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BIOMARKERS OF CARDIAC INJURY IN PATIENTS UNDERGOING THORACIC RADIATION THERAPY

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Radiation therapy (RT) as part of the management for cancers of the chest is associated with increased dose-dependent risk of delayed-onset heart disease. This delay from RT symptoms has driven the interest in serum biomarkers as a way to detect subclinical cardiac damage at an earlier time point. High-sensitivity assays to detect plasma levels of cardiac troponin I (TnI) have been developed as biomarkers of acute myocardial injury. N-terminal probrain natriuretic peptide (NT-proBNP) is a useful biomarker for myocardial strain. Galectin-3 (Gal-3) is a beta-galactoside-binding lectin that appears to be a marker and mediator of cardiac fibrosis. We hypothesized that early damage to the myocardium could be detected during, and shortly after RT using hsTnI, NT-proBNP, and Gal-3 in patients undergoing thoracic RT for lung or breast cancer.

Patients undergoing clinically indicated RT, with or without chemotherapy, were enrolled in a prospective study in which blood samples were collected before and at different times after RT. Sixteen patients undergoing thoracic RT for lung and/or left-sided breast cancer with maximum heart radiation doses greater than 1,000 centigray (cGy) were included as the RT group. We also included 9 patients undergoing pelvic RT for prostate adenocarcinoma to serve as control without a measurable radiation dose to the heart. Biomarkers were assessed at baseline, after the first treatment, mid-point into the RT, at the end of the RT, and at 6 months follow up, when available. Missing data was not inputted.

Analysis of hsTnI and Gal-3 were performed on the Abbott Architect™ (Longford, Ireland). Immunoassay for the quantitative determination of NT-proBNP was performed using Roche reagents (Mannheim, Germany).

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The entire heart was contoured, including atria and ventricles, on the computerized tomography (CT) images used for planning RT delivery (Figure) and the total treatment max and mean heart doses were determined at time of each blood draw point so that temporal analyses could be performed. Frequencies are reported as N and %. Continuous data are expressed as medians and interquartile range for potential deviation from a Gaussian distribution. Non-paired and paired continuous data were compared using the Mann Whitney and the Wilcoxon non-parametric tests.

Individual patient characteristics are shown in the Table. Median age was 60 years in the thoracic and pelvic RT group. There were 7 males (44%) in the thoracic RT group and all patients in the pelvic RT group were male. In the thoracic group, 10 of the 16 patients had lung cancer (62%) with varying stages and histologies. The remaining 6 thoracic patients had left invasive ductal carcinoma (38%) with all but one having early stage disease.

Cardiac risk factor characteristics are shown in Table 1. There were no statistically significant differences between the two groups. Previous myocardial infarction had occurred in 3 patients (19%) receiving thoracic RT and 1 patient (11%) receiving pelvic RT (P=0.63).

Radiation therapy and cardiac dosimetry details are shown in Table 1.

Plasma samples were obtained for all 25 patients before RT. However, 8 follow up samples in 6 patients that were scheduled to be collected during RT were not obtained, and 8 of the 25 patients were not able to provide serum samples after RT.

In all 25 patients, the hsTnI levels were considered within normal limits (<30 ng/L), before, during and after RT. In the thoracic RT group (N=16), hsTnI levels were 3.5 [2.0–5.2] ng/L before RT, 4.0 [2.0–6.0] ng/L during RT, 3.5 [2.0–7.2] ng/L after RT, and 3.5 [1.5–5.6] ng/L 6 months later. There were no significant differences in hsTnI levels before RT and after RT at any follow up time point (all P>0.20). No increases in hsTnI levels were found with RT in the pelvic RT group (N=9) (all P>0.20)[Figure].

There were no significant changes in NT-proBNP in the thoracic RT group: 94 [28–312] pg/ml before RT, 126 [36–508] pg/ml during RT, 98 [23–210] pg/ml after RT, and 176 [33–297] pg/ml 6 months after RT (all P values >0.20). No significant changes in NT-proBNP were seen in the pelvic RT group (all P>0.20)[Figure].

In the thoracic RT group, Gal-3 levels did not change over time (all P>0.20). Gal-3 levels were 16.1 [11.8–19.2] ng/mL before RT, 16.4 [11.6–19.1] ng/mL during RT, 15.5 [11.5–19.0] ng/mL after RT, and 12.5 [8.3–12.5] ng/mL 6 months after (all P values >0.20). Similarly, no significant changes were seen in the pelvic RT group (all P values >0.20) [Figure].

In summary, the data shows that hsTnI, NT-proBNP and Gal-3 levels were all unchanged and not affected by thoracic RT (maximum heart dose up to 6,456 cGy), and not affected by pelvic RT.

Nellessen et al.¹ had reported data on 23 patients receiving large doses of radiation to the chest and reported a non-significant change in hsTnI from 5.0 ng/L to 7.5 ng/L (normal

value <30 ng/L after 6 weeks of radiation. Skyttä et al.² found that high sensitivity troponin T (hsTnT) levels were within the normal range and without significant change in 58 patients with early stage breast cancer undergoing adjuvant breast RT without prior chemotherapy. Hughes-Davies et al.³ measured TnT levels in 50 left-sided breast cancer patients being treated with adjuvant RT using and only 1 of the 50 patients before or after RT had TnT>20 ng/L. Kozak et al.⁴ quantified TnT 30 patients receiving thoracic RT and TnT was detectable (>10 ng/L) in only 1 of 30 patients. Lastly, Gomez et al.⁵ studied patients receiving RT >45 Gy to the thorax with a median heart dose of 2,590 cGy and only two patients had elevated TnI and BNP.

The lack of significant increase in troponin levels in our study is in contrast with the literature on subclinical cardiotoxicity seen with anthracyclines. Additionally, BNP monitoring during chemotherapy has been associated with early detection of diastolic dysfunction in lymphoma patients receiving doxorubicin.

The difference between the data obtained with chemotherapy vs RT suggests that the mechanisms of myocardial injury are different. Additional studies to identify measures of acute cardiac effects of radiation therapy, i.e. with imaging (echocardi-Doppler strain analysis or magnetic resonance imaging) are needed.

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Figure.

Radiation therapy treatment plans with prescription isodose lines are shown in a patient with left sided breast cancer (case 1) and in a patient with lung cancer (case 2). The overlap between the isodose lines and the heart contours represents the dose that the heart receives. Red indicates tumor. Purple lines indicate contour of the heart. Yellow lines indicate areas receiving 4500cGy. Turquoise lines indicate areas receiving 2500cGy. Dark blue lines indicate areas receiving 1000cGy. Cardiac biomarkers were measured before, during and after RT. Troponin I levels in patients undergoing thoracic RT (panel A) or pelvic RT (panel

D). NT-proBNP levels in patients undergoing thoracic RT (B) or pelvic RT (E). Galectin-3 levels in patients undergoing thoracic RT (C) or pelvic RT (F).

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Table 1

Characteristics of the patients

Patient	Site of Irradiation	Age	Gender	Radiation to the Heart (cGy)		Prior history of heart disease	Hypertension	Diabetes	Hyperlipidemia	Tobacco use
				Maximum Dose	Mean Dose					
#1	Thoracic	56	M	6,950	460	Y	Y	N	Y	Y
#2	Thoracic	65	M	1,410	129	Y	Y	Y	N	Y
#3	Thoracic	86	F	3,946	127	N	Y	N	Y	N
#4	Thoracic	55	F	2,674	101	N	N	N	N	Y
#5	Thoracic	56	F	3,879	92	N	Y	N	N	N
#6	Thoracic	60	F	2,258	343	N	N	N	N	N
#7	Thoracic	72	F	2,707	72	N	Y	Y	N	N
#8	Thoracic	55	F	6,709	1,040	N	N	N	N	N
#9	Thoracic	62	F	1,152	88	N	Y	N	N	N
#10	Thoracic	60	M	7,100	2,500	Y	Y	N	N	Y
#11	Thoracic	56	M	4,940	2,003	N	N	N	N	Y
#12	Thoracic	64	M	5,683	2,060	N	Y	N	N	Y
#13	Thoracic	81	F	7,265	866	N	Y	N	N	Y
#14	Thoracic	74	M	6,437	1,320	N	Y	Y	N	Y
#15	Thoracic	60	M	6,456	1,704	N	Y	N	N	Y
#16	Thoracic	49	F	7,409	2,084	N	N	N	N	Y
#17	Pelvic	57	M	0	0	N	Y	Y	N	N
#18	Pelvic	52	M	0	0	N	N	Y	N	N
#19	Pelvic	65	M	0	0	Y	Y	N	N	N
#20	Pelvic	75	M	0	0	N	N	Y	N	N
#21	Pelvic	68	M	0	0	N	Y	Y	N	N
#22	Pelvic	71	M	0	0	N	Y	Y	Y	N
#23	Pelvic	48	M	0	0	N	Y	Y	Y	N
#24	Pelvic	53	M	0	0	Y	N	Y	N	Y
#25	Pelvic	60	M	0	0	Y	Y	N	Y	N

Abbreviations: cGy – Centigray, F – Female, M – Male, N – No, Y – Yes