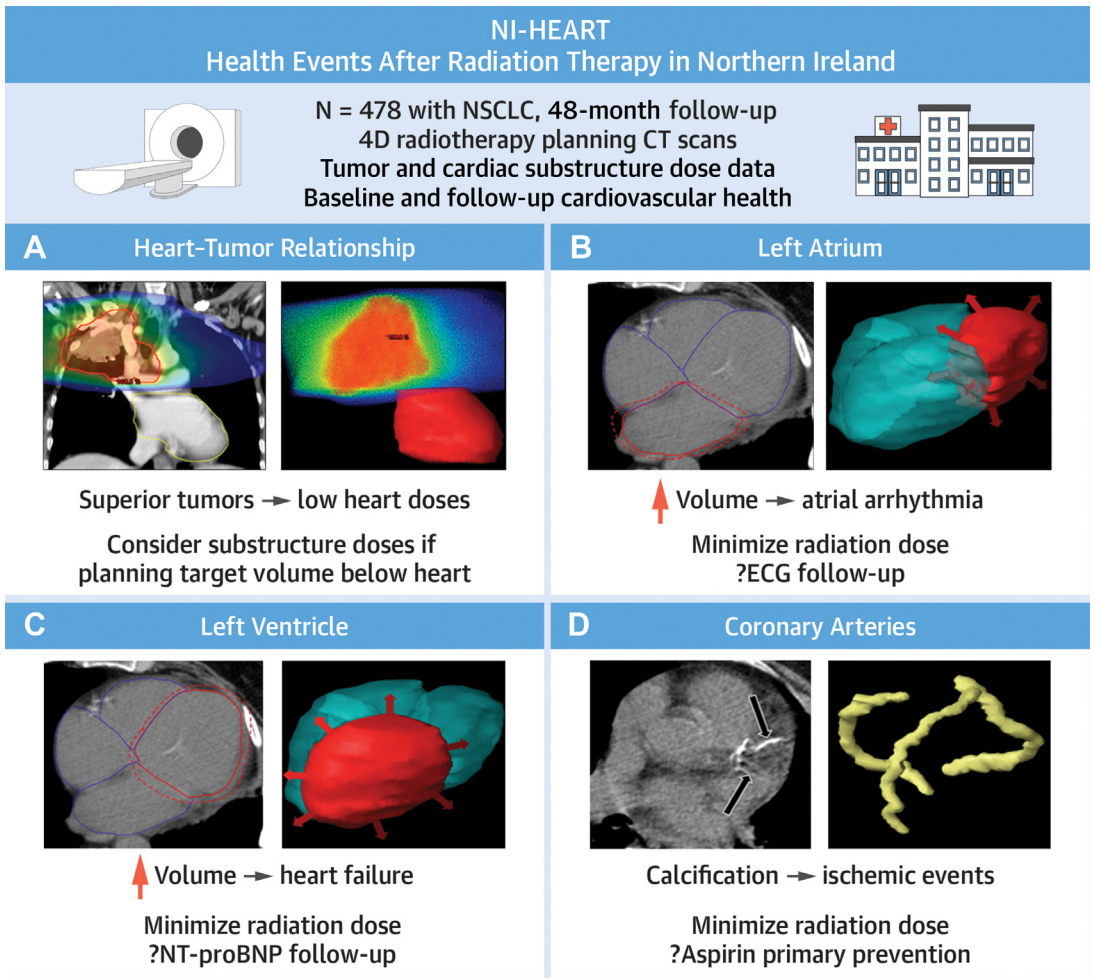
at 53.0 months. Higher QRISK3 scores, when dichotomized at the median, were associated with a greater cumulative incidence of MACE at 5 years: 22% (95% CI: 14%-30%) compared with 12% (95% CI: 7%-20%; $P = 0.042$). However, these scores did not predict worse OS (HR: 0.81; 95% CI: 0.61%-1.08%; $P = 0.27$).

TUMOR LOCATION AND ASSOCIATIONS WITH CARDIAC DOSE AND MACE. The majority of patients (78% [n = 374]) had planning target volumes below the superior aspect of the heart, resulting in significantly higher incidental radiation doses to cardiac substructures compared with those with targets above the heart ($P < 0.001$ for all substructures) (Supplemental Table 1). Specifically, for structures associated with MACE, the differences between superior and inferior tumor locations were notable: the LA (median 1.3 Gy vs 14.9 Gy), the LV (median 0.5 Gy vs 3.8 Gy), and the LAD (median 0.0 Gy vs 12.3 Gy). The impact of tumor height on the radiation dose distribution is summarized in the **Central Illustration**.

Interestingly, the cumulative incidence of MACE was similar regardless of tumor location: 19% (95% CI: 15%-24%) for tumors below the heart vs 23% (95% CI: 12%-26%) for tumors above ($P = 0.80$). Similarly, OS rates were also comparable, with a HR of 1.05 (95% CI: 0.81%-1.37%; $P = 0.55$) (Supplemental Figure 1). This similarity in OS may be potentially influenced by a higher burden of established cardiac diseases in the latter group, although this difference was not statistically significant (Supplemental Table 2).

CARDIAC STRUCTURAL CHARACTERISTICS AND ASSOCIATIONS WITH MACE. The **Central Illustration** highlights multiple functionally relevant scan parameters correlating with MACE. Baseline LA volume showed the highest predictive capacity for atrial arrhythmia (C index = 0.70; 95% CI: 0.61-0.78) at 66.5 months (Supplemental Table 3). The median LA volume was 98.1 mL (Q1-Q3: 81.3-120 mL). A significantly higher cumulative incidence of atrial

CENTRAL ILLUSTRATION **Overall Study Design and Relevant Radiotherapy Planning Scan Characteristics With Suggested Clinical Management Options**



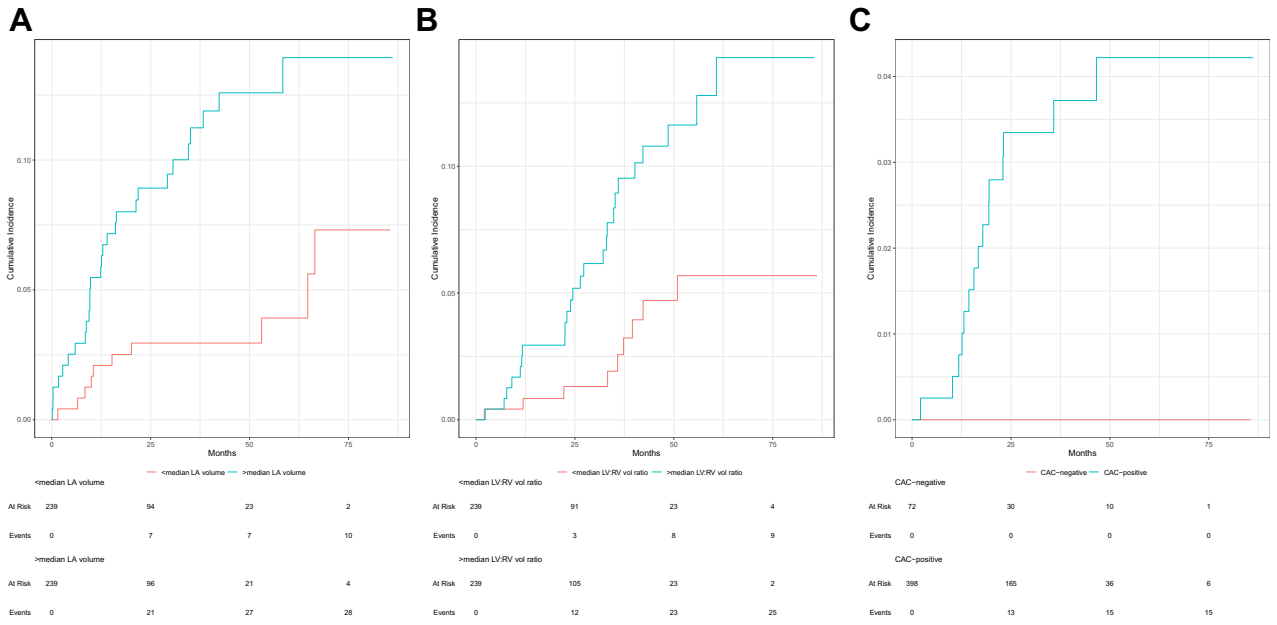
Walls GM, et al. JACC CardioOncol. 2024;6(4):529-540.

(A) No craniocaudal tumor-heart overlap is demonstrated in the coronal plane (left) and in 3 dimensions from the anterior perspective (right) in a representative patient. (B) The left atrium is demonstrated in the axial plan (left) and in 3 dimensions from the left perspective (right) in a representative patient. (C) The left ventricle is demonstrated in the axial plan (left) and in 3 dimensions from the left perspective (right) in a representative patient. (D) Coronary artery calcification of the left anterior descending and left circumflex coronary arteries is demonstrated (black arrows) in the axial plane (left) and the 3-dimensional geometry of the coronary arteries from the anterior perspective (right) in a representative patient. 4D = 4-dimensional; CT = computed tomographic; ECG = electrocardiographic; NI-HEART = Northern Ireland Cardiovascular Health Events After Radiation Therapy; NSCLC = non-small cell lung cancer; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

arrhythmia was observed for LA volumes greater than the median compared with less than the median at 5 years: 14% (95% CI: 9%-20%) vs 4% (95% CI: 2%-8%) ($P = 0.001$) (**Figure 2A**). LA volume remained significantly associated with atrial arrhythmia events after accounting for clinically relevant covariates and the competing risk for death ($P = 0.024$) (**Table 2**). Higher LA volume did not show a significant association with OS on Kaplan-Meier analysis (HR: 0.87; 95% CI: 0.71-1.08; $P = 0.21$), except after adjusting for heart base dose in patients with low median LA volumes (Supplemental Figure 2). Notably, no significant association was observed with LAD dose.

The chamber geometry metric with the highest predictive capacity for heart failure was the baseline LV/RV volume ratio (C index = 0.71; 95% CI: 0.60-0.82) at 60.8 months (Supplemental Table 3). The median LV volume was 218.8 mL (Q1-Q3: 180.5-

FIGURE 2 **Radiation Therapy Scan Characteristics and Risk for Cardiac Events**



Cumulative incidence of the atrial arrhythmia (A), heart failure (B), and myocardial infarction (C) after adjustment for the competing risk for death, stratified by relevant cardiac characteristics on radiation therapy planning scan. Gray tests were performed for the 60-month time point. LA = left atrial; LV = left ventricular; RV = right ventricular.

266.6 mL), and the median RV volume was 139 mL (Q1-Q3: 118.7-163.1 mL), resulting in a median LV/RV ratio of 1.55 (Q1-Q3: 1.43-1.72 mL). The cumulative incidence of heart failure was significantly higher for LV/RV ratios greater than the median compared with less than the median at 5 years: 13% (95% CI: 8%-18%) vs 6% (95% CI: 3%-10%) ($P = 0.007$) (**Figure 2B**). A higher LV/RV volume ratio was associated with heart failure events after accounting for clinically relevant covariates and the competing risk for death ($P = 0.028$) (**Table 3**). However, the LV/RV volume ratio was not associated with OS on Kaplan-Meier analysis (HR: 1.11; 95% CI: 0.90-1.37; $P = 0.33$) across the whole cohort or after adjusting for LAD dose, but it was after adjusting for heart base dose (Supplemental Figure 3).

CAC was observed in the majority of patients (85%), graded as mild (32%), moderate (32%), or severe (21%), with no changes in grading upon verification. Eight patients lacked noncontrast scans. Myocardial infarction cases were graded as mild, moderate, or severe CAC in 67%, 20%, and 19%, respectively, compared with 6% for CAC-negative cases. Numerically, there was a higher cumulative incidence of myocardial infarction among CAC-positive patients compared with CAC-negative patients at 5 years: 4.2% (95% CI: 2%-7%) vs 0% (95% CI: 0%-0%) ($P = 0.094$), although the difference was not statistically significant (**Figure 2C**). Multivariable analysis was not feasible, because of the low event rate. CAC positivity was not associated with OS on Kaplan-Meier analysis (HR: 1.08; 95% CI: 0.80-1.45; $P = 0.63$), except after adjusting for the heart base dose in CAC-positive cases (Supplemental Figure 4), with no significant association observed with LAD dose.

MULTIVARIABLE ANALYSIS FOR OS. In a Cox regression model for OS, only the association of atrial volume reached statistical significance, although the magnitude of effect was not clinically significant (HR: 0.992; 95% CI: 0.987-0.999; $P = 0.002$) in terms of imaging features, as shown in **Table 4**. Notably, several anticipated clinical factors (performance status, T stage, and chemotherapy) and RT-related factors (heart base dose and statin therapy) were also found to be statistically significantly associated with OS.

DISCUSSION

Radiation cardiotoxicity manifests as MACE in the months to years following definitive RT for NSCLC,

TABLE 2 Fine and Gray Regression Model for Post-Radiation Therapy Atrial Arrhythmias

	N	Number of Events	Adjusted HR (95% CI)	*P* Value
Age	478	38	1.00 (0.96-1.04)	0.97
Sex				
Female	224	15	1.00 (reference)	
Male	254	23	0.96 (0.46-1.98)	0.90
LA volume	478	38	1.01 (1.00-1.02)	0.024
LA Dmax	478	38	1.01 (0.99-1.03)	0.290
CAD	478	38	1.92 (0.93-4.00)	0.080
Alcohol, units/wk				
None	296	22	1.00 (reference)	
0-6	123	11	1.45 (0.67-3.13)	0.35
≥7	59	7	1.26 (0.47-3.34)	0.65
Antidysrhythmic agent	478	38	0.92 (0.44-1.90)	0.81

Multivariable regression analysis for post-radiation therapy atrial arrhythmias, adjusting for LA volume and clinically relevant cardiovascular and dosimetric factors, with death considered a competing risk.

CAD = coronary artery disease; Dmax = maximum dose; LA = left atrial.

significantly affecting patient survivorship.[22] Despite not having metastatic disease, patients with NSCLC eligible for definitive RT have poor OS (eg, a median of 23 months in this study). Therefore, urgent identification of holistic approaches to optimizing health is crucial.

In this study, baseline cardiac status, as assessed by the burden of pre-existing established cardiac diseases and features from routine pre-RT imaging, was associated with MACE. The established cardiovascular stratification tool, QRISK3, demonstrated modest utility in identifying patients at high risk for MACE.

Our findings align with those of recent studies. Atkins et al[21] showed that the 2-year rate of post-RT MACE was significantly higher for patients with known cardiac comorbidities (12% vs 3%). Similarly, Dess et al[4] observed a greater 2-year rate of grade 3 cardiac events in patients with pre-existing heart disease (21% vs 7%), and Yegya-Raman et al[20] reported a higher 4-year incidence of symptomatic cardiac events with baseline coronary artery disease (52% vs 23%). Interestingly, 2 smaller studies (n = 76 and n = 120) with low event rates (4% and 8%) failed to identify an association between baseline cardiac disease and radiation cardiotoxicity.[23,24]

To our knowledge, this study is the first to examine the spatial relationship between the heart and tumor in the context of radiation cardiotoxicity outcomes. Given that RT is typically delivered in the axial plane with patients in the supine position, we hypothesized that tumors not extending caudally to the level of the heart would result in lower incidental radiation doses to substructures. Although this hypothesis was supported by our findings, we observed that the rate of MACE was not significantly lower than in cases in which tumors overlapped the craniocaudal height of the heart. This unexpected observation could potentially be explained by the higher prevalence of established cardiac diseases in cases in which the tumor was positioned above the heart or other unaccounted factors in this retrospective analysis. This observation is consistent with findings from a North American group that reported no significant differences in substructure doses between patients with and those without MACE in a small, matched case analysis.[25]

This study is also the first, to our knowledge, to investigate cardiac substructure volumes for the risk for endpoint-specific radiation cardiotoxicity. Although atrial arrhythmias span a wide range of mechanisms and pathologic tissues within the atria, LA enlargement has been identified as an important predictor for future arrhythmias in cardiology studies.[26] Using data derived from the RT planning CT, LA volume was identified as the best predictor for pooled atrial arrhythmias of different subtypes. This association remained significant after adjusting for key clinical covariates such as pre-existing coronary disease, alcohol use, and radiation dose to this structure.

Similarly, a notable relationship was observed for the LV concerning the outcome of heart failure. LV enlargement, which is indicative of cardiac pump dysfunction, was found to be associated with heart failure after RT. Enlargement of both LA and LV structures exhibited a higher cumulative incidence of their respective MACE in this cohort.

On the basis of routinely available RT imaging, the presence of CAC was not associated with an increased

TABLE 3 Fine and Gray Regression Model for Post-Radiation Therapy Heart Failure

	N	Number of Events	Adjusted HR (95% CI)	*P* Value
Age	478	34	1.05 (1.01-1.09)	0.012
Sex				
Female	224	15	1.00 (reference)	
Male	254	19	0.75 (0.49-1.48)	0.41
LV/RV volume ratio	478	34	4.51 (1.18-17.23)	0.028
LV mean dose	478	34	1.05 (1.01-1.09)	0.027
Heart failure	478	34	1.44 (0.46-3.14)	0.002
Angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors	478	34	1.25 (0.60-2.60)	0.55

Multivariable regression analysis for post-radiation therapy heart failure, adjusting for LV/RV volume ratio and clinically relevant cardiovascular and dosimetric factors, with death as a competing risk.

LV = left ventricular; RV = right ventricular.

cumulative incidence of acute myocardial ischemic events post-RT, after adjusting for the competing risk for death. This contrasts with recent studies[27,28] that demonstrated such an association. This finding may be attributed to the small number of events or could be related to the grading of calcification on motion-adapted RT planning scans, for which there is currently no agreed protocol. Analyzing the cohort as CAC positive and CAC negative for an overall OS analysis also revealed no difference, consistent with other recent studies.[28,29] However, a study using quantitative calcium assessment showed that this more detailed approach was prognostic for OS,[30] suggesting that quantitative calcium scoring may offer greater utility compared with semiquantitative methods.

The absence of associations between the metrics and overall OS likely reflects the multifactorial nature of lung cancer mortality, involving cardiac morbidities, noncardiac comorbidities, cancer relapse, and treatment toxicity. Only 3 small studies in NSCLC have shown that acute cardiac events are associated with reduced OS,[4,20,24] consistent with cardiac events' not being closely linked to cardiotoxicity-related deaths. It is possible that cardiac parenchymal damage remains subclinical until the onset of acute physiological systemic stress, such as sepsis, manifesting to impair recovery and increase the risk for death from the medical insult.[31] A recent study on physical functionality might provide supportive evidence for this phenomenon.[32] Notably, a greater LA volume was associated with a slight but statistically significant improvement in survival on the basis of the multivariable analysis, possibly because atrial arrhythmias may prompt cardiovascular optimization while carrying a low mortality risk themselves.

Heart chamber volumes are typically assessed using dedicated cardiac imaging modalities such as echocardiography, but there are limited data on this in NSCLC. One study showed that the functional metric of global longitudinal strain was significantly associated with MACE, whereas LV ejection fraction was not predictive.[33] In a study of 112 patients with stage III NSCLC treated with dose-escalated 3-dimensional conformal chemoradiation, the cardiac event rate was 18%. The CLARITY (Cardiotoxicity in Locally Advanced Lung Cancer Patients Treated With Chemoradiation Therapy; NCT04305613) study, an ongoing multicenter North American trial recruiting 210 patients with stage II or III NSCLC undergoing chemoradiation, includes serial echocardiography, positron emission tomography/CT, and quality-of-life assessments. This study is likely to provide high-quality data to assess the utility of such tests in NSCLC RT.

A paper released alongside the 2022 International Cardio-Oncology Society consensus also highlighted

TABLE 4 Cox Proportional Hazards Model for Survival

	N	Number of Deaths	Adjusted HR (95% CI)	*P* Value
Age	470	333	1.01 (1.00-1.04)	0.019
Gender				
Female	222	145	1.00 (reference)	
Male	248	188	1.56 (1.21-2.01)	<0.001
Performance status				
0	44	25	1.00 (reference)	<0.001
1	229	170	2.41 (1.53-3.81)	<0.001
2	174	124	2.43 (1.51-3.91)	0.002
3	23	14	3.09 (1.51-6.34)	<0.001
T stage				
0	19	8	1.00 (reference)	
1	117	76	1.47 (0.68-3.22)	0.33
2	133	92	1.40 (0.65-3.05)	0.39
3	98	76	1.81 (0.83-3.94)	0.14
4	103	81	2.45 (1.12-5.34)	0.024
N stage				
0	152	106	1.00 (reference)	
1	77	56	0.85 (0.60-1.21)	0.37
2	206	146	0.83 (0.62-1.13)	0.24
3	35	25	0.76 (0.45-1.27)	0.30
Subtype				
Adenocarcinoma	151	102	1.00 (reference)	
Squamous cell	217	162	1.17 (0.90-1.53)	0.23
Clinical	66	42	0.78 (0.51-1.19)	0.25
Other	36	27	0.97 (0.63-1.52)	0.92
Chemotherapy[a]				
None	324	236	1.00 (reference)	
Neoadjuvant	94	72	0.88 (0.64-1.21)	0.44
Concurrent	52	25	0.63 (0.40-1.00)	0.048
Heart Dmax	470	333	1.01 (1.00-1.01)	0.033
Lung V20	470	333	1.03 (1.01-1.05)	0.001
CVRFs				
0	3	1	1.00 (reference)	0.17
1	102	76	4.12 (0.54-31.75)	0.28
2	183	127	3.04 (0.40-23.16)	0.21
3	141	101	3.70 (0.48-28.35)	0.20
4	41	28	3.85 (0.48-30.63)	0.17
Established cardiac diseases[b]				
0	305	212	1.00 (reference)	
1	124	93	1.17 (0.89-1.54)	0.25
2	32	21	1.06 (0.65-1.75)	0.81
3	9	7	2.14 (0.86-5.35)	0.10
Statin therapy	279	188	0.65 (0.51-0.83)	0.001
Left atrial volume	470	333	0.992 (0.987-0.997)	0.002
Ventricular volume ratio	470	333	0.96 (0.61-1.53)	0.88
Coronary artery calcification	470	333	1.10 (0.76-1.59)	0.61

Multivariable regression Cox proportional hazards model for overall survival among all patients with coronary artery calcium grading available (n = 470), adjusting for clinically relevant cardiovascular and oncological factors. [a]Patients receiving both neoadjuvant and concurrent chemotherapy were classified as having had concurrent chemotherapy. [b]History of coronary artery disease, arrhythmia, or heart failure.

CVRF = cardiovascular risk factor; Dmax = maximum dose; V20 = organ volume receiving ≥20 Gy.

other imaging options for cardiac assessment.[34] Cardiac magnetic resonance imaging remains a limited resource but may offer a superior method for evaluating cardiac baseline, with encouraging preliminary data.[35] Data for cardiac CT are lacking for intrathoracic cancer. Cardiac CT typically involves electrocardiographic gating and breath-hold for cardiorespiratory motion management, and when combined with beta-blocker administration and high-resolution protocols, it provides sufficient scan quality for detailed coronary artery characterization.[36,37] Results from the ACCOLADE (Avoiding Cardiac Toxicity in Lung Cancer Patients Treated With Curative-Intent Radiotherapy; NCT03645317) trial, a prospective cohort study evaluating cardiac CT alongside matched echocardiography and serial blood markers, are eagerly awaited.

Previous literature on troponin and B-type natriuretic peptide is confined largely to small studies of mixed primary tumor types, in which statistically insignificant transient increases were noted.[38,39] A recent larger study specific to NSCLC, involving baseline N-terminal pro-B-type natriuretic peptide levels for 200 patients, showed an association between blood marker levels and electrocardiogram changes.[40] However, this represents only the third NSCLC-specific study examining conduction changes.[19,41]

As cardiac substructure autosegmentation becomes increasingly integrated into clinical RT workflows,[9] chamber metrics represent a readily available, simple, and pragmatic method with enormous potential for quantitatively screening patients, along with coronary calcification assessment. The potential cost-effective clinical opportunities related to these data encompass education, primary prevention, dosimetry, and enhanced monitoring (see the **Central Illustration**). To complement the pretreatment assessment of CVRFs, established cardiac diseases, and QRISK3 scores, along with the evaluation of RT imaging, select cases could undergo routine blood marker and electrocardiographic assessments during follow-up appointments after treatment. Patients and their primary physicians should be informed about the results of their baseline cardiovascular assessments. Aspirin and statin therapy could be considered for patients with CAC, particularly if a coronary artery lies within or near high-dose regions.

For patients with tumors located inferior to the upper limit of the heart, minimizing the dose to cardiac substructures may be advisable if safely achievable, with possible prioritization of substructures exhibiting abnormalities described herein. However, it is important to note the lack of prospective evidence for this approach and outstanding data for the dosimetric safety and clinical benefits of prioritizing specific substructures over others.

In summary, our study demonstrates that established cardiology parameters can be used in thoracic radiation oncology to predict cardiac morbidity after RT. These findings align with several European recommendations,[5] such as baseline evaluations of CVRFs (including a risk score) and established cardiac disease, supported by NSCLC-specific evidence. Additionally, although the association was not statistically significant ($P = 0.094$), that the cumulative risk for post-RT myocardial infarction was 4.2% among patients with CAC and 0% among those without potentially lends some support to the International Cardio-Oncology Society consensus statement[42] that advises CAC evaluation before initiating cancer therapy.

Finally, we introduce novel parameters, including cardiac chamber volumes, as baseline predictors of specific cardiac events: LA volume for supraventricular arrhythmia and LV/RV volume ratio for cardiac failure. When combined with CVRFs, established cardiac diseases, and CAC assessments, these chamber volume metrics identified in our study may help identify a high-risk population. Patients identified as high risk may benefit from cardiovascular assessments before RT and personalized radiation treatment planning that account for substructure-specific risks, such as individualized substructure dose-sparing prioritization.

STUDY LIMITATIONS. Apart from the retrospective design, the primary limitation of this study is the relatively low incidence of MACE, especially concerning myocardial infarction, relative to the number of statistical tests performed on the cohort. The low rates of chemotherapy contribute to isolating the effects of radiation but also limit the generalizability of the findings. Therefore, caution is advised when interpreting the results of this study, and validation in large prospective studies during the adjuvant durvalumab era is necessary.

CONCLUSIONS

Radiation cardiotoxicity represents a significant clinical concern after treatment in patients with unresectable NSCLC, often resulting in hospitalizations and premature mortality. This study's RT-treated cohort underscores the utility and value of cardiac history and planning computed tomography

scan parameters for prospectively assessing the risk for cardiotoxicity after definitive RT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Clinical risk factors and routine RT imaging contribute to predicting the risk for cardiac events after lung cancer RT, although not OS.

TRANSLATIONAL OUTLOOK: Further studies are needed to optimize and monitor baseline risk assessment and to explore how RT planning strategies can incorporate this information.

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