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Are we ready to change treatment planning for left-side breast cancer radiotherapy?

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Comment on "What new dose distribution statistics may be included in the optimization of dose distribution in radiotherapy for post-mastectomy patients" by Piotr Mężyński and Paweł Kukołowicz [NOWOTWORY J Oncol 2021; 71(5): 267–273]

The standard treatment for breast cancer is either breast-conserving surgery or, in high-risk patients, mastectomy. Surgery is typically followed by adjuvant whole breast radiotherapy [1, 2]. Breast irradiation is intended to deliver a high therapeutic dose to the entire breast, minimising the doses in healthy tissues, defined as organs at risk (OARs). Previously, the fundamental law of radiobiology [3] postulated that highly differentiated organs with a low mitotic index are radioresistant and therefore described the heart as the quintessential radioresistant organ. Multiple studies on breast cancer treatment have refuted this claim, demonstrating a significant cardiac risk when portions of the heart are irradiated [4]. Routinely, the whole heart is considered as a single OAR. It is based on findings of the population-based case-control study published by Darby et al. [5], where a linear relationship between radiation dose and heart disease was defined. Darby's group showed that each additional 1 Gy of mean heart dose (MHD), predicted a 7.4% increase in a major coronary event over 20 years with no threshold below which there was no risk. Even though MHD has since become the prime restrictor of doses to the heart, numerous studies have shown that the impact of the radiation dose also depends on the heart substructures and, thus, dose restrictions should be modified accordingly [6]. One of these substructures is the left anterior descending coronary artery (LAD). Atkins et al. found the importance of limiting the dose to this substructure [7]. Because of its close proximity to the anterior chest wall, LAD is often exposed to high doses during breast irradiation and is a significant predictor of heart complications. Generally, the mean LAD dose is monitored as a surrogate predictor of cardiotoxicity.

Recently, Mężyński and Kukołowicz [8] presented an interesting planning study where they evaluated the doses delivered to various heart substructures and calculated normal tissue complication probability (NTCP) for the intensity modulation radiotherapy (IMRT) irradiated group of left-sided post-mastectomy patients. The study's conclusion recommends contouring cardiac substructures for a reliable assessment of the dose distribution as the MHD is not sufficient for cardiac risk evaluation for modern radiotherapy techniques. The LAD was one of all delineated substructures in this study where doses and NTCP were analysed. The authors found that below 30 Gy of the mean LAD dose, the NTCP seems to be negligible (the average value of LAD toxicity was below 0.2%). Nevertheless, their findings were based on a relatively small group (30) of patients. The study performed by Zureick et al. [9] was based on a more representative group (375) of patients treated with the 3D conformal technique, and investigated whether dose to LAD correlates with adverse cardiac events. The median

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follow-up time in this study was 48 months. 36 patients experienced some cardiac event, and 23 patients experienced a major cardiac event. The analysis showed that the increased mean and maximum LAD and mean heart doses were associated with an increased risk of some cardiac event and a major event. Based on the ROC (receiving operator curve) analysis, the authors identified the thresholds of 2.8, 6.7, and 0.8 Gy for the mean and max LAD dose, and MHD, respectively.

Another issue that could affect Mężyński and Kukołowicz's results was the difficulty in precise contouring of the heart substructures (especially LAD). As shown by Biedka and Żmuda [10], contouring the LAD is complicated due to its volume and location. Nevertheless, based on the analysis performed on the group of 50 patients, the authors of this study delivered valuable tips that could be helpful during the manual contouring of the LAD. To reduce the probability of wrong contouring (contour does not cover structure), applying a 1 cm margin to the contoured structure is recommended [10]. Current technology in structure segmentation based on artificial intelligence automatically produces contours of heart substructures. The recent study by van Velzen et al. [11] develops and validates an auto segmentation algorithm for the whole heart and its substructures and evaluates the association between heart dose, hospitalisation, and death due to heart disease in a large clinical dataset. In general, van Velzen et al. found that the risk of heart disease requiring hospitalisation was higher in patients receiving a high dose to cardiac substructures than in patients who had lower doses. Unfortunately, they could not distinguish the effects of MHD from dose to respective substructures on the risk of developing heart disease. A similar problem for predicting cardiac complications exists in lung cancer treatment [12]. Inability to establish such a relation may be due, in our opinion, to the multifactorial nature of radiation-induced cardiovascular disease. The disease can be associated with damage caused by doses deposited in multiple heart substructures. The role of several substructures would also support the hypothesis that IMRT offers better treatment than the 3D conformal option by giving a low dose to a large volume of the heart instead of a high dose to a small volume.

Most studies on this subject were focused on conformal 3D techniques including Zureick et al. [9]. Only Mężyński and Kukołowicz performed their analysis on breast treatment realised by IMRT. Unfortunately, their study is based on a relatively small group of patients, and we recommend a larger patient cohort investigation. Also, it would be interesting to include the data on LAD motion in different patients as an important factor in the correct contouring of this OAR [13].

We currently lack strong evidence demonstrating that heart avoidance by high doses using dose constraints for cardiac substructures rather than MHD improves clinical outcomes. This remains especially true in an era when 3D treatments are being replaced by IMRT and thus we need more data. Meanwhile, MHD should continue to be the standard of care in routine practice until the relationship of cardiac complications is unequivocally linked to the selected heart substructures.

Conflict of interest: none declared

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