SUMMARY

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Preclinical and clinical studies reveal that breast cancer radiotherapy is associated with an increased rate of major coronary events. This is especially true for women with left-sided breast cancer. Consequently, when irradiating women with left-sided breast cancer, specific measures should be taken to decrease the heart dose as much as possible and avoid radiation-induced coronary artery disease.

This thesis contains three chapters. In each chapter we focussed on relevant aspects of decreasing the heart dose in whole breast irradiation. In **chapter 1** we focussed on optimising the target volume delineation. Optimal definition of the target is the first step in radiation treatment. Improperly defined target volumes may lead to a systematic geographical miss during the full course of radiation treatment. An increased visibility of the glandular breast tissue (Clinical Target Volume; CTV breast) and the lumpectomy cavity (LC) may be obtained by using Magnetic Resonance Imaging (MRI) based delineation instead of Computed Tomography (CT) based delineation. Therefore, we examined if adding MR images, scanned in supine position, might be beneficial. The latter may enable a decrease in the interobserver variability of delineating the CTV breast as well as that of the LC. In our studies we compared, amongst others, the interobserver variability of the delineation of the CTV Breast and that of the LC in 10 breast cancer patients after breast-conserving surgery. Two radiologists and two radiation oncologists delineated the relevant target volumes based on the co-registered CT-MR images. We found that the addition of MR images did not improve consistency of the delineation of the CTV breast nor for the LC. For the LC the mean conformity index, when using the Cavity Visualisation Score (CVS), increased when this target volume was clearly visible on the CT and MR images. In cases with low CVS the use of clips may be helpful to define the LC with more precision. Furthermore, after comparing five different registration methods, surgical clips evidently were not always clearly visible on MR images. We found that multimodality breast markers are obligatory in performing an optimal CT-MR registration. A breast-marker-based co-registration of CT and MR data sets gave the best results in terms of the rest volume.

In **chapter 2** the results of 3 treatment-planning studies of whole breast irradiation are presented. In using the most optimal 3D-conformal radiotherapy treatment technique in left-sided breast cancer to reduce the dose in the organs at risk, it became clear that the Left Anterior Descending (LAD) coronary artery still could receive a relatively high maximum dose. We found that the mean LAD dose could be reduced by 50% when using a breath-hold technique. Several methods for performing a breath-hold technique are available. Most important is that the patient performs a moderate Deep Inspiration Breath-Hold (mDIBH) to achieve the largest distance between the heart and the border of the tangential radiation fields. In our institution, we noted that 98% of the patients was able to complete the Active Breathing Control method.

Furthermore, the treatment-planning studies give insight into the pros and cons of the several treatment techniques when using a breath-hold technique. All this can be used to decide whether a new technique should be performed in daily practice. Our treatment-planning studies revealed higher dose homogeneity when using tangential Intensity Modulated Radiotherapy (IMRT) in breath-hold compared to a 3D-conformal Radiotherapy (3D-CRT) technique in breath-hold; this tangential IMRT technique is less complex and succeeds in significantly lowering the dose in the heart and in the LAD coronary artery. Specifically the caudal part of the treatment fields, including the LAD, received a lower dose. Therefore, we concluded that a tangential IMRT technique in

breath-hold adds a substantial gain to lowering the dose, especially in the caudal part of the heart, and, hence, in the caudal part of the LAD.

Furthermore, we studied the added value of TomoTherapy and a proton technique when using a breath-hold technique. The TomoTherapy treatment study revealed that the mean dose of the heart and LAD-region was reduced when using TomoTherapy in breath-hold in comparison to tangential IMRT in breath-hold. However, we found that the combination of a breath-hold technique with TomoTherapy cannot be performed in daily clinical practice, due to the long beam-on time. The lowest dose in the heart and coronary arteries was found in the proton therapy study, with and without using a breath-hold technique. Protons would, theoretically, be the treatment of choice. However, as yet, proton therapy is not available in The Netherlands. If a limited use of proton therapy would be at our disposal, we would recommend a comparative assessment between the expected treatment efficacy, the degree of expected treatment-related toxicity, the possibility to apply "Accelerated Partial Breast Irradiation" (APBI) and costs.

Summarising, performing a tangential IMRT technique in breath-hold is currently the most optimal combination. Whether the use of a breath-hold technique reduces the risk of coronary heart disease could not be confirmed in these planning studies.

The results of our study on coronary artery calcium (CAC) scores were presented in **chapter 3**. The CAC scores, as obtained by CT scanning without using contrast enhancement, accurately predicts the risk of subsequent cardiovascular events. The CAC score is seen as a surrogate marker of coronary artery damage. Firstly, we found that the coronary artery calcium (CAC) scores (determined before the start of the radiotherapy treatment) in the age category 55-64 years were significantly higher than the CAC scores in an asymptomatic female American cohort. These data suggest that breast cancer patients are at a higher risk of developing coronary artery disease.

Secondly, three years after whole breast irradiation we found significantly less increase of CAC scores of the LAD in the group irradiated using a breath-hold technique when compared to patients irradiated without the use of breath-hold. When in each patient the Right Coronary Artery (RCA) CAC score was subtracted from the LAD CAC score, the group of left-sided breast cancer patients, treated with a breath-hold technique, showed less increase in CAC score 3 years after whole breast irradiation. Therefore, the risk of cardiac heart disease may have decreased. However, drawbacks of our study are the small numbers and the relatively short follow-up period.

In the **general discussion** several **future perspectives** were pointed out. As for the delineation of target volumes we do not advise to use MR images in addition to the CT scan when delineating either the glandular breast tissue or the lumpectomy cavity. We concluded that currently a tangential IMRT technique combined with a breath-hold technique is the most optimal treatment technique for left-sided breast cancer whole breast radiotherapy. This recommendation is based on the observations that in all studied patients an increase in dose homogeneity was found, as well as a reduction in dose in the heart, specifically in the caudal part of the LAD. Based on literature data and our study results we advise the following constraints when performing radiotherapy in left-sided breast-conserving radiotherapy (using a fractionation scheme of 42.56 Gy in 16 fractions), since no absolute thresholds could be defined.

1. Mean heart dose < 2 Gy;
2. Mean lung dose < 5 Gy;
3. Mean dose outside the Planning Target Volume (PTV) as low as reasonably achievable.
4. In patients younger than 45 years the dose in the contralateral breast should be as low as possible. In BRCA 1/2 carriers this is of even more importance.

Our treatment planning studies revealed that these constraints are feasible.
We also advise to perform a breath-hold technique in all left-sided breast cancer patients, regardless of age and breast size.

Finally, some **concluding remarks** were given. We have described that improvements in breast cancer radiotherapy have been achieved. However, the surrounding healthy tissue will still receive a radiation dose, when the glandular breast tissue is irradiated. Focussing on individualisation of the radiation treatment is of the utmost importance. In future research we have to aim at decreasing the (late) side-effects of the radiotherapy and increasing the quality of life further. Introducing APBI into daily practice should be the objective of future clinical research. Research should also focus on the question whether breast radiotherapy can be omitted after breast-conserving surgery. Finally, this needs to be tailored according to the patient's preferences, by means of shared decision-making.