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Cardiovascular Screening and Prevention in Female Breast Cancer Patients Receiving Radiotherapy

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Abstract

Aims: Breast cancer patients receiving radiotherapy have an excellent oncological prognosis. However, these patients are at risk for long-term cardiovascular iatrogenic events and currently no individualized cardiovascular screening and prevention is routinely performed.

Methods and Results: By integrating data of the SCORE risk charts and radiotherapy excess ratios, we were able to develop 10-year cardiovascular mortality risk charts based on mean heart dose, age, systolic blood pressure, smoking-status and cholesterol for high- and low-risk regions in Europe.

Conclusion: Breast cancer patients are long-term survivors and individualization of breast radiotherapy and cardiovascular screening and prevention is warranted, not only based on cardiovascular risk factors but also heart dose.

Keywords: Breast cancer; Radiotherapy; Cardiovascular mortality

Breast Cancer Patients at High Cardiovascular Risk

Breast cancer is the most frequently diagnosed malignancy in females and has a favorable oncological prognosis. One in eight women will develop breast cancer and nine out of ten breast cancer patients are still alive 5-years after breast cancer diagnosis [1]. However, these long-term survivors are at risk of cardiovascular morbidity and mortality due to common risk factors (i.e. smoking, sedentary life style, obesity, etc.) and iatrogenic effects related to Radiotherapy (RT) and systemic treatments including chemotherapy, targeted therapy and hormonal therapy. Breast cancer patients have a hazard ratio of 1.8 for cardiovascular mortality [2]. European and American cardio-oncological directives have been established in order to optimize cardiovascular prevention, screening, monitoring and treatment for cancer patients [3-6].

Cardiovascular morbidity due to breast cancer treatment includes valvular disease, ischemic heart disease, dysrhythmias, hypertension, heart dysfunction or failure, pulmonary hypertension and pericarditis. For example, the risk of left ventricular dysfunction due to doxorubicinis 3% to 5%, 7% to 26% and 18% to 48% for cumulative doses of 400 mg/m, 550 mg/m and 700 mg/m, respectively [4,6]. Currently there is a trend towards more intensified treatments, including dose dense chemotherapy and combination therapies (dual HER2 blockade, etc.), even potentially increasing cardiovascular risk. Left ventricular ejection fraction surveillance is performed during and after anthracycline therapy and/or HER2-directed therapy [5]. While RT-induced cardiovascular morbidity and mortality is well documented no routine screening and prevention is currently performed [7-10].

Radiotherapy Induced Cardiac Morbidity and Mortality

Radiotherapy plays an essential part in breast cancer treatment; it halves the recurrence risk and decreases breast cancer death by about one sixth after breast sparing surgery [11]. Until the 90s it was widely accepted that the heart was relatively radioresistant and therefore no heart protection was performed. Afterwards it became apparent that left- *vs.* right-sided breast cancer patients had more risk of fatal myocardial infarction due to increased heart dose. Neither the radiation induced dose/volume-effect relationship, nor the pathophysiology of radiation-induced cardiac morbidity are entirely understood. It is probably interplay between myocyte ischemia/injury, inflammation, fibrosis, oxidative stress and microvascular dysfunction [6].

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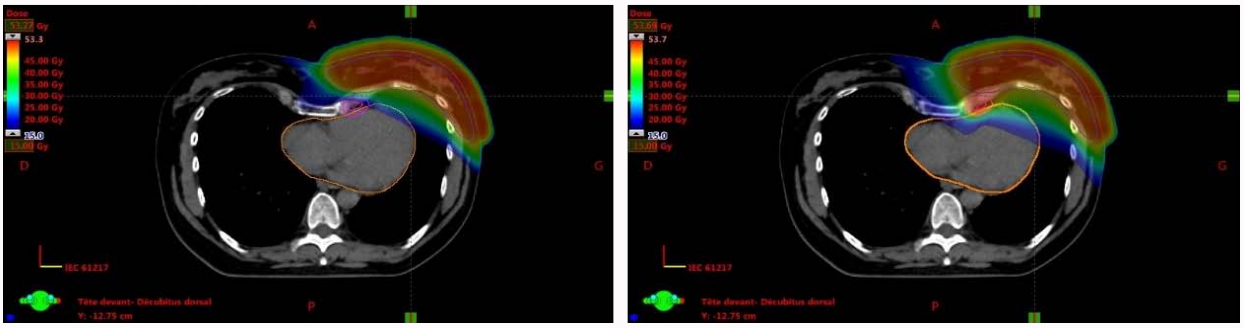

Figure 1: Isodose distribution of a patient treated without (left) and with (right) the inclusion of the internal mammary chain region (indicated in pink), resulting in a higher cardiac dose.

A recent cohort study involving 1,934,248 patients from 22 countries with an inter quartile range of breast cancer diagnosis during 1987-2002 [7], demonstrated that cardiac mortality was higher in left- *vs.* right-sided cancer with a rate ratio of 1.13, when chemotherapy was administered the rate ratio even increased to 1.42. Moreover cardiac mortality risk was higher in younger patients, increased from time since cancer diagnosis and lasted into the third decade after exposure. A meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) including 75 randomized radiotherapy versus no radiotherapy trials showed a radiotherapy-induced cardiac death rate ratio of 1.30 [8], especially due to coronary heart disease. A linear relationship has been found between heart dose and cardiac morbidity and mortality [8-10]. The higher the heart dose the higher the risk of major coronary events including death from ischemic heart disease, myocardial infarction and coronary revascularization, with no apparent threshold dose. This cardiovascular risk starts within the first 5 years after radiotherapy and is related with individual cardiovascular risk factors including hypertension and smoke status [8-10].

Breast radiotherapy varies between patients, mainly due to differences in individual anatomy, treatment side or regions, RT techniques and protocols. It has evolved over the past decades resulting in a decreased heart dose due to advanced treatment techniques, position alterations, inspiration related techniques or combinations [12]. Still in some patients it is difficult to achieve a low heart dose, for example in a patient with a pectus excavatum or when internal mammary chain irradiation is performed, which is located intra-thoracic posterolateral of the sternum. Figure 1 shows a treatment plan for the same patient without (left-side) and with (right-side) the inclusion of the internal mammary lymph node region, resulting in an increased heart dose. These individual differences in breast radiotherapy results in a wide variability in heart doses and hence cardiovascular risk.

Individualizing Cardiovascular Screening and Prevention after Breast Radiotherapy

In the EBCTCG-meta-analysis the absolute cardiac mortality risk from modern RT is estimated as 1% for smokers and 0.3% for non-smokers [8]. However there is a large range in individual cardiovascular risk factors and heart dose as shown in Figure 1. Breast radiotherapy varies between patients and should be taken into account in order to estimate the cardiovascular mortality risk. A breast cancer patient with a low cardiovascular risk profile might become a high-risk patient when receiving a high heart dose. Recently, we published individualized 10-year cardiovascular mortality risk charts in the Journal of the European Society of Radiation Oncologists by integrating data from the SCORE risk charts with data from the EBCTCG-trial [8,13,14]. Enabling us to estimate the individual 10-year cardiovascular mortality based on mean heart dose, gender, age, systolic blood pressure, smoking-status and cholesterol for high- and low-risk regions in Europe [13].

Example 1: A 56-year old, non-smoking patient from France (low-risk region) with cholesterol 220 mg/dL and a systolic blood pressure of 160 mmHg has a 10-year cardiovascular mortality risk of 1%, adding breast radiotherapy with a mean heart dose of 2 Gy or 8 Gy will increase her risk with 0.1% or 0.2% respectively.

Example 2: A 64-year old, smoking patient from Bosnia (high-risk region) with cholesterol 260 mg/dL and a systolic blood pressure of 160 mmHg has a 10-year cardiovascular mortality risk of 13%, adding breast radiotherapy with a mean heart dose of 2 Gy or 8 Gy will increase her risk with 0.7% or 2.7% respectively.

These risk charts might be useful for cardiovascular screening and prevention but also to individualize RT treatment not only based on tumor but also cardiovascular characteristics. For example including the internal mammary chain will highly increase heart and lung dose (Figure 1), while reducing 8-year breast cancer mortality with 2.5% in lymph node positive patients [15]. For patient 2, the iatrogenic risks might outweigh the benefit. However when cardiovascular prevention is performed this will subsequently decrease cardiovascular risk and might therefore rebalance oncological gains *vs.* long-term iatrogenic effects.

The cardiovascular risk models are not applicable for patients with known coronary heart disease or other atherosclerotic disease and diabetes type 2 or diabetes type 1 with target organ damage, which should be considered as high or very high cardiovascular risk patients [14]. The cardiovascular risk might be underestimated in obese patients, patients with a family history of premature cardiovascular disease, socially deprived patients, patients who have preclinical atherosclerosis, moderate to severe kidney disease, impaired glucose regulation, triglycerides and fibrinogen, but also in patients receiving cardiotoxic agents like anthracyclines and HER2 directed therapies. These data emphasize the importance of lifestyle optimization including smoking cessation, dietary patterns and physical activity. The long-term cardiac effects of current used hypofractionated (a higher dose per fraction and less fractions) schedules and altered dose distribution i.e. more low and less high heart dose by advanced radiation techniques remains unknown.

Breast cancer patients receiving RT have an excellent oncological

prognosis, therefore individualized long-term prevention and screening of cardiovascular morbidity is warranted, not only based on cardiovascular risk factors but also heart dose.

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