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Opinion

Modern Radiotherapy and Cardiac Toxicity in Breast Cancer

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Abstract

Radiotherapy (RT) is a mainstay of Breast Cancer (BC) patients therapy. Nonetheless, unintended irradiation of the heart and its substructures can result in cardiac toxicity, jeopardizing long-term survivors' quality of life (QOL). Advances in RT delivery techniques deeply impacted this clinical scenario. Indeed, given the non-negligible burden of cardiotoxicity, modern cardiac sparing approaches have a pivotal role. Nonetheless, further evidence is eagerly awaited regarding patients' selection, clinical predictors, biological markers, and particularly heart substructures dose-constraints.

Keywords: breast cancer; radiotherapy; cardiac toxicity; DIBH; QOL; cardiac sparing

1. Introduction

A crucial goal for modern cancer care is maintaining the balance between achieving optimal disease control and minimizing the risk of late-induced sequelae, particularly in patients with more prolonged expected survival. In terms of radiotherapy (RT), thoracic cancers can be particularly challenging due to the presence of "critical" organs at risk (OARs), namely the heart and lungs. Breast cancer (BC) is the first female cancer worldwide [1]. In Italy, about 55,000 new cases of BC were diagnosed in 2020 [2]. Postoperative RT is a mainstay of BC treatment, drastically impacting disease control and leading to survival benefits [3–6].

Nonetheless, unintended irradiation of the heart and its substructures can result in cardiac toxicity, jeopardizing survivors' quality of life (QOL) [3,4,7,8]. Indeed, although patients identify the cure as their most important treatment outcome, late complications related to treatment are a recognized problem as follow-up increases among those cured within this oncologic setting.

2. Breast RT and Heart Disease Risk

All cancer treatment modalities are associated with long-term morbidities, magnified in long-term survivors [9]. In terms of cardiac toxicity, anthracycline-based chemotherapy (ChT) regimens are associated with a risk of ventricular or coronary artery alterations, increasing when RT doses to large heart volumes are involved [10]. Radiation-induced heart diseases (RIHD) have several pathogenic pathways, such as microvascular injury, myocardial remodeling, oxidative stress, inflammation, fibrosis, and apoptosis, contributing to: vessels micro- and macroangiopathy leading to coronary artery disease (CAD), damage of the atrioventricular node/conduction system, accelerated atherosclerosis, and myocardial fibrosis [11–14]. These pathways and the corresponding clinical implications are under the research spotlight [15,16]. Indeed, long-term radiation-related cardiac toxicity can be seen as arrhythmias, pericarditis, congestive or ischemic heart disease, and valvular damage [17].

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, comparing surgery plus RT versus surgery alone in BC patients, showed an increase of 27% in mortality from cardiac events, mainly caused by coronary artery disease [3]. Moreover, the 15-year follow-up update of the EBCTCG confirmed a correlation between the mortality related to cardiac disease and the doses to the heart [4]. There is evidence that this correlation is stronger in trials reporting larger mean cardiac doses and that the risk of death from heart disease increases by 3% per Gy ($p < 0.00001$) [18]. Another series showed a 7% risk of developing late coronary artery disease following RT [11]. After a median follow-up time of 12 years, a cardiac stress test was performed in 82 patients. Alterations in the stress tests were significantly different between left- and right-sided BC patients (59% *vs* 8% respectively, $p = 0.001$) and up to 70% of the alterations involved the left anterior descending coronary artery (LAD-CA) territory, suggesting a correlation between left-sided irradiation and the increased risk of late radiation-induced coronary artery disease [11].

Overall, BC patients receiving incidental cardiac radiation have been estimated to have a relative risk of developing cardiac events between 1.2 and 3.5 in a 15-year follow-up period, compared with patients that did not receive RT [3,7,19–21]. A dose >30 Gy, younger age of radiation exposure, and the cardiovascular risk factors in medical history, are documented risk factors for developing RIHD within a year or 2 of exposure [7]. However, the correlation between heart damage and dose radiation exposure still needs to be fully defined. The low-dose contribution should also be furtherly clarified [22]. Radiotherapy has

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evolved during the past decades. Mean heart doses (MHD) have certainly benefited from the delivery technique improvements and the advent of advanced image guidance. Currently, mean doses of radiation to the whole heart from right-sided breast RT are typically about 1 or 2 Gy [7]. For left-sided breast RT, the doses are usually higher but widely variable: MHD of 5 Gy is generally observed [7], and in some cases, e.g., in case of a small distance between the heart and the thoracic wall and when internal mammary irradiation is required, the mean dose may be around 10 Gy [23–26]. MHD of 3 Gy during breast RT is likely to increase the risk of death from cardiac cause from 1.9 to 2.4% and, particularly, the risk of an acute coronary event from 4.5 to 5.4% [7]. Darby *et al*. [7] showed an increase of 7.4% in the risk of major coronary events per each Gy of MHD, with no apparent threshold and regardless of prior cardiac risk factors. The increase starts within the first 5 years following RT and continues to the third decade after RT [7].

Furthermore, left-sided breast RT and chest-wall irradiation have been associated with more significant mortality in patients developing cardiac toxicity after a decade from treatment [27–29].

A cohort study by van den Bogaard *et al*. [30] included 910 consecutive female patients with BC treated with postoperative RT. The primary end point was cumulative incidence of acute coronary events (ACEs) within 9 years of follow-up. The median MHD was 2.37 Gy. The cumulative incidence of ACEs increased by 16.5% per Gy ($p = 0.042$). The volume of the left ventricle receiving 5 Gy (LV-V5) was the main prognostic dose-volume metric [30].

The Breast Cancer and Cardiotoxicity Induced by Radiotherapy (BACCARAT) prospective study consisted of left or right unilateral BC patients treated with 3D-Conformal RT (3D-CRT) between 2015 and 2017 [31]. Dose distributions were generated for 89 left-sided BC patients (MHD = 2.9 ± 1.5 Gy, Dmean_LAD = 15.7 ± 3.1 Gy) and 15 right-sided BC patients (MHD = 0.5 ± 0.1 Gy; Dmean_right coronary artery = 1.2 ± 0.4 Gy). From the study analysis MHD emerged as a parameter not sufficient to predict with confidence individual patient dose to the LV and coronary arteries, in particular the LAD [31].

Indeed, assessing the substructures doses is the key to reduce the risk of cardiac complications [23]. Moreover, coronaries motion and the use of compensatory expansion margins should be taken into account [32].

Thus, modern cardiac avoidance approaches during BC irradiation have become a significant matter of interest due to the potential benefit of decreasing cardiac toxicity and its related clinical manifestations, particularly for left-sided disease [3,7].

3. Cardiac Sparing Approaches

Over the last decades, a significant contribution to minimizing the dose to the heart during BC irradiation and, subsequently, to potentially reduce the risk of radiation-induced cardiovascular events has been reached thanks to the development of modern RT techniques.

Intensity-modulated RT (IMRT) and volumetric arc therapy (VMAT) have been increasingly adopted in breast RT, especially for left-sided presentations [33–35]. Compared to 3D-CRT, intensity-modulated techniques can improve cardiac dosimetry [36–39].

Before generating treatment plans, particularly for left-sided and young BC patients, an accurate choice of the plan technique should be made [40].

Modern RT may also be combined with breathing-adapted approaches to achieve significant reduction in the heart dose [41,42].

The breath-hold approach is one of the most well-investigated cardiac-avoidance strategies. Indeed, inspiration breath-hold gives the best cardiac dislocation since the heart moves away from the chest wall, decreasing the heart volumes exposed to irradiation [43–46]. Moreover, such an approach may allow for expansion margins reduction, resulting in OARs' major protection [47]. Deep inspiration breath hold (DIBH) has several technical options [48–56].

Sakka *et al*. [35] reported a significant reduction in the dose to the heart and the LAD-CA observed with DIBH compared to free-breathing (FB) by increasing the heart-to-chest wall distance in both IMRT and VMAT plans.

Korreman *et al*. [57] showed a drastic reduction in the heart V50 and the median LAD-CA volume for DIBH in left-sided presentations. An extensive systematic meta-analysis comparing DIBH and FB in a large left-sided BC patients cohort showed a significant DIBH dosimetric benefit regarding both the heart and LAD-CA ($p < 0.01$) [58]. DIBH may also offer some advantages in patients receiving RT to the internal mammary chain [59].

Noteworthy, the role of partial breast (PB) irradiation as a cardiac sparing approach has also been evaluated.

Compared to the whole breast irradiation (WBI), accelerated partial breast irradiation (APBI) can decrease the heart and surrounding OARs exposure [60–64]. However, few studies compared APBI and WBI or focused on cardiovascular toxicity [62–64].

Chiang *et al*. [64] recently conducted a planning comparison study comparing the critical OARs dosimetry among PB irradiation, including both Interstitial Brachytherapy (ISBT) and external beam radiotherapy (PB-EBRT), and WBI in 12 left-sided BC patients. The MHDs in both APBI techniques were all significantly lower compared to the WBI technique ($p < 0.05$): the MHDs were 1.05, 0.47 and 3.24 Gy in the ISBT plan, the PB-EBRT plan, and the WBI plan, respectively [64]. The LAD-CA mean dose and Dmax were significantly lower in both the APBI plans (with no significant difference between the ISBT and PB-EBRT plans) compared to the WBI plan: LAD-CA mean doses were 1.68, 0.49, and 3.34 Gy, and LAD-CA Dmax(s) were 3.08, 1.80 and 12.13 Gy for ISBT, PB-EBRT and WBI respectively [64].

Finally, proton therapy (PT) has to be taken into account when mentioning modern RT approaches. Given unique ballistic properties, extreme OARs avoidance can be reached when treating the thoracic district with PT [17].

Fagundes *et al*. [65] compared PT with 3D-CRT, helical tomotherapy, and VMAT in 10 patients with stage III left-sided BC. The MHD was significantly ($p < 0.001$) decreased with the use of PT (1.2 $\pm$ 0.42 Gy (relative biological effectiveness (RBE)) compared with 3D-CRT (6.8 $\pm$ 2.08 Gy), helical tomotherapy (10.2 $\pm$ 1.6 Gy), and VMAT (8.2 $\pm$ 1.13 Gy). The PT heart-sparing benefit emerged even for plans including the internal mammary nodes compared to the photon ones not including the internal mammary nodes [65].

In a systematic review of published clinical data, Kammerer *et al*. [66] highlighted that PT often decreases the MHD by a factor of 2 or 3, i.e., 1 Gy with PT versus 3 Gy with 3D-CRT and 6 Gy for IMRT [66].

Nevertheless, PT uncertainties have to be considered [17,67], including mainly the RBE changes along the beam path and uncertainties due to tissue density variations/organ motion [67]. Thereafter, coronary arteries certainly represent the structures at the highest risk in this context [67].

4. Conclusions

Cardiotoxicity can unfavorably counterbalance the oncological benefits of RT. Modern RT, based on upgraded delivery techniques, positively impacts such adverse events risk reduction. Indeed, given the non-negligible burden of cardiotoxicity in long-term survivors, modern cardiac sparing techniques have a pivotal role in this clinical scenario. Nonetheless, further evidence is awaited regarding patients' selection, clinical predictors, biological markers, and heart substructures dose-constraints.

Author Contributions

GCI and VC gave the idea and wrote the main manuscript text. GCI, VC and UR decided the method of the literature review. GCI, VC and UR reviewed references. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Giuseppe Carlo Iorio is serving as one of the Guest editors of this journal. We declare that Giuseppe Carlo Iorio had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Felix Wong.

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