Physics and Imaging in Radiation Oncology 25 (2023) 100410

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

Association of cardiac calcium burden with overall survival after radiotherapy for non-small cell lung cancer

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Radiotherapy
Coronary calcifications

ABSTRACT

Background and purpose: Coronary calcifications are associated with coronary artery disease in patients undergoing radiotherapy (RT) for non-small cell lung cancer (NSCLC). We quantified calcifications in the coronary arteries and aorta and investigated their relationship with overall survival (OS) in patients treated with definitive RT (Def-RT) or post-operative RT (PORT).

Materials and methods: We analyzed 263 NSCLC patients treated from 2004 to 2017. Calcium burden was ascertained with a Hounsfield unit (HU) cutoff of > 130 in addition to a deep learning (DL) plaque estimator. The HU cutoff volumes were defined for coronary arteries ($Plaque_{Coro}$) and coronary arteries and aorta combined ($Plaque_{Coro+Ao}$), while the DL estimator ranged from 0 (no plaque) to 3 (high plaque). Patient and treatment characteristics were explored for association with OS.

Results: The median $Plaque_{Coro}$ and $Plaque_{Coro+Ao}$ was 0.75 cm^3 and 0.87 cm^3 in the Def-RT group and 0.03 cm^3 and 0.52 cm^3 in the PORT group. The median DL estimator was 2 in both cohorts. In Def-RT, large $Plaque_{Coro}$ (HR:1.11 (95%CI:1.04–1.19); p = 0.008), and $Plaque_{Coro+Ao}$ (HR:1.06 (95%CI:1.02–1.11); p = 0.03), and poor Karnofsky Performance Status (HR: 0.97 (95%CI: 0.94–0.99); p = 0.03) were associated with worse OS. No relationship was identified between the plaque volumes and OS in PORT, or between the DL plaque estimator and OS in either Def-RT or PORT.

Conclusions: Coronary artery calcification assessed from RT planning CT scans was significantly associated with OS in patients who underwent Def-RT for NSCLC. This HU thresholding method can be straightforwardly implemented such that the role of calcifications can be further explored.

1. Introduction

Lung cancer is the leading cause of cancer-related death. Radiotherapy (RT) is a key treatment modality for non-small cell lung cancer (NSCLC) and can be used in a variety of settings, including definitive treatment for patients with early and locally-advanced staged disease and post-operatively for selected high-risk patients with locally-advanced disease.

Cardiac toxicity is a central concern in patients undergoing RT for lung cancer. The randomized phase III RTOG 0617 trial, which investigated dose escalation of definitive RT (Def-RT) to 74 Gy compared to 60 Gy with concurrent chemotherapy in patients with stage III NSCLC

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https://doi.org/10.1016/j.phro.2023.01.001
Received 17 August 2022; Received in revised form 5 December 2022; Accepted 3 January 2023
Available online 5 January 2023
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[1], identified a survival decrement in the high dose group, which was hypothesized to be primarily driven by a higher heart dose [2–4]. In parallel, other retrospective studies have found an association between heart dose and cardiac events among patients undergoing Def-RT for locally advanced NSCLC [5,6]. Patients undergoing post-operative RT (PORT) have also been found to have increased cardiac toxicity, and higher heart doses have been shown to lower overall survival [7,8]. Additionally, the LungART trial found that patients with pathological stage N2 disease who were randomized to PORT experienced increased cardiopulmonary toxicity [9].

Coronary artery calcium (CAC) is associated with coronary artery disease [10], and while traditional quantification of CAC has been performed using study-specific imaging techniques and/or qualitative assessments, CAC can be measured quantitatively on non-contrast enhanced CT scans of the chest [11]. For instance, CAC quantified from RT planning CT scans for patients undergoing breast cancer RT have been associated with coronary artery disease [12], and a similar association has been identified in lung cancer patients [13,14]. There is currently no data demonstrating an association between CAC assessed from RT treatment planning scans and overall survival (OS) in locally-advanced NSCLC.

Herein, we evaluated the association between quantitative cardiac calcium burden, assessed using two different methods, and OS in two cohorts of patients with NSCLC who underwent either Def-RT or PORT. Aortic calcification burden has not traditionally been considered as a risk factor for cardiovascular disease but given the prevalence of aortic calcifications and our clinical observation of high aortic calcification burden in some patients, we also assessed whether aortic calcifications were associated with OS.

2. Materials and methods

2.1. Patient population

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by our Institutional Review Board. In total, 524 locally-advanced NSCLC patients were identified who had been consecutively treated with Def-RT, with concurrent chemotherapy, (n = 240) or PORT (n = 284) at our institution from May 2004 to January 2017, prior to the introduction of consolidation immunotherapy into the standard of care for Def-RT with chemotherapy. These two cohorts have been described in greater detail previously [7,15–17]. Exclusion criteria for the current analysis were use of intravenous contrast during treatment planning CT scan, and poor CT quality such as a high level of imaging artifacts. The CT quality was assessed in every case by a single observer (JMH).

Of the 524 patients identified, 263 of the 320 non-contrast CT scans were determined to be of sufficient quality, which included 130 scans in Def-RT and 133 scans in PORT.

2.2. Radiation therapy

All patients were immobilized using a custom mold and were treated with 6 MV photon radiation using either 3-dimensional conformal RT or intensity-modulated RT (IMRT). For Def-RT [18], following delineation of the gross tumor volume, expansions were made for the internal target volume, clinical target volume (CTV), and planning target volume (PTV) where a 4D CT scan was obtained, or expansion for only CTV and PTV in cases where a breath-hold scan was obtained. The Def-RT prescription dose ranged from 58 Gy to 80 Gy in 2.0 Gy fractions administered daily. For PORT, as previously described [17], the CTV included affected nodal stations, bronchial stump, and ipsilateral hilum extending into the ipsilateral lower paratracheal and subcarinal spaces, and the prescription dose ranged from 45 Gy to 70 Gy in 1.8 or 2.0 Gy fractions administered daily. Standard dosimetric constraints for locally advanced NSCLC treatment were applied to our patient population. The volume of the heart receiving 30 Gy was constrained to < 50%.

2.3. Cardiac calcium burden ascertainment

Two cardiac calcium burden estimation methods were explored: Hounsfield Unit (HU) thresholding in addition to a published Deep Learning (DL) plaque estimator, which yielded a categorical assessment of coronary plaque ranging between 0 and 3 within the CT field-of-view in which 0 represents no calcified plaque (HU = 0), 1 low plaque intensity (HU = 1–100), 2 moderate plaque intensity (HU = 101–300), and 3 high plaque intensity (HU > 300) [19]. For the HU thresholding approach, the pericardium and aorta were auto-segmented using our open-source DL segmentation algorithm [20,21]. The aorta contour included ascending aorta, aortic arch, and descending aorta to approximately the level of the cardiac apex. Plaque was defined as the volume with HU > 130 - according to the Agatston plaque score [10]. Two plaque volumes were defined: the volume encompassed within the pericardium contour ($Plaque_{Coro}$), as suggested by others as a surrogate for CAC [13], and the volume within the aorta and the pericardium ($Plaque_{Coro+Ao}$). All segmentations were qualitatively post-processed by a single observer (JMH) to exclude image artifacts and high HU devices, such as port catheters, surgical clips, and pacemaker wires. The code for the DL plaque estimator was implemented as available.

2.4. Statistical analysis

The two plaque volumes from the HU thresholding method ($Plaque_{Coro}$ and $Plaque_{Coro+Ao}$), the plaque estimator from the DL method were explored for association with OS (reference: time since RT completion). The method of association with OS was Cox Proportional Hazards regression, and a variable was considered a predictor if presenting with a Benjamini Hochberg false-discovery rate (FDR) adjusted p-value of ≤ 0.05. In addition, the association between OS and age, Karnofsky Performance Status (KPS), mean heart dose (MHD, corrected for fractionation effects via the equivalent uniform dose in 2 Gy fractions using $\alpha/\beta = 3$ Gy), prescribed dose, RT technique (3D-CRT vs IMRT), sex, smoking status (never vs former/current), and stage (Def-RT: IIIA vs IIB; PORT: I vs II + III, and I + II vs III) was explored.

3. Results

Baseline disease, patient and treatment characteristics are summarized in Table 1. The median follow-up time for OS was 21 (IQR: 10–42) months in Def-RT and 33 (IQR: 17–57) months in PORT with corresponding 2-year OS of 45% and 73%, respectively.

In Def-RT, the population median $Plaque_{Coro+Ao}$ was 0.87 (IQR: 0.15–3.76) cm^3. This was attributed primarily to the amount of $Plaque_{Coro}$ being 0.75 (IQR: 0.14–2.96) cm^3 compared to $Plaque_{Ao}$ being only 0.09 (IQR: 0–0.65) cm^3. For smaller $Plaque_{Coro+Ao}$ in particular, $Plaque_{Coro}$ was strongly correlated with $Plaque_{Coro+Ao}$ ($R^2 = 0.98$; Fig. 1C). In PORT the median $Plaque_{Coro+Ao}$ was lower: 0.52 (IQR: 0.06–1.36) cm^3. In contrast to Def-RT, accumulation of plaque in PORT was constituted by aortic plaque ($Plaque_{Ao}$: 0.31 (IQR: 0.02–0.93) cm^3 vs 0.03 (IQR: 0.004–0.28) cm^3 for $Plaque_{Coro}$). These plaque patterns for both cohorts are summarized in Fig. 1A-1D. The median DL plaque estimator was 2 (IQR: 1–3) and 2 (IQR: 2–3) in Def-RT and PORT, respectively.

In Def-RT, $Plaque_{Coro}$ (HR: 1.11 (95%CI: 1.04–1.19); $p_{FDR} = 0.008$) and $Plaque_{Coro+Ao}$ (HR: 1.06 (95%CI: 1.02–1.11); $p_{FDR} = 0.03$) were significantly associated with OS. This association was likely driven by $Plaque_{Coro}$ given that a median of 86% of $Plaque_{Coro+Ao}$ was constituted by $Plaque_{Coro}$ (Fig. 1C), and that a relationship between $Plaque_{Coro}$ and OS was more pronounced. Among the other investigated characteristics, only KPS was significantly associated with OS in Def-RT (HR: 0.97 (95% CI: 0.94–0.99); p = 0.03). The Kaplan-Meier curves between high- and low-risk for both $Plaque_{Coro}$ and $Plaque_{Coro}$ combined with KPS were

Table 1
Disease, patient, and treatment characteristics for each of the two studied cohorts, and their univariable association with Overall Survival.

Characteristic	Def-RT (N = 130[1])	HR (95%CI)	p-value*	PORT (N = 133[1])	HR (95%CI)	p-value*
Age (Years)	66 (59–72)	1.01 (0.99–1.03)	0.27	67 (58–72)	1.02 (1.00–1.05)	0.13
Sex		1.42 (0.95–2.11)	0.15			
Female (ref.)	67 (52%)			84 (63%)	1.59 (0.96–2.63)	0.13
Male	63 (48%)			49 (37%)		
KPS baseline		0.97 (0.94–0.99)	0.03**		1.01 (0.98–1.04)	0.45
60	2 (2%)			0 (0%)		
70	17 (13%)			9 (7%)		
80	53 (41%)			52 (39%)		
90	58 (45%)			50 (38%)		
100	0 (0%)			22 (17%)		
Stage[2]		1.04 (0.70–1.56)	0.49		2.02 (1.06–3.81), 1.62 (0.97–2.70)	0.13, 0.13
IA	0 (0%)			21 (16%)		
IB	0 (0%)			15 (11%)		
IIA	0 (0%)			10 (8%)		
IIB	0 (0%)			5 (4%)		
IIIA	67 (52%)			78 (59%)		
IIIB	63 (48%)			4 (3%)		
Smoking history			0.15		1.21 (0.65–2.24)	0.45
Never (ref.)	8 (6%)	2.67 (0.88–7.66)		28 (21%)		
Former	79 (61%)			97 (73%)		
Current	43 (33%)			8 (6%)		
RT technique		–	–		1.26 (0.74–2.14)	0.41
IMRT (ref.)	130 (100%)			95 (71%)		
3D-CRT	0 (0%)			38 (29%)		
Prescribed dose (Gy)		0.97 (0.94–1.00)	0.15		1.03 (0.98–1.09)	0.31
45–<54	8 (6%)			58 (44%)		
54–<60	17 (13%)			56 (42%)		
60–65.99	44 (34%)			17 (13%)		
66.–<74	54 (42%)			2 (2%)		
74–80	7 (5%)			0 (0%)		
MHD $EQD2_3$ (Gy)	14 (8.2–14)	1.02 (0.99–1.04)	0.20	7.8 (4.0–12)	1.07 (1.03–1.11)	0.01**
$Plaque_{Ao}$ (cm^3)	0.09 (0–0.65)	1.06 (0.96–1.18)	0.27	0.31 (0.02–0.93)	1.10 (0.98–1.23)	0.17
$Plaque_{Coro}$ (cm^3)	0.75 (0.14–2.96)	1.11 (1.04–1.29)	0.009**	0.03 (0.004–0.28)	1.25 (0.99–1.57)	0.13
$Plaque_{Coro+Ao}$ (cm^3)	0.87 (0.15–3.76)	1.06 (1.02–1.11)	0.03**	0.52 (0.06–1.36)	1.10 (1.00–1.20)	0.13

[1] Median (IQR) or n (%); [2]Ref: Stage IIIA in Def-RT; Stage I or Stage I + II in PORT. *P-values from a Benjamini Hochberg false-discovery rate adjustment; **Denoting significance. *Abbreviations: $EQD2_3$: Equivalent Dose in 2 Gy fractions; Gy: Gray; RT: HR: Hazard Ratio; IMRT: Intensity-Modulated Radiation Therapy; KPD: Karnofsky Performance Status; MHD: Mean Heart Dose; Radiation Therapy; 3D-CRT: Three-dimensional Conformal Radiation Therapy.*

significantly distinguishable ($p_{FDR} = 0.03$, 0.003; Fig. 2A and 2C) and deceased patients presented typically with larger $Plaque_{Coro}$ for each KPS category (Fig. 2C). In PORT, no plaque volume was associated with OS (Table 1), and the DL plaque estimator did not predict OS in either cohort but did present with a weak significant linear correlation with $Plaque_{Coro+Ao}$ in both cohorts (Def-RT: R^2: 0.23, $p < 0.0001$; PORT: R^2: 0.05, $p = 0.006$).

4. Discussion

In this study, we found that increased cardiac calcium burden prior to RT, assessed from straightforward HU thresholding in non-contrast enhanced treatment planning CT scans, is associated with worse OS in patients treated with definitive RT (Def-RT) for locally-advanced NSCLC. This novel finding extends upon previous indications of an increased risk of cardiac toxicity among patients with greater coronary artery calcium (CAC) burden [13]. We also employed a Deep Learning (DL) plaque estimation method [19] in addition to the more standard HU cutoff approach to estimate calcium. Further, we have extended the commonly studied parameter of CAC to evaluate the effect of calcium in the aorta as well.

A significant relationship between either $Plaque_{Coro}$ or $Plaque_{Coro+Ao}$ and OS was established in Def-RT, but a similar pattern was not observed in PORT. Patients in Def-RT had a higher calcification burden ($Plaque_{Coro+Ao}$), and the distribution of calcium differed between Def-RT and PORT with patients in Def-RT having more coronary calcifications and patients in PORT more aortic calcifications (Def-RT vs PORT: $Plaque_{Coro}$ median: 0.75 cm^3 vs 0.03 cm^3; $Plaque_{Ao}$ median: 0.09 cm^3 vs 0.27 cm^3). The Def-RT cohort may represent a selection of patients with more medical comorbidities that undergo Def-RT rather than surgery, which is supported by the lower KPS in Def-RT compared to in PORT (median KPS: 80 vs 90). The more fit PORT patients with lower disease burden together with the suggestion that the $Plaque_{Ao}$ burden observed here does not substantially impact upon a patient's survival may explain why no association was identified between the plaque volumes and OS in PORT. In the Def-RT group, lower KPS was associated with poor OS (HR: 0.97 (95%CI: 0.94–0.99); $p_{FDR} = 0.03$), which has been observed previously as well [22]. While this association was weaker compared to that between OS and $Plaque_{Coro}$ (HR: 1.11 (95%CI: 1.04–1.19; $p_{FDR} = 0.008$), combining $Plaque_{Coro}$ with KPS improved discrimination between low and high risk patient populations (Fig. 2B).

In breast [12] and lung [13] cancers, others have found an association between coronary calcium detected on treatment planning CT scans and cardiac toxicity. The study by Gal et al., in which cardiovascular disease (CVD) was obtained and CAC quantified using a DL method for over 15,000 patients, found that risk of CVD increased from 5% in patients with no CAC to 28% in patients in the most severe plaque group. Additionally, for patients in the most severe plaque group, there was a strong association between CAC and coronary artery disease (HR = 7.8, 95%CI: 5.5–11). Wang et al. segmented coronary calcifications in treatment planning CT scans with a HU > 130 cutoff categorizing the 109 locally-advanced lung cancer patients as having no, low, or high calcium burden, and a strong association was identified between their three-categorical CAC burden and cardiac toxicity (low vs none: HR 7.0, $p = 0.005$, high vs none: HR 10.6, $p < 0.001$). While in the current study we did establish a solid association between HU thresholding-based CAC and OS (HR = 1.1, 95%CI: 1.0–1.3), which is a highly objective and relevant outcome, we did not explore a similar causative association

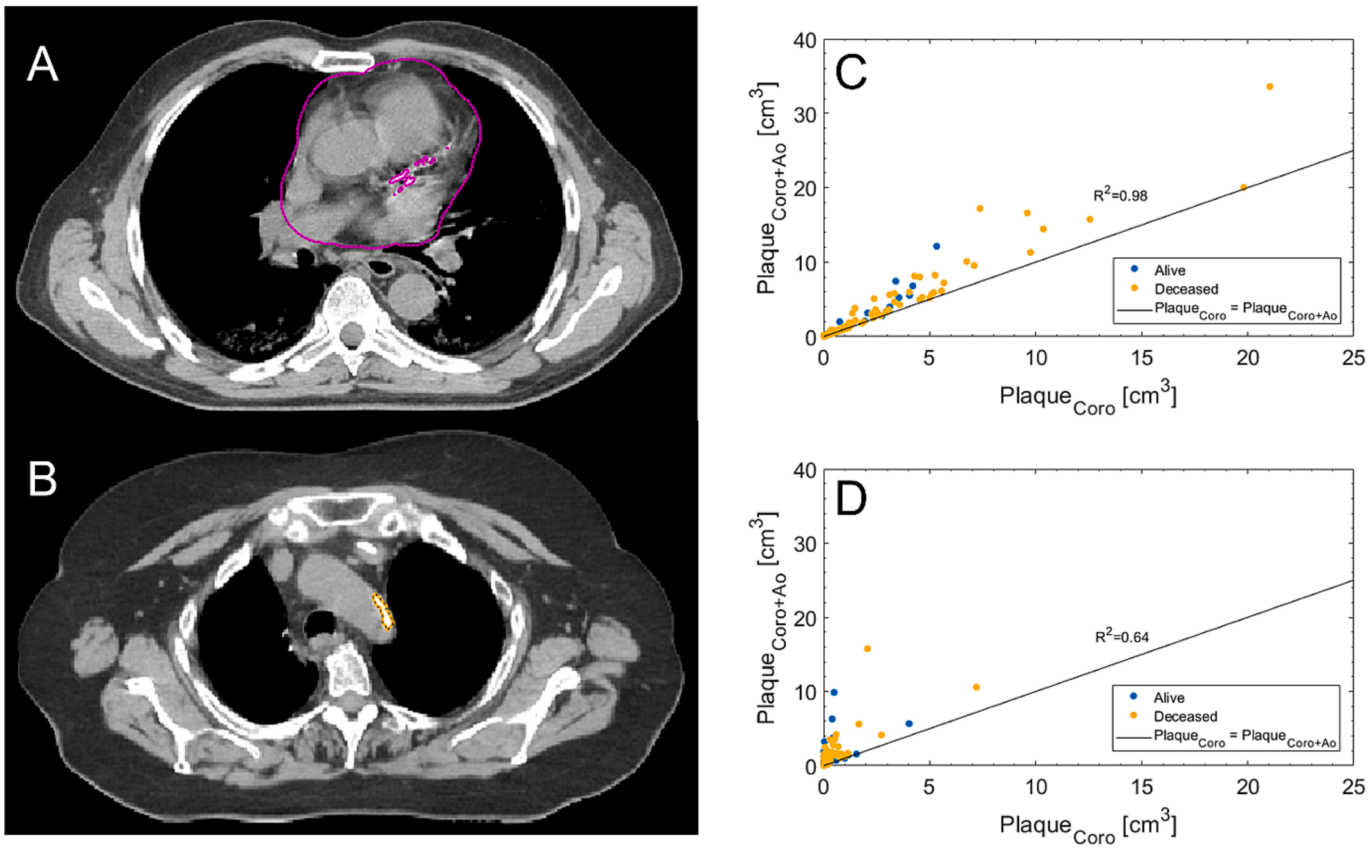

Fig. 1. A patient with a total plaque volume ($Plaque_{Coro+Ao}$) around the cohort median in Def-RT (0.87 cm^3; **1A**), and around the cohort median $Plaque_{Coro+Ao}$ in PORT (0.52 cm^3; **1B**). Scatter plot between $Plaque_{Coro}$ and $Plaque_{Coro+Ao}$ separated for OS status in the Def-RT (**1C**) and in PORT (**1D**).

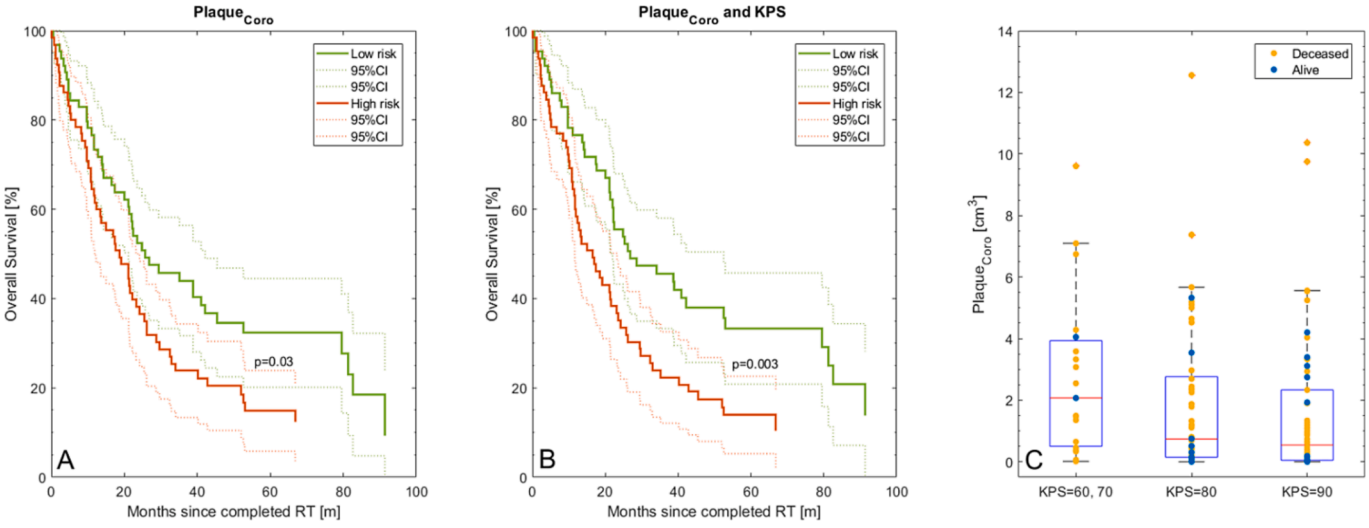

Fig. 2. A-C. Def-RT cohort. Kaplan-Meier curves stratified with respect to the median value of $Plaque_{Coro}$ (**2A**), and with respect to the median value of the prognostic index (PI=(0.11* $Plaque_{Coro}$)+(-0.03*KPS)) combining $Plaque_{Coro}$ and KPS (**2B**; p-values from a log-rank test). **2C:** Boxplots with individual patients as scatter representations of $Plaque_{Coro}$ stratified between KPS 60 and 70 combined, KPS 80 and KPS 90 and color-coded with respect to survival status. *Note: The y-axis in Fig. 2C has been truncated for improved visualization excluding two data points (*$Plaque_{Coro}$ *= 21.05 cm³ and KPS = 80;* $Plaque_{Coro}$ *= 19.81 cm³ and KPS = 90).*

with atherosclerosis risk as cholesterol is not assessed routinely in our standard practice. Additionally, our ability to retrospectively ascertain cardiac events is limited as most of our patients receive cardiology care outside of our institution.

Interestingly, the four categorical DL method [19] used to assess calcification burden in the current study correctly classified $Plaque_{Coro}$ and $Plaque_{Ao}$ in Def-RT and $Plaque_{Coro}$ alone in PORT, but was not significantly associated with OS in either cohort (Def-RT: $p = 0.55$; PORT: $p = 0.23$). To fully exploit the potential of the DL algorithm we believe that the open-source code from Zeleznik et al. [19] could benefit from visualizing the segmented plaque volumes in addition to retaining continuous over the four categorical representations of identified

plaque.

A potential drawback of the plaque estimation methods used here is the inability to detect non-calcified plaques, which can lead to plaque underestimation. Overestimation of plaque may occur in cases where there are calcifications inside the pericardial contour that are not coronary calcifications, such as in cases of valvular calcifications. Also and beyond the scope of this study, other auto-segmentation methods such as those in [23–26] could potentially be explored.

In conclusion and to the best of our knowledge, this is the first study to report on the association between cardiac calcium burden as assessed from routinely acquired non-contrast enhanced treatment planning CT scans and OS in patients with locally advanced NSCLC. We established a significant association between increased coronary plaque and worse OS in patients treated with Def-RT. The plaque algorithm uses HU thresholding within the aorta and pericardium, which together with our open-source cardiac substructure DL algorithm can be easily implemented to further assess the role of pre-treatment plaque on outcomes and to stratify patients in prospective studies involving Def-RT and immunotherapy in locally-advanced NSCLC.

Funding

This research was partially supported by the NIH/NCI Cancer Center Support Grant/Core Grant (P30 CA008748). No sponsor participated in study design, data analysis or interpretation, writing the report, or the decision to submit the article for publication. The funding source was not involved in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Author contributions statement

We certify that all authors have contributed meaningfully to this manuscript and meet criteria for authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements: None

Data sharing:

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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