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Radiation-Induced Heart Disease after Lung Cancer

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Radiation Induced Heart Disease after Lung Cancer

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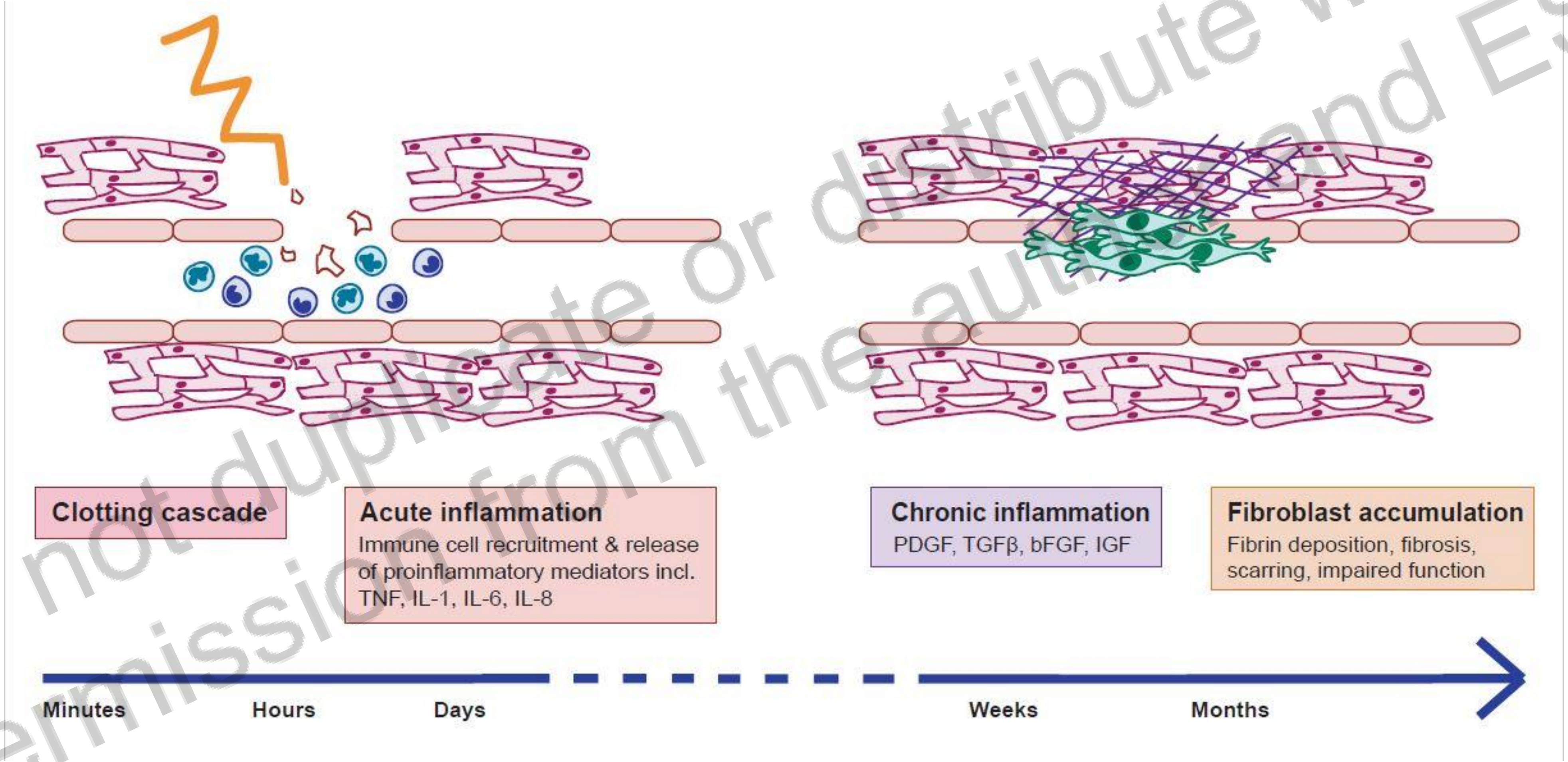
Overview

- Radiation induced heart disease
- Radiotherapy for lung cancer
- Heart dose and outcome
- Coronary artery calcium
- Cardiac biomarkers
- Cardiac substructure avoidance
- Management of RIHD

Please ask questions/send comments any time

Pathophysiology of RIHD



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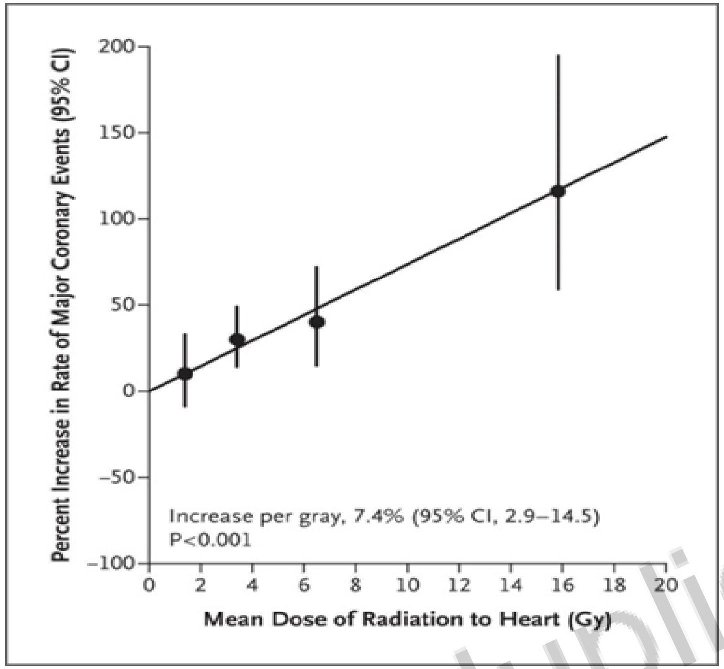
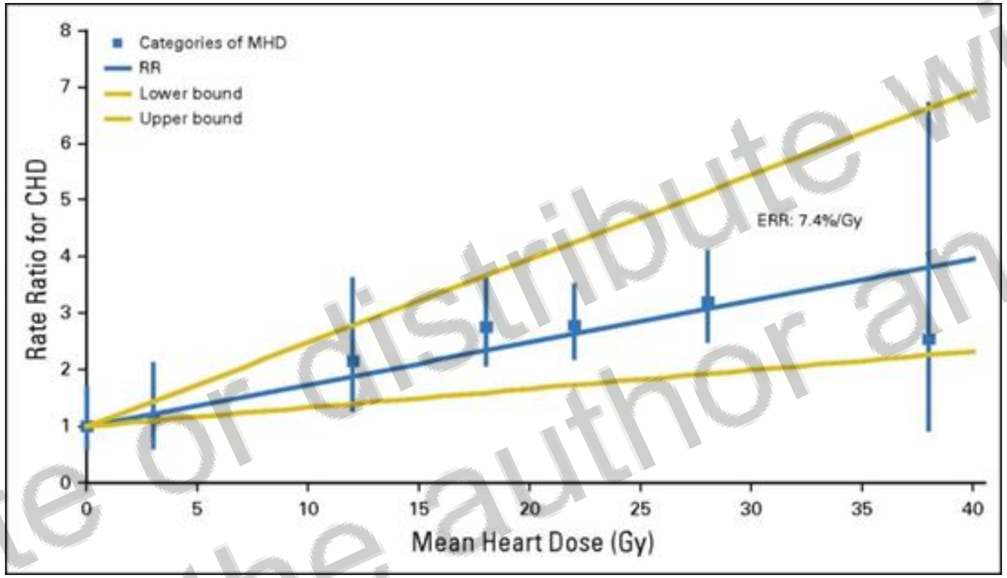
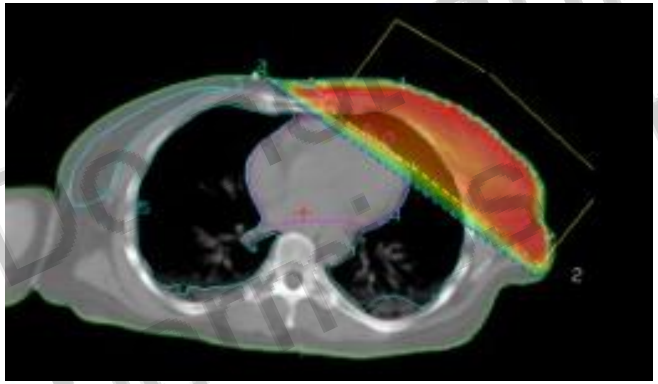
Radiotherapy for breast cancer and lymphoma

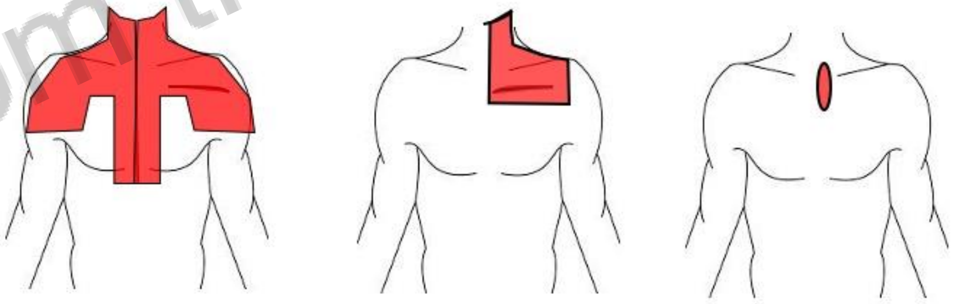




Darby 2013,
Van Nimwengen 2016

- Old radiotherapy techniques
- Dose to heart estimated from from 2D plans
- What about chemotherapy?





REGIONAL RT (ie, MANTLE RADIATION)

INVOLVED-FIELD RT

INVOLVED-NODE RT

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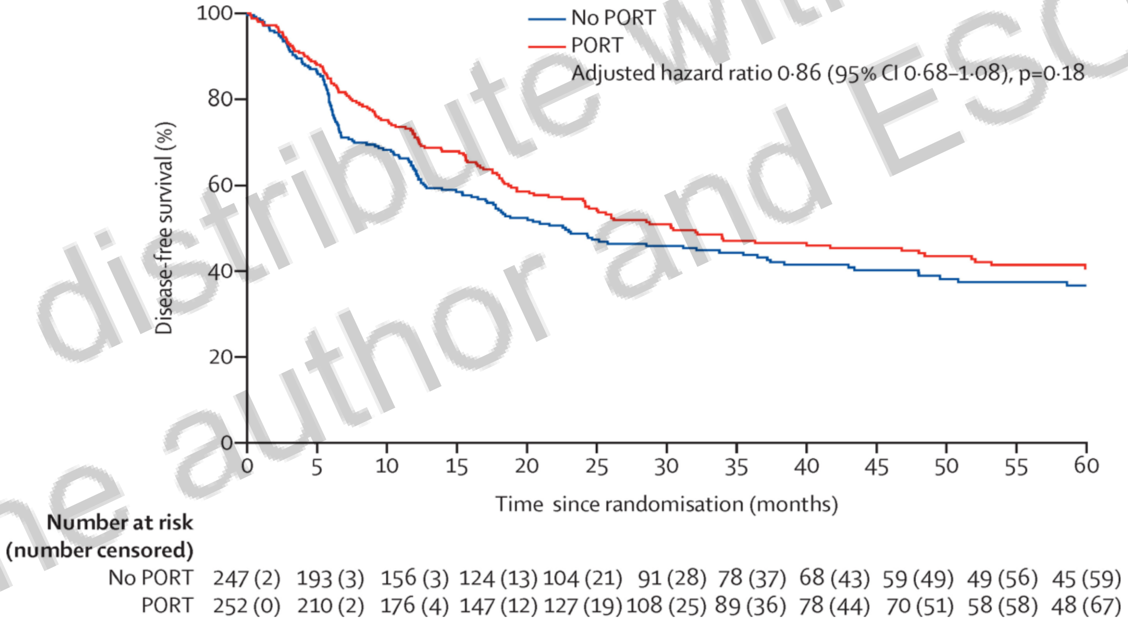
Radiotherapy in the treatment of lung cancer

Stage at diagnosis	SCLC	NSCLC
1	40.8%	20.4%
2	58.4%	26.5%
3	57.8%	41.8%
4	37%	29.3%
Unknown	28.8%	9.5%

- Alternative to surgery
- Stereotactic ablative body radiotherapy in early stage lung cancer
- Concurrent or sequential chemotherapy in stage 3 lung cancer – usually platinum based
- Following surgery



Le Pechoux 2022

- No improvement in DFS with PORT
- Improved locoregional control
- 16% of deaths in PORT arm due to cardiopulmonary disease

Improving Outcome in Lung Cancer

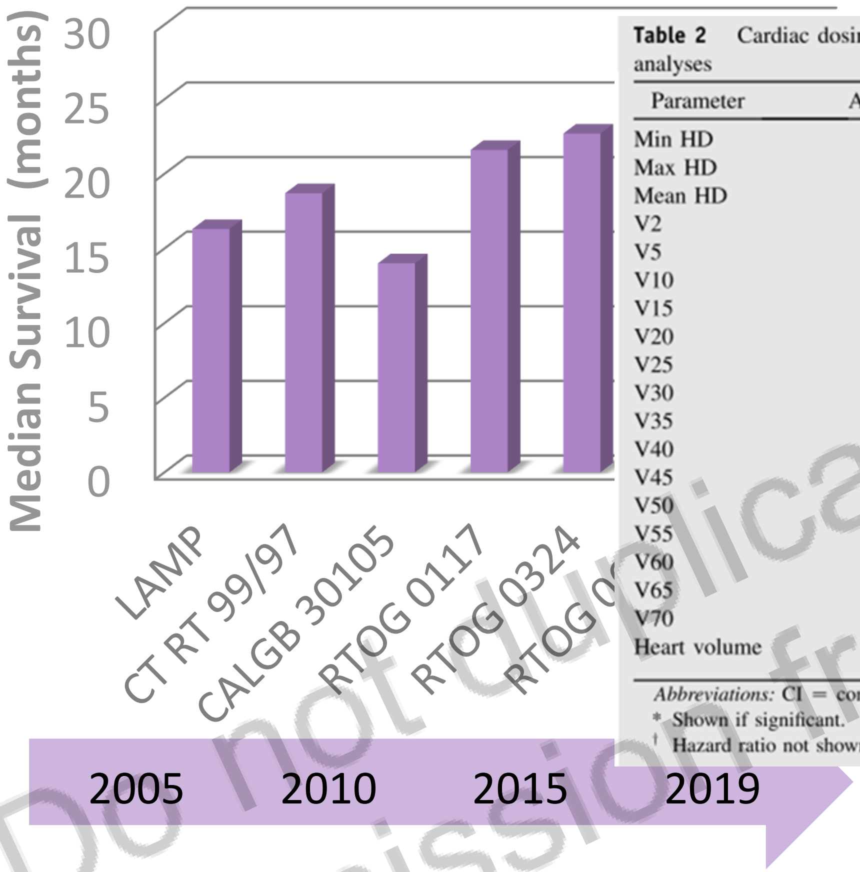


Figure adapted from Brown et al, *BJR* 2019

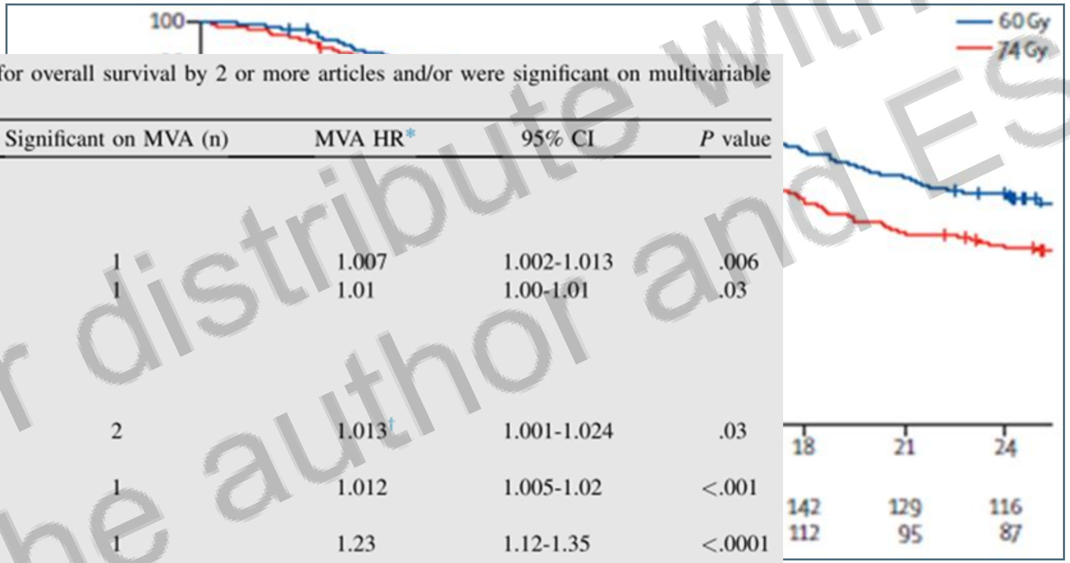


Table 2 Cardiac dosimetric parameters assessed for overall survival by 2 or more articles and/or were significant on multivariable analyses

Parameter	Articles assessed (n)	Significant on MVA (n)	MVA HR*	95% CI	*P* value
Min HD	2				
Max HD	7				
Mean HD	8				
V2	1	1	1.007	1.002-1.013	.006
V5	11	1	1.01	1.00-1.01	.03
V10	4				
V15	3				
V20	4				
V25	3				
V30	12	2	1.013†	1.001-1.024	.03
V35	4				
V40	5	1	1.012	1.005-1.02	<.001
V45	4				
V50	5	1	1.23	1.12-1.35	<.0001
V55	3				
V60	3				
V65	2				
V70	2				
Heart volume	1	1	1.12	1.06-1.19	<.0001

Abbreviations: CI = confidence interval; HD = heart dose; HR = hazard ratio; MVA = multivariable analysis.
* Shown if significant.
† Hazard ratio not shown for second study.

- MHD ↑major adverse cardiac events [3]

1 Bradley et al, *Lancet Oncol* 2015; 2 Wang et al, *J Clin Oncol*, 2017; 3 Atkins et al, *J Am Coll Cardiol*. 2019; 4 Zhang et al, IJROBP 2019

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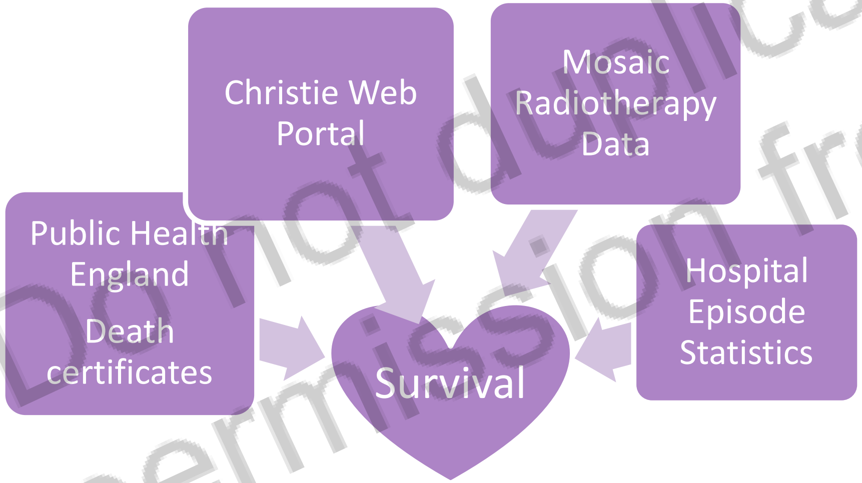
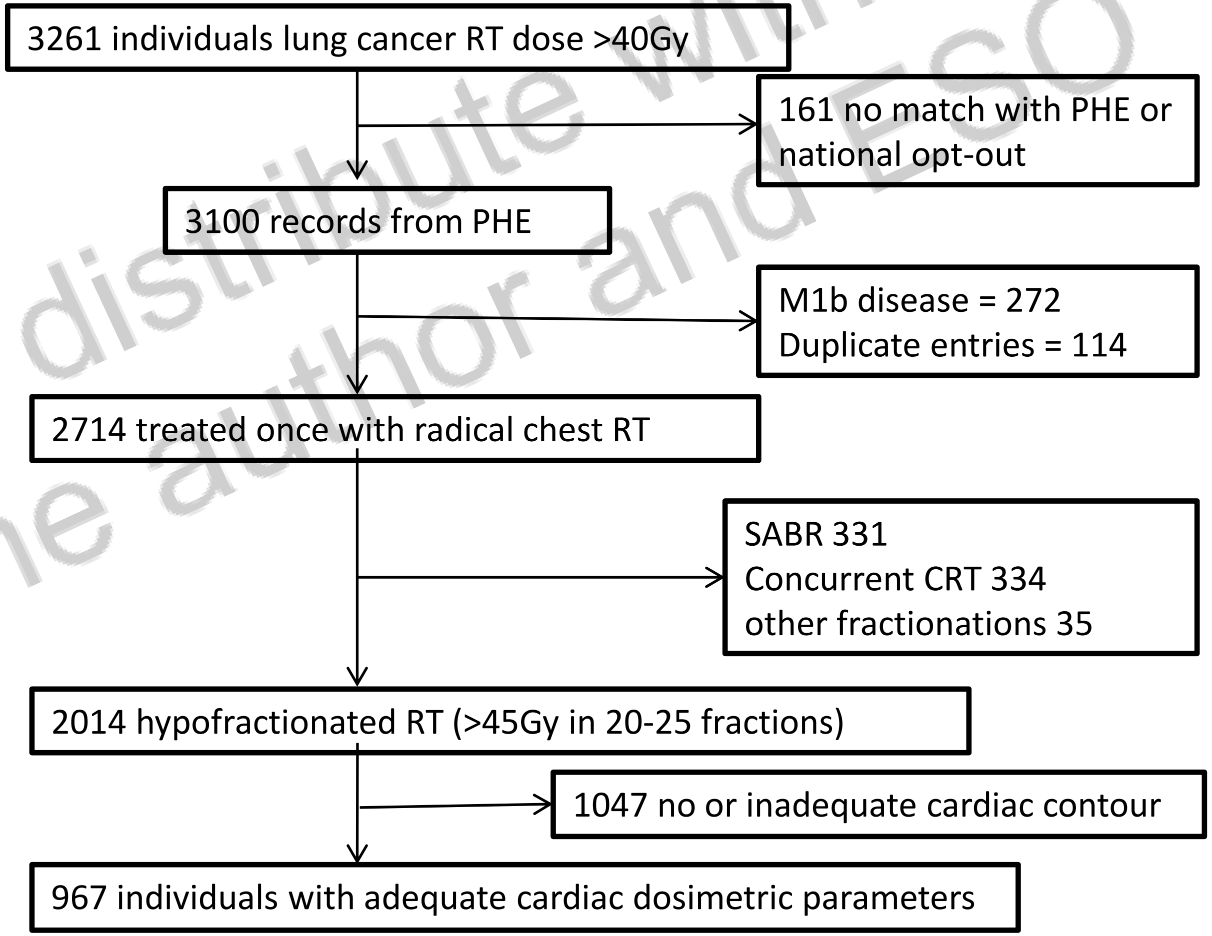
Do whole heart dose parameters predict for cardiac death?

- 3261 patients treated with radical RT for lung cancer at The Christie 1/1/2010 and 31/12/2016
- Cardiac cause of death
- Follow up censored at Nov 2017





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Baseline characteristics or patients with cardiac dosimetric parameters

Variable		No cardiac comorbidity N = 675	Cardiac comorbidity N = 292	P value
Age at radiotherapy (years)	median	72.2 (52.9-87.3)	75.8 (59.1-88.5)	**<0.001**
Sex	Female	340 (50.4)	112 (38.4)	**0.001**
	Male	335 (49.6)	180 (61.6)	
Performance Status	0	55 (8.1)	20 (6.8)	0.348
	1	317 (47.0)	123 (42.1)	
	2	241 (35.7)	115 (39.4)	
	3	57 (8.4)	31 (10.6)	
	(Missing)	5 (0.7)	3 (1.0)	
Tstage	T1	99 (14.7)	47 (16.1)	0.366
	T2	235 (34.8)	111 (38.0)	
	T3	175 (25.9)	80 (27.4)	
	T4	155 (23.0)	53 (18.2)	
	(Missing)	11 (1.6)	1 (0.3)	
Nstage	N0	227 (33.6)	107 (36.6)	**0.022**
	N1	111 (16.4)	59 (20.2)	
	N2	223 (33.0)	99 (33.9)	
	N3	111 (16.4)	27 (9.2)	
	(Missing)	3 (0.4)	0 (0.0)	
Deprivation	least deprived	92 (13.6)	37 (12.7)	0.304
	2	70 (10.4)	28 (9.6)	
	3	96 (14.2)	53 (18.2)	
	4	149 (22.1)	74 (25.3)	
	most deprived	268 (39.7)	100 (34.2)	
Smoking Status	Current	196 (29.0)	54 (18.5)	**0.004**
	Ex-smoker	312 (46.2)	161 (55.1)	
	Never	10 (1.5)	7 (2.4)	
	Not known	8 (1.2)	5 (1.7)	
	(Missing)	149 (22.1)	65 (22.3)	

- Median MHD =12.75Gy (0.7Gy – 28Gy)
- Median Heart V5Gy = 47.9% (0.04% - 99.5%)
- Median Heart V30Gy = 14.9% (0-39.3%)
- Median Heart V50Gy = 4.1% (0-15.8%)
- Median follow up 61 weeks

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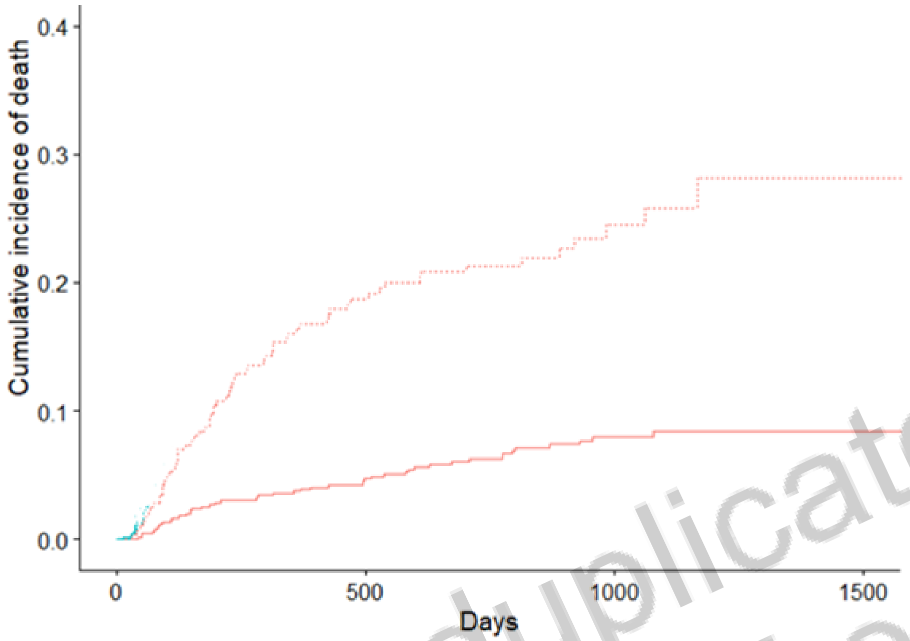
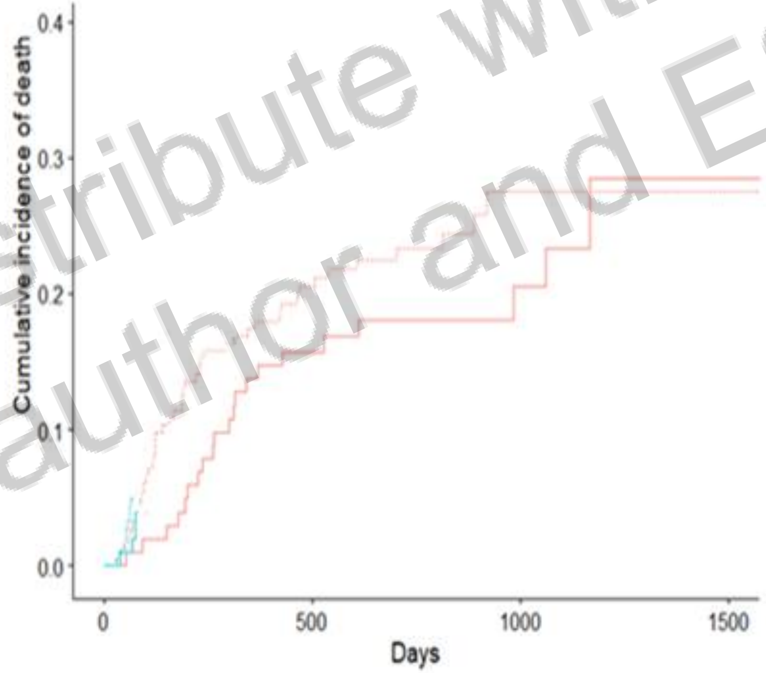
Patients with pre-existing cardiac comorbidities





- 2 year cumulative incidence of death with a cardiac cause 21.3% in patients with a cardiac comorbidity

- 2 year cumulative incidence of death with a cardiac cause 18.1% if MHD <10Gy
- 23.3% if MHD≥10Gy

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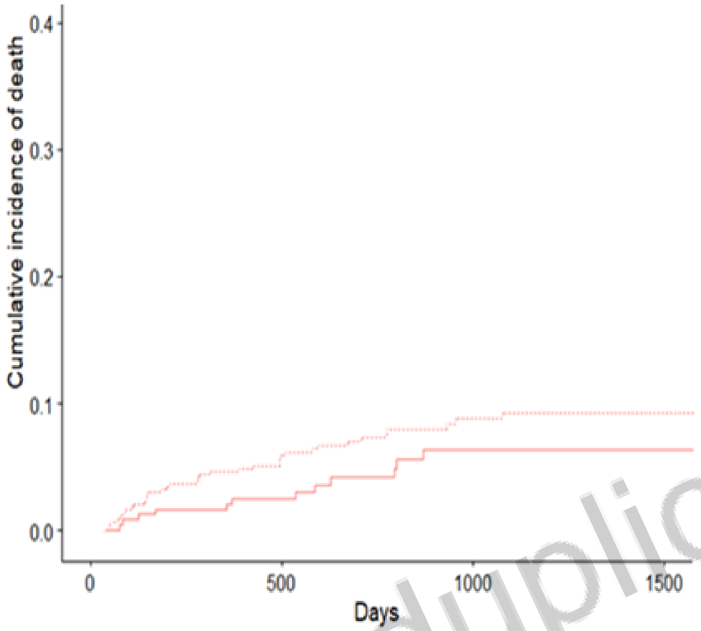
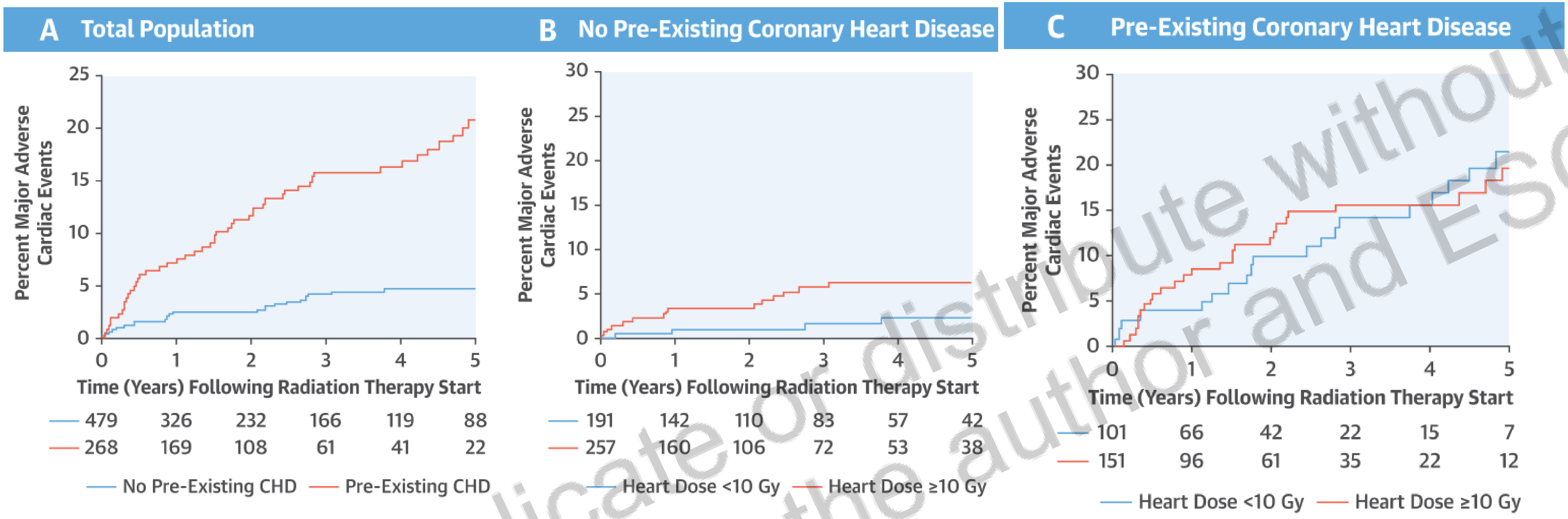
Patients without pre-existing cardiac comorbidities



Variable	aHR
Age	1.06 (1.02-1.09)
Sex Male	NS
PS	NS
T stage	NS
N stage	NS
Deprivation quintile	NS
Laterality Right	NS
Histology	NS
MHD	1.07 (1.01-1.13)
MLD	NS

- 2 year cumulative incidence of death with a cardiac cause 4.1% if MHD <10Gy
- 7.3% if MHD≥10Gy



Atkins JACC 2019; 73, 2976-2987

- MHD ≥10Gy associated with increased risk of MACE and all cause mortality in patients without a history of CHD
- LAD dose associated with increased MACE in patients without CHD
- 50-80% of patients with intermediate/high cardiovascular risk are not on statins

Avoiding CardiaC tOxicity in Lung cAncer radiotherapy (ACCOLADE)

136 patients undergoing radical RT

Stage I-III patients having SABR, concurrent/sequential chemoRT or RT alone

Prior to RT

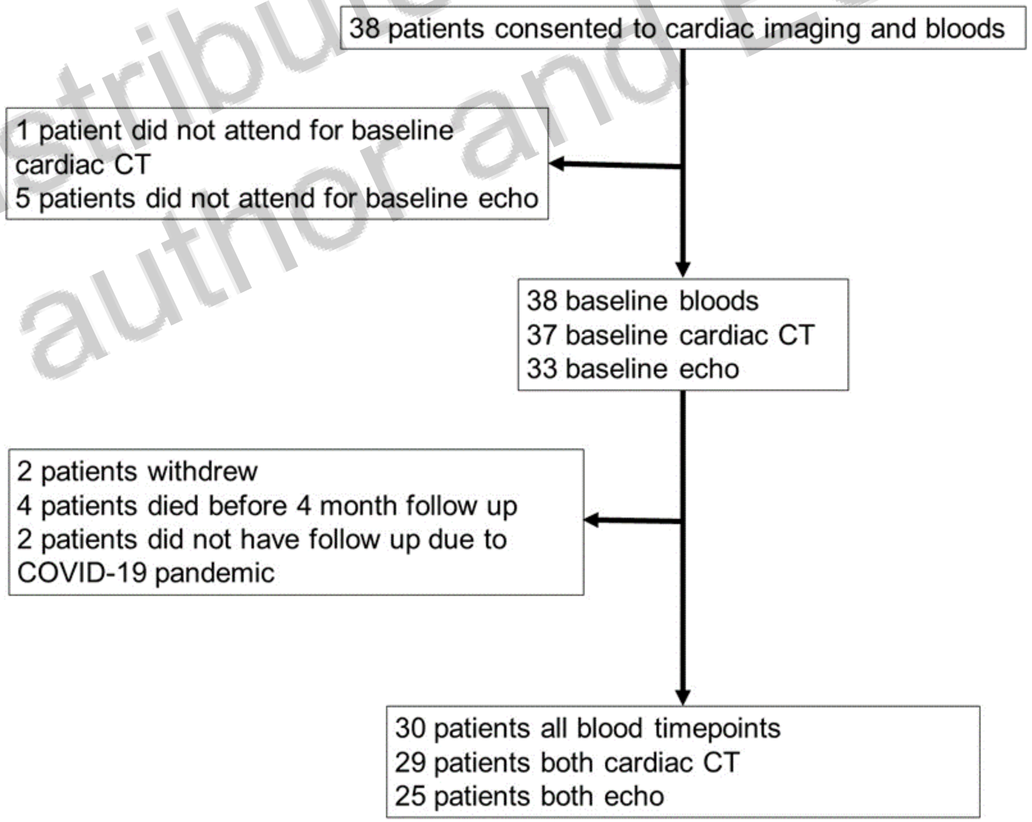
Blood FBC, lipids, cholesterol, high sensitivity troponin I, CRP, NT-proBNP, Q-risk 3 score	Cardiac CT + echo in 35 patients

At end of RT

Blood FBC, lipids, cholesterol, high sensitivity troponin I, CRP, NT-proBNP

4 months after RT

Blood FBC, lipids, cholesterol, high sensitivity troponin I, CRP, NT-proBNP	Cardiac CT + echo



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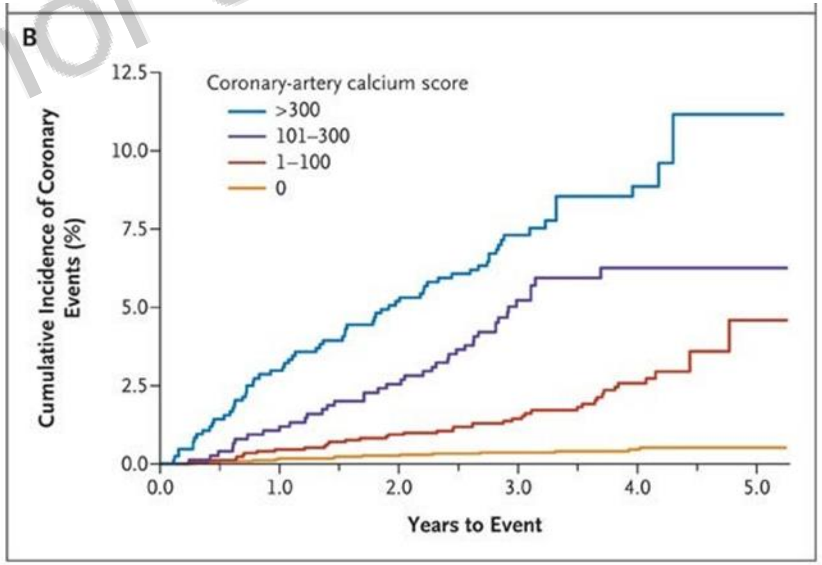
Coronary Artery Calcium Scoring

- Calcified lesion is >130 HU over ≥3 pixels
- CAC volume score = number of voxels x volume of each voxel
- Agatston = lesion area x density factor

Table 3. Risk of Coronary Events Associated with Increasing Coronary-Artery Calcium Score after Adjustment for Standard Risk Factors.*

Coronary-Artery Calcium Score	Major Coronary Event† No./No. at Risk	Major Coronary Event† Hazard Ratio (95% CI)	Major Coronary Event† P Value	Any Coronary Event No./No. at Risk	Any Coronary Event Hazard Ratio (95% CI)	Any Coronary Event P Value
0	8/3409	1.00		15/3409	1.00	
1–100	25/1728	3.89 (1.72–8.79)	<0.001	39/1728	3.61 (1.96–6.65)	<0.001
101–300	24/752	7.08 (3.05–16.47)	<0.001	41/752	7.73 (4.13–14.47)	<0.001
>300	32/833	6.84 (2.93–15.99)	<0.001	67/833	9.67 (5.20–17.98)	<0.001
Log_2(CAC+1)‡		1.20 (1.12–1.29)	<0.001		1.26 (1.19–1.33)	<0.001

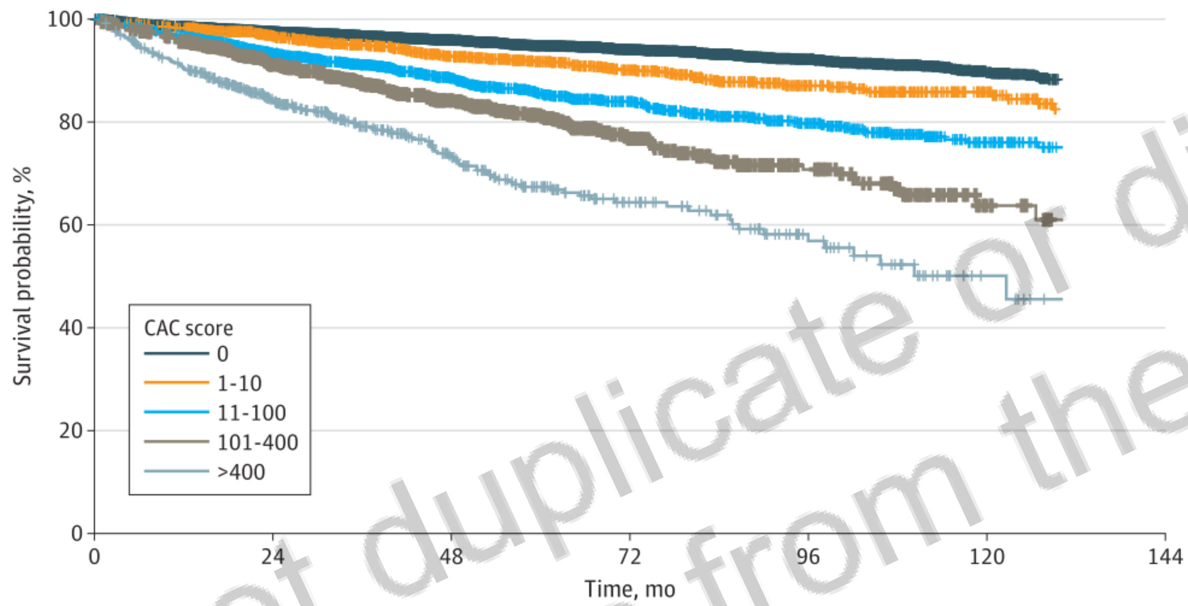
* CAC denotes coronary-artery calcium score, and CI confidence interval.
† Major coronary events were myocardial infarction and death from coronary heart disease.
‡ Each unit increase in log_2(CAC+1) represents a doubling of the coronary-artery calcium score.



Detrano R et al. N Engl J Med 2008;358:1336-1345.

CAC score in patients with cancer

Figure. Kaplan-Meier Plot for Fatal and Nonfatal Cardiovascular Disease by Coronary Artery Calcium (CAC) Score Category



No. at risk (No. censored)

0	11 179 (0)	9102 (1818)	6117 (4678)	3663 (7031)	1716 (8925)	631 (9980)
1-10	1584 (0)	1267 (268)	874 (617)	543 (928)	317 (1139)	141 (1311)
11-100	1825 (0)	1429 (281)	923 (726)	580 (1027)	316 (1267)	118 (1455)
101-400	830 (0)	600 (162)	366 (360)	177 (523)	87 (602)	27 (656)
>400	497 (0)	322 (101)	180 (210)	91 (281)	45 (320)	11 (349)

- CAC score can be measured on radiotherapy planning scans
- Coronary artery calcium is predictive of OS and coronary events in patients having radiotherapy

Gal R et al JAMA oncology 2021

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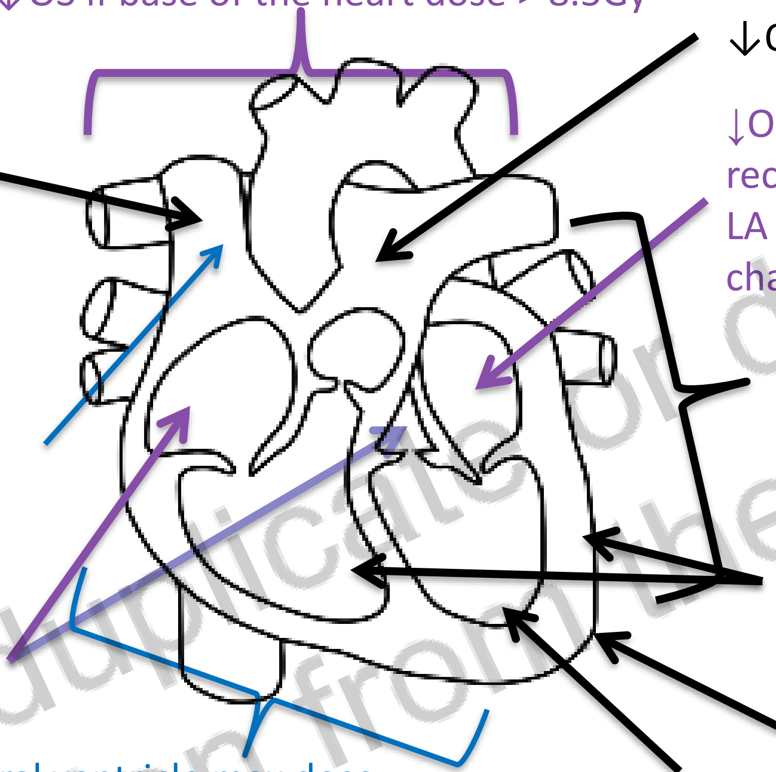
Which Cardiac Substructures are important?

↓OS if base of the heart dose > 8.5Gy [1]



Min dose to SVC significantly associated with non-specific ECG changes [10]

Min dose to SVC and max dose to LA significantly associated with non-cancer death [9]

Max dose to RA, AV and RCA > 19.5Gy associated with worse OS [8]

Bilateral ventricle max dose significantly associated with non-cancer death [7]

LV V5Gy and V30Gy associated with symptomatic CE in patients with IHD [6]

↓OS if PA V40Gy >80%[2]

↓OS if >2.2% of LA wall received >63Gy

LA dose associated with ECG changes [3]

Pericardial V30 ≥ 29% associated with worse OS [4]

Dose to LAD, LV and RV significantly associated with CE in patients with IHD [5]

LAD V15>10% associated with ↑MACE[11]

Black: 1.8 – 2Gy per fraction

Purple: >2Gy per fraction

Blue: SABR

1. McWilliam et al, *Eur J Cancer*. 2017
2. Ma et al, *Radiat Oncol*. 2017
3. Vivekanandan et al *IJROBP*. 2017
4. Xue et al, *Radiother Oncol*. 2019
5. Yegya-Raman et al, *JTO*. 2018
6. Wang et al, J Clin Oncol. 2017
7. Wong et al, Clin Lung Cancer. 2018
8. McWilliam et al, IJROBP 2020
9. Stam et al, Radiother Oncol 2017
10. Hotcha et al, CTRO 2019
11. Atkins et al, JAMA Oncology 2021

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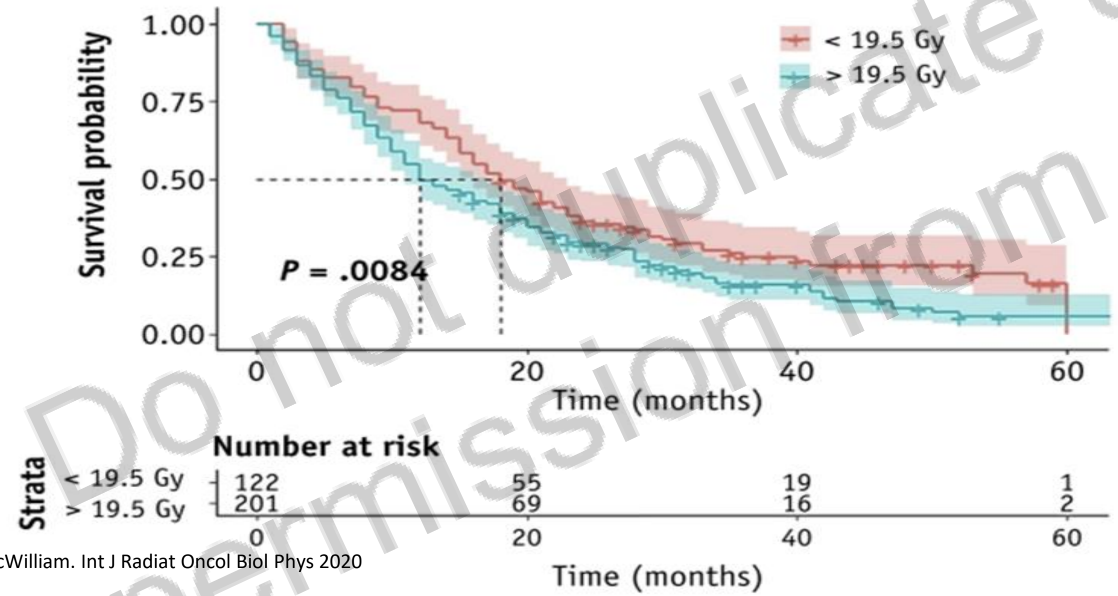
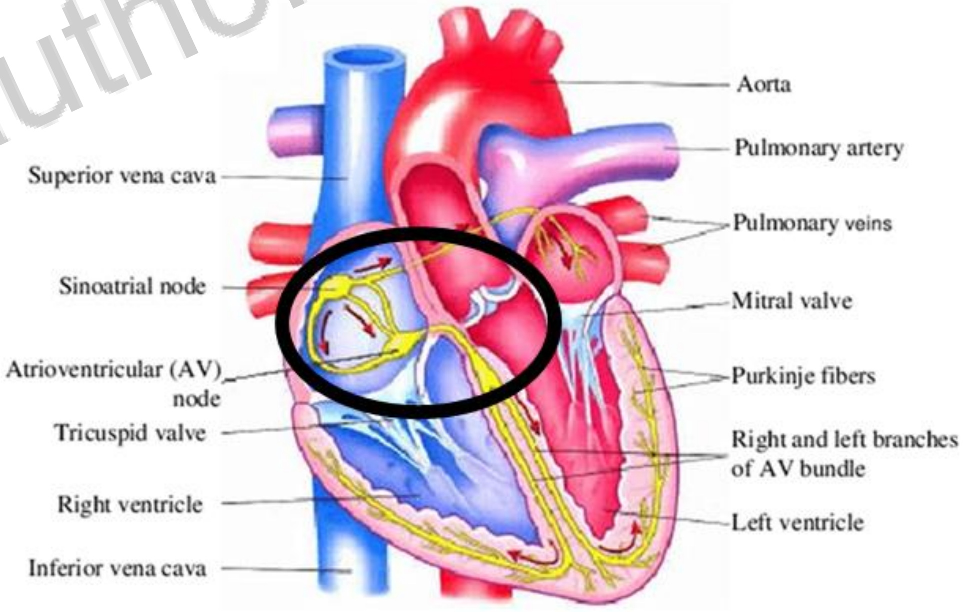
Cardiac substructure avoidance

- Radiation to cardiac substructures is associated with cardiac events and death
- Maximum dose to right atrium, right coronary artery and ascending aorta significant for OS in 978 patients treated for NSCLC with hypofractionated RT
- Dose threshold 19.5Gy in 2.75Gy/fraction

Aims
- Define a cardiac avoidance area (CAA)
- Investigate the ability of optimised photon and proton plans to spare this area



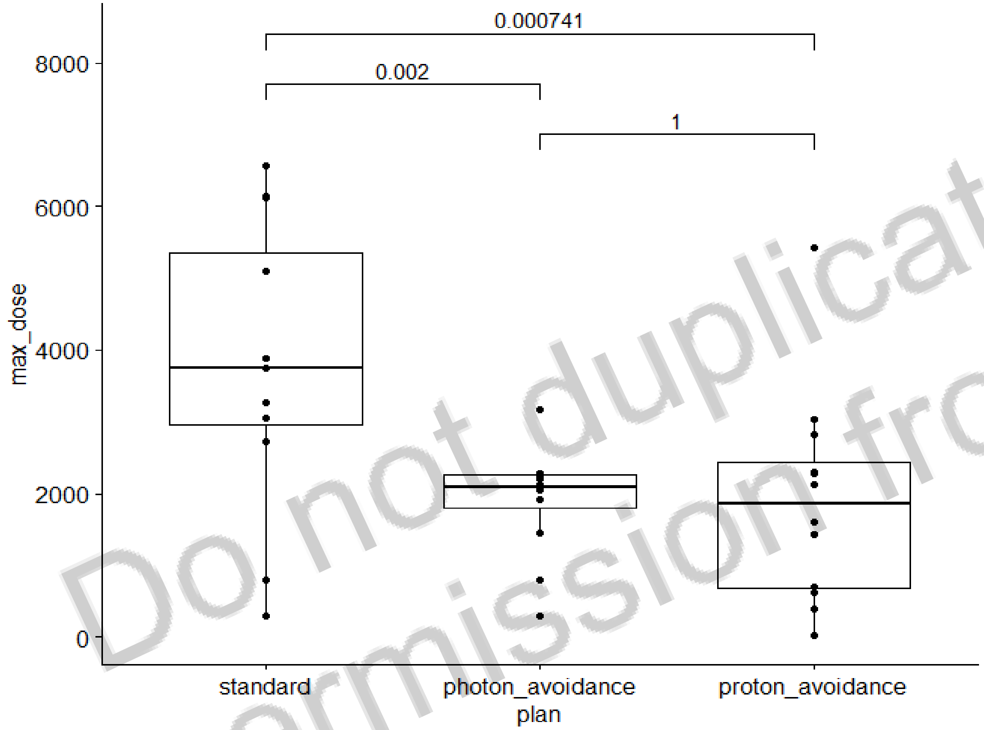
McWilliam. Int J Radiat Oncol Biol Phys 2020

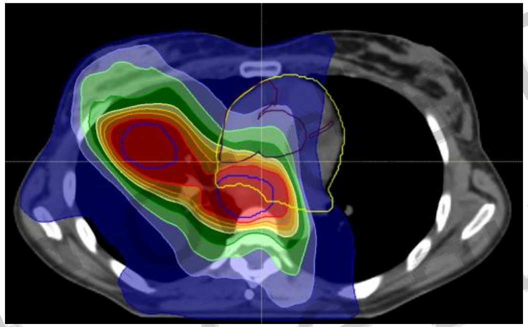


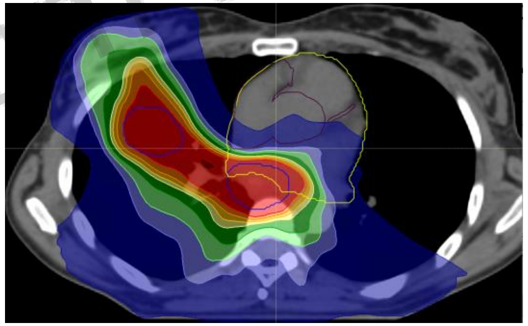
Results

- 6 right sided and 6 left sided tumour
- Mean ITV volume 219cc (sd 66cc)
- Mean CAA volume 15% of cardiac volume

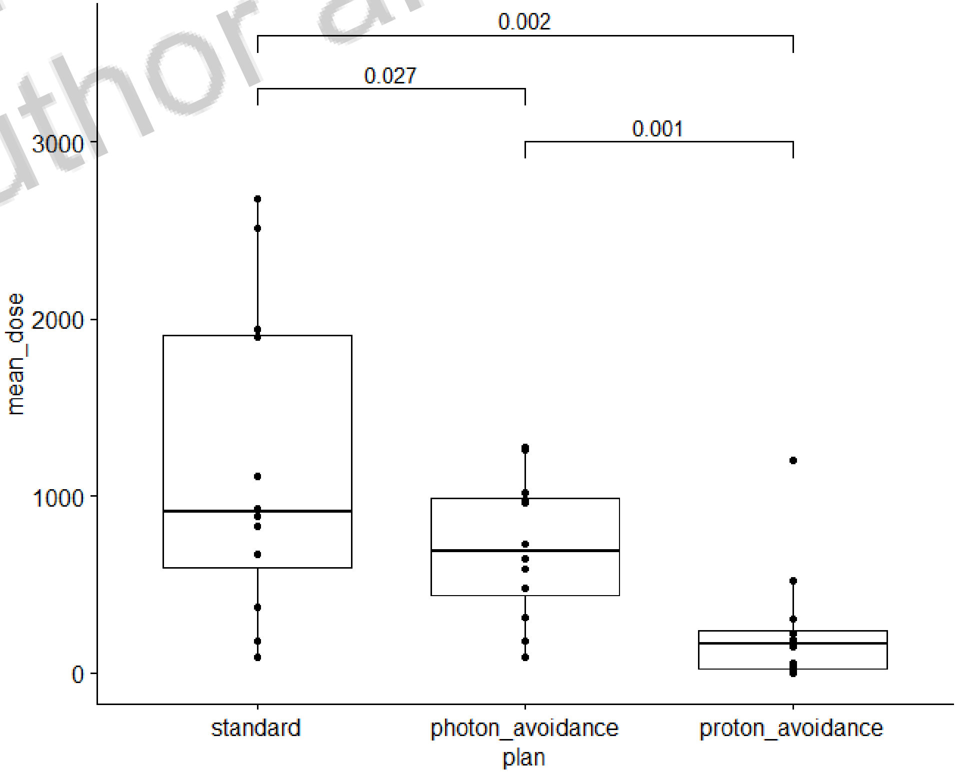
D1cc to cardiac avoidance area







Mean dose to avoidance area



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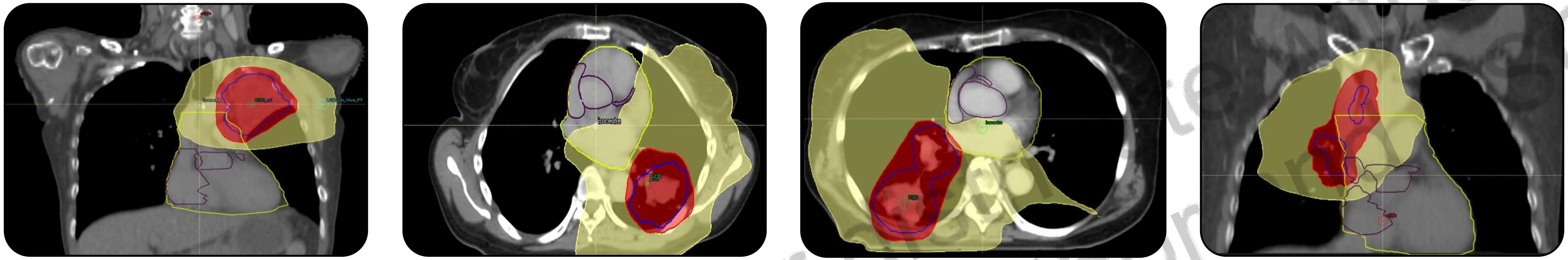
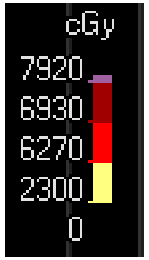
Location, Location, Location



ITV is not on same axial plane as CAA	ITV on same axial plane as CAA ≥1cm away	ITV <5mm from CAA	ITV and CAA overlap
No requirement for CAA dose reduction with proton and photon planning	Best CAA dose reduction achieved with proton planning D1cc<23Gy achievable with protons and photons	No dose reduction to CAA with proton planning D1cc <23Gy to CAA not achievable with protons but could be achieved with photons	Dose reduction to CAA not achievable with proton and photon planning Unable to achieve D1cc <23Gy to CAA without compromising ITV dose



Management of RIHD

Pathology	Symptoms and signs	Investigation	Management
Pericardium			
Acute pericarditis	Fever, chest pain, pericardial rub	Echo, CMR	Symptomatic pain relief with anti-inflammatory medications (eg NSAIDs or aspirin) Colchicine
Pericardial effusion	Dyspnoea, cardiac tamponade, quiet heart sounds	Serial Echo	Pericardiocentesis if patient acutely unwell secondary to cardiac constriction/tamponade
Constrictive pericarditis	Dyspnoea, oedema, fatigue, pericardial rub	Echo, CMR, CCT to identify calcification	Diuretics if heart failure present Surgery in intractable cases
Myocardium			
Cardiomyopathy and heart failure	Dyspnoea, oedema, fatigue, cough	Blood NT pro-BNP Echo CMR	Diuretics, B-blockers, ACE inhibitors, angiotensin receptor blockers /angiotensin receptor-neprilysin inhibitors
Coronary Arteries			
IHD	Chest pain	Blood troponin levels ECG, Echo, CCT, Angiography	Cardiac risk factor optimisation and secondary prevention with statins and aspirin B-blockers, Ca-channel blockers Antianginals eg. Nitroglycerine, ivadrabine, ranolazine, nicorandil Re-vascularisation
Valves			
Regurgitation and stenosis	Dyspnoea, oedema, fatigue, cough, chest pain, cardiac murmur	Echo, CMR, CCT	Diuretics, anti-coagulation, blood pressure control Valve replacement with surgery or TAVI
Conduction system			
Arrythmia	Palpitations, dizziness, dyspnoea, chest pain	ECG (ambulatory) Echo CMR	Anti-arrythmics Pacemaker Cardiac resynchronisation

Reducing Cardiac Toxicity of Radiotherapy

Cardiac Avoidance	Optimal Cardiac Health	Monitoring Cardiac Toxicity
• Image guided radiotherapy • Proton beam therapy	• Primary and secondary prevention	• Consistent recording and follow up

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