



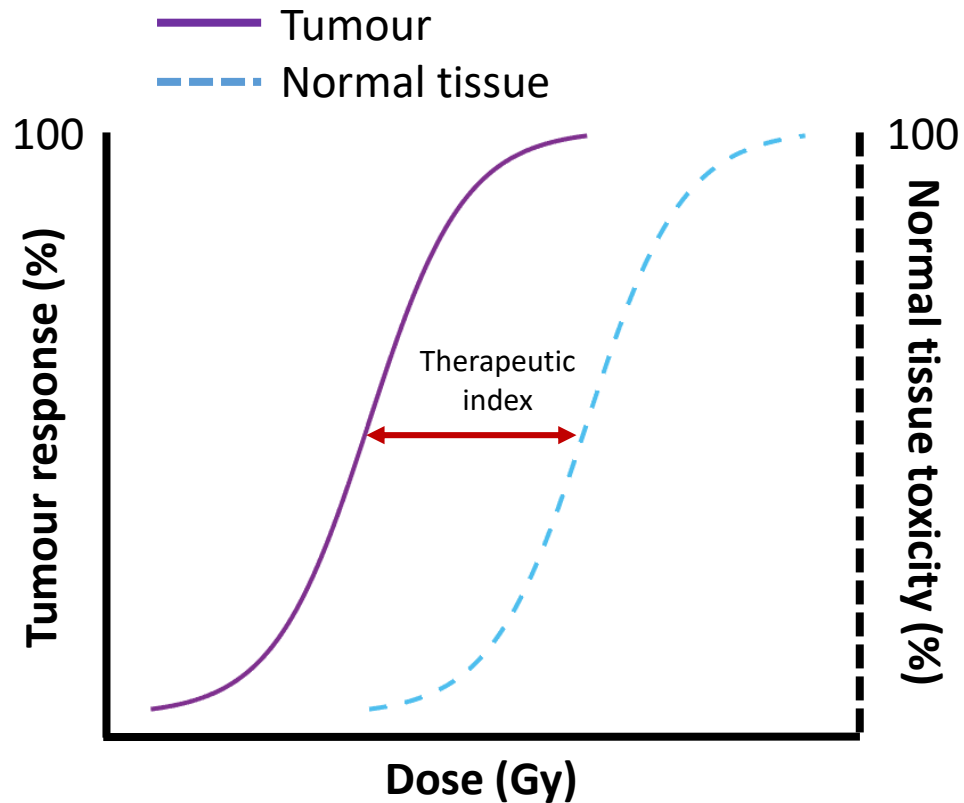
Preclinical models for radiation induced normal tissue toxicities



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Background



The goal of radiation therapy is to reduce or eliminate tumor burden while sparing normal tissues from long-term injury.

Modern radiation therapy (RT) techniques generally yield non-uniform dose distributions in non-target tissues.

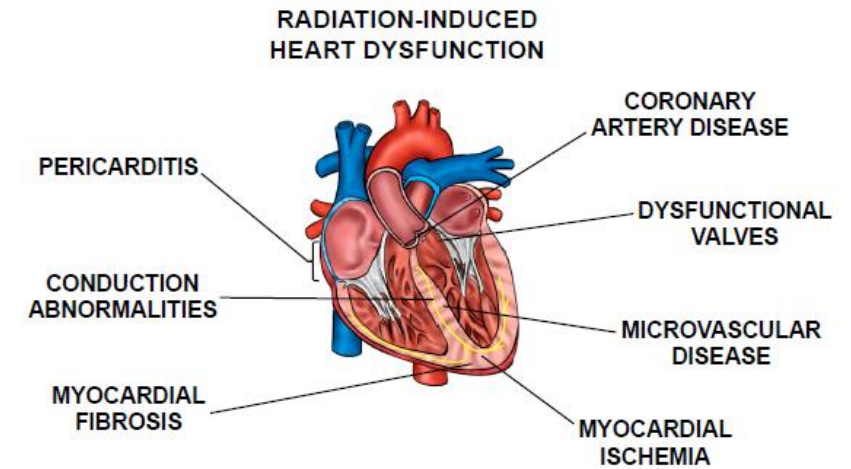
The limitations of conventional cancer therapies do not derive from their inability to ablate tumor, but rather from limits on their ability to do so without excessively damaging adjacent normal tissue.

- *continued development of robust normal tissue endpoints including patient reported outcomes to further our understanding of the relationship between toxicity and quality of life.*
- *Improved understanding of the interaction between dose distribution on one hand and dose per fraction or administration of other modalities on the other*

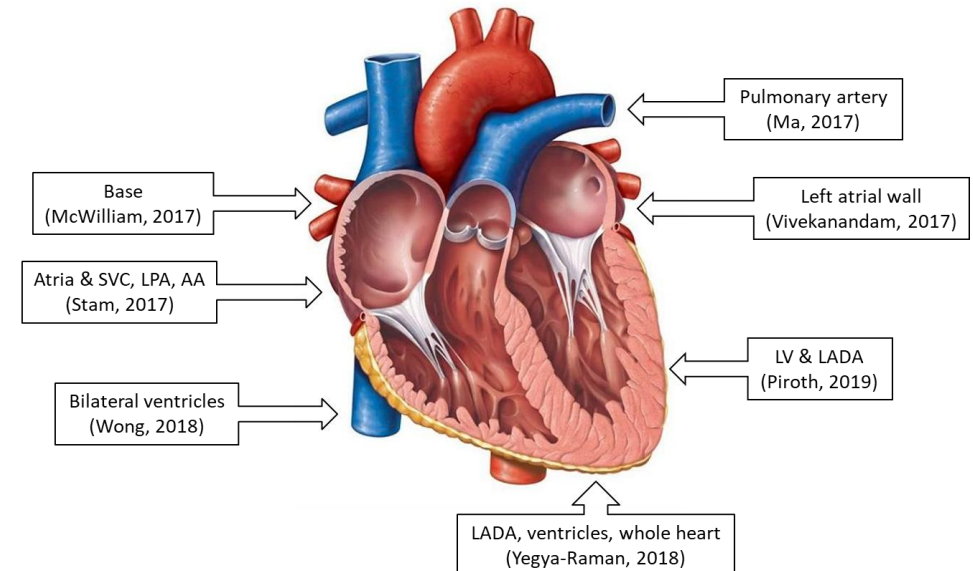
Thoracic radiation presents a unique challenge because of the inherent sensitivity of normal lung tissue to radiation. Radiation induced lung toxicity (RILT) is the most common dose limiting adverse sequelae in patients receiving thoracic irradiation

Background

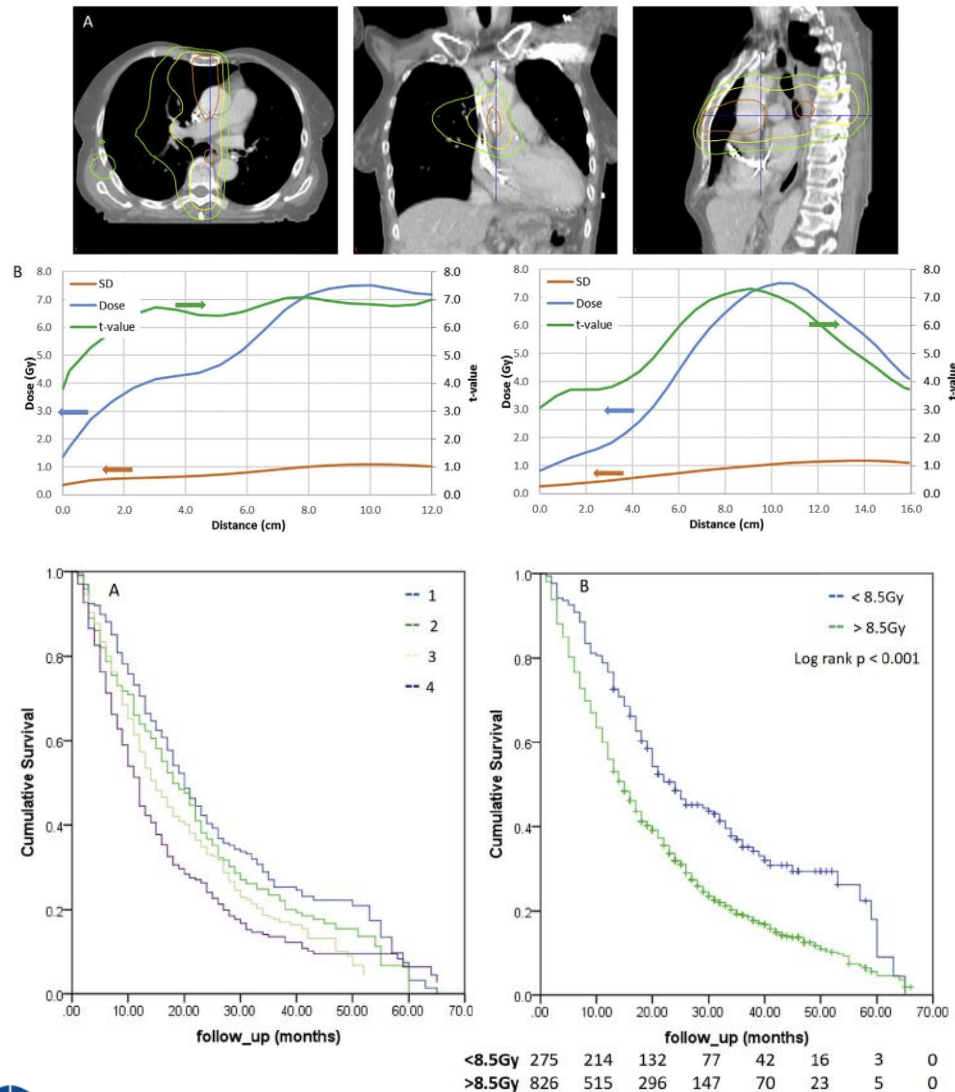
- Side effects of RT for thoracic tumors, cardiac and pulmonary toxicities, can cause morbidity and mortality in long-term cancer survivors.
- Advances in radiation oncology have made radiation more precise , allowing a more effective dose delivery to the target volume
- Numerous studies have shown that modern RT has not fully eliminated the risk or RICT
- the use of small animal image-guided RT with treatment planning systems that allow more accurate dose determination has the potential to revolutionize knowledge of clinically relevant tumor and normal tissue radiobiology
- challenges related to radiation delivery, including dose verification and calibration, determination of doses received by adjacent normal tissues that can affect outcomes, and motion management and identifying variation in doses due to animal heterogeneity.



Schlaak et al. Cancers 2020



Background



- Incidental cardiac irradiation is associated with changes in cardiac function
- A total of **1163** lung cancer patients treated between 2010 and 2013 at a single academic cancer centre, with routine curative-intent RT (55 Gy in 20 fractions), with or without induction chemotherapy, were randomly selected for analysis.
- High dose delivered to the base of the heart associated with poor survival.
- Dose region, tumour volume, performance status and nodal stage correlated with survival.
- No correlation with mean cardiac dose, V5 and V30.
- Threshold at 8.5 Gy.**

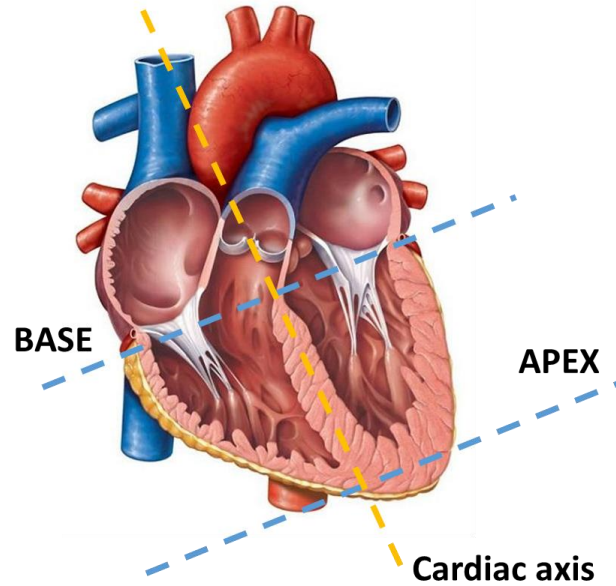
Background

- 109 breast cancer survivors treated with RT between 2005 and 2011
- The aim of the study was to assess the relationship between the radiation dose to the *LV* , dose to the *coronary arteries* and LV systolic and diastolic functions.
- Prescribed dose was 50.4 Gy delivered in 28 fractions to the whole breast with a boost of 14 or 16.8 Gy
- DVH parameters that were selected for this endpoint were based on ***dose to the coronary arteries***

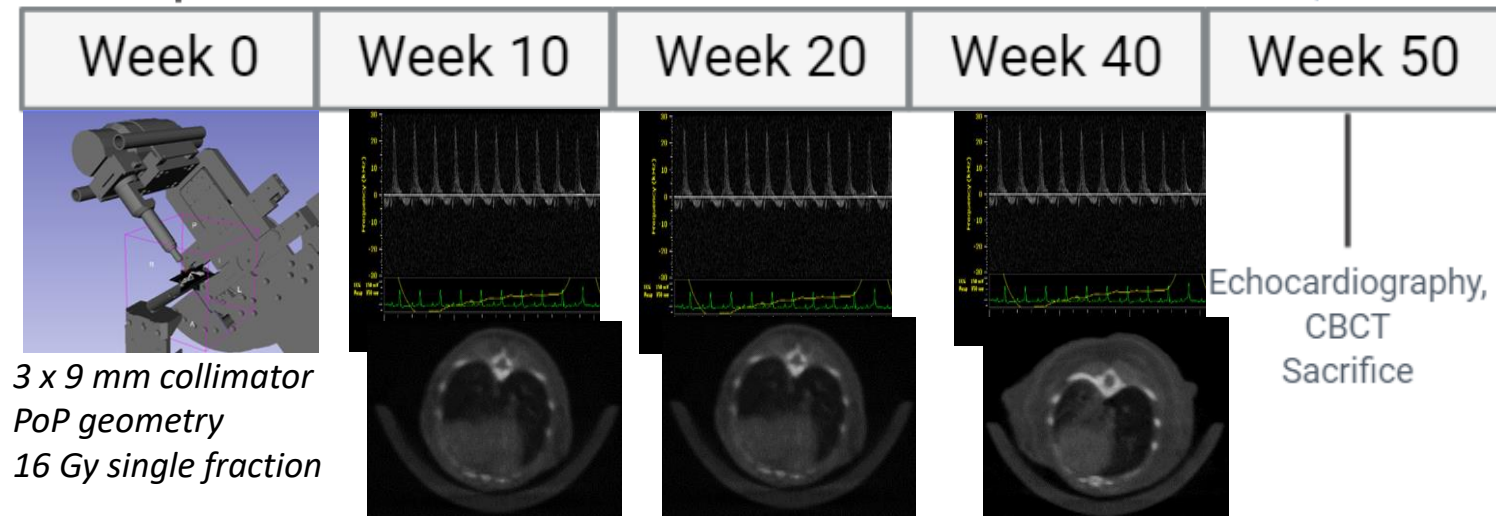
*Because a decreased ejection fraction indicates relatively late and severe cardiac damage, an additional analysis was performed using the subclinical parameter **global longitudinal strain (GLS)** of the LV as an endpoint.*

Left ventricular ejection fraction (%) based on 107 patients with BC*		
Mean	58.04	
Range	41.00-71.00	
Missing	2	1.8
Abnormal left ventricular ejection fraction [†]		
Yes	15	13.8
No	92	84.4
Missing	2	1.8
Left ventricle global longitudinal strain (%) based on 52 patients with BC [‡]		
Mean	-16.95	
Range	-23.26 to -9.44	
Missing because of limited quality	57	52.3
Left ventricle diastolic function (cm/s) based on 109 patients with BC [§]		
Mean	9.00	
Range	3.45-16.05	
Missing	0	0.0
Abnormal left ventricle diastolic function		
Yes	43	39.4
No	66	60.6
Missing	0	0.0

Study Design



Baseline CBCT and
echocardiography.
RT 16 Gy



- C57 BL6 mice, irradiated with a single dose of 16 Gy targeted to the Base, Middle or Apex of the heart
- Longitudinal Trans Thoracic Echocardiography – to detect functional changes in the heart
- Serial longitudinal CBCT to detect lung fibrosis



LVEDD = left ventricular end diastolic diameter (mm).

LVEDD = left ventricular end diastolic diameter (mm)

Derived functional parameters

Left Ventricular Fractional Shortening (FS): Percent change in LV cavity dimensions at the base with systolic contraction, measurement of systolic function and cardiac contractility

Left Ventricular Ejection Fraction (EF): a measurement of the percentage of blood leaving the heart each time it contracts.

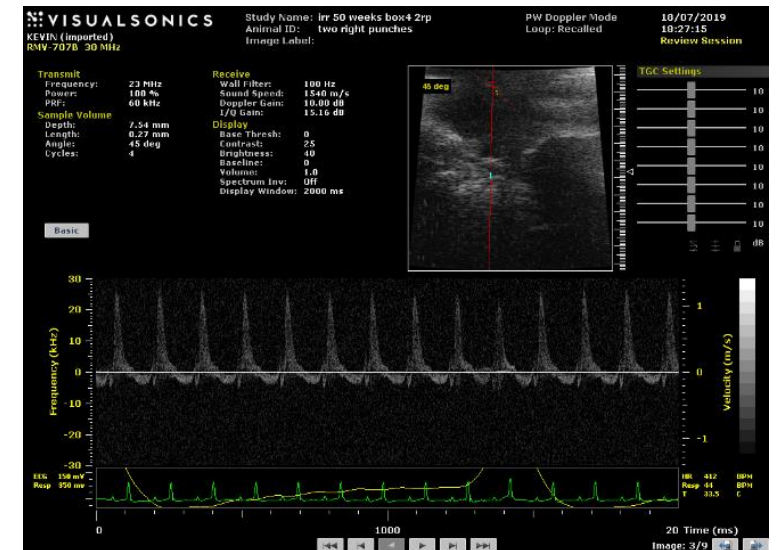
LV diastolic function is measured from ***Pulsed Wave Doppler mode***

- LV filling waves : **early (E wave)** and **atrial** (late, **A wave**)
- isovolumic contraction time, **IVCT**
- ejection time (**ET**)
- isovolumic relaxation time (**IVRT**)

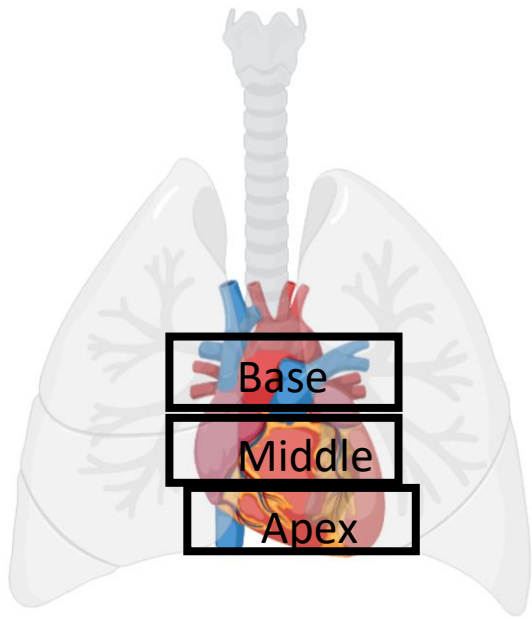
Derived functional parameters

E/A ratio - relationship between early and late filling

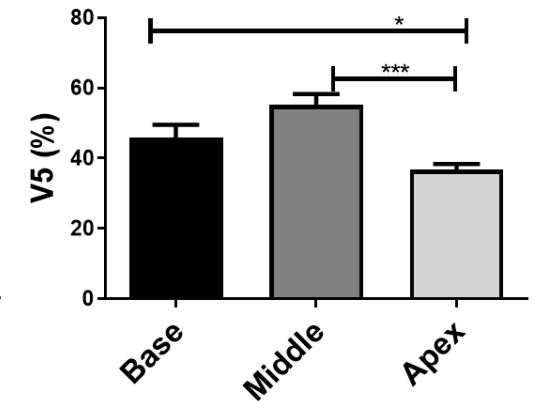
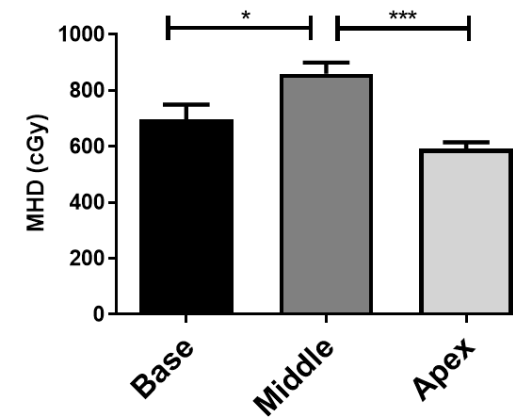
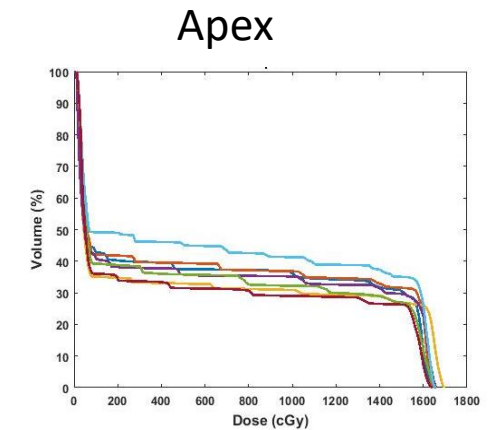
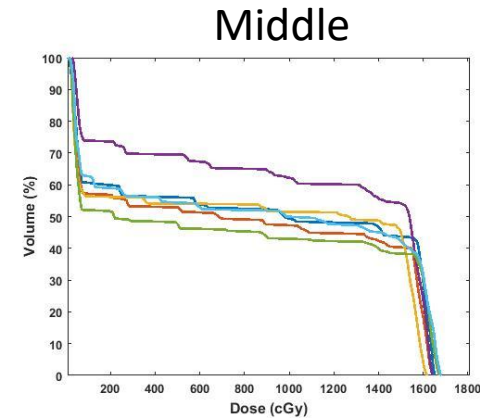
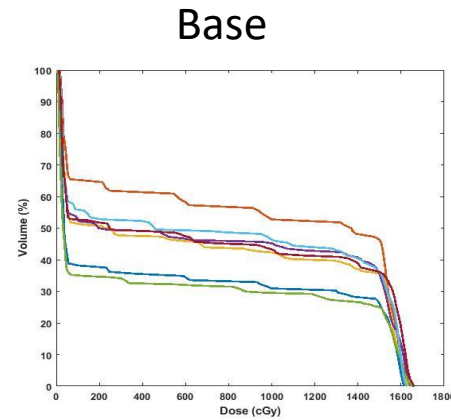
Myocardial Performance Index (MPI) -an index that incorporates both systolic and diastolic time intervals in a global systolic and diastolic ventricular function.



Study Design



- The heart anatomy leads to variation in the irradiated volume and mean dose delivered for all experimental arms.
- Significantly higher Mean Heart Dose for the Middle and Base irradiated experimental arms
- Significantly lower average V5 for the Apex irradiated mice



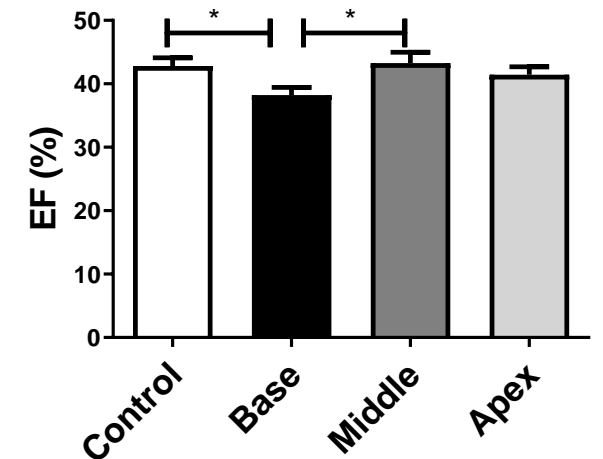
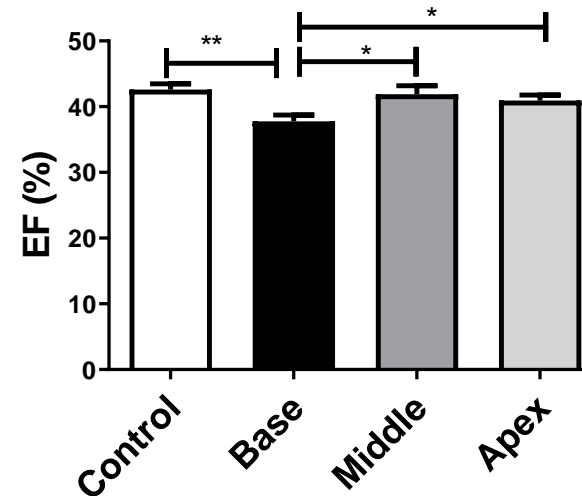
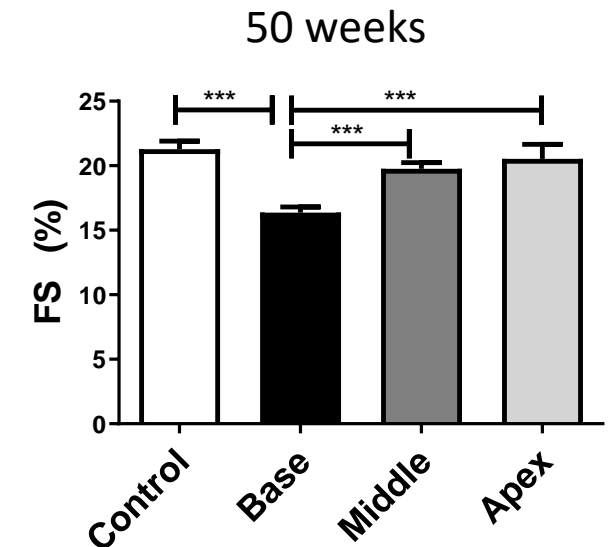
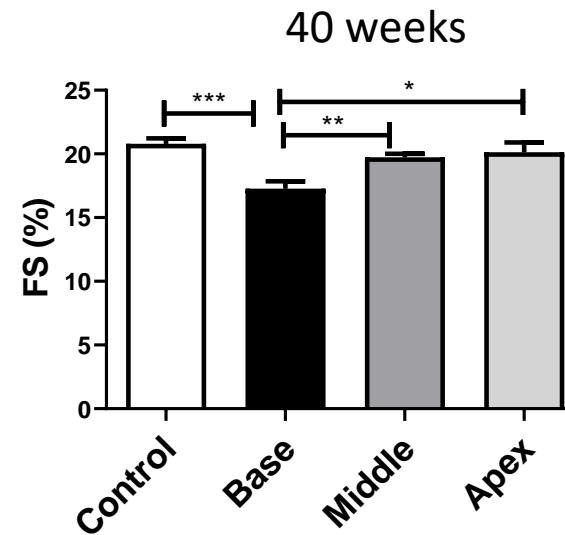
Results

Sub-volume targeting induces differential effects on the systolic function

Only mice in which the base of the heart was irradiated showed significant changes ($p < 0.001$) in the fractional shortening (FS).

At 50 weeks, the observed decrease in FS in the base irradiated cohort was significantly different to the middle and apex irradiated groups ($p < 0.003$).

Similarly, reduced left ventricular EF was observed for the base-irradiated cohort ($p = 0.02$)



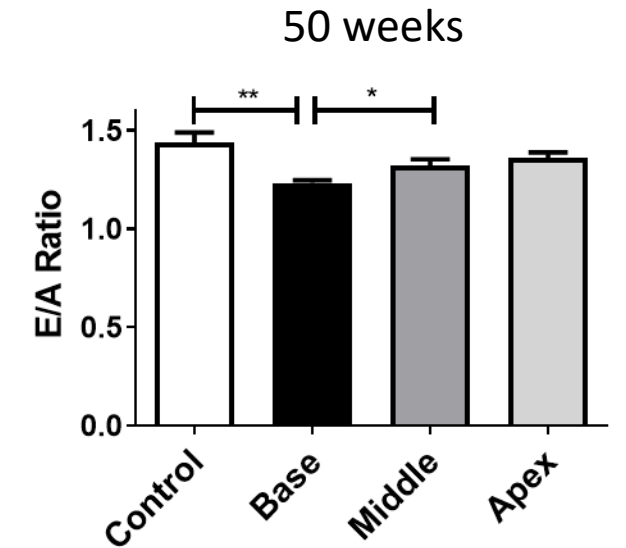
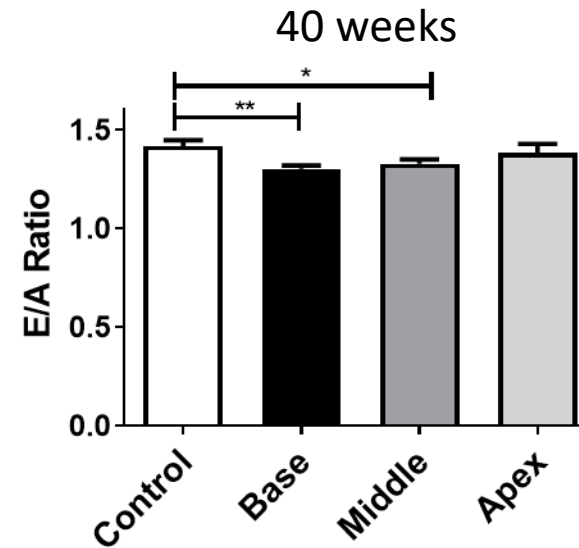
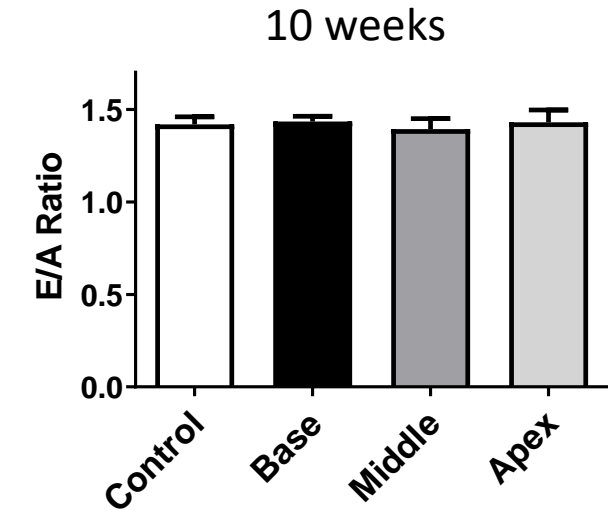
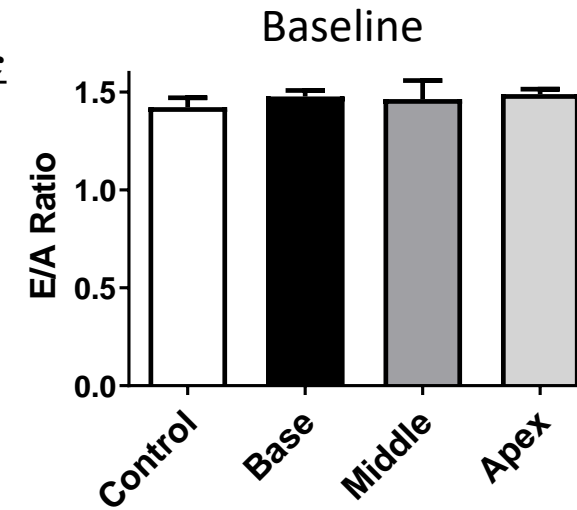
* $P < .05$, ** $P < .01$ and *** $P < .001$.

Sub-volume targeting induces differential effects on the diastolic function

Early and late filling ratio as a measure of the diastolic function

A significant decrease in the E/A ratio of early and late filling of the left ventricle indicating diastolic dysfunction.

This was observed for the base and middle irradiated cohorts

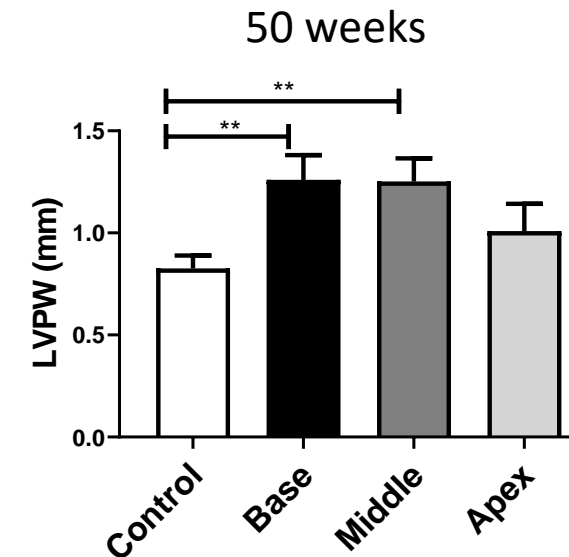
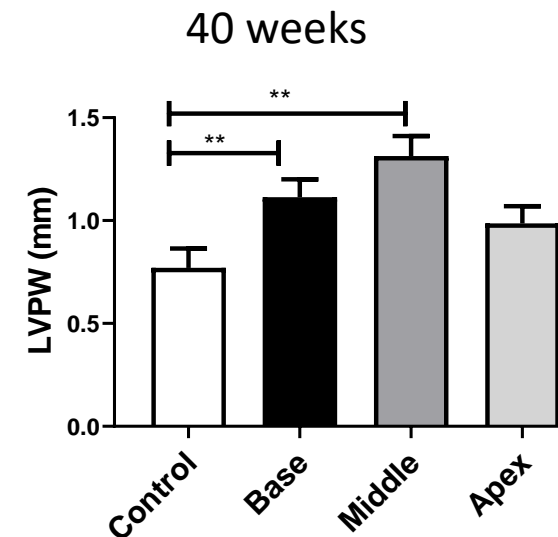
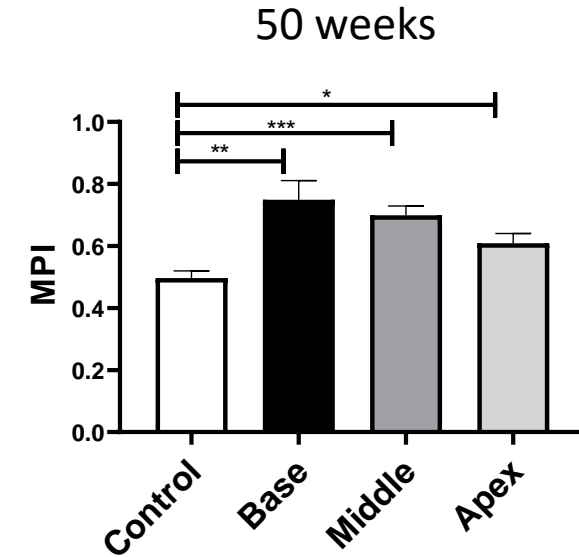
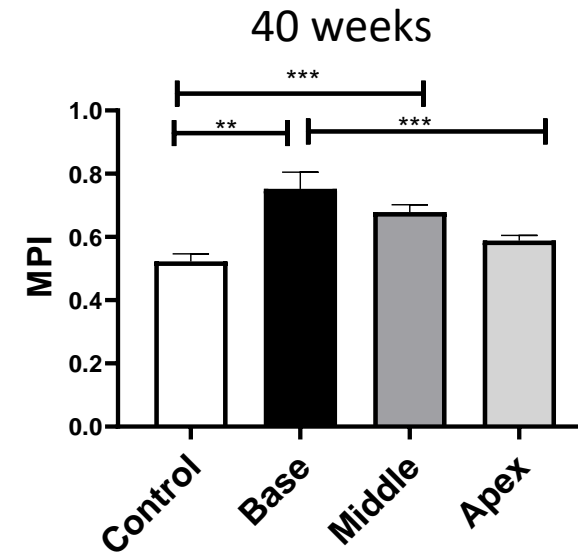
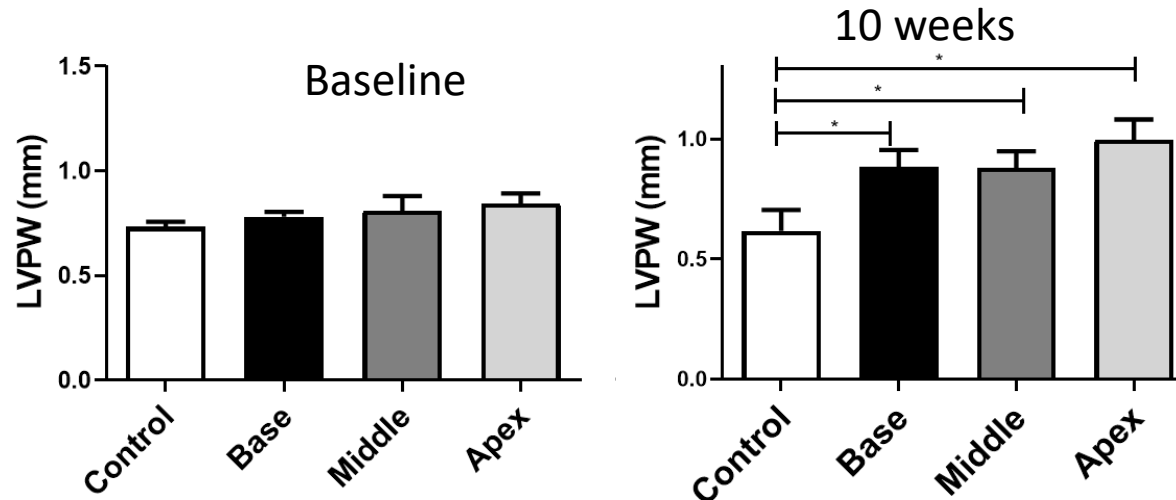


* $P < .05$, ** $P < .01$ and *** $P < .001$.

Results

Sub-volume targeting induces effects on the global and structural parameters

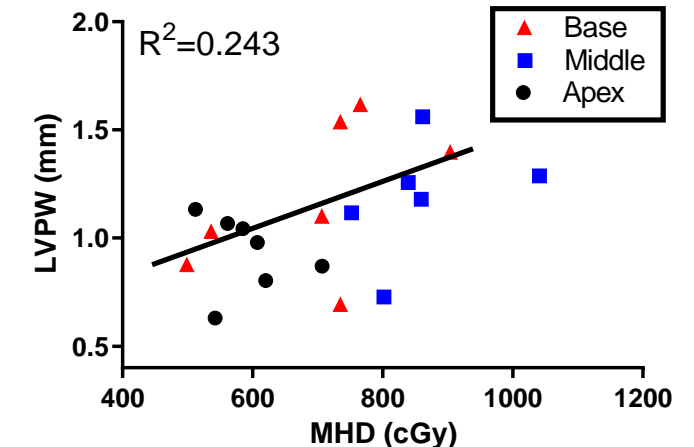
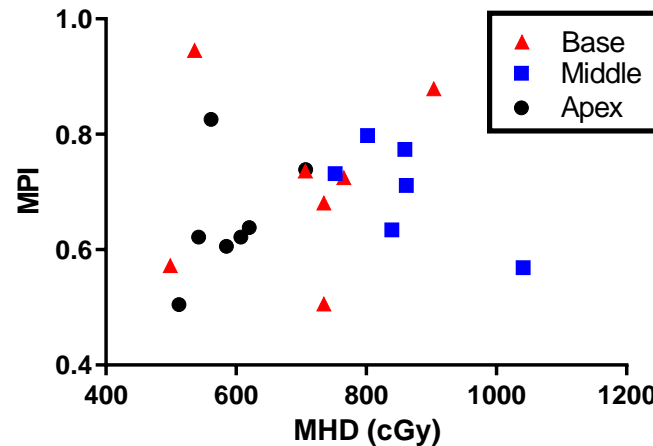
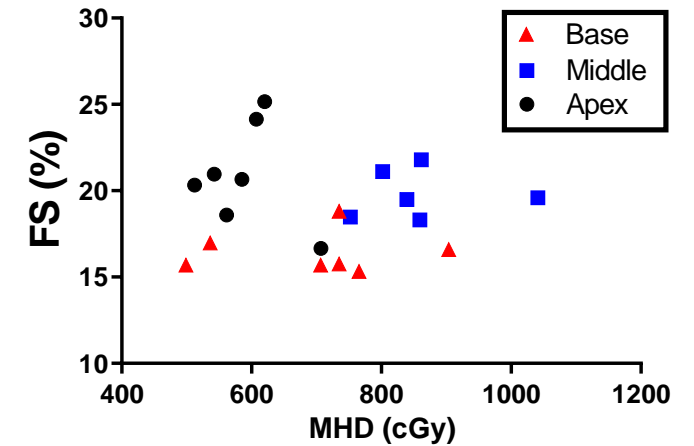
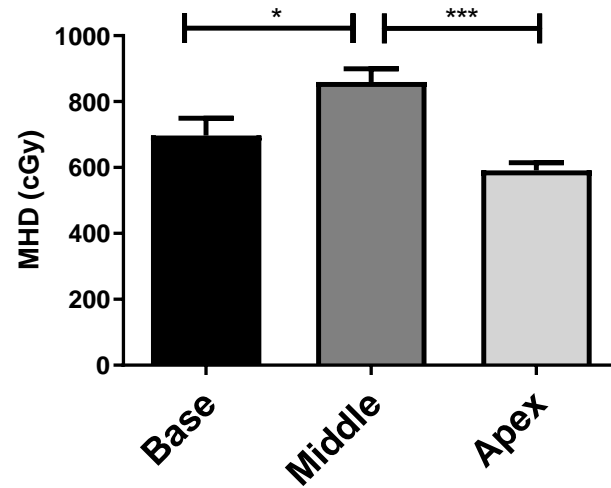
- Changes in MPI were significant for both Base and middle irradiated mice, and less significant for apex irradiated mice ($p=0.018$) at 50 weeks post irradiation.
- Significant changes in the LVPW thickness in diastole starting at 10 weeks post irradiation



* $P < .05$, ** $P < .01$ and *** $P < .001$.

Cardiac function and structure and the MHD

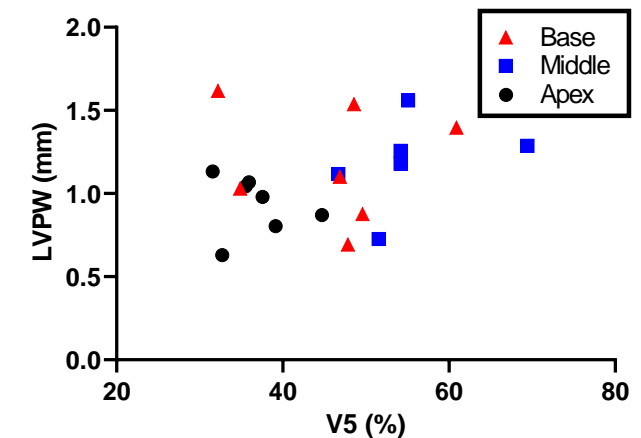
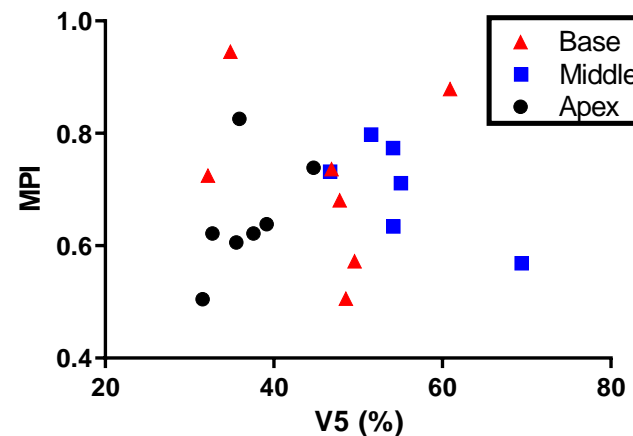
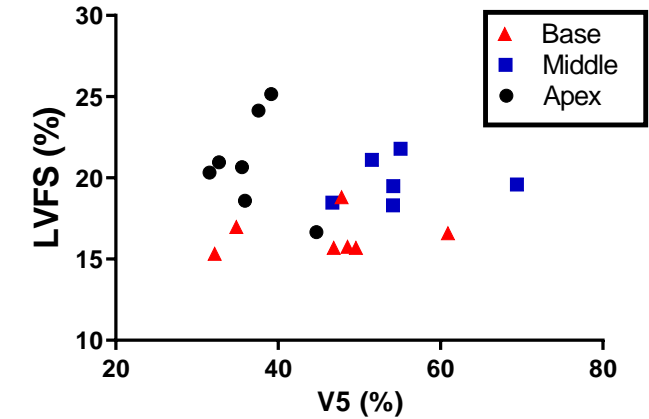
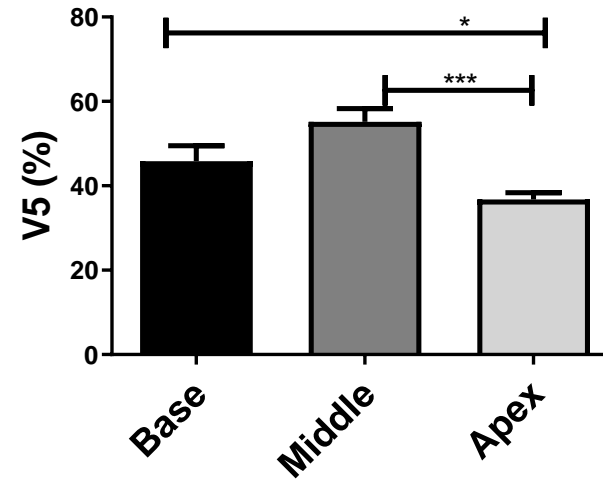
- An average MHD of 8.6 ± 1.8 Gy was delivered to the middle region cohort which had the highest volume of the heart irradiated.
- Base-irradiated animals received an average of 7.0 ± 2.1 Gy followed by the apex irradiated mice with an MHD average of 5.9 ± 0.3 Gy.
- Interestingly, LVPW thickness showed a weak but significant correlation with MHD



* $P < .05$, ** $P < .01$ and *** $P < .001$.

Cardiac function and structure and V5

- Middle irradiated mice had $55 \pm 14\%$ heart volume irradiated with 5 Gy or more
- Base irradiated animals had $46 \pm 11\%$ heart volume irradiated with ≥ 5 Gy. Apex irradiated animals had only $37 \pm 7\%$ heart volume irradiated with ≥ 5 Gy
- Similar to the observed correlations with MHD, no correlations were detected for FS or MPI ($R^2 < 0.05$). Interestingly, LVPW was not significantly correlated with V5 ($p = 0.81$).

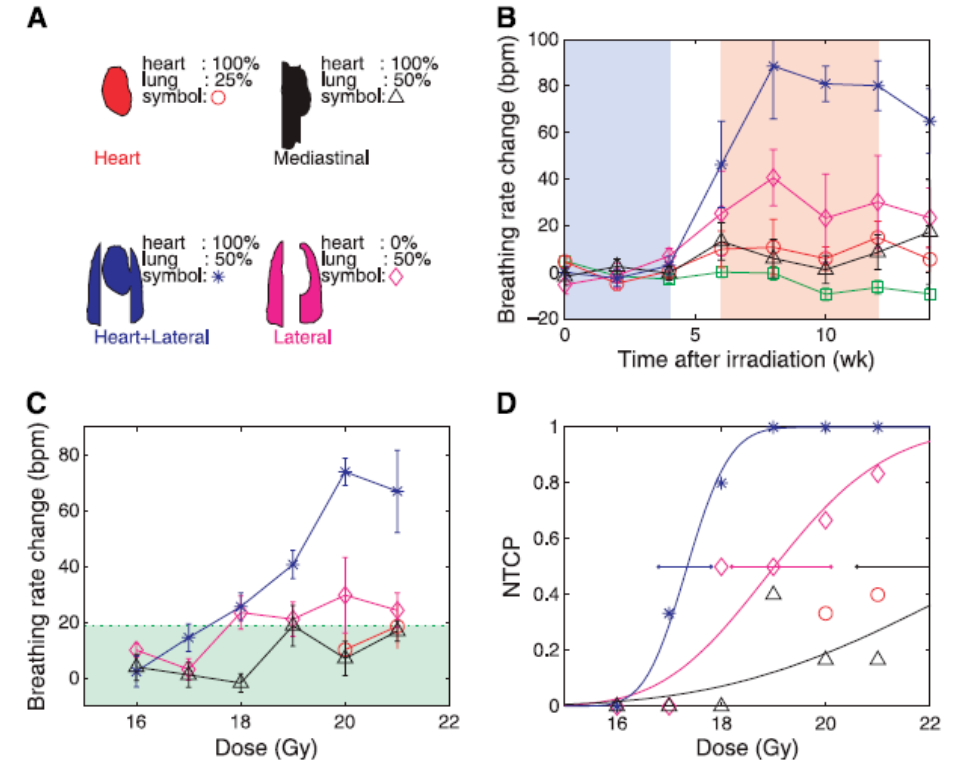
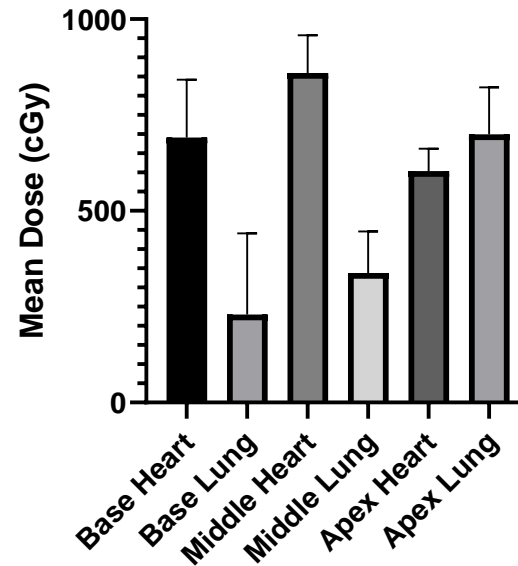
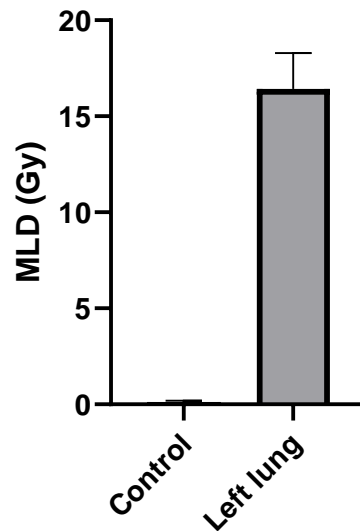


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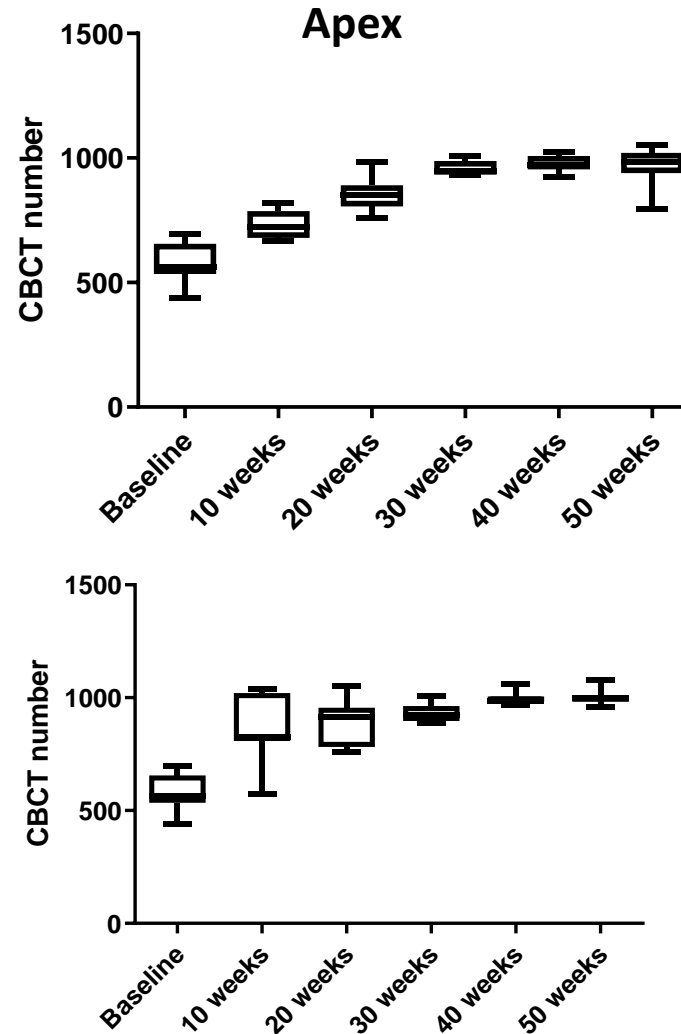
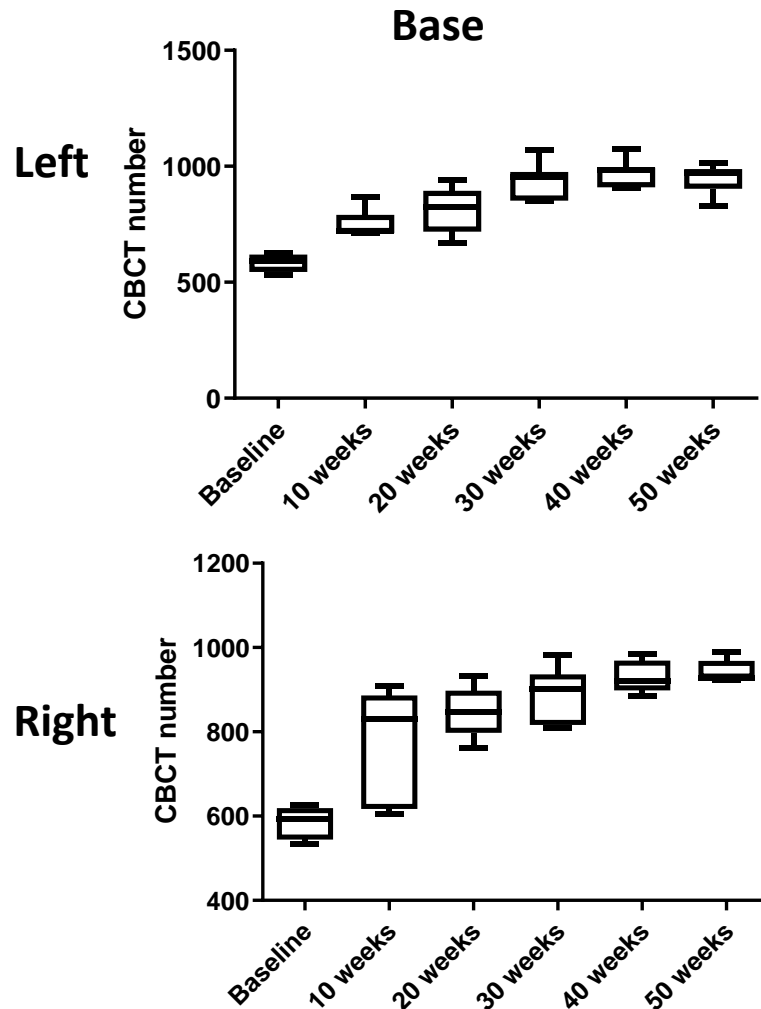
Results

Cardio-pulmonary interaction

- The response of an organ to irradiation does not necessarily depend on the dose distribution in that organ alone.
- The tolerance dose for early lung function damage depends not only on the lung region that is irradiated but also that **concomitant irradiation of the heart severely reduces the tolerance of the lung.**



Results



We observed a steady increase in the CBCT numbers up to 50 weeks for all experimental groups

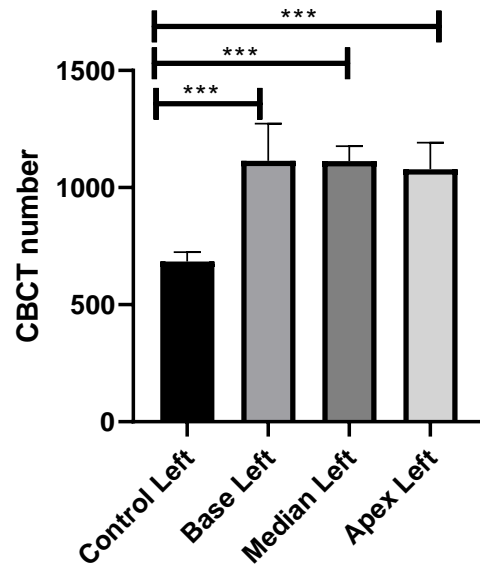
This was observed for both left and right lungs

Variations in the CBCT numbers may account for the movement within the radiation field

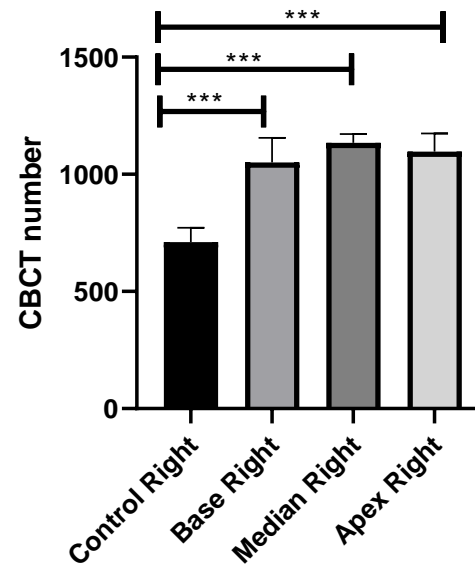
The CBCT numbers increase is consistent with a previous study analysing the lung irradiation only, for a fraction of the dose directly delivered to the lungs

Results

Left Lung 30 weeks



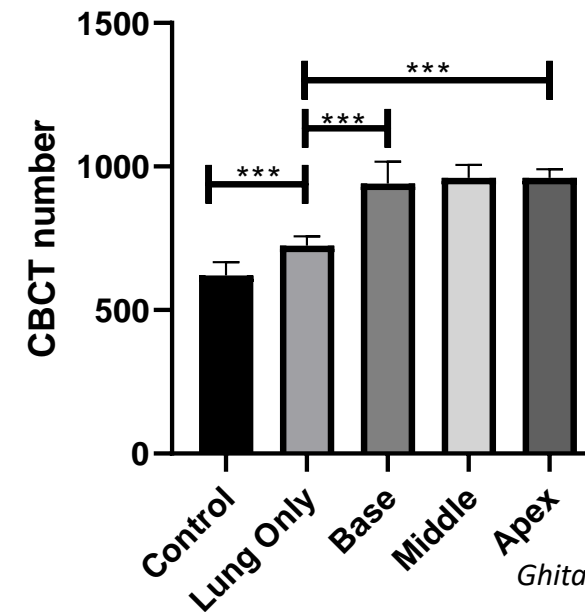
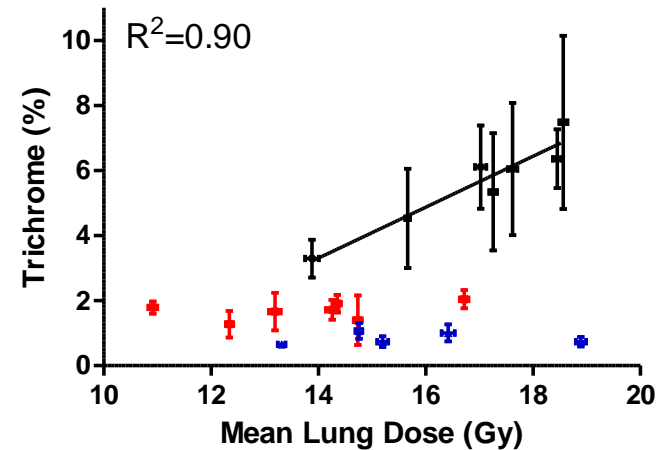
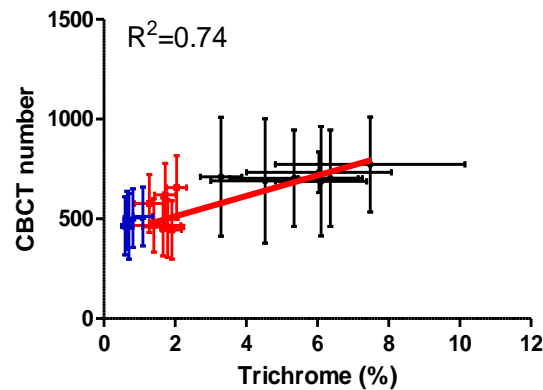
Right Lung 30 weeks



Effects in the lung after cardiac irradiation seem to be significantly higher when compared to the effects after lung irradiation only.

This is very interesting considering the variation in the mean dose for both cases

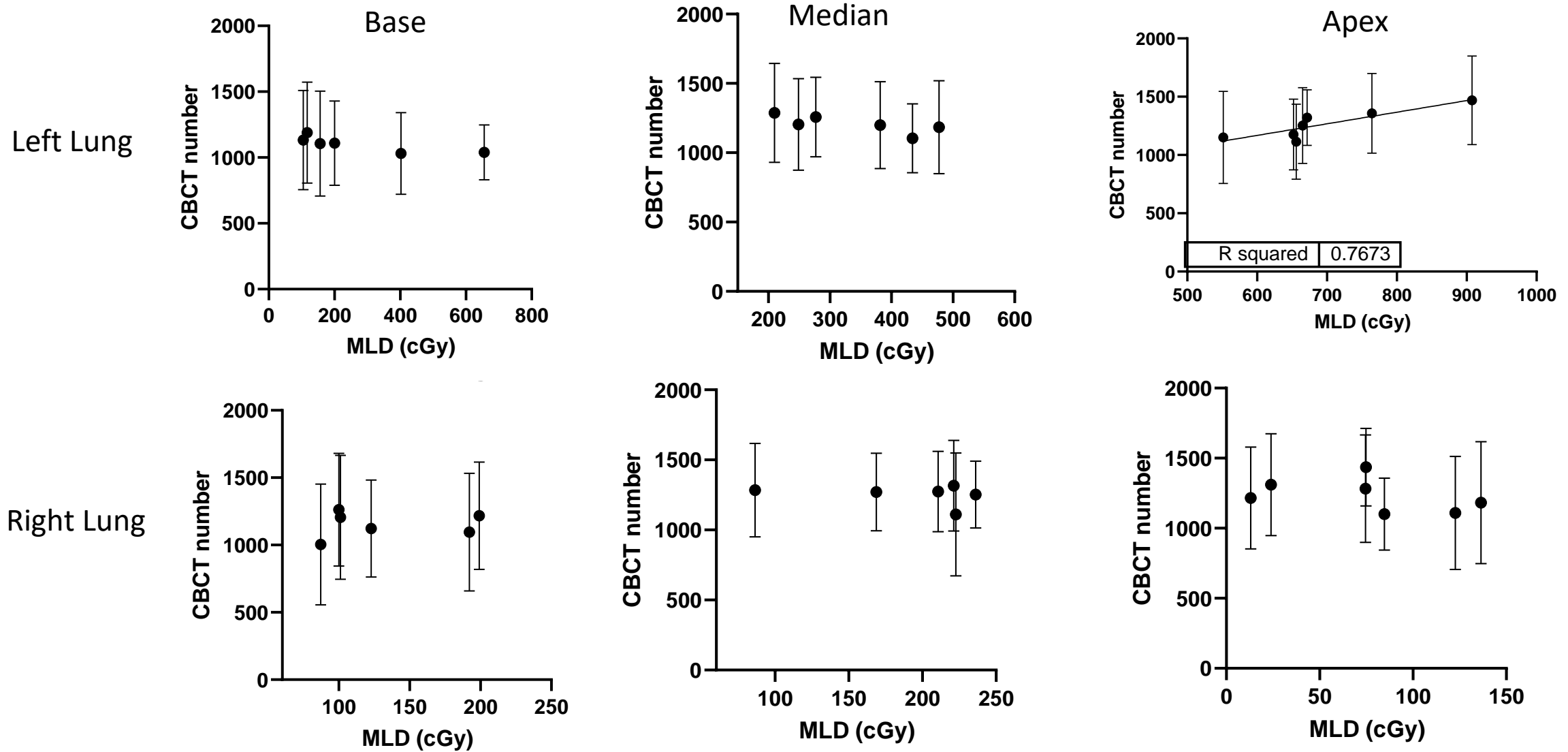
This indicates a complex cardio-pulmonary interaction of interest for further analysis.



Ghita et al. in preparation

Ghita et al. IRJOBP 2019

Results



Conclusions and future work

- Radiation delivered to the base of the heart showed a significant effect on the functional EF, FS, MPI and E/A
- Radiation induced changes in the left ventricular posterior wall thickness as early as 10 weeks post irradiation.
- Some of these changes will recover, leaving the base and middle irradiated cohorts with significant increase in LVPW at 50 weeks post irradiation
- LVPW shows a correlation with the MHD
- Functional parameters show no correlation with MHD or V5 indicating underlying biological mechanisms
- CBCT numbers in the left lung have increased with no correlation with the dose deposition in the left lung
- Further analysis is required to elucidate any mechanistic insight into the radiation induced cardiac and lung toxicity, and further studies need to be carried out considering different fractionation schedules as well as various comorbidities observed in patients.

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