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Evaluation of the Irradiated Volume of the Heart and Cardiac Substructures After Left Breast Radiotherapy

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Abstract. *Backround/Aim: Adjuvant radiotherapy in patients with cancer of the left breast may lead to impaired cardiac function. The aim of our prospective study is to evaluate (i) doses to the irradiated volume of the heart and its substructures and (ii) determine whether their correlation with changes in strain echo measurements contribute to the prediction of subclinical heart morbidity. Patients and Methods: Twenty-five patients were enrolled in our study. We retrospectively assessed the radiation doses to the whole heart, left anterior descending artery (LAD) and left ventricle (LV). Results: The mean heart dose (MHD) was 152 cGy (SD=50.56 cGy) and the range was 74-279 cGy. The LAD was the most exposed structure, with a mean dose of 448.91 cGy (SD=490.53 cGy) and range of 120-2,057cGy. Finally, the mean LV dose was 149.12 cGy (SD=69.57) with a range of 63-317 cGy. Conclusion: The early results of our study showed low radiation exposure of the whole heart and left ventricle, and higher exposure of the LAD. The data that will emerge from the evaluation of strain echo parameters should show whether these associations might be useful in clinical practice for the prediction of early subclinical cardiac changes.*

Breast cancer is the most common malignancy in women worldwide, accounting for approximately 15 to 30% of new cancer cases in females in the USA in 2019 (1). The role of adjuvant breast radiotherapy (RT) is well established concerning both improved local control of the disease and the reduction of the mortality rate. Indeed, a great reduction of local recurrence, which may approach even 80% might be observed after 50 Gy dose of adjuvant RT, while overall mortality may be reduced by 5.3% at 15 years after adjuvant RT (2, 3). However, this treatment modality may be accompanied by adverse effects on surrounding normal tissues, including the ipsilateral lung and the heart in patients with left breast cancer (4). During previous decades, major scientific concern was raised regarding potential cardiotoxicity due to the observation of characteristically increased cardiac mortality after RT in patients with left compared to right breast cancer (5). However, this unfavorable outcome was attributed to older radiotherapeutic techniques, which were unable to effectively protect heart tissue (6).

In contrast to past common practice, modern radiotherapeutic equipment including the use of tangential fields, intensity-modulated radiotherapy and deep-inspiration breath hold, manage to offer improved protection of the heart (7, 8). Nevertheless, a small part of the whole heart tissue or even cardiac substructures such as the left anterior descending artery (LAD) and the left ventricle (LV) may receive low doses of RT, which may be responsible for subsequent findings of heart reactions (9). Consequently, we considered it useful to evaluate the radiation doses by using tangential fields, not only to the whole heart, which is most commonly assessed in each RT treatment planning, but also to its substructures, LAD and LV, for their potential contribution to an increased risk of cardiac dysfunction in patients who undergo left breast RT.

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As well as the evaluation of radiation doses to heart tissue, certain serum biomarkers may possess significant role in early detection of cardiac dysfunction after left breast RT. Indeed, cardiac troponins I and T, and the natriuretic hormones brain natriuretic peptide (BNP) and its amino-terminal fragment (NT pro-BNP) have been occasionally studied for their potential capacity to predict early cardiac dysfunction after left breast RT (10-13). Despite some promising data, more studies with stronger statistical results are needed to evaluate their predictive role after RT. In addition to this, although a large number of studies have extensively investigated the association between increased levels of C-reactive protein and cardiotoxicity after chemotherapy, more data are required to establish its predictive value after RT (14-16).

Strain and strain rate imaging calculated by 2-dimensional speckle tracking echocardiography (2D-STE) might also constitute a useful tool for the early prediction of heart failure after RT in patients with cancer of the left breast. Specifically, strain imaging was found to be capable of both predicting early cardiotoxicity in patients undergoing chemotherapy and revealing cardiac damage in various diseases (17-21). Being inspired by the sensitiveness of this echocardiographic tool to predict cardiac dysfunction in several conditions, some investigators studied the role of strain imaging in revealing early cardiac abnormalities in patients after left breast RT. More specifically, decreased levels of strain parameters were found in various periods after RT (from a few weeks to 2 years post-radiation) in some studies, changes which were actually found to be related to the RT dose (22-27). This finding generates great interest about the potential contribution of strain echocardiographic imaging to the prediction of early heart dysfunction in patients after left breast RT.

For this purpose, we designed our prospective study. The first step of our study was the retrospective assessment of the radiation doses to the whole heart and specific cardiac substructures (LAD and LV). Additionally, 2D strain echocardiography was to be performed for each patient before and 1 year after the end of each RT planning. In this way, we secondly aim to investigate the potential correlation between findings in dosimetric planning and changes in 2D strain echocardiography which might be a valuable tool for the early prediction of subclinical cardiac changes in patients after left breast RT.

Our study is still ongoing and the end is foreseen for late 2020. The first results are presented in this article, while the final results are estimated to be published in approximately 1 year.

Patients and Methods

Twenty-five female patients with early-stage left-sided breast cancer after breast-conserving therapy and without history of any cardiac disease were enrolled in our prospective study. Internal Ethics Committee of the Medical Department of the University of Thessaly concluded that our study fulfilled all necessary moral and ethical requirements (Larisa 12.02.2019, Protocol Number: 07, 1st/11.02.2019 meeting). The free and informed consent of all patients was obtained. The inclusion period lasted from November 2018 to November 2019. The age of included patients ranged from 37 to 71 years at the time of treatment. All patients were node-negative and had not previously received chemotherapy. Patients with any personal history of myocardial and coronary artery disease, echocardiographic abnormalities or previous RT to the thorax were excluded from the study. All patients were treated to 42.56 Gy in 16 daily fractions (five fractions a week) to the tissue of the whole left breast with 3D-conformal RT without breath-hold gating. Tangential fields with 6- and 18-MV photon beams were used. An additional boost of 10 Gy was applied to the tumor site with electron beams, with electron energy from 6 to 18 MeV. All patients were treated in the same position with their arms above the head and the Oncentra External Beam treatment planning system (Version 4.5.3, Software 4.5.3.15; Nucletron B.V., Veenendaal, the Netherlands) was used to perform the dose calculations.

In order to evaluate the potential association between the irradiated volume of the heart and cardiac substructures and the probability of causing subclinical cardiac changes, both the whole heart and cardiac substructures (LAD and LV) were retrospectively manually delineated on individual computed tomographic scans using a published peer-reviewed cardiac atlas (28). Additionally, dose–volume histograms were created for the heart, LAD and LV based on the RT plan. In particular, the volumes that we measured include the mean heart dose (MHD), the volume of the heart receiving more than 20 Gy ($V20_{heart}$), the volume of the heart receiving more than 25 Gy ($V25_{heart}$), 30 Gy ($V30_{heart}$) and 40 Gy ($V40_{heart}$); the mean LAD dose, the volume of LAD receiving more than 20 Gy ($V20_{LAD}$), 30 Gy ($V30_{LAD}$) and 40 Gy ($V40_{LAD}$), the mean LV dose; the volume of the LV receiving more than 5 Gy ($V5_{LV}$) and 23 Gy ($V23_{LV}$).

For the evaluation of our findings in dose–volume histograms, we considered as baseline the recommended guidelines for doses to heart and cardiac substructures in accordance with Quantitative Analysis of Normal Tissue Effects in the Clinic Guidelines, Danish Breast Cancer Cooperative Group and the German Breast Cancer Expert Group (29-31). In particular, MHD should be kept under 2.5 Gy, $V20_{heart}$ and $V25_{heart}$ under 10%, $V30_{heart}$ under 46% and $V40_{heart}$ below 5% (32). Moreover, the mean LAD dose should be kept under 10 Gy, while $V30_{LAD}$ and $V40_{LAD}$ should be below 2% and 1%, respectively. Regarding $V20_{LAD}$, it is considered high when it exceeds 10% (33). Finally, the mean LV dose should be kept under 3 Gy while $V5_{LV}$ and $V23_{LV}$ should be below 17% and 5%, respectively.

Furthermore, before the first fraction of RT, 2D strain echocardiography was performed for all patients, while a second 2D strain echocardiography is planned to be done 1 year after the end of RT. Global and segmental longitudinal strain and strain rate will be measured in order to evaluate subclinical cardiac events. All the measurements in strain echo before RT will be considered as the reference values. Baseline measurements for global and segmental longitudinal strain and strain rate have been proposed for use in a wide clinical setting. Specifically, a 5% decrease was found to be predictive of a subclinical cardiac change, while $-16.5\% \pm 2.1\%$ and $-1.00/s \pm 0.13/s$ were proposed as reference values for the mean global longitudinal strain before RT (34).

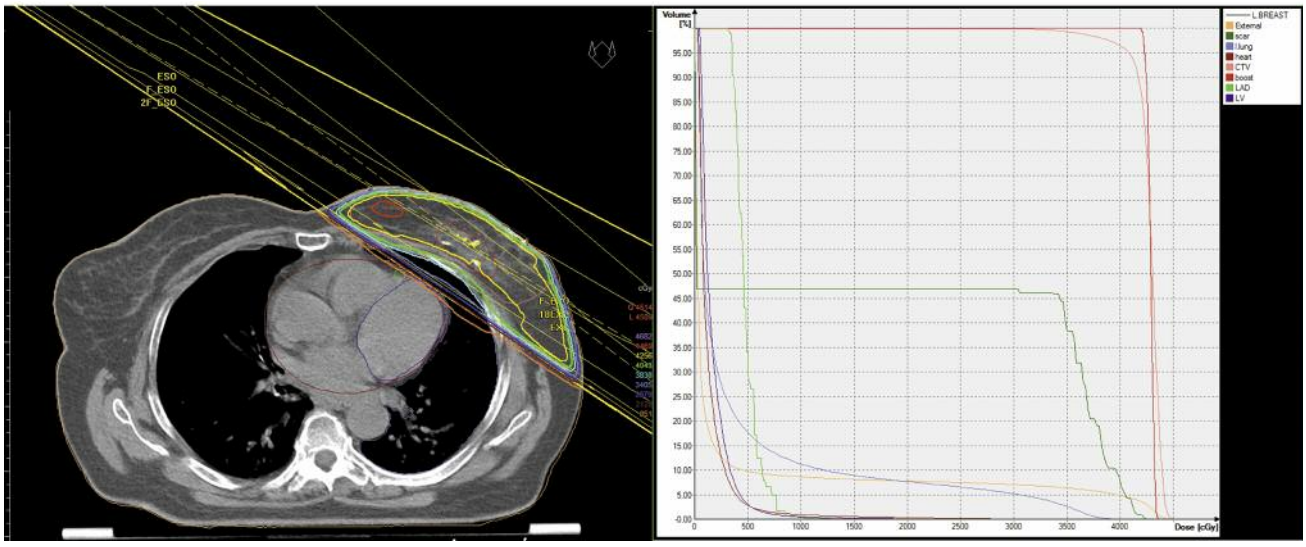

Figure 1. *A: 3D treatment planning with normal breathing; Clinical target volume (CTV) contoured in pink, heart contoured in red, left ventricle contoured in purple, left anterior descending artery (LAD) contoured in green. B: Dose–volume histogram. CTV in pink, whole heart in red, left ventricle in purple, LAD in green.*

Results

The average age of the 25 women of our study was 53.2 years (SD=10.51) and the range was 34 years (range=37-71 years). Dose–volume histograms for all patients were included (Figure 1). Regarding the whole heart, all patients presented MHD <250 cGy except for one (279 cGy) (Table I). The mean MHD was 152 cGy (SD=50.56) and the range among patients was 205 cGy (range=74-279 cGy) (Table I). In addition, $V20_{heart}$, $V25_{heart}$, $V30_{heart}$ and $V40_{heart}$ were well below the recommended thresholds for all patients, with a maximum $V20_{heart}$ value of 3.87%, $V25_{heart}$ value of 3.41%, $V30_{heart}$ value of 2.97% and $V40_{heart}$ value of 0.25%, respectively (Tables I and II). Furthermore, 50% of V20, V25, V30 and $V40_{heart}$ values were between 0.9 and 1.48, 0.20 and 1.16, 0 and 0.85 and 0 and 0.03, respectively (Table II). In contrast to the whole heart, LAD was the most exposed structure with a mean LAD dose of 448.91 cGy (SD=490.53) and the range among patients was 1937 cGy (range=120-2057 cGy) (Table I). Specifically, four patients presented a mean LAD dose higher than the recommended threshold [1577, 1180, 2057 and 1213 cGy; (Table I)]. The range among patients in mean LAD dose was higher than observed for the whole heart. Moreover, although $V20_{LAD}$ and $V30_{LAD}$ were higher than the recommended thresholds for six (29.38%, 17.40%, 56.32%, 21.99%, 10.62%, 11.08%) and five (5.93%, 2,73%, 37.15%, 3.37%, 2.01%) cases respectively with a maximum $V20_{LAD}$ value of 56.32% and $V30_{LAD}$ value of 37.15%, all patients presented low $V40_{LAD}$ (<1%) with a maximum $V40_{LAD}$ of 0.34% (Tables I and II). Furthermore, 50% of V20, V30 and $V40_{LAD}$ values were between 0 and 8, 0 and 0 and 0 and 0 respectively (Table II). The great variability of LAD dose is potentially explained by the fact that due to the anatomic location of LAD (in the anterior region of the heart), its radiation exposure is dependent on the variation of breast and heart size of each patient, which are factors that determine the volume of LAD in the radiation field. Finally, regarding LV all patients presented low mean LV dose (<300 cGy) except for one (317 cGy) (Table I). Mean LV dose was 149.12 cGy (SD=69.57) and the range among patients was 254 cGy (range=63-317 cGy) (Table I). The range among patients in mean LV dose was higher than observed for the whole heart. $V5_{LV}$ and $V23_{LV}$, respectively, were below the recommended thresholds in all patients, with a maximum $V5_{LV}$ value of 9.44% and $V23_{LV}$ value of 3.43% (Tables I and II). Finally, 50% of $V5_{LV}$ and $V23_{LV}$ values were between 0 and 4.19 and 0 and 0.53 respectively (Table II).

Discussion

Breast cancer is the second most frequently diagnosed malignancy after lung cancer (35). Breast RT has a main role in the therapeutic management in the adjuvant setting offering excellent local control and an increased long-term survival (36). However, regarding the fact that breast RT was found to be associated with increased risk of heart toxicity even two decades after RT and that this risk is significantly correlated to

Table I. *Dosimetric parameters for heart and cardiac substructures.*

		Heart					LAD				LV		
ID	Age (years)	V20 (%)	V25 (%)	V30 (%)	V40 (%)	Mean dose (cGY)	V20 (%)	V30 (%)	V40 (%)	Mean dose (cGY)	V5 (%)	V23 (%)	Mean dose (cGY)
1	39	0.13	0.08	0.05	0.00	112.8	0	0	0	219	0.015	0	109
2	46	0.38	0.24	0.14	0.00	128	0	0	0	139	1.26	0.07	129
3	42	1.48	1.21	0.93	0.03	183	0	0	0	261	4.19	0.53	181
4	59	1.08	0.82	0.59	0.02	170	0	0	0	383	5.87	0.49	216
5	61	0.21	0.10	0.03	0.00	107.2	0	0	0	177	0.048	0	109
6	50	1.60	1.34	1.09	0.18	194	0	0	0	301	1.61	0.016	153
7	71	1.30	1.06	0.85	0.25	172	0	0	0	225.8	4.52	1.07	230
8	46	0.01	0.00	0.00	0.00	133	0	0	0	189	0.52	0	162
9	65	0.32	0.19	0.07	0.00	108	0	0	0	178	0	0	63
10	70	0.50	0.28	0.11	0.00	168	0	0	0	267	0.01	0	132
11	52	2.11	1.73	1.34	0.22	226	29.38	5.93	0	1577	0	0	100
12	44	0	0.00	0.00	0.00	112	0	0	0	452	0	3	84
13	69	0	0.00	0.00	0.00	74	0	0	0	247	0.06	0	81
14	43	0.43	0.30	0.16	0.00	126	17.40	2.73	0	1180	0	0	86
15	45	0.00	0.00	0.00	0.00	78	0.00	0.00	0	120	0	0	63
16	51	0.00	0.00	0.00	0.00	74	0.00	0.00	0	183	0	0	76
17	41	1.49	1.16	0.81	0.04	190	56.32	37.15	0.34	2057	0	0	103
18	44	3.87	3.41	2.90	0.49	279	0	0	0	200	7.52	3.43	293
19	60	1.73	1.35	0.93	0.00	222	21.99	3.37	0	1213	4.94	0.63	234
20	63	1.63	1.31	2.97	0.06	205	10.62	2.01	0	400	9.44	2.58	317
21	68	0.69	0.46	0.24	0.00	143	11.08	0.85	0	450	0	0	115
22	62	0.92	0.71	0.48	0.00	191	0.69	0.00	0	220	6.15	0.43	242
23	55	0.01	0.00	0.00	0.00	120	0.00	0.00	0	196	0.19	0.00	130
24	47	0.09	0.02	0.00	0.00	154	7.48	0.00	0	190	2.94	0.01	180
25	37	0.50	0.39	0.18	0.00	130	8	0	0	198	1.20	0.70	140

LAD: Left anterior descending artery; LV: left ventricle; V#: volume of tissue receiving more than a close of #Gy.

Table II. *Summary of dose–volume data for the heart, left anterior descending artery (LAD) and left ventricle (LV).*

Tissue	Parameter	Minimum	25th Percentile	Median	75th Percentile	Maximum
Whole heart	V20 (%)	0.000	0.090	0.500	1.480	3.870
	V25 (%)	0.000	0.020	0.300	1.160	3.410
	V30 (%)	0.000	0.000	0.160	0.850	2.970
	V40 (%)	0.000	0.000	0.000	0.030	0.490
LAD	V20 (%)	0.000	0.000	0.000	8.000	56.320
	V30 (%)	0.000	0.000	0.000	0.000	37.150
	V40 (%)	0.000	0.000	0.000	0.000	0.340
LV	V5 (%)	0.000	0.000	0.190	4.190	9.440
	V23 (%)	0.000	0.000	0.000	0.530	3.430

V#: Volume of tissue receiving more than a close of #Gy.

the radiation dose to which the heart is exposed, there is major interest in the potential methods that might predict those patients who are at a greater risk of developing cardiac dysfunction early (37, 38). In particular, many investigators highlighted the significance of including dose constraints for the cardiac subvolumes LAD and LV besides the whole heart in order to increase heart protection. Characteristically, in 2005, Carr *et al*. found significantly increased risk for coronary heart disease when 5% of the heart volume received more than 12.9 Gy (39). In 2011, Darby *et al*. illustrated increased risk for coronary events per 1 Gy MHD higher than 2 Gy (40). Moreover, in 2015, Skytta *et al*. observed increased levels of

serum troponin T when MHD was 4 Gy *versus* no increase with MHD 2.8 Gy (41). Furthermore, the mean LV dose of 6.7 Gy was associated with increased troponin T compared to no increase with a mean LV dose of 4.5 Gy. Finally, regarding LAD, increased levels of troponin T were observed when either the mean dose of LAD was 23.8 *versus* 17.5 Gy, or 55.4% *versus* 36.2% of LAD volume received 20 Gy and when 45% *versus* 29.3% of LAD volume received 30 Gy. Finally, in 2017 van den Bogaard *et al*. declared that the incidence for acute coronary events was increased by 16.5% per 1 Gy MHD (42). In addition, they observed acute coronary events when 29.3% of the LV received 5 Gy, while no event was found when the 16.9% of the LV received the same dose. The early results of our study have shown low radiation exposure of the whole heart in all cases; only one patient presented a MHD higher than the recommended threshold and this patient might be at a higher risk of developing coronary events according to Darby *et al*. (40). Similarly, LV received low radiation doses in all cases and only one patient presented a mean LV dose higher than the recommended threshold. However, this value is low according to Skytta *et al*. and thus potentially incapable of raising the serum troponin T level (41). On the contrary, LAD was found to be the most exposed structure. Specifically, six patients in total presented higher mean LAD, $V20_{LAD}$ or $V30_{LAD}$ dose than the recommended thresholds. However, only one patient exceeded the thresholds according to Skytta *et al*. and consequently was at a higher risk of developing an increase of serum troponin T.

The early results of our study will be further evaluated when the second session of 2D strain echocardiography will be performed for all patients. By analyzing both the changes in strain echo parameters before RT and 1 year after, and the correlation between those changes and the irradiated volume of the heart and its substructures (LAD and LV), we hope to be able to declare safe conclusions about this association. In this way, we aim to at offer a potentially useful strategy in clinical practice for the prediction of early subclinical cardiac changes in patients after RT for left breast cancer.

Limitations

There are some limitations to our study. First of all, the sample size may be too small to predict significant changes either in RT planning or in 2D strain echocardiography. Additionally, performing strain echo 1 year after RT may be too early to detect subclinical cardiac changes. However, reduced strain parameters were previously found from as early as 2 months up to 14 months after RT (12, 25, 26). Moreover, all patients were treated with a 3D-conformal RT without breath-hold gating. Given the fact this technique is still not available in our Department, we lack the ability to investigate the association between changes in strain echographic parameters and the irradiated volume of the heart and its substructures by comparing 3D-conformal RT with and without breath-hold gating. Finally, our study includes patients without history of any cardiac disease and consequently our results will probably not be appropriate for generalization to all patients who undergo whole left breast RT.

Conclusion

The early prediction of post radiation cardiac toxicity should be the priority of the whole therapeutic approach. The cardiac substructures LAD and LV should be assessed besides the whole heart in each RT treatment planning in order to achieve improved heart protection. Further data arising from the evaluation of strain echographic parameters will enlighten the potential of this strategy in predicting early cardiac morbidity in patients undergoing RT for left breast cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

All the Authors participated in the writing and revision of this article and take responsibility for its content. The present publication is approved by all Authors and by the responsible authorities where the work was carried out. The Authors confirm that the content of the article has not been published or submitted for publication elsewhere.

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