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Research paper

Measuring early changes in heart function due to radiation treatment in breast cancer patients

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In breast cancer (BC) patients, a challenge in identifying root causes of cardiac toxicity and effective interventions is that major cardiac events often do not present until 5–10 years post-therapy [1]. Our goal of this research is to develop, validate and apply tools to quantify sub-clinical changes in heart function early after treatment to identify patients at risk for future cardiac events and to correlate cardiac graded dysfunction with patient and treatment factors. Our on-going study is approved by the University of Florida's human subjects in research institutional review board, and all patients provide informed consent. The study includes patients receiving conventional three-dimensional (3D) intensity-modulated X-ray based radiation therapy (IMRT), and those receiving proton therapy. We acquire 3D cardiac magnetic resonance imaging (cMRI) before and after radiation treatment in patients with left-sided breast cancer. In-house software tools are used to segment the left ventricular (LV) endocardial wall in each view, accurately model the 3D LV endocardial surface [2], and precisely measure LV ejection fraction (LVEF) [3]. A preliminary analysis in 10 patients finds that proton therapy patients ($n = 6$) have a significantly lower mean heart dose (MHD) (0.3 ± 0.2 Gy) compared with IMRT patients ($n = 4$; 4.1 ± 1.1 Gy; $p < 0.001$). A two-tailed, unpaired student's t-test was used for all p-value calculations. At 6–9 months post-treatment we observed a decrease in LVEF that correlated strongly with MHD (R-squared = 0.75) with a slope of around 5 %. The mean change in LVEF was overall positive for the proton therapy group ($+8.3 \pm 5.2$ %) indicating improved LVEF function after treatment. LVEF change was negative for the IMRT group (-9.6 ± 2.1 %) and significantly different between the treatment groups ($p < 0.001$). If confirmed with additional subjects, this would be the first demonstration of a cardiac health benefit of proton therapy over X-ray-based radiation treatment (RT) in breast cancer. We hypothesize that the improvement in LVEF in the proton therapy group is a result of our patients having received chemotherapy prior to acquisition of the baseline cMRI. Perhaps all patients had diminished LVEF at baseline which was exacerbated in the IMRT group because of additional radiation insult, but where in the absence of substantial MHD with the proton therapy group the hearts were able to somewhat recover. A follow-up study is underway to address the impact of chemotherapy on sub-clinical changes in LVEF. In patients with BC it is also possible using cMRI to measure changes in regional perfusion in myocardial tissue [4], and regional myocardial mechanical strains [5] via MRI cardiac tagging [6–8] with the potential advantage of related regional radiation exposure to regional changes in perfusion and function. Conveniently, each of these cMRI exams can be performed in our cancer patients within the same 1-h imaging session. However, these additional techniques require further refinement and streamlining to be practical for routine clinical use. The greatest barrier to clinical implementation is the time required to segment the heart endocardial and epicardial surfaces for each view and time. Model-based and artificial intelligence approaches hold promise for fully automating these tasks.

CRediT authorship contribution statement

Walter G. O'Dell: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **Shruti Siva Kumar:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft. **Christopher L. Klassen:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Michael S. Rutenberg:** Data curation, Investigation, Methodology, Resources,

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Validation, Writing – original draft. **Raymond B. Mailhot Vega:** Data curation, Investigation, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. **Nancy P. Mendenhall:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Paul G. Okunieff:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft. **Julie A. Bradley:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics statement

The study was performed under an IRB-approved protocol in accordance with all federal, state and institutional guidelines for human subjects in research. All patient subjects provided informed consent to participate in this study.

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