

## Radiation Therapy in Breast Cancer Patients and Cardiac Toxicity - New Perspectives

**Rušinová L\* and Soumarová R**

*Department of Radiotherapy and Oncology, Third Faculty of Medicine, Charles University and Královské Vinohrady University Hospital, Prague, Czech Republic*

**\*Corresponding Author:** Rušinová L, Department of Radiotherapy and Oncology, Third Faculty of Medicine, Charles University and Královské Vinohrady University Hospital, Prague, Czech Republic.

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### Abstract

Adjuvant radiotherapy after breast cancer surgery is an important part of breast cancer treatment, improving local control and overall survival. However, a higher risk of cardiac mortality was observed when conventional radiotherapy techniques were used. In those focused on modern radiotherapy techniques, cardiac morbidity and mortality were no longer presented. However, an extremely long follow-up period was required. In the era of personalized medicine, it is essential not only develop new radiotherapy techniques and monitor dose distribution to different anatomical cardiac structures during radiotherapy but also to identify breast cancer patients with a higher risk of radiation-induced cardiac morbidity and define preventative strategies.

**Keywords:** *Breast Cancer; Radiotherapy; Cardiac Toxicity*

Breast cancer is the most common cancer among women and the importance of adjuvant radiotherapy (RT) following breast cancer surgery as part of the treatment protocol for improving local control and overall survival has been confirmed in several meta-analyses. Radiotherapy after breast-conserving surgery reduces the risk of local recurrence by 50% and contributes to the improvement of overall survival among patients with node-positive and node-negative disease [1].

The probability of radiotherapy long-term side effects generally depends on the volume of heart irradiated, dose per fraction and total radiation dose. It is also important to take into consideration the younger age at the time of radiotherapy, concomitant cardiotoxic chemotherapy and trastuzumab, pre-existing cardiac disease, and conventional cardiac risk factors such as diabetes, hypertension, hyperlipidemia, obesity, and smoking. For instance, a synergistic effect was observed between smoking and RT on the risk of heart attack and the presence of hypertension was associated with a higher risk of coronary artery disease after left-sided breast radiotherapy [2,3].

Heart irradiation can cause many changes manifesting as radiotherapy-induced heart disease (RIHD). Cardiac dysfunction due to radiation involves not only coronary heart disease (CHD) and pericardial disease (acute pericarditis, delayed and constrictive pericarditis) but also congestive heart failure, valvular damage, cardiomyopathies and arrhythmias. The main pathology is radiation-induced fibrosis and microvascular damage leading to ischemia. Capillaries are the most radiosensitive because they have just a single layer of endothelium, which is highly susceptible to ionizing radiation [4]. Acute radiation side effects reflect a combination of epithelial and vascular damage. Ionizing radiation can induce apoptotic cell death of endothelial cells (EC), accelerated senescence of EC, dysregulation of cytokines, disorganization of cell adhesion molecules, persistence of reactive oxygen species and alteration in coagulation.

Pre-existing cardiac disease is probably very important for developing radiotherapy-induced cardiac morbidity. A population-based study of patients treated between 2000 and 2010 using modern radiotherapy techniques showed higher risk of coronary interventions among patients with left-sided tumors and higher risk of cardiac mortality. However, the risk was limited to women with previous cardiac

disease [6]. The largest meta-analysis to date, published by Cheng in 2017, examined data of 1.191,371 women from 39 studies and 11 randomized trials between 1966 and 2015. The risk of coronary artery disease and cardiac mortality was increased among patients with left-sided radiotherapy compared to those undergoing right-sided radiotherapy and, also, among patients with radiation therapy compared to those without radiotherapy. The risk started to increase within the first decade for coronary artery disease and in the second decade for cardiac mortality. While current modern radiotherapy techniques reduce the risks, they cannot completely eliminate cardiotoxicity [7].

Results from clinical trials suggesting an increase in cardiovascular morbidity and mortality, especially after left-sided radiotherapy, led to the development of new techniques such as deep inspiration breath holding (DIBH) or accelerated partial breast irradiation (APBI). The aim of DIBH is to deliver a dose only during the particular phase of the respiratory cycle when breast and chest wall are as far as possible from the heart [8,9]. This technique is very effective for a significant heart dose reduction [10]. APBI considerably reduces the dose delivered to the heart by focusing radiation on the tumor bed. In selected patients, it is currently considered the standard technique, replacing whole breast irradiation [11].

Although breast cancer radiotherapy has gained widespread acceptance, there are relatively few clinical data supporting proton radiotherapy. A systematic review of 13 studies analyzing proton therapy published last year has shown that the mean doses delivered to the heart and lungs are reduced with proton therapy compared to photon therapy. However, large well-designed controlled clinical trials are needed to confirm a clinical benefit of proton therapy. Several studies are currently underway including the phase III RADCOMP study, comparing photon versus proton radiation therapy after partial mastectomy with lymph node involvement. The study was launched in 2016 and is due to be completed by 2020, following enrolment of 1,720 patients. The results are expected in 2030 [12].

Taking into account the high survival rate of breast cancer patients there is an urgent need to focus on detection of early subclinical cardiac dysfunction and implementation of primary prevention strategies. Some subclinical cardiac events that occur over weeks, months or first years after RT, can be detected via echocardiography and myocardial changes, coronary changes or circulating biomarkers.

Walker, *et al.* recently published a prospective study, investigating the associations between breast cancer RT-induced cardiac doses and subclinical left ventricle dysfunction defined as a global longitudinal strain reduction (GLS) > 10% based on 2D speckle-tracking echocardiography, 6 months after RT. In the patient study group, consisting of 79 BC patients treated with radiotherapy without chemotherapy, a mean decrease of 6% in GLS was observed [13]. However, longer follow-up and larger size of population is required to investigate the associations. A large multicentre European study (MEDIRAD EARLY-HEART study) is already ongoing and could provide more answers [14].

From the radiation oncologist's point of view, our aim is to reduce the radiation dose delivered to the heart by using modern radiotherapy techniques and treatment individualization. However, the final balance between sufficient protection of cardiac structures versus optimal target volume coverage remains in our hands. Ongoing clinical trials detecting early subclinical changes based on cardiac imaging and circulating biomarkers could provide insights into strategies to identify breast cancer patients at highest risk of, and thus prevent, radiation-induced cardiac complications. Although further research is needed, this concept opens a new area for cooperation between radiation oncologists and cardiologists.

### Bibliography

1. Clarke M., *et al.* "Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials". *Lancet* 366.9503 (2005): 2087-2106.
2. Hooning MJ., *et al.* "Long-term risk of cardiovascular disease in 10-year survivors of breast cancer". *JNCI: Journal of the National Cancer Institute* 99.5 (2007): 365-375.

3. Harris EE., *et al.* "Late cardiac mortality and morbidity in early-stage breast cancer patients after breast conservation treatment". *Journal of Clinical Oncology* 24.25 (2006): 4100-4106.
4. Dimitrievich GS., *et al.* "Radiosensitivity of vascular tissue. I. Differential radiosensitivity of capillaries: a quantitative in vivo study". *Radiation Research* 99.3 (1984): 511-535.
5. Bhanu Prasad Venkatesulu., *et al.* "Radiation-induced endothelial vascular injury. A review of possible mechanisms". *JACC: Basic to Translational Science* 3.4 (2018): 563-572.
6. Boero IJ., *et al.* "Modern Radiation Therapy and Cardiac Outcomes in Breast Cancer". *International Journal of Radiation Oncology, Biology, Physics* 94.4 (2016): 700-708.
7. Cheng YJ., *et al.* "Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer". *Journal of the American Heart Association* 6.5 (2017): e005633.
8. Lin A., *et al.* "The benefit of deep inspiration breath hold: evaluating cardiac radiation exposure in patients after mastectomy and after breast-conserving surgery". *Breast Cancer* 24.1 (2017): 86-91.
9. Al-Hammadi N., *et al.* "Voluntary Deep Inspiration Breath-hold Reduces the Heart Dose Without Compromising the Target Volume Coverage During Radiotherapy for Left-sided Breast Cancer". *Radiology and Oncology* 52.1 (2018): 112-120.
10. Rice L., *et al.* "An effective deep-inspiration breath-hold radiotherapy technique for left-breast cancer: impact of post mastectomy treatment, nodal coverage, and dose schedule on organs at risk". *Breast Cancer* 79 (2017): 437-446.
11. Correa C., *et al.* "Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence- Based Consensus Statement". *Practical Radiation Oncology* 7.2 (2017): 73-79.
12. NCT02603341 - Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial.
13. Valentin Walker., *et al.* "Early detection of subclinical left ventricular dysfunction after breast cancer radiation therapy using speckle-tracking echocardiography: association between cardiac exposure and longitudinal strain reduction (BACCARAT study)". *Radiation Oncology* 14 (2019): 204.
14. Walker V., *et al.* "Early detection of cardiovascular changes after radiotherapy for breast Cancer: protocol for a European multicenter prospective cohort study (MEDIRAD EARLY HEART study)". *JMIR Research Protocols* 7.10 (2018): e178.

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