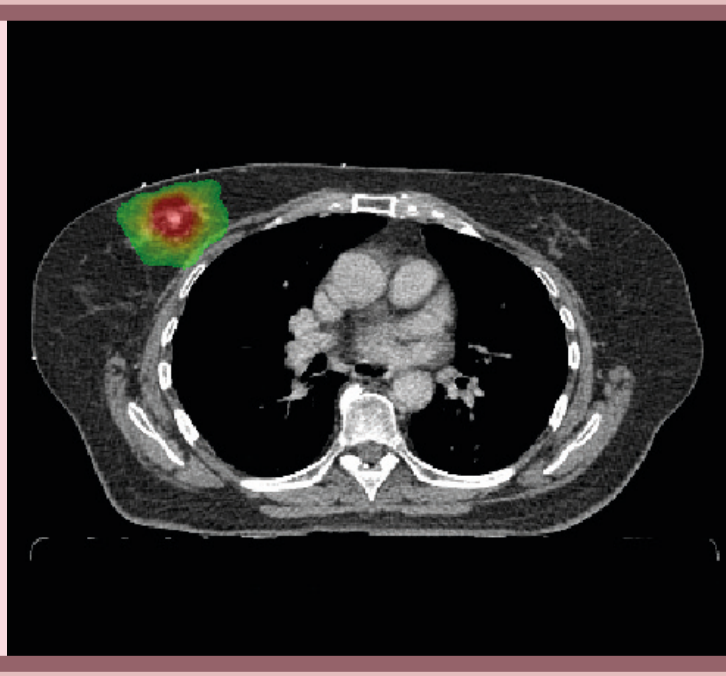
TREATMENT DE-ESCALATION FOR EARLY-STAGE BREAST CANCER

MRI-GUIDED SINGLE DOSE PREOPERATIVE ABLATIVE RADIOTHERAPY



RAMONA K.
CHARAGHVANDI-DAYERIZADEH

Treatment de-escalation for early-stage breast cancer: MRI-guided single dose preoperatieve ablative radiotherapy

De-escalatie in behandeling voor vroeg-stadium borstkanker: eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie
(met een samenvatting in het Nederlands)

proefschrift

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“Voor mijn ouders”

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Chapter 1
Introduction

Historical background of breast cancer treatment

The first mentioning of breast cancer and treatment attempts go back to ancient Egypt, where in the Edwin Smith Surgical Papyrus (2500-3000 BC) cancer cases were clinically described, clearly differentiating this fatal disease entity from infections of the breast [1-2]. Ever since, developments in breast cancer treatment were prone to the social and cultural beliefs of that timeframe, ranging from temple offerings to Asclepius in ancient Greece, diet, purgation and surgery-attempts in Roman times, stagnating developments in Europe of the Dark Ages, and pursue of surgical progress in the Arabic, Moorish and Middle-Eastern cultures [1-2]. Anatomical breast and lymphatic's explorations in Western Europe during the 16th-18th century Renaissance were followed by a Golden Age of surgery due to several discoveries such as sterilization of instrumentation, the use of surgical gloves and anesthesia in the 19th century [1-2]. The first milestone in breast cancer treatment – the famous radical mastectomy approach of the American surgeon Halsted – was first reported in 1894, which expanded upon previous work on pectoral muscle, fascia and en bloc resection and axillary lymph nodes dissections by German and English colleagues [2]. In the 1930's in France, François Baclesse showed that it was possible to cure breast cancer patients with radiotherapy alone. Later on, he demostrated that feasibility of breast conserving therapy by combining radiotherapy with surgical tumor resection, which was unfortunately associated with severe late sequelae [3]. Also the 1930's, the English surgeon Keynes proposed the combination of a simple mastectomy with radium needle implantation in the lymph nodes, as an alternative to radical mastectomy [4]. Despite promising clinical results similar to radical surgery, Keynes eventually abandoned his research due to negative publicity. The Scottish radiologist McWhirter, convinced by Keyne's results, started to combine simple mastectomy with thoracic wall and lymph nodes irradiation and published in 1949 improved survival rates from previous approaches [2,4]. Nonetheless, the first radiotherapy milestone in breast cancer treatment was reached in 1981 when Veronesi reported no survival benefit and poorer cosmetic outcomes in women with early-stage breast cancer treated with radical mastectomy compared to quadrantectomy and axillary lymph node dissection followed by whole breast irradiation [5]. Other milestones such as the introduction of chemotherapy and endocrine therapy (i.e. Tamoxifen), the growing use of screening mammographies since the 1970's, the introduction of breast conserving surgery and whole breast irradiation as alternative for mastectomy in the 1980's, advances in genetic profiling from the mid 1990's on, the discovery of the Her2 protein therapy in 2001 and introduction of aromatase inhibitors in 2004 have had a significant positive impact on the prognosis of breast cancer patients and further refined current breast cancer treatment [6].

Epidemiology of breast cancer

Breast cancer is currently the most frequently diagnosed cancer among women in the world, with 1.7 million new cases diagnosed in 2012, accounting for 25% of all cancer cases [7]. In the Netherlands, the number of new cases of breast cancer and ductal carcinoma in situ is around 16.000 per year, with a 12-14% lifetime risk for a Dutch women to develop breast cancer, should she reach the age of 85 years [8]. In the great majority of the breast cancer patients, 75%, early-stage breast cancer (i.e. stage I-II) is diagnosed, mainly due to the introduction of the national breast screening program in 1995 [9]. This has resulted in increasing incidence rates the past decades. In addition, due to systemic treatment, improved overall survival of 76% at 10 year and locoregional recurrence rates as low as 2.5% are encountered at 5 years [9]. Furthermore, with growing knowledge on the long-term impact of oncological treatment on health (e.g. cardiotoxicity caused by chemotherapy or radiotherapy), physical (e.g. functional morbidity following surgery) and emotional functioning (e.g. toxicity caused by endocrine treatment), the importance of other endpoints than survival, such as quality of life (QoL) became more clear, for patients as well as for medical professionals [10].

Local treatment of early-stage breast cancer

Whole breast irradiation

Breast-conserving therapy (BCT), consisting of breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) with or without a boost to the tumor bed, is currently the standard of care for early-stage breast cancer [5, 11-14]. The addition of WBI following BCS results in decreased locoregional recurrence rates, distant disease recurrence or breast cancer associated death, depending on the patient's or tumor's characteristics [14]. Breast-conserving treatment has demonstrated equivalent oncological efficacy to mastectomy in early-stage breast cancer, and is therefore preferred in current clinical practice [5, 11-12]. The past years, the conventional WBI (i.e. 50 Gy in 2 Gy fractions, ≥25 fractions) has been replaced by the equally oncological effective hypofractionated WBI (i.e. fraction size >2 Gy, 15-16 fractions), enabling a shorter RT fractionation schedule [15].

For women with early-stage breast cancer and a low-risk of local recurrence, alternatives have been sought for the protracted RT fractionation schedule (i.e. 15-23 fractions during a three to five weeks interval), but also for its associated treatment burden and toxicity. For example, the omission of postoperative RT in elderly patients treated with endocrine therapy resulted in increased loco(regional) recurrence rates, but without an impact on survival [16,17]. Another strategy aiming at reduction of the treatment burden for early-stage breast cancer patients was evaluated within the FAST phase II trial with a 30 Gy or 28.5 Gy hypofractionated RT-schedule in 5 weekly fractions [18]. A 1.3% ipsilateral local recurrence rate and 100% rate of good or excellent cosmesis was evaluated at 3 years follow-up [19]. In addition, the FAST-FORWARD phase III clinical testing a 1-week WBI course (26 Gy or 27 Gy/5 fractions) versus the standard of care 3 week regimen in the United Kingdom (i.e. 40 Gy/15 fractions) evaluated low incidence rates of clinically significant acute skin toxicity with both schedules [19]. The long term-oncological outcomes of the FAST-trials are still under investigation.

Partial breast irradiation

Partial breast irradiation (PBI), aiming at the delivery of RT only on the high-risk breast tissue surrounding the tumor bed is an alternative for WBI for selected patients with early-stage breast cancer and low-risk of local recurrence [20-23]. The necessity of irradiation of the whole breast leading to breast and adjacent organ toxicity has been questioned, since the majority of recurrences (i.e. 62-88%) of small invasive carcinomas occur in the vicinity of the previous tumor location [24-26]. Since target volumes in PBI are smaller compared to

WBI, dose escalation per fraction can lead to shorter RT fractionation schedules, so-called accelerated partial breast irradiation (APBI). Compared to WBI, both a PBI and APBI approach result in a decreased irradiated volume and possibly less associated RT-toxicity. In addition, the treatment time reduction associated with APBI might result in a reduced treatment burden for the patient.

Several APBI techniques are available, each with their own advantages and disadvantages [28-29]. Interstitial multicathether brachytherapy-based APBI is the technique with the longest available follow-up. Intraoperative RT is a more recently developed APBI-method, which has the major advantage of completing RT in one single session at the operation theater following BCS. A drawback of both of these approaches concerns the necessity of additional equipment and trained personnel, thereby limiting the availability of these techniques. External beam based APBI is a non-invasive, widespread available technique in medical centers, however in comparison to interstitial multicatheter brachytherapy or intraoperative RT, larger treatment volumes are usually irradiated. Also, it should be mentioned that external beam APBI can be delivered in either the supine or the prone treatment position. The great majority of the radiation oncology departments treat patients in the supine position, since this approach is more robust for positioning on the treatment table (i.e. less set-up errors). Some institutions perform external beam APBI in the prone treatment position, which might be more beneficial to normal tissue dosimetry in subsets of patients, e.g. left-breast cancer in large breasts [30].

Several randomized controlled trials on WBI versus (A)PBI with various RT-delivery techniques have been performed, revealing conflicting oncological and toxicity results [23, 31-39]. The majority of these studies have been included in a systematic-review and meta-analysis, showing a significant increase in local recurrence and new primaries in the ipsilateral breast in partial breast irradiation compared to WBI, with similar overall survival rates [38-39]. Breast and skin toxicity profiles varied substantially across treatment arms and, not surprisingly, also across (A)PBI-techniques [30-37]. These results reflect the heterogeneity in (A)PBI studies, with the included patients at a high- and low-risk for local recurrence, and ascertain the intrinsic RT dosimetry characteristics of the various techniques. The American Society for Radiation Oncology (ASTRO) and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO), divide breast cancer patients in three risk-categories for local recurrence and thus APBI eligibility within clinical practice or clinical trials [20-22]. The recommended 'low-risk' patient and tumor characteristics suitable for (A)PBI are summarized in table 1.

A recent randomized controlled trial, the UK IMPORT-LOW, evaluated external beam based RT approaches in low-risk breast cancer patients [23]. The three treatment arms were 40 Gy to the whole breast versus 40 Gy to the partial breast, versus the combination 36 Gy whole breast RT plus 40 Gy to the partial breast, all delivered in 15 fractions. In 2018 patients treated between 2007 and 2010, no significant differences in the 5 years local recurrence rates were assessed in the PBI-arm only (i.e. 0.5%) versus the conventional WBI-arm (i.e. 1.1%) only. Furthermore, in the PBI compared to the WBI-arm, significantly less changes in breast appearance (i.e. 27% versus 38%) and less firmer breast tissue (i.e. 14% versus 28%) were reported. QoL, as evaluated with the breast cancer specific EORTC-QLQ-B23 questionnaire, showed no differences between the treatment arms. The authors therefore conclude that a 40 Gy in 15 fractions PBI schedule delivered using an external beam technique, is safe and effective and could be easily implemented within most radiotherapy centers worldwide.

Table 1. Summary of eligibility criteria for accelerated partial breast irradiation according to American Society for Radiation Oncology (ASTRO) and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (ESTRO) guidelines

ASTRO-suitable	ESTRO-low-risk
• ≥ 50 years • Non-lobular carcinoma • Free surgical excision margins ≥2mm • Unifocal tumor • pT1N0 (including isolated tumor cells) • No extended DCIS • ER-receptor positivity • No limitations grading • If screen detected, then DCIS up to 2.5cm, grade 1-2, with free excision margins ≥3mm.	• ≥ 50 years • Non-lobular carcinoma • Free surgical excision margins ≥2mm • pT1-2(max 3.0cm)N0 • Unifocal tumor • No solely DCIS or extended DCIS • No limitations grade, ER or PR receptor

Consequently, the IMPORT-LOW PBI-schedule has recently been introduced in the Netherlands as an alternative for WBI in clinical practice, for selected low-risk patients with early-stage breast cancer. Furthermore in the Netherlands, intraoperative-based APBI within standard clinical practice is being performed in two Dutch medical centers.

The greatest variation in APBI toxicity results is found for external beam technique, and is probably due to variations in RT-schedules, radiation dose-time effect (i.e. one-daily versus two-daily schedule) or delivery techniques (e.g. volumetric modulated arc therapy is more conformal to treatment volumes and enables less high-dose volumes compared to 3D conformal radiotherapy). Furthermore, the importance of treatment volumes is illustrated by preliminary results of the RAPID randomized controlled trial evaluating conventional or hypofractionated WBI versus an APBI 38.5 Gy schedule in 10 twice daily fractions reported significantly more fair and poor cosmesis in the APBI arm at 5 years follow-up (13% versus 33%, respectively) [33]. Interestingly, another randomized controlled trial evaluating a WBI-schedule of 48 Gy in 2 Gy fractions (with or without a boost), versus an almost similar to RAPID APBI schedule of 37.5 Gy in 10 fractions twice daily, found no differences in the treatment arms with 100% good cosmetic results during 5 years follow-up [35]. Possible explanations for the increased toxicity in the APBI-arm of the RAPID trial concerns the short interfraction interval of 6 hours, and the low percentage of boost-patients (i.e. 21%) in the WBI-arm. In multivariate analysis, factors evaluated with adverse cosmesis were smoking, advanced age and larger seroma volume [41]. Furthermore, in the previously mentioned APBI-studies, different maximum acceptable ratio's of RT target volume to ipsilateral breast were employed (e.g. in the RAPID-trial up to 35% thereby exceeding the 25% ESTRO recommendation), which might have lead to variations in treatment volumes [21]. Inconsistencies in toxicity profiles might therefore also partly be explained by the extent of RT target volumes, since large treatment volumes correlate with increased treatment toxicity such as fibrosis [42].

Preoperative versus post-operative partial breast irradiation

Preoperative APBI aims for RT delivery to the intact tumor and tumor bed, before surgical artefacts occur in the affected breast. Subsequently, RT dosimetry studies have shown that this approach results in small, limited treatment volumes (figure 1) and improved inter-observer agreement between radiation oncologists on target

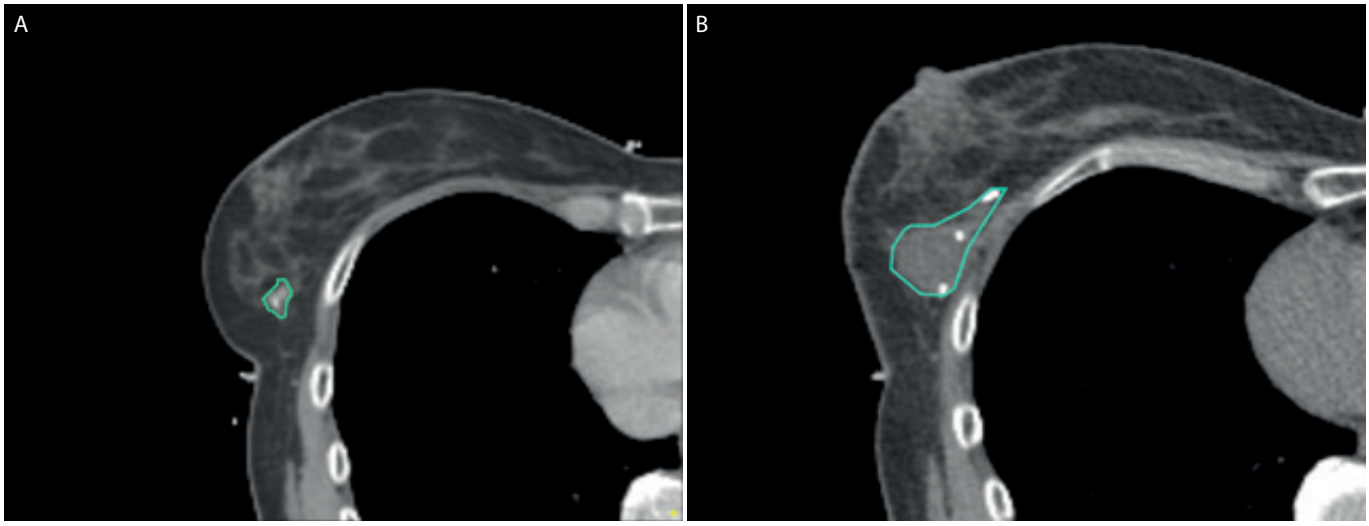

Figure 1. A planning-CT in the same breast cancer patient (A) illustrating a preoperative radiotherapy approach with the intact tumor versus (B) a postoperative approach with a (larger volume) tumor bed. *(courtesy of dr. M.D. den Hartogh)*

volumes delineations, compared to a post-operative APBI approach [43-44].

Furthermore, a preoperative approach might open a new window of opportunities in refinement of current breast cancer treatment through dose escalation per fraction, downstaging and evaluation of the pathologic tumor response to RT.

High-dose RT delivery to the intact tumor might redefine the role of radiotherapy for early-stage breast cancer from adjuvant to breast conserving surgery towards a primary radiosurgical role. Radiotherapy as an alternative for a surgical approach has gained ground as primary treatment for several oncological sites, such as stage I lung cancer, specific brain malignancy or oligometastatic disease [46]. In line with these developments, high-dose RT might enable the eradication of cancerous tissue in the breast, thereby facilitating an ablative RT approach in breast cancer treatment as an alternative for lumpectomy. Previous studies on primary RT have mainly focused on locally advanced breast cancer with locoregional RT schedules, ranging from 50 Gy in 25 fractions to 65-75 Gy in 30 fractions, combined with chemotherapy [47,48] These combined regimens showed impressive local control results even without surgery with a 26% local relapse rate at 10 year, and downsizing of the tumor in inoperable breast cancer thereby still enabling a mastectomy in 75% of the patients. Van Limbergen *et al* evaluated local control following WBI alone in 221 breast cancer patients staged Tis-T3N0N1, and found 5 year local control rates ranging from 40 to 100% for T1 carcinomas treated with 45-110 Gy, respectively [49].

In current clinical practice, the individual RT fractionation schedule and target volumes are mainly based on patient's (e.g. age) and gross pathological characteristics (e.g. tumor size, resection status, number of tumor positive involved lymph nodes). This is in contrast to (neo)adjuvant systemic treatment where gene expression profiling tests (e.g. MammaPrint®) and immunomolecular assays (e.g. human epidermal growth factor receptor-2) are clinically available for treatment individualization. With preoperative APBI, the direct tumor response to RT might be evaluated, thereby hopefully unraveling genetic and immunomolecular patterns of RT-sensitivity and enabling the development of predictive or prognostic RT-biomarkers and assays for the clinical practice.

Current experience with preoperative APBI is rare, with a very limited number of phase I-II EBRT-based studies. The largest study on preoperative APBI evaluated a 40 Gy schedule in 10 fractions over 2 weeks followed by a wide local excision at 6 weeks, in 70 low-risk breast cancer patients [50]. At 23 months follow-up, local tumor recurrence was observed in 2 patients. Limited fibrosis in a small volume of the breast was encountered with, interestingly, improving cosmetic outcome over time. Another study on preoperative APBI evaluated a 38.5 Gy schedule in ten 3.85 Gy fractions twice daily in tumors up to 3 cm, with lumpectomy being performed ≥21 days [51]. At a median follow-up of 3.6 years, good to excellent cosmetic outcome was reported by 78% of women, with grade 0-1 toxicity only. A pathologic complete response following RT was evaluated in 15% of the cases.

MRI-guided single dose preoperative ablative radiotherapy

When only a part of the breast is irradiated as with (A)PBI, MRI-guidance is a requisite for treatment accuracy, crucial for targeting the tumor [52-53]. A preoperative MRI of the breasts may have a role in the assessment APBI eligibility, since 11% of women are no longer APBI candidates after undergoing additional MRI following standard

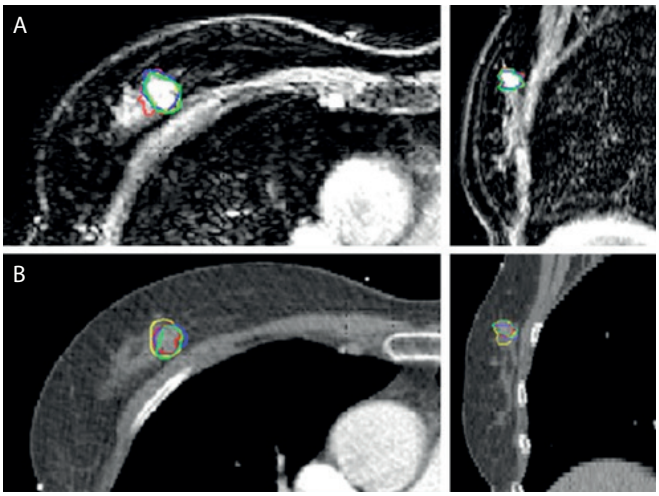

Figure 2. Gross tumor volume delineation of 4 different observers in the transversal plane on (A) preoperative contrast-enhanced MRI versus (B) preoperative contrast-enhanced CT. *(courtesy of dr. M.D. den Hartogh)*

assessment [54]. Preoperative MRI washout kinetics in combination with histopathology features could accurately identify breast cancers of limited extent . Also, it increases the tumor visibility by comparison to the poor imaging quality of the standard radiotherapy planning-CT scan [52-53, **figure 2**].

Previously, MRI-guided single dose external beam RT has been evaluated as clinically feasible in a phase I dose escalation trial in 32 women ≥55 years with cT_1N_0 invasive ductal carcinomas or DCIS ≤2.0 cm, treated with single 15, 18 or 21 Gy dose to the intact tumor, followed by lumpectomy within 10 days [55]. At a median follow-up of 23 months, no recurrences were encountered, with good to excellent physician rated cosmetic outcomes in all patients and limited grade 1-2 toxicity. A single dose preoperative APBI approach combines the main advantages of intraoperative RT and external beam RT, by enabling a minimal burdening schedule, using a widespread available non-invasive technique. In the current thesis, a new concept of an ablative MRI-guided single dose APBI is introduced, since high-dose RT to the intact tumor might enable tumor downstaging up to a pathologic complete response. Single dose ablative APBI is an innovative concept in breast-cancer treatment, and aims at facilitating a radiosurgical approach to early-stage disease, thereby making breast-conserving surgery redundant for selected patients. The main aim with this approach is treatment de-escalation for early-stage breast cancer patients with a low risk on local recurrence, thereby enabling a minimal burdening and effective therapy at the same time.

Online MRI-guided single dose preoperative ablative radiotherapy

Since in curent clinical practice RT-delivery is mainly CT-scan based, some preparations are required for MRI-guided APBI. First, fiducial markers are placed in the tumor in order to enable tumor visibility on the RT treatment planning scans and on the treatment table of the linear accelerator. A planning-MRI and a planning-CT are performed, and co-registered, in order to delineate the tumor and organs at risk. In addition, the planning-CT enables RT-dose calculations for treatment planning. Furthermore, when the patient lies on the treatment table before RT-delivery, imaging with a low-dose CT-scan enables localization of the correct RT treatment volume based on the inserted fiducial markers, patient's bony anatomy and patient's body surface.

The University Medical Center Utrecht has, in collaboration with Elekta® and Philips®, designed the world's first hybrid linear accelerator (MRI-linac) consisting of a RT delivery system and a 1.5 Tesla MRI scanner [56-57]. This system is currently commercially available. Recently, an MRI-linac based treatment in patients with lumbar spine metastasis has been evaluated as clinical feasible [58]. The MRI-linac enables real-time imaging during the actual RT delivery and may thus provide very accurate soft-tissue differentiation between RT target (i.e. breast tumor) and non-target volumes (i.e. healthy surrounding tissue). This online treatment approach has thus the potential to improve RT target definition, reduce treatment volumes and allow RT dose escalation to the tumor at the same time. Clinically, this might result in improved local tumor control and less associated toxicity for breast cancer patients. In addition, compared to CT-based MRI-guided APBI, an MRI-linac online treatment might not require the insertion of fiducial markers for position verification or the performance of a planning-CT scan. Also, the omission of fiducial markers might prevent artifacts and improve the radiologic response evaluation on diagnostic MRIs following RT. At the same time, RT-delivery in the presence of a magnetic field (i.e. due to the MRI-component of the MRI-linac) might impact the RT-dose distribution at the skin surface, and poses thus some dosimetric challenges [59-60].

Outline of the current thesis

The general goal of the current thesis is to set-up and evaluate a new de-escalating treatment approach for early-stage low-risk breast cancer, namely MRI-guided single dose ablative APBI. However, in order to know where you are heading, it is important to know where you came from. **Chapter 2** describes the impact of current standard of care, the hypofractionated RT schedule consisting of 16-23 fractions. The functional, cognitive and emotional capacity is evaluated within the growing population of women over 60 years of age with early-stage breast cancer or ductal carcinoma in situ, which are suitable candidates for APBI. The following three chapters focus on the feasibility of MRI-guided single dose preoperative ablative RT. **Chapter 3** describes the dosimetric feasibility for single fraction ablative radiotherapy by comparing 2 contrasting APBI techniques, namely volumetric modulated arc therapy (i.e. an external beam RT technique) with an interstitial multicatheter brachytherapy approach. **Chapter 4** focuses on logistics and feasibility and describes the challenges and considerations within the design of the ABLATIVE study - the first prospective, single arm, multicenter study evaluating MRI-guided preoperative single dose ablative radiation treatment in patients with early-stage breast cancer with a low risk of local recurrence. **Chapter 5** addresses preliminary acute toxicity results from the first 15 treated patients within the ABLATIVE study. Furthermore, dosimetry parameters are compiled with data from the previously described dose escalation APBI trial in order to develop practical guidelines and recommended treatment constraints for future single dose APBI studies. **Chapter 6** describes the dosimetric feasibility using an MRI-linac based treatment approach. Single dose APBI plans in the prone versus supine radiotherapy position, in the presence of a magnetic field were performed and evaluated for with respect to predefined constraints and compared to actual delivered plans in treated patients. The findings of this thesis are summarized and discussed in **chapter 7.**

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Chapter 2

Patient reported outcomes following postoperative radiotherapy for (non)invasive breast cancer in women ≥60 years of age

Submitted

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ABSTRACT

Purpose: Commonly used survival endpoints in oncological research are not appropriate to assess the impact of treatment in older breast cancer patients. Therefore, we evaluated patient-reported outcomes (PROs) in women ≥60 years undergoing postoperative radiotherapy (RT) for (non)invasive breast cancer.

Methods and materials: Between October 2013 and July 2018, we identified all ductal carcinoma in situ and breast cancer patients from the prospective UMBRELLA cohort. Clinical data and PROs (e.g. EORTC-QLQ-C30 and Hospital Anxiety and Depression Scale) were collected at baseline (i.e. after surgery, and before or shortly after RT), 3, 6, 12, 18, and 24 months following treatment. Changes in PROs and determinants of quality of life (QoL), cognitive and physical functioning, fatigue, anxiety and depression during a 24 months follow-up were assessed using linear mixed effect models.

Results: A total of 702 patients ≥60 years were included, with 34% of women being ≥70 years. QoL, physical functioning and fatigue deteriorated within the first 6 months after RT, and returned to baseline levels thereafter. For QoL and fatigue, a significant improvement above baseline scores was observed from 18 months onwards. Anxiety improved from baseline values at any time point during follow-up. Comorbidity was the major factor significantly associated with all PROs deterioration. Extended RT volumes were associated with worse PROs.

Conclusion: Women ≥60 years of age with (non)invasive breast cancer experienced a temporary decline in QoL, physical functioning and more fatigue up to 6 months following RT. Comorbidity, but not advanced age, was the major factor associated with long-term deterioration in PROs. These results may be used during shared-decision making, when discussing pros and cons of RT for elderly patients with breast cancer.

INTRODUCTION

In Western populations, comorbidity is the most important factor influencing overall survival in elderly breast cancer patients [1-2]. The commonly used survival endpoints in breast cancer research may therefore not be the most appropriate to adequately evaluate treatment efficacy in older women. Hence, the International Society of Geriatric Oncology recommends evaluating cancer treatments also in terms of impact on functional, cognitive and emotional status [3-4].

Whole breast radiotherapy (RT) following breast-conserving surgery and post-mastectomy RT reduce recurrence rates patients with low- or intermediate risk breast cancer, but little is known about the impact of RT on the physical and emotional functioning of patients ≥60 years of age [5-10]. In the current landscape of shared decision-making, adequately informing patients on the consequences of oncological treatment is essential.

Therefore, we aimed to evaluate changes in global health status (QoL), physical and emotional functioning, fatigue, anxiety and depression symptoms following postoperative RT for (non) invasive breast cancer patients above 60 years of age. Secondly, we aimed to identify which patient, tumor or treatment characteristics were associated with worse patient-reported outcomes (PROs). We hypothesized that comorbidity, advanced age and intensified treatment schedules (e.g. mastectomy, locoregional RT, axillary lymph node dissection, systemic treatment) would negatively influence PROs.

MATERIAL & METHODS

Between October 2013 and July 2018, all patients with breast cancer and ductal carcinoma in situ (DCIS) referred to the department of Radiation Oncology of the University Medical Center Utrecht (The Netherlands), were invited to participate within the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA-cohort) [11]. Patients consented to standardized prospective collection of clinical data and PROs after surgery, before or shortly after initiation of RT (i.e. baseline), and at predefined intervals hereafter (i.e. 3, 6, 12, 18 and 24 months). All patients within the UMBRELLA who were ≥60 years of age, and who completed at least one PROs questionnaire were identified. In addition, only patients treated with current standard of care hypofractionated RT schedule (i.e. shorter schedule with fraction dose >2Gy versus conventional 2Gy and ≥25 fractions–schedule) were included for analysis [12].

Data collection

Demographics, functional status, tumor and treatment characteristics were obtained from the Netherlands Cancer Registry [13]. Data on comorbidity, RT target volumes and fractionation were retrieved from medical records. The Charlson Comorbidity Index was calculated based on comorbidity and medication from the medical record [14-15]. Patient-reported QoL, physical and cognitive functioning, and fatigue levels were assessed with the European Organization for Research and Treatment of Cancer (EORTC) validated core

questionnaire EORTC-QLQ-C30 [16]. The data were linearly transformed according to the EORTC-manual, into scores ranging from 0-100, with higher scores indicating better functioning. To evaluate the fatigue scores accordingly, these were inversed, thus extracted from the maximum of 100 points. Anxiety and depression symptoms were evaluated with the Hospital Anxiety and Depression Scale (HADS), a validated questionnaire for symptom screening purposes [17-18]. These scores range from 0 -21, with higher scores indicating worse symptoms. The HADS threshold for clinically relevant symptoms is 8 points [19].

Paper or electronic PROs questionnaires, depending on the patient's preference, were acquired at baseline and at 3, 6, 12, 18 and 24 months follow-up. No HADS questionnaires were acquired at the 3 months timepoint.

Statistical analysis

Patients were categorized according to age (i.e. 60-69 versus ≥70 years), comorbidity (i.e. none versus 1 mild comorbidity versus >1 mild comorbidity), breast surgery type (i.e. breast-conserving versus mastectomy), axillary surgery type (i.e. none/with sentinel node procedure only versus axillary lymph node dissection), systemic treatment (i.e. none versus endocrine therapy versus (neo)adjuvant chemotherapy combined with any other systemic treatment), RT type (i.e. local (i.e. breast or chest wall) versus (loco)regional (including axillary levels I-IV).

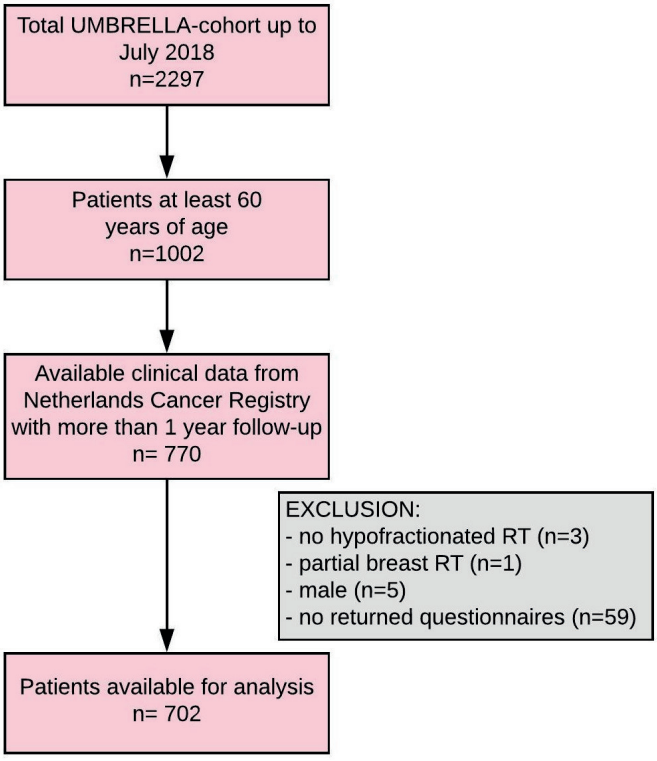
Categorical data were summarized using frequencies and percentages. Continuous data were summarized using a median, (interquartile) range (IQR), mean values or standard deviation (SD). Changes in PROs over time were assessed with linear mixed models analysis. Linear mixed effect models for repeated measures take correlations between PROs measurements at different time-points within patients into account. An autoregressive covariance structure was used to account for correlations among observations, assuming that correlations are higher between measurements that were closer together than further apart. Six models for QoL, physical functioning, cognitive functioning, fatigue, depression and anxiety were constructed. All models included a random intercept per patient in order to account for PROs' variation in baseline. The categorized variables age, comorbidity, breast surgery type, axillary surgery type, systemic treatment, RT-schedule and target volumes, and time-points were included as fixed factors. An interaction between time and age was included in the model.

Absolute changes in PROs' scores between baseline and follow-up were calculated. The proportion of patients at different time points with improved, stable or worsened PROs from baseline was evaluated according to evidence-based guidelines for clinically relevant changes of the EORTC QLQ-C30-scores [20]. The percentages of patients with at least moderate anxiety and depression symptoms were evaluated [19]. Furthermore, PROs' scores were compared to an age-matched female Dutch reference population without a history of breast cancer [21].

All analyses were performed in SPSS version 24. Statistical tests were two-sided and performed at a significance level <0.05.

RESULTS

Between October 2013 and July 2018, 2.297 patients were included in the UMBRELLA-cohort, with 702 patients meeting our inclusion criteria (figure 1). The response rates at baseline and at 3, 6, 12, 18 and 24 months were 87%, 84%, 81%, 73%, 68% and 62%, respectively.



*RT: radiotherapy

Figure 1. CONSORT diagram to illustrate the patient selection.

Patient and treatment characteristics in women between 60-69 years (n=464) and ≥70 years of age (n=234) are reported in table 1. Patients ≥70 years had more often comorbidity (47% versus 35%), received less often a RT boost dose (i.e. 21-26 fractions) on the tumor bed (20% versus 39%), and less often systemic treatment (44% versus 52%) compared to patients aged 60-69 years. Overall, disease stage, surgery type and most frequent comorbidities were similar across age groups. Chronic pulmonary disease was reported in 12% versus 10%, peripheral vascular disease in 13% versus 8%, and diabetes in 9% versus 7% in women ≥70 years versus 60-69 years of age, respectively.

Changes in PROs over time

In the total group (figure 2, table 2-3), QoL decreased significantly between baseline and 3 months, and a significant improvement above baseline was observed at 18 and 24 months. Cognitive functioning was significantly lower than baseline up to 12 months, with the lowest scores observed at 3 months after the start of RT. Symptoms of fatigue worsened significantly at 3 and 6 months, and improved significantly above baseline at 18 and 24 months following RT. A significant deterioration in physical functioning compared to baseline was observed at 3 and at 6 months after RT. Anxiety symptoms significantly improved compared to baseline from 6 months onward. Depression scores remained stable over time.

Compared to the mean scores of the normative cohort (n=355), patient's QoL scores were similar up to 6 months and significantly higher from 12 months onwards. Patients experienced significantly more fatigue and anxiety from baseline up to 12 and 18 months follow-up, respectively. Patients scored lower on the cognitive domain than the reference population at all time points. No differences between the reference and patient population were found for physical functioning or depressive symptoms.

Table 1. Patient characteristics before the delivery of radiotherapy and administered treatment across age groups

	< 70 years (n=464)	≥ 70 years (n=238)
Median age (range)	64 (60-69)	73 (70-84)
Charlson Comorbidity Index		
– no comorbidity	294 (63%)	126 (53%)
– 1 mild comorbidity	121 (26%)	56 (24%)
– > 1 mild comorbidity	43 (9%)	54 (23%)
– unknown	6 (1%)	2 (1%)
WHO performance status		
– 0	234 (50%)	101 (42%)
– 1	72 (16%)	41 (17%)
– 2	1 (0%)	7 (3%)
– unknown	157 (34%)	89 (37%)
Breast surgery		
– breast conserving	414 (89%)	203 (85%)
– mastectomy	48 (11%)	35 (15%)
– none	1 (0%)	0 (0%)
Axillary surgery		
– sentinel node	384 (83%)	192 (81%)
– axillary lymph node dissection	40 (9%)	24 (10%)
– none	40 (9%)	22 (9%)
Pathological disease stage		
– 0*	12 (3%)	0 (0%)
– in situ	70 (15%)	26 (11%)
– I	254 (55%)	120 (50%)
– II	97 (21%)	67 (28%)
– III	20 (4%)	16 (7%)
– IV	1 (0%)	0 (0%)
– unknown	10 (2%)	9 (4%)
Radiotherapy		
– median no. of fractions (range)	16 (21-26)	16 (21-26)
– no. of patients (%)		
• 16x2.67 Gy	283 (61%)	190 (80%)
• 21x2.67 Gy	143 (31%)	14 (6%)
• 23x2.67 Gy	37 (8%)	33 (14%)
• 26x2.67 Gy	1 (0.2%)	1 (0.4%)
– local	376 (81%)	189 (79%)
– locoregional	82 (18%)	44 (19%)
– regional	6 (1%)	5 (2%)
Systemic treatment **		
– none	223 (48%)	133 (56%)
– any neoadjuvant therapy	51 (11%)	10 (4%)
– adjuvant chemotherapy	96 (21%)	12 (5%)
– adjuvant endocrine therapy	198 (43%)	97 (41%)
– adjuvant endocrine- and chemotherapy	97 (21%)	6 (3%)

* no residual disease following surgery ** scores do not add up to 100% since the adjuvant chemotherapy, endocrine therapy and adjuvant endocrine – and chemotherapy group overlap.

Determinants of PROs

Comorbidity was the main factor negatively influencing all PROs: patients with one mild comorbidity reported significantly lower QoL, physical and cognitive functioning and more fatigue and depression symptoms (**figure 3A, table 2-3**). More than one mild comorbidity significantly impaired all PROs scores even further, including anxiety symptoms.

Also, the extent of RT-volumes was significantly associated with worse PROs (**table 2**). Patients treated with locoregional RT reported significantly lower QoL scores, impaired physical and cognitive functioning and experienced more fatigue compared local RT only. This effect was not observed for anxiety or depression symptoms.

Advanced age did not negatively influence PROs, except for the physical functioning domain (**figure 3B, table 2-3**). Patients ≥70 years of age had significantly lower physical functioning scores at all time points from baseline onwards, with the largest difference at 18 months follow-up, compared to younger patients. In addition, physical functioning scores in the older group worsened significantly from baseline at all time points during follow-up, except 3 months. In patients aged 60-69 years, physical functioning scores significantly worsened up to 6 months following RT, and recovered to baseline thereafter. An interaction between time and age category was also observed for fatigue. For patient ≥70 years of age, fatigue symptoms remained stable over time. In the younger group, fatigue worsened significantly at 3 and 6 months and improved above baseline at 18 and 24 months follow-up, respectively. Also, patients aged 60-69 years experienced significantly more fatigue compared to their older counterparts at 3 months follow-up, with no differences at other time points. For QoL, cognitive functioning, anxiety and depression, no differences in scores were observed over time across age category.

Patients treated with chemotherapy (± endocrine treatment) experienced significantly more fatigue and had lower QoL scores, compared to patients not receiving any systemic treatment at all (**table 2**). Other PROs were not impaired by the use of systemic treatment.

Clinically relevant changes in PROs

At 3 months follow-up, a clinically relevant worsening compared to baseline was observed in 23% of patients for QoL, 22% for physical functioning, 45% for fatigue symptoms, and 27% for cognitive functioning (**Appendix 1**). At 6 months, a clinically relevant worsening was observed for physical functioning scores (23% of patients), fatigue symptoms (37% of the patients), and in cognitive functioning (27% of the patients). A clinically relevant improvement (compared to baseline) in QoL and fatigue from 18 months onwards was observed in 39% and 38% of patients, respectively.

The percentage of women experiencing at least moderate anxiety symptoms was 22% at baseline, and varied between 17%-18% during follow-up. In the reference population, 18% of women experience moderate anxiety symptoms. The percentage of patients experiencing at least moderate depression symptoms was 11% at baseline, and ranged between 11%-13% during follow-up. In the reference population, 15% of women experienced depressive symptoms.

DISCUSSION

Our study provides relevant information on the short and long-term from the patient's perspective on physical and emotional functioning following postoperative RT. Patients ≥60 years experience temporarily lower QoL and more fatigue within the first six months after RT, with PROs scores returning to post-surgery and pre-RT levels thereafter. From 18 months on, a significant recovery above baseline is observed for fatigue. Physical functioning was significantly impaired, with the younger group experiencing a temporary decline within the first 6 months of follow-up. For patients ≥70 years of age this lasted up to 24 months. Anxiety symptoms recovered significantly above baseline from 6 months following RT. Depressive symptoms remained stable over time. Comorbidity was the major detrimental factor for PROs. Compared to the normative population, patients experienced more fatigue and anxiety symptoms up to 18 months follow-up, though their QoL was significantly higher from 12 months on following RT. The CALBG randomized controlled study evaluated the omission

LEGEND
- the blue graph illustrates unadjusted mean values and associated 95%confidence interval
- represents a statistically significant change during follow-up from baseline PROs
- higher EORTC-QLQ-C30 scores (A, range 0-100) indicate better well-being
- higher Hospital Anxiety and Depression Scale scores (B, range 0-21) indicate worse symptoms
- green dashed line represents the mean PROs value for the Dutch reference population

Figure 2. Patient reported outcome measures according to the EORTC-QLQ-C30 (2A) and Hospital Anxiety and Depression Scale (2B) subscales at various time points from baseline in the UMBRELLA cohort

of RT following breast-conserving surgery in stage I breast cancer for patients ≥70 years of age treated with Tamoxifen [5]. This study showed a reduction in 5-years loco(regional) recurrence rates with additional RT compared to Tamoxifen alone (1% vs. 4% recurrence, p<0.001). Survival did not improve when adding RT. A recent retrospective study in patients ≥65 years of age with 1-3 tumor positive lymph nodes showed a benefit of additional post-mastectomy RT for recurrence free survival in tumors above 5cm, also without any impact on overall survival at a median follow-up of 50 months [10]. The impact on PROs was not evaluated.

A hypothesized benefit for QoL for older patients by omitting RT has previously been discarded in a randomized controlled trial [22]. In low-risk node-negative breast cancer patients (stage 0-2), the omission of RT after breast-conserving surgery did not result in an improved QoL or other EORTC-QLQ-C30 subdomains at 15 months, 3 or 5 years follow-up. However, omitting RT resulted in a significant

Table 2. Results of mixed model analysis on determinants of patient reported outcome measures scores

	MEAN ESTIMATES OF DIFFERENCES [95% CI]					
VARIABLES	**QUALITY of LIFE**	**PHYSICAL FUNCTIONING**	**COGNITIVE FUNCTIONING**	**FATIGUE**	**ANXIETY**	**DEPRESSION**
Intercept	81.3 [79.1 – 83.5]	90.1 [88.0 – 92.3]	89.0 [86.6 – 91.4]	79.5 [76.7 – 82.3]	5.1 [4.5- 5.5]	2.6 [2.2 – 3.1]
Age						
– 60-69 years						
– ≥ 70 years	-1.4 [-4.5 – 1.6]	-3.0 [-5.9 – -0.2]	2.2 [-1.1 – 5.4]	-0.1 [-3.8 – 3.9]	-0.5 [-1.1 – 0.1]	-0.1 [-0.7 – 0.5]
Comorbidity						
– none						
– 1 mild comorbidity	-6.5 [-9.0 – -3.0]	-7.5 [-10.1 – -4.9]	-4.5 [-7.4 – -1.7]	-6.0 [-9.3 – -2.7]	0.3 [-0.3 – 0.9]	1.0 [0.5 – 1.6]
– > 1 mild comorbidity	-8.6 [-11.9–-5.3]	-13.9 [-17.3 –-10.6]	-4.8 [-8.5 – -1.2]	-10.2 [-14.4 –-5.9]	1.3 [0.5 – 2.0]	1.4 [0.7 – 2.1]
Radiotherapy *						
– local						
– (loco)regional	-3.7 [-7.0– -0.4]	-5.0 [-8.4 – - 1.7]	-4.4 [-8.1 – -0.8]	-4.7 [-8.9 –-0.5]	0.7 [-0.1 – 1.4]	0.3 [-0.4 – 1.1]
Systemic treatment						
– none						
– endocrine therapy alone	0.7 [-2.0 – 3.3]	0.7 [-2.0 – 3.4]	0.2 [-2.8 – 3.1]	-0.2 [-3.6 – 3.3]	0.2 [-0.4 – 0.8]	-0.2 [-0.7 – 0.4]
– chemotherapy with or without endocrine therapy	-3.9 [-7.1 – -0.6]	-0.5 [-3.8-2.9]	-2.6 [-6.2 – 1.1]	-4.5 [-8.7 –- 0.3]	0.5 [-0.2 – 1.2]	0.4 [-0.2 – 1.2]
Breast surgery						
– breast conserving						
– mastectomy	-1.2 [-5.4 – 2.9]	-4.0 [-8.2 – 0.3]	-0.1 [-4.5 – 4.7]	-3.7 [-9.0 – 1.7]	0.7 [-0.3 – 1.6]	1.1 [0.2 – 2.0]
Axillary surgery						
– sentinel node or no surgery						
– axillary lymph node dissection	-1.7 [-6.1 – 2.6]	-3.4 [-7.8 – 1.1]	1.2 [-3.7 – 6.1]	-0.9 [-6.6 – 4.7]	-0.7 [-1.7 – 0.3]	0.0 [-1.0 – 0.9]
Time						
Baseline						
3 months	-2.7[-4.3 – -1.1]	-2.9 [-4.1 – -1.7]	-3.3 [-4.9 – -1.7]	-7.3 [-9.2 – -5.3]	-	-
6 months	-0.9 [-2.7 – 0.8]	-2.7 [-4.1 – -1.4]	-2.2 [-4.0 – -0.4]	-2.5 [-4.6 – -0.4]	-0.9 [-1.2 – -0.6]	0.2 [-0.1 – 0.4]
12 months	1.0 [-0.8 – 2.9]	-0.3[-1.3 – 1.7]	-2.2 [-4.1 – -0.3]	0.9 [-1.3 – 3.1]	-0.9 [-1.2 – -0.6]	-0.1 [-0.4 – 0.2]
18 months	2.7 [0.8 –2.9]	0.2 [-1.3 – 1.7]	-1.2 [-3.2 – 0.8]	4.6 [2.2 – 6.9]	-0.9 [-1.2 – -0.5]	-0.3 [-0.6 – 0.0]
24 months	2.5 [0.4 – 4.6]	-1.3 [-3.0 – 0.3]	-0.3 [-2.5 – 1.8]	5.0 [2.4 – 7.5]	-1.0 [-1.3 – -0.6]	-0.1 [-0.4 – 0.2]

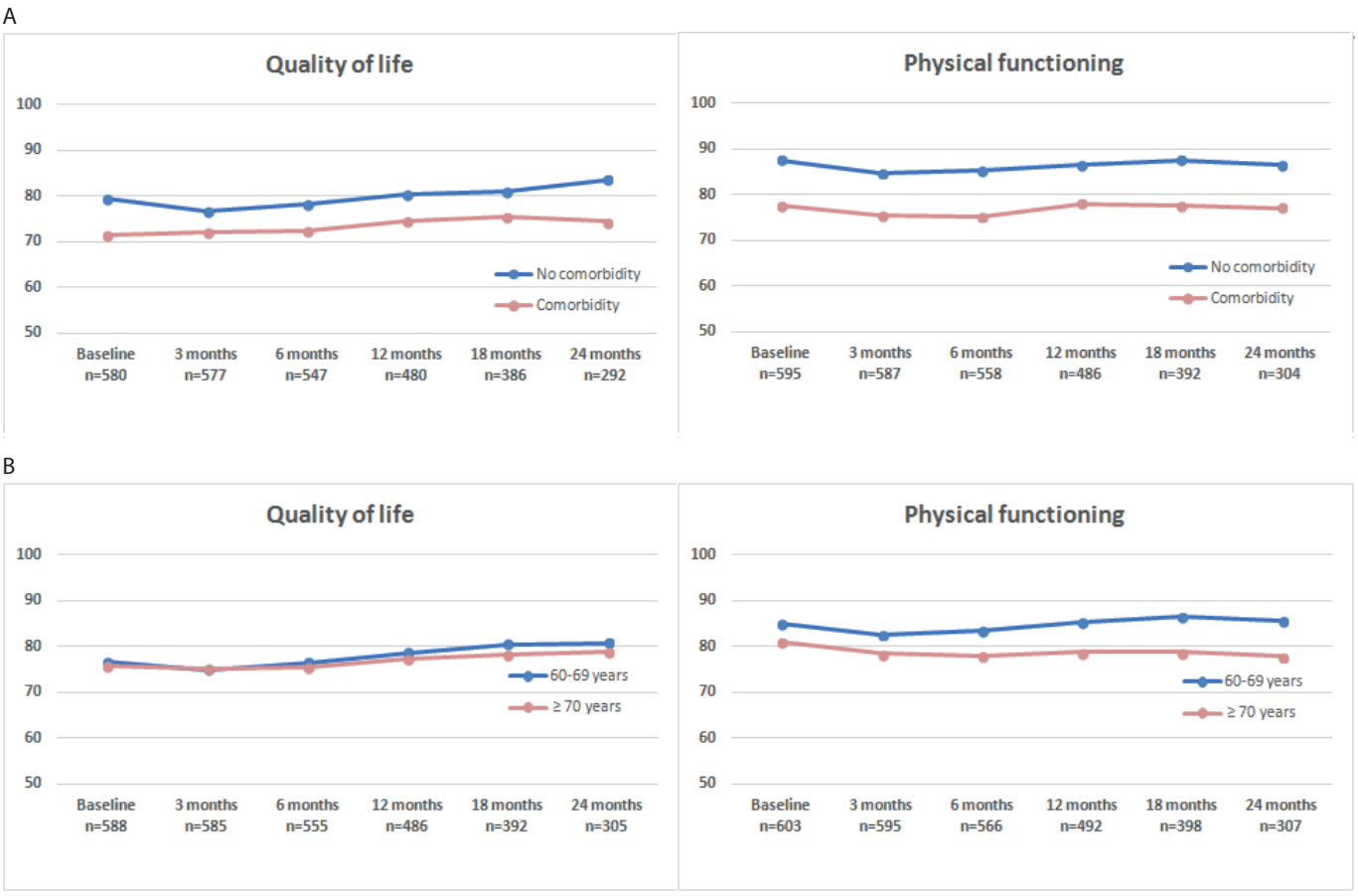
Dark grey highlight: significant change from reference category, i.e. the first mentioned category for each variable.

LEGEND:
- no anxiety or depression PROs-questionnaires were collected at 3 months.
- the interaction between time*age, which was included in the analysis, is not shown in the table, but reported in the results section of the manuscript
- * local radiotherapy: breast or chest wall; (loco)regional radiotherapy: including axillary levels I-II/IV after sentinel node procedure or II-IV after axillary
- lymph node dissection

Table 3. Patient reported outcome measures according to the EORTC-QLQ-C30 (2A) and Hospital Anxiety and Depression Scale (2B) sub-scales at baseline and during a 24 months follow-up

	Baseline	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**
	mean (95%CI)	**mean (95%CI)**	**mean (95%CI)**	**mean (95%CI)**	**mean (95%CI)**	**mean (95%CI)**
EORTC-QLQ-C30 scale						
- global health	76.3 (75.0-77.7)	75.0* (73.5-76.5)	76.1 (74.5-77.7)	78.2 (76.6-78.8)	79.1* (77.5-80.8)	80.1* (78.2-81.9)
- physical functioning	83.7 (82.3-85.0)	81.3* (79.8-82.7)	81.6* (80.1-83.1)	83.2 (81.6-84.8)	84.1 (82.3-85.8)	83.2 (81.2-85.2)
- cognitive functioning	86.8 (85.4-88.3)	84.7* (83.1-86.3)	85.2* (83.6-86.8)	85.3* (83.5-87.0)	85.5 (83.7-87.3)	86.4 (84.3-88.4)
- fatigue	74.2 (72.4-76.0)	69.4* (67.5-71.3)	72.8* (70.8-74.7)	75.7 (73.7-77.7)	79.1* (77.1-81.1)	79.2*(76.8-81.5)
HADS scale						
- anxiety	5.4 (5.1-5.7)	N/A	4.6 (4.3-4.9)*	4.6 (4.3-5.0)*	4.7 (4.4-5.1)*	4.6 (4.2-5.0)*
- depression	3.2 (2.9-3.5)	N/A	3.4 (3.1-3.7)	3.2 (2.9-3.5)	3.0 (2.7-3.3)	3.2 (2.8-3.6)

LEGEND:
- the scores represents unadjusted mean values as calculated in univariable analysis
- * represents a statistically significant change during follow-up from baseline PROs
- higher EORTC-QLQ-C30 scores (range 0-100) indicate better well-being;
- higher Hospital Anxiety and Depression Scale scores (range 0-21) indicate worse symptoms
- N/A : non applicable since no questionnaires were collected at 3 months



LEGEND
- the graph represents unadjusted mean values as calculated in univariable analysis
- higher EORTC-QLQ-C30 scores (range 0-100) indicate better well-being

Figure 3. Quality of life and physical functioning scores according to the EORTC-QLQ-C30 questionnaire at various time points from baseline, across comorbidity (A) and age group (B)

increase of the 5 years ipsilateral breast tumor recurrence (i.e. 1.3% to 4.1%) [6].

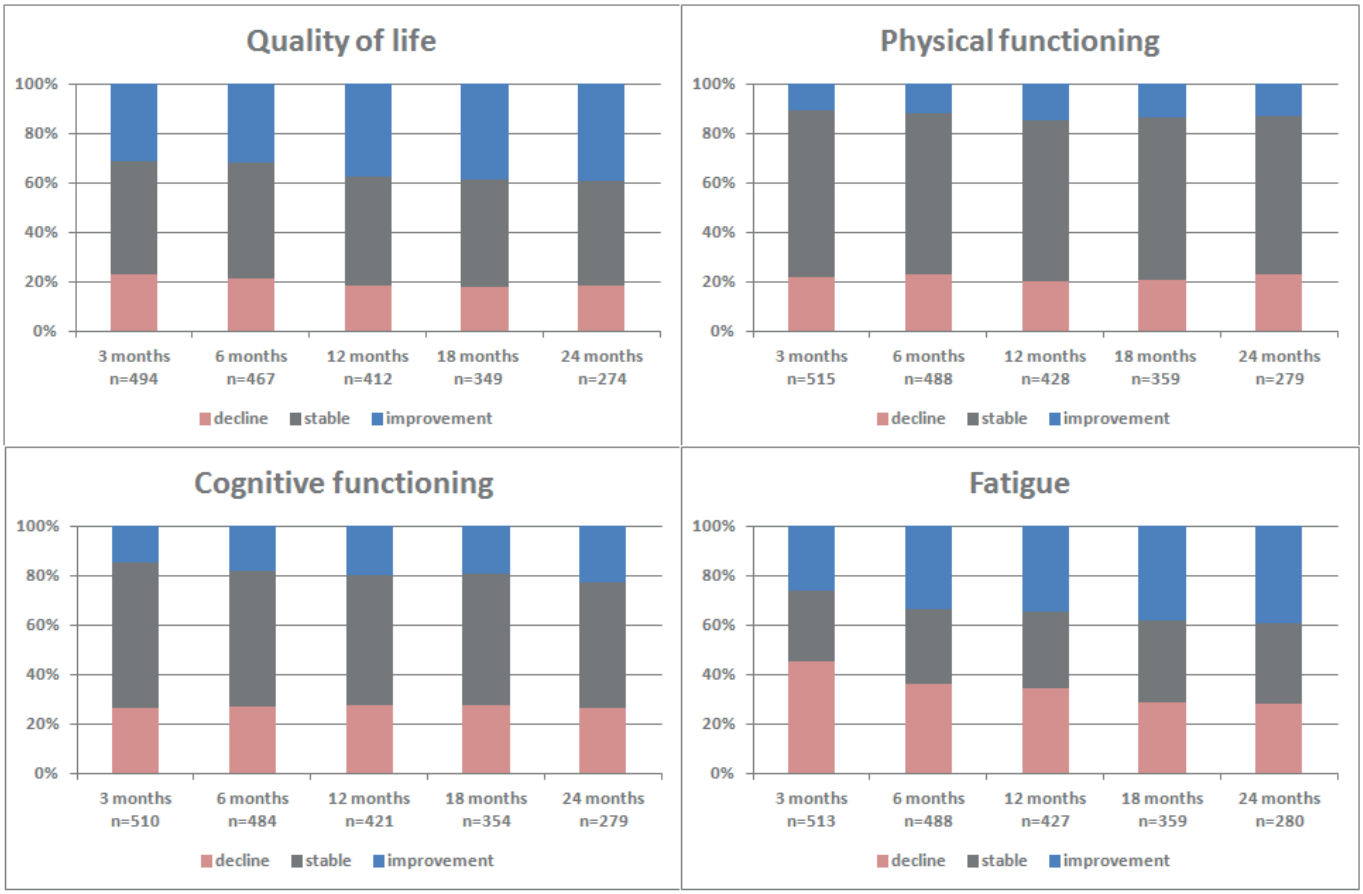
Overall, these studies show a reduction in breast cancer recurrence when undergoing RT after surgery, but the impact on QoL remains under evaluated. In line with the current geriatric recommendations, we used non-survival endpoints for oncological treatment evaluation. A main finding of our study is that a hypofractionated RT schedule has only short-term negative consequences on QoL up to 3 months follow-up, independent of patient's age. Also, no differences in QoL were found compared to the Dutch reference population up to 6 months follow-up, with significant better scores thereafter. An explanation for these study findings is a phenomenon called response-shift, where during follow-up an internal shift in perceived QoL and functioning has occurred [23].

Three previous studies have addressed the impact of treatment in an older population treated with breast-conserving surgery and whole breast irradiation [24-26]. All studies used the same PROs instrument as we did (i.e. EORTC QLQ-C30). However, these studies evaluated a conventionally fractionated RT schedule in contrast to our study where current standard of care hypofractionated RT-schedule was investigated.

Bantema-Joppe et al studied the impact of age on PROs in Dutch breast cancer survivors (n=1420) during a 5-year follow-up across age groups (≤50, 51-70, and ≥70 years) [24]. Consistent to our findings, the presence of comorbidity negatively influenced all functional scales. In contrast to our cohort, no temporary decline was observed in QoL shortly after RT, which might be explained by questionnaires not acquired at fixed points, but during the course of the first year of follow-up. Furthermore, the authors reported significantly more fatigue in younger (i.e. ≤ 50 years) compared to middle-aged patients (i.e. 51-70 years), but not older patients (i.e. ≥70 years).

Arraras et al evaluated the impact of treatment in Spanish breast cancer patients ≥65 years of age (n=173) before RT, the final day of RT and 6 weeks following RT, focusing on differences between axillary surgery groups (i.e. axillary lymph node dissection, sentinel lymph node biopsy and no surgery) [25]. In line with our findings, a temporary decline in QoL, physical functioning and worsening of fatigue, followed by a recovery to baseline was observed. Also, the type of axillary treatment was not an independent factor negatively influencing PROs.

Derks et al investigated physical functioning in post-menopausal patients treated within the TEAM randomized controlled trial, designed to compare two types of endocrine therapies (n=431) [26]. The percentage of women undergoing conventionally fractionated RT between 60-69 years, and ≥70 years of age was 71% and 51%, respectively, with the smaller remaining proportion of patients undergoing hypofractionated RT [27-28]. Interestingly, in contrast to our findings, comorbidity was not associated with physical decline



Appendix 1. Percentage of patients with clinically deteriorated, stable, and improved quality of life, fatigue, physical and cognitive functioning scores according to the EORTC-QLQ-C30 questionnaires, compared to baseline scores

over time. In line with our findings, the oldest group experienced a significant decline in physical functioning, compared to their younger counterparts.

The course of anxiety and depression symptoms was investigated within the START-trials comparing the efficacy of a hypofractionated to a conventionally fractionated regimen for early-stage breast cancer (n=2208) [12,29]. A minority of 38% of the patients was >60 years of age. In line with our findings, anxiety symptoms significantly improved over time, whereas no time trend was observed for depression. Young age was a predictor of worse anxiety scores, which was not observed in our study. We believe this is most likely due to age differences in the reference category, with younger women <60 years of age in the START-trials, compared to our 60-69 years group.

A strength of our study is the evaluation of a contemporary RT schedule for breast cancer, using a diverse range of PROs within a prospective cohort at various points during 24 months follow-up. Moreover, reliable clinical data were used from the Netherlands Cancer Registry, complementing our institution registries with accurate medical history from other peripheral hospitals. Since our study illustrated the impact of treatment on various PROs, our results can be used to guide shared decision making in current clinical landscape.

Some study limitations have to be addressed. First, specific elderly questionnaires (e.g. QLQ-ELD14, Geriatric 8 screening) could have given additional insights on patient's mobility, frailty aspects and experienced treatment burden [30-31]. These questionnaires are not yet part of the UMBRELLA-cohort measurements. Secondly, PROs at time of breast cancer diagnosis are not yet collected at our institution, since UMBRELLA was set up as cohort where primarily RT patients were included. Thirdly, no patients were treated with partial breast irradiation, which is an emerging treatment option for low-risk patients ≥60 years of age. Future studies should evaluate the impact of partial breast irradiation on PROs specifically in the elderly.

Based on our study findings, hypofractionated RT is a manageable treatment option for patients for whom maximum oncological safety is important. However, it should be discussed with patients that extended locoregional RT volumes were significantly associated with lower QoL, physical functioning, and more fatigue compared to local RT. Our results may be used to select the best treatment option as part of shared decision-making depending on each patient's personal treatment goals. It is eventually up to the patient to decide whether the best possible QoL or lowest risk of local recurrence is the most important factor to base treatment on.

Since comorbidity was the major factor negatively influencing PROs, we advise future strategies for treatment burden improvement to also focus on this subgroup. The least burdening treatment option is often considered to be adjuvant endocrine therapy. However, due to polypharmacy, systemic side-effects and therapy compliance, local short-interval strategies such as partial breast irradiation might be more appropriate [32-35]. Other initiatives evaluating less burdening treatment approaches currently investigate the omission of postoperative RT in patients ≥70 years of age without an indication for endocrine therapy [36].

CONCLUSION

Breast cancer patients ≥60 years of age experienced a temporary decline in QoL, physical functioning, and worsening of fatigue within the first 6 months following postoperative hypofractionated radiotherapy. Symptoms of psychological distress improved or remained stable over time. Comorbidity, was the major factor associated with deterioration in overall well-being. Compared to the reference population, patients experienced more fatigue and anxiety symptoms up to 18 months follow-up, though their QoL was significantly higher from 12 months on following RT. Our findings illustrate the patient's perspective on the impact of RT following breast surgery, which is useful for shared decision-making in current radiation-oncology practice.

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Chapter 3

MRI-guided single fraction ablative radiotherapy for early-stage breast cancer: a brachytherapy versus volumetric modulated arc therapy dosimetry study

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ABSTRACT

Background and purpose: A radiosurgical treatment approach for early-stage breast cancer has the potential to minimize the patient's treatment burden. The dosimetric feasibility for single fraction ablative radiotherapy was evaluated by comparing volumetric modulated arc therapy (VMAT) with an interstitial multicatheter brachytherapy (IMB) approach.

Methods and materials: The tumors of 20 patients with early-stage breast cancer were delineated on a preoperative contrast-enhanced planning CT-scan, co-registered with a contrast-enhanced magnetic resonance imaging (MRI), both in radiotherapy supine position. A dose of 15 Gy was prescribed to the planned target volume of the clinical target volume (PTV_{CTV}), and 20 Gy integrated boost to the PTV of the gross tumor volume (PTV_{GTV}). Treatment plans for IMB and VMAT were optimized for adequate target volume coverage and minimal organs at risk (OAR) dose.

Results: The median $PTV_{GTV/CTV}$ receiving at least 95% of the prescribed dose was ≥99% with both techniques. The median PTV_{CTV} unintentionally receiving 95% of the prescribed PTV_{GTV} dose was 65.4% and 4.3% with IMB and VMAT, respectively. OAR doses were comparable with both techniques.

Conclusion: MRI-guided single fraction radiotherapy with an integrated ablative boost to the GTV is dosimetrically feasible with both techniques. We perceive IMB less suitable for clinical implementation due to PTV_{CTV} overdosage. Future studies have to confirm the clinical feasibility of the single fraction ablative approach.

INTRODUCTION

The current standard treatment in early-stage breast cancer is breast-conserving therapy (BCT), consisting of breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) with or without a boost [1,2]. Despite its proven effectiveness [3], the protracted radiotherapy (RT) duration ranging from 3 to 7 weeks with a hypofractionated or conventional regimen, can provide a substantial treatment burden. Post-operative accelerated partial breast irradiation (APBI) to the tumor bed offers a promising alternative to WBI in low-risk breast cancer patients due to reduced treatment volume and RT duration. Furthermore, Palta et al. have shown that preoperative APBI for stage I breast cancer results in substantial treatment volume reduction when compared to a post-operative approach [4]. Preoperative ABPI could therefore enable treatment acceleration [5] to further decrease treatment burden. However, when aiming at alternatives to BCT with minimal treatment burden, the role of RT could be exchanged for a radiosurgical approach, as already employed in certain patients, e.g. with lung cancer or brain metastasis. For a radiosurgical approach, accurate tumor localization is critical. Since tumor size on magnetic resonance imaging (MRI) is highly correlated to microscopic tumor size, MRI-guidance is required in addition to planning CT-scan, in order to adequately identify tumor extent [6,7]. The MRI-linac, a hybrid system consisting of an 8 MV accelerator and an integrated 1.5 Tesla MRI scanner, and MRI-guided brachytherapy, is currently being investigated for several tumor sites [8,9]. For breast oncology, our department focuses on MRI-guided radiotherapy developments as a substitute for surgical treatment for early-stage breast cancer with low-risk characteristics according to European and American Society for Radiation Oncology APBI guidelines [10,11].

The purpose of this study was to evaluate the dosimetric feasibility for MRI-guided single fraction ablative RT for early-stage breast cancer. We conducted a planning study by comparing a volumetric modulated arc therapy (VMAT) versus interstitial multicatheter brachytherapy (IMB) approach.

MATERIALS AND METHODS

Patient characteristics

This study included patients from the pre-existing NTR3198 study, approved by our institutional review board [7]. Patients with tumors up to 30 mm, scheduled for breast-conserving surgery and whole breast irradiation were included. Baseline characteristics of the 20 patients are shown in Table 1. Patients underwent a contrast-enhanced (CE) CT and CE-MRI in supine RT treatment position on a wedge board at 10° of inclination, with arms in abduction above the head. Details on patient positioning and preoperative imaging parameters were previously reported [7].

Target definition and organs at risk

All delineations were performed using software developed at our department, Volumetool® [12]. Gross tumor volumes (GTVs) and organs at risk (OARs) were delineated by an experienced breast radiation oncologist on CE-CT, co-registered with CE-MRI **(Appendix 1A).** The GTV was uniformly expanded by 2 cm to create a clinical target volume (CTV), excluding the skin and chest wall. For VMAT, both GTV and CTV were uniformly expanded by

3 mm to obtain the planning target volumes PTV_{GTV} and PTV_{CTV}, respectively, excluding the skin. For IMB, the PTV_{GTV} and PTV_{CTV} were equal to the GTV and CTV, respectively. The ipsilateral breast was contoured using a CT/MRI compatible demarcation wire around the palpable glandular breast tissue. The lungs were automatically contoured. The skin was defined as the area within the first 5 mm under the ipsilateral breast surface, extended with a uniform 3.5 cm margin from the breast borders. The chest wall was delineated as one structure, including the bony structures (i.e. ribs, sternum, scapula) and muscles (i.e. intercostal, pectoral and part of the rotator-cuff). The heart contour started below the pulmonary trunk bifurcation and included the pericardium [13].

Treatment plan acquisition

The preoperative planning CT-images and delineations were exported from Volumetool® into the Oncentra Brachy 4.3® planning software (Elekta Ltd.) for the IMB plans and Monaco 3.2® (Elekta Ltd.) for the VMAT plans. Two radiotherapy dose levels were concomitantly prescribed in one single fraction: 15 Gy to the PTV_{CTV} and 20 Gy to the PTV_{GTV}. The 20 Gy single dose is equivalent to a 73.7 Gy dose in 2 Gy fractions (EQD2, a/b 4.7 Gy), resulting in a 100% 5 year tumor control probability for cT1N0 tumors [14]. The single 15 Gy dose corresponds to an EQD2 of 44.1 Gy (a/b 4.7 Gy), similar to the standard hypofractionated schedule of 16 fractions of 2.66 Gy at our institution.

OAR constraints were set to minimize the normal tissue volume receiving the prescription dose without compromising target volume coverage. Dose constraints for lungs and heart were converted from the QUANTEC 2 Gy fractions recommendations to a single dose equivalent using an a/b of 3 Gy [15]. The recommendation for both lungs, a mean lung dose < 7 Gy (physical dose) was converted to < 3.6 Gy in a single dose. In this study, a constraint of the mean ipsilateral lung dose < 3.6 Gy was maintained. A lower heart constraint than the QUANTEC recommendation (i.e. V25 Gy < 10%) was maintained, using V5Gy < 10% (physical dose), in concordance to our clinical practice. This implied V2.8 Gy < 10% of the heart in a single dose delivery. The chest wall objective was extrapolated from stereotactic lung RT studies. In order to avoid RT associated chest wall pain, a D20cc < 16.3 Gy objective was formulated [16]. No reference data are available for acceptable skin dose in single dose irradiation. Since 15 Gy was prescribed to the CTV and no restrictions on tumor distance to skin were provided, a skin objective D1cc < 16 Gy was perceived as minimum feasible.

Plans were optimized for adequate target volume coverage and a dose as low as possible to the OARs. Adequate target volume coverage was defined as 99% or more of the PTV receiving at least 95% of the prescribed dose, thus at least 19 Gy for the PTV_{GTV} and 14.3 Gy for the PTV_{CTV}.

For IMB planning, Oncentra Brachy 4.3® software was used. The implant configuration consisted of catheters centrally placed through the GTV and at the periphery of the CTV. IMB plans were generated using inverse planning simulated annealing (IPSA). For the plan optimization process, PTV and OAR weighting factors and dose objectives were set, depending on tumor location. The plans were also optimized with respect to the dose nonuniformity ratio (DNR) recommendation of the GEC-ESTRO APBI trial. This implied a ratio between 150% (22.5 Gy) and 100% (15 Gy) of the prescribed CTV dose of 0.35 or less. If adequate coverage or optimal DNR was not achieved, catheters were subsequently displaced or additional catheters in a triangular configuration were placed throughout the CTV. The spacing between the needles was less than 20 mm. The microselectron Elekta Ltd.) HDR Iridium-192 was used as stepping source with 2.5 mm distance between dwell positions. With VMAT, plans were generated using Monaco 3.2® software, starting at a 180° angle, using two partial arcs (clockwise and counter clockwise) and a total angle of 210–240°. For the plan optimization process, PTV and OAR weighting factors and dose objectives were set, depending on tumor location.

Table 1. Baseline characteristics

	VALUE	RANGE
Breast		
left	11 (55%)	
right	9 (45%)	
Tumor location in breast		
lateral	13 (65%)	
medial	4 (20%)	
central	3 (15%)	
Median		
clinical tumor size	14 mm	5 mm – 30 mm
gross tumor volume	1.8 cc	0.2 cc – 12.7 cc
distance to skin	10 mm	0 mm – 38.0 mm
distance to chest wall	9 mm	0.5 mm – 46 mm
ipsilateral breast volume	867.8 cc	479.1cc – 3390.6 cc

Plan evaluation and data analysis

For each patient and planning modality, median values on target volume coverage, OAR dose and high dose volumes in the PTV_{CTV} and breast were assessed. High dose volumes to the PTV_{GTV} were not reported since our study design investigated the feasibility of an ablative dose to the tumor. The paired data were evaluated using the non-parametric Wilcoxon signed-rank test and IBM SPSS Statistics 20 (Chicago, IL, USA), with a significance level below 0.05.

RESULTS

The tumor and ipsilateral breast characteristics are presented in table 1. Tumors were mainly laterally located in the left breast. The median tumor size was 13.5 mm, with a median distance of 10.0 mm and 9.0 mm to the skin and chest wall, respectively.

Due to the additional 3 mm PTV margin required with VMAT, IMB resulted in a lower median PTV_{GTV} (1.8 cc vs. 6.1 cc, $p < 0.05$) and PTV_{CTV} (74.8 cc vs. 100.9 cc, $p < 0.05$) (Table 2). The median PTV_{GTV} and PTV_{CTV} receiving at least 95% of the prescribed dose was ≥99% for both treatment modalities (Table 2 and Fig. 1). In two IMB plans, a cranio-caudal instead of a medio-lateral catheter insertion was required for adequate target volume coverage due to an extreme lateral and medial tumor localization. For IMB plans, the median DNR was 0.33 (range 0.19–0.38), with four plans slightly exceeding the dose homogeneity recommendation. The median PTV_{CTV} outside PTV_{GTV} receiving 95% of the prescribed PTV_{GTV} dose (V19Gy) differed substantially, i.e. 4.3 cc and 48.9 cc for the VMAT and IMB plans, respectively (Table 2). Fig. 2 shows a representative IMB plan illustrating a great proportion of the PTV_{CTV} receiving the prescribed PTV_{GTV} dose. The median volume ipsilateral breast receiving 15 Gy outside the CTV was 11.8 cc (range 4.2–43.4) and 9.6 cc (range 3.7–27.6) in VMAT and IMB plans, respectively. The median D1cc in the PTV_{CTV} was 20.3 Gy for the VMAT plans (Table 2). With IMB, the median D1cc in the PTV_{CTV} of 78.8 Gy was found in the high dose sleeves encompassing the

Table 2. Dosimetric parameters for IMB and VMAT treatment plans for a single dose ablative radiotherapy, with a 20 Gy and 15 Gy dose prescription to GTV and CTV, respectively

	IMB median	[range]	VMAT median	[range]	p value
TREATMENT PLANNING					
PTV_{GTV} *(cc)**	1.8	0.2-12.7	6.1	1.4-24.3	< 0.05
PTV_{CTV} *(cc)**	74.8	44.4-147.4	100.9	61.6-183.2	< 0.05
Ratio PTV_{CTV} to ipsilateral breast *(%)*	6.9	4.4-21	9.2	5.4-26.0	< 0.05
COVERAGE					
V_{19Gy} PTV_{GTV} *(%)*	100	[98.6-100]	99.7	[98.9-100]	0.116
$V_{14.3Gy}$ PTV_{CTV} *(%)*	98.6	[98.5-99.5]	99.2	[98.8-100]	< 0.05
Number of catheters	16	[10-20]	-		
HIGH DOSE VOLUMES					
excluding PTV_{GTV}					
V_{19Gy} PTV_{CTV} *(cc)*	48.9	[20.5-92.5]	4.3	[1.9-13.0]	< 0.05
$V_{200\%}$ PTV_{CTV} *(cc)*	7.6	[3.2-15.8]	-		
$V_{400\%}$ PTV_{CTV} *(cc)*	1.7	[0.8-2.8]	-		
D_{1cc} PTV_{CTV} *(Gy)*	78.8	[53.6-102.3]	20.3	[19.6-20.9]	< 0.05
excluding PTV_{CTV}					
V_{15Gy} ipsilateral breast *(cc)*	9.6	[3.7-27.6]	3.9	[0.25-16.4]	< 0.05
OAR EVALUATION					
D_{mean} contralateral breast *(Gy)*	0	[0-0.2]	0.2	[0.1-0.4]	< 0.05
Mean ipsilateral lung dose *(Gy)*	0.8	[0-1.2]	1.3	[0.4-2.5]	< 0.05
D_{1cc} skin *(Gy)*	15.9	[4.6-21.2]	15.2	[10.2-18.3]	0.167
Mean heart dose *(Gy)*	0.4	[0.1-1.8]	0.7	[0.2-1.1]	< 0.05
$V_{2.8Gy}$ heart *(%)*	0	[0-0.2]	0.3	[0-5.9]	< 0.05

V_{xGy} = volume in cc or percentages receiving at least x Gy;
D_{xcc} = dose in Gy to at least x cc volume.
OAR = organ at risk.

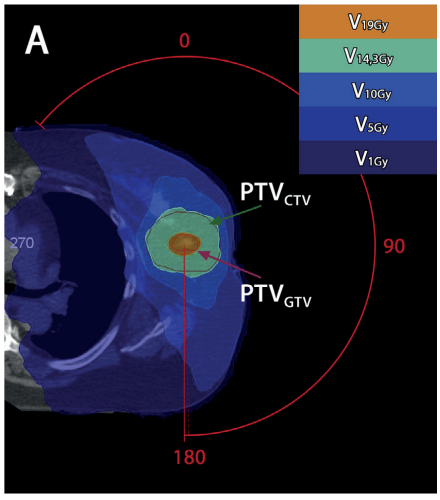


Figure 1. Dose distribution in VMAT (A) versus IMB (B) plan. Volumes receiving a certain dose are illustrated within the corresponding colored isodose lines.

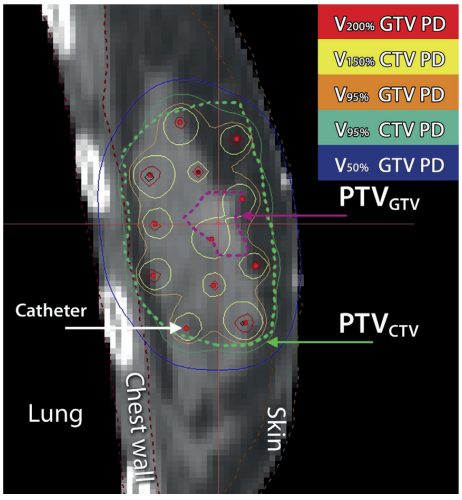


Figure 2. High dose volumes in IMB plan. Volumes receiving a certain percentage of the prescription dose (PD) to the GTV or CTV (V% PD) are illustrated within the corresponding colored isodose lines

catheters. The predefined ipsilateral lung (mean dose < 3.6 Gy), heart (V2.8Gy < 10%) and chest wall constraints (D20cc < 16.3 Gy) were achieved in all plans. The D1cc skin dose was higher than 16 Gy in three VMAT and eight IMB plans, respectively. The median D1cc skin was 15.2 Gy and 15.9 Gy with VMAT and IMB, respectively **(Table 2).** The mean ipsilateral breast dose was 4.6 Gy (range 3.4–7.7 Gy) with VMAT and 3.9 Gy (range 2.5–7.2 Gy) with IMB, respectively.

DISCUSSION

A comparative planning study on single fraction treatment was performed to evaluate the dosimetric feasibility of single dose MRguided ablative radiotherapy for early-stage breast cancer. The VMAT and IMB treatment approach resulted in adequate target volume coverage for all cases.

Due to the additional PTV margin required for VMAT, the PTV_{CTV} was significantly lower with IMB. However, the extent of high dose volumes in the PTV_{CTV} was considerably lower with VMAT compared to IMB. **Appendix 1B** shows a representative dose volume histogram in an IMB versus a VMAT plan. The dose to the contralateral breast, ipsilateral lung and heart were negligible with IMB and low with VMAT **(Table 2).** Skin and ipsilateral breast dosimetric parameters were comparable.

No other comparative VMAT (or external beam RT) versus IMB planning studies have been performed to investigate a single fraction ablative RT approach. However, preoperative single fraction RT has previously been evaluated as feasible by Palta et al. using a three-dimensional conformal radiation therapy (3D-CRT) planning technique. In seventeen virtual plans, a 15 Gy dose was planned for T1 tumors [4] and resulted in a lower OAR dose compared to our study. In the Palta study, the median dose of to the ipsilateral lung and heart were 0.30 Gy and 0.13 Gy, respectively. The D10cc of the skin was 4.9 Gy, whereas in our study 13.2 Gy and 11.7 Gy was evaluated in VMAT and IMB plans, respectively. However, the prescription dose was lower, i.e. 15 Gy and the CTV 1.5 cm margin was less extensive compared to our planning study (20 Gy and 2 cm, respectively). In addition, Palta et al. defined the skin as the first 3 mm of the breast surface whereas in our study 5 mm was employed. Furthermore, tumors were located at least 1 cm from the skin while our study had no restrictions regarding tumor location. Horton et al. performed a phase I dose escalation trial of a single radiosurgery treatment. In this study breast cancer patients with T1 tumors were irradiated to a single dose of 15, 18 or 21 Gy followed by breast-conserving surgery at two weeks after RT [5]. The skin dose to 1 cc and 10 cc (11.0 Gy and 7.0 Gy, respectively) was more favorable when compared to our results. Compared to Horton et al., we used a different CTV expansion, skin definition and tumor location restriction. During a median follow-up of 23 months, no dose limiting toxicity was observed, along with good or excellent cosmetic outcome in all patients.These encouraging preoperative clinical results are not in accordance with the observations by Pinnarò et al. who evaluated single fraction partial breast 3D-CRT in the post-operative setting. After a median follow-up of 3 years, a dose of 21 Gy significantly increased the treatment related toxicity and resulted in fair and poor cosmesis in 36% and 5% of the patients, respectively [17]. These conflicting toxicity and cosmetic results between the study by Horton et al. and Pinnarò et al. could be attributed to differences in follow-up time and a substantial reduction in ipsilateral breast tissue dose observed with preoperative versus post-operative APBI [5]. In the post-operative APBI study, grade 2 fibrosis or higher was associated with ≥ 66 cc of the ipsilateral breast receiving more than 21 Gy [17]. Contrary, in our study, no cases of V21Gy > 66 cc of the breast volume were observed in the VMAT plans. This is most likely due to our two-dose level RT approach including a lower, 15 Gy prescribed dose to the PTV_{CTV}. A V21Gy ≥ 66 cc was noted in three IMB plans. In addition, Pinnarò et al. observed that impaired cosmesis was correlated with a mean ipsilateral breast dose above 9 Gy. In our study, no VMAT or IMB plans acquired a mean ipsilateral breast dose above 9 Gy.

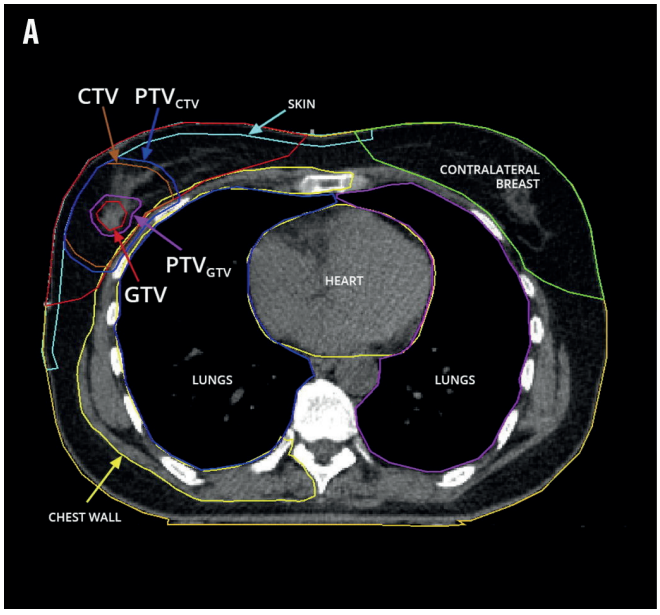
To our knowledge, no studies have been performed evaluating preoperative single dose ablative RT using the IMB approach. Following BCS for early-stage breast cancer, Polgár et al. found that IMB partial breast irradiation delivered in 7 fractions up to a total of 36.4 Gy gives equivalent local control and significantly better cosmetic outcome by comparison to external beam WBI, during a ten year follow-up [18]. These long-term good clinical results with IMB based post-operative APBI cannot be directly extrapolated to a preoperative ablative APBI approach given the more complex catheter configuration of our two-dose levels RT and the higher prescription dose. In the present study, the PTV_{CTV} required numerous catheters in the IMB plans, due to the extensive 2 cm CTV margin around the GTV. This resulted in a median of 65.4% (or 48.9 cc) of the PTV_{CTV} receiving the prescribed dose for the PTV_{GTV} resulting in PTV_{CTV} overdosage. In VMAT plans substantially less overdosage was observed, with a median of 4.3% (or 4.3 cc) for the PTV_{CTV}. In the current study, a clear advantage of IMB over VMAT concerns the significant smaller PTV_{CTV} with a median absolute reduction of 26.1 cc. On the contrary, VMAT resulted in a median absolute reduction in PTV_{CTV} overdosage of 44.6 cc when compared to IMB. In brachytherapy, limited regions of PTV_{CTV} overdosage are perceived as an inherent advantage of the characteristic dose distributions. However, for IMB based breast cancer treatment there is a distinction between uniform post-operative APBI and our two-dose level preoperative APBI. In this specific study, the integrated ablative high-dose boost is intended for the macroscopic tumor, not for microscopic disease and breast tissue within the PTV_{CTV}. Since PTV_{CTV} overdosage can result in unnecessary toxicity, e.g. fibrosis or fat necrosis and decreased cosmetic results, at our department we prefer the VMAT technique for implementing the single dose ablative RT in clinical practice. Previous dosimetric studies on post-operative APBI delivered in 10 fractions up to a total of 38.5 Gy, have evaluated the VMAT technique as feasible with respect to OAR dose, together with superior dose conformity and a shortened treatment time when compared to intensity-modulated arc therapy or conventional 3-dimensional conformal radiation therapy [19,20].

An important aspect on the clinical applicability of the single dose ablative RT is local tumor control. The importance of managing high and low-risk patient criteria is illustrated by the intraoperative (IORT) single dose APBI versus WBI randomized controlled trial. The ELIOT trial evaluating post-lumpectomy single 21 Gydose electron IORT showed an acceptable 5-year local recurrence (LR) of 1.9% in good candidates but a 7.4% LR in possible candidates and 7.7% in patients with a contraindication for APBI according to Groupe Européen de Curiethérapie European Society for TherapeuticRadiology and Oncology [21]. When considering the delivery of APBI in low-risk patients, a precise imaging method is crucial for successfully targeting high-risk (breast or tumor) tissue only and minimizing the treatment volume in favor of toxicity and cosmesis. MRI-guidance in addition to mammography findings and histopathology features has the potential to accurately identify breast cancers of limited extent [6] and is therefore suitable for the delivery of the ablative treatment in clinical practice. Furthermore, in order to ensure safe treatment delivery, the GTV was expanded to CTV by 2 cm.

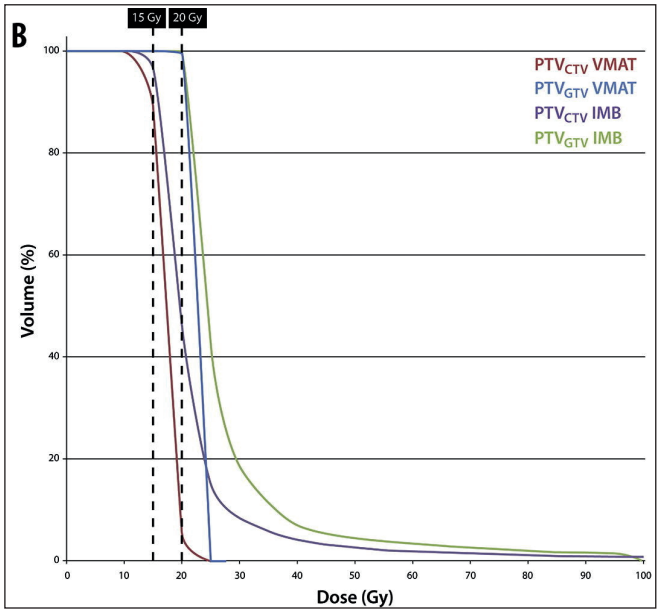
A drawback of our study is the reproducibility of our planning study observations in clinical practice, especially for IMB. The static CT-based catheter tracks in this IMB planning study can differ from implants achievable in practice. Nevertheless, PTV_{CTV} overdosage as a result of the characteristic brachytherapy dose distribution together with the two level, high prescription dose approach, remains the main limiting factor for IMB implementation of single fraction ablative RT. Furthermore, in this comparative study, differences in dose calculation algorithms between VMAT and IMB planning software

are possible. In addition, we observed minor absolute differences in OAR dose with VMAT and IMB plans despite statistically significant differences evaluated with the Wilcoxon signed rank test. Therefore only a substantial dosimetric difference such as PTV_{CTV} overdosage (65.4% IMB versus 4.3% VMAT) was considered clinically relevant. Finally, the value of the linear-quadratic model for the conversion of EQD2 constraints to single dose constraints is limited. Moreover, for the clinical implementation of a single fraction ablative RT, there is a lack of evidence-based OAR constraints. In particular for the skin, the permitted dose could not be easily determined given the limited number of studies. The current planning study evaluated the D1cc dose, nevertheless, the clinical implications of a 1 cc skin dose above 16 Gy remain unknown. In one post-operative single fraction APBI study, late toxicity such as grade 1 or 2 telangiectasia was observed in 26.5% of the patients and was associated with a previous acute erythema episode [17]. Acute erythema was correlated to the mean skin dose of 5.4 Gy. We therefore estimate that high doses to the skin are reasonably tolerated. However, a comparison with the mean skin dose in our study is impracticable due to differences in skin volume definition in several studies. We observed low median skin doses of 1.9 Gy and 2.2 Gy for the IMB and VMAT plans, and therefore can expect acceptable skin toxicity. Nevertheless, OAR toxicity has to be confirmed in further clinical studies.

In conclusion, we found that MRI-guided single fraction radiotherapy with an integrated ablative boost to the GTV is dosimetrically feasible using VMAT and IMB. For this two-dose level treatment approach, we perceive IMB less suitable for clinical implementation due to PTV_{CTV} overdosage. Recently, we initiated a clinical study investigating the feasibility for MRI-guided single dose ablative preoperative external beam radiotherapy using VMAT planning for low-risk, early-stage breast cancer patients. In order to assess the ablative effect, breast-conserving surgery is performed 6 months after radiotherapy. The primary study endpoint the pathological complete response. For the future, we hope to implement the single dose ablative treatment approach using the MRI-linear accelerator that is currently being developed at our department.



Appendix 1A. Planning target volumes and organs at risk delineations. Transverse planning CT slide illustrating delineations of the planning target volumes in a VMAT plan and organs at risk such as contralateral breast, lungs, heart, chest wall and skin. NOTE: For VMAT, both GTV and CTV were uniformly expanded by 3 mm to obtain the planning target volumes PTV_{GTV} and PTV_{CTV}. For IMB planning, the PTV_{GTV} and PTV_{CTV} were equal to the GTV and CTV, respectively



Appendix 1B. Dose volume histograms. Representative dose volume histogram illustrating that 58% of the PTV_{CTV} receives 95% of the prescribed PTV_{GTV} dose (19 Gy) with IMB, in contrast to 8% with VMAT. The VMAT and IMB plans are compared in the same patient.

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Chapter 4

Redefining radiotherapy for early-stage breast cancer with single dose ablative treatment: a study protocol

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ABSTRACT

Background: A shift towards less burdening and more patient friendly treatments for breast cancer is currently ongoing. In low-risk patients with early-stage disease, accelerated partial breast irradiation (APBI) is an alternative for whole breast irradiation following breast-conserving surgery. MRI-guided single dose ablative APBI has the potential to offer a minimally burdening, non-invasive treatment that could replace current breast-conserving therapy.

Methods: The ABLATIVE study is a prospective, single arm, multicenter study evaluating preoperative, single dose, ablative radiation treatment in patients with early-stage breast cancer. Patients with core biopsy proven non-lobular invasive breast cancer, (estrogen receptor positive, Her2 negative, maximum tumor size 3.0 cm on diagnostic MRI) and a negative sentinel node biopsy are eligible. Radiotherapy (RT) planning will be performed using a contrast enhanced (CE) planning CT-scan, co-registered with a CE-MRI, both in supine RT position. A total of twenty-five consecutive patients will be treated with a single ablative RT dose of 20 Gy to the tumor and 15 Gy to the tumorbed. Follow-up MRIs are scheduled within 1 week, 2, 4 and 6 months after single-dose RT. Breast-conserving surgery is scheduled at six months following RT. Primary study endpoint is pathological complete response. Secondary study endpoints are the radiological response and toxicity. Furthermore, patients will fill out questionnaires on quality of life and functional status. Cosmetic outcome will be evaluated by the treating radiation oncologist, patient and 'Breast Cancer Conservation Treatment cosmetic results' software. Recurrence and survival rates will be assessed. The patients will be followed up to 10 years after diagnosis. If patients give additional informed consent, a biopsy and a part of the irradiated specimen will be stored at the local Biobank and used for future research on radiotherapy response associated genotyping.

Discussion: The ABLATIVE study evaluates MRI-guided single dose ablative RT in patients with early-stage breast cancer, aiming at a less burdening and non-invasive alternative for current breast-conserving treatment.

Trial registration: ClinicalTrials.gov registration number NCT02316561. The trial was registrated prospectively on October 10th 2014.

BACKGROUND

In the field of breast cancer treatment a shift towards less burdening and more patient friendly therapies is currently ongoing. Breast-conserving therapy consisting of breast-conserving surgery (BSC) followed by whole breast irradiation (WBI) is the standard treatment for early-stage disease [1-2]. The WBI benefit with respect to local recurrence and breast cancer associated mortality varies substantially, depending on clinical and tumor characteristics [3-4].

A main shortcoming of WBI is the protracted schedule of 16 to 23 RT fractions, ranging from 3 to 5 weeks treatment duration. Since the risk of local recurrence is low, and 62 to 88% of local recurrences are found within the vicinity of the tumor bed [5-6], accelerated partial breast irradiation (APBI) has been investigated as an alternative to WBI. APBI can deliver a higher radiation dose solely on breast tissue directly surrounding the tumor bed in a reduced treatment time [7–9]. APBI instead of WBI following breast-conserving surgery can represent a less burdening treatment, however adequate patient selection is essential. APBI, when compared to WBI, can be associated with an increased local recurrence rate in high-risk patients, without compromising regional and distance recurrence or overall survival [10–18]. In selected patients with early-stage and low-risk characteristics, APBI can be regarded as an equivalent to WBI [18-19]. Patient eligibility guidelines for APBI have been set up by the American Society for Radiation Oncology (ASTRO) and European Society for Radiotherapy and Oncology (ESTRO) [7-8].

Adequate delivery of APBI is critical given that RT is aimed for high-risk tissue only and not the whole breast. Target volume definition is more precise before surgical tumor removal, when compared to a post-operative approach [20]. In addition, there is with less variability in target volume delineation across radiation oncologists [20-21]. Also, a substantial reduction in treatment volumes can be achieved with preoperative APBI when compared with post-operative APBI, possibly leading to less treatment-related toxicity [20, 22-23].

MRI-guided single dose APBI, prior to breast-conserving surgery, has been investigated in women with early-stage and low-risk breast cancer due to its potential to minimize RT treatment duration and toxicity [24]. However, a primary ablative RT approach to the tumor, without the performance of breast-conserving surgery, may represent an additional gain for the clinical practice. As with stereotactic RT for stage I non-small-cell lung cancer [25], noninvasive, ablative RT might be feasible as definitive treatment for early-stage breast cancer. Single dose ablative APBI has the potential to decrease the burden of multiple RT fractions, and at the same time replace breastconserving

surgery for selected patients. This could offer non-invasive and minimally burdening treatment for women with early-stage breast cancer.

A multicenter, single-arm prospective study has been initiated in The Netherlands, in order to evaluate MRI-guided single dose ablative RT as definitive treatment for early-stage breast cancer. This paper describes the study design, which assesses an ablative treatment approach following single dose MRI-guided APBI in breast cancer.

METHODS/DESIGN

Study design

The ABLATIVE trial was initiated as a single-arm prospective interventional study at the Radiotherapy Department of the University Medical Center (UMC) Utrecht in The Netherlands and was subsequently extended to 3 regional peripheral hospitals. The purpose of the study is to evaluate the feasibility of single dose radiotherapy as definitive treatment for early-stage breast cancer. To evaluate the pathological tumor response, breast-conserving surgery is performed at 6 months after RT. The primary study endpoint is the pathological complete response (pCR) as assessed by microscopic evaluation of the excision specimen. The secondary endpoints include radiological response, toxicity, cosmetic outcome, local, regional and distant relapse rates, and disease-free and overall survival. Also,patient reported outcome measures such as quality of life, functionality, psychological symptoms and frailty are evaluated. Furthermore, if patients provide additional informed consent for Biobank purposes, future research will evaluate radiotherapy response genotyping.

Ethical matters

This study is set-up in agreement with the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and is conducted in accordance with the Dutch Medical Research Involving Human Subjects Act (http://www.ccmo.nl). The study protocol has been approved by the Medical Research Ethics Committee of the UMC Utrecht (NL46017.041.13) and has been recorded in an international trial registry (ClinicalTrial.gov: NCT02316561). The study has been approved by the Institutional Review Board of each participating institute. Written informed consent is obtained from all patients before inclusion.

Quality assurance

Study monitoring will be carried out centrally at the UMC Utrecht, by an independent monitor contracted by the sponsor, according to national guidelines on quality control for university medical centers [26].

Patient recruitment and selection

Women presenting at the Department of Surgery of the UMC Utrecht and Diakonessenhuis hospital in Utrecht, non-invasive and minimally burdening treatment for St. Antonius Hospital in Nieuwegein/Utrecht or Rivierenland Hospital in Tiel are eligible for inclusion after a diagnosis of invasive breast cancer. The study initially included patients at least 60 years of age with early-stage and low-risk (cT1N0Mx) invasive ductal or ductulobular breast cancer without an indication for systemic treatment according to Dutch National Guidelines. Recently, eligibility criteria were broadened to include patients from 50 years or older, and the use of endocrine treatment was permitted. Table 1 gives an overview on the inclusion and exclusion criteria, which are in concordance to the ASTRO and ESTRO guidelines for partial breast irradiation [7-8]. The surgeon informs patients on the possibility of a study intervention evaluating single dose RT with postponed surgical treatment instead of standard of care 16–23 fractions postoperative radiotherapy. Patients interested in trial participation receive additional information from the coordinating investigator. Furthermore, these patients are referred to the radiation oncologist at the UMC Utrecht for preoperative consultation to receive information about the standard RT treatment.

Table 1. Overview inclusion and exclusion criteria ABLATIVE study

INCLUSION
World Health Organization performance status 0-2
Females ≥ 50 years* with cT1N0 tumor
Females ≥ 70 years with cT1-2*$_{(maximum\ 3\ cm)}$N0 tumor
Tumor histology as assessed on biopsy:
– Ductal or ductolobular invasive carcinoma
– Estrogen receptor positivity
– HER2 receptor negative
Unifocal tumor
Tumor negative sentinel node procedure
Adequate understanding of the Dutch language
EXCLUSION
Legal incapacity
Known BRCA gene mutation
MRI contra-indication
Previous history of ipsilateral breast surgery and impaired cosmetic outcome, as assessed by the treating surgeon or radiation-oncologist.
Signs of extensive ductal carcinoma in situ on mammogram or histological biopsy.
History of breast cancer
Other type of malignancy within 5 years before breast cancer diagnosis[1*]
Collagen synthesis disease

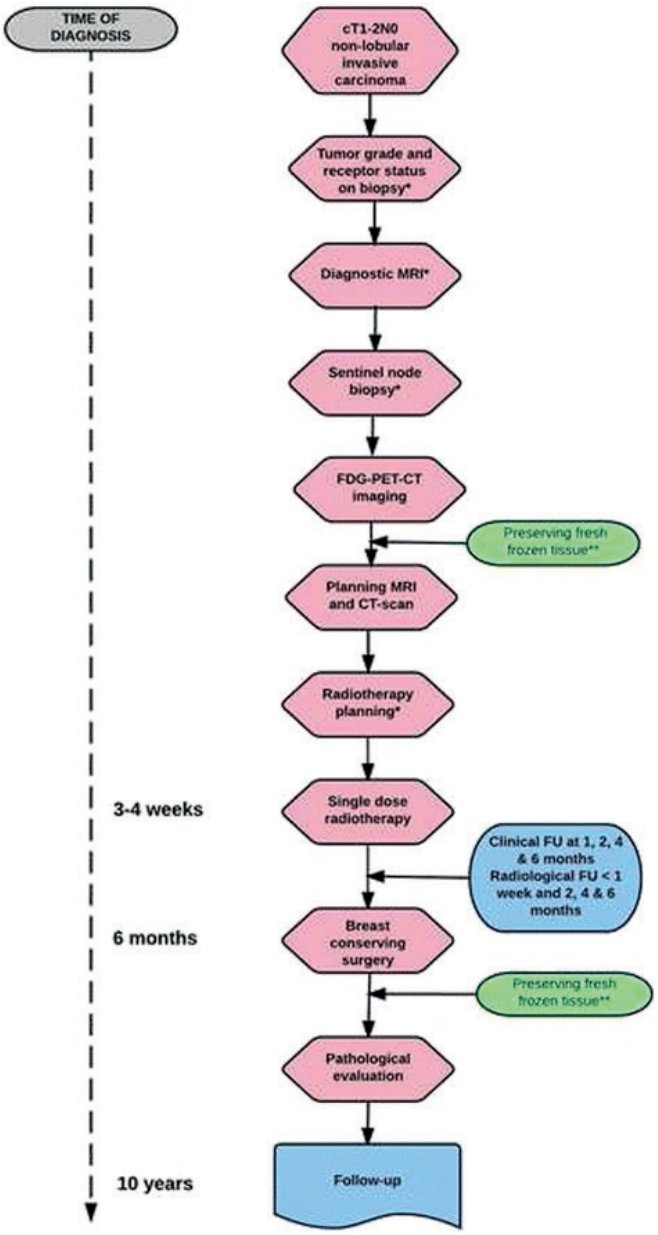
[1] *For adequately treated carcinoma in situ of the cervix or basal cell carcinoma of the skin no specific time span is required.* * *Criterion adjusted following the amendment.*

Procedures

An overview of the required study procedures for single dose ablative radiotherapy is illustrated in Fig. 1. All patients will undergo the RT study procedures at the UMC Utrecht. Study patients from the participating teaching hospitals will undergo the standard of care sentinel node procedure and breast-conserving surgery in the referral hospital.

Diagnostic work-up

Following informed consent, eligibility criteria are assessed stepwise. First, the estrogen, progesterone and HER2 receptor, and Bloom & Richardson tumor grade are assessed on a 14-gauge histological biopsy [27]. Second, a diagnostic MRI (in prone position) is performed to assess the tumor diameter and exclude tumor multifocality or multicentricity [28]. A third step is the performance of a sentinel node procedure, using blue dye, separately from breast-conserving surgery. Only patients with a pN0 nodal status are eligible [7-8]. For the purpose of RT response assessment, an FDG-PET-CT of the breasts



Legend: * reassessment eligibility criteria following procedure ** additional informed consent required

Figure 1. Overview study design.

is performed to acquire a baseline standard uptake value (SUV) of the tumor before irradiation.

Radiotherapy preparations

For position verification purposes during RT delivery, an MRI compatible clip will be placed in the tumor under ultrasound guidance. For RT treatment planning, a contrast-enhanced (CE) CT-scan as well as CE and functional MRI-scan in supine RT treatment position are performed on the same day. The gross tumor volume (GTV) is delineated on CE-CT, and co-registered with the findings on CE-MRI by a radiation oncologist specialized in breast cancer. GTV delineation is verified by a dedicated breast radiologist. To account for microscopic disease, the GTV is uniformly expanded by 2 cm to create a clinical target volume (CTV), thereby excluding

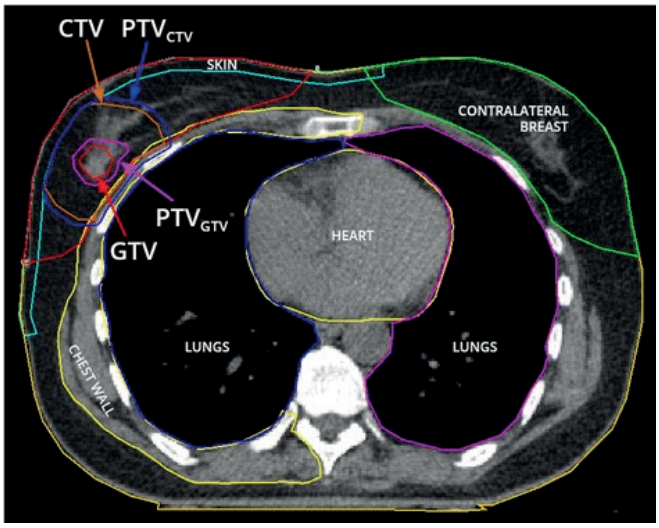


Figure 2. Contouring of planning target volumes and organs at risk. Legend: GTV represents the gross tumor volume, CTV the clinical target volume and PTV the planning target volume

the first 5 mm beneath the skin and the chest wall. Both GTV and CTV are uniformly expanded by 3 mm to obtain the planning target volumes PTV_{GTV} and PTV_{CTV}, respectively, thereby excluding the first 5 mm beneath the skin [29-30]. Organs at risk (OARs), such as skin, ipsilateral and contralateral breast, lungs, heart and chest wall are delineated according to predefined protocols [29]. **Figure 2** illustrates the delineations of the target volumes and OARs.

Volumetric modulated arc therapy (VMAT) plans are created using 2 separated partial arcs, clockwise and counter clockwise. Two radiotherapy dose levels are concomitantly prescribed in one single fraction: 15 Gy to the PTV_{CTV} and 20 Gy to the PTV_{GTV}. The 20 Gy single dose is equivalent to a 73.7 Gy dose in 2 Gy fractions (EQD2, α/β 4.7), resulting in a 100% 5 yeartumor control probability for cT1N0 tumors [31, 32]. The single 15 Gy dose corresponds to an EQD2 of 44.1 Gy (α/β 4.7), similar to the standard hypofractionated schedule of 16 fractions of 2.66 Gy at our institution. Adequate target volume coverage is defined as 99% or more of the PTV receiving at least 95% of the prescribed dose **(Fig. 2)**. VMAT plans are optimized for target volume coverage and a dose as low as possible to the OARs, thereby not exceeding the predefined constraints **(Additional file 1)** [29]. **Figure 3** illustrates an example of a single dose ablative APBI treatment plan.

Radiotherapy treatment delivery

For position verification purposes 2 cone beam CTs (CBCT) are performed before RT delivery. The first CBCT is used for treatment position assessment, and the second one to check the tumor location after position correction. The clip in the tumor is used for position verification. Also the position of the clip relative to the chest wall is determined to quantify changes in target location or deformations. To account for intra-fraction motion, position verification and correction is performed after the first arc using a third CBCT. A last CBCT is taken after RT delivery to determine the intra-fraction motion during the second arc.

Follow-up after single dose ablative treatment

Following the ablative boost treatment, frequent clinical and MRI monitoring will be performed. For (early) treatment response

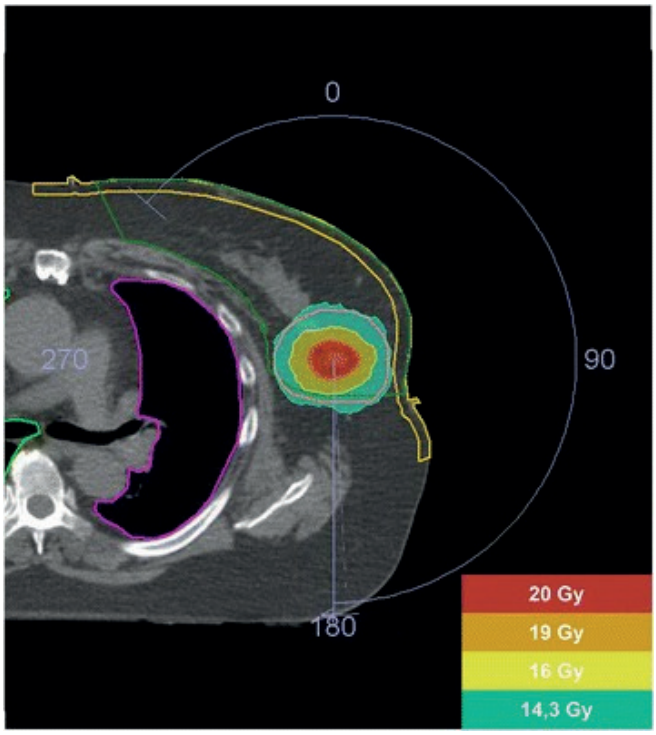


Figure 3. Dosimetry treatment plan single dose ablative radiotherapy. Legend: The red isodose (20 Gy) represents the prescribed dose to the gross tumor volume (GTV), the orange isodose (19 Gy) represents 95% of the prescribed dose to the GTV, the yellow isodose (16 Gy) represents 107% of the prescribed dose to the clinical target volume (CTV) and the green isodose (14.3 Gy) represents 95% of the prescribed dose to the CTV

assessment, MRIs are scheduled within 1 week and at 2, 4 and 6 months after RT. The radiologic response will be evaluated according the 'Response Evaluation Criteria in Solid Tumors' guidelines [33]. Breast-conserving surgery In order to assess the ablative RT effect on the tumor, breast-conserving surgery is scheduled at 6 months following RT treatment. If disease progression is clinically or radiologically suspected, surgery is performed earlier. The surgical specimen is evaluated for radiotherapy response. Cell viability is assessed using hematoxylin and eosin staining, and additional cytokeratin 8 immunohistochemistry. The excision specimens will be revised centrally at the UMC Utrecht by one dedicated breast pathologist.

The pathological response is categorized as [34]:

1. Complete pathologic response = either no residual carcinoma or no residual invasive carcinoma but DCIS may be present.
2. Partial response to therapy:
   - near complete response = minimal residual disease (<10% tumor cells)
   - evidence of response (10–50% tumor cells)
   - >50% tumor cellularity remains evident with features of response present
3. No evidence of response

Follow-up

In our institute, follow-up visits after treatment usually consist of a yearly consultation at the outpatient department of Surgery or Radiation Oncology including mammography during 5 years. If systemic therapy is indicated, additional consultations with the medical oncologist are planned. Figure 4 illustrates the additional study procedures and follow-up time points for the study patients. Consultations with the radiation oncologist are scheduled at baseline and at predefined time points up to 10 years post diagnosis to assess long-term toxicity (Common Toxicity Criteria Adverse events version 4.03) [35]. Reporting and follow-up of (serious) adverse events is carried out according to predefined regulations of the study protocol. Cosmetic outcome is assessed (as excellent, good, fair and poor) by the radiation oncologist, thereby taking into account breast changes such as telangiectasia or fibrosis following treatment. For additional cosmetic evaluation, digital photographs of the breasts are taken and will be examined using the BCCT.core software program [36]. Patients will also fill out questionnaires on the cosmetic outcome of their breasts. Radiological follow-up will consist of yearly mammograms in the first 5 years and in the 6th, 8th and 10th year after RT. In addition, a diagnostic MRI of the breasts will be performed at 1 year after diagnosis.

Patient reported outcome measures

Patients are requested to fill out questionnaires on quality of life (EORTC QLQ-C30, EORTC QLQ-B23) [37], emotional symptoms (Hospital Anxiety and Depression Scale) [38], frailty (Groningen Frailty Indicator) [39] and functionality (Multidimensional Fatigue Inventory; Short Questionnaire to Assess Health enhancing Physical activity) [40-41] at baseline and predefined time points up to 10 years after diagnosis. Furthermore, the patient's satisfaction with the cosmetic outcome is assessed with a standardized set of questions.

Other procedures

Even though RT is a key modality for breast cancer treatment, no gene-expression profiles enabling a personalized treatment approach are available for the clinical practice [42]. In order to also contribute to the evolving field of radiogenomics, study patients will be required to give additional consent for a future study on radiotherapy response genotyping. For this purpose, an additional breast biopsy will be performed at baseline, and this tissue will be fresh frozen at the UMC Utrecht Biobank. Also, following breast-conserving surgery, a part of the irradiated excision specimen will be preserved.

Sample size calculation

We expect to find a pathological complete response in 95% of the patients, as determined in the surgical specimen at six months after radiotherapy (with or without endocrine treatment). The sample size calculation is performed with the Power Analysis and Sample Size software program PASS 2008, (Hintze J, 2008. PASS 2008, NCSS, LCC. Kaysville, Utah, USA. www,ncss,com), using the exact (Clopper-Pearson) confidence interval formula in the 'Confidence intervals for one proportion' procedure. With an estimated pCR of 95% a sample size of 20 patients would produce a two-sided 95% confidence interval running from 75 to 100%. A total of 25 patients will be included to compensate for drop out or loss to follow-up.

Statistical methods

The proportion of patients with pCR will be evaluated and a two-sided 95% confidence interval will be calculated. The secondary study objectives will be described without the performance of an official statistical test.

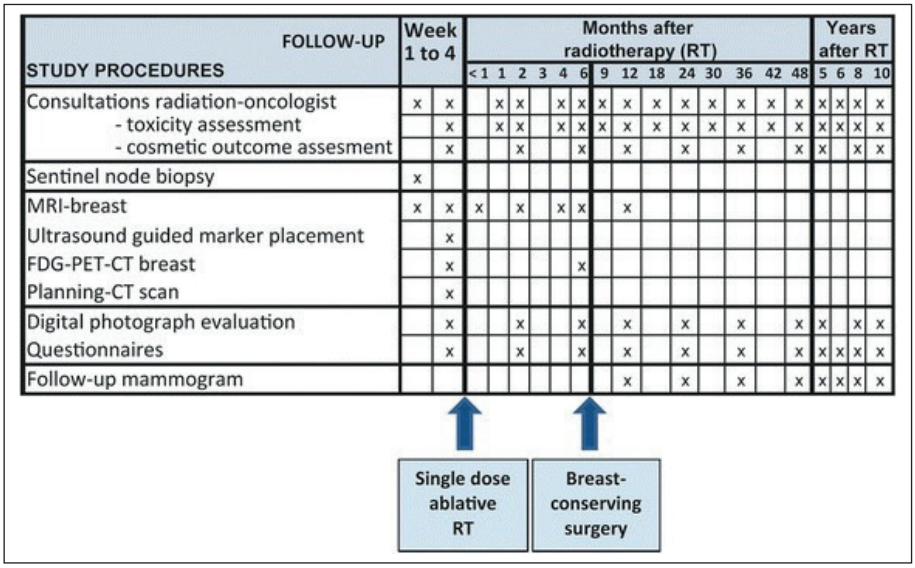


Figure 4. Overview study procedures and follow-up time

DISCUSSION

The ABLATIVE study is, to the best of our knowledge, the first study to evaluate the ablative effect of single dose APBI for early-stage breast cancer in current era of image-guided radiotherapy. When pursuing a minimally burdening ablative treatment for early-stage breast cancer, external beam APBI offers the least invasive technique with the most widespread availability, when compared to brachytherapy or intraoperative techniques. A phase I dose escalation trial with 15, 18 or 21 Gy single dose RT delivered to T1 tumors has previously been evaluated in prone treatment approach [24]. Breast-conserving surgery was performed at 10 days after RT. During a median follow-up of 23 months, no dose limiting toxicity or local recurrences were observed, along with good or excellent cosmetic outcomes in all single dose APBI treated patients.

Pathological complete response following single dose APBI will be assessed by breast-conserving surgery 6 months afterwards. Local tumor control following whole breast RT only has been reported as feasible in two previous studies, performed more than two decades ago [32, 43]. In breast cancer patients with T1 carcinomas treated with a hyperfractionated 45–110 Gy schedule, the 5-year local control rates ranged from 40 up to 100% [32]. Another retrospective study evaluated hyperfractionated whole breast RT alone (median dose 76 Gy) in 319 patients with stage I-IV disease, unfit for surgery or with unresectable tumors [38]. For the total group of patients, local control rates were 56 and 44%, at 5 and 10 years follow-up, respectively. High-risk characteristics such as tumor size above 4 cm and high tumor grade were independent factors associated with local recurrence. The mean time to maximal response was 6.4 months. In another study in rectal adenocarcinoma, a time interval around 15–16 weeks after neoadjuvant chemoradiotherapy was evaluated as most adequate to result in a pathological complete response [44]). For the current study, a 6 months interval up between radiotherapy and breastconserving surgery was considered acceptable from a patient's perspective. Our results will show if 6 months follow-up is sufficient to enable the evaluation of a complete ablative effect. We consider a 95% pCR rate as minimum rate to take the investigational treatment to a future randomized controlled trial with breast-conserving therapy as standard treatment arm. Irrespective of the proportion of patients with a pathological complete response, the current study might have other benefits for clinical practice. A non-ablative preoperative single dose treatment is an appealing alternative to multiple postoperative RT fractions. In addition, extending the time to surgery might be considered if the treatment is not ablative at 6 months following RT. Regardless of the feasibility of an ablative treatment approach, studying preoperative RT has great potential towards a personalized and tailored RT approach. Whereas RT is an essential part of current earlystage breast cancer treatment, its effect cannot be directly evaluated since surgery is performed before WBI. For the individual patient in clinical practice, there are no predictors or biomarkers of RT response available yet. With preoperative RT, its effect can be directly investigated in the excised specimen, enabling future explorations towards RT response predictors and biomarkers.

A challenge of the current study design is setting-up the radiological follow-up between RT and surgery. The first MRI scan, performed within 1 week after RT, aims at identifying early-stage characteristics of treatment response. Data from neoadjuvant chemotherapy (NAC) for locally advanced breast cancer, have shown that the ADC values following the first cycle of NAC significantly increased from baseline, in complete and partial responders [45]. Furthermore, the previously mentioned single dose preoperative APBI study evaluated changes in CE-parameters (e.g. area under the contrast curve) and increase in ADC-values on the MRI performed at 1 week after radiotherapy. However, the clinical implications of these early MRI changes ought to be further explored [46]. Since there is no experience on RT response monitoring in breast cancer patients, additional MRIs were pragmatically scheduled at 2, 4 and 6 months following single fraction APBI. In addition, we incorporated 2 FDG-PET-CTs at baseline and preoperatively at 6 months, in order to evaluate other modalities for response assessment. MRI combined with FDG-PET-CT might have a complementary role for pCR assessment, as suggested in neoadjuvant chemotherapy studies [47]. The study results will have to identify the most useful imaging modality and time point for response assessment.

For future implementation of non-invasive ablative APBI, the performance of a separate sentinel node biopsy (SNB) has to be addressed. A SNB is performed for staging purposes only, and not with a therapeutic intent. For a select group of low-risk patients, axillary ultrasound instead of SNB might be perceived as sufficient to exclude (clinically relevant) gross nodal involvement [48], given its high specificity (range 82–98%) [49]. The impact of non-detection

of micrometastases is limited, with similar survival in women with stage IA (node negative) versus stage IB disease (micrometastases) [50]. Currently, the omission of SNB is being prospectively evaluated for cT1-2 N0 disease as assessed with axillary ultrasound, treated with breast-conserving therapy [51].

At our department, the ABLATIVE study with a single dose treatment is a preparatory step towards on-line MRI-guided RT in early-stage breast cancer. The UMC Utrecht has, in collaboration with Elekta® and Philips®, designed and prototyped the world's first hybrid linear accelerator (MRlinac) consisting of a RT delivery system and a 1.5 Tesla MRI scanner [52]. The MR-linac provides real-time softtissue imaging during the actual radiation delivery [53]. Due to this targeted approach, smaller RT target volumes possibly reducing RT related toxicity, and RT dose escalation may be facilitated at the same time. The MR-linac has thus the potential to offer non-invasive, utterly precise, high-dose RTas an alternative for surgical treatment.

In conclusion, the ABLATIVE study is a multicenter prospective trial evaluating MRI-guided single dose ablative radiotherapy as definitive treatment in patients with low-risk and early-stage breast cancer.

Additional file 1. Overview dose prescription and constraints

STRUCTURE/TARGET VOLUME	PRESCRIPTION DOSE or SINGLE DOSE CONSTRAINTS*
Gross tumor volume (GTV)	20 Gy
Clinical target volume (CTV)	15 Gy
Planning target volume GTV (PTV_{GTV})	95% of the GTV dose in ≥ 99% volume
Planning target volume CTV (PTV_{CTV})	95% of the CTV dose in ≥ 99% volume
Ipsilateral breast	PTV_{CTV} < 25% of total volume ipsilateral breast
Heart	$V_{2.8\,Gy}$ < 10% $V_{4.7Gy}$ < 5%
Ipsilateral lung	Mean lung dose < 3.6 Gy
Chest wall	D_{20cc} < 16.3 Gy
Skin	Dose as low as possible, aim Dmax < 12 Gy. If this not feasible (e.g. CTV aligns skin) aim Dmax < 16 Gy.
Contralateral breast, trachea and esophagus	No constraint, dose as low as possible.

* Rationale and methods dose contraint conversion previously described [29]

ABBREVIATIONS

APBI: Accelerated partial breast irradiation; ASTRO: American Society for Radiation Oncology; BSC: Breast-conserving surgery; CBCT: Cone beam CT scan; CE: Contrast enhanced; CTV: Clinical target volume (CTV); ESTRO: European Society for Radiotherapy and Oncology; GTV: Gross tumor volume; MR-linac: MRI linear accelerator; NAC: Neoadjuvant chemotherapy; OAR: Organ at risk; pCR: Pathological complete response; PTV_{CTV}: Planning target volume of the clinical target volume; PTV_{GTV}: Planning target volume of the gross tumor volume; SNB: Sentinel node biopsy; VMAT: Volumetric modulated arc therapy; WBI: Whole breast irradiation

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Chapter 5
Treatment constraints for single dose external beam preoperative partial breast irradiation in early-stage breast cancer

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ABSTRACT

Background: Following breast-conserving surgery and post-operative 3D-conformal accelerated partial breast irradiation (APBI), suboptimal cosmetic results have been reported. Preoperative radiation delivery to the intact tumor enables better target visualization and treatment volume reduction. Single dose preoperative APBI has the potential to improve toxicity profiles, reduce treatment burden and enable in vivo exploration of breast cancer radiogenomics.

Purpose: Develop practical guidelines for single dose external beam preoperative APBI.

Methods: Recommended dose constraints were derived from pooled dosimetry estimates from 2 clinical trials. In an American dose escalation trial, a uniform 15, 18 or 21 Gy dose has previously been evaluated for non-lobular cT1N0 or low/intermediate grade DCIS <2 cm in prone position (n = 32). In the Netherlands, the feasibility of ablative APBI (20 Gy to GTV, 15 Gy to CTV) to non-lobular cT1N0 in supine position, is currently being explored (n = 15). The dosimetric adherence to the developed constraints was evaluated in new APBI plans with a 21 Gy uniform dose but an extended CTV margin (n = 32).

Results: Dosimetric data pooling enabled the development of practical guidelines for single dose preoperative APBI.

Conclusion: The developed guidelines will allow further explorations in the promising field of single dose preoperative external beam APBI for breast cancer treatment.

INTRODUCTION

Accelerated partial breast irradiation (APBI) has been explored as an alternative to whole breast irradiation (WBI) following breast-conserving surgery [1-9]. In selected patients with early-stage breast cancer and low-risk of local recurrence, APBI efficacy appears to be equivalent to WBI with respect to local control and survival rates [3,6-10].

Several randomized controlled trials have evaluated different approaches to deliver APBI following breast-conserving surgery, each with its own advantages and disadvantages. Interstitial multicatheter brachytherapy (IMB) is the technique with the longest clinical follow-up available and good clinical results when compared to WBI with equivalent efficacy, and comparable toxicity profiles [6, 9]. However, due to the invasiveness of the technique, the required physician's expertise and brachytherapy equipment, IMB has not been widely implemented. Second, intra-operative radiotherapy (IORT) is an appealing technique due to the single treatment approach at the time of surgery but requires costly and cumbersome equipment. External beam APBI has the advantage of widespread equipment availability and expertise, but when compared to the previous techniques, larger treatment volumes have typically been utilized. As a result, an increase in soft tissue fibrosis and suboptimal cosmetic outcomes has been seen with 3-dimensional conformal external beam radiation therapy (3D-CRT) [4]. However, more dose conformal techniques such as intensity-modulated radiotherapy (IMRT), have the potential for superior toxicity and cosmetic outcome profiles when compared to WBI, suggesting that the results of external beam APBI could be improved upon [8].

In an effort to overcome the disadvantages and capitalize on the advantages of the previous APBI techniques, the concept of MRI-guided single dose external beam partial breast irradiation delivered prior to surgical resection has been developed [11-13]. The single dose concept of IORT using a non-invasive external beam technique can minimize the treatment duration and burden for patients, without the purchase of any supplementary radiotherapy equipment. In addition, the delivery of radiation (RT) preoperatively to the intact tumor allows more precise targeting when compared to post-surgery, resulting in significantly smaller treatment volumes and possibly less RT-induced toxicity [11,14]. Another advantage of preoperative APBI concerns the uniformity of treatment volume definition, with less interobserver variation in target volume delineation when compared to a postoperative approach [15]. MRI-guided preoperative target definition can further improve the tumor visualization (i.e. tumor spiculae) [16]. This could facilitate dose escalation, enabling an ablative, definitive treatment approach for early-stage breast cancer. Finally, preoperative APBI allows the direct evaluation of RT effects in breast tumors, aiming at the identification of radiation response predictors and biomarkers, which may help to guide personalized treatment for future patients [17].

Single dose external beam preoperative APBI has great potential in clinical practice to deliver a precise and uniform, minimally burdensome treatment with less associated toxicity, and opens a new window of opportunity in radiogenomics. Based on the clinical experience with this approach in two university medical centers, this manuscript introduces practical guidelines for the delivery of single dose external beam preoperative radiotherapy.

Table 1. Overview of treatment planning in the different cohorts

	Dose escalation cohort 15, 18 or 21Gy (total n=32)	Integrated boost cohort 20/15Gy (n=15)	Replanned cohort 21Gy (n=32)
Set-up	Prone*	Supine	Prone*
Gross tumor volume (GTV)	Delineated based on fused CT-MR findings and intratumoral fiducial marker.	Delineated based on fused CT-MR findings and intratumoral fiducial marker.	Delineated based on fused CT-MR findings and intratumoral fiducial marker.
Clinical target volume (CTV)	15 mm around GTV, excluding the first 5 mm from the body as well as chest wall > 1cm from the GTV	20 mm around GTV, excluding the first 5 mm from the body as well as the chest wall	20 mm around GTV, excluding the first 5 mm from the body as well as the chest wall
Evaluated planning target volume (PTV)	3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue	- 3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue ($PTV_{(CTV)}$) - 3 mm margin from GTV, excluding the first 5 mm of subcutaneous tissue (PTV_{GTV})	3 mm margin from CTV, excluding the first 5 mm of subcutaneous tissue and chest wall
Prescription dose (PD)	15, 18 or 21 Gy to the CTV	15 Gy for the CTV 20 Gy for the GTV	21 Gy for the uniform CTV
Definition adequate coverage	At least 95% of PD to 100% of CTV	At least 95% of PD to at least 99% of PTV_{CTV} or PTV_{GTV}, respectively.	At least 95% of PD to at least 98% of CTV. Secondary objective: 95% of PD to 95% of PTV_{CTV}
Treatment planning approach	Intensity modulated radiation therapy with 5-7 (non)coplanar beam arrangement.	Volumetric modulated arc therapy with 2 partial arcs.	Intensity modulated radiation therapy with 4-7 noncoplanar beam arrangement.

* 2 patients were treated supine

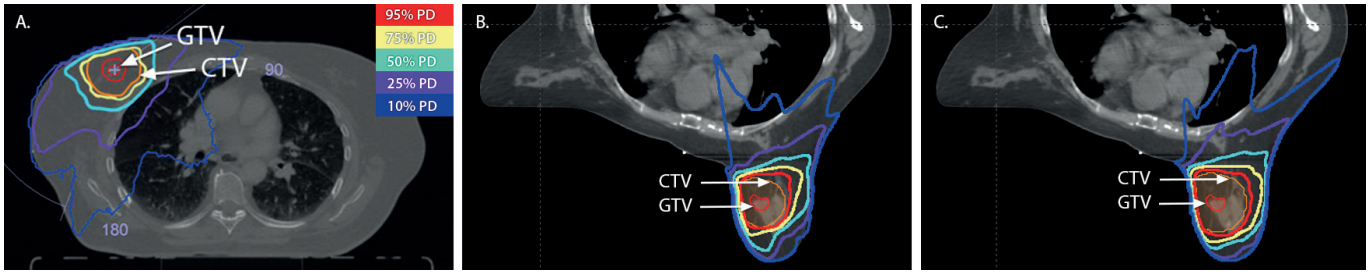


Figure 1. Dose distributions treatment. (A) VMAT plan in supine treatment position with 20 Gy prescription dose (PD) to the gross tumor volume (GTV) and 15 Gy PD to the clinical target volume (CTV). Isodose illustrate the GTV prescription dose. (B) IMRT plan in prone treatment position plan with 21 Gy prescription do se (PD) and a 15 mm CTV margin. (C) IMRT plan in prone treatment position plan with 21 Gy prescription dose (PD) and a 20 mm CTV margin.

METHODS

Study population

The current study includes data from 2 pre-existing studies and was approved by the Institutional Review Boards of the participating institutes. In both trials, toxicity was prospectively evaluated at predefined, overlapping time points using the Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version_4.03).

At Duke University Medical Center, Durham, Unites States of America, a phase I dose escalation trial (ClinicalTrial.gov NCT00944528) was conducted between August 2010 and March 2013 in order to determine the maximum tolerated dose of single dose preoperative APBI in prone RT position. A total of 32 patients ≥55 years with cT_1N_0 invasive ductal carcinomas or DCIS ≤2.0 cm were included [12]. A lumpectomy was performed within 10 days following RT. The updated treatment toxicity at a median of 37 months follow-up is in line with the previous published results, with chronic grade 1-2 local fibrosis, dermatitis and breast pain being the most common toxicities [12]. In all patients treated with single dose APBI only, good to excellent cosmetic outcomes were assessed by the treating physician.

At the University Medical Center Utrecht, The Netherlands, an ongoing trial evaluates the clinical feasibility of a radiosurgical approach for early-stage breast cancer (ClinicalTrial.gov NCT02316561). A lumpectomy is performed at 6 months following RT in the supine position, in order to evaluate the pathological response. The current study included the first 15 study patients ≥50 years with $cT_1N_{0(sn)}$ invasive ductal carcinoma. At time of analysis, eleven (of the planned 25) patients had a lumpectomy performed, and only grade 1-2 toxicity has been observed at a median follow-up of 7 months **(appendix 1).**

Treatment planning

At Duke, IMRT was used to deliver 15Gy, 18Gy or 21Gy to the gross tumor volume (GTV) and the clinical target volume (CTV) (Eclipse®version 10). At Utrecht, a single dose Volumetric Arc Therapy (VMAT) treatment was concomitantly prescribed to deliver two dose levels, 20Gy to the GTV and 15Gy to the CTV (Monaco®version 19). Study details have been previously published [12,13,18]. **Table** and **figure 1** illustrate treatment planning characteristics.

Table 2. Treatment volume characteristics in the clinical and replanned cohorts

	Dose escalation prone cohort 15, 18, 21 Gy (N=32) median (IQR)*	Integrated boost supine cohort 15/20 Gy (N=15) median (IQR)*	Replanned prone cohort 21 Gy (N=32) median (IQR)*
Affected breast n (%)			
- left	18 (56%)	7 (47%)	18 (56%)
- right	14 (44%)	8 (53%)	14 (44%)
Ipsilateral breast volume (cc)	1589.6 (1098.1-1887.0)	1099.9 (821.1-1245.0)	1470.9** (974.7-1727.3)
TREATMENT VOLUMES			
Gross tumor volume (cc)	0.9 (0.5-1.3)	1.3 (1.0-2.9)	0.9 (0.5-1.3)
Clinical tumor volume (cc)	43.2 (35.0-49.3)	74.1 (69.4-96.0)	75.6 (64.2-88.4)
Planning target volume (cc)	63.3 (54.3-73.5)	107.4 (97.0-154.9)	101.4 (85.3-122.6)
Ratio PTV to ipsilateral breast volume (%)	4.6 (2.9-5.5)	12.8 (8.5-13.8)	8.1 (4.9-9.5)
OVERDOSAGE			
$V_{105\%}$ PTV (%)	7.3 (0-35.8)	0*** (0-0)	0 (0-0.2)
$V_{110\%}$ PTV(%)	0 (0-0)	0*** (0-0)	0 (0-0)
D_{max} PTV(%)	106.8 (105.6-109.7)	104.5*** (104.0-105.5)	103.2 (101.8-104.7)

** unless otherwise specified ** represents consensus breast volumes*** 105% (21Gy) and 110% (22Gy) respectively of the prescription dose to the GTV in the $PTV_{(CTV)}$ (thereby excluding the GTV);*

Guidelines development

Since the initial dosimetric parameters of interest differed between the institutions, a new protocol for treatment plan evaluation was reached in consensus. Using the original treatment plans, this protocol evaluated target volume coverage and dose to organs at risk (OAR) with respect to NSABP B39/RTOG 0413 and QUANTEC guidelines for target and normal tissue constraints, converted to a single-dose prescription [13,19]. Furthermore, in order to achieve a uniform evaluation between institutions the chest wall delineation was adjusted, and two different skin definitions were assessed (i.e. first 3 and 5mm subcutaneous tissue).

Since no dose limiting toxicity has been encountered, no normal tissue complication probability curves were developed. Reasonable constraints were pragmatically defined based on descriptive statistics of the pooled dosimetric parameters in the clinical cohorts. Overall median, interquartile range (IQR) and 10th and 90th percentile doses were determined for target volume and OAR parameters. Optimal and acceptable dosimetry was defined as an OAR value that did not exceed the 75th (upper IQR) and 90th percentile of the pooled dosimetric parameter, respectively.

Dosimetric feasibility guidelines

To determine the feasibility of these new dose constraints for future studies, new treatment plans were performed for the patients in the dose escalation cohort (n=32) using Eclipse®version 13.6. Given the variation in breast delineations, some ipsilateral and contralateral breast contours were adjusted, following consensus [20]. A uniform 21Gy dose was prescribed to the intact tumor with a 2.0cm margin in order to assess our guidelines using a larger CTV margin that more closely approximates existing post-operative external-beam APBI data. Due to the 0.5cm CTV extension from the initial treatment plans, this would more often align the skin. Adequate target volume coverage was therefore defined as ≥95% of prescription dose to ≥98% of the CTV. Table 1 illustrates RT planning characteristics for this replanned cohort. The new plans were evaluated for adherence to the previously defined optimal or acceptable dosimetry from the clinical cohorts.

RESULTS

Dosimetry across cohorts

The median GTV and CTV receiving ≥95% of the prescribed dose (PD) was ≥99% in all 3 cohorts. The median PTV receiving ≥95% of the PD was ≥97% in the clinical cohorts and 95% in the replanned cohort. Table 2 gives an overview of the treatment volumes. In the integrated boost cohort treatment volumes are larger compared to the dose escalation cohort, given the 0.5cm additional CTV extension. When evaluating PTV overdosage in relation to the CTV PD in the integrated boost cohort, the median $V_{110\%}$ and $V_{105\%}$ was 29% and 43%, respectively. Higher mean ipsilateral breast and skin dosimetry are encountered with higher PD (table 3). Lower PD fall-off is observed in the integrated boost cohort.

Optimal or acceptable plan dosimetry

Optimal and acceptable dosimetry was defined from the clinical cohorts as a value up to the 75th percentile (i.e. upper IQR) and 90th percentile of the pooled dosimetric parameter, respectively (table 4). Table 5 summarizes treatment recommendations for single dose preoperative APBI.

Dosimetric adherence to constraints

In the replanned cohort, at least acceptable $V_{100\%}$ and $V_{50\%}$ PD in the ipsilateral breast was achieved in 100% and 91% of the cases despite smaller consensus breast volumes (table 2). An acceptable mean ipsilateral breast dose was evaluated in 56% of the patients. Optimal dosimetry was achieved for the contralateral breast, ipsilateral lung and chest wall in 97%, 94% and 97% of cases, respectively. At least acceptable D_{max} and D_{mean} heart was encountered in 97% and 100% of patients. For the first 3 mm of subcutaneous tissue, at least acceptable skin dosimetry was achieved for the D_{1cc} and D_{10cc} in 19% and 63% of cases, respectively. For the first 5 mm of subcutaneous tissue, this was achieved in 19% and 28% of patients, respectively.

Table 3. Dose to organs at risk across the clinical cohorts

	Dose escalation prone cohort 15Gy (N=8) median (IQR)	Dose escalation prone cohort 18Gy (N=8) median (IQR)	Dose escalation prone cohort 21Gy (N=16) median (IQR)	Integrated boost supine cohort 15/20Gy (N=15) median (IQR)
IPSILATERAL BREAST				
$V_{100\%}$ CTV prescription dose (%)	4.2 (3.1-4.9)	3.2 (2.2-3.7)	4.2 (2.5-5.9)	10.2 (6.8-11.0)
$V_{50\%}$ CTV prescription dose (%)	14.4 (10.3-17.6)	11.6 (8.7-14.1)	14.2 (10.1-19.7)	27.3 (19.6-30.7)
$V_{100\%}$ GTV prescription dose (%)	**	**	**	0.4 (0.3-0.8)
$V_{50\%}$ GTV prescription dose (%)	**	**	**	21.9 (15.8-24.0)
Mean dose (Gy)	2.9 (2.2-3.3)	2.8 (2.4-3.0)	3.8 (2.8-4.7)	5.0 (4.0-5.4)
SKIN (3 mm)*				
D_{1cc} (Gy)	8.8 (7.1-10.9)	10.6 (9.1-11.9)	12.5 (10.9-15.8)	12.9 (11.6-13.3)
D_{10cc} (Gy)	5.9 (4.4-6.6)	7.2 (6.2-8.3)	7.8 (7.0-9.1)	9.7 (7.7-10.5)
SKIN (5 mm)*				
D_{1cc} (Gy)	12.1 (9.0-12.9)	12.9 (11.4-15)	17.1(15.9-18.8)	14.5 (13.3-15.8)
D_{10cc} (Gy)	7.9 (6.3-8.9)	9.5 (8.5-10.4)	11.6 (10.6-13.9)	12.3 (10.4-12.7)
HEART				
D_{max} (Gy)	3.1 (1.0-4.0)	1.6 (0.5-3.0)	0.8 (0.3-2.4)	3.0 (1.9-3.9)
Mean dose (Gy)	0.1 (0.0-0.2)	0.2 (0.0-0.5)	0.1 (0-0.2)	0.7 (0.5-1.2)
OTHER				
D_{max} contralateral breast (Gy)	1.2 (0.2-2.2)	0.3 (0.2-1.1)	0.4 (0.3-0.7)	1.5 (0.8-3.1)
Mean dose ipsilateral lung (Gy)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.4 (0.2-0.6)	1.4 (0.9-1.6)
D_{20cc} dose chest wall (Gy)	2.8 (1.7-7.7)	2.4 (1.0-4.0)	3.9 (2.4-5.0)	12.3 (9.4-13.4)

** the first 3 mm or 5 mm of subcutaneous tissue from body surface ** CTV prescription dose is GTV prescription dose*

Table 4. Dose to organs at risk in the pooled (clinical) cohort of patients, and in the replanned 21Gy cohort

	Clinical cohorts 15, 18, 21 (dose escalation) and 15/20Gy (integrated boost) median (IQR) [10^{th}-90^{th} percentile] (N=47)	Replanned prone cohort 21Gy median (IQR) (N=32)
IPSILATERAL BREAST		
$V_{100\%}$ CTV prescription dose (%)	4.6 (3.1-7.2) [2.1-10.8]	1.4 (0.1-6.6)
$V_{50\%}$ CTV prescription dose (%)	16.3 (12.1-20.9) [8.2-29.8]	20.0 (16.0-26.7)
Mean dose (Gy)	3.6 (2.8-4.8) [2.3-5.4]	5.2 (4.2-5.8)
SKIN (3 mm)*		
D_{1cc} (Gy)	11.7 (10.4-13.2) [8.2-15.3]	16.4 (15.6-17.0)
D_{10cc} (Gy)	7.7 (6.6-9.5) [5.7-10.6]	10.2 (9.1-11.0)
SKIN (5 mm)*		
D_{1cc} (Gy)	14.5 (12.5-16.3) [11.0-18.2]	19.0 (18.4-19.4)
D_{10cc} (Gy)	10.5 (9.0-12.4) [7.7-13.9]	15.4 (13.7-16.0)
HEART		
D_{max} (Gy)	2.3 (0.8-3.4) [0.2-4.2]	2.6 (1.0-3.3)
Mean dose (Gy)	0.2 (0.1-0.6) [0-1.0]	0.2 (0.1-0.4)
OTHER		
D_{max} contralateral breast (Gy)	0.5 (0.3-1.6) [0.2-2.4]	0.2 (0.2-0.5)
Mean dose ipsilateral lung (Gy)	0.4 (0.2-1.0) [0.1-1.6]	0.6 (0.3 -0.7)
D_{20cc} dose chest wall (Gy)	4.6 (2.5-10.2) [1.3-13.2]	4.1 (3.1-5.6)

** the first 3 mm or 5 mm of subcutaneous tissue from body surface*

Table 5. Treatment planning recommendations for single dose preoperative external beam partial breast irradiation

	DEFINITION	RECOMMENDATION or CONSTRAINTS	POOLED CONSTRAINT (IQR) [10th-90th percentile]
ELIGIBILITY			
Patient characteristics	-	- women ≥ 50 years of age - eligible for breast conservation treatment	-
Tumor characteristic	-	- unifocal non-lobular cT_1N_0Mx or low/ intermediate grade c$T_{is}N_0Mx$ ≤2cm - ER or PR receptor positive - Her2 negative	-
TARGET VOLUMES			
Prescription dose (PD)	-	- 15 to 21 Gy uniform dose, in case of short interval (≤ 10 days) to surgery - the recommended dose and interval to surgery for a radiosurgical approach is currently under evaluation in the integrated boost cohort. (ClinicalTrial.gov NCT02316561)	-
GTV	Delineation according to findings on fused contrast-enhanced CT-MRI.	Aim at: - ≥ 95% dose to 99% volume - D_{max} ≤ 107%	
CTV	- uniform PD: 1.5 to 2.0cm - integrated boost approach: 2.0cm - first 5mm of subcutaneous tissue and chest wall are excluded.	Aim at: - ≥ 95% dose to 98% volume - uniform PD: D_{max} ≤ 110% - D_{max} ≤ 140% with an integrated boost approach	-
Planning target volume (PTV) [18, 32]	- uniform PD: 3mm expansion from CTV - integrated boost approach: additional 3mm expansion from GTV. - first 5 mm of subcutaneous tissue are excluded.	Aim at: - ≥ 95% dose in ≥97% volume - D_{max} < 110%	-
ORGANS AT RISK			
Ipsilateral breast [20]	According to radiopaque wire markings of breast tissue following palpation, as well as breast contouring atlas guidelines	Aim at: - ≤ 8.5% PTV to breast ratio - ≤ 4.8Gy mean dose - $V_{100\%}$ CTV PD ≤7.2% - $V_{50\%}$ CTV PD ≤20.9%	Ratio PTV/breast (3.5-**8.5**); [2.0-13.8] Mean breast dose (2.8-**4.8**); [2.3-5.4] V100% CTV PD (3.1-**7.2**); [2.1-10.8] V50% CTV PD (%) (12.1-**20.9**); [8.2-29.8]
Skin	The first 3 to 5 mm of subcutaneous tissue of the ipsilateral breast.	Aim at: - D_{max} ≤ 100% PD - 3 mm: D_{1cc} ≤ 13.2Gy - 3 mm: D_{10cc} ≤ 9.5Gy - 5 mm: D_{1cc} ≤ 16.3Gy - 5 mm: D_{10cc} ≤ 12.4Gy	Skin 3 mm D_{1cc} (10.4-**13.2**); [8.2-15.3] D_{10cc} (6.6-**9.5**); [5.7-10.6] Skin 5 mm D_{1cc} (12.5-**16.3**); [11.0-18.2] D_{10cc} (9.0-**12.4**); [7.7-13.9]
Chest wall	Sternum, ribs and (intercostal, pectoralis) muscles aligning the ipsilateral breast.	Aim at: - D_{20cc} ≤ 10.2Gy	D20cc (2.5-**10.2**) [1.3-13.2]
Heart [33]	The heart contour starts below the pulmonary trunk bifurcation and includes the pericardium.	Aim at: - mean dose ≤0.6Gy - D_{max} ≤3.4Gy	Mean dose (0.1-**0.6**); [0-1.0] Max dose (0.7-**3.4**); [0.2-4.2]
Contralateral breast [21]	According to findings on CT-scan as well as breast contouring atlas guidelines, not extending past midline.	Aim at: - D_{max} ≤1.6Gy	Dmax (0.3-**1.6**) [0.2-2.2]
Lungs	Delineation of ipsilateral, contralateral and both lungs according to CT findings.	Aim at mean dose: - ipsilateral lung ≤ 1.0Gy - contralateral lung ≤ 0.4Gy - both lungs ≤ 0.7Gy	Ipsilateral (0.2-**1.0**); [0.1-1.6] Contralateral (0-**0.4**); [0-0.5] Both lungs (0.2-**0.7**); [0.1-1.0]

Value: optimal organ at risk constraint — Value: acceptable organ at risk constraint

DISCUSSION

The current study provides consensus recommendations for single dose preoperative APBI target and OAR constraints based on the clinical data from 2 university medical centers (**table 5, appendix figure 1**). Optimal and acceptable dose constraints were formulated from clinically correlated data. In patients treated with preoperative single dose APBI only, no dose limiting toxicity has been observed, possibly placing these constraints at the lower, safe end of the toxicity spectrum [12, **appendix table 1**]. In addition, the dosimetric feasibility of single dose 21Gy APBI with CTV margin expansion was evaluated. Acceptable and optimal OAR dosimetry could be achieved in the great majority of the cases, except for the skin, with at least acceptable metrics ranging from 19-63%. Additional target volume expansion would likely preclude use of skin constraint and require additional clinical investigation to determine the impact of high skin doses on acute and chronic toxicity (**appendix figure 2**).

To our knowledge, no other centers have evaluated the feasibility of single dose preoperative external beam APBI. Single dose 18-21Gy 3D-CRT based APBI following surgery has been previously reported for $pT_{1\text{-}2(max.3cm)}N_{0\text{-}1}$ non-lobular carcinoma (n=64) [21]. The study stopped prematurely due to unexpected grade 2-3 subcutaneous fibrosis and fair-poor cosmesis in 44% and 41% of the patients, respectively. This is in contrast to our results and is likely due to our smaller preoperative target volumes. For example, our median PTV was 72.2cc (30.1-203.7cc) versus 96cc (range 17-290cc) compared to the post-lumpectomy APBI study. Furthermore, increased toxicity in the post-lumpectomy 3D-CRT based APBI could be explained by differences in techniques, with less dose inhomogeneity for the IMRT-VMAT approach used at our institutes [22]. Also, we hypothesize that preoperative APBI is more favorable with respect to the cosmesis because a portion of the breast tissue receiving high-dose RT prone to development of fibrosis will be excised. In the post-lumpectomy APBI study, a mean ipsilateral breast dose ≥9Gy was the only factor associated with impaired cosmesis. Their mean dose was 9.7Gy (range 4.4-14.1Gy), whereas the pooled mean estimate in the clinical cohorts was 3.8Gy (range 1.6-7.8Gy) and 5.0Gy (range 2.9-7.3Gy) in the replanned cohort.

Van der Leij *et al* evaluated preoperative multiple fraction APBI for $cT_{1\text{-}2(max.3.0\ cm)}N_0$ (n=70) by delivering forty Gy in 10 fractions over 2 weeks with 3D-CRT, IMRT or VMAT, followed by lumpectomy at 6 weeks [23]. Interestingly, induration fibrosis actually declined over time and cosmetic outcome improved. At 24 months, 46% and 2% of the patients experienced mild-moderate local fibrosis and 80% were satisfied to very satisfied with the cosmetic result. A phase 2 trial by Nichols *et al* evaluated 3D-CRT preoperative APBI for $T_{1\text{-}2(max.\ 3.0cm)}N_0$ (n=27) with 38.5Gy in 3.85Gy fractions twice daily and lumpectomy performed ≥21 days after RT [24]. At a median follow-up of 3.6 years, good-excellent cosmetic outcome was reported by 78% of women. Expected grade 0-1 toxicity (CTCAE_version_3), such as fatigue, skin erythema, hyperpigmentation, fibrosis, breast discomfort, edema and dyspnea was encountered. A direct comparison with our cohorts is difficult due to fractionation and/or RT technique differences, nonetheless, these studies show that preoperative APBI is a feasible option for low-risk breast cancer patients and give a sense of expected clinical outcomes.

Furthermore, our clinical preoperative irradiated cohorts illustrate a great advantage in target volume reduction compared with postoperative APBI. In the APBI-arm of the RAPID trial, women ≥40 years with $pT_{1\text{-}2(max\ 3.0cm)}N_0$ were treated to a total of 38.5Gy in twice daily 10 fractions following breast-conserving surgery [4,25]. The mean volume receiving 95% of PD was 332cc (standard deviation (SD) 153cc), with a mean ratio to ipsilateral breast of 22% (SD 7%) (25). In our clinical cohorts, the mean PTV volume was 72cc (SD 37cc) with a mean 7% (SD 4%) PTV to ipsilateral breast ratio. Even in the replanned cohort with an extended CTV margin, the mean PTV was 99cc (SD 31cc) with a mean 8% (SD 3%) ratio PTV to ipsilateral breast. We therefore believe that preoperative external beam APBI has great potential in clinical practice to deliver a precise treatment with smaller treatment volumes, enabling a reduction in RT associated toxicity and improvement in treatment burden.

To our knowledge, no other clinical studies assessed skin toxicity following single dose RT. Setting constraints based on data from hyperfractionated or multiple fraction hypofractioned treatment would not be appropriate from a radiobiological point of view. If acceptable skin dosimetry cannot be achieved in clinical practice, a reduction of the CTV margin from 20 to 15mm could provide an alternative in order to still deliver a single dose treatment. Another option to consider when skin constraints cannot be achieved, is accepting a higher dose given that no dose limiting toxicity has been observed so far. It should be noted though that additional single dose RT clinical studies are needed to determine whether larger target volumes with higher associated skin doses maintain clinically acceptable skin toxicity.

With postoperative APBI, the CTV definition has mainly evolved from Holland's work in mastectomy specimens, where even in small tumors ≤2.0cm, 92% of microscopic disease extended up to 30 mm from the index lesion [26]. Nowadays, an MRI of the breasts is typically utilized to assess the possibility of extensive disease in APBI candidates, resulting in 11% of patients eventually deemed ineligible [27]. An MRI and histopathology correlation study showed that in the absence of extensive intraductal component, no subclinical invasive disease was present in 93% of lumpectomy cases more than 10mm beyond the edge of the lesion as measured on MRI [28]. In a recent prospective pathology study on the appropriate CTV margin for APBI, the maximum radial extension of residual carcinoma was assessed in 133 women requiring re-excision or completion mastectomy after initial lumpectomy [29]. In the 58% patients with non-involved initial margins, residual disease, if present, was ≤10 mm in 97.4% of the cases. In the 42% patients with involved margins, disease extended beyond 20mm in 10.7% of cases. Large extension of microscopic disease was associated with involved margins, tumorsize ≥30 mm and premenopausal status, which are characteristics that do not apply to our patient population. We acknowledge that the appropriate preoperative CTV margin is a subject up for debate, however for low-risk patients with biologically favorable and limited extent of disease assessed on MRI, we perceive 15mm as a minimum, up to 20mm, as a recommended CTV margin [30-31, table 5]. This is also supported by our clinical outcomes with only 1 local recurrence so far in our dose-escalation cohort at a median follow-up of 37 months.

Similarly, the optimal time between surgery and resection is not known. In the dose escalation 'proof of principle' trial, the investigators did not wish to delay definitive surgical resection and therefore surgery was perfomed ≤10 days. In the integrated boost cohort where a radiosurgical approach is currently explored, surgery is undertaken 6 months after RT in order to evaluate the complete pathologic response. Given that the latter approach is still under investigation, we suggest a short interval to surgery.

The current study has certain drawbacks that should be addressed. First, the recommended constraints originate from a heterogeneous population, treated in the prone or supine position, with a VMAT or IMRT technique, different optimization techniques and various fractionation schedules. Nonetheless, we believe that

the radiobiological impact of single dose highly-conformal APBI ≥15 Gy is sufficiently similar, and rare, to justify this pooling of data. Combining the scarce experience will eventually define the safety aspects of this treatment approach. Also, this heterogeneous population reveals variation across different medical centers and illustrates current clinical practice, that should be considered in study design. We expect that ongoing and future trials will provide a sufficient number of patients to enable subgroup analysis. Second, the patients in the simultaneous boost cohort have a limited 229 days follow-up. Though toxicity has been limited thus far, additional data will be required to confirm the safety of treatment planning with the suggested constraints. Nonetheless, given the scarce experience with single dose APBI, guidelines to ensure consistent treatment planning will be critical for ongoing assessment of clinical feasibility with this technique.

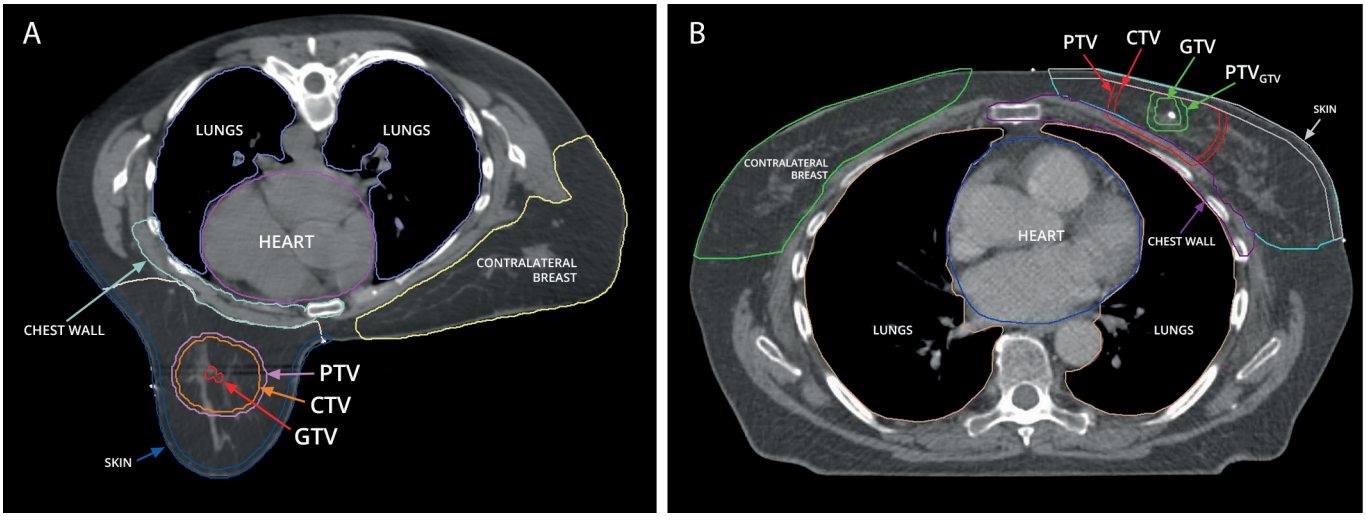
We believe single dose preoperative RT is a compelling treatment approach and our practical recommendations could reach further than a low-risk APBI eligible population. Future studies could focus on locally advanced breast cancer in conjunction with immunotherapy, for example [34]. Furthermore, if single dose RT proves to be ablative for early-stage breast cancer, future studies could focus on the minimally invasive treatment for functionally impaired, medically inoperable breast cancer patients. However to minimize the possibility of adverse events for study patients, carrying out single dose ultra hypofractionated RT studies should be confined to stringent protocols, taking pre-existing experience into account. We perceive our current experience and recommendations a basic, but helpful foundation for future explorations in the promising field of single dose preoperative RT.

In conclusion, dosimetric data pooling acquired from clinical cohorts of 15Gy, 18Gy, 21Gy, and simultaneous integrated 15/20Gy boost, enabled the development of practical guidelines for single dose APBI in women ≥50 years of age with low-risk cT_1N_0 non-lobular breast cancer or limited DCIS. The dosimetric adherence to developed OAR constraints was demonstrated in new APBI plans with a 21Gy uniform dose but an extended CTV margin. However, caution remains warranted and possible adaptation of skin constraints might be required following future single dose APBI clinical trials. Our short-term results support the importance of further developments in the field of single dose preoperative APBI which has the potential to further minimize treatment burden, reduce target volumes and treatment toxicity, and allow the in-vivo exploration of breast cancer radiogenomics.

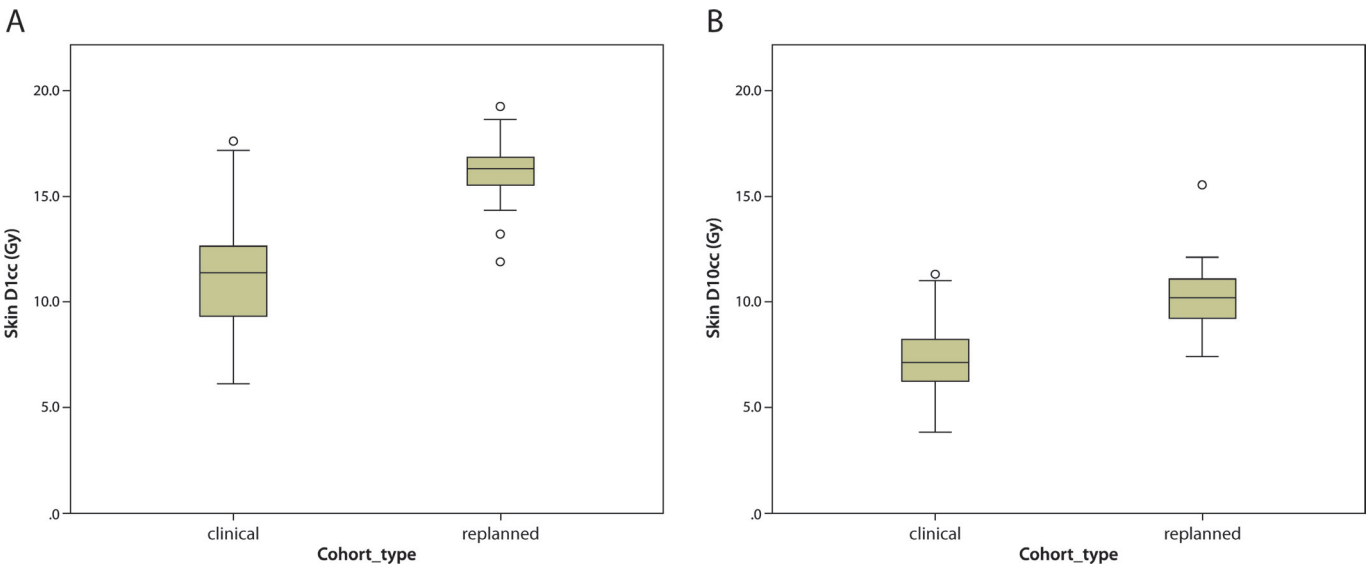
Appendix 1 – table . Overview of main treatment toxicities and post-operative complications following single dose preoperative accelerated partial breast irradiation in the integrated boost cohort (ClinicalTrial.gov NCT02316561)

	Percentage toxicity n=15 (%)
Toxicity grade 1 (%)	
Local fibrosis	87%
Fatigue	80%
Breast discomfort	67%
Dermatitis	0%
Toxicity grade 2 (%)	
Pain breast*	13%
Post-operative complications (%)	
Haematoma (grade 2)	7%
Chronic seroma	**

* resolved following analgesic treatment and lymphedema therapy. ** chronic seroma rates cannot be reported due to the limited median follow-up of 69 days following surgery.



Appendix 1 – figure. Recommended delineations organs at risk and target volumes in prone (A) and supine treatment approach (B).



Appendix 2 – figure. The impact of CTV increase (from 15 to 20 mm) and 21 Gy prescription dose in the clinical versus replanned prone cohort for D1cc (A) and D10cc (B) in the first 3 mm of subcutaneous tissue.

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Chapter 6

Single dose partial breast irradiation using an MRI linear accelerator in the supine and prone treatment position

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ABSTRACT

Background: In selected patients with early-stage and low-risk breast cancer, an MRI-linac based treatment might enable a radiosurgical, non-invasive alternative for current standard breast conserving therapy.

Aim: To investigate whether single dose accelerated partial breast (APBI) to the intact tumor in both the prone and supine radiotherapy positions on the MRI-linac is dosimetrically feasible with respect to predefined coverage and organs at risk (OAR) constraints.

Material & methods: For 20 patients with cTis or low-risk cT1N0M0 non-lobular breast carcinoma, previously treated with single dose preoperative APBI in the supine (n = 10) or prone (n = 10) position, additional intensity modulated radiotherapy plans with 7 coplanar beams in the presence of a 1.5T magnetic field were generated. A 20 Gy and 15 Gy dose was prescribed to the gross tumor and clinical target volume, respectively. The percentage of plans achieving predefined organ at risk (OAR) constraints, currently used in clinical practice, was assessed. Dosimetry differences between the prone versus supine approach and the MRI-linac versus clinically delivered plans were evaluated.

Results: All MRI-linac plans met the coverage and predefined OAR constraints. The prone approach appeared to be more favorable with respect to the chest wall, and ipsilateral lung dose compared to the supine position. No dosimetric differences were observed for the ipsilateral breast. No treatment position was clearly more beneficial for the skin or heart, since dosimetry varied among parameters. Overall, the MRI-linac and clinical plans were comparable, with minor absolute dosimetric differences.

Conclusion: MRI-linac based single dose APBI to the intact tumor is a promising and a dosimetrically feasible strategy in patients with low-risk breast cancer. Preliminary OAR dosimetry favored the prone radiotherapy position.

INTRODUCTION

Accelerated partial breast irradiation (APBI) following breast-conserving surgery has proven to be an alternative to whole breast irradiation (WBI) in early-stage low-risk breast cancer [1-6]. In current clinical practice however, APBI target volume definition can be difficult due to post-surgical breast tissue changes. The use of surgical markers and contouring guidelines improves the tumor bed delineation consistency among clinicians [7]. Nonetheless, a preoperative APBI approach with the tumor in situ has proven to be more beneficial with respect to target definition and treatment volumes, compared to postoperative APBI [8,9].

For APBI, an MRI-based strategy enables adequate visualization of tumor extent and selection of eligible patients [10-12]. MR-guided CT-linac based single dose APBI delivered preoperatively in the prone treatment position has recently been evaluated as feasible for low-risk non-lobular carcinoma or ductal carcinoma in situ (DCIS) [13]. Furthermore, an MR-guided supine preoperative approach has also been shown to be dosimetrically feasible and is currently under clinical investigation with promising preliminary results [15]. This single dose preoperative RT delivery results in a burden minimizing treatment for patients, and opens a new window of opportunity to evaluate a radiosurgical approach for breast cancer patients [15-17].

The MRI linear accelerator (MRI-linac) is a hybrid system, consisting of a 7MV linear accelerator (Elekta AB, Stockholm), and a 1.5 Tesla MRI scanner (Philips®) [18-20]. In contrast to MRI-guided CT-based RT currently employed in clinical practice, the MRI-linac provides on-line high soft-tissue contrast during the actual radiation delivery, thereby differentiating between target and non-target surrounding normal tissue. Furthermore, real-time target volume MR-imaging allows for potential plan adaptation strategies, such as smaller margins for target volumes and dose escalation. This may result in less radiotherapy-induced toxicity, while simultaneously enhancing the local tumor control probability. This might enable a radiosurgical approach to the intact tumor, possibly making breast conserving surgery and the subsequent radiotherapy (RT) schedule redundant for selected patients with early-stage low-risk breast cancer eligible for APBI. Also, due to real-time target volume MRI-imaging during RT, fiducial markers required for a position verification or a planning CT-might not be required, making single dose APBI MRI-linac based treatment less burdensome for selected breast cancer patients. Nonetheless, at least three major issues should be considered for treatment planning on the MRI-linac. First, the trajectories of secondary electrons are modified due to the presence of a magnetic field. As a result of a shorter build-up region and increased exit dose in the skin (i.e. due to the electron return effect), the dose distribution can be impacted [21-22]. Second, certain technical specifications of the MRI-linac such as the fixed collimator and fixed couch position relative to the isocenter, could impact treatment planning. Furthermore, both the prone and supine treatment position on the MRI-linac might have specific challenges in practical and dosimetric feasibility. The main objective of the current study was therefore to

investigate whether single dose APBI in both the prone and supine treatment positions to the intact tumor is dosimetrically feasible on the MRI-linac with respect to predefined coverage and organs at risk constraints.

MATERIAL & METHODS

Patient selection

This study was designed as a RT predicate study for evidence based-introduction of the MRI-linac according to the R-IDEAL framework for clinical evaluation of technical innovations in radiation oncology [23]. Twenty patients were selected from 2 earlier studies on MRI-guided preoperative single-dose partial breast irradiation. At Duke University Medical Center, Durham, United States of America, 32 women (≥55 years with cT_1N_0 ductal carcinoma or low-intermediate grade DCIS ≤2.0cm) were treated in the prone position with a single dose of 15Gy, 18Gy or 21Gy to the tumor plus margin [13]. At Utrecht University Medical Center, Utrecht, The Netherlands, a study on the feasibility of preoperative single dose ablative radiotherapy in the supine position has recently been completed (≥50 years of age with $cT_{1\text{-}2(\max 3.0cm)}N_0$ non-lobular carcinoma), delivering 20Gy to the tumor and 15Gy to the clinical target volume. Details on these studies have been previously published [13,15,16,24].

For the current study, data was obtained from the first 10 patients treated in the supine position in the Dutch study and 10 patients treated with 21Gy in the prone position, matched for breast size. A waiver exempting additional informed consent was acquired from the Institutional Review Boards of both participating institutes.

Treatment imaging and planning

For patients treated in the prone position, a preoperative diagnostic or treatment planning 1.5T or 3.0T contrast-enhanced (CE)-MRI and planning CT-scan using a CDR® prone breast board were available. For patients treated in the supine position, a preoperative diagnostic 1.5T or 3.0T CE-MRI, and a CE-planning 1.5T MRI and CE-planning CT-scan in the supine position were available. The first two patients were scanned on a supine board at 10° incline on a C-qual® and MRI-compatible Thorawedge board®. The remaining 8 patients were scanned at 5° incline on an adapted MRI-compatible Macromedics® breast board. For all patients, the gross tumor volume (GTV) had been contoured previously on the planning-CT by the treating breast radiation oncologist based on the fused images with the diagnostic and/or planning MRI. The GTV was uniformly expanded by 20mm to create a clinical target volume (CTV). The chest wall and the first 5mm from the external body surface were excluded from the CTV. A 3mm margin was employed to generate the planning target volume (PTV). The first 5mm from the external body surface were excluded from the PTV. This PTV margin is in concordance to the PTV margin employed in the supine clinical study, aiming at an objective dosimetric comparison to the clinical plans. A PTV was defined for the GTV as well as the CTV, resulting in a PTV_{GTV} and PTV_{CTV}, respectively. Organs at risk (OAR) such as heart, lungs, breasts, and chest wall had been previously delineated [16]. The skin was defined as the first 5mm of the external body surface in the ipsilateral breast.

Intensity modulated radiotherapy (IMRT) plans with 7 coplanar beams in the presence of a 1.5T magnetic field were created using Monaco® (version 5.19.01, Elekta AB, Stockholm, Sweden) on the planning CT-scans. The MRI-linac technical features are incorporated in this software. The linac is equipped with a multileaf collimator housing 160 leaves with a projected width of a single leaf of 0.72cm at the isocenter [25]. In the MRI-linac, the flattening filter free 7MV photon beam can rotate a full 360° around the patient with maximum field size of 22cm longitudinal and 57.4cm lateral. The isocenter is fixed at 14.3 cm above the treatment couch.

All plans were generated by one experienced radiation dosimetrist. The maximum amount of segments in the treatment planning software was set at 100. Dose prescription, coverage requirements and organ at risk (OAR) constraints were utilized as currently employed in the Dutch study for single dose APBI in the supine position [15]. The rationale for this possibly ablative treatment approach, prescribed dose and development of the organs at risk constraints have been previously described [15]. An integrated boost was utilized, with 20Gy delivered to the GTV and 15Gy delivered to the CTV, since this is also the intended prescription dose for future MRI-linac treatments. Adequate coverage of the target volume with doses as low as reasonably possible to the OAR was prioritized. Adequate coverage was defined as at least 99% of the $PTV_{GTV/CTV}$ receiving at least 95% of the prescribed dose to the GTV or CTV, respectively. The employed OAR constraints were a D_{mean} <3.6Gy to the ipsilateral lung, a $V_{2.8Gy}$ <10% and $V_{4.7Gy}$ <5% to the heart, a D_{20cc}<16.3Gy to the chest wall, and a D_{1cc}<12Gy to the skin or a D_{1cc}<16Gy if the CTV aligned the skin [15]. Dose to the ipsilateral and contralateral breast was kept as low as possible.

Comparison to clinical treatment plans

In order to compare the MRI-linac plans to the actual delivered clinical plans in the prone or supine position, the OAR dosimetry was extracted from the clinical treatment planning systems. For the supine treatment position, the clinical plans attained the same prescription dose, target volume definition, and OAR constraints, however volumetric modulated arc therapy (VMAT) instead of IMRT was utilized for treatment plan optimization. For the prone position, the main differences compared to the MRI-linac treatment characteristics were a uniform dose prescription (i.e. 21Gy to the GTV and CTV), a smaller CTV definition (i.e. 1.5cm instead of 2.0cm from the GTV) and different OAR-constraints [24]. Given the variation in techniques and prescribed dose, a pairwise individual comparison was not applied between the MRI-linac and the clinical plans.

Statistical analysis

According to the R-IDEAL design for RT-based innovations, a sample size of 20 patients should be adequate for this predicate study [23]. The primary study endpoint was defined as the percentage of feasible plans with respect to target coverage and OAR constraints. Secondary study endpoints entailed the dosimetric differences between the prone versus the supine treatment position, and dosimetric differences between the MRI-linac plans versus the corresponding clinical treatment plans. These differences were described quantitatively; no statistical tests were performed given the limited number of 10 patients. Patient and treatment planning characteristics were evaluated using descriptive statistics. Medians and interquartile ranges (IQR) were employed for continuous variables and frequencies for discrete variables. All analyses were performed in IBM SPSS Statistics® version 22.

Table 1. Baseline and target volume characteristics

	Prone position Median (IQR)* (n=10)	Supine position Median (IQR)* (n=10)
Tumor lateralisation (%)		
– Left	40%	50%
– Right	60%	50%
Tumor location (%)		
– Central	50%	20%
– Medial quadrant	20%	30%
– Lateral quadrant	30%	50%
Gross tumor volume (cc)	0.6 (0.3-1.3)	1.1 (0.7-2.0)
Clinical target volume (cc)	74.0 (58.7-85.6)	72.9 (67.5-86.3)
Planning target volume(PTV) (cc)**	100.1 (78.4-113.1)	104.9 (95.5-121.9)
Ipsilateral breast volume (cc)	1119.8 (824.3-1480.1)	1116.5 (1000.2-1269.7)
Ratio PTV/ipsilateral breast (%)	8.9% (7.2-9.8)	11.6% (7.6-13.8)

**median and interquartile range unless otherwise specified ** clinical target volume with an additional 3mm margin*

RESULTS

Baseline characteristics

Tumor and target volume characteristics of the 20 patients are presented in table 1. For the total group of patients (n=20), the median GTV, CTV and PTV_{CTV} was 0.9cc (IQR 0.5-1.4cc), 73.4cc (IQR 66.5-84.0cc), and 103.0cc (IQR 94.8-115.2cc), respectively, with a median PTV_{CTV} to ipsilateral breast ratio of 9.0% (IQR 7.6-12.8%).

MRI-linac plans overall

Adequate target coverage and the predefined ipsilateral lung, heart, and chest wall constraints were achieved in all plans. The CTV extended to the first 5mm of the external body surface (i.e. skin) in 19 out of 20 patients. The D_{1cc}<12Gy skin constraint was only feasible in 2 patients, one treated in the prone and one treated in the supine position. The D_{1cc} of the skin was below 16Gy in all patients. In the total group of patients, the mean ipsilateral breast volume receiving half of the prescription dose to the GTV (i.e. 10Gy) was 20% (IQR 15.6-22.8%).

Prone versus supine MRI-linac plan

Coverage, inhomogeneity (i.e. overdosage) and OAR dosimetry across the two treatment approaches are illustrated in table 2. Representative dose distributions are illustrated in figure 1. In the MRI-linac plans, the differences in median D_{20cc} chest wall and mean lung dose were Δ8.1Gy and Δ0.5Gy, respectively, in favor of the prone position (table 2, figure 2). Differences in heart and skin dosimetry between the two approaches fluctuated across various parameters (table 2, figure 3) and therefore no treatment position was clearly more beneficial. The dose to the ipsilateral or contralateral breast appeared not to be associated with a specific treatment position (table 2).

Clinical versus MRI-linac plan in the supine treatment position

In the actual delivered plans in the supine group, the median values of the mean ipsilateral breast, ipsilateral lung, and heart dose were 4.5Gy (IQR 3.9-5.3Gy), 1.4Gy (IQR 0.8-1.6Gy), and 0.7Gy (IQR 0.5-0.9Gy), respectively (data not shown). In the MRI-linac plans,

Table 2. Dosimetry of single dose MR-linac based treatment in the prone and supine position with a 20Gy and 15Gy prescribed dose to the gross tumor volume (GTV) and clinical tumor volume (CTV), respectively.

	Prone position Median (IQR) (n=10)	Supine position Median (IQR) (n=10)
Coverage		
– $V_{95\%}$ PTV_{GTV} (%)*	99.7 (99.1-100)	99.3 (98.7-99.9)
– mean dose PTV_{GTV} (Gy)	20.1 (20.0-20.1)	20.1Gy (20.0-20.1)
– $V_{95\%}$ PTV_{CTV} (%)*	99.6 (99.2-99.8)	99.0 (99.0-99.3)
– mean dose PTV_{CTV} (Gy)	15.7 (15.7-15.9)	16.1 (15.9-16.3)
Overdosage (%)		
– V_{19Gy} PTV_{CTV}	5.1 (4.1-6.5)	8.8 (6.1-10.5)
– V_{21Gy} PTV_{CTV}	0 (0-0)	0 (0-0)
Dose to organs at risk		
Ipsilateral breast		
– $V_{100\%}$ PD^{**}_{CTV} (%)	7.2 (5.7-8.1)	7.8 (6.9-10.8)
– $V_{50\%}$ PD_{CTV} (%)	25.6 (20.8-28.9)	26.3 (20.3-29.6)
– $V_{100\%}$ PD_{GTV} (%)	0.2 (0.1-0.3)	0.4 (0.2-0.6)
– $V_{50\%}$ PD_{GTV} (%)	20.0 (16.6-22.9)	19.9 (14.8-23.2)
– mean dose (Gy)	4.6 (3.9-5.0)	4.6 (3.8-5.4)
Skin		
– D_{1cc}	15.0 (14.7-15.3)	14.7 (14.0-15.4)
– D_{10cc}	13.4 (12.4-13.9)	11.8 (10.6-12.9)
– V_{12Gy}	17.3 (11.7-22.8)	9.6 (5.9-13.9)
Heart		
mean dose (Gy)	0.8 (0.5-1.0)	0.8 (0.5-1.1)
– $V_{2.8Gy}$ (%)	0 (0-0.7)	3.2 (0-4.6)
Chest wall		
– D_{20cc} (Gy)	4.3 (2.2-5.2)	12.4 (9.9-13.5)
Ipsilateral lung		
– mean dose (Gy)	0.4 (0.3-0.6)	0.9 (0.6-1.1)
Contralateral breast		
– D_{max} (Gy)	2.7 (2.4-3.1)	2.0 (1.6-3.1)
Treatment delivery		
– no. segments	95.5 (93.0-96.3)	82.4 (79.0-90.3)
– no. monitor units	4765.9 (4450.0-5047.9)	5442.6 (5014.6-6024.7)
– delivery time (s)	852.5 (766.7-870.1)	892.3 (839.6-984.3)

**Vxx% = volume receiving xx% of the prescribed dose to the CTV (15Gy), GTV (20Gy) or a certain no. of Gy. **prescribed dose ; IQR = interquartile range; $PTV_{GTV/CTV}$ - planning target volume of the CTV/GTV;*

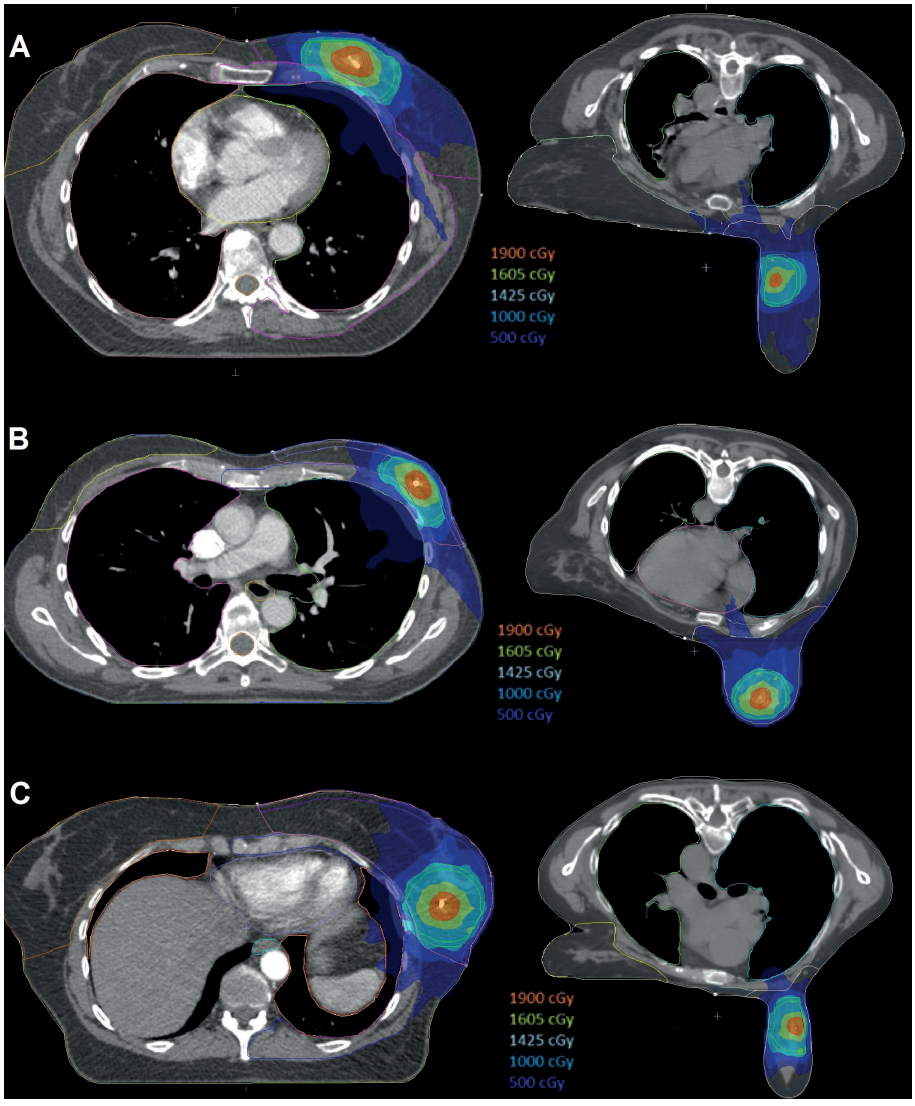

Figure 1. Representative dose distributions for a medial (A), central (B) and lateral (C) tumor illustrating heart, ipsilateral lung and chest wall volumes receiving less dose in the prone versus supine treatment position.

the median differences in mean ipsilateral breast, ipsilateral lung, and heart dose were below 1Gy (i.e. +Δ0.1Gy, -Δ0.5Gy and +Δ0.1Gy, respectively (table 2)), compared to the clinical plans.

Clinical versus MRI-linac plan in the prone treatment position

In the actual delivered plans in the prone group, the median values of the mean ipsilateral breast, ipsilateral lung, and heart dose were 3.8Gy (IQR 3.1-4.4Gy), 0.3Gy (IQR 0.2-0.4Gy) and 0.1Gy (IQR 0.0-0.3Gy), respectively (data not shown). In the current prone MRI-linac plans, the median differences in mean ipsilateral breast, ipsilateral lung, and heart dose were again below 1Gy (i.e. +Δ0.8, +Δ0.1 and +Δ0.7), despite a larger target volume compared to the actual delivered plans.
Differences in various skin parameters between the MRI-linac and clinical delivered plans are illustrated in table 3.

Technical feasibility

In all patients treated in the supine position, the isocenter was located within the body contour, mostly at mid-mediastinal position. In patients treated in the prone position, the fixed isocenter was located outside the body contour, in the midline, due to the position of the breast board.All patients treated in the prone position, would have fit the 70cm MRI-linac bore, given that the largest measured distance from the table to the most posterior extent of the patient was 44cm. No virtual collision issues were encountered in patients treated in either position.

DISCUSSION

To our knowledge, the current study is the first to address the dosimetric feasibility of a prone and supine treatment approach using an MRI-linac for single dose preoperative APBI. When setting up the current study, we presumed that certain technical specifications of the MRI-linac and treatment position might negatively alter treatment planning and therefore dosimetric feasibility of the predefined OAR constraints, compared to conventional CT-linac based treatment. Nonetheless, our results showed that single dose APBI on the MRI-linac is feasible with respect to adequate target volume coverage and acceptable normal tissue doses, in both the prone and supine treatment position. Preliminary OAR dosimetry favored a prone approach.

Two previous studies have focused on magnetic field dose effects for postoperative RT in the supine position [26-27]. Van Heijst *et al*

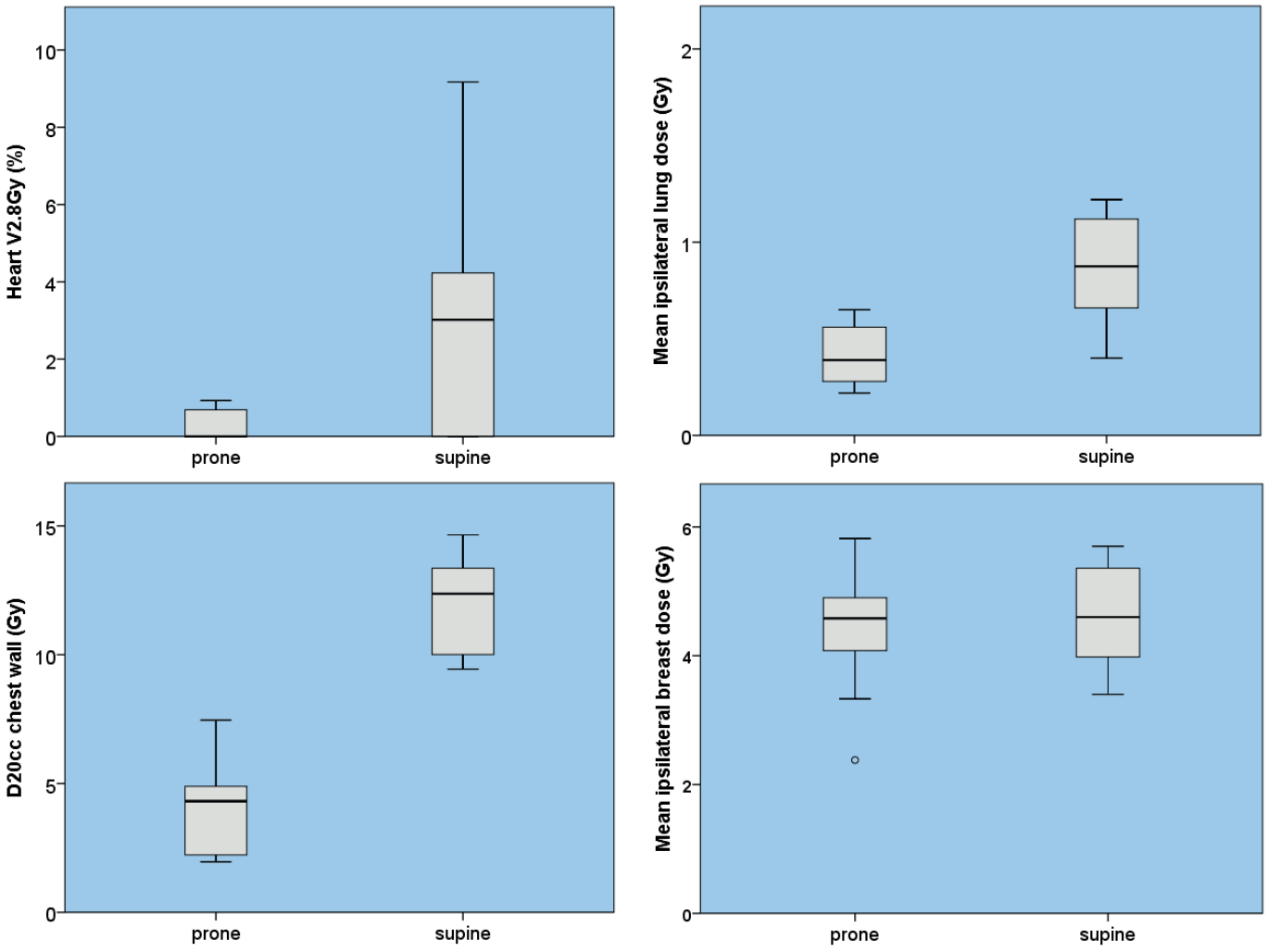

Figure 2. Boxplot illustrating the V2.8Gy dose to the heart, mean ipsilateral lung dose, D20cc dose to the chest wall and mean ipsilateral breast dose with the prone versus supine treatment position.

investigated the magnetic-field impact on skin dose with WBI (42.56 Gy in 16 fractions, 2-field forward IMRT) and APBI (38.5 Gy in 10 fractions, 7-field IMRT) at 0T, 0.35T and 1.5T [26]. A negative impact of the magnetic field was more prominent in WBI, whereas with APBI, its effect on the skin was perceived as negligible. Other OARs were not adversely influenced by the magnetic field. Kim *et al* analyzed the 1.5T magnetic field dose effects using a tangential beam arrangement, 5-beam IMRT, and VMAT for APBI delivered in 8 fractions of 5Gy [27]. Heart and lung doses were minimally impacted by the magnetic field. Depending on the skin parameter and definition (i.e. first 3mm versus 5mm subcutaneous tissue), some negative impact on dosimetry could be observed. Nonetheless, for some skin parameters (e.g. D_{1cc}) this could be mitigated by increasing the number of beams (i.e. 5-beam IMRT versus tangential field). At first glance, these two studies might appear conflicting with respect to the evaluated impact of the magnetic field in APBI, probably due to variations in skin definition and parameters (e.g. mean dose, D_{1cc}, D_{2cc}), and significance level of observed differences (i.e. α 0.05 versus 0.10). Nonetheless, both studies conclude that additional beams reduce the skin dose and the magnetic field does not compromise other OAR dosimetry. In our study, we observed that for both positions the OARs were not compromised. This is further strengthened by the comparison of the clinical and MRI-linac plans in supine position with the same prescribed dose, and similar constraints during treatment plan optimization, with minor absolute dosimetric differences, including skin parameters (table 3). Therefore, limited clinical impact is anticipated, nonetheless these findings will need to be confirmed

Table 3. Comparison of skin parameters between the clinical and MRI-linac treatment plans in the prone and supine treatment position.

	Supine position Median (IQR) (n=10)		**Prone position* Median (IQR) (n=10)**	
	MRI-linac plan	**Clinical plan**	**MRI-linac plan**	**Clinical plan**
D_{1cc} skin (Gy)	14.7 (14.0-15.4)	14.7 (13.6-15.7)	15.0 (14.7-15.3)	16.8 (14.2-18.3)
D_{10cc} skin (Gy)	11.8 (10.6-12.9)	12.2 (10.1-12.7)	13.4 (12.4-13.9)	11.9 (10.4-14.6)
V_{12Gy} skin (cc)	9.6 (5.9-13.9)	10.8 (4.5-13.4)	17.3 (11.7-22.8)	9.8 (4.7-18.0)

. in the clinical plans, a uniform 21Gy dose was prescribed to the clinical target volume (CTV) including the gross tumor volume (GTV) whereas in the MRI-linac plans an integrated boost of 15/20Gy was prescribed to the CTV/GTV, respectively.*

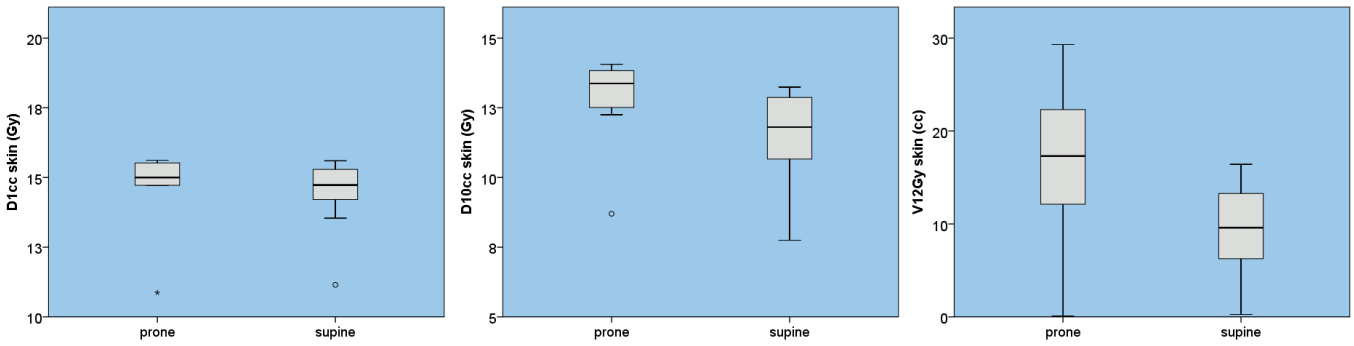

Figure 3. Boxplot illustrating the variation in dosimetric skin parameters between the prone and supine treatment position.

in future MRI-linac clinical trials to establish safety and tolerability. For the prone MR-linac plans, a direct comparison of the MRI-linac to the actual delivered plans is partially impeded by differences in CTV margin, prescription dose (i.e. 21Gy versus 15/20Gy) and OARs constraints for plan optimization. Still, one observation is interesting for description: despite the lower 15/20Gy prescribed dose with the MRI-linac plans, the median V_{12Gy} was higher, 17.3cc versus 9.8cc compared to the prone clinical plans with a 21Gy prescribed dose (table 3). This is likely attributable to the increase in CTV margin from 1.5cm utilized in the clinical plans to a 2.0cm extension from GTV in the MRI-linac plans.

Our institutions have focused on the concept of single dose preoperative APBI to enable a radiosurgical approach in low-risk breast cancer. Since CT-based target delineation may be suboptimal due to the reduced soft tissue contrast differentiation, MRI-guided targeting may be uniquely suited to this approach [11-12]. The MRI-linac could have the potential to minimize the PTV margin. Moreover, since the set-up error might increase in prone compared to supine treatment position, on-line imaging could also account for position verification issues. This might result in decreased irradiated volumes and a further decrease of RT-induced toxicity. In the context of post-operative APBI, due to the elongation of the tumor bed in the prone position, the mean CTV and PTV volumes are significantly higher for patients treated prone versus supine [28]. At the same time, prone positioning appears to be more beneficial with respect to non-target tissue dosimetry, especially in patients with right-breast cancers or left-breast cancers in women with large breasts [29]. This is in line with our observation given the mean dose to the ipsilateral lung, $V_{2.8Gy}$ heart and especially D_{20cc} chest wall which appear to be smaller in the prone treatment position (table 2, figure 2). A prerequisite for a radiosurgical approach in early-stage breast cancer concerns adequate dose prescription and the importance of high biological effective doses (BED) for local tumor control, as illustrated in the case of stereotactic RT in early-stage lung cancer [31]. Compared to an offline, MRI-guided approach to the intact tumor, real-time tumor imaging with the MRI-linac allows potentially for plan adaptation strategies, and thus BED escalation for high-risk tissue, possibly further enhancing the local tumor control probability. Furthermore, from a patient's perspective, an MRI-linac based single dose APBI might provide less burdening invasive procedures, e.g. no additional fiducial marker is required for position verification. Moreover, a pseudo-CT-scan based on the online MR-images, instead of a separate RT planning-CT, might be sufficient for treatment planning.

Still, certain limitations of the current study have to be addressed. First, the practical feasibility of the single dose MRI-linac treatment approach for breast cancer patients is still under investigation. Also, similar PTV margins to the clinical plans were used for the MRI-linac, since at this stage of research it is yet unknown what the extent of this PTV margin should be, whereas smaller MRI-linac margins would more easily result in feasible coverage and OAR dosimetry. At our department, a clinical study is currently ongoing towards the development of an adaptive MRI-linac workflow in the supine and the prone position, thereby also including the practical feasibility of various breast boards, treatment time delivery considerations, comfort evaluation for breast cancer patients and evaluation of the most adequate PTV-margin. Second, evaluation of the prone and supine treatment approach has been done with distinct patients (e.g. variation in Body Mass Index, tumor localization in breast quadrant, more left-sided breast cancer in patients treated in the supine position) rather than in a pairwise fashion and thus may not fully capture dosimetric differences between the supine and prone position when using an MRI-linac. We therefore cannot elaborate on specific treatment positions being more favorable for specific patients. Furthermore, it has to be noted that the clinical and MRI-linac plans in the prone position have been performed with a different prescribed dose, CTV and PTV definitions and therefore a direct dosimetric comparison was not possible. Nonetheless, our main study goal was to investigate the dosimetric feasibility according to actually utilized clinical predefined constraints, which we could evaluate based on our data. Our results thus far are encouraging in both treatment positions, nonetheless MRI-linac based single dose ablative APBI as radiosurgical alternative to current breast conserving therapy in early-stage breast cancer will of course need to be confirmed in the clinical setting

CONCLUSION

Single dose APBI on the MRI-linac to the intact tumor is dosimetrically feasible in both the supine and prone position for early-stage low-risk breast cancer. Although dose contraints were met for both treatment positions, OAR dosimetry might favor a prone treatment position.

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Chapter 7
Summary and general discussion

The past years hypofractionated whole breast irradiation (WBI) has been the standard of care for early-stage breast cancer following breast conserving surgery (BCS) [1]. Recently, postoperative partial breast irradiation (PBI) has been established as an alternative for WBI in patients with a low-risk of local recurrence [2-5]. With PBI, solely the portion of the breast at highest risk for local recurrence – the tumor bed – is targeted, resulting in decrease irradiated volumes. In addition, by increasing the dose per fraction, the current number of 15-23 radiotherapy (RT) fractions can be reduced, leading to shorter RT schedules (i.e. accelerated partial breast irradiation (APBI)). From a patient's perspective, APBI enables treatment de-escalation with possibly less treatment related toxicity, reduced treatment burden, and less impact on the physical and emotional wellbeing, compared to WBI.

The goal of the current thesis was to address whether further treatment de-escalation for early-stage breast cancer is feasible by evaluating several aspects of MRI-guided single dose preoperative ablative RT. Preoperative APBI targets the intact tumor, instead of the post-surgery tumor-bed, allowing treatment volume reduction and dose escalation per fraction, thereby further shortening the RT-schedule [6-8]. Also, preoperative APBI may enable tumor downstaging and direct evaluation of tumor response to RT and has therefore great potential for the development of predictive and prognostic biomarkers, RT-sensitivity genetic profiles and refinement of the current adjuvant role of RT in breast cancer treatment. Nonetheless, the most interesting aspect of preoperative APBI concerns the delivery of high-dose RT on the intact tumor in the breast, prior to surgical artifacts. This might facilitate a radiosurgical – ablative – treatment approach which may replace breast conserving surgery and protracted RT-schedules, thereby minimizing the impact of treatment for the individual patient. For this scenario, MRI-guidance is crucial for adequately targeting malignant tissue in the breast [9-10].

An essential step towards adequate evaluation of an innovative treatment concerns assessment of the starting point, i.e. description of the current clinical practice in the low-risk breast cancer population. Therefore, **chapter 2** of this thesis focused on the patient's perspective of currently employed hypofractionated RT schedule and its impact on patient-reported outcome measures (PROs) during a 2 year follow-up in women ≥60 years of age with breast cancer or ductal carcinoma in situ (DCIS). This group of women might benefit most from partial breast RT innovations, since they are very suitable for treatment de-escalation approaches due to their age and high-percentage of early-stage and low-risk breast cancer diagnoses [11]. At the same time, older patients have a widespread heterogeneity in performance status due to the presence of comorbidity [12-14]. Assessing the impact of treatment on functional, emotional and cognitive capacities is thus even more crucial for this patient population [13-14]. We found that women ≥60 years of age with DCIS or breast cancer experienced a temporary decline in quality of life (QoL), physical functioning and more fatigue up to 6 months following postoperative RT. Compared to an age-matched Dutch population without breast cancer, patients experienced more fatigue and anxiety symptoms up to 18 months follow-up, though their QoL was significantly higher from 12 months on following RT. Comorbidity, but not advanced age, was the major factor associated with deterioration in overall well-being. Also, extended RT volumes (i.e. (loco)regional RT) were significantly associated with lower QoL, physical functioning, and more fatigue compared to local RT. Previous studies in elderly breast cancer patients have shown that the addition of whole breast RT to adjuvant endocrine therapy resulted in a significant reduction of loco(regional) recurrences, however without any benefit for overall survival [15-19]. Endocrine therapy, which is often postulated as an appropriate alternative for whole breast RT in the elderly, also has important drawback in clinical practice, such as low treatment compliance due to (musculoskeletal) side-effects and protracted treatment duration [20-21]. Our study adds up that there is also room for improvement on the impact of whole breast hypofractionated RT schedule on the functional and emotional capacities in women ≥60 years of age. The current evaluation of PROs might be a useful tool for shared decision making in clinical practice by discussing the best treatment option for the individual patient. It is eventually up to the patient to decide whether the best possible QoL or lowest risk of local recurrence is the most important factor to base definite treatment on.

Chapter 2 also provides important information on the impact of hypofractionated WBI on PROs for elderly patients [13-14]. Geriatric societies acknowledge the lack of evidence based treatment approaches for the patients at least 70 years of age, and encourage future collection of clinical data to focus on non-conventional oncological outcomes, such as PROs [13]. Data for this study were obtained from the UMBRELLA cohort, which is integrated in routine care at the department of Radiation Oncology of the UMC Utrecht [22]. It should be noted though that our patients might not be completely representative for the entire population of elderly breast cancer patients, since the PROs were collected in women treated with RT. Recently, we have expanded the UMBRELLA cohort to other hospitals to also include patients treated without RT.

In contrast to systemic treatments (e.g. chemotherapy, endocrine therapy), the phase I-IV trial framework is not suitable for evaluation of all new treatments in radiation oncology [23]. Instead, the R-IDEAL criteria provide a framework for systematic clinical evaluation of technical innovations in radiation oncology. R-IDEAL is based on the IDEAL criteria for surgical innovations [23-24]. The first stage of this process is stage 0, the so-called radiotherapy-predicate studies, evaluating technical aspects of new RT approaches. Subsequent R-IDEAL stages focus on the evaluation of technical feasibility and safety, technical development, evaluation of early effectiveness, and formal comparison to the standard of care during a long-term follow-up. **Chapter 3** of this thesis therefore first focuses on the dosimetric feasibility of MR-guided single dose preoperative APBI by comparing a state of the art non-invasive external beam technique, i.e. volumetric modulated arc therapy (VMAT) with an interstitial multicatheter brachytherapy approach, an invasive APBI technique with the longest clinical follow-up currently available. The most crucial assumption in this study concerned the single dose prescription intended to be ablative in future clinical studies on low-risk breast cancer. Furthermore, in contemporary literature with intraoperative based APBI, single doses as high as 21Gy to the tumor bed have been evaluated as safe [25-26]. For our dosimetry study on MRI-guided single dose approach, two dose levels were pragmatically designed with an integrated 20Gy boost to the gross tumor volume (GTV) (i.e. equivalent to a 73.7Gy dose in 2Gy fractions (EQD2, α/β 4.7Gy) and a 15Gy dose intended for microscopical disease, thus clinical target volume (CTV) (i.e. equivalent to 44.1Gy (EQD2, α/β 4.7Gy) and standard hypofractionated 16 fractions of 2.66Gy

schedule). These assumptions were set up before the publication of the adjusted α/β value of 3.5Gy (95% CI 1.2–5.7) for local regional relapse within the START-A and START pilot trial, or the results of the START-B 15 fractions RT schedule [1]. Our planning study evaluated differences in target volumes and dose dosimetry to organs at risk (OAR) initially in concordance to our expectations based on set-up requirements (i.e. planning target volume required for VMAT but not IMB) and characteristic dose fall-off of the two techniques (e.g. larger planning volumes with VMAT and slightly lower mean dose to the ipsilateral lung, contralateral breast or heart with IMB). Nonetheless, our dosimetry study unexpectedly revealed that the integrated boost approach, resulted in extensive CTV overdosage for interstitial multicatheter brachytherapy, with a median of 49% of CTV receiving a higher dose, intended to the GTV. With VMAT, only 4% CTV overdosage was observed. We therefore concluded that single dose RT with an integrated ablative boost to the GTV is dosimetrically feasible with both techniques. Brachytherapy though is less suitable for clinical implementation due to two-dose level based CTV overdosage, which can possibly result in more RT-induced toxicity. This is in stark contrast to clinical results from postoperative APBI data showing consistently good toxicity results with uniform, one dose-level prescription, brachytherapy and conflicting toxicity results with an external bream RT approach [27-32]. In addition, a recent single arm study in 20 low-risk breast cancer patients treated with uniform, single dose 18Gy interstitial multicatheter brachytherapy based post-operative APBI evaluated during 24 months follow-up evaluated only 2 grade two toxicities in 2 separate cases, with good to excellent cosmetic outcome in 80% of the women [33]. **Chapter 3** therefore illustrates the importance of systematic evaluation of new RT interventions, given the possibility of totally contrasting results to long-term established clinical experience. Furthermore, our findings in **chapter 3** set ground to the development of the first prospective clinical study evaluating MRI-guided single dose ablative preoperative partial breast RT in early-stage breast cancer using a VMAT technique.

The ABLATIVE study is designed to evaluate the clinical feasibility of an MRI-guided ablative – or radiosurgical - partial breast approach in early-stage low-risk patients. It challenges hereby the position of RT as previously evaluated in post- and preoperative APBI studies or currently employed with standard of care WBI or PBI in these low-risk patients. **Chapter 4** describes the study protocol, which includes the extensive diagnostic work-up (i.e. MRI, FDG-PET-CT and sentinel node procedure) before the single-dose partial breast RT. To evaluate radiologic tumor downstaging following RT, several MRIs are being performed. In addition, extensive clinical follow-up (e.g. questionnaires for physician and patients) were performed in order to evaluate RT-induced toxicity and patient-reported outcome measures. At first glance, this complex logistics oppose the mindset of MRI-guided single dose ablative APBI having the potential to offer a minimally burdening, non-invasive treatment. However, at this stage of development, all possible pathologic, radiologic, radiobiologic, dosimetric, surgical or patient related factors ought to be evaluated in order to further refine this treatment approach for the future. The collected data within the ABLATIVE study will give more insight in the most useful imaging modality and time points, genetic profile or tumor biology in relation to RT response. The best-case scenario is that the great majority of treated cases will comply with the primary study endpoint, namely a pathologic complete response (pCR) at six months following RT. A preliminary conclusion would then be that MRI-guided single dose ablative RT is clinically feasible instead of multiple fractionated RT with the potential to omit a surgical treatment. Subsequent studies might focus on the radiologic or clinical predictors of pCR, and the comparison with standard of care breast-conserving therapy in low-risk breast cancer patients.

Nonetheless, we believe that even a modest scenario envisaging only a minority of treated cases achieving pCR, will still be of great gain for the clinical practice, even if breast-conserving surgery is still required. From a societal perspective, replacing a multiple fraction postoperative RT schedule with single dose non-ablative preoperative APBI, is appealing with respect to work-load and associated treatment costs at a radiation-oncology department, maybe even for countries in less economically developed regions. From the individual patient's perspective, replacing a multiple fraction RT schedule with one single non-ablative RT dose is expected to positively impact the perceived treatment burden, and potentially functional or emotional status. A strength of the ABLATIVE study is that the future results may be extended beyond the low-risk patient population. Since the effects of preoperative RT can be directly evaluated in the excised specimen, biomarkers of RT response could be incorporated in future studies on preoperative RT for locally advanced breast cancer. Another application of MRI-guided single dose ablative RT might be in frail (and therefore inoperable) elderly patients with hormone sensitive breast cancer where currently primary endocrine therapy is perceived as the best alternative for local surgical treatment. In these frail patients with comorbidity, survival is mainly determined by non-breast cancer related causes, thus local breast disease instead of systemic disease is most threatening. A local RT-approach might therefore be more suitable compared to systemic endocrine therapy. Furthermore, additional drug therapy can be prevented in these patients with polypharmacy. Therefore, single high-dose RT to the intact tumor has the potential to be a more efficient and less burdening treatment alternative compared to primary endocrine therapy in frail inoperable patients. This approach will be studied at the Universitary Medical Center Utrecht, where a new clinical trial on "Single dose rAdiation treatment in medically inopeRAble breast cancer patients (SARA-study) " is currently being developed.

An essential prerequisite for further evaluation of the above mentioned promising clinical scenarios are of course acceptable toxicity results following MRI-guided single dose preoperative APBI. **Chapter 5** therefore describes treatment constraints based on the acute toxicity data in the first 15 treated patients within the ABLATIVE study. The median follow-up was 7 months following the investigational treatment. Furthermore, an update on the late toxicity is given for the dose escalation trial on single dose preoperative trial. At Duke Cancer Institute (Durham, NC, United States), 32 women with cT_1N_0 non-lobular carcinoma or DCIS <=2.0 cm were treated with a uniform non-ablative 15, 18 or 21Gy single dose RT followed by lumpectomy within 10 days [34]. No dose-limiting toxicity has been observed in both studies. Subsequently, as described in **chapter 5**, treatment constraints for single dose preoperative RT were pragmatically defined based on pooled dosimetric parameters within the two clinical cohorts. Current APBI guidelines for organs at risk (OARs) dosimetry lack absolute physical dose constraints and solely recommend a maximum dose percentages to OARs from the initial prescription dose [2]. The previously conducted external beam post-operative APBI-studies showed a variation in experienced toxicity and associated determinants of toxicity [27-31]. It is postulated that, besides patient and dose related factors, differences in dose-volume parameters and interfraction interval are also likely to account for differences in toxicity [35-37]. Defining OAR constraints to prevent RT-induced toxicity for our treatment approach is even more crucial given that the linear-quadratic model is not applicable for single doses higher than 8 Gy. At the same time, the past years several studies have been set up to explore the role of stereotactic ablative body or

neoadjuvant RT in early-stage breast cancer patients [38-39]. In order to minimize the possibility of adverse events for study patients, carrying out studies on ultra hypofractionated neoadjuvant RT studies should be confined to stringent protocol, taking pre-existing experience from various medical centers into account. With lessons learned from the postoperative external beam APBI toxicity experience, we should aim consistent treatment planning in order to ensure the future clinical feasibility of ultra fractionated neoadjuvant RT. We therefore believe that the dosimetric data pooling acquired in **chapter 5** from clinical cohorts of 15 Gy, 18 Gy, 21 Gy, (i.e. at Duke Cancer Institute) and simultaneous integrated 15/20 Gy boost (i.e. ABLATIVE-study), will be a helpful foundation for future explorations in the field of single dose preoperative RT. Furthermore, of importance to mention is the interesting dosimetric aspect of preoperative APBI compared to postoperative APBI, where breast tissue receiving the highest-dose RT is excised, likely to result in less ipsilateral breast toxicity such as fibrosis. However, preoperative RT could result in an increased post-operative complication risk. Long-term follow-up will have to unravel the definitive toxicity balance between postoperative APBI and preoperative, single dose APBI on smaller target volumes, likely to be excised.

As previously described, the potential of single dose preoperative APBI is versatile and **chapter 6** of this thesis brings us back to a new predicate dosimetry study, exploring this concept on the MRI-linac [40-41]. Recently, the MRI-linac based treatment in patients with lumbar spine metastasis has been evaluated as clinical feasible [42]. An important note on the MRI-linac treatment strategy concerns the current limited availability, though at the same time expanding over radiation-oncology departments world-wide. Several European and American institutes are collaborating within the MRI-linear accelerator consortium aiming at systematic evaluation and evidence-based introduction in clinical practice [43]. With 9 preliminary tumor sites selected as possible indications for the MRI-linac treatment as alternative for surgical treatment, and each collaborating institute coordinating subsequent studies, an effective evaluation of this innovative treatment can be accomplished, making it easily to implement in other non-consortium centers in the near future.

The results of the planning study described in **chapter 3** and preliminary outcomes of the ABLATIVE study show that MRI-guided single dose preoperative ablative RT is dosimetrically, technically and clinically feasible. Nonetheless, an online MRI-linac based treatment where the tumor is visualized real-time during the actual RT delivery has additional advantages. Online treatment strategies might enable dose escalation within the tumor altogether with smaller target volume margins, possibly resulting in enhancement of local tumor control probability and reduced RT-toxicity at the same time. Also, due to the real-time target volume imaging, additional fiducial markers for position verification or a planning CT might not be required in the future, making it a minimally burdensome treatment for patients. The omission of a fiducial marker might prevent MRI-artefacts and improve the radiologic response evaluation on MRIs following treatment. This simplistic view on the MRI-linac's potential is in stark contrast to the various technical and dosimetric issues that ought to be considered for single dose APBI treatment planning [44-45]. The variation in patient position on the treatment table (i.e. prone versus supine patient positioning), certain technical specification of the MRI-linac (i.e. fixed collimator and fixed couch position relative to the isocenter in anterior, posterior and lateral directions) and modified trajectories of secondary electrons due to the presence of a magnetic field need to be studied first. **Chapter 6** therefore evaluates the dosimetric and technical feasibility of single dose APBI to the intact tumor in 20 patients previously treated with single dose preoperative APBI in the supine (n=10) (i.e. within the ABLATIVE study) or prone (n=10) position (i.e. the dose escalation study at Duke Cancer Center). Additional intensity modulated radiotherapy plans with 7 coplanar beams in the presence of a 1.5T magnetic field were generated, with a 20Gy and 15Gy dose prescribed to the GTV and CTV, respectively – in accordance to the ABLATIVE study. A "worst case" scenario for MR-linac treatment planning was employed, with similar target volume margins as utilized within the ABLATIVE-study. Nonetheless, all MRI-linac plans met the predefined coverage and OAR constraints whereas minor absolute differences were observed compared to the clinical plans. A trend was observed towards more favorable OAR dosimetry for patients treated in the prone RT position. At our department of Radiation Oncology at the University Medical Center Utrecht, a RT predicate study is currently ongoing evaluating the MRI-only workflow for the MRI-linac using single-dose preoperative APBI delivered in the prone versus supine position in breast cancer patients.

In the field of oncology, a shift towards less invasive and less burdening treatments for patients is currently ongoing. Single dose preoperative ablative APBI has the great potential to become a de-escalating alternative for multiple fractionated radiotherapy schedules, and even an alternative for breast-conserving surgery in selected low-risk breast cancer patients. The current thesis emphasizes that for breast cancer, a new promising treatment era has begun with the implementation of MRI-based radiotherapy approaches.

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Nederlandse samenvatting

De-escalatie van behandeling voor vroeg-stadium borstkanker: eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie

Voor vrouwen over de hele wereld is borstkanker de meest voorkomende oncologische diagnose. De ziekte komt steeds vaker voor in zowel economisch ontwikkelde, als minder economisch ontwikkelde landen. In Nederland wordt jaarlijks bij 16.500 vrouwen borstkanker of een voorloper van borstkanker (zogenaamde ductaal carcinoom in situ (DCIS)) ontdekt. De gemiddelde Nederlandse vrouw heeft een 12-14% risico om borstkanker gedurende haar leven te ontwikkelen, mocht zij de 85-jarige leeftijd bereiken. Bij de overgrote meerderheid van de patiënten (i.e. 75%) wordt borstkanker in een vroeg stadium ontdekt. Dit komt mede door de introductie van het bevolkingsonderzoek in 1995 in Nederland en verbeteringen in de radiologische beeldvorming. Tegelijkertijd heeft de behandeling van borstkanker de afgelopen decennia ook een snelle ontwikkeling doorgemaakt door verbeterde werking van systemische behandelingen (bijvoorbeeld chemotherapie en anti-hormonale therapie), verbetering van bestralingstechnieken en minder invasieve chirurgische benaderingen (bijvoorbeeld mogelijkheid voor borstsparende operatie in plaats van borstamputatie). In Nederland is het totale overlevingspercentage 10 jaar na de diagnose borstkanker 76%. Door de toename in overleving en groeiende kennis over de korte en lange termijn bijwerkingen van de kankerbehandelingen, wordt het steeds belangrijker om ook de gevolgen van een behandeling op het lichamelijk en emotioneel functioneren van patiënten te evalueren, zodat tijdig met de juiste behandeling van deze negatieve gevolgen kan worden gestart.

De meest gangbare behandeling voor vroeg-stadium borstkanker is de borstsparende therapie. Hierbij wordt de tumor verwijderd middels een borstsparende operatie en de gehele borst wordt vervolgens bestraald om eventuele achterblijvende kankercellen te vernietigen. De laatste jaren is er meer belangstelling voor gedeeltelijke borstbestraling (PBI) als alternatief voor gehele borstbestraling. Met PBI wordt het gedeelte van de borst te bestraald waar de tumor heeft gezeten voor de operatie (dit is het tumorbed) en waar de grootste kans bestaat dat de ziekte terugkeert. Aangezien alleen een gedeelte van de borst wordt bestraald, kunnen omliggende organen ook meer gespaard worden hetgeen kan leiden tot minder bijwerkingen van de bestraling. Een ander voordeel is dat de totale dosis bestraling in een kortere tijd kan worden toegediend, de zogenaamde geaccelereerde gedeeltelijke borstbestraling (APBI). De huidige behandelingstijd waarbij patiënten 15-16 keer worden bestraald gedurende 3 weken kan hiermee worden verkort. Vanuit het perspectief van de patiënt kan APBI resulteren in minder bijwerkingen en een kortere behandelingsduur met hierbij een beperkter impact van de bestraling op het lichamelijk en emotioneel functioneren. Op basis van eerdere wetenschappelijke onderzoeken hebben Europese en Amerikaanse radiotherapie verenigingen voorwaarden opgesteld waaraan patiënten dienen te voldoen voordat ze voor (A)PBI in aanmerkingen komen. Samenvattend, betreft dit patiënten met vroeg-stadium borstkanker die tenminste 50 jaar oud zijn met een kleine hormoongevoelige tumor zonder uitzaaiingen naar de lymfeklieren.

Een nieuwe ontwikkeling binnen de APBI betreft de zogenaamde preoperatieve borstbestraling. Door de tumor en het tumor bed te bestralen voorafgaande, in plaats van na de borstsparende operatie, kan een bestralingsarts nauwkeuriger bepalen welk gedeelte van de borst behandeld dient de worden. Hierdoor kan het bestraalde borstvolume nog verder worden beperkt, hetgeen kan leiden tot minder bijwerkingen aan de omliggende organen of de aangedane borst. Ook kan door voorafgaande aan de borstsparende operatie te bestralen, het directe effect van de bestraling op de tumor worden geëvalueerd en zou de effectiviteit van borstbestraling kunnen worden voorspeld. Het meest interessante aspect van het primair bestralen van een borsttumor betreft het bewerkstelligen van een *ablatieve* behandeling. Hierbij is het doel om de borstkankercellen alleen met bestraling te vernietigen, zonder dat daar nog een borstsparende operatie aan te pas hoeft te komen.

Voor een ablatieve behandeling middels een hoge dosis bestraling is het van cruciaal belang goed onderscheid te kunnen maken tussen tumor en gezond weefsel. In de huidige klinische praktijk wordt het te bestralen volume bepaald en het bestralingsplan opgesteld op een CT-scan, waarbij het contrast tussen verschillende weefsels in de borst niet optimaal is. Wanneer de gehele borst wordt bestraald is het gebruik van een CT-scan niet bezwaarlijk. Bij de voorbereidingen voor bestraling van een niet-geopereerde tumor in de borst, is het echter wenselijk gebruik te maken van een MRI-scan waarop de tumor beter zichtbaar is dan op een CT-scan. Een MRI-scan bewerkstelligt veel contrast tussen weefsels en kan dus goed onderscheid maken tussen tumor en gezond weefsel. Deze MRI-gestuurde radiotherapie kan verder worden geoptimaliseerd door de tumor af te beelden tijdens de bestralingsbehandeling. De bestralingsafdeling an het Universitair Medisch Centrum Utrecht heeft samen met Philips® en Elekta® een bestralingsapparaat ontwikkeld met een geïntegreerde MRI-scanner, de zogenaamde MRI-versneller.

In dit proefschrift worden de voorbereidingen beschreven naar eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie voor vroeg-stadium borstkanker, waarvan het primaire doel is om voor patiënten een uiterst effectieve, echter minimaal invasieve behandeling tot stand te brengen met verminderde bijwerkingen en een minimale impact op de kwaliteit van leven.

In **hoofdstuk 2** van dit proefschrift werd de impact van de huidige oncologische behandeling geëvalueerd in borstkanker patiënten die tenminste 60 jaar oud zijn, vanaf de bestraling gedurende 2 jaar follow-up. Deze patiëntengroep heeft een hoog percentage vroeg-stadium borstkanker diagnoses die een laag risico hebben op ziekte terugkeer (zogenaamde laag-risico patiënten die ouder zijn dan 50 jaar en kleine, hormoon-gevoelige tumoren hebben zonder uitzaaiingen naar de lymfeklieren). Deze patiënten zijn daarom geschikt voor minimaal invasieve behandelingen zoals APBI. Daarbij hebben oudere patiënten vaker comorbiditeit en dus beperkingen, waardoor het van belang is om de impact van oncologische behandeling op het functioneren te evalueren. In het Universitair Medisch Centrum Utrecht worden alle patiënten die verwezen worden naar de bestralingsafdeling gevraagd om mee te doen aan de Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluation (UMBRELLA) onderzoek waarbij op vaste tijdstippen vragenlijsten worden afgenomen over o.a. bijwerkingen van de behandeling, lichamelijk en emotioneel functioneren en ervaren kwaliteit van leven (zogenaamde *patient reported outcome measures* (PROMs)). In **hoofdstuk 2** werd de impact van de oncologische behandeling onderzocht middels PROMs in patiënten ≥60 jaar binnen het UMBRELLA-onderzoek die volgens de huidige richtlijnen

voor borstkanker zijn bestraald. In de eerste 6 maanden werd tijdelijk een achteruitgang geëvalueerd in het fysiek functioneren en ervaren kwaliteit van leven en meer vermoeidheid ten opzichte van voor start van de bestraling. Daarbij hadden patiënten meer angstsymptomen en meer vermoeidheid bij vergelijking met Nederlandse vrouwen ≥60 jaar zonder borstkanker. Vanaf 12 maanden was de ervaren kwaliteit van leven in de groep patiënten verbeterd ten opzichte van vrouwen zonder borstkanker. Comorbiditeit was de grootste beperkende factor voor alle PROMs. Daarbij ervoeren patiënten die met (loco)regionale (i.e. lymfeklieren in de oksel, hals of rondom het borstbeen) bestraling werden behandeld lagere kwaliteit van leven, meer beperkingen in fysiek functioneren en meer vermoeidheid in vergelijking met patiënten die lokaal (i.e. gehele borst of borstwand) zijn bestraald. Eerdere onderzoeken in oudere patiënten met vroeg-stadium borstkanker behandeld met anti-hormonale therapie hebben aangetoond dat aanvullende bestraling na de borstsparende operatie de kans op lokale terugkeer van borstkanker halveert, met gelijkblijvende overleving. Hierdoor is in de huidige klinische praktijk, de bestralingsbehandeling van oudere patiënten met borstkanker een onderwerp van discussie. Anti-hormonale therapie wordt soms geopperd als een alternatief voor gehele borstbestraling in oudere patiënten, echter heeft deze behandeling ook nadelen zoals een lage therapie compliance door bijwerkingen (zoals opvliegers, spier- en gewrichtspijnen en stemmingsstoornissen) en lange behandelduur. De evaluatie van PROMs in **hoofdstuk 2** kan in het kader van gedeelde besluitvorming door zorgverleners worden gebruikt om patiënten boven 60 jaar adequaat te informeren omtrent de verwachte impact van de huidige oncologische behandeling op het fysiek en emotioneel functioneren om tot een passende behandelkeuze te komen.

In tegenstelling tot behandeling met geneesmiddelen zoals chemotherapie, is het gangbare fase I-IV studieopzet niet altijd geschikt voor de evaluatie van nieuwe bestralingsinterventies. Een eerste stap binnen de radiotherapie betreft het evalueren van technische aspecten van de nieuwe behandeling, een zogenaamde *predicate*-studie. **Hoofdstuk 3** beschrijft een vergelijking in haalbare bestralingsdosis tussen 2 verschillende APBI technieken voor eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie in vroeg-stadium borstkanker. De *volumetric modulated arc therapy* (VMAT) is een vorm van uitwendige bestraling waarbij de bundels tijdens het stralen om de patiënt roteren, om zo een meest optimale dosisverdeling bewerkstellingen. *Interstitial multicatheter brachytherapy* (IMB) is een vorm van inwendige bestraling waarbij multipele katheters in de tumor(bed) worden ingebracht. Het voordeel van VMAT boven IMB is dat het een niet-invasieve techniek betreft. Aangezien de tumor niet inwendig wordt behandeld, waardoor onzekerheden ten aanzien van de positionering bestaan door bijvoorbeeld de ademhaling, wordt bij VMAT een extra veiligheidsmarge genomen rondom het te bestralen volume. Een voordeel van IMB is dat een kleiner gebied inwendig kan worden bestraald in vergelijking met een uitwendige techniek zoals VMAT.

Een bestralingsdosis van 20 Gy op de tumor en 15 Gy op de omliggende 2 cm aan borstweefsel met mogelijk hierin microscopische tumoruitbreiding, werd voorgeschreven. Deze dosering werd op basis van eerdere literatuur als potentieel ablatief geacht voor de tumor, echter nog binnen de veiligheidsvoorschriften voor het gezond omliggende weefsel. De onderzochte behandeling bleek haalbaar met betrekking tot voldoende dosis voor de tumor volumes zonder overschrijding van de toegestane dosis voor de gezonde organen, met zowel de VMAT als IMB-techniek. Met IMB werd een significant lagere gemiddelde dosis geëvalueerd voor het hart en de ipsilaterale long, echter met minimale absolute verschillen, ten opzichte van VMAT. Daarbij, om voor de IMB-techniek voldoende bestralingsdosis te krijgen in de tumor volumes waren multipele katheters nodig, wat gepaard ging met een overdosering in het borstweefsel rondom de tumor. De IMB-techniek werd daarom minder geschikt geacht voor de eenmalige MRI-gestuurde ablatieve radiotherapie, bij vergelijking met VMAT. De resultaten in **hoofdstuk 3** vormen de basis voor het eerste prospectieve klinisch onderzoek naar eenmalige dosis MRI-gestuurde ablatieve preoperatieve radiotherapie in vroeg-stadium borstkanker.

Hoofdstuk 4 beschrijft het ABLATIVE studieprotocol waarbij de klinische haalbaarheid van eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie middels een VMAT-techniek wordt onderzocht in patiënten met laag-risico en vroeg-stadium borstkanker. Met een ablatieve behandeling zou de huidige complementaire rol van de radiotherapie kunnen worden gewijzigd naar volwaardige alternatief voor de huidige borstsparende therapie. Voor de klinische praktijk zou dat betekenen dat patiënten niet meer geopereerd en 15-16 keer postoperatief bestraald zouden hoeven te worden. **Hoofdstuk 4** beschrijft o.a. de uitgebreide benodigde diagnostische work-up (deze zijn de benodigde MRI-scans, schildwachtklierprocedure voorafgaande aan bestraling i.p.v. tijdens de borstsparende operatie, FDG-PET-CT-scans) en vervolgcontroles voor studiepatiënten. Alle mogelijke radiologische, radiobiologische, bestralingsdosis, tumor- en patiënt gerelateerde factoren worden geëvalueerd in de ABLATIVE-studie om de behandeling oncologisch veilig te kunnen verfijnen voor toekomstige patiënten. De primaire studie uitkomst betreft een volledige pathologisch respons, wat bewijzend is voor een ablatieve behandeling voor vroeg stadium borstkanker. In een groter vervolgstudie zou dan bevestigd dienen te worden dat eenmalige MRI-gestuurde ablatieve radiotherapie een volwaardig alternatief is voor de borstsparende chirurgie en 15-16 postoperatieve bestralingen. Indien geen complete pathologische respons na bestraling volgt, dan heeft eenmalige niet-ablatieve behandeling alsnog voordelen voor de klinische praktijk. Voor patiënten zou dat betekenen dat een traject met 15-16 postoperatieve bestralingen gedurende 3 weken kan worden gereduceerd naar 1 bestraling voorafgaande aan de borstsparende operatie. Daarnaast kan in de ABLATIVE-studie het directe effect van de bestraling op de tumor wordt onderzocht. *Biomarkers* van respons kunnen geselecteerd en gebruikt worden voor toekomstige studies. Een andere toepassing voor de eenmalige MRI-gestuurde radiotherapie betreft medisch-inoperabele kwetsbare oudere patiënten, waarbij in de huidige klinische praktijk anti-hormonale therapie als *second best* alternatief voor de chirurgie wordt beschouwd. In het Universitair Medisch Centrum Utrecht wordt momenteel hier een onderzoek naar opgezet.

Een essentiële voorwaarde voor een vervolg van de ABLATIVE-studie betreft het evalueren van acceptabele toxiciteit na de eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie. In **hoofdstuk 5** wordt de acute toxiciteit data beschreven in de eerste 15 patiënten behandeld in de ABLATIVE-studie. Daarbij wordt ook nog een overzicht gegeven van de toxiciteit in een Amerikaanse dosis escalatie studie waarbij 32 vrouwen met vroeg-stadium mammaborstkanker of DCIS behandeld zijn middels eenmalige 15 Gy, 18 Gy of 21 Gy niet-ablatieve MRI-gestuurde radiotherapie. In beide onderzoeken wordt tot nu toe geen ernstige toxiciteit geobserveerd. De data uit deze twee studies met betrekking tot bestralingsdosis in de tumor en gezonde organen werd vervolgens samengevoegd, met als doel richtlijnen te creëren voor toekomstige klinische studies naar eenmalige MRI-gestuurde radiotherapie. Dit is van toegevoegde waarde voor de klinische praktijk omdat bij zowel Europese als Amerikaanse radiotherapie verenigingen geen bestralingsdosis aanbevelingen worden gedaan voor gedeeltelijke borstbestraling. Om de kans op toxiciteit te minimaliseren voor (studie)patiënten, is het cruciaal om

kaders op te stellen voor toegestane bestralingsdosis voor de tumor en gezonde organen, waarin eenmalige MRI-gestuurde behandeling veilig mag worden toegepast.

Hoofdstuk 6 borduurt voort op het concept van eenmalige MRI-gestuurde ablatieve gedeeltelijke borstbestraling en beschrijft een nieuwe *predicate*-studie naar de haalbaarheid van deze behandeling op de MRI-versneller. Een behandeling op de MRI-versneller heeft als grootste voordeel dat de tumor gevisualiseerd kan worden tijdens het bestralen. Hierdoor zou een tumor nog nauwkeuriger kunnen worden bestraald, zelfs met een hogere bestralingsdosis waarbij tegelijkertijd het gezonde omliggend weefsel nog beter kan worden bespaard. Tegelijkertijd kan de geïntegreerde MRI-scanner op een bestralingstoestel de behandeling technisch complexer maken. In hoofdstuk 6 werd daarom de haalbaarheid geëvalueerd van eenmalige MRI-gestuurde ablatieve radiotherapie met betrekking tot voldoende dosis voor de tumor volumes, zonder overschrijding van de toegestane dosis voor de gezonde organen. Hiervoor werd gebruik gemaakt van eerdere scans van patiënten binnen het ABLATIVE-onderzoek (patiënten die in rugligging zijn behandeld) en de eerder beschreven Amerikaanse dosis escalatie studie (patiënten die in buikligging zijn behandeld). Daarbij werden deze MRI-versneller radiotherapie plannen vergeleken met de klinische plannen van patiënten. Alle MRI-versneller plannen voldeden aan de voorafgedefinieerde kaders met betrekking tot adequate dosis in tumorvolumes en gezonde organen. Er werd een trend gezien dat een bestralingsbehandeling in buikligging mogelijk gunstiger uitpakt voor de borstwand, long en hart dosis. Op basis van deze resultaten is een vervolgonderzoek opgezet in het Universitair Medisch Centrum Utrecht waarin een MRI-versneller *worfklow*, zowel in rug- en buikligging, wordt onderzocht.

Concluderend kan er gesteld worden dan eenmalige MRI-gestuurde ablatieve preoperatieve radiotherapie de potentie heeft om een uiterst effectieve en tegelijkertijd minimaal invasieve behandeling te bewerkstellingen voor patiënten met laag-risico vroeg-stadium borstkanker. Dit proefschrift beschrijft de eerste stappen van een nieuw veelbelovende behandelingstijdperk van MRI-gestuurde radiotherapie voor de behandeling van borstkanker.

Dankwoord

There is a time for everything, and a season for every activity under the heavens:
a time to plant and a time to uproot,
a time to kill and a time to heal,
a time to tear down and a time to build,
a time to weep and a time to laugh,
a time to mourn and a time to dance,
a time to scatter stones and a time to gather them,
a time to embrace and a time to refrain from embracing,
a time to search and a time to give up,
a time to keep and a time to throw away,
a time to tear and a time to mend,
a time to be silent and a time to speak,
a time to love and a time to hate,
a time for war and a time for peace.

(Ecclesiastes 3; 1-10)

Een promotietraject brengt een rollercoaster van emoties met zich mee. Achteraf, kijk ik terug op de afgelopen jaren vooral met een gevoel van dankbaarheid voor de kansen die ik heb gekregen en een gevoel van waardering voor de mensen die mij op weg hebben geholpen.

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For My thoughts are not your thoughts,
Neither are your ways My ways, declares the LORD
For as the heavens are higher than the earth,
So are My ways higher than your ways,
And My thoughts than your thoughts.

(Isaiah 55:8-9)

List of publications

Patient reported outcomes following postoperative radiotherapy for (non) invasive breast cancer in women ≥60 years of age. **KR Charaghvandi**, HJGD van den Bongard, DA Young-Afat, ML Gregorowitsch, CH van Gils, B van Asselen, HM Verkooijen. *Submitted.*

Single dose partial breast irradiation using an MRI linear accelerator in the supine and prone treatment position. **KR Charaghvandi**, T van't Westeinde, S Yoo, AC Houweling, A Rodrigues, HM Verkooijen, MEP Philippens, B van Asselen, JK Horton, HJGD van den Bongard. *ClinTransl Radiat Oncol 2018.*

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Curriculum vitae

Kejal-Ramona Charaghvandi was born in Cluj-Napoca in the Transylvania region of Romania on the 15th of October 1986, to Romanian and Kurdish parents. In 2000, she resettled together with her family in the Netherlands where she attended Ter Kemenade College and later on Jan van Brabant College in Helmond.

Following her graduation in 2005, she started medical school at the University Medical Centre (UMC) Utrecht. In 2010, she temporarily interrupted her medical study to attend the Conflict Studies minor programme at the faculty of Humanities at the Utrecht University. During her clinical rotations, she published her personal experiences as an intern in the online "Arts in spé" platform for medical students. She also worked as a research-assistant at the Imaging Sciences Institute at the UMC Utrecht and a triage-assistant at the general practitioner office in 's Hertogenbosch. Her interest for the field of breast cancer was awakened while attending consultations at the breast clinic at St. Antonius Hospital in Nieuwegein. She subsequently opted for a final internship at the Medical Oncology Department at the UMC Utrecht and a final research project on mammographic breast density at the Radiology Department – under supervision of then associate professor dr. H.M. Verkooijen. In her last year of medical school, she unexpectedly found her true medical calling while she completed an internship at the Radiation Oncology Department under supervision of dr. M. Intven.

After obtaining her medical degree in 2012, she started working as a resident (ANIOS) on the Intensive Care Unit at the St. Elisabeth Ziekenhuis in Tilburg, this in order to broaden her clinical experience. In 2013 she started her PhD fellowship at the Radiation Oncology Department at the UMC Utrecht, thereby setting up and coordinating the ABLATIVE-study on MRI-guided single dose preoperative ablative radiotherapy for early-stage breast cancer, under supervision of dr. H.J.G.D. van den Bongard, dr. B. van Asselen, prof. dr M. van Vulpen, and later on prof. dr. H.M. Verkooijen. In 2016, she got the opportunity to perform a research internship at the Radiation Oncology Department at Duke Cancer Center in Durham in the United States, where she focused on dosimetric and pathologic aspects of single dose preoperative radiotherapy for early-stage breast cancer, under supervision of associate professor dr. J.K. Horton, dr. S. Yoo and dr. E. Parilla-Castellar. During her PhD-trajectory she also completed her postgraduate master of Epidemiology in 2017. In June 2017, she started her training as a radiation oncologist at the Radboud University Medical Center in Nijmegen under supervision of prof. dr. J. Bussink and dr. H. Rütten.

Ramona got married to Nader Dayerizadeh on her 30th birthday in 2016. They currently live with their daughter Lauren Ava Rosa in Nijmegen.

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