JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 23, 2019

Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer

Katelyn M. Atkins, MD, PhD,[a] Bhupendra Rawal, MS,[b] Tafadzwa L. Chaunzwa, BS,[c,d] Nayan Lamba, BA,[e] Danielle S. Bitterman, MD,[a] Christopher L. Williams, PhD,[d] David E. Kozono, MD, PhD,[d] Elizabeth H. Baldini, MD, MPH,[d] Aileen B. Chen, MD, MPP,[d] Paul L. Nguyen, MD,[d] Anthony V. D'Amico, MD, PhD,[d] Anju Nohria, MD,[f] Udo Hoffmann, MD,[g] Hugo J.W.L. Aerts, PhD,[d,h] Raymond H. Mak, MD[d]

ABSTRACT

BACKGROUND Radiotherapy-associated cardiac toxicity studies in patients with locally advanced non-small cell lung cancer (NSCLC) have been limited by small sample size and nonvalidated cardiac endpoints.

OBJECTIVES The purpose of this analysis was to ascertain whether cardiac radiation dose is a predictor of major adverse cardiac events (MACE) and all-cause mortality (ACM).

METHODS This retrospective analysis included 748 consecutive locally advanced NSCLC patients treated with thoracic radiotherapy. Fine and Gray and Cox regressions were used to identify predictors for MACE and ACM, adjusting for lung cancer and cardiovascular prognostic factors, including pre-existing coronary heart disease (CHD).

RESULTS After a median follow-up of 20.4 months, 77 patients developed ≥1 MACE (2-year cumulative incidence, 5.8%; 95% confidence interval [CI]: 4.3% to 7.7%), and 533 died. Mean radiation dose delivered to the heart (mean heart dose) was associated with a significantly increased risk of MACE (adjusted hazard ratio [HR]: 1.05/Gy; 95% CI: 1.02 to 1.08/Gy; $p < 0.001$) and ACM (adjusted HR: 1.02/Gy; 95% CI: 1.00 to 1.03/Gy; $p = 0.007$). Mean heart dose (≥10 Gy vs. <10 Gy) was associated with a significantly increased risk of ACM in CHD-negative patients (178 vs. 118 deaths; HR: 1.34; 95% CI: 1.06 to 1.69; $p = 0.014$) with 2-year estimates of 52.2% (95% CI: 46.1% to 58.5%) versus 40.0% (95% CI: 33.5% to 47.4%); but not among CHD-positive patients (112 vs. 82 deaths; HR: 0.94; 95% CI: 0.70 to 1.25; $p = 0.66$) with 2-year estimates of 54.6% (95% CI: 46.8% to 62.7%) versus 50.8% (95% CI: 41.5% to 60.9%), respectively (p for interaction = 0.028).

CONCLUSIONS Despite the competing risk of cancer-specific death in locally advanced NSCLC patients, cardiac radiation dose exposure is a modifiable cardiac risk factor for MACE and ACM, supporting the need for early recognition and treatment of cardiovascular events and more stringent avoidance of high cardiac radiotherapy dose. (J Am Coll Cardiol 2019;73:2976–87) © 2019 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/).

From the [a]Harvard Radiation Oncology Program, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts; [b]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [c]Yale School of Medicine, New Haven, Connecticut; [d]Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts; [e]Harvard Medical School, Boston, Massachusetts; [f]Department of Cardiovascular Medicine, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts; [g]Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the [h]Department of Radiology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts. Dr. Williams has received research grants from Varian Medical Systems. Dr. Nguyen has received consulting fees from Blue Earth, Ferring, Janssen, Astellas, Cota, Nanobiotix, Genome DX, Augmenix, Boston Scientific, Dendreon, and Bayer; and has received grants (to institution) from Janssen and Astellas. Dr. Nohria has received a research grant (to institution) from Amgen; and has served as a consultant for Takeda Oncology. Dr. Hoffmann has received research grants (to institution) from Medimmune, Kowa, and HeartFlow Inc. Dr. Aerts has received consulting fees from Sphera and Genospace. Dr. Mak has served on the Scientific Advisory Board of AstraZeneca; and has received an honorarium from NewRT. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 2, 2019; revised manuscript received March 19, 2019, accepted March 20, 2019.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2019.03.500

Cardiac toxicity following radiotherapy has been observed in long-term breast cancer and Hodgkin lymphoma survivors, with a typical latency period of more than a decade and increased incidence with higher heart dose, younger age at treatment, and pre-existing cardiac risk factors (1–3). However, although these malignancies portend a more favorable prognosis, lung cancer is conversely the leading cause of cancer-related death in the United States (4). Thus, the clinical relevance of radiotherapy-associated cardiac toxicity in locally advanced non-small cell lung cancer (NSCLC) patients has historically been minimized given the competing risk of cancer-specific death and presumption of prolonged latency to cardiotoxicity (5,6).

SEE PAGE 2988

However, recent multicenter trials have reported improved 5-year survival rates of 15% to 20% and median survival times >2 years (7,8), while encouraging results have been observed with lung cancer screening in high-risk populations, molecularly targeted therapies in advanced disease, and consolidative immunotherapy for locally advanced disease (9–11). Moreover, recent studies have reported that cardiac events in NSCLC patients treated with radiotherapy are common, associated with cardiac radiation dose and baseline cardiac risk (12,13), and predict for mortality (7,14). However, these studies were limited by small sample size, inconsistent endpoints, and variable baseline cardiac risk assessment (5–7,12,13,15,16). To the best of our knowledge, no prior NSCLC studies have utilized American Heart Association (AHA)/American College of Cardiology (ACC)-defined endpoints (17), thus precluding rational extrapolation to baseline Framingham risk (18) and guideline-based cardiovascular risk prevention interventions (19). Therefore, given improving NSCLC outcomes together with clinically significant cardiac events post-radiotherapy, there remains an urgent need for improved cardiac risk assessment using validated cardiac endpoints, identification of predictive factors, and maximized risk reduction strategies with optimized radiotherapy approaches.

The primary objective of the current study was to determine whether cardiac radiation dose exposure was associated with an increased risk of AHA/ACC-defined major adverse cardiac events (MACE) (17) and all-cause mortality (ACM) in a large cohort of locally advanced NSCLC patients treated with thoracic radiotherapy, adjusting for traditional lung cancer and cardiovascular prognostic factors, including pre-existing coronary heart disease (CHD). The secondary objective included analyzing cardiac event subgroups using oncology clinical trial common terminology criteria for adverse event (CTCAE) scales (20). This study provides a deeper understanding of the relationship between CHD and the incremental risk of cardiac radiation dose exposure as a potentially modifiable risk factor, thereby substantially affecting national guidelines on radiotherapy planning and providing a shared framework among radiation oncologists, primary care physicians, and cardiologists to increase recognition and treatment of cardiovascular events and inform post-radiotherapy cardiac risk prevention strategies.

ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality

CHD = coronary heart disease

CTCAE = common terminology criteria for adverse event

CVD = cardiovascular disease

MACE = major adverse cardiac events

MHD = mean heart dose

NSCLC = non-small cell lung cancer

METHODS

PATIENT POPULATION. Single-institution retrospective cohort study of 748 consecutive locally advanced NSCLC patients treated between November 30, 1998, and January 27, 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 had 2010 American Joint Commission on Cancer clinical stage II (medically inoperable or unresectable) or III NSCLC treated with thoracic radiotherapy using conventional (3-dimensional conformal radiotherapy) or intensity-modulated radiotherapy techniques. Patients treated with stereotactic body radiotherapy were excluded. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

TREATMENT. Patients were treated with definitive concurrent chemoradiotherapy (without surgery), neoadjuvant radiotherapy or chemoradiotherapy (prior to surgical resection), or adjuvant radiotherapy or chemoradiotherapy (following surgical resection). Chemotherapy was typically administered as a platinum doublet, including cisplatin or carboplatin plus a cytotoxic agent (pemetrexed, docetaxel, paclitaxel, gemcitabine, or vinorelbine). A 3-dimensional or 4-dimensional computed tomography (CT) scan was obtained for radiotherapy planning, and when available, diagnostic CT and/or positron emission tomography scans were coregistered to the planning CT to aid delineation of tumor and normal anatomy structures. Radiation was targeted to the gross tumor and/or areas most at risk for microscopic tumor and was typically delivered in daily fractions (treatments) of 1.8 to 2.0 Gy (range 1.8 to 4.0 Gy; 99.2% [742 of 748] received 1.8-2.0 Gy fractions) to cumulative doses of 50 to 66 Gy. Radiotherapy was planned using Varian

TABLE 1 Patient and Treatment Characteristics

	Total (N = 748)	CHD Negative (n = 480)	CHD Positive (n = 268)	p Value
Age, yrs	65 (57-73)	62 (55-71)	68 (62-76)	<0.0001
Sex				
Female	368 (49.2)	252 (52.5)	116 (43.3)	
Male	380 (50.8)	228 (47.5)	152 (56.7)	0.018
ECOG PS				
0-1	660 (88.2)	439 (91.5)	221 (82.5)	
2	69 (9.2)	32 (6.7)	37 (13.8)	
3-4	19 (2.5)	9 (1.9)	10 (3.7)	0.001
Weight loss	237 (31.7)	157 (32.7)	80 (29.9)	0.46
Tobacco				
Never	60 (8.0)	52 (10.8)	8 (3.0)	
Current	298 (39.8)	201 (41.9)	97 (36.2)	
Former	390 (52.1)	227 (47.3)	163 (60.8)	<0.001
PY	43 (30-60)	40 (28-60)	48 (30-72)	0.0004
Medical history				
Hypertension	375 (50.1)	189 (39.4)	186 (69.4)	<0.001
Hyperlipidemia	359 (48.0)	184 (38.3)	175 (65.3)	<0.001
Diabetes mellitus	105 (14.0)	43 (9.0)	62 (23.1)	<0.001
DVT/PE	34 (4.6)	19 (4.0)	15 (5.6)	0.36
Arrhythmia	103 (13.8)	43 (9.0)	60 (22.4)	<0.001
Valvulopathy	42 (5.6)	18 (3.8)	24 (9.0)	0.004
PAD	61 (8.2)	–	61 (22.8)	
Stroke	14 (1.9)	–	14 (5.2)	
CAD	216 (28.9)	–	216 (80.6)	
Prior MI	86 (11.5)	–	86 (32.1)	
CHF	61 (8.2)	–	61 (22.8)	
Prior thoracic RT	21 (2.8)	11 (2.3)	10 (3.7)	0.26
Prior chemotherapy	15 (2.0)	13 (2.7)	2 (0.8)	0.10
Framingham risk				
Median, %	14.8 (8.4-26.1)	14.8 (8.4-26.1)		
Low (<10%)	134 (17.9)	134 (27.9)		
Moderate (10%-20%)	120 (16.0)	120 (25.0)		
High-risk (>20%)	226 (30.2)	226 (47.1)		
NSCLC clinical stage				
II	79 (10.6)	40 (8.3)	39 (14.6)	
IIIA	418 (55.9)	272 (56.7)	146 (54.5)	
IIIB	251 (33.6)	168 (35.0)	83 (31.0)	0.028
Tumor laterality				
Right	417 (55.8)	279 (58.1)	138 (51.5)	
Left	281 (37.6)	174 (36.3)	107 (39.9)	0.12
NSCLC histology				
Adenocarcinoma	331 (44.3)	229 (47.7)	102 (38.1)	
SCC	234 (31.3)	128 (26.7)	106 (39.6)	
Large cell carcinoma	133 (17.8)	89 (18.5)	44 (16.4)	
Other	50 (6.7)	34 (7.1)	16 (6.0)	0.004
Chemotherapy type				
Induction	158 (21.1)	101 (21.0)	57 (21.3)	1.00
Concurrent	641 (85.7)	424 (88.3)	217 (81.0)	0.007
Adjuvant	247 (33.0)	173 (36.0)	74 (27.6)	0.019
RT/surgery sequence				
Definitive CRT	433 (57.9)	266 (55.4)	167 (62.3)	
Neoadjuvant RT/CRT	171 (22.9)	132 (27.5)	39 (14.6)	
Adjuvant RT/CRT	88 (11.8)	55 (11.5)	33 (12.3)	
RT alone	56 (7.5)	27 (5.6)	29 (10.8)	<0.001

Continued on the next page

Eclipse (Varian Medical Systems, Palo Alto, California) and prioritized meeting the prescription dose to the tumor while minimizing dose to the spinal cord and lung. Specifically, the dose constraints were (VX Gy = volume [%] receiving X Gy): spinal cord (maximum <50 Gy), lungs (mean <17 Gy, V20 Gy <30%, V5 Gy <50%). Cardiac dose constraints were not adopted until 2008 (V30 Gy <50%, V45 Gy <40%, and V60 Gy <20%).

DOSIMETRIC ANALYSIS. Individual radiotherapy dose distributions were reviewed manually, and dose-volume histograms were generated in MIM (MIM Software, Cleveland, Ohio). Hearts were recontoured manually per cardiac radiotherapy atlas definitions (21) by 2 investigators (K.M.A. and D.S.B.) and independently reviewed (R.H.M.). Bilateral lungs were contoured using automated thresholding and excluding gross tumor volume. Mean heart dose (MHD) was individually calculated for each patient and defined as the mean radiation dose (Gy) delivered to the whole heart (including pericardium) by the completion of radiotherapy.

BASELINE CARDIAC RISK AND COMORBIDITIES. In-depth manual medical record review was performed to determine the presence (or absence) of pre-existing CHD, defined as coronary artery disease, congestive heart failure, or a CHD risk equivalent (peripheral vascular disease or stroke). Past medical history, notes (consultation, follow-up, emergency department visits, and admissions), reports (imaging, procedure, and electrocardiograms), and laboratory data were reviewed to identify prior diagnoses and/or cardiac events. Patients with coronary artery calcifications reported on diagnostic chest CT were categorized as having coronary artery disease.

For CHD-negative patients, 10-year Framingham cardiovascular disease (CVD) risk was calculated (body mass index utilized when lipids were unavailable) (18). Pre-existing arrhythmia and valvulopathy were defined as symptomatic, requiring medical intervention, or any ventricular arrhythmia or moderate or greater echocardiogram abnormality, respectively. Performance status was assessed using the Eastern Cooperative Oncology Group scale. Weight loss was defined as unintentional and within 6 months of diagnosis. Smoking was defined as never (<100 lifetime cigarettes), current (or quit <1 year prior to diagnosis), or former (quit ≥1 year prior to diagnosis). Prior thoracic radiation therapy (RT) and/or chemotherapy included treatment for prior (nonlung cancer) malignancies.

CARDIAC ENDPOINTS. The primary endpoint of AHA/ACC-defined MACE (22) and the secondary endpoint of grade ≥3 CTCAE (version 4.03) (20) were defined as occurring after day 1 of radiotherapy or ≥30 days post-operatively (if applicable). Categories of MACE included cardiac death, unstable angina, myocardial infarction (MI), heart failure hospitalization or urgent visit, and coronary revascularization. Individual CTCAE were grouped into coronary/cardiac arrest, arrhythmia, heart failure/cardiomyopathy, valvulopathy, pericardial, and cardiopulmonary (nonpleural effusion)/other categories. Events were determined by in-depth manual medical record review (as described in the previous text). Patients with pre-existing cardiac comorbidities that remained stable after radiotherapy (by comparison to 6-month interval preceding radiotherapy) were not recorded as having events.

FOLLOW-UP AND DETERMINATION OF CAUSE OF DEATH. Patients were typically seen in follow-up with chest imaging every 3 to 6 months following radiotherapy. Cause of death was determined by medical record review. Lung cancer–specific death was defined as death as a result of active or progressive disease. Cardiac-specific death was defined as sudden cardiac death, or death due to acute MI, heart failure, cardiovascular procedure, cardiovascular hemorrhage, or other (17).

STATISTICAL ANALYSIS. Descriptive statistics were used to report the distribution of clinical characteristics by pre-existing CHD status. Continuous covariates were evaluated using a Wilcoxon rank sum test, whereas categorical covariates were compared using a Fisher exact test. Cumulative incidence estimates (23) of MACE and CTCAE subgroups, with noncardiac death as a competing risk, and 1 − Kaplan-Meier estimates (24) of ACM were calculated and graphically displayed, stratified by CHD or cardiac dose. Estimates were compared using a 2-sided Gray's p value for MACE and CTCAE and a log-rank 2-sided p value for ACM, respectively. The proportional hazards assumption was assessed by chi-square goodness-of-fit (25). The selected dose threshold of 10 Gy was based on published dose stratifications (12,13), cutpoint analysis (26), and our clinical threshold for toxicity. The relationship between MACE and heart dose was depicted graphically by plotting 2-year MACE cumulative incidence estimates by increments of 5 Gy MHD.

Univariable and multivariable Fine and Gray (27) regressions (with noncardiac death as a competing risk) and Cox (28) regressions were performed to ascertain whether clinical or dosimetric variables were associated with MACE, CTCAE, or ACM, adjusting for lung cancer and cardiovascular prognostic and treatment factors. For the models, time 0 was the start date of radiotherapy and concluded by the date of first MACE/CTCAE (or death for ACM) or last observation, whichever came first. Unadjusted hazard ratios (HRs) and adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) were calculated. Multivariable models included covariables with $p \leq 0.05$ on univariable analysis and MHD and CHD (regardless of p value). The interaction between MHD (continuous variable) and pre-existing CHD (categorical variable) was tested. A 2-sided $p \leq 0.05$ was considered statistically significant except in the case of multiple testing, where $p \leq 0.025$ (0.05/2) was considered significant. Stata version 15.1 (StataCorp LLC, College Station, Texas) and SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) statistical software were used for all analyses.

TABLE 1 Continued

	Total (N = 748)	CHD Negative (n = 480)	CHD Positive (n = 268)	p Value
RT technique				
3D-CRT	584 (78.1)	367 (76.5)	217 (81.0)	
IMRT	164 (21.9)	113 (23.5)	51 (19.0)	0.17
RT year				
<2008	273 (36.5)	175 (36.5)	98 (36.6)	
≥2008	475 (63.5)	305 (63.5)	170 (63.4)	1.00
Prescribed RT dose, Gy	64.0 (54.9-66.0)	63.5 (54.0-66.0)	64.0 (60.0-66.0)	0.99
Dose	701*	449*	252*	
Heart mean, Gy	12.3 (5.9-19.0)	11.8 (5.9-19.0)	12.9 (6.1-19.5)	0.37
Heart V5Gy, %	35.7 (19.2-57.3)	34.1 (18.6-55.5)	37.5 (19.9-62.4)	0.22
Heart V30Gy, %	15.3 (6.4-27.2)	14.6 (6.2-27.1)	16.3 (6.9-27.9)	0.49
Esophagus mean, Gy	23.7 (17.1-30.6)	24.0 (17.6-30.7)	23.4 (15.3-29.7)	0.11
Lung mean, Gy	14.9 (11.6-17.2)	15.2 (11.4-17.4)	14.6 (11.8-17.0)	0.34
Lung V5Gy, %	42.9 (32.8-52.1)	42.8 (32.7-52.4)	43.0 (33.5-51.7)	0.92
Lung V20Gy, %	25.2 (19.2-29.6)	25.2 (19.3-29.7)	25.1 (19.2-29.2)	0.63

Values are median (interquartile range), n (%), or n. *Based on dose plan information available for n = 701 total patients. The distributions of continuous variables were compared using the Wilcoxon rank sum test, while categorical covariates were compared using the Fisher exact test.

3D-CRT = 3-dimensional conformal radiation therapy; CAD = coronary artery disease; CHD = coronary heart disease; CHF = congestive heart failure; CRT = chemoradiotherapy; DVT = deep venous thrombosis; ECOG = Eastern Cooperative Oncology Group; Gy = Gray; IMRT = intensity modulated radiation therapy; MI = myocardial infarction; NSCLC = non-small cell lung cancer; PAD = peripheral artery disease; PE = pulmonary embolism; PS = performance status; PY = pack-years; RT = radiation therapy; SCC = squamous cell carcinoma.

RESULTS

CLINICAL CHARACTERISTICS. The median age was 65 years (interquartile range [IQR]: 57 to 73 years), 49.2% were women, and 35.8% had pre-existing CHD (n = 268) (Table 1). Compared with CHD-negative patients, CHD-positive patients were older ($p < 0.0001$), more likely male ($p = 0.018$), with greater smoking history ($p = 0.0004$), less likely to be treated with chemotherapy ($p = 0.007$) or surgery ($p = < 0.001$),

with no difference in radiotherapy technique or dose parameters ($p > 0.05$). Among CHD-negative patients, the median Framingham risk was 14.8% (IQR: 8.4% to 26.1%). The median prescription radiation dose delivered to gross tumor or areas most at risk for microscopic tumor was 66.0 Gy (IQR: 54.9 to 66.0 Gy) and a median mean radiation dose delivered to the heart (mean heart dose [MHD]) of 12.3 Gy (IQR: 5.9 to 19.0 Gy).

ANALYSIS OF MACE. With a median follow-up of 20.4 months (IQR: 8.4 to 45.0 months), 77 of 748 (10.3%) patients developed ≥1 MACE (27 of 480 [5.6%] CHD-negative vs. 50 of 268 [18.7%] CHD-positive; $p < 0.0001$) with a median time to first MACE of 18.5 months (IQR: 5.4 to 33.6 months). A total of 28 patients developed an MI, 28 had a heart failure event, 27 had a cardiac-specific death, and 20 required coronary revascularization (MI at time of revascularization [n = 8], stent [n = 11], coronary artery bypass grafting [n = 3], revascularization unsuccessful/unattempted [n = 6]) (Online Table 1). There was an increased risk of MACE in CHD-positive versus CHD-negative patients (unadjusted HR: 3.58; 95% CI: 2.25 to 5.71; $p < 0.001$) with 2-year cumulative incidence estimates of 11.7% (95% CI: 8.2% to 15.9%) versus 2.5% (95% CI: 1.4% to 4.2%), respectively (**Table 2, Central Illustration**). The risk of MACE had no apparent threshold below which the risk was decreased (Online Figure 1). Cutpoint analysis identified an optimal MHD of 13.5 Gy for MACE and 11.5 Gy for ≥3 CTCAE, although these were poorly discriminatory with concordance indexes of 0.57 and 0.56, respectively.

After adjustment for age, baseline CHD or arrhythmia, and radiotherapy technique, a significant increase in the risk of MACE was observed in patients with increasing MHD (AHR: 1.05/Gy; 95% CI: 1.02 to 1.08/Gy; $p < 0.001$) (**Table 3**). Moreover, there was a significant interaction between MHD and CHD (AHR: 0.95; 95% CI: 0.91 to 0.99; $p = 0.007$). Specifically, for the 480 CHD-negative patients, treatment with MHD ≥10 Gy versus <10 Gy was associated with a significantly higher risk of MACE (19 events vs. 5 events; HR: 3.01; 95% CI: 1.15 to 7.89; $p = 0.025$), with 2-year estimates of 3.5% (95% CI: 1.7% to 6.3%) versus 1.1% (95% CI: 0.2% to 3.5%), respectively (**Central Illustration**). Conversely, among the 268 CHD-positive patients, there was no observed increased risk of MACE with MHD ≥10 Gy versus <10 Gy (27 events vs. 19 events; HR: 0.99; 95% CI: 0.55 to 1.77; $p = 0.98$), with 2-year cumulative incidence estimates of 12.1% (95% CI: 7.5% to 17.9%) versus 10.0% (95% CI: 5.1% to 16.8%), respectively (**Central Illustration**).

ANALYSIS OF ACM. A total of 533 patients died (71.3%), 357 of lung cancer (67.0%), 41 of known noncardiac causes (7.7%), and 27 of cardiac causes (5.1%). Among the 27 cardiac deaths, 17 of 268 (6.3%) versus 10 of 480 (2.1%) occurred in CHD-positive versus CHD-negative patients ($p = 0.0028$), respectively. The median OS was 22.3 months (IQR: 9.8 to 45.7 months). There was an increased risk of ACM in CHD-positive versus CHD-negative patients (unadjusted HR: 1.31; 95% CI: 1.10 to 1.56; $p = 0.003$) with 2-year estimates of 53.2% (95% CI: 47.3% to 59.3%) versus 46.4% (95% CI: 42.0% to 51.0%), respectively (**Figure 1A**).

After adjustment for age, sex, performance status, unintentional weight loss, baseline CHD or arrhythmia, treatment regimen, and RT year, a significant increase in the risk of ACM was observed in patients with increasing MHD (AHR: 1.02/Gy; 95% CI: 1.01 to 1.03/Gy; $p = 0.003$) (**Table 3**). Furthermore, a significant interaction was observed between MHD and CHD (AHR: 0.98; 95% CI: 0.96 to 1.00; $p = 0.030$). Specifically, for the 480 CHD-negative patients, treatment with MHD ≥10 Gy versus <10 Gy was associated with a significantly higher risk of ACM (178 deaths vs. 118 deaths; HR: 1.34; 95% CI: 1.06 to 1.69; $p = 0.014$), with 2-year estimates of 52.2% (95% CI: 46.1% to 58.5%) versus 40.0% (95% CI: 33.5% to 47.4%), respectively (**Figure 1B**). Among the 268 CHD-positive patients, there was no observed increased risk of ACM with MHD ≥10 Gy versus <10 Gy (112 deaths vs. 82 deaths; HR: 0.94; 95% CI: 0.70 to 1.25; $p = 0.66$), with 2-year estimates of 54.6% (95% CI: 46.8% to 62.7%) versus 50.8% (95% CI: 41.5% to 60.9%), respectively (**Figure 1C**).

ANALYSIS OF CTCAE CARDIAC SUBGROUPS. Of 748 patients, 240 (32.1%) developed ≥1 grade ≥3 CTCAE (126 of 480 [26.3%] CHD-negative vs. 112 of 268 [41.8%] CHD-positive; $p < 0.0001$) with a median time to first event of 10.4 months (IQR: 3.2 to 26.2 months). There was an increased risk of grade ≥3 CTCAE in CHD-positive versus CHD-negative patients (unadjusted HR: 1.78; 95% CI: 1.39 to 2.30; $p < 0.001$) with 2-year cumulative incidence estimates of 31.0% (95% CI: 25.5% to 36.6%) versus 19.0% (95% CI: 15.6% to 22.6%), respectively (**Table 2**, Online Figure 2A). The 2-year cumulative incidences of CTCAE subgroups by CHD (**Table 2**) and individual absolute events (Online Table 1) were determined.

After adjustment for baseline CHD or arrhythmia and treatment regimen, a significant increase in the risk of grade ≥3 CTCAE was observed in patients with increasing MHD (AHR: 1.03/Gy; 95% CI: 1.01 to 1.04; $p = 0.002$) (Online Table 2). There was a trend toward

TABLE 2 Cumulative Incidences at 2 Years of Cardiac Event Subgroups by Pre-Existing CHD Status

	Total (N = 748)		CHD Negative (n = 480)		CHD Positive (n = 268)		
Event Type	n (%)	2-Year % (95% CI)	n (%)	2-Year % (95% CI)	n (%)	2-Year % (95% CI)	p Value
AHA/ACC MACE							
MACE, any	77 (10.3)	5.8 (4.3-7.7)	27 (5.6)	2.5 (1.4-4.2)	50 (18.7)	11.7 (8.2-15.9)	<0.001
CV death	27 (3.6)	1.6 (0.9-2.7)	10 (2.1)	0.6 (0.2-1.7)	17 (6.3)	3.4 (1.7-6.1)	0.004
CV death/nonfatal MI	49 (6.6)	3.3 (2.2-4.7)	18 (3.8)	1.7 (0.8-3.2)	31 (11.6)	6.0 (3.6-9.4)	<0.001
Grade ≥3 CTCAE							
Any	240 (32.1)	23.3 (20.3-26.4)	126 (26.3)	19.0 (15.6-22.6)	112 (42.5)	31.0 (25.5-36.6)	<0.001
Arrhythmia	128 (17.1)	11.9 (9.7-14.4)	64 (13.3)	9.5 (7.1-12.3)	64 (23.9)	16.2 (12.1-20.9)	0.001
Coronary/cardiac arrest	45 (6.0)	2.3 (1.4-3.6)	20 (4.2)	0.8 (0.3-2.0)	25 (9.3)	4.9 (2.8-8.0)	<0.001
Heart failure/CM	73 (9.8)	5.5 (4.1-7.4)	27 (5.6)	2.7 (1.5-4.5)	46 (17.2)	10.5 (7.2-14.6)	<0.001
Pericardial, all types	49 (6.6)	4.6 (3.3-6.3)	36 (7.5)	6.1 (4.2-8.5)	13 (4.9)	1.9 (0.7-4.1)	0.14
*Effusion, benign cyto.	21 (2.8)	1.8 (1.0-2.9)	16 (3.3)	2.8 (1.5-4.5)	5 (1.9)	0 (no events yet)	0.24
Valvulopathy	16 (2.1)	1.0 (0.4-1.9)	8 (1.7)	0.6 (0.2-1.8)	8 (3.0)	1.5 (0.5-3.6)	0.24
Cardiopulmonary/other	56 (7.5)	5.4 (3.9-7.2)	33 (6.9)	5.2 (3.5-7.5)	23 (8.6)	5.7 (3.3-8.9)	0.42

*Patients requiring pericardiocentesis with cytology showing no evidence of malignant cells. Estimates were compared using a 2-sided Gray's p value.

ACC = American College of Cardiology; AHA = American Heart Association; CM = cardiomyopathy; CTCAE = common terminology criteria for adverse event; CV = cardiovascular; cyto. = cytology; MACE = major adverse cardiac event; other abbreviations as in Table 1.

significant interaction between MHD and CHD (AHR: 0.98; 95% CI: 0.95 to 1.00; p = 0.073) and CHD-negative patients with MHD ≥10 Gy versus <10 Gy had a significantly higher risk of grade ≥3 CTCAE (77 events vs. 38 events; HR: 1.63; 95% CI: 1.11 to 2.39; p = 0.013), with 2-year estimates of 22.8% (95% CI: 17.9% to 28.1%) versus 13.7% (95% CI: 9.3% to 19.0%), respectively (Online Figure 2B). There was no significant increased risk of grade ≥3 CTCAE among CHD-positive patients with MHD ≥10 Gy versus <10 Gy (64 events vs. 40 events; HR: 1.10; 95% CI: 0.74 to 1.63; p = 0.64), with 2-year cumulative incidence estimates of 29.6% (95% CI: 22.5% to 37.1%) versus 29.9% (95% CI: 21.3% to 39.0%), respectively (Online Figure 2C).

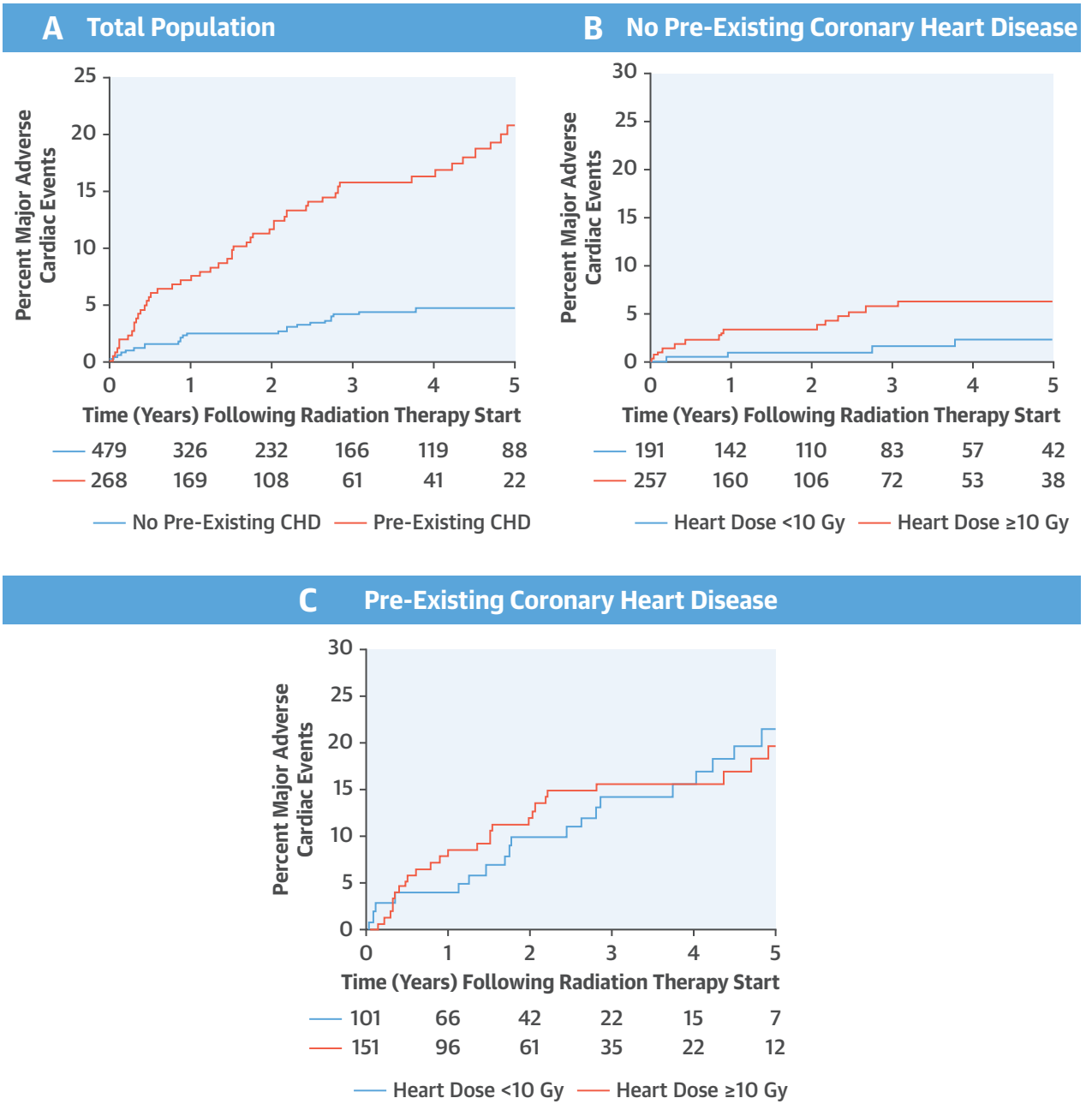
DISCUSSION

Despite the competing risk of cancer-specific death and short life expectancy of locally advanced NSCLC patients, we observed a high risk for MACE within 2 years post-radiotherapy, and cardiac radiation dose exposure was an independent predictor of MACE, grade ≥3 CTCAE, and ACM. As cardiac radiation dose is modifiable during the radiotherapy planning process, these results underscore the importance of more stringent avoidance of high cardiac radiotherapy dose, highlight the importance of early recognition and treatment of cardiovascular events, as well as inform the design of prospective trials incorporating baseline cardiac risk stratification with cardiac radiation dose reduction techniques and post-radiotherapy cardiac preventative care.

Strengths of this study include cardiac radiation dose analysis in one of the largest locally advanced NSCLC cohorts that expands substantially on recent smaller reports, the first application of AHA/ACC-defined MACE as a primary endpoint in this patient population, and comprehensive detailing of cardiac risk factors and validated cardiac endpoints to provide a shared framework between radiation oncologists, primary care physicians, and cardiologists to identify high-risk patients and inform post-radiotherapy cardiac risk prevention strategies.

Several points require further discussion. First, our observed MACE rates among CHD-negative patients (harboring moderate median Framingham risk) exceed rates in high-risk Framingham Heart Study participants, even within a narrow time frame post-radiotherapy (29,30). For example, the 1-year rate of atherosclerotic CVD and CV death/nonfatal MI was approximately 0.6% in Framingham participants eligible for lung cancer screening (29) or with high-risk Agatston coronary calcium scores (30). By contrast, we observed a 1-year cumulative incidence of CV death/nonfatal MI and total MACE of 1.7% and 2.5%, respectively (**Table 2**). Such rates surpass guideline thresholds for recommending aggressive risk reduction (19). Moreover, large database and epidemiological studies estimate that >40% of patients with lung cancer have pre-existing CVD, and shared risk profiles exist between CVD and cancer-related mortality (31,32) with higher cancer-related mortality in individuals meeting guideline-based statin eligibility (33). However, less than one-half of these patients are treated with guideline-directed

CENTRAL ILLUSTRATION Cardiac Radiation Dose and Lung Cancer Mortality



Atkins, K.M. et al. J Am Coll Cardiol. 2019;73(23):2976–87.

Cumulative incidence of MACE stratified by **(A)** pre-existing CHD (Gray's $p < 0.001$) or MHD in **(B)** patients without pre-existing CHD (Gray's $p = 0.025$) and **(C)** patients with pre-existing CHD (Gray's $p = 0.98$). CHD = coronary heart disease; MACE = major adverse cardiac events; MHD = mean heart dose.

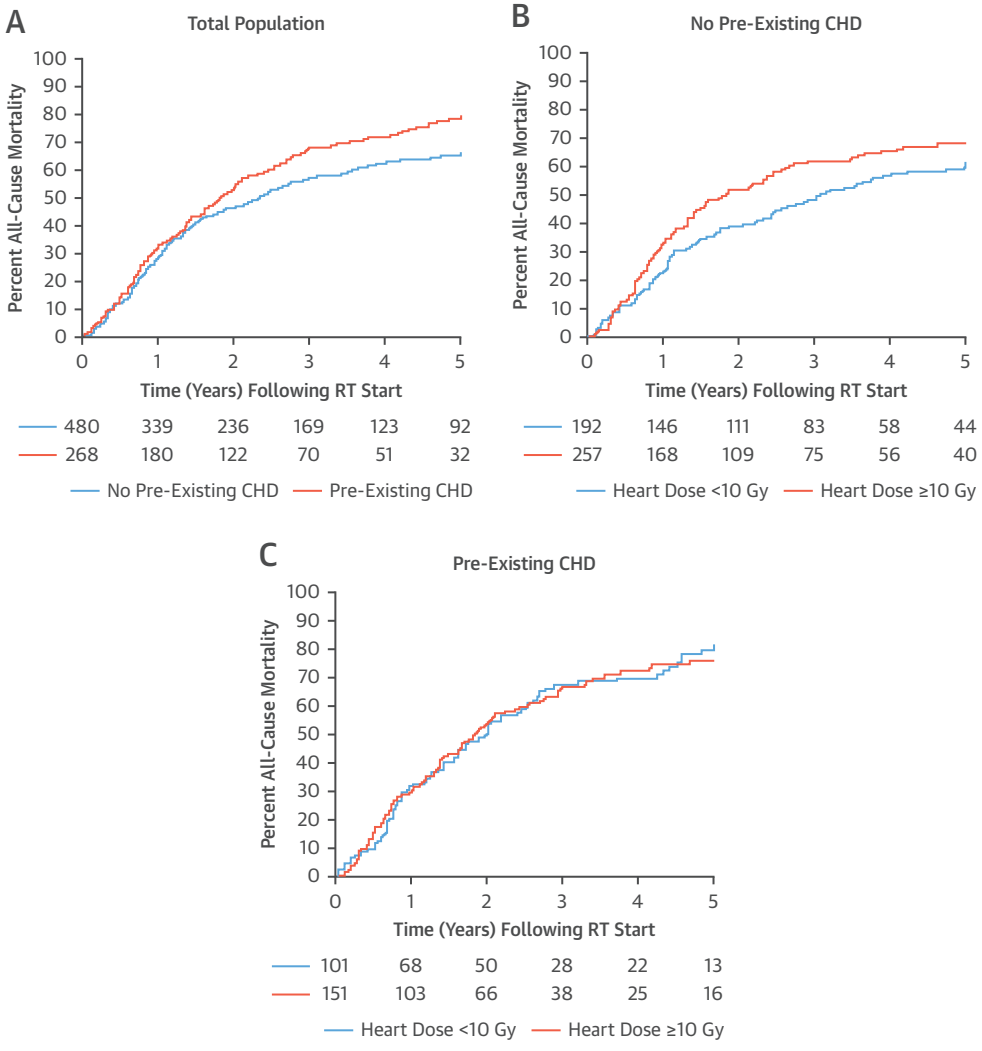
TABLE 3 Competing Risks and Cox Regression Analyses for Major Adverse Cardiac Events and All-Cause Mortality

		Major Adverse Cardiac Events					All-Cause Mortality				
			Univariable		Multivariable			Univariable		Multivariable	
	N	No. MACE	HR (95% CI)	p Value	AHR (95% CI)	p Value	No. of ACD	HR (95% CI)	p Value	AHR (95% CI)	p Value
Lung cancer factors											
Age, yrs*	748	77	1.03 (1.01–1.05)	0.007	1.01 (0.99–1.04)	0.30	533	1.02 (1.01–1.03)	<0.001	1.00 (0.99–1.01)	0.41
Sex*											
Female	368	38	1.00 (Referent)				251	1.00 (Referent)		1.00 (Referent)	
Male	380	39	1.00 (0.64–1.56)	1.00			282	1.20 (1.01–1.43)	0.034	1.14 (0.95–1.36)	0.16
ECOG PS											
0–1	660	68	1.00 (Referent)				458	1.00 (Referent)		1.00 (Referent)	
2–4	88	9	0.98 (0.49–1.96)	0.96			75	1.63 (1.28–2.09)	<0.001	1.57 (1.21–2.03)	0.001
Smoking*											
Never	60	5	1.00 (Referent)				40	1.00 (Referent)			
Ever	688	72	1.27 (0.51–3.16)	0.61			493	1.30 (0.94–1.80)	0.11		
Weight loss*											
No	511	59	1.00 (Referent)				360	1.00 (Referent)		1.00 (Referent)	
Yes	237	18	0.67 (0.40–1.13)	0.13			173	1.33 (1.10–1.59)	0.002	1.23 (1.01–1.49)	0.037
Stage											
II	79	11	1.00 (Referent)				53	1.00 (Referent)			
III	669	66	0.71 (0.38–1.33)	0.28			480	1.18 (0.89–1.57)	0.25		
Tumor laterality											
Right	417	36	1.00 (Referent)				300	1.00 (Referent)			
Left	281	35	1.51 (0.95–2.41)	0.080			200	0.97 (0.81–1.16)	0.71		
Histology											
Adeno	331	33	1.00 (Referent)				232	1.00 (Referent)			
Nonadeno	417	44	1.09 (0.70–1.71)	0.70			301	1.17 (0.99–1.40)	0.07		
Baseline cardiac factors											
CHD											
No	480	27	1.00 (Referent)		1.00 (Referent)		324	1.00 (Referent)		1.00 (Referent)	
Yes	268	50	3.58 (2.25–5.71)	<0.001	7.00 (3.20–15.31)	<0.001	209	1.31 (1.10–1.56)	0.003	1.37 (0.99–1.89)	0.054
Arrhythmia											
No	645	59	1.00 (Referent)		1.00 (Referent)		453	1.00 (Referent)		1.00 (Referent)	
Yes	103	18	2.07 (1.21–3.54)	0.008	1.55 (0.85–2.81)	0.15	80	1.36 (1.08–1.73)	0.011	1.26 (0.98–1.62)	0.075
Treatment factors											
RT/surgery sequence											
Definitive RT/CRT	489	51	1.00 (Referent)				398	1.00 (Referent)		1.00 (Referent)	
Neoadjuvant/adjuvant RT/CRT	259	26	0.97 (0.60–1.55)	0.89			135	0.40 (0.33–0.48)	<0.001	0.41 (0.33–0.51)	<0.001
Chemo (any)											
No	42	4	1.00 (Referent)				32	1.00 (Referent)			
Yes	706	73	1.04 (0.38–2.86)	0.94			501	0.75 (0.52–1.07)	0.11		
RT technique											
3D-CRT	584	69	1.00 (Referent)		1.00 (Referent)		423	1.00 (Referent)			
IMRT	164	8	0.43 (0.21–0.89)	0.023	0.39 (0.18–0.84)	0.017	110	1.14 (0.9–1.41)	0.23		
RT year											
<2008	273	28	1.00 (Referent)				235	1.00 (Referent)		1.00 (Referent)	
≥2008	475	49	1.14 (0.72–1.80)	0.57			298	0.83 (0.70–0.99)	0.042	0.79 (0.66–0.95)	0.013
Mean heart dose, Gy	701	70	1.02 (1.00–1.04)	0.090	1.05 (1.02–1.08)	<0.001	490	1.01 (1.00–1.02)	0.015	1.02 (1.01–1.03)	0.003
Interaction											
†Cardiac dose × CHD	701	70	0.95 (0.92–0.99)	0.008	0.95 (0.91–0.99)	0.007	490	0.98 (0.96–1.00)	0.049	0.98 (0.96–1.00)	0.030

*Both a lung cancer and cardiac prognostic factor. †Interaction term between heart dose (continuous variable) and pre-existing CHD (categorical variable).

ACD = all-cause death; adeno = adenocarcinoma; AHR = adjusted hazard ratio; chemo = chemotherapy; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

FIGURE 1 All-Cause Mortality Estimates Stratified by Pre-Existing CHD and MHD



All-cause mortality estimates stratified by **(A)** pre-existing CHD (log-rank p = 0.003) or MHD in **(B)** patients without pre-existing CHD (log-rank p = 0.014), and **(C)** patients with pre-existing CHD (log-rank p = 0.66). The proportional hazards assumption was not violated (**A**, p = 0.127; **B**, p = 0.838; **C**, p = 0.099). CHD = coronary heart disease; MACE = major adverse cardiac events; MHD = mean heart dose; RT = radiation therapy.

medical therapy and/or are medically optimized according to AHA/ACC recommendations (31,34). Together, these findings illustrate that patients with locally advanced NSCLC represent a distinctly high cardiovascular-risk population both at baseline and due to radiation exposure with an unmet need for optimized cardiac risk reduction.

Second, utilization of MACE endpoints (17) allows comparison to comprehensive radiotherapy-associated cardiotoxicity studies in breast cancer and Hodgkin lymphoma (1-3). Indeed, Darby et al. (3) reported that major coronary event (MI, revascularization, CV death) rates increased linearly with MHD by 7.4% per Gy, beginning within 5 years post-radiotherapy (3), and Van Nimwegen et al. (1,2) similarly showed 7.4% per Gy excess relative risk of CHD with a median interval to CHD of >18 years. Although we observed a similar absolute risk of MACE (HR: 1.05/Gy) in NSCLC patients with no apparent threshold below which the risk was decreased (Online Figure 1), these events occurred over a considerably more contracted timeframe (1 to 2 years) in patients with high baseline cardiac risk and a significant competing risk of lung cancer mortality. Together,

these results suggest that cardiac events may be under-measured after high-dose thoracic radiotherapy and may impart an even greater clinical effect as competing risks decrease with improved NSCLC outcomes (7-11), thereby further illustrating the importance of cardiac dose reduction.

Third, our observed cumulative incidence of grade ≥3 CTCAE (23% at 2 years) was higher than recent studies reporting 2-year rates of 10% and 11% for "symptomatic cardiac events" or grade ≥3 CTCAE, respectively (12,13). These differences may be due, in part, to a higher proportion of CHD-positive patients in our cohort (36% vs. 14% to 27%), as MHD was similar (12,13). Notably, our study included 748 patients, perhaps providing more robust estimates of cardiac events and baseline risk compared with smaller cohorts (n = 112 [12] or n = 125 [13]), which may be reflected by the interaction between CHD and MHD observed in our study compared with Dess et al. (13).

Given the global burden of NSCLC and improving outcomes in the era of immunomodulatory and molecularly targeted therapies (9,11), post-radiotherapy cardiac events present a formidable health problem for which aggressive risk mitigation strategies are imminently needed and adequate practice guidelines are lacking. Indeed, American Society of Clinical Oncology recommendations focus on anthracycline and anti-HER2-associated cardiotoxicity with echocardiogram-based monitoring (35), but are insufficient for radiotherapy-based risk assessment, particularly in high cardiac-risk NSCLC patients. Accordingly, we recommend that all NSCLC patients undergo age appropriate screening for cardiac risk factors with estimation of 10-year cardiovascular risk using either Framingham or AHA/ACC risk scores. Cardiac risk factors (i.e., blood pressure, cholesterol, and hemoglobin A1c) should be optimized per current guideline recommendations. Given the increased prevalence of CVD in this population (36), a detailed history and physical to assess for signs or symptoms concerning for ischemia and CHD should be performed, and if present or if very poor functional capacity, further workup, including functional stress test with imaging, should be considered. The optimal method for risk assessment, monitoring, and risk reductive measures beyond current recommended guidelines warrants prospective testing.

For radiotherapy planning, we suggest a more stringent avoidance of high cardiac radiotherapy dose and reconsideration of stricter cardiac radiation dose constraints than those recently published (MHD <20 Gy) (12) or in national guidelines (MHD <20 Gy in 2019 guidelines but previously ≤26 Gy) (36). Specifically, we recommend MHD <10 Gy, based on a comparison with recently published dose stratifications (12,13) and our clinical threshold for toxicity, as a cutoff <10 Gy correlated with MACE and grade ≥3 CTCAE 2-year cumulative incidences of 1% and 14%, respectively, in CHD-negative patients, and 10% and 30%, respectively, in CHD-positive patients, and was conservatively just below cutpoint analysis thresholds (13.5 and 11.5 Gy for MACE and grade ≥3 CTCAE, respectively). If recommended doses must be exceeded due to tumor location and/or lung dose safety, we advocate for early, frequent cardiology follow-up for primary or secondary prevention with aggressive risk factor management.

Although we did not observe an association between cardiac dose and risk of MACE/CTCAE/ACM in CHD-positive patients, we suspect this is due to surpassing an observable dose-response relationship in the setting of elevated baseline cardiac risk with high-dose thoracic RT, rather than cardiac dose not being important in these patients. Indeed, among the 50 CHD-positive patients who received <5 Gy MHD, the 2-year cumulative incidence of MACE was already 10.1% while patients receiving ≥10 Gy had rates of 12.1%. Furthermore, the absolute increase in the 2-year cumulative incidence of MACE with MHD ≥10 Gy versus <10 Gy in CHD-negative versus CHD-positive patients was similar (2.4% vs. 2.1%, respectively), which may reflect an effect of cardiac dose being masked in CHD-positive patients who have elevated baseline cardiac event rates, even at MHD <5 Gy. Thus, there may not be a "safe" cardiac dose threshold in this setting, and these patients may warrant dose limits that are significantly lower, although this warrants further investigation.

STUDY LIMITATIONS. Potential limitations of this study include the heterogeneous treatment regimens and its retrospective nature. Indeed, more than one-third of treatment regimens included surgery, which was associated with reduced risk of ACM and likely a surrogate for better baseline cardiac and performance status. Nonetheless, after accounting for treatment regimens, chemotherapy use, and radiotherapy technique, cardiac dose remained an independent predictor of MACE, CTCAE, and ACM, suggesting that our results may be generalizable to a broad range of locally advanced NSCLC treatment paradigms that include radiotherapy. Importantly, despite MACE and CTCAE events commonly occurring post-radiotherapy in this study, retrospective assessment may in fact underestimate true cardiac risk, particularly in patients with limited follow-up due to competing risks or medical care received locally and incompletely

captured despite in-depth medical record review. Similarly, although we observed a 36% prevalence of CHD, consistent with studies from others (13,31), this may be an underestimate in the retrospective setting.

CONCLUSIONS

Our study strongly suggests that despite the competing risk of cancer-specific death and short life expectancy of locally advanced NSCLC patients, there is a high risk for MACE within 2-years post-radiotherapy and cardiac radiation dose exposure is an independent predictor of MACE, grade ≥3 CTCAE, and ACM. The results of this study highlight the importance of early recognition and treatment of cardiovascular events and inform the design of future prospective trials that incorporate baseline cardiac risk stratification with cardiac radiation dose reduction techniques and post-radiotherapy cardiac preventative care. Indeed, as cardiac dose exposure is a modifiable predictor, we suggest more stringent avoidance of high cardiac radiotherapy dose and reconsideration of stricter cardiac radiation dose constraints in national radiotherapy guidelines.

ADDRESS FOR CORRESPONDENCE: Dr. Raymond H. Mak, Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, 450 Brookline Avenue, Boston, Massachusetts 02115. E-mail: rmak@partners.org. Twitter: @Dr_RayMak.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: Despite the competing risks of cancer-related death, patients with locally advanced NSCLC may benefit from reduction of cardiac radiation dose, preventive post-radiotherapy cardiac care, and earlier recognition and treatment of cardiovascular events.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to assess the effect of combined cardiac risk stratification, cardiac radiation dose reduction techniques, and post-radiotherapy preventive care on survival and quality of life in patients with lung cancer.

REFERENCES

1. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175:1007–17.

2. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–43.

3. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98.

4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

5. Schytte T, Hansen O, Stolberg-Rohr T, Brink C. Cardiac toxicity and radiation dose to the heart in definitive treated non-small cell lung cancer. Acta Oncol 2010;49:1058–60.

6. Hardy D, Liu CC, Cormier JN, Xia R, Du XL. Cardiac toxicity in association with chemotherapy and radiation therapy in a large cohort of older patients with non-small-cell lung cancer. Ann Oncol 2010;21:1825–33.

7. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99.

8. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2016;34:953–62.

9. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. Lancet 2017;389:299–311.

10. Aberle DR, Adams AM, Berg CD, et al., for the National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

11. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–50.

12. Wang K, Eblan MJ, Deal AM, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. J Clin Oncol 2017;35:1387–94.

13. Dess RT, Sun Y, Matuszak MM, et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. J Clin Oncol 2017;35:1395–402.

14. Speirs CK, DeWees TA, Rehman S, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. J Thorac Oncol 2017;12:293–301.

15. Tucker SL, Liu A, Gomez D, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. Radiother Oncol 2016;119:495–500.

16. Guberina M, Eberhardt W, Stuschke M, et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial. Ann Oncol 2017;28:1084–9.

17. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Nucl Cardiol 2015;22:1041–144.

18. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.

19. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

20. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. NCI (2010, June 14, 2010). Available at: https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed August 29, 2017.

21. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study

cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10–8.

22. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403–69.

23. Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993;88:400–9.

24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

25. Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika 1980;67:145–53.

26. Liu X. Classification accuracy and cut point selection. Stat Med 2012;31:2676–86.

27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

28. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187–220.

29. Lu MT, Onuma OK, Massaro JM, D'Agostino RB Sr., O'Donnell CJ, Hoffmann U. Lung cancer screening eligibility in the community: cardiovascular risk factors, coronary artery calcification, and cardiovascular events. Circulation 2016;134:897–9.

30. Hoffmann U, Massaro JM, D'Agostino RB Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular event prediction and risk reclassification by coronary, aortic, and valvular calcification in the Framingham Heart Study. J Am Heart Assoc 2016;5:e003144.

31. Al-Kindi SG, Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: the unmet need for onco-cardiology. Mayo Clin Proc 2016;91:81–3.

32. Rasmussen-Torvik LJ, Shay CM, Abramson JG, et al. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk In Communities study. Circulation 2013;127:1270–5.

33. Pursnani A, Massaro JM, D'Agostino RB Sr., O'Donnell CJ, Hoffmann U. Guideline-based statin eligibility, cancer events, and noncardiovascular mortality in the Framingham Heart Study. J Clin Oncol 2017;35:2927–33.

34. Hitchcock W, Dess RT, Hartman HE, et al. Optimizing cardiac medications in patients with locally advanced non-small cell lung cancer undergoing definitive radiation. J Radiat Oncol Biol Phys 2017;99:E462.

35. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893–911.

36. National Comprehensive Cancer Network (NCCN) Guidelines. Non-Small Cell Lung Cancer (Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed May 1, 2019.

KEY WORDS cardiac toxicity, cardiotoxicity, non-small cell lung cancer, NSCLC, radiotherapy

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