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GENERAL INTRODUCTION

Over the past decades, an increasing incidence in breast cancer has been observed in Europe [1]. Arnold et al. showed an estimated annual percentage change (APC): of 1.1% for women in the age group 35-49 years and of 0.7% in the age group 50-74 years during 1998-2007. An APC of 1.1% and 0.7% stands for an increasing trend in breast cancer incidence [2]. Female breast cancer represents around 30% of all new cancer cases in Europe [3]. In comparison to other countries, The Netherlands shows one of the highest breast cancer rates. In 2012, over 14,000 women were diagnosed with invasive breast cancer and around 2,200 women with breast carcinoma in situ [4].

Mastectomy was the standard local treatment modality in the early years of breast cancer treatment. However, several large prospectively randomised controlled trials showed that the overall survival after breast conserving surgery followed by radiation therapy was comparable to that of mastectomy [5-8]. Based on these findings, breast conserving therapy (including whole breast irradiation) was introduced around 1980. As it was unclear at that time whether a boost dose was meaningful, the EORTC boost-no boost trial was launched. This phase-III trial showed that a boost dose improved the local control in all age categories (with hazard ratios varying from 0.49-0.76). The absolute risk reduction was most pronounced in patients under 40 years that received a boost dose [9].

Furthermore, in 2011 the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that breast cancer recurrences were decreased by 50% when using radiotherapy after breast conserving surgery in breast cancer patients with different absolute risks. Apart from this, a decrease of breast cancer death (after 15 years) and any death was noted when applying radiotherapy [10]. Finally, it appeared that the use of adjuvant systemic therapy significantly contributed to obtaining a lower risk of ipsilateral recurrent disease [11].

These results show that radiotherapy is of importance, and is, therefore, an integral part of the breast conserving therapy. However, several improvements in the radiation therapy treatment can be realised. A relatively new development is the introduction of hypofractionation schemes. Several randomized studies reported comparable local control rates and breast cosmesis for the hypofractionation schedule compared to those of the standard treatment (25x2Gy per fraction) [12,13]. According to Whelan et al. the hypofractionation schedule is more convenient for patients and less costly, which may result in an increase in the number of women receiving whole breast irradiation after breast conserving surgery [13]. The implementation of Accelerated Partial Breast Irradiation (APBI) techniques is the latest step in adapting the radiation treatment, applied following the ASTRO and ESTRO guidelines for the "low risk" group [14,15].

Over the past few years, radiation therapy techniques in breast cancer treatment have changed. Since 2000, planning computed tomography (CT) scans have been applied and radiation oncologists have started delineating target volumes (i.e. the glandular breast tissue and the lumpectomy cavity) as well as the critical structures surrounding the target volumes, in order to obtain information about the dose in these volumes. The used treatment planning techniques changed from 2D planning techniques to 3D conformal radiotherapy planning techniques (3D-CRT). And in just one decade other techniques such as Intensity Modulated Radiotherapy (IMRT), rotational therapy (Volumetric Modulated Arc Therapy (VMAT), TomoTherapy) have made their appearance. Furthermore, within a few years, the Magnetic Resonance Imaging (MRI) accelerator will make its clinical entrance in The Netherlands, which accordingly will result in new insights [16].

However, as it is the case for every medical treatment, side effects occur when applying radiotherapy [17]. Preclinical and clinical studies suggest that breast cancer radiotherapy is associated with an increased rate of major coronary events [6,18,19]. This is especially applicable for patients with left-sided breast cancer [20-25]. Consequently, irradiation of left-sided breast cancer patients implies that special attention should be paid to avoid late radiation induced coronary artery toxicity by applying optimised treatment techniques.

MRI and target volume delineation of the glandular breast tissue and the lumpectomy cavity

Before starting with the treatment planning process the target volume needs to be defined. Several authors studied the differences in delineating the glandular breast volume and the lumpectomy cavity volume [26-28]. Li et al. showed that differences in target volume delineation for whole breast irradiation were of significance both clinically and dosimetrically. For example, in one of the case studies, the heart volume receiving 20 Gy varies from 0% to 7% according to the various delineations performed by nine radiation oncologists [29]. This indicates that guidelines for defining the target volume and the heart are needed.

Besides using delineation protocols, the used imaging modalities are of importance in delineating the target volumes. In radiation therapy, the standard imaging modality is the CT scan. MRI is a diagnostic imaging modality that has proven to increase the visualisation of soft tissues [30], and has shown to improve the agreement between observers in delineating the breast cancer lumpectomy cavity volume in an APBI study using brachytherapy [31]. Therefore, an increased visibility of the glandular breast tissue and the lumpectomy cavity may be obtained by using MRI based delineation instead of CT based delineation. The latter may enable a further decrease of the interobserver variation in delineating the glandular breast tissue as well as that of the lumpectomy cavity. Therefore, we hypothesised that an MRI technique could improve the delineation of the glandular breast cancer target volume and the lumpectomy cavity in external beam radiation treatment. We performed two studies to examine the differences in glandular breast tissue (GBT) and lumpectomy cavity (LC) volume delineation on the MRI and the CT. And we assessed the inter-observer variability for both volumes on both imaging modalities as well. For a total of 15 patients, who underwent a MRI and CT scan in supine position, it appeared that no differences were found delineating the volumes on MRI compared to CT. Also the inter-observer variability was comparable for both imaging modalities [32,33]. However, still the question remained if the observers agreement could be improved after co-registration of the MRI and the CT.

Treatment planning studies in whole breast irradiation to reduce heart and left anterior descending (LAD) coronary artery dose

The literature shows that reducing the heart and LAD coronary artery dose is a major issue when applying radiotherapy [24], even in today's improved treatment planning techniques [23]. A breath-hold technique can be used to reduce the dose in the heart and the heart vessels. Over the past few years, several authors carried out studies to evaluate the pros and cons of various breath-hold techniques and these have proven to be easy performable and reproducible [34-38]. In 2008 the Active Breathing Control (ABC) method, a breath-hold technique, was introduced in our institution (Radiotherapy Centre West, RCWEST). Because of the ALARA (As Low As Reasonably Achievable) principle, and in the absence of a threshold dose for the radiation-induced damage to the heart and the main coronary artery, the LAD dose should be minimised in all patients. Therefore, all left-sided breast cancer patients were treated with this breath-hold technique, without setting an age limit, since 2010. After two years, the feasibility of our ABC method was evaluated. It appeared that 98% of our breast cancer patients were able to undergo the breath-hold technique [39].

As RCWEST aims to continuously improve radiation treatment we tried to identify which treatment technique would be best in the reduction of the dose to the critical structures, i.e. the heart and the LAD. Therefore, several treatment planning studies were carried out.

Yartsev et al. confirmed that treatment planning studies are valuable to explore if (new) treatment planning techniques meet the constraints according to the department requirements [40]. Our hypothesis was, that Intensity Modulated Radiotherapy (IMRT), proton therapy and TomoTherapy would be superior in sparing the heart and LAD than a standard 3D-Conformal Radiotherapy (3D-CRT) technique.

Vascular heart damage before and after whole breast irradiation

Several risk factors play a role in developing breast cancer [2,39]. In the Dutch national guideline of diagnosis and treatment of breast cancer the various risk factors are summarised, see Figure 1 [41].

The relative risk of physical inactivity and a high Body Mass Index were indicated as risk factors in the overview (Figure 1). Acccording to the World Heart Federation (WHF), both were also indicated as risk factors of heart disease as well.

The WHF reported that 6% and 5% of global deaths were attributed to physical inactivity and a high Body Mass Index, respectively; the leading risk factor of heart disease is hypertension, to which 13% of global deaths are attributed. Furthermore, women experience an increased risk of heart disease with increasing age [42].

Taking into account the above described risks the question arose whether breast cancer patients have an a priori higher risk for developing heart disease.
The Framing Risk Score (FRS) is the most commonly used Coronary Artery Disease (CAD) risk prediction score [43]. However, Oudkerk et al. state that the FRS does not take lifestyle factors and the extent of atherosclerotic disease burden into account [44]. The calcium score (number of calcium deposits) in the coronary arteries (CAC scores), as a surrogate of total atheroma burden, appears to predict the risk of subsequent cardiovascular events in cases without symptomatic CAD [44,45]. The calcium score measurement is based on a non-invasive CT scan and appears to improve the FRS predictions [46]. Therefore, we investigated the calciumscores in three cohorts of breast cancer patients.

As was stated above, radiation therapy has side effects on critical organs surrounding the glandular breast tissue, such as the lungs, the contralateral breast and the heart and the coronary arteries. Several studies pointed out that radiation treatment for left-sided breast cancer increased the risk of heart disease [20-25].

We hypothesised that patients with left-sided breast cancer were more at risk for an increase in CAC scores than patients with right-sided breast cancer or left-sided breast cancer treated with a heart sparing radiation technique. Therefore, a longitudinal study was conducted to follow a cohort of breast cancer patients before and 3 years after the radiation treatment in order to evaluate the possible effects on the CAC scores.

Factor	Relative risk	Reference
Older age (over age 45 versus under age 25)	< 10	Dumitrescu 2005 McPherson 2000
Mutations in BRCA1/2	6 – 8	Dumitrescu 2005 McPherson 2000
Geographic region (North American and Northern Europe versus the Far East, Africa and South America)	5 - 10	Dumitrescu 2005
High density mammogram	4 - 6	Boyd 2010
Atypical benign breast laesions: Atypical (ductal or lobular) hyperplasia, flat epithelial atypia, lobular carcinoma in situ, papillary laesions and complex sclerosing laesions (radial scars)	4 - 5	Dumitrescu 2005 McPherson 2000 Morrow 1999 Santen 2005
Prior history of radiation; chest and/or axillary radiation, e.g. due to Hodgkin's lymphoma before age 40	3 - 20	De Bruin 2009 Van Leeuwen 2003 Aleman 2003
Breast carcinoma or DCIS in medical history	2 - 4	Morrow 1999
Late age at the time of first child, over age 35 vs. before age 20	2	Dumitrescu 2005 McPherson 2000
High postmenopausal bone density	2 - 3.5	Dumitrescu 2005
Diethylstillbestrol (DES) use during pregnancy	2	McPherson 2000
Late menopause, after age 54	≤ 2	Dumitrescu 2005 McPherson 2000 Morrow 1999
Nulliparity	< 2	Dumitrescu 2005 McPherson 2000 Morrow 1999
Hormone replacement therapy (HRT) use for over 10 years	1.4 - 3	Dumitrescu 2005
Alcohol intake, risk is dose-dependent, 2-5 units per day vs. no alcohol intake	1.2 - 1.5	Brennan SF 2010 Key 2006 Li 2010
Oral contraception Recent use Past use	 1.2 -2.4 1.0-1.2	Dumitrescu 2005 Cibula 2010
Mutations in other highly penetrant genes; p53, PTEN	1 - 6	Dumitrescu 2005
Early menarche, before age 11	1 - 3	Dumitrescu 2005 McPherson 2000 Morrow 1999
Physical exercise 5x per week vs. inactivity	0.85	Patterson 2010 Bernstein 2009
In vitro fertilisation	Not clearly elevated	Salhab 2005 Dor 2002 Zreik 2010
Obesity Premenopausal, body mass index > 35 Postmenopausal, body mass index > 35	 0.7 2	McPherson 2000

Figure 1: Risk factors for developing breast cancer [41].

Outline of this thesis
The first and second parts of this thesis focus on optimizing the radiation treatment technique. In **chapter 1** we analyse the optimization of the breast target volume delineation and the additional value of coregistered CT/MR images.

As confirmed in the literature, sparing the heart when applying a radiation therapy technique is of great importance. We evaluated the use of the Active Breathing Control method, as used in RCWEST. Furthermore, three planning studies are described in **chapter 2**, evaluating the best treatment planning technique.

In **chapter 3**, the cardiac side-effects of radiation therapy are described. Firstly, the baseline characteristics of a cohort of breast cancer patients in RCWEST are analysed and compared to a cohort of healthy Caucasian women. Secondly, we prospectively analysed if there were differences in calcium scores before and three years after radiation treatment found in three groups of patients treated with radiation treatment for breast cancer.

Finally, the main findings of this thesis are summarised and discussed and recommendations for clinical practice are given.

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