Research Article

The "Neglected" and the "Unexpected" in Radiotherapy-Induced Cardiotoxicity-Insights from a Monocentric Study on Myocardial Perfusion Imaging in Early Breast Cancer Patients

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Abstract

Background: Radiotherapy (RT) for early breast cancer (EBC) increases the subsequent rate of ischemic heart disease (IHD), often with the gender-specific

microvascular phenotype. The goal of our study was to analyze the potential value of a baseline myocardial perfusion imaging (MPI) and a proactive monitoring on RT cardiotoxicity in early breast cancer patients.

Methods: 70 EBC patients with an indication for RT, had a baseline stress/rest MPI, in 25 patients Coronary Flow Reserve (CFR) was also estimated. All patients received a 3-dimensional conformal RT with an average mean heart dose of 3.29 Gy. A 20-year cardiology follow-up was scheduled.

Results: At baseline 12/70 patients showed MPI abnormalities; 11/12 had IHD risk factors (RF). 21/70 patients with chest pain after RT performed post-RT MPI: 7 patients showed "de novo" abnormalities, 3 increased their pre-RT abnormalities. 90% of patients with MPI abnormalities showed angiographically normal epicardial coronary arteries. 90% of patients with MPI abnormalities had risk factors for IHD, including pregnancy-related hypertension. One patient with no RF for IHD and normal baseline MPI reported post-RT abnormalities likely due to a genetic predisposition. No major cardiologic events were recorded in a 9-year follow-up in patients with baseline MPI abnormalities.

Conclusions: A baseline stress/rest MPI is useful in EBC patients with a high likelihood of IHD, MPI abnormalities call for a proactive monitoring and an aggressive treatment of IHD risk factors that may reduce the burden of IHD. A gender-oriented approach and the search for genetic predisposition smooth the way towards precision medicine.

Keywords: Radiotherapy; Breast cancer; Cardiotoxicity; Myocardial perfusion imaging; Gender-specific risk factors; genetic predisposition

1. Introduction

RT has dramatically changed the natural history of breast cancer reducing local recurrences and deaths [1]. RT-induced cardiotoxicity is a wide spectrum disease that can develop immediately or gradually and can occur even decades after chest radiation and has a great impact on mortality and morbidity [2]. An excess in the late cardiovascular mortality in irradiated women and a higher incidence of Ischemic Heart Disease (IHD) in early left breast cancer patients compared to right-sided ones have also been reported [3-7]. Cardiovascular risk factors, high cumulative dose (>30 Gy) or high dose of radiation fractions (>2 Gy/day), concomitant chemotherapy (e.g. anthracycline) are some of the risk factors reported for RT-induced cardiotoxicity [2]. Although modern RT delivery techniques have significantly reduced the dose and cardiac involvement, late cardiotoxicity (20-30 years after RT) is still an issue with modern therapeutic regimens [2, 5-7], the identification of early signs of RT-induced cardiovascular damage has yet to be clarified. RT-induced cardiovascular diseases may affect all parts of the heart, in this paper, we refer to IHD, a common phenotype of RT-induced cardiotoxicity. Electrocardiographic changes detected soon after RT have long been described and have been considered "functionally insignificant" [8] even though post RT ST-T abnormalities may be the epiphenomenon of an endothelial impairment or of an

inflammatory response and deserve further attention. Echocardiography, coronary computed tomography angiography (CCTA) and circulating biomarkers are also evaluated in the early detection of RT-cardiotoxicity [9]. Myocardial perfusion imaging abnormalities in irradiated left breast cancer have been extensively described, but the clinical meaning of baseline abnormalities and the role of MPI as early marker of RT-induced vascular damage still remain unclear [10-14]. The aim of our study was to investigate the role of a careful baseline investigation in predicting the likelihood of RT-induced IHD, we have a few data on post-RT MPI and 2 intriguing cases.

2. Methods

Eighty early breast cancer patients with an indication for adjuvant RT were enrolled from 2007 to 2012: 10 withdraw, 70 patients were recruited in a longitudinal study.

2.1 Cardiologic evaluation

At baseline patients underwent a thorough cardiovascular examination with an accurate anamnesis that included gynecologic history. Traditional risk factors such as type 2 diabetes and hypertension were evaluated as well as female-specific risk factors and chronic inflammatory conditions. These last two categories of risk are defined risk *enhancers* in the 2019AHA/ACC Prevention Guidelines [15]. Lifestyle behavior was also investigated and a healthy lifestyle shift was suggested to all patients. Electrocardiographic and echocardiographic recordings were registered; a stress/rest perfusion scan was performed in all patients with exercise test in 45 patients and Dypiridamole administration in 25 patients. In these last 25 patients we also estimated CFR.

MPI was obtained with a single-day stress–rest 99mTc-tetrofosmin by gated SPECT according to the European Association of Nuclear Medicine and European Society of Cardiology recommendations [16]. A commercially available software program (Cedars-Sinari Medical Center, Los Angeles, CA) was used to calculate left ventricular ejection fraction. MPI was considered abnormal when reversible and /or fixed defects were detected. CFR was assessed in 25 patients: regional CFR is defined as the ratio between dypiridamole and baseline myocardial blood flow. We administered Dypiridamole at the dosage of 0.56 mg/kg in 4 minutes with continuous electrocardiographic monitoring. Dypiridamole estimated myocardial blood flow can be assessed by measuring first transit counts in the pulmonary artery and myocardial count rate from G-SPECT images, baseline myocardial blood flow is estimated afterwards. Such methodology has been tested in several settings and was definitely found to correlate to oxygen-15-labeled water ([(15)O]H(2)O) PET which is gold standard technique for CFR and to intracoronary Doppler [17, 18].

All patients were scheduled for a clinical 20-year-follow-up with a reassessment of cardiovascular risk factors with a particular emphasis on lifestyle behavior. The protocol was approved by the local institutional board of ethics and all patients gave written informed consent.

2.2 Radiotherapic administration

All patients received Radiotherapy with an average mean heart dose of 3.29 Gy. RT was delivered with a linear accelerator, at the dose of 50 Gy in 25 fractions (2 Gy/die) to the whole breast and a boost of 10-16 Gy

to the tumor. A 3-dimensional conformal radiation therapy technique was used. Two tangential fields were applied covering the breast and the edges of the field were shaped based on patients'anatomy; this technique includes a small part of the lung (about 2 cm). Photons were more widely used than electrons, and the photon beam energy was usually 6 MV. For large breasts a higher energy was used (usually 15MV). To obtain more homogeneity, two wedges with 10-30° angles were used. According to the recommendations of the International Commission on Radiation Units and Measurements, an optimal plan requires the entire planning target volume to be between 95% and 107% levels relative to 100% prescription point. We used two direct fields and a dynamic multi leaf collimator to modulate the radiotherapy dose across the boost. To evaluate the proper execution of the radiotherapy plan, we analyzed the Dose-Volume Histogram that provides the relation between radiation dose to tissue volume [19].

2.3 Systemic therapy

Adjuvant anthracycline-containing chemotherapy was administered to 44 out of 70 patients (62.8%) (Table 1). HER status was tested in all patients. Trastuzumab was given to all positive patients (16). Hormone therapy was administered to 33 patients (47%): 21 premenopausal women received Tamoxifene, 12 postmenopausal women received Aromatase Inhibitors.

2.4 Statistical analysis

Mean and SD were used for quantitative variables, absolute and relative frequencies were used to describe qualitative variables. An explorative analysis of MPI abnormalities detection at baseline and follow-up and presence/absence of risk factors was also performed using chi square test. Significance level was set at 0.05. SPSS 20 software was used for the analysis.

3. Results

Characteristics of patients are showed in Table 1. Breast cancers were most frequently left-sided (94.3%). Eighty-one per cent of early breast cancer patients reported at least one traditional risk factor for IHD (diabetes, hypercholesterolemia, hypertension, smoking habit, family history). In five patients female specific risk factors namely preeclampsia (3), pregnancy related hypertension (1) and gestational diabetes (1) were found. Two cases of autoimmune disorders were also reported. All patients received RT. Sixty-six patients received RT in our institution. Full radiotherapy plan is showed in Table 2.

At baseline 58 patients (83%) had a normal MPI and 12 patients (17%) showed myocardial perfusion defects (11 stress-induced defects, 1 fixed defect). In 50% of cases the myocardial perfusion defects affected the anterior wall and in 66.7% the apex (Table 3). Eleven out of twelve patients (91.7%) with baseline abnormalities of MPI had at least one risk factors for IHD: 8 patients (66%) had hypertension, 6 (50%) dyslipidemia, 4 (33%) had a family history of IHD, 2 (16%) had diabetes, 2 (16%) were active smokers, 1 (8%) had a history of preeclampsia, 1 (8%) had autoimmune disease and only one did not have any cardiovascular risk factors. At the exploratory analysis no statistical significance was found (p=0.306).

Number of patients	70
Age	Mean 55.72 (10.62 SD)
Comorbidities	
Coronary artery disease	0
Hypertension	36
Diabetes Mellitus	2
Hypercholesterolemia	21
Smoking habit	8
Female specific cardiovascular risk factors	
Pregnancy complications	5
Laterality	
Left breast	66
Right breast	4
Histology type	
IDC	59
ILC	29
DCIS	8
Others	1
Tumor stage	
0	8
I	23
II	26
III	13
IV	0
Hormonal status (positive)	33
HER2 status	Positive 16 Negative 54
Surgery	
Mastectomy	13 (19%)
Quadrantectomy	57 (81%)
Chemotherapy	45
Anthracycline	44
Hormonotherapy	33
Tamoxifen	21
Aromatase inhibitors	12

Data are expressed as numbers; SD-standard deviation; IHD-ischemic heart disease; IDC-Invasive ductal carcinoma; ILC-invasive lobular carcinoma; DCIS-ductal carcinoma in situ (Intraductal breast cancer); HER2-human epidermal growth factor receptor 2; CHT-chemotherapy

Table 1: Characteristics of patients.

3D-CRT	**n**
	70
IMRT	0
Tangential fields only	0
Tangential fields+boost	50
Tangential fields+boost+supraclavicular lymph nodes	4
Tangential fields+supraclavicular lymph nodes	12
Dose Heart (Gy)	
Median (range)	2.84 (0.01-11.3)
Mean	3.29

Data are expressed as numbers; CRT-Conformal Radiotherapy IMRT intensity modulated radiation Therapy; Gy Gray

Table 2: RT plan.

MPI normal pattern	58
MPI abnormalities	12
Antero-septal fixed	1
Stress induced ischemia	11
Anterior	4
Infero-apical ischemia	2
Antero-lateral ischemia	2
Infero-lateral	2
Pure apical	1

Table 3: Myocardial perfusion imaging results.

21/70 patients (30%) were referred for chest pain soon after RT and they performed an early post RT MPI. In detail, post RT- MPI was available for 17 out of 58 normal baseline MPI and for 4 out of 12 abnormal MPI patterns. Of the 58 patients with a normal pre-RT, 7 out of 17 (41%) showed myocardial *de novo* perfusion defects after RT, in 85.7% of these patients cardiovascular risk factors were present, including a case of pre-eclampsia and a family history of premature CVD. Three of them have been also treated with anthracycline systemic therapy and Trastuzumab therapy. The four available post-RT MPI for patients with baseline myocardial perfusion defects underlined three cases of increased myocardial perfusion defects, and 1 case with no modification. All four patients reported a personal history of cardiovascular risk factors. Globally risk factors have been reported in 83.3% of increased or *de novo* myocardial perfusion defects even if no statistical significance was found at the exploratory analysis (p=0.224). Nine out of ten

(90%) *de novo* and increased myocardial perfusion defects, showed angiographically normal epicardial coronary arteries. Only 1 out of the 3 with increased perfusion defects showed a stenosis of distal Left Anterior Descending Artery.

4. Case studies

Two patients of the 70 previously described deserve particular attention. The first one is a 56-year-old hypertensive woman with ductal invasive adenocarcinoma, stage pT2N0, G3, Estrogen Receptor (ER) and Progesteron Receptor (PgR) positive, HER2-, Mib 1 30%, a history of preeclampsia and a family history for IHD; she had a baseline reversible apical-anterior myocardial perfusion defect and reduced estimated values of CFR (1.6 for global CFR, 1.47, 1.61 and 1.38 respectively for Left Anterior Descending Artery, Circumflex and Right Coronary Artery CFR). Twenty days after RT, she complained of chest pain, her electrocardiogram showed T wave inversion in anterolateral leads, her stress/rest MPI showed an increased reversible myocardial perfusion defect (apical-anterior and mid-anterior) and a 19% reduction of global CFR, an 8% reduction of Left Anterior Descending CFR, a 31% reduction of Circumflex CFR and a 4% reduction of Right Coronary Artery CFR. She had also received anthracycline therapy. Multislice Computed Tomography showed normal epicardial coronary arteries. Thirty-eight months after the end of RT she had 2 episodes of atrial fibrillation converted to sinus rhythm with amiodarone, She was on antiarrhythmic therapy, but 8 years after RT she had another episode of atrial fibrillation. No more episodes of chest pain were reported, she is on a healthy diet and she is exercising regularly.

The second patient, a 38-year-old woman with no risk factors for IHD and left breast G3 ER-PgR-intraductal adenocarcinoma, had a baseline normal MPI and normal estimated CFR values: global-CFR 2.48, Left Anterior Descending, circumflex and right coronary artery-CFR 2.67, 2.59 and 2.80, respectively. No anthracycline therapy was administered before RT. Immediately after RT, she was referred for atypical chest pain, her ECG showed T wave inversion in anterior leads and a small myocardial perfusion defect in the apical region of the left ventricle was found. Global CFR was 2.06 (-17% vs baseline value), Left Anterior Descending, Circumflex and Right Coronary Artery-CFR values were 2.10 (-21%), 2.59 and 2.48 (-11%), respectively. She refused noninvasive evaluation of coronary arteries. Two years later she performed a stress-echo that did not show abnormalities of left ventricular contraction. She has always had a healthy lifestyle behavior.

4.1 Follow-up (mean follow up period: 9 years (7-12 years)

We have oncologic follow up data of 60 patients after a mean time of 9 years from the end of RT. Two patients died for progressive disease, 7 patients had recurrent disease or metastases, 51 are alive with no evidence of disease. Ten patients were lost at follow up, we have cardiologic follow up data of 60 patients with a mean time of 9 years from the end of RT (range 7-12 years). In a small number of patients baseline estimated CFR values were confronted to post-RT values. Patients with baseline or post RT myocardial perfusion defects did not experience coronary events, a patient presented episodes of atrial fibrillation, a hypertensive patient with normal baseline MPI had an acute myocardial infarction 9 years after RT with normal epicardial coronary arteries.

5. Discussion

RT improves prognosis of breast cancer, but RT-induced cardiotoxicity has a relevant impact on long term survivors' cardiovascular mortality even with modern therapies. In long-term (12 years of follow-up), irradiated breast cancer patients, especially left-sided ones, have an increased risk of RT-associated coronary damage (anatomic coronary stenosis) [3, 20]. Darby documented that "rates of major coronary events increases linearly with the mean dose to the heart by 7.4% per gray" [21]. A direct link between radiation and location of coronary stenoses has been documented by Nilsson, who reported an increase in stenoses in mid-distal Left Anterior Descending, in distal Diagonal Artery in irradiated left early breast cancer patients and in proximal Right Coronary Artery in right internal mammary chain irradiation [22]. An increased risk of cardiac disease seems also to be reported in RT breast cancer patients who also received anthracycline-containing chemotherapy [20].

Radiotherapy causes structural and functional abnormalities of coronary vessels, valves, pericardium, and myocardium. RT for breast, lung and esophageal cancer, thymoma, and mediastinal lymphoma has a high probability of enclosing the heart in the RT portal. Endothelial damage seems to be the first step of RT-induced cardiotoxicity with an inflammatory response and oxidative damage in large vessels [23]; RT-induced plaques may determine ostial stenoses with a significant higher incidence of left main disease followed by ostial Right Coronary and Left Anterior Descending arteries [24]. Radiation therapy is an independent risk factor for accelerated atherosclerosis. This manifests as both micro- and macrovascular disease and can be progressive, despite being clinically silent until years after treatment. Any arteries or arterioles within the radiation field are potentially at risk.

In particular, radiation-induced inflammation results in accumulation of myofibroblasts and intimal proliferation with aggregation of lipid-rich macrophages. These inflammatory, pro-thrombotic plaques are more likely to rupture than more stable, less lipid-rich plaques. The likelihood of RT-induced IHD is magnified and accelerated by traditional cardiovascular risk factors, particularly hypercholesterolemia [25]. As far as myocardial fibrosis is concerned, we know that RT and anthracycline-containing-chemotherapy can induce interstitial fibrosis, therefore the "ischemic" pattern of MPI can be due to RT-induced fibrosis and/or could be biased by the anthracycline-induced fibrosis. And some patients with MPI abnormalities received also trastuzumab. The "multiple hit" hypothesis may hold true for the combination of anthracycline injury, trastuzumab-induced impairment of compensatory mechanisms and RT-induced damage. And, finally, we know the role of baseline risk factors, but what is the impact of cardiac risk factors that occur some years after RT? Postmenopausal overweight patients in follow-up may be very different from the young, slim patients seen at the baseline evaluation.

SPECT MPI is widely used in women to investigate suspected or known coronary artery diseases (CAD) and to stratify risk of IHD events [26]. Myocardial perfusion abnormalities both at rest and after stress are reported as reliable predictors of subsequent cardiac events in patients with ischemic heart disease, but we do not know the true meaning of post-RT MPI

abnormalities [27-29], CT coronary angiography yields greater accuracy than nuclear stress myocardial perfusion imaging for identifying anatomic lesions of the epicardial coronary arteries, but myocardial perfusion scan is able to identify a functional microvascular impairment. As reported in the recent JACC Scientific Expert Panel of Prevention, Diagnosis and Management of Radiation Associated Cardiac Disease, "single-photon emission CT and positron emission tomography can assess myocardial ischemia in RT-induced IHD. Studies are limited by small numbers, but show that 12% of asymptomatic patients have stress induced perfusion defects; and in patients receiving both RT and chemotherapy, a high proportion of new perfusion defects" is seen [2].

The lack of coronary stenosis does not mean the absence of IHD, we know that the gender-related phenotype of IHD in women is more likely a non-obstructive coronary artery disease. In this light MPI could be more effective that CT coronary angiography in identifying microvascular disease, and perfusion defects could appear earlier than contractile abnormalities detected with stress echocardiography. Moreover, advancements in SPECT technology with a decrease of the radiation dose and the potential to quantify myocardial blood flow, will likely increase the diagnostic yield of SPECT MPI in irradiated breast cancer patients. CFR estimated values <= 2.5 may be a valuable tool to evaluate the coronary arteries and may be considered a "sentinel" of "coronary endothelial health" [30], this value may be more sensitive than MPI abnormalities to detect early sign of RT-induced endothelial dysfunction.

The need to focus on traditional cardiovascular risk factors in RT-induced cardiotoxicity is commonly underlined, since the interaction of RT-induced endothelial dysfunction with other traditional cardiovascular risk factor may lead to clinical events. The 2013 Expert consensus defined the relative risk of Radiation-Induced-Heart Disease between 2 and 5.9 in irradiated high-risk patients with left early breast cancer patients and with >1 risk factors for Radiation-Induced inflammatory cascade [31]. Even with the limit of our exploratory analysis, our sample and the two case studies, highlight the pivotal role of traditional risk factors in baseline MPI abnormalities suggesting that a stress test at baseline may be useful to identify patients at highest risk of RT-induced cardiotoxicity In this regard it seems crucial to pay attention to the baseline MPI in patients with a history of hypertensive disorders of pregnancy. The cardiovascular system of these women that failed the stress of pregnancy has a permanent widespread endothelial dysfunction that is particularly vulnerable to the multifactorial vasculotoxicity of RT. MPI abnormalities are the epiphenomenon of this liability and call for a close monitoring and an aggressive control of all risk factors.

Furthermore, the unpredictable cardiotoxicity observed in a young female patient without known cardiovascular risk factors raises the intriguing issue of genetic predisposition to RT-induced cardiotoxicity. Radiation sensitivity seems to be influenced but the cumulative effect of multiple genetic polymorphisms [32].

6. Limits

The main limits of our study are represented by the small sample, the medium term clinical follow- up and the impossibility to evaluate CFR for all patients. Only a longer follow up (e.g.10-15 years) will tell us what is

the value of RT-induced early myocardial perfusion defects and how "safe" are ***normal*** epicardial coronary arteries that we found in 90% of our patients with MPI abnormalities. Regarding the exploratory analysis of baseline and post-RT MPI abnormalities in our population with a high prevalence of risk factors, a deep investigation with balanced samples of patients with and without risk factors would have probably offered more interesting insights.

7. Conclusions

Cardiovascular diseases are the leading cause of death in women. Even with the remarkable progress in radiotherapy techniques, RT-induced manifestations of IHD in early breast cancer patients has not to be underestimated. Considering the peculiar microvascular non–obstructive phenotype of IHD in women, in patients with a high suspicion of endothelial "vulnerability" a ***functional*** stress test with imaging modalities and CFR estimation could be more useful than ***anatomic*** tests to detect baseline microvascular disease and to predict how that cardiovascular system is going to cope with a stressful situation like a multiple-step cancer therapy. Unfortunately this scintigraphic modality is hampered by the radiation issue; while waiting for nuclear imaging techniques with less radiation impact, echocardiography-derived CFR should be considered.

Focusing on RT cardiotoxicity risk factors, the "uniqueness" of the "female specific" risk factors, such as hypertensive disorders of pregnancy, has not been fully addressed yet, resulting widely underestimated. Since the antiangiogenic-like status of women with a history of preeclampsia will likely interact with potentially vasculotoxic treatment such as thoracic RT, gynecologic history should become routine in the baseline evaluation of all early breast cancer female patients. A vulnerable endothelium is a call for aggressive treatment of all cardiovascular risk factors and for a healthy lifestyle to reduce the impact of RT-induced cardiotoxicity. And this was the case with the patient we described who radically changed her lifestyle behavior towards a "healthy type". MPI abnormalities in patients with no risk factors for cardiovascular disease might be due to genetic predisposition, research of genetic polymorphism should be strongly encouraged to smooth the way towards precision medicine. In a near future we will probably have tailored *gene-based-* and *"sex&gender"*-oriented oncologic treatments to select, as Hertz says, "the right dose for the right drug for the right patient" [33] and maybe the " right Grays for the right chest for the right *gende*r for the right patient". In the meantime, in early breast cancer irradiated patients, an accurate evaluation of traditional and emerging risk factors for IHD and a careful cardiac follow up, to aggressively treat baseline and subsequent risk factors for CAD is mandatory to limit the late clinical presentation of coronary events. Remarkable progresses have been made and the next future will see the widespread use in the clinical practice of the developing RT delivery protocols that minimize the chances of RT-induced cardiotoxicity. Meanwhile a close cardiac follow up is mandatory, it should start immediately after RT to treat oncoming risk factors and to counsel for a healthy lifestyle behavior. Multimodality imaging-based screening protocols to adequately identify early markers of RT-induced cardiotoxicity have to be implemented. As suggested by Pizzino et al. multimodality imaging with three-dimensional and speckle-tracking echocardiography [34] and cardiac Magnetic Resonance Imaging enriched with CFR estimate may

be a suitable option to monitor cardiotoxicity in early breast cancer patients. The final goal is to reduce the impact of RT-induced IHD in these patients.

Data Availability Statement

All data generated and analyzed during this study are included in this published article.

Conflict of Interest Statement

Authors declared no conflict of interest.

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