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Original Article

Association between statin therapy dose intensity and radiation cardiotoxicity in non-small cell lung cancer: Results from the NI-HEART study

Gerard M. Walls [a,b,*], John O'Connor [b], Mark Harbinson [c,d], Eamon P. McCarron [d,e], Frances Duane [f,g], Conor McCann [c], Peter McKavanagh [h], David I. Johnston [a], Jayaraj Erekkath [a], Valentina Giacometti [b], Anna T. Gavin [i], Jonathan McAleese [a], Alan R. Hounsell [a,b], Aidan J. Cole [a], Karl T. Butterworth [b], Conor K. McGarry [a,b], Gerard G. Hanna [a,b,1], Suneil Jain [a,b,1]

[a] *Cancer Centre Belfast City Hospital, Belfast Health & Social Care Trust, Lisburn Road;* [b] *Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Jubilee Road;* [c] *Department of Cardiology, Belfast City Hospital, Belfast Health & Social Care Trust, Lisburn Road;* [d] *Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Jubilee Road;* [e] *Department of Clinical Biochemistry, Royal Victoria Hospital, Belfast Health and Social Care Trust, Falls Road, Belfast, Northern Ireland, United Kingdom;* [f] *St. Luke's Radiation Oncology Network, St. Luke's Hospital;* [g] *Trinity St James's Cancer Institute, St. James's Hospital, Dublin, Ireland;* [h] *Department of Cardiology, Ulster Hospital, South Eastern Health & Social Care Trust, Upper Newtonards Road, Dundonald; and* [i] *Northern Ireland Cancer Registry, Queen's University Belfast, Falls Road, Belfast, Northern Ireland, United Kingdom*

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ABSTRACT

Introduction: Radiation cardiotoxicity is a dose-limiting toxicity and major survivorship issue for patients with non-small cell lung cancer (NSCLC) completing curative-intent radiotherapy, however patients' cardiovascular baseline is not routinely optimised prior to treatment. In this study we examined the impact of statin therapy on overall survival and post-radiotherapy cardiac events.

Methods: Patients treated between 2015–2020 at a regional center were identified. Clinical notes were interrogated for baseline patient, tumor and cardiac details, and both follow-up cancer control and cardiac events. Three cardiologists verified cardiac events. Radiotherapy planning scans were retrieved for application of validated deep learning-based autosegmentation. Pre-specified Cox regression analyses were generated with varying degrees of adjustment for overall survival. Fine and Gray regression for the risk of cardiac events, accounting for the competing risk of death and cardiac covariables was undertaken.

Results: Statin therapy was prescribed to 59% of the 478 included patients. The majority (88%) of patients not prescribed a statin had at least one indication for statin therapy according to cardiovascular guidelines. In total, 340 patients (71%) died and 79 patients (17%) experienced a cardiac event. High-intensity (HR 0.68, 95%CI 0.50–0.91, p = 0.012) and medium-intensity (HR 0.70, 95%CI 0.51–0.97, p = 0.033) statin therapy were associated with improved overall survival after adjustment for patient, cancer, treatment, response and cardiovascular clinical factors. There were no consistent differences in the rate or grade of cardiac events according to statin intensity.

Conclusions: Statin therapy is associated with improved overall survival in patients receiving curative-intent radiotherapy for NSCLC, and there is evidence of a dose–response relationship. This study highlights the importance of a pre-treatment cardiovascular risk assessment in this cohort. Further studies are needed to examine if statin therapy is cardioprotective in patients undergoing treatment for NSCLC with considerable incidental cardiac radiation dose and a low baseline cardiac risk.

The definitive treatment of non-small lung cancer (NSCLC) in patients deemed inoperable for medical reasons is radiotherapy, although this treatment also poses a significant physiological cardiopulmonary challenge [1,2]. Radiation cardiotoxicity in NSCLC is now a significant survivorship issue in the context of improved clinical outcomes in the era of advanced radiotherapy technology [3] and immunotherapy [4]. Acute cardiac events such as

* Corresponding author at: Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Lisburn Road, Belfast BT9 7AB, Northern Ireland, United Kingdom.
E-mail address: g.walls@qub.ac.uk (G.M. Walls).
[1] These authors contributed equally.

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arrhythmias [5–7], infarction [8–9] and heart failure [8,9] are observed as early as months after treatment, and incidental dose to the heart base region has been associated with excess deaths [10–14]. Proposed mechanisms by which cardiac dose leads to death include fatal acute cardiac events, subclinical impairment that compounds acute medical problems [15,16] and hematological toxicity [17].

The likelihood of radiation-induced cardiotoxicity is dependent on the radiation dose incidentally delivered to select heart structures [18,19]. The co-morbidity burden of the lung cancer population is large, with 30% of patients having had a previous cardiovascular event [20,21] and a further 50% having risk factors pre-disposing them to future cardiac events [20]. Potentiating this risk, social deprivation in this cohort [22] may beget suboptimal health services access and engagement, meaning patients may be less likely to have their risk factors medically optimised [23]. Further, this situation potentially represents a missed opportunity given the preclinical data purporting multiple cardiovascular drugs as radioprotectants [24], including statin therapy [25,26].

Whilst historically prescribed to lower serum lipid levels [27], cardiology guidelines now recommend statin therapy for a myriad of cardiovascular risk factors, owing to their pleiotropic anti-inflammatory, anti-oxidant and anti-fibrotic properties [28]. Patients with an elevated predicted 10-year risk of cardiovascular events according to tools such as QRISK3 or the Framingham score are usually offered statin therapy as 'primary prevention' [29,30]. Despite patients with NSCLC undergoing curative-intent radiotherapy commonly meeting the criteria for being 'high risk', statin therapy is only prescribed to 41–47% patients [20,31], most likely due to reduced healthcare access or suboptimal primary care prescribing practices [32]. The first study examining the relationship of statins in NSCLC found a negative association between statins and survival and no impact on cardiac events, but did not investigate statin dose intensity, cardiac substructure doses, or other concomitant cardiovascular drugs [31]. As high statin dose intensity has been linked with a greater degree of cardiovascular protection than low intensity in randomised clinical studies [33], statin dose is an important consideration. The primary objective of this retrospective cohort study was to determine the impact of statins on cardiac events and survival over a range of statin dose intensities, adjusting for cardiovascular baseline and substructure radiation dose metrics.

Methods

A retrospective analysis of 478 consecutive patients with NSCLC treated with curative-intent (chemo)radiotherapy between January 1, 2015, and December 31st, 2020, was conducted at the Cancer Centre Belfast City Hospital. Data analysis was conducted between February 1, 2022, and June 30, 2022. Patients were excluded if they had any previous left-sided breast or intrathoracic radiotherapy (e.g. mantle, lung, esophageal), if their radiotherapy plan could not be obtained, or if they subsequently received radical re-irradiation for locoregional relapse. Radiotherapy was delivered as volumetric modulated arc therapy (VMAT), intensity-modulated radiotherapy (IMRT) or 3D-conformal radiotherapy (Varian Eclipse, Varian Medical Systems Inc), in 1.8–2.75 Gy fractions. A contrast-enhanced 4-dimensional (4D) computed tomography (CT) scan was obtained for planning and the diagnostic positron emission tomography scan was fused with this for target and organ-at-risk delineation. Platinum-doublet concurrent and neoadjuvant chemotherapy were administered where patient fitness permitted. Governance approvals were provided and ethical approval waived, by the Belfast Health & Social Care Trust, and findings were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [34].

The cardiac chambers (left and right atria and ventricles) and great vessels (superior and inferior venae cavae and pulmonary artery) were segmented using a validated deep learning-based autosegmentation tool [35] and inspected by a clinical oncologist (GW). The coronary arteries [36] (left main, left anterior descending, left circumflex, and right), conduction nodes [37], pulmonary veins and ascending aorta, were manually delineated by a clinical oncologist (GW) on the Varian contouring module Eclipse (Varian Medical Systems, Palo Alto, CA, USA). A composite cardiac base structure was created using CERR (Computer Environment for Radiotherapy Research) [38], comprising the right atrium, superior vena cava, aortic root and proximal left anterior descending and right coronary arteries [39]. This cardiac sub-region was chosen to account for the radiation dose distribution within the heart as it has been consistently shown to relate to prognosis in this patient population [10–14]. A randomly selected 5% of contours were verified by a radiation oncologist (FD, arteries; GH (veins, nodes)), owing to their susceptibility to interobserver variation, and dose-volume histograms were re-calculated using the Varian AAA 16.1.0 dose calculation algorithm: mean, maximum (0.01 cc), and volume percentages receiving a specific xGy dose in 5 Gy increments.

As pre-specified in the study design, clinical records were interrogated for baseline patient, tumor and cardiovascular status details and subsequent cancer and cardiovascular outcomes, from initiation of radiotherapy until death, or last follow-up. Statin therapy dose intensity was graded as low, medium or high according to international consensus [40]. Cardiovascular risk factors (CVRFs) were classified as hypertension, dyslipidemia, diabetes mellitus, and smoking status. Established cardiac diseases (ECDs) were classified as a history of coronary artery disease, arrhythmia or heart failure. 'Other vascular history' included cerebrovascular events, peripheral vascular disease, and aortic aneurysm. The 10-year predicted risk of each patient developing a cardiac event was calculated with QRISK3 where there was no prior history [30]. Symptomatic cardiac events occurring post-radiotherapy were graded according to the clinical trial common terminology for adverse events (CTCAE) version 5 scale and were verified by a cardiology subspecialist (MH, CMC, PM). Events were defined by an increased grade compared with the 6 months prior to radiotherapy in patients with a previous history of the disease, in order to prevent labile pre-existing cardiac disease being classified as a radiation-related cardiac event following radiotherapy.

Acute coronary syndrome, arrhythmia and acute heart failure were assessed; pericardial and valve-related endpoints were not as the limited echocardiogram data available were not at standardised endpoints. Episodes of recurrent atrial fibrillation were also excluded from the study due to their ubiquitous nature. Mean cardiac substructure dose-volume metrics were calculated, except for the coronary arteries which had the maximum values calculated, given their clear serial tissue organisation. Patients underwent clinical assessment 36 monthly for 5 years after treatment, with CT imaging routinely at 3 months, 2 years and 5 years. Primary cause of death was extracted from death certificates.

Statistical analysis

Patient characteristics were summarised using descriptive statistics. Differences between categorical and continuous covariables were assessed with Fisher exact or Chi-squared tests, and student t tests respectively. One-way ANOVA was performed for intensity subgroup comparisons. Kaplan-Meier analysis was used to assess the effect of heart base radiation dose (in quartiles, and at a 3 Gy threshold to identify a very low dose group) and baseline

cardiovascular risk (as a 10-year risk threshold ≥ 10% according to QRISK3). Three Cox proportional hazards regressions were used to model all-cause mortality: unadjusted, adjusted for tumor and cardiovascular risk factors only and adjusted for all clinically relevant factors, using the time between the radiotherapy start date and date of death or last follow-up. This iterative plan was designed to demonstrate the consistent trend of statin dose intensity in an intermediate and full version of the model. Cardiac event cumulative incidence was adjusted for CVRFs, ECDs, key substructure doses and non-cardiac death as a competing risk using Fine and Gray regression, using the time between the radiotherapy start date and the date of the first cardiac event [41]. All statistical analyses were performed using R Studio [42].

Results

Of the 535 patients treated in this period, 478 patients were eligible for inclusion, and the median follow-up was 21.1 months. A total of 254 (53%) were male and the median age was 70 years (interquartile range (IQR) 64–76). Most patients received curative-intent radiotherapy alone (326, 58%) planned with VMAT (245, 51%). Two-hundred and eighty-three (59%) patients were receiving statin therapy, mostly at medium- (95, 20%) or high- (168, 35%) intensity, and twenty patients received low-intensity statin therapy (4%), as listed in Supplementary Table 1. Patients on statin therapy had a higher baseline QRISK3, and higher frequency of CVRFs and ECDs (Table 1). Of the patients not on statin therapy, the majority had at least one indication (171, 88%), and 4 were on an alternate lipid lowering therapy, suggesting an intolerance to statins (Supplementary Table 2). Patients on statin therapy also received other common cardiovascular drugs more frequently, eg. anti-angiotensins (52% versus 17% ($p < 0.0001$)) and beta blockers (38% versus 11% ($p < 0.0001$), and were likely to have been assessed by a cardiologist in the past (28% versus 12% ($p < 0.0001$)).

Body mass index, CCI and PS were also significantly worse in the statin cohort. There was no significant difference in disease staging, IMRT usage or incidental lung dose, but there were less histological diagnoses, less chemotherapy and lower heart base doses in patients receiving statin therapy. The statin dose intensity subgroups were well matched except for clinically insignificant variation in age, PS, T-stage and rates of previous cardiology assessment (Supplementary Table 3). There were no statistically significant differences in cardiac substructure doses between groups. Rates of palliative radiotherapy and systemic therapy for disease progression were low, and were balanced between groups. Locoregional (29.7 months, 95% confidence interval (95%CI) 20.1–50.9) versus 40.5 months, (95%CI 24.1–not reached)) and distant (34.1 months, 95%CI 17.8–not reached versus 51.9 months, 95%CI 35.9–not reached) control rates were not significantly different between statin-treated patients (all doses) and no-statin cases (log rank

Table 1
Baseline patient, tumor, treatment and cardiovascular characteristics of the cohort.

	All Patients (%)	No Statin (%)	Statin (%)	p value
Number of Patients	478	195 (41)	283 (59)	
Age (median, IQR)	70 (64–76)	67 (60–75)	71 (66–76)	**<0.0001**
Gender				
Female	224 (47)	100 (51)	124 (44)	0.1137
Male	254 (53)	95 (49)	159 (56)	
Performance Status				
0	45 (9)	26 (13)	19 (7)	
1	234 (49)	100 (51)	134 (61)	**0.029**
2	176 (37)	62 (32)	114 (40)	
3	23 (5)	7 (4)	16 (6)	
BMI* (median, IQR)	26.5 (23.0–29.9)	24.9 (22.2–28.9)	27.2 (24–30.5)	**0.0014**
CCI (median, IQR)	5.0 (5.0–6.0)	5.0 (4.0–6.0)	6.0 (5.0–7.0)	**<0.0001**
Previous SACT				
Cytotoxic Therapy	10 (2)	4 (1)	6 (1)	
Endocrine Therapy	8 (2)	5 (1)	3 (1)	0.3698
Both	1 (<1)	1 (<1)	0	
T-stage				
0	20 (4)	10 (4)	10 (4)	
1	117 (24)	42 (22)	75 (27)	
2	134 (28)	54 (28)	80 (28)	0.6796
3	101 (21)	43 (22)	58 (20)	
4	106 (22)	46 (24)	60 (21)	
N-stage				
0	152 (32)	59 (30)	93 (33)	
1	78 (16)	28 (14)	50 (18)	0.6093
2	210 (44)	91 (47)	119 (42)	
3	38 (8)	17 (9)	21 (7)	
Subtype				
Squamous cell carcinoma	223 (43)	86 (44)	137 (48)	
Adenocarcinoma	153 (32)	72 (37)	81 (29)	**0.0002**
Clinical	66 (14)	19 (10)	47 (17)	
Other	36 (8)	18 (9)	5 (2)	
Dose Fractionation**				
52–55Gy/19–20#	461 (96)	184 (94)	278 (98)	**0.0351**
60–66Gy/30–33#	14 (3)	8 (4)	5 (2)	
72–79Gy/40–44#	3 (1)	3 (2)	0	
Radiotherapy planning**				
3DCRT	139 (29)	57 (29)	82 (29)	
IMRT	94 (20)	52 (27)	42 (15)	>0.9999
VMAT	245 (51)	86 (44)	159 (56)	
Intravenous contrast				

(continued on next page)

Table 1 (*continued*)

	All Patients (%)	No Statin (%)	Statin (%)	p value
Yes	345 (72)	141 (72)	204 (72)	>0.9999
No	133 (28)	54 (28)	79 (28)	
Chemotherapy**				
No	325 (68)	120 (62)	205 (72)	
Concurrent	50 (10)	26 (13)	24 (8)	
Neoadjuvant	100 (21)	47 (24)	53 (19)	**0.0121**
Neoadjuvant & Concurrent	3 (1)	2 (1)	1 (<3)	
Adjuvant durvalumab	5 (1)	2 (<1)	3 (1)	>0.999
MBD (Gy) (median, IQR)	9.3 (5.2–15.1)	9.8 (5.1–16.9)	9.0 (5.4–13.8)	**0.0249**
Lung V20 (%) (median, IQR)	20.0 (14.8–27.1)	20.9 (15.0–27.8)	19.4 (14.7–26.2)	0.2773
Palliative RT for PD	30 (6)	11 (6)	19 (7)	0.7041
Palliative SACT for PD	57 (12)	29 (6)	28 (6)	>0.999
Hypertension	242 (51)	61 (31)	181 (64)	**<0.0001**
Dyslipidemia	272 (57)	50 (26)	159 (56)	**<0.0001**
Diabetes Mellitus**				
No	375 78)	178 (91)	197 (70)	
Type 1	6 (1)	3 (2)	3 (1)	**<0.0001**
Type 2	94 (20)	14 (7)	80 (28)	
Pre-Diabetes	3 (1)	0	3 (1)	
Smoking**				
Never	29 (6)	12 (6)	6 (2)	
Previous	308 (64)	130 (67)	178 (63)	0.8447
Current	152 (32)	53 (27)	89 (31)	
Pack Years (median, IQR)	40.0 (30.0–50.0)	40.0 (30.0–50.0)	40 (30.0–60.0)	**0.0164**
QRISK3 Score***	18.7 (11.9–27.2)	15.5 (8.9–24.5)	21.7 (15.2–29)	**<0.0001**
Coronary artery disease**,†				
No	403 (84)	175 (90)	196 (69)	
Stable Angina	57 (12)	13 (7)	44 (16)	
Acute Coronary syndrome	66 (14)	7 (4)	59 (21)	**<0.0001**
Any	109 (23)	20 (10)	89 (11)	
Arrhythmia**,†				
No	426 (89)	181 (92)	245 (87)	
Atrial Fibrillation	36 (8)	8 (4)	28 (10)	
Ventricular Arrhythmia	5 (1)	1 (1)	4 (1)	**<0.0001**
Other	13 (3)	6 (3)	7 (2)	
Any	52 (11)	14 (7)	38 (13)	
Heart Failure	41 (9)	9 (5)	32 (11)	**0.012**
Cerebrovascular Disease**,†				
No	411 (86)	187 (96)	229 (81)	
Ischemic	33 (7)	4 (2)	29 (10)	
Hemorrhagic	3 (1)	1 (1)	2 (<1)	
Transient Ischemic Attack	30 (6)	3 (2)	27 (10)	**<0.0001**
Amaurosis Fugax	1 (<1)	0	1 (<1)	
Any	62 (13)	7 (4)	55 (19)	
Peripheral Vascular Disease	46 (10)	8 (4)	38 (13)	**0.0008**
Aneurysm	24 (5)	4 (2)	20 (7)	**0.0174**
Valvulopathy	30 (6)	8 (4)	22 (8)	0.1256
Anti-thrombotic Therapy**				
No	255 (53)	152 (78)	103 (36)	
Antiplatelet	183 (38)	34 (17)	149 (53)	**<0.0001**
Anticoagulant	40 (8)	9 (5)	31 (11)	
Anti-angiotensin Therapy**				
No	318 (67)	162 (83)	156 (55)	
ACE inhibitors	115 (24)	22 (11)	93 (33)	**<0.0001**
AR2 Blockers	45 (9)	11 (6)	34 (12)	
Beta Blockers	128 (27)	21 (11)	107 (38)	**<0.0001**
Diuretics	108 (23)	25 (13)	83 (29)	**<0.0001**
Nitrate Tablets	36 (8)	6 (3)	30 (11)	**0.0023**
Previous Cardiologist Review	102 (21)	24 (12)	78 (28)	**<0.0001**

(BMI = body mass index; CCI = Charlson Comorbidity Index; SACT = systemic anti-cancer therapy; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric modulated arc therapy; MBD = mean base dose; RT = radiotherapy; PD = progressive disease; SACT = systemic anticancer therapy; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker).

* = available for 459 patients.

** = significance test performed on top row versus the other rows.

*** = calculable for 277 patients.

† = several patients are included on more than one row.

p = 0.450 and p = 0.089 respectively), or by statin dose intensity (log rank for trend p = 0.860 and p = 0.270 respectively) (Supplementary Figures 1–2).

A total of 340 patients died, 259 (76.1%) of NSCLC, 46 (13.5%) of non-cardiac causes, and 11 (3.2%) of cardiac causes; cause was not available for 15 (4.4%) patients (Supplementary Table 4). The median overall survival was 23.0 months (IQR 10.7–34.9 months). Overall survival (OS) was significantly lower in patients with higher mean heart base doses, and there was evidence of a dose response relationship (Supplementary Figure 3). The two-year

cumulative incidence of death was 55.6% (95%CI 48.1–62.3), 35.0% (95%CI 10.3–52.9), 45.5% (95%CI 34.5–54.7) and 51.4% (95%CI 43.0–58.5) for no statin and low-, medium- and high-intensity statin respectively. In unadjusted analyses, statin therapy was not associated with a significant improvement in OS in the whole cohort (p = 0.061), nor was dose intensity (p = 0.150).

(Supplementary Figure 4). In subgroup analyses the study was not specifically powered for, for patients receiving considerable heart base irradiation (i.e. dose of > 3 Gy, n = 416), the survival benefit of statin therapy was significant (p = 0.036), whereas the difference was not significant in the smaller subgroup receiving negligible heart base doses (n = 62) (p = 0.570) (Fig. 1**A–B**). In patients with a high QRISK3 score, there was a significant survival benefit with statin treatment (p = 0.007) (Fig. 1**B**) which was not present in the low QRISK3 group (n = 57) (p = 0.850) (Fig. 1**D**).

In a Cox proportional hazards regression model for all-cause mortality with adjustment for all the relevant clinical parameters, low- (HR 0.89, 95%CI 0.49–1.62), medium- (HR 0.70, 95%CI 0.51–0.97) and high- (HR 0.68, 95%CI 0.50–0.91) intensity statin therapy were associated with reduced mortality and were significant for medium (p = 0.033) and high intensity (p = 0.012) (Table 2). In the partially adjusted model, the association of high-intensity was also significant for a survival benefit (HR 0.76, 95%CI 0.58–1.00, p = 0.047) but medium- was not (HR 0.73, 95%CI 0.54–1.00, p = 0.052). The hazard ratio for low-intensity statin did not meet the pre-specified significance level in the partial or fully adjusted models (p = 0.851, p = 0.709 respectively). Differences in effect size between the partially (ten tumor, patient and CVRF covariables) and unadjusted models were similar to those between the fully (all covariables including ECDs) and partially adjusted model for medium (partial 0.07, full 0.03) and high intensity (partial 0.07, full 0.08) statin subgroups (Fig. 2; Supplementary Tables 5–6).

Seventy-nine patients developed 90 cardiac events, with a median time-to-event of 16.3 months (IQR, 9.5–33.9) and a median grade of 3 (IQR 3.0–3.5) (Supplementary Table 7). Arrhythmia, heart failure and acute coronary syndrome were observed in 41, 35 and 15 patients respectively. Ten patients experienced 2 events, and 1 patient experienced 3 events. There were no significant differences in the frequency of cardiac events, or time-to-event between statin therapy or dose intensities (Fig. 3), and the grade was higher in high-intensity statin therapy patients, particularly for acute coronary syndrome (p < 0.0001) (Supplementary Table 7). Cardiac substructure doses were similar between patients with and without cardiac events at each statin dose intensity, except for higher doses in the right coronary artery (p = 0.039) for patients with events in the high-intensity statin group.

There were similar rates of both CVRFs and ECDs between patients having events compared with those not. In the no-statin group there was significantly more ECDs (7 (24.1%) versus 13 (7.8%), p = 0.015) and higher left anterior descending coronary artery doses (mean 27.8 Gy versus 20.8 Gy, p = 0.039) in patients having cardiac events. When adjusting for baseline CVRFs and ECDs, key substructure dose metrics, and the competing risk of death, statin therapy dose intensity was not associated with cardiac events (Table 3).

Discussion

In this study, statin dose intensity was independently associated with improved survival following curative radiotherapy for NSCLC after adjusting for cancer, cardiovascular and radiotherapy covariables. The association of high-intensity statin was stronger than that of medium-intensity, despite patients at both dose levels

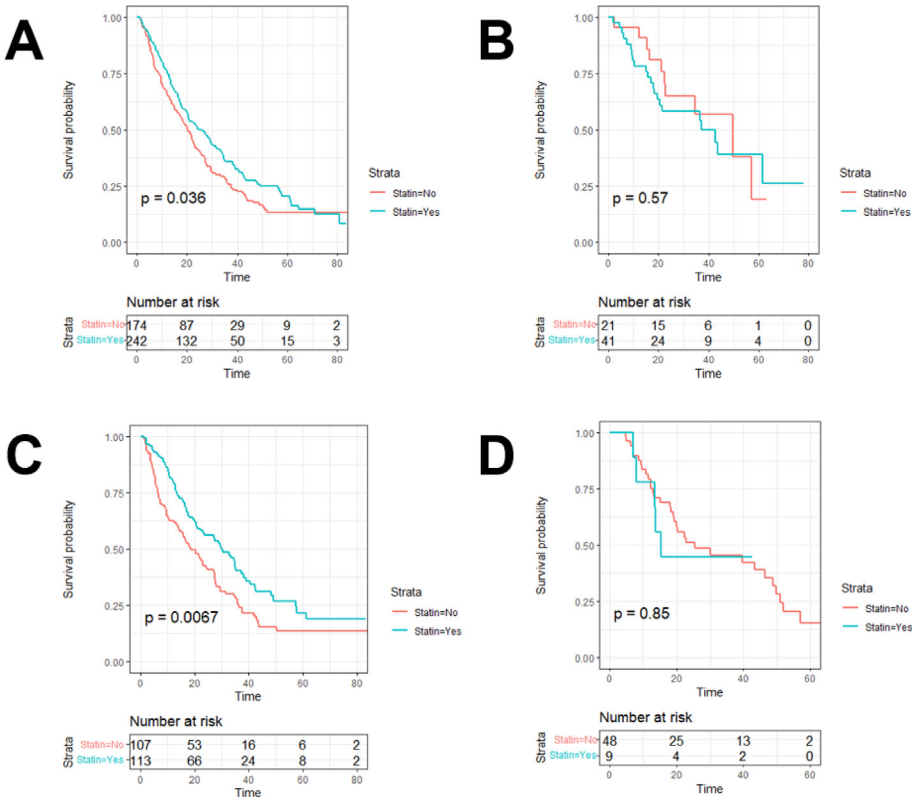

Fig. 1. Overall survival (months) by Kaplan-Meier according to incidental radiation dose to the mean heart base (A = ≥3 Gy; B < 3 Gy) and QRISK3 score (A = ≥10% risk at 10 years; B < 10% risk at 10 years), with p-values calculated by the log-rank test.

Table 2
Fully adjusted Cox proportional hazards model for overall survival.

Patient Characteristics	No Patients	No Deaths	Adjusted Hazard Ratio (95% CI)	p value
Age	472	335	1.02 (1.00–1.03)	0.108
Gender				
Male	248	189	1 [reference]	
Female	224	146	0.67 (0.52–0.86)	**<0.001**
Performance Status				
0	45	26	1 [reference]	
1	230	171	2.50 (1.60–3.91)	**<0.001**
2	174	124	2.54 (1.59–4.08)	**<0.001**
3	23	14	2.47 (1.19–5.12)	**<0.001**
Charlson Comorbidity Index*				
3	17	13	1 [reference]	
4	89	60	0.73 (0.36–1.47	0.371
5	171	123	0.66 (0.32–1.35)	0.253
6	112	78	0.68 (0.31–1.50)	0.343
7	45	36	0.72 (0.31–1.70)	0.455
8	26	17	0.51 (0.20–1.31)	0.164
9	12	8	0.48 (0.15–1.55)	0.221
T-stage				
0	20	8	1 [reference]	
1	117	76	1.74 (0.79–3.86)	0.171
2	130	89	1.69 (0.76–3.77)	0.196
3	100	78	2.23 (0.99–4.99)	0.052
4	100	84	2.96 (1.31–6.67)	**0.009**
N-stage				
0	150	105	1 [reference]	
1	77	56	0.88 (0.62–1.25)	0.474
2	207	146	0.88 (0.64–1.20)	0.41
3	38	28	0.78 (0.47–1.29)	0.344
Subtype				
Adenocarcinoma	152	103	1 [reference]	
Squamous cell	220	165	1.09 (0.84–1.43)	0.484
Clinical	64	40	0.94 (0.61–1.46)	0.795
Other	36	27	0.84 (0.53–1.33)	0.463
Chemotherapy**				
None	320	231	1 [reference]	
Neoadjuvant	103	79	1.05 (0.76–1.46)	0.756
Concurrent	52	25	0.63 (0.40–1.01)	0.056
Mean Base Dose (Gy)	472	335	1.01 (0.99–1.02)	0.545
Lung V20 (%)	472	335	1.09 (1.04–1.14)	**<0.001**
Hypertension	239	168	0.86 (0.65–1.13)	0.297
Dyslipidemia	268	197	1.07 (0.84–1.36)	0.571
Diabetes Mellitus	99	68	0.95 (0.67–1.35)	0.778
Pack Years	472	335	1.00 (0.99–1.00)	0.177
Coronary Artery Disease	120	90	1.27 (0.91–1.76)	0.155
Arrhythmia	50	33	0.74 (0.48–1.13)	0.166
Heart Failure	39	26	1.00 (0.63–1.58)	0.999
Other Vascular History	111	88	1.61 (1.17–2.22)	**0.003**
Previous Cardiologist Review	100	67	0.98 (0.71–1.34)	0.882
Anti-thrombotic Drug	215	153	1.33 (0.98–1.80)	0.067
Anti-angiotensin Drug	125	93	0.89 (0.66–1.20)	0.461
Statin Therapy				
None	192	145	1 [reference]	
Low-Intensity	20	15	0.89 (0.49–1.62)	0.709
Medium-Intensity	94	65	0.70 (0.51–0.97)	**0.033**
High-Intensity	166	110	0.67 (0.50–0.91)	**0.011**

* = patients with Charlson scores of 2 (n = 2) and 10 (n = 4) were not included given their small proportions and lack of variation (all but 1 died).
** = total > 472 as 3 patients received both neoadjuvant and chemotherapy.

having a greater burden of baseline cardiac morbidity than low- and no-statin patients. A survival benefit was observed in unpowered subgroup analyses of patients with a considerable heart radiation dose, or patients with an unfavorable cardiovascular risk profile, which is hypothesis-generating for a dual cardioprotective role for statin therapy in the NSCLC population. Cancer control outcomes were comparable between statin-treated and no-statin groups. Together, these data suggest a benefit for high-intensity statin therapy, or medium- where necessary, to patients embarking on radiotherapy for NSCLC, and possibly for those patients with considerable cardiac base radiation doses (i.e. >3 Gy) or pre-existing CVRFs or ECDs in particular.

Investigating the precise mechanisms by which cardiac dose leads to death is complicated by the central role of the heart in the systemic response to medical conditions, the difficulty of accurately ascertaining cause of death in patients with lung cancer [20], the absence of systematic and sensitive post-radiotherapy cardiac surveillance data, and the convention of exclusively reporting 'whole heart' dose metrics in clinical physics studies [43]. Within these limitations, the low rate of fatal acute cardiac events reported in the literature does not fully account for the increased death rate observed with higher heart doses in NSCLC, positing subclinical cardiac substructure insults as a vector for increased mortality. It is plausible that non-event cardiotoxicity remains

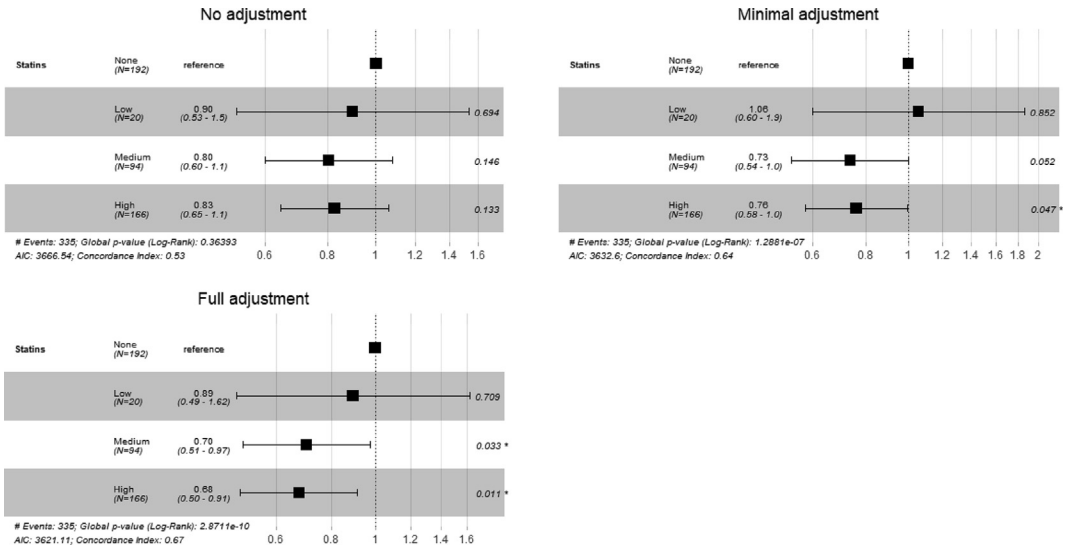

Fig. 2. Forest plots of the hazard ratios for different statin dose intensities in the unadjusted, partially adjusted and full adjusted Cox regression models for overall survival.

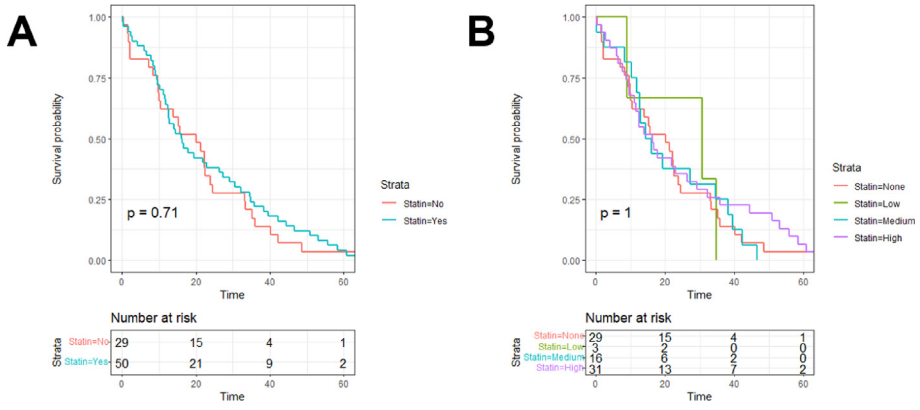

Fig. 3. Cardiac event-free survival (months) plotted by Kaplan-Meier analysis by statin prescription (A), and by dose intensity (B), for the patients that developed cardiac events, with p-values calculated by the log-rank (A) and log-rank for trend (B) tests.

Table 3
Fine and Gray regression model for first cardiac event, adjusting for the relevant clinical cardiovascular and dosimetric factors, with death as a competing risk.

Patient Characteristics	No Patients	No Events	Adjusted Hazard Ratio (95% CI)	p value
Age	472	79	1.024	0.082
Female Gender	224	34	1.058	0.83
Any Chemotherapy	153	4	0.725	0.55
Hypertension	242	47	1.228	0.43
Dyslipidemia	272	46	1.098	0.69
Diabetes Mellitus	103	19	1.011	0.97
Pack Years	472	79	1.002	0.58
Coronary Artery Disease	75	31	1.587	0.098
Arrhythmia	52	16	1.274	0.54
Heart Failure	41	17	3.01	**0.0043**
Other Vascular History	114	23	1.053	0.86
Sinoatrial Node Maximum	472	79	1.008	0.32
Total Coronary Artery V15	472	79	2.245	0.15
Statin Therapy				
None	195	29	1 [reference]	
Low-Intensity	20	3	0.657	0.47
Medium-Intensity	95	16	0.849	0.63
High-Intensity	478	30	0.852	0.6

subclinical until an acute medical stressor such as sepsis or hemorrhage, where it manifests to hamper recovery, increasing the risk of death from the medical stressor [15,16]. As such, all-cause mortality may serve as a surrogate metric for radiation cardiotoxicity in NSCLC cohorts after accounting for relevant patient and tumor factors, as demonstrated in studies examining the cardiac base as a dose-sensitive region [10–14]. In this study, statin therapy was specifically associated with improved OS in the 416 patients with

a higher heart radiation dose, suggesting that statins partially counter the deleterious effects on the heart. Furthermore, lung cancer control outcomes were comparable between the statin and no-statin groups of patients.

In contrast with our data, the only other published patient-level study assessing statins [31] found a negative association with OS and hypothesised that increased mortality rate is explained by the adverse CVRF profile of the statin group. Our data and that of Atkins had similar rates of baseline CVRFs and ECDs, but statins were prescribed more frequently in our cohort (59% versus 41%). Atkins et al. found a positive association between statin therapy and survival for a subgroup of patients with higher cardiac radiation doses, which was also seen in this study. Importantly, in our cohort there were no differences in locoregional or distant cancer control based on statin dose intensity, implying that survival gains in the statin-treated patients were not due to better cancer outcomes as the result of statin therapy acting as a radiosensitiser. In agreement with Atkins et al. [31], neither statin therapy or its dose intensity in the presented cohort were significantly associated with a reduction in the frequency of, or interval to, cardiac events. This raises the possibility that the potential cardioprotective effect of statin therapy is diminished above a radiation dose threshold.

Our finding that patients with a favorable QRISK3 score did not derive a survival benefit from statin therapy in unadjusted analyses suggests that a proportion of post-radiotherapy cardiac disease is due to intrinsic cardiovascular ill-health. It is likely that the risk of developing a post-radiotherapy cardiac event is dependent on a complex interaction of cardiometabolic risk factors, established cardiac pathology, inter-related substructure radiation doses and individual radiosensitivity. Furthermore, it is anticipated that radioprotective therapies have a finite capacity for off-setting these factors from preclinical research [25,26,44–46].

The strengths of this study are that, to our knowledge, it is the first to analyse statin dose intensity for cardiac radioprotection and the first to implement individual cardiac base region contouring. By integrating validated cardiovascular risk scores, and subspecialist event verification, this work fosters better mutual understanding between radiation oncologists and cardiologists. The cohort described benefited from a contemporary radiotherapy workflow including 4D-planning, cone-beam CT image-guidance and IMRT/VMAT delivery, and this study utilised evidence-based substructure dose metrics, from a validated, deep learning-based autosegmentation tool [35]. In addition, matching cancer control outcomes and cause of death data were available for oncological context, which is relevant given the mixed evidence for statin therapy improving tumor radiation responses [47]. The weaknesses of this work relate to its retrospective nature; patient adherence to statin therapy was not available, and it is possible that cardiac events were missed during follow-up, although data missingness levels were low elsewhere and patient attrition was rare. The rate of cardiac events was modest, pericardial and valve disease endpoints were not included, and the diagnosis of CVRFs following treatment were not available. Finally, the absence of any survival benefit for low-dose statin, and distinct cardiac event type analyses, should be regarded with caution given the small numbers involved. Despite these limitations, this comprehensive individual patient-level dataset presents compelling evidence for an association of medium-, and moreso high-intensity statin therapy, with improved survival in patients with NSCLC treated with curative radiotherapy.

Conclusion

High- and medium-intensity statin therapy conferred a benefit in OS in this contemporary NSCLC cohort treated with curative radiotherapy, however the risk of acute cardiac events was not altered. These findings remain to be validated prospectively, but serve to prompt radiation oncologists to avail of the opportunity for optimisation of modifiable CVRFs in patients undergoing thoracic radiotherapy.

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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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109762.

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