Proton therapy preserves acute left ventricular ejection fraction relative to conventional X-ray therapy in breast cancer

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I. INTRODUCTION

- There are now over 3.5 million long-term breast cancer (BC) survivors in the United States.[1]
- Radiotherapy (RT) is a critical component of breast cancer management, yielding a substantial survival benefit[2] but can result in inadvertent exposure of large volumes of normal tissues to low and moderate doses of radiation (up to ~50 Gy).
- The relative risk of cardiac disease increases for each Gy increase in mean heart dose; 35% total for the typical patient.[3]
- Left-sided BC patients who receive chest wall RT have a 4-fold higher risk of cardiac events than right-sided BC patients.[4]
- Because cardiac injury is a known risk of RT in BC, early markers of heart injury could benefit follow-up management in these patients and may help identify new techniques to improve the therapeutic ratio of treatment.

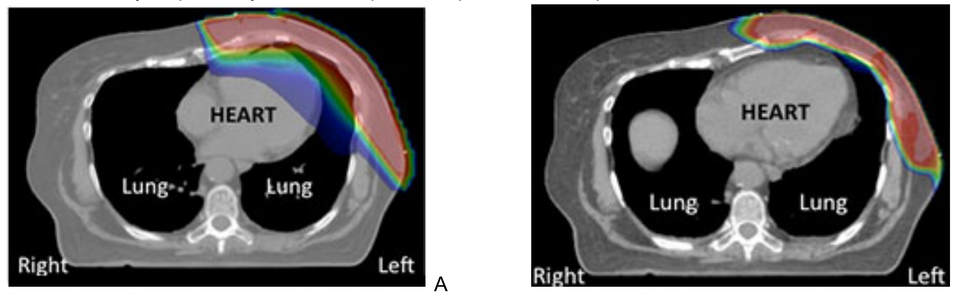

Figure 1 . Comparison of breast cancer radiation treatment plans using electrons/photons versus protons. [A] is an RT plan using a medial electron field matched to narrow photon tangents and [B] is a plan using proton therapy. The color overlay represents the spatial dose distribution with red indicating the prescription dose of 50 Gy. Both plans are designed to irradiate the chest wall and regional and internal mammary lymph nodes. Through the unique property of the proton Bragg peak, the proton treatment plan results in less volume of the heart exposed to radiation.

STUDY HYPOTHESES : (1) pre-symptomatic decline in global left-ventricular (LV) function can be quantified using careful analysis of cardiac magnetic resonance images (CMRI); (2) the decline in LV ejection fraction (LVEF) correlates with heart dose; and (3) proton therapy preserves cardiac function better than X-ray therapy as measured by change in LVEF.

II. METHODOLOGY

IMAGE ACQUISITION

CMRI were acquired at 8-10 time points over the systolic phase of the cardiac cycle using True-FISP in patients with left-sided BC under an approved protocol. CMRI were acquired before and 6-12 months after completion of RT. **(Figure 1)**

HEART LEFT VENTRICULAR VOLUME AND EJECTION FRACTION COMPUTATION

An in-house semi-automatic snake-based segmentation program was used to gather geometric information and a conformal 3D mathematical model of the LV endocardial surface was generated at each time frame. The LV cavity volume (LVV) at each cardiac phase was computed numerically from the 3D surface model. **(Figure 2D).** The LVEF was then calculated as:

$$\textbf{Left Ventricular Ejection Fraction (LVEF)} = \frac{\text{End Diastolic Volume} - \text{End Systolic Volume}}{\text{End Diastolic Volume}} \qquad \textbf{Eqn. 1}$$

Three investigators performed the segmentation and LVEF computation process independently, with each investigator blinded to the type of therapy each patient received and to the findings of the other investigators.

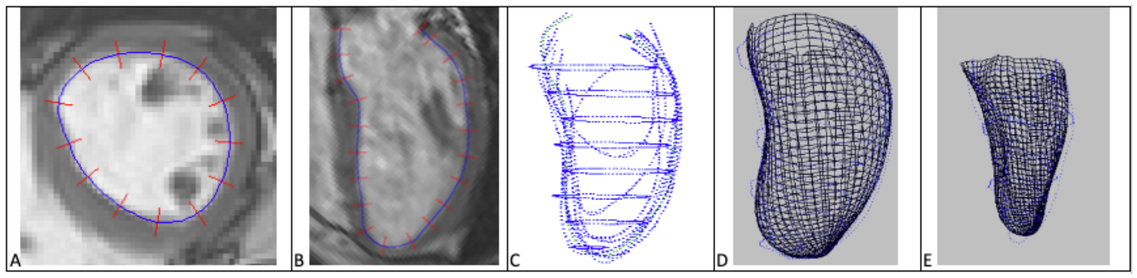

Figure 2. Anatomical cardiac MR Images, border segmentation, and surface fitting: [A] and [B] show representative short- and long-axis anatomical True-FISP CMR images in a breast cancer patient, prior to radiation, overlaid with endocardial contours (blue curves and red slashes) generated semi-automatically using our in-house interactive 'snake' software. [C] shows the combined contours from all slices and views at end-diastole. [D] & [E] show endocardial surface meshes generated from fitting the contour data to 3D surface models at end-diastole and end-systole, respectively, in the same patient and at same size scale. These figures illustrate the ability to model the convoluted LV endocardial surface, and to account for large changes in LV cavity volume.

MEAN HEART DOSE VS LVEF

The mean heart dose (MHD) was extracted from the treatment planning systems and correlated with the LVEF changes for each patient. Protons delivered lower average MHDs (0.3 +/- 0.2 Gy RBE) than X-rays (4.1 +/- 1.1 Gy). The % volume of heart tissue receiving >= 5 Gy (V5) was also lower with PT (14.2 +/- 9.9%) versus X-ray RT(1.5 +/- 1.1%): p value of 0.01.

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III. RESULTS

X-RAY RT VS PROTON THERAPY LVEF QUANTIFICATION

The 3D LV surface modeling approach has been shown to have LVV error < 2.5% and LVEF error < 4% for physiological heart filling/ejection in a canine heart preparation[5]. The trend of progression of LVEF change (either increased/decreased) with respect to the type of therapy received by the patients was consistent among the three blinded investigators.

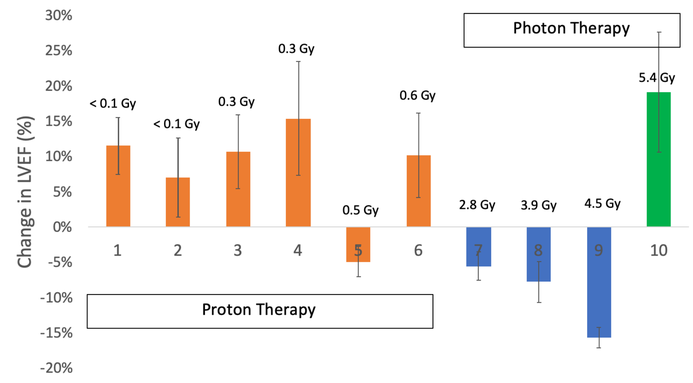

Figure 3 . Plot of LVEF percent change in breast cancer patients treated with proton vs X-ray therapy:

This figure shows the plots of percent change in LVEF pre and post radiation therapy. The first six bar graphs in orange represent patients who received protons and the other four in blue and green represent patients who received X-ray RT. The mean heart dose is indicated on top of each bar graph. The green bar graph represents the patient who had highest MHD and received a beta-blocker post-radiation due to indications of heart failure; the improved LVEF post-radiation is attributed to this medical intervention. The average % LVEF change was +8.28 ± 5.23% and -9.65± 2.14%. for the proton and X-ray RT cohorts, respectively

MEAN HEART DOSE VS LVEF

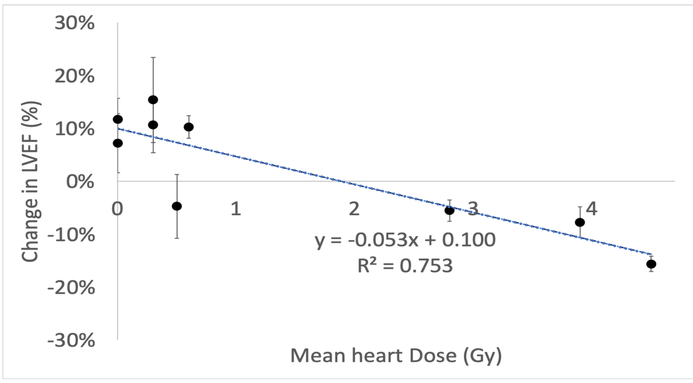

Figure 4. Plot of Mean Heart Dose vs Ejection Fraction percent change:

This figure illustrates the plot of mean heart dose (MHD) vs %LVEF change. A correlation coefficient of -0.87 confirmed the hypothesis that incidence of cardiac injury is directly proportional to the radiation dose. The dashed line shows the fitted regression line with the goodness of fit being close to 75%. The extrapolation to 0 Gy shows a ~10% increase in LVEF that is hypothesized to result from recovery from chemotherapy-induced LVEF reduction at our baseline scan. This figure illustrates that with every increase in 1-Gy mean heart dose, there is a decline in LVEF of ~5%, starting from 10% increase at 0 Gy.

STATISTICAL ANALYSIS

A repeated measures ANOVA showed that the LVEF change pre- to post-therapy was significantly ($p = 0.006$) different between the two treatment cohorts while the effect of inter-user variability in contour measurements was not ($p = 0.267$).

A one-way ANOVA revealed that, while the MHD and V5 were significantly different [p value of $0.01 < 0.05$ (α)] between the two cohorts, the patient ages and time-interval to follow-up were not. [p value of $0.10 > 0.05$ (α)]

A Fisher's exact test revealed no significant differences in the use of doxorubicin, BMI, smoking history, or prior cardiac history between the two cohorts. [p value of $0.10 > 0.05$ (α)]

III. DISCUSSION & CONCLUSIONS

- For every 1 Gy increase in mean heart dose, LVEF at 6-12 months post-RT decrease by ~5%.
- Proton therapy preserved ED global cardiac function (LVEF) better than conventional X-ray therapy, with the majority of PT patients experiencing improvement in LVEF at 6-12 months post-RT (from baseline being post-chemotherapy).
- CMRI and 3D conformal surface modeling can identify significant changes in sub-clinical heart function at early time points.

- These analysis techniques are hoped to enable the field to address several key clinical questions, including:
  - ❑ Does PT improve the therapeutic ratio of breast cancer RT via reduction the severity of long-term cardiac toxicity?
  - ❑ Can we predict which breast cancer patients before treatment who are at an elevated risk for cardiac toxicity and may benefit from proton therapy, altered RT, or pre-treatment administration of mitigating agents?
  - ❑ What is the optimal role for CMRI in routine follow-up care of breast cancer patients for sub-clinical cardiac toxicity?

IV. REFERENCES

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