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From heart to heart for breast cancer patients—cardiovascular toxicities in breast cancer radiotherapy

A recent paper by Darby et al. [1] on heart toxicities after radiotherapy of breast cancer generated a strong debate in the medical and nonmedical press [2]. In the modern era of 3D conformal radiation oncology, few of us have seen patients with heart toxicities, but does this mean that the topic is obsolete? The paper by Darby et al. [1] is a landmark in this field of clinical research. It is a large and very carefully designed case–control study on radiation-induced major coronary events (i.e., myocardial infarction, coronary stenting, or death from ischemic heart disease) after postoperative radiotherapy of breast cancer. By using a case–control design, the authors reduced the influence of changing treatment concepts and techniques of radiation treatment over time. Furthermore, the study not only analyzed death from coronary events, but incidence of any major coronary event. In the modern era of cardiology and radiation oncology, minimizing the risk of coronary events for every age should be our next goal [3, 4]. Therefore, the study deserves careful and critical evaluation. Based on our experience as the coordinator of the European research project CARDIORISK [5, 6], we see the need to discuss the clinical relevance of the data in greater depth.

The radiosensitivity of the heart was first demonstrated by the American pathologist Louis Fajardo (1968) in the follow-up of patients treated with mantle field radiotherapy for Hodgkin's disease [7]. He described two special clinical manifestations of radiation-induced heart disease which differed in clinical symptoms, latency, and pathology, namely pericarditis and myocardial fibrosis leading to congestive heart failure. Numerous studies in survivors of Hodgkin's disease followed. They established five different heart diseases as potential late radiation damage and established the heart as a radiosensitive organ [8]:

- myocardial infarction/ischaemic heart disease,
- congestive heart failure,
- pericarditis,
- arrhythmias or conduction defects, and
- valvular diseases.

Myocardial infarction is a consequence of coronary artery atherosclerosis. High total doses to the coronary arteries may cause myocardial infarctions 5–20 years after irradiation. There is no evidence that low doses to large volumes of the myocardium may cause myocardial infarction (A-bomb survivor studies) [9].

Congestive heart failure in patients suffering from radiation-induced heart disease is mainly related to interstitial myocardial fibrosis causing "backward failure". It is the consequence of microvascular radiation injury which, according to the findings of the European CARDIORISK project is slowly progressive over long periods and may be induced by relatively low doses of a few Gy [5, 6].

Pericarditis is a typical exudative inflammatory response of the epithelium of the heart, the epicardium, and similar to the radiation response of other surface epithelia. The critical parameter for the development of clinically significant symptoms is the area of the epicardium which receives a radiation dose in excess of the threshold for exudative inflammation (>30 Gy) [10].

Arrhythmias and conduction defects are caused by damage to the sinus or AV node or to the conduction system in the interventricular septum which may be interrupted by local ischemia or by fibrosis. Therefore, the interventricular septum may also be a critical substructure of the heart [11].

The pathogenesis of valvular damage by radiotherapy is still not well understood. Investigations by Schellong et al. [12] suggest that it is a critical late effect particularly after radiotherapy of children. No reliable data are available on dose thresholds for either conduction defects or valvular damage.

Which of these five above described heart toxicities can be expected after breast cancer radiotherapy? What is the evidence we have coming from the publications of the last decade?

The 2005 meta-analysis of the randomized trials organized by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [13] demonstrated an increased rate ratio (RR 1.27) of mortality from ischemic heart disease in women treated with radiotherapy as compared with women treated with surgery only. In the 2011 published update of EBCTCG on 10-year recurrence and 15-year breast cancer death, the mortality rate from nonbreast cancer causes is mentioned in only one sentence. No significant difference in the mortality rate from nonbreast cancer causes in patients who underwent radiotherapy vs. surgery only (RR 1.09, 95%

confidence interval 0.97–1.22, p=0.14) was found [14]. However, the mortality from nonbreast cancer causes did include several death causes: death by circulatory diseases (heart disease, stroke, pulmonary embolism), cancers (lung cancers, esophageal cancers, leukemia, soft tissue sarcomas), or other causes (e.g., respiratory diseases). A very detailed up to date report on nonbreast cancer mortality of EBCTCG is not yet published. On the other hand, it is important to note that there are published retrospective data on the causes of and latency to death in breast cancer patients with right-sided and left-sided breast cancer. In patients who did not receive radiotherapy, there was no influence of breast cancer laterality on causes of death [15]. In contrast, in patients who received postoperative radiotherapy, after a latency of >10 years, the rate of death from heart diseases increased significantly in patients with left-sided breast cancer compared to right-sided breast cancer. Congestive heart failure and valvular diseases are only documented in retrospective studies in breast cancer patients treated with internal mammary nodal irradiation [16, 17].

These and most other epidemiological studies on radiation-induced heart diseases have so far not separated the different heart diseases, but combined all types of heart diseases as one potential radiation effect. The epidemiological approach demonstrated the importance of late cardiac complications after various forms of radiotherapy but it provided little assistance in resolving the clinical problem.

Based on our experience as the coordinator of the European research project CARDIORISK [5, 6], we see the need to discuss the clinical relevance of the recent data published by Darby et al. [1] in greater depth.

The study included patients treated in Sweden and Denmark. The patients received irradiation treatment during the time period from 1958–2001. In all, 2168 women who underwent radiotherapy for breast cancer in Sweden and Denmark were included. All women who received radiotherapy were cross-matched with nationwide registers of diagnosis at the time of hospital discharge and cause of death (up to 2002 in Sweden and 2007 in Denmark) with a total of 963 patients with major coronary events and 1205 controls being assessed. Surely, the study had some important drawbacks, including the following:

- Most of the patients were treated with techniques that now would be considered suboptimal (i.e., 2D conformal radiotherapy plans).
- The study does not state how many patients had a direct internal mammary field, which is considered to be one of the very important risk factors for radiation-induced heart toxicity.
- No individual dosimetric data were available. In order to assess the mean heart doses and the mean dose to the anterior descending coronary artery, the 2D plans were recalculated on a "typical" patient. Available evidence, however, suggests that even in a small group of 20 patients, the mean heart dose can vary by a factor of two between patients. Moreover, the mean dose to the left anterior coronary artery can vary by a factor of ten between patients [18].
- For 26% of the patients with major coronary events, no relevant record could be found. Nonetheless the remaining 74% had cardiology hospital records or autopsy reports that confirmed the diagnosis of heart disease.

Independent of the above listed drawbacks, several issues raised by the 2013 study of Darby et al. [1] should be considered:

- The study emphasized that the incidence of major coronary events started to increase very early (about 5 years after radiotherapy) with 44% of the major coronary events occurring within the first 10 years.
- The excess absolute risk of the entire cohort (left- and right-sided breast cancer patients) is about 1% and is compatible with a proportional increase of incidence with increasing mean heart dose. The overall average radiation dose to the heart was 6.6 Gy for women with tumors in the left breast and 2.9 Gy for patients with tumors in the right breast. The authors found a significant higher rate of coronary events in left-sided breast cancer patients which could be explained by the higher dose in this group. Nonetheless, they also found a correlation with dose, despite the laterality of cancer. The linear dose–risk relationship found in the study does not imply that every breast cancer patient who is treated with postoperative radiotherapy has a risk of 1% of developing radiation-induced myocardial infarction. Table S13 (supplementary appendix, page 17) of the Darby publication [1] provides risk estimations of at least one acute coronary event induced by radiotherapy. This risk of lethal myocardial infarction is compared to the rates of death from ischemic heart disease for 15 countries of the European Union (data from 2010, table S11, supplementary appendix, page 14). We could approximate the risk by using the tables of the Darby publication [1]. If we assume that we irradiate a 50-year-old breast cancer patient without cardiac risk factors with a mean heart dose of 3 Gy, the risk of having at least one acute coronary event by the age of 80 years rises from 4.5% to 5.4%. If the patient has preexistent cardiac risk factors, her risk of having at least one acute coronary event by the age of 80 years rises from 8% to 9.7%. If her mean heart dose would be 10 Gy and she would have cardiac risk factors her risk increases from 8% to 13.5%. Thus, patients with cardiac risk factors and/or unfavorable anatomical features (e.g., pectus excavatum) may have a much higher absolute risk of 5% or more. This is more than 50% higher than in a patient without radiotherapy. It has to be the goal of clinical research in cardiology and radiation oncology to identify this critical group of patients and develop methods to minimize the risk of coronary events.
- Another interesting finding of the Darby publication [1] is that the mean dose of radiation to the heart was a better predictor of the rate of major coronary events than the mean dose to the left anterior descending coronary artery. An interpretation of this result is difficult. It might be due to the method to use "typical" patient anatomy for dose distribution calcu-

lations from 2D treatment plans and the lack of real 3D dose distributions for each patient (considering the volume of the whole heart including the region of the anterior descending coronary artery). We think that the mean radiation dose to the heart is likely to be more related to late damage of the microvasculature of the myocardium. This potentially causes congestive heart damage rather than myocardial infarction. However, there might be functional interactions between both pathogenic pathways [10].

We draw from the recent Darby paper [1] consequences for our research regarding cardiotoxicity and also for our daily clinical practice in adjuvant, curative radiation treatment of breast cancer patients:

- We performed a retrospective pilot study on 250 left-sided breast cancer patients, treated between 2009 and 2010 in our clinic. In our daily practice mean doses to the heart for left-sided breast cancer radiotherapy were seldom higher than 3 Gy. We, thus, consider 3 Gy as a high mean heart dose. In these patients (≥3 Gy mean doses), we found that doses to critical substructures in the heart vary considerably between patients as a consequence of differences in the anatomy of the thorax.
- Prospectively contouring of heart and subvolumes of the heart will be standardized according to the RTOG contouring atlases [19]/Danish Breast Cancer Cooperative Group recommendations [20].
- The maximum of the total dose (in conventional fractionation with single doses of 1.8 or 2 Gy) of the anterior descending coronary artery will be specified and limited. There are no data available, yet, on which to define a dose threshold below which radiation-induced myocardial infarction would be unlikely.
- The volume of the left and right ventricles exposed to a dose which might lead to progressive reduction of microvascular density will be specified and limited. The studies by Marks et al. [21] suggest a dose/volume limit of >10 Gy to >10% of the ventricular myocardium.
- Those patients in whom either of the two dose/volume criteria exceed, will undergo a gated treatment planning by active breathing control.
- For patients in whom either of the two dose/volume criteria will not be met or patients with preexistent risk factors (i.e., women with cardiac risk factors or which underwent cardiotoxic systemic therapy), a basic cardiological evaluation and standardized follow-ups will be developed jointly with cardiologists [22] and according to the recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography [23].

In conclusion, we propose our approach and these anatomical dose distribution limits for discussion.

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References

1. Darby SC, Ewertz M, McGale P et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:987–998
2. Dunst J (2013) [Cardiac risks associated with adjuvant radiotherapy for breast cancer]. Strahlenther Onkol 189:590–591
3. Sedlmayer F, Sautter-Bihl ML, Budach W et al (2013) Is the simultaneously integrated boost (SIB) technique for early breast cancer ready to be adopted for routine adjuvant radiotherapy? Statement of the German and the Austrian Societies of Radiooncology (DEGRO/OGRO). Strahlenther Onkol 189:193–196
4. Sautter-Bihl ML, Sedlmayer F, Budach W et al (2012) When are breast cancer patients old enough for the quitclaim of local control? Strahlenther Onkol 188:1069–1073
5. Cardiorisk. http://www.cardiorisk.eu/. Accessed 11 Nov 2013
6. Andratschke N, Maurer J, Molls M, Trott KR (2011) Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention. Radiother Oncol 100:160–166
7. Fajardo LF, Stewart JR, Cohn KE (1968) Morphology of radiation-induced heart disease. Arch Patho 86:512–519
8. Adams MJ, Lipsitz SR, Colan SD et al (2004) Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 22:3139–3148
9. Shimizu Y, Kodama K, Nishi N et al (2010) Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. BMJ 340:b5349
10. Carmel RJ, Kaplan HS (1976) Mantle irradiation in Hodgkin's disease. An analysis of technique, tumor eradication, and complications. Cancer 37:2813–2825
11. Larsen RL, Jakacki RI, Vetter VL et al (1992) Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults. Am J Cardiol 70:73–77
12. Schellong G, Riepenhausen M, Bruch C et al (2010) Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer 55:1145–1152
13. Early Breast Cancer Trialists' Collaborative Group. (2000) Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 355:1757–1770
14. Darby S, McGale P, Correa C et al (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707–1716
15. Darby SC, McGale P, Taylor CW, Peto R (2005) Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 6:557–565
16. Harris EE, Correa C, Hwang WT et al (2006) Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 24:4100–4106
17. Hooning MJ, Botma A, Aleman BM et al (2007) Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 99:365–375
18. Taylor CW, Povall JM, McGale P et al 2008) Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys 72:501–507
19. Kong FM, Ritter T, Quint DJ et al (2011) Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 81:1442–1457
20. Nielsen MH, Berg M, Pedersen AN et al (2013) Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol 52:703–710
21. Marks LB, Yu X, Prosnitz RG et al (2005) The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys 63:214–223
22. Jaworski C, Mariani JA, Wheeler G, Kaye DM (2013) Cardiac complications of thoracic irradiation. J Am Coll Cardiol 61:2319–28
23. Lancellotti P, Nkomo VT, Badano LP et al (2013) Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 14:721–740