Final Report
Executive Summary

HSC Public Health Agency
Research and Development

HSC R&D Division Final Progress Report

Final Reports should be submitted via electronic copy to HSC R&D Division within 6 weeks of the request.
The report should be completed on the attached form in clear typescript. Please extend boxes as required.
Please adhere to any word limits. These reports may be subject to external peer review.
Details from the Final Report may be placed on the HSC R&D Division website and shared with appropriate key stakeholders or members of the public.

HSC Public Health Agency
Research and Development

HSC R&D Division Award Details

HSC R&D File Reference	
HSC R&D Funding Scheme	Wellcome-HRB Irish Clinical Academic Training Programme
Project Title	Biophysical correlates of base-mediated cardiotoxicity in non-small cell lung cancer
Award Holder Name (Employer)	Dr Gerard Walls
Host Research Organisation	Queen's University Belfast
Award Duration	3 years
Award Start Date	August 2019
Award End Date	December 2023 (includes COVID redeployment for 4 months)
Name of Lead Supervisor: ***(only applicable to training awards)***	Dr Karl Butterworth

HSC Public Health Agency
Research and Development

Evidence Brief

(1 page: which may be used for dissemination by HSC R&D Division)

Why did we start? (The need for the research and/or Why the work was commissioned)	The base region of the heart had recently been identified as a region that should be spared radiation in patients with lung cancer who are getting curative-intent chemoradiation. Although a mouse study had shown the same findings in Belfast, the biologic basis of this had not been elucidated.
What did we do? (Methods)	A 500 patient database (NI-HEART) was built with granular detail on patient, tumour and cardiovascular baseline details, plus cardiac substructure dose information. A novel lab technique called spatial transcriptomics was employed to delve into the biology of the problem in a mouse experiment also.
What answer did we get? (Findings)	We validated the base region as a dose-sensitive region in NI-HEART. We also found that statin therapy was protective in patients. This was tested in animals and was also found to be the case. The transcriptomic experiment was a world-first and identified that different regions of the heart respond differently to irradiation.
What should be done now? (Practice/Policy Implications and/or Recommendations)	Those international societies responsible for writing guidelines for lung cancer radiotherapy should consider our data in their next iterations. We also published pre-clinical guidelines for how the yield from animal studies can be maximized to progress the field in a way that translates into better outcomes for patients.

Final Report

(no more than 20 pages)

Please structure the report using the headings below

- **Background**

Radiation cardiotoxicity (RC) is as an important treatment sequela for patients with locally advanced lung cancer. Depending on the dose and distribution of radiation, asymptomatic ECG changes (30–60% incidence), symptomatic cardiac events (20% incidence) can each manifest, with onset typically in the months to years after treatment, and often with a chronic component. Furthermore, multiple retrospective and prospective studies have demonstrated a detriment in survival with greater cardiac doses after adjusting for tumour and cardiovascular factors.

Despite the widespread availability of IMRT, for many patients avoidance of the heart is not possible to due to intimate tumour proximity eg lung and oesophageal cancers. With the advent of adjuvant immunotherapy in the curative setting, and re-irradiation and immunotherapy in the advanced disease setting, plus the patient advocates' priority of survivorship, reducing cardiac disease after radiotherapy for lung cancer is paramount.

In recent years, cardiac subregions have been identified that might be prioritised for dose sparing for radioprotection of the heart. One region with the most data is the cardiac base, the superior-right aspect of the heart. Furthermore, there is emerging evidence that drugs such as statin therapy might have some capacity to mitigate against radiation heart disease. The purpose of this research was to quantify the biophysical correlates of base-mediated radiation heart disease.

- **Aims and objectives**

  - To validate and characterise the radiosensitive nature of the cardiac base
  - To assess if statins can be radioprotective for the heart

- **Methods**

  - Systematic review
  - Spatial transcriptomics
  - Mouse study of partial heart irradiation
  - Clinical radiotherapy cardiotoxicity database
  - Deep learning-based autosegmentation
  - Design of novel contouring atlas

- **Personal and Public Involvement (PPI)**

  - The Northern Ireland Cancer Research Consumer Forum with Sister Ruth Boyd provided expert feedback during the development of this project that helped very much to shape it into what is.

- **Findings**

- Spatial transcriptomics was deployed to identify regional variation in the impact of base irradiation on gene expression at 30 weeks. Gene dysregulation was not restricted to the cardiac anatomy that was irradiated, demonstrating how the cardiac substructures are biologically inter-related.

- The pre-clinical literature on statin therapy is consistent with a prophylactic role in radiation cardiotoxicity. Long-term follow-up data was generated in a second mouse study, and this confirmed persistent abrogation of radiation effects on functional endpoints.

- A cohort of 478 NSCLC cases was used to evaluate the relationship between statin therapy and cardiac outcomes in the clinical setting, accounting for incidental radiation dose to the heart base. A significant relationship was found to exist between statin therapy dose intensity and survival. Cardiac events did not differ by statin intensity in frequency or severity however.

- Finally, the clinical data evidencing the base region of the heart as a key anatomical volume for dose-sparing is based on the endpoint of overall survival, a surrogate measure of radiation cardiotoxicity.

- In the clinical cohort above, cardiac substructures were auto-contoured with a validated tool for 4-dimensional planning scans. Additional substructures were manually delineated, including the pulmonary veins using an atlas presented here.

- Dose volume histogram metrics for the heart base were found to be associated with both survival and cardiac events. Furthermore, the dose to several cardiac substructures within the base corresponded to relevant clinical endpoints.

- Relationships were also observed for some substructures outside the formal base definition

- **Conclusion**

  - This work confirmed that the heart base radiation dose influences the cardiac response to irradiation, and that statin therapy partially off-sets deleterious radiation effects

- **Practice and Policy Implications/Recommendations**

  - First guideline for future clinically relevant mouse models of radiation heart disease experiments.

  - First validation of the cardiac base as a radiosensitive cardiac subregion using individual patient delineations.

- First evidence for a dose-response for statin therapy as a radioprotectant in lung cancer for reduced cardiotoxicity.

- **Pathway to Impact**

  - First demonstration of spatial transcriptomics in the setting of radiotherapy.

  - Atlas is published, which will serve as a foundation for future research to establish radiotherapy dose constraints for the pulmonary veins.

- **References**

1. **Walls GM** et al. Validation of an established deep learning auto-segmentation tool for cardiac substructures in 4D planning scan. Phys Imaging Radiat Oncol 2022;14:61-6.

2. **Walls GM** et al. Murine models of radiation cardiotoxicity: a systematic review and recommendations for future studies. Radiother Oncol 2022;173:19-31.

3. **Walls GM** et al. Spatial gene expression changes in the mouse heart following basetargeted irradiation. Int J Radiat Oncol Biol Phys 2023;115(2):453-463.

4. **Walls GM**, Hanna GG. Sinoatrial node radiation dose and atrial fibrillation in patients with lung cancer. JAMA Oncol 2023;in press.

5. **Walls GM et al.** A pulmonary vein atlas for radiotherapy planning. Radiother Oncol 2023.

6. **Walls GM et al.** The association of incidental radiation dose to the heart base with overall survival and cardiac events after curative-intent radiotherapy for non-small cell lung cancer: results from the NI-HEART Study. Radiother Oncol 2023.