Assessing Acute Cardiac Inflammation One Month after Left-sided Breast Cancer Radiotherapy with Hybrid PET/MRI

Oi Wai Chau (ochau@uwo.ca)
London Regional Cancer Program https://orcid.org/0000-0002-1127-4504
Ali Islam
Lawson Health Research Institute
Michael Lock
London Regional Cancer Program
Edward Yu
London Regional Cancer Program
Robert Dinniwell
London Regional Cancer Program
Brian Yaremko
London Regional Cancer Program
Muriel Brackstone
London Health Sciences Centre
William Pavlosky
Lawson Health Research Institute
John Butler
Lawson Health Research Institute
Heather Biernaski
Lawson Health Research Institute
Michael Kovacs
Lawson Health Research Institute
Chantelle Graf
Lawson Health Research Institute
Gerald Wisenberg
Lawson Health Research Institute
Frank S Prato
Lawson Health Research Institute
Stewart Gaede
London Regional Cancer Program

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Abstract

Purpose: To investigate the utility of hybrid ^{18}FDG-PET/MRI and serial blood work to detect early inflammatory response and cardiac functionality changes at one-month post-radiation therapy (RT) in patients with left-sided breast cancer.

Methods: Fifteen left-sided breast cancer patients enrolled in the RICT-BREAST study underwent hybrid PET/MRI cardiac imaging at baseline and one-month after standard RT. Eleven patients received deep-inspiration breath-hold RT, while others received free-breathing RT. A list-mode ^{18}FDG/PET scan with glucose suppression was acquired. Myocardial inflammation was quantified by the change of mean ^{18}FDG standard uptake and analyzed based on the coronary vascular territory (left anterior descending (LAD), left circumflex or right coronary artery).

MR assessments, including LV functional and extracellular volume matrices (ECV), were extracted from T1 (pre and during-constant infusion of gadolinium) and cine images, respectively, acquired simultaneously during PET acquisition. Cardiac injury and inflammation biomarker measurements of hs-TnT, hs-CRP and erythrocyte sedimentation rate were compared at the 1-month follow-up in this study.

Results: At one-month follow-up, a significant increase (10%) of ^{18}FDG/PET myocardial uptake (meanSUV_{bw}) in LAD segments ($p=0.04$) and ECV in slices at the apex (6%) and base (5%) were detected ($p \leq 0.02$). Further, a significant reduction of LV stroke volume (-7%) was seen ($p < 0.02$). No significant changes in all circulating biomarkers at follow-up were shown.

Conclusions: ^{18}FDG/PET myocardial uptake and functional MR, including SV and ECV were sensitive to changes at one-month after breast cancer RT with findings suggesting an acute cardiac inflammatory response which is an important cardiotoxicity surrogate to RT.

The clinical pilot study (NCT03748030, November 16, 2018) was approved by the Western University Human Research Ethics Board (HSREB ID 112991), funded by Lawson Strategic Research Fund (R19-292).

Introduction

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer death in females worldwide [1]. Adjuvant radiation therapy (RT) of the breast plays a critical role in curative breast cancer management with local and regional control benefits and lower mortality rates [2]. However, patients with left-sided breast cancer are at an increased risk of radiation-related cardiac disease [3] [4], with an increase in the risk for undergoing percutaneous coronary intervention [5] and cardiac mortality [6], due to the proximity of the heart to the irradiated breast.

A worldwide systematic review on whole breast RT studies after 2014 reported that the heart received a mean of 3.6 Gy heart dose based on 84 left-sided breast cancer studies [7]. The left anterior descending

artery (LAD), however, had a substantially higher dose compared to the whole heart, with a mean dose of 12.4 Gy [7]. A linear relationship between major coronary events and mean heart dose from 2D-breast RT without a threshold, of 7.4% per Gy was also reported in a population-based case-control study [8]. However, the early effects of radiation are not well understood and the clinical symptoms do not typically manifest until 10–15 years after RT. It is therefore important to limit the exposure of the heart to ionizing radiation during RT to limit the development of cardiac sequelae.

A previous pre-clinical study of five canines imaged with hybrid ^{18}FDG/PET showed a progressive global inflammatory response during the initial year following RT [9]. ^{18}FDG/PET can identify an inflammatory reaction, as the activated proinflammatory macrophages preferentially sequester glucose. The increased inflammatory signal uptake was detected as early as one-week post single fraction irradiation of a biologically equivalent LAD dose compared to a standard left breast RT under breath-hold condition [9]. The dose delivered to the whole heart and other coronary arteries were likewise the typical values observed in left breast RT [7]. Immunohistochemistry (CD45) at 12-months confirmed the presence of inflammatory cells [9].

If inflammation occurs early, preceding but predictive of subsequent cardiac manifestations, then there may be a role for early treatment with anti-inflammatory and/or cardio-protective medication. With the use of multimodality imaging including hybrid positron emission tomography (PET) and magnetic resonance imaging (MRI), simultaneous acquisition over the same anatomical site allows assessment of acute cardiac inflammation and early cardiac irradiation functional changes non-invasively and longitudinally after RT. For optimal ^{18}FDG/PET assessment of the cardiac inflammatory response, suppressing the normal myocardial uptake of ^{18}FDG is required [10].

Functional MR imaging including cine imaging assesses left ventricular function throughout the cardiac cycle with a short breath-hold of about 15 seconds. It is considered the gold standard for quantifying left ventricular ejection fraction (LVEF), end-diastolic volume (LVEDV) and end-systolic volumes (LVESV) [11]. In addition, T1-mapping has the ability to detect pre-clinical myocardial fibrosis. The combination of pre- and post-contrast T1 maps can give a measure of the extracellular volume (ECV), where an increase relates to myocardial fibrosis and correlates to an increasing likelihood of cardiac events [12]. The optimal means of quantifying ECV is during a slow constant infusion of a gadolinium tracer, where a constant concentration of a tracer is supplied to the myocardium during the capture of 3D T1 maps [13]. Lastly, T2 relaxation rate increases correlate with an increase in extracellular water, i.e., edema.

Serial blood work such as high-sensitivity Troponin T (hs-TnT), high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) are the common surrogate markers of myocardial injury and inflammation. Hs-TnT level has great diagnostic accuracy in detecting acute myocardial infarction [14]. Meanwhile, hs-CRP with a level greater than 3 mg/L is associated with higher cardiovascular risk [15]. ESR can identify acute inflammation by measuring the plasma viscosity [16]. These biomarkers can provide subclinical evidence of cardiotoxicity during RT.

Aim

In this study, we investigate the utility of hybrid PET/MRI and serial blood work to detect an early inflammatory response/cardiac functionality changes after radiation therapy in patients with left-sided breast RT.

Methods

Radiation Treatment and delivery

The clinical pilot study (NCT03748030) was approved by the Western University Human Research Ethics Board (HSREB ID 112991). Of 17 recruited left-sided breast cancer patients, stage T0-T3, one patient was ineligible, and one did not consent. All patients did not have a prior cardiac disease history and one patient was diagnosed with diabetes mellitus. None of the patients received any prior RT to the thorax or breast.

Patients in the study received their RT during 2020–2021. The majority of patients (73%) received standard deep inspiration breath-hold (DIBH) forward planned intensity-modulated radiotherapy (IMRT), 42.5 Gy in 16 fractions and did not receive adjuvant chemotherapy (67%). 7 of the 11 DIBH RT patients received additional boost doses of 10 Gy in 5 fractions. One patient only completed the first five fractions of her radiation treatment and discontinued due to breast swelling, pain and erythema.

Fifteen left-sided breast cancer patients treatment plans were retrospectively reviewed. Treatment planning optimization was performed using the Pinnacle^3 treatment planning system (Philips Radiation Oncology Systems, Fitchburg, USA). Contours of the heart, left ventricle (LV), and left anterior descending artery (LAD) were manually delineated on the treatment planning CT performed on the Philips Brilliance Big Bore CT scanner (Philips Medical Systems) using Mim maestro (Mim Software Inc., Cleveland, USA). The mean values for each dose metrics are shown in table 1. Note that this cohort of patients received a low dose in the reported cardiac regions.

Imaging

PET/MR imaging was performed on a 3T-hybrid PET/MRI scanner (Biograph mMR Siemens Medical Systems, Malvern, USA) prior with serial blood work drawn at baseline, within 1-month and within 1-year following the completion of RT. Patients were imaged in the supine position. In this paper, we are reporting the results at 1-month follow-up.

PET imaging (Myocardial inflammation)

The suppression of glycolysis was achieved through fasting (12 hours prior imaging) and a 24-hour diet which was high in fat, low in carbohydrate and low in protein prior to the PET scan. Furthermore, the

injection of heparin at 45 minutes (5 μg/kg) and 30 minutes (10 μg/kg) was performed prior to the injection of ^{18}FDG. A 60-minute list-mode scan of ^{18}FDG with a bolus injection at 5 MBq/kg was conducted. All PET data were reconstructed using an iterative three-dimensional ordered subset expectation maximization algorithm (OSEM) [17] with 3 iterations, 21 subsets, 10-minutes intervals, 172 x 172 x 127 matrix size and a 4 mm-Gaussian smoothing filter, yielding a voxel size of 2.08 x 2.08 x 2.03 mm. Attenuation was corrected for all PET scans using a two-point Dixon MR imaging pulse sequence (MRAC), which automatically segments and substitutes discrete attenuation coefficients of the lung, adipose tissue and soft tissue [18]. Myocardial contours were manually delineated on the PET images fused with the MRAC images using Mim maestro, according to the American Heart Association 16-segment model [19].

Myocardial inflammation was assessed using the change from the baseline pre-radiation treatment study in the mean ^{18}FDG/PET standard uptake based on body weight (meanSUV_{bw}) in the myocardial tissue between 40–60 minutes post tracer injection. SUV at 1-month follow-up compared to baseline was calculated where the change was segmented based on each coronary vascular territory: left anterior descending (LAD), left-circumflex (LCX) or right coronary (RC) artery.

Mr Imaging

T2-weighted images of the heart using 3 slice locations (apex, mid and base) were acquired concurrently with PET imaging using TrueFISP 2D sequence with 224.03 ms repetition time, 1.31 ms echo time, flip angle: 60, FOV matrix of 288 x 360 and slice thickness of 6 mm.

The T2-weighted images were followed by a 2D stack of standard non-contrast steady state free precession cine images and T1-weighted images of the whole heart before and during a gadolinium contrast (Gadovist; Bayer Inc, Mississauga, ON) infusion. The cine images were acquired using TrueFISP sequence, flip angle: 50, 43.5 ms repetition time, 1.58 ms echo time, FOV matrix = 253 x 300, and a slice thickness of 6 mm.

The gadolinium contrast was injected as a bolus over 2 minutes (0.1 mmol/kg) and then followed by a constant infusion over 30 minutes 0.002 mmol/kg/min). The T1-weighted post gadolinium constant infusion images were acquired 10 minutes into the constant infusion. Both sets of T1-weighted images were acquired using the MOLLI sequence with 293.92 ms repetition time, 1.22 ms echo time, flip angle: 35, FOV matrix = 255 x 300 and slice thickness 6 mm.

Circle CVI42 v5.11 (Circle Cardiovascular Inc., Calgary, Canada) was used to assess cardiac function, including LV functional parameters (LVEDV, SV and LVEF) and a radiologist (AI) provided clinical assessment of the T2-weighted and T1-weighted post-contrast images. The extracellular volumes (ECV) were calculated using Eq. (1) with the extraction of T1 values of the blood pool and the myocardium between pre- and during- constant infusion, grouped based into three slices locations (apex, mid and basal). The hematocrit ratio was determined from the blood sample.

$$(1)\ ECV = (1 - hematocritratio)\left(\frac{\frac{1}{PostcontrastT1myocardium} - \frac{1}{nativeT1myocardium}}{\frac{1}{PostcontrastT1LVbloodpool} - \frac{1}{nativeT1LVbloodpool}}\right)$$

Bloodwork

Blood for the parameters noted earlier were drawn prior to the baseline pre-radiation scan and measured at 1-month follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS IBM v.23 (IBM SPSS Statistics for Windows, Armonk, NY). Shapiro-Wilk normality test was utilized to check for normality among the values of standard uptake of ^{18}FDG per supplied coronary region, left ventricular functional parameters, blood work and ECV measurements before and 1-month after RT. Based on the Shapiro-Wilk test, all the blood work measurements (hs-TnT, hs-CRP and ESR) were not normally distributed ($p < 0.03$). Consequently, tests of significance for these parameters were performed using the Wilcoxon signed rank test. A Paired t-test was performed for all other parameters. A bivariate correlation test was performed to compare these changes to relevant dosimetric parameters of the heart and substructures presented in table 1.

Dosimetric parameters of the heart and its substructures were tested for significance between the DIBH and free-breathing-RT group using Mann-Whitney U test. If any of the changes of the ^{18}FDG regional uptake, LV functional parameters, blood work and ECV measurements were significant at follow-up, Mann-Whitney U test was further performed to check for significance between the DIBH and Free-breathing-RT group.

Results

Table.1 Patient demographics of fifteen left-sided breast cancer patients along with the radiation dose metrics of the heart, left ventricle and the left anterior descending artery. the mean value is indicated with *

Age of patients n = 15	*60y/o (38–79)
Staging	3
T_{CIS}	8 (1 recurrence BC)
T1	3
T2	1
T3	
Radiation Treatment (RT)	4 (27%)
Free-breathing RT	2
Tomotherapy	1
IMRT	1
VMAT	11 (73%)
DIBH IMRT	
Prescription dose	14
42.5 Gy in 16 fractions	7
With 10 Gy in 5 fractions boost	1
48 Gy in 16 fractions	
Mean Heart Dose	*1.79 Gy
Mean LV Dose	*2.07 Gy
Mean LAD dose	*2.78 Gy
$V5_{Gy}$ Heart	*9.46%
Max Heart Dose	*1.96 Gy
Max LAD dose	*8.41 Gy
Adjuvant chemotherapy	5 (33%)
Yes	4
Herceptin	10 (67%)
No	

Patient demographics of the observational study are shown in table 1. Results of regional uptake of ^{18}FDG/PET, LV functional parameters, ECV and blood work measurements are presented in Figs. 2–4. A significant increase in the ^{18}FDG/PET mean standard uptake (meanSUVbw) in the LAD territory (p = 0.04, 10%) was seen in average across patients (9 of the 10 patients) at 1-month follow-up. A non-

significant correlation was observed between the increase of ^{18}FDG/PET uptake in the LAD territory and the (mean and max) LAD dose metrics with a r-value range of − 0.23 to − 0.24, $p > 0.5$. A non-significant correlation was observed with the heart dose metrics (mean heart dose and $V5_{Gy}$Heart) with a r-value of 0.12–0.17, $p > 0.6$ (see table 2). The SV was significantly reduced ($p < 0.02$, 7%, 9 of 12 patients) at 1-month follow-up while LVEDV and LVEF were not significantly changed ($p > 0.08$) The majority of the LV functional parameters were within the normal range, except one patient who had borderline LV dilation [20]. The reduction in SV was insignificantly correlated to all the heart and substructure dose metrics (r-value of 0.14–0.27, $p > 0.27$). In addition, a significant increase for ECV in apex and basal slices were identified ($p \leq 0.02$ by 6%, 10 of 12 patients and 5%, 11 of 12 patients), while no significant change of ECV was observed for mid slices of the heart ($p > 0.5$). The ECV in apex and basal slice locations were weak to moderately correlated to all the heart, LV and LAD dose metrics (r-value of 0.19–0.57).

No significant changes ($p > 0.3$) of all blood work (hs-TnT, hs-CRP, ESR) measurements were reported. No gross abnormal enhancement, fibrosis or edema measured with T1- and T2-weighted images at both baseline and 1-month follow-up were detected. One patient had borderline LV dilation at 1-month follow-up.

For dose metrics, only the mean heart dose ($p = 0.04$) was significantly higher in free-breathing RT compared to DIBH RT patients. Maximum heart and LAD dose, $V5_{Gy}$Heart, mean LV and LAD dose were insignificant ($p \geq 0.06$). Changes of ^{18}FDG/PET uptake at the LAD territory, SV, ECV in apex and basal slices were not different ($p \geq 0.2$) between RT groups.

Table.2 Presented are the mean values of ^{18}FDG/PET standard uptake of the myocardium based on body weight (SUVbw) sorted according to the respective supplying coronary arteries using the AHA heart model, LV functional parameters (EDV, SV and EF), extracellular volume matrix values (at apex, mid and basal slice locations of the heart) and blood work measurements of high-sensitivity Troponin-T, high-sensitivity C-reactive protein and erythrocyte sedimentation rate at baseline and 1-month follow-up. The percentage comparing baseline and 1-month follow-up change of each respective measurement were reported.

N = 15		LCX	LAD	RC
^{18}FDG/PET meanSUVbw	baseline	1.52	1.47	1.61
	1-month follow-up	1.62	1.61	1.67
	% change	6%	10%	4%
		EDV (ml)	**SV (ml)**	**EF (%)**
Mean values of LV functional parameters	baseline	123	79.27	65.4
	1-month follow-up	115.92	74	64.25
	% change	-6%	-7%	-2%
		Apex	**Mid**	**Base**
Mean extracellular volume (ECV)	baseline	0.289	0.271	0.268
	1-month follow-up	0.307	0.275	0.279
	% change	6%	3%	5%
		hs-TnT (ng/L)	**hs-CRP (mg/L)**	**ESR (mm/h)**
Mean value of Blood Work measurements	baseline	10	3.39	12.64
	1-month follow-up	7.92	2.53	11.42
	% change	-21%	-25%	-10%

Table.3 Pearson bivariate correlation coefficient r-values and p-values between the changes of ^{18}FDG/PET standard uptake value in LAD supplied myocardial segments, stroke volume and extracellular volume matrices at apex and basal slices compared to the heart and substructure dose metrics.

Change of parameter		mean Heart dose	mean LV dose	mean LAD dose	$V5_{Gy}$ Heart	max Heart dose	max LAD dose
^{18}FDG LAD	r-value	0.12	0.04	-0.23	0.17	0.07	-0.24
	p-value	0.74	0.91	0.53	0.63	0.85	0.51
SV	r-value	0.25	0.32	0.22	0.21	0.14	0.37
	p-value	0.46	0.34	0.52	0.53	0.69	0.27
ECV apex	r-value	0.34	0.38	0.19	0.30	0.36	0.33
	p-value	0.28	0.22	0.55	0.35	0.26	0.30
ECV base	r-value	0.44	0.44	0.57	0.41	0.41	0.55
	p-value	0.17	0.18	0.07	0.21	0.21	0.08

Discussion

Currently, dose-sparing guidelines for cardiac substructures are not well established in breast RT. In terms of the whole heart, consensus guidelines recommend that the volume of the heart irradiated should be minimized as much as possible without compromising the breast target coverage. Quantitative Analyses of Normal Tissue Effects in Clinic (QUANTEC) recommended limiting the volume of heart receiving at least 25 Gy ($V25_{Gy}$) less than 10% to maintain the risk of cardiac mortality under 1% [21]. In our study, the cardiac dose values among patients were lower than the QUANTEC guideline with a mean whole heart $V5_{Gy}$ of 9.46%. However, it is important to note that the LAD and LV can still receive a substantially higher dose than the remainder of the heart structures [7]. The mean LAD dose in our study was 2.78 Gy, which was recognized as a high regional dose region compared to the overall heart (mean heart dose of 1.79 Gy, see table 1).

While cardiac risk reduction strategies including the role of active breathing modalities [22], patient positioning [23] [24], or accelerated partial breast irradiation [25] are discussed, few efforts in randomized controlled trials have validated the cardiac-sparing techniques or looked into the cardiac substructure early response to radiation in breast RT. In exploring differences that three patients received a higher mean heart dose in free-breathing RT, but no differences in other dosimetric parameters of the heart and its substructures, this may have implications that DIBH RT can achieve better sparing in terms of the

whole heart compared to free-breathing RT. With the use of hybrid PET/MRI, the significantly elevated uptake of ^{18}FDG/PET in LAD segments along with the increase of ECV in apical and basal slices with a reduction of SV suggested acute regional inflammation/functional changes in the myocardium as early as 1-month after the end of RT. It is important to note that the changes were observed in patients even with low dose myocardial irradiation compared to the recommended guidelines regardless of breath-hold techniques.

Jo et al. [26] conducted a retrospective study evaluating the irradiated myocardium segmented based on dose threshold in both the staging and post-RT PET/CT images of breast cancer patients who underwent 3D-CRT. The ^{18}FDG/PET uptake of the myocardium irradiated with more than 30 Gy significantly increased after RT even at the one-year follow-up. The degree of ^{18}FDG/PET uptake increase significantly correlated with the radiation dose to the myocardium. However, glucose suppression was not performed. In our study, where glucose was suppressed and the radiated dose to the myocardium was low, the ^{18}FDG/PET uptake increase in the LAD segments was weakly correlated to the whole heart dose metrics. Also of note, the myocardium was segmented according to the AHA heart model, which can provide better location of the radiosensitive substructure of the heart, i.e. the LAD myocardial segments.

In terms of MR functional parameters, our study demonstrated a significant reduction of SV at 1-month follow-up, no significant changes were shown in LVEDV and LVEF. This corresponds to the results of a systematic review conducted by Kaidar-Person et al. [27], which reported five out of six studies without LVEF reduction using SPECT imaging at 6-months follow-up and four studies with perfusion defects. Bergom et al. [28] evaluated ECV and LV functional parameters in a pilot study of breast cancer patients who received 3D-CRT and adjuvant anthracycline-based chemotherapy using cardiac MR and did not report any clinically abnormal findings at a median follow-up of 8.3 years post RT. No evidence of increased ECV with increasing heart or ventricular radiation doses was reported, [28] in contrary to our study which identified a weak to moderate correlation between the increase of ECV (at apex and basal slice locations) and the heart and substructure metrics. However, this study only performed a median long-term follow-up scan; hence, the changes in the LV functional parameters and ECV were not determined. Without measurements performed prior to 6 months, any early postulated effects of radiation on myocardial metabolism are purely conjecture.

Limitations of our study reported here include two patients had insufficient glucose suppression in their baseline ^{18}FDG/PET scan and two patients did not complete the one-month post-RT imaging. However, in the literature, it is reported that five percent of the time the suppression fails even under the best diet and fasting protocols [29]. The sample size of patients between breath-hold and free-breathing RT techniques was small; hence, in future a larger sample size is needed to increase the power of comparison of early cardiac response between RT techniques.

It is unlikely that the 70-minute hybrid PET/MRI protocol used in our study would be routinely used for patient management. Furthermore, it is noted that within 1-month post-RT, none of the patients have had clinically significant cardiac events, and therefore, we do not recommend that these findings influence

present clinical practice. However, scar could manifest at a later stage, such that additional care to minimize the volume of cardiac substructure (LAD/LV) in the RT field and longitudinal follow-up are recommended. With patients returning for their 1-year post-RT imaging, longitudinal 1-year follow-up would increase the power to detect subsequent inflammation changes into cardiac sequelae such as progressive fibrosis or scar formation. Such evidence-based information can help establish guidelines to determine the need of cardiovascular risk assessment of patients prior to initiation of RT and long-term cardiovascular monitoring of breast cancer survivors, in addition to the modification of the cardiovascular risk-based RT regimen.

Conclusion

In summary, we were successfully able to detect a significant increase of ^{18}FDG/PET uptake in the myocardial territory of the LAD along with a significant increase of extracellular volume matrices at the apex and basal locations of the heart at 1-month following the end of left-sided breast cancer radiotherapy. This may be related to a significant decrease in the left ventricular stroke volume noted at follow-up. No significant changes in blood work measurements including Troponin T, high-sensitivity C-reactive protein and erythrocyte sedimentation rate were seen. Among the fifteen left-sided breast cancer patients, our pilot study demonstrated the feasibility of using hybrid PET/MR imaging to assess cardiac responses to radiotherapy as early as one month follow-up. Validation of these metrics in the prediction of radiation-induced cardiac disease in a larger cohort could prompt a change in management of left-sided breast cancer patients with early cardiac changes detected with non-invasive imaging.

Declarations

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Competing Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions

O-W.C., A.I, F.S.P and S.G. conceived and designed research; O-W.C., A.I, J.B., H.B., M.K., C.G. acquired and process the data; O-W.C., and A. I. analyzed data; O-W.C., A.I, M.L., J.B., G.W., F.S.P and S.G. interpreted

results of data; O-W.C prepared figures; O-W.C., and A.I. drafted manuscript; O-W.C., A.I., M.L, E.Y., M.B., G.W., F.S.P. and S.G. edited and revised manuscript; O-W.C., A.I., M.L, E.Y., R.D., B.Y., M.B., W.P., J.B., H.B., M.K., C.G., G.W., F.S.P and S.G approved final version of manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The clinical pilot study (NCT03748030**,** November 16, 2018) was approved by the Western University Human Research Ethics Board (HSREB ID 112991).

Consent to participate

Written informed consent was obtained from the parents.

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Figures

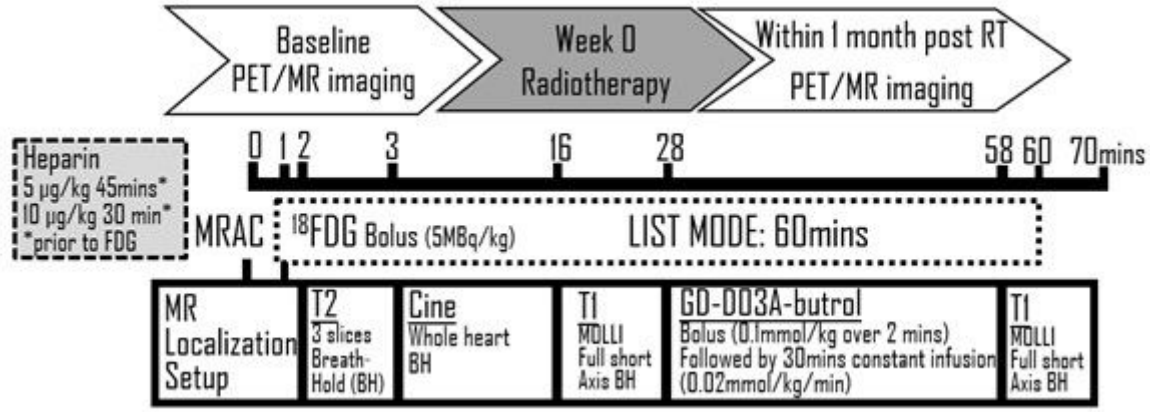

Figure 1

Overview of the timeline and hybrid PET/MR imaging protocol

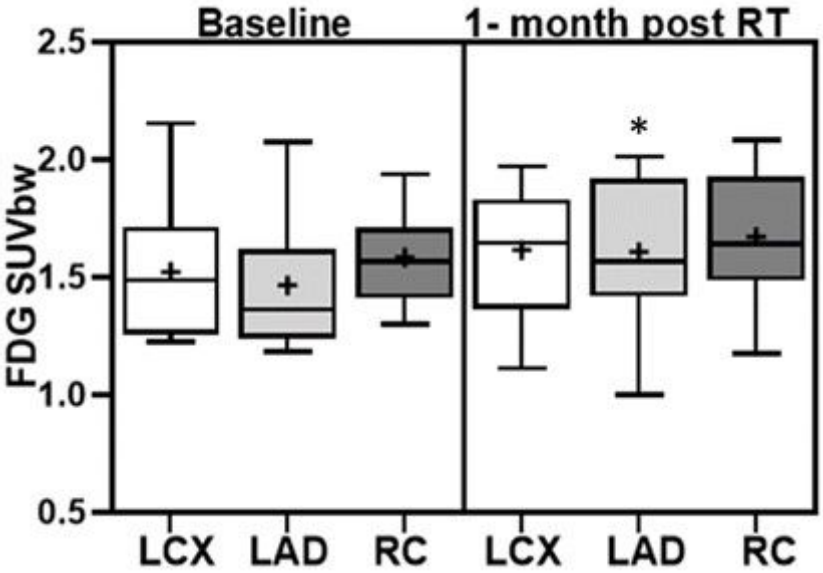

Figure 2

^{18}FDG/PET mean standard uptake values of the myocardium based on body weight (SUVbw) of fifteen patients at baseline and 1-month follow-up. The uptake values for the entire myocardium were broken down to regions supplied by the LAD, LCX and RC. Note the mean standard uptake value is indicated with ' + ' and the median value is indicated as the median bar in the boxplot, any significant differences at 1-month follow-up were marked with *

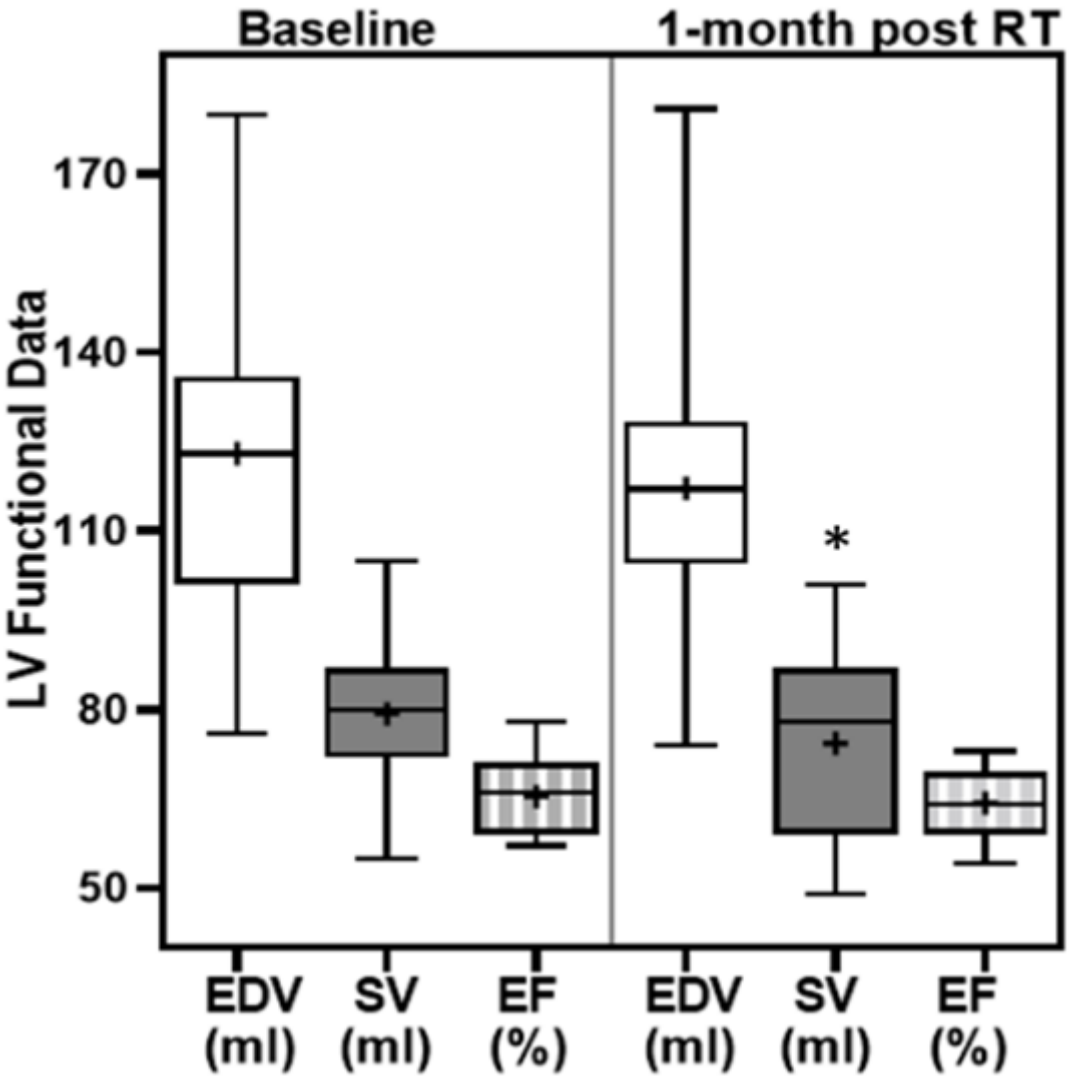

Figure 3

Mean cardiac functional parameters including the left ventricular end-diastolic volume (EDV), stroke volume (SV) and the left ventricular ejection fraction (EF) for the fifteen patients before and 1-month after radiotherapy. Significant reduction at 1-month post-RT was shown in SV

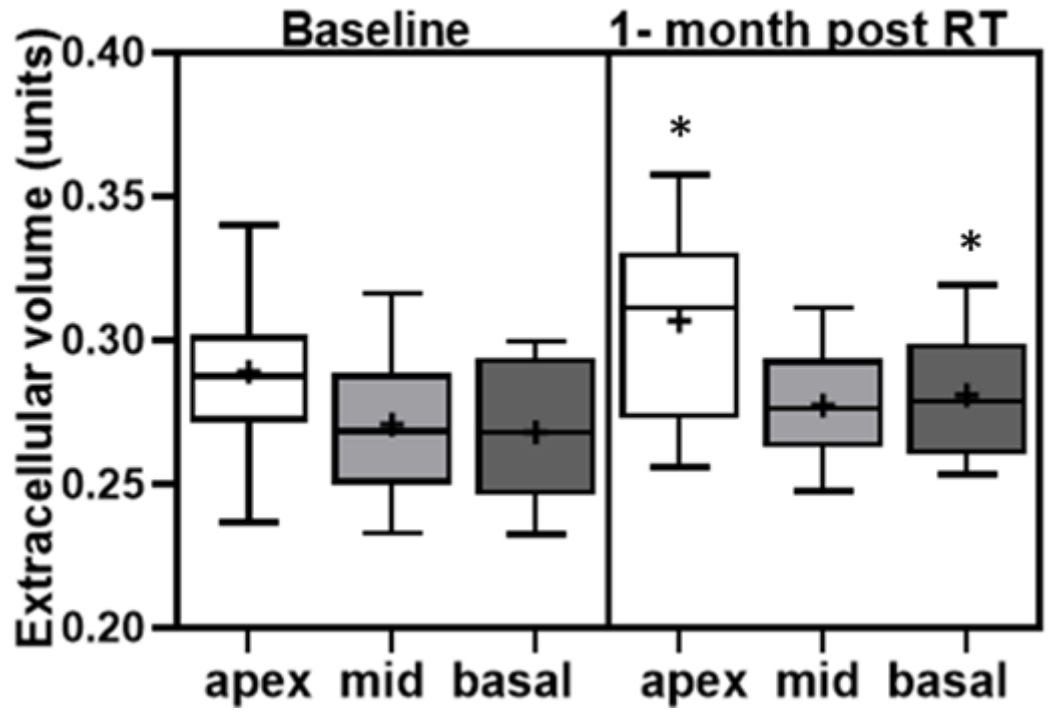

Figure 4

Mean Extracellular volume before and 1-month after radiotherapy.

Significant increases of ECV in apex and basal slices were observed at 1-month follow-up

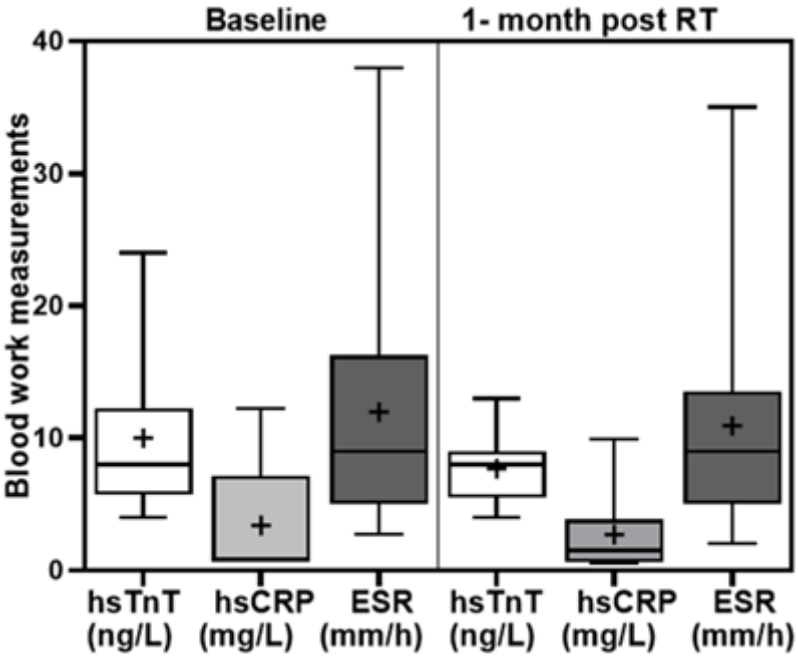

Figure 5

Presented are the mean blood work measurements of high-sensitivity Troponin T (hs-TnT) high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) before and 1-month after radiotherapy.