Cardiac Risks in Multimodal Breast Cancer Treatment

Wilfried Budach[1]

Almost all breast cancer patients receive one or more adjuvant treatments consisting of tamoxifen, aromatase inhibitors, LHRH-antogonists, chemotherapy, trastuzumab, and radiotherapy. These treatments have been shown to considerably improve overall survival [1–3, 6, 15–17]. As a result, long term survival for 15 and more years is achieved in more than two thirds of newly diagnosed breast cancer patients. Therefore, more interest in short and long term risks of adjuvant treatments has been arisen. The focus of this article is the long term cardiac risks of adjuvant radiotherapy in breast cancer patients and possible interactions with chemotherapy and trastuzumab.

Adjuvant radiotherapy is used in approximately 75% of all breast cancer patients. The latest meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) provides unequivocal evidence that adjuvant radiotherapy after breast conserving surgery and after mastectomy in high risk patiens (N+) results in a significant survival benefit [6]. What is the prize to pay for the benefits of radiotherapy? Based on the data of more than 20,000 women with at least 15 years follow up, three relevant risks can be identified that are associated with the use of radiotherapy [6]: The relative risks to develop a contralateral breast cancer (1), to die from heart disease (2), and to die from lung cancer (3) are increased by the factors 1.18 (p = 0.002), 1.27 (p = 0.0001), and 1.78 (p = 0.0004), respectively. The relative risk for non breast cancer deaths is in total enhanced by factor 1.12 (p = 0.001). The effects were not age dependent. However, the absolute effects are quite small. At 15 years, an increase of all non breast cancer deaths from 14.6% to 15.9% was observed. More than 50% of the excess risk of non breast cancer deaths are the result of circulatory disease, in particular myocardial infarctions. The excess risk for heart disease is not detectable before 10 years after irradiation, but seems to increase continuously afterwards, especially after more than 15 years follow up [6, 12]. The long term effects of radiotherapy on the development of heart disease and dose and volume dependence of these effects are poorly understood. Two recent publications shed some light on this issue [12, 18]. According to Schultz-Hector and Trott [18] a mean heart dose of as little as 1.5–2.0 Gy is already associated with an approximately 1.5-fold increase in the risk of heart disease after more than 10 years after radiotherapy (Figure 1). This data is mainly based on atomic bomb survivors [14, 19] and the outdated experience of radiotherapy of peptic ulcer disease [5] as well as on radiotherapy on lung cancer and breast cancer patients [1, 6, 7]. Since atomic bomb survivors have also a higher risk to develop hypertension and may have other unknown factors that influences the risk of heart disease, this data should be interpreted with caution. The same is true for the peptic ulcer patients, because radiotherapy of the stomach, especially with radiation techniques used more than have a century ago, was invariantly associated with considerable doses to the kidneys and parts of liver. More relevant appear the data of the EBCTC [1, 6] and of the SEER database [7]. However, the mean heart doses taken form these publication are rough estimates with unknown error bars. The data of Hooning et al. [12] solely based on breast cancer patients and more reliable dose estimates indicate that the risk of radiation induced heart disease starts to increased at a mean heart dose of approximately 4 Gy (Figure 1). Although this indicates a considerable higher tolerance dose than proposed by Schultz-Hector and Trott [18], this is still much lower compared to tolerance

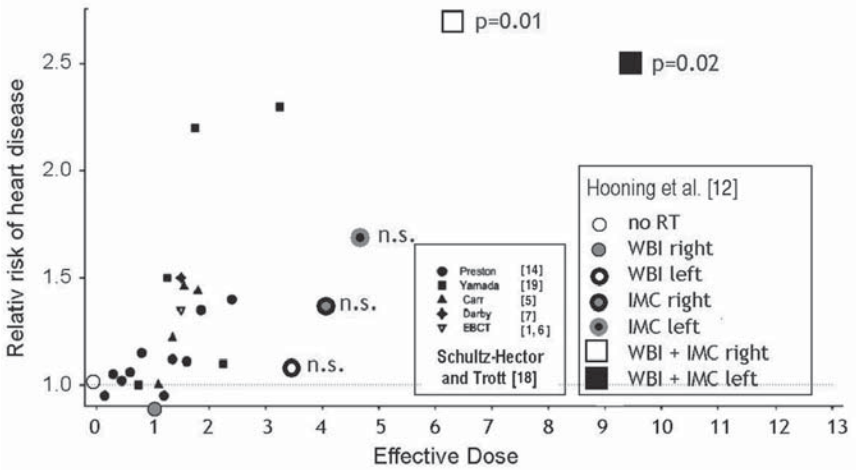

Figure 1. (modified from Schultz-Hector and Trott [18]): The relative risk of cardiac events more than 10 years after radiotherapy in dependence of the mean heart dose for different treatments in different publications. The mean heart doses were corrected according to the linear-quadratic model assuming an α/β of 3 Gy. (n.s. = not significant; RT = radiotherapy; WBI = whole breast irradiation; IMC internal mammary chain).

Key Words: Breast cancer · Cardiotoxicity · Radiotherapy · Chemotherapy · Trastuzumab

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[1]Dept of Radiation Oncology, University of Düsseldorf

dose of 30 Gy (TD5/5) that is currently reported in the textbooks of radiotherapy [8]. Importantly, the estimated mean heart doses for radiotherapy (2 Gy fractions equivalent assuming an α/β of 3 Gy) of right sided and left sided breast cancers were approximately 1.0 Gy and 3.4 Gy, respectively, if no irradiation or the internal mammary lymphatic chain (IMC) was administered. This is well below the threshold dose for an excess risk of heart disease in their database. In case of IMC radiotherapy, mean heart doses of 7–9 Gy are typically seen, at least, if radiotherapy is administered mainly by photons. An approximately 2.5-fold excess risk of heart disease was observed at these doses [12].

Since the majority of patients in the data of Hooning et al. [12] received radiotherapy between 1970 and 1984, that is, with a kind of outdated radiation technique, the question arises, whether the same risks are observed with modern radiation techniques. The EBCTCG [6] reported a considerably higher excess risk for heart disease for radiotherapy of left sided breast cancer compared to right sided breast cancer. In a recently published meta-analysis [9], no difference in the incidence of ischemic heart disease was seen 15 years after radiotherapy between left and right sided cancers, if the radiotherapy was administered later than 1984. In the combined analysis of the Danish post mastectomy trials [11] no excess risk of heart disease was found in irradiated patients at 12 years after treatment, even though radiotherapy of the IMC (with electrons) was routinely used. These observations suggest that critical doses at the heart are usually not reached, if modern radiation techniques are used.

However, an increasing number of patients receive beside radiotherapy other cardiotoxic treatments like anthracyclines and trastuzumab. Anthracyclins were initially thought to induce only acute an subacute cardiotoxicity, but cumulating evidence indicates that late toxicity 5 or more years after treatment is also not uncommon [13]. Systematic investigations about a possible interaction of radiotherapy and anthracyclin treatment are scares [4]. Hooning et al. [12] reported a rate of cardiac events 20 years after adjuvant treatment in 2.5%, 8.5%, and 22% of patients receiving no treatment or tamoxifen, radiotherapy ± tamoxifen, and radiotherapy and chemotherapy ± tamoxifen, respectively. Importantly, the differences between the three treatment strategies were still incognizable at 15 years, indicating that chemotherapy seem to enhance the probability of radiation induced very late occurring cardiotoxicity.

Trastuzumab has been shown to induce considerable acute cardiotoxicity especially in combination with anthracyclins. The toxicity seems to be reversible in most cases after cessation of therapy. However, long term follow up is lacking. Little is know about a possible interaction with radiotherapy. In the NCCTG N9831 trial [15] patients were randomised to adjuvant trastuzumab or no treatment after the chemotherapy About 70% of the patients received radiotherapy concurrently to trastuzumab. After a median follow up of 2.5 years, no excess risk of cardiac events was detected in irradiated patients. IMC radiotherapy was not allowed in this study [10]. Hence, based on this limited data, no evidence for an interaction between trastuzumab and radiotherapy in the short term was found, however, further follow up is needed.

In summary, recently published data indicate that the radiation tolerance of the heart is in the long term (> 15 years) considerably lower than was previously thought. However, modern radiation techniques assure that radiation induced cardiotoxicity is minimal. Anthracylins enhance the radiation induced cardiotoxicity, especially when IMC radiotherapy is given. Trastuzumab and concurrent radiotherapy seems not to aggravate the cardiotoxicity of trastuzumab in the short term, but no long term experience is available.

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Wilfried Budach
Dept of Radiation Oncology, University of Düsseldorf
University Hospital Düsseldorf
Moorenstr. 5
40225 Düsseldorf
Germany
wilfried.budach@uni-duesseldorf.de