Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: an NI-HEART analysis

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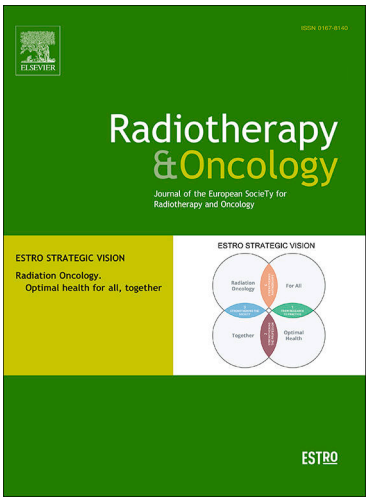

Original Article

Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: an NI-HEART analysis

Gerard M Walls, Conor McCann, John O'Connor, Anna O'Sullivan, David I Johnston, Jonathan McAleese, Conor K McGarry, Aidan J Cole, Suneil Jain, Karl T Butterworth, Gerard G Hanna

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Full Title

Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: an NI-HEART analysis

Short Title

Pulmonary vein dose and atrial fibrillation

Authors

Gerard M Walls FRCR PhD[1,2]

Conor McCann MD[3]

John O'Connor PhD [4]

Anna O'Sullivan[5]

David I Johnston MRCP[2]

Jonathan McAleese FRCR[1]

Conor K McGarry PhD[1,2]

Aidan J Cole FRCR PhD[11]

Suneil Jain FRCR PhD[11,2]

Karl T Butterworth PhD[2]

Gerard G Hanna FRCR PhD[1,2]

1

Cancer Centre Belfast City Hospital,
Belfast Health & Social Care Trust,

Lisburn Road,
Belfast,
Northern Ireland.

2
Patrick G Johnston Centre for Cancer Research,
Queen's University Belfast,
Jubilee Road,
Belfast,
Northern Ireland.

3
Department of Cardiology,
Belfast City Hospital,
Belfast Health & Social Care Trust,
Lisburn Road,
Belfast,
Northern Ireland.

4

School of Engineering,

University of Ulster,

York Street,
Belfast,
Northern Ireland.

5

School of Medicine,

University College Dublin,

Belfield,

Dublin 4,

Ireland.

Corresponding Author

Dr Gerard Walls

Patrick G Johnston Centre for Cancer Research

Queen's University Belfast

Lisburn Road

Belfast BT9 7AB

Northern Ireland

g.walls@qub.ac.uk

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GW = speaker fee from Astra Zeneca

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HIGHLIGHTS

- AF is a common form of radiation cardiotoxicity in patients with NSCLC
- the pulmonary veins have been postulated as arbitrators of AF in radiotherapy
- dose to the pulmonary veins was associated with probability of AF in this study
- validation is needed to confirm this finding before implantation of PV-sparing
- patients with high PV doses could undergo pulse check +/- ECG during follow-up

Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: an NI-HEART analysis

Background and purpose

Symptomatic arrhythmia is common following radiotherapy for non-small cell lung cancer (NSCLC), frequently resulting in morbidity and hospitalization. Modern treatment planning technology theoretically allows sparing of cardiac substructures. Atrial fibrillation (AF) comprises the majority of post-radiotherapy arrhythmias, but efforts to prevent this cardiotoxicity have been limited as the causative cardiac substructure is not known. In this study we investigated if incidental radiation dose to the pulmonary veins (PVs) is associated with AF.

Material and methods

A single-centre study of patients completing contemporary (chemo)radiation for NSCLC, with modern planning techniques. Oncology, cardiology and death records were examined, and AF events were verified by a cardiologist. Cardiac substructures were contoured on planning scans for retrospective dose analysis.

Results

In 420 eligible patients with NSCLC treated with intensity-modulated (70%) or 3D-conformal (30%) radiotherapy with a median OS of 21.8 months (IQR 10.8–35.1), there were 26 cases of new AF (6%). All cases were grade 3 except two cases of grade 4. Dose metrics for both the left (V55) and right (V10) PVs were associated with the incidence of new AF. Metrics remained statistically significant after accounting for the competing risk of death and cardiovascular covariables for both the left (HR 1.02, 95%CI 1.00–1.03, p=0.005) and right (HR 1.01 (95%CI 1.00–1.02, p=0.033) PVs.

Conclusion

Radiation dose to the PVs during treatment of NSCLC was associated with the onset of AF. Actively sparing the PVs during treatment planning could reduce the incidence of AF during follow-up.

INTRODUCTION

Radiotherapy (RT) is the only definitive treatment option available to patients with non-small cell lung cancer (NSCLC) deemed to be technically or medically inoperable. Contemporary RT results have been improved by the recent introduction of adjuvant immunotherapy, but outcomes remain poor, with <50% 5-year survival (1), one-third experience grade 3–4 toxicity, and poor quality of life (2).

Morbidity and mortality following RT are typically attributed to progression of cancer or chronic comorbidities, but treatment toxicity is increasingly recognized (3), including radiation cardiotoxicity. Although a latency period of many years is classically described for cardiac radiation effects, accumulating evidence suggests cardiac RT injury is a problem in the short-term for patients with NSCLC (4,5). Cardiac dose has been linked to the incidence of symptomatic cardiac events, affecting approximately 25% patients (6). Hospitalizations and morbidity resulting from cardiac events are detrimental for quality of life during cancer survivorship (7,8).

Symptomatic arrhythmia affects up to 11% patients following lung cancer RT (9), and the most commonly observed arrhythmia subtype is atrial fibrillation (AF). Kim et al demonstrated that the maximum dose (Dmax) to the sinoatrial node (SAN), the specialized pacemaker region of cardiac cells in the right atrial (RA) wall, best predicted new AF from the available cardiac substructure dose volume histogram (DVH) metrics in a cohort of 321 patients with NSCLC (10). In recent esophageal cancer series, left atrium (LA) DVHs were associated with incident AF (11,12).

The pathological cardiac tissue responsible for AF is typically located at the junction of the pulmonary veins and the left atrium. In AF, the sleeve of myocardial tissue embedded in the overlapping walls of these structures becomes altered, causing abnormal propagation of electrical potentials (13). Pulmonary vein (PV) isolation is the definitive treatment for AF, involving radiofrequency ablation of the PVs via cardiac catheterization (14,15).

As RT is known to cause short- and long-term cardiac tissue injury, it is plausible that dose deposited in the PVs may in part explain the significant rates of AF observed following RT. The PVs are adjacent to the left atrium In this study, the DVH metrics of the PVs were interrogated for an association with the development of AF in patients who completed definitive RT for NSCLC.

METHODS AND MATERIALS

Patients and Treatment

Consecutive patients completing curative-intent (chemo)RT for NSCLC between January 1st 2015 and December 31st 2020 were retrospectively included, as previously described in other NI-HEART analyses (16,17). Patients were excluded if they had previous left-sided breast or intrathoracic RT, or a history of AF, or if they received dose-escalated RT (in a clinical trial). Radiotherapy was delivered as 3D-conformal (3DCRT) or intensity-modulated radiotherapy (IMRT) including volumetric modulated arc therapy (VMAT) (Varian Eclipse, Varian Medical Systems Inc), as 55 Gy in 20 once-daily fractions over 4 weeks. 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 XXXXXXXXXXXXXXXXXX, findings were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (18).

Baseline Cardiac Profiles

Oncology records were interrogated for baseline and subsequent cardiovascular outcomes, from initiation of RT until death or last follow-up. Baseline cardiovascular risk factors were collected. ie. hypertension, dyslipidaemia, diabetes mellitus and tobacco. Established cardiovascular conditions were recorded. These were defined as coronary artery disease (stable and unstable angina, and myocardial infarction), heart failure and non-AF arrhythmia. Vascular disease was also collected including cerebrovascular disease (ischaemic/haemorrhagic stroke, transient ischaemic attach and amaurosis fugax), and peripheral vascular disease (lower limb ischaemia, aortic or pelvic aneurysm). Pre-existing prescriptions of anti-dysrhythmic drugs (eg. beta-blockers or calcium channel blockers) and alcohol consumption ≥22 units per week = 4) were also recorded since these impact the incidence of AF. Those patients with no available information were assigned the median value. ie. 0 units per week. Time-to-AF and -death were measured from the RT start date. Events were graded by CTCAEv5 and were verified by an electrophysiology subspecialist cardiologist (CMC).

DVH Metrics

The PVs and SAN were manually segmented by a clinical oncologist (GW) (19,20) (**Figure 1**). The LA was auto-contoured using a validated open-source deep learning algorithm (21). Verification was performed on 5% cases randomly selected by a radiation oncologist (GH). DVH metrics were calculated using the AAA 16.1.0 algorithm. A small selection of PV metrics was prospectively chosen for the analysis through consensus discussions based on the correlation profiles of the metrics, and to represent the range of different dose levels. The volume receiving ≥10Gy (V10), the mean dose, and the volume receiving ≥55Gy (V55), representing the low-, medium- and high-dose baths respectively. Dmax and V20 were used for the SAN and LA respectively, based on previous studies (10,11).

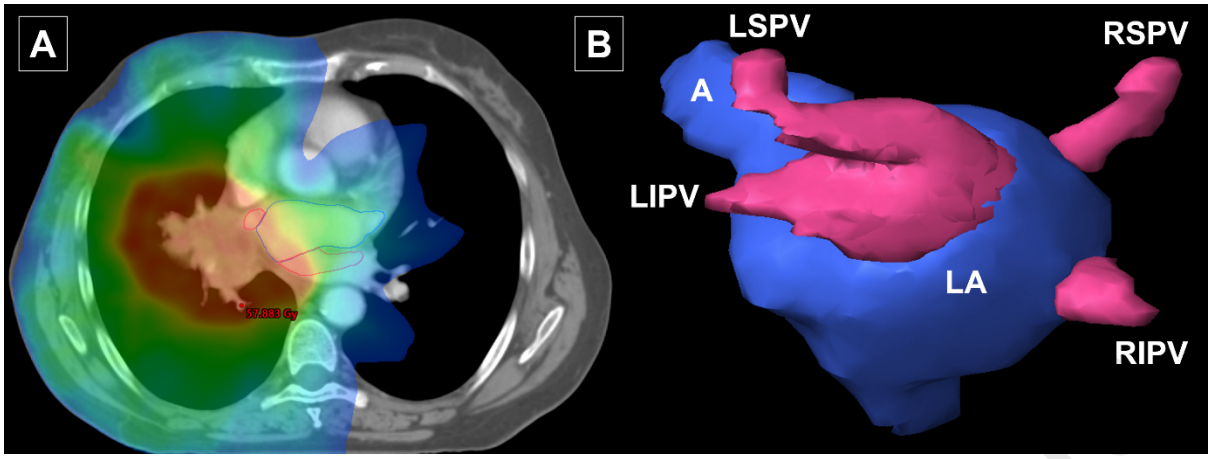

Figure 1. A) A representative axial image from a 4-dimensional CT planning scan with the radiation dose color wash overlaid (blue = 10Gy, red = 55Gy). The left atrium is outlined in blue and the pulmonary veins are outlined in mauve. **B)** A 3-dimensional reconstruction of the left atrium and pulmonary veins from the posterior view.

(LA = left atrium; A = Auricle; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein)

Statistical Analyses

Mann-Whitney tests and Chi squared were used to assess the significance of baseline differences between patients that developed AF versus those did not, as much of the continuous data for the non-AF cases was not normally distributed (Shapiro-Wilk). Correlograms based on Spearman's correlation coefficients were generated to assess the collinearity of the PV DVH metrics to inform metric selection (**Supplementary Figure 1**), having been shown to be normally distributed on Shapiro-Wilk. Fine and Gray regression was performed with each candidate metric (V10, mean, V55) in turn, with adjustment for cardiovascular covariables and death, leading adjusted hazard ratios (aHR). The area under the curve (AUC) for prediction of AF events was calculated for PV metrics with the strongest associations with AF, and for the SAN Dmax (10) and LA V20 (11) for comparison, in order to determine optimal cut-points (Youden method) for visualising the impact of PV dose on cumulative incidence of AF after accounting for the competing risk of death. Cox regression was used to assess the association of PV DVHs and post-radiotherapy AF with death, accounting for baseline and follow-up factors. All statistical analyses were performed using R Studio (22).

RESULTS

Of 420 eligible patients available, 200 (52%) were female, the median age was 70 years, and most patients had involved lymph nodes (69%), as shown in **Table 1**. Patients were mostly planned with volumetric modulated arc therapy (50%) or static gantry intensity-modulated RT (20%). Chemotherapy was administered in a minority of patients (33%). The burden of pre-existing cardiovascular morbidity was high, with 78% having ≥2 cardiovascular risk factors, and 46% having ≥1 established cardiovascular disease. Alcohol consumption was low across the cohort, with most patients either not drinking (40%) or drinking ≤6 units per week (26%), and data was available for 322 patients. The median OS was 21.8 months (IQR 10.8–35.1 months).

The median volume of the RPV was 5.0cc (IQR 3.8–6.3), and was 6.4cc (IQR 4.9–8.4) for the LPV. The median V10, mean, V55 and maximum dose to the pulmonary veins were the 59.0% (IQR 0.0–100), 12.9 Gy (IQR 3.8–33.6), 0.0% (0.0–7.7) and 25.1 Gy (9.0–56.8) on the right, and 84.1% (37.3–100.0), 19.6 Gy (9.2–38.4), 0.0% (0.0–13.6) and 49.7 Gy (18.8–57.3) on the left. Doses to the PVs were not improved in patients treated with IMRT compared with 3D-conformal RT, although VMAT was associated with improved values for several metrics, as shown in **Table 2**.

Twenty-six patients (6%) developed AF with a median onset time of 13.3 months (IQR, 8.4–13.3). All cases were grade 3 except for two grade 4s. In terms of baseline demographics, hypertension (20/26 v 195/394) and non-AF arrhythmia (3/26 v 6/394) were statistically significantly more common in patients that developed AF. For the LPV, the DVH parameter with the strongest association with the development of AF was the V55, with an aHR 1.02 (95%CI 1.00–1.03, p=0.005), as shown in **Table 3**. For the RPV, the DVH parameter with the strongest association with the development was the V10, with an aHR 1.01 (95%CI 1.00–1.02, p=0.033),, as shown in **Table 3**. Alcohol consumption was the only clinical covariable significantly associated with AF events.

The AUC for prediction of AF events was 0.64 (p=0.02) and 0.61 (p=0.03) for the LPV V55 and RPV V10 respectively and the optimal thresholds for predicting AF were 2% for the LPV V55, and 54% for the RPV V10. The RPV V10 and LPV V55 thresholds were met by 225 patients (54%) and 167 patients (40%) respectively, and 102 patients (24%) met both.

	All Patients (%)	**No Post-Radiotherapy AF (%)**	**Post-Radiotherapy AF (%)**	**P value**
Number of Patients	420 (100)	394 (94)	26 (6)	-

Age (median, IQR)	70 (63–75)	70 (63 – 75)	71 (66 – 76)	0.279
Gender				
Female	200 (48)	191 (48)	9 (35)	0.224
Male	220 (52)	203 (52)	17 (65)	
Performance Status				
0	43 (10)	40 (10)	3 (12)	
1	206 (49)	196 (50)	10 (38)	0.690
2	152 (36)	140 (36)	12 (46)	
3	19 (1)	18 (5)	1 (4)	
CCI* (median, IQR)	5 (5 – 6)	5 (5 – 6)	5 (4 – 6)	0.581
Units of Alcohol Per Week				
None	167 (40)	161 (41)	6 (23)	
1–6	109 (26)	98 (25)	11 (42)	
7–14	28 (7)	27 (7)	1 (4)	0.063
15–21	3 (1)	3 (1)	0 (0)	
≥22	15 (4)	12 (3)	3 (12)	
Unknown	98 (23)	93 (24)	5 (19)	
T-stage				
0	18 (4)	17 (4)	1 (4)	
1	102 (24)	96 (24)	6 (23)	0.773
2	119 (28)	110 (28)	9 (35)	
3	87 (21)	84 (21)	3 (12)	
4	94 (22)	87 (22)	7 (27)	
N-stage				0.748

0	129 (31)	120 (30)	9 (35)	
1	72 (17)	69 (18)	3 (12)	
2	189 (45)	176 (45)	13 (50)	
3	30 (7)	29 (7)	1 (4)	
Subtype				
Squamous cell carcinoma	199 (47)	186 (47)	13 (50)	
Adenocarcinoma	139 (33)	132 (34)	7 (27)	0.638
Clinical	53 (13)	48 (12)	5 (19)	
Other	29 (7)	28 (7)	1 (4)	
Chemotherapy				
No	265 (63)	261 (66)	20 (77)	
Concurrent	45 (11)	44 (11)	3 (11)	0.086
Neoadjuvant	89 (21)	87 (22)	2 (8)	
Neoadjuvant & Concurrent	3 (1)	2 (1)	1 (4)	
Lung V20 (%) (median, IQR)	20.3 (15.3 – 27.1)	20.3 (15.3 – 26.7)	20.4 (15.0 – 27.4)	0.868
Hypertension	215 (51)	195 (49)	20 (77)	**0.007**
Dyslipidemia	250 (60)	231 (59)	19 (73)	0.146
Diabetes Mellitus	88 (21)	81 (21)	7 (27)	0.440
Pack Years (median, IQR)	40 (30 – 56)	40 (30 – 55)	50 (40 – 69)	0.101
QRISK3 Score**	18.1 (11.8 – 26.8)	18.1 (11.0 – 26.6)	21.5 (14.9 – 35.4)	0.075
Coronary Artery Disease	107 (25)	97 (25)	10 (38)	0.117

Non-AF Arrhythmia	9 (2)	6 (2)	3 (12)	**<0.001**
Heart Failure	22 (5)	19 (5)	3 (12)	0.137
Cerebrovascular Disease	48 (11)	47 (12)	1 (4)	0.210
Peripheral Vascular Disease	54 (13)	53 (13)	1 (4)	0.156
Valvulopathy	14 (3)	12 (3)	2 (8)	0.201
Statin Therapy	194 (46)	181 (46)	13 (50)	0.688
Anti-Dysrhythmic Drug	105 (25)	97 (25)	7 (27)	0.792

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

(IQR = interquartile range; CCI = Charlson Comorbidity Index; AF = atrial fibrillation,

V20 = volume receiving ≥20Gy)

* = calculable for n=234 non-AF, n=15 AF; * = CCI was binned for Chi squared significance testing as 0–4, 5 and 6–10.

Metric	3DCRT (IQR) n=126	IMRT (IQR) n=84	VMAT (IQR) n=210	IMRT v 3DCRT p value	VMAT v 3DCRT p value
RPV Mean (Gy)	12.9 (5.8–33.3)	21.7 (7.5–43.1)	10.2 (2.9–29.8)	0.0567	0.2696
RPV Dmax (Gy)	24.1 (12.8–57.0)	50.4 (16.6–56.9)	21.6 (6.7–56.7)	0.0642	0.3004
RPV V10 (%)	60.3 (19.7–100.0)	76.2 (32.6–100.0)	42.6 (0.0–100.0)	0.1915	**0.0247**
LPV Mean (Gy)	25.0 (10.4–41.8)	21.8 (10.0–41.6)	15.8 (8.0–35.0)	0.7627	**0.0068**
LPV Dmax	55.2 (23.6–58.2)	51.4 (19.3–	44.1 (16.1–	0.4689	**0.0159**

(Gy)		56.5)	57.1)		
LPV V55 (%)	0.0 (0.0–29.8)	0.0 (0.0–10.2)	0.0 (0.0–7.9)	**0.0046**	**<0.0001**

Table 2. Doses delivered to the pulmonary veins by treatment planning solution

(3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc modulated therapy; RPV = right pulmonary vein; Dmax = maximum dose; V10 = volume receiving ≥10 Gray; LPV = left pulmonary vein; V55 = volume receiving ≥55 Gray)

Table 3. Fine-Grey regression models for the incidence of atrial fibrillation according to pre-specified pulmonary vein dose metrics, with adjustment for relevant cardiovascular characteristics.

	Right Pulmonary Vein		**Left Pulmonary Vein**	
	aHR (95%CI)	**p value**	**aHR (95%CI)**	**p value**
Volume Receiving ≥10Gy				
DVH	1.01 (1.00 – 1.02)	**0.033**	1.01 (0.99–1.02)	0.350
Age	1.03 (0.98 – 1.07)	0.210	1.02 (0.98–1.07)	0.290
Sex	1.80 (0.77 – 4.23)	0.180	1.80 (0.76–4.22)	0.180
HF	2.35 (0.64 – 8.55)	0.200	2.26 (0.61–8.37)	0.220
Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.42 (1.08 – 5.42)	**0.032**	2.51 (1.08 – 5.84)	**0.033**
2	1.80 (0.40 – 8.11)	0.440	1.75 (0.39 – 7.78)	0.460
3	0.00 (0.00 – 8.11)	0.000	0.00 (0.00 – 0.00)	0.000
4	4.78 (0.98 – 23.50)	0.054	5.40 (1.10 – 26.60)	**0.038**
Drug	0.79 (0.31 – 2.01)	0.620	0.80 (0.32–2.01)	0.640
Chemo	1.70 (0.73 – 3.94)	0.220	1.56 (0.69–3.52)	0.280
Statin	1.11 (0.46 – 2.66)	0.840	1.03 (0.43–2.46)	0.940
CAD	2.03 (0.80 – 5.14)	0.140	2.04 (0.81–5.17)	0.130

Mean Dose				
DVH	1.01 (0.99–1.03)	0.490	1.02 (1.00–1.04)	0.100
Age	1.03 (0.98–1.07)	0.280	1.03 (0.98–1.07)	0.240
Sex	1.77 (0.76–4.16)	0.190	1.76 (0.75–4.12)	0.190
HF	2.26 (0.61–8.46)	0.220	2.34 (0.64–8.59)	0.200
Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.61 (1.14 – 5.97)	**0.023**	2.37 (1.00 – 5.59)	**0.050**
2	1.88 (0.42 – 8.33)	0.410	1.79 (0.40 – 7.93)	0.450
3	0.00 (0.00 – 0.00)	0.000	0.00 (0.00 – 0.00)	0.000
4	5.43 (1.09 – 26.90)	**0.038**	5.02 (1.02 – 24.58)	**0.047**
Drug	0.75 (0.29–1.96)	0.590	0.77 (0.31–1.91)	0.570
Chemo	1.47 (0.65–3.30)	0.350	1.56 (0.70–3.49)	0.270
Statin	1.06 (0.43–2.62)	0.850	1.01 (0.42–2.39)	0.990
CAD	2.09 (0.83–5.29)	0.120	2.06 (0.81–5.23)	0.130
Volume Receiving ≥55Gy				
DVH	1.00 (0.98–1.02)	0.840	1.02 (1.00–1.03)	**0.005**
Age	1.02 (0.98–1.07)	0.330	1.03 (0.98–1.07)	0.230
Sex	1.80 (0.77–4.20)	0.180	1.81 (0.80–4.09)	0.150
HF	2.27 (0.61–8.45)	0.220	2.26 (0.66–7.72)	0.140

Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.62 (1.15 – 5.98)	**0.022**	2.46 (1.05 – 5.74)	**0.038**
2	1.87 (0.42 – 8.28)	0.410	1.77 (0.39 – 8.00)	**0.460**
3	0.00 (0.00 – 0.00)	**0.000**	0.00 (0.00 – 0.00)	0.000
4	5.32 (1.09 – 26.0)	**0.039**	5.16 (1.11 – 24.00)	0.036
Drug	0.78 (0.31–1.99)	0.610	0.75 (0.30–1.87)	0.530
Chemo	1.41 (0.63–3.18)	0.400	1.57 (0.70–7.72)	0.280
Statin	1.05 (0.45–2.45)	0.910	1.03 (0.44–2.41)	0.940
CAD	2.06 (0.81–5.23)	0.130	2.01 (1.63–4.91)	0.120

(aHR = adjusted hazard ratio; DVH = dose volume histogram; HF = heart failure; CAD = coronary artery disease)

By comparison, the AUC for the SAN Dmax (0.61, p=0.05) and LA V20 (0.57, p=0.24) were lower and not statistically significant. The 24-month cumulative incidence of AF with PV doses above these thresholds was 15 versus 3 events compared for below (p=0.11), after accounting for the competing risk of death (**Figure 2**).

When adjusting for clinically relevant comorbidity, oncology and cardiovascular covariables the survival of patients was onset of AF post-radiotherapy was improved in patients that developed atrial fibrillation (aHR 0.53, 95%CI 0.32–0.88, p=0.014 (**Table 4**).

Patient Characteristics	No Patients	No Deaths	Adjusted Hazard Ratio (95% CI)	p value
Age	420	300	1.01 (0.99–1.00)	0.067

Gender				
Female	200	131	1 [reference]	
Male	220	166	1.38 (1.08–1.76)	**0.010**
Performance Status				
0	43	25	1 [reference]	
1	206	154	2.20 (1.39–3.46)	**<0.001**
2	152	108	2.31 (1.43–3.72)	**<0.001**
3	19	13	3.14 (1.52–6.47)	**0.002**
T-stage				
0	18	8	1 [reference]	
1	102	70	1.20 (0.55–2.61)	0.654
2	119	80	1.13 (0.52–2.46)	0.763
3	87	68	1.54 (0.70–3.37)	0.283
4	94	74	2.17 (0.99–4.75)	0.054
N-stage				
0	129	94	1 [reference]	
1	72	52	0.96 (0.67–1.38)	0.830
2	189	133	0.93 (0.68–1.28)	0.660
3	30	21	0.76 (0.44–1.31)	0.323
Subtype				
Adenocarcinoma	139	95	1 [reference]	
Squamous cell	199	150	1.08 (0.82–1.42)	0.580
Clinical	53	34	0.79 (0.50–1.25)	0.324
Other	29	21	0.79 (0.48–1.31)	0.367
Chemotherapy**				
None	281	207	1 [reference]	

Neoadjuvant	89	69	0.96 (0.68–1.34)	0.804
Concurrent	50	24	0.59 (0.36–0.97)	**0.037**
Mean Base Dose (Gy)	435	300	1.01 (0.99–1.03)	0.419
Lung V20 (%)	435	300	1.03 (1.01–1.06)	**0.007**
Coronary Artery Disease	107	83	1.25 (0.95–1.64)	0.111
Non-AF Arrhythmia	9	5	0.51 (0.20–1.29)	0.157
Heart Failure	41	16	1.22 (0.71–2.10)	0.470
Other Vascular History	95	75	1.42 (1.06–1.91)	**0.020**
Statin Therapy	282	167	0.71 (0.55–0.91)	**0.07**
Post-Radiotherapy AF	26	19	0.53 (0.32–0.88)	**0.014**
Post-Radiotherapy Locoregional Relapse	169	144	0.91 (0.70–1.18)	0.487
Post-Radiotherapy Distant Relapse	176	160	2.05 (1.57–2.67)	**<0.001**

Table 4. Fully adjusted Cox proportional hazards model for overall survival.

(V20 = volume receiving ≥20Gy; AF = atrial fibrillation)

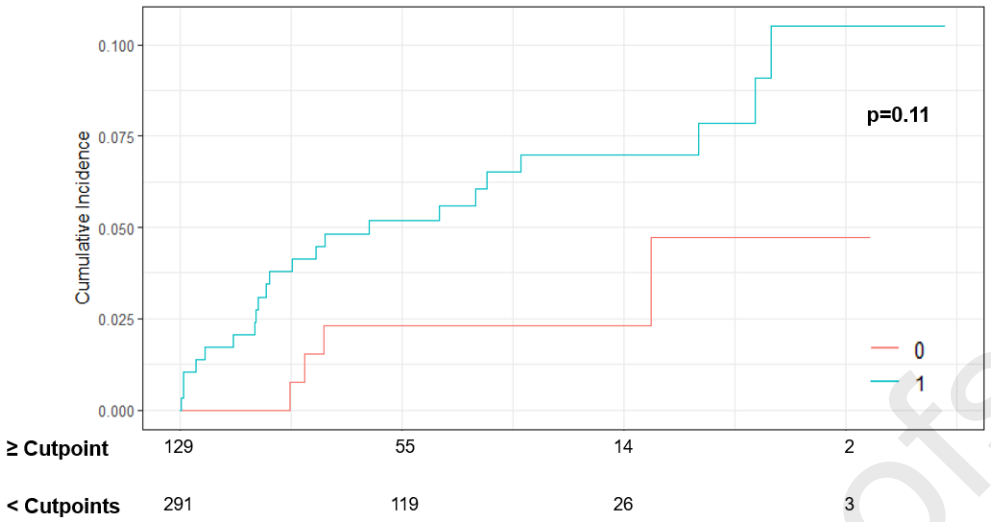

Figure 2. The cumulative incidence plot for the occurrence of atrial fibrillation after radiation therapy, with adjustment for the competing risk of death, comparing patients where either PV optimal dose cut-point was met (blue) with those where neither was met (red).

DISCUSSION

Whether the incidental radiation dose to the cardiac substructures increases the probability of subsequent AF during the treatment of intrathoracic cancer is not currently known. In this first study examining the PVs, the arrhythmogenic origin of AF, the radiation dose received was associated with the onset of AF. In this NSCLC cohort, the rate of AF was 6% and two-thirds of cases occurred within 24 months. The hazard of AF was found to increase by 2% and 1% per percentage point increase in the LPV V55 and RPV V10 respectively, and the associations were statistically significant after accounting for cardiovascular factors and the competing risk of death. The implications of these data are that actively sparing these structures could reduce the incidence of AF, and where this is not possible, patients identified as being at high risk of AF could undergo active screening during follow-up. Validation of these novel findings in external datasets would be prudent prior to implementation.

As AF arises in the general population due to pathology localised to the myocardial sleeve tissue of the central portion of the PVs (13), it was postulated in this study that the established effects of fractionated, high-dose RT on the cardiac parenchyma could be implicated in post-radiotherapy AF. The aetiology of AF involves the autonomous initiation of a depolarization throughout the atria by a cardiomyocyte in the PV myocardial sleeve in 95% cases (23). Underlying this automaticity is typically a combination of age-related autonomic nervous system changes and cardiovascular risk factors, leading to aberrant electrophysiology at the level of the sodium and calcium ion channels of the PV cardiomyocytes (24). If re-entry circuits

of electrical conduction are established, the atria contract at approximately 600 beats per minute, instead of 70–90 beats per minute, resulting in the loss of meaningful atrial contractions. AF can be asymptomatic, but for most patients causes problems such as palpitation, dizziness, shortness of breath, but can accompany other acute illnesses to worsen the severity of those presentations, and common complications include heart failure and stroke (23,24).

Curiously, the occurrence of AF post-treatment was associated with improved survival in this cohort of patients, and although a survival detriment was not anticipated, a survival benefit was surprising. One possible explanation for this is that the medical assessment for AF might provoke clinicians to evaluate other cardiovascular risk factors and address these with investigations and treatments, although data on this was not collected however. Also of note, although VMAT was associated with better sparing of the PVs compared with 3DCRT, IMRT was not. IMRT was the smallest planning solution subgroup, but this observation could also be interpreted that segmenting the PVs and providing a dose constraint, is necessary to harness the potential for cardiac substructure dose-sparing inherent to IMRT. It was noted that patients that developed AF had elevated rates of hypertension and non-AF arrhythmia compared with those that did not. Hypertension was not included in multivariate analyses for the AF endpoint as it is a ubiquitous cardiovascular risk factor. The relevance of the non-arrhythmia diagnoses is likely to be low as none of the 3 were atrial tachyarrhythmias.

The dose received by left anterior descending coronary artery (LAD) has been linked to the established cardiology composite endpoint major adverse cardiac events (MACE) (25,26) and some centres have implemented LAD-sparing approaches. However, the MACE endpoint does not include arrhythmia events, meaning the risk of RT-related arrhythmias is possibly not addressed by this approach. Almost one half of patients with AF are hospitalized per year (27), which is a reliable surrogate of quality of life (7,8) and healthcare expenditure for a condition (28). Therefore, there is an urgent need to conduct specific studies into arrhythmia, so that the most relevant cardiac substructures can be identified for treatment planning and post-treatment monitoring.

Although it has been demonstrated that the SAN Dmax is associated with the onset of AF events (10), this specialized pacemaker tissue in the lateral wall of the right atrium does not normally have a role in the pathophysiology of AF. The SAN is located 1–2 cm anterior to the RPV, and approximately 4cm to the right of the LPV, and therefore it is possible that the SAN behaves as a DVH surrogate for the PVs. The investigators did not examine the PVs in their cohort, possibly because the first atlas for contouring these structures was published subsequent to their study (19). Interestingly, the PVs are also intimately related to the cardiac base region, for which there is a emerging evidence of a capacity for cardiotoxicity mediation (29).

Murine models of radiation cardiotoxicity have shown upregulation of conduction-related ion channels such, as $Na_V1.5$, and gap junction proteins, such as Cx43 in single-fraction studies, without impacting CM surface area and or collagen levels (30). Other investigators have also found focal electrical change, such as brady- and tachyarrhythmias (31,32), as well as atrioventricular and bundle branch blocks (33), and prolonged PR and QT intervals, premature atrial complexes and ST segment depression (34). Most of these latter findings were

exploratory endpoints however, rather than from dedicated experimental procedures, which has been recommended recently (35). Aligning the latency period observed in this study, the timing of arrhythmia was typically weeks–months in these studies, indicating that radiation cardiotoxicity events can occur earlier than previously described (36).

The conduct of clinical dosimetric toxicity studies is typically complicated by an abundance of DVH metrics and a dearth of non-cancer covariable data, leading to multiple testing dilemmas and unmeasured biases respectively (37). In this study, a limited number of rationale DVH metrics were selected for analysis in advance, and a comprehensive range of cardiovascular details was available for adjustment. In this study, superior and inferior PVs were segmented together for the RPV and LPVs in order to streamline the analysis. Single PV studies will be informative in future as ultra-central SABR is implemented for select patients. While the AUC values generated during the calculation of optimal cut-points were similar to that of the recent LAD V15 (0.64) and SAN (0.66) papers, and likely reflect the multifactorial nature of AF in this cohort of patients, validation of PVs in other datasets would be prudent.

Large retrospective thoracic radiation datasets with PV structures are required to elicit the dose-response relationship of the PVs for AF endpoints. From a radiobiology perspective, assuming AF is a deterministic effect, sufficient dose to a single point within any of the four PVs may result in local disruption of cardiomyocytes to lead to arrhythmogenesis, in keeping with a serial model. The safe dose thresholds may be impacted by other risk factors for AF, such as alcohol, which was shown in the data presented. Furthermore, the role played by the four PVs is not equal , as suggested by the current data also. The non-uniform dose thresholds apparent for the RPV and LPV in this analysis are in keeping with the electrophysiological phenomenon whereby the arrhythmogenic focus more often originates in the LPV than the RPV (13), although not all studies are in agreement (19). It is therefore rational that the LPV might have a lower dose threshold for the development of an arrhythmogenic focus, compared with the RPV.

The strengths of this study are the multidisciplinary nature of the study design, the inclusion of the relevant clinical factors such as cardiac history and drugs, the contemporary nature of RT planning, and the low levels of cytotoxic chemotherapy, which carry an independent risk of arrhythmogenesis. It is therefore possible that the current study underestimated the relationship between PV irradiation and new AF, which should be considered in future validation studies, such as large multicenter, prospective registries. The main limitations of this study are its retrospective nature, a lack of information on locoregional relapse which could have directly involved a PV, and the modest number of events for multivariate analysis with the critically relevant clinical parameters. External validation in the conventional fractionation context would be beneficial for enhanced transferability of these findings globally, and will require conversion of the dose thresholds depending on the dose prescription to the planning target volume. ie. LPV V63 and RPV V11 when 60 Gy / 30# is planned for an NSCLC case (heart α/β 3).

CONCLUSION

Dose to the pulmonary veins was associated with the onset of AF after definitive RT in patients with NSCLC. If confirmed in other datasets, consideration should be given to dose-sparing of the PVs, and proactive screening of patients after treatment where this isn't possible.

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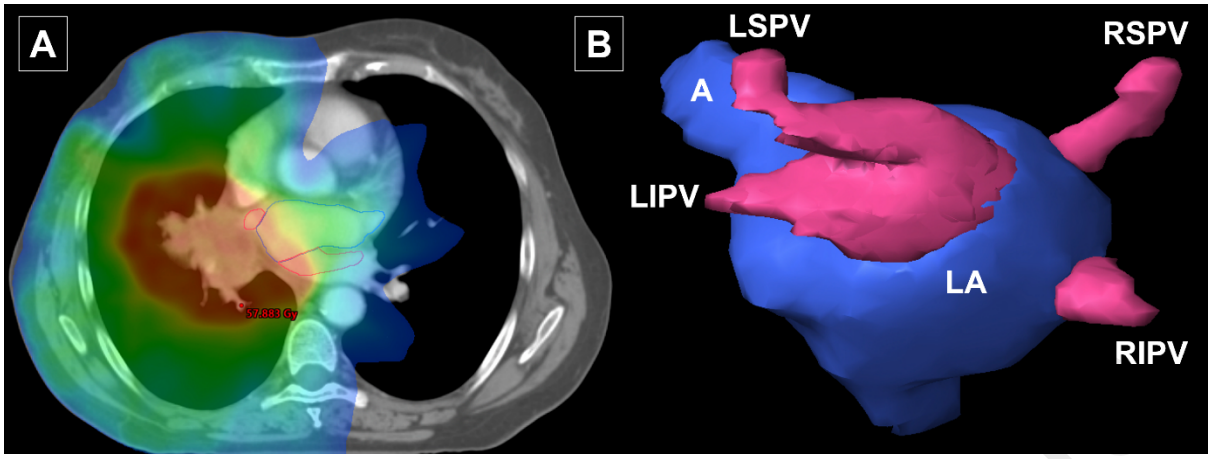
Figure 1. A) A representative axial image from a 4-dimensional CT planning scan with the radiation dose color wash overlaid (blue = 10Gy, red = 55Gy). The left atrium is outlined in blue and the pulmonary veins are outlined in mauve. **B)** A 3-dimensional reconstruction of the left atrium and pulmonary veins from the posterior view.



(LA = left atrium; A = Auricle; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein)

Figure 2. The cumulative incidence plot for the occurrence of atrial fibrillation after radiation therapy, with adjustment for the competing risk of death, comparing patients where either PV optimal dose cut-point was met (blue) with those where neither was met (red).

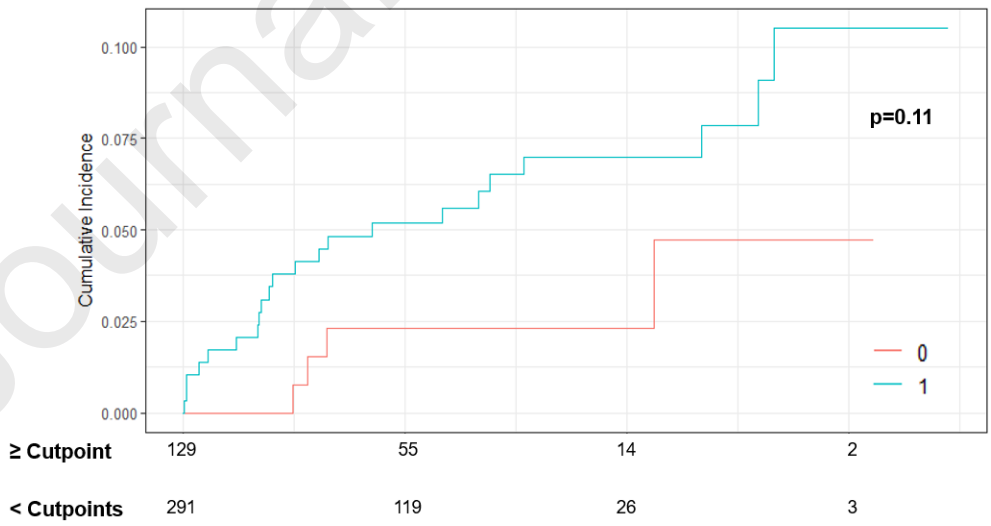


Table 1. Baseline patient, tumour, treatment and cardiovascular characteristics of the cohort

	All Patients (%)	No Post-Radiotherapy AF (%)	Post-Radiotherapy AF (%)	P value
Number of Patients	420 (100)	394 (94)	26 (6)	-
Age (median, IQR)	70 (63–75)	70 (63 – 75)	71 (66 – 76)	0.279
Gender				
Female	200 (48)	191 (48)	9 (35)	0.224
Male	220 (52)	203 (52)	17 (65)	
Performance Status				
0	43 (10)	40 (10)	3 (12)	
1	206 (49)	196 (50)	10 (38)	0.690
2	152 (36)	140 (36)	12 (46)	
3	19 (1)	18 (5)	1 (4)	
CCI* (median, IQR)	5 (5 – 6)	5 (5 – 6)	5 (4 – 6)	0.581
Units of Alcohol Per Week				
None	167 (40)	161 (41)	6 (23)	
1–6	109 (26)	98 (25)	11 (42)	0.063
7–14	28 (7)	27 (7)	1 (4)	
15–21	3 (1)	3 (1)	0 (0)	
≥22	15 (4)	12 (3)	3 (12)	

Unknown	98 (23)	93 (24)	5 (19)	
T-stage				
0	18 (4)	17 (4)	1 (4)	
1	102 (24)	96 (24)	6 (23)	0.773
2	119 (28)	110 (28)	9 (35)	
3	87 (21)	84 (21)	3 (12)	
4	94 (22)	87 (22)	7 (27)	
N-stage				
0	129 (31)	120 (30)	9 (35)	
1	72 (17)	69 (18)	3 (12)	0.748
2	189 (45)	176 (45)	13 (50)	
3	30 (7)	29 (7)	1 (4)	
Subtype				
Squamous cell carcinoma	199 (47)	186 (47)	13 (50)	
Adenocarcinoma	139 (33)	132 (34)	7 (27)	0.638
Clinical	53 (13)	48 (12)	5 (19)	
Other	29 (7)	28 (7)	1 (4)	
Chemotherapy				
No	265 (63)	261 (66)	20 (77)	
Concurrent	45 (11)	44 (11)	3 (11)	0.086
Neoadjuvant	89 (21)	87 (22)	2 (8)	
Neoadjuvant & Concurrent	3 (1)	2 (1)	1 (4)	
Lung V20 (%) (median, IQR)	20.3 (15.3 – 27.1)	20.3 (15.3 – 26.7)	20.4 (15.0 – 27.4)	0.868
Hypertension	215 (51)	195 (49)	20 (77)	**0.007**

Dyslipidemia	250 (60)	231 (59)	19 (73)	0.146
Diabetes Mellitus	88 (21)	81 (21)	7 (27)	0.440
Pack Years (median, IQR)	40 (30 – 56)	40 (30 – 55)	50 (40 – 69)	0.101
QRISK3 Score**	18.1 (11.8 – 26.8)	18.1 (11.0 – 26.6)	21.5 (14.9 – 35.4)	0.075
Coronary Artery Disease	107 (25)	97 (25)	10 (38)	0.117
Non-AF Arrhythmia	9 (2)	6 (2)	3 (12)	**<0.001**
Heart Failure	22 (5)	19 (5)	3 (12)	0.137
Cerebrovascular Disease	48 (11)	47 (12)	1 (4)	0.210
Peripheral Vascular Disease	54 (13)	53 (13)	1 (4)	0.156
Valvulopathy	14 (3)	12 (3)	2 (8)	0.201
Statin Therapy	194 (46)	181 (46)	13 (50)	0.688
Anti-Dysrhythmic Drug	105 (25)	97 (25)	7 (27)	0.792

(IQR = interquartile range; CCI = Charlson Comorbidity Index; AF = atrial fibrillation, V20 = volume receiving ≥20Gy)

* = calculable for n=234 non-AF, n=15 AF; * = CCI was binned for Chi squared significance testing as 0–4, 5 and 6–10.

Table 2. Doses delivered to the pulmonary veins by treatment planning solution

Metric	3DCRT (IQR) n=126	IMRT (IQR) n=84	VMAT (IQR) n=210	IMRT v 3DCRT p value	VMAT v 3DCRT p value
RPV Mean (Gy)	12.9 (5.8–33.3)	21.7 (7.5–43.1)	10.2 (2.9–29.8)	0.0567	0.2696
RPV Dmax (Gy)	24.1 (12.8–57.0)	50.4 (16.6–56.9)	21.6 (6.7–56.7)	0.0642	0.3004
RPV V10 (%)	60.3 (19.7–100.0)	76.2 (32.6–100.0)	42.6 (0.0–100.0)	0.1915	**0.0247**
LPV Mean (Gy)	25.0 (10.4–41.8)	21.8 (10.0–41.6)	15.8 (8.0–35.0)	0.7627	**0.0068**
LPV Dmax (Gy)	55.2 (23.6–58.2)	51.4 (19.3–56.5)	44.1 (16.1–57.1)	0.4689	**0.0159**
LPV V55 (%)	0.0 (0.0–29.8)	0.0 (0.0–10.2)	0.0 (0.0–7.9)	**0.0046**	**<0.0001**

(3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc modulated therapy; RPV = right pulmonary vein; Dmax = maximum dose; V10 = volume receiving ≥10 Gray; LPV = left pulmonary vein; V55 = volume receiving ≥55 Gray)

Table 3. Fine-Grey regression models for the incidence of atrial fibrillation according to pre-specified pulmonary vein dose metrics, with adjustment for relevant cardiovascular characteristics.

	Right Pulmonary Vein		**Left Pulmonary Vein**	
	aHR (95%CI)	**p value**	**aHR (95%CI)**	**p value**
Volume Receiving ≥10Gy				
DVH	1.01 (1.00 – 1.02)	**0.033**	1.01 (0.99–1.02)	0.350
Age	1.03 (0.98 – 1.07)	0.210	1.02 (0.98–1.07)	0.290

Sex	1.80 (0.77 – 4.23)	0.180	1.80 (0.76–4.22)	0.180
HF	2.35 (0.64 – 8.55)	0.200	2.26 (0.61–8.37)	0.220
Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.42 (1.08 – 5.42)	**0.032**	2.51 (1.08 – 5.84)	**0.033**
2	1.80 (0.40 – 8.11)	0.440	1.75 (0.39 – 7.78)	0.460
3	0.00 (0.00 – 8.11)	0.000	0.00 (0.00 – 0.00)	0.000
4	4.78 (0.98 – 23.50)	0.054	5.40 (1.10 – 26.60)	**0.038**
Drug	0.79 (0.31 – 2.01)	0.620	0.80 (0.32–2.01)	0.640
Chemo	1.70 (0.73 – 3.94)	0.220	1.56 (0.69–3.52)	0.280
Statin	1.11 (0.46 – 2.66)	0.840	1.03 (0.43–2.46)	0.940
CAD	2.03 (0.80 – 5.14)	0.140	2.04 (0.81–5.17)	0.130
Mean Dose				
DVH	1.01 (0.99–1.03)	0.490	1.02 (1.00–1.04)	0.100
Age	1.03 (0.98–1.07)	0.280	1.03 (0.98–1.07)	0.240
Sex	1.77 (0.76–4.16)	0.190	1.76 (0.75–4.12)	0.190
HF	2.26 (0.61–8.46)	0.220	2.34 (0.64–8.59)	0.200
Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.61 (1.14 – 5.97)	**0.023**	2.37 (1.00 – 5.59)	**0.050**
2	1.88 (0.42 – 8.33)	0.410	1.79 (0.40 – 7.93)	0.450

3	0.00 (0.00 – 0.00)	0.000	0.00 (0.00 – 0.00)	0.000
4	5.43 (1.09 – 26.90)	**0.038**	5.02 (1.02 – 24.58)	**0.047**
Drug	0.75 (0.29–1.96)	0.590	0.77 (0.31–1.91)	0.570
Chemo	1.47 (0.65–3.30)	0.350	1.56 (0.70–3.49)	0.270
Statin	1.06 (0.43–2.62)	0.850	1.01 (0.42–2.39)	0.990
CAD	2.09 (0.83–5.29)	0.120	2.06 (0.81–5.23)	0.130
Volume Receiving ≥55Gy				
DVH	1.00 (0.98–1.02)	0.840	1.02 (1.00–1.03)	**0.005**
Age	1.02 (0.98–1.07)	0.330	1.03 (0.98–1.07)	0.230
Sex	1.80 (0.77–4.20)	0.180	1.81 (0.80–4.09)	0.150
HF	2.27 (0.61–8.45)	0.220	2.26 (0.66–7.72)	0.140
Alcohol				
0	1.0 [reference]		1.0 [reference]	
1	2.62 (1.15 – 5.98)	**0.022**	2.46 (1.05 – 5.74)	**0.038**
2	1.87 (0.42 – 8.28)	0.410	1.77 (0.39 – 8.00)	**0.460**
3	0.00 (0.00 – 0.00)	**0.000**	0.00 (0.00 – 0.00)	0.000
4	5.32 (1.09 – 26.0)	**0.039**	5.16 (1.11 – 24.00)	0.036
Drug	0.78 (0.31–1.99)	0.610	0.75 (0.30–1.87)	0.530
Chemo	1.41 (0.63–3.18)	0.400	1.57 (0.70–7.72)	0.280
Statin	1.05 (0.45–2.45)	0.910	1.03 (0.44–2.41)	0.940
CAD	2.06 (0.81–5.23)	0.130	2.01 (1.63–4.91)	0.120

(aHR = adjusted hazard ratio; DVH = dose volume histogram; HF = heart failure; CAD = coronary artery disease)

Table 4. Fully adjusted Cox proportional hazards model for overall survival.

Patient Characteristics	No Patients	No Deaths	Adjusted Hazard Ratio (95% CI)	p value
Age	420	300	1.01 (0.99–1.00)	0.067
Gender				
Female	200	131	1 [reference]	
Male	220	166	1.38 (1.08–1.76)	**0.010**
Performance Status				
0	43	25	1 [reference]	
1	206	154	2.20 (1.39–3.46)	**<0.001**
2	152	108	2.31 (1.43–3.72)	**<0.001**
3	19	13	3.14 (1.52–6.47)	**0.002**
T-stage				
0	18	8	1 [reference]	
1	102	70	1.20 (0.55–2.61)	0.654
2	119	80	1.13 (0.52–2.46)	0.763
3	87	68	1.54 (0.70–3.37)	0.283
4	94	74	2.17 (0.99–4.75)	0.054
N-stage				
0	129	94	1 [reference]	
1	72	52	0.96 (0.67–1.38)	0.830
2	189	133	0.93 (0.68–1.28)	0.660
3	30	21	0.76 (0.44–1.31)	0.323

Subtype				
Adenocarcinoma	139	95	1 [reference]	
Squamous cell	199	150	1.08 (0.82–1.42)	0.580
Clinical	53	34	0.79 (0.50–1.25)	0.324
Other	29	21	0.79 (0.48–1.31)	0.367
Chemotherapy**				
None	281	207	1 [reference]	
Neoadjuvant	89	69	0.96 (0.68–1.34)	0.804
Concurrent	50	24	0.59 (0.36–0.97)	**0.037**
Mean Base Dose (Gy)	435	300	1.01 (0.99–1.03)	0.419
Lung V20 (%)	435	300	1.03 (1.01–1.06)	**0.007**
Coronary Artery Disease	107	83	1.25 (0.95–1.64)	0.111
Non-AF Arrhythmia	9	5	0.51 (0.20–1.29)	0.157
Heart Failure	41	16	1.22 (0.71–2.10)	0.470
Other Vascular History	95	75	1.42 (1.06–1.91)	**0.020**
Statin Therapy	282	167	0.71 (0.55–0.91)	**0.07**
Post-Radiotherapy AF	26	19	0.53 (0.32–0.88)	**0.014**
Post-Radiotherapy Locoregional Relapse	169	144	0.91 (0.70–1.18)	0.487
Post-Radiotherapy Distant Relapse	176	160	2.05 (1.57–2.67)	**<0.001**

(V20 = volume receiving ≥20Gy; AF = atrial fibrillation)