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Association of Left Anterior Descending Coronary Artery Radiation Dose With Major Adverse Cardiac Events and Mortality in Patients With Non–Small Cell Lung Cancer

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IMPORTANCE Radiotherapy accelerates coronary heart disease (CHD), but the dose to critical cardiac substructures has not been systematically studied in lung cancer.

OBJECTIVE To examine independent cardiac substructure radiotherapy factors for major adverse cardiac events (MACE) and all-cause mortality in patients with locally advanced non–small cell lung cancer (NSCLC).

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort analysis of 701 patients with locally advanced NSCLC treated with thoracic radiotherapy at Harvard University–affiliated hospitals between December 1, 2003, and January 27, 2014, was performed. Data analysis was conducted between January 12, 2019, and July 22, 2020. Cardiac substructures were manually delineated. Radiotherapy dose parameters (mean, maximum, and the volume [V, percentage] receiving a specific Gray [Gy] dose in 5-Gy increments) were calculated. Receiver operating curve and cut-point analyses estimating MACE (unstable angina, heart failure hospitalization or urgent visit, myocardial infarction, coronary revascularization, and cardiac death) were performed. Fine and Gray and Cox regressions were adjusted for preexisting CHD and other prognostic factors.

MAIN OUTCOMES AND MEASURES MACE and all-cause mortality.

RESULTS Of the 701 patients included in the analysis, 356 were men (50.8%). The median age was 65 years (interquartile range, 57-73 years). The optimal cut points for substructure and radiotherapy doses (highest C-index value) were left anterior descending (LAD) coronary artery V15 Gy greater than or equal to 10% (0.64), left circumflex coronary artery V15 Gy greater than or equal to 14% (0.64), left ventricle V15 Gy greater than or equal to 1% (0.64), and mean total coronary artery dose greater than or equal to 7 Gy (0.62). Adjusting for baseline CHD status and other prognostic factors, an LAD coronary artery V15 Gy greater than or equal to 10% was associated with increased risk of MACE (adjusted hazard ratio, 13.90; 95% CI, 1.23-157.21; $P = .03$) and all-cause mortality (adjusted hazard ratio, 1.58; 95% CI, 1.09-2.29; $P = .02$). Among patients without CHD, associations with increased 1-year MACE were noted for LAD coronary artery V15 Gy greater than or equal to 10% (4.9% vs 0%), left circumflex coronary artery V15 Gy greater than or equal to 14% (5.2% vs 0.7%), left ventricle V15 Gy greater than or equal to 1% (5.0% vs 0.4%), and mean total coronary artery dose greater than or equal to 7 Gy (4.8% vs 0%) (all $P \leq .001$), but only a left ventricle V15 Gy greater than or equal to 1% increased the risk among patients with CHD (8.4% vs 4.1%; $P = .046$). Among patients without CHD, 2-year all-cause mortality was increased with an LAD coronary artery V15 Gy greater than or equal to 10% (51.2% vs 42.2%; $P = .009$) and mean total coronary artery dose greater than or equal to 7 Gy (53.2% vs 40.0%; $P = .01$).

CONCLUSIONS AND RELEVANCE The findings of this cohort study suggest that optimal cardiac dose constraints may differ based on preexisting CHD. Although the LAD coronary artery V15 Gy greater than or equal to 10% appeared to be an independent estimator of the probability of MACE and all-cause mortality, particularly in patients without CHD, left ventricle V15 Gy greater than or equal to 1% appeared to confer an increased risk of MACE among patients with CHD. These constraints are worthy of further study because there is a need for improved cardiac risk stratification and aggressive risk mitigation strategies.

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Supplemental content

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Development of cardiac adverse events is a well-recognized risk following radiotherapy in patients with locally advanced non–small cell lung cancer (NSCLC).[1-5] Radiation exposure of arterial vessels alters the natural history of coronary artery disease by inducing inflammation that subsequently triggers accelerated progression of the disease.[6,7] Cardiac events in patients with NSCLC are common, are associated with cardiac radiation dose and baseline cardiac risk,[3,4] and estimate the probability of mortality.[8-10] These studies have evaluated radiation exposure to the entire heart with measures such as mean heart dose (MHD). However, MHD has been shown to be a poor surrogate for coronary artery dose exposure,[11] thereby precluding direct association of injury with substructures and specific events (eg, coronary dose exposure associating with coronary events). Thus, cardiac substructure dose constraints to determine the probability of major adverse cardiac events (MACE) and mortality in patients with NSCLC are needed.

Locoregional recurrence remains a significant barrier to prolonging survival in patients with locally advanced NSCLC.[12-14] In an attempt to overcome this challenge, radiation dose escalation was performed in Radiation Therapy Oncology Group 0617; however, the high-dose arm of the trial was associated with worse survival, and secondary analyses suggested that higher cardiac doses, among other factors, may have contributed to the lower survival rate.[8,10] There has since been increasing interest in characterizing the association between cardiac dose and outcomes in lung cancer, although these analyses have been limited by small sample size, nonstandard or inconsistent cardiac end points, absence of cardiac substructure data, and variable assessment of baseline cardiac risk.[1,3,4,15,16]

A 2019 study showed that MHD was associated with MACE and all-cause mortality in one of the largest cohorts of patients with locally advanced NSCLC, building upon earlier reports with comprehensive inclusion of cardiac risk factors and validated cardiac end points.[5] The primary objective of the present study was to expand upon the prior work by determining independent cardiac substructure radiotherapy factors associated with MACE and all-cause mortality in patients with locally advanced NSCLC, adjusting for preexisting heart disease and traditional lung and cardiovascular prognostic factors.

Key Points

Question What radiotherapy dose exposure thresholds to critical cardiac substructures can estimate the probability for major adverse cardiac events and mortality in patients with non–small cell lung cancer?

Findings In this cohort study of 701 patients with non–small cell lung cancer, left anterior descending coronary artery dose exposure appeared to be an independent factor associated with major adverse cardiac events and all-cause mortality, and baseline coronary heart disease status appeared to interact significantly with dose exposure.

Meaning These findings suggest that newly identified cardiac substructure dose thresholds should alert clinicians to consider implementing more stringent cardiac radiotherapy planning parameters, but these thresholds require further study for validation, and optimized risk mitigation strategies are warranted.

Methods

A retrospective analysis of a cohort of 701 consecutive patients with locally advanced NSCLC treated with thoracic radiotherapy between December 1, 2003, and January 27, 2014, was conducted at Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts. Data analysis was conducted between January 12, 2019, and July 22, 2020. Radiotherapy was delivered using 3D-conformal radiotherapy or intensity-modulated radiotherapy techniques (excluding stereotactic body radiotherapy). Radiotherapy was planned (Varian Eclipse, Varian Medical Systems Inc) and delivered in 1.8- to 2.0-Gy fractions.[5] Dose constraints were used for the spinal cord (maximum <50 Gy), lungs (mean <17 Gy, volume [V] percentage) receiving a specific gray dose: 20 Gy <30%, V5 Gy <50%), and heart (V30 Gy <50%, V45 Gy <40%, and V60 Gy <20%; adopted in 2008).

This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board under a waiver of consent owing to its retrospective nature with minimal risk. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Cardiac substructures, including the coronary arteries (left main, left anterior descending [LAD], left circumflex, right, and posterior descending), chambers (left and right atria and ventricles), and whole heart, were manually delineated on archived planning computed tomographic scans in MIM Maestro, version 6.9.6 (MIM Software Inc) according to guidelines[17] by 4 of us (K.M.A., T.L.C, N.L., and D.S.B.) and independently reviewed by 3 of us (A.N., U.H., and R.H.M.). Radiotherapy dose-volume histograms were recalculated in MIM Maestro; mean (gray), maximum (gray), and volume (percent) receiving a specific (X) gray dose (VX Gy [5-Gy increments]) were calculated.

In-depth manual medical record review was performed.[5] Preexisting coronary heart disease (CHD) was defined as coronary artery disease, congestive heart failure, or a CHD risk-equivalent (peripheral vascular disease, stroke, or extensive coronary artery calcifications).[5] Ten-year Framingham cardiovascular disease risk was calculated.[18] MACE (unstable angina, heart failure hospitalization or urgent visit, myocardial infarction, coronary revascularization, and cardiac death)[19] were assessed after initiation of radiotherapy and 30 days or more postoperatively, if applicable, until death or the last follow-up. Patients with preexisting cardiac comorbidities (eg, congestive heart failure) were counted as having a MACE if the event was either greater in severity compared with the 6-month interval preceding radiotherapy or of a different event class (eg, myocardial infarction or cardiac death). Follow-up and determination of cause of death were previously described.[5]

Statistical Analysis

The distribution of clinical characteristics was assessed using descriptive statistics. Categorical covariables were evaluated using a Fisher exact test and continuous covariables were compared using a Wilcoxon rank-sum test. Area under the receiver operating characteristic curve was calculated. Comparative analyses of area under the curve and cut-point analyses were performed using the Liu method.[20] MACE cumulative incidence estimates were adjusted for noncardiac death as a competing risk,[21] compared using a 2-sided Gray *P* value. Kaplan-Meier estimates[22] of all-cause mortality were compared using a 2-sided log-rank *P* value. Fine and Gray[23] regressions, adjusted for noncardiac death as a competing risk, and Cox proportional hazards[24] regressions were performed. Time 0 was the start date of radiotherapy and concluded by the date of the first MACE, death, or last observation, whichever came first. Multivariable models included covariables with $P \leq .05$ determined on univariable analysis and cardiac dose variables. Multicollinearity was assessed by variance inflation factor and tolerance. A *P* value ≤.05 (2-sided) was considered statistically significant. All analyses were performed with Stata, version 15.1 (StataCorp LLC) statistical software.

Results

Clinical Characteristics

Of the 701 patients included in the analysis, 356 were men (50.8%) and 345 were women (49.2%); the median age was 65 years (interquartile range [IQR], 57-73 years). Most patients (405 [57.8%]) were treated with definitive chemoradiotherapy. Among patients without CHD (449 [64.1%]), baseline cardiovascular risk according to the Framingham criteria was high in 217 patients (48.3%), moderate in 111 patients (24.7%), and low in 121 patients (26.9%). There was no significant difference in tumor laterality, radiotherapy technique, or radiotherapy dose between patients with and without CHD (**Table 1**).

Comparative Area Under the Curve Analysis

Analysis of the area under the curve demonstrated that cardiac dose variables had significantly higher C-index levels using MACE vs all-cause mortality as the end point. For example, for the total population, the median C-index value was 0.54 (IQR, 0.52-0.57) with MACE as the end point vs 0.52 (IQR, 0.51-0.53) for all-cause mortality ($P < .001$) (eTable 1 in the Supplement). By cardiac substructure, LAD dose variables had significantly higher C-index values for MACE compared with the whole heart, right ventricle, posterior descending artery, left atrium, right atrium, and right coronary artery, but not significantly higher than the left circumflex, total coronary, or left main arteries. Moreover, cardiac dose variables had significantly higher C-indices in patients without vs with CHD for each cardiac substructure. For example, the C-indices for the LAD coronary artery were 0.68 in patients without CHD vs 0.49 in patients with CHD, and for the left circumflex coronary artery were 0.71 in patients without CHD vs 0.49 in patients with CHD ($P < .001$) (eTable 2, eTable 3, eFigure 1, and eFigure 2 in the Supplement).

Cut-Point Analysis

The optimal cut-point (C-index) levels for dose variables with the highest C-index level per structure were V15 Gy greater than or equal to 10% (0.64) for the LAD coronary artery, V15 Gy greater than or equal to 14% (0.64) for the left circumflex coronary artery, V15 Gy greater than or equal to 1% (0.64) for the left ventricle, mean greater than or equal to 7 Gy (0.62) for the total coronary arteries, mean greater than or equal to 27 Gy (0.59) for the left main artery, and V25 Gy greater than or equal to 14% (0.59) for the whole heart (included for clinical relevance). Cut points and descriptive statistics for all dose variables are reported (eTable 4 and eTable 5 in the Supplement).

MACE Analysis

The median follow-up was 20.4 months (IQR, 8.2-44.6 months) overall and 47.8 months (IQR, 31.6-75.4 months) in patients alive. Seventy patients developed greater than or equal to 1 MACE (1-year cumulative incidence, 3.9%; 95% CI, 2.6-5.5), with a median time to first MACE of 20.6 months (IQR, 8.8 months to 43.3 months). After adjusting for age, hypertension, diabetes, arrhythmia, CHD, and radiotherapy technique, a significant increase in the risk of MACE was observed with an LAD coronary artery V15 Gy greater than or equal to 10% (adjusted hazard ratio [aHR], 13.90; 95% CI, 1.23-157.21; $P = .03$) (**Table 2**). Although peripheral vascular disease, coronary artery disease, and congestive heart failure were significantly associated with MACE on univariable analysis, given the limited number of MACE, only CHD was included in the multivariable analysis, because the former disease states represent CHD/CHD-risk equivalents. Given modest multicollinearity (eTable 6 in the Supplement), we repeated the multivariable analysis using individual (non-LAD) cardiac dose variables, each of which was significantly associated with MACE. For example, a left circumflex coronary artery V15 Gy greater than or equal to 14% (aHR, 8.13; 95% CI, 2.80-23.58; $P < .001$) and left ventricle V15 Gy greater than or equal to 1% (aHR, 6.67; 95% CI, 2.30-19.30; $P < .001$) (eTables 7-12 in the Supplement).

There was a significant interaction between CHD and LAD V15 Gy greater than or equal to 10% ($P = .04$). Specifically, among patients without CHD (n = 449), LAD V15 Gy greater than or equal to 10% vs <10% was associated with a significantly increased risk of MACE (23 vs 1 event; HR 24.8; 95% CI, 3.49-176.42; $P = .001$) with 1-year estimates of 4.9% (95% CI, 2.6-8.3) vs 0%, respectively (**Figure 1**, **Table 3**). By contrast, among patients with CHD (n = 252), there was not a statistically significant increase in the risk of MACE with LAD coronary artery V15 Gy greater than or equal to 10% vs less than 10% (30 vs 16 events; hazard ratio, 1.42; 95% CI, 0.78-2.60; $P = .25$) with 1-year estimates of 7.6% (95% CI, 4.0-12.6) for V15 Gy greater than or equal to 10% vs 4.7% (95% CI, 1.8-10.0) for V15 Gy less than 10%. We observed similar findings among other dose variables stratified by cut point, including left circumflex coronary artery V15 Gy greater than or equal to 14% vs less than 14%, with 1-year MACE estimates of 5.2% vs 0.7% in patients without CHD ($P < .001$), and 9.0% vs 4.3% in patients with CHD ($P = .08$). Only left ventricle V15 Gy greater than or equal to 1% vs less than 1% was associated with an increased risk of MACE among both pa-

Table 1. Patient and Treatment Characteristics by CHD Status

Characteristic	No. (%)			
		CHD		
	Total (n = 701)	Negative (n = 449)	Positive (n = 252)	*P* value[a]
Patient characteristics				
Age, median (IQR), y	65 (57-73)	62 (55-71)	69 (62-76)	<.001
Sex				
Women	345 (49.2)	238 (53.0)	107 (42.5)	<.008
Men	356 (50.8)	211 (47.0)	145 (57.5)	
ECOG performance				
0-1	616 (87.9)	410 (91.3)	206 (81.8)	.001
2	67 (9.6)	31 (6.9)	36 (14.3)	
3-4	18 (2.6)	8 (1.8)	10 (4.0)	
Weight loss	224 (32.0)	148 (33.0)	76 (30.2)	.50
Tobacco use				
Never	56 (8.0)	49 (10.9)	7 (2.8)	<.001
Current	279 (39.8)	49 (10.9)	94 (37.3)	
Former	366 (52.2)	215 (47.9)	151 (59.9)	
Pack-years, median (IQR)	43 (30-60)	40 (26-60)	46 (30-75)	<.001
Medical history				
Hypertension	362 (51.6)	185 (41.2)	177 (70.2)	<.001
Hyperlipidemia	341 (48.6)	175 (39.0)	166 (65.9)	<.001
Diabetes	97 (13.8)	40 (8.9)	57 (22.6)	<.001
DVT/PE	30 (4.3)	18 (4.0)	12 (4.8)	.70
Arrhythmia	99 (14.1)	43 (9.6)	56 (22.2)	<.001
Valvulopathy	41 (5.8)	18 (4.0)	23 (9.1)	.007
PVD	55 (7.8)	NA	55 (21.8)	NA
Stroke	13 (1.9)	NA	13 (5.2)	NA
CAD	202 (28.8)	NA	202 (80.2)	NA
Myocardial infarction	82 (11.7)	NA	82 (32.5)	NA
Congestive heart failure	58 (8.3)	NA	58 (23.0)	NA
Prior thoracic RT	20 (2.9)	11 (2.5)	9 (3.6)	.48
Prior chemotherapy	15 (2.1)	13 (2.9)	2 (0.8)	.10
Framingham risk	NA	NA	NA	NA
Median, % (IQR)	NA	15.1 (8.6-26.4)	NA	NA
Low (<10%)	NA	121 (26.9)	NA	NA
Moderate (10%-20%)	NA	111 (24.7)	NA	NA
High (>20%)	NA	217 (48.3)	NA	NA
NSCLC clinical stage				
II	78 (11.1)	39 (8.7)	39 (15.5)	.02
IIIA	390 (55.6)	254 (56.6)	136 (54.0)	
IIIB	233 (33.2)	156 (34.7)	77 (30.6)	
NSCLC clinical nodal stage				
0-1	179 (25.5)	104 (23.2)	75 (29.8)	.29
2	359 (51.2)	237 (52.8)	122 (48.4)	
3	162 (23.1)	107 (23.8)	55 (21.8)	
Tumor laterality				
Right	392 (55.9)	261 (58.1)	131 (52.0)	.18
Left	263 (37.5)	163 (36.3)	100 (39.7)	

(continued)

Table 1. Patient and Treatment Characteristics by CHD Status (continued)

Characteristic	No. (%)			P value[a]
		CHD		
	Total (n = 701)	Negative (n = 449)	Positive (n = 252)	
NSCLC histologic characteristics				
Adenocarcinoma	314 (44.8)	216 (48.1)	98 (38.9)	.007
SCC	223 (31.8)	122 (27.2)	101 (40.1)	
Large cell carcinoma	115 (16.4)	78 (17.4)	37 (14.7)	
Other	49 (7.0)	33 (7.4)	16 (6.4)	
Chemotherapy type				
Induction	133 (19.0)	87 (19.4)	46 (18.3)	.76
Concurrent	594 (84.7)	393 (87.5)	201 (79.8)	.008
Adjuvant	238 (34.0)	165 (36.8)	73 (29.0)	.04
Treatment sequence				
Definitive				
Chemoradiotherapy	405 (57.8)	247 (55.0)	158 (62.7)	<.001
RT alone	56 (8.0)	27 (6.0)	29 (11.5)	
Neoadjuvant	154 (22.0)	121 (27.0)	33 (13.1)	
Adjuvant	86 (12.3)	54 (12.0)	32 (12.7)	
RT technique				
3D-CRT	539 (76.9)	337 (75.1)	202 (80.2)	.14
IMRT	162 (23.1)	112 (24.9)	50 (19.8)	
RT year				
<2008	230 (32.8)	147 (32.7)	83 (32.9)	>.99
≥2008	471 (67.2)	302 (67.3)	169 (67.1)	
Prescribed RT dose, median (IQR), Gy	66.0 (56.0-66.0)	66.0 (54.0-66.0)	66.0 (60.0-66.0)	.91
Dose, median (IQR), Gy				
Heart, mean	12.3 (5.9-19.0)	11.8 (5.9-19.0)	12.9 (6.1-19.5)	.37
Esophagus, mean	23.7 (17.1-30.6)	24.0 (17.6-30.7)	23.4 (15.3-29.7)	.11
Lung				
Mean	14.9 (11.6-17.2)	15.2 (11.4-17.4)	14.6 (11.8-17.0)	.34
V5, %	42.9 (32.8-52.1)	42.8 (32.7-52.4)	43 (33.5-51.7)	.92
V20, %	25.2 (19.2-29.6)	25.2 (19.3-29.7)	25.1 (19.2-29.2)	.63

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; 3D-CRT, 3-dimensional conformal radiotherapy; DVT, deep venous thrombosis; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; NA, not applicable; NSCLC, non–small cell lung cancer; PE, pulmonary embolism; PVD, peripheral vascular disease; RT, radiotherapy; SCC, squamous cell carcinoma; V, volume.

[a] The distributions of categorical covariates were compared using the Fisher exact test; continuous variables were compared using the Wilcoxon rank-sum test.

tients with and without CHD, with 1-year MACE estimates of 5.0% vs 0.4% (V15 Gy ≥1% vs <1%) in those without CHD ($P < .001$), and 8.4% vs 4.1% (V15 Gy ≥1% vs <1%) in those with CHD ($P = .046$) (Table 3).

All-Cause Mortality Analysis

A total of 490 died, 325 (66.3%) of lung cancer, 37 (7.8%) of known noncardiac causes, and 25 (5.1%) of cardiac-specific causes; the remainder (n = 103) were of unknown causes. The median overall survival was 22.2 months (IQR, 9.8-45.1 months). After adjustment for age, sex, performance status, unintentional weight loss, stroke, peripheral vascular disease, myocardial infarction, congestive heart failure, arrhythmia, CHD, treatment paradigm, and treatment year, we observed a significant increase in the risk of all-cause mortality with the LAD coronary artery V15 Gy greater than or equal to 10 Gy (aHR, 1.58; 95% CI, 1.09-2.29; $P = .02$) (Table 2). Similar to our evaluation of MACE, given modest multicollinearity (eTable 6 in the Supplement), we repeated the analysis using individual (non-LAD coronary artery) cardiac dose variables, of which the mean total coronary artery dose greater than or equal to 7 Gy, MHD greater than or equal to 10 Gy, and whole heart V25 Gy greater than or equal to 14% were significantly associated with all-cause mortality. For example, mean total coronary arteries greater than or equal to 7 Gy (aHR, 1.33; 95% CI, 1.05-1.67; $P = .02$) and MHD greater than or equal to 10% (aHR, 1.32; 95% CI, 1.04-1.67; $P = .02$) (eTables 7-12 in the Supplement).

There was a significant interaction between baseline CHD and LAD coronary artery V15 Gy ($P = .01$). Specifically, for the 449 patients without CHD, the LAD coronary artery V15 Gy greater than or equal to 10% vs less than 10% was associated

Table 2. Competing Risks and Cox Proportional Hazards Regression Analyses for MACE and ACM

Covariable	No. of patients	MACE					ACM				
		No. MACE	Univariable		Multivariable[a]		No. ACM	Univariable		Multivariable[a]	
			HR (95% CI)	*P* value	aHR (95% CI)	*P* value		HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Lung cancer factors											
Age, y[b]	701	70	1.03 (1.01-1.05)	.01	1.00 (0.98-1.03)	.79	490	1.02 (1.01-1.03)	<.001	1.00 (0.99-1.01)	.50
Sex[b]											
Women	345	33	1 [Reference]		NA		231	1 [Reference]		1 [Reference]	
Men	356	37	1.11 (0.70-1.77)	.67	NA		259	1.21 (1.01-1.44)	.04	1.15 (0.95-1.39)	.15
ECOG performance status											
0-1	616	62	1 [Reference]		NA		418	1 [Reference]		1 [Reference]	
2-4	85	8	0.93 (0.44-1.94)	.84	NA		72	1.69 (1.32-2.18)	<.001	1.56 (1.19-2.04)	.001
Smoking[b]											
Never	56	4	1 [Reference]		NA		36	1 [Reference]		NA	
Ever	645	66	1.46 (0.53-4.03)	.47	NA		454	1.34 (0.95-1.88)	.09	NA	
Weight loss											
No	477	54	1 [Reference]		NA		330	1 [Reference]		1 [Reference]	
Yes	224	16	0.64 (0.37-1.12)	.12	NA		160	1.30 (1.07-1.57)	.007	1.25 (1.02-1.52)	.03
Overall stage											
II	78	11	1 [Reference]		NA		52	1 [Reference]		NA	
III	623	59	0.67 (0.36-1.27)	.22	NA		438	1.17 (0.87-1.56)	.30	NA	
Nodal category											
0-1	179	20	1 [Reference]		NA		115	1 [Reference]		NA	
≥2	521	50	0.83 (0.50-1.39)	.48	NA		375	1.21 (0.99-1.50)	.07	NA	
Tumor laterality											
Right	392	35	1 [Reference]		NA		277	1 [Reference]		NA	
Left	263	30	1.35 (0.83-2.19)	.23	NA		184	1.00 (0.83-1.20)	.98	NA	
Histologic characteristics											
Adenocarcinoma	314	32	1 [Reference]		NA		218	1 [Reference]		NA	
Non-adenocarcinoma	387	38	1.0 (0.62-1.59)	.99	NA		272	1.14 (0.96-1.36)	.15	NA	
Baseline cardiac factors											
Hypertension	362	55	3.61 (2.05-6.36)	<.001	2.66 (1.47-4.81)	.001	259	1.09 (0.91-1.30)	.33	NA	
Hyperlipidemia	341	37	1.19 (0.75-1.90)	.46	NA		241	1.03 (0.87-1.23)	.71	NA	
Diabetes	97	17	2.09 (1.21-3.59)	.008	1.13 (0.62-2.06)	.69	72	1.11 (0.87-1.43)	.41	NA	
Stroke	13	3	2.52 (0.81-7.83)	.11	NA		11	1.87 (1.03-3.41)	.04	1.19 (0.61-2.32)	.61
PVD	55	13	2.86 (1.58-5.18)	.001	NA		46	1.41 (1.04-1.91)	.03	1.09 (0.77-1.53)	.64
Coronary artery disease	202	33	2.34 (1.47-3.74)	<.001	NA		149	1.14 (0.94-1.39)	.17	NA	

(continued)

Table 2. Competing Risks and Cox Proportional Hazards Regression Analyses for MACE and ACM (continued)

Covariable	No. of patients	MACE					ACM				
		No. MACE	Univariable		Multivariable[a]		No. ACM	Univariable		Multivariable[a]	
			HR (95% CI)	*P* value	aHR (95% CI)	*P* value		HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Myocardial infarction	82	12	1.60 (0.86-2.96)	.14	NA		68	1.45 (1.12-1.87)	.005	1.32 (0.96-1.80)	.08
Congestive heart failure	58	17	4.04 (2.33-6.99)	<.001	NA		47	1.34 (0.99-1.81)	.06	0.91 (0.64-1.29)	.59
Arrhythmia	99	17	2.09 (1.20-3.64)	.009	1.66 (0.91-3.02)	.10	76	1.34 (1.05-1.71)	.02	1.26 (0.97-1.64)	.09
Valvulopathy	41	4	1.02 (0.36-2.85)	.98	NA		31	1.35 (0.94-1.95)	.11	NA	
CHD	252	46	3.68 (2.26-6.02)	<.001	25.4 (3.10-208.72)	.003	194	1.32 (1.10-1.58)	.003	1.30 (0.89-1.89)	.17
Treatment factors											
RT/chemoradiotherapy sequence											
Definitive	461	47	1 [Reference]		NA		370	1 [Reference]		1 [Reference]	
Neoadjuvant/adjuvant	240	23	0.95 (0.58-1.55)	.83	NA		120	0.39 (0.31-0.47)	<.001	0.41 (0.33-0.51)	<.001
Chemotherapy (any)	659	66	1.01 (0.37-2.78)	.98	NA		458	0.74 (0.52-1.06)	.10	NA	
Radiotherapy factors											
Technique											
3D-CRT	539	63	1 [Reference]		1 [Reference]		382	1 [Reference]		NA	
IMRT	162	7	0.38 (0.17-0.83)	.02	0.41 (0.18-0.93)	.03	108	1.14 (0.92-1.41)	.24	NA	
Radiotherapy year										NA	
<2008	230	22	1 [Reference]		NA		195	1 [Reference]		1 [Reference]	
≥2008	471	48	1.21 (0.74-1.98)	.45	NA		295	0.83 (0.69-1.00)	.05	0.76 (0.62-0.92)	.004
Cardiac RT dose factors, Gy[c]											
LAD coronary artery V15											
<10%	329	17	1 [Reference]		1 [Reference]		223	1 [Reference]		1 [Reference]	
≥10%	372	53	2.97 (1.73-5.12)	<.001	13.90 (1.23-157.21)	.03	267	1.16 (0.97-1.39)	.09	1.58 (1.09-2.29)	.02
Left circumflex coronary artery V15											
<14%	415	25	1 [Reference]		1 [Reference]		288	1 [Reference]		1 [Reference]	
≥14%	286	45	2.85 (1.75-4.62)	<.001	1.88 (0.52-6.85)	.34	202	1.08 (0.90-1.29)	.40	0.81 (0.55-1.19)	.29
Left ventricle V15											
<1%	369	20	1 [Reference]		1 [Reference]		251	1 [Reference]		1 [Reference]	
≥1%	332	50	2.96 (1.77-4.96)	<.001	1.07 (0.35-3.31)	.90	239	1.12 (0.94-1.34)	.21	0.80 (0.53-1.21)	.29
Mean total coronary artery, Gy											
<7	331	18	1 [Reference]		1 [Reference]		227	1 [Reference]		1 [Reference]	
≥7	370	52	2.78 (1.64-4.73)	<.001	2.24 (0.39-13.00)	.37	263	1.16 (0.97-1.38)	.10	1.32 (0.82-2.13)	.25
Mean left main coronary artery, Gy											
<27	338	23	1 [Reference]		1 [Reference]		231	1 [Reference]		1 [Reference]	
≥27	368	47	1.90 (1.16-3.13)	.01	0.61 (0.11-3.42)	.57	259	1.04 (0.87-1.24)	.71	0.85 (0.58-1.24)	.40

(continued)

Table 2. Competing Risks and Cox Proportional Hazards Regression Analyses for MACE and ACM (continued)

Covariable	No. of patients	MACE					ACM				
		No. MACE	Univariable		Multivariable[a]		No. ACM	Univariable		Multivariable[a]	
			HR (95% CI)	*P* value	aHR (95% CI)	*P* value		HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Whole heart V25											
<14%	294	19	1 [Reference]		1 [Reference]		203	1 [Reference]		1 [Reference]	
≥14%	407	51	2.03 (1.20-3.42)	.008	0.80 (0.18-3.65)	.78	287	1.13 (0.94-1.35)	.18	0.97 (0.61-1.56)	.92
Mean heart, Gy											
<10	293	24	1 [Reference]		NA		200	1 [Reference]		1 [Reference]	
≥10	408	46	1.45 (0.89-2.36)	.14	NA		290	1.19 (0.99 - 1.43)	.06	1.21 (0.74-1.99)	.45
Interaction[d]											
LAD coronary artery V15 Gy ≥10% × CHD	701	70	0.06 (0.01-0.46)	.007	0.06 (0.00-0.89)	.04	490	0.59 (0.41-0.86)	.005	0.45 (0.25-0.82)	.01
Left circumflex artery V15 Gy ≥14% × CHD	701	70	0.20 (0.06-0.66)	.008	0.79 (0.15-4.02)	.77	490	0.72 (0.50-1.04)	.08	1.26 (0.70-2.28)	.44
Left ventricle V15 Gy ≥1% × CHD	701	70	0.28 (0.08-0.95)	.04	1.54 (0.31-7.58)	.59	490	0.77 (0.54-1.11)	.16	1.10 (0.58-2.12)	.75
Mean total CA ≥ 7 Gy × CHD	701	70	0.14 (0.03-0.67)	.01	0.54 (0.07-4.10)	.56	490	0.62 (0.43-0.90)	.01	0.79 (0.37-1.66)	.53
Mean LM ≥ 27 Gy × CHD	701	70	0.25 (0.07-0.85)	.03	1.17 (0.16-8.86)	.88	490	0.70 (0.49-1.01)	.05	1.08 (0.56-2.07)	.82
Heart V25 ≥ 14% × CHD	701	70	0.35 (0.10-1.20)	.10	1.31 (0.21-8.20)	.77	490	0.70 (0.48-1.00)	.05	1.51 (0.60-3.82)	.38
Mean heart ≥ 10 Gy × CHD	701	70	0.33 (0.11-1.03)	.06	NA		490	0.70 (0.48-1.01)	.05	0.74 (0.32-1.73)	.49

Abbreviations: ACM, all-cause mortality; aHR, adjusted hazard ratio; CA, coronary artery; CHD, coronary heart disease; 3D-CRT, 3-dimensional conformal radiation therapy; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiation therapy; LAD, left anterior descending; LM, left main; MACE, major adverse cardiac events; NA, not applicable; PVD, peripheral vascular disease; RT, radiotherapy.

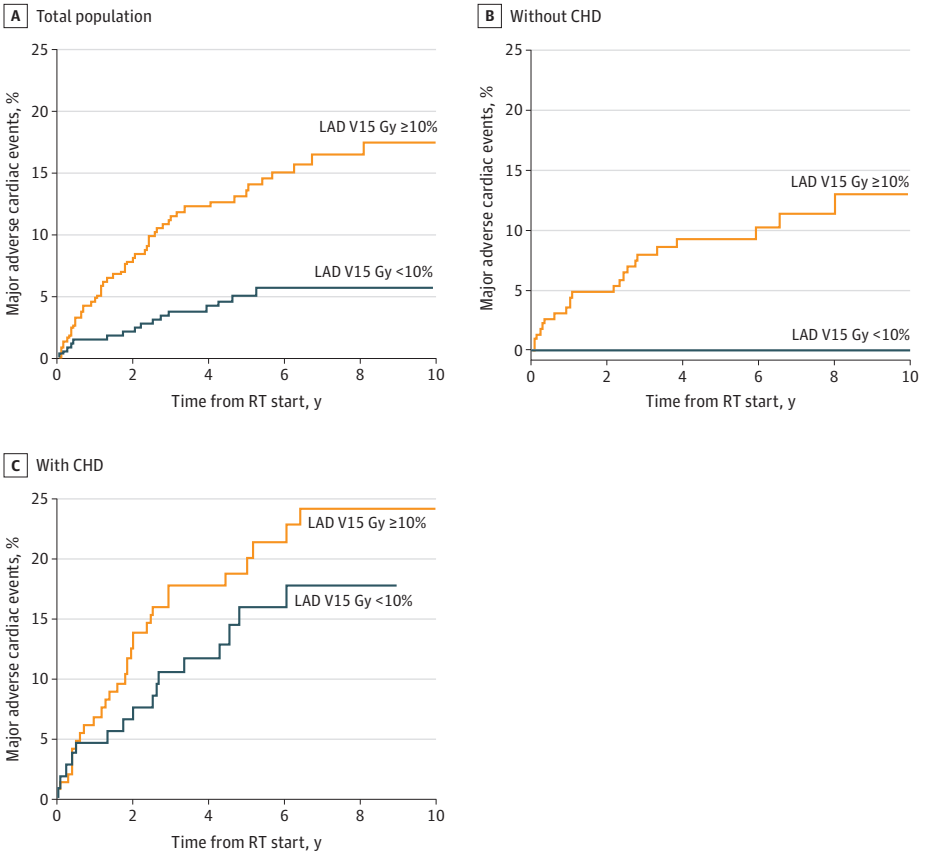
[a] Multivariable models included covariables with $P \leq .05$ on univariable analysis and cardiac dose variables. Entries given as NA did not meet the criteria to be included in the multivariable model.

[b] Both a lung cancer and cardiac prognostic factor.

[c] Radiotherapy dose factors are dichotomous variables.

[d] Interaction term between heart dose factor (dichotomous variable) and preexisting CHD (dichotomous variable).

Figure 1. Cumulative Incidence of Major Adverse Cardiac Events (MACE) Stratified by Left Anterior Descending (LAD) Coronary Artery Volume (V)15 Gy Less Than 10% or Greater Than or Equal to 10%



Cumulative incidence of MACE in the total population (P < .001) (A), patients without preexisting coronary heart disease (CHD) (P = .001) (B), or patients with preexisting CHD (P = .25) (C). RT indicates radiotherapy.

with a significantly increased risk of all-cause mortality (158 vs 138 deaths; hazard ratio, 1.36; 95% CI, 1.08-1.71; P = .009), with 2-year estimates of 51.2% (95% CI, 44.7%-57.9%) for V15 Gy greater than or equal to 10% vs 42.2% (95% CI, 35.9%-49.0%) V15 Gy less than 10% (**Figure 2**, Table 3). Among the 252 patients with CHD, there was no statistically significant increase in the risk of all-cause mortality with the LAD coronary artery V15 Gy greater than or equal to 10% vs less than 10% (109 vs 85 deaths; hazard ratio, 0.80; 95% CI, 0.60-1.06; P = .12), with 2-year estimates of 47.9% (95% CI, 40.1%-56.4%) for V15 Gy greater than or equal to 10% vs 61.1% (95% CI, 51.9%-70.4%) for V15 Gy less than 10%. We observed similar findings with mean total coronary artery dose greater than or equal to 10% 7 Gy and whole heart V25 Gy greater than or equal to 14% (Table 3).

Discussion

Despite the competing risk of lung cancer death, we observed that LAD coronary artery dose exposure (V15 Gy ≥10%) is an independent factor associated with MACE and all-cause mortality and that optimal cardiac dose constraints may differ based on preexisting cardiac status. The LAD coronary artery V15 Gy greater than or equal to 10%, left circumflex coronary artery V15 Gy greater than or equal to 14%, left ventricle V15 Gy greater than or equal to 1%, and mean total coronary artery dose greater than or equal to 7 Gy appeared to confer a 5% absolute increase in 1-year MACE estimates in patients without CHD, but only left ventricle V15 Gy greater than or equal to 1% appeared to confer an increased risk among patients with CHD (Table 3). Similarly, LAD coronary artery V15 Gy greater than or equal to 10% and mean total coronary artery dose greater than or equal to 7 Gy appeared to confer a nearly 10% absolute increase in 2-year all-cause mortality estimates in patients without but not with CHD. These findings support more precise cardiac risk stratification based on coronary and left ventricle dose exposure and baseline status of CHD.

The most robust data for radiotherapy-associated cardiac events are from breast cancer and lymphoma studies.[25-27] However, it is challenging to extrapolate these findings to NSCLC given the higher doses of radiotherapy used in NSCLC, with more widely varying dose exposure to cardiac substructures based on primary tumor and nodal locations (eFigure 3 in the Supplement), the more contracted time (1-2 years) during which cardiac events are observed, and the elevated baseline cardiac risk in these patients.[3-5,28] Furthermore, it warrants discussion that the most commonly used cardiac dose constraint is MHD. Although Atkins et al[5] recently reported that MHD is an independent factor associated with MACE and

Table 3. Cumulative Incidence of MACE and All-Cause Mortality Stratified by Dose Cut-Point and CHD Status

	Total population (n = 701)			CHD					
				Negative (n = 449)			Positive (n = 252)		
DVH variable	No. (%)	Incidence, % (95% CI)	*P* value	No. (%)	Incidence, % (95% CI)	*P* value	No. (%)	Incidence, % (95% CI)	*P* value
MACE cumulative incidence, 1-y estimates[a]									
LAD coronary artery									
V15 Gy <10%	17 (5.2)	1.5 (0.6-3.4)	<.001	1 (0.5)	0[b]	.001	16 (15.1)	4.7 (1.8-10.0)	.25
V15 Gy ≥10%	53 (14.3)	5.9 (3.8-8.7)		23 (10.2)	4.9 (2.6-8.3)		30 (20.6)	7.6 (4.0-12.6)	
Left circumflex coronary artery									
V15 Gy <14%	25 (6.0)	1.9 (0.9-3.6)	<.001	4 (1.5)	0.7 (0.2-2.5)	<.001	21 (14.9)	4.3 (1.8-8.5)	.08
V15 Gy ≥14%	45 (15.7)	6.7 (4.2-10.0)		20 (11.4)	5.2 (2.5-9.2)		25 (22.5)	9.0 (4.6-15.2)	
Left ventricle									
V15 Gy <1%	20 (5.4)	1.6 (0.7-3.4)	<.001	4 (1.6)	0.4 (0.0-2.1)	<.001	16 (13.2)	4.1 (1.6-8.8)	.046
V15 Gy ≥1%	50 (15.1)	6.4 (4.1-9.3)		20 (10.0)	5.0 (2.6-8.7)		30 (22.9)	8.4 (4.5-14.0)	
Total coronary artery									
Mean <7 Gy	18 (5.4)	0.9 (0.3-2.5)	<.001	2 (0.9)	0[b]	.001	16 (14.4)	2.7 (0.7-7.1)	.12
Mean ≥7 Gy	52 (14.1)	6.5 (4.3-9.4)		22 (9.6)	4.8 (2.6-8.2)		30 (21.3)	9.2 (5.2-14.7)	
Left main coronary artery									
Mean <27 Gy	23 (6.9)	2.4 (1.1-4.5)	.01	4 (1.8)	1.4 (0.4-3.7)	.004	19 (16.8)	4.4 (1.7-9.4)	.51
Mean ≥27 Gy	47 (12.8)	5.2 (3.2-7.8)		20 (8.7)	3.5 (1.7-6.5)		27 (19.4)	7.9 (4.2-13.2)	
Whole heart									
V25 Gy <14%	19 (6.5)	2.1 (0.9-4.2)	.008	4 (2.0)	1.0 (0.2-3.4)	.01	15 (15.3)	4.1 (1.3-9.4)	.28
V25 Gy ≥14%	51 (12.5)	5.2 (3.3-7.7)		20 (7.9)	3.6 (1.8-6.4)		31 (20.1)	7.8 (4.3-12.8)	
All-cause mortality, 2-y estimates[c]									
LAD coronary artery									
V15 Gy <10%	223 (67.8)	47.9 (42.7-53.5)	.09	138 (61.9)	42.2 (35.9-49.0)	.009	85 (80.2)	61.1 (51.9-70.4)	.12
V15 Gy ≥10%	267 (71.8)	50.0 (44.9-55.2)		158 (69.9)	51.2 (44.7-57.9)		109 (74.7)	47.9 (40.1-56.4)	
Left circumflex coronary artery									
V15 Gy <14%	288 (69.4)	48.3 (43.6-53.3)	.40	176 (64.2)	45.0 (39.3-51.2)	.13	112 (79.4)	55.4 (47.4-63.8)	.34
V15 Gy ≥14%	202 (70.6)	49.7 (44.0-55.7)		120 (68.6)	49.3 (42.0-57.1)		82 (73.9)	50.1 (41.2-59.8)	
Left ventricle									
V15 Gy <1%	251 (68.0)	46.4 (41.4-51.6)	.21	157 (63.3)	43.3 (37.4-49.8)	.11	94 (77.7)	53.4 (44.8-62.6)	.52
V15 Gy ≥1%	239 (72.0)	51.7 (46.3-57.2)		139 (69.2)	50.9 (44.1-58.1)		100 (76.3)	52.7 (44.4-61.5)	
Total coronary artery									
Mean <7 Gy	227 (68.6)	44.7 (39.5-50.3)	.10	136 (61.8)	40.0 (33.9-46.9)	.01	91 (82.0)	54.8 (45.8-64.3)	.22
Mean ≥7 Gy	263 (71.1)	52.6 (47.6-57.9)		160 (69.9)	53.2 (46.8-59.9)		103 (73.1)	51.6 (43.6-60.2)	
Left main coronary artery									
Mean <27 Gy	231 (69.4)	47.9 (42.6-53.4)	.70	139 (63.2)	42.9 (36.6-49.7)	.18	92 (81.4)	58.5 (49.5-67.7)	.13
Mean ≥27 Gy	259 (70.4)	50.3 (45.3-55.6)		157 (68.6)	50.4 (44.0-57.1)		102 (73.4)	50.2 (42.1-58.8)	
Whole heart									
V25 Gy <14%	203 (69.1)	44.3 (38.8-50.2)	.18	122 (62.2)	40.3 (33.7-47.5)	.04	81 (82.7)	53.4 (43.9-63.5)	.38
V25 Gy ≥14%	287 (70.5)	52.2 (47.4-57.2)		174 (68.8)	52.2 (46.1-58.6)		113 (73.4)	52.8 (45.1-61.0)	

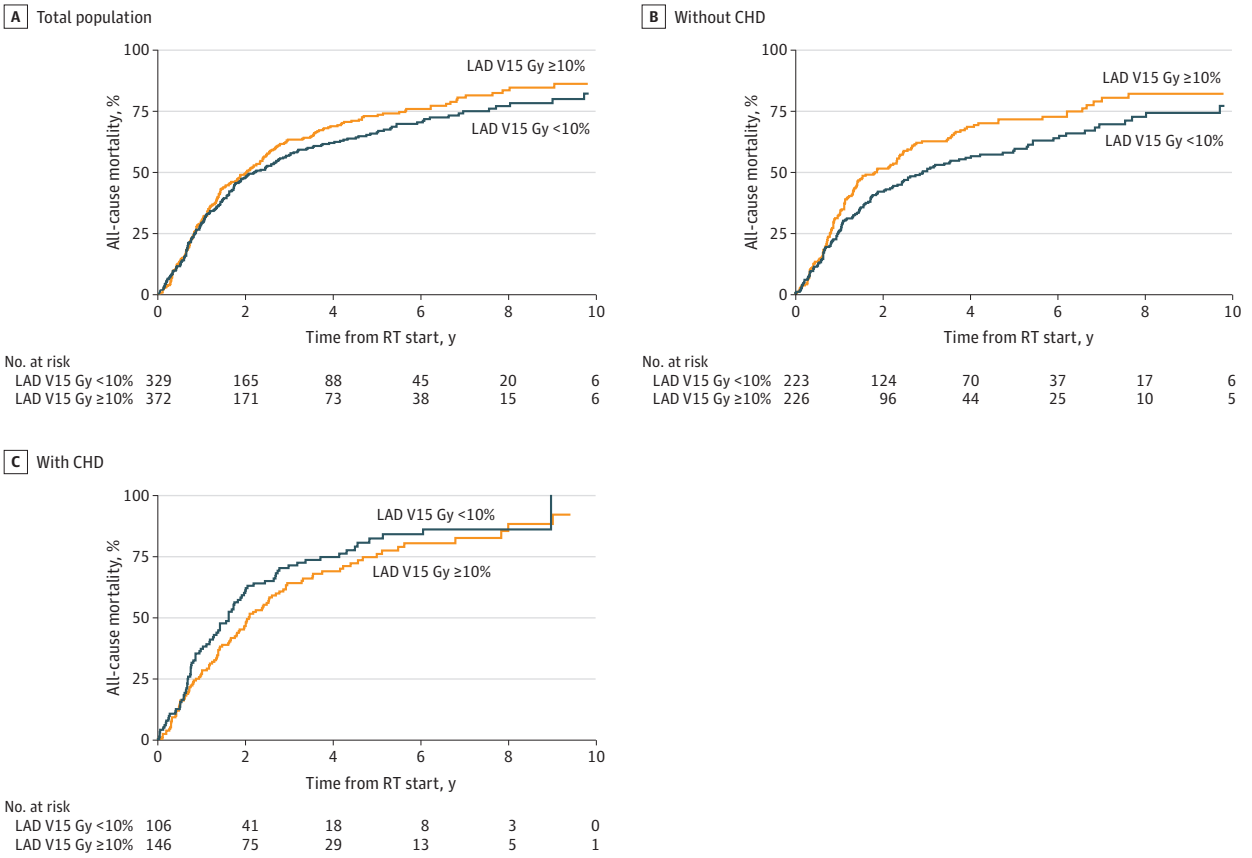
Abbreviations: CHD, coronary heart disease; DVH, dose-volume histogram; LAD, left anterior descending; MACE, major adverse cardiac events; V, volume.

[a] Estimates were compared using a 2-sided, Gray *P* value.

[b] No events by time point.

[c] Estimates were compared using a 2-sided, log-rank *P* value.

Figure 2. All-Cause Mortality Stratified by Left Anterior Descending (LAD) Coronary Artery Volume (V)15 Gy Less Than 10% or Greater Than or Equal to 10%



All-cause mortality in the total population (log-rank *P* = .09) (A), patients without preexisting CHD (log-rank *P* = .009) (B), or patients with preexisting CHD (log-rank *P* = .12) (C). RT indicates radiotherapy.

all-cause mortality in patients with NSCLC, this dose variable is limited because it is unable to account for the variability and steepness of dose distributions across cardiac regions (eFigure 3 in the Supplement) and is insufficient to indicate the probability of left ventricle and coronary artery dose exposure.[11] Together, these findings underscore the need for more nuanced cardiac dosimetry to improve cardiac risk estimation.

A recent systematic review failed to identify consistent cardiac radiation dose parameters associated with survival in patients with NSCLC.[29] However, this study was performed before Atkins et al[5] published findings on what was, to our knowledge, the largest NSCLC cohort describing individual cardiac (MACE and grade ≥3 Common Terminology Criteria for Adverse Events) and survival outcomes with analysis of MHD. The review included 4 small (112-250 patients each) studies with a primary end point of cardiac events.[1,3,4,15,16] However, these studies had limited events, used variable and/or nonvalidated cardiac end points, and had inconsistent accounting of baseline cardiac risk. A single study analyzed the coronary (LAD coronary artery) dose, but limited sample size, and thus, limited cardiac events, precluded multivariable analysis of cardiac events and only disease progression was associated with mortality.[15] There have been more series analyzing cardiac dose variables associated with survival.[8-10,30-41] The largest of these studies was RTOG 0617, showing heart doses of V5, V30, and V40 Gy to be associated with survival,[8,10,31,32] and more recently identifying atria dose to 45% greater than 44 Gy, pericardium mean dose to the hottest 55% greater than 51 Gy, and ventricles mean dose to the hottest 5% greater than 56 Gy.[39] However, these studies only analyzed pericardium, atria, and ventricles (without coronary arteries), and did not assess cardiac events or account for baseline cardiac risk. Moreover, these NSCLC series largely evaluated whole heart dosimetry,[9,30,33-41] and some analyzed the pulmonary artery,[35] base of heart,[36] and left atrium.[41] The only study to evaluate coronary dosimetry used a noncontouring method to match 1161 patients to 5 template anatomies with 14 cardiac substructures delineated (including the LAD, left circumflex coronary, and right coronary arteries), and found that the right atrium, right coronary artery, and ascending aorta were associated with survival, proposing a 23-Gy maximum dose limit, but without assessment of cardiac events or accounting for baseline cardiac risk.[37] Together, the limitations of these heterogeneous reports underscore the value of robust clinical data sets with validated and/or standardized cardiac event end points and the need for com-

prehensive cardiac substructure dosimetry (including coronary arteries).

Given the shared risk profiles between CHD and cancer and the high prevalence of CHD among patients with NSCLC,[28,42] careful assessment of preexisting cardiac risk is necessary, because optimal cardiac dose constraints may differ based on preexisting cardiac status. Although we did not observe a significant association between coronary dose and risk of MACE or all-cause mortality in patients with CHD, we posit that this lack of association is the result of exceeding an observable dose response in an ultra-high-risk group. Consistent with this hypothesis, patients with vs without CHD harbor a similar absolute increase in 1-year MACE rates with LAD coronary artery V15 Gy greater than or equal to 10% vs less than 10% (3% vs 5%), left circumflex coronary artery greater than or equal to 14% vs less than 14% (5% vs 5%), left ventricle V15 Gy greater than or equal to 1% vs less than 1% (4% vs 5%), and mean total coronary arteries greater than or equal to 7 Gy vs less than 7 Gy (7% vs 5%) (Table 3). However, only the left ventricle V15 Gy greater than or equal to 1% was statistically significant among patients with CHD. The cause of these differences is unclear, but possible mechanistic reasons include a potential for greater susceptibility to sequalae from radiation-induced microvascular disease or myocardial fibrosis in the presence of baseline epicardial coronary obstructive patterns.[6,7,43] Moreover, the absence of a more dominant LAD coronary artery-mediated effect in patients with CHD may, in part, have been confounded by the increased LAD coronary artery dose in patients with vs without CHD (mean, 8.7 vs 7.0 Gy, $P = .03$) (eTable 5 in the Supplement).

The association between lung dose-volume parameters and symptomatic pneumonitis and mortality has been well characterized.[44,45] Together with our current and recent observations demonstrating the association between cardiac and coronary artery radiation dose, cardiac events, and mortality,[5] we recommend a balanced approach in radiotherapy planning optimization. Specifically, we do not recommend exceeding lung dose constraints or prioritizing cardiac dose constraints such that tumor coverage is not maintained. Rather, we recommend minimizing cardiac and left coronary artery radiation doses as low as reasonably allowable while achieving safe lung dose-volume exposure and maintaining tumor coverage (eg, with the goal of achieving LAD coronary artery V15 Gy <10% and MHD<10 Gy[5]). Although modern treatment planning techniques may allow improved optimization of lung and cardiac constraints in a subset of patients, strategies evaluating treatment planning optimization techniques with appropriate cardiac risk stratification are of high clinical interest and are being actively pursued.[46] Furthermore, identifying patients at highest risk of cardiac events might help identify who may benefit most from experimental technologies, such as proton radiotherapy.

Strengths and Limitations

Strengths of this study are that, to our knowledge, it represents the largest cohort of individual patient cardiac and coronary dosimetry in thoracic radiotherapy with manual delineation of cardiac substructures.[17] Combined with comprehensive detailing of cardiac risk factors and use of a validated MACE end point, the study provides an improved means for identifying patients at high cardiac risk for whom more aggressive cardiac risk mitigation strategies, including more stringent cardiac and coronary artery radiation dose avoidance, may be warranted. The association of precisely calculated radiation dose exposure to critical cardiac substructures (eg, coronary arteries) that have a directly relevant pathophysiologic mechanism of injury (eg, coronary artery stenosis) to clearly defined toxic cardiac events (eg, myocardial infarction, coronary revascularization) is the key novel contribution of this work and an important point of understanding for oncologists and cardiologists.

Limitations of this study include its retrospective design and absence of a validation cohort. Therefore, prospective validation of these newly identified cardiac constraints is warranted. In addition, the known multicollinearity of radiation dose variables precludes thorough direct comparison among these variables. In addition, although the validated MACE end point is ideal for incorporating baseline cardiovascular risk (eg, Framingham or atherosclerotic cardiovascular disease risk) and guideline-based cardiac risk factor optimization, radiotherapy-relevant end points, such as arrhythmias and pericardial events, were not addressed, and the limited number of MACE introduces the potential for data overfitting. Atkins et al[5] recently reported the cumulative incidence rates of these individual grade 3 or greater MACE and Common Terminology Criteria for Adverse Events and their differential association with baseline cardiac risk; however, detailed analysis of the relevant cardiac substructure dose variables and their association with these end points was outside of the scope of this report.

Conclusions

Our study suggests that LAD coronary artery V15 Gy greater than or equal to 10% is an independent factor associated with MACE and all-cause mortality in patients with NSCLC and optimal cardiac dose constraints may differ based on preexisting cardiac status. We noted that LAD coronary artery V15 Gy greater than or equal to 10%, left circumflex coronary artery V15 Gy greater than or equal to 14%, left ventricle V15 Gy greater than or equal to 1%, and mean total coronary arteries greater than or equal to 7 Gy appeared to confer a 5% absolute increase in 1-year MACE estimates in patients without CHD, but only left ventricle V15 Gy greater than or equal to 1% conferred an increased risk among patients with CHD. Similarly, an LAD coronary artery V15 Gy greater than or equal to 10% and mean total coronary artery dose greater than or equal to 7 Gy appeared to confer a nearly 10% absolute increase in 2-year all-cause mortality estimates in patients without but not with CHD. These cardiac constraints are worthy of further study for validation because critical cardiac substructure dose constraints for radiotherapy planning are lacking and there is a need for identifying patients for whom more aggressive risk mitigation strategies are warranted.

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