

Breast Radiotherapy and Early Adverse Cardiac Effects. The Role of Serum Biomarkers and Strain Echocardiography

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Abstract. Breast cancer radiotherapy has a clear benefit for both long-term survival and local recurrence rate. However, there is still much concern about the early radiation-induced heart toxicity. This article aimed to clarify the impact of certain cardiac biomarkers and strain echocardiographic imaging on the detection of early cardiac dysfunction. Several studies that reported changes in either echocardiographic and/or serum levels measurements after breast radiotherapy were searched. Despite the established role of cardiac biomarkers to predict late cardiotoxicity after radiotherapy, data concerning early cardiac damage are still lacking. Furthermore, although strain echocardiography represents a specific tool for the detection of cardiac morbidity in certain diseases, much interest concerns its role in the prediction of early heart failure after radiotherapy. Identification of new tools for the detection of early cardiotoxicity after breast radiotherapy may minimize the side-effects of therapeutic modalities in the clinical setting.

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Radiotherapy constitutes one of the most effective management methods for solid malignancies. Data from the Global cancer statistics (GLOBOCAN) indicate that there will be about 18.1 million new cancer cases worldwide in 2018 (1). Among these patients, more than 2 million will suffer from breast malignancies. There is no doubt that radiotherapy accompanied by other therapeutic modalities, including surgery and chemotherapy, has greatly contributed to reduced local recurrences and increased long-term survival rates for these patients (2). Although the major benefit of adjuvant radiotherapy in the local control of the disease is well established, many questions remain regarding the treatment-associated heart toxicity, which may adversely affect the quality of life of cancer survivors (3). Cardiac toxicity after breast cancer radiotherapy results from the exposure of a substantial volume of the heart to a dose, which is capable of adversely affecting the heart tissue. However, whether this could be averted by the most advanced radiation techniques still remains uncertain. Modern radiotherapeutic techniques and advances in treatment planning achieve reduced cardiac radiation exposures with the use of respiratory gating or blocking the heart in tangential field. Nevertheless, these contemporary newer techniques may still affect, to some degree, part of the heart, including the left ascending artery, increasing, thus, the risk of heart disease (4).

Several studies analyzed and confirmed the association between the radiation dose to heart and the increased risk of

heart disease (5-7). Available data suggest that as the dose of radiation rises, the risk of developing heart complications rises too. Specifically, patients with left side breast cancer clearly present higher possibility to develop cardiac events in comparison with right-sided cancers, while those with previous cardiac disease history obviously have an increased risk of heart damage, which can be observed even by exposure to low radiation doses (8, 9). In addition to the dose and the irradiated volume of the heart, the administration of certain chemotherapeutic agents comprises an additional risk factor of cardiotoxicity (10). However, patient-related factors that may also accelerate the development of radiation-induced cardiotoxicity consist of: younger age at radiotherapy, history of circulatory disease, diabetes and some known harmful lifestyle factors such as obesity, lack of activity, alcohol, smoking and hypertension (11).

The cardiotoxic effect of RT can be seen several years after irradiation and the increased risk may remain for at least two decades past radiotherapy (9). Various published data on radiation-induced heart disease have clearly highlighted the unfavorable impact of radiation on the heart tissue many years after radiotherapy, thus, influencing, the lifestyle of long-term cancer survivors (12, 13). Consequently, a prolonged follow-up seems mandatory for the observation of radiation induced cardiac events. Pericarditis, valvular dysfunction, cardiomyopathy and coronary artery disease are some of the severe late cardiotoxic effects, making the incidence of radiation-induced heart disease to be between 10–30 % within 5-10 years following irradiation (14).

Materials and Methods

We included any paper offering any data concerning strategies and measures for detecting early cardiotoxicity after breast radiotherapy in women treated for left breast cancer. Electronic databases were searched using synonyms for radiation therapy, cardiotoxicity, biomarkers and echocardiography in women with breast cancer. A filter was not used since any type of study was considered, without restriction to randomized controlled trials. PubMed, Cochrane Database of Controlled Trials, and SCOPUS were searched from 1993 to 2018 and with no language restrictions. Cross references from the included studies were hand searched. All titles and abstracts retrieved were printed and reviewed manually by two reviewers independently. The studies that clearly did not meet the inclusion criteria were excluded.

Impact of Radiation Dose on the Heart

Despite considerable uncertainty, it seems that cardiac effects of radiation are fairly dependent on both dose and fractionation of radiotherapy. In earlier studies it was noted that a radiation dose of 30 Gy might be the threshold dose for developing heart damage (15). In particular, patients who had received doses lower than 30 Gy for Hodgkin disease, presented much lower incidence of developing pericarditis.

Furthermore, one recent population control study including more than 2,000 women who were treated for breast cancer, highlighted that even extremely low radiation doses may adversely affect the heart tissue (16). Characteristically, it was observed that the risk of developing major coronary events increases linearly by 7.4 percent per one gray of radiation, with a mean radiation dose to the heart being 4.9 Gy. More specifically, this risk may be elevated for at least twenty years after irradiation and is related to the co-existence of other risk factors, such as circulatory and vascular disease. Moreover, a recent large meta-analysis including 39 studies with breast cancer survivors, revealed a higher risk of coronary disease and mortality during the first and second decade respectively, after radiation exposure (17). Nevertheless, the absolute risk seems to be too low to be able to offset the benefit of radiation. An even smaller cohort investigating the dose of radiation in the heart tissue, characteristically demonstrated a significant association between higher radiation dose and higher frequency of cardiac outcomes (18). Notably, they found that the risk of a coronary event increases by 16.5% per gray of radiation to the heart tissue, with the dose of 5 Gy to the left ventricle being the most predictive component.

However, despite improved treatment modality and different cardiac-sparing techniques, such as enhanced inspiration gating (EIG), deep inspiration breath hold (DIBH) and intensity-modulated radiotherapy (IMRT), there is still a risk of cardiac toxicity after breast radiotherapy (19). Consequently, according to the Quantec (Quantitative Analysis of Normal Tissue Effects in the Clinic-) guidelines, the whole organ of the heart should always be contoured as an organ at risk for left-sided breast cancer at each treatment planning (20). Specifically, the dose of 25 Gy must not affect more than 10% of the whole heart volume, while the mean heart dose must be kept lower than 26 Gy for standard fractionated radiotherapy. Furthermore, with regard to partial irradiation, it is estimated that by following classic fractionated radiotherapy the risk of cardiac mortality is lower than 1 percent for 15 years when one tenth of the whole heart volume receives less than 25 Gy (21). Nonetheless, given the fact that there is still a lack of studies about the radiation effect on different substructures of the heart, in the era of personalized medicine, the definition of more specific components regarding the association between radiation dose volume parameters and subsequent toxicity constitutes one of the biggest challenges.

Early Cardiotoxicity

Although much research has already been focused on the analysis of late radiation effects on the heart, more information is still needed concerning the early radiation toxicity, whose clinical assessment still remains difficult.

Actually, the early identification of radiation damage to the heart tissue might prove to be vital for the improvement of the quality of life of the breast cancer survivors. Therefore, specific cardiac serum biomarkers and strain rate imaging may play a significant role in the detection of early subclinical cardiac changes. Thus, those patients who are at a higher risk and may need close follow-up in order to achieve better outcomes, will be identified.

Serum Biomarkers

Serum biomarkers might play an important role in the detection of heart damage after radiotherapy. Several classical biomarkers have already been studied for their impact on the discovery of cardiac dysfunction after radiotherapy. Cardiac Troponin I (TnI) and cardiac Troponin T (TnT) are sensitive and specific markers of cardiac morbidity. During the past years, many researchers have extensively studied the significant role of TnI and TnT as useful biomarkers of cardiotoxicity in oncologic patients after chemotherapy (22, 23). However, data regarding the value of these cardiac markers after breast radiotherapy are missing. Furthermore, brain natriuretic peptide (BNP) and its amino-terminal fragment (NT pro-BNP) are natriuretic hormones that are released from the heart into the circulation, predicting heart failure (24). Many studies revealed increased levels of these peptides after radiotherapy, which suggests that these proteins can become potential markers for the early detection of radiation-induced cardiotoxicity. Characteristically, in 1995 Hughes-Davies L *et al.* enrolled 50 patients with left breast cancer aiming to investigate the potential elevation of TnT levels during radiotherapy (25). However, they found no differences comparing the concentration of the protein before and after irradiation. Furthermore, Nellessen *et al.* analyzed the cardiac biomarkers TnI and BNP before and during the first week of radiotherapy (26). Although they showed elevated levels of both cardiac biomarkers after radiotherapy, the outcomes were not characterized clinically significant. In agreement with the foregoing, D'Errico *et al.* found no changes in the levels of TnT in left-sided breast cancer patients 5 to 22 months after radiotherapy. Nevertheless, they clearly demonstrated increased levels of NT-pro BNP (27). On the contrary, Erven *et al.* found elevated mean levels of TnI in 51 left-sided breast cancer patients after irradiation (28). In line with the above, one recent prospective, non-randomized study revealed a positive correlation between increased TnT levels and higher radiation dose for the whole heart and the left ventricle in 58 left-sided breast cancer patients (29). As a matter of fact, these outcomes attract a great deal of interest on whether elevated levels of the above-mentioned biomarkers after breast radiotherapy could be related to an increased risk of developing cardiovascular morbidity in the near future.

Moreover, since radiation has a tendency of motivating inflammatory processes, C- reactive protein (CPR), an acute phase protein, whose expression is related to inflammatory cytokines such as interleukin (IL)-1, IL-6 and tissue necrosis factor- α (TNF- α), may be an additional potential predictive marker of cardiotoxicity after irradiation. Many studies have previously highlighted the strong association between elevated levels of high-sensitivity C-reactive protein (hsCRP) and adverse prognosis in patients with heart failure (30-32). Although numerous studies have examined the potential clinical value of CRP measurements in the detection of cardiotoxicity in patients after chemotherapy, there is lack of data about the established role of CRP in the early prediction of myocardial changes. Indeed, Morris *et al.*, after measuring cardiac Troponin I (cTnI) and CRP levels in 95 breast cancer patients during their chemotherapeutic schema, found no relationship between these biomarkers and changes in left ventricular ejection fraction (LVEF) (33). Moreover, two further studies aimed to illustrate the value of cardiac biomarkers as a most promising tool to predict early cardiac injury in patients after chemotherapy (34, 35). They similarly found no significant association between elevated levels of CRP and early echocardiographic changes. On the contrary, Lipshultz *et al.* enrolling 201 childhood cancer survivors demonstrated a higher clinical value of CRP. In particular, increased levels of this protein were found to be related to lower levels of left ventricular (LV) mass, regardless of prior exposure to cardiotoxic therapy (36).

According to these findings, it seems that despite the variability of outcomes, certain serum biomarkers may represent a promising tool for the prediction of early myocardial dysfunction, leading to a more appropriate stratification of those patients who demand closer monitoring. Nevertheless, further studies with more specific biomarkers are certainly needed to empower this association. Therefore, this could lead to a deep and multidisciplinary comprehension of all the potential biological mechanisms involved in heart dysfunction after radiotherapy, so that patients receive the greatest benefit possible.

Strain Rate Imaging

Speckle tracking echocardiography may be used as a valuable tool for the quantification of regional myocardial function, which could be proven vital, taking into account the association between abnormalities of the left ventricle and lower survival rates (37). Specifically, strain and strain rate imaging calculated by 2-dimensional speckle tracking echocardiography (2D-STE) might constitute a highly specific clinical approach for the detection of early subclinical abnormalities of the heart tissue. Indeed, by measuring myocardial viability, these parameters could be used for the assessment of early myocardial damage (38-40).

Several studies have well defined the superiority of strain imaging over LVEF regarding the evaluation of left ventricular function, thus highlighting the higher prognostic value of the aforementioned and accordingly its ability to show which patients have a higher risk of developing heart damage in the near future (41, 42). Furthermore, a lot of studies have already proposed the role of strain imaging in revealing subclinical heart damage in various conditions. For instance, Kato *et al.* previously calculated strain and strain rate parameters in 50 patients in order to illustrate the sensitivity of this method to adequately differentiate hypertrophic cardiomyopathy (HCM) from hypertensive left ventricular hypertrophy (H-LVH) (43). A more recent study led to similar results some years later (44). Moreover, it was well shown that strain imaging can effectively detect subclinical left ventricular changes in diabetic patients (45, 46). Apart from that, many investigators have also demonstrated the relationship between strain imaging and the detection of early heart dysfunction after the administration of chemotherapeutic agents. Actually, Stoodley *et al.* found reduced post-chemotherapy strain parameters in 52 women with breast cancer; the capacity of strain imaging to predict early cardiotoxicity was also confirmed by Sawaya *et al.* one year later (47, 48). More recent studies also supported the decrease of strain parameters after chemotherapy, hence, declaring the potential ability of this method to predict early dysfunction of the heart tissue (49, 50).

Although several researchers have examined the potential role of strain imaging in revealing myocardial changes in several diseases, only few succeeded to investigate the impact of these parameters on the detection of the early heart damage in breast cancer patients after radiotherapy. Specifically, Wang *et al.* assessed early heart changes after thoracic radiotherapy by analyzing various data of strain rate in the left ventricular walls (51). Notably, they separated 40 patients into three groups according to the time of the radiotherapeutic process: 1-3 days before radiotherapy, 2-3 weeks and 5-6 weeks during radiotherapy, respectively. What they observed was that the lowest strain and conventional echocardiographic parameters were found among patients with the longest duration and highest dose of radiotherapy, demonstrating, that strain rate imaging can successfully indicate early radiation cardiac effects. Similar results have also been illustrated by Chang *et al.* in 40 patients a few years later, highlighting the value of strain rate imaging in the detection of early cardiac dysfunction after thoracic radiotherapy (52). Specifically, by dividing patients into 5 groups according to dose and duration of radiotherapy, they evaluated all the echocardiographic and strain rate data. As a result, they detected a significant relationship between longer duration and higher dose of radiotherapy and lower strain rate and echocardiographic parameters, declaring that strain rate may reveal earlier the radiation induced heart damage in patients who have had

previous thoracic radiotherapy. Similarly, to the previous observations, Tsai *et al.* demonstrated lower left ventricular systolic function and strain rate parameters in 47 patients at least two decades after previous thoracic radiotherapy with or without chemotherapy (53).

Moreover, the same year, Erven *et al.* published their data about the role of strain rate imaging in revealing early myocardial dysfunction after breast cancer radiotherapy (54). In particular, studying the changes of strain parameters in 20 patients with left breast cancer and 10 with right breast before radiotherapy, at the end of it and after two months, they characteristically found reduced post-radiation strain and strain rate levels in all patients with left breast cancer. More recently, a further study conducted by the same researcher also confirmed decreased strain measurements, mainly in anterior segments, in 51 patients with left-sided breast cancer 8 and 14 months after radiotherapy (28). Two years later, Lo *et al.* showed that the strain parameters remained decreased 6 weeks after the end of radiotherapy in 40 women with left-sided breast cancer, thus, stressing the possibly severe role of 2-dimensional strain imaging (SI) in the early detection of left ventricular dysfunction (55). Finally, quite different results have been reported by Heggemann *et al.* in 49 patients where they demonstrated reduced measurements of longitudinal strain in some segments, but also, stabilized global strain levels 24 months after radiotherapy (56). Thereafter, it seems to be clear that strain rate echocardiography may successfully reveal early subclinical cardiac abnormalities after radiotherapy in some subregions of the heart.

In conclusion, it appears that early negative effects on the heart and specifically on the myocardium and left ventricle may be detected by strain echocardiographic imaging. Many studies clearly demonstrated decreased levels of strain parameters after radiotherapy promoting this approach as a promising method for the better quantification of early changes in heart function after radiotherapy. However, much more systematic research with larger studies and longer follow-up is surely required for an improved assessment and exploitation of this sensitive echocardiographic tool regarding the field of cardiotoxicity after radiotherapy.

Conclusion

Breast cancer constitutes the most frequent type of neoplastic disease among females, a fact that arises major concern regarding the potential effects of the whole therapeutic management, which is required on a case-by-case basis. During the last two decades the relationship between breast radiotherapy and late toxicity of the heart tissue has been extensively described. However, taking into account the high survival rate of breast cancer patients and subsequently how important it is for these patients to reduce morbidity to a minimum, much information is further needed for the

establishment of the most appropriate methods that could early predict those who are at a higher risk. Actually, several biomarkers have been well documented for their relation to the prediction of heart changes after radiotherapy. Nevertheless, there is still a lack of robust results regarding the establishment of characteristic biomarkers capable of revealing early cardiotoxicity. Thus, an intensive evaluation of the changes of specific cardiac biomarkers during a longer follow up after radiotherapy might be a highly useful tool for the early detection of potential toxicity to different subregions of the heart. In addition, conventional echocardiography has been widely used for the assessment of radiation-induced cardiotoxicity for more than two decades. However, strain imaging seems to be a more sensitive method for the evaluation of heart function after radiotherapy, which has already been reported by certain studies. Nonetheless, further research is certainly required for the establishment of this promising echocardiographic parameter as a valuable method for the detection of heart failure early after radiotherapy. Accordingly, this could enhance the management of breast cancer patients and improve their quality of life.

In conclusion, it is imperative that prevention and early diagnosis of post-radiation heart toxicity is the priority of the whole therapeutic process. Thereafter, novel ideas based on this aim are considered fruitful leading to more appropriate therapeutic techniques individually for each patient.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

All the Authors have 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 manuscript has not been published, or submitted for publication elsewhere.

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