

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/32932> holds various files of this Leiden University dissertation

Author: Mast, Mirjam

Title: Avoiding the heart : about optimising whole breast irradiation

Issue Date: 2015-06-23



AVOIDING THE HEART

About optimising whole
breast irradiation

Mirjam Mast

AVOIDING THE HEART

About optimising whole breast irradiation

Mirjam Mast

Cover idee **Floris Mast**
Grafisch ontwerp **Suze Swarte grafisch ontwerp i.s.m. Laura Bolczek**
Printed by **Cito Repro Groep, Amsterdam**
ISBN **978-90-822415-1-8**

© **Mirjam Mast, The Netherlands, 2015**

Avoiding the heart. About optimising whole breast irradiation.
Thesis, Leiden University, The Netherlands, 2015

All rights reserved.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic or mechanical, including photocopying, and recording, or otherwise, without the written permission of the author.

AVOIDING THE HEART

About optimising whole breast irradiation

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 23 juni 2015 klokke 15.00 uur

door

Mirjam Esther Mast

geboren te Haarlem
in 1970

Promotiecommissie

Promotor	Prof. dr. H. Struikmans
Co-promotores	Dr. A.L. Petoukhova, MCHaaglanden, Den Haag Dr. A.N. Scholten, NKI-AvL, Amsterdam
Overige leden	Prof. dr. J.W.R. Nortier Prof. dr. J.P. Pignol, Erasmus Universiteit, Rotterdam Prof. dr. E.J.Th. Rutgers, Universiteit van Amsterdam

Te weten wat men weet,
en te weten wat men niet weet,
dat is kennis.

Confucius (China 551-479 v.Chr.)

CONTENTS

General introduction	11
Chapter 1	23
MRI and target volume delineation of the glandular breast tissue and the lumpectomy cavity	
Optimal registration method of MRI and CT for delineation in radiotherapy planning of breast cancer patients treated with breast conserving therapy	25
Target volume delineation in breast conserving radiotherapy: are co-registered CT and MR images of added value?	43
Chapter 2	
Treatment planning studies in whole breast irradiation to reduce heart and LAD dose	57
A heart sparing technique in women with left-sided breast cancer. Results of 4 years of experience in Radiotherapy Centre West	59
Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further?	69
Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients Reduction of heart dose in left-sided whole breast irradiation: IMRT versus TomoTherapy in breath-hold	81
Tangential IMRT versus TomoTherapy with and without breath-hold in left-sided whole breast irradiation	95

Chapter 3	105
Vascular heart damage before and after whole breast irradiation	
Preradiotherapy calcium scores of the coronary arteries in a cohort of women with early-stage breast cancer: A comparison with a cohort of healthy women	107
Less increase of CT based calcium scores of the coronary arteries three years after breast-conserving radiotherapy using breath-hold	119
General discussion	133
Concluding remarks	144
Summary	153
Samenvatting	159
Appendices	165
Abbreviations	
List of publications	
Curriculum Vitae	
Dankwoord	

The page features two large, abstract, orange-colored shapes that resemble stylized hands or wings. The top shape is positioned in the upper right quadrant, and the bottom shape is in the lower left quadrant. Both shapes have a white, angular cutout in their center, creating a sense of depth and movement. The background is plain white.

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). According 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 calcium scores 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
Diethylstilbestrol (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.

References

1. Karim-Kos H, de Vries E, Soerjomataram I, et al. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008; 44: 1345-1389.
2. Arnold M, Karim-Kos H, Coebergh J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. *Eur J Cancer* 2013 Oct 8. S0959-8049(13)00842-3.
3. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18(3):581-592.
4. IKNL: http://www.cijfersoverkanker.nl/selecties/dataset_1/img540624c12bc8c?type=bar; assessed 28-11-2014.
5. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med*. 1981;305(1):6-11.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and surgery in early breast cancer. An overview of randomized trials. *N Engl J Med* 1995;333:1444-1455.
7. van Dongen J, Voogd A, Fentiman I, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;92:1143-1150.
8. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation or the treatment of invasive breast cancer. *N Engl J Med*, 2002;347(16):1233-1241.
9. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2014 [Epub ahead of print].
10. EBCTCG Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378(9804):1707-1716.
11. EBCTC Group Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-1717.
12. TART Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9(4):331-341.
13. Whelan T, Pignol J, Levine M, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362(6):513-20.
14. Smith B, Arthur D, Buchholz T, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO) *Int J Radiat Oncol Biol Phys* 2009;74(4):987-1001.
15. Polgár C, van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence. *Radiother Oncol* 2010;94:264-273.
16. Lagendijk J, Raaymakers B and Van Vulpen M The Magnetic Resonance Imaging-Linac System. *Semin Radiat Oncol* 2014;24(3):207-209.
17. Petersen C and Würschmidt F Late Toxicity of Radiotherapy: A Problem or a Challenge for the Radiation Oncologist? *Breast Care (Basel)*. 2011;6(5):369-374.
18. Schultz-Hector S and Trott K Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with

- the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007;67:10–18.
19. Stewart F, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE_{-/-} mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649–658.
 20. Darby S, McGale P, Taylor C, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557–565.
 21. Hoening M, Botma A, Aleman B, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365–375.
 22. Borger J, Hoening M, Boersma L, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. *Int J Radiat Oncol Biol Phys* 2007;69(4):1131–1138.
 23. Taylor C, Povall J, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 2008;72(2):501–507.
 24. Darby S, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
 25. Henson K, McGale P, Taylor C, et al. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer* 2013;108:179–182.
 26. Weiss E and Hess C The impact of gross tumor volume (GTV) and clinical target volume (CTV) definition on the total accuracy in radiotherapy theoretical aspects and practical experiences. *Strahlenther Onkol* 2003;179(1):21–30.
 27. Struikmans H, Wárlám-Rodenhuis C, Stam T, et al. Interobserver variability of target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005;76(3):293–299.
 28. Van Mourik A, Elkhuisen P, Minkema D, et al. Multi institutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010;94(3):286–291.
 29. Li X, Tai A, Arthur D, et al. Variability of target and normal structure delineation for breast-cancer radiotherapy: a RTOG multi-institutional and multi-observer study(2009). *Radiation Therapy Oncology Group (RTOG)*. *Int J Radiat Oncol Biol Phys* 2009;73:944–951.
 30. Whipp E and Halliwell M Magnetic resonance imaging appearances in the postoperative breast: the clinical target volume-tumor and its relationship to the chest wall. *Int J Radiat Oncol Biol Phys* 2008;72:49–57.
 31. Jolicoeur M, Racine M, Trop I, et al. Localization of the surgical bed using supine magnetic resonance and computed tomography scan fusion for planification of breast interstitial brachytherapy. *Radiother Oncol* 2011;100:480–484.
 32. Giezen M, Kouwenhoven E, Scholten A, et al. MRI versus CT based volume delineation of the lumpectomy cavity (LC) in supine position in breast conserving therapy: an exploratory study. *Int J Radiat Oncol Biol Phys* 2012;82:1332–1340.
 33. Giezen M, Kouwenhoven E, Scholten A, et al. Magnetic Resonance Imaging- Versus Computed Tomography-Based Target Volume Delineation of the Glandular Breast Tissue (Clinical Target Volume Breast) in Breast-Conserving Therapy: An Exploratory Study. *Int J Radiat Oncol Biol Phys* 2011;81:804–811.
 34. Korreman S, Pedersen A, Aarup LR, et al. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1375–1380.
 35. Cao J, Roeske J, Chmura S, et al. Calculation and prediction of the effect of respiratory motion on whole breast radiation therapy dose distributions. *Med Dosim* 2009;34:126–132.
 36. Vikström J, Hjelstuen M, Mjaaland I, et al. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold

- with audio-visual guidance, without compromising target coverage. *Acta Oncol* 2011;50:42–50.
37. Swanson T, Grills I, Hong Y, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36:24–30.
 38. Alderliesten T, Sonke JJ, Betgen A, et al. Accuracy Evaluation of a 3-Dimensional Surface Imaging System for Guidance in Deep-Inspiration Breath-Hold Radiation Therapy *Int J Radiation Oncol Biol Phys* 2013;85(2): 536-542.
 39. Mast M, van der Klein J, van Geen S, et al. Een hartsparende bestralingstechniek bij vrouwen met linkszijdige borstkanker. De resultaten van vier jaar ervaring in Radiotherapiecentrum West. *Ned. Tijdschr Oncol* 2012;9(6):270-276.
 40. Yartsev S, Muren L and Thwaites D Treatment planning studies in radiotherapy. Editorial / *Radiother Oncol* 2013;109:342–343.
 41. Comprehensive Cancer Centre the Netherlands. Breast cancer Dutch Guideline, version 2.0, 2012.
 42. <http://www.world-heart-federation.org/press/fact-sheets/cardiovascular-disease-risk-factors/> assessed 28-11-2014.
 43. Anderson K, Odell P, Wilson P, et al. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293-298.
 44. Oudkerk M, Stillman A, Halliburton S, et al: Coronary artery calcium screening: current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging. *Eur Radiol* 2008;18:2785–2807.
 45. Greenland P, Bonow R, Brundage B, et al. ACCF/AHA 2007 Clinical Expert Consensus Document on Coronary Artery Calcium Scoring by Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients With Chest pain. A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA writing committee to update the 2000 expert consensus document on electron beam computed tomography). *Circulation*. 2007;115:402-426.
 46. Kavousi M, Elias-Smale S, Rutten J, et al: Evaluation of Newer Risk Markers for Coronary Heart Disease Risk Classification. A Cohort Study. *Ann Intern Med* 2012;156:438-444.

The page features two large, stylized orange geometric shapes. The top shape is a jagged, upward-pointing form with a white notch in the center. The bottom shape is a similar jagged, downward-pointing form, also with a white notch in the center. These shapes are positioned symmetrically around the central text.

CHAPTER 1

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

Registration of MRI and CT for target volume delineation in breast conserving radiotherapy

Anna Petoukhova^a, Mirjam Mast^a, Erik Kouwenhoven^a, Wim Jansen^b,
Astrid Scholten^c and Henk Struikmans^{a,b}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of Clinical Oncology, Leiden University Medical Centre,
The Netherlands;

^c Department of Radiation Oncology, Netherlands Cancer Institute –
Antoni van Leeuwenhoek Hospital, The Netherlands.

Acta Oncol submitted 14-11-2014

Abstract

Background

To assess the optimal method of MRI to CT registration of the glandular breast tissue (GBT) and the lumpectomy cavity (LC).

Materials and methods

After breast conserving surgery 10 breast cancer patients underwent a planning-CT and a MRI (1.5 T, T1 weighted) in supine radiotherapy treatment position. Co-registration of the CT and MR images was performed with five different methods (breast-markers, thoracic-markers, surgical (titanium) clips, normalized mutual information and local correlation). Parameters of the rigid-body transformation (3D translation and 3D rotation) to match the CT and MRI were recorded. Accuracy was evaluated by comparing the misalignment between CT and MR for breast-markers, thoracic-markers, surgical clips and all fiducials. Additionally, an evaluation was performed by delineating the GBT based on CT and MRI by four observers (two radiation oncologists and two radiologists). We determined which registration procedure yields the smallest non-overlapping (rest) volume.

Results

The thoracic-marker-based registration resulted in smallest MRI-CT distances between breast markers. For the surgical clip evaluation, the mean MRI-CT distance for the breast-marker-based registration is the lowest. But the use of surgical clips for MRI-CT registration resulted in large rotations ($> 3^\circ$) for 7 out of 8 patients. Moreover, clips were not always well visible on the MR images. The thoracic-marker-based and breast-marker-based registrations resulted in the smallest MRI-CT displacements between all fiducials.

Co-registration of CT and MR data sets based on breast-markers gave the best result for the GBT delineation in terms of the rest volume.

Conclusions

The use of breast markers for MRI-CT co-registration gives the best results and is recommended not only for delineation of the GBT, but also for delineation of the lumpectomy cavity. For lumpectomy cavity delineation the clip-based registration is an alternative to the breast-marker-based registration.

Introduction

In radiotherapy, target volume delineation is based on computed tomography (CT), while magnetic resonance imaging (MRI) is able to complement the CT data for its superior soft tissue visualisation. The added value of co-registration of CT together with MR images was clearly assessed for various tumour sites such as brain, head-and-neck and prostate [1-3]. However, this added value was not studied in detail for breast cancer radiotherapy [4]. There are some published data available about registration of MR images with mammography and ultrasound [5]. Kirby et al. [6] and Jolicoeur et al. [7] described co-registration of CT to MR images (in prone position and supine position, respectively) for breast cancer radiotherapy. These two studies focussed on co-registration of CT/MRI for surgical bed volumes. For patients in supine position, comparison of CT and MRI remains difficult due to the limited bore size of conventional closed MRI scanners (for example, 60 cm in diameter for a Siemens Magnetom Symphony MRI scanner), respiratory motion artifacts, and distortion of breast tissue by overlying MR receiver coils. In our previous studies [8,9], a first attempt to find an added value of MRI was described for delineation of the glandular breast tissue (GBT) and lumpectomy cavity, respectively. In these studies non-registered CT and MR scans were used. To investigate whether MRI indeed improves GBT and lumpectomy cavity delineation, a method has to be developed for accurate rigid registration of MR and CT in breast cancer.

The majority of registration algorithms in medical imaging can be classified as being either frame based [10], point based [11] or voxel based [12]. Stereotactic frame-based registration is very accurate, but not suitable for breast imaging. The anatomical point-based registration methods are labour-intensive and their accuracy depends on the accurate identification of corresponding landmarks in all modalities. Voxel-based registration methods [12] optimize the similarity of all geometrically corresponding voxel pairs for some features. The overall registration accuracy should be within an acceptable tolerance for 3D treatment planning (2–5 mm) [13]. According to Fraass et al. 3D registration results in about 2 mm accuracy, including distortions and transfer of MRI contours to CT dataset [13].

Nowadays rigid image registration has become more accurate [4,14]. According to Devic et al. [4] the MRI to CT image co-registration error is of the order of 1–2 mm, except for deformable methods. However, the magnitude of the co-registration error depends on the co-registration technique and also on the anatomical site. Skerl et al. [14] compared 12 similarity measures for the rigid registration of multi-modal head images. They concluded that the results for the registration of CT to MR images and MR to CT images indicate that such methods as normalized mutual information are the most accurate similarity measures and have the smallest risk of being trapped in a local optimum.

In addition to the clinically used large region of interest (ROI), a registration of multiple ROIs can be used (mROI). Van Kranen et al. [15] proposed to use this method (based on mROI registration of cone beam computed tomography scans and the planning CT) and van Beek et al. [16] reported the first clinical experience with this method for head-and-neck cancer patients.

In our study, CT and MR images of ten breast cancer patients who were candidates for breast conserving therapy were made in supine position after surgery and before starting the radiotherapy treatment. On the breast of these patients breast markers were placed. For these patients co-registration of the CT and MR images was performed with five different methods (breast-markers, thoracic-markers, surgical clips, anatomical markers, normalized mutual information (NMI) [12] and local correlation

[17]. The rigid-body transformation consists of a 3D translation and 3D rotation, and these parameters were recorded for each registration method. Registration accuracy was evaluated by performing a comparison of the misalignment between CT and MR by breast-markers, thoracic-markers, surgical clips and all fiducials (breast-markers, thoracic-markers and surgical clips). Additionally, an evaluation was performed by delineating the GBT on CT and MRI by four observers (two radiation oncologists and two radiologists). Thereafter, we investigated which registration procedure yields the smallest non-overlapping volume (rest volume).

The aim of this manuscript is to describe advantages and disadvantages of each registration method and to find the best possible MRI to CT registration of the GBT and the lumpectomy cavity.

Materials and methods

Patients

Ten patients with early stage breast cancer (clinically T1-2; N0-1) were treated with breast conserving therapy (patients did not undergo en bloc axillary dissection). After referral to the radiotherapy department a planning-CT scan and directly afterwards an MRI scan were performed. Patient and tumour characteristics are presented in Table 1. All patients confirmed participation in our study by signing an informed consent. The study was approved by the regional institutional review board METC Zuidwest Holland [18].

Mean age in years (range)	Menopausal status	Left (L) - or right (R) sided	Breast quadrant	Pathological TN (2002)	Days since surgery (range)	Ductal (D) or lobular (L) carcinoma
57 (44 - 86)	†post: 4x *pre: 6x	L:3x R:7x	upper outer: 3x upper inner: 1x lower outer: 2x sub areolar/ nipple complex: 2x upper 12 o' clock: 1x lower 6 o' clock: 1x	pT1: 6x pT2: 4x pN0: 8x pN1: 2x	27 (12 - 41)	D: 10x

Table 1. Patient and tumour characteristics.

Abbreviations: *pre = premenopausal; †post = postmenopausal.

CT and MR images of patients

Patients underwent planning CT followed by MRI in the same supine radiotherapy treatment position. No intravenous contrast was used. Patients were imaged in supine position with back, shoulders and arms supported by a CT and MRI compatible wedge (Thorawedge, CIVCO Medical Solutions, The Netherlands) at 5° slope angle and with a knee support for comfort. Both arms were in abduction with both hands jointed above the head. CT and MR images were obtained using 3 mm slice thickness from lung apices up to diaphragm. The field of view covered the whole of the patient's chest and both breasts. CT scans (using a 512 x 512 matrix and a 1.07 mm pixel size) were performed using an AcQSim single slice CT scanner (Philips Medical Systems, Cleveland, OH, USA) with a bore size of 85 cm. MR images were taken using a Magnetom Symphony 1.5 T scanner (Syngo MR 2004A MRI, Siemens, The Netherlands) with a bore size of 60 cm. Only MR images in one direction: T1 weighted TSE (Turbo Spin Echo) transverse MRI scans (256 x 204 matrix and voxel size 1.6 x 1.6 x 3 mm³, no slice-gap) were used in this study.

No fat suppression was used as the entire GBT including the lumpectomy cavity was intended to be visualized. The MRI body coil was set at a bandwidth of 150.0 Hz/pixel with a signal-to-noise ratio of 1. An additional phased-array coil was positioned over the affected breast supported by foam blocks aside to the breast to prevent changes of the original breast shape and to keep the breast in radiotherapy treatment position. The border of palpable GBT was marked with a thin plastic tube by the radiation oncologist (HS) just prior to CT scanning. The position of the tube remained the same during both CT and MR scanning. For CT and MR imaging the tube was filled with either a copper wire or lipiodol, respectively. During CT and MR scans multimodality hydrogel filled markers (MedCaT B.V., Erica, The Netherlands) were used to evaluate MR-CT matching possibilities. The donut shaped markers were 15 mm in diameter and had a thickness of 3.5 mm with a hole in the middle with a diameter of 5 mm. Four markers were placed along the laser lines on the thorax and four markers were placed on the breast (see Figure 1) of each patient. Surgical (titanium) clips (Teleflex Medical, Morrisville, NC, USA) within the breast, applied by surgeons to mark the borders of the lumpectomy cavity, were no contra-indication for MRI. In two of the remaining ten patients no surgical clips were placed in the lumpectomy cavity.

CT and MR image registration

CT and MR images were registered using Syntegra software of the Pinnacle3 treatment planning system (version 8.0, Philips Medical Systems, The Netherlands). Syntegra provides manual and point-based image registration, and three automated methods of gray value voxel-based image registration.

NMI registration is nowadays the state of the art for many clinical sites. For ten breast patients, the registration of the MR with CT images was performed with five different methods: four point-based (breast-markers, thoracic-markers, and surgical clips) and two automated voxel-based (NMI and local correlation) methods.

Multimodality markers (thoracic-markers or breast-markers) matching was achieved by using the midpoint of each marker by one observer (ALP). The midpoints were manually identified on each of the CT and MR scans. Misalignment between CT and MR markers was calculated in terms of the distance, defined as the mean of the distances between all point pairs. Syntegra software allows for automatic minimization of this distance between two sets.

The centre of gravity of the hole of each donut was manually determined on the axial slices of the CT and MR scans, sagittally and coronally reconstructed images were used for verification. For each clip, an identical procedure of identification of the centre of gravity was manually performed. Impaired visibility of the surgical clips on the MR images of some patients [9] made registration on the surgical clips difficult. Moreover, the surgical clips were often located close to each other (see e.g. Figure 2).

NMI and local correlation are two automated image registration algorithms in Pinnacle³. They are based on maximizing of similarity measures: NMI is based on probability distributions of the gray values in each image set [12], whereas local correlation assumes a local linear relationship between gray values. Local correlation is the default option in Syntegra for registration of CT and MR images because it works best for different image sets in which equivalent features can easily be seen. After a preliminary study for NMI and local correlation the complete set of CT and MR scans were used. Alternatively, a bounding box was used to limit the image set to a rectangular box defined by the user. An attempt to define the bounding box around the breast of each patient has failed probably because of the absence of high-contrast structures such as bones in the breast. Likewise, the use of a ROI to limit the existing image set was not preferred because this method is time consuming and subjective since the results strongly depend on the ROI delineation.

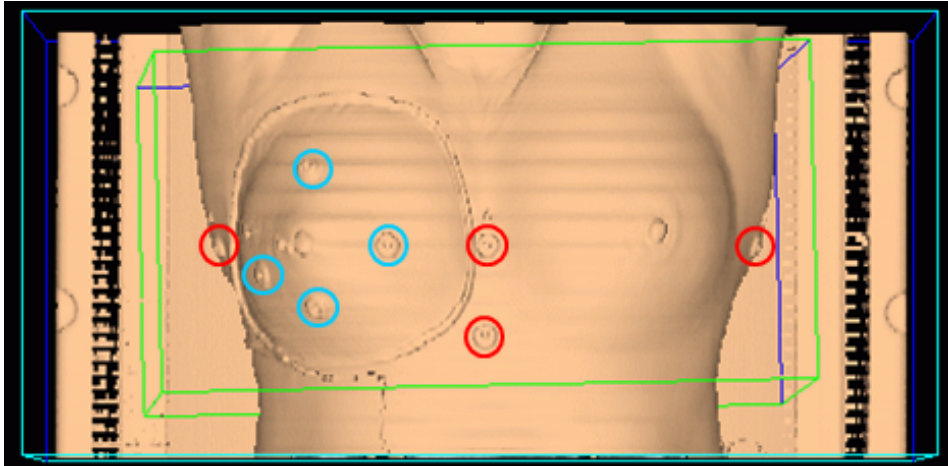


Figure 1. Patient 1 lying in the supine radiotherapy position on a Thorawedge with 5° slope angle. Four multimodality markers were placed along the laser lines on the thorax (red circles) and four markers were placed on the breast (aqua circles). The border of palpable GBT was marked with a thin copper wire. Thin blue and green lines indicate the CT and MR scan volumes, respectively.

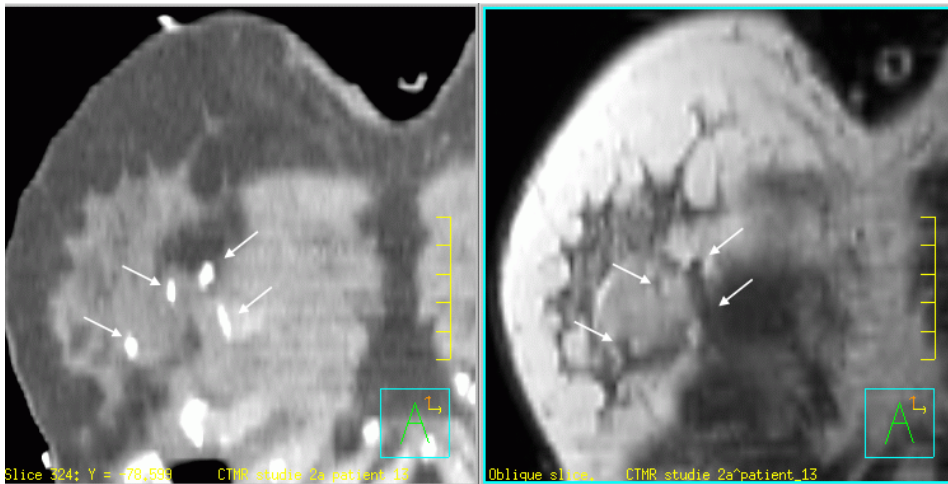


Figure 2. Patient 8 (54 years, premenopausal status) with four surgical clips in the breast: sagittal CT (left) and MR (right) images registered using breast markers. Note that the four clips, which can be seen on these images, are located very close to each other.

Evaluation of the registration accuracy

For each patient and each registration method the rigid-body transformation was recorded, defined as a 3D translation along the x-, y- and z-axis and 3D rotation around the x-, y- and z-axes. Note that according to the patient's CT scans, in all cases the x-axis is directed from patient's right to left, the y-axis is directed from posterior to anterior and the z-axis is directed from cranial to caudal. Although each patient underwent the CT and MR scans in the same treatment position, limited rotations between two scans can occur.

Each registration method started with the movement of the centre of the MR data set to the centre of the CT data set. Consecutively the translations and rotations were adjusted according to the applied registration method. For each evaluation method the fiducials (breast-markers or thoracic-markers or the clips) remained on the same place during the CT and MR. For each patient the registration accuracy of each method was evaluated (post-registration) by comparison of the average MR-CT displacement of the breast-markers or the surgical clips, the thoracic-markers or all fiducials.

In addition to the other registration method evaluations, target delineations (Clinical Target Volume) of the GBT by four observers (two radiation oncologists and two radiologists) [8] were used. The GBTs were delineated blind to the viewing contours of others and using written delineation instructions according to Giezen et al. [8]. For each individual patient, the mean, range and standard deviation values of the GBT delineation were calculated to evaluate the inter-observer variability in GBT delineation. For each registration method an averaged rest volume over the four observers on CT and MR images was determined according to Rasch et al. [19]. The rest volume (CT, MRI) was determined for each observer and consisted of specific parts of the GBT volumes, which were delineated on CT but not on MRI.

MR image distortion and validation of the methods used

Sources of MRI distortion can be divided into two groups: machine related distortions and object induced (i.e. patient dependant) effects [4]. Machine related distortions could be quantified and subsequently corrected for. Modern MRI scanners compensate for the majority of machine-derived distortions [4]. Object induced distortions arise from magnetic susceptibility effects, which modify the local magnetic field and tend to be most pronounced at air/tissue boundaries. The other major source of object induced distortions is chemical shift. Protons in fatty tissues resonate at slightly lower frequencies than those in water. The difference in frequency is called chemical shift [20] and water-fat shift (WFS) for the specific case of body fat. Susceptibility-induced distortions of the markers were minor. The markers are used for evaluation of registration accuracy without any correction for shift. Motion is an additional problem in MR imaging which can result in blurring, misregistration and artifacts within the scanned images. Both cardiac as well as respiratory movements affect the thorax.

Statistics

For the statistical analysis SPSS version 17 (SPSS Inc. Chicago, IL, USA) was used. To analyze the differences between the different registration methods a Wilcoxon signed-rank test was used to compare the differences of the average values between both imaging modalities. The level of statistical significance was considered $p < 0.05$ (two-sided) for all calculations.

Results

CT and MR images registration

The translations of MRI relative to CT images along the x-, y-, and z-axes, as determined with five registration algorithms, are presented in Table 2.

Differences between various registration methods for the translation along the same axis are limited within a few millimetres. The angles of rotations of the MR image data sets along the x-, y-, and z-axes after completing MRI/CT fusion with the five registration algorithms are shown in Table 3. Figure 3 shows an example of the breast-marker-based and clip-based registrations for patient 4. For the clip-based registration a rotation of the MR image along the z-axis relative to the CT image can be seen clearly.

Translations and distance d (cm)																						
Pa- tient	Breast-markers				Thoracic-markers				Surgical clips				Local Correlation				Normalized Mutual Information					
	#	x	y	z	d	x	y	z	d	x	y	z	d	x	y	z	d	x	y	z	d	
1	-0.4	-48.0	2.1	48.0	0.2	-47.8	2.1	47.9	-0.3	-47.7	2.2	47.7	-0.4	-47.7	2.1	47.7	-0.4	-47.7	2.3	47.7		
2	0.7	-48.2	0.3	48.2	0.1	-47.5	0.7	47.5	0.7	-49.1	1.4	49.1	0.1	-47.4	0.7	47.4	0.0	-47.3	0.6	47.3		
3	0.2	-46.3	3.0	46.4	0.0	-46.4	3.1	46.5	-0.2	-47.3	4.2	47.5	-0.2	-46.4	3.5	46.6	-0.2	-46.4	3.6	46.6		
4	-0.3	-50.5	1.7	50.5	-0.1	-50.4	1.7	50.4	-1.6	-51.1	2.1	51.2	-0.5	-50.4	2.1	50.5	-0.5	-50.4	2.2	50.4		
5	-1.8	-46.7	-2.3	46.8	-2.2	-46.8	-2.0	46.9	-2.2	-46.9	-3.2	47.1	-2.3	-46.8	-2.2	46.9	-2.3	-46.8	-2.1	46.9		
6	0.5	-47.2	-8.4	47.9	0.6	-47.0	-8.2	47.7	n.a.*	n.a.*	n.a.*	n.a.*	0.4	-47.2	-8.3	48.0	0.4	-47.2	-8.4	47.9		
7	1.3	-47.5	-7.4	48.1	1.4	-47.0	-7.5	47.6	n.a.*	n.a.*	n.a.*	n.a.*	1.0	-47.2	-7.2	47.7	1.0	-47.1	-7.1	47.7		
8	-0.1	-50.9	-8.1	51.5	0.0	-50.9	-7.9	51.5	-0.4	-50.9	-7.4	51.5	-0.2	-50.8	-7.8	51.4	-0.2	-50.8	-7.8	51.4		
9	-2.3	-47.1	-1.9	47.2	-2.0	-47.1	-1.4	47.2	-2.2	-47.0	-0.9	47.0	-1.9	-47.1	-1.2	47.1	-1.9	-47.1	-1.1	47.1		
10	3.1	-48.8	-6.4	49.3	2.8	-48.9	-6.5	49.4	3.1	-49.0	-6.0	49.4	2.7	-48.7	-6.6	49.2	2.6	-48.8	-6.4	49.2		

Table 2. CT and MR image registration parameters found for breast-marker, thoracic-marker, surgical-clip-based registration, local correlation and normalized mutual information (NMI). The Table shows the translation of MR images along the x-, y-, and z-axes and the distance (d) between the two imaging modalities.

Rotations (degree)																
Patient	Breast-markers			Thoracic-markers			Surgical clips			Local Correlation			Normalized Mutual Information			
	#	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
1		-2.1	1.2	-3.1	-2.0	0.6	-1.3	1.0	-1.0	-1.1	-0.9	0.3	-1.1	-0.9	0.5	-0.9
2		-3.6	-2.1	7.5	-3.8	-1.3	2.8	-3.0	2.7	10.5	-1.8	-0.6	2.2	-1.4	-0.5	2.0
3		-3.8	-0.7	-0.1	-2.2	-0.4	-1.1	-10.2	-4.1	-2.8	-2.0	-0.3	-0.2	-1.2	-0.3	-0.4
4		-2.8	1.6	0.0	-1.8	2.2	2.2	-1.4	-1.6	-6.1	-1.2	2.3	0.3	-1.0	2.0	1.0
5		-0.1	-1.5	0.0	-2.3	0.3	-0.2	3.1	-4.1	1.1	-1.1	0.7	0.0	-0.8	0.8	-0.3
6		-0.8	-2.3	0.6	-2.0	-2.2	1.4	n.a.*	n.a.*	n.a.*	-1.4	-2.3	0.4	-1.4	-2.3	0.4
7		-1.8	-1.2	-2.2	-2.3	-0.3	-0.1	n.a.*	n.a.*	n.a.*	-2.2	0.5	0.4	-1.8	0.2	0.6
8		-2.8	1.3	-0.3	-3.0	0.6	0.3	-4.3	-1.3	-1.8	-2.3	0.3	-0.4	-2.5	0.4	-0.1
9		-1.2	0.5	0.9	-1.7	-0.4	1.7	-4.7	-3.2	2.1	-2.0	-1.2	0.2	-1.6	-1.3	0.6
10		-1.3	0.4	-0.3	-0.5	0.3	0.1	-1.9	3.1	0.6	-0.2	1.4	0.4	-0.2	1.6	0.4

Table 3. The same as Table 2, but for rotation of MR images around the x-, y-, and z-axes.

Rotations larger than 3° are highlighted by shadowing.

*In patients 6 and 7 no surgical clips were placed in the lumpectomy cavity.

Registration accuracy

The registration accuracy for the five registration methods evaluated using breast-markers; surgical clips, thoracic-markers and all fiducials are presented in Figures 4a, 4b, 4c and 4d, respectively. The various registration methods are given in the Figures in an increasing level of misalignment between the CT and MR scans according to the breast-marker evaluation, shown in Figure 4a. For the other three evaluation methods the same order was used. Note that the smallest MRI-CT distances for the breast markers are achieved for breast-multimodality-marker registration (breast-mmm). This is not surprising, since here the same breast markers are used for matching and evaluation. This result can be considered as an indicator of the best achievable accuracy of the markers themselves.

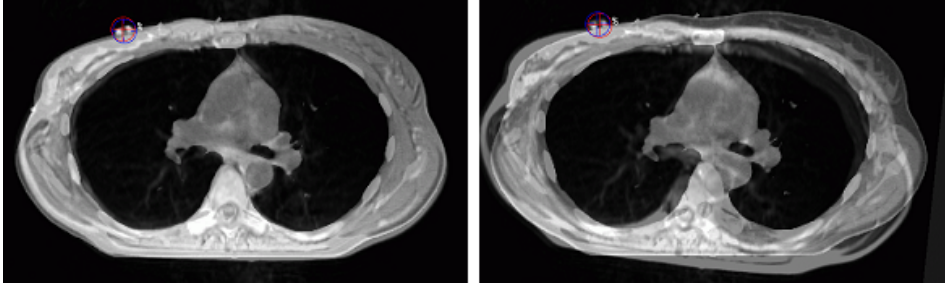


Figure 3. Axial scans of the fused CT and MR images of patient 4 (44 years, premenopausal status) with a breast-marker: the left panel shows the result of breast-marker based registration the right panel shows that for surgical clips based registration. The red and blue circles show the position of the marker on the CT and MR images, respectively.

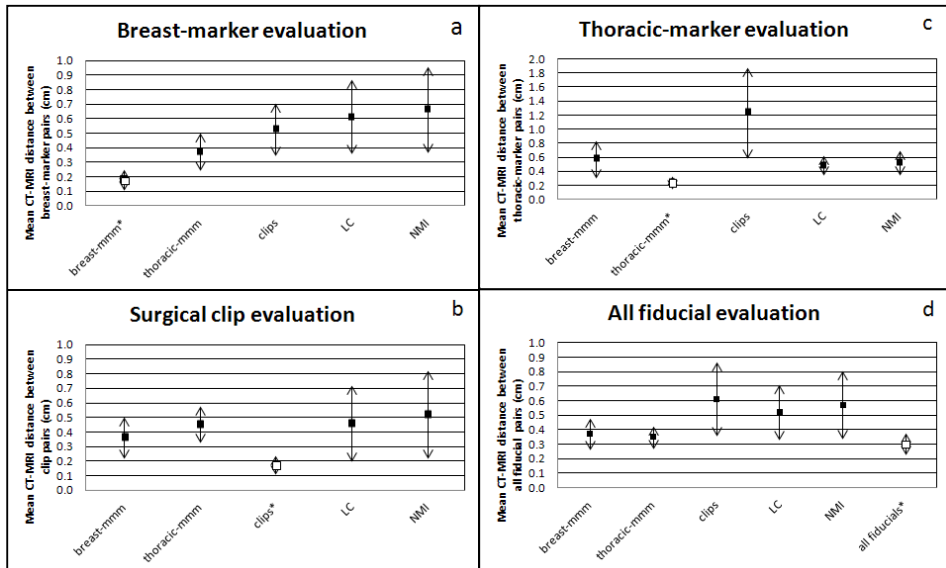


Figure 4. Analysis of CT/MRI fusion accuracy for five registration methods: breast-multimodality-markers (breast-mmm), thoracic-multimodality-markers (thoracic-mmm), surgical clips (clips), local correlation (LC) and normalized mutual information (NMI). Evaluation of each registration is performed using the breast-markers (a), surgical clips (b) or thoracic-markers (c) or all fiducials (d). Each registration result is presented as the mean value with the arrows for ± 1 SD. Note that the y-scale is twice as large for evaluation based on thoracic-markers compared to breast-markers, surgical clips and all fiducials. The (biased) method used for the evaluation is marked with a star (*) and an open symbol. In Figure 4d registration method based on fusion of all fiducials is added.

The thoracic-marker-based registration resulted in smallest MRI-CT distances between breast markers (see Figure 4a). If measured using the breast marker MRI-CT distance, the difference between the thoracic-marker-based and the clip-based ($p=0.05$) or local correlation based ($p \leq 0.01$) registration was significant, whereas the local correlation based and NMI based registration methods showed worse results than the thoracic-marker-based and the clip-based methods.

For the surgical clip evaluation, the mean MRI-CT distance for the breast-marker-based

registration is the lowest (see Figure 4b). The mean value of the clip MRI-CT distance for breast-marker-based registration is not significantly lower ($p=0.09$) than that for the thoracic-marker-based registration.

Evaluation by delineating the GBT on MRI and CT

Figure 5 shows the glandular breast tissue delineations by 4 observers on CT and MRI for patient 7. For each patient in this study, a mean rest volume as percentage of the mean GBT volume is presented in Table 4 for each of the five registration methods. The mean rest volume is the smallest on CT and on MRI for the breast marker registration (followed by the local correlation registration).

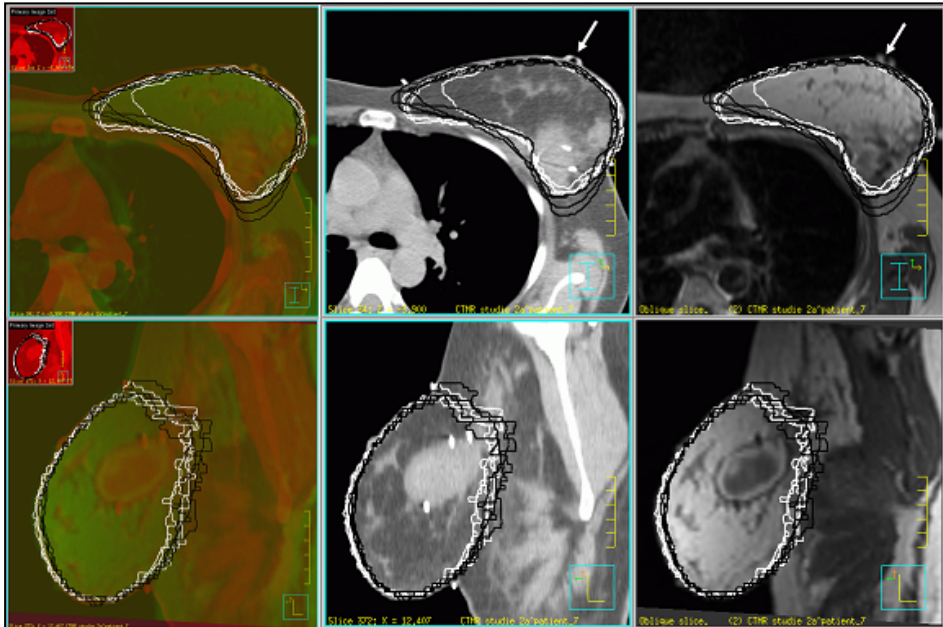


Figure 5. Axial scans (top panels) and sagittally reconstructed scans (bottom panels) of the fused CT and MR images of patient 2 (49 years, premenopausal status) for breast-marker-based registration: the glandular breast tissue delineations by 4 observers on fused CT and MRI (left, CT in red and MRI in green), CT (middle) and MRI (right). The GBT delineations on CT and MRI are shown in black and white, respectively. The arrow in the top panels points to a breast marker. On the axial and sagittally reconstructed scans respectively two and three markers around the seroma, are visible. Note that the GBT volume is well fused with breast marker registration, although a rotation up to 7.5 degrees between CT and MRI took place.

(a)

patient #	Mean GBT (CT)	Mean rest volumes* (CT, MRI) (%)				
	(cm ³) Mean (range, SD)	Breast-markers	Thoracic-markers	Surgical clips	LC	NMI
1	643 (592-675, 37)	12.5	15.5	12.8	12.9	12.4
2	919 (865-977, 46)	10.7	10.6	13.7	10.5	10.4
3	863 (826-902, 40)	7.7	7.0	14.5	6.8	7.9
4	326 (309-360, 23)	16.9	19.4	35.0	17.9	18.6
5	364 (343-413, 33)	15.0	17.6	24.3	14.7	18.5
6	672 (595-767, 81)	15.8	16.3	n.a.#	15.7	15.8
7	408 (366-487, 54)	16.1	17.7	n.a.#	16.4	16.7
8	495 (430-594,76)	13.3	15.8	12.9	12.6	13.1
9	808 (727-1008, 142)	11.7	12.8	11.6	14.3	14.2
10	410 (366-524, 77)	22.8	21.7	22.6	22.6	22.1
Mean	591	14.2	15.4	18.4	14.4	15.0
SD	220	4.1	4.3	8.2	4.3	4.3

(b)

patient #	Mean GBT (MRI)	Mean rest volumes* (MRI, CT) (%)				
	(cm ³) Mean (range, SD)	Breast-markers	Thoracic-markers	Surgical clips	LC	NMI
1	614 (549-667, 59)	8.3	11.5	8.6	8.7	8.2
2	893 (752-974, 100)	8.0	8.0	11.2	7.9	7.7
3	951 (804-1038, 115)	16.1	15.5	22.3	15.3	16.3
4	347 (290-388, 41)	21.9	24.2	38.9	22.9	23.5
5	361 (271-410, 63)	14.2	16.8	23.7	13.9	17.8
6	621 (495-733, 99)	8.8	9.4	n.a. #	8.7	8.9
7	392 (296-441, 66)	12.9	14.6	n.a. #	13.2	13.5
8	497 (361-558, 92)	13.6	16.1	13.2	12.9	13.4
9	808 (653-971, 130)	11.7	12.8	11.6	14.3	14.2
10	354 (307-421, 49)	10.5	9.3	10.4	10.3	9.8
Mean	584	12.6	13.8	17.5	12.8	13.3
SD	232	4.2	4.8	10.3	4.4	5.0

*defined as the average volume delineated by the same observer on MRI, but not on CT.

In patients 6 and 7 no surgical clips were placed in the lumpectomy cavity.

Table 4. GBT volume delineation on CT (a) and MR (b) images and rest volumes for CT (a) and MRI (b) found for breast-marker, thoracic-marker, surgical-clip-based registration, local correlation (LC) and normalized mutual information (NMI). For each patient the rest volume is given as the percentage of the corresponding mean GBT volume.

Discussion

Comparison of five different registration methods (breast-markers, thoracic-markers, surgical clips, normalized mutual information and local correlation) was performed for the GBT and the lumpectomy cavity. The use of breast markers for MRI-CT co-registration gives the best results and is recommended not only for delineation of the GBT, but also for delineation of the lumpectomy cavity. For lumpectomy cavity delineation the clip-based registration is an alternative to the breast-marker-based registration.

CT and MR images registration

We have chosen, because of the absence of the established gold standard in assessment of the registration accuracy of retrospective intermodality image registration [21], for the comparison of five different registration methods for the GBT and the lumpectomy cavity. The performance of the methods was evaluated by the agreement between delineations [8,9] and by the size of the standard deviation of registration parameters. A rigid transformation was chosen based on our previous results [8]. In this article, Giezen et al. showed that the GBT volumes were comparable on CT and MR scans (mean [SD] ratio MRI to CT GBT volumes, 1.04 [0.06]). In the present study, the mean [SD] ratio MRI to CT GBT volumes was 0.98 [0.07]. In literature breast deformation was observed for MRI in prone position and for CT in supine position [22]. Further investigation of non-rigid transformation is beyond the scope of this study.

MRI-CT translation parameters were comparable for different registration methods (see Table 2), while the rotations were for some registration methods larger than 3°. For the registration using surgical clips, rotations larger than 3° were found for 7 out of 8 patients. We believe that these rotations occur due to small distances between the clips rather than a rotation of the clips relative to patient anatomy.

Results for GBT

Delineation of the CTV of GBT based on CT scans remains a challenge in spite of relatively low interobserver variability [23,24], because of the difficulty of differentiating between fatty (involved) breast tissue and fatty non-breast tissue. Struikmans et al. [23] found a mean conformity index (CI), calculated as an average of the ratios between the common volume and encompassing volume for all possible pairs of delineations, on CT scans of 0.87 (range, 0.75–0.92) for five observers (two radiation oncologists, two radiation oncologist trainees, and one radiologist) averaged over 18 patients. Hurkmans et al. [24] reported the interobserver variability of GBT delineations by four radiation oncologists in seven breast cancer patients ($C_{\text{common}} = 0.43$, where C_{common} was calculated as a ratio of the volume commonly delineated by all observers to the encompassing volume). According to Giezen et al. [8] interobserver variability of the delineation of the CTV of GBT on CT and MRI is comparable.

As can be seen in Table 4, the mean rest volume was the smallest for the breast marker registration and the largest for the clip registration but the differences between various registration methods were small and not statistically significant because of the interobserver variability.

For the breast-marker evaluation, the misalignment between CT and MRI was the smallest for the thoracic-marker registration (except for the breast-marker registration). The breast- and thoracic-marker-based registration resulted in the smallest MRI-CT distances between all fiducials.

In our study the mean MRI-CT distance between the breast marker pairs averaged over 10 patients was 1.8 mm [SD = 0.7 mm] for the breast-marker-based registration. The last results are comparable with the mean clip misalignment described below. Note, that the matching region is larger for the breast-markers (GBT) than for the clips (lumpecto-

my cavity). The local correlation and NMI methods use a larger region than the breast to match. This probably results in additional misalignment, for instance due to distortion of the contra lateral breast by overlying MR receiver coils.

The thoracic-marker evaluation requires a significantly larger region to match. A larger matching region can make registration more difficult due to machine-related and patient-induced image distortions and cardiac and respiratory movements. The mean misalignment between CT and MR across 10 patients was found to be 2.4 mm [SD = 0.9 mm] for the registration based on the same fiducials, which is only slightly larger than the result for breast markers. For thoracic-marker-based evaluation the local correlation showed lowest misalignment between CT and MR scans, followed by the NMI. To our knowledge, CT and MR images co-registration for the GBT was not discussed in literature so far. We therefore cannot compare our results with other studies.

Results for lumpectomy cavity

Delineation of the lumpectomy cavity is based on surgical titanium clips attached to the cavity wall by the surgeon [6]. The interobserver variability in the delineation of the lumpectomy cavity on CT scans is high even in the presence of delineation guidelines: Struikmans et al. [23] reported the mean CI of 0.56 (range 0.39 – 0.74), according to van Mourik et al. [25] considerable delineation variation was present (mean CI = 0.42, range 0.19 - 0.59); partially because of the relatively small volume of the cavity. Addition of MR images to CT/clip data can probably improve interobserver variability [6,9]. Further investigation based on delineation of lumpectomy cavity on MR-CT co-registered images is needed.

For the surgical clip evaluation, which is a reasonable approach for the lumpectomy cavity, the mean CT-MR distance for the breast-marker-based registration was the lowest (except for the clips themselves) 3.6 mm [SD=1.4 mm].

If the thoracic markers were used for registration, the mean misalignment between CT and MR for the clips was 4.5 mm [SD=1.3 mm]. However, if the clips were used for registration the mean misalignment of thoracic markers was larger by more than a factor of two, 12 mm [SD=6 mm]. This large difference can be related to the fact that the clips were close to each other while the thoracic markers were much further away. As a result, small uncertainties in the registration using clips will be greatly enhanced when the thoracic markers were used for the evaluation. The situation is distinctly different when the thoracic markers were used in the registration while clips are exploited for the evaluation.

Kirby et al. [6] used surgical clips to register MRI with CT images of 30 patients in prone position. As a matching structure, clips have the advantage over the chest wall to overcome the problem of accurately identifying bony boundaries on MR images. Moreover, according to Kirby et al. the use of the clips for registration led to a smaller field of view and, therefore, reduced machine-related image distortion. They registered a mean clip misalignment between CT and MRI across all 30 cases of 0.8 mm (medial-lateral), 0.6 mm (superior-inferior), and 1.0 mm (anterior-posterior), yielding a mean misalignment distance of 1.4 mm.

This result is in good agreement with the MRI-CT distance of 1.7 mm [SD = 0.6 mm] averaged over 8 patients for the registration based on the surgical clips in our study.

Surgical-clip-based registration resulted in large rotations (see Table 3 and Figure 3) for 7 out of 8 patients in the present study. This effect is not described by Kirby et al. [6], probably because of smaller rotations in their study due to larger number of the surgical clips (6 to 12 versus 4 to 6 in our case). Moreover, not all the patients have surgical clips for various reasons. In our case 2 out of 10 patients did not have any surgical clips. Jolicœur et al. [7] used the predefined fusion points (the nipple, the tip of scapula, the sternal notch and the carina) for MRI-CT registration. A qualitative evaluation was

then performed using the skin surface markers on the surgical scar and the nipple. They reported a mean MRI-CT distance of 5.6 mm (range: 1.9–11.6 mm). For the breast-marker-based evaluation and clip registration, the mean MRI-CT distance was 5.3 mm [SD=1.8 mm] (range: 2.8–7.7 mm). These results are difficult to compare because of absence of clips in the study by Jolicoeur et al. [7].

Conclusions

For the breast-marker evaluation, the misalignment between CT and MRI was the smallest for the thoracic-marker registration. For the surgical clips evaluation, the misalignment between CT and MRI was the smallest for the breast-marker registration. The use of surgical clips for MRI-CT registration resulted in large rotations ($> 3^\circ$) for 7 out of 8 patients. Moreover, the clips were not always clearly visible on MR images. The thoracic-marker-based and breast-marker-based registrations resulted in the smallest MRI-CT displacements between all fiducials. Co-registration of CT and MR data sets based on breast-markers gave the best result for the glandular breast tissue delineation in terms of the rest volume.

Considering all observed results, we recommend breast markers for MRI-CT co-registration for both glandular breast tissue and lumpectomy cavity delineation in radiotherapy. For lumpectomy cavity delineation the clip-based registration is an alternative to the breast marker registration. Further work is required to optimize registration methods using deformable registration.

Acknowledgments

The authors are grateful to Dr. Wilbert Bartels, Dr. Martijn Eenink and Wilco Schillemans for useful remarks, Bart Hemmes for help with MR images and Thomas Vissers for bibliographical assistance.

References

1. Zhang Y, Chu JC, Hsi W, Khan A J, Mehta P S, Bernard D, et al. Evaluation of four volume-based image registration algorithms. *Med Dosim* 2009;34:317-322.
2. Webster GJ, Kilgallon JE, Ho KE, Rowbottom CG, Slevin NJ, Mackay RI. A novel imaging technique for fusion of high-quality immobilised MR images of the head and neck with CT scans for radiotherapy target delineation. *Br J Radio* 2009; 82:497-503.
3. Parker CC, Damyanovich A, Haycocks T, Haider M, Bayley A, Catton CN. Magnetic resonance imaging in the radiation treatment planning of localized prostate cancer using intra-prostatic fiducial markers for computed tomography co-registration. *Radiother Oncol* 2003;66:217-224.
4. Devic S. MRI simulation for radiotherapy treatment planning. *Med Phys* 2012;39: 6701-6711.
5. Sivaramakrishna R. 3D breast image registration--a review. *Technol Cancer Res Treat* 2005;4:39-48.
6. Kirby AM, Yarnold JR, Evans PM, Morgan VA, Schmidt MA, Scurr ED, et al. Tumor bed delineation for partial breast and breast boost radiotherapy planned in the prone position: what does MRI add to X-ray CT localization of titanium clips placed in the excision cavity wall? *Int J Radiat Oncol Biol Phys* 2009;4:1276-1282.
7. Jolicoeur M, Racine ML, Trop I, Hathout L, Nguyen D, Derashodian T, et al. Localization of the surgical bed using supine magnetic resonance and computed tomography scan fusion for planification of breast interstitial brachytherapy. *Radiother Oncol* 2011;100:480-484.
8. Giezen M, Kouwenhoven E, Scholten AN, Coerkamp EG, Heijnenbrok M, Jansen WP, et al. Magnetic resonance imaging-versus computed tomography-based target volume delineation of the glandular breast tissue (clinical target volume breast) in breast-conserving therapy: an exploratory study. *Int J Radiat Oncol Biol Phys* 2011;81:804-811.
9. Giezen M, Kouwenhoven E, Scholten AN, Coerkamp E G, Heijnenbrok M, Jansen WP, et al. MRI- Versus CT-Based Volume Delineation of Lumpectomy Cavity in Supine Position in Breast-Conserving Therapy: An Exploratory Study. *Int J Radiat Oncol Biol Phys* 2012;82:1332-1340.
10. Yan CH, Whalen RT, Beupre GS, Sumanaweera TS, Yen SY, Napel S. A new frame-based registration algorithm. *Med Phys* 1998;25:121-128.
11. Maurer CR, Jr., Fitzpatrick JM, Wang MY, Galloway RL Jr, Maciunas RJ, Allen GS. Registration of head volume images using implantable fiducial markers. *IEEE Trans Med Imaging* 1997;16:447-462.
12. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image registration by maximization of mutual information. *IEEE Tran Med Imaging* 1997;16:187-198.
13. Fraass B, Doppke K, Hunt M, Kutcher G, Starkschall G, Stern R, et al. American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: quality assurance for clinical radiotherapy treatment planning. *Med Phys* 1998; 25:1773-1829.
14. Skerl D, Likar B, Fitzpatrick JM, Pernus F. Comparative evaluation of similarity measures for the rigid registration of multi-modal head images. *Phys Med Biol* 2007;52:5587-5601.
15. van Kranen S, van Beek S, Rasch C, van Herk M, Sonke JJ. Setup uncertainties of anatomical subregions in head-and-neck cancer patients after offline CBCT guidance. *Int J Radiat Oncol Biol Phys* 2009;73:1566-1573.
16. van Beek S, van Kranen S, Mencarelli A, Remeijer P, Rasch C, van Herk M, et al. First clinical experience with a multiple region of interest registration and correction method in radiotherapy of head-and-neck cancer patients. *Radiother Oncol* 2010; 94: 213-217.
17. Rösch MP, Blaffert T, Weese J. Multi-modality image registration using local correlation. In: Lemke HU, editor. *Computer Assisted Radiology and Surgery (CARS '99)*. Amsterdam: Elsevier;

- 1999:228-232.
18. METC Zuidwest Holland, ABR nr. 17089, 2007, dossier nr. NL 17089.098.07.
 19. Rasch C, Keus R, Pameijer FA, Koops W, de Ru V, Muller S, et al. The potential impact of CT-MRI matching on tumor volume delineation in advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 1997;39:841-848.
 20. Atkinson DJ, Martin JF, Brown MA, Koutcher JA, Burt CT, Ballon D. Clinicaspectroscopy. In: Edelman RR, Hesselink JR, editors. *Clinical magnetic resonance imaging*. Philadelphia (PA): W.B. Saunders Company; 1990:269-313.
 21. Loi G, Dominietto M, Manfreda I, Mones E, Carriero A, Inglese E, Krenkli M, et al. Acceptance test of a commercially available software for automatic image registration of computed tomography (CT), magnetic resonance imaging (MRI) and ^{99m}Tc-methoxyisobutylisonitrile (MIBI) single-photon emission computed tomography (SPECT) brain images. *J Digit Imaging* 2008;21:329-337.
 22. Pathmanathan P, Gavaghan DJ, Whiteley JP, Chapman SJ, Brady JM Predicting tumor location by modeling the deformation of the breast. *IEEE Trans Biomed Eng* 2008;55:2471-2480.
 23. Struikmans H, Warlam-Rodenhuis C, Stam T, Stapper G, Tersteeg R J, Bol GH, et al. Interobserver variability of clinical target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005;76:293-299.
 24. Hurkmans CW, Borger JH, Pieters BR, Russell NS, Jansen EP, Mijnheer BJ. Variability in target volume delineation on CT scans of the breast. *Int J Radiat Oncol Bio Phys* 2001;50:1366-72.
 25. van Mourik AM, Elkhuisen PH, Minkema D, Duppen J C; Dutch Young Boost Study Group and van Vliet-Vroegindewij C et al. Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010;94:286-291.

Target volume delineation in breast conserving radiotherapy:
are co-registered CT and MR images of added value?

Mirjam Mast^a, Emile Coerkamp^b, Mark Heijenbrok^b, Astrid Scholten^c, Wim Jansen^c, Erik Kouwenhoven^a, Jasper Nijkamp^d, Stephanie de Waard^b, Anna Petoukhova^a and Henk Struikmans^{a,c}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of radiology, Medical Center Haaglanden, The Hague, The Netherlands;

^c Department of Clinical Oncology, Leiden University Medical Centre, The Netherlands;

^d Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, The Netherlands.

Radiat Oncol 2014;9:65

Abstract

Introduction

In breast conserving radiotherapy differences of target volume delineations between observers do occur. We evaluated whether delineations based on co-registered computed tomography (CT) and magnetic resonance (MR) imaging may result in an improved consistency between observers. We used the delineation conformity index (CI) to compare clinical target volumes of glandular breast tissue (CTV breast) and lumpectomy cavity (LC) on both imaging modalities.

Materials and methods

Four observers delineated CTV breast and LC on co-registered CTMR images in ten breast cancer patients. CIs were determined for CT and CTMR. Furthermore, the Cavity Visualization Score (CVS) of LC was taken into account.

Results

The mean CI for CTV breast ($CI_{CT;CTV}$: 0.82 and $CI_{CT-CTMR;CTV}$: 0.80) and LC ($CI_{CT;LC}$: 0.52 and $CI_{CT-CTMR;LC}$: 0.48) did not differ significantly ($p = 0.07$ and $p = 0.33$, respectively). Taking CVS into account for the LC, with a $CVS \geq 4$ the mean CI was 0.62 for both $CI_{CT;LC}$ and $CI_{CT-CTMR;LC}$.

Conclusion

The mean volume of the delineated glandular breast tissue based on CT was significantly larger compared to the volume based on CTMR. For patients with a $CVS \geq 4$, the mean CIs of the LC were higher compared to $CVS < 4$ for volumes delineated on both CT as well as CTMR images. In our study cohort no significant differences between the CIs of the CTV breast and the LC delineated on CTMR co-registered images were found compared to the CIs on CT images only. Adding MR images does not seem to improve consistency of the delineation of the CTV breast and the LC, even though the volumes were copied from CT images. Since we included only ten patients, caution should be taken with regard to the results of our study.

Background

There can be substantial differences in identification of the target volumes among radiation oncologists specialized in breast cancer radiotherapy [1]; even when written delineation guidelines are used [2-4]. Compared to computed tomography (CT) magnetic resonance imaging (MRI) may reveal more relevant details [5]. And, according to Jolicoeur et al., the use of MRI improved the level of agreement between observers delineating the lumpectomy cavity compared to CT [6]. In our former study, published in 2011, we noted that the concordance for delineation of the volumes on CT differed only slightly from the concordance based on magnetic resonance (MR) images [7]. Whether the use of a co-registration of the two imaging modalities could lead to an improvement of the agreement between observers remained unclear.

Therefore, we analyzed the delineation conformity, when based on CT as well as on CTMR co-registered images. In our study, we have evaluated the delineated clinical target volumes of the glandular breast tissue (CTV breast) and the lumpectomy cavity (LC) in ten patients referred for radiation therapy after breast conserving surgery.

Materials and methods

Between July 2007 and August 2008, fifteen patients with early stage breast cancer (clinically T1-2; N0-1) and treated with breast conserving surgery were included in our study. The mean age was 57 years; 8 patients had right-sided and 7 patients had left-sided breast cancer; the tumor was mostly situated in the upper outer quadrant of the breast. Patient and tumor characteristics were described in detail earlier [7]. Since the rigid co-registration was performed on breast markers which were used only in patients 6–15, we included only these ten patients in the present study [8]. After referral for whole breast radiotherapy, a planning-CT scan and directly afterwards a MRI scan were performed, both in supine treatment position. The procedure was described in detail by Giezen et al. [7].

The study was approved by the regional institutional review board METC Zuidwest Holland. All patients agreed to participate in our study by signing an informed consent. Four observers, i.e. two radiation oncologists and two radiologists, participated in the study and delineated the glandular breast tissue (CTV breast) [7] as well as the lumpectomy cavity (LC) [9]. The four observers delineated CTV breast and LC according to the determined delineation instructions, Table 1 [9].

For all ten patients this resulted in the, for each observer, delineated CTV breast and LC, based on CT images only. After ten weeks, the observers re-evaluated these CTV breast and LC delineations copied on the co-registered CTMR images, and made adaptations when judged necessary. By choosing an interval time of ten weeks it was likely that the observers had forgotten specific details of their CT-based delineations of each specific case. By doing so a more reliable comparison (and eventually an adaptation) between the CT based images and the CTMR images may be achieved. The alternative method of delineating the co-registered CTMR images was not used because this would imply an intra-observer variability.

After defining all CTV breast volumes, a scripting tool was applied to trim all CTV breast volumes up to 5 mm below the skin surface.

To quantify the variability of one delineation compared to another we used the Conformity Index (CI). A CI of 0 indicates no overlap is present between delineations; a CI of 1 indicates completely identical delineations. A method for calculating the CI was used, that is unbiased by the number of observers delineating a target volume [10]. We determined two types of CI of the CTV breast and LC enabling us to assess the influ-

ence of imaging modality on delineation variability, and the inter-observer variation, respectively. Firstly, for each observer, the delineated volumes on CT were compared to CTMR, indicated with the symbols $CI_{CT-CTMR;CTV}$ and $CI_{CT-CTMR;LC}$. The resulting CIs were thereafter averaged over the patient population. Secondly, for every delineated target volume we determined the CIs for CT based and CTMR based delineations separately, by comparing the delineations of the different observers to each other.

	CTV Breast	Lumpectomy Cavity
Window/Level (WL); Window Width (WW)	<ul style="list-style-type: none"> - Fixed: WL 0 Hounsfield Unit (HU) and WW of 500 HU for CT and variable WL and WW for MRI; - Change of WL and WW during delineation permitted for CT and MRI. 	<ul style="list-style-type: none"> - Fixed: WL 0 Hounsfield Unit (HU) and WW of 500 HU for CT and variable WL and WW for MRI; - Change of WL and WW during delineation permitted for CT and MRI.
Appearance	<ul style="list-style-type: none"> - The location of the marking wire, positioned around the palpable Glandular Breast Tissue (GBT), will be used as an aid for CTV Breast delineation; - The clinical target volume (CTV) breast was defined to comprise all GBT including fatty (involved) lobes - Margin of the GBT is (ventrally) assumed to be situated 5 mm below the skin surface; in case of MRI the visible GBT fat is (ventrally) delineated as GBT margin; - Delineation is performed on all CT or MRI slices that are judged to contain GBT; - Appearance of the contralateral breast (by comparing with the ipsilateral breast) on CT or MR images; - The preoperative mammographies and location of the palpable GBT marking wire, visible on CT or MRI, all will serve as an aid for GBT delineation. 	Appearance of contralateral breast (comparing with ipsilateral breast) serves as aid for LC delineation.
Clips	Surgical clips (if applicable) should all be included within the delineated GBT.	All surgical clips (if applicable) should be included within delineated LC.
Seroma	Postoperative seroma/hematoma present in LC should be included within delineated GBT.	Postoperative seroma/hematoma present in LC should be included within delineated LC.

Table 1. Delineation instructions for CTV Breast and the lumpectomy cavity. Abbreviations: LC Lumpectomy Cavity, WL window level, WW window width, HU Hounsfield Units, MRI Magnetic Resonance Imaging, CT computed tomography.

The resulting values are indicated with the symbols $CI_{CT;CTV}$, $CI_{CTMR;CTV}$, $CI_{CT;LC}$ and $CI_{CTMR;LC}$. Again, an average over the patient population was calculated. Furthermore, the earlier assessed ‘‘Cavity Visualization Score’’ (CVS) [9] of the lumpectomy cavity was taken into account in the analysis as well. With the CVS according to Smitt et al. [11] depiction of the lumpectomy cavity is categorized from 1, cavity not visualized, to 5, all cavity margins clearly defined. Finally, a median 3D surface of the CTV breast and LC of all four observers was calculated [12] (local surface variation) in order to analyze and visualize the local inter-observer variation for each patient.

Statistical analysis

Wilcoxon Signed Rank Test was performed to compare all data, CT versus CTMR, since the number of eligible data was less than 30. For analysis we used SPSS Statistics version 17.0. The level of statistical significance was considered $p < 0.05$ (two sided) for all tests.

Results

Glandular breast tissue (CTV breast)

Delineated volumes

The mean volume of the delineated glandular breast tissue based on CT (mean 576 cc; range 303–900) was significantly larger compared to the volume based on CTMR (mean 557 cc; range 287–892) ($p < 0.01$).

CT versus CTMR: conformity indices and local surface variation

On the CTMR images few adaptations to the delineated volume were carried out. The range in CIs ($CI_{CT-CTMR,CTV}$) for each observer was 0.89 – 1.00 (mean SD 0.03), Table 2. The mean CI for all observers between $CI_{CT,CTV}$ and $CI_{CTMR,CTV}$ did not differ significantly, Table 3.

The local surface variation in Figure 1 shows again that few adaptations were carried out on the co-registered CTMR images. We found a mean local standard variation between observers of 2.2 mm and 2.6 mm for CT and CTMR, respectively ($p = 0.05$). In seven out of ten patients the local standard variation increased on CTMR. For patient 8, 11, 12, 13 and 15 the differences were mostly present in the medial part of the CTV breast.

	$CI_{CT-CTMR,CTV}$ (SD)	$CI_{CT-CTMR,LC}$ (SD)
Observer_1	0.99 (0.01)	0.84 (0.09)
Observer_2	0.89 (0.05)	0.70 (0.23)
Observer_3	1.00 (0.00)	0.91 (0.17)
Observer_4	0.97 (0.05)	0.85 (0.30)

Table 2. Conformity indices of the CTV Breast and lumpectomy cavity (LC) delineations for each observer, CT compared to CTMR.

	CTV breast; Mean CI_{All} (SD)	LC; Mean CI_{All} (SD)
CI_{CT}	0.82 (0.04)	0.52 (0.20)
CI_{CTMR}	0.80 (0.06)	0.48 (0.21)
p-value $CI_{CT-CTMR}$	0.07	0.33

Table 3. Conformity indices ($CI_{CT,CTMR}$) of the CTV breast and lumpectomy cavity (LC) delineations based on CT and CTMR for all observers.

Inter-observer variability

In considering the variation in the local surface distance, it became apparent that the delineations of the observers varied, on CT as well as CTMR, predominantly in the medial and lateral part of the CTV breast, Figure 1.

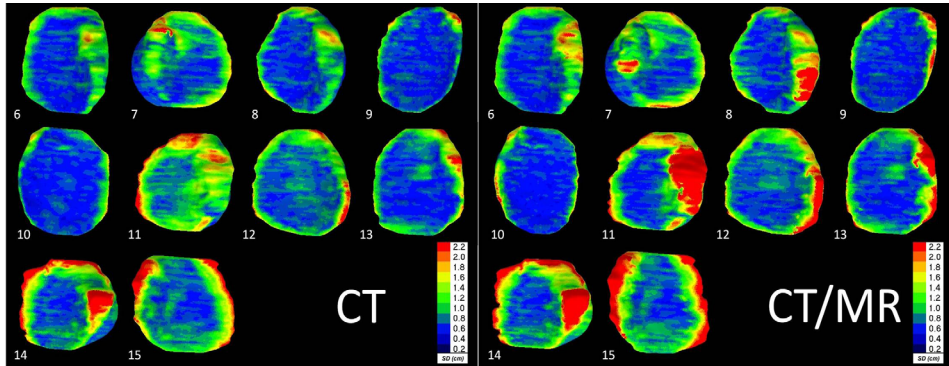


Figure 1. Left: Coronal posterior view of the ten delineated Clinical Target Volume (CTV) breast Computed Tomography (CT) volumes. Right: Coronal view of the ten delineated CTV breast CTMR volumes. The local surface distance variation of the four observers is projected on the median surface of each CTV breast. Colour map: Blue: high agreement between observers; Red: low agreement between observers according to the scale given.

Lumpectomy cavity (LC)

Delineated volumes

The mean volumes of the delineated LC based on CT (mean 24 cc; range 4–73) did not differ ($p = 0.2$) compared to those based on CTMR (mean 26 cc; range 7–71), Table 4.

	Mean Lumpectomy Cavity Volume CT	Mean Lumpectomy Cavity Volume CTMR
Patient_6	28	25
Patient_7	73	71
Patient_8	14	13
Patient_9	7	7
Patient_10	11	11
Patient_11	29	32
Patient_12	4	9
Patient_13	30	34
Patient_14	8	13
Patient_15	33	45

Table 4. Mean volumes for all observers of the lumpectomy cavity (LC) delineations based on CT and CTMR.

CT versus CTMR: conformity indices and local surface variation

For LC more adaptations were carried out than for CTV breast, since the range in CIs ($CI_{CT-CTMR;LC}$) for each observer decreased: 0.70 – 0.91 (mean SD 0.20), Table 2. The mean CI for all observers between $CI_{CT;LC}$ and $CI_{CTMR;LC}$, however, did not differ significantly, Table 3.

When taking the CVS into account, we found that, if the CVS was ≥ 4 , the mean CI appeared to increase. An increase of the CI to 0.62 was found for $CI_{CT;LC}$ as well as for $CI_{CTMR;LC}$ delineations in all 5 cases with a CVS of ≥ 4 . In Figure 2 we display the mean CI of both CT and CTMR on the CVS scale from 0 to 5; see Figure 3 as well.

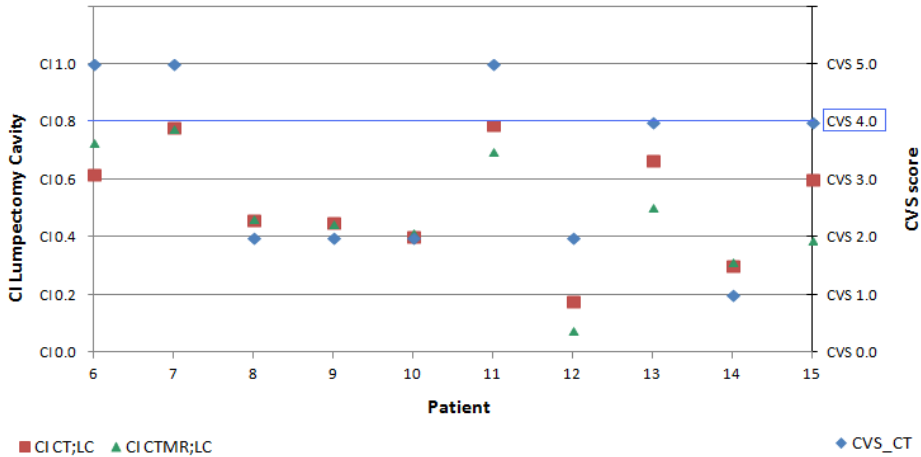


Figure 2. For each patient for the lumpectomy cavity the Conformity Index (CI) on CT, The CI on CTMR and the Cavity Visualization Score (CVS) were determined.

The local surface distance variation showed more variation in the delineation of the LC compared to CTV breast. We found a mean local standard variation between observers of 2.4 mm and 2.8 mm for CT and CTMR, respectively ($p = 0.13$). In five out of ten patients (patient 11, 12, 13, 14 and 15) the degree of variability increased on the co-registered CTMR images and in two patients (patient 6 and 7) the degree of variability was larger on the CT images. For the other two patients, no major variability was noted. As an example, in patient 12, a premenopausal patient, no seroma was found, no clips were placed and the CVS was 2, Figure 4.

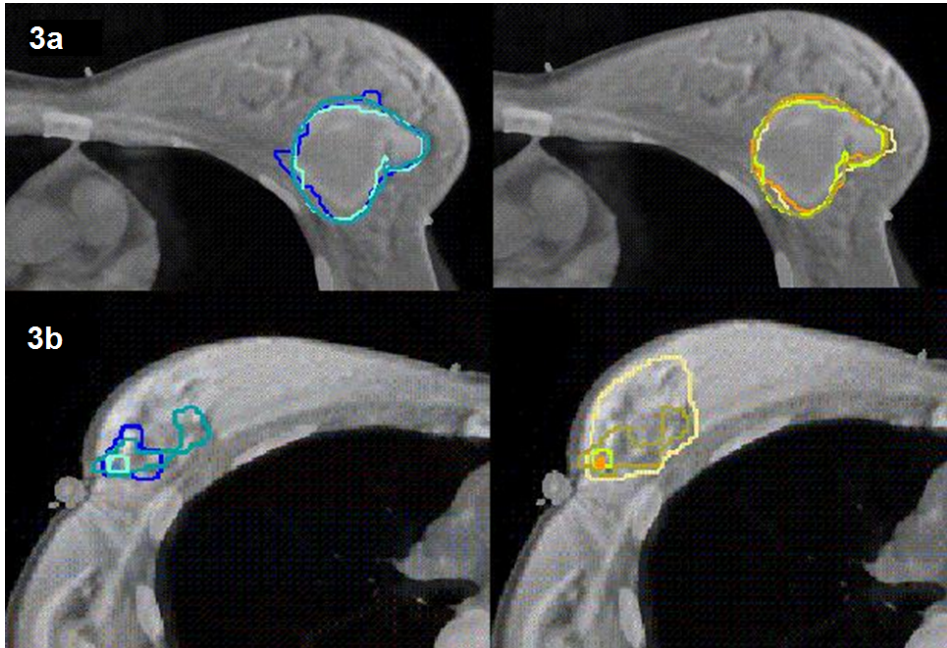


Figure 3. Differences between the 4 observers on co-registered CTMR images; Left: volumes delineated on CT. Right: volumes delineated on CTMR; a. Example of a patient with seroma, a CVS of 5; b. Example of a patient with a CVS of 2.

Discussion

CT versus CTMR

In this study we investigated the potential merits of CTMR co-registration on the delineation of the CTV breast and the Lumpectomy Cavity (LC). Concerning the study outline, we only focused on the advantages of CTMR co-registration. Therefore, to avoid intra-observer variability, we copied the CTV breast and LC delineated on the CT to the co-registered CTMR images. Thereafter each observer considered to adapt (yes or no) the CTV breast or LC, respectively when based on the CTMR images. Finally, the differences between the CT based and CTMR based delineations were analyzed. This method could have introduced a bias, since the observers did not delineate the CTMR co-registered images. Comparisons and eventually adaptations were, after an interval time of 10 weeks, done directly on the CTMR co-registered images. In doing so the observers could have been distracted by the copied volume. But the alternative method of delineating the co-registered CTMR images had the disadvantage that this would result in an intra-observer variability between the CT based and the CTMR based delineations.

We found that the CT based CTV breast volumes, when compared with CTMR based volumes, were significantly larger. In our study cohort, it became apparent that the CIs for CTMR co-registered images, when compared to those based on CT images only, did not differ significantly from those based on CT images only, neither for CTV breast nor for LC. With respect to LC, in the 5 cases with a CVS \geq 4, the mean CI values increased to 0.62, whereas for the cases with a CVS $<$ 4 a mean CI of 0.50 was found.

Compared to the results of our first investigation [9] the CI for the LC increases from 0.32 for MR to 0.48 for the co-registered CTMR.

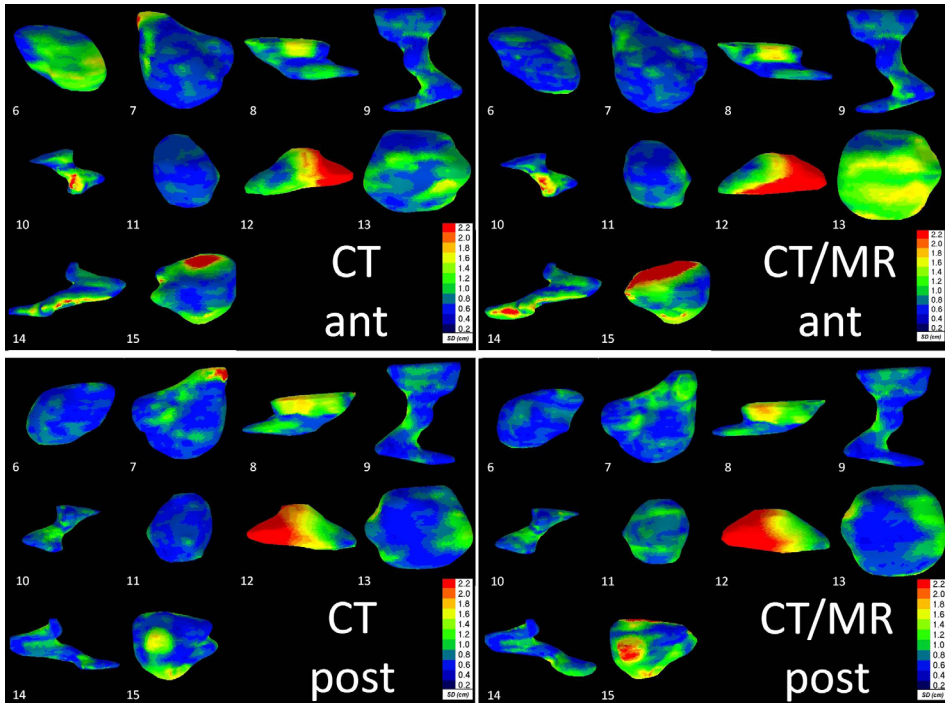


Figure 4. Left: Coronal posterior view of the ten delineated Lumpectomy Cavity (LC) Computed Tomography (CT) volumes in both anterior as well as posterior view. Right: Coronal view of the ten delineated LC CTMR volumes in both anterior as well as posterior view. The local surface distance variation of the four observers is projected on the median surface of each LC. Colour map: Blue: high agreement between observers; Red: low agreement between observers according to the scale given.

Remarkably, we found higher CIs (Lumpectomy Cavity) for both CT and CTMR compared to the results of Boersma et al. although our volumes were smaller and in our study the lumpectomy cavity was defined instead of the CTV boost [4]. The CTV boost in the study of Boersma et al. was defined as the 1.5 cm rim of tissue that had surrounded the primary tumor. Also, manual adaptation of the co-registration by each observer could be a reason for the lower CI in the study of Boersma et al., since this could be a bias in the analysis of the delineated structures. In our study, the co-registration was locked after performing the co-registration. Furthermore, in our study clips were placed directly in several segments in the lumpectomy cavity wall representing the extensions of the primary tumor, whereas in the Boersma study clips only had been placed at the deepest (dorsal) border of the lumpectomy cavity [4].

CTV breast

The major differences in delineation of the target volume between observers were located in the medial and lateral part of the CTV breast. This was confirmed in the study of Li et al. In their study, the effect of these variations on the dose in the organs at risk was studied as well. They concluded, that variations in normal structure dose were found

and that large variations in the medial-lateral borders contributed mostly to the variation in the normal structure dose [13]. Therefore, consistency in delineation of the CTV breast is of great importance. In our study cohort specific guidelines (Table 1) were used and consensus meetings had taken place. The latter could explain the non-significant differences in the CTV breast when MR imaging was added.

Lumpectomy cavity

Delineations of the lumpectomy cavity were done by experienced radiation oncologists and trained radiologists. They used written delineation guidelines (Table 1). All this was in line with the findings of various recent studies. As Wong et al. showed in their study cohort, “trained” oncologists consistently produced smaller target volumes in seroma contouring compared to an “untrained” cohort. The implementation of guidelines reduced the inter-observer variability in volume delineation in their study. These data indicated that improved consistency among radiation oncologists may be achieved by consensus guidelines.[14].

Furthermore, our results reveal that, when the CVS was ≥ 4 , the CI was increased for both CT as well as CTMR defined volumes. This finding was reported before by Landis et al. [1]. This could indicate that, for lumpectomy cavities with a CVS of < 4 , specific landmarks such as surgical clips or gold markers may enable a more precise defined CTV boost [3,15]. According to Topolnjak et al. and Park et al., the position of these clips and markers remain stable throughout the treatment course [16,17]. Nevertheless, it seems important to be aware of interfractional target deformations as reported by Ahunbay et al. [18]. Concerning the use of surgical clips, Jolicoeur et al. did not use clips and found a concordance ratio of 0.66 on CT and 0.96 on MR [6]. Finally, as Van Mourik et al. also suggested [3], we confirm that a multi-disciplinary approach is what should be aimed at in target delineation; especially in the delineation of the LC and when the CVS is lower than 4, since every specialist can contribute to a better understanding. If an inconsistency of the surgical clips and at the edge of the seroma was found, as described by Yang et al., this should be part of the multidisciplinary discussion [19].

Conclusion

The mean volume of the delineated glandular breast tissue based on CT was significantly larger compared to the volume based on CTMR. For patients with a CVS ≥ 4 , the mean CIs of the LC were higher compared to CVS < 4 for volumes delineated on both CT as well as CTMR images. In our study cohort no significant differences between the CIs of the CTV breast and the LC delineated on CTMR co-registered images were found compared to the CIs on CT images only. Adding MR images does not seem to improve consistency of the delineation of the CTV breast and the LC, even though the volumes were copied from CT images. Since we included only ten patients, caution should be taken with regard to the results of our study.

Acknowledgements

We thank T.F.H. Vissers for bibliographical assistance, J. van Egmond for his assistance with Excel and J.F.D. Bouricius for critically editing this article.

References

1. Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, Killoran JH, Gelman R, Harris JR: Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. *Int J Radiation Oncology Biol Phys* 2007, 67:1299–1308.
2. Struikmans H, Wárlám-Rodenhuis C, Stam T, Stapper G, Tersteeg RJHA, Bol GH, Raaijmakers CPJ: Inter-observer variability of target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005, 76:293–299.
3. van Mourik AM, Elkhuizen PH, Minkema D, Dutch Young Boost Study Group, van Vliet-Vroegindeweij C: Collaborators (15). Multi institutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010, 94:286–291.
4. Boersma LJ, Janssen T, Elkhuizen PHM, Poortmans P, van der Sangen M, Scholten AN, Hanbeukers B, Duppen JC, Hurkmans C, van Vliet C: Reducing inter-observer variation of boost-CTV delineation in breast conserving radiation therapy using a pre-operative CT and delineation guidelines. *Radiother Oncol* 2012, 103:178–182.
5. Whipp EC, Halliwell M: Magnetic resonance imaging appearances in the postoperative breast: the clinical target volume-tumor and its relationship to the chest wall. *Int J Radiation Oncology Biol Phys* 2008, 72:49–57.
6. Jolicoeur M, Racine M, Trop I, Hathout L, Nguyen D, Derashodian T, David S: Localization of the surgical bed using supine magnetic resonance and computed tomography scan fusion for planification of breast interstitial brachytherapy. *Radiother Oncol* 2011, 100:480–484.
7. Giezen M, Kouwenhoven E, Scholten AN, Coerkamp EG, Heijenbrok M, Jansen WPA, Mast ME, Petoukhova AL, Struikmans H: Magnetic resonance imaging – versus computed tomography-based target volume delineation of the glandular breast tissue (clinical target volume breast) in breast-conserving therapy: an exploratory study. *Int J Radiation Oncology Biol Phys* 2011, 81:804–811.
8. Petoukhova A, Mast ME, Kouwenhoven E, Jansen WPA, Scholten AN, Struikmans H: Optimal registration method of mri and ct for delineation in radiotherapy planning of breast cancer patients treated with breast conserving therapy. *Int J Radiation Oncology Biol Phys* 2013, 87:S209.
9. Giezen M, Kouwenhoven E, Scholten AN, Coerkamp EG, Heijenbrok M, Jansen WPA, Mast ME, Petoukhova AL, Struikmans H: MRI- versus CT-based volume delineation of lumpectomy cavity in supine position in breast-conserving therapy: an exploratory study. *Int J Radiation Oncology Biol Phys* 2012, 82:1332–1340.
10. Kouwenhoven E, Giezen M, Struikmans H: Measuring the similarity of target volume delineations independent of the number of observers. *Phys Med Biol* 2009, 54:2863–2873.
11. Smitt MC, Birdwell RL, Goffinet DR: Breast electron boost planning: Comparison of CT and US. *Radiology* 2001, 219:203–206.
12. Deurloo KEI, Steenbakkers RJHM, Zijp LJ, de Bois JA, Nowak PJCM, Rasch CRN, van Herk M: Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy. *Int J Radiation Oncology Biol Phys* 2005, 61:228–238.
13. Li XA, Tai A, Arthur DW, Buchholz TA, MacDonald S, Marks LB, Moran JM, Pierce LJ, Rabinovitch R, Taghian A, Vicini F, Woodward W, White JR: Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG multi-institutional and multiobserver study. *Int J Radiation Oncology Biol Phys* 2009, 73:944–951.
14. Wong EK, Truong PT, Kader HA, Nichol AM, Salter L, Petersen R, Wai ES, Weir L, Olivetto IA: Consistency in seroma contouring for partial breast radiotherapy: impact of guidelines. *Int J Radiation*

- Oncology Biol Phys 2006, 66:372–376.
15. Dzhugashvili M, Pichenot C, Dunant A, Balleyguier C, Delalogue S, Mathieu M, Garbay J, Marsiglia H, Bourcier C: Surgical clips assist in the visualization of the lumpectomy cavity in three-dimensional conformal accelerated partial-breast irradiation. *Int J Radiation Oncology Biol Phys* 2010, 76:1320–1324.
 16. Topolnjak R, de Ruiter P, Remeijer P, Vliet-Vroegindewij C, Rasch C, Sonke JJ: Image-guided radiotherapy for breast cancer patients: surgical clips as surrogate for breast excision cavity. *Int J Radiation Oncology Biol Phys* 2011, 81:187–195.
 17. Park CK, Pritz J, Zhang GG: Validating fiducial markers for image-guided radiation therapy for accelerated partial breast irradiation in early-stage breast cancer. *Int J Radiation Oncology Biol Phys* 2012, 82:e425–e431.
 18. Ahunbay EE, Robbins J, Christian R, Godley A, White J, Li A: Interfractional target variations for partial breast irradiation. *Int J Radiation Oncology Biol Phys* 2012, 82:1594–1604.
 19. Yang Z, Chen J, Hu W, Pan Z, Cai G, Yu X, Mei X, Zhagn Q, Liu T, Guo X: Planning the breast boost: How accurately do surgical clips represent the CT seroma? *Radiother Oncol* 2010, 97:530–534.

The page features two large, stylized orange geometric shapes. The top shape is a jagged, upward-pointing form with a white notch in its center. The bottom shape is a similar jagged, downward-pointing form, also with a white notch. The shapes are positioned symmetrically around the central text.

CHAPTER 2

Treatment planning studies in
whole breast irradiation to reduce heart
and LAD dose

A heart sparing technique in women with left-sided breast cancer.
Results of 4 years of experience in Radiotherapy Centre West

Mirjam Mast, Joke van der Klein, Saskia van Geen, Monique Jacobs,
Ko van Wingerden, Anna Petoukhova and Henk Struikmans

Radiotherapy Centre West, The Hague

Ned Tijdschr Oncol 2012;9:270-276

Summary

The literature shows that, with the increasing survival of breast cancer patients after breast conserving therapy, the various therapies are associated with an increased risk of fatal cardiovascular events. Furthermore, the data also indicate that even today, recent techniques in left-sided breast cancer radiotherapy administer high doses radiation to the heart, and more specifically to the left anterior descending coronary artery.

A breathing adapted technique in left-sided breast cancer can be used to reduce the dose in the heart and in the coronary arteries. This technique is easy to use in daily practice. In Radiotherapy Centre West (RCWEST) the Active Breathing Control (ABC) method was used. We found that the preparation time increased once only by one hour; the time spent by the patient at the linear accelerator was not increased compared to the time without using the breathing adapted technique. The ABC method is well-suited to daily practice; 99% of the patients with clinical T1-2, N0-2, M0 left-sided breast cancer who were treated with the ABC technique, could complete the treatment. Until a threshold has been found to reduce heart damage after breast conserving radiation therapy, RCWEST administers the ABC method to all patients with left sided-breast cancer, as every reduction in heart dose is of importance.

Introduction

Breast cancer is the most common type of all cancers in The Netherlands. Breast-conserving therapy (BCT) is offered only if a good cosmetic result and optimal loco-regional tumour control can be achieved. In all other cases breast ablative surgery is opted for. Fractionated whole breast irradiation is seen as an integral part of breast conserving therapy [1]. Due to the improved survival probability of breast cancer patients, Darby et al. reported in 2005 that the probability of the occurrence heart diseases as caused by the various treatment modalities, is increased. The latter specifically applies to left-sided radiation, chemotherapy (including anthracyclines) and biologicals (trastuzumab). Due to improved irradiation techniques the increased risk of heart disease after irradiation clearly decreased over the years and is, after more than 10 years of follow-up, no longer present [2]. However, Taylor et al. stated that parts of the heart (the myocardium, but especially the Left Anterior Descending coronary artery (LAD) still receive high radiation doses with current radiation techniques [3]. The systematic review of Sardaro et al. shows that still much is unclear with respect to the resulting radiation-induced heart damage in breast cancer patients [4]. Various (preclinical and clinical) studies show the occurrence of atherosclerosis and arterial wall thickening after irradiation [5-7]. Decreasing the heart dose in breast cancer patients is, therefore, of (great) importance. In recent years, several authors reported that a breathing-adapted irradiation technique could be used. This method, in which irradiation is applied only during a period of breath-hold, leads to a marked decrease of the heart dose. Breathing-adapted irradiation can be carried out by various methods. Active Breathing Control (ABC) is one of these methods (see Figure 1). In a recent article Swanson et al. described that the ABC method leads to a significantly lowered heart dose. They also showed that this method is well able to be sustained in patients with breast cancer. In the mean time, they have applied the ABC method for 6 years [8]. Breathing-adapted method appears to be feasible for loco-regional irradiation as well [9-11].

After an extensive literature study conducted by Van der Klein et al., we started an ABC pilot study in mid 2008 [12]. The aim of this study was to evaluate the feasibility of the routine implementation of the ABC method. In addition to providing support to the patient in the linear accelerator, the training of the patient on the computed tomography

(CT) -simulator and performing the CT scan differs from the routine procedure. The technique proved feasible for various patients [13]. From January 2010 onwards, the ABC method was implemented for all left-sided irradiation of breast cancer in our clinic. In The Netherlands (and outside of The Netherlands as well), little is known about the feasibility of the ABC method in a radiotherapy department. For this reason, we present our experiences.

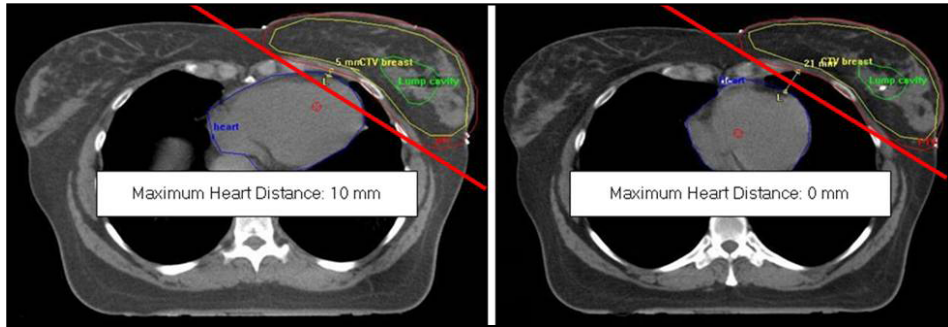


Figure 1. Example of a specific case planned to be irradiated in "Radiotherapiecentrum West" for left sided breast cancer with free-breathing (FB) (left) and with breath hold (BH) (right). These axial slides show that the cardiac dose is lower for the BH-case. In yellow the CTV breast; green: lumpectomy cavity; red: dorsal radiotherapy field border. The anatomy differs slightly between the left and right side of the Figure because of the performed breath-hold.

Materials and methods

First of all, a dedicated radiation therapist (RTT) informs the patient on the radiotherapy as well as on the necessary preparations. The latter is illustrated by a PowerPoint presentation. Then a training session takes place. In this training session, the patient practices with the Active Breathing Coordinator (ELEKTA, Crawley, United Kingdom) equipment. During this training session the lung volume of each patient and the threshold, above which she should inhale, is determined. For each patient, the number of seconds during which she is able to hold her breath, is registered. Once the patient understands the method well and can carry out the instructions of the radiation therapist (RTT), a CT scan in free-breathing (FB) and a CT scan breath-hold (BH) are performed.

If the patient, at a later time, is unexpectedly unable to follow the instructions of the ABC method correctly, the FB CT scan can be used. The glandular breast tissue is, using the ABC method, irradiated with two tangential opposing fields. A dose of 16×2.66 Gy is administered. Only on indication a boost dose was given. This boost dose was directed to the lumpectomy cavity. In this review on patients irradiated with BH at Radiotherapy Centre West (RCWEST) we limit ourselves to the period of January 1st in 2010 to December 31st in 2011. During this time, a total of 284 patients with left-sided breast cancer were irradiated. Forty of these patients were irradiated with another technique, e.g. irradiation of only the supraclavicular nodes or single dose radiotherapy during breast conserving surgery, the so-called intraoperative radiation therapy (IORT). A total of 52 patients (18%) was not irradiated with the ABC method due to a prior estimate of the radiation oncologist or because the method was not feasible. In Table 1 we summarised the reasons why the ABC method could not be carried out. Ultimately, 192 patients were irradiated with ABC. Of this group, only the patients with cT1-2;N0-2;M0 left-sided breast cancer, that were irradiated locally or loco-regionally,

were included in this study. The following characteristics of each patient were registered: whether only a local or a locoregional radiation technique was applied; whether the ABC method could be completed by the patient or not; above which threshold (after the training) the patient ought to inhale; how long (in seconds) the patient could hold her breath; how many breath-holds had to be carried out during each session of irradiation; and whether the patient was familiar with pre-existing lung disease.

	Not irradiated with the breath-hold technique
Age (>95 years)	1
Physical limitations:	
- pulmonary diseases: e.g. COPD	5
- other	4
Communicative limitations (language, deafness, etc.)	8
Psychological limitations	5
Other; estimation of the radiation oncologist, e.g. latex allergy	29

Table 1. Summary of limitations of patients with cT1-2; N0-2; M0 left-sided breast cancer prone to be irradiated with the ABC breath-hold technique.

Finally, in 20 consecutive patients of our study population we examined whether the dose in the heart and the left coronary artery (LAD) could be reduced when using the ABC method. For these analyses the following values were determined and compared to each other: (i) V50 %, the volume that receives 50% of the dose; (ii) D10, the dose that encompasses 10% of the volume; (iii) D50, the dose that encompasses 50% of the volume.

When performing the statistical analysis we used a ‘Wilcoxon Signed Rank Test’ and a p-value of <0.05 was considered as significant.

Results

Three (1.6 %) out of 192 patients were not able to complete the ABC procedure during their irradiation course. Retrospectively, we concluded that these patients had not completely understood the procedure.

A total of 175 patients, 174 women and 1 male, bearing a cT1-2;N0-2;M0 left sided breast cancer, had been included in the study. A total of 18 patients were affected by a restriction, but still were treated with the ABC-method (see Table 2). For example, a patient was irradiated who could only speak a foreign language. After defining a number of clear agreements the ABC-method could be completed. The mean age of the cohort was 56 years, ranging from 28 to 85 years. Twenty-five percent of the patients was irradiated loco-regionally.

The mean number of seconds that the patients could hold their breath was 26, ranging from 18 to 33. The mean of all lung volumes was 1.7 litres; with a range of 0.7 litres-2.5 litres. The limited lung volume of 0.7 litres for one particular patient appeared to place no restriction on completing her treatment sessions without any problem. We noted that a difference in lung volume of at least 0.2 litres must be achieved, because a smaller difference leads to a very limited chest wall extension and, hence, will result in a too small increase in the distance between the heart and the radiation fields. The total

irradiation time takes about 2-3 minutes. For this reason the patient is asked to hold her breath over and over again. During each session of radiotherapy, on average 5 periods of breath-hold, with a range of 2-10 breath-holds, were necessary. The highest number of breath-holds was needed when irradiating loco-regionally. The same threshold values were used in patients receiving a boost dose (directed at the lumpectomy cavity). Again, on average 5 breathing-holds, with a range of 3-9 breath-holds, were needed.

Prematurely stopped with the ABC-breath-hold technique	Irradiated with the ABC-breath-hold technique	Prematurely stopped with the ABC-breath-hold technique
Age (>95 years)	0	0
Physical limitations:		
- pulmonary diseases: e.g COPD	13	0
- other	0	0
Communicative limitations (language, deafness, etc.)	4	0
Psychological limitations	1	1

Table 2. Summary of limitations of patients with cT1-2; N0-2; M0 left-sided breast cancer irradiated with and without the ABC breath-hold technique.

With the introduction of the ABC method the preparation time, when compared to the situation without using the ABC method, lasted about one hour longer; in one and a half hours, the patient has undergone the training and the two CT scans were made (FB and BH). After going through the learning curve of the radiation therapist, for which temporary extra time was given to accompany the patient on the radiation device to control the breathing, the time that is scheduled per patient lasts no longer than was previously the case (without the use of the ABC method), and is the same for a right-sided breast cancer irradiation. For local irradiation 10 minutes and for loco-regional irradiation 15 minutes is scheduled. Apart from the patients whose ABC method was not feasible in the long run, we noted no further challenges or emergency stops during the full course of the radiation therapy.

The analyses of the radiation treatment plans show that the ABC-method results in a significantly lower dose in the heart and the heart vessels and at the same time appear to have a comparable coverage of the irradiated target volume (see Table 3).

Mean; n=20	BH	FB	p-value
Heart V50 (%)	1,4	4,9	<0,01
Heart D10 (Gy)	3,0	7,3	<0,01
Heart D50 (Gy)	0,8	1,0	<0,01
LAD V50 (%)	16,9	41,6	<0,01
LAD D10 (Gy)	20,9	33,0	<0,01
LAD D50 (Gy)	7,3	19,7	<0,01

Table 3. Dose volume values for the heart and the 'Left Anterior Descending coronary artery' (LAD): For the 'breath-hold'(BH) technique and in 'Free-breathing'(FB).

Discussion

The breathing-adapted irradiation is well enforceable in daily practice; of patients with cT1-2;N0-2;M0 left-sided breast cancer, and being irradiated with the ABC-method, 99% can completely sustain the treatment. Little is known about the feasibility of the ABC method. Massaccesi et al. indicated that 90% of the patients the method can insist, however, they have examined a group of only 20 patients [14].

But data are available on another method of heart sparing: the ‘Gating’ technique. Irradiation with this technique is administered only when the breathing cycle of the patient is within a certain predefined phase. In their institute, Berson et al. noted beforehand that 20% of their patients (n=136) were not suitable to undergo the ‘Gating’-technique [15]. The latter was partly due to reasons other than not being able to perform the technique. They reported that 97% of the patients who started the treatment with the “Gating” method could sustain it till the end [15].

Our study showed that 29 patients (15%) were irradiated without the ABC method. The radiation oncologist had judged beforehand that these patients were not suitable to undergo the ABC method. This assessment did not only take place in the start-up phase, but was kept up regularly in the past 2 years. For example, patients have been irradiated without ABC. One of the considerations was a latex allergy. But the ABC-respiratory equipment contains no latex, so in that respect, this patients could have undergone the irradiation with the ABC method. Thus, eventually more patients could have been irradiated with the ABC method. We recommend that radiation therapists perform an assessment to judge whether (yes/no) the patient is able to complete irradiation combined with the ABC method. The radiation oncologist decides on medical grounds whether (yes/no) the patient is eligible for the ABC method.

Since RCWEST is located in the centre of The Hague, relatively a large number of patients of foreign origin is referred for treatment to RCWEST (patients living in the ‘Schilderswijk’, patients working at the embassies). Many of them do not speak the Dutch language properly. We did not explicitly investigate this item. Despite the observed language barrier, we observed that the ABC method could successfully be carried out regularly in this group. Massaccesi et al. noted in their feasibility study that the workload increased [14]. However, we noticed that when the ABC method is administered to all patients with left-sided breast cancer, this technique is no longer an exception and, hence, the radiation therapists feel familiar with this method. For this reason, there is no need anymore to schedule extra time on the linear accelerator. The preparation time, though, remained increased by about one hour. This extra time is required to prepare the patient in a proper manner for the breathing adapted irradiation. Based on these findings, we plan to pass the FB scan, thus reducing the preparation time.

To handle a maximum age to propose (or not to propose) the option with ABC is a matter of opinion and grounds for debate. However, a paper by Van Schoor et al. makes clear that the expected mean median survival duration of women aged 75 years is 10 years [16]. Also, Louwman et al. indicate that the relative survival (taking into account the risk of mortality due to causes other than breast cancer) of a 70-year old patient with breast cancer lasts 3-10 years after breast cancer diagnosis. This is similar to the relative survival duration of breast cancer patients aged 40-70 years. The relative survival 3-5 years after diagnosis of breast cancer of 80-year old female breast cancer patients is 5% lower than breast cancer patients of 40-70 years; it should be kept in mind that the stage distribution in this 80-year old group was often worse and that this group of patients was regularly undertreated [17].

Since the effects of irradiation for cardiovascular damage may become manifest after 10 years, using the ABC method of patients over 70 years of age can be justified [2]. In RCWEST, no age limit is used when proposing the ABC method. Wang et al. indicate that, by means of an automatic planning process, insight is obtained into which patients may benefit from a breathing adapted irradiation technique [18]. They opt for a dose reduction at the heart of a small group of patients (the threshold $V50 > 10 \text{ cm}^3$), which implies that only in 15-20% of all left-sided breast cancer patients the ABC method would be useful [18]. Taylor et al., however, do not expect that the dose of the current irradiation techniques, when compared to those of the older techniques, is reduced. And a threshold dose is not yet determined [19]. For this reason, the aim of RCWEST is to reduce the dose to the heart and the heart vessels to zero.

Qi et al. indicated that because of the intrinsic motion the position of the heart and the heart vessels on the CT scan varies and appears to be only a snapshot in time. On a 4D-CT, this is a CT scan in which the patients were scanned in several phases of respiration; the location of both varies over a short period of time. They reconfirm that the lowest dose in the heart and the LAD was found at the end of the normal inspiration. In RCWEST, when using the ABC method, the patient is irradiated at a level of 75% of the patient's deep inspiration [20]. Wang et al. have also investigated the displacement of the heart and the coronary arteries, which shows that during the deep inspiration, the LAD was displaced around 2.3 mm. For this reason, they suggest to implement an extra safety margin of ≥ 5 mm between the LAD and the radiation field edge [21]. Follow-up studies to examine further reduction of the dose in the heart and the cardiac vessels (to compensate for the displacement of the heart) will take place in RCWEST.

Conclusion

The Active Breathing Control method appeared to be feasible in daily practice; in 99% of the left-sided breast cancer patients (cT1-2;N0-2;M0), treated with the ABC method, it can be sustained. Until it becomes clear which threshold dose should be used for evaluating the risk of reducing heart damage, in RCWEST the breathing adapted irradiation technique is offered to all patients with left-sided breast cancer. Furthermore, any reduction in heart dose is judged to be of importance, especially in patients who are prone to receive cardio toxic chemotherapy (e.g., adriamycin and trastuzumab).

Recommendations

1. We advise to combine the breath-hold technique with irradiation for all women bearing left-sided breast cancer, because this technique is easy to implement into daily practice.
2. More research is needed to assess the threshold dose.

Acknowledgements

We would like to thank the following people for the various efforts they have made R. Gangabisoensingh and L. Kwakkel-Huizenga for the datamanagement. J. van Egmond for his assistance with Excel. I. Korteland for retrieving patient data. L. van Kempen, M. Heijenbrok, H. Rozema and Y. Kalidien for their contribution in the planning study. And finally, M. van Dalum, A. van Hek, J. Kuipers and L. Versluis for implementing the ABC method and training their colleagues.

References

1. Richtlijn mammacarcinoom. Versie: 2.0, Consensus based 2012-02-13. NABON, Landelijke richtlijn. Te raadplegen via www.oncoline.nl/mammacarcinoom (Accessed 17 augustus 2012).
2. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300.000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-65.
3. Taylor CW, Povall JM, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 2008;72:501-7.
4. Sardaro A, Petruzzelli MF, D'Errico MP, et al. Radiation-induced cardiac damage in early left breast cancer patients: risk factors, biological mechanisms, radiobiology, and dosimetric constraints. *Radiother Oncol* 2012; 103:133-42.
5. Stewart FA, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE^{-/-} mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649-58.
6. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007;67:10-8.
7. Dorresteijn LD, Kappelle AC, Scholz NM, et al. Increased carotid wall thickening after radiotherapy on the neck. *Eur J Cancer* 2005;41:1026-30.
8. Swanson T, Grills IS, Hong Y, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36(1):24-30.
9. Stranzl H, Zurl B, Langsenlehner T, et al. Wide tangential fields including the internal mammary lymph nodes in patients with left-sided breast cancer influence of respiratory-controlled radiotherapy (4D-CT) on cardiac exposure. *Strahlenther Onkol* 2009;185:155-60.
10. Jaggi R, Phil D, Moran J, et al. Evaluation of four techniques using intensity-modulated radiation therapy for comprehensive locoregional irradiation of breast cancer. *Int J Radiat Oncol Biol Phys* 2010;78:1594-1603.
11. Hjelstuen M, Mjaaland I, Vikström J, et al. Radiation during deep inspiration allows loco-regional treatment of left breast and axillary-, supraclavicular- and internal mammary lymph nodes without compromising target coverage or dose restrictions to organs at risk. *Acta Oncol* 2011; Early online:1-12.
12. Van der Klein JN. Een literatuurstudie naar ABC bij het mammacarcinoom en het longcarcinoom. *Gamma Professional* 2007;57:36-9.
13. Benschop E, Limpens KM, Reurink NM, et al. Introductie en implementatie van de Active Breathing Control methode in de praktijk. *Gamma Professional* 2008;58:31-3.
14. Massaccesi M, Caravatta L, Cilla S, et al. Active Breathing Coordinator in adjuvant three-dimensional conformal radiotherapy of early stage breast cancer: a feasibility study. *Tumori* 2010;96:417-23.
15. Berson AM, Emery R, Rodriguez L, et al. Clinical experience using respiratory gated radiation therapy: comparison of free-breathing and breath-hold techniques *Int J Radiat Oncol Biol Phys* 2004;60:419-26.
16. Van Schoor G, Otten JD, Den Heeten GJ, et al. Breast cancer among women over 75 years: an important public health problem? *Eur J Public Health* 2012;22:422-4.
17. Louwman WJ, Vulto JC, Verhoeven RH, et al. Clinical epidemiology of breast cancer in the elderly. *Eur J Cancer* 2007;43:2242-52.
18. Wang W, Purdie TG, Rahman M, et al. Rapid automated treatment planning process to select breast cancer patients for active breathing control to achieve cardiac dose reduction. *Int J Radiat Oncol Biol Phys* 2012;82:386-93.
19. Taylor CW, Bronnum D, Darby SC, et al. Cardiac dose estimates from Danish and Swedish breast cancer radiotherapy during 1977-2001. *Int J Radiat Oncol Biol Phys*

- 2011;100:176-83.
20. Qi XS, Hu A, Wang K, et al. Respiration induced heart motion and indications of gated delivery for left-sided breast irradiation. *Int J Radiat Oncol Biol Phys* 2012;82:1605-11.
 21. Wang X, Pan T, Pinnix C, et al. Cardiac motion during deep-inspiration breath-hold: implications for breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:708-14.

Left-sided breast cancer radiotherapy with and without breath-hold:
Does IMRT reduce the cardiac dose even further?

Mirjam Mast^a, Loes van Kempen-Harteveld^a, Mark Heijenbrok^b, Yamoena Kalidien^a,
Hans Rozema^a, Wim Jansen^c, Anna Petoukhova^a and Henk Struikmans^{a,c}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of Radiology, Medical Center Haaglanden, The Hague,
The Netherlands;

^c Department of Clinical Oncology, Leiden University Medical Center,
The Netherlands

Radiother Oncol 2013;108(2):248-253

Abstract

Purpose

In radiotherapy for left-sided breast cancer, Active Breathing Control enables a decrease of cardiac and Left Anterior Descending (LAD) coronary artery dose. We compared 3D-Conformal (3D-CRT) to Intensity Modulated Radiotherapy (IMRT) treatment plans based on free-breathing (FB) and breath-hold (BH). We investigated whether IMRT enables an additional decrease of cardiac dose in radiotherapy plans with and without BH.

Materials and methods

Twenty patients referred for whole breast irradiation were included. The whole breast, heart and LAD-region were contoured. Four treatment plans were generated: FB_3D-CRT; FB_IMRT; BH_3D-CRT; BH_IMRT. Several doses were obtained from Dose Volume Histograms and compared. Results were compared statistically using the Wilcoxin Signed Rank Test.

Results

For heart and LAD-region, a significant dose reduction was found in BH ($p < 0.01$). For both BH and FB, a significant dose reduction was found using IMRT ($p < 0.01$). By using IMRT an average reduction of 5% was noted in the LAD-region for the volume receiving 20 Gy.

In 5 cases, the LAD-region remained situated in the vicinity of the radiation portals even in BH. Nevertheless, with IMRT the LAD dose was reduced in these cases.

Conclusion

IMRT results in a significant additional decrease of dose in the heart and LAD-region in both breath-hold and free-breathing.

Introduction

Left-sided breast cancer radiotherapy has been associated with an increased risk of fatal cardiovascular events [1]. These findings were confirmed in population-based studies carried out in Denmark, Sweden and The Netherlands. In these series, the risk of developing ischemic heart disease, pericarditis and valvular disease was increased [2,3]. Several (pre)clinical studies established that a higher risk on atherosclerotic lesions was found after radiation treatment [4,5]. Nilsson et al. and Correa et al. described the effect of radiotherapy on the development of stenosis after several years [6,7]. Recently, Darby et al. found that the incidence of ischemic heart disease was proportional to the mean dose to the heart and started to increase within a few years to at least 20 years after exposure [8]. Patients with pre-existing cardiac risk factors had higher absolute risks after radiotherapy than those without [8]. Correa et al. described that, in modern radiotherapy, a reduction in risk of coronary damage was noticed [7]. However, Taylor et al. found that, even in modern radiotherapy techniques, the anterior part of the heart, including the LAD, still receives doses of over 20 Gy [9]. These findings confirm the importance of taking the coronary arteries (i.e. the Left Anterior Descending coronary artery (LAD)) into account as an “Organ At Risk” when defining a radiation treatment plan. Therefore, sparing the heart and the coronary arteries, specifically, the LAD, seems highly relevant to reduce cardiac morbidity risk in contemporary radiotherapy.

Various techniques are available to decrease the cardiac dose; the Active Breathing Control (ABC) method is one of these techniques. When using the ABC method the patient holds her breath during the administration of radiotherapy for left-sided breast cancer patients. In doing so, the distance between the heart and the radiation fields is enlarged. The use of ABC results in a significant decrease of the dose applied to the heart as well as of the dose applied to the LAD [10,11]. Intensity Modulated Radiotherapy (IMRT) is successfully used as a class solution for various tumor sites. Subsequently, several authors described the use of IMRT for the dose reduction in the heart during breast cancer irradiation. Coon et al. showed that the dose to the heart can be lowered in patients with unfavorable cardiac anatomy, when using an IMRT technique. And Schubert et al. found that inversely planned IMRT, when compared to a 3D-CRT technique, resulted in a lower dose to the heart without compromising the dose in the target volume [12,13].

In the present study, we examined whether the use of IMRT enabled an additional decrease of the cardiac dose as well as a further decrease of the dose to the LAD, in cases with and without the use of the ABC breath-hold technique. Therefore, we compared 3D-Conformal Radiotherapy (3D-CRT) treatment plans to IMRT treatment plans based on either a free-breathing or a breath-hold CT scan. In this way we were able to distinguish between the contributions of the breath-hold technique and those of the IMRT technique in lowering the cardiac dose and the dose to the LAD.

Materials and methods

Twenty consecutive patients, diagnosed with left-sided ductal carcinoma in situ or infiltrative breast cancer, were included in this planning study. All patients underwent breast-conserving surgery (and axillary staging). Thereafter, they were treated with whole breast radiotherapy using the breath-hold technique. No regional radiotherapy was given. All patients underwent a free-breathing CT scan and a breath-hold CT scan in the same treatment position, i.e. they were placed on a carbon fiber breast board (Sinmed B.V., Reeuwijk, The Netherlands) with both arms abducted above the head. A copper wire was placed around the palpable breast tissue as an aid for Clinical Target Volume (CTV) delineation.

Single-slice CT images (AcQSim Inc., Philips Medical Systems, Cleveland, OH, United States) were obtained using 3-mm inter-slice thickness from lung apices to the diaphragm. The breath-hold CT scan was executed using the ELEKTA Active Breathing Coordinator™ device (ELEKTA, Crawley, United Kingdom), the threshold was determined at 75% of the moderate deep inspiration as described by Remouchamps et al. [10]. Patients were trained on the CT-simulator to hold their breath for a maximum duration of 30 s, using a mouth piece, nose clip and prism glasses. The duration of the breath-hold was defined for each patient individually. The method described above has been the standard procedure in our department since October 1st, 2010 for all left-sided breast cancer radiotherapy patients [14].

Target delineation and organs at risk

To avoid inter-observer-based differences, the glandular breast tissue, heart and the LAD-region were delineated for each breath-hold- and free-breathing-scan by one observer only (by MLKH). All delineations were performed in the Pinnacle³ planning system (version 8.0m, Philips Medical Systems, United States). The glandular breast tissue was contoured according to RTOG delineation guidelines [15] and was defined as the CTV. PTV was created by expanding the CTV 5 mm in the transversely, 6 mm cranially, and 9 mm caudally. The PTV was retracted 5 mm from the patient surface to minimize high-dose levels in the build-up regions for IMRT plans (PTV_{trim}).

The heart was delineated according to the University of Michigan cardiac atlas of Feng et al., from the cranial border of the left atrium to the apex of the heart [16]. As no contrast was used during the planning-CT scan, the LAD was in some slices difficult to visualize and, therefore, the LAD-region was contoured instead [9,16]. To contour this region we followed the anatomic borders of the pericardium, which served as the anterior border. The superior border was defined as the origin of the LAD from the left main coronary artery and followed the anterior-interventricular groove; the caudal border was situated at the apex cordis. When, in some slices the LAD was difficult to visualize, its location was inferred from the course of the interventricular groove and interpolated between slices. Delineations of the heart and LAD-region were reviewed by the radiologist (MH).

Our 3D-CRT technique consisted of two opposing wedged tangential fields. If optimal dose homogeneity was not achieved an additional field was added. With our IMRT technique, 60% of the dose was given with two open tangential fields and 40% with four inversely planned IMRT fields, with a 'Step-and-Shoot' technique. For the optimization a Direct Machine Parameter Optimization (DMPO) was used with the following criteria: the maximum number of segments was constricted to 12; the minimum segment area was set to 9 cm²; and the threshold for the minimum number of monitor

units (MUs) per segment was 4 MUs. For the heart we started to define a maximum equivalent dose of 20 Gy after weights for the heart and the LAD-region were set individually for each individual patient to enable a maximum sparing of these structures. For the PTV_{trim} several constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy) and minimum dose (40.6 Gy).

All plans were calculated with a Collapsed Cone algorithm using heterogeneity correction (Philips Medical Systems 2006 Pinnacle³. Physics REFERENCE GUIDE Release 8.0). For 3D-CRT as well as for IMRT plans identical gantry angles and beam energies were used. In this way a more reliable comparison of the two techniques could be obtained. Moreover, the dose to the contralateral breast was not biased due to the use of identical gantry angles. All treatment plans had to meet the criterion that 97% of the PTV_{trim} was covered by at least of the 95% isodose (and <108% isodose). The plans were judged and approved by one radiation oncologist (HS).

The prescribed dose was 42.56 Gy in 16 fractions in all cases. For both techniques (3D-CRT and IMRT), the treatment plans based on the breath-hold and free-breathing scans were compared for all patients. For PTV_{trim}, the percentages of volumes receiving 95% and 107% of the prescribed dose (V95%; V107%) were determined and compared. Furthermore, for the heart and the LAD-region, various dose volume parameters were generated and evaluated; the choice was based on those published in the literature. As far as the lung tissue was concerned, the mean lung dose and the volume receiving 20 Gy (V20 Gy) (averaged over both lungs) were analyzed for both techniques. And finally, the total body dose, the volume receiving 5% of the prescribed dose (V5%), and the number of monitor units were compared.

Statistics

A Wilcoxon Signed Rank Test was performed to compare doses and volume differences since the number of eligible cases was less than 30. For analysis, we used SPSS Statistics version 17.0 (IBM Corporation, Armonk, NY, United States). The level of statistical significance was considered at a p-value of <0.05 for all tests.

Results

Heart and LAD-region

For both the heart and the LAD-region a significant dose reduction ($p < 0.01$) was found when comparing the treatment plans based on breath-hold to those based on the free-breathing scans. In the LAD-region an average volume reduction for the 20 Gy (V20 Gy) of 20% was achieved by using the breath-hold technique.

Another 5% reduction in irradiated volume for the 20 Gy (V20 Gy) could be achieved by using an IMRT technique. Furthermore, for the IMRT technique when compared to the 3D-CRT technique, a significant dose reduction ($p < 0.01$) was found (Table 1).

However, in 6 out of 20 patients over 30% of the LAD-region still received 20 Gy in 3D-CRT, even when using the breath-hold technique. In these cases, IMRT resulted in a reduction of the V20 Gy with an average of 15%.

Figure 2 shows that the caudal part of the heart in particular, and thus the LAD-region, is situated in the vicinity of the radiation portals, even in the breath-hold treatment plans. With IMRT, a lower dose was attained in the LAD-region, and in doing so, in all patients

a decrease of the dose in the caudal part of the LAD-region was found. This was attained by the fact that the multileaves enclosed the PTV_{trim} better by rotating the collimator angle (Figure 3). Nevertheless, in five patients the caudal part of the LAD-region, i.e. around 45 mm from the apex cordis, still received doses between 21 and 34 Gy.

Table 1.		Mean (SD) (n=20)				p-value	
		Breath-hold (BH)		Free-breathing (FB)		BH compared to FB, for both 3D-CRT and IMRT	3D-CRT compared to IMRT, for both BH and FB
		3D-CRT	IMRT	3D-CRT	IMRT		
Heart	Mean (Gy)	1.8 (0.8)	1.5 (0.5)	3.3 (1.6)	2.7 (1.3)	p < 0.01	p < 0.01
	Dmax (Gy)	15.8 (13.0)	8.6 (6.2)	29.2 (14.6)	24.7 (14.7)	p < 0.01	p < 0.01
	V5Gy (%)	3.8 (3.0)	2.5 (2.1)	8.9 (5.0)	7.4 (4.7)	p < 0.01	p < 0.01
	V20Gy (%)	1.5 (1.5)	0.6 (0.8)	5.0 (3.5)	3.5 (3.0)	p < 0.01	p < 0.01
	V30Gy (%)	1.0 (1.1)	0.3 (0.4)	4.0 (3.1)	2.4 (2.3)	p < 0.01	p < 0.01
LAD-region	Mean (Gy)	9.6 (6.9)	6.7 (5.1)	18.6 (9.3)	14.9 (9.3)	p < 0.01	p < 0.01
	Dmax (Gy)	25.2 (15.3)	18.8 (13.6)	35.5 (11.6)	31.4 (13.0)	p < 0.01	p < 0.01
	V5Gy (%)	39.4 (26.4)	30.3 (25.9)	62.6 (23.0)	54.9 (25.1)	p < 0.01	p < 0.01
	V10Gy (%)	25.0 (23.8)	18.2 (21.5)	49.9 (25.2)	42.9 (26.6)	p < 0.01	p < 0.01
	V20Gy (%)	17.8 (20.1)	9.7 (15.1)	42.5 (25.6)	32.8 (27.1)	p < 0.01	p < 0.01
Lung	Mean (Gy)	3.0 (1.0)	2.6 (0.9)	3.3 (1.1)	2.9(1.1)	p < 0.02	p < 0.01
	Dmax (Gy)	36.1 (8.0)	33.4 (5.7)	18.0 (6.9)	35.5 (5.0)	p < 0.01	p < 0.01
	V5Gy (%)	11.4 (3.3)	10.1 (3.1)	11.3 (3.3)	10.1 (3.3)	3D-CRT: p = 0.94 / IMRT: p = 0.90	p < 0.01
	V20Gy (%)	6.2 (2.4)	5.1 (2.2)	6.8 (2.8)	5.7 (2.6)	3D-CRT: p < 0.01 / IMRT: p = 0.06	p < 0.01
Total body	V5% (%)	18.3 (5.0)	16.2 (4.8)	20.0 (5.2)	17.4 (5.2)	P < 0.02	p < 0.01
Monitor Units		462	340	467	342	p > 0.7	p < 0.01

Table 1. Overview of mean doses and volumes, including the p-value. Abbreviations: BH: Breath-hold. FB: Free-breathing. V5 Gy, 10 Gy, 20 Gy, 30 Gy: volume receiving 5 Gy, 10 Gy, 20 Gy, 30 Gy respectively. Dmax: dose encompassing 2% of the volume. V95%, V107%: volume receiving $\geq 95\%$ and 107% of the prescribed dose respectively. V5%: volume receiving $\geq 5\%$ of the prescribed dose.

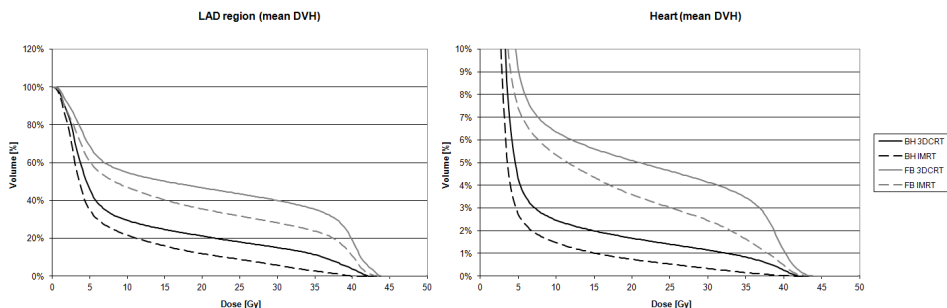


Figure 1. Mean Dose Volume Histograms of the 20 patients of the study; Left: the Left Anterior Descending coronary artery region; Right: the heart. In black the breath-hold technique; in grey the free-breathing technique. The dotted lines represent the Intensity Modulated Radiotherapy technique. Note that the y-scale is different for the left and right graphs.

The mean doses and volumes, averaged over 20 patients, are presented in Table 1. In Figure 1, mean Dose Volume Histograms (DVHs) of the LAD-region and the heart were reproduced for both breath-hold and free-breathing, as well as for the 3D-CRT and IMRT technique.

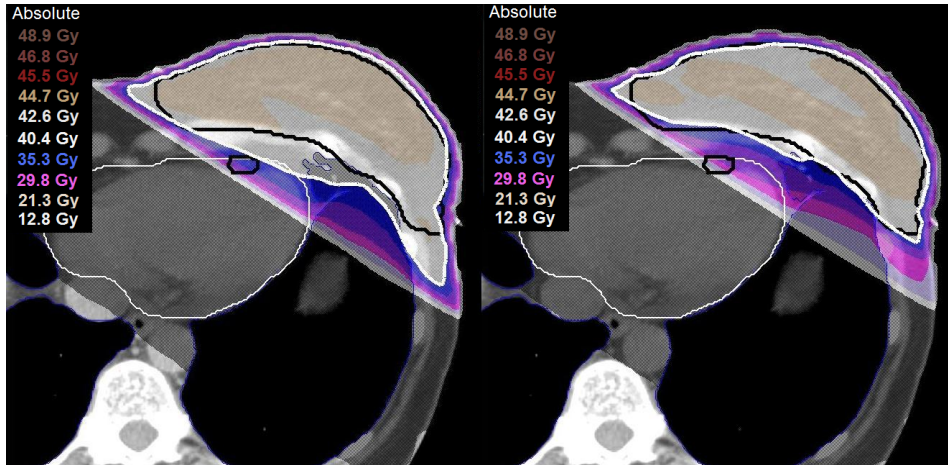


Figure 2. Comparison of the 95% isodose (white line) in the caudal part of the radiation fields for the 3D-Conformal Radiotherapy (left) and the Intensity Modulated Radiotherapy (right) technique on the breath-hold scan. Black line = PTV_{trim} .

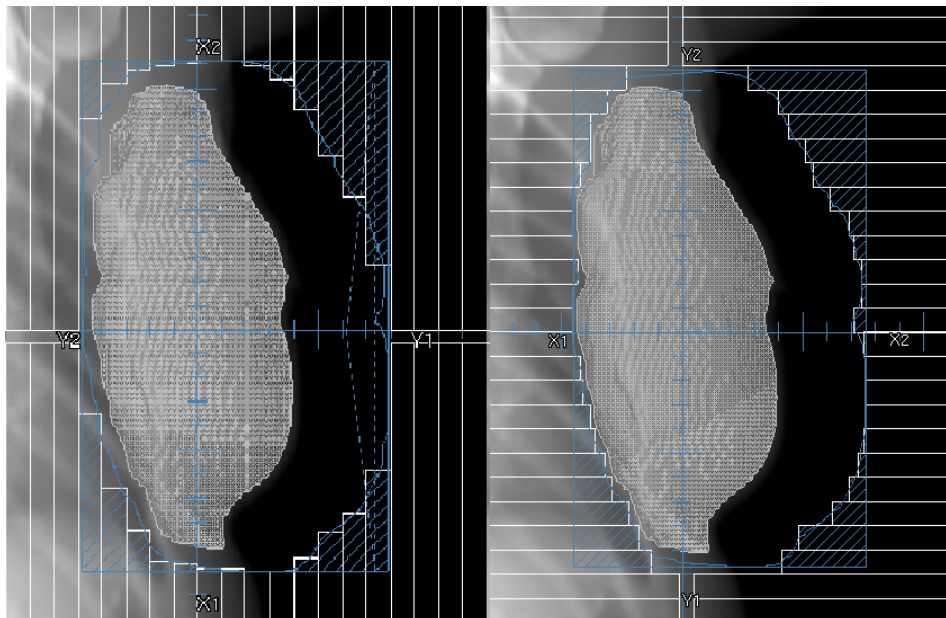


Figure 3. Beams Eye View of the left anterior oblique treatment field; Left: the 3D-Conformal Radiotherapy technique; Right: the Intensity Modulated Radiotherapy technique. The collimator was turned to adapt the treatment field as much as possible to the PTV_{trim} . This collimator adaption is not possible for 3D-Conformal radiotherapy because of the wedge. In grey PTV_{trim} was visualized.

Lung

For the 3D-CRT plans, the lung volume receiving 20 Gy was significantly reduced in breath-hold ($p < 0.01$). In the IMRT plans, a borderline significant reduction was found for the lung volume that received 20 Gy in breath-hold ($p = 0.06$). For the mean lung dose a significant reduction was found in breath-hold ($p < 0.02$).

Total body

The volume of the total body receiving 5% of the prescribed dose was significantly reduced when using the breath-hold technique ($p < 0.02$). Also, a significant reduction of irradiated volume ($p < 0.01$) was found when 3D-CRT and IMRT techniques were compared (Table 1).

Delineated volumes

For the delineated volume of the LAD-region no significant differences ($p = 0.15$) were found in treatment plans in breath-hold (mean 10.5 cm³, range 6.3–19.2) when compared to those in free-breathing (mean 10.9 cm³, range 6.8–14.2). The delineated heart volumes in breath-hold treatment plans appeared to be significantly smaller compared to free-breathing; mean of 682 cm³ (range 516–884) and 741 cm³ (range 561–883) respectively ($p < 0.01$). Significantly larger lung volumes were found in breath-hold than in free-breathing ($p < 0.01$); mean lung volume in breath-hold was 5506 cm³ (range 4681–6476) and in free-breathing 3049 cm³ (range 1341–4718).

Monitor units

Significantly less monitor units ($p < 0.01$) were needed using the IMRT technique when compared to the amount of monitor units used in the 3D-CRT technique. We found an average of 465 monitor units versus 341 respectively (Table 1).

Discussion

In general, we found that the breath-hold technique resulted in a significant dose reduction in the heart and of the dose in the LAD-region. Furthermore, with IMRT a significant further dose reduction could be attained. IMRT enables a decrease in the dose in the LAD-region in the caudal part of the radiation fields as well. Even when using the breath-hold technique, the LAD-region is situated close to the radiation fields, because of the position of the heart, and more specifically of the LAD, in the thorax. Sparing the caudal part of the LAD seems to be of great (clinical) relevance, since Nilsson et al. found a four- to sevenfold increase of high-grade coronary artery stenosis after radiation therapy in the mid- and distal LAD when comparing women with left- and right-sided breast cancer [6]. In our study we defined the caudal part of the LAD-region, comparable to the distal branch of the LAD Nilsson et al. described [6]. However, the cranial border of the distal branch was difficult to define, therefore we chose the cranial border of the distal branch arbitrarily at a distance of 15 slices (3 mm/slice) on the planning CT scan, starting from the apex cordis in cranial direction.

Kirby et al. delineated the LAD itself without using contrast, they made use of the course of the anterior-interventricular groove, when the LAD was difficult to find and added an isotropic 10 mm margin around the defined LAD to take delineation uncertainties and heart/respiratory motion into account [17]. In our cases, the pericardium was defined as the border of the LAD-region [16], and in this way the LAD-region could remain at a somewhat larger distance from the high-dose areas of the radiation fields. Because of these delineation differences between the two investigations the LAD doses were difficult to compare. As for the significantly smaller volumes of the heart in

the breath-hold scan, the breath-hold probably influences the heart volume as well. No studies were identified to confirm this finding.

Neither for the dose in the heart nor for the dose in the LAD any specific thresholds could be defined according to several authors, summarized in the systematic review performed by Sardaro et al. [18]. Since no threshold doses for the heart and LAD are available and the clinical effect of low doses is not completely clear, we think it would be best clinical practice to keep the dose in the heart and LAD as low as achievable. Therefore, we decided to use the breath-hold technique for all left-sided breast cancer patients. It is a simple method, which has been completely implemented in our clinic. Other breathing adapted radiation techniques could be useful as well, such as the fluoroscopy-guided Deep Inspiration Breath-hold (DIBH) irradiation technique [19], the gated technique [20] and the voluntary inspiration breath-hold [21].

No significant differences were found according to the PTV_{trim} coverage for both the breath-hold and free-breathing scans; however, a significantly lower dose outside the PTV_{trim} was observed for IMRT in comparison to 3D-CRT. Since Remouchamps et al. and Schubert et al. reported that, with IMRT, generally a more homogeneous dose distribution will be achieved in comparison to a 3D-CRT technique, dose homogeneity was not involved in our study [10,13]. According to Cao et al. the influence of breathing motion should be considered and thus the choice for an optimal treatment technique should be made. Using IMRT and a breathing adapted radiation treatment technique, the dosimetric coverage may be more optimal [22]. Furthermore, significantly less monitor units were determined for the IMRT technique compared to 3DCRT; this was also found in the study of Remouchamps et al. [10]. The significant reduction in mean lung dose, found for both lungs, was confirmed in the study by Borst et al. [19].

Finally, the ABC method in our experience is a simple and well-tolerated technique. Also, Swanson et al. report 6 years of experience in their clinic with this method [10]. In the evaluation study of Mast et al. it was stated that 99% of the patients with clinical T1–2, N0–2, M0 left-sided breast cancer who were treated with the ABC technique, completed the treatment without any problem [14].

Conclusion

We confirmed that the breath-hold technique in left-sided breast cancer radiotherapy leads to a significant dose reduction in the heart and the LAD-region. IMRT enables an additional dose reduction in these critical organs in both free-breathing and breath-hold. Applying an IMRT technique can reduce the dose in the caudal part of the radiation fields in both free-breathing and breath-hold as well.

Role of the funding source

We want to acknowledge the American Women's Club of The Hague for funding this planning study. The study sponsors had no involvement in the content of the study, and neither in the collection, analysis and interpretation of the study.

Acknowledgements

We thank T.F.H. Vissers for bibliographical assistance, J. van Egmond for his assistance with Excel and J.F.D. Bouricius for critically editing this article.

References

1. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300.000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557–65.
2. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011;100:167–75.
3. Hoening MJ, Botma A, Aleman BMP, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365–75.
4. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007;67:10–8.
5. Stewart FA, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE^{-/-} mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649–58.
6. Nilsson G, Holmberg L, Garmo H, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012;30:380–6.
7. Correa CR, Litt HI, Hwang W, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007;25:3031–7.
8. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after RT for breast cancer. *N Engl J Med* 2013;368:987–98.
9. Taylor CW, Povall JM, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 2008;72:501–7.
10. Remouchamps VM, Letts N, Vicini FA, et al. Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:704–15.
11. Swanson T, Grills IS, Hong Y, Entwistle A, Teahan M, Letts N, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36:24–30.
12. Coon AB, Dickler A, Kirk MC, et al. Tomotherapy and multifield intensitymodulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavourable cardiac anatomy. *Int J Radiat Oncol Biol Phys* 2010;78:104–10.
13. Schubert LK, Gondi V, Sengbusch E, Westerly DC, Soisson ET, Paliwal BR, et al. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. *Radiother Oncol* 2011;100:241–6.
14. Mast ME, van der Klein JN, van Geen S, et al. Een hartsparende bestralingstechniek bij vrouwen met linkszijdige borstkanker. De resultaten van vier jaar ervaring in Radiotherapiecentrum West. *Ned Tijdschr Oncol* 2012;9:270–6.
15. <http://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE%3d&ctabid=236>; visited 1-7-2013.
16. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 2011;79:10–8.
17. Kirby AM, Evans PM, Donovan EM, Convery HM, Haviland JS, Yarnold JR. Prone versus supine positioning for whole and partial-breast radiotherapy: a comparison of non-target tissue dosimetry. *Radiother Oncol* 2010;96:178–84.
18. Sardaro A, Petruzzelli MF, D'Errico MP, Grimaldi L, Pili G, Portaluri M. Radiation-induced cardiac damage in early left breast cancer patients: risk factors,

- biological mechanisms, radiobiology, and dosimetric constraints. *Radiother Oncol* 2012;103:133–42.
19. Borst GR, Sonke JJ, den Hollander S, et al. Clinical results of image-guided deep inspiration breath hold breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;78:1345–51.
 20. Vikström J, Hjelstuen MHB, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. *Acta Oncol* 2011;50:42–50.
 21. Korreman SS, Pedersen AN, Aarup LR, Nottrup TJ, Specht L, Nystrom H. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1375–80.
 22. Cao J, Roeske JC, Chmura SJ, et al. Calculation and prediction of the effect of respiratory motion on whole breast radiation therapy dose distributions. *Med Dosim* 2009;34:126–32.

Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients

Mirjam Mast^a, Eline Vredeveld^b, Herman Credoe^b, Jaap van Egmond^a, Mark Heijenbrok^c, Eugen Hug^d, Patrick Kalk^b, Loes van Kempen-Harteveld^a, Erik Korevaar^b, Hans Paul van der Laan^b, Hans Langendijk^b, Hans Rozema^a, Anna Petoukhova^a, Marco Schippers^{b,e}, Henk Struikmans^{a,f} and John Maduro^b

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of Radiation Oncology, University Medical Center, Groningen, The Netherlands;

^c Department of Radiology, Medical Center Haaglanden, The Hague, The Netherlands;

^d ProCure Proton Therapy Centers, Somerset, USA;

^e Paul Scherrer Institut, Villingen, Switzerland;

^f Department of Clinical Oncology, Leiden University Medical Center, The Netherlands.

Breast Cancer Res Treat 2014;148(1):33-39

Abstract

Purpose

In left-sided breast cancer radiotherapy, tangential intensity modulated radiotherapy combined with breath-hold enables a dose reduction to the heart and left anterior descending (LAD) coronary artery. Aim of this study was to investigate the added value of intensity modulated proton therapy (IMPT) with regard to decreasing the radiation dose to these structures.

Materials and methods

In this comparative planning study, four treatment plans were generated in 20 patients: an IMPT plan and a tangential IMRT plan, both with breath-hold and free-breathing. At least 97 % of the target volume had to be covered by at least 95 % of the prescribed dose in all cases. Specifically with respect to the heart, the LAD, and the target volumes, we analyzed the maximum doses, the mean doses, and the volumes receiving 5–30 Gy.

Results

As compared to IMRT, IMPT resulted in significant dose reductions to the heart and LAD-region even without breath-hold. In the majority of the IMPT cases, a reduction to almost zero to the heart and LAD-region was obtained. IMPT treatment plans yielded the lowest dose to the lungs.

Conclusions

With IMPT the dose to the heart and LAD-region could be significantly decreased compared to tangential IMRT with breath-hold. The clinical relevance should be assessed individually based on the baseline risk of cardiac complications in combination with the dose to organs at risk. However, as IMPT for breast cancer is currently not widely available, IMPT should be reserved for patients remaining at high risk for major coronary events.

Introduction

Postoperative radiotherapy is considered standard of care after breast-conserving surgery for breast cancer [1]. After mastectomy, radiotherapy is required in case of intermediate or high risk of locoregional failure [2,3]. Previous studies [4,5] have shown that radiotherapy is associated with an increased rate of major coronary events, especially in patients treated for left-sided breast cancer. However, it should be noted that the follow-up period in these studies is relatively short [4, 5]. With improved survival, more patients will be at risk for long-term radiation-induced toxicity, thus making it even more important to reduce the dose to all organs at risk (OARs).

Recently, Darby et al. found that the rate of major coronary events was proportional to the mean dose to the heart starting within a few years after exposure. Patients with pre-existing cardiac risk factors had higher absolute risks after radiotherapy than those without [6]. Given its anatomical location, the left anterior descending (LAD) coronary artery is most at risk for developing atherosclerosis after left-sided breast-conserving radiotherapy [7]. Taylor et al. showed that even with contemporarily delivered tangential fields, the mean dose to the LAD was considerable: 7.6 Gy. Furthermore, half of the patients appeared to receive more than 20 Gy in the ventral part of the heart [8]. As the rate of ischemic heart disease is proportional to the mean heart dose, Darby et al. advised to reduce the dose to the heart as much as possible. In order to reduce the dose to the heart and the LAD using photons, intensity modulated radiotherapy (IMRT), either combined or not combined with breath-hold techniques, has been investigated [9–11] and compared to 3D-conformal radiotherapy (3D-CRT) with and without breath-hold [11].

A commonly used IMRT technique for breast cancer treatment is an IMRT technique based on the standard tangential fields with additional smaller subfields in order to improve dose homogeneity [12]. The advantage of this technique, compared to the full inversed planned multiple beam IMRT, is, that the dose redistribution is confined to the same area as the tangential fields, thus avoiding an excessive low dose to surrounding OARs. In addition, breath-hold techniques can be used to decrease the heart dose. With a breath-hold technique, a patient holds her breath during 25–30 s intervals in which radiation is administered. In doing so, the distance between the heart and the radiation fields increases and, consequently, the dose to the heart decreases [10].

However, due to anatomical variations in some patients, the radiation dose to the heart remains relatively high, even with the use of advanced photon-based techniques. Due to its physical characteristics, proton therapy may eventually enable a further decrease of dose to the heart. In contrast to a photon beam, a proton beam is characterized by a very narrow width of a relatively high peak of maximum dose administration: the Bragg peak. In other words, a proton beam is characterized by a dose distribution that is finite and adjustable in depth depending on the energy of the proton beam. Theoretically, these characteristics of protons enable a very precise irradiation of the target volume, while at the same time better sparing of the surrounding normal tissue can be obtained [13]. Therefore, we assumed that proton therapy may enable an improved sparing of the heart and LAD in left-sided breast cancer patients, especially in cases where the heart dose remains (relatively) high with advanced photon techniques [14–16]. In a previous paper, we found that tangential IMRT in combination with a breath-hold procedure resulted in a significant decrease of the dose to the heart and LAD-region compared to 3D-CRT in breathhold, while retaining optimal target volume coverage [11]. Furthermore, compared to standard photon 3D-CRT, tangential IMRT improves overall cosmesis and reduces the risk of skin telangiectasia [17]. However, to the best of our knowledge, planning compar-

ative studies are lacking, which focus on the additional value of protons for whole breast irradiation compared to that of tangential IMRT (both with and without breath-hold).

Therefore, the aim of this planning comparative study was to determine whether a further dose reduction to the heart and LAD could be obtained with proton therapy (either with or without breath-hold).

Materials and methods

We used the same methods as described in our previous planning comparative study comparing conformal photon radiotherapy (3D-CRT) and tangential IMRT (with and without breath-hold) [11]. The current study population consisted of 20 consecutive female breast cancer patients (pT1-2; pN0-1; M0). All patients underwent breast-conserving surgery and axillary staging with a sentinel node procedure.

To avoid interobserver-based delineation differences, the glandular breast tissue was contoured by one experienced radiation oncologist (LKH), according to RTOG delineation guidelines [18], and defined as the CTV. The PTV was created by expanding the CTV with 5 mm in transverse directions, 6 mm cranially, and 9 mm caudally according to the guidelines of our department for 3D-CRT and IMRT. The PTV was retracted 5 mm from the patient surface (PTV_{trim}) to minimize high-dose levels in the buildup regions for IMRT plans. No adaptations for PTV_{trim} were performed in the direction of the lungs, in doing so the thoracic wall may be included in PTV_{trim} . In order to be able to compare the same volumes, we applied the same margins to the proton plans. Furthermore, the heart and the LAD-region were delineated by one experienced radiation oncologist (LKH) and were subsequently reviewed by an experienced cardiac radiologist (MH). All volumes were delineated on each breath-hold scan and free-breathing scan. For the breath-hold scan, the Active Breathing Control (ABC) method was used (ELEKTA Active Breathing CoordinatorTM device, Crawley, United Kingdom) [19]. A high feasibility rate was reported when using the ABC method [10,20]. Details concerning the ABC method were described by Mast et al. [11].

Treatment planning techniques

Tangential IMRT-planning

All IMRT plans were produced by one experienced dosimetrist (HR), who was blinded for the IMPT plans. The applied IMRT technique was a tangential IMRT technique. According to this technique, approximately 60 % of the dose was given with two tangential open fields, and 40 % with four inversely planned tangential IMRT fields using the same gantry angles, with a 'step-and-shoot' technique [11,12]. The nominal energy used was 6 MV in most of the cases, and occasionally 10 MV.

Proton planning

Spot scanning intensity modulated proton therapy (IMPT) plans were planned by two experienced IMPT dosimetrists (HC, PK) using a research version of the Pinnacle3 planning system (version 9.1, Philips Medical Systems, Cleveland, OH, United States). Both were blinded for the IMRT plans. With spot scanning, a pencil beam of protons is regulated in a highdose spot. This spot can be positioned for a specified period of time; by superimposing several spots, the desired radiation dose can be composed. Generally, for protons a RBE of 1.1 is used over the full depth of the proton beam, and the dose is represented as CGE (Cobalt Gray Equivalent, which is Relative Biological Effectiveness (RBE) 9 physical dose in Gy) [15]. In the doses we report here, this RBE has been taken into account.

IMPT dose calculations and field configurations were planned according to Ares et al. [21]. In all plans, the gantry angles were 345° (-15°), 27° , and 75° . The different beams were set to distribute the spots in such a way that no spot was more than 0.2 cm outside the PTV_{trim}. Spots were placed over the PTV_{trim} with 8 mm separation in the plane perpendicular to the beam direction; while in depth, spot layers were positioned and interspaced with 5 mm between each spot.

Energy layers ranged from 7.7 to 23.0 g/cm² (representing the depth of the Bragg peak location) or 100–185 MeV. Corresponding lateral spot sizes ranged approximately from 15 to 8 mm full-width-at-half-maximum at the isocenter in air and without range shifter. A range shifter of 75 mm water equivalent thickness was used so that the spot positions ranged from 2 to 155 mm water equivalent depth. Note that the range shifter and air gap between range shifter and patient skin increase the spot size.

All plans were adapted to the individual target volumes and critical organs, using the “trial-and-error” method.

IMRT and IMPT treatment plan optimization

The prescribed dose was 42.56 Gy in 16 fractions in all cases. For all IMRT and IMPT plans, 97 % of the PTV_{trim} had to be covered by at least 95 % of the prescribed dose with a maximum of 2 % receiving more than 107 % of the prescribed dose [22]. No compromises on the PTV coverage with either of the techniques were made to ensure a fair comparison. For the PTV_{trim}, the following constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy, point dose), and minimum dose (40.6 Gy). The maximum dose (D_{max}) was defined as the maximal dose to a volume of at least 2 % of that specific volume; according to the ICRU 83. All further planning objectives used were similar again to obtain fair dosimetric comparisons between the two techniques. For the purposes of our study, IMRT and IMPT treatment plans based on the breath-hold and free-breathing scans were compared in all patients.

Furthermore, various dose volume parameters of PTV_{trim}, heart, LAD-region, and lung (both lungs as well as the left lung separately) were generated and evaluated. The choice of these dose volume parameters (D_{max}; mean; V5–V30 Gy) was based on those published in the literature [10,22,23]. Finally, all plans were evaluated and approved by two experienced breast cancer radiation oncologists (HS and JM).

Statistics

A Wilcoxon signed-rank test was performed to compare dose and volume differences since the number of eligible cases was less than 30. For this analysis, we used SPSS Statistics version 20.0. The level of statistical significance was defined by a p value of 0.05 (two-sided) for all tests. (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.)

Results

Heart and LAD-region

The mean doses for the heart and LAD-region, for IMRT and IMPT, in breath-hold and free-breathing, in all cases are presented in Figure 1.

Despite the use of tangential IMRT with breath-hold in some patients, the dose to the LAD-region remained relatively high (Table 1; Figure 1). With breath-hold IMRT, still 9 out of 20 patients received a mean dose to the LAD-region exceeding 5 Gy, while in 4 out of 20 patients the dose remained beyond 10 Gy. In 3 patients, the mean heart dose was more than 2 Gy (Figure 1).

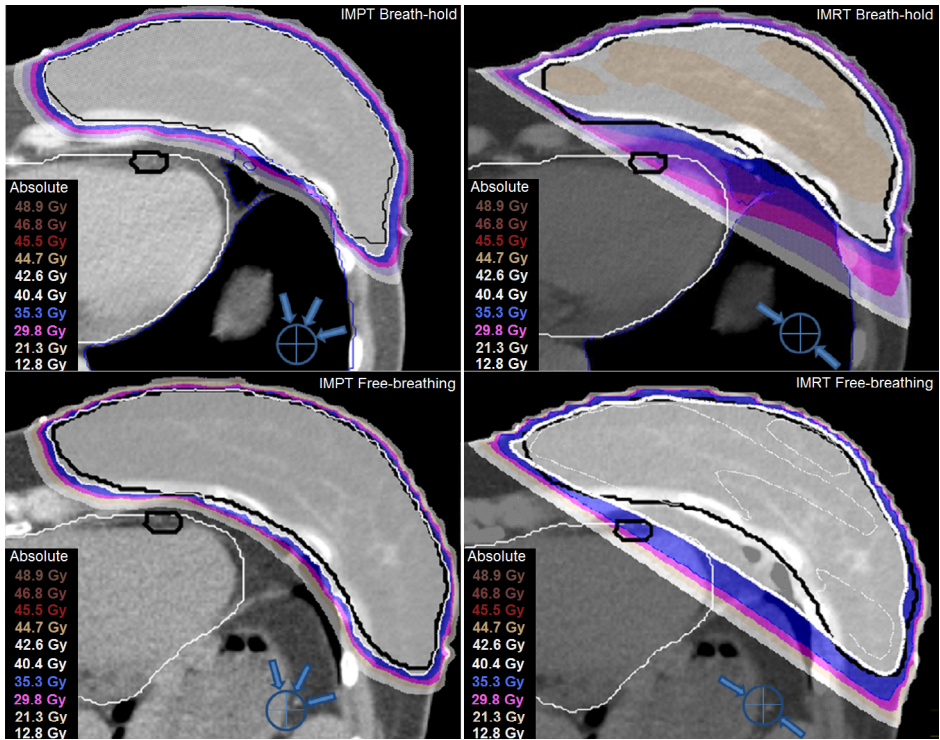


Figure 1 Isodose lines in the caudal part of the patient on the breathhold scan. Delineated organs at risk: white line heart; black line region of the left anterior descending coronary artery. Planning target volume: black line PTV_{trim}; thick white line 95 % isodose line. At the bottom right, the used gantry angles were pointed out, represented by the small arrows.

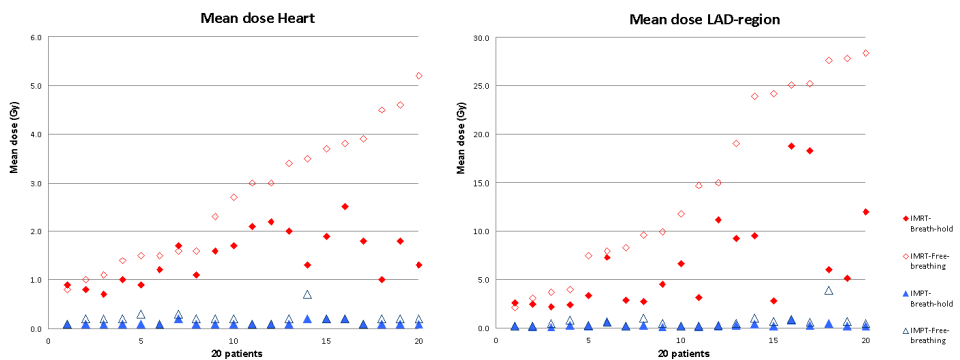


Figure 2 Left: Mean dose administered to the heart. Right: Mean dose administered to the LAD-region; both with intensity modulated radiotherapy (IMRT) and intensity modulated proton therapy (IMPT) in breath-hold (BH) and free-breathing (FB). The cases were rearranged using the increasing (from left to right) IMRT FB technique values.

An additional reduction of the various dose parameters could be obtained with IMPT as well as with breath-hold IMPT. The volume of the heart and LAD-region receiving 20 Gy (V20 Gy) could be reduced to almost zero in all patients (Figure 1 and 2; Table 1).

Lung

As compared to IMRT, the mean lung dose, the V5 Gy, and the V20 Gy in both lungs and in the left lung could be reduced significantly. In particular, the mean V20 Gy value for both lungs could be reduced from 5.1 % (SD 2.2) with breath-hold IMRT to 1.3 % (SD 0.8) with breath-hold IMPT (Table 1).

Table 1. Dose distribution parameters		Mean (SD) (n=20)				p-value	
		BH		FB		BH compared to FB, for both IMPT and IMRT	IMPT compared to IMRT, for both BH and FB
		IMPT	IMRT	IMPT	IMRT		
Heart	Mean (Gy)	0.1 (0)	1.5 (0.5)	0.2 (0.1)	2.7 (1.3)	p < 0.01	p < 0.01
	Dmax (Gy)	0.3 (0.3)	8.6 (6.2)	1.2 (1.7)	24.7 (14.7)	p < 0.01	p < 0.01
	V5Gy (%)	0.1 (0.2)	2.5 (2.1)	0.5 (0.8)	7.4 (4.7)	p < 0.01	p < 0.01
	V20Gy (%)	0	0.6 (0.8)	0.1 (0.2)	3.5 (3.0)	IMPT: p = 0.02 / IMRT: p < 0.01	p < 0.01
	V30Gy (%)	0	0.3 (0.4)	0	2.4 (2.3)	IMPT: p = 1.80 / IMRT: p < 0.01	p < 0.01
LAD-region	Mean (Gy)	0.3 (0.2)	6.7 (5.1)	0.7 (0.8)	14.9 (9.3)	p < 0.01	p < 0.01
	Dmax (Gy)	1.8 (1.9)	18.8 (13.6)	4.5 (3.4)	31.4 (13.0)	p < 0.01	p < 0.01
	V5Gy (%)	0.4 (0.9)	30.3 (25.9)	2.8 (5.8)	54.9 (25.1)	p < 0.01	p < 0.01
	V10Gy (%)	0.1 (0.3)	18.2 (21.5)	0.8 (2.7)	42.9 (26.6)	IMPT: p = 0.04 / IMRT: p < 0.01	p < 0.01
	V20Gy (%)	0	9.7 (15.1)	0.1 (0.6)	32.8 (27.1)	IMPT: p = 0.06 / IMRT: p < 0.01	BH: p = 0.20 / FB: p < 0.01
Bilateral lung	Mean (Gy)	0.8 (0.4)	2.6 (0.9)	0.9 (0.3)	2.9 (1.1)	IMPT: p = 0.10 / IMRT: p < 0.02	p < 0.01
	Dmax (Gy)	14.6 (8.0)	33.4 (5.7)	18.0 (6.9)	35.5 (5.0)	p < 0.05	p < 0.01
	V5Gy (%)	3.6 (1.9)	10.1 (3.1)	4.0 (1.2)	10.1 (3.3)	IMPT: p = 0.08 / IMRT: p = 0.90	p < 0.01
	V20Gy (%)	1.3 (0.8)	5.1 (2.2)	1.5 (0.7)	5.7 (2.6)	IMPT: p = 0.06 / IMRT: p = 0.03	p < 0.01
Lung Left	Mean (Gy)	1.5 (0.6)	5.4 (1.8)	1.6 (0.6)	6.1 (2.3)	IMPT: p = 0.20 / IMRT: p < 0.01	p < 0.01
	Dmax (Gy)	23.6 (8.2)	37.1 (2.8)	27.0 (7.0)	38.7 (2.3)	p < 0.04	p < 0.01
	V5Gy (%)	7.1 (2.7)	21.4 (6.6)	7.7 (2.7)	21.9 (7.1)	IMPT: p = 0.17 / IMRT: p = 0.59	p < 0.01
	V20Gy (%)	2.5 (1.4)	10.9 (4.7)	2.8 (1.4)	12.4 (5.7)	IMPT: p = 0.04 / IMRT: p = 0.02	p < 0.01
PTV _{trim}	V95% (%)	99.6 (0.32)	97.9 (0.15)	99.7 (0.19)	97.9 (0.18)	IMPT: p = 0.09 / IMRT: p = 0.70	p < 0.01
	V107% (%)	0	0.4 (1.0)	0	0.2 (0.4)	IMPT: p = 1.00 / IMRT: p = 0.47	p < 0.02

Table 1. Non-significant data is presented in bold. BH breath-hold, FB free-breathing, IMPT intensity modulated proton therapy, IMRT intensity modulated radiotherapy, V5, V10, V15, V20, V30, and V40 Gy volume receiving 5, 10, 15, 20, 30, and 40 Gy, respectively, Dmax dose encompassing 2 % of the volume. V95 % and V107 % volume receiving 95 and 107 % of the prescribed dose, respectively.

Discussion

The main objective of this study was to investigate if the dose to the heart and LAD-region could be reduced using spot scanning IMPT. The results showed that, with both IMPT techniques (with and without breath-hold), the doses to the heart as well as to the LAD-region could be reduced significantly compared to IMRT with breath-hold. This could be achieved without compromising the doses to the target volumes. It should be stressed that, with IMPT, a further reduction to almost zero to the heart and LAD-region could be obtained in the majority of cases. The results show that a breath-hold technique had no added value when using IMPT. However, using breath-hold may improve the robustness of the IMPT technique, since the tissue shift will be less in breath-hold. Protons are more sensitive than photons to the effects of motion due to the range of the Bragg Peak. When using a proton field from a perpendicular direction, a tissue shift could cause thickness changes and thus range changes.

Recently Darby et al. reported a dose–effect relationship between the dose to the heart and the rate of major coronary events [6]. The authors could not identify any threshold dose for the development of coronary events, emphasizing the need to reduce the dose to as low as possible. The average mean heart dose of the left-sided breast cancer patients in their cohort was 6.6 Gy [6]. However, we noted lower mean heart doses with our tangential IMRT (2.7 Gy with free-breathing and 1.5 Gy with breath-hold). With IMPT further reductions could be obtained (0.2 Gy with free-breathing and 0.1 Gy with breath-hold).

Our study compares two techniques using the same fractionation scheme, with a fraction dose of 2.66 Gy and a total dose of 42.65 Gy. However, if the effects on reduction in cardiac dose of this study are being compared to the results of other planning studies, this needs to be taken into account.

It has been shown that decreasing of the mean heart dose is relevant [6]. The lifetime risk of radiation-induced ischemic heart disease for breast cancer patients increases linearly with an increase of the mean dose to the heart of 7.4 % per Gy (95 % confidence interval, 2.9–14.5) [6]. Consequently, the baseline risk should be taken into account. Recently, Duma et al. [24] approximated the increased rate of absolute radiation-induced ischemic heart disease by using the tables of the Darby publication [6]. They reported that, irradiating a 50-year-old breast cancer patient without cardiac risk factors with a mean heart dose of 3 Gy, the risk of having at least one acute coronary event by the age of 80 years rises from 4.5 to 5.4 %. They subsequently noted that in the presence of pre-existent cardiac risk factors, the risk of having at least one acute coronary event by the age of 80 years would rise from 8 to 9.7 %. If the mean heart dose would be 10 Gy and in the presence of cardiac risk factors, this risk would increase from 8 to 13.5 % [24]. Although, with breath-hold IMPT, the mean heart dose could be reduced to almost zero, the question arises whether all left-sided breast cancer patients will have clinically relevant benefit from proton irradiation. Recently, Langendijk et al. described the so-called modelbased approach, to define which patients could be selected for proton therapy. In this model-based approach, the estimated benefit in terms of risk reduction can be obtained by integrating dose differences in prediction models [25]. The excess risk on ischemic heart disease depends on the dose, and the relative increase per Gy is independent of the baseline risk on cardiac events, meaning that the absolute excess risk can be easily estimated by calculating the baseline risk, e.g., the Reynolds score [26], in addition to the mean heart dose.

Apart from the mean heart dose, there are data suggesting that the dose to the LAD coronary artery is most at risk for developing atherosclerosis after left-sided breast-conserving radiotherapy due to its anatomical position in relation to the breast [7]. In the current study, the average mean dose to the LAD-region was 6.7 Gy with breath-hold IMRT which could be reduced to 0.3 Gy with breath-hold IMPT. These doses are lower when compared to the mean LAD doses of 20 and 9.4 Gy, without using breath-hold [6, 8]. It should be noted that the methodologies of defining the LAD or LAD-region varied widely among these three studies [6,8,11].

As in most treatment planning comparative studies, some critical notes also apply to this study. First, set-up errors and geometric changes during radiation treatment are more likely to affect the dose distributions when using IMPT. It should be noted that the effect of range uncertainties and patient breathing motion using IMPT were relatively small, as shown by Ares et al. [21] which is in line with the results of Xu et al. [27]. However, Wang et al. compared a passive scattered proton beam with a spot scanning IMPT technique and stated that IMPT is more sensitive for set-up uncertainties and breathing motion [28]. With advanced position verification procedures and adaptive treatment strategies in combination with a breath-hold technique, these uncertainties are expected to be minimized. Furthermore, as pointed out by other authors, set-up errors and range uncertainties need to be accounted for by applying robust IMPT treatment planning techniques rather than by using the traditional CTV-PTV margin concept [29,30].

Second, some authors reported higher skin dose when using protons and, hence, worse cosmetic outcome can be expected. Girodet et al. reported worse cosmetic outcome in accelerated partial breast irradiation (APBI) when using protons. However, they used a single field per treatment and stated that multiple proton beam scanning and advances in patient set-up could result in decreased margins [31]. In our planning comparative study, we were not able to compare the dose to the skin since a treatment planning system is not able to adequately calculate the dose to the skin. Therefore, the clinical experience when using protons in breast cancer treatment is of importance. Several phase-II studies report on the cosmetic results after proton beam therapy [31,32].

Third, for the current study, we decided to use tangential IMRT with 60 % of the dose given with two open tangential fields. Further dose reductions to the heart could be obtained by using IMRT with a larger degree of freedom. However, in most cases this can only be achieved at the expense of dose to other OARS and normal tissue [20, 33]. Ares et al. showed that, using proton irradiation, in left-sided breast cancer the dose to the OARs can significantly be reduced when compared to photons [21]. As yet, no planning study has compared proton and photon irradiation in combination with breath-hold in left-sided breast cancer radiotherapy. In most departments, a 3D-CRT photon technique is considered the current standard. However, recently it has been shown that tangential IMRT with breath-hold further reduces the dose to the heart and LAD-region without increasing the dose to other normal tissues [11].

Based on the radiation principles that dose should be “As Low As Reasonably Achievable” (ALARA) there is no doubt that patients will benefit from protons at least to some extent. Due to limited accessibility of proton therapy and higher costs, it will not be feasible to offer protons to all breast cancer patients. A model-based approach will enable the identification of patients who will benefit most from this new technology and thus will ensure a more costeffective use. For all other left-sided breast cancer patients, a tangential IMRT technique with breath-hold can be used to reduce the dose to the heart

and LAD-region. In future, it may be possible to make choices based on individual planning comparisons in order to individualize the radiation treatment.

Conclusion

In left-sided breast cancer irradiation, IMPT is the most promising technique to maximally reduce the dose to heart and LAD-region, even without a breath-hold technique. However, as IMPT for breast cancer is currently not widely available, IMPT should be reserved for patients remaining at high risk for major coronary events.

Acknowledgments

We thank T. F. H. Vissers for bibliographical assistance and J. F. D. Bouricius for critically editing this article.

Conflict of interest

The authors have nothing to disclose and indicate no potential conflict of interest.

Open Access

This article is distributed under the terms of the Creative Commons Attribution Non-commercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P (2011) Effect of radiotherapy after breast surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 378(9804):1707–1716.
2. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366(9503):2087–2106.
3. Kyndi M, Overgaard M, Nielsen HM, Sørensen FB, Knudsen H, Overgaard J (2009) High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol* 90(1):74–79.
4. Darby SC, McGale P, Taylor CW, Peto R (2005) Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 6(8):557–565.
5. Hooning MJ, Botma A, Aleman BM et al (2007) Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 99(5):365–375.
6. Darby SC, Ewertz M, McGale P et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 368(11):987–998.
7. Nilsson G, Holmberg L, Garmo H et al (2012) Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 30(4):380–386.
8. Taylor CW, Povall JM, McGale P et al (2008) Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 72(2):501–507.
9. Schubert LK, Gondi V, Sengbusch E et al (2011) Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and tomotherapy. *Radiother Oncol* 100(2):241–246.
10. Swanson T, Grills IS, Ye H et al (2013) Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 36(1):24–30.
11. Mast ME, van Kempen-Hartevelde L, Heijenbrok MW et al (2013) Left-sided breast cancer radiotherapy with and without breathhold: does IMRT reduce the cardiac dose even further? *Radiother Oncol* 108(2):248–253.
12. van Asselen B, Schwarz M, van Vliet-Vroegindewij C, Lebesque JV, Mijnheer BJ, Damen EM (2006) Intensity-modulated radiotherapy of breast cancer using direct aperture optimization. *Radiother Oncol* 79(2):162–169.
13. Levin WP, Kooy H, Loeffler JS, DeLaney TF (2005) Proton beam therapy. *Br J Cancer* 93:849–854.
14. Weber DC, Ares C, Lomax AJ et al (2006) Radiation therapy planning with photons and protons for early and advanced breast cancer: an overview. *Radiat Oncol* 20(1):22.
15. Moon SH, Shin KH, Kim TH et al (2009) Dosimetric comparison of four different external beam partial breast irradiation techniques: three dimensional conformal radiotherapy, intensitymodulated radiotherapy, helical tomotherapy, and proton beam therapy. *Radiother Oncol* 90(1):66–73.
16. Hoppe BS, Flampouri S, Su Z et al (2012) Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 84(2):449–455.
17. Mukesh MB, Barnett GC, Wilkinson JS et al (2013) Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *Am J Clin Oncol* 31(36):4488–4497
18. <http://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE%3d&tabid=236>; visited 13 June 2014.

19. Remouchamps VM, Letts N, Vicini FA et al (2003) Initial clinical experience with moderate deep-inspiration breath-hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 56(3):704–715.
20. Mast ME, van der Klein JN, van Geen S et al (2012) Een hartsparende bestralingstechniek bij vrouwen met linkszijdige borstkanker. De resultaten van vier jaar ervaring in Radiotherapiecentrum West. *Ned Tijdschr Oncol* 9(6):270–276.
21. Ares C, Khan S, Macartain AM et al (2010) Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 76(3):685–697.
22. Borst GR, Sonke JJ, den Hollander S et al (2010) Clinical results of image-guided deep inspiration breath-hold breast irradiation. *Int J Radiat Oncol Biol Phys* 78(5):1345–1351.
23. Tan W, Liu D, Xue C et al (2012) Anterior myocardial territory may replace the heart as organ at risk in intensity-modulated radiotherapy for left-sided breast cancer. *Int J Radiat Oncol Biol Phys* 82(5):1689–1697.
24. Duma MN, Molls M, Trott KR (2014) From heart to heart for breast cancer patients: cardiovascular toxicities in breast cancer radiotherapy. *Strahlenther Onkol* 190(1):5–7.
25. Langendijk JA, Lambin P, De Ruyscher D, Widder J, Bos M, Verheij M (2013) Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol* 107(3):267–273.
26. Ridker PM, Buring JE, Rifai N, Cook NR (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 297(6):611–619.
27. Xu N, Ho MW, Li Z, Morris CG, Medenhall NP (2013) Can proton therapy improve the therapeutic ratio in breast cancer patients at risk for nodal disease? *Am J Clin Oncol*. 2014;37(6):568-574.
28. Wang X, Zhang X, Li X et al (2013) Accelerated partial-breast irradiation using intensity-modulated proton radiotherapy: do uncertainties outweigh potential benefits? *Br J Radiol*86:1029–1040.
29. Unkelbach J, Bortfeld T, Martin BC et al (2009) Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. *Med Phys* 36:149–163.
30. Fredriksson A, Forsgren A, Hårdemark B (2011) Minimax optimization for handling range and setup uncertainties in proton therapy. *Med Phys* 38:1672–1684.
31. Galland-Girodet S, Pashtan I, MacDonald SM et al (2014) Longterm cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1 trial. *Int J Radiat Oncol Biol Phys*. 90(3):493-500.
32. Bush DA, Do S, Lum S et al (2014) Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys*. 90(3):501-505.
33. Borges C, Cunha G, Monteiro-Grillo I, Vaz P, Teixeira N (2014) comparison of different breast planning techniques and algorithms for radiation therapy treatment. *Phys Med* 30(2):160–170.

Tangential IMRT versus TomoTherapy with and without breath-hold in left-sided whole breast irradiation

Mirjam Mast^a, Truus Reynders^b, Mark Heijenbrok^c, Loes van Kempen-Harteveld^a, Hilde Van Parijs^b, Hans Rozema^a, Anna Petoukhova^a, Dirk Verellen^b, Mark De Ridder^b and Henk Struikmans^{b,d}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Radiotherapy Department, Oncology Center, UZ Brussel, Brussels, Belgium;

^c Department of Radiology, Medical Center Haaglanden, The Hague, The Netherlands;

^d Department of Clinical Oncology, Leiden University Medical Center, The Netherlands.

Acta Oncol Accepted 26-04-2015

Abstract

Purpose

Active Breathing Control enables a decrease of cardiac and Left Anterior Descending (LAD) coronary artery dose in left-sided breast cancer radiotherapy. Applying a tangential IMRT technique results in an additional decrease in these organs of risk (OAR). Other studies showed that TomoTherapy decreases the dose in the OARs when compared to tangential IMRT. We investigated whether TomoTherapy enables an additional decrease of cardiac dose in radiotherapy plans with and without breath-hold (BH).

Materials and methods

We compared tangential Intensity Modulated Radiotherapy (IMRT) and TomoTherapy treatment plans based on free-breathing (FB) as well as on BH. Twenty patients referred for whole breast irradiation were included. The glandular breast tissue, heart and LAD-region were contoured. Four treatment plans were generated: FB_IMRT; FB_TomoTherapy; BH_IMRT; BH_TomoTherapy. Several doses were obtained from Dose Volume Histograms and compared.

Results

For the mean dose in the heart and LAD-region a significant reduction of the dose was found when using TomoTherapy instead of tangential IMRT in both breath-hold and free-breathing. For the LAD-region TomoTherapy in breath-hold resulted in a significant lower mean dose of 4.9 Gy, with tangential IMRT in breath-hold a mean dose of 6.7 Gy was found. The doses in the contralateral lung, both lungs and planning target volume (PTV) were comparable for both techniques in breath-hold. However, for the V107% in the PTV significant lower doses were found when using TomoTherapy in breath-hold.

Conclusion

In daily clinical practice tangential IMRT in breath-hold is the preferred technique to maximally reduce the dose to heart and LAD-region in left-sided whole breast irradiation.

Introduction

Whole breast irradiation (WBI), with or without a boost dose, is seen as the standard therapy after breast conserving surgery. But WBI may, amongst others, induce ischaemic heart disease. The incidence of ischaemic heart disease appears to be proportional to the mean dose to the heart and starts within a few years after exposure [1]. It is, therefore, of importance to define the most optimal radiation treatment technique for left-sided WBI. The aims are achieving the lowest dose in the critical structures as well as achieving optimal target coverage.

Using a breath-hold technique during left-sided breast cancer radiotherapy reduces the dose in the heart [2]. Tangential beam intensity modulated radiotherapy (IMRT) in combination with a breath-hold technique, when compared to 3D-CRT with breath-hold, resulted in a significantly larger decrease of the dose in the heart and left anterior descending coronary (LAD) artery [3]. However, others reported that TomoTherapy resulted in less dose in the critical structures when compared to tangential IMRT [4, 5]. The question is, does this finding still hold when tangential IMRT is used with a breath-hold technique?

The aim of this comparative planning study, therefore, was to determine whether a further dose reduction to the heart and the LAD-region could be obtained with TomoTherapy compared to tangential IMRT, with (and without) breath-hold.

Materials and methods

The study population consisted of 20 consecutive female breast cancer patients (pT1-2; N0-1; M0). All patients underwent breast-conserving surgery. Axillary staging was carried out by performing a sentinel node biopsy. We used the same methods as described in our former treatment planning comparison studies 3D-CRT and tangential IMRT (with and without breath-hold), and comparing tangential IMRT to proton therapy (with and without breath-hold) in the Pinnacle3 planning system (Philips Medical Systems, Cleveland, OH, United States). The delineated volumes were described in these studies as well [3, 6].

The PTV was retracted 5 mm from the patient surface (PTV_{trim}) [3, 6], in order to be able to compare the same volumes; we applied the same margins to the TomoTherapy plans. For all tangential IMRT and TomoTherapy plans, 97% of the PTV_{trim} had to be covered by at least 95% of the prescribed dose with a maximum of 2% receiving more than 107% of the prescribed dose [7]. No compromises on the PTV coverage with either of the techniques were made to ensure a fair comparison. The prescribed dose was 42.56 Gy in 16 fractions in all cases.

Tangential IMRT-planning

With the applied tangential IMRT technique, approximately 60% of the dose was given with two tangential open fields, and 40% with four inversely planned tangential IMRT fields, using the same gantry angles, with a ‘step-and-shoot’ technique [8]. The nominal energy used was 6 MV in most of the cases, and occasionally 10 MV.

For the PTV_{trim} the following constraints were used: uniform dose (42.56 Gy), maximum dose (45.5 Gy, point dose) and minimum dose (40.6 Gy). The maximum dose (D_{max}) was defined as the maximal dose to a volume of at least 2% of that specific volume; according to ICRU 83.

For tangential IMRT and TomoTherapy treatment plans, based on the breath-hold as well as on the free-breathing scans, were compared in all patients. Furthermore, various

dose volume parameters of PTV_{trim} , heart, LAD-region and lung (both lungs as well as the left lung separately) were generated and evaluated, and were the same as in the earlier study [3].

For treatment optimisation, the Direct Machine Parameter Optimization (DMPO) [7] was used with the following criteria: the maximum number of segments was restricted to 12 (to achieve a better sparing of the critical structures; and to keep the same time slot as for conventional treatment, in order to make a breath-hold treatment feasible); the minimum segment area was set to 9 cm². For the heart we started defining a maximum dose (point dose) of 20 Gy; after which the weights for the heart and LAD-region were set individually per patient to make a maximum sparing of these structures possible. All plans were calculated with a Collapsed Cone algorithm.

TomoTherapy planning

The TomoTherapy Hi-ART treatment planning system used a different set of factors than Pinnacle to control the dose administration. For treatment, only ‘tight’ pitch factors were applied between 0.25 and 0.30. The primary collimation jaws were set to a field width of 2.45 cm at isocentre to determine the fan beam width. A modulation factor of 2.0 was used for all plans. Using TomoTherapy for breast cancer cases demands the addition of a constraint to the contralateral breast. Since TomoTherapy is a rotational technique, the contralateral breast needs to be avoided. This technique was also used in another planning comparison study. We used these dose constraints which were described by Reynders et al. [9].

Statistics

A Wilcoxon Signed Rank Test was carried out to compare dose and volume differences, since the number of eligible cases was less than 30. For the convenience of comparison the values in Table 1 were averaged over twenty patients. For this analysis, we used SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). The level of statistical significance was defined by a p-value of ≤ 0.05 (two-sided) for all tests.

Results

For the mean dose in the heart a significant reduction of the dose was found when using TomoTherapy instead of IMRT in both breath-hold and free-breathing. The mean dose for TomoTherapy in breath-hold was reduced to 1.1 Gy compared to 1.5 Gy when using IMRT. For the LAD-region TomoTherapy in breath-hold, when compared to IMRT in breath-hold, resulted in a significant lower mean dose of 4.9 Gy versus 6.7 Gy, respectively. See the Table 1 and Figure 1.

For the other dose-volume values (V5Gy, V10Gy, V20Gy, V30Gy) no significant differences were noted between the two techniques for the heart and LAD-region, when using breath-hold. With breath-hold in both IMRT and TomoTherapy, a significant lower dose could be achieved in all dose-volume values, see Table 1.

The doses in the contralateral lung and both lungs were comparable for both techniques in breath-hold; a mean dose of 5.2 Gy and 5.4 Gy was found for the left lung for TomoTherapy and IMRT, respectively. For PTV_{trim} comparable dose values were found for both techniques as well; however, for the V107% significant lower doses were found when using TomoTherapy in breath-hold. See Table 1.

Dose distribution parameters		Mean (SD) (n=20)				p-value	
		BH		FB		BH compared to FB, for both IMRT and Tomo	IMRT compared to Tomo, for both BH and FB
		Tomo	IMRT	Tomo	IMRT		
Heart	Mean (Gy)	1.1 (0.4)	1.5 (0.5)	2.1 (1.0)	2.7 (1.3)	p < 0.01	p < 0.01
	Dmax (Gy)	6.5 (5.4)	8.6 (6.2)	17.0 (9.7)	24.7 (14.7)	p < 0.01	p < 0.01
	V5Gy (%)	2.1 (1.8)	2.5 (2.1)	6.9 (4.2)	7.4 (4.7)	p < 0.01	BH: p = 0.06 / FB: p = 0.55
	V20Gy (%)	0.4 (0.6)	0.6 (0.8)	1.9 (1.9)	3.5 (3.0)	p < 0.01	p < 0.03
	V30Gy (%)	0.1 (0.2)	0.3 (0.4)	0.6 (1.0)	2.4 (2.3)	p < 0.01	BH: p = 0.06 / FB: p < 0.01
LAD-region	Mean (Gy)	4.9 (3.8)	6.7 (5.1)	11.3 (6.7)	14.9 (9.3)	p < 0.01	p < 0.01
	Dmax (Gy)	15.0 (11.2)	18.8 (13.6)	27.1 (11.2)	31.4 (13.0)	p < 0.01	p < 0.04
	V5Gy (%)	26.3 (23.9)	30.3 (25.9)	55.2 (23.4)	54.9 (25.1)	p < 0.01	BH: p = 0.05 / FB: p = 1.0
	V10Gy (%)	15.3 (18.2)	18.2 (21.5)	40.8 (24.9)	42.9 (26.6)	p < 0.01	p > 0.10
	V20Gy (%)	5.4 (9.7)	9.7 (15.1)	22.4 (22.2)	32.8 (27.1)	p < 0.01	BH: p = 0.05 / FB: p < 0.01
Bilateral lung	Mean (Gy)	2.7 (0.8)	2.6 (0.9)	2.8 (0.9)	2.9 (1.1)	IMRT: p = 0.02 / Tomo: p = 0.79	p > 0.10
	Dmax (Gy)	37.5 (3.4)	33.4 (5.7)	29.7 (8.0)	35.5 (5.0)	p < 0.01	p < 0.01
	V5Gy (%)	10 (2.4)	10.1 (3.1)	11 (2.3)	10.1 (3.3)	IMRT: p > 0.10 / Tomo: p < 0.02	BH: p > 0.10 / FB: p < 0.02
	V20Gy (%)	4.9 (1.9)	5.1 (2.2)	4.4 (2.5)	5.7 (2.6)	IMRT: p < 0.03 / Tomo: p > 0.10	BH: p > 0.10 / FB: p < 0.04
Lung Left	Mean (Gy)	5.2 (1.5)	5.4 (1.8)	5.3 (1.8)	6.1 (2.3)	IMRT: p < 0.01 / Tomo: p > 0.10	p > 0.10
	Dmax (Gy)	37.5 (3.4)	37.1 (2.8)	34.1 (6.1)	38.7 (2.3)	IMRT: p > 0.10 / Tomo: p < 0.02	p < 0.03
	V5Gy (%)	20.5 (5)	21.4 (6.6)	23.0 (5)	21.9 (7.1)	IMRT: p > 0.10 / Tomo: p < 0.01	p > 0.10
	V20Gy (%)	9.8 (3.9)	10.9 (4.7)	8.8 (5.2)	12.4 (5.7)	IMRT: p < 0.02 / Tomo: p > 0.10	BH: p > 0.10 / FB: p < 0.02
PTV _{trim}	V95% (%)	98.2 (1.0)	97.9 (0.15)	97.8 (1.4)	97.9 (0.18)	p > 0.10	p > 0.10
	V107% (%)	0	0.4 (1.0)	0 (0.1)	0.2 (0.4)	p > 0.10	BH: p = 0.03 / FB: p = 0.06

Table 1. Non-significant data is presented in bold. BH breath-hold; FB free-breathing; IMRT intensity modulated radiotherapy; Tomo TmoTherapy; V5, V10, V15, V20, V30, and V40 Gy volume receiving 5, 10, 15, 20, 30, and 40 Gy, respectively; Dmax dose encompassing 2 % of the volume; V95 % and V107 % volume receiving 95 and 107 % of the prescribed dose, respectively.

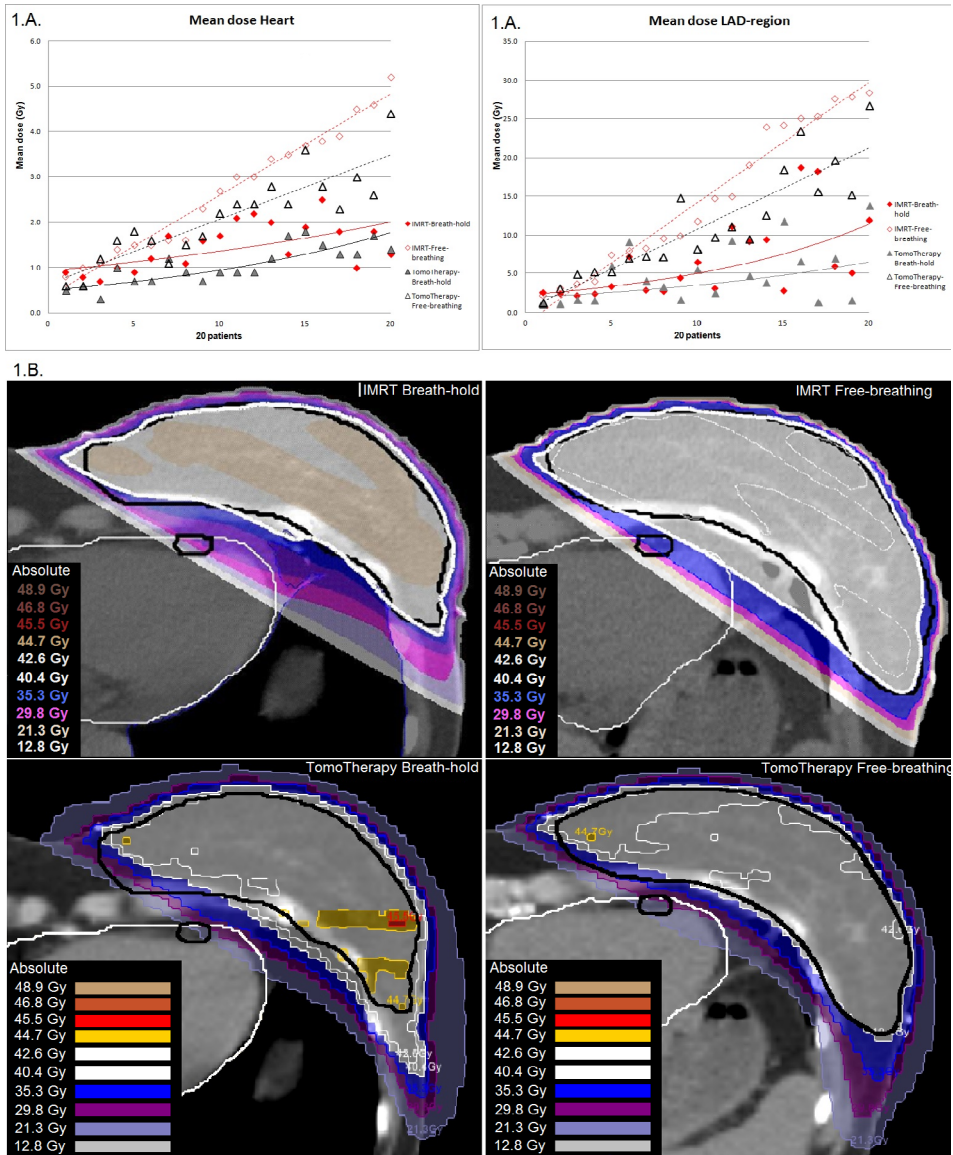


Figure 1A: Left: Mean dose administered to the heart in breath-hold and free-breathing for Intensity Modulated Radiotherapy (IMRT) and TomoTherapy (Tomo). Right: Mean dose administered to the LAD-region in breath-hold and free-breathing for Intensity Modulated Radiotherapy (IMRT) and TomoTherapy (Tomo). The cases were rearranged using the increasing (from left to right) IMRT FB technique values. For the convenience of comparison regression lines were added in the graphs.

Figure 1B: Isodose lines in the caudal part of the patient on the breath-hold scan. Delineated Organs at Risk: white line = heart; thick black line = region of the Left Anterior Descending coronary artery; Planning Target Volume: black line = PTV_{min}; 95% isodose = thick white line. Left: IMRT and TomoTherapy in breath-hold. Right: IMRT and TomoTherapy in free-breathing.

Discussion

The results show that, with TomoTherapy in breath-hold, when compared to tangential IMRT in breath-hold, the mean doses to the heart as well as to the LAD-region could be reduced significantly. This was achieved without compromising the doses to the target volumes. For the other dose values both techniques in breath-hold were comparable. The difference between the mean heart dose when using a tangential IMRT technique in breath-hold compared to TomoTherapy in breath-hold, was limited 1.5Gy (SD 0.5Gy) and 1.1Gy (SD 0.4Gy), respectively. However, it should be emphasised that the combination of a breath-hold technique with TomoTherapy cannot be performed in daily clinical practice, due to the longer beam-on time (a TomoTherapy treatment session in free-breathing fraction lasts about 20 minutes) and rotating technique [9]. Therefore, TomoTherapy can only be applied without breath-hold. We also showed, that less dose to the heart and LAD-region will be administered when using tangential IMRT in breath-hold compared to TomoTherapy in free-breathing, see Figure 1. Theoretically, the tangential IMRT technique could be optimised. A higher dose reduction to the heart could be achieved by using a multiple field IMRT technique. However, Borges et al., reported that this could only be achieved at the expense of a higher dose in OARs and normal tissue [10]. Furthermore, we did not evaluate the dose in the contralateral breast as this item was analysed in other studies. Shiau et al. found no significant difference in mean doses in the contralateral breast between TomoTherapy and tangential IMRT. However, as the low dose (V5Gy) in the contralateral breast was higher for TomoTherapy compared to tangential IMRT, this should be taken into account when using a TomoTherapy technique [5]. Recently, TomoDirect was introduced, allowing the administration of radiation using fixed gantry angles. As Qi et al. described in their study, the TomoDirect technique leads to less dose in the contralateral breast compared to helical TomoTherapy [11]. Finally, we underline the statement of Qi et al., that individualised radiation treatment is of importance and that the appropriate radiation technique needs to be selected according to the patients risk factor [11].

Conclusion

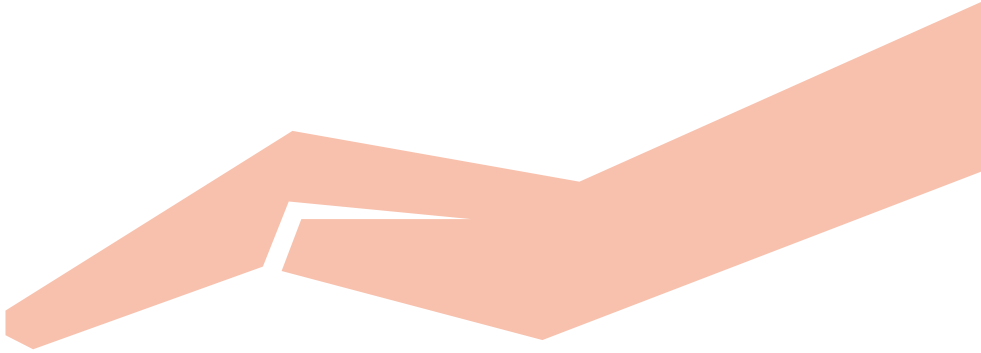
In daily clinical practice tangential IMRT in breath-hold is the preferred technique to maximally reduce the dose to heart and LAD-region in left-sided whole breast irradiation.

Acknowledgements

We thank T.F.H. Vissers for bibliographical assistance, J. van Egmond for his assistance with Excel, K. Leysen for her assistance with the figures and J.F.D. Bouricius for critically editing this article.

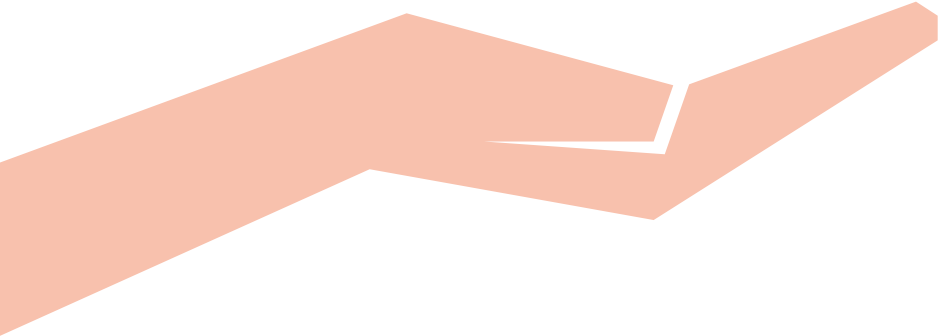
References

1. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368(11):987-998.
2. Swanson T, Grills IS, Ye H, et al. Six-year Experience Routinely Using Moderate Deep Inspiration Breath-hold for the Reduction of Cardiac Dose in Left-sided Breast Irradiation for Patients With Early-stage or Locally Advanced Breast Cancer. *Am J Clin Oncol* 2013; 36(1):24-30.
3. Mast ME, van Kempen-Harteveld L, Heijenbrok MW, et al. Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? *Radiother Oncol* 2013; 108(2):248-53.
4. Coon A, Dickler A, Kirk MC, et al. TomoTherapy and multifield intensity-modulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavorable cardiac anatomy. *Int. J. Radiation Oncology Biol. Phys.* 2010; 78(1):104-110.
5. Shiau A, Hsieh C, Tien H, et al. Left-Sided Whole Breast Irradiation with Hybrid-IMRT and Helical Tomotherapy Dosimetric Comparison *BioMed Res Int.* 2014, 741326.
6. Mast ME, Vredeveld EJ, Credoe H, et al. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. *Breast Cancer Res Treat* 2014;148(1):33-9.
7. Borst GR, Sonke JJ, den Hollander S, et al. Clinical results of image-guided deep inspiration breath-hold breast irradiation. *Int J Radiat Oncol Biol Phys* 2010; 78(5):1345-1351.
8. van Asselen B, Schwarz M, van Vliet-Vroegindeweyj C, Lebesque JV, Mijnheer BJ, Damen EM. Intensity-modulated radiotherapy of breast cancer using direct aperture optimization. *Radiother Oncol* 2006; 79(2):162-169.
9. Reynders T, Tournel K, De Coninck P, et al. Dosimetric assessment of static and helical TomoTherapy in the clinical implementation of breast cancer treatments 2009; 93(1):71-79.
10. Borges C, Cunha G, Monteiro-Grillo I, Vaz P, Teixeira N. Comparison of different breast planning techniques and algorithms for radiation therapy treatment. *Phys Med* 2014; 30(2):160-70.
11. Qi XS, Liu TX, Liu AK, et al. Left-sided breast cancer irradiation using rotational and fixed- field radiotherapy *Medical Dosimetry* 2014; 39:227-234.



CHAPTER 3

Vascular heart damage before and after
whole breast irradiation



Preradiotherapy Calcium Scores of the Coronary Arteries in a Cohort of Women with Early-Stage Breast Cancer: A Comparison with a Cohort of Healthy Women

Mirjam Mast^a, Mark Heijenbrok^b, Anna Petoukhova^a, Astrid Scholten^c,
Joop Schreur^d and Henk Struikmans^{a,c}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of Radiology, Medical Center Haaglanden, The Hague,
The Netherlands;

^c Department of Clinical Oncology, Leiden University Medical Centre,
Leiden, The Netherlands;

^d Department of Cardiology, Medical Center Haaglanden, The Hague,
The Netherlands

Int J Radiat Oncol Biol Phys 2012;83(3):853-858

Abstract

Purpose

Breast cancer radiotherapy has been associated with an increased risk of cardiac toxicity. However, no data are available on the probability of developing coronary artery disease (CAD) in breast cancer patients when compared with healthy women. Therefore, baseline coronary artery calcium (CAC) scores, as an accepted tool to predict CAD, were determined and compared with the CAC scores of a healthy, asymptomatic cohort, the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.

Materials and methods

Eighty consecutive patients with ductal carcinoma in situ or infiltrative breast cancer referred for radiotherapy after breast-conserving surgery were included in our study. Their cardiovascular risk profile was registered, and a 64 multislice CT scan was performed. The CAC scores of an unselected (Caucasian only) Radiotherapy Centre West (RCWEST) cohort, as well as of those of a selected (comorbidity and race adjusted) RCWEST cohort, were determined. The scores of both cohorts were compared with those of the female (Caucasian only) MESA cohort.

Results

For the unselected RCWEST cohort (n = 62) we found significant ($p < .01$) higher scores for women in the 55-64 age category compared with those of the MESA cohort. In the selected cohort (n = 55) the CAC scores of the women in the age category 55-64 were significantly ($p = .02$) higher compared with the MESA cohort. No significant differences were noted in the other age categories.

Conclusion

Both cohorts revealed that CAC scores in the 55-64 age category were significantly higher than the CAC scores in the asymptomatic (female) MESA population. These data suggest that breast cancer patients bear a higher risk of developing coronary heart disease before the start of radiotherapy. Therefore, measures to decrease cardiac dose further in breast cancer radiotherapy are even more important.

Introduction

According to the data of the Early Breast Cancer Trialists Collaborative Group, breast cancer radiotherapy, as it was administered in 1970-1990, was associated with an increased risk of fatal cardiovascular events (1). This finding was confirmed in a retrospective study in the Dutch Late Effects Breast Cancer cohort (2). Taylor et al. concluded that the heart dose from lefttangential radiotherapy had decreased considerably over the past 40 years. However, they also noted that for approximately half of left-sided patients, part of the heart still receives ≥ 20 Gy and found that the left anterior descending coronary artery, of all main coronary arteries, received the highest dose (3). Marks et al. found that the radiation induced heart perfusion defects are located in the anterior parts of the left ventricle (4). These data indicate that even today, left-sided breast cancer radiotherapy is potentially harmful to the heart, and specifically to the left anterior descending coronary artery. This is relevant because radiotherapy is frequently applied in the primary treatment of breast cancer. In a Dutch population-based study, it was shown that about 63% of women with breast cancer received radiotherapy as part of their primary treatment (5).

However, no data are available on the frequency of risk factors predicting the probability of coronary artery disease (CAD) for the group of women diagnosed with early-stage breast cancer before starting radiotherapy. Specifically, when compared with healthy women, no data are available on the number of CAC (i.e., coronary artery calcium, or CAC) deposits. Therefore, in our study, these baseline CAC scores were compared with the CAC scores of a healthy female population. In doing so, the CAC scores in 80 consecutive female breast cancer patients were compared with the CAC scores of a healthy, asymptomatic female cohort, the MESA cohort (6).

The reasons for the use of CAC scores in our study design were as follows: a number of studies concluded that the amount of calcium deposits in the coronary arteries predicts the risk of subsequent cardiovascular events in cases without symptomatic CAD (7-11). Furthermore, Pletcher et al. stated in their systematic review and meta-analyses that CAC is an independent predictor of CAD (7). Finally, it was suggested that CAC deposits can be useful in deciding whether further diagnostic testing is necessary in asymptomatic patients or patients with nonanginal chest pain and was shown that low-dose CT has proved to be a sensitive, noninvasive method for quantifying CAC deposits (8). With this study we attempted to identify differences in CAC scores for several cohorts to assess the risk on CAD before starting the radiation treatment.

Materials and methods

From September 2008 until October 2010, 80 women were included in this study. Consecutive patients with either ductal carcinoma in situ (< 4 cm) or infiltrative breast cancer (< 5 cm) and treated with breast-conserving surgery were considered eligible. If indicated, chemotherapy started after radiotherapy. The study was approved by the local ethical committee (Dutch southwestern region), and written informed consent was obtained for all participants. A low-dose, nongated 64 multislice CT scan, the Lightspeed VR 64-MSCT (GE, UK), was performed within 10-15 min. No intravenous contrast enhancement was used. The performed CT scan took place before the start of radiotherapy.

The overall CAC score consists of the sum of all the calcium lesions present in the left main artery, left anterior descending coronary artery, left circumflex artery, and right coronary artery and was estimated with a GE Advantage Workstation Volume (share 2,

version 4.4 (2007), rev. 1, DFOV 25 cm, pixel area 0.5 x 0.5 mm²). The method we used was described by Agatston et al. (12). All scans were evaluated by one radiologist (MH) specialized in determining CAC scores. To determine the inter-observer variability of the CAC values, a random selection (n = 58) of the available CAC scans was done. A second radiologist, blinded to the scores of the first observer, determined for each of the 58 cases a second CAC score.

The MESA study was designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease in a population-based sample of 6,814 men and women aged 45-84 years. All participants were free of clinically apparent cardiovascular disease (6). To compare the results of the Radiotherapy Centre West (RCWEST) cohort to that of the MESA cohort, several risk factors of developing cardiac disease were registered. Age, height, body mass index (BMI, defined as weight in kilograms divided by height in square meters) and CAD risk factors: history of heart and vascular disease, including diabetes mellitus, hypertension, and hypercholesterolemia (the latter three only applicable when medication was used), were registered in specially designed questionnaires before starting the radiotherapy sessions. Smoking habits were registered and defined by the number of pack years. One pack year was defined by smoking a total of 20 cigarettes each day during 1 year. In the RCWEST cohort a woman was classified as a former smoker if she had stopped smoking more than one year before starting radiotherapy.

As a first step, the CAC scores of the Caucasian RCWEST cohort were compared with those of the (female) Caucasian MESA cohort. We then excluded patients suffering from diabetes mellitus and those diagnosed beforehand with cardiovascular diseases. By doing so, we created a cohort that was better comparable (specifically with respect to cardiac risk factors) to that of the MESA cohort. Finally, the CAC scores of this latter selected RCWEST cohort were compared with the (female) Caucasian MESA data. The calcium scores were classified into percentiles, e.g., the 25th percentile implies that 25% of all cases have a CAC value lower than the given value.

According to Bax et al. (13), the determined CAC values are categorized as follows: low-risk calcium scores—CAC values 0-100; medium-risk calcium scores—100 < CAC values <400; high-risk calcium scores—CAC values >400.

For optimal comparison with the MESA cohort, three age categories of patients were created: 45-54, 55-64, and 65-74. Two age categories of patients were excluded from our analysis because the youngest age group in our cohort (<45) is not included in the MESA cohort, and the oldest age group (75-84) consisted only of two patients.

Statistical analysis

Because the data were heavily skewed with 36% of the patients having a CAC score of zero, a log transformation was computed on all CAC values. On the log scale, the data were normally distributed. A paired t test was performed to determine the inter-observer variability of the overall CAC values. The inter-observer variability of the CAC values was also evaluated for each single artery (left main artery, left anterior descending coronary artery, left circumflex artery, and right coronary artery). A Wilcoxon signed rank test was performed for the latter analysis because the number of eligible data was <30. For a comparison of the RCWEST cohort to the MESA cohort, the distribution of the CAC scores was analyzed with the Chi-square test. The MESA CAC distribution for each age group was computed into a ratio (expected) and was compared to the CAC distribution of the RCWEST cohort (observed). A Chi-square test was also performed for the comparison of age, race, smoking, and BMI between both cohorts.

For analysis, we used SPSS Statistics version 17.0. The level of statistical significance was considered $p < 0.05$ for all tests. (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.)

Results

Eighty women diagnosed with either pure ductal carcinoma in situ (<4 cm; 5% of all cases) or infiltrative breast cancer (<5 cm; 95% of all cases) were included. Sixty-four percent of the women were postmenopausal. Thirteen percent of the patients in the RCWEST cohort had a history of cardiac disease; two patients had experienced a myocardial infarction in the past, and two patients mentioned that they had experienced signs of myocardial ischemia (angina pectoris). Furthermore, 8 patients suffered from diabetes mellitus. In three of these eight patients, a combination of the excluding factors were present. Seven patients were not Caucasian.

The mean age of the patients included in the RCWEST cohort was 56 years (range, 29-81), and for the MESA cohort, the mean age was 62 (range, 45-84). The mean BMI in the RCWEST cohort was 26 (range, 18-39); for the MESA cohort, no mean BMI was available. A significant difference between the RCWEST and the MESA cohort was found in the distribution of BMI categories; specifically, the BMI categories <25 and 30 to <40 seem to be different. A significant difference was also found for the age categories: in the RCWEST cohort, a higher percentage of women in the 55- to 64-year age category was included; in the MESA cohort, more women were included in the 45- to 54-year age category. Furthermore, the distribution of race was significantly different: in the RCWEST cohort, a larger number of Caucasian women was included. Finally, the smoking status of the RCWEST cohort differed significantly from those of the MESA cohort, specifically in the current smokers category (Table).

The mean overall CAC was 82 with a range of 0-779, with 53% of the CAC scores being zero.

Inter-observer variability CAC values

For 73% ($n = 58$) of the patients, the inter-observer variability between the two radiologists was evaluated. No significant differences ($p = 0.3$) in the overall CAC values were found. However, for each separate artery, it was difficult in some patients to determine to which artery the specific CAC value belonged. In these cases, the proportion of calcium deposits was situated near the bifurcation of two arteries. Both radiologists scored an overall CAC value of zero in the same patients.

Comparison with the MESA cohort

For the unselected Caucasian RCWEST cohort ($n = 65$; the 15 patients <45 and >74 were excluded, see Materials and methods) we found significantly ($p < 0.01$) higher CAC scores when compared to those of the (female) Caucasian MESA cohort. This applied specifically for the CAC distribution for women in the age category of 55-64 years old. In the other age categories, no significant differences were found (age category 45-54: $p = 0.84$; age category 65-74: $p = 0.07$).

Percentiles of CAC scores for three age categories of Caucasian patients only (45-54, 55-64, and 65-74; $n = 62$) are shown in the Figure for both the RCWEST cohort and the MESA cohort. These scores showed that in the 45-54 age category ($n = 11$), the numbers of patients with the value 0 were approximately the same (25th-75th percentile values), but the 95th percentile CAC value was higher in the MESA data. The CAC values of the RCWEST 55-64 age category ($n = 33$) increased more rapidly than the

MESA cohort, and the CAC values of the 65-74 age category (n = 18) seem to be of the same magnitude.

The selected RCWEST cohort was created by excluding the cases with a history of cardiac disease, diabetes mellitus, and non-Caucasians and consisted of 55 patients. This selected cohort also showed a significantly ($p = 0.02$) higher CAC distribution for the women in the 55-64 age category compared with that of the MESA cohort. For the other age categories, no significant differences were found.

	RCWEST (Number)	RCWEST (%)	MESA (%)	P-value	Selected RCWEST cohort
Age (years)					
< 45	13*	16.3	0		9*
45-54	13	16.3	30.1		11
55-64	33	41.3	27.7	< 0.001	27
65-74	19	23.8	28.6		17
75-84	2^	2.5	13.6		2^
Race					
Caucasian	73	91.3	40.2		66
Chinese	0	0	11.4		n.a.
Black	2	2.5	27.8	< 0.001	n.a.
Hispanic	1	1.3	20.6		n.a.
Hindustani	4	5	0		n.a.
Diabetes Mellitus (DM)					
Yes	6	7.5	n.a.	n.a.	n.a.
No	74	92.5	n.a.		n.a.
Hypertension[§]					
Yes	11	13.8	43.8		19
No	67	83.8	56.2	n.a. [¶]	47
Combined with DM	2	2.5	n.a.		n.a.
Smoking cigarettes					
Never	39	48.8	58.8		33
Former	23	28.8	29.2	0.02	25
Current	18	22.5	12.0		8
BMI (kg/m²)					
< 25	34	42.5	31.8		31
25-<30	31	38.8	34.6	0.02	25
30-40	15	18.8	28.5		10
≥ 40	0	0	5.0		0

*Excluded from analysis, no data available in MESA cohort

^ Excluded from analysis, too few patients in RCWEST cohort

§ RCWEST cohort: Only if a patient received medication for hypertension

¶ N.a. since different definitions were used in both cohorts

Table. Patient characteristics of the unselected RCWEST, The MESA and the selected RCWEST cohort.

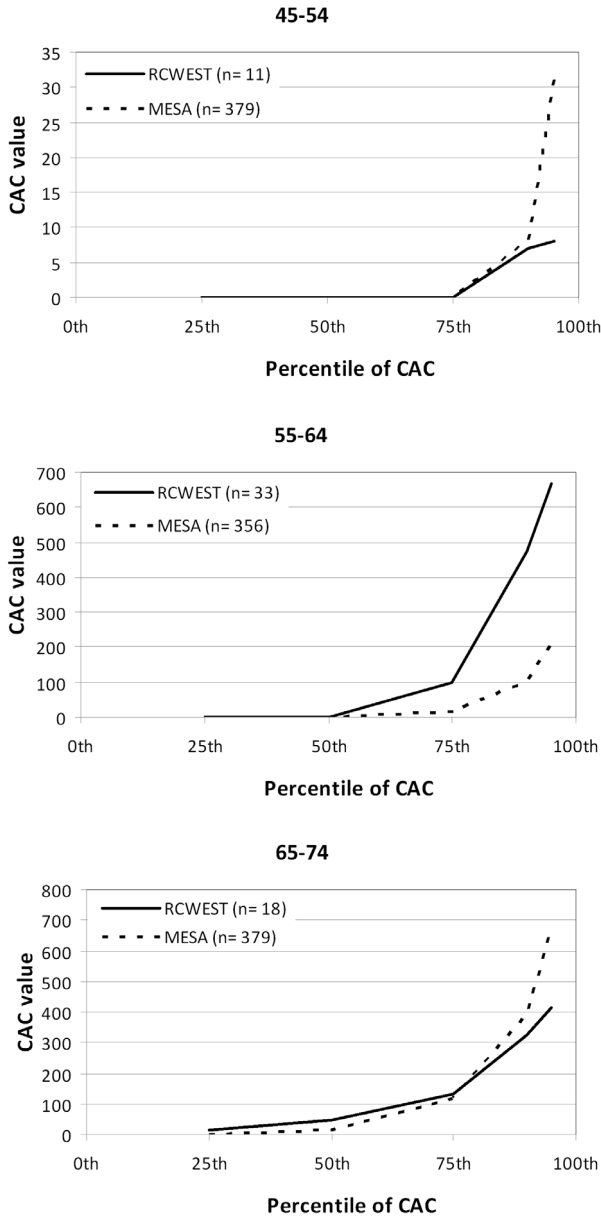


Figure. Percentiles of coronary artery calcium (CAC) scores for three Caucasian age categories (45-54, 55-64, and 65-74 years) for both the Radiotherapy Centre West (RCWEST) cohort (blackline) and the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (dashed line).

Discussion

A comorbidity and race adjusted comparison revealed that the RCWEST cohort CAC scores in the 55-64 age category were significantly higher than the CAC scores in the (asymptomatic) MESA cohort. This applies both to the unselected Caucasian RCWEST cohort and to the selected RCWEST cohort, in which only Caucasian and “healthy” patients were included.

However, to compare our data reliably to the MESA data, we needed to divide the cohort into specific age categories. Because the RCWEST cohort consisted of 80 women, this resulted in a small number of patients for each category. Therefore, the results of the chi-square test are less reliable. Possibly because of the small number of patients in the age categories 45-54 and 65-74, no differences were found compared with those of the MESA cohort (6).

Although we did not find significant differences between the observers, the determination of the CAC values for each separate artery was difficult in some patients. Therefore, we restricted ourselves by using the values of one radiologist and, in doing so, eliminated a possible inter-observer bias.

The number of CAC values of zero in the Caucasian RCWEST cohort was 44%, which is lower than the 62% in the MESA cohort of McClelland (6). Also, in the Caucasian RCWEST cohort, fewer women older than 65 had a CAC value of zero (50th percentile 46 for RCWEST and 13 for Caucasian MESA). This confirms the findings that significantly higher CAC values were found in one of the age categories of the RCWEST cohort.

According to Bax and colleagues (13), the relationship between CAC scores and CAD may be weakened because extensive calcification could possibly represent a more stable stage of CAD. Noncalcified and mixed lesions could be more vulnerable, but this is still a point of debate (14,15).

A drawback of our study is that we had to compare the Dutch RCWEST cohort with that of a healthy cohort, the American MESA cohort. However, no such data were available for the (healthy) Dutch female population. The MESA cohort consists of American women, and it is conceivable that those women experience different cardiac risk factors than Dutch women because of the different lifestyles in the United States (i.e., more dietary fat consumption, less physical activity, and higher BMI). Also, the number of current smokers in the RCWEST cohort is higher than in the MESA cohort; because we could not find the definition “formersmoker” in the MESA cohort, we applied the definition “smoker” if the patient had stopped less than 1 year before radiotherapy. Thereafter, we classified a patient as “former smoker” if the patient had stopped smoking without a time limitation. In that analysis, no significant differences were found between cohorts ($p = 0.18$). Furthermore, we compared our overall results for Caucasian women with those of the German Heinz Nixdorf Recall (HNR) study, a population-based study that recruited unselected participants in the German Ruhr area. This population would, theoretically, be better comparable to the Dutch RCWEST cohort, although the HNR study did not stratify for race (16). It was remarkable that in Caucasian women aged up to 60 years, the 50th percentile CAC values were all zero in both the HNR study and the RCWEST cohort.

However, in the selected RCWEST cohort, we found CAC 50th percentile values that were around 8 times higher compared with the HNR study (22 vs. 2.6) for Caucasian women in the 65-69 age category ($n = 15$). For this comparison, we again had to divide

our group of patients into comparable age groups; in doing so, only a small number of patients remained in each age category.

As for the BMI, a BMI of >25 kg/m² is classified as overweight according to the World Health Organization guidelines. We found a smaller number of patients in the Dutch RCWEST cohort who could be classified as overweight (58%) than in the American MESA cohort (68%) (11), but we found higher BMI values in our study compared with the general Dutch female population according to Statistics Netherlands (CBS). In the Dutch female population aged ≥ 20 years old, the number of overweight patients in 2007 was 40% (17). However, the fact that the women in the RCWEST cohort experience a higher BMI compared with the Dutch female population corresponds to the finding that overweight is a risk factor for breast cancer. Remarkably, a BMI higher than 30 kg/m² seems to correlate with a worse disease-free survival in breast cancer patients (18, 19).

Because this cohort is not selected, our results might be representative of breast cancer patients treated with breastconserving therapy. Our study underlines the necessity to compare treatment associated CAD in patients with left-sided breast cancer with other cohorts of breast cancer patients, because those women may also eventually be more predisposed to develop CAD. In 2008, a heart-sparing breath-hold technique (20) was introduced in our department to decrease cardiac dose for leftsided breast cancer cases. We intend to quantify the efficacy of the heart-sparing technique by comparing the number of calcium deposits in the coronary arteries of breast cancer patients treated with and without use of the ABC technique before radiotherapy until 3 years after completion of the radiation treatment.

Conclusion

Despite the relatively small number of patients, the RCWEST cohorts revealed that the CAC scores in the 55-64 age category were significantly higher than the CAC scores in the asymptomatic (female) MESA cohort. These data suggest that breast cancer patients bear a higher risk of developing CAD. Therefore, measures to decrease cardiac dose further in breast cancer radiotherapy are even more important.

Acknowledgments

We thank R. Wolterbeek for his analytical assistance and statistical advice, the medical receptionists for arranging the appointments for the calcium CT scans, J. van Egmond for creating the Access database and his assistance with Excel, Mrs. A. Otten for her assistance with the data management, T.F.H. Vissers for bibliographical assistance, and Mrs. J.F.D. Bouricius for critically editing this article.

References

1. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300.000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-565.
2. Hooning MJ, Botma A, Aleman BMP, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365-375.
3. Taylor CW, Povall JM, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 2008;72:501-507.
4. Marks LB, Yu X, Prosnitz RG, Zhou S, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys* 2005;63:214-223.
5. Struikmans H, Aarts MJ, Jobsen J, et al. An increased utilisation rate and better compliance to guidelines for primary radiotherapy for breast cancer from 1997 till 2008: A population-based study in The Netherlands. *Radiother Oncol* 2011;100:320-325.
6. McClelland RL, Chung H, Detrano R, et al. Distribution of coronary artery calcium by race, gender and age: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;113:30-37.
7. Pletcher MJ, Tice JA, Pignone M, et al. Using the coronary artery calcium score to predict coronary heart disease events. A systematic review and meta-analysis. *Arch Intern Med* 2004;164:1285-1292.
8. Rozanski A, Gransar H, Wong ND, et al. Use of coronary calcium scanning for predicting inducible myocardial ischemia: Influence of patients' clinical presentation. *J Nucl Cardiol* 2007;14: 669-679.
9. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain. A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA writing committee to update the 2000 expert consensus document on electron beam computed tomography). *Circulation* 2007;115:402-426.
10. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2009;158:554-561.
11. Jacobs PC, Prokop M, van der Graaf Y, et al. Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers. *Atherosclerosis* 2009;209:455-462.
12. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of corpora artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-832.
13. Bax JJ, Schuijff JD. Can coronary calcification define the warranty period of a normal myocardial perfusion study [editorial]? *Mayo Clin Proc* 2008;83:10-12.
14. van Velzen JE, Schuijff JD, de Graaf FR, et al. Plaque type and composition as evaluated noninvasively by MSCT angiography and invasively by VH IVUS in relation to the degree of stenosis. *Heart* 2009;95:1990-1996.
15. Schaar JA, Mastik F, Regar E, et al. Current diagnostic modalities for vulnerable plaque detection. *Curr Pharm Des* 2007;13:995-1001.
16. Schmermund A, Möhlenkamp S, Berenbein S, et al. Populationbased assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. *Artherosclerosis* 2006;185:177-182.
17. Centraal Bureau voor de Statistiek 'Statistics Netherlands (CBS)'. Persbericht 'Press Report' PB08-018. Available at: <http://www.cbs.nl/nl-NL/menu/themes/gezondheid-welzijn/publicaties/artikelen/archief/2008/2008-018-pb.htm>. Accessed March 7, 2011.
18. Sparano JA, Wang M, Martino S, et al.

- Obesity at diagnosis is associated with inferior outcomes in hormone receptor positive breast cancer [abstract]. 2010. Available at: http://www.abstracts2view.com/sabcs10/view.php?nuZSABCS10L_500. Accessed March 7, 2011.
19. Hepp PGM, Rack B, Annecke K, et al. Multivariate analysis of obesity and disease free survival in patients with nodal positive primary breast cancer—The ADEBAR trial [abstract]. 2010. http://www.abstracts2view.com/sabcs10/view.php?nuZSABCS10L_280/http://www.breastcancer.org/risk/new_research/20101214.jsp. Accessed March 7, 2011.
 20. Remouchamps VM, Letts N, Vicini FA, et al. Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:704-715.

Less increase of CT based calcium scores of the coronary arteries three years after breast-conserving radiotherapy using breath-hold

Mirjam Mast^a, Mark Heijenbrok^b, Loes van Kempen–Harteveld^a, Anna Petoukhova^a, Astrid Scholten^c, Ron Wolterbeek^d, Joop Schreur^c and Henk Struikmans^{a,f}

^a Radiotherapy Centre West, The Hague, The Netherlands;

^b Department of Radiology, Medical Center Haaglanden, The Hague, The Netherlands;

^c Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

^d Leiden University Medical Centre, department of medical statistics and bioinformatics, Leiden, The Netherlands

^e Department of Cardiology, Medical Center Haaglanden, The Hague, The Netherlands

^f Department of Clinical Oncology, Leiden University Medical Centre, Leiden, The Netherlands;

Int J Radiat Oncol Biol Phys Submitted 15-02-2015

Summary

The aim of this prospective longitudinal study was to identify differences in Coronary Artery Calcium (CAC) scores between three groups of breast cancer patients (right-sided, left-sided treated with and without breath-hold) by comparing the CAC scores before the start of radiotherapy to those determined three years after radiotherapy. Breath-hold in breast-conserving radiotherapy leads to a less pronounced increase of CT based CAC scores.

Abstract

Purpose

The aim of this prospective longitudinal study was to identify differences in Coronary Artery Calcium (CAC) scores between three groups of breast cancer patients by comparing the CAC scores before the start of radiotherapy to those determined three years after radiotherapy.

Materials and methods

Multi-slice CT scans were carried out in 99 consecutive patients, referred for radiotherapy after breast-conserving surgery. No regional radiotherapy was given. The patients were subdivided in three groups: left- and right-sided radiotherapy, and left-sided radiotherapy using a breath-hold technique. The differences in increase of the overall and Left Anterior Descending (LAD) coronary artery CAC scores were determined. Within each patient the LAD minus RCA scores were also analyzed, representing the CAC scores of the LAD minus those of the Right Coronary Artery (RCA).

Results

After three years, a non-significant lower increase in overall CAC scores and a significant lower increase in mean CAC scores in the LAD was found for the group with left-sided breast cancer treated with breath-hold compared to the group without breath-hold. Furthermore, the LAD minus RCA scores in patients treated for left-sided breast cancer without breath-hold were higher when compared to those with right-sided breast cancers and those with left-sided breast cancer treated with breath-hold.

Conclusion

Breath-hold in breast-conserving radiotherapy leads to a less pronounced increase of CT based CAC scores. Therefore, breath-hold is probably useful to prevent the development of radiation-induced coronary artery disease. The drawbacks of our study were the small numbers and the relatively short follow-up period.

Introduction

Radiotherapy for left-sided breast cancer has been associated with an increased risk of Coronary Artery Disease (CAD) [1,2]. This rate of major coronary events started to increase within a period of 5 years of exposure of radiotherapy. Also was determined that the incidence of major coronary events was proportional to the mean dose to the heart [3]. Furthermore, Nilson et al. found a higher amount of calcium deposits in the LAD coronary artery after radiation therapy for left-sided breast cancer compared to the same situation for right-sided breast cancer [4]. Whetal et al. confirmed that the presence of radiation-induced calcium deposits is seen as a surrogate marker for radiation-induced atherosclerotic lesions. They found more atherosclerotic lesions in the LAD of irradiated Hodgkin's lymphoma survivors than in non-irradiated patients. These patients were treated with mediastinal or mantle field radiotherapy (including the pre-cranial arteries and/or coronary arteries) with a median dose of 40 Gy [5]. According to Greenland et al. and Oudkerk et al., the amount of calcium deposits in the coronary arteries (CAC scores) predicts the risk of subsequent cardiovascular events [6,7]. Another study showed that CAC scores, when compared with 11 other newer coronary heart disease risk markers, were the best predictors of the occurrence of cardiovascular disease in persons who were initially without CAD [8]. Moreover, it appeared that adding CAC scores to the Framingham Risk score (FRS) improved the accuracy of risk predictions [8]. It should be emphasized that the FRS is the most commonly used CAD risk prediction score [9].

To the best of our knowledge, no studies have been carried out that compared the amount of CAC before and after radiotherapy in breast cancer patients treated with radiotherapy. Therefore, we prospectively determined CAC scores at baseline as well as three years after radiotherapy in 99 consecutive female breast cancer patients receiving breast-conserving radiotherapy.

The aim of this prospective longitudinal study was to identify possible differences in CAC scores between patients irradiated for right-sided breast cancer and patients irradiated for left-sided breast cancer. The latter group comprised both patients irradiated using a breath-hold technique and those irradiated without using a breath-hold technique.

Materials and methods

Patients

Patients with either DCIS (< 4 cm) or breast cancer (< 5 cm) and treated with breast-conserving surgery and whole breast radiotherapy were considered eligible. No regional radiotherapy was given. Every eligible patient referred to our department, Radiotherapy Centre West (RCWEST), was asked to participate in this study. Seventy percent of all eligible patients agreed to participate. From September 2008 until July 2011, 109 consecutive patients were included in this prospective study. The study was approved by the local ethical committee (METC Zuidwest Holland). Written informed consent was obtained from all participants. If indicated, adjuvant systemic therapy and/or chemotherapy was given, starting after radiotherapy. Our patient population consisted of three groups: i) 21 patients treated with left-sided radiotherapy (group L-BH); ii) 23 patients treated with right-sided radiotherapy (group R); and iii) 65 patients treated with left-sided radiotherapy using a breath-hold technique (group L+BH). From January 2010 onwards, in all left-sided breast cancer patients in RCWEST the Active Breathing Control (ABC) breath-hold method [10,11] was used. Therefore, the third

group (group L+BH), consisted of patients receiving radiotherapy using a breath-hold technique. Subsequently, from October 2010 hypofractionation schemes were routinely administered [12,13]. In 33 of these 65 left-sided breast cancer patients, treated with breath-hold, a hypofractionation scheme was used.

CAC CT scan

CAC CT scans were carried out at baseline and after three years. CAC was measured using non-contrast, low-dose non-gated cardiac CT studies on a GE 64-slice MDCT scanner (LightSpeed VCT, General Electric Medical System®, Milwaukee, WI). The non-invasive CT scan was performed within 10-15 minutes. A 2.5 mm reconstructed slice thickness was used.

The CAC score was calculated according to Agatston et al. [14]. The Agatston score requires three contiguous voxels of >130 Hounsfield units. The overall coronary calcium score was determined on a GE Advantage Workstation Volume (share 2, version 4.4 (2007), DFOV 25 cm, pixel size 0.5x0.5 mm²), by summing individual lesion scores from each of the main epicardial coronary arteries: Left Main Artery (LMA), Left Anterior Descending (LAD) artery, Left Circumflex (LCX) artery, and Right Coronary Artery (RCA).

To avoid interobserver variations, all scans were evaluated by one radiologist (MH), specialized in determining CAC scores, and one cardiologist (JS), in order to reach a consensus on all calculated calcium scores. Both were blinded for the side of the radiotherapy (right of left breast). All scans were reviewed separately. When different scores were found, a joint review took place, and a final decision was reached based on consensus. CAC scores were categorized into three groups: i) a low-risk group: 0 – 100; ii) a medium risk group: 100-400; iii) a high-risk group: > 400 [15]. We compared the distribution of these three risk groups in time within each of the three patients groups: R, L-BH and L+BH.

Radiotherapy

Details on the patient position, the CT scan before the radiation treatment, the breath-hold technique and the delineation of the target and critical organs were described earlier [11]. A 3D-Conformal Radiation Therapy (3D-CRT) technique was used. Details about this technique and dose specification were also described earlier [11]. Total doses were: 50 Gy in 25 fractions for the conventionally fractionated cases, and 42.56 Gy in 16 fractions for the cases irradiated with a hypofractionation scheme. If indicated according to the national guidelines, a boost dose, using a photon based technique, was added to the tumor bed. This boost dose was given after completion of the whole breast irradiation. The boost doses ranged from 13.30 Gy-26 Gy, in 5 to 13 fractions respectively, see Table 1.

Risk factors

The following cardiac risk factors were obtained before starting radiotherapy: age, height, BMI (Body Mass Index, defined as weight in kilograms divided by height in square meters), postmenopausal status, smoking habits. Also, specific CAD risk factors were obtained: history of heart and vascular disease, including diabetes mellitus, hypertension and hypercholesterolemia (the latter three were only found applicable when medication was used).

CAC scores analyses

Since we were interested in the difference between the baseline score and the score three years after radiation therapy, the patients who were not able to undergo a CAC CT scan after three years were excluded from the CAC analyses.

Concerning the CAC scores we determined:

1. the (mean) overall CAC scores and the (mean) LAD CAC scores at baseline and at three years after radiation for group L-BH, group R and group L+BH.
2. the (mean) differences between CAC scores within each patient in the LAD and the RCA (LAD minus RCA CAC scores), at baseline and at three years after radiation, for the three groups. Representing the differences in the individual patient. The RCA is the coronary artery that receives the lowest dose when administering whole breast radiotherapy, since the RCA is lying furthest away from the radiation treatment fields, both in left-sided as well as right-sided breast cancer radiotherapy. Therefore, this artery was used as a reference.

Statistical analysis

A descriptive analysis of the change of the CAC scores in time was carried out, reporting the mean, median, standard deviation and Standard Error (SE). The presence or absence of statistical significance of categorical values was determined using the Chi-square test. We fitted mixed models for the various outcome variables assuming no differences at baseline, and carried out a one-way analysis of variance (ANOVA) for the continuous values. For analysis, we used SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). P-values ≤ 0.05 (two-sided) were considered statistically significant for all tests.

Results

General characteristics of the patients and risk factors

For all 109 women a baseline CAC score was calculated. After three years of follow-up, ten women were lost to follow-up since they had either died, suffered from metastases or had received cardiac vessel metal implants which seriously distorted the quality of the CAC CT images. Hence, after three years of follow-up, in 99 women both a baseline and a follow-up CAC score were available (see Table 3 for the range when the follow-up calcium CT scan had taken place).

Of the 99 women 12% were diagnosed with pure DCIS (<4 cm) and 88 % with breast cancer (< 5cm). Forty percent of the patients received adjuvant chemotherapy, the latter was anthracycline based in all patients, Table 1.

The mean age of the patients was 56 years (range 28-74). Patient and treatment characteristics are summarized in Table 1. Sixty-eight percent of all 99 women had a post-menopausal status at baseline; 83% of the left-sided breast cancer patients irradiated without breath-hold; 70% of the right-sided breast cancer patients; and 62% of the left-sided breast cancer patients irradiated with breath-hold. Of all the women 91% was Caucasian, 3% was Spanish, 2% was Black and 4% was Hindustani.

The mean BMI in the RCWEST cohort was 26 (range 18-39), corresponding with overweight on the BMI scale [16]. Seventeen percent in the total RCWEST cohort had a BMI higher or equal to 30, corresponding with obesity on the BMI scale [16].

Table 1		Mean age at RT (years)	Left/Right sided breast cancer	RT with ABC (yes/no)	RT dose (Gy)	RT boost dose (Gy)	Chemotherapy
R	(n=20)	55.6 [39-71]	Right	no	50.00	16 (n=5) / 20 (n=3) / 26 (n=3)	6
L-BH	(n=18)	61.2 [44-74]	Left	no	50.00	16 (n=8) / 20 (n=1)	8
L+BH	(n=28)	54.3 [28 - 72]	Left	yes	50.00	16 (n=13) / 20 (n=3)	26
	(n=1)		Left	Yes	42.00 *		
	(n=32)		Left	yes	42.56		

* Radiotherapy stopped prematurely, hence the planned dose of 50 Gy was not given

Table 1: Patient and treatment characteristics of the three RCWEST groups.

Seventeen percent of the women were smoking before they started with the radiation treatment. Around 52% of the women had a smoking history with a mean number of history pack years of 11 (range 0 – 56). Also, before the start of the radiation therapy 20% of the women were used to drinking more than 2 units of alcohol each day, 27% of them less than 1 unit per day.

One patient had experienced a cardiac arrest in the past and two patients reported that they had experienced signs of angina pectoris in the past. During the follow-up period no coronary vascular events or other (new) heart diseases had been reported. Furthermore, 23 patients suffered from hypertension and eleven patients suffered from diabetes mellitus. No differences were seen between the three groups, see Table 2.

Table 2

Group (n = 99)	R (n=20)	L-BH (n=18)	L+BH (n=61)	p-value
Postmenopausal at baseline	14	15	38	p = 0.2
Smoking	3	2	12	p = 0.7
History pack years >= 10	10	8	24	p = 0.7
Alcohol; > 2 units per day	5	7	8	p = 0.05
BMI < 25	6	8	29	p = 0.4
BMI >= 25	14	10	32	
History of cardiac diseases *	3**	4	5	p = 0.3
Hypertension ***	5	5	13	p = 0.8
DM ***	4	1	6	p = 0.3

* mostly arrhythmias

** one patient with a cardiac arrest

*** some patients suffer from both hypertension and DM

Table 2: Distribution of the risk factors in the three RCWEST groups. Calcium scores: mean scores LAD and overall score.

At baseline, a comparable distribution of the risk factors between the three groups: L-BH, R and L+BH, was noted, see Table 2. After three years, only a small non-significant shift was noted in the CAC risk distribution ($p > 0.1$), Table 3.

Table 3		Baseline								3 years (1095 days) after RT **									
		Mean / median Calcium-score LAD	Range	Mean / median Calcium-score Overall	Range	CAC low risk*	CAC medium risk*	CAC high risk*	Percentage with zero Calciumscore Overall	Mean / median Calcium-score LAD	Range	Mean / median Calcium-score Overall	Range	CAC low risk*	CAC medium risk*	CAC high risk*	Percentage with zero Calciumscore Overall		
R	(n=20)	14.5 / 0.0	0 - 105	80.1 / 0.0	0 - 825	n=17	n=1	n=2	60%	29.9 / 0.0	0 - 255	138.0 / 0.0	0 - 1334	n=16	n=2	n=2	55%		
L-BH	(n=18)	49.3 / 6.5	0 - 334	75.2 / 11.0	0 - 477	n=14	n=3	n=1	28%	77.3 / 9.5	0 - 634	138.3 / 25.5	0 - 1055	n=13	n=3	n=2	28%		
L+BH	(n=61)	19.3 / 0.0	0 - 401	35.7 / 0.0	0 - 645	n=54	n=6	n=1	66%	28.8 / 0.0	0 - 509	64.9 / 0.0	0 - 1039	n=51	n=7	n=3	51%		
								p-value = 0.4								p-value = 0.8			

* low-risk group: 0 – 100; medium risk group: 100-400; high-risk group: > 400

** R = mean 1165 (974-1399); L-BH = mean 1161 (960-1398); L+BH = mean 1094 (889-1337)

Table 3: Calcium scores (mean and median; range; CAC risk group; percentage of calcium score 'zero') in all patients at baseline and three years after radiation therapy.

The mean overall CAC score at baseline was 52 with a range of 0 - 825. For the LAD at baseline we found a mean CAC score of 24 (range 0 – 401). After three years, the mean overall CAC score was 93 (range 0 – 1334) and for the LAD the mean CAC score was 38 (range 0 - 634). For the three groups the mean and median calcium scores of the overall and the LAD score were summarized in Table 3.

After analyzing the three cohorts it became apparent that the increase in the LAD calcium scores after three years was higher in group L-BH, see Figure 1: red line in the left part of the Figure. The mean increase in CAC scores for the overall and the LAD score in all three cohorts is visualized in Figure 1.

In comparing the observed differences in calcium scores over time, less increased mean calcium scores were found for the left-sided breast cancer patients treated with breath-hold (group L+BH) and right-sided (R) breast cancer patients compared to left-sided patients treated without breath-hold (L-BH). For the overall CAC scores these changes were non-significant ($p>0.10$). For the LAD, comparing left-sided without breath-hold (L-BH) and right-sided breast cancer (R), no significant difference was found ($p=0.2$); for left-sided breast cancer patients treated with the breath-hold technique (L+BH) versus left-sided patients without the breath-hold technique (L-BH) a significant lower calcium score was found ($p=0.04$; 95%CI: -42.7 to -1.15).

Calcium scores: LAD minus RCA

Concerning the calcium scores in the LAD minus the RCA, we found significant differences in the three groups ($p=0.03$). Lower scores were observed in the group of patients treated for left-sided breast cancer with breath-hold (L+BH) compared to left-sided breast cancer patients treated without a breath-hold technique (L-BH). See Figure 2 for mean differences in LAD minus RCA scores between baseline and three years after radiotherapy.

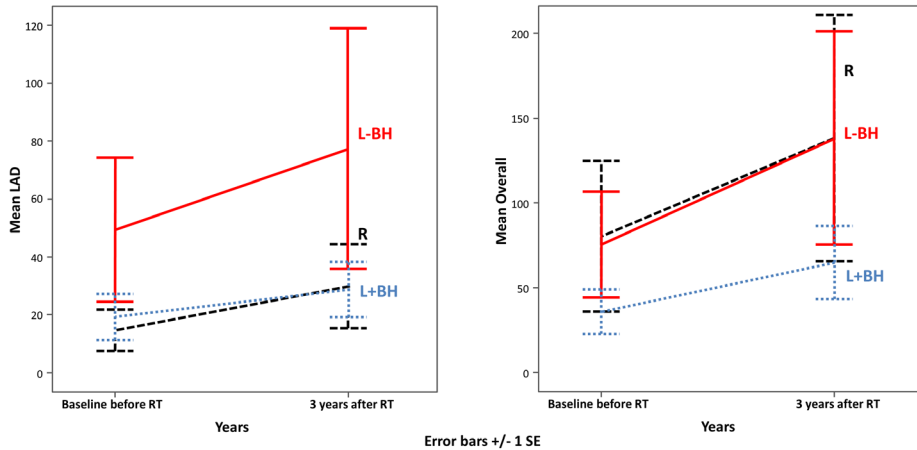


Figure 1: Mean calcium score increase in time with 1 Standard Error (SE) at baseline and at three years after radiotherapy. LAD score (left) and overall score (right); note: the scales in both Figures differ. Red solid line: Left-sided breast cancer patients, group L-BH. Black dashed line: Right-sided breast cancer patients, group R. Blue dotted line: Left-sided breast cancer patients treated in breath-hold, group L+BH.

Discussion

In this prospective longitudinal study we found a less pronounced increase in coronary artery calcium scores in patients with left-sided radiotherapy when using a breath-hold technique (L+BH) compared to those with left-sided radiotherapy without breath-hold (L-BH). Specifically with respect to the CAC scores of the Left Anterior Descending (LAD) coronary artery, this difference was statistically significant. Furthermore, three years after radiotherapy, significant differences were found for the CAC scores of the LAD minus the CAC scores of the RCA for left-sided breast cancer without breath-hold (L-BH), right-sided radiotherapy (R) and left-sided radiotherapy with breath-hold (L+BH). The increased CAC scores three years after radiotherapy, administered without a breath-hold technique, are indicative for a more pronounced development of (radiation-induced) atherosclerosis. These findings are consistent with the preclinical data of Stewart et al. [17]. They found that irradiation accelerates the development of macrophage-rich, inflammatory atherosclerotic lesions in carotid arteries of mice. Similar findings were reported by Schultz-Hector & Trott [18] and Basavaraju & Easterly [19].

Some drawbacks and strong points of our study should be mentioned.

In our cohort, the radiotherapy regimens were identical. As only breast-conserving radiotherapy was administered, regional radiotherapy was given in none of the patients. All patients were treated with 3D-conformal radiotherapy techniques in the same institute. The biological effective breast doses were identical [20, 21].

Drawbacks were the limited sample size of our cohort and the relatively short follow-up period of three years. Probably, larger differences will be found after a longer follow-up period. Whetal et al. did find an increased number of calcified and non-calcified atherosclerotic lesions of the pre-cranial artery in irradiated Hodgkin's lymphoma survivors (HLSs) [5]. The relative number of calcified lesions in the pre-cranial arteries of irradiated compared to non-irradiated patients they found was, however, comparable. The HLSs were examined 5-13 years after radiotherapy [5]. In this study no baseline CAC

scores were determined; and the control group were non-irradiated patients referred for CT angiography of the pre-cranial arteries due to the suspicion of a recent stroke or TIA [5]. Conversely, Chang et al. performed coronary calcium CT scans in twenty asymptomatic breast cancer patients five to fourteen years after their radiation treatment. Chang et al. did not find increased calcium scores in left-sided breast cancer patients. The latter was probably due to the fact that most of them had a calcium score ‘zero’; also, no baseline CAC values were available [22].

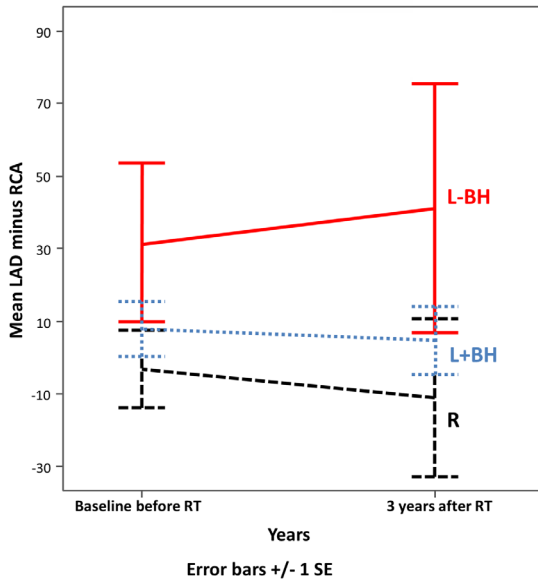


Figure 2: Mean CAC score: LAD minus RCA with 1 Standard Error (SE) at baseline and at three years after radiotherapy. Mean difference between baseline and 3 years after radiotherapy. Red solid line: Left-sided breast cancer patients (group L-BH). Black dashed line: Right-sided breast cancer patients (group R). Blue dotted line: Left-sided breast cancer patients treated in breath-hold (group L+BH).

Another drawback of our study was, that we did not investigate, for each individual patient, the relation between the amount of CAC and the delivered dose levels to the heart and the LAD. However, for a 3D conformal radiotherapy technique as well as for an IMRT technique without breath-hold, we have reported that the mean heart dose and the mean LAD dose could be decreased significantly by using a breath-hold technique [11]. These findings are in line with earlier reported decrease in LAD dose when using a breath-hold technique [23-26].

A strong point of our study was that the relevance of the use of the CT based CAC score is well supported by the literature. The CT based CAC score is known for its highly predictive value of developing cardiac vascular events. Kavousi et al. stated in 2012 that CAC scores even improved the Framingham Risk Score (FRS) predictions. However, they indicated that these scores may not be generalizable to younger or non-Caucasian populations. We want to stress that only very few non-Caucasian patients were included in our study. Besides this, although the mean age in the RCWEST groups was lower than that in the study performed by Kavousi et al., 56 years (SD 10.5) compared to 69.1 years (SD 8.5) respectively; the patients in our RCWEST cohort could not be classified as “young” [8].

Raggi et al. reported the relevance of low CAC scores. They found that a low CAC value was associated with higher survival rates (concerning all cause death) in all ages [27]. Also, a systematic review stated that the absence of an increased CAC score was associated with a low risk of future cardiovascular events [28]. In the RCWEST patients, it was not possible to calculate the FRS, since we did not measure the serum cholesterol levels and blood pressure.

A potential drawback seemed to be the differences of the CAC scores 'zero' between the three groups. Three years after radiotherapy 55% of the right-sided breast cancer patients of RCWEST still had a CAC score 'zero'. In the left-sided breast cancer patients it was 28% and in the left-sided breast cancer patients treated with a breath-hold technique it was 51%, see Table 2. The cohort of left-sided breast cancer patients treated with breath-hold consisted of relatively many patients with a CAC score 'zero' at baseline, i.e. 66%. With respect to these findings we want to emphasize that every consecutive patient was asked to participate in this study and that about 70% agreed to participate. Findings mentioned above can, therefore, be interpreted as a coincidence. The risk factors for cardiovascular disease in the three RCWEST patient groups (L-BH, R and L+BH) were comparable, including the CAC risk distribution, Tables 2 and 3. We found small differences in age and postmenopausal status at baseline, we therefore added the LAD minus RCA value in the analysis. This value represents the differences in CAC scores in the individual patient.

According to these findings summarized above we suggest that decreasing the heart dose in radiotherapy would be of great importance in breast cancer patients.

Conclusion

Breath-hold in breast-conserving radiotherapy leads to less increase in time of CT based CAC scores. A breath-hold technique therefore is probably useful to protect left-sided breast cancer patients against the development of radiation induced coronary artery disease. Drawbacks of our study are the small numbers and the relatively short follow-up period.

Acknowledgements

We thank the patients for participating in this study; the radiation oncologists: J. Biesta, H. Ceha, H. De Jager, P. Koper, T. Stam, S. Swank-Bordewijk, A. Verbeek-de Kanter, R. Wiggenraad for including the patients in this study; the medical receptionists for arranging the appointments for the calcium CT scans; colleagues of the radiology department in MCH Antoniushove for arranging and performing the Calcium CT scans; I. Korteland for processing the letters to the general practitioners and the patients; J. van Egmond for creating the Access database and his assistance with Excel; T. Vissers for bibliographical assistance; and F. Bouricius for critically editing this article.

References

1. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300.000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-565.
2. Hooning MJ, Botma A, Aleman BMP, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365-75.
3. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-998.
4. Nilsson G, Holmberg L, Garmo H, et al. Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer. *J Clin Oncol* 2012;30:380-386.
5. Wethal T, Nedregard B, Andersen R, et al. Atherosclerotic lesions in lymphoma survivors treated with radiotherapy. *Radiother Oncol* 2014;110:448-454.
6. Greenland P, Bonow RO, Brundage BH, et al. Clinical Expert Consensus Document on Coronary Artery Calcium Scoring by Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients With Chest pain. A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA writing committee to update the 2000 expert consensus document on electron beam computed tomography). *Circulation. Journal of the American heart association* 2007;115:402-426.
7. Oudkerk M, Stillman A, Halliburton S, et al. Coronary artery calcium screening: current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging. *Eur Radiol* 2008;18:2785-2807.
8. Kavousi M, Elias-Smale S, Rutten J, et al. Evaluation of Newer Risk Markers for Coronary Heart Disease Risk Classification. A Cohort Study. *Ann Intern Med* 2012;156:438-44.
9. Anderson K, Odell P, Wilson P, et al. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293-8.
10. Swanson T, Grills IS, Hong Y, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36:24-30.
11. Mast ME, van Kempen-Harteveld L, Heijnenbroek MW, et al. Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? *Radiother Oncol* 2013;108:248-53.
12. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *START Trialists' Group, Lancet Oncol* 2008;9:331-41.
13. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513-520.
14. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of corpora artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology* 1990;15:827-832.
15. Bax JJ, Schuijff JD. Can Coronary Calcification Define the Warranty Period of a Normal Myocardial Perfusion Study? *Editorial Mayo Clinic Proceedings* 2008;83:10-12.
16. World Health Organisation. Obesity and overweight. Fact sheet N°3 11 March 2013 [assessed 7th August 2014]. <http://www.who.int/mediacentre/factsheets/fs311/en/>
17. Stewart FA, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649-658.
18. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol*

- Biol Phys 2007;67:10-18.
19. Basavaraju SR, Easterly CE. Pathophysiological effects of radiation on atherosclerosis development and progression, and the incidence of cardiovascular complications. *Med Phys* 2002;29:2391-2403.
 20. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467-71.
 21. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. START Trialists' Group. *Lancet* 2008;371:1098-107.
 22. Chang M, Suh J, Kirtani V, et al. Coronary calcium scanning in patients after adjuvant radiation for early breast cancer and ductal carcinoma in situ. *Frontiers in oncology* 2013;3:253.
 23. Korreman SS, Pedersen AN, Aarup LR, Nottrup TJ, Specht L, Nystrom H. Reduction of cardiac and pulmonary complication probabilities after breathing adapted radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1375-80.
 24. Borst GR, Sonke JJ, den Hollander S, et al. Clinical results of image-guided deep inspiration breath hold breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;78:1345-51.
 25. Vikström J, Hjelstuen MHB, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. *Acta Oncol* 2011;50:42-50.
 26. Vennarini S, Fourier-Bidoz N, Aristei C, et al. Visualisation of the left anterior descending coronary artery on CT images used for breast radiotherapy planning. *Br J Radiol* 2013;86:1025.
 27. Raggi P, Gongora MC, Gopal A, et al. Coronary Artery Calcium to Predict All-Cause Mortality in Elderly Men and Women. *Journal of the American College of Cardiology* 2008;52:17-23.
 28. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification. *JACC: Cardiovascular Imaging* 2009;6:675-688.



**GENERAL
DISCUSSION**



Radiotherapy is an integral part of breast conserving therapy. It substantially improves treatment efficacy by decreasing local recurrence rates and results in an increased breast cancer specific survival [1-6]. With the introduction of the planning CT scan over the last decades, it was possible to gather more precise information on both dose homogeneity in the target volume and mean and maximum dose in the organs at risk. In recent years the knowledge concerning the side effects of this radiation treatment has increased further and, amongst others, the effect on the heart was documented [7,8]. Based on this knowledge, important aspects of the treatment delivery have been changed in order to minimise the dose in the heart. Still, a number of unanswered questions remain and further improvements in the treatment delivery seem possible. In this thesis, several strategies to optimise the radiation treatment for patients with breast cancer were analysed. First, we focussed on optimising the target volume delineation. Subsequently, several treatment planning techniques were compared in order to decrease the dose to the heart. Also, with decreasing the dose in the heart, changes of calcium scores in the coronary arteries of the various patient categories were followed in the years after treatment.

Delineation of volumes in breast cancer radiotherapy

Optimal definition of the target is the first step in the radiation treatment process. Improperly defined target volumes may lead to a systematic geographic miss in the individual patient during the whole course of radiation treatment [9-11]. Ultimately, this may negatively affect the treatment efficacy and could also lead to an increased dose to organs at risk.

Several uncertainties, (e.g. positioning inaccuracies; technical inaccuracies), were defined influencing the efficacy of the radiation treatment. As was stated by several authors the inter-observer differences in delineating the target volume is a large uncertainty in the radiotherapy process [12,13]. These uncertainties can be defined by, for example the Conformity Index (CI), a tool for quantification of the variability of delineation. For the special circumstance where the number of observers equals two, it is defined as the volume of agreement divided by the total encompassing volume. This has been generalised to any number of observers by Kouwenhoven et al. [14]. This tool, the generalised CI (CIgen), was used in our delineation studies [15-17].

In breast conserving radiotherapy, the target volume delineation aims at delineating the glandular breast tissue (CTV Breast) and the Lumpectomy Cavity (LC). In order to improve the uniformity of the delineation of these structures the following measures seem relevant:

1. Use of guidelines;
2. Allocating breast cancer dedicated staff members.
3. Addition of MR images.

Ad 1: The use of guidelines improved the consistency of the target delineation [12,18,19], however, this was questioned by Van Mourik et al. They still reported considerable variation between observers despite the use of delineation guidelines for the LC [13]. Also, Boersma et al. stated that the interpretation of guidelines is the weakest link in the chain of delineating the LC, even when using a pre-operative CT scan [20]. Therefore, a dedicated team of radiation oncologists is necessary.

Ad 2: Radiation oncologists with expertise in breast cancer radiotherapy should consult each other when delineating the LC, since the interpretation of the LC is difficult and large differences exist. Several studies revealed that some observers delineate the target

volume systematically larger or smaller than others [12,21]. As peer review of the delineated volumes might improve the consistency of delineating the target volume, and as the review by radiologists seems to be of importance, radiologists should be readily available for consultation [13]. Furthermore, consultation of radiologists improves the image interpretation and could also contribute to a better use of the optimal window/level settings in delineating the target volume.

Ad 3: Adding MR imaging may improve the visibility of the target volume [10]. Therefore, in our delineation studies we compared the delineation of the CTV Breast and the LC of 10 patients (delineated by two radiologists and two radiation oncologists) on both the CT and MR images separately and on the co-registered CT-MR images. In these studies the conformity indices were compared. However, in our study we found that adding MR images did not improve the consistency of the delineated volumes [15-17].

For the CTV Breast the largest variations were found in the medial and lateral borders of the target volume. Apart from the effect of these variations on the dose in the glandular breast tissue, Li et al. pointed out that these variations have the largest impact on the dose in the surrounding structures [22] and could thus increase the dose in the organs at risk (OAR). Another study analysing the additional value of using an MR imaging in target delineation of breast tissue also showed that the use of these images did not improve the consistency between observers [23], this is in line with our results.

Concerning the delineation of the LC, we found that the delineated volumes differ widely between observers. Also, the addition of MR images in these cases did not improve the consistency. A joint review of the delineated LC might provide a more consistent volume, and could avoid a geographic miss of the LC.

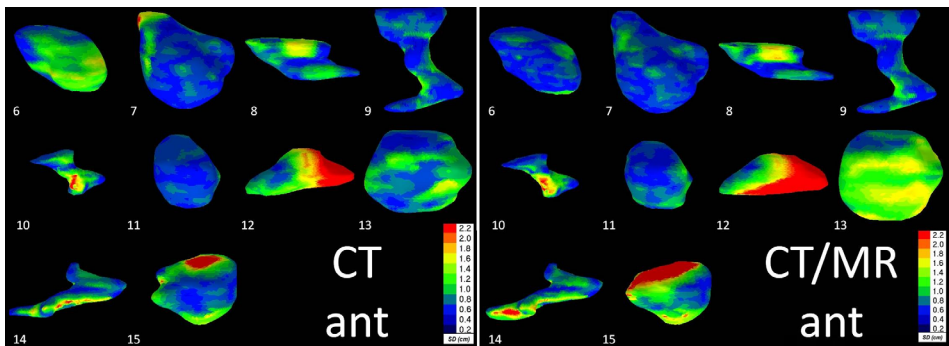


Figure 1. Coronal view of ten delineated lumpectomy cavity (LC) volumes in anterior and posterior view.

Colour map: blue, high agreement between observers; red, low agreement between observers, according to the scale given.

In both CT and CT-MR delineated LC volumes we found a CI of roughly 0.50. To note is that delineation differences in small volumes (when compared to larger volumes) appear to have a large impact on the calculated CIs. Furthermore, registration of CT and MRI remains difficult due to respiratory motion artefacts, together with distortion of breast tissue by overlying MR receiver coils. We found that multimodality breast markers are obligatory in performing an optimal CT-MR registration [24]. Avoiding the adjustment of CT-MR registration manually is important since this influences the definite LC volumes [20]. Adding surgical clips is a prerequisite to determine the lumpectomy volume according to the systematic review of Yang et al. [10]. The surgical clips are visible on the CT scan

and can be used as a helping tool in delineating the LC. However, defining the LC with the use of clips appear to be difficult as well, since the clips represent only a few points of the LC's border and an interpolation is usually required, resulting in delineation inaccuracies [10].

Apart from the variations reported in delineating the target volumes, Lorenzen et al. also described that variations can be found when delineating the heart and the coronary arteries. The use of guidelines for delineation of the heart improved the consistency considerably. However the use of guidelines did not improve the consistency of the left anterior descending (LAD) coronary artery delineation, since the LAD was not visible on all CT slices [25]. Therefore, aiming at delineating the LAD region instead of the LAD itself seems more appropriate.

Future perspectives: delineation of volumes

Based on our study results 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. It was demonstrated that differences in the delineated volume had great impact on the dose in the OAR. Therefore, we strongly suggest the following procedure in the delineating process. Firstly, we recommend that each observer should take advantage of the full potential of the planning system. By using the CT information in all three projections the observer keeps a better overview of the delineated structures. As a second recommendation, we expect that implementation of auto-contouring in the clinic may further improve the consistency in the generated structures. But, still, the expected conformity in delineation of the lumpectomy cavity needs to be proven. Thirdly, the ability of the radiation therapists to delineate the glandular breast tissue could further increase the efficiency in a radiation therapy department [26]. However, we are aware that a shift in activities and responsibilities of the radiotherapy team needs to be implemented gradually.

Treatment planning techniques in breast cancer radiotherapy

Performing treatment planning studies

Treatment planning studies have proven their value. The results give insight into the pros and cons of the several available treatment techniques. The results can be used to decide whether a new technique should be used in daily practice [27]. However, in order to make a true comparison of the various techniques, it is essential to define the same initial conditions for each separate technique. Depending on the defined hypothesis either the level of target coverage can be set equally, and in doing so enable the evaluation of the dose in the OAR, or the doses in the OAR are set equally, allowing evaluation of the differences in target coverage for the various compared treatment techniques. Also, the level of details of the calculated treatment technique needs to be described extensively, e.g. in a supplementary Table, in order to maximise the usefulness of the described planning techniques [27]. This is certainly helpful to the radiotherapy staff enabling them to reproduce the described radiation technique. Consequently, both reviewer and the journal, to which the manuscript was submitted, need to take their responsibility in maintaining uniformity in the described treatment planning studies.

Apart from these treatment-planning studies in daily practice the radiation oncologist will approve the final treatment plan. But he or she may decide to compromise the planning target volume coverage to spare an OAR.

Sparing organs at risk in breast cancer radiotherapy

Contralateral breast cancer (CBC)

Some patients with breast cancer have an elevated risk of developing a second breast cancer in the contralateral breast after radiotherapy [28,29]. Especially women who are diagnosed with breast cancer at young age (younger than 35 years old) and with a family history of breast cancer or an oestrogen receptor negative primary tumour, have a higher incidence of contralateral breast cancer [30]. Furthermore, Stovall et al. stated that for young patients (younger than 40 years old) an increased risk was found for doses in the contralateral breast higher than 1 Gy [31]. Also, Hoening et al. calculated the CBC risk and found a hazard ratio of 1.23 on the risk of medial contralateral breast cancer when receiving a radiation dose to the medial part of the contralateral breast up to 3.6 Gy in women < 45 years old [32]. For each individual patient the radiation oncologist should always decide if a higher dose in the contralateral breast outweighs a higher dose in the heart and the LAD-region. Recently, Abo-Madyan et al. stated that the use of multiple beam IMRT or VMAT increases the risk of CBC, although the absolute risk was low. Tangential IMRT results in a lower CBC risk [33].

Heart and coronary arteries

It is important to always reduce the dose in the heart and coronary arteries as much as possible, since several studies state that a higher dose in these arteries is associated with an increased risk of cardiovascular disease [7,8,34,35]. Paszat et al. found a higher risk of anterior myocardial infarction when larger volumes of the heart were incorporated in the treatment fields [36]. Interestingly, radiation techniques have changed over time and have led to a reduced heart dose. Graham et al. investigated the dose differences before and after routine 3D planning or cardiac contouring (before and after contouring era). They reported a significant lower mean heart dose in low risk patients (without treatment of internal mammary nodes or a boost dose), but no difference in the mean LAD dose. However, a correlation was reported between the Maximum Myocardial Depth (MMD) and the LAD dose; the mean doses in the inferior part of the LAD increased from 49% to 84% of the prescribed breast dose when the MMD was >15 mm. They also identified a 15-mm MMD as a useful transition point from low to high mean inferior-LAD doses [37]. On the opposite Aznar et al. stated that the dose delivered to the coronary arteries and the dose delivered to the heart are not necessarily correlated and that both organs at risk need to be delineated in order to get proper information of the applied doses [38]. Delineating the LAD is, however, difficult, and as Vennarini et al. stated, only one-third of the artery could be objectively visualised [39]. Therefore, delineating an LAD-region, instead of just the LAD, would be more appropriate in order to avoid a misinterpretation of the received dose [40,41].

Lung

The Quantec tolerance guidelines provide organ-specific dose/volume/outcome data. For the lungs, a dose tolerance has been described to avoid radiation pneumonitis, i.e. the volume that receives 20 Gy needs to remain below 30% for both lungs [42]. Also, the risk of radiation induced secondary lung cancers was increased, especially after a long term follow up period of 20 years [43,44]. A recently published review clearly showed that the risk of second lung cancers after breast cancer radiotherapy increases gradually in time. A dose-response relation for lung cancer has also been described, indicating a risk that seems to increase linearly with 8.5% (95% CI 3.1% to 23.3%) per delivered Gy to the lung [44]. A nested case-control study by Grantzau et al. confirmed that this risk was enhanced in ever smokers, with an excess rate of 17.3% per Gy [45].

Treatment planning techniques in breast cancer radiotherapy

With IMRT the dose homogeneity is increased and a 3-7% decrease of hotspots can be achieved. Two phase-III trials demonstrated that women in the IMRT treatment arms had less acute toxicity, long-term telangiectasia and fibrosis compared to women irradiated with 3D-CRT techniques [46]. The phase-III trial of Donovan et al. points out that doses higher than 105% can result in more induration of the breast [47]. However, the used IMRT techniques were more complex than the tangential IMRT technique we currently use [47-50]. The authors of both trials concluded that an IMRT technique should specifically be used for patients with large breasts. Munshi et al. report the same findings, they advise to perform a 2D technique in patients with small breasts [51]. In our treatment planning studies we see a higher homogeneity when using tangential IMRT compared to a 3D-CRT technique; this tangential IMRT technique is less complex and succeeds to significantly lower the dose in the heart and LAD, regardless of the volume of the breast.

It is remarkable that Graham et al. did not find a significant reduction of the cardiac dose in a comparison study from 2D to 3D CT-treatment planning [37]. They reported that the inferior part of the LAD received a high mean dose which could be lowered by using a breath-hold technique. Aznar et al. confirmed this finding. They performed a study on the dose levels in the specific parts of the heart [38]. In our treatment planning comparison study we found that, when using an IMRT technique, the dose decreased, in the heart as well as in the LAD-region. Specifically the caudal part of the treatment fields, including the LAD, received a lower dose. We, therefore, concluded that an IMRT technique adds a substantial gain in lowering the dose, especially in the caudal part of the heart, and, hence, in the caudal part of the LAD.

Finally, in defining the most optimal radiotherapy treatment technique with the lowest heart dose, one must not forget that the heart moves in and out (to some degree) of the radiotherapy treatment fields. Several studies quantified the movement of the heart [52,53]. Wang et al. advised more than 5 mm of distance between the LAD and the field edge because of the motion of the heart itself [54]. These variations should be kept in mind when evaluating the radiotherapy treatment plans. Adding a margin around the critical structures could be helpful.

Future perspectives: treatment planning

As several studies have shown, it is important to avoid as much radiation dose as possible in the heart and coronary arteries. Epidemiological studies show that even low doses need to be avoided as well. Based on literature [45,55] and our study results we advise the following arbitrary constraints when performing radiotherapy in left-sided breast conserving radiotherapy, since no absolute thresholds could be defined. The constraints, we advice, appear to be feasible from our treatment planning studies (using a fractionation scheme of 42.56 Gy in 16 fractions):

1. Mean heart dose < 2 Gy;
2. Mean lung dose < 5 Gy;
3. Mean dose outside the 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.

We propose to perform a tangential IMRT technique in all patients, regardless of age and size of the breast, since 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 treatment fields. By using a tangential IMRT technique the dose will better encompass

the target volume and the dose in the heart and LAD will be decreased as well. Moreover, when using a tangential IMRT technique no increase in the low dose regions in the normal tissue was found, even when applying a multiple beam IMRT technique. Another important aspect of the radiation treatment is to achieve the lowest dose in the normal tissue outside the treatment fields. In our treatment planning studies the proton therapy technique results in the lowest dose in the heart and coronary arteries and would, therefore, be the treatment of choice. However, an increased risk of skin toxicity could be expected when using protons [56]. The used proton technique (i.e. using multiple proton beams instead of a single beam) or the use of scanning techniques, advances in patient positioning and fractionation schedules seem to be important in reducing the skin dose [56,57]. Furthermore, as yet, proton therapy is not available in the Netherlands. However, if a limited use of proton therapy would be available, we would recommend a comparative assessment between costs, toxicity and the urgency of a dose reduction.

Another option to reduce the dose in the surrounding structures is the Accelerated Partial Breast Irradiation (APBI) technique. To determine if a patient is eligible for an APBI technique guidelines are available (ASTRO and ESTRO guidelines) [58,59]. According to these guidelines a patient could be classified in the so called “low risk” group. APBI techniques are widely available and appear to be feasible. The lower number of fractions is convenient for the patient. Furthermore, aiming only at the lumpectomy cavity the dose in the heart is lower. This is specifically valid for Intra Operative Radiotherapy (IORT) since the dose in the surrounding structures remains low by using proper shielding.

Breath-hold techniques in left-sided breast cancer radiotherapy

When 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 LAD coronary artery still could receive a relatively high maximum dose (2.7 Gy - 41.7 Gy; to note: some patients received nodal irradiation as well) [39]. We found that the mean LAD dose could be reduced with 50% when using a breath-hold technique, and for the high dose region this reduction was even larger. This was confirmed in other studies as well [60,61]. However, the randomised trial from Zellars et al. showed that ABC was not significantly associated with prevention of perfusion deficits compared before and six months after the radiation treatment. The reason that in four years time only 50 patients could be enrolled to this study remains unclear. Furthermore, a longer follow-up is needed to confirm their findings [62].

Several methods for performing a breath-hold technique are available, e.g. Active Breathing Control (ABC), voluntary breath-hold in combination with on-line registration of the patient position, Real-time Position Management system. [60,63-65]. The reproducibility of the various breath-hold methods was studied, all methods proved to be safe, including the ABC technique [66]. Recently Mittauer et al. investigated the dosimetric impact of breath-hold variations when using ABC. The estimated effect for the target coverage was negligible, however a large impact was estimated for the OARs [67]. One needs to consider this when applying breath-hold techniques. Most important is that the patient performs a moderate deep inspiration breath-hold (mDIBH) to achieve the largest distance between the heart and the radiation fields [68]. Remouchamps et al. defined a breath-hold threshold level of 75% of the maximum aspiratory capacity of the patient. The mDIBH level was chosen as a balance between achieving substantial heart displacement and maintaining patient comfort [68]. However, in a randomised cross-over study, the Royal Marsden found that a voluntary breath-hold

and the ABC technique were comparable as regards the reproducibility and the dose in the OARs, but that patients and staff preferred the voluntary breath-hold technique. It remains unclear why 136 of the in total 159 patients were excluded from the study [69]. In the diversity of treatment planning techniques for some patients the heart dose appears to be low as well without breath-hold, see Figure 2. In these patients treatment without a breath-hold technique could be an option, especially since no threshold for the heart and LAD dose could be defined in the literature. Also, the introduction of an age restriction could be considered, although Darby et al. recently found that cardiac events were observed within just 5 years after the radiation treatment and were independent of age [8]. In our institution 98% of the patients were able to complete the active breathing control method [64]. Moreover, this method potentially enables a more individualised approach. Summarising, the ABC technique is a reproducible and reliable technique. Therefore, we decided to use this type of breath-hold technique in all patients. Recently, Register et al. confirmed that no specific anatomic surrogate for the dosimetric benefits of DIBH technique could be identified; only the heart volume in the treatment field predicted the reduction in mean heart dose. They stated that a breath-hold technique should be used for all patients receiving left-sided breast cancer irradiation [70].

The results of our planning studies (Figure 2) clearly show that the breath-hold technique significantly reduces both the dose in the heart and the LAD-region. From our treatment planning studies TomoTherapy in breath-hold, when compared to tangential IMRT in breath-hold, appears to add an extra dose reduction. Unfortunately, it is not possible yet to combine TomoTherapy with breath-hold in a clinical setting. Furthermore, the mean heart dose reduction when using the TomoTherapy technique is limited, 1.5Gy (SD 0.5Gy) for IMRT in breath-hold and 1.1Gy (SD 0.4Gy) for the TomoTherapy technique in breath-hold. Therefore, the most optimal treatment technique for left-sided breast cancer radiotherapy appears to be the tangential IMRT technique combined with a breath-hold technique.

Whether the use of a breath-hold technique reduces the risk of coronary heart disease cannot be confirmed, although our calcium score study revealed a positive effect. Three years after whole breast irradiation we found a significantly smaller increase of LAD calcium scores in the group irradiated using a breath-hold technique when compared to patients irradiated without the use of breath-hold. Specifically, the individual findings of the coronary artery calcium (CAC) score in each patient are important. When the RCA CAC score was subtracted from the LAD CAC score it became clear that in the group of left-sided breast cancer patients, treated with a breath-hold technique, a significantly smaller increase in CAC score was noted 3 years after whole breast irradiation. Therefore, the risk of cardiac heart disease may have decreased as well, since the amount of CAC scores predicts the risk of subsequent cardiovascular events [71,72]. Drawbacks of our study are the small numbers and the relatively short follow-up period.

Finally, in performing treatment-planning studies, guidelines need to be formulated in order to be able to compare the results of studies. The scientific journals could be helpful in designing these guidelines. In combination with the ICRU recommendations, guidelines for planning studies can be helpful to optimise the radiation treatment techniques in daily practice.

Future perspectives: breath-hold techniques

With the increased knowledge concerning the several applied breath-hold techniques, it seems that aiming at an optimal enlargement of the thoracic volume is of importance.

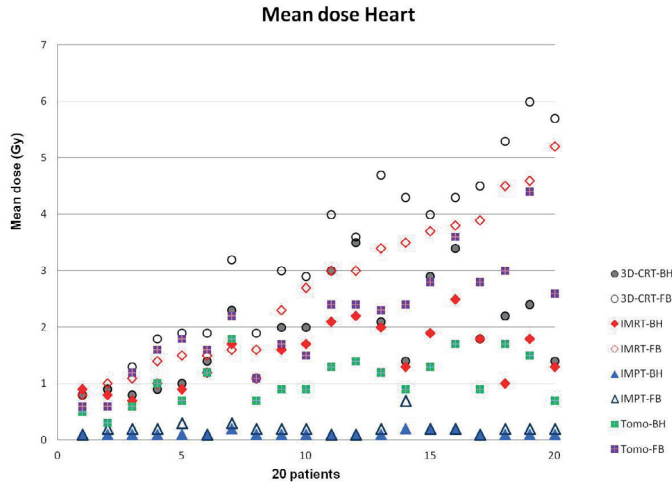


Figure 2. The various treatment planning techniques, with and without breath-hold. The 20 cases were rearranged using the increasing (from left to right) IMRT FB technique values.

A mean deep inspiration breath-hold of 75% of the maximum aspiratory capacity of the patient needs to be achieved to attain the largest thoracic amplitude. With a shallow breath-hold without increasing this amplitude the heart still may receive a relatively high radiation dose. The ABC method informs the staff with vital information about the maximal amplitude of each individual patient.

A breath-hold technique can also be used to reduce the dose in the ipsilateral lung. This is valid for patients with right-sided breast cancer radiotherapy as well. In all patients decreasing the risk of developing a secondary lung cancer is of importance and, therefore, the dose in the lungs should be kept as low as possible, which specifically applies to smokers [45].

Finally, when combining a breath-hold technique with a tangential IMRT technique a further dose reduction was found, especially in the caudal part of the treatment fields. Therefore, nowadays we advise to use a tangential IMRT technique in combination with a breath-hold technique. To note: the Active Breathing Control technique has the advantage of taking into account the thoracic amplitude. Whether the CTV-PTV margins can be decreased, with the use of a breath-hold technique, needs to be examined in future studies.

Coronary artery disease and breast cancer radiotherapy

Several pre-clinical studies reported that arteries are particularly sensitive to radiation [73-75]. It appeared that the carotid intima-media thickness increased linearly with increasing length of time after radiotherapy [76]. Stewart recently suggested that microvascular changes and atherosclerosis in experimental studies are the likely underlying causes of radiation-induced cardiovascular damage, at $\geq 2\text{Gy}$ and $\geq 8\text{Gy}$, respectively, to the whole heart or a part of the heart [77,78].

Whetal et al. confirmed that the presence of radiation-induced calcium deposits is considered as a surrogate marker for radiation-induced atherosclerotic lesions in patients treated for Hodgkin's lymphoma [79]. Also Daniels et al. found a high prevalence of asymptomatic coronary artery disease. They stated that this might justify the screening of Hodgkin disease survivors who had received mediastinal radiotherapy. However, they performed a computed tomographic coronary angiography, which is an invasive method [80].

Gondrie et al. tried to incorporate unexpected image findings, such as arterial calcium scores, and outcome data relevant to patients. They state that truly meaningful conclusions about the prognostic value of unexpected and emerging image findings can be reached and used to improve patient-care [81]. Jairam et al. presented in 2014 a calculation tool, which can be used in daily practice by radiologists to determine whether a subject has high calcifications scores relative to other patients with the same age and gender [82].

Groarke et al. claimed that a low threshold for screening with non-invasive imaging might help to identify injury at a stage where timely intervention may reduce cardiovascular morbidity and mortality in cancer survivors. But much cheaper and easier would be to use the low dose planning CT scan used for radiation treatment planning [83] together with the calculation tool of Jairam et al. [82].

Future perspective: coronary artery disease

The calculation tool of Jairam et al. [82] could be applied to identify patients with a high rate of calcifications on the CT scan and, therefore, having a high risk of developing a coronary vascular event. These patients could be proposed for a radiation technique with a low dose in the heart and the coronary arteries: e.g. the proton technique or if applicable an APBI technique.

Position verification in breast cancer radiotherapy

Another crucial step in the radiation treatment process is the position verification procedure on the linear accelerator. Several studies aimed at improving this process in order to achieve daily optimal patient positioning. It appeared that an on-line clip match procedure improves the localisation of the treatment volume [84-88]. In our institution we studied the optimal position verification procedure since 2008 [89]. In 2014 we started with an on-line surgical tantalum clips match as a position verification procedure for the boost fields [90].

Future perspective: position verification

To reduce the risk of geographical miss an on-line position procedure is of fundamental importance in administering a boost or external APBI. Instead of aiming at the bony structures we aim directly at the lumpectomy cavity by matching on the tantalum clips that represent the lumpectomy cavity. Tantalum clips are widely available and less expensive compared to gold markers. These clips can be placed in the lumpectomy cavity on a routinely basis. It is, therefore, easy to incorporate this procedure into daily practice.

Concluding remarks

As was stated before, lessons can be learned from the various published studies. Improvements in radiation techniques have been achieved. However, the surrounding healthy tissue will still receive a radiation dose, when the glandular breast tissue is irradiated after breast conserving surgery. Only omitting radiation treatment completely will prevent this. Up until now no subgroup of patients can be defined in whom radiotherapy can be safely omitted, since the risk on ipsilateral recurrence is significantly reduced when applying radiotherapy. However, in selected subgroups, for example in patients older than 70 years, with low-grade, small ductal carcinoma in situ [91], omitting radiation therapy after complete excision of the tumour and perform a wait and see policy could be an option.

In future, we need to focus on individualisation of the radiation treatment, taking into account tumour and patient-related risk factors, to try to cure the patient with the optimal and most convenient type of treatment, and reduce the treatment-related consequences as much as possible. In order to achieve the most optimal treatment we need to aim at an optimal definition of target volumes. Furthermore, several radiation treatment techniques could be used to reduce the dose in the heart and the LAD: i.e. tangential IMRT in combination with breath-hold, external APBI, IORT or, in specific cases by using protons. And, as a last step in the radiation treatment process, performing an optimal procedure to correct for positioning inaccuracies is a prerequisite. Thereby, preserving the patient's quality of life is of utmost importance. Finally, this needs to be tailored according to the patient's preferences, by means of a process of shared decision making.

References

1. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981;305(1):6-11.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and surgery in early breast cancer. An overview of randomized trials. *N Engl J Med* 1995;333:1444-1455.
3. van Dongen J, Voogd A, Fentiman I, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;92:1143-1150.
4. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation or the treatment of invasive breast cancer. *N Engl J Med* 2002;347(16):1233-1241.
5. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2014 [Epub ahead of print].
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378(9804):1707-1716.
7. McGale P, Darby S, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011;100:167-175.
8. Darby S, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-998.
9. Weiss E, Hess C The Impact of Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) Definition on the Total Accuracy in Radiotherapy. *Strahlenther Onkol* 2003;179:21-30.
10. Yang T, Tao R, Elkhuizen P, et al. Tumor bed delineation for external beam accelerated partial breast irradiation: A systematic review. *Radiother Oncol* 2013;108(2):181-189.
11. Poortmans P, Aznar M and Bartelink H Quality Indicators for Breast Cancer: Revisiting Historical Evidence in the Context of Technology Changes. *Semin Radiat Oncol* 2012;22(1):29-39.
12. Weiss E and Hess C The Impact of Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) Definition on the Total Accuracy in Radiotherapy. Theoretical Aspects and Practical Experiences. *Strahlenther Onkol* 2003;179:21-30.
13. van Mourik A, Elkhuizen P, Minkema D, et al. Multi institutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010;94:286-291.
14. Kouwenhoven E, Giezen M and Struikmans H. Measuring the similarity of target volume delineations independent of the number of observers. *Phys Med Biol* 2009;54:2863-2873.
15. Giezen M, Kouwenhoven E, Scholten A, et al. MRI versus CT based volume delineation of the lumpectomy cavity (LC) in supine position in breast conserving therapy: an exploratory study. *Int J Radiat Oncol Biol Phys* 2012;82:1332-1340.
16. Giezen M, Kouwenhoven E, Scholten A, et al. Magnetic Resonance Imaging- Versus Computed Tomography-Based Target Volume Delineation of the Glandular Breast Tissue (Clinical Target Volume Breast) in Breast-Conserving Therapy: An Exploratory Study. *Int J Radiat Oncol Biol Phys* 2011;81:804-811.
17. Mast M, Coerkamp E, Heijenbrok M, et al. Target volume delineation in breast conserving radiotherapy: are co-registered CT and MR images of added value? *Radiat Oncol* 2014;9:65.
18. Wong E, Truong P, Kader H, et al. Consistency in seroma contouring for

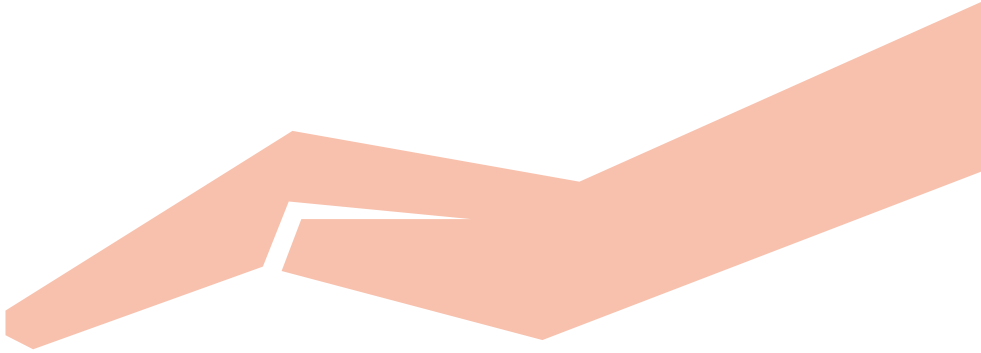
- partial breast radiotherapy: impact of guidelines. *Int J Radiat Oncol Biol Phys* 2006;66:372–376.
19. Nielsen M, Berg M, Pedersen M, et al. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group (2013). *Breast Cancer Cooperative Group. Acta Oncol* 2013; 52:703–710.
 20. Boersma L, Janssen T, Elkhuizen P, et al. Reducing interobserver variation of boost-CTV delineation in breast conserving radiation therapy using a pre-operative CT and delineation guidelines. *Radiother Oncol* 2012;103:178–182.
 21. Struikmans H, Wárlám-Rodenhuis C, Stam T, et al. Interobserver variability of target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005;76:293–299.
 22. Li X, Tai A, Arthur D, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG multi-institutional and multiobserver study. *Int J Radiat Oncol Biol Phys* 2009;73:944–951.
 23. Den Hartogh M, Philippens M, van Dam I, et al. MRI and CT imaging for preoperative target volume delineation in breast-conserving therapy. *Radiat Oncol* 2014;9:63.
 24. www.estro.org/search/MeshLevelOne/Surgical/MeshLevelTwo/Magnetic+Resonance+Imaging/MeshLevelThree/Mastectomy,+Segmental?page=46; assessed 17-01-2015.
 25. Lorenzen E, Taylor C, Maraldo M, et al. Inter-observer variation in delineation heart and left anterior descending coronary artery in radiotherapy for breast cancer: A multi-centre study from Denmark and the UK. *Radiother Oncol* 2013;108(2):254–258.
 26. Batumalai V, Koh E, Delaney G, et al. Interobserver Variability in Clinical Target Volume Delineation in Tangential Breast Irradiation: a Comparison between Radiation Oncologists and Radiation Therapists. *Clin Oncol* 2011;23:108–113.
 27. Yartsev S, Muren L and Thwaites D Treatment planning studies in radiotherapy. *Radiother Oncol* 2013;109:342–343.
 28. Soerjomataram I, Louwman W, de Vries E, Primary malignancy after primary female breast cancer in the south of the Netherlands, 1972–2001. *Breast Cancer Res Treat* 2005;93:91–95.
 29. Molina-Montes E, Perez-Nevot B, Marina Pollan M, et al. Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer: A systematic review and meta-analysis. *The Breast* 2014;23:721–742.
 30. Lizarraga I, Sugg SL, Weigel R, et al. Review of risk factors for the development of contralateral breast cancer. *Am J Surg* 2013;206:704–708.
 31. Stovall M, Smith S, Langholz B, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. *Int J Radiat Oncol Biol Phys* 2008;72(4):1021–1030.
 32. Hooning M, Aleman B, Hauptmann M, et al. Roles of Radiotherapy and Chemotherapy in the Development of Contralateral Breast Cancer. *J Clin Oncol* 2008;26(34):5561–5568.
 33. Abo-Madyan Y, Aziz M, Aly M, et al. Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. *Radiother Oncol* 2014;110(3):471–476.
 34. Borger J, Hooning M, Boersma L, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. *Int J Radiat Oncol Biol Phys* 2007;67:1131–1138.
 35. Stewart F, Hoving S and Russell N Vascular Damage as an Underlying Mechanism of Cardiac and Cerebral Toxicity in Irradiated Cancer Patients. *Radiat Res* 2010;174(6b):865–869.
 36. Paszat L, Vallis K, Benk V, et al. A population based case cohort study of the risk of myocardial infarction following radiation therapy for breast cancer.

- Radiother Oncol 2007;82:294-300.
37. Graham P. Cardiac dosimetry for adjuvant left-sided breast radiotherapy: Patterns with 2D- versus 3D-era planning and correlates of coronary dose with maximum depth of myocardial exposure J Med Imaging Radiat Oncol 2014;58:517–522.
 38. Aznar M, Korreman S, Pedersen A, et al. Evaluation of dose to cardiac structures during breast irradiation. Br J Radiol 2011;84:743-746.
 39. Vennarini S, Fournier-Bidoz N, Aristei C, et al. Visualisation of the left anterior descending coronary artery on CT images used for breast radiotherapy planning. Br J Radiol 2013;86:20120643.
 40. Taylor C, Povall J, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys 2008;72(2):501-507.
 41. Feng M, Moran J, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10–18.
 42. Marks L, Yorke E, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3):S10–S19.
 43. Henson K, McGale P, Taylor C, et al. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 2013;108:179–182.
 44. Grantzau T and Overgaard J Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. Radiother Oncol. 2014 [Epub ahead of print].
 45. Grantzau T, Thomsen M, Væth M, et al. Risk of second primary lung cancer in women after radiotherapy for breast cancer. Radiother Oncol 2014;111:366–373.
 46. McCormick B and Hunt M Intensity-modulated radiation therapy for breast: is it for everyone? Semin Radiat Oncol 2011;21:51-54.
 47. Donovan E, Bleakley N and Denholm E Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007;82:254–264.
 48. Evans P, Donovan E, Partridge M, et al. The delivery of intensity modulated radiotherapy to the breast using multiple static fields. Radiother Oncol 2000;57:79-89.
 49. Mihai A, Rakovitch E, Sixel K, et al. Inverse vs. Forward breast IMRT planning. Med Dosim 2005;30(3):149-154.
 50. Pignol J, Olivotto I, Rakovitch E, et al. A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis. J Clin Oncol 2008;26(13):2085-2092.
 51. Munshi A, Pai R, Phurailatpam R, et al. Do all patients of breast carcinoma need 3-Dimensional CT-based planning? A dosimetric study comparing different breast sizes. Med Dosim 2009;34(2):140-144.
 52. McIntosh A, Shoushtari A, Benedict S, et al. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inhalation breath hold for left breast cancer patients treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys 2011;81(4):569-576.
 53. Topolnjak R, Borst G, Nijkamp J, et al. Image-guided radiotherapy for left-sided breast cancer patients: geometrical uncertainty of the heart. Int J Radiat Oncol Biol Phys 2012;82(4):647-655.
 54. Wang X, Pan T, Pinnix C, et al. Cardiac motion during deep-inspiration breath-hold: implications for breast cancer radiotherapy. Int J Radiat Oncol Biol Phys 2012;82(2):708-714.
 55. Stewart F, Seemann I, Hoving S, et al. Understanding Radiation-induced Cardiovascular Damage and Strategies for Intervention Clin Oncol 2013;25:617-624.
 56. Galland-Girodet S, Pashtan I, MacDonald S et al. Longterm cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1

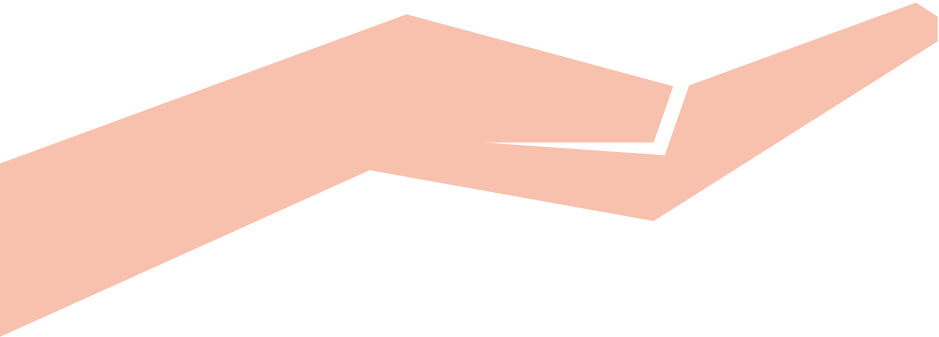
- trial. *Int J Radiat Oncol Biol Phys* 2014;90(3):493-500.
57. Bush D, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys* 2014;90(3):501-505.
 58. Smith B, Arthur D, Buchholz T, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO) *Int J Radiat Oncol Biol Phys* 2009;74(4):987-1001.
 59. Polgár C, Van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiothérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence. *Radiother Oncol* 2010;94:264-273.
 60. Swanson T, Grills I, Hong Y, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol* 2013;36:24-30.
 61. Beck R, Kim L, Yue N, et al. Treatment techniques to reduce cardiac irradiation for breast cancer patients treated with breast-conserving surgery and radiation therapy: a review. *Front Oncol*. 2014;14(4):327.
 62. Zellars R, Bravo P, Tryggstad E, et al. SPECT Analysis of Cardiac Perfusion Changes After Whole-Breast/Chest Wall Radiation Therapy With or Without Active Breathing Coordinator: Results of a Randomized Phase 3 Trial. *Int J Radiat Oncol Biol Phys*, 2014;88(4):778-785.
 63. Vikström J, Hjelstuen M, Mjaaland I, et al. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. *Acta Oncol* 2011;50:42-50.
 64. Mast M, van der Klein J, van Geen S, et al. Een hartsparende bestralingstechniek bij vrouwen met linkszijdige borstkanker. De resultaten van vier jaar ervaring in Radiotherapiecentrum West. *Ned. Tijdschr. Oncol.* 2012;9;6:270-276.
 65. Alderliesten T, Sonke JJ, Betgen A, et al. Accuracy Evaluation of a 3-Dimensional Surface Imaging System for Guidance in Deep-Inspiration Breath-Hold Radiation Therapy *Int J Radiat Oncol Biol Phys* 2013;85(2):536-542.
 66. Remouchamps V, Letts N, Yan D, et al. Three-dimensional evaluation of intra- and interfraction immobilization of lung and chest wall using active breathing control: A reproducibility study with breast cancer patients. *Int J Radiat Oncol Biol Phys* 2003;57(4):968-978.
 67. Mittauer K, Deraniyagala R, Li J, et al. Monitoring ABC-assisted deep inspiration breath hold for left-sided breast radiotherapy with an optical tracking system. *Med Phys* 2015;42(1):134.
 68. Remouchamps V, Letts N, Vicini F, et al. Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:704-715.
 69. Bartlett F, Colgan R, Carr K, et al. The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol* 2013;108(2):242-247.
 70. Register S, Takita C, Reis I, et al. Deep inspiration breath-hold technique for left-sided breast cancer: An analysis of predictors for organ-at-risk sparing. *Med Dosim* 2014 [Epub ahead of print].
 71. Greenland P, Bonow R, Brundage B, et al. Clinical Expert Consensus Document on Coronary Artery Calcium Scoring by Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients With Chest pain. A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA writing committee to update the 2000

- expert consensus document on electron beam computed tomography). *Circulation* 2007;115:402-426.
72. Oudkerk M, Stillman A, Halliburton S, et al. Coronary artery calcium screening: current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging. *Eur Radiol* 2008;18:2785-2807.
 73. Basavaraju S and Easterly C Pathophysiological effects of radiation on atherosclerosis development and progression, and the incidence of cardiovascular complications *Med Phys* 2002;29(10):2391-2403.
 74. Stewart F, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE_{-/-} mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006; 168:649-658.
 75. Schultz-Hector S and Trott K Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007;67:10-18.
 76. Huang T, Hsu H, Chen H, et al. Long-term effects on carotid intima-media thickness after radiotherapy in patients with nasopharyngeal carcinoma *Radiother Oncol* 2013;8:261.
 77. Stewart F, Mechanisms and dose-response relationships for radiation-induced cardiovascular disease *Ann ICRP* 2012;41(3):72-79.
 78. Stewart F, Seemann I, Hoving S, et al. Understanding Radiation-induced Cardiovascular Damage and Strategies for Intervention *Clin Oncol* 2013;25:617-624.
 79. Wethal T, Nedregaard B, Andersen R, et al. Atherosclerotic lesions in lymphoma survivors treated with radiotherapy. *Radiother Oncol*. 2014;110(3):448-454.
 80. Daniëls L, Krol A and De Graaf M Screening for coronary artery disease after mediastinal irradiation in Hodgkin lymphoma survivors: phase II study of indication and acceptance. *Annals of Oncology* 2014;25:1198-1203.
 81. Gondrie M, Mali W and Buckens C The PROgnostic Value of unrequested Information in Diagnostic Imaging (PROVIDI) Study: rationale and design. *Eur J Epidemiol* 2010;25:751-758.
 82. Jairam P, De Jong P, Mali W, et al. Age and sex based reference values for incidental coronary artery and thoracic aorta calcifications on routine clinical chest CT: A powerful tool to appreciate available imaging findings. *Atherosclerosis* 2014;235:546-553.
 83. Groarke J, Nguyen P, Nohria A, et al. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. *Eur Heart J* 2014;35:612-623.
 84. Kim L, Wong J, Yan D On-line localization of the lumpectomy cavity using surgical clips. *Int J Radiat Oncol Biol Phys* 2007;69:1305-1309.
 85. Hasan Y, Kim L, Martinez A, et al. Image guidance in external beam accelerated partial breast irradiation: comparison of surrogates for the lumpectomy cavity. *Int J Radiat Oncol Biol Phys* 2008;70(2):619-625.
 86. Penninkhof J, Quint S, Baaijens M, et al. Practical use of the extended no action level (eNAL) correction protocol for breast cancer patient with implanted surgical clips, *Int J Radiat Oncol Biol Phys* 2011;82:1031-1037.
 87. Topolnjak R, de Ruiter P, Remeijer P, et al. Image-guided radiotherapy for breast cancer patients: surgical clips as surrogate for Breast excision cavity, *Int J Radiat Oncol Biol Phys* 2011;81:187-195.
 88. Coles C, Harris E and Donovan E Evaluation of implanted gold seeds for breast radiotherapy planning and on treatment verification: A feasibility study on behalf of the IMPORT trialists. *Radiother Oncol* 2011;100(2):276-281.
 89. Mast M, Van Egmond J, Kuipers J, et al. Positieverificatie bij de 2-velden techniek bestraling van het borstklierweefsel in het kader van de sparende behandeling van borstkanker. *Gamma professional*.

- 2008;58(4):34-37.
90. van der Drift M, Mast M, Van Egmond J, et al. On-line positieverificatie op tantalum clips bij de sequentiële en partiële bestraling van de lumpectomieholte in de borst. *Gamma Professional*, Juli 2014, jaargang 64(3):3-7.
 91. Donker M, Litière S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol*. 2013;31(32):4054-4059.



SUMMARY



Summary

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.

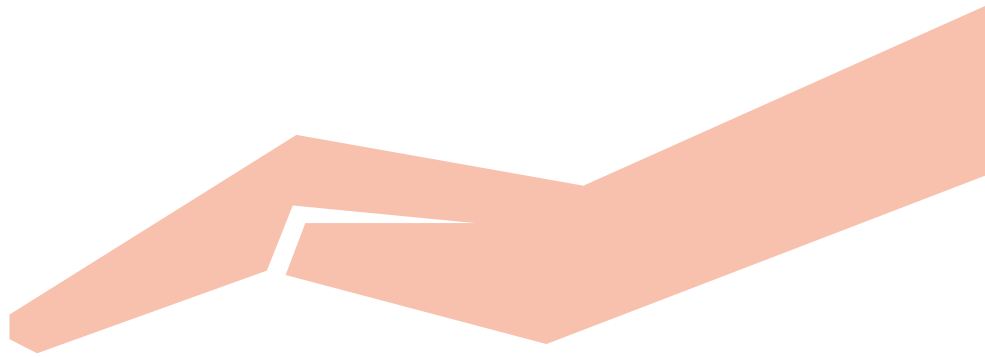
Secondly, three years after whole breast irradiation we found significantly less increase of CAC scores of the LAD in the group irradiated using a breath-hold technique when compared to patients irradiated without the use of breath-hold. When in each patient the Right Coronary Artery (RCA) CAC score 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.

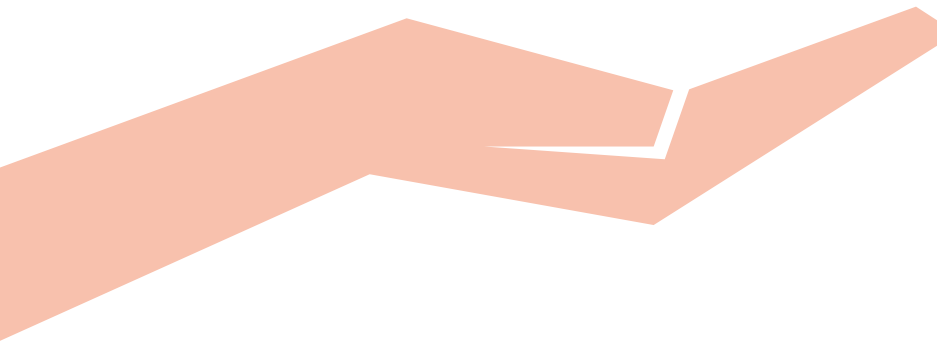
1. Mean heart dose < 2 Gy;
2. Mean lung dose < 5 Gy;
3. Mean dose outside the Planning Target Volume (PTV) as low as reasonably achievable.
4. In patients younger than 45 years the dose in the contralateral breast should be as low as possible. In BRCA 1/2 carriers this is of even more importance.

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.



SAMENVATTING



Samenvatting

In preklinische en klinische studies is aangetoond dat vrouwen die bestraald worden voor borstkanker, ten gevolge van die bestraling een grotere kans hebben op het ontstaan van hart- en vaatziekten. Dit geldt vooral voor vrouwen met linkszijdige borstkanker. Daarom is het van belang dat met name voor deze laatste categorie vrouwen specifieke maatregelen genomen worden om de hartdosis zo veel mogelijk te beperken opdat coronair lijden veroorzaakt door bestraling wordt voorkomen.

Dit proefschrift bevat drie hoofdstukken. De bespreking van een aantal relevante aspecten om de hartdosis tijdens electieve borstbestraling waar mogelijk te verlagen, staat in elk hoofdstuk centraal.

In **hoofdstuk 1** wordt het optimaliseren van de wijze van intekenen van het te bestralen doelgebied besproken. Dit is de eerste stap op weg naar het opstellen van een bestralingsplan. Niet optimaal ingetekende doelgebieden kunnen tijdens de gehele bestralingsperiode leiden tot het onjuist bestralen van deze doelgebieden. Zowel het borstklierweefsel (Clinical Target Volume; CTV breast) als het operatiegebied (lumpectomieholte; Lumpectomy Cavity; LC) is met Magnetic Resonance Imaging (MRI) in plaats van Computed Tomography (CT), waarschijnlijk met meer nauwkeurigheid te bepalen. Daarom onderzochten wij in dit proefschrift of het toevoegen van MR beelden, gescand in rugligging, van meerwaarde zou kunnen zijn. Dit laatste zou tot gevolg kunnen hebben dat de interobserver variatie bij het intekenen van het CTV breast en de LC kleiner wordt. In onze studies vergeleken we dit in tien patiënten die een CT scan hadden ondergaan na een borstsparende operatie. Twee radiologen en twee radiotherapeuten hebben de relevante doelgebieden ingetekend gebaseerd op geregistreerde CT-MR beelden en gebaseerd op de reguliere CT beelden. Uit het onderzoek bleek dat door toevoegen van MR beelden de interobservervariatie van de intekeningen voor zowel het CTV breast als voor de LC niet kleiner was geworden. Bij het gebruik van de “Cavity Visualisation Score” (CVS) bleek dat de gemiddelde conformityindex groter werd, hetgeen duidt op een betere overeenkomst tussen de intekenaars, als het doelvolumen duidelijk zichtbaar was op CT en MR beelden. Wanneer er sprake is van een lage CVS zouden clips een goed hulpmiddel kunnen zijn om de LC beter te kunnen definiëren.

Ook werd onderzocht wat de beste methode is om de MR beelden met die van de CT te fuseren. Nadat we vijf verschillende registratiemethoden hebben vergeleken, blijkt dat chirurgische clips niet altijd zichtbaar zijn op MR beelden, en dat “multimodality” markers gebruikt dienen te worden om een optimale CT-MR registratie te laten plaatsvinden. Wij concludeerden dat het beste resultaat wordt bereikt wanneer de markers, geplaatst op de te bestralen borst, worden gebruikt.

In **hoofdstuk 2** worden de resultaten van drie planningstudies, betreffende de electieve linkszijdige bestraling van het borstklierweefsel, beschreven. Uit onze studies werd duidelijk dat de gemiddelde dosis in de LAD met 50% kan worden verlaagd wanneer een ademhalingsgecontroleerde techniek wordt toegepast tijdens de bestraling. Er zijn verschillende ademhalingsgecontroleerde technieken beschikbaar. In RCWEST wordt de “Active Breathing Control” (ABC) methode toegepast. We hebben aangetoond dat 98% van de patiënten in staat is om deze methode uit te voeren.

Ook is de waarde van een aantal bestralingstechnieken onderzocht. Deze planningstudies laten zien dat een betere homogeniteit kan worden bereikt als een tangentiële Intensity Modulated Radiotherapy (IMRT) techniek wordt toegepast; dit vergeleken met

3D-conformatie radiotherapie (3D-CRT) techniek beide in combinatie met een ademhalingsgecontroleerde techniek. Deze tangentiële IMRT techniek is goed uitvoerbaar en leidt tot een significante verlaging van de dosis in het hart en de Left Anterior Descending (LAD) coronair arterie. Vooral het caudale gedeelte van het hart, inclusief de LAD, krijgt een lagere dosis. We concluderen dan ook dat een tangentiële IMRT techniek in combinatie met een ademhalingsgecontroleerde techniek een substantiële bijdrage levert aan het verlagen van de dosis in het hart, vooral in het caudale gedeelte van het hart.

Tevens werd de meerwaarde van een TomoTherapie en een protonen techniek onderzocht. In beide gevallen werd eveneens de waarde van een ademhalingsgecontroleerde techniek onderzocht. Als we gebruik maken van de ademhalingsgecontroleerde techniek blijkt uit deze planningsstudie dat, vergeleken met een IMRT-techniek, de gemiddelde dosis die het hart en de LAD ontvangen lager uitkomt. Echter, vanwege de lange bestralingstijden is het uitvoeren van een ademhalingsgecontroleerde TomoTherapie-techniek (nog) niet uitvoerbaar. De laagste hart- en LAD-dosis werd bereikt met het toepassen van een protonentechniek. Dit laatste gold zowel mét, als zonder het toepassen van de ademhalingsgecontroleerde techniek. Om deze reden zou de protonentechniek theoretisch gezien de voorkeur hebben. Momenteel is een protonentechniek nog niet toepasbaar in Nederland. Indien de protonen techniek beschikbaar zou zijn, raden we aan om alvorens te besluiten deze techniek bij patiënten met borstkanker toe te passen eerst een afweging te maken waarin worden meegenomen: de verwachte efficiency van de behandeling, de te verwachten toxiciteit van de behandeling, mogelijkheden voor het uitvoeren van “Accelerated Partial Breast Irradiation” (APBI) en kosten.

Wij concluderen dat het uitvoeren van een tangentiële IMRT-techniek in combinatie met een ademhalingsgecontroleerde techniek de beste combinatie is. Of door het toepassen van deze ademhalingsgecontroleerde bestralingstechnieken daadwerkelijk de kans op het ontstaan van hart-en vaatziekten na bestraling verkleind wordt, kan niet uit deze planningsstudies worden geconcludeerd.

De resultaten van de coronair-arterie-calcium (CAC) studie worden uiteengezet in **hoofdstuk 3**. De CAC scores werden bepaald op een CT scan die zonder toevoegen van contrast werd uitgevoerd. Volgens de literatuurgegevens blijken deze scores een uitstekende voorspeller te zijn voor het ontstaan van hart- en vaatziekten. Daarom wordt de CAC-score gezien als een surrogaat voor schade in de coronair-arteriën. In de eerste studie hebben we aangetoond dat de CAC-scores (bepaald voor de start van de bestraling) van vrouwen met borstkanker in de leeftijdscategorie van 55-64 jaar significant hoger waren dan de CAC-scores in een cohort asymptomatische Amerikaanse vrouwen zonder borstkanker. Deze bevinding wekt de suggestie dat vrouwen met borstkanker meer risico met zich mee dragen op het ontwikkelen van hart- en vaatziekten.

In de tweede studie hebben we drie jaar na afloop van de radiotherapie een significant lagere stijging gevonden van de CAC scores in de LAD in de groep van vrouwen met linkszijdige borstkanker en bestraald met de ademhalingsgecontroleerde techniek vergeleken met vrouwen bestraald voor linkszijdige borstkanker zonder de ademhalingsgecontroleerde techniek. Tevens bleek, in de groep vrouwen die linkszijdig werden bestraald met de ademhalingsgecontroleerde techniek, dat het verschil tussen de CAC score van de LAD en de CAC score van de rechter coronair arterie (RCA), bepaald voor elke individuele patiënt, drie jaar na de bestraling minder stijgt in vergelijking met vrouwen die linkszijdig werden bestraald zonder de ademhalingsgecontroleerde techniek. Beperkingen van deze studie zijn de kleine aantallen en de relatief korte follow-up. In het **discussie**-hoofdstuk worden diverse toekomstperspectieven uiteengezet. Ten aan-

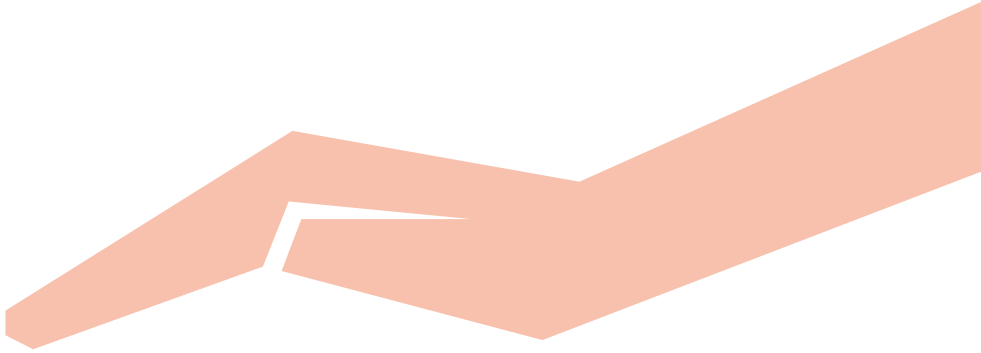
zien van het intekenen van het doelvolume ontraden we om MR beelden routinematig te gebruiken naast de CT beelden. Dit geldt voor zowel het intekenen van het borstklierweefsel als voor het intekenen van de lumpectomieholte. Verder concluderen we dat de tangentiële IMRT-techniek in combinatie met een ademhalingsgecontroleerde, de beste techniek is voor het electief bestralen van linkszijdige borstkanker. Dit is gebaseerd op het feit dat uit onze planningsstudies naar voren is gekomen dat in alle onderzochte patiënten een betere dosishomogeniteit was gevonden, en tevens een verlaging van de dosis in het hart, met name in het caudale gedeelte van de LAD. Omdat geen absolute drempelwaarden kunnen worden gedefinieerd, adviseren wij, gebaseerd op onze bevindingen en daaromtrent gepubliceerd onderzoek, om de volgende drempelwaarden voor linkszijdige borstbestralingen toe te passen.

We gaan uit van een fractioneringsschema van 42.65Gy in 16 fracties.

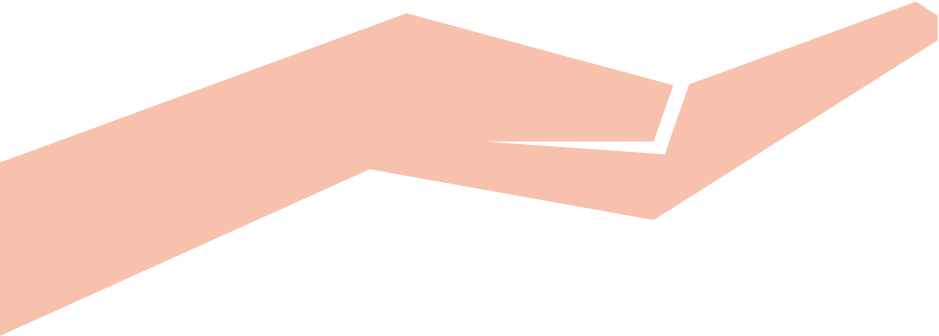
1. Gemiddelde hart dosis < 2 Gy;
2. Gemiddelde long dosis < 5 Gy;
3. Gemiddelde dosis buiten het te bestralen gebied, Planning Target Volume (PTV), zo laag mogelijk.
4. Bij patiënten jonger dan 45 jaar moet de dosis in de contralaterale borst zo laag mogelijk gehouden worden. In patiënten met een BRCA 1/2 genafwijking is dit zo mogelijk van nog groter belang.

Onze planningstudies tonen aan dat deze drempelwaarden haalbaar zijn. Verder adviseren we de ademhalingsgecontroleerde techniek toe te passen bij alle patiënten met linkszijdige borstkanker, zonder een leeftijdsgrens aan te houden of criteria te stellen aan de grootte van de te bestralen borst.

Conclusie: we hebben beschreven dat verbeteringen in radiotherapie-technieken bij borstkanker kunnen worden behaald. Echter, ondanks deze inspanningen zal het gezonde weefsel nog steeds een zekere dosis ontvangen als de gehele borst wordt bestraald. Mede hierom is het individualiseren van de bestralingsbehandeling van groot belang. Vervolgonderzoek zal tot doel moeten hebben negatieve (late) effecten van de radiotherapie te beperken en de kwaliteit van leven van de patiënt te verhogen. De introductie van partiële borstbestraling (APBI) zal verder onderzocht moeten worden. Dit geldt eveneens voor de vraag of de electieve borstbestraling wellicht volledig achterwege gelaten kan worden na borstsparende operatie. Besluitvorming hieromtrent kan niet worden geforceerd zonder de patiënt hierin te kennen en kennis te nemen van haar wensen. In samenspraak met de patiënt kan het behandelend team dan de meest optimale behandeling kiezen.



APPENDICES



Abbreviations

3D-CRT	3D-Conformal Radiotherapy
ABC	Active Breathing Control
APBI	Accelerated Partial Breast Irradiation
BCT	Breast Conserving Therapy
BH	Breath-Hold
BMI	Body Mass Index
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CI	Conformity Index
CI ^{CT;CTV}	Conformity Index on CT for the CTV Breast
CI ^{CTMR;CTV}	Conformity Index on CT compared to CTMR for the CTV Breast
CI ^{CT;LC}	Conformity Index on CT for the Lumpectomy Cavity
CI ^{CTMR;LC}	Conformity Index on CT compared to CTMR for the Lumpectomy Cavity
CT	Computer Tomography
CVS	Cavity Visualisation Score
CTV	Clinical Target Volume
DCS	Dice Similarity Coefficient
mDIBH	moderate Deep Inspiration Breath Hold
DVH	Dose Volume Histogram
FB	Free-Breathing
FRS	Framingham Risk Score
GBT	Glandular Breast Tissue
HLSs	Hodgkin's Lymphoma Survivors
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated RadioTherapy
IORT	Intra Operative RadioTherapy
LAD	Left Anterior Descending (coronary artery)
LC	Lumpectomy Cavity
LMA	Left Main Artery
LMx	Left Circumflex artery
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	Magnetic Resonance Imaging
MST	Mamma Sparende Techniek
NMI	Normalized Mutual Information
PTV	Planning Target Volume
RBE	Relative Biological Effectiveness
RCA	Right Coronary Artery
RCWEST	Radiotherapy Centre West
RT	Radiation Therapy
SD	Standard Deviation
SE	Standard Error
TSE	Turbo Spin Echo
VMAT	Volumetric Arc Therapy
WFS	Water-Fat Shift
WHF	World Health Federation

List of publications in peer reviewed journals

1. Mast M, Vredeveld J, Credoe M, Van Egmond J, Heijenbrok M, Hug E, Kalk P, van Kempen-Harteveld M, Korevaar E, van der Laan HP, Langendijk J, Rozema J, Petoukhova A, Schippers J, Struikmans H, Maduro J. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. *Breast Cancer Res Treat* 2014;148(1):33-39.
2. Mast M, Coerkamp E, Heijenbrok M, Scholten A, Jansen W, Kouwenhoven E, Nijkamp J, de Waard S, Petoukhova A, Struikmans H. Target volume delineation in breast conserving radiotherapy: are co-registered CT and MR images of added value? *Radiat Oncol* 2014;9:65.
3. Mast M, Van Kempen-Harteveld L, Heijenbrok M, Kalidien Y, Rozema H, Jansen W, Petoukhova A, Struikmans H. Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further? *Radiother Oncol* 2013;108(2):248-253.
4. Mast M, Struikmans H, Schreur J. In reply to Gyenes and Butler. *Int J Radiat Oncol Biol Phys* 2013;85(3):579-580.
5. Wiggenraad R, Verbeek-de Kanter A, Mast M, Molenaar R, Kal H, Lycklama A, Nijeholt G, Vecht C, Struikmans H. Local progression and pseudo progression after single fraction or fractionated stereotactic radiotherapy for large brain metastases: A single centre study. *Strahlenther Onkol* 2012;188(8):696-701.
6. Mast M, Heijenbrok M, Petoukhova A, Scholten A, Schreur J, Struikmans H. Preradiotherapy calcium scores of the coronary arteris in a cohort of women with early stage breast cancer; a comparison with a cohort of healthy women. *Int J Radiat Oncol Biol Phys* 2012;83(3):853-858.
7. Giezen M, Kouwenhoven E, Scholten A, Coerkamp E, Heijenbrok M, Jansen W, Mast M, Petoukhova A, Struikmans H. MRI versus CT based volume delineation of the lumpectomy cavity (LC) in supine position in breast conserving therapy: an exploratory study. *Int J Radiat Oncol Biol Phys* 2012;82:1332-1340.
8. Mast M, Van der Klein J, Van Geen S, Van Wingerden, Petoukhova A, Struikmans H. Een hartsparende bestralingstechniek bij vrouwen met linkszijdige borstkanker: de resultaten van 4 jaar ervaring in Radiotherapiecentrum West. *Ned Tijdschr Oncol* 2012;9:270-276.
9. Giezen M, Kouwenhoven E, Scholten A, Coerkamp E, Heijenbrok M, Jansen W, Mast M, Petoukhova A, Struikmans H. Magnetic Resonance Imaging- Versus Computed Tomography-Based Target Volume Delineation of the Glandular Breast Tissue (Clinical Target Volume Breast) in Breast-Conserving Therapy: An Exploratory Study. *Int J Radiat Oncol Biol Phys* 2011;81:804-811.
10. Wiggenraad R, Mast M, Van Santvoort J, Hoogendoorn M, Struikmans H. A 3D conformal parotid gland sparing irradiation technique for bilateral neck treatment as an alternative to IMRT. *Strahlenther Onkol* 2005;181(10):673-682.

List of publications in non-peer reviewed journals

1. Mast M, Crama M, Roering R, Kwakkel – Huizenga L, Petoukhova A, Struikmans H. Radiotherapie bij een patiënt met zeer pijnlijke wratten op beide voeten: beschrijving van een casus. *Gamma Professional* 2015;65(1):3-5.
2. El Kadaoui M, Mast M, Marinelli A, Peeters M, Petoukhova A, Tan J, Van der Sijp J, Van Wingerden J, Koper P, Struikmans H. Borstsparende behandeling van borstkanker; klaar in 1 dag. *Gamma Professional* 2014;64(4):16-17.
3. Van der Drift M, Mast M, Van Egmond J, Kuipers J, Van Santvoort J, Struikmans H. On-line positieverificatie op tantalum clips bij de sequentiële en partiële bestraling van de lumpectomieholte in de borst. *Gamma Professional* 2014;64(3):3-7.
4. Struikmans H, Mast M, Petoukhova A. Case report: radiotherapy for disabling bilateral verrucae plantares (plantar warts). *ESTRO News* July 2014.
5. Roos J, Mast M, Van Egmond J, Struikmans H, Petoukhova A. Van wig naar plat: wat is het effect op de dosis in het normale weefsel bij borstsparende bestraling. *Gamma Professional* 2013;63(1):22-25.
6. Mast M, Struikmans H. Radiotherapy for breast cancer during pregnancy. A case report. *ESTRO News* February 2013.
7. Renes G, Tieben J, Tijssen N, Mast M, Struikmans H. Straal met je hart, straal minder hart. Hartsparing bij de 2 velden bestraling van de borst met toepassing van de ABC techniek: een vergelijkende planning studie van IMRT versus 3D-CRT. *Gamma Professional* 2010;60(1):14-16.
8. Mast M, Van Egmond J, Kuipers J, Jansen W, Pieterse A, Van Santvoort J, Struikmans H. Positieverificatie bij de 2-velden techniek bestraling van het borstklieerweefsel in het kader van de sparende behandeling van borstkanker. *Gamma professional* 2008;58(4):34-37.
9. Benschop E, Limpens K, Reurink N, Mast M. Active Breathing Control methode in de praktijk Introductie en implementatie van de Active Breathing Control methode in de praktijk bij bestraling van patiënten met borstkanker. *Gamma Professional* 2008;58(4):31-33.
10. Giezen M, Jansen W, Mast M, Petoukhova A, Scholten A, Struikmans H. Relevance of decreasing the heart dose for whole breast irradiation with left-sided breast cancer after breast conserving surgery. *Gamma professional* 2007;57(1):33-35.

Books

Froma A, Mast M, Welleweerd H, editors, *Techniek in de radiotherapie*, 2nd edition, Maarssen: Elsevier gezondheidszorg; 2007.

Curriculum Vitae

The author of this thesis was born on November 12th, 1970 in Haarlem, The Netherlands.

After practising nine years as a radiation therapist in Medical Center Haaglanden she took a Masters Course at the Graduate School of Health, Haarlem, The Netherlands. In 2003 she obtained her MSc degree Radiation Therapy in Europe. Since then she worked as a staff member Research&Development (R&D) in Radiotherapy Centre West (RCWEST). In 2009 she received her MSc in Epidemiology, at the Institute for Research in Extramural Medicine, EMGO instituut, VUMC, Amsterdam. Thereafter, she started working on her PhD.

Dankwoord

Promoveren is een lange weg, en tijdens de wandeling die je maakt lopen er veel mensen met je mee. De reis begon met het opzetten van de functie 'Research&Development medewerker' en de kans die de afdeling radiotherapie van het MCH Westeinde in het algemeen en Henk Struikmans in het bijzonder mij bood. Dank Henk, voor het vertrouwen in mij, en voor je ondersteuning.

Allereerst wil ik me graag richten tot de vrouwen met borstkanker die bestraald zijn op de afdeling radiotherapie van het MCH Westeinde en die bereid waren mee te werken aan onze onderzoeken. Dank voor het gestelde vertrouwen in ons.

Daarnaast mijn beide co-promotores, Anna en Astrid. Anna, samen met Henk stond je zo ongeveer dag en nacht klaar om op mijn mails te reageren. Een betere ondersteuning kon ik me niet wensen. Astrid, ik heb je heldere blik op de materie zeer gewaardeerd. Het is geweldig om in zo'n fijn promotie team gewerkt te hebben.

Alle mede-auteurs, dank voor jullie geduld als ik jullie weer eens bestookte met vragen of korte deadlines. Emile en Mark, dank voor de vele intekenuren, wat hebben jullie veel werk verzet; Mark, naast het intekenen heb je alle CAC CT's beoordeeld en samen met Joop consensus gezocht ten aanzien van deze scores. Ook dit heeft vele uren van jullie gekost. Joop, dank voor het meedenken, je bemoedigende woorden en de klap op mijn schouder om vooral vol te houden. Loes, dank voor alle goede tips, zelfs tot midden in de nacht werkte je door om commentaar aan te leveren, ook jij moedigde me aan vol te houden. Dank ook voor de kritische blik op de materie. Wim, dank voor je bijdragen in de vele hartsparringsoverleggen en dat je bereid was steeds naar Den Haag te komen. Ron, dank voor de analyses van de calciumwaarden, het waren intensieve overleggen, waar we beiden enthousiast uit kwamen. Het was ontzettend leerzaam, ook om te mogen samenwerken met collega's uit het NKI-AvL, UMCG, VU Brussel en het LUMC. Allen dank voor het meedenken en jullie kritische blik. Ik heb het als zeer leerzaam en prettig ervaren!

Freek, wat heb je ontzettend veel voor me gedaan! Het redigeren van alle Engelse teksten. Hoe strak de deadline ook was, je stond voor me klaar. Thanks a million!! Wopke, dank voor het redigeren van de Nederlandse teksten en je kritische blik op de stellingen.

Alle (ex)collega's van de afdeling radiotherapie dank ik voor alle geboden ondersteuning, aanmoedigingen, getoonde interesse, meelevens en begrip. Het heeft me geholpen om door te zetten. Heleen, dank dat je, ondanks je drukke schema, de introductie en discussie door wilde nemen en aanvullingen hebt gegeven. En Paul Rietveld, dank dat je de teksten op vergeten spaties en typefouten hebt gecontroleerd.

Thomas en Pauline van de medische bibliotheek, jullie waren onmisbaar voor het aanleveren van de literatuur; Thomas voor alle zoekopdrachten die je hebt gemaakt, dank, ze waren van essentieel belang.

Zonder administratieve ondersteuning ben je nergens; het verwerken van alle brieven door Ina; het versturen van documenten of nalopen van de studiemappen door Ineke; het bij elkaar zetten van documenten en de administratie rondom de promotie door Esther; het regelen van alle CT afspraken en meedenken hierin door de dames van de balie. Dank allemaal voor alle geboden hulp.

De collega's van de afdeling radiologie wil ik bedanken voor het uitvoeren van de vele scans, en het management van de afdeling radiologie van het MCH WZ dank voor de flexibiliteit bij het maken van alle MRI- en calciumscore CT scans.

Floris Mast, Suze Swarte en Laura Bolczek, zonder jullie zag mijn boekje er niet zo mooi uit. Dank voor jullie kunstzinnig inzicht!

Mijn lieve familie en vrienden, die me bijna zagen vergroeien met de computer. Dank voor het meeleven en meedenken, en voor jullie geduld en begrip. Blij dat jullie zo dicht om me heen staan! Rob, wat jammer dat ik niet met je heb kunnen sparren over mijn boekje. Ik weet zeker dat je me het vuur aan de schenen had gelegd en me had uitgedaagd te discussiëren over de zin en onzin van promoveren. Ik mis je nog steeds.

Lieve pap en mam en mam van Egmond, dank voor jullie grenseloos vertrouwen in me, jullie begrip, aanmoediging en het meeleven. Ik ben dankbaar dat jullie de oplevering van het boekje kunnen meemaken. Mijn maatje Maarten, de vele wandelingen met jou zorgde voor de broodnodige ontspanning, zo jammer dat je er niet meer bent. 'Nicht Layki' heeft de taak van je overgenomen, en met verve. Fijn! En tot slot, Jaap, dank dat je altijd voor me klaar stond, je begrip, je bemoedigende woorden en het steeds meeslepen van mijn computer op de boot.

AVOIDING THE HEART

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

With respect to whole breast irradiation we concluded that:

- the routine use of MR images in addition to the CT scan, when delineating either the glandular breast tissue or the lumpectomy cavity, does not have added value.
- tangential IMRT technique combined with a breath-hold technique should be the treatment technique of choice for left-sided breast cancer.
- a breath-hold technique should and can be used in all left-sided breast cancer patients, regardless of age and breast size.
- breath-hold in left-sided whole breast radiotherapy results in a less pronounced increase of coronary calcium score and, hence, could result in less radiation-induced cardio vascular damage.