Cardiac Toxicity in Lung Cancer Radiotherapy

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What is Radiotherapy?
Improving outcome in lung cancer

Bradley et al Lancet Oncol 2015

- Included patients PS0-1, age < 75 with good lung function
- Cardiac dose constraint V40Gy<100%
- Heart V5Gy and V30Gy associated with increased risk of death
What cardiac dose?

Cumulative incidence of cardiac and non-cardiac death following radical fractionated RT for lung cancer in 928 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Articles assessed (n)</th>
<th>Significant on MVA (n)</th>
<th>MVA HR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Min HD</td>
<td>2</td>
<td>1</td>
<td>1.007</td>
<td>1.002-1.013</td>
<td>.006</td>
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<td>Max HD</td>
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<td>1</td>
<td>1.01</td>
<td>1.00-1.01</td>
<td>.03</td>
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<td>Mean HD</td>
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<td>1</td>
<td>1.001</td>
<td>1.001-1.001</td>
<td>.0001</td>
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<tr>
<td>V2</td>
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<td>2</td>
<td>1.013</td>
<td>1.001-1.024</td>
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<td>V3</td>
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<td>1.005-1.02</td>
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<td>V10</td>
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<td>V15</td>
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<td>1</td>
<td>1.12</td>
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<tr>
<td>Heart volume</td>
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<td>1</td>
<td>1.12</td>
<td>1.06-1.19</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

No association between cardiac death and MHD, heart V5, V30 or V50

Heart V30 > 15% associated with an increased incidence of non-cardiac death (p=0.01)

**As a continuous variable**: $HR = 1.091$ per mm ($p = 0.007$)  
(positive shifts = shifts towards heart)

- Imaging patients during treatment affects survival
- Dose to the heart affects survival

McWilliam et al EJC 2017
- 1101 Patients who had 55Gy in 20 fractions
- Dose to base of heart associated with survival
Cardiac substructures

Is the RA a surrogate for the cardiac conduction system?

Sinoatrial node
Arrhythmia
Heart block

Atrioventricular node
Heart block

Coronary arteries
Accelerated plaque formation
Calcification
Plaque rupture

Pericardium
Restrictive pericarditis
Pericardial effusion
Cardiac tamponade

Valves
Valvular stenosis or regurgitation

Myocardium
Cardiomyopathy
Heart failure

Cardiac tamponade
Comorbidities

25% of people with lung cancer have cardiac problems
70% have at least 1 other health problem
920 patients from Manchester Lung Screening Pilot

- 93% patients had Q-risk2 > 10%
- 1 in 3 were not on a statin

1 Islam et al, Cancer Epidemiology, Biomarkers and Prevention 2015
2 Balata et al, Lung Cancer 2018
3 Abravan et al, Rad Onc (Suppl 1 – ESTRO 2019)
# Avoiding Cardiac Toxicity in Lung Cancer Radiotherapy (ACcoLade)

200 patients undergoing radical RT  
Stage I-III patients having SABR, concurrent/sequential chemoRT or fractionated RT alone

**Prior to RT**  
- Blood FBC, lipids, cholesterol, high sensitivity troponin I, CRP, NT-proBNP, Q-risk 3 score  
- Cardiac CT + echo in 50 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 in 50 patients

- 18 patients recruited  
- 7 cardiac imaging  
- Unable to carry out CT angiogram in 2 patients  
- Median age 69 years  
- 6 patients with previous cardiac problems  
- Q-risk3 predicted 10 year CVD risk > 10% in all patients
Rapid learning can use routine data to improve patient care

- Change cardiac dose limits
- Measure survival and lung toxicity
- Decide on outcomes (e.g., survival and lung toxicity)

Anonymized routine data can be used in a pipeline to improve patient care.
Phase 2 trial of Protons in stage 3 NSCLC

All comers

R (1:1)

Proton chemoRT (IMPT)

Photon chemoRT (IMRT)

RT dose in both arms: 60Gy (RBE) in 30Fx

Biomarkers:
- Cardiac MRI (baseline & 6m)
- Lymphopenia (baseline, w3 & after chemoRT)
- Lung functions (baseline & 6m)
- % of patients who start durvalumab & dose intensity

Phase 3 trial in un-selected population*

Primary endpoint: Cardiac GIII or higher adverse-event free survival

Secondary endpoints: HRQoL, toxicity, LRC, metastatic control

Protons non-inferior to photons?

Yes

Protons superior to photons?

Yes

Protons likely inferior, no phase 3 trial

No

Biomarker analysis

Cardiac MRI
Lymphopenia
Immunotherapy
Lung function test

Phase 3 trial in selected population
Big data informed clinical trials

Clinical Trial – RTOG 0617

Big Data analysis

Clinical Trial – ACCOLADE

Define dose sensitive cardiac substructures

All patients having chemoradiotherapy for stage 3 lung cancer

R (1:1)

Proton chemoradiotherapy (IMPT)

Photon chemoradiotherapy (IMRT)

Cardiac substructure avoidance