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TITLE
Determining radiation-induced subclinical cardiac toxicity in left sided breast cancer patients using pre- and post-
treatment magnetic resonance imaging

HYPOTHESIS:
Our hypothesis is that cardiac magnetic resonance (CMR) images can be used to quantify subclinical changes in heart
function and regional myocardial strains in breast cancer patients who received radiation therapy (RT) to the chest wall
and axilla. Our goal is to establish whether early detection of cardiac radiation injury could be beneficial for follow-up
management of cancer patients, and determine whether proton therapy decreases the severity of cardiac toxicity
compared with standard X-ray based radiation therapy.

BACKGROUND/AIMS:
Systemic therapy with large-field radiotherapy (RT) to the chest wall and lymph nodes in the mediastinum and axilla
yields a substantial survival benefit but can result in inadvertent exposure of large volumes of normal tissues to low
and moderate doses of radiation. Recent studies have shown a 27% increase in lifetime risk for adverse cardiac
events in breast cancer patients who receive RT. Moreover, left-sided breast cancer patients who receive RT to the
chest wall have a 4-fold higher risk of adverse cardiac events than patients with right-sided breast cancer. We
developed and implemented methodologies to accurately measure left ventricular volume and ejection fraction from
standard anatomical CMRI, and to quantify regional myocardial mechanical strains from CMRI with cardiac tagging.
These tools were applied in a cohort of left-sided breast cancer patients to correlate global and regional subclinical
heart injury with regional radiation exposure.

METHODS: CMR images were acquired at 8-10 time-frames over the systolic phase of the cardiac cycle in patients
with left-sided breast cancer under protocol UFPTI 1419-BR02. 8-10 short- and long-axis views were acquired before
and 6 to 12 months after completion of RT. Contrast-enhanced images were obtained to assess left ventricular volume
and ejection fraction. Parallel-tagging images were acquired for wall strain analysis. An in-house semi-automatic
snake-based contouring toolkit was used to segment the left ventricular (LV) endocardial and epicardial borders on
each image slice and time frame (Fig. 2A-C). Mathematical models for each surface were defined in a prolate
spheroidal coordinate system. A novel deformable image registration approach was used to de-warp the heart from
the follow-up time frame back to the reference time point when the tags were generated. A 3-D mesh of myocardial
material points was defined around the LV at which the 3-D Lagrangian strain tensor and a wall thickening parameter
were computed. Finally, the 3D dose field, defined on the RT planning CT images, was mapped onto the MR-based
heart volume to associated regional wall dose with changes in regional mechanical strains.

RESULTS & CONCLUSIONS
We have developed tools to accurately quantify LV volume and ejection fraction, and regional heart wall function to
assess sub-clinical cardiac toxicity in breast cancer patients. A significant decrease in LV ejection fraction at 6-12
months post-RT was found in patients receiving conventional X-ray therapy compared with proton therapy. A
significant decrease in magnitude of mean mid-wall circumferential strain and thickening strain at 12-months post-RT
were found in a patient who received conventional RT (p < 0.05). These initial results suggest that sub-clinical
changes in cardiac function are present and measurable in breast cancer patients, and that proton therapy is
associated with a reduction in cardiac injury. These findings are hoped to motivate and precipitate the application of
these tools to address key clinical questions such as whether proton therapy substantially reduces the severity of
radiation toxicity to the heart compared with conventional RT and whether there a role for cardiac imaging in routine
clinical follow-up care of breast cancer patients for management of cardiac toxicity.