

V5 and High Sensitivity Cardiac Troponin T for Early Detection of Cardiac Toxicity During Left Breast Cancer Irradiation

VERA CIRNIGLIARO¹, SILVIA PIETROSANTI², CHIARA DEMOFONTI¹, MARTINA DE ANGELI³, DOROTEA GIOVENCO³, LAURA CEDRONE³, CECILIA SCIOMMARI³, ALESSANDRA CAROSI³, FRANCA PIETRASANTA³, SARA RAMELLA¹ and ROLANDO MARIA D'ANGELILLO³

¹Radiation Oncology, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy;

²Radiation Oncology, INI s.p.a Divisione Città Bianca, Rome, Italy;

³Radiation Oncology, Department of Biomedicine and Prevention, Università Tor Vergata di Roma, Rome, Italy

Abstract. *Background/Aim:* The high sensitivity cardiac troponin T (Hs-cTnT) is a myocardial damage biomarker that could have a predictive value in patients who undergo radiotherapy for left sided breast cancer. The aim of this study was to evaluate the early effect of left whole breast radiotherapy (WB-RT) on serum Hs-cTnT levels and its correlation with pre-existing factors. *Patients and Methods:* The study was conducted from December 2017 to May 2018. Forty-five patients with early stage left-sided breast cancer who received adjuvant breast hypofractionated RT without prior chemotherapy were included. Serum levels of Hs-cTnT were obtained before, weekly during RT, and within one week after the end of treatment. Considering the physiological variations of serum levels, an increase in Hs-cTnT (Δ Hs-cTnT) of more than 30% from the baseline value was chosen as a threshold. The main cardiovascular risk factors were recorded. Dose volume histograms (DVHs) were used to provide a quantitative analysis for the whole heart, left ventricle, and left anterior descending artery (LAD). *Results:* Twelve of 45 patients (26.6%) showed a Δ Hs-cTnT \geq 30%. The maximum Hs-cTnT level was recorded in the last

week of treatment. Δ Hs-cTnT was strongly associated with heart V5 ($p=0.05$) and hypertension ($p=0.05$). Multivariate analysis confirmed the importance of the heart V5 and correlated with Δ Hs-cTnT. *Conclusion:* The increase in Hs-cTnT serum levels during adjuvant WB-RT suggested a correlation with the cardiac radiation dose in chemotherapy-naive breast cancer patients. A longer follow-up is needed to correlate Hs-cTnT values with cardiac events.

Adjuvant radiotherapy is a standard treatment for early stage breast cancer. Radiotherapy reduced the 10-year risk of any first recurrence from 35.0% to 19.3% and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (1), however there is potential for cardiac and pulmonary toxicity (2). Darby *et al.* recorded in 2013 that the rate of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray in patients with left-sided breast cancer. Cardiovascular events could occur within the first 5 years after radiotherapy (RT) completion and continue up to 30 years after treatment (3). Damage to cardiac micro and macro-vasculature is the pathophysiological cause of radiation-related heart disease, with a predominance of ischaemic heart disease (4). This indicates that the coronary arteries, and the left anterior descending artery (LAD), may be a critical structure for the development of late radiation-induced heart morbidity. The risk of radiation-induced cardiotoxicity may be increased by baseline patient cardiac risk factors and systemic therapies (5, 6), such as anthracyclines, trastuzumab, taxanes, tamoxifen (7, 8). Furthermore, serum biomarkers may play an important role in the detection of heart damage after radiotherapy. Cardiac biomarkers have been applied for early identification, evaluation, and monitoring cardiotoxicity during chemotherapy (9).

High-sensitivity cardiac troponin T (Hs-cTnT) is a biomarker of myocardial damage and may have a predictive value in patients who underwent radiotherapy for left sided breast cancer (10, 11). Cardiac troponins (cTn) are structural

Correspondence to: Vera Cernigliaro, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo, 21-00128 Rome, Italy. Tel: +39 3383419437, e-mail: vera.cernigliaro@libero.it

Key Words: High-sensitivity troponin T, cardiac toxicity, radiotherapy, breast cancer, V5.

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Table I. Patient characteristics.

Baseline characteristics	Number (%)
Number of patients	45
Age (mean)	60 years
Hypertension	18 (40%)
Diabetes	5 (11%)
Hypothyroidism	17 (37%)
Dyslipidemia	7 (15%)
Smoking	13 (28%)
Hormonal therapy	36 (80%)
Troponin ng/ml; T0 – mean (range)	3.1 (3.0-5.7)

proteins that bind to the actin complexes in myofilaments and regulate muscle contraction by interacting with calcium ions and inhibiting the ATPase activity of actinomyosin. cTn represents a complex composed of three subunits: troponin T (cTnT), troponin I (cTnI), and troponin C (cTnC) (12). cTn have high specificities and high sensitivity for myocardial injury and are used in the diagnosis and risk stratification of acute coronary syndromes.

The aim of this study was to evaluate the early effect of left whole breast radiotherapy (WB-RT) on serum Hs-cTnT levels and to correlate them with radiation dose, to the whole heart, to its substructures and to patients' clinical features.

Patients and Methods

Population. We conducted a prospective observational study between December 2017 and May 2018. A total of 45 consecutive patients with early stage left-sided breast cancer or ductal carcinoma *in situ* (DCIS) were analyzed. Exclusion criteria were: age over 75 years, previous chemotherapy treatment, pre-existing heart disease, severe lung disease, kidney failure, and autoimmune disease. Patients with pharmacologically treated hypertension were included. The main cardiovascular risk factors were recorded. All patients were treated with adjuvant conformal 3D RT after surgery in the supine position using “wing board” with arms above heads, computed tomography scan was performed with 2.5 mm thickness, without intravenous contrast. Conformal treatment plans were obtained using the Pinnacle treatment planning system (Phillips Medical Systems, Andover, MA, USA) and were delivered using an Elekta Precise linear accelerator. Treatment was given to a total dose of 42.5 Gy in 16 fractions over 3 weeks with eventually an additional boost to tumor bed.

High sensitivity cardiac troponin (Hs-cTnT) was analyzed in serum samples taken before RT (T0), weekly during the first, (T1), the second (T2) and the third week (T3) and one week after the end of the treatment (T4). Blood sampling was carried out in the timeslot between 8:00 and 9:00 am, since diurnal variation of troponin were observed with a decline in values of 0.8% per hour from 8:30 am to 2:30 pm (13).

Considering the physiological variations of serum levels, a significant increase in Hs-cTnT levels during RT was predefined to exceed 30% from baseline value in this protocol. Dose volume histograms (DVHs) were used to provide a quantitative analysis.

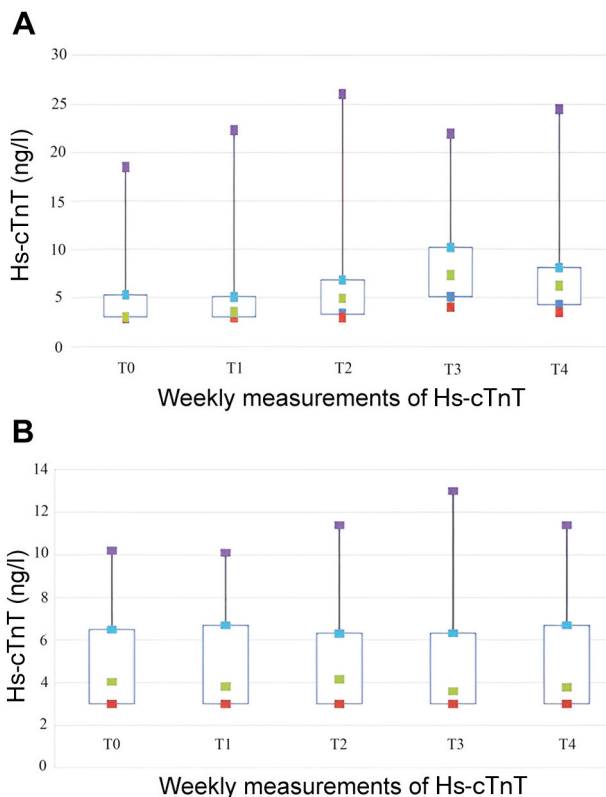


Figure 1. Box plot. A) Box plot figure showing the high sensitivity of cardiac troponin T (Hs-cTnT) before radiotherapy (RT), weekly during RT, and one week after the end of treatment in patients with increased Hs-cTnT release (N=12). B) Box plot showing the Hs-cTnT before RT, weekly during RT, and one week after the end of treatment in patients without Hs-cTnT release (N=33).

The maximum dose and the mean dose and dose-volume parameters V5, V10, V15, V20, V25, and V30 were evaluated for the whole heart, left ventricle, and LAD. A comprehensive echocardiography study and 12-lead electrocardiogram (ECG) were performed at the baseline and at the end of RT. The study was approved by the local Ethics Committee and written consent was obtained for all patients.

Statistical analysis. Data are expressed as means±standard deviation (SD) for normally distribute continuous variables and as medians with inter-quartile range (IQR) for variables with non-normal distribution.

Statistical analyses were performed using MedCalc for Windows, version 17.9.6 (Medcalc Software, Ostend, Belgium). The χ^2 test was performed for the correlation between Δ Hs-cTnT and clinical and dosimetric variables. Multivariate analysis was performed using binary logistic regression. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of the patients are presented in Table I. Median Hs-cTnT for the whole study population was 3.1 ng/l before RT (IQR=3.0-5.7), 3.4 ng/l at 1 week (IQR=3-6), 4.8 ng/l

Table II. Dose-volume parameters.

	Max dose (Gy) Median/Mean (IQR)		VDose (%) Median/Mean (IQR)					
	V5	V10	V15	V20	V25	V30		
Heart	41.7/34.4 (16.3-43.2)	1.51/1.85 (1.0-2.0)	3.1/4.3 (1.1-5.3)	1.5/2.5 (0.2-0.8)	1.0/1.9 (0.1-2.2)	0.7/1.5 (0.0-1.9)	0.5/1.2 (0.0-1.6)	0.3/0.9 (0.0-1.3)
LAD	33.7/29.3 (14.4-42.1)	6.4/10.1 (3.3-11.7)						
Left ventricle	40.2/32.2 (17.5-42.3)	2.2/3.4 (1.4-3.5)	2.8/4.3 (0.1-4.9)	1.8/3.2 (0.0-3.7)	1.1/2.6 (0.0-2.9)	0.7/2.1 (0.0-2.4)	0.3/1.6 (0.0-1.9)	

LAD: Anterior descending artery.

at 2 weeks (IQR=3.0-6.0), 5.1 ng/l at 3 weeks (IQR=3.2-7.0) and 5.5 ng/l after RT (IQR=3.3-7.5). Hs-cTnT increased over 30% from the baseline value in 12/45 (26%) patients.

In these 12 patients, median Hs-cTnT was 3.1 ng/l before RT (IQR=3.0-5.3), 5.0 ng/l at 1 week (IQR=3.3-6.8), 3.5 at 2 weeks (IQR=3.0-5.0), 7.4 at 3 weeks (IQR=4.1-10.2), 6.3 after RT (IQR=4.3-8.1) (Figure 1A). An increase in Hs-cTnT was not accompanied by early clinical changes in ECG or echocardiography. Finally, for the remaining 33 patients, median values at the same time points were: 4 ng/l (IQR=3.0-6.5), 3.8 ng/l (IQR=3.0-6.7), 4.2 ng/l (IQR=3.0-6.3), 3.6 ng/l (IQR=3.0-6.3), and 3.8 ng/l (IQR=3.0-6.7), respectively (Figure 1B).

Dose-volumes parameters are shown in Table II. The following maximum and average dose values [median (IQR)] were recorded for LAD: 33.7 Gy (IQR=14.4-42.1) and 6.4 Gy (IQR=3.3-11.7). For the maximum and average doses, the following values for the left ventricle were recorded [median (IQR)]: 40.2 Gy (IQR=17.5-42.3) and 2.2 Gy (IQR=1.4-3.5).

Univariate analysis (Table III) revealed that Δ Hs-cTnT is strongly associated with heart V5 ($p=0.05$) and pre-existing hypertension ($p=0.05$). Multivariate analysis confirmed the correlation between heart V5 and Δ Hs-cTnT (HR=3.75, 95%CI=0.9-14.8; $p<0.005$).

Discussion

Several studies have shown the correlation between heart exposure to irradiation and an increased risk of heart disease (14). Although morbidity of radiation induced heart disease (RIHD) has been reduced by optimizing treatment plan and techniques, recent studies have shown that modern technology does not eliminate the risk of RIHD (15, 16).

Specifically, patients with left side breast cancer clearly present higher risk for developing cardiac events in comparison with right-sided one's (3). The early detection of radiation-induced cardiac toxicity may potentially

Table III. Univariate analysis.

	Troponin $\geq 30\%$ <i>p</i> -Value
Clinical variables	
Smoking (yes vs. no)	0.59
Diabetes (yes vs. no)	0.62
Hypertension (yes vs. no)	0.05
Dyslipidemia (yes vs. no)	0.93
Hypothyroidism (yes vs. no)	0.79
Heart	
Dose mean (Gy) (≤ 2.2 Gy vs. ≥ 2.2 Gy)	0.17
Dose max (\leq median vs. $>$ median)	0.67
V10 (%) (\leq median vs. $>$ median)	0.54
V15 (%) (\leq median vs. $>$ median)	0.28
V20 (%) (\leq median vs. $>$ median)	0.09
V25 (%) (\leq median vs. $>$ median)	0.28
V30 (%) (\leq median vs. $>$ median)	0.28
V5 (%) (\leq median vs. $>$ median)	0.05
LAD	
Dose max (Gy) (\leq median vs. $>$ median)	0.605
Dose mean (Gy) (≤ 8.7 Gy vs. > 8.7 Gy)	0.300
LV	
Dose max (Gy) (\leq median vs. $>$ median)	0.38
Dose mean (Gy) (≤ 1.7 Gy vs. > 1.7 Gy)	0.46
V10 (%) (\leq median vs. $>$ median)	0.09
V15 (%) (\leq median vs. $>$ median)	0.09
V20 (%) (\leq median vs. $>$ median)	0.08
V25 (%) (\leq median vs. $>$ median)	0.07
V30 (%) (\leq median vs. $>$ median)	0.21

LAD: Anterior descending artery; LV: left ventricular.

indicate patients that will develop late toxicity among breast cancer survivors. The cardiac troponin has been extensively studied as early detector of cardiac toxicity resulting from anticancer therapies (17). Several studies have evaluated the

increased levels of this biomarker after radiotherapy and suggested that the cardiac troponin could be a potential marker of early radiation-induced heart damage. Cramer *et al.* found a correlation between irradiation doses to cardiac tissue and Hs-cTnT (18). In patients with increased levels of this biomarker, the mean heart dose and mean LV were significantly higher (18). In our observational prospective study, we analyzed Hs-cTnT before, during, and after radiotherapy in chemotherapy-naïve breast cancer patients.

The Hs-cTnT is a well-established biomarker of acute myocardial infarction (AMI) (19, 20). In addition, elevated Hs-cTnT levels can be detected in chronic heart failure (21) and LV hypertrophy (22, 23). The values of Hs-cTnT in healthy individuals show variations in the different published studies; the 99th percentile differs from 12 ng/l (24) to 20 ng/l (25) and it has been shown that these values are influenced by patient age, sex and comorbidities (26). Excluding patients with known heart diseases, it is estimated that the median Hs-cTnT in women aged 55 to 75 years is 3 ng /l (26). Based on these data and considering the physiological weekly and diurnal changes in Hs-cTnT, an increase more than 30% from baseline value was interpreted as significant (17). In our series, 12/45 (26%) patients recorded an increase in the levels of this biomarker, mainly during the last week of RT; however, during a median of 3 years follow-up, no cardiac event was recorded. To correlate the rise in troponin levels with the risk of long-term cardiovascular morbidity and mortality, a longer follow-up is needed, since the cardiotoxic effects of RT tend to increase even after long periods of irradiation (3).

Moreover, a correlation with hearth V5 was also observed. This suggests that V5 and its correlation with a serum biomarker could represent a potential tool to predict myocardial damage leading to an appropriate stratification of patients at greater risk for long-term cardiac toxicity. A prolonged follow-up seems mandatory to obtain long-term results.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

All Authors participated in the study design and coordination and discussed the outcome during the study.

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