Is the risk of ischemic heart disease in women after radiotherapy for breast cancer nowadays still (linearly) associated with the mean heart dose?

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1. The reported ‘relative excessive risks relative per Gy’ for these six studies varied substantially (0%–19%) [2, 3, 4, 5, 9];
2. In the Darby study, analyses were based on ‘a standard patient’ and in early cases only analogue RT-charts, to estimate dose levels, were available, negatively impacting the reliability of their findings [2, 3, 5];
3. RT details differed or were absent. In contrast to the older studies, in the more recent studies, the majority of patients were treated after 2000 [4, 9, 10]. Whereas after 2000, more homogeneous and conformal 3D dose calculation and delivery was feasible [11, 12];
4. van den Bogaard et al. concluded that their multivariable normal tissue complication probability model, predicting the occurrence of an acute coronary event, included the 5 Gy left ventricle volume, but not MHD [4];
5. Age-restrictions as well as countries of residence differed, while age-standardized prevalence of coronary vascular diseases as well as death rates from ischemic heart disease for women vary substantially between European countries, impacting the correct interpretation of these studies [13–15];
6. Only relative risks were provided, whereas clinical relevance is determined also by absolute figures;
7. Information about tobacco use was unknown in >50% of cases [2] and not considered in two other studies [5, 9]. This is relevant since tobacco use is associated with an increased risk of developing MCEs after BC-RT [16–18]. For the combination of tobacco use and BC-RT, even a synergistically increased rate of fatal myocardial infarction was noted [16].

Subsequently, we investigated results of (more recent) phase-III trials, because its prospective design ensures that the reliability of findings of phase-III trials is not hampered by observed differences and methodological flaws. And to confirm whether the reported higher MHD values for locoregional RT, including the internal mammary chain (IMC) [11, 12, 19, 20] coincide with significantly higher MCE-incidence rates. To summarise, firstly the DBCG-82bc trial (n = 3,083), after 30-year follow-up, reported no significant excess deaths of ischemic heart disease [21]. Patients were randomized (1982–1990) between yes or no postoperative RT to the chest wall and nodal regions (including IMC). Secondly, in 2023, the meta-analysis of the ‘Early Breast Cancer Trialists’ Collaborative Group’, evaluating the role of regional lymph node irradiation (RNI) in 16 phase-III trials (n = 14,324), was reported. With 15 years of follow-up, no increased non-breast cancer-related mortality (including cardiac deaths) was noted in the eight more recent trials (n = 12,167), in which patients were treated from 1989 till 2008 [22]. Thirdly, in the EORTC 22922-10925 trial (1996–2004), 4,004 patients were randomised between irradiation of the ipsilateral IMC and ipsilateral medio-supraclavicular chain or not [23]. Special attention was given to prospectively assess incidences of late side effects. After 15.7 years, cardiac death rates were identical in both arms (1.4%). No differences were found between left-sided versus right-sided cases. While cumulative incidence rates for any heart disease after nodal RT showed a limited increase of 1.7%, no increased incidence rates of cross-sectionally registered...
cardiac diseases, with a score of 2 or higher (CTC-AE 2, assessed every 5 years after treatment), were seen. Moreover, a RT-planning study using a fractionation scheme of 40.05Gy/15fr and representing >75% (concerning irradiation technique) of the participants of the EORTC 10925-22922 trial, revealed that the mean of the MHD values after left-sided whole breast RT and IMC-RT, when compared to that after whole breast RT only, was 13.9 Gy higher (Figure 1A) [19].

This contradicts the findings of Darby et al., predicting an increased MCE-incidence in the treatment arm of this trial of about 100% (13.9 × 7.4%) [2]. According to the results of two similar studies, even more pronounced increased MCE incidences were predicted [4, 5]. The following changes over time should be considered also, between 1970 and 2000, for women in Western Europe, an almost linear decline in death rates, ranging from 65% to 50%, for ischemic heart disease was noted [15]. After 1990, a significant lowering of heart doses in radiotherapy was achieved [11, 12]. More recently, introduction of 3D-treatment planning and, subsequently, intensity-modulated RT (IMRT) and respiratory control enabled even further improved heart sparing [19, 24] (Figure 1A+1B). Another RT-planning study (not considering IMRT), concluded that breath-hold as well as volumetric arc therapy enabled improved heart sparing after nodal RT (including IMC) [20]. After 2008, total RT-doses of 50 Gy/25 fr decreased towards 40 Gy/15 fr [25], resulting in correspondingly decreased mean heart physical doses. Furthermore, according to the results of the ‘Fast-Forward trial’; RT doses for local treatment are decreasing further towards 26Gy/5fr [26]. Radiobiological calculations, though, show that hypofractionation does not increase the probability of RT-associated MCE incidences. Finally, MHD is not a specific tool to predict the incidence of (major) atherosclerotic coronary artery disease, because the dose distribution in the heart is inhomogeneous, especially when using tangential beam-based RT techniques [10, 27]. We conclude that MHD cannot be seen as a reliable tool predicting increased MCE-incidences after BC-RT. Hence, nowadays there is no convincing evidence to support the use of MHD as a normative RT-planning parameter in daily practice nor in studies. The reliability of future findings of studies still using MHD as a normative RT planning parameter is hampered. We state that, in daily practice as well as in studies, cardiac risk assessment in BC-RT is of importance and preferably determined according to reported ‘evidence-based’ guidelines [14]. To predict radiation associated major coronary event incidence rates, we recommend evaluating the relevance of dose-volume relationships for both coronary arteries and left ventricle.

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**Conflict of interest**

All authors state that no actual or potential conflicts of interest exist in relation of the contents of this manuscript.

**Ethical approval**

No ethical approval was requested since no own data were used.

**Data availability statement**

No specific data were used to compose this letter.

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