Myocardial perfusion years after radiation therapy for left-sided breast cancer: Normal or abnormal? This is the question

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Breast cancer is the most commonly occurring cancer in women and the second most frequent cancer overall, with over 2 million new cases in 2018.[1] Multiple advances in screening, classification of tumors into biologic subtypes, surgical techniques, and chemotherapy have contributed to earlier diagnosis of breast cancers and better management. Given the better prognosis of these patients, adverse effects from therapies, including those developing over long times, are becoming increasingly important.[2,3]

Treatment of breast cancer often consists in a combination of surgery, chemotherapy, and post-operative adjuvant radiation therapy (RT) to the breast or chest wall, possibly extended to regional lymph nodes. It is well known that both chemotherapy with anthracycline or trastuzumab and RT may be cause cardiac toxicity through different mechanisms, namely activation of cell death pathways and inhibition of mitochondrial biogenesis by anthracyclines,[4] inhibition of HER2 signaling in the heart by trastuzumab,[5] and radiation-induced cardiac damage. This last can manifest as coronary artery atherosclerosis, cardiomyopathy due to microvascular dysfunction, and possibly also pericarditis or valve disease.[6] The risk of radiation-induced heart disease increases by about 7% per Gy of mean absorbed dose; the goal of RT planning is then to keep the dose to the heart as low as possible through target-specific dose delivery (limiting cardiac irradiation to the anterior wall), and various heart-sparing techniques: respiratory gating to irradiate the breast region only during deep inspiration (when the heart is farthest from the chest wall), and 3D computed tomography (CT) planning to restrict cardiac irradiation to the anterior wall, perfused by the left anterior descending (LAD) artery.[6] Since macro- or microvascular damage can result in clinically manifest cardiac ischemia only over years or decades, and long follow-up periods are then required, the impact of contemporary radiation protocols remains to be determined. Impaired myocardial perfusion or coronary artery calcium score (CACS) may represent useful surrogate endpoints, denoting an early damage that may become clinically evident over time.

Several studies reported myocardial perfusion deficits following RT for breast cancer, although they dated back to 1990s or 2000s, and employed single-photon emission computed tomography (SPECT) and cardiac magnetic resonance (CMR) instead of the gold standard technique for *in vivo* quantification of myocardial blood flow (MBF), namely positron emission tomography/computed tomography (PET/CT).[7–16] In the only study so far available, 15 women with breast cancer (9 of whom with left-sided breast cancer) underwent resting and adenosine PET/CT with the ^{15}O-H_2O tracer before RT (which was administered at 42.5 or 45.0 Gy over 17 or 20 sessions, respectively, plus an additional dose for patients with intact breasts), and then 2 and 8 months after completion of RT.[17] A RT technique restricting irradiation to the anterior cardiac wall was adopted. Accordingly, compared to baseline, resting myocardial blood flow (MBF) was reduced at 2 and 8 months only in the 7th left ventricular segment, and

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reduced stress perfusion was mostly confined in the LAD territory. Changes in myocardial perfusion were apparently not influenced by cancer side, age, cardiovascular risk factors, or additional cancer therapies.[17]

The study by Rasmussen et al, published in the present issue of the *Journal*, adds to our knowledge on this topic.[18] The authors evaluated 20 women receiving adjuvant RT (48 Gy over 24 sessions) for left-sided breast cancer, using a state-of-the-art RT technique. After 7 ± 2 years, patients underwent a ^{13}N-NH_3 PET/CT scan to assess CACS and myocardial perfusion. The median CACS was 4, and coronary calcifications were primarily located in the LAD territory. Resting MBF and myocardial flow reserve (MFR) in the irradiated and non-inferior zones did not differ significantly. Indeed, ''no differences were observed for rest MBF (1.29 ± 0.29 vs 1.33 ± 0.29 mL·g^{-1}·minute^{-1}, P = ns), stress MBF (2.74 ± 0.59 vs 2.78 ± 0.66 mL·g^{-1}·minute^{-1}, P = ns), or MFR (2.22 ± 0.62 vs 2.17 ± 0.65, P = ns) between anterior and inferior wall myocardium.'' The authors conclude that contemporary RT protocols do not seem to affect resting and stress myocardial perfusion after several years from treatment.

Although the authors correctly acknowledge most limitations of their analysis, we deem it useful to further discuss some points. First, the study population could be too small for a small difference in myocardial perfusion to emerge. Indeed, the comparison between 20 irradiated and 20 non-irradiated regions would have yielded a significant difference (with 5% alpha error probability and 80% power) only if Cohen's effect size was 0.42 (2-tail test) or 0.37 (1-tail test), over a scale from 0 to 1 (G-power software, version 3.1). In other words, a difference in myocardial perfusion would have been detectable only if irradiation was quite harmful to the heart, which is quite unlikely when using contemporary RT protocols. The study was then probably underpowered to detect significant differences in myocardial perfusion between irradiated and non-irradiated zones. Other important limitations are the lack of baseline PET/CT imaging and the absence of a control group, which could have allowed a more meaningful assessment of MBF and MFR values measured during follow-up. On the other hand, the finding of MBF and MFR values in the irradiated region approaching reference values for healthy women[19] gives some support to the conclusion that myocardial perfusion is not significantly altered by RT, at least over a 7-year timespan. Nonetheless, some RT-induced damage is suggested by an uneven distribution of calcifications, which were more represented in irradiated segments, and might represent the earliest evidence of vascular damage by RT. Overall, further studies with longer follow-up periods are advisable to properly investigate the consequences of RT on coronary anatomy and myocardial perfusion. These studies should also try to dissect the effects of RT from those of anthracyclines, which have been found to cause perfusion deficits in CMR studies.[20]

In conclusion, Rasmussen et al should be congratulated for addressing this topic of outmost clinical relevance, but their study should probably be regarded as hypothesis-generating rather than a clear demonstration that myocardial perfusion is not reduced following RT for left-sided breast cancer.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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