Elevated Coronary Artery Calcium Quantified by a Validated Deep Learning Model From Lung Cancer Radiotherapy Planning Scans Predicts Mortality

ARTIFICIAL INTELLIGENCE

original reports

Elevated Coronary Artery Calcium Quantified by a Validated Deep Learning Model From Lung Cancer Radiotherapy Planning Scans Predicts Mortality

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abstract

PURPOSE Coronary artery calcium (CAC) quantified on computed tomography (CT) scans is a robust predictor of atherosclerotic coronary disease; however, the feasibility and relevance of quantitating CAC from lung cancer radiotherapy planning CT scans is unknown. We used a previously validated deep learning (DL) model to assess whether CAC is a predictor of all-cause mortality and major adverse cardiac events (MACEs).

METHODS Retrospective analysis of non–contrast-enhanced radiotherapy planning CT scans from 428 patients with locally advanced lung cancer is performed. The DL-CAC algorithm was previously trained on 1,636 cardiac-gated CT scans and tested on four clinical trial cohorts. Plaques ≥ 1 cubic millimeter were measured to generate an Agatston-like DL-CAC score and grouped as DL-CAC = 0 (very low risk) and DL-CAC ≥ 1 (elevated risk). Cox and Fine and Gray regressions were adjusted for lung cancer and cardiovascular factors.

RESULTS The median follow-up was 18.1 months. The majority (61.4%) had a DL-CAC ≥ 1. There was an increased risk of all-cause mortality with DL-CAC ≥ 1 versus DL-CAC = 0 (adjusted hazard ratio, 1.51; 95% CI, 1.01 to 2.26; $P = .04$), with 2-year estimates of 56.2% versus 45.4%, respectively. There was a trend toward increased risk of major adverse cardiac events with DL-CAC ≥ 1 versus DL-CAC = 0 (hazard ratio, 1.80; 95% CI, 0.87 to 3.74; $P = .11$), with 2-year estimates of 7.3% versus 1.2%, respectively.

CONCLUSION In this proof-of-concept study, CAC was effectively measured from routinely acquired radiotherapy planning CT scans using an automated model. Elevated CAC, as predicted by the DL model, was associated with an increased risk of mortality, suggesting a potential benefit for automated cardiac risk screening before cancer therapy begins.

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INTRODUCTION

Individuals with lung cancer represent a high cardiovascular risk group, with more than 40% harboring pre-existing cardiovascular disease and shared risk profiles existing between cardiovascular disease and cancer-related mortality.[1,2] However, these patients are often incompletely medically optimized, with only half of high-risk patients treated with guideline-directed cardiovascular medical therapy, including statins, at the time of diagnosis.[1,3] Moreover, most patients with locally advanced disease are ultimately treated with thoracic radiotherapy, which has been associated with increased risk of cardiac events and mortality.[4-7] These findings highlight the need for comprehensive cardiac risk assessment at the time of lung cancer diagnosis and improved cardiac risk mitigation strategies.

Coronary artery calcium (CAC), which is routinely quantified from cardiac-gated computed tomography (CT) scans, is one of the strongest predictors of atherosclerotic coronary vascular disease and major adverse cardiac events (MACEs).[8-10] The Agatston score is the gold standard method for quantifying CAC, which generates a summed score of all calcified coronary lesions, reflecting the product of each lesion area and a density (peak attenuation) weighting factor.[11] CAC is embedded in the current American College of Cardiology and American Heart Association primary prevention guidelines and frequently used to improve clinical risk prediction,[12,13] and deeper analysis of CAC features, such as volume, mass, density, number of involved segments and arteries, and even radiomics-based assessment of complex radiographic features, have been shown to further improve the predictive value of CAC.[14-18] However, the measurement of CAC has traditionally been limited to specialized, ECG-gated cardiac CT scans, requiring considerable radiologic expertise and manual effort,

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To quantify coronary artery calcium (CAC) from radiotherapy planning computed tomography (CT) scans in patients with locally advanced lung cancer using a previously validated automated deep learning model and assess whether elevated CAC at the time of radiotherapy is associated with increased risk of mortality.

Knowledge Generated

In this proof-of-concept study, CAC was effectively measured from routinely acquired radiotherapy planning CT scans in patients with locally advanced lung cancer using an automated deep learning model. Elevated CAC, as predicted by the model, was associated with an increased risk of mortality, adjusting for lung cancer and cardiovascular prognostic factors.

Relevance

These findings support further validation of applying this approach to routinely acquired radiotherapy planning CT scans to take full advantage of the potentially valuable, but currently untapped, imaging information for automated cardiac risk stratification in patients with cancer.

and the feasibility and utility of automated CAC quantitation from non–ECG-gated, nonrespiratory-gated (free breathing) radiotherapy planning CT scans is unknown.

Recently, deep learning (DL) has demonstrated significant progress in image recognition tasks, enhancing automated evaluation of complex patterns and allowing more unbiased extraction of quantitative imaging features. Convolutional neural networks, frequently trained on millions of photographic images, have been successfully implemented through transfer learning to oncology images to analyze disease states and predict outcomes.[19-22] Indeed, DL in medical imaging can perform complex tasks, which have only been feasible in the past few years. Notably, patients with lung cancer undergo a multitude of high-resolution imaging studies as part of oncologic standard of care, which can be repurposed for biometric measurements, including cardiovascular risk assessment.

The primary objective of the current study was to quantify CAC from non–ECG-gated, nonrespiratory-gated (free breathing) radiotherapy planning CT scans in patients with locally advanced non–small-cell lung cancer using a previously validated automated DL model trained on ECG-gated cardiovascular medical imaging and validated in non-ECG, respiratory-gated low-dose lung cancer screening CT scans.[23] Our goal was to quantify CAC and assess whether elevated DL-CAC at the time of radiotherapy planning is a predictor of all-cause mortality (ACM) and MACEs, adjusting for traditional lung cancer and cardiovascular prognostic factors.

METHODS

Patient Population

This was a retrospective study of 748 consecutive patients with locally advanced lung cancer treated with thoracic radiotherapy at Dana-Farber Cancer Institute (DFCI), Brigham and Women's Hospital (BWH), and DFCI/BWH at Milford Regional Medical Center between November 1998 and January 2014. Eligible patients included those with an available nonintravenous contrast radiotherapy planning CT and verified dose-volume histogram. Participants with missing CT data, intravenous contrast enhancement, incompatible slice thickness, or scans in which heart autosegmentation failed were excluded, resulting in 428 eligible participants (Fig 1). This study was approved by the DFCI/Harvard Cancer Center Institutional Review Board with a waiver of consent.

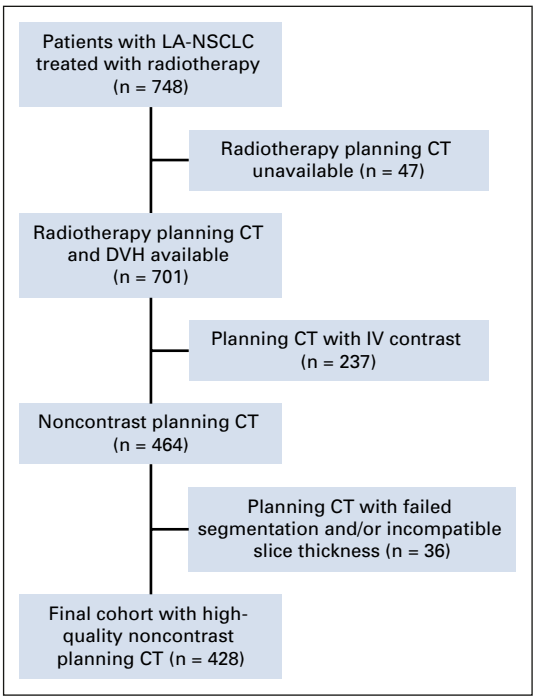

FIG 1. Patient selection criteria. Schematic showing eligible patients included for deep learning coronary artery calcium analysis. CT, computed tomography; DVH, dose-volume histogram; IV, intravenous; LA-NSCLC, locally advanced non-small cell lung cancer.

Treatment and Clinical Outcomes

Oncologic treatment included curative-intent radiotherapy plus chemotherapy and/or surgery for patients with 2010 American Joint Committee on Cancer stage II (medically inoperable or unresectable) or III non–small-cell lung cancer. Radiotherapy was planned using Varian Eclipse (Varian Medical Systems Inc, Palo Alto, CA) using 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy techniques (excluding patients treated with stereotactic body radiotherapy). Radiotherapy dose to the heart was determined on the basis of heart volumes delineated manually as previously reported.[4,7,24] Baseline cardiac risk factors, medical history, comorbidities, and postradiotherapy MACEs and death were assessed by detailed manual medical record review as previously described.[4] MACE included the categories of cardiac death, unstable angina, myocardial infarction, heart failure hospitalization or urgent visit, and coronary revascularization[25] and was defined as occurring after the start of radiotherapy or ≥ 30 days postoperatively (when applicable).

Deep Learning–Based Coronary Calcium Measurement

Eligible patients underwent non–ECG-gated, nonrespiratory-gated (free breathing) helical CT simulation (General Electric Medical Systems, Milwaukee, WI) with slice distances ≤ 3.0 mm. The DL convolutional neural network CAC algorithm was previously trained and tuned on 1,636 ECG-gated CT scans from the Framingham Heart Study, manually segmented by expert readers, and consisted of three consecutive DL networks for segmentation.[23] Independent testing and validation was performed on 20,084 CT scans from four different clinical trial cohorts, including the Framingham Heart Study (without overlap with the training cohort; n = 663), the National Lung Screening Trial (n = 14,959), the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial (n = 4,021), and the Rule out Myocardial Infarction using Computer-Assisted Tomography II (ROMICAT-II) trial (n = 441). Plaques ≥ 1 cubic millimeter were volumetrically measured and multiplied by a maximum plaque density factor to generate an Agatston-like DL-CAC score in a fully automated fashion.[11,24] Risk groups were assigned on the basis of DL-CAC score, defined as DL-CAC = 0 (very low risk) and DL-CAC ≥ 1 (elevated risk).

Statistical Analysis

The distribution of clinical characteristics was reported and compared using descriptive statistics. Although continuous covariates were evaluated using a Wilcoxon rank-sum test, categorical covariates were compared using a Fisher's exact test. Kaplan-Meier estimates of ACM were calculated and graphically displayed, stratified by DL-CAC risk group, with survival estimates compared using a two-sided log-rank *P* value. The cumulative incidence estimates of MACEs were calculated, accounting for noncardiac death as a competing risk and compared using a two-sided Gray's *P* value.[26] Univariable and multivariable Cox regressions[27] were performed to assess whether DL-CAC was associated with ACM and MACE, adjusting for lung cancer and cardiovascular factors. For these models, time zero was the start of radiotherapy and concluded at the date of death. For the above analyses, a two-sided $P \leq .05$ was considered statistically significant. Stata version 16.1 (StataCorp LLC, College Station, TX) statistical software was used for all analyses.

RESULTS

Clinical Characteristics

By DL-CAC risk group, 38.6% (n = 165) had very low risk (DL-CAC = 0) and 61.5% (n = 263) had elevated risk (DL-CAC ≥ 1). Patients with elevated DL-CAC (≥ 1 *v* 0) were more likely to be older (median age 69 *v* 59 years; $P < .001$), male (56.3% *v* 43.6%; $P = .007$), with greater smoking history (50 *v* 40 pack-years; $P < .001$), and more likely to harbor cardiovascular disease risk factors such as hypertension (62.7% *v* 33.9%; $P < .001$), hyperlipidemia (56.3% *v* 31.5%; $P < .001$), and diabetes mellitus (17.5% *v* 5.5%; $P < .001$; Table 1). Half (50.2%) of patients with DL-CAC ≥ 1 had known coronary heart disease (CHD) or CHD equivalent (eg, peripheral vascular disease, stroke) versus 15.8% of those with DL-CAC = 0. Of those without known CHD, the median 10-year Framingham cardiovascular risk score was higher in patients with DL-CAC ≥ 1 versus DL-CAC = 0 (23.1% *v* 11.9%; $P < .001$), respectively. There was no difference in mean heart radiotherapy dose delivered between DL-CAC ≥ 1 versus DL-CAC = 0 (11.9 Gy *v* 11.5 Gy; $P = .83$).

ACM Analysis

The median follow-up was 18.1 months (interquartile range [IQR], 7.9-45.1 months) overall and 53.0 months (IQR, 33.1-80.3 months) in patients alive. There were 323 deaths, of which 72.1% (n = 233) were from lung cancer, 8.4% (n = 27) from known noncancer causes, 5.0% (n = 16) from known cardiac-specific causes, and 22.9% (n = 74) from unknown causes. The median time to death was 20.8 months (IQR, 9.0-46.4 months), with an overall 2-year ACM estimate of 51.8% (95% CI, 47.2 to 56.7).

Adjusting for lung and cardiovascular prognostic factors, including age, sex, performance status, smoking, unintentional weight loss, cancer stage, histology, hypertension, hyperlipidemia, and diabetes, as well as mean heart radiotherapy dose, there was an increased risk of ACM with DL-CAC≥ 1 versus DL-CAC = 0 (209 *v* 114 deaths; hazard ratio [HR], 1.51; 95% CI, 1.01 to 2.26; $P = .04$) (Table 2), with 2-year estimates of 56.2% (95% CI, 50.3 to 62.3) versus 45.4% (95% CI, 38.2 to 53.4), respectively (Fig 2). There was no statistically significant interaction between DL-CAC and mean heart radiotherapy dose ($P = .31$).

MACE Analysis

The median time to first MACE was 19.4 months (IQR, 8.2-44.3 months) with a 2-year cumulative incidence estimate

TABLE 1. Patient and Treatment Characteristics

Characteristic	CAC = 0 (n = 165)	CAC ≥ 1 (n = 263)	*P*
Age, median (IQR, years)	59.0 (54.0-65.0)	69.0 (61.0-76.0)	<.001
Sex			
Female	93 (56.4)	115 (43.7)	
Male	72 (43.6)	148 (56.3)	.007
ECOG performance status			
0-1	148 (89.7)	221 (84.0)	
2	14 (8.5)	31 (11.8)	
3-4	3 (1.8)	11 (4.2)	.23
Unintentional weight loss	57 (34.6)	87 (33.1)	.75
Tobacco			
Never	22 (13.3)	15 (5.7)	
Current	76 (46.1)	94 (35.7)	
Former	67 (40.6)	154 (58.6)	<.001
Pack-years, median (IQR)	40.0 (27.0-50.0)	50.0 (32.5-75.0)	<.001
Medical comorbidities			
Hypertension	56 (33.9)	165 (62.7)	<.001
Hyperlipidemia	52 (31.5)	148 (56.3)	<.001
Diabetes mellitus	9 (5.5)	46 (17.5)	<.001
Peripheral vascular disease	5 (3.0)	31 (11.8)	.001
Stroke	3 (1.8)	5 (1.9)	.63
Coronary artery disease	19 (11.5)	108 (41.1)	<.001
Myocardial infarction	8 (4.9)	43 (16.4)	<.001
Congestive heart failure	3 (1.8)	32 (12.2)	<.001
CHD	26 (15.8)	132 (50.2)	<.001
Framingham Risk[a]	n = 139 CHD neg[a]	n = 131 CHD neg[a]	
Median, % (IQR)	11.9 (7.7-21.8)	23.1 (12.7-32.1)	<.001
Low (< 10%)	55 (39.57)	20 (15.3)	
Moderate (10%-20%)	39 (28.1)	21 (16.0)	
High-risk (> 20%)	45 (32.4)	90 (68.7)	<.001
NSCLC clinical overall stage			
II	8 (4.9)	38 (14.5)	
IIIA	91 (55.2)	144 (54.8)	
IIIB	66 (40.0)	81 (30.8)	.003
NSCLC clinical nodal stage			
N0-1	27 (16.4)	83 (31.6)	
N2-3	138 (83.6)	180 (68.4)	<.001
NSCLC histology			
Adenocarcinoma	80 (48.5)	109 (41.1)	
Squamous cell carcinoma	40 (24.2)	95 (36.1)	
Others	45 (27.3)	59 (22.4)	.06
Radiotherapy dose (Gy)			
Prescribed dose, median (IQR)	64.0 (54.0-66.0)	66.0 (60.0-66.0)	.49
Mean whole heart dose, median	11.0 (5.5-17.0)	12.2 (5.0-19.4)	.45
Mean lung dose, median	14.4 (10.9-17.0)	14.2 (10.6-17.0)	.85

NOTE. Values are listed as No. (%) unless otherwise specified. The distributions of categorical covariates were compared using the Fisher's exact test, whereas continuous variables were compared using the Wilcoxon rank-sum test.

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NSCLC, non–small-cell lung cancer.

[a]Framingham Risk assessed only among the n = 270 CHD-negative patients.

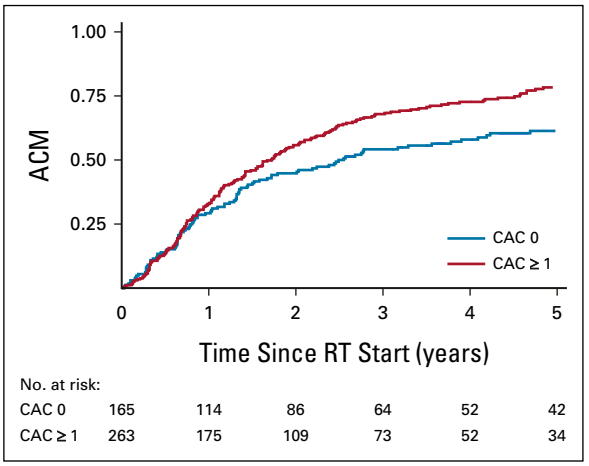

FIG 2. ACM estimates stratified by the DL-CAC group. ACM estimates stratified by DL-CAC score ≥ 1 versus DL-CAC 0 (log-rank $P = .006$). ACM, all-cause mortality; DL-CAC, deep learning coronary artery calcium; RT, radiation therapy.

of 5.0% (95% CI, 3.2 to 7.3). In total, 43 patients developed at least one MACE, including myocardial infarction (n = 18), heart failure hospitalization or urgent visit (n = 13), coronary revascularization (n = 12), unstable angina (n = 2), and cardiac death (n = 16).

Adjusting for age, sex, unintentional weight loss, and histology, there was a trend toward increased risk of MACE in patients with DL-CAC ≥ 1 versus DL-CAC = 0 (32 *v* 11 MACE; HR, 1.80; 95% CI, 0.87 to 3.74; $P = .11$), with 2-year MACE estimates of 7.3% (95% CI, 4.6 to 10.9) versus 1.2% (0.2 to 4.0), respectively (Appendix Table A1, Fig 3). Among patients without baseline CHD, adjusting for age, sex, histology, and mean heart radiotherapy dose, there was no significant difference in the risk of MACE in patients with DL-CAC ≥ 1 versus DL-CAC = 0 (7 *v* 9 MACEs; HR, 0.90; 95% CI, 0.37 to 2.24; $P = .83$), although MACE numbers were limited (n = 16; Appendix Table A2).

DISCUSSION

In this proof-of-concept study, DL-CAC was effectively measured from routinely acquired, non-ECG and nonrespiratory-gated (free breathing) radiotherapy planning CT scans in patients with locally advanced lung cancer using an automated DL model. This model was trained on ECG-gated cardiovascular imaging and previously validated in more than 20,000 patients from four independent clinical trial cohorts,[23] including 14,959 participants from the low-dose chest CT arm of the National Lung Screening Trial with respiratory-gated (single, maximal breath-hold), non–ECG-gated CT scans.[28,29] We observed that elevated DL-CAC was associated with an increased risk of ACM, adjusting for lung cancer and cardiovascular prognostic factors. There was a trend toward increased risk of MACEs with elevated DL-CAC, although this did not reach statistical significance in the setting of limited events. Together, these findings support further validation of applying this approach to routinely acquired radiotherapy planning CT scans to take full advantage of the potentially valuable, but currently untapped, imaging information for automated cardiac risk stratification in patients with cancer.

Strengths of this study are that it represents, to our best knowledge, the first report of opportunistic quantitation of CAC in a high-risk population using a validated DL system and the first study observing that elevated DL-predicted CAC is associated with an increased risk of mortality in patients with lung cancer. Notably, the application of automated DL methods to routine clinical imaging for cardiovascular risk prediction has been demonstrated from images such as retinal fundus photographs and lung cancer screening CT scans.[23,30-32] However, the use of routine oncologic imaging, such as radiotherapy planning CT scans, for cardiovascular risk prediction has been less well characterized. Importantly, DL studies analyzing CAC from various cardiac CT and chest CT protocols have demonstrated success,[33] including DL models specifically measuring CAC from breast cancer radiotherapy CT scans.[34] For example, the ongoing Bragatston multicenter cohort study from the Netherlands uses automated DL-CAC measurement to assess cardiovascular risk prediction.[35] Together, these studies support the feasibility of applying DL methods to automate complex assessments of medical imaging, such as CAC quantitation, highlighting the potential to improve upon existing cardiac risk stratification methods from standard-of-care imaging.

Practically, our observations support the assessment of CAC from radiotherapy planning CT scans in patients with lung cancer to improve cardiac risk stratification. Indeed, we previously reported that these high cardiovascular risk patients are often incompletely medically optimized with guideline-based antilipid therapy,[3] suggesting that

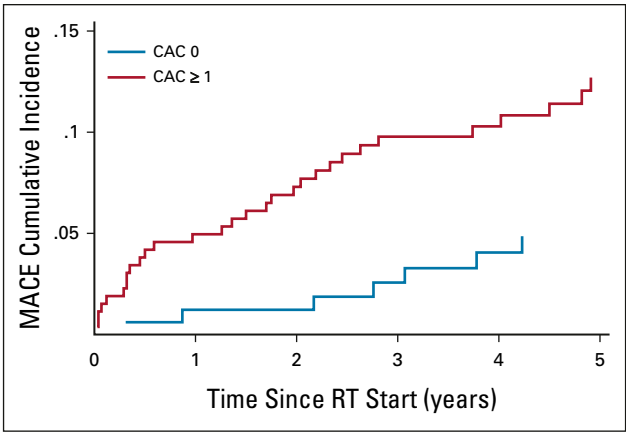

FIG 3. MACE estimates stratified by the DL-CAC group. MACE estimates stratified by DL-CAC ≥ 1 versus DL-CAC 0 (Gray's $P = .055$). DL-CAC, deep learning coronary artery calcium; MACE, major adverse cardiac event; RT, radiation therapy.

TABLE 2. Cox Regression Analysis for All-Cause Mortality

Covariable	No. of Patients	No. of ACD	Univariable		Multivariable	
			HR (95% CI)	*P*	AHR (95% CI)	*P*
Age, years	428	323	1.01 (1.00 to 1.03)	.008	1.01 (1.00 to 1.02)	.08
Sex						
Female	208	150	1.0 (referent)		1.0 (referent)	
Male	220	173	1.19 (0.96 to 1.48)	.12	1.10 (0.87 to 1.38)	.43
ECOG performance status						
0-1	369	270	1.0 (referent)		1.0 (referent)	
2-4	59	53	1.79 (1.33 to 2.41)	<.001	1.72 (1.25 to 2.37)	.001
Smoking						
Never	37	26	1.0 (referent)		1.0 (referent)	
Ever	391	297	1.43 (0.96 to 2.14)	.08	1.16 (0.77 to 1.76)	.47
Unintentional weight loss	144	113	1.35 (1.07 to 1.70)	.01	1.30 (1.03 to 1.65)	.03
Overall stage						
II	46	36	1.0 (referent)		1.0 (referent)	
III	382	287	1.02 (0.72 to 1.44)	.93	0.92 (0.57 to 1.49)	.75
Nodal stage						
0-1	110	74	1.0 (referent)		1.0 (referent)	
≥ 2	318	249	1.26 (0.97 to 1.64)	.08	1.59 (1.12 to 2.26)	.009
Histology						
Adenocarcinoma	189	142	1.0 (referent)		1.0 (referent)	
Nonadenocarcinoma	239	181	1.13 (0.90 to 1.41)	.29	1.01 (0.80 to 1.27)	.93
Hypertension	221	170	1.08 (0.97 to 1.35)	.47	0.90 (0.70 to 1.16)	.41
Hyperlipidemia	200	152	1.01 (0.82 to 1.26)	.90	0.92 (0.73 to 1.17)	.49
Diabetes	55	45	1.17 (0.85 to 1.61)	.33	1.15 (0.82 to 1.61)	.42
CAC						
DL-CAC = 0	165	114	1.0 (referent)		1.0 (referent)	
DL-CAC ≥ 1	263	209	1.38 (1.09 to 1.73)	.006	1.51 (1.01 to 2.26)	.04
Radiotherapy dose						
Mean heart dose (per Gy)	428	323	1.01 (1.00 to 1.02)	.02	1.02 (1.00 to 1.04)	.02
Interaction[a]						
DL-CAC × mean heart dose	428	323	1.00 (0.97 to 1.02)	.78	0.99 (0.97 to 1.01)	.31

Abbreviations: ACD, all-cause death; AHR, adjusted hazard ratio; CAC, coronary artery calcium; DL, deep learning; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

[a]Interaction term between CAC (categorical variable) and heart radiotherapy dose (continuous variable).

identification of CAC on lung cancer workup or radiotherapy planning imaging in the absence of known CAD should alert the treating clinicians to prompt a cardiovascular workup, including calculation of the 10-year risk of atherosclerotic cardiovascular disease and determination of statin therapy and optimized medical management.[36] Furthermore, cardiac radiotherapy dose,[4] particularly dose exposure to the left anterior descending coronary artery,[7,24] is associated with increased risk of MACE and mortality and is a potentially modifiable risk factor during the radiotherapy planning process. Therefore, cardiovascular risk stratification via automated CAC calculation at the point of care (eg, at the time of radiotherapy planning) may facilitate multidisciplinary medical management and personalized radiotherapy planning to optimize cardiac risk reduction in high-risk patients.

The application of advanced machine learning methods, such as DL, to analyze CT data beyond the initial clinical indication is a rich methodology with promising scientific potential. For instance, enhanced body composition profiling, including quantitative assessment of skeletal muscle, visceral and subcutaneous adipose, liver fat, and bone mineral density, has been linked with metabolic, cardiovascular, and cancer outcomes.[37-40] As CT scans are standard-of-care imaging for lung cancer workup, radiotherapy planning

and delivery, and follow-up surveillance, these patients harbor a wealth of 3-dimensional, high-resolution volumetric imaging, which can be used to train DL models to predict outcomes and additionally repurposed for assessment of biometrics (both at baseline and serially).[22,41] Together, these findings represent a unique opportunity to expand the value of routine oncologic imaging data by adding an additional layer of automatically extracted prognostic information. This information has the potential to improve cardiovascular risk prediction and help mitigate the morbidity and health care burden of radiotherapy-associated cardiac toxicity without increasing provider workload or health care costs. Moreover, predictive models and methodologies such as these have the potential to be retrained and adapted to a variety of malignancies and cancer therapies, which could dramatically alter cancer-related toxicity prediction.

Potential limitations of this study include its retrospective nature and cohort size precluding more nuanced stratification of CAC risk groups in both primary and secondary prevention cohorts. Indeed, the necessity to eliminate contrast-enhanced CT scans reduced our cohort size, thereby limiting absolute MACE numbers and reducing overall power for this analysis and the ability to more broadly incorporate clinical metadata, for which a larger and expanded data set is warranted. Furthermore, the exclusion of contrast-enhanced CT scans might have introduced bias, as there may be unaccounted clinical differences among these patients. Together, these limitations support further studies evaluating the feasibility of analyzing CAC from specific phases of a respiratory 4-dimensional CT (which are routinely obtained without contrast). In addition, the DL-CAC algorithm was directly applied to the nonrespiratory-gated radiotherapy planning CT scans without retraining, which may affect performance and potentially impart bias toward artificially high CAC scores given the added motion artifact. Indeed, similar work in breast cancer radiotherapy planning CT scans demonstrated good, but slightly higher reliability and proportion of agreement of CAC scores between automated and manual expert scoring in breath-hold (*v* free breathing) scans, suggesting that respiratory-gated scans may harbor an advantage when feasible.[34] Finally, it should be noted that the use of CAC in the general population is currently validated using cardiac-gated CT scans with manual segmentation, and we do not have CAC scores calculated in this gold standard fashion to serve as a baseline comparator in our cohort. Finally, we did not assess longitudinal CAC changes from baseline images in comparison with surveillance and follow-up imaging, which would provide additional insight into more specific radiotherapy-associated cardiac risk assessment.

In conclusion, our proof-of-concept study strongly suggests that a previously developed DL system trained on cardiovascular imaging can be repurposed and applied to cancer-specific, radiotherapy planning CT scans to generate a quantitative CAC score that is associated with the risk of mortality, despite the high competing risk of lung cancer death. Together, these observations illustrate a significant potential to apply this approach for automated cardiac risk stratification before the initiation of cancer therapy.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Fine and Gray Regression Analysis for MACEs

			Univariable		Multivariable	
Covariable	**No. of Patients**	**No. of MACEs**	**HR (95% CI)**	***P***	**SHR (95% CI)**	***P***
Age, years	428	43	1.02 (0.99 to 1.05)	.25	1.01 (0.98 to 1.05)	.50
Sex						
Female	208	22	1.0 (reference)		1.0 (reference)	
Male	220	21	0.90 (0.50 to 1.63)	.73	1.05 (0.55 to 2.01)	.87
ECOG performance status						
0-1	369	37	1.0 (reference)			
≥ 2	59	6	1.00 (0.42 to 2.36)	1.0		
Smoking						
Never	37	4	1.0 (reference)			
Ever	391	39	0.94 (0.33 to 2.67)			
Unintentional weight loss	144	8	0.45 (0.21 to 0.96)	.039	0.45 (0.21 to 0.98)	.045
Overall stage						
II	46	6	1.0 (reference)			
III	382	37	0.77 (0.33 to 1.79)	.55		
Nodal stage						
0-1	110	11	1.0 (reference)			
≥ 2	318	32	0.97 (0.49 to 1.92)	.93		
Histology						
Adenocarcinoma	189	25	1.0 (reference)		1.0 (reference)	
Nonadenocarcinoma	239	18	0.57 (0.31 to 1.04)	.07	0.55 (0.30 to 1.03)	.06
Mean heart RT dose, Gy	428	43	1.01 (0.98 to 1.03)	.63		
CAC						
DL-CAC = 0	165	11	1.0 (reference)		1.0 (reference)	
DL-CAC ≥ 1	263	32	1.93 (0.99 to 3.78)	.055	1.80 (0.87 to 3.74)	.11

Abbreviations: CAC, coronary artery calcium; DL, deep learning; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MACEs, major adverse cardiac events; RT, radiotherapy; SHR, subdistribution hazard ratio.

TABLE A2. Fine and Gray Regression Analysis for MACEs in Patients Without Coronary Heart Disease

			Univariable		Multivariable	
Covariable	**No. of Patients**	**No. of MACEs**	**HR (95% CI)**	***P***	**SHR (95% CI)**	***P***
Age, years	270	16	1.00 (0.95 to 1.05)	.92	1.01 (0.95 to 1.07)	.79
Sex						
Female	139	10	1.0 (reference)		1.0 (reference)	
Male	131	6	0.64 (0.24 to 1.75)	.39	0.89 (0.36 to 2.20)	.80
ECOG performance status				.60		
0-1	244	15	1.0 (reference)			
≥ 2	26	1	0.59 (0.08 to 4.20)			
Smoking						
Never	32	2	1.0 (reference)			
Ever	238	14	0.93 (0.21 to 4.07)	.92		
Unintentional weight loss	94	3	0.44 (0.13 to 1.54)	.20		
Overall stage						
II	21	1	1.0 (reference)			
III	249	15	1.33 (0.19 to 9.16)	.78		
Nodal stage						
0-1	63	4	1.0 (reference)			
≥ 2	207	12	0.83 (0.27 to 2.59)	.75		
Histology						
Adenocarcinoma	126	13	1.0 (reference)		1.0 (reference)	
Nonadenocarcinoma	144	3	0.21 (0.06 to 0.73)	.01	0.16 (0.04 to 0.59)	.006
Mean heart RT dose, Gy	270	16	1.04 (1.01 to 1.06)	.01	1.06 (1.02 to 1.10)	.004
CAC						
DL-CAC = 0	139	9	1.0 (reference)		1.0 (reference)	
DL-CAC ≥ 1	131	7	0.84 (0.31 to 2.23)	.72	0.90 (0.37 to 2.24)	.83

Abbreviations: CAC, coronary artery calcium; DL, deep learning; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MACEs, major adverse cardiac events; RT, radiotherapy; SHR, subdistribution hazard ratio.