Archives of Cardiovascular Disease (2016) xxx, xxx—xxx

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Elsevier Masson France EM|consulte www.em-consulte.com/en

SCIENTIFIC EDITORIAL

Breast cancer radiotherapy: A case of double jeopardy

Radiothérapie pour le cancer du sein : une double peine

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Received 25 August 2016; received in revised form 5 September 2016; accepted 7 September 2016

KEYWORDS
Radiotherapy;
Cardiovascular diseases;
Cardiotoxicity;
Cardiac imaging;
Biomarkers

MOTS CLÉS
Radiothérapie ;
Maladies cardiovasculaires ;
Cardiotoxicité ;
Imagerie cardiaque ;
Biomarqueurs

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women. Death rates have been decreasing in many developed countries over the past 25 years, largely as a result of early detection through mammography and improved treatments, and the 5-year relative survival rate is now around 85%, reaching nearly 100% for stage 0 or stage I [1].

There are several ways to treat breast cancer, depending on its type and stage: local treatments, including surgery and radiation therapy, possibly combined with systemic treatments, including chemotherapy such as anthracyclines or paclitaxel, hormonal therapy, such as tamoxifen, and targeted therapy for HER2-positive breast cancer, such as trastuzumab (Herceptin®).

Cardiotoxicity is a well-recognised adverse effect of many commonly used cancer therapies. If systemic treatment-related cardiotoxicity — particularly chemotherapy — has been studied extensively and has a major place in cardio-oncology field, radiotherapy-induced cardiotoxicity is somewhat relegated to the background of the specialty and research [2]. Why? First, because most patients have a combination of systemic treatment and radiotherapy; only about 30% have radiotherapy without chemotherapy. Second, since the 1970s, a clear association has been shown between therapeutic doses of thoracic irradiation and an increased risk of cardiovascular disease in cancer survivors, although these effects may take decades to become

Abbreviations: CI, confidence interval; Gy, Grays; MRI, magnetic resonance imaging; RR, relative risk.

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http://dx.doi.org/10.1016/j.acvd.2016.09.001

Please cite this article in press as: Jacob S, Ferrières J. Breast cancer radiotherapy: A case of double jeopardy. Arch Cardiovasc Dis (2016), http://dx.doi.org/10.1016/j.acvd.2016.09.001

symptomatic [3]. However, as awareness of radiotherapy cardiotoxicity has grown and technology has developed, in terms of breast cancer radiotherapy regimens, the range of doses to the heart has changed over the past few decades, as a result of the development of new techniques, beam energies and target doses, and different volumes, etc. [4]. Nevertheless, some residual risk of cardiac side effects remains.

Breast radiotherapy can lead to side effects because of the presence of neighbouring normal cardiac tissue within the irradiation field, and all the structures of the heart, including the pericardium, the myocardium, the valves, the conduction system and the coronary arteries have the potential to be damaged by irradiation. For these women, the breast is irradiated to about 50 Grays (Gy) in 2 Gy fractions, although only a small part of the heart is exposed to high doses, and dose distributions vary considerably depending on tumour location and the radiotherapy technique used. For breast cancers treated between the 1950s and the 1990s, the average dose to the entire heart ranged from 0.9 to 14 Gy for a left breast cancer and from 0.4 to 6 Gy for a right breast cancer, reaching 3 to 17 Gy and 2 to 10 Gy, respectively, when the internal mammary chain was also irradiated [5]. These doses were divided by a factor of 5 between the 1970s and the 2000s. Nevertheless, some regions of the heart, especially at the apex of the left ventricle or the left anterior descending artery, still receive high doses exceeding 20 Gy [6], which may continue to induce cardiac lesions.

Increased cardiac morbidity and mortality rates are well documented after breast radiotherapy, especially after some of the radiotherapy techniques that were used in the past, with long-term cardiac toxicities — such as heart failure, coronary artery disease, myocardial infarction and, finally, cardiovascular death — appearing more than 10 years after radiotherapy. The Early Breast Cancer Trialists' Collaborative Group carried out a meta-analysis of mortality from randomized trials of radiotherapy versus no radiotherapy, which showed a significant excess of cardiovascular death in women who received radiotherapy (relative risk [RR]: 1.27, standard error: 0.07; $P = 0.0001$), and the risk of cardiac death was greater for women with left-sided cancer (mean cardiac doses 12 Gy, RR: 1.44, standard error: 0.11; $P = 0.001$) than for those with right-sided cancer (mean cardiac dose 5 Gy, RR: 1.18, standard error: 0.06; $P = 0.001$). Another recent study by McGale et al. [7] analysed the incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden from 1976 to 2006, and found that left cancer radiotherapy versus right cancer radiotherapy incidence rate ratios were significantly increased for acute myocardial infarction (RR: 1.22, 95% confidence interval [CI]: 1.06—1.42), angina (RR: 1.25, 95% CI: 1.05—1.49), pericarditis (RR: 1.61, 95% CI: 1.06—2.43) and valvular heart disease (RR: 1.54, 95% CI: 1.11—2.13). Based on this population, a case-control study was performed, including 963 women who experienced a major coronary event after radiotherapy compared with 1205 controls who were also irradiated, but did not have a major coronary event [8]. This analysis showed that the rate of major coronary events increased linearly with mean cumulative dose to the heart, by 7.4% per Gy (95% CI: 2.9—14.5; $P < 0.001$).

Long before the onset of the clinically significant cardiac events that occur many years after radiotherapy, several studies using anatomical and functional imaging have shown that heart injury is usually subclinical, and may occur over the first weeks, months or years after completion of treatment. This injury is usually irreversible, and its prediction is the most important challenge. Echocardiography can be used to evaluate myocardial dysfunction. Global longitudinal strain and strain rate assessed using automated two-dimensional speckle-tracking echocardiography is a recent technique for detecting and quantifying subtle disturbances in left ventricular systolic function. In particular, this method was used in the context of detecting cardiotoxicity of recent breast radiotherapy: strain and strain rate were significantly decreased (by a mean 5%) during the first year following radiotherapy [9,10]. This suggested that a change in global longitudinal strain could be used to detect early subclinical changes in left ventricular systolic function, and is concordant with the recent publication of European recommendations for the evaluation of cardiovascular complications after radiotherapy in adults, including, in particular, echocardiography examination [11]. Cardiac magnetic resonance imaging (MRI), which is the gold standard for the measurement of ventricular volumes and function, has the unique ability to characterize myocardial tissue, and to potentially identify early signs of cardiac injury. A recent German study, which combined speckle-tracking echocardiography and cardiac MRI in a 2-year follow-up of a sample of 50 breast cancer patients treated with radiotherapy, also observed subclinical cardiac changes [12]. More advanced use of cardiac MRI, such as estimation of extracellular volume fraction using T1 mapping, can identify diffuse patterns of myocardial injury likely to be associated with cancer drug therapy [13], but requires further investigation, in particular for radiation-induced cardiotoxicity. At the coronary artery level, retrospective studies based on records of patients treated with breast radiotherapy who had undergone coronary angiography many years after radiotherapy, revealed a link between radiation and location of stenosis, as stenoses were often present in the left anterior descending artery, which showed the importance of simultaneous consideration of the location of radiation doses at the structures of the heart combined with localized effects, particularly in the coronary arteries [14,15]. With a much shorter follow-up, coronary computed tomography angiography was used for patients treated with radiation therapy to the chest for Hodgkin's lymphoma [16,17]. Based on the precise analysis of 15 segments of coronary arteries per patient, an increase in calcified and non-calcified plaques during a 2-year follow-up was detectable, and could probably also be observed for breast radiotherapy patients.

There are no specific circulating biomarkers of radiation-induced heart damage at the present time. Potentially relevant biomarkers differ depending on the type of injury (microvascular rarefactions, coronary damage, tissue inflammation). Among classical biomarkers, N-terminal pro-B-type natriuretic peptide and troponin have been shown to be potential biomarkers for cardiac damage after radiotherapy [18—20]. Circulating blood-based biomarkers are actively under investigation as possible alternatives or

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