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Neoadjuvant single-dose irradiation in low-risk breast cancer

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Neoadjuvant single-dose irradiation in low-risk breast cancer

Neoadjuvante eenmalige bestraling voor laagrisicoborstkanker
(met een samenvatting in het Nederlands)

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Jeanine Else Vasmel

geboren op 30 december 1989 te Amsterdam

Promotor:	Prof. dr. H.M. Verkooijen
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GENERAL INTRODUCTION AND THESIS OUTLINE

BREAST CANCER

Every year approximately 17,000 women and 130 men in the Netherlands are diagnosed with breast cancer [1]. Women diagnosed through the national breast cancer screening program account for almost 50% of the breast cancer diagnoses [2]. Within the national screening program, Dutch women aged between 50 and 74 years receive an invitation for a mammogram every two years, and are subsequently referred for additional diagnostic tests to the hospital in case of suspicion of a tumor. The additional diagnostic tests can consist of a repeated (three-dimensional) mammography, ultrasound imaging, magnetic resonance imaging (MRI), and biopsy of the suspected tumor and lymph nodes.

Following confirmation of breast cancer, the disease stage is determined by the TNM-criteria. In this the T stands for the size of the tumor, the N for the presence of affected lymph nodes, and the M for the presence of distant metastases (Figure 1) [3,4]. From the TNM-criteria the disease stages (0 up to IV) are formed. Disease stage 0 up to IIA are considered early stage breast cancer. Disease stages IIB and III are considered locally advanced disease, and stage IV is metastasized disease. Correct determination of disease stage at the moment of diagnosis is important to construct the most suitable treatment approach and to communicate the prognosis to patients and their relatives.

Currently, the 10-year relative survival rate for breast cancer patients with stage I disease is 95% , and for patients with stage II 83% [1]. These survival rates have increased over the past decades, as for patients who were diagnosed between 1989 and 1992 the 10-year relative survival rate was 86% for stage I disease, and 64% for stage II disease [1]. This improvement in survival can be attributed to both earlier detection of breast cancer as well as improved treatment, through more effective systemic treatment and advanced radiotherapy techniques [5,6]. Earlier detection of breast cancer, and thus an increase in the incidence of early stage breast cancer, has been achieved by the implementation of the national screening program and progression in imaging techniques, such as three-dimensional mammography, digital mammography, and MRI [7,8].

In this thesis, we focus on a novel treatment approach for the increasing number of women diagnosed with low-risk early stage breast cancer. The treatment approach consists of a single dose of neoadjuvant partial breast irradiation, aiming to completely eradicate all tumor cells, and with the opportunity to omit breast conserving surgery in future patients. To be more specific, this involves patients with T1N0M0 and T2N0M0 (with a maximum tumor size of 3 cm) disease, without nodal involvement, and with an estrogen receptor-positive and HER2-negative tumor (stage 1A and 2A in figure 1) [9,10].

These kind of tumors are considered to have a low-risk of local and distant recurrence of disease, as they slowly proliferate and thus take a long time to grow or metastasize to lymph nodes or other organs [11]. Low-risk early stage breast cancer patients have a 5 and 10-year local recurrence risk of approximately 1% and 3%, respectively [12,13].

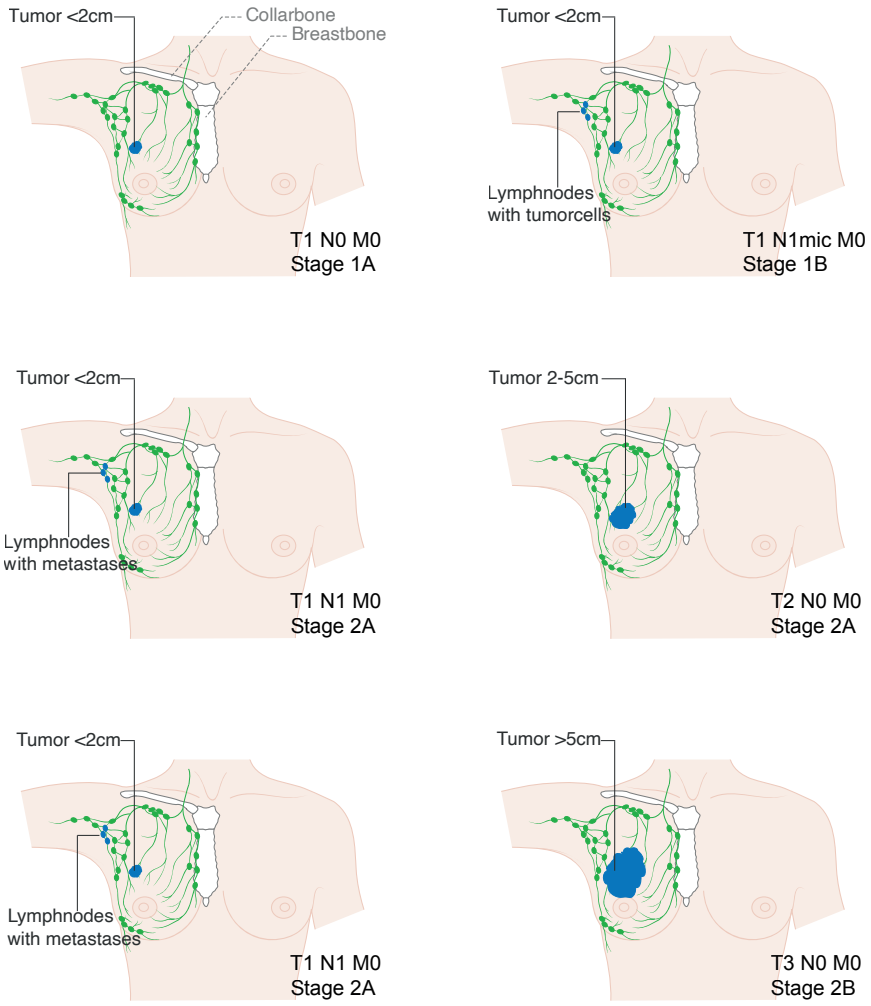

FIGURE 1. Disease stage 1 and 2 according to TNM-criteria (Adapted from Cancer Research UK - Original email from CRUK, CC BY-SA 4.0).

STANDARD TREATMENT OF EARLY STAGE BREAST CANCER

History

Breast cancer treatment as we currently know it, started with the radical mastectomy as introduced by the surgeon Halsted in 1894. During this invasive surgery the entire breast, the underlying chest wall muscles and axillary lymph nodes were removed. This surgery was first further extended by removing supraclavicular and mediastinal lymph nodes as well, before reducing the extent by leaving the chest wall muscles intact: the modified radical mastectomy [14]. It was not until the end of the twentieth century that breast-conserving surgery was introduced as a standard treatment for breast cancer, as it resulted in equal survival rates when combined with adjuvant radiotherapy in comparison to mastectomy [15,16]. Earlier in the 20th century radiotherapy had been widely studied, but without definitive recommendations on the timing, dose or patient selection [17]. Nowadays, Breast-conserving surgery is performed to remove the tumor, while adjuvant breast radiotherapy is prescribed to further decrease the risk of local recurrence of disease resulting in an increased survival [5,18,19].

Multidisciplinary approach

Currently, early stage breast cancer, as all breast cancers, is treated according to a multidisciplinary approach, which can involve a combination of surgery, oncoplastic or reconstructive surgery, radiotherapy, and systemic treatment [20]. In the Netherlands, treatment options for all patients are discussed within a multidisciplinary meeting by surgeons, plastic surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, and clinical geneticist according to national and local guidelines [21]. The final treatment approach is made, ideally, after discussing the treatment options with the patient and their relatives, which is known as 'shared decision making' [22].

In addition to surgery and adjuvant radiotherapy, systemic treatment can be indicated in low-risk breast patients to further reduce the risk of recurrence of disease and improve survival. The indication for the type of systemic treatment depends on tumor size and grade. However, low-risk breast cancer patients rarely have an indication for chemotherapy, while they regularly receive endocrine treatment.

Radiotherapy for low-risk breast cancer

Adjuvant radiotherapy can consist of whole breast radiotherapy (WBI) or partial breast radiotherapy (PBI) [12,13,23–26]. In the Netherlands, during WBI the entire breast can be irradiated in 5 up to 15 fractions (5x 5.2 Gray (Gy), , or 15x 2.67 Gy) [27]. Until 2011, patients were treated with WBI schedules consisting of 25 fractions of 2 Gy [28]. The reduction in

number of fractions, also known as hypofractionation, has been implemented because the risk of locoregional recurrence appeared to be equal to 25 fractions with a decrease in treatment-induced toxicity [24,29]. In addition, hypofractionation results in decreased treatment burden for patients.

During PBI, only the tumor bed, which is the part of the breast where the tumor was originally located including a margin to include microscopic disease, is irradiated. (Since the risk of locoregional recurrence is low, most local recurrences occur in or near the tumor bed the majority of low-risk breast cancer patients are eligible for treatment with PBI [9,10,30]. External beam radiotherapy schedules with PBI consists mainly of 5 or 15 fractions [12,13,27]. PBI resulted in further reduction of treatment-induced toxicity and improved patient-reported outcomes when compared to WBI, without compromising the risk of recurrence of disease [12,31].

To deliver radiotherapy, a treatment plan is made using a radiotherapy planning computed tomography (CT) scan of the chest of the patient in supine treatment position. On this CT-scan the target volume is defined, as well as the organs at risk. For PBI, the target volume is the tumor bed including a margin to account for microscopic disease. For WBI, the target volume is the whole breast. The organs at risk are the normal tissues near the target volume that should be spared from the radiotherapy dose. The surrounding organs at risk during breast cancer radiotherapy are the ipsilateral breast in PBI, and in PBI and WBI the contralateral breast, the heart, and both lungs. Since it is not possible to completely spare the normal tissue, treatment constraints are used which describe to what extent the organs at risk can tolerate radiotherapy dose to minimize the risk of toxicity[32].

Even when the treatment constraints are met, radiotherapy may lead to treatment-induced toxicity. This toxicity can be defined as acute (occurring within the first three months after treatment) or late (occurring after three months). Acute toxicity may include fatigue and radiation dermatitis, causing breast edema, pain and itchiness [33]. Late toxicity may include breast fibrosis (changing breast appearance or shrinkage), lymphedema, hyperpigmentation, radiation pneumonitis, and cardiovascular disease [34–36]. Both acute and late toxicity may impair patient-reported outcomes such as the level of physical functioning, the emotional well-being, and general quality of life [31,37,38]. Hypofractionation and (accelerated) PBI can reduce the risk of treatment-induced toxicity, and improve quality of life compared to conventional fractionation and WBI.

POTENTIAL OF NEOADJUVANT SINGLE-DOSE PARTIAL BREAST IRRADIATION

This thesis focuses on a novel treatment method for low-risk early stage breast cancer patients. The treatment method consists of neoadjuvant single-dose ablative PBI followed by breast-conserving surgery.In recent years, neoadjuvant single-dose PBI has been introduced within clinical trials as a treatment approach for low-risk breast cancer patients[39,40]. As opposed to adjuvant PBI, neoadjuvant PBI is administered before surgical treatment. Benefits of neoadjuvant PBI include the smaller irradiated target volumes enabling a higher radiotherapy dose per fraction, and better definition of the tumor, which could result in better cosmesis and improved patient reported outcomes [39,41].

The advantage of neoadjuvant PBI is that the tumor is still *in situ*, meaning still in the original place. An *in situ* tumor can be better defined as a target volume for irradiation compared to the postoperative tumor bed, due to the absence of postoperative changes such as seroma (fluid collection within the surgical planes) and swelling of the surrounding breast tissue. Additionally to standard radiotherapy treatment planning, an MRI improves the target definition for neoadjuvant PBI by improved visualization of the tumor spiculae [41]. Due to the addition of an MR images for the development of a treatment plan, the term MRI-guided neoadjuvant PBI has been coined.

A point of interest for neoadjuvant PBI is that the radiosensitivity, the so-called a/b ratio, is relatively low for breast tumor cells [24,42–45]. The a/b ratio describes the relation between the radiation dose and amount of surviving tumor cells. Tumors with a high a/b ratio (between 7 and 20 Gy), respond within days to weeks to radiotherapy, while tumors with a low a/b ratio (between 0.5 and 6 Gy) can take up to years to respond to radiotherapy. For breast cancer, the currently accepted a/b ratio is between 2.7 and 3.5 Gy [24,46]. Through combining the low a/b ratio and the intention to spare the surrounding healthy tissue, an extremely hypofractionated treatment schedule of a single dose could be developed. In the trial described in this thesis, for this an a/b ratio of 4.7 Gy was used, as this was the accepted ratio during the initiation of the trial (Figure 2) [39,43]. Due to the slow proliferation of breast tumors in low-risk patients, the breast tumors are expected to respond very well, but slowly, to the high dose, which can translate to a high rate of pathologic complete response at a long interval after radiotherapy [11].

Neoadjuvant PBI may achieve tumor downstaging, including pathologic complete response, which is an important feature. Tumor downstaging is already widely studied in breast cancer patients treated with neoadjuvant chemotherapy, the standard

treatment for more advanced breast cancer patients [47,48]. When neoadjuvant partial breast irradiation results in a pathologic complete response, omission of the subsequent breast-conserving surgery can be considered. This could lead to a further reduction in treatment-induced toxicity and treatment burden for patients [49,50]. Therefore, if low-risk breast cancer patients could be adequately treated with neoadjuvant PBI with a high chance of pathologic complete response, this could lead to a paradigm shift in breast cancer treatment for selected low-risk patients.

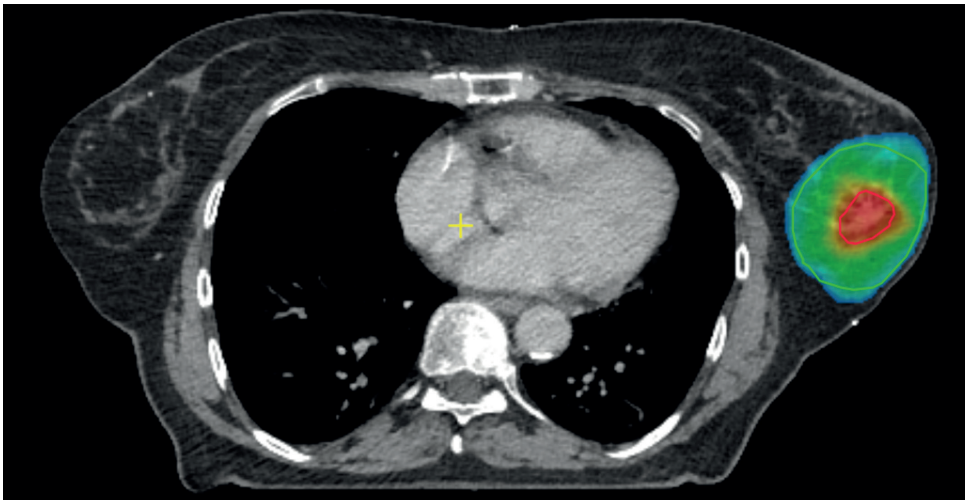

FIGURE 2. Dosimetry of treatment plan for neoadjuvant single-dose PBI in a patient with left-sided breast cancer.

AIM AND OUTLINE OF THE THESIS

To assess whether neoadjuvant single-dose PBI could be used as a safe and effective treatment for low-risk breast cancer patients, we initiated a feasibility study in which neoadjuvant single-dose PBI was followed by breast-conserving surgery [39]. The aim of this study (the ABLATIVE study), was to evaluated the efficacy and safety of neoadjuvant single-dose PBI. It is currently not known what proportion of patients who undergo neoadjuvant single-dose PBI will achieve pathologic complete response. In the ideal situation where all patients treated with neoadjuvant single-dose PBI would achieve pathologic complete response, surgery could be omitted in all patients. However, if not all patients achieve pathologic complete response, it could still be of great interest to be able to identify the patients in which the irradiation has an ablative effect, so surgery

could be omitted in only these patients. The rate and possible determinants of pathologic complete response have been widely studied in breast cancer patients treated with neoadjuvant chemotherapy. In these more advanced stage breast cancer patients, tumor grade, hormone receptor status, MRI, and tumor infiltrating lymphocytes, can be used to predict the pathologic response [51–53]. In low-risk breast cancer patients treated with MR-guided neoadjuvant PBI, the potential predictors for pathologic response still need to be researched. However, it can be hypothesized that the predictors for pathologic response in patients treated with neoadjuvant chemotherapy correspond to those in patients treated with neoadjuvant irradiation.

The aim of this thesis is to describe MR-guided irradiation for breast cancer patients, to evaluate the effect of MR-guided neoadjuvant single-dose PBI in low-risk breast cancer patients, and to explore options for the future differentiation between responders and non-responders after neoadjuvant single-dose PBI.

In **chapter 2** of this thesis, challenges and benefits of MRI in breast cancer radiotherapy planning are discussed. It covers the paradigm shift to neoadjuvant radiotherapy for breast cancer patients, including the possibilities to treat these patients on a linac with an integrated MR-scanner (MR-linac).

In **chapter 3**, the development and evaluation of expert-based international consensus guidelines on the delineation of breast tumors on MRI for neoadjuvant irradiation are discussed. International consensus on tumor delineation is necessary for comparison between studies and for potential future implementation of neoadjuvant irradiation in standard practice.

In **chapter 4**, the effects of neoadjuvant single-dose PBI in low-risk breast cancer in terms of the rate of pathologic complete response and toxicity are reported.

Chapter 5 provides insight in the immune response to neoadjuvant breast irradiation in low-risk breast cancer patients, which could aid in the early identification of complete responders.

In **chapter 6**, the correlation between semi-quantitative parameters derived from repeated MRI scans and pathologic response to neoadjuvant single-dose PBI is evaluated in order to identify excellent responders in whom surgery might be omitted.

In **chapter 7**, the agreement and reliability between three different methods for evaluation of cosmetic results following neoadjuvant irradiation and breast-conserving surgery are evaluated. With the aim to assess whether these methods can be used interchangeably.

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OPTIMIZING MR-GUIDED RADIOTHERAPY FOR BREAST CANCER PATIENTS

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ABSTRACT

Current research in radiotherapy for breast cancer is evaluating neoadjuvant as opposed to adjuvant partial breast irradiation with the aim of reducing the volume of breast tissue irradiated and therefore the risk of late treatment-related toxicity. The development of MR-guided radiotherapy, including dedicated MR-guided radiotherapy systems (hybrid machines combining an MR-scanner with a linear accelerator (MR-linac) or ^{60}Co sources) could potentially reduce the irradiated volume even further by improving tumour visibility before and during each radiotherapy treatment. In this position paper we discuss MR-guidance in relation to each step of the breast radiotherapy planning and treatment pathway, focussing on the application of MR-guided radiotherapy to neoadjuvant partial breast irradiation.

INTRODUCTION

The combination of a worldwide rising incidence of breast cancer together with decreasing mortality following breast cancer treatment has resulted in increasing numbers of breast cancer survivors living with late treatment-related toxicity [1–3]. In recent decades this has led to prioritization of treatment de-escalation aiming to reduce treatment-related toxicity without impeding survival [4]. Studies comparing adjuvant whole breast irradiation (WBI) versus adjuvant partial breast irradiation (PBI) in women with lower risk breast cancers have demonstrated that PBI is as effective as WBI in terms of 5-year local recurrence rates and survival but with lower rates of late patient-reported and clinician-reported toxicity [5–8]. Nonetheless, late treatment-related toxicity remains an issue in a significant proportion of patients [6,8].

With neoadjuvant PBI, smaller target volumes can be irradiated compared to conventional adjuvant PBI, potentially resulting in less radiotherapy-related toxicity and therefore a higher quality of life [9–11]. This is because, for neoadjuvant PBI, the gross target volume (GTV) is tumour rather than tumour bed, presenting a smaller, more easily definable target. Furthermore, the breast tissue at risk of local relapse remains in the closest possible proximity to the GTV thereby reducing uncertainty around location of the clinical target volume (CTV). This is increasingly important in the current era of oncoplastic surgery in which the tissue that was adjacent to the tumour, the edge of which is usually marked by titanium surgical clips, may be mobilised and placed at some distance from its original location in order to ensure a good cosmetic result. This can lead to a larger CTV in the adjuvant setting than would have been necessary in the neoadjuvant setting. One problem with irradiating tumours in the neoadjuvant setting using the current standard computed tomography (CT)-based radiotherapy planning pathway however is that primary breast cancers can be difficult to see on a standard non-contrast-enhanced radiotherapy planning CT scan.

The development of magnetic resonance (MR) guided radiotherapy has greatly improved the possibilities for image-guided radiotherapy and greater sparing of healthy tissue by providing excellent soft tissue visualization. MR-guided radiotherapy can refer to treatment on a conventional linear accelerator (linac) with the use of additional imaging on an MR-scanner to plan treatment, or to treatment on a hybrid machine. A hybrid machine is an MR-scanner combined with a linac (MR-linac, Unity Elekta and MRIdian linac, ViewRay) or with ^{60}Co sources (MRIdian, ViewRay) [12–15]. For breast cancer patients, MR-guided radiotherapy is expected to be most beneficial in the neoadjuvant setting treating *in situ* tumours which can be more clearly visualised on MR images than on CT, both at the time of radiotherapy planning and during radiotherapy treatment. The latter

would facilitate reduction in set-up error margins in both the neoadjuvant and adjuvant setting. In addition, administering MR-guided radiotherapy on a hybrid machine could reduce the radiation exposure associated with the daily cone beam CT (CBCT) required during treatment on a conventional linac.

In this position paper we discuss MR-guidance in relation to each step of the breast radiotherapy planning and treatment pathway from simulation to contouring, to treatment planning and then delivery. We review what is already known, what is under evaluation, and potential obstacles to clinical implementation, highlighting where optimization of techniques and/or workflow is still required (Table 1).

SIMULATION

Patient set-up

The main challenge for patient set-up in treatment position for breast radiotherapy in an MRI scanner or a hybrid machine is the limited MRI bore size (60-70 cm) compared to the CT bore size of 80-90 cm [16–18]. This limits the size and inclination of a positioning device as well as the number of possible positions for patient set-up.

For patients treated in supine position with arms raised above their head, the elbow span in combination with an inclined position can be problematic. A solution for this is to put the arms closer together and/or to use either a wedge with smaller inclination or no wedge at all. Placement of an anterior receiver coil on a patient in supine position could lead to deformation of the breast [19]. However, coil bridges can be used as support for the coil to prevent deformation (Figure 1) [9,20–22].

In the prone position, the proportion of patients who can fit into the MR-scanner bore is limited by the space needed for a pendulous breast to hang freely without touching the table top in combination with the requirement to place an additional receiver coil on the back of the patient (Figure 2). The additional receiver coil is necessary as the full body contour is needed for radiotherapy (RT) planning purposes, which is not a requirement for diagnostic prone breast imaging.

Standard RT immobilization equipment may not necessarily be MR-compatible and standard MR equipment (e.g. the dedicated prone breast coil) is not designed for set-up reproducibility. Therefore, it is necessary to develop dedicated RT immobilization equipment that is MR-compatible (i.e. non-conductive, low density material). This equipment must also fit inside the MR bore and leave room for the MR receiver coils (e.g.

flexible receiver coils in a prone breast board), while not degrading image quality [17,22]. Because of the electron stream effect (ESE), further discussed in section 4, simulation should include the chin and upper abdominal region.

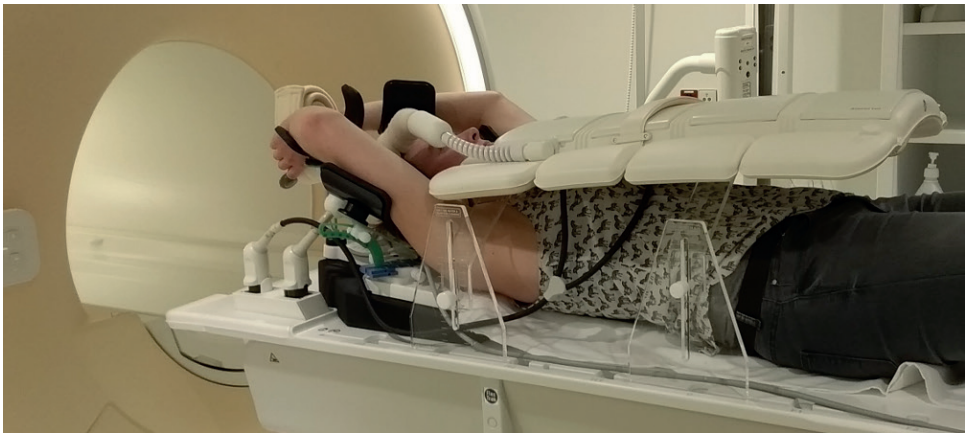

FIGURE 1. Supine patient set-up for MRI simulation. In this set-up a 5 degrees inclined wedges is used. Height-adjustable coil bridges are used as support for the anterior receiver coil to prevent deformation of the body contour.

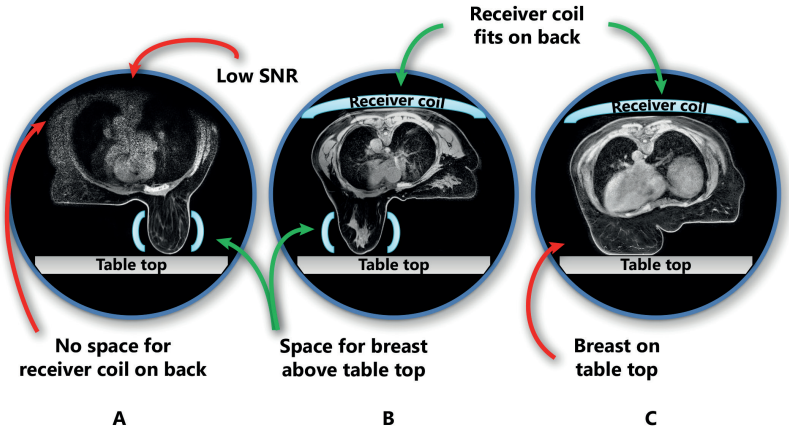

FIGURE 2. Patient and receiver coil positioning in prone position, including challenges in this position. The images show three different patients. (A) No space for the receiver coil on the back of the patient if the breast hangs freely without touching the scanner table; (B) The receiver coil fits above the patient while also the breast hangs freely; (C) When the receiver coil is fitted in the MRI bore above the patient the breast touches the table top and is deformed. Light blue shapes represent the receiver coils (horizontal: receiver coil array; vertical: single flex coil). SNR – signal-to-noise ratio

Image quality

For optimal quality of MR images, the receiver coil should be placed close to the target volume. Therefore, a strategic set-up for the additional coils should be chosen, specific to the selected patient position (e.g. supine or prone). Because RT immobilization devices, such as the supine and prone breast boards and coil bridges increase the gap between the patient and the receiver coils (i.e. the distance to the posterior coil located in the scanner table, and to the anterior coil on top of the patient), it was initially thought that the positioning requirements for breast cancer radiotherapy might have a negative impact on MR image quality. However, multiple studies have reported good quality of MR images for breast RT in both supine and prone treatment positions acquired at 1.5 T and 3.0 T MR scanners [19,21,22].

Another factor that might impair MR image quality is organ motion, including respiratory and cardiac motion, during scanning. Imaging in prone position has the advantage of minimizing breast motion due to respiration and may also minimize motion artefacts [19]. Batumulai et al. found no significant effect of the breathing artefacts on image quality in both prone and supine position by instructing their volunteers to maintain shallow breathing and choosing a right-left phase encoding direction in their MRI scans [22]. Additionally, to preventing the motion, artefact reduction (e.g. gating or triggering) or motion correction (e.g. MR navigators) techniques can be used to minimize motion effects on MRI scans. However, it is important to realize how the anatomy relates to the breathing state during radiotherapy [18]. To prevent step-like displacements in different slices in the scan volume caused by motion during scanning, a 3D sequence can be used, although motion in a 3D scan will lead to blurring [23].

In studies that evaluated prone breast MRI for RT, a dedicated breast coil is usually used [19,22,24]. While this coil provides optimal image quality for the breasts, it cannot capture the full body contour and all organs at risk (OAR) with adequate quality (Figure 2). However, for MR-guided radiotherapy on a conventional linac, this may be sufficient, provided that enough anatomical landmarks are visible to register the MR-scan to the planning CT scan. Scanning with an additional receiver coil on top of the patient could help to overcome this issue, but may not be possible in all patients due to the limited MR bore size.

In case of radiotherapy treatment on a hybrid MR-guided radiotherapy system, it is not possible to irradiate through the standard dedicated prone breast coils that are used in diagnostic MR imaging. For that reason the receiver coils dedicated to hybrid machines have a 'window' through which irradiation is possible [15,25]. Since these dedicated coils have different properties to the standard receiver coils (i.e. fewer coil arrays, which

restricts acceleration of imaging) and are not breast specific, the image quality can be inferior. Another restriction is that the coil cannot be placed too closely to the patient due to the electron return effect (ERE; see section 4), which restricts the signal-to-noise ratio of the imaging. In general, a higher field strength gives a better signal-to-noise ratio, which may place a 1.5 T hybrid system in favour over a 0.35 T system. However, experiences with the 0.35 T hybrid system show that patient setup and online tracking for breast cancer could be performed successfully based on imaging at this lower magnetic field strength [26]. To assure appropriate image quality, the MRI sequences and image quality for breast imaging on the hybrid systems should therefore be tested and optimized for the use of the dedicated coil and each system specifically.

Geometric accuracy

The impact of geometric distortions on MR-based contouring and planning should be taken into account when optimizing image quality and MRI sequences for radiotherapy on a hybrid machine [18,27]. The effect of distortions on image quality is described in this section, whilst the effect of distortions on dose distributions is described in section 4.

Distortions arise from system-related factors (i.e. main magnetic field inhomogeneity and gradient non-linearities) and patient-related factors (i.e. chemical shift and susceptibility effects), and depend on the specific scanner and sequence parameters [18,28–31].

System-related distortions due to gradient non-linearities increase with increasing distance of the target volume from the MRI isocentre and can range up to 12 mm [25,27,28,30,32]. For the Elekta MR-linac (1.5 T) maximum displacements of 2.0 mm were found within 17.5 cm from the isocentre [25]. For the ViewRay ^{60}Co-system (0.35 T) this was 1.9 mm, but larger distortions were observed further from the central axis [33]. To minimize the effect of image distortion by gradient non-linearities, the target volume should be positioned as close to the scanner isocentre as possible [17], which may be challenging for laterally located target volumes, such as lateral breast tumours. A possible solution may be to shift the patient on the scanner table towards the contralateral side such that the ipsilateral breast moves closer to the machine isocentre, if this is possible within the limited space inside the bore. Furthermore, to minimize system-related distortions it is also important to always use the scanner's software for gradient non-linearity correction [23,30]. By using a 3D scan, the gradient non-linearity correction can be applied in all directions.

Distortions caused by main magnetic field inhomogeneities and by susceptibility effects induced by the patient's presence in the scanner also need to be corrected for.

Distortion caused by patient-induced susceptibility can be particularly large, especially at the tissue-air interface, with mean maximum distortions at 3.0 T having been found to increase from 1.4-3.7 mm in a phantom to 3.7-11.3 mm in patients (including set-up uncertainties) [29]. Susceptibility effects scale with the main magnetic field strength [31]. A lower field strength or a high receiver bandwidth can help to reduce both main magnetic field inhomogeneity and patient-induced susceptibility, but reduces signal-to-noise ratio [30,31]. Patient-specific correction methods (e.g. using the B0 map) may be helpful to correct for these distortions [18,30].

Choice of MR image contrast

Several MRI sequences have been recommended for MR-guided radiotherapy. For use of MRI in the adjuvant breast RT setting, use of T1-weighted 3D sequences without fat suppression resulted in the best visualization of surgical clips, while T1-weighted images with fat suppression (e.g. mDixon) best enabled differentiation between glandular breast tissue and seroma [9,20,34]. 2D or 3D T2-weighted MRI with fat suppression (e.g. STIR or water selective excitation) or without fat suppression was preferred for visualization of lumpectomy cavity and associated seroma, and for discrimination between glandular breast tissue and tumour bed [17,19,21,22,24].

In the neoadjuvant setting, the use of T1-weighted fat suppressed contrast-enhanced MRI is recommended for optimal tumour and tumour spiculae visualization, since differences in contrast uptake provide a clear distinction between tumour and glandular breast tissue (Figure 3) [35–38]. Additionally, T2-weighted images might aid in the differentiation between tumour and post-biopsy changes [35]. mDixon fat suppression methods proved to be reliable and are recommended because they are relatively insensitive to main magnetic field inhomogeneities [39,40]. Use of diffusion-weighted imaging (DWI) was only described in one study, where it was used in the context of response evaluation after RT and not for target delineation [35]. Use of DWI for radiotherapy could help in differentiation between benign and malignant lesions, but magnetic susceptibility induced geometric distortions make it more suitable for diagnostic imaging than for MR-guided radiotherapy [41,42]. All studies presented above used fusion of MRI with a planning-CT scan on which the OARs were delineated. Therefore, no recommendations focusing on OAR visualization on different MRI sequences have been published. Based on expert opinion, OARs are clearly visualized on any of the sequences mentioned above, except for DWI. All sequences described were acquired on stand-alone MRI scanners. Hybrid treatment machines may come with only a fixed set of available MRI sequences in clinical mode [15,43]. Therefore, not all sequences described may be available on these machines during treatment. A summary of online available MRI sequences on hybrid machines is presented in table 2.

CONTOURING

With regards to target volume delineation in the adjuvant partial breast irradiation setting, delineation of the tumour bed on CT should, according to guidelines, include visible seroma and representative surgical clips, the tumour location on preoperative imaging, and take into account the microscopic tumour-free margins [44–47]. The added value of MRI to a standard planning CT scan for delineation in the adjuvant setting is disputed for several reasons [48,49]. Firstly, surgical clips lead to voids on MRI potentially leading to less accurate target volume definition [34]. Secondly, studies have shown both a significant increase as well as a decrease of the target volume when either a pre- or postoperative MRI scan was available for delineation in addition to a postoperative planning CT [20,21,34,50]. Thirdly, in three separate studies, MRI did not lead to a reduction in interobserver variation [20,24,50]. However, in a more recent larger study, a significant reduction in interobserver variation was reported for delineation on MRI in patients without surgical clips [51]. Therefore, the added value of using MRI for contouring in the adjuvant setting seems likely to be limited to those patients in whom tumour bed clips have not been placed.

In the context of neoadjuvant partial breast irradiation, given that this is not yet a standard of care in breast cancer management, delineation of in-situ breast tumours is a relatively new concept to most radiation oncologists and new guidelines are needed. Guidelines for the delineation of primary breast tumours on MRI for use in neoadjuvant PBI setting have recently been developed by the Breast Tumor Site Group of the International MR-Linac Atlantic Consortium [36]. These recommend the use of contrast-enhanced MRI which , due to increased contrast uptake in tumours compared to the surrounding glandular breast tissue, allows for better visualization of breast tumours than using CT (Figure 3) [9,38]. Contrast-enhanced MRI has been used for the delineation of target volumes in several recent studies of neoadjuvant PBI [37,52]. In these studies, insertion of an additional fiducial marker by a radiologist was necessary both to help localise the tumour for subsequent surgical resection in case of tumour downstaging and for tumour position verification since the tumour cannot be visualized on CBCT in most patients. These markers cause artefacts on MRI, which can be observed as voids (Figure 3). The size of these artefacts depends on the material and geometry of the marker. As the artefact can obscure tumour tissue, the void of a marker should be included in the target volume. If omission of surgery after an ablative dose RT becomes clinically feasible, insertion of a fiducial marker in the tumour might not be necessary anymore. This would be beneficial for both target volume definition and follow-up imaging, as well as patient satisfaction [53].

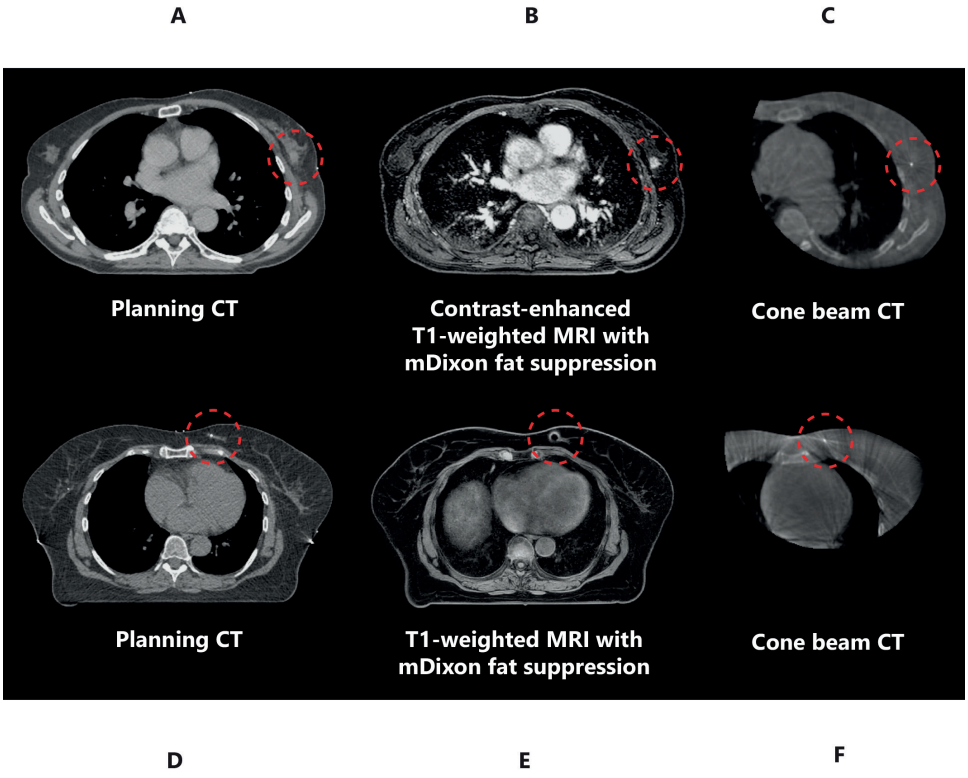

FIGURE 3. Imaging of a primary breast tumour on CT (A, D), (contrast-enhanced) MRI (B, E) and CBCT (C, F) scans indicating the difference in tumour visibility (inside the red circle) between these modalities in two different patients (A-C and D-F). D-F: the marker inserted in the tumour medial in the left breast is observed as a void on MRI (indicated by the red circles).

TREATMENT PLANNING FOR A HYBRID MACHINE

For MR-guided radiotherapy on a conventional linac, treatment planning is performed according to the standard practice. This includes registering the MRI scan to the planning CT scan used for delineation and producing a dose distribution using a standard treatment planning system. However, when treatment is to be delivered on a MR-guided hybrid machine, several additional factors need to be considered, all of which will be incorporated into the dedicated treatment planning systems. These factors are inherently related to the design of the hybrid machines. Firstly, given that the magnetic field influences the path of secondary electrons, the electron return effect

(ERE) and the electron stream effect (ESE) in air have to be taken into account. Secondly, the influence of geometric accuracy of the MR images on treatment planning must be considered. Thirdly, there are some restrictions for planning to bear in mind.

Electron return effect (ERE)

The Lorentz force acting on moving charged particles in a magnetic field causes several effects during irradiation in a magnetic field [54–59]. One of these is the ERE, which refers to the fact that the path of electrons is bent in the presence of a magnetic field, resulting in exit electrons re-entering the body after a helical path in air [55]. Studies have shown that skin dose is increased for patients undergoing WBI in a magnetic field due to the ERE [60,61]. According to van Heijst et al. the mean skin dose increased from 29.5 Gy at 0 T to 32.3 Gy at 0.35 T and to 33.2 Gy at 1.5 T for 2-beam WBI. For 7-beam WBI the mean skin dose increased from 27.9 Gy at 0 T to 30.2 Gy at 0.35 T and to 29.8 Gy at 1.5 T [60]. Given these findings, WBI is not thought to be a good indication for treatment on a hybrid machine, irrespective of the field strength. Although, van Heijst et al. found that the mean skin dose for PBI also increased, from 5.2 Gy at 0 T to 5.6 Gy at 0.35 T and 5.8 Gy at 1.5 T, the absolute mean skin dose was small compared to WBI. Therefore, the increase in skin dose for PBI in a magnetic field would be highly unlikely to translate into a higher risk of radiation dermatitis. Furthermore, it has been reported that increasing the number of beam angles helps in decreasing the skin dose [60,62]. Therefore, although PBI is a good indication for breast RT on a hybrid machine, one should remain aware of the risk of increased skin dose and use more rather than fewer beams. Since the ERE effect is also present at the lung-tissue interface, it is also important to check the maximum lung and chest wall dose [57,62]. Previous planning studies concluded that effects of the magnetic field on OARs, other than the skin, are generally negligible and doses were within clinical constraints [60,62,63].

Electron stream effect (ESE)

The second effect that should be kept in mind for breast cancer treatment on a hybrid machine is the electron stream effect (ESE) in air which can lead to dose being deposited in tissues well outside the irradiated field (Figure 4). This was first observed and evaluated by Park et al. who, in the context of accelerated PBI delivered on the 0.35 T ^{60}Co ViewRay system, observed an electron stream in air extending towards the head and ipsilateral arm [64]. This ESE is caused by electrons generated inside the body that, instead of scattering in random directions when leaving the body, start spiralling along the magnetic field [65]. If unobstructed, this electron stream would reach the chin and arm, causing unwanted irradiation of the skin in these areas. In an extreme case the maximum dose measured was as high as 16.1% of the prescribed dose [64]. Dose to

the skin outside the treatment field was highest in patients with tumours located in the cranial part of the breast. Depending on the location of the high dose region in the breast, this electron stream can also be directed towards the feet (Figure 4). Studies on phantoms and early clinical experiences suggest that the treatment planning system is able to fully describe the ESE and that the use of bolus material to shield the body parts located in the electron stream showed effective reduction of the dose in these regions [64–66].

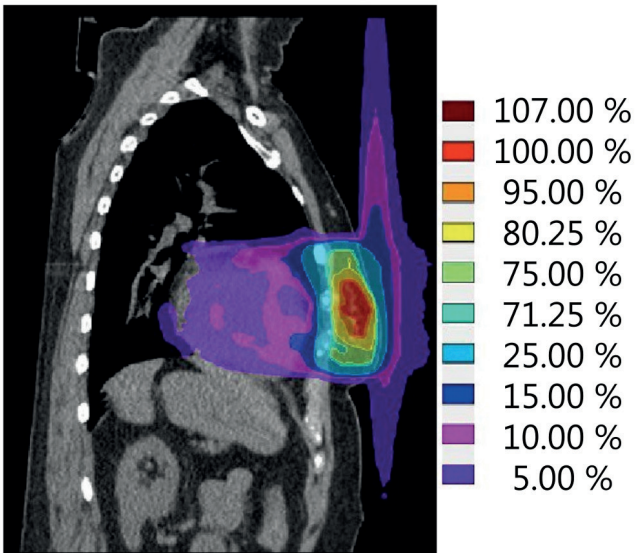

FIGURE 4. Simulation of a single fraction neoadjuvant PBI treatment plan (ABLATIVE trial approach, 1x20 Gy to GTV) for the 1.5 T MR-linac. The calculated dose distribution shows the electron stream effect in air resulting in dose outside of the treatment field in both cranial and caudal directions. Scale is set to 100% reference dose = 20 Gy.

Impact of geometric distortions

Since the breast is located peripherally in the body and geometric distortions increase with distance from the isocentre and susceptibility effects arise near tissue-air interfaces (as described in section 2), the effects of these distortions on dosimetry for breast RT may be significant [27,30]. The system-specific distortions together with patient-related distortions, may result in unacceptable dosimetric variations, as has already been shown for WBI [29]. This issue still requires investigation in the context of PBI, such as investigation of the impact of distortion at the edges of the breasts which would lead to inaccurate assignment of air versus tissue electron density and therefore inaccurate

dose calculations when these are based on the MRI. Geometric distortions inside the target region should be carefully considered in choosing adequate planning target volume (PTV) margins in the context of breast RT on an hybrid machine [33].

Planning restrictions

Technical specifications such as the magnetic field strength, beam energy, source-to-axis distance, and maximum field size are system-specific and are accounted for in the treatment planning systems [13–15]. However, there are some specific issues to highlight that will be different from treatment planning for breast irradiation on a conventional linac. Firstly, for the ViewRay MR-linac system angles between 30° and 33° are not available, while for the Elekta system 8° to 18° degrees need to be avoided due to the cryostat-pipe [15,67]. Furthermore, some beam angles commonly used for breast radiotherapy on conventional systems should preferably not be used on the Elekta system, i.e. angles around 130°-150° and 210°-230°, with exact angles depending on the tumour location [66,67]. This is because of high density material in the treatment couch edges that may cause unwanted dose effects during daily plan adaptation. Because of the design of the hybrid machines, rotations of the table with respect to the gantry angle and, therefore, irradiation with non-coplanar beams are not possible. No problems are expected because of this since good plan quality for PBI can be achieved with coplanar IMRT [26,63,68].

With respect to the methods currently used for dose calculation, co-registration of the planning CT to the pre-treatment and/or online MR images or bulk density assignment are currently used for electron density information for both the ViewRay and Elekta hybrid machines [15,67,69]. Strategies for creating a synthetic CT directly from an MRI scan, such as atlas-based, voxel-intensity based or deep learning approaches, are in development [70,71]. However, data on the use of synthetic CT for the breast or thoracic region are limited. Recent data have shown encouraging results for synthetic CT generation for the thoracic region based on (a combination of) voxel-intensity and atlas-based approaches, with a mean absolute error <50 HU in the body, and dosimetric differences ≤1.7% inside lung tumour PTVs [72,73]. Inclusion of bone density information, specifically the spine in this study on lung tumour treatment plans, proved to be important to reduce local hot spots in the differences between the simulated dose distributions on CT and synthetic CT [73]. Ahunbay et al. proposed to continue using a planning CT scan for each patient [74]. Their approach with inclusion of bone density and the use of deformably registered lung density, both of which may be necessary for breast RT treatment planning as well, may enable accurate full online re-planning on the daily anatomy. In an online workflow, options may be limited by the specific system, but aforementioned issues should be taken into account as well as speed of synthetic CT generation.

TREATMENT ON A HYBRID MACHINE

For MR-guided radiotherapy on a conventional linac, the treatment and position verification can be performed according to the current standard radiotherapy workflow. Using a hybrid machine with daily online MRI both before and during treatment, new opportunities become available for daily set-up and positioning accuracy, online adaptive RT based on daily anatomy, and intra-fraction motion management.

Daily set-up and positioning accuracy

Experiences from hospitals that have treated breast cancer patients in the adjuvant setting with the 0.35 T ^{60}Co system have shown that initial patient set-up verification based on location of lumpectomy cavity, and online motion monitoring could be beneficial for PBI patients in terms of reducing the CTV to PTV margin and therefore irradiated volume and thereby the risk of late toxicity [26,43,69,75]. A >52% reduction in treatment volume was achieved by applying no PTV margin for the lumpectomy cavity with the help of online MRI for set-up [26,75]. Although a 0 mm PTV margin neglects correction of other uncertainties that would normally be incorporated in the CTV to PTV margin (e.g. mechanical equipment and dosimetric uncertainties) [76], this illustrates that online MRI for set-up may help to reduce the PTV margin compared to treatment on a conventional linac. With the aid of an online motion monitoring approach, a mean difference of less than 1% between planned and delivered dose to 95% of the target volume was achieved [26]. For treatment in the neoadjuvant setting, patient set-up and positioning accuracy on a hybrid machine are still to be evaluated.

Online adaptive radiotherapy

On hybrid machines, a new treatment plan can be made during each fraction based on online MR imaging. Depending on the specific system, different strategies are available. These range from dose recalculation on the new patient anatomy to full online re-contouring and re-planning [15,77,78]. Requirements for online re-planning are somewhat different than for pre-treatment planning. In particular, the time available for target and OAR re-delineation and plan optimization is much reduced since the patient is on the treatment table. The choice of plan adaptation strategy will therefore depend on a trade-off between plan quality and speed of plan adaptation. In general, it is expected that a full reoptimization plan adaptation method will lead to improved dosimetry in most patients, especially in the case of deformations in the tumour or organs at risk, but will take more time [78,79]. In the group reporting on adjuvant PBI on a ^{60}Co system, where online MRI proved beneficial for set-up and PTV margin reduction, no online plan adaptation was performed and yet retrospective comparison of planned versus delivered dose

showed adequate coverage, suggesting that, in the context of PBI, use of a simpler plan adaptation strategy may be reasonable [26,43]. Currently, injection of contrast agent is not performed during treatment on a hybrid machine, although it could help to re-contour the tumour volume in case of neoadjuvant PBI. However, gadolinium chelates, the most commonly used contrast agent for breast cancer, could have a radiosensitizing effect [80]. Due to the uncertainty of the effect and safety of irradiation when a contrast agent has been injected and concern about stability and toxicity of irradiated gadolinium, it is not recommended to use contrast enhanced sequences for imaging during treatment.

Intra-fraction motion management

Generally three types of intra-fraction motion can be distinguished: 1) regular breathing motion, 2) irregular transient motion, and 3) non-transient bulk motion. Breast intra-fraction motion evaluated on 2D and 3D MR images (2-20 minutes duration) has been reported to be generally regular and limited to <3 mm [26,81]. Larger displacements have been observed, but these were mostly transient. Acharya et al. calculated that a mean PTV margin of 0.7 mm would be sufficient to cover 90% of the lumpectomy cavity for 90% of the treatment time for a mean fraction duration of 12.7 minutes. However, intra-fraction displacement seemed to differ substantially between patients, reaching a mean displacement range of 6 mm in AP direction for one patient [26]. One possibility to handle intra-fraction displacement might be to individualize the PTV margin based on cine MR data from simulation. Larger whole-body shifts of up to 14 mm over a 21 minute duration have been observed infrequently, although for the majority of patients motion evaluated up to 20 minutes was generally regular and small [81]. The impact of intra-fraction motion on current standard hypofractionated treatment is therefore likely to be limited. However, for extremely hypofractionated treatment schedules (1-2 fractions) delivered on hybrid machines, treatment times will increase significantly due to the online delineation and planning procedure and due to increased beam on time because of a lower dose rate of the hybrid machines and use of IMRT compared to volumetric modulated arc therapy [68,82,83]. This will increase the risk of systematic non-transient patient displacement both before and during treatment and may also negatively affect patient comfort. Although not yet available, real time plan adaptation during RT delivery will be the ultimate goal to account for intrafraction motion management [84]. Henke et al. noted that online motion tracking and gating on the lumpectomy cavity was beneficial for accelerated PBI treatment with regard to reduction of PTV margin [26,43]. A disadvantage of gating is that, although it is a solution for intrafraction motion management, it will even further increase the treatment time. Solutions for online monitoring and management of intra-fraction motion such as cine MRI-based gated irradiation are not yet implemented for the 1.5 T Elekta MR-linac.

First clinical experiences

Several publications have reported on neoadjuvant MR-guided PBI on a conventional linac including favourable toxicity profiles [35,37,85]. However, no patients have yet been treated with neoadjuvant PBI on a hybrid machine. A planning study has shown that neoadjuvant PBI in a single fraction in prone or supine position on the 1.5 T Elekta MR-linac would be dosimetrically feasible with adequate target coverage and within predefined constraints for OAR [63].

Experiences with adjuvant PBI on a hybrid system have been published. For patients treated on the 0.35 T ^{60}Co Viewray system with single fraction adjuvant PBI, up to 12 months follow-up is available, and no local recurrences have been reported. The first clinical results showed good tolerability, low toxicity with a maximum of grade 2 toxicity, and good-to-excellent cosmetic outcome assessed by both patients and physician [86,87]. Usage of this system resulted in benefits for initial patient set-up on lumpectomy cavity and online motion monitoring by which the PTV margin was diminished to 0 mm, which led to a large reduction in treatment volume of 52% [26,43,69,75]. The first patient has also been successfully treated with adjuvant PBI in 15 fractions on a 1.5 T Elekta MR-linac, which led to only grade 1 toxicity of the breast with adequate protection of the chin to prevent unwanted irradiation due to the ESE [66].

Patients are currently being recruited for several studies on MR-guided PBI. On clinicaltrials.gov, two trials are registered aiming to treat patients in the adjuvant setting on a hybrid machine, looking primary at either reproducibility of treatment and cosmetic outcome [88,89]. Three other trials are being conducted to further explore the effect of neoadjuvant MR-guided partial breast irradiation on a conventional linac [90–92]. The primary outcomes of these trials are postoperative complication rate, reproducibility of treatment and pathologic response, respectively.

CONCLUSION

The addition of MR-guidance to the breast radiotherapy planning pathway facilitates target volume delineation in the neoadjuvant partial breast irradiation setting whilst treatment on a hybrid MR and linac or ^{60}Co machine could lead to reduced CTV to PTV margins in the neoadjuvant and adjuvant partial breast irradiation settings through clearer visualisation of the target volume during treatment. Although challenges for treatment of breast cancer patients on these systems remain (table 1), the first breast

cancer patients have been treated successfully with adjuvant PBI on a hybrid system, and studies of MR-guided neoadjuvant partial breast irradiation will open shortly, through which technical approaches and workflow are likely to be further refined.

TABLE 1. Overview of challenges for the implementation of MR-guided radiotherapy on a hybrid machine for breast cancer patients

Challenge	Effect	Potential solution
Simulation		
Patient positioning inside MR bore	Prone: breast deformation on table and fitting of receive coil (Figure 2)	Development of a thinner coil or a dedicated MR-linac breast coil
	Supine: difficulties fitting arms inside bore in standard RT position	Use a minimal or no inclined wedge support, move arms closer together above the head
Deformation of body contour by receiver coil	Disturbed body contour	Use coil bridges to support the coil (Figure 1)
Body contour visibility in prone position	With dedicated prone breast coil, body contour and OARs not visible further away from coil	Use an additional coil placed on top of the patient
Electron stream effect	Irradiation dose outside the treatment field in an inferior to superior direction (Figure 4)	Include chin, arm and abdominal region in the simulation plan
Breathing and cardiac motion during scanning	Motion artefacts	Use a 3D sequence, signal averaging, and left-right phase encoding in protocol design, or use triggering or breath-hold for acquisition
Contouring		
Surgical clip and/or marker visualization on MRI	Magnetic field distortion and artefacts impeding contouring of target volume (Figure 3)	1. Use or develop markers or clips with smaller artefacts 2. No marker insertion (only possible in the neoadjuvant setting if no further surgery is required)
Simulation and planning		
Geometric accuracy (gradient non-linearities) in combination with lateral target volumes	Reduced geometric accuracy, increasing with distance from isocentre	1. Use distortion correction software on scanner 2. Position target as close to scanner isocentre as possible (e.g. shift patient on the table) 3. Include remaining inaccuracy in PTV margin
Geometric accuracy (magnetic field inhomogeneities and patient-induced distortions)	Reduced geometric accuracy, especially near tissue-air interfaces	1. Use high bandwidth acquisition 2. Acquisition of B0 map to assess patient-induced distortion.

TABLE 1. Continued

Challenge	Effect	Potential solution
Planning		
Electron return effect	Possible skin dose, chest wall or lung dose increase (dose increase at tissue-air interfaces)	Pay attention to skin, chest wall and lung dose constraints in planning, carefully choose beam set-up (e.g. use enough beams)
Electron stream effect	Irradiation dose outside the treatment field in an inferior to superior direction (Figure 4)	Use of bolus material to shield irradiation outside of field
Missing electron density information in MR-only workflow	Inaccurate dose calculation without correct electron density assignments	Development of methods for synthetic CT generation from MRI
High density treatment couch material	Unpredictable dose effects by daily replanning	Avoid beam angles passing through the treatment couch edges
Treatment		
Irradiation through coil	No irradiation through MR receiver coils, only through dedicated hybrid machine coils. Dedicated prone breast coil cannot be used	1. Try to fit the dedicated MR-linac coil on top of prone patient (only for smaller patients) 2. Design a thinner, more flexible coil for the hybrid system 3. Design a new prone coil for the hybrid system
Fixed treatment couch	Interfractional changes in position cannot be corrected by moving the treatment couch	Use online plan adaptation strategies to account for interfractional changes in anatomy
Motion during treatment	Geographical miss during treatment or increased PTV margins	Use online gating or tracking when available, e.g. only beam-on when the target volume is within pre-specified boundaries

Abbreviations: MRI - Magnetic Resonance Imaging; MR - Magnetic Resonance; OAR - Organ At Risk; PTV - Planning Target Volume; CT - Computed Tomography; RT - Radiotherapy.

TABLE 2. Overview of recommended MR sequences and commercial online availability for clinical breast cancer treatment on hybrid machines

Type of MR sequence	Advantages (+) and disadvantages (-)	Availability on Unity (Elekta AB)	Availability on MRIdian® (ViewRay®)
Postoperative			
T1-weighted with fat suppression [9,20,34]	+ Differentiation between glandular breast tissue and seroma	Not available*	Not available
T1-weighted without fat suppression [9,20,34]	+ Best visualization of surgical clips	3D T1-weighted FFE	3D T2/T1-weighted TRUFI
T2-weighted with or without fat suppression [17,19,21,22,24]	+ Visualization of lumpectomy cavity and seroma + Differentiation between glandular breast tissue and seroma	3D T2-weighted TSE without fat suppression*	3D T2/T1-weighted TRUFI
DWI [35]	+ Differentiation between malignant and benign tissue in case of irradical resection - Susceptible to geometric distortions	Not available*	Not available*
Preoperative			
T1-weighted contrast-enhanced with fat suppression [35–38]	+ Visualization of tumour and tumour spiculae - Injection of and irradiation with contrast agent	No standard contrast injection available	No standard contrast injection available
T2-weighted with or without fat suppression [35]	+ Differentiation between tumour and post-biopsy changes	3D T2 TSE without fat suppression*	3D T2/T1-weighted TRUFI
DWI [35]	+ Differentiation between malignant and benign tissue - Susceptible to geometric distortions	Not available*	Not available*

Abbreviations (with generic sequence names in brackets): TSE - Turbo Spin Echo (fast spin echo); FFE – Fast Field Echo (spoiled gradient echo); TRUFI – True Fast Imaging with Steady State Precession (balanced steady state free precession)

**Not available in online treatment setting. Acquiring DWI and MR sequences with fat suppression is possible offline – outside online treatment setting mode.*

Note: this table does not provide an exhaustive overview of all imaging possibilities but only refers to MR sequences mentioned in this article and currently commercially available imaging options.

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3

CONSENSUS ON CONTOURING PRIMARY BREAST TUMORS ON MRI IN THE SETTING OF NEOADJUVANT PARTIAL BREAST IRRADIATION IN TRIALS

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ABSTRACT

Purpose: To present and evaluate expert-developed guidelines for contouring primary breast tumors on MRI in the setting of neoadjuvant partial breast irradiation.

Methods: Contouring guidelines for target definition of primary breast tumors on contrast-enhanced (CE) MRI have been developed by an international team of experienced breast radiation oncologists and a dedicated breast radiologist during three meetings. At the first meeting, draft guidelines were developed through discussing and contouring two cases. At the second meeting six breast radiation oncologists delineated gross tumor volume (GTV) in 10 early-stage breast cancer patients (cT1N0) according to guidelines. Isotropic expansion of GTV (20 mm) was used to generate clinical target volume (CTV), excluding skin and chest wall. Delineations were reviewed for disagreement and guidelines were clarified accordingly. At the third meeting five radiation oncologists re-delineated 6 cases, using final guidelines. Interobserver variation of GTV and CTV was assessed using the generalized conformity index (CI). CI was calculated as the sum of volumes each pair of observers agreed upon, divided by the sum of encompassing volumes for each pair of observers.

Results: For the two delineation sessions combined, mean GTV ranged between 0.19 and 2.44 cc, CI for GTV ranged between 0.28 and 0.77, and CI for CTV ranged between 0.77 and 0.94. The largest interobserver variation in GTV delineations was observed in cases with extended tumor spiculae, blood vessels near or markers within the tumor, or increased enhancement of glandular breast tissue. Final guidelines stated to delineate all visible tumor on CE-MRI scan 1 to 2 minutes following contrast injection and if a marker was inserted in the tumor this should be included.

Conclusion: Expert-consensus guidelines for contouring primary breast tumors on MRI have been developed. Final guidelines resulted in low interobserver variation for CTV in the context of a uniform 20 mm GTV to CTV expansion margin.

INTRODUCTION

Breast conserving therapy for early stage breast cancer patients consists of breast conserving surgery (BCS) and adjuvant whole breast irradiation (WBI) [1]. Recently, adjuvant partial breast irradiation (PBI) has been introduced for breast cancer patients at low risk of local recurrence [2–5]. The focus of current clinical trials in external beam adjuvant PBI for low-risk breast cancer patients has shifted towards delivering PBI in the neoadjuvant setting (NA-PBI) [6–12]. Through neoadjuvant irradiation of the *in situ* tumor, as opposed to the usually much larger tumor bed, together with a small volume of breast tissue around the tumor, the aim is to further reduce treatment-induced toxicity of PBI without increasing the risk of local recurrence. For adjuvant PBI the tumor bed needs to be delineated, based on reconstruction of the original tumor location using diagnostic imaging, tumor bed clips and surgery-associated architectural distortion [2,13]. This may or may not accurately represent the position of the original tumor and has been associated with high interobserver variation in contouring of the target volume [13–15]. In the context of NA-PBI, the tumor is still *in situ*, such that target delineation would be expected to be more accurate than in the postoperative setting and with less interobserver variation [16,17]. In addition, tumor visibility on MRI is improved when compared to standard radiotherapy planning CT [16]. As a result, using MRI for target contouring can result in smaller target volumes, less interobserver variation, and therefore smaller irradiated volumes thereby further contributing to reduce treatment-induced toxicity and improve cosmesis [6,9,11,18].

To underpin research on MR-guided NA-PBI, written guidelines on tumor contouring are required to minimize the interobserver variation in target volume definition, and to be able to compare outcomes between clinical trials. This manuscript describes the expert consensus development and evaluation of contouring guidelines for primary breast tumors on MRI in the context of MR-guided NA-PBI.

MATERIALS AND METHODS

Case selection and imaging

A non-random sample of 10 early-stage breast cancer cases was selected from the ABLATIVE study population (ClinicalTrials.gov identifier: NCT02316561). This trial was approved by the institutional review board of the University Medical Center Utrecht, the Netherlands. All patients had given written informed consent for use of their data [9]. Cases were selected to represent the population variation in tumor size and location, as well as reflecting variations in tumor shape, diagnostic marker placement, and degree

of enhancement of glandular breast tissue. Before participation in the trial in all patients standard diagnostic imaging (i.e. mammography and ultrasound) was performed. Following participation all patients underwent a diagnostic contrast-enhanced MRI in prone position to assess tumor size and unifocality (voxel size of 0.89 x 0.89 x 0.90 mm).

For radiotherapy planning all patients underwent MR-imaging in supine treatment position with both arms raised above the head. Patients were positioned on a ThoraxSupport™ (MacroMedics, Waddinxveen, the Netherlands) with an incline of 5 degrees. Images were obtained on a 1.5T wide bore MRI scanner (Ingenia, Philips Medical Systems, Best, the Netherlands) using an anterior receive coil, which was placed on a support to prevent deformation of the breast. MRI scanning consisted of contrast-enhanced (CE) series. This consisted of 1 pre- and 5 post-contrast T1-weighted 3D fast field echo scans with fat suppression using the Dixon technique (voxel size of 1.15 x 1.15 x 1.25 mm). The 5 post-contrast scans were acquired with an interval of 60 seconds following an intravenous contrast injection containing gadobutrol (Gadovist 0.1ml/kg, 1ml/s, Bayer, Leverkusen, Germany).

Guideline development

MRI-based guidelines for contouring primary breast tumors were developed by an international team of experienced breast radiation oncologists and a dedicated breast radiologist (specialized in MRI) during three meetings. At the first meeting two cases were delineated by four breast radiation oncologists, differences in delineations between observers were discussed and the first written guidelines were drafted. Thereafter, two delineation meetings were held to evaluate and optimize these guidelines. At the second meeting, six breast radiation oncologists delineated gross tumor volume (GTV) of ten cases and interobserver variation in delineation was assessed. Interobserver variation and the causes thereof were discussed subsequently via an online meeting and by reviewing delineations with a dedicated breast radiologist, and the guidelines were clarified accordingly. At the third meeting, held six months after the second meeting, five breast radiation oncologists re-delineated a subset of six cases (five with the highest levels of interobserver variation and one with the lowest interobserver variation at the second meeting) using the final guidelines and the interobserver variation in tumor delineation was assessed. Three radiation oncologists were common to both delineation meetings. Both delineation meetings started with an educational session on the current guidelines.

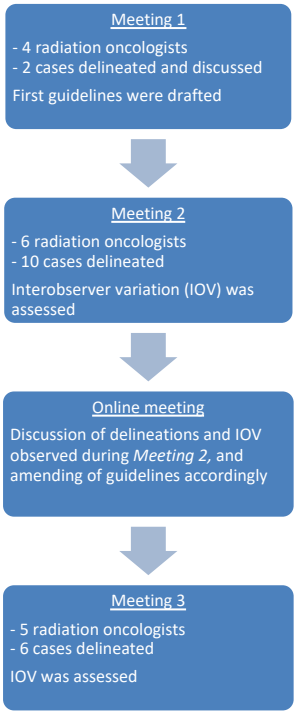

FIGURE 1. Overview of the in-person and online meetings, three radiation oncologists were present at all meetings.

Target volume delineation

For target volume delineation, the radiotherapy planning CE-MRI scans in supine position, the diagnostic MRI scan in prone position, which also included CE-MRI, and diagnostic mammogram were presented to the observers. All observers delineated the gross tumor volume (GTV) according to the written contouring guidelines. The clinical target volume (CTV) was created by adding a uniform margin of 20 mm to the GTV, excluding the skin and chest wall and, by definition, not exceeding ipsilateral breast tissue. The skin, chest wall, and ipsilateral breast were delineated by one observer per case during the second meeting. Delineation was performed in Monaco 5.11 (Elekta AB, Stockholm, Sweden).

Data analysis

Tumor size was assessed by a dedicated breast radiologist on the diagnostic MRI in prone position. Breast volume was defined as the volume of the delineated ipsilateral breast on MRI. All delineations were visually inspected for discrepancies. Interobserver variation in GTVs and CTVs was evaluated separately for the two delineation sessions, using the mean delineated volume, generalized conformity index (CI), and mean difference in center of mass (dCOM) (Figure 2). Volume was measured in cubic centimeter (cc), dCOM in millimeter (mm), and CI was calculated as the sum of the volumes each pair of observers agreed upon, divided by the sum of the encompassing volumes for each pair of observers using the following equation: [19].

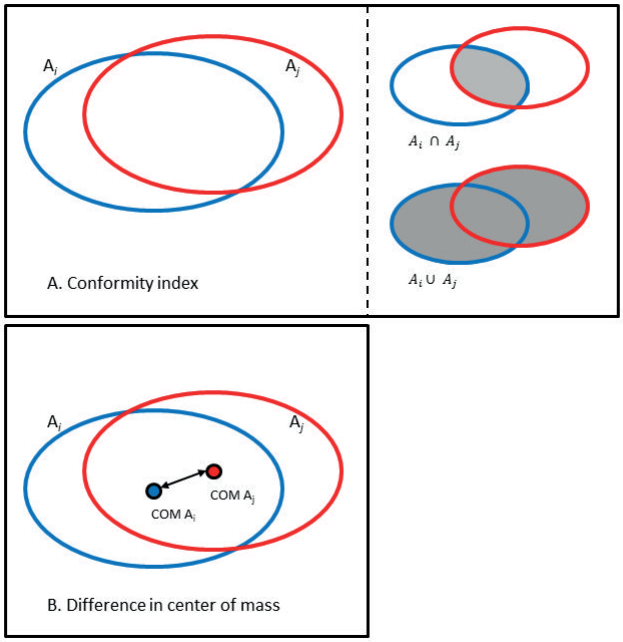

FIGURE 2. A_i is the delineation by observer i, A_j is the delineation by observer j. A: Conformity index (sum of the volumes each pair of observers agreed upon, divided by the sum of the encompassing volumes for each pair of observers:); B: Difference in center of mass (dCOM).

RESULTS

During the first meeting GTVs of two cases were delineated on the DCE-MRI in supine position, with access to the diagnostic MRI in prone position. For maximum contrast uptake in the tumor, the MRI approximately 4 minutes after contrast injection was used for GTV delineation. GTV delineation incorporated all visible enhanced tumor, including extensive tumor spiculae that could be best assessed on the diagnostic MRI in prone position. Consequently, the diagnostic MRI was used to assess tumor position and the extensiveness of tumor spiculae. In cases with a biopsy marker in or adjacent to the tumor, the marker was included in the delineation, in order to take into account possible tumor cells close to the marker that could not be adequately visualized due to imaging artifacts caused by the marker.

Evaluation of the ten cases delineated during the second meeting showed that one structure other than the tumor was delineated by one observer (case 10) and this delineation was therefore removed from the analysis. The cases had a median tumor diameter of 15 mm (range 5-20) and median breast volume of 836 cc (range 199-1487) (Table 1). The mean volumes of the delineated GTVs ranged between 0.19 and 2.44 cc, the CI ranged between 0.28 and 0.77, and the mean dCOM ranged between 0.5 and 4.2 mm (Table 2A). For the CTVs, which were restricted by the same contours of the breast, skin, and chest wall for all observers, the mean volumes ranged between 29 and 88 cc, the CI ranged between 0.77 and 0.94, and the mean dCOM ranged between 0.4 and 3.7 mm. When visually assessing the delineations, the largest variations were observed in tumors with an adjacent blood vessel (e.g. case 3, Figure 3A), with increased background enhancement (e.g. case 4, Figure 3B), with extended tumor spiculae (e.g. case 6, Figure 3C) or with a marker adjacent to the tumor (e.g. case 10, Figure 3D).

During reviewing of the interobserver variation via the online meeting the optimal MRI for delineation was discussed since in several cases it was difficult to differentiate between tumor and glandular breast tissue at 4 minutes after contrast injection. Furthermore, it was noticed that not all observers included the biopsy marker in the GTV delineation. When reviewing the cases with a dedicated breast radiologist, it was recommended to use the scan approximately 1 to 2 minutes after contrast injection, since this will facilitate differentiation between tumor and glandular breast enhancement. Tumors show increased contrast uptake immediately following contrast injection, while the glandular breast tissue does not yet have increased uptake. Additionally, the final guidelines reinforced to include the entire marker in the GTV delineation and to use coronal images to determine cranial and caudal edges of the tumor.

TABLE 1. Patient and tumor characteristics

Case	Age (years)	Breast size (cc)	Tumor diameter (mm)	Tumor location	Side
1*	65	1,441	19	Medio-cranial	Left
2	64	973	5	Medio-cranial	Left
3*	51	199	20	Medio-cranial	Right
4*	68	363	14	Medio-cranial	Right
5*	66	431	14	Latero-cranial	Left
6	62	605	15	Central	Left
7	55	991	15	Latero-cranial	Right
8	64	1,144	10	Latero-caudal	Right
9*	69	1,487	20	Latero-cranial	Right
10*	73	699	15	Medio-cranial	Left

**: Case 1, 3, 4, 5, 9, and 10 were delineated during both delineation sessions.*

TABLE 2A. Interobserver variation in contouring by 6 breast radiation oncologists of the 10 cases during the second session (cases listed by volume).

	GTV			CTV		
Case	Mean volume (cc)	CI	Mean dCOM (mm)	Mean volume (cc)	CI	Mean dCOM (mm)
2	0.19	0.48	1.0	37	0.89	1.2
4	0.62	0.42	1.0	34	0.87	3.2
8	0.64	0.64	0.7	55	0.92	0.6
6	0.93	0.66	0.9	48	0.93	0.8
3	1.03	0.57	2.4	29	0.82	3.2
5	1.36	0.64	0.8	67	0.91	0.8
10§	1.46	0.28	4.2	55	0.77	3.7
1	2.20	0.77	0.5	60	0.94	0.4
7	2.22	0.67	0.8	88	0.88	1.0
9	2.44	0.65	0.9	85	0.90	0.9

§: Based on 5 observers.

TABLE 2B. Interobserver variation in contouring by 5 breast radiation oncologists of the 6 cases during the third session.

	GTV			CTV		
Case	Mean volume (cc)	CI	Mean dCOM (mm)	Mean volume (cc)	CI	Mean dCOM (mm)
4	0.62	0.43	1.5	34	0.83	1.5
3	0.47	0.54	1.0	23	0.88	1.4
5	1.29	0.68	0.6	66	0.93	0.6
10	2.02	0.34	4.2	60	0.78	3.3
1	2.22	0.77	0.3	59	0.94	0.4
9	2.41	0.69	1.0	84	0.90	1.2

Final guidelines stated that all tumors should be visualized on contrast enhanced fat suppressed MR images at 1 to 2 minutes following contrast injection. All enhancing tumor tissue, as well as markers within or adjacent to the tumor should be included in the delineation. If distinction between tumor and glandular breast tissue is challenging, one can toggle between different contrast images or use a maximum intensity projection. To determine the cranial and caudal border of the tumor, it is advised to use the coronal images. At least a T1 fat suppressed gadolinium contrast enhanced series is required to be able to adhere to the guidelines. This includes one pre-contrast, and multiple post-contrast images ranging 1 minute up to 5 minutes following contrast injection. The final guidelines are presented in Table 3.

The six cases re-delineated according to the final guidelines during the third meeting had a median tumor diameter of 17 mm (range 14-20) and median breast volume of 565 cc (range 199-1487) (Table 1). The mean volumes of the delineated GTVs ranged between 0.47 and 2.41 cc, the CI ranged between 0.34 and 0.77, and the mean dCOM ranged between 0.3 and 4.2 mm (Table 2B). For the CTVs, which again were restricted by the same contours of the breast, skin, and chest wall for all observers, the mean volumes ranged between 23 and 84 cc, the CI ranged between 0.78 and 0.94, and the mean dCOM ranged between 0.4 and 3.3 mm. Interobserver variation seemed to be consistent during the two delineation sessions (Figure 4).

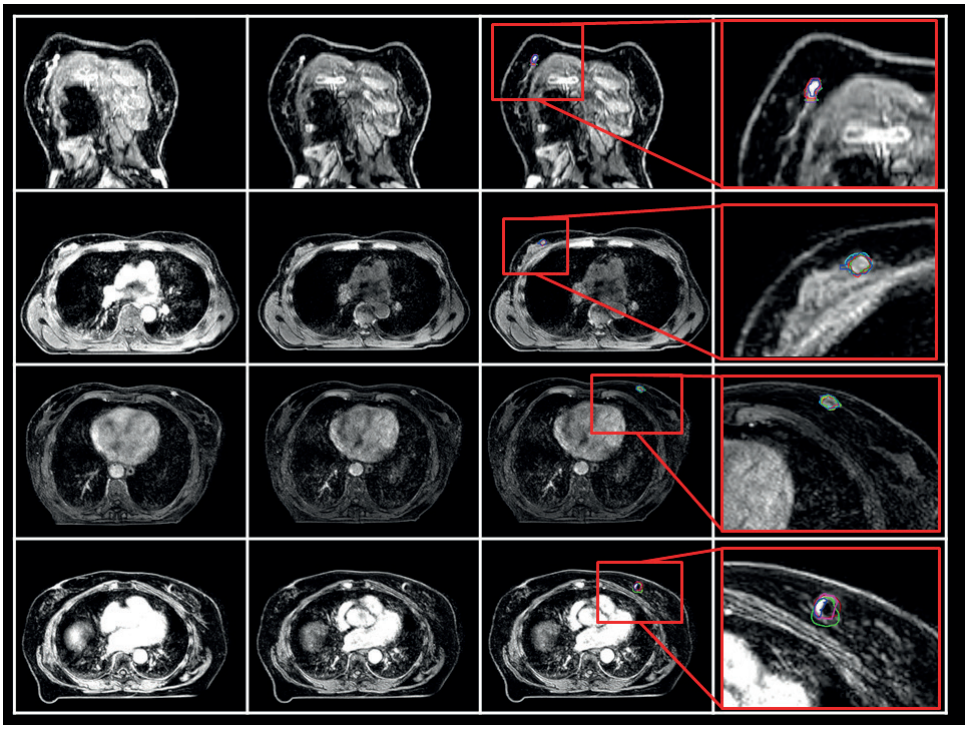

FIGURE 3. Example of four cases (A-D) in whom large interobserver variation was observed. In the first column MR images at approximately 5 minutes following contrast injection are shown without delineations, in the second column MR images at approximately 1 minute following contrast injection are shown without delineations, in the third column the same MR images at approximately 1 minute following contrast injection are shown with delineations by the different observers, in the fourth column these MR images and delineations are enlarged. A: Adjacent vessel (case 3, coronal plane); B: Background enhancement (case 4, transversal plane); C: Extended tumor spiculae (case 6); D: Biopsy marker close to tumor (case 10).

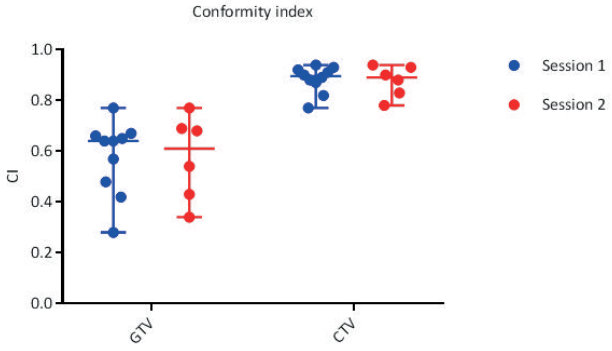

FIGURE 4. Conformity indices from delineations during the two sessions, including median and range.

DISCUSSION

This manuscript describes the development and evaluation of guidelines for contouring primary breast tumors on MRI. The delineated tumors were small with a maximum mean delineated volume of 2.4 cc, reflecting the case selection from a patient population treated in a NA-PBI study. The CI of the GTVs ranged from 0.34 to 0.77 using the final guidelines, and after expanding the GTV to CTV by adding a uniform margin of 20 mm (adapted to skin, ipsilateral breast, and chest wall), the CI increased to a range of 0.78 to 0.94 (Figure 4). These CI compare favorably to the existing literature on tumor bed delineation in the standard adjuvant setting [13–15].

For standard postoperative contouring of the tumor bed in breast radiotherapy, a postoperative radiotherapy planning CT is used. In a systematic review on interobserver variation in postoperative tumor bed delineation by Yang et al., high interobserver variation was reported with CIs ranging from 0.10 up to 0.61 [14]. In addition, Boersma et al. reported a mean CI of 0.36 (SD 0.21) for tumor bed delineation on CT using guidelines for external beam radiotherapy boost on the tumor bed [15]. Aiming to decrease interobserver variation, observers were provided with an additional preoperative planning CT, but the mean CI remained 0.36 (SD 0.19). One of the challenges in using additional preoperative imaging for postoperative treatment, lies in the process of matching preoperative to postoperative imaging where significant anatomical changes have occurred due to surgery. This may explain the lack of improvement in CI with provision of preoperative imaging.

Since all mean tumor volumes were below 2.5cc in our study, small variations in delineation resulted in a low CI of the GTV, due to the correlation between tumor volume and CI. Small variations in delineation of a small tumor lead to a low CI, since the volume observers agree upon will rapidly diminish, opposed to a large tumor, in which small variations in delineation only have a marginal effect on the volume observers agree upon, while the total encompassing volume remains the same. Despite the small GTVs, the CIs of GTV within our study for the preoperative contouring of primary breast tumors are well above the reported mean CI for postoperative tumor bed delineation, which is currently standard clinical practice [13–15,20,21]. Likewise, approximately half of the CIs of GTV within our study were above the upper limit of 0.61 reported by Yang et al. [14].

In this study on the contouring of primary tumors on MRI, the actual observed value of CI of the GTV seemed to be mostly affected by the presence of markers (leading to a void on MRI), adjacent blood vessels, and degree of enhancement of the glandular breast tissue. Further improvement of target volume delineation could be achieved through

improved imaging of markers on MRI or development of new markers (resulting in smaller artifacts on MRI), or by omitting the insertion of markers. Currently, omission of marker insertions is not feasible, since NA-PBI will be followed by surgery and a marker is necessary for adequate (irradiated) tumor resection.

The CIs of the CTV, created by expanding the GTV by 20 mm, were, as expected, higher than the CIs of the delineated GTV, due to the uniform expansion. The margin to create the CTV is added to take into account microscopic tissue within 2 cm of the tumor and can also handle small inaccuracies in tumor delineation. Additionally, the boundaries of CTV largely consist of anatomical borders, such as the ipsilateral breast, chest wall, and skin, which were delineated only once by one single observer per patient and might therefore affect CI. However, little interobserver variation in delineation of the chest wall and skin is expected, since the chest wall is clearly visualized on MRI and the skin is deducted from the external body contour. Furthermore, delineation of the breasts is expected to be automated through an atlas or deep learning in the near future, aiming to reduce the interobserver variation in delineation and minimize the effect on CI of the CTV [22,23]. For improvement of target delineation of primary breast tumors, auto contouring could also be further studied. However, it is reported that this could be unreliable due to various tumor locations and tumor boundaries, including the tumor markers, and variations in enhancement of the ipsilateral glandular breast tissue [24].

Since breast tumors are better visualized on MRI compared to CT, the current guidelines are only applicable to delineation on MRI. With the clinical introduction of the MR-linac (a linear accelerator with integrated MR scanner), we expect the demand for guidelines using only MR images for delineation to rise [25]. For institutions without access to an MR-linac these guidelines can be used for delineation of the target, while treatment is being performed on a conventional linac. Currently a standard radiotherapy planning CT should always be performed for breast cancer patients who will be treated on an MR-linac to derive the Hounsfield Units necessary for treatment planning. In the future, MR-only treatment planning will become widely available once a robust method for the development of a synthetic CT from an MRI has been introduced [26].

In the case where a structure other than the tumor was delineated by one observer, this would not be covered by any PTV margin. This problem can be overcome by a second reading of the delineated target volume by a breast radiologist. Patients in whom the tumor cannot be visualized on CE-MRI due to marker artefacts are not eligible for NA-PBI and should be treated according to local standard of care.

Several limitations are applicable to this study. Firstly, a small and homogeneous sample of cases regarding tumor size and receptor status was used for the development and evaluation of guidelines. We have deliberately chosen this sample of low-risk patients since this represents the population that is currently eligible for PBI [27]. Secondly, we cannot evaluate the differences between the two delineation meetings, since not all observers were present at both meetings and a subset of cases was delineated at the last meeting. Nonetheless, since these cases showed, within the possibilities, a range of variations in tumor shape and enhancement of glandular breast tissue, and all radiation oncologists were all involved in the process of evaluation and adaptation of these guidelines, we may conclude that these guidelines resulted in acceptable interobserver variation. When compared to current clinical guidelines for postoperative delineation of the tumor bed on the radiotherapy planning CT, the interobserver variation we observed was equal or even lower [13–15]. Broader implementation of these guidelines should be accompanied by teaching sessions among breast radiation oncologists and radiologists. Thirdly, implementation of the guidelines can be complicated by the fact that not all radiation facilities have access to an MRI-scanner [28]. However, in patients who have undergone a diagnostic MRI in prone position but an additional MRI in supine position is not available, these guidelines could be used by institutions who treat patients in prone position as well. For optimal treatment of low-risk breast cancer patients with NA-PBI, we believe delineation of the target volume should be done using MRI, keeping in mind possible future treatment on the MR-linac.

CONCLUSION

Guidelines for contouring primary breast tumors on MRI have been developed by an international team of experienced breast radiation oncologists and a dedicated breast radiologist. The final guidelines resulted in low interobserver variation for CTV in the context of a uniform 20 mm expansion margin of GTV to CTV, supporting the use of these contouring guidelines in future clinical trials of MR-guided NA-PBI.

TABLE 3. Final contouring guidelines for primary breast tumors on MRI for NA-PBI.

GTV
• Prior to delineation the diagnostic prone MR images and mammograms should be referred to in order to define position of the primary tumor, expected tumor volume, and extent of spiculae. NB Spiculae can be distinguished from vessels by the fact that they do not extend all the way back to chest wall. This is easier to appreciate on the prone diagnostic images.
• Delineation of the tumor should be made on the dynamic T1 gadolinium-enhanced sequence (=master), approximately 1 to 2 minutes after contrast injection.
• Due to gadolinium administration the tumor is visible on the dynamic T1 gadolinium sequence as a hyper intense structure.
• Delineate the tumor including any bright spiculated growth (also hyper intense on T1 gadolinium-enhanced sequence) but do not delineate associated less intense (greyer) areas.
• Where contrast enhancement is maximal, include it in GTV, but where contrast enhancement is less intense, toggle between the 0, 1, 2, and 4 minutes post-contrast sequences to determine whether or not contrast-enhancement is in tumor or vessels/glandular breast tissue. Enhancement in vessels usually peaks at 2 minutes post-contrast injection. Enhancement in tumor usually peaks early (1 minute post-contrast administration) and then gradually decreases. Enhancement in glandular tissue usually peaks more slowly than tumor and washes out more slowly. Alternatively, a MIP (maximum intensity projection) can be used.
• If a marker has been placed within or adjacent to the tumor, the artifact created by that marker needs to be delineated in its entirety.
• As a final cross-check, use the coronal view to determine if the edges of the GTV are correct (i.e. to aid discrimination from vessels and glandular breast tissue).
• Potential artifacts: Inadequate fat suppression at peripheries can cause artifacts (such as high signal intensity at peripheries of breast). This is more likely to occur with larger breasts or where breasts are close to the edge of the bore.
CTV
• To be created by adding a uniform margin of 20 mm to GTV.
• Excludes chest wall and skin (edited to 5 mm below the body contour).
• By definition does not exceed the ipsilateral breast tissue.

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4

TUMOR RESPONSE FOLLOWING NEOADJUVANT MR-GUIDED SINGLE ABLATIVE DOSE PARTIAL BREAST IRRADIATION

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ABSTRACT

Purpose: To assess the pathologic and radiologic response in low-risk breast cancer patients, treated with MR-guided neoadjuvant partial breast irradiation (NA-PBI), and to evaluate toxicity and patient reported outcomes (PROs).

Patients and methods: For this single-arm prospective trial, women with unifocal, non-lobular tumors, with a maximum diameter of 20 mm (50-70 years) or 30 mm (≥70 years), and tumor-negative sentinel node(s) were eligible. Patients were treated with single ablative dose NA-PBI followed by breast conserving surgery after an interval of six to eight months. Target volumes were defined on radiotherapy planning CT-scan and additional MRI. Prescribed doses to gross tumor volume (GTV) and clinical target volume (GTV plus 20 mm margin) were 20 Gy and 15 Gy, respectively. Primary outcome was pathologic complete response (pCR). Secondary outcomes were radiologic response (on MRI), toxicity (CTCAE), PROs (EORTC QLQ-BR23 and Hospital Anxiety and Depression Scale), and cosmesis (assessed by patient, radiation oncologist and BCCT.core software).

Results: 36 patients were treated with NA-PBI, pCR was reported in 15 patients (42%; 95%-CI, 26%-59%). Radiologic complete response was observed in 15 patients, 10 of whom had pCR (positive predictive value 67%; 95%-CI, 39%-87%). After a median follow-up of 21 months (range 12-41), all patients experienced grade 1 fibrosis in treated breast volume. Transient grade 2 and 3 toxicity was observed in 31% and 3% of patients, respectively. Local recurrences were absent. No deterioration in PROs or cosmetic results was observed.

Conclusions: NA-PBI has the potential to induce pCR in a substantial proportion of patients with acceptable toxicity. This treatment seems a feasible alternative to standard postoperative irradiation, and could even result in postponement or omission of surgery, if pCR can be accurately predicted in selected low-risk patients.

INTRODUCTION

The incidence of low-risk breast cancer has increased due to the introduction of breast cancer screening programs and improved imaging [1–3]. Furthermore, breast cancer survival has improved with close to 80% of women surviving at least 10 years following primary diagnosis [4,5]. This results in a growing number of women with late treatment-induced toxicity [6,7]. Consequently, the focus of breast cancer treatment and research is shifting towards reducing toxicity and improving quality of life, while maintaining optimal oncological outcomes.

Recently, postoperative partial breast irradiation (PBI) following breast-conserving surgery (BCS) has been introduced as standard treatment option in early-stage breast cancer patients with low-risk on local recurrence [8–11]. In PBI only the tumor bed is irradiated resulting in smaller irradiated volumes compared to whole breast irradiation. Consequently, late adverse effects, including breast fibrosis, can be reduced resulting in improved cosmetic results [12–15].

MR-guided neoadjuvant PBI (NA-PBI) may be an alternative for postoperative PBI [16–19]. Since the tumor is still *in situ* and the irradiated volume is smaller compared to postoperative PBI, radiotherapy can be delivered in one single ablative dose instead of multiple fractions radiotherapy (i.e. 15-25 fractions) [18]. This can reduce the treatment burden and can radiotherapy-induced toxicity, which could improve quality of life. MR-guided NA-PBI could lead to tumor regression, which can be assessed using pathology and imaging, potentially resulting in a smaller surgical intervention or even omission of surgery [20,21].

In this feasibility study, we report pathologic response after MR-guided single ablative dose NA-PBI in low-risk breast cancer patients. In addition, we report the radiologic response, toxicity, and patient reported outcomes (PROs) of this treatment approach.

METHODS AND MATERIALS

In this single arm prospective multicenter study patients underwent MR-guided single ablative dose NA-PBI followed by BCS after an interval of 6 or 8 months [22]. The primary endpoint was the proportion of patients with pathologic complete response (pCR).

Patient recruitment

The Institutional Review Board of the University Medical Center (UMC) Utrecht, the Netherlands, approved this study and all patients gave written informed consent (ClinicalTrials.gov identifier: NCT02316561). Patients were recruited in the UMC Utrecht and three regional hospitals. Patients eligible for enrolment were women with low-risk invasive breast cancer eligible for postoperative PBI according to international guidelines, i.e. primary non-lobular, unifocal breast cancer, without clinical evidence of lymphatic and distant spread of disease, and without indication for (neo)adjuvant chemotherapy [23,24]. Patients in the *suitable* group according to the ESTRO criteria were included, yet patients with lymphovascular invasion were excluded. (Neo)adjuvant endocrine treatment was allowed according to national guidelines [25]. Other inclusion criteria were age ≥50 years, maximum tumor diameter of 20 mm on MRI (maximum tumor diameter of 30 mm if age ≥70 years), ER-positive, and Her2 neu-negative tumor [22]. Patients were excluded if they had a BRCA1/2 or CHEK2 gene mutation, a collagen synthesis disease, or signs of extensive ductal carcinoma in situ as assessed on mammography and MRI. Within 1 week following enrolment, tumor diameter and unifocality were confirmed by 3T MRI exam in prone position (3.0T Ingenia wide bore, Philips Medical Systems, Best, the Netherlands) at UMC Utrecht. The MRI protocol included T1- and T2-weighted imaging, dynamic contrast enhanced (DCE) imaging, and diffusion weighted (DW) imaging [26]. Within 1 month following enrolment patients underwent a sentinel node biopsy to confirm node negative disease.

Radiation therapy treatment

All patients were treated with single-dose NA-PBI at UMC Utrecht. For radiotherapy (RT) target volume delineation and treatment planning, a contrast-enhanced CT (Brilliance Big bore CT, Philips Medical Systems, Best, The Netherlands) and, in addition to standard practice, a contrast-enhanced MRI exam (Ingenia 1.5T, Philips Medical Systems, Best, The Netherlands) were obtained in supine position on the ThoraxSupport™ (MacroMedics, Waddinxveen, the Netherlands) with the arms raised above the head. A gold fiducial marker (Visicoil™, IBA Dosimetry, Schwarzenbruck, Germany) was inserted in the tumor for tumor visualization on the cone beam CT-scan on the linear accelerator, before acquisition of the planning CT. CT and MR images were imported into an in-house developed software tool (Volumetool®) for manual rigid registration and delineation [27]. The gross tumor volume (GTV) and organs at risk (i.e. heart, lungs, chest wall and breasts) were delineated by an experienced breast radiation oncologist, followed by verification of the GTV delineation by a breast radiologist. The clinical target volume (CTV) was created by uniformly expanding the GTV with a margin of 20 mm, while excluding the skin and chest wall, never exceeding the ipsilateral breast. Both GTV and CTV were

expanded by a margin of 3 mm to create the planning target volume (PTV). Prescribed dose to the PTV-GTV and PTV-CTV was a single fraction of 20 Gy and 15 Gy, respectively [28]. Using an α/β of 4.7 Gy and 2 Gy fractions, the single dose of 20 Gy is equivalent to 73.7 Gy and 15 Gy equivalent to 44.1 Gy using the linear quadratic (LQ) model [29]. Adequate target coverage was determined to be achieved if at least 99% of the PTV-GTV and 99% of the PTV-CTV received 95% of the prescribed dose ($V_{95\%}$≥99%). The mean dose (D_{mean}) was set to be between 99% and 101% of the prescribed dose, and volume receiving ≥107% ($V_{107\%}$) of the prescribed dose to be as low as possible. RT planning was performed using volumetric modulated arc therapy with 2 partial arcs in the Monaco Treatment planning system (Elekta AB, Stockholm, Sweden). The volume of the heart receiving ≥2.8 Gy ($V_{2.8Gy}$) was restricted at a maximum of 10%, the maximum dose in the skin (D_{1cc}) at <16 Gy, the D_{mean} in the ipsilateral lung at <5 Gy, the D_{max} of the spinal cord at <18 Gy, and the dose in esophagus and trachea (supplementary material 1). The lung constraint was converted from the QUANTEC recommendation of mean lung dose <7 Gy for 2 Gy per fraction to a single dose of 20 Gy using the LQ-model with an α/β of 3 Gy [28,30]. For the heart, we used a lower constraint than the QUANTEC recommendations, according to our clinical practice (V_{5Gy} ≤10% and V_{10Gy} ≤5%), and converted these from 2 Gy per fraction to a single dose of 20 Gy using the same LQ-model with an α/β of 3 Gy. The constraint for skin was determined based on what was deemed minimum feasible with a prescribed dose of 15 Gy to PTV-CTV. Position verification was performed before, during and after the RT delivery using cone beam CT. If discrepancies in patient positioning were observed when compared to the RT planning CT, position correction was applied according to standard procedure. Following single dose radiotherapy patients had no indication for additional adjuvant breast radiotherapy.

Imaging response assessment

A 3T diagnostic MRI was used as baseline measurement for response assessment. Radiological response was assessed at 1 week, 2 months, 4 months, 6 months, and if applicable 8 months, after NA-PBI using 3T MRI with the same protocol as the diagnostic MRI. Routine MRI reports by dedicated breast radiologists were used to extract details on response [31]. Radiologic complete response was defined as complete absence of pathologic contrast enhancement and complete absence of diffusion restriction in the original tumor.

Histological outcome assessment

All patients underwent BCS in the referring hospital. For the first 15 patients, the interval between NA-PBI and BCS was 6 months. For the subsequent 21 patients the interval was 8 months. In case of progressive disease on MRI, BCS would be performed immediately

and in case of tumor-positive resection margins a re-excision would be performed. Pathologic response was assessed by dedicated breast pathologists using the surgical specimen according to EUSOMA criteria [32]. Pathologic response was categorized as pCR (no residual tumor cells), near pCR (<10% residual tumor cells), partial response (10-50% residual tumor cells), stable disease (>50% residual tumor cells with features of response to treatment), or no evidence of response.

Toxicity

Following NA-PBI, patients visited the UMC Utrecht after 1, 2, 4 and 6 months, and additionally after 8 months for patients who underwent surgery 8 months following NA-PBI. Thereafter, patients visited the department 1 month following BCS and every year following NA-PBI. During each visit, toxicity was scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [33]. Patients reported breast symptoms, anxiety, and depression at baseline, before BCS (at 6 or 8 months following NA-PBI), and every year following NA-PBI through validated questionnaires (EORTC-QLQ-BR23, Hospital Anxiety and Depression Scale (HADS) [34–37]. At the same time points, the cosmetic result was assessed by the patient, treating radiation oncologist and BCCT. core software[38,39].

Statistical analysis

The primary endpoint was the proportion of patients who attained pCR. Secondary endpoints, proportion of patients with radiologic complete response, toxicity and cosmetic results, were evaluated using descriptive analytics. Positive and negative predictive value (PPV and NPV) of preoperative MRI for the prediction of pCR were calculated. PPV was defined as the probability radiologic complete response predicts pCR, i.e. the number of patients with pCR and radiologic complete response divided by all patients with radiologic complete response. NPV was defined as the probability no radiologic complete response predicts residual disease, i.e. the number of patients with residual disease and without radiologic complete response divided by all patients without radiologic complete response. Changes in patient-reported anxiety, depression and breast symptoms were analyzed using a linear mixed model for repeated measures. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software (IBM SPSS version 25 Statistics for Windows, Armonk, NY: IBM Corp.).

RESULTS

Between May 2015 and January 2018, 67 patients were screened for eligibility, 31 of whom were excluded. Six patients had a positive sentinel node, in 4 patients the tumor size was too large on MRI, 18 patients were excluded due to secondary findings on MRI or PET-CT and 3 patients withdrew informed consent (Supplementary material 2). Of the remaining 36 patients, 15 patients underwent surgery 6 months and 21 patients 8 months following NA-PBI. In one patient a re-excision was indicated due to tumor positive resection margins. The median age was 65 years (range 51-78) and median tumor size as assessed on MRI was 13 mm (range 5-20). Six patients (17%) received neoadjuvant endocrine treatment according to standard care, which was initiated after NA-PBI (Table 1).

TABLE 1. Patient and tumor characteristics of breast cancer patients undergoing NA-PBI.

	N=36
Median age in years (range)	65 (51-78)
Median tumor diameter in mm[a] (range)	13 (5-20)
Patients with neoadjuvant endocrine treatment[b]	6 (17%)
Bloom-Richardson (BR) grade	
I	24 (67%)
II	9 (25%)
III	2 (6%)
NA[c]	1 (3%)
Histology type carcinoma	
Ductal	35 (97%)
Mucinous	1 (3%)

All patients had ER-positive, HER2-negative tumors and tumor-negative sentinel nodes as per protocol.

[a]: Tumor diameter as assessed on MRI.

[b]: Initiated after NA-PBI.

[c]: NA: Not assessable; BR grade not assessable due to small tumor biopsy.

The mean volumes of the GTV, CTV and ipsilateral breast were 1.6 ml (range 0.3-3.8), 73.9 ml (range 27.9-130.0), and 1,036 ml (range 284-2027), respectively. Adequate target coverage of the PTV-CTV (V95%≥99%) was achieved in 34 patients. In 2 patients minor compromises of the PTV-CTV coverage were accepted (95% and 96%, respectively) due to close proximity of the caudally located breast tumor to the chest wall and heart. Only in two patients, the $V_{107\%}$ of the PTV-GTV was more than 0% (0.07% and 0.18%,

respectively), the mean D_{max} of PTV-GTV was 21.0 Gy (range 20.5-21.5). The mean ratio of PTV-CTV to ipsilateral breast was 11.2% (range 5.5-20.6) and the average D_{mean} of the ipsilateral breast was 4.7 Gy (range 1.7-7.8).

The average D_{max} in the heart was 3.2 Gy (range 0.2-11.1), the average D_{mean} in the ipsilateral lung was 1.2 Gy (range 0.5-1.9.), and the average D_{1CC} of the skin was 14.9 Gy (range 9.4-18.1). Treatment constraints for spinal cord, trachea, and esophagus were met in all patients. Only the treatment constraint of the skin (D_{max} <16 Gy) was not achieved in all patients.

Fifteen out of 36 patients attained pCR (42%; 95%-CI, 26%-59%). pCR was observed in five of 15 patients at 6 months post-NA-PBI (33%; 95%-CI, 13%-61%) and in ten of 21 patients at 8 months post-NA-PBI (48%; 95%-CI, 26%-70%) (Table 2).

Table 2. Pathologic response of low-risk breast cancer following MR-guided single ablative dose NA-PBI according to EUSOMA criteria.

	All patients (N=36)	**6 months following NA-PBI (N=15)**	**8 months following NA-PBI (N=21)**
Pathologic complete response	15 (42%)	5 (33%)	10 (48%)
Near pathologic complete response	12 (33%)	5 (33%)	7 (33%)
Partial response	7 (19%)	4 (27%)	3 (14%)
Stable disease	2 (6%)	1 (7%)	1 (5%)
No response	0 (0%)	0 (0%)	0 (0%)

Response according to EUSOMA criteria. Pathologic complete response: either (i) no residual carcinoma or (ii) no residual invasive tumor but DCIS present. Near pathologic complete response: minimal residual disease/near total effect (e.g. < 10% of tumor remaining) Partial response: evidence of response to therapy but with 10–50% of tumor remaining. Stable disease: > 50% of tumor cellularity remains evident, when compared with the previous core biopsy sample, although some features of response to therapy present. No response: No evidence of response to therapy.

Twelve patients attained near pCR (33%), seven patients partial response (19%) and two patients stable disease (6%). There were no patients with no evidence of response. Of the six patients who received neoadjuvant endocrine treatment, two patients attained pCR, three patients near pCR and one patient partial response. Thus 33% achieved pCR

with and 43% achieved pCR without neoadjuvant endocrine treatment. All six patients receiving neoadjuvant endocrine treatment had an indication to continue endocrine treatment in the adjuvant setting, and in one additional patient endocrine treatment was initiated following BCS. Two patients stopped endocrine treatment prematurely due to toxicity, at 3 and 6 months following BCS, respectively. Radiological response assessment showed an increase in radiologic complete response during the interval between NA-PBI and breast-conserving surgery (Figure 1). Radiologic complete response occurred in 15 out of 36 patients (42%) at the final pre-surgery MRI. Ten of the 15 patients with complete radiological response had pCR. This resulted in a PPV of MRI to predict pCR of 67% (95%-CI, 39%-87%) (Figure 3). Of the 21 patients in whom the final pre-surgery MRI showed residual disease, five patients had pCR. This resulted in an NPV of MRI to predict pCR of 76% (95%-CI, 52%-91%) (Figure 2).

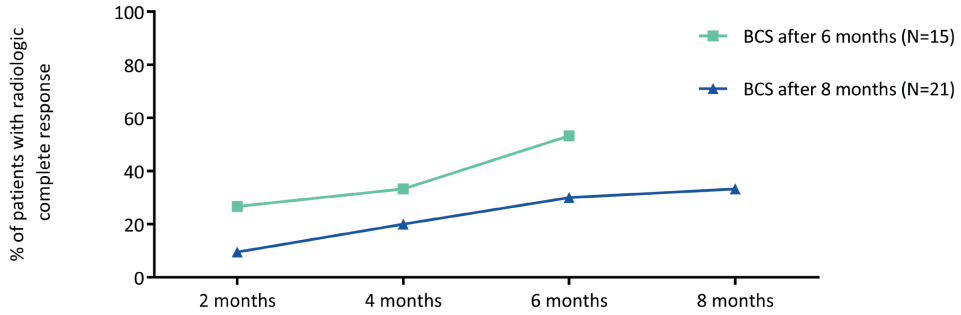

FIGURE 1. Increasing proportion of radiologic complete response during longer follow-up.

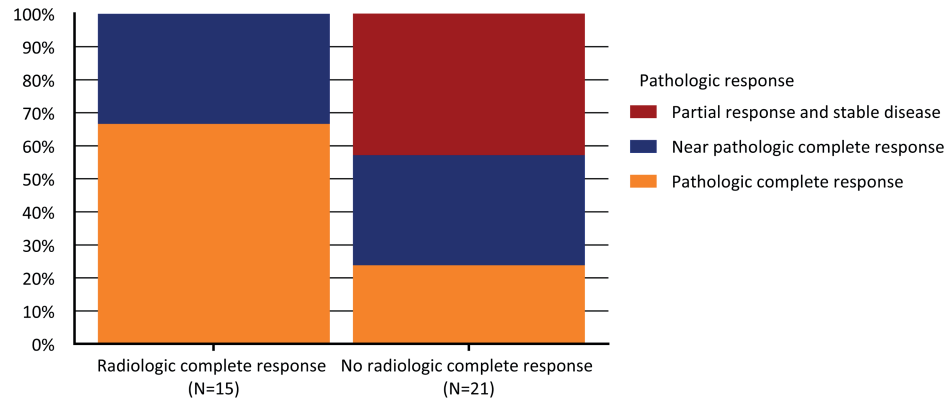

FIGURE 2. Correlation between pathologic response and radiologic response at final pre-surgery MRI.

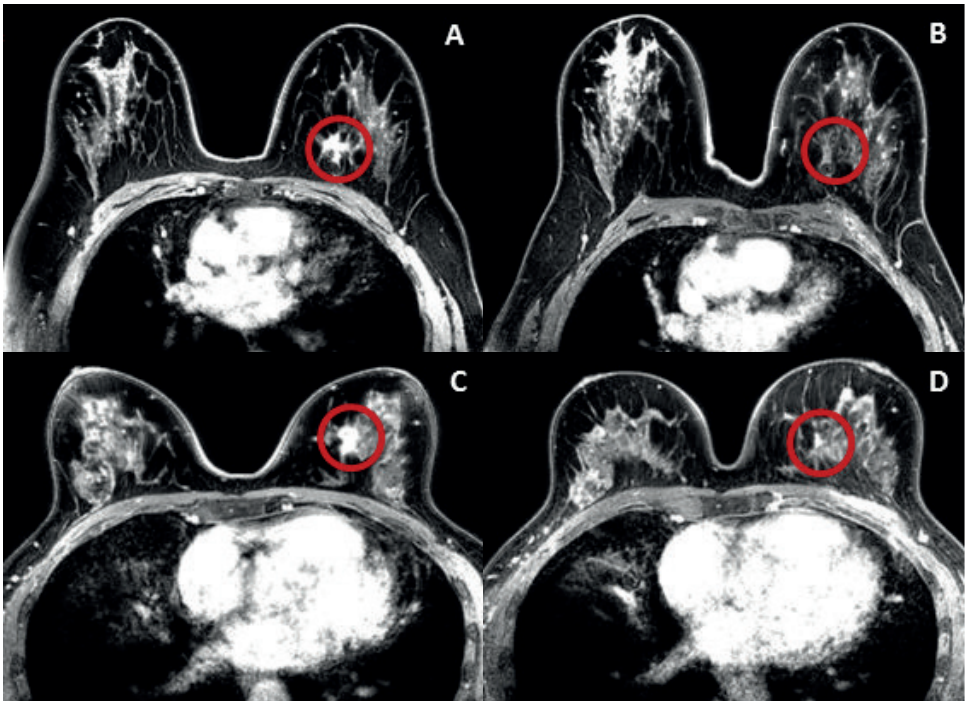

FIGURE 3. A: Diagnostic DCE-MRI of patient 1; B: DCE-MRI at 6 months following NA-PBI showing radiologic complete response in patient 1; C: Diagnostic DCE-MRI of patient 2; D: DCE-MRI at 6 months following NA-PBI showing residual disease in patient 2.

Acute skin toxicity, as assessed by the treating radiation oncologist, was observed in 19% of patients within 1 month following NA-PBI, and no grade 2 toxicity or higher was observed. All acute skin toxicity was resolved within 2 months following NA-PBI. After median follow-up of 24 months (range 12-47), all patients developed grade 1 fibrosis restricted to the treated breast volume, 58% developed grade 1 breast discomfort or pain, and 31% grade 1 breast edema. Grade 2 toxicity was observed in 17% of patients (breast pain, chest wall pain, arm pain and breast edema) and was transient in all patients. Additionally, 14% of patients experienced a postoperative wound infection that was treated conservatively with oral antibiotics (grade 2) and 3% a postoperative wound infection that required surgical incision (grade 3) (Table 3). Following an alteration in the study protocol, patients received perioperative antibiotics according to local protocol and no additional postoperative infections occurred. No lung and cardiac toxicities were observed.

No changes in patient-reported breast symptoms, anxiety, and depression scores were observed. Mean reported values were comparable to an age-matched population of Dutch women without a diagnosis of cancer (Supplementary material 3). At 1 year following NA-PBI, 94% of the patients was very satisfied, satisfied or not unsatisfied with the cosmetic results (Supplementary material 3.)

No local recurrences or deaths were observed. In one patient, who prematurely stopped anti-estrogen therapy, regional and distant recurrence was simultaneously diagnosed in the ipsilateral axillary lymph nodes, vertebrae and pelvis, without a local recurrence, at 21 months following NA-PBI. The 2-year disease-free survival rate was therefore 97%. In another patient, a primary contralateral breast cancer (cT2N0) was diagnosed on MRI during the interval between NA-PBI and surgery.

TABLE 3. Radiotherapy- and surgery-induced toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

	Before BCS (6 or 8 months following NA-PBI) (N=36)		**12 months following NA-PBI (N=36)**			**18 months following NA-PBI (N=32)**	
	Grade 1	**Grade 2**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**
Breast fibrosis/ induration*	31 (86%)	0 (0%)	36 (100%)	0 (0%)	0 (0%)	32 (100%)	0 (0%)
Breast discomfort/ pain	21 (58%)	1 (3%)	17 (47%)	2 (6%)	0 (0%)	4 (13%)	0 (0%)
Chest wall pain	2 (6%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Breast edema	11 (31%)	1 (3%)	18 (50%)	0 (0%)	0 (0%)	4 (13%)	0 (0%)
Wound infection	0 (0%)	0 (0%)	0 (0%)	5 (14%)	1 (3%)	0 (0%)	0 (0%)

** only inside the treated breast volume*

DISCUSSION

In this single arm prospective study, MR-guided single ablative dose NA-PBI of low-risk breast cancer induced pCR in 42% (95%-CI, 26%-59%) and near pCR in 33% of the patients. Preoperative MRI was only modestly able to predict pCR, with a PPV of 67% (95%-CI, 39%-87%) and an NPV of 76% (95%-CI, 52%-91%). After a median follow-up period of 21 months, only limited toxicity was observed without any local recurrences. These findings demonstrate that MR-guided single ablative dose NA-PBI is a feasible treatment approach for low-risk breast cancer patients.

Few studies on NA-PBI in early-stage breast cancer patients have been published [16,19,40–42]. The advantage of NA-PBI potentially consists of decreased irradiated volumes ad reduced radiotherapy-induced toxicity compared to postoperative PBI. Additionally, NA-PBI can result in tumor regression, potentially requiring less extensive surgery. Horton et al. have investigated MR-guided single dose NA-PBI in 32 patients treated in a dose-escalation study with a single dose of 15, 18 or 21 Gy and BCS within 10 days after radiotherapy [18]. No dose-limiting toxicity was found during 23 months of follow-up, and patient-reported cosmetic outcome was good or excellent in all but one patient. In the European-wide PAPBI trial 70 patients were treated with 40 Gy in 10 fractions and BCS after an interval of 6 weeks. With a postoperative infection rate of 11% and 2 patients having a local recurrence within 2 years, NA-PBI was concluded to be an acceptable alternative for postoperative irradiation [40]. Pathologic (near) complete response was observed in 6 out of 65 patients [41]. Nichols et al. treated 27 low-risk breast cancer patients with NA-PBI with a total of 38.5 Gy over 10 fractions in 5 days[42]. pCR occurred in 4 patients (15%) after an interval of at least 21 days. No unexpected adverse events were observed and cosmetic outcome was good to excellent in the majority of patients. However, none of the above-mentioned trials was designed for tumor downstaging with a maximum interval between NA-PBI and surgery of 6 weeks. Arriagada et al. reported that maximum tumor response in 463 breast cancer patients staged cT1-4N0-3 after doses up to >80 Gy, was seen after 6 months [43]. Since the aim of our trial on MR-guided NA-PBI was to achieve pCR, we pragmatically initiated our trial with an interval of 6 months, and prolonged this to 8 months after the first 15 patients, with continuous assessment of the radiological response during this interval.

For assessment of tumor response after NA-PBI and preoperative identification of patients with pCR we have used MRI [44]. In our trial, not all patients with pCR were identified using MRI, and some patients with residual tumor were assessed as radiologic complete responders on MRI. Wang et al. used DCE- and DW-MRI for response assessment and found a significant increase in initial area under the concentration curve in the CTV after NA-PBI, but no change in regional apparent diffusion coefficient [45]. Research into gene expression profiles in the PAPBI trial showed an inflammatory response and changes in p53 signaling and cell cycle regulation following neoadjuvant irradiation. However, no distinction between responders and non-responders was possible using the gene expression profiles, which could be attributed to the relatively short interval between NA-PBI and BCS [41]. These techniques, including assessment of changes in gene expression profiles and additional preoperative biopsies, might be feasible options for future trials on response assessment following NA-PBI [41,45–47].

If pCR can be adequately predicted with a high positive predictive value following NA-PBI in future patients, a surgical intervention might be omitted or postponed, which could lead to further reduction of treatment-induced toxicity [20,21,48,49]. Following a high predicted probability of pCR thorough follow-up including imaging is warranted to enable intervention as soon as recurrence of disease is diagnosed. For patients with predicted incomplete response, the advantage remains of having been treated with a single radiotherapy dose to a smaller volume as compared to multiple fractioned postoperative.

NA-PBI was well tolerated by all patients, with only mild late toxicity reported. In all patients grade 1 breast fibrosis was observed, restricted to the treated volume. The rate of postoperative wound infections in our trial is comparable to standard BCS followed by WBI for breast cancer patients [50]. Nevertheless, we amended our study protocol to treat all patients with preoperative antibiotics to minimize the risk of postoperative wound infections. Patients within our trial did not report more symptoms of anxiety or depression when compared to an age-matched population of Dutch women without a diagnosis of cancer. The patient-reported breast symptoms, anxiety, and depression scores did not seem worse compared to other cohorts in which early-stage breast cancer patients were treated with whole and partial breast irradiation [10,51].

Several limitations apply to this study. Firstly, the small sample size of 36 patients resulted in a fairly wide 95%-CI around the pCR proportion. Second, due to selection of patients, the reported PROs might be too optimistic for the entire population of low-risk breast cancer patients. Third, only short-term follow-up is presented at this moment. Longer follow-up of will be important for further evaluation of local control, toxicity, and PROs, including cosmesis. Fourth, due to the extensive diagnostic work-up including MRI and sentinel node biopsy, and intensive follow-up with MRI, clinical implementation of NA-PBI at this stage could be a challenge for smaller institutions. Since no disease progression was observed during the interval between NA-PBI and surgery, a reduced number of MRIs during follow-up may improve implementation without compromising oncological safety. Since only a limited number of patients received neoadjuvant endocrine treatment, we were not able to determine the exact impact of endocrine treatments on NA-PBI and the pathologic response. One could expect an increased rate of pCR in patients receiving additional endocrine treatment, since this can also induce pCR [52]. Nonetheless, these patients had an indication for adjuvant endocrine treatment if treated with standard breast-conserving treatment according to the Dutch guidelines. Therefore, we allowed (neo)adjuvant endocrine treatment in participating patients, including its possible influence on tumor downstaging.

Breast cancer patients treated with MR-guided single ablative dose NA-PBI might have several benefits over being treated with standard postoperative partial or whole breast irradiation. First, a smaller volume of the breast is irradiated with the potential to decrease the risk of treatment-induced toxicity. Second, the entire radiotherapy treatment is delivered in one single dose compared to a 3-5 week fractionated schedule within the standard breast-conserving treatment. Third, if pCR can be accurately predicted in future patients, surgery might safely be omitted in these selected patients resulting in further reduction of treatment burden and health care costs.

CONCLUSION

MR-guided single ablative dose NA-PBI resulted in tumor regression in all low-risk breast cancer patients, and in complete tumor ablation in over 40%. Treatment-induced toxicity and PROs were acceptable after a median follow-up of 21 months. This treatment approach is a promising alternative for standard postoperative irradiation after breast-conserving surgery, and could result in postponement or omission of surgery in selected patients if pCR can be accurately predicted.

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5

TUMOR-INFILTRATING LYMPHOCYTES IN LOW-RISK PATIENTS WITH BREAST CANCER TREATED WITH SINGLE-DOSE PREOPERATIVE PARTIAL BREAST IRRADIATION

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ABSTRACT

Purpose: Preoperative partial breast irradiation (PBI) has the potential to induce tumor regression. We evaluated the differences in the numbers of pre-irradiation tumor infiltrating lymphocytes (TILs) between responders and non-responders after preoperative PBI in low-risk patients with breast cancer. Furthermore, we evaluated the change in number of TILs before and after irradiation.

Methods and Materials: In the prospective ABLATIVE study, low-risk patients with breast cancer underwent treatment with single-dose preoperative PBI (20 Gy) to the tumor and breast-conserving surgery after 6 or 8 months. In the pre-irradiation diagnostic biopsy and post-irradiation resection specimen, numbers of TILs in 3 square regions of 450 x 450 mm were counted manually. TILs were visualized with CD3, CD4, and CD8 immunohistochemistry. Differences in numbers of pre-irradiation TILs between responders and non-responders were tested using Mann-Whitney U test. Responders were defined as pathologic complete or near-complete response, and non-responders were defined "as all other response." Changes in numbers of TILs after preoperative PBI were evaluated with the Wilcoxon signed rank test.

Results: Pre-irradiation tissue was available from 28 patients, post-irradiation tissue from 29 patients, resulting in 22 pairs of pre-irradiation and post-irradiation tissue. In these 35 patients, 15 had pathologic complete response (43%), 11 had a near complete response (31%), 7 had a partial response (20%), and 2 had stable disease (6%). The median numbers of CD3+TILs, CD4+ TILs, and CD8+TILs in the pre-irradiation tumor tissue were 49 (interquartile range [IQR], 36-80), 45 (IQR, 28-57), and 19 (IQR, 8-35), respectively. The number of pre-irradiation TILs did not differ significantly between responders and non-responders. The median numbers of CD3+ TILs, CD4+ TILs, and CD+ TILs in post-irradiation tumor tissue were 17 (IQR, 13-31), 26 (IQR, 16-35), and 7 (IQR, 5-11), respectively.

Conclusions: After preoperative PBI in this limited cohort, the number of TILs in tumor tissue decreased. No differences in numbers of pre-irradiation TILs between responders and non-responders were observed.

INTRODUCTION

Pre-operative partial breast irradiation (PBI) has the potential to induce tumor regression in breast cancer patients [1]. In our previous study (the ABLATIVE trial) a single dose (20 Gy) of pre-operative PBI, 15 out of 36 low-risk breast cancer patients resulted in a pathologic complete response after an interval of six to eight months between irradiation and breast-conserving surgery [2]. Complete tumor regression following pre-operative PBI could allow omission of breast surgery in future patients with no clinical evidence of residual disease [3,4]. In order to assess which patients will achieve or have achieved pathologic complete response (pCR), adequate response assessment is eminent.

Response assessment during standard pre-operative systemic treatment currently consists of magnetic resonance imaging (MRI) and/or 18F-FDG positron emission tomography computed tomography (PET/CT). Several studies have shown that the predictive value of both MRI and PET/CT for pathologic response is insufficient to identify patients in whom surgery following pre-operative systemic treatment (PST) can be omitted [5–7].

To increase the predictive value of response assessment following pre-operative systemic treatment or radiotherapy, assessment of immune infiltrates, so-called tumor infiltrating lymphocytes (TILs) have been proposed as a biomarker [8–11]. Increased numbers of TILs in resection specimens of patients with triple negative breast cancer (TNBC) treated with PST have been associated with improved outcome, such as disease-free survival and overall survival [8]. The explanation for the association between the number of TILs and improved clinical outcome lies within the activation of the immune system following PST, which can result in inhibition of tumor growth and induction of immunogenic cell death [12–14]. The number of TILs can be evaluated as a representation of the activation of the immune system. However, not in all patients TILs can be identified, complicating the research of TILs as a biomarker [15,16]. The important types of TILs in breast cancer patients that we studied are CD3-postive TILs, CD4-positive TILs, and CD8-positive TILs. The expression of CD3 is crucial for the activation of T-cells in an anti-tumor response, activation of CD4 directly activates CD8+ T-cells and leads to the production of tumor necrosis factor-a [17–19] . CD8 is expressed on cytotoxic T-cells and increases sensitivity of the T-cell to the presented antigen [17,20].

In this study we assessed TILs before and after pre-operative PBI in low-risk breast cancer patients, and evaluated the differences in numbers of pre-operative TILs between responders and non-responders as a possible biomarker for future response monitoring.

MATERIALS AND METHODS

Patient selection

The pre-irradiation diagnostic core needle biopsies and post-irradiation resection specimens of low-risk luminal breast cancer patients included in the ABLATIVE trial on single dose pre-operative PBI were evaluated [2]. The ABLATIVE trial was approved by the institutional review board of the UMC Utrecht, the Netherlands, and registered in ClinicalTrials.gov (NCT06863301). After informed consent, patients with unifocal ductal or mucinous invasive breast cancer with a maximum diameter of 3 cm, ER positive and HER2 negative tumor, a negative sentinel lymph node biopsy, and no indication for (pre) operative chemotherapy and/or immunotherapy were enrolled. Participating patients were treated with a single ablative radiotherapy dose of 20 Gy to the tumor and 15 Gy to the breast tissue within 2 cm of the tumor. Patients underwent breast conserving surgery (BCS) after an interval of six or eight months following pre-operative PBI. The pathologic response following pre-operative PBI was assessed using the EUSOMA criteria according to the national guidelines [21,22]. The response could be (a) pathologic complete response (pCR); (b) near pCR (<10% residual disease); (c) partial response (10-50% residual disease); (d) stable disease (>50% residual disease); or (e) no evidence of response. Thirty-six women were included in the clinical trial, but of one case no additional pre- and post-irradiation tumor tissue could be retrieved. From 22 cases both the diagnostic biopsy and the resection specimen were available, from six cases only the pre-irradiation diagnostic biopsy was available, and from seven cases only the post-irradiation resection specimen was available.

Assessment of tumor infiltrating lymphocytes

Consecutive slides of 4 µm were obtained from formalin-fixed paraffin-embedded tissue blocks of the diagnostic tumor biopsy and resection specimen. These slides were stained by immunohistochemistry for CD3, CD4, and CD8, using rabbit anti-CD3 polyclonal antibody (DAKO, A0452, dilution 1:100, Glostrup, Denmark), rabbit anti-CD4 monoclonal antibody (Cellmarque, 104R-16, dilution 1:20, Rocklin, USA), and mouse anti-CD8 monoclonal antibody (DAKO, M7103, dilution 1:100), respectively. If available, an additional slide was stained with HE. All slides were digitalized with a NanoZoomer-XR digital slide scanner (Hamamatsu, Hamamatsu City, Japan) at a ×40 magnification.

The pre- and post-irradiation slides were assessed separately. The clinical information and histopathologic reports were available during annotation of representative tumor areas. This annotation was performed by a researcher, MD and an experienced breast pathologist on HE stained slides, and copied to the IHC stained slides. When no HE

slide was available, the first annotation was performed on CD3 stained slides. On the pre-irradiation slides the tumor was annotated and on the post-irradiation slides the irradiated tumor and area of tumor regression was annotated. The irradiated tumor and area of regression was identified by reactive changes such as scar-like fibrosis and iron-loaded macrophages. If distinction between area of regression and surrounding stroma was not clear, stroma with the same density as the definitive area of regression was included in the annotation. Following tumor or area of regression annotation, three square fields of 450 µm by 450 µm were randomly selected in all slides and the number of TILs was manually quantified by dotting each lymphocyte in these fields. TILs assessment was performed blinded to clinical information and histopathologic reports.

Statistical analysis

Pathologic response was grouped to responders (defined as pCR and near-pCR) and non-responders (defined as partial response, stable disease, and no evidence of response). The number of TILs was expressed as the mean of the three selected squares, and calculated for both the diagnostic biopsy and resection specimen. The number of pre- and post-irradiation TILs and change in number of TILs were presented using median and interquartile range (IQR). Differences in numbers of pre-irradiation TILs between responders and non-responders were tested using Mann-Whitney test. Differences in numbers of TILs between pre- and post-irradiation were tested using Wilcoxon signed rank test. Statistical tests were 2-sided and performed at a significance level of 0.05. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Of the 35 analyzed low-risk breast cancer patients, the median age was 64 years (range 51-78) and the median tumor size was 13 mm (range 5-20) (table 1). Of the total of 35 cases, fifteen achieved pCR (43%), 11 near pCR (31%), seven partial response (20%), and two stable disease (6%). Of the 28 pre-irradiation samples, 13 achieved pCR (46%), 9 near pCR (32%), 5 partial response (18%), and 1 stable disease (4%). Of the 29 cases post-irradiation samples, 12 achieved pCR (41%), 10 near pCR (35%), 6 partial response (21%), and 1 stable disease (3%). For some cases only the pre-irradiation (six cases) or post-irradiation (seven cases) slide was available, since no tumor material was left for IHC staining after the necessary clinical pathology assessment. In five cases the pre-irradiation slide did not contain enough tumor material to select three square fields of 450 µm by 450 µm, therefore fewer fields were selected. Due to technically inadequate staining, not all IHC staining could be assessed for every case.

TABLE 1. Patient and tumor characteristics of 35 low-risk breast cancer patients studied for the association between tumor infiltrating lymphocytes and pathologic response after pre-operative PBI.

	Median (range) or N (%)
Tumor diameter (mm) [a]	13 (5-20)
Age (years)	64 (51-78)
Bloom Richardson grade	
1	24 (69%)
2	9 (26%)
3	1 (3%)
NA [b]	1 (3%)
Histology type	
Ductal	34 (97%)
Mucinous	1 (3%)
Pathologic response	
Pathologic complete response	15 (43%)
Near complete response (<10% residual tumor cells)	11 (31%)
Partial response (10-50% residual tumor cells)	7 (20%)
Stable disease (>50% residual tumor cells)	2 (6%)
No response	0 (0%)

[a]: Tumor diameter as assessed on MRI.

[b]: NA: Not assessable; BR grade not assessable due to small tumor biopsy.

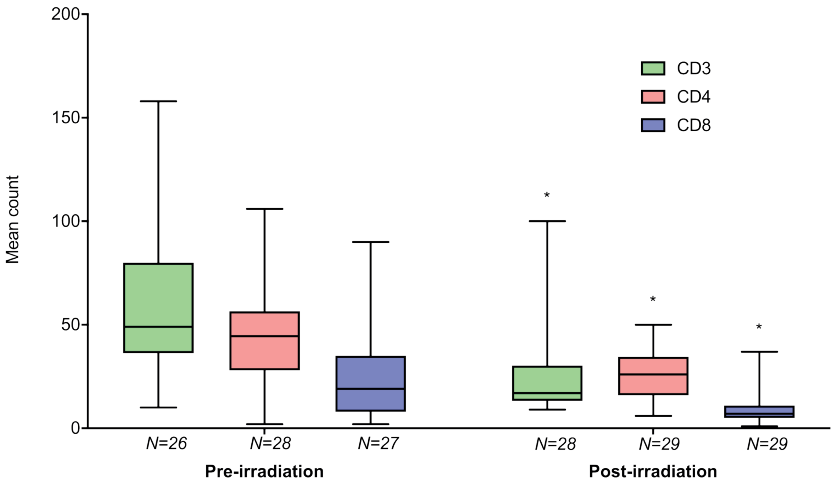

FIGURE 1. Numbers of pre- and post-irradiation (six to eight months after irradiation) TILs of breast cancer patients treated with pre-operative PBI. *: P-value <0.05 for difference with pre-irradiation number of TILs.

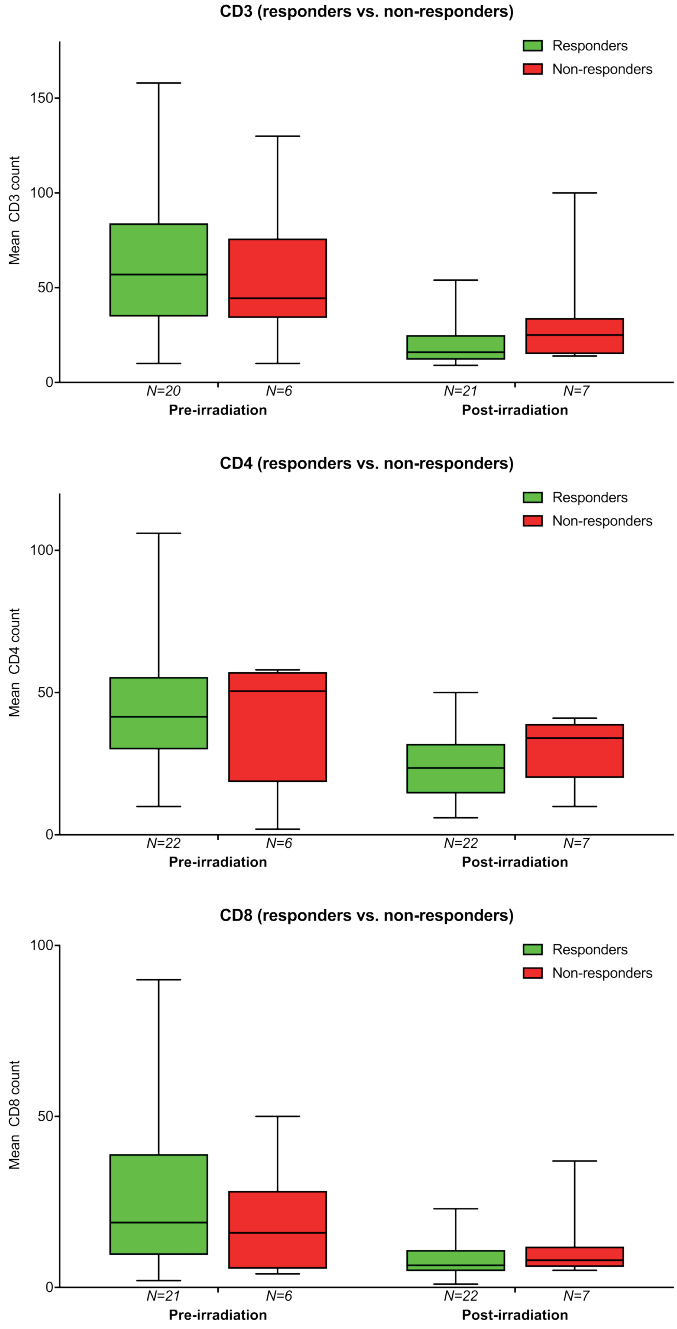

FIGURE 2. Numbers of pre- and post-irradiation (six to eight months after irradiation) TILs in low-risk breast cancer patients treated with pre-operative PBI according to pathologic response. No significant differences in numbers of pre-irradiation TILs between responders and non-responders were found.

In the pre-irradiation slides the median number of CD3+ TILs was 49 (IQR 36-80), of CD4+ TILs 45 (IQR 28-57), and of CD8+ TILs 19 (IQR 8-35) (figure 1). For responders and non-responders, the median number of CD3+ was 57 and 45 (p=0.74), of CD4+ 42 and 50 (p=0.98), and of CD8+ 19 and 16 (p=0.48), respectively (figure 2). In the post-irradiation slides the median number of CD3+, CD4+, and CD8+ TILs was 17 (IQR 13-31), 26 (IQR 16-35), and 7 (IQR 5-11), respectively (figure 1). In the 22 cases in whom both the pre- and post-irradiation number of TILS could be assessed, a statistically significant decrease in TILs was observed. In these 22 cases the median pre-irradiation number of CD3+ TILs was 45 (IQR 33-79), and median post-irradiation 16 (IQR 12-22), for CD4+ TILs 44 (IQR 30-55) pre-irradiation and 25 (IQR 13-35), respectively, for CD8+ TILs 17 (IQR 7-37) and 6 (IQR 5-9) respectively. For CD3+ a median decrease of 69%, (p=0.002) was observed, for CD4+ a median decrease of 27%, (p=0.003), and for CD8+ a median decrease of 74% (p=0.004).

DISCUSSION

TILs could be clearly identified in all low-risk breast cancer patients, both pre- and post-irradiation (figure 3). We observed no differences in the number of pre-irradiation TILs between responders and non-responders.

We observed a large range in the number of pre- and post-irradiation TILs with the largest range in the number of CD3+ lymphocytes. Similarly, a large range in pre-treatment TILs in breast cancer patients treated with PST has been reported. Denkert et al. evaluated the percentage of intratumoral and stromal TILs prior to PST of cT1-3N0-2M0 breast cancer patients [23]. In core biopsies of 1,058 cases they observed tumors without any TILs as well as tumors with over 50% TILs. In a study that evaluated CD8+ TILs in the resection specimen of 1,334 breast cancer patients (pT1-2N0-2M0) after primary surgery within the Nottingham Tenovus Primary Breast Carcinoma series, a median of 11 TILs was observed in a field of 0.28 mm^2 (interquartile range 2-34) [20]. This number of TILs is comparable to the median of 19 CD8+ TILs (IQR 8-35) in the pre-irradiation tumor tissue within our study, despite the low-risk luminal breast cancer patients in our study in contrast to the more advanced disease in the Nottingham series. Kovács et al. did evaluate a more comparable patient group of early-stage breast cancer patients, and found that patients with luminal A and B type tumors had the lowest percentage of TILs [11].

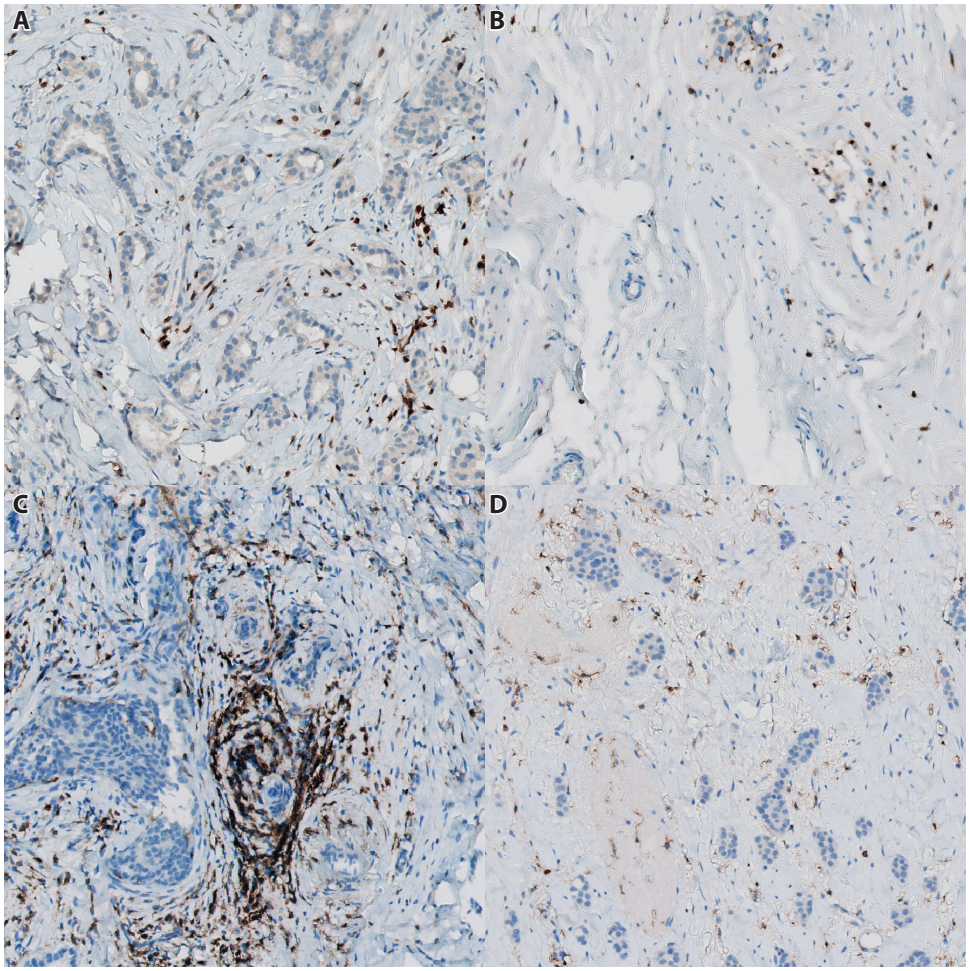

FIGURE 3. Immunohistochemical positive staining of lymphocytes in low-risk breast cancer patients. A: pre-irradiation CD3 staining, B: post-irradiation CD3 staining in a case with pathologic complete response (eight months after irradiation), C: pre-irradiation CD4 staining, D: post-irradiation CD4 staining in a case with partial response (six months after irradiation).

The observed decrease in number of TILs after pre-operative irradiation was higher than in previous studies on pre-operative systemic treatment in locally advanced and inflammatory breast cancer patients [15,24]. In addition to the different treatment approach, this could be attributed to the lower number of pre-irradiation TILs and longer interval of up to eight months between irradiation and post-irradiation assessment of TILs in our study. This resulted in tumor regression after an ablative dose of radiotherapy, including fewer vital tumor cells for immune cells to respond to.

Pre-treatment TILs have been shown to be a significant predictor of pathologic complete response and prolonged survival after PST in breast cancer patients [10,20,23]. In our small series, we did not observe an association between pre-treatment TILs and pathologic response. Most of the affirmative studies on TILs during PST included patients with a more advanced disease stage than the low-risk breast cancer patients in the present study. In addition, many studies reported the predictive value of pre-treatment TILs for response to PST in TNBC, and not in ER+ breast cancers [25–27]. Moreover, all cases in our study, except for one, had a Bloom Richardson grade 1 or 2 tumor. Low grade tumors have been reported to have lower numbers of TILs than high grade tumors [11,28], which could also explain why we were not able to demonstrate an association between pre-treatment TILs and pathologic response.

A strength of the current study is the availability of both pre- and post-irradiation slides of the same breast cancer patients, enabling us to assess the effect of irradiation on the number of TILs. Secondly, the number of TILS was assessed through several different IHC stainings that highlight TIL subtypes and can help us in understanding the contribution of the different types of immune cells to response to pre-operative PBI. Even though a significant decrease in TILs following pre-operative PBI was observed, we could not differentiate between responders and non-responders using the number of pre-operative TILs, an important step in the ultimate treatment de-escalation, i.e. omission of surgery. Nevertheless, it is remarkable that even after the long interval of six to eight months after pre-operative PBI, TILs were stills observed in all cases. In several publications, TILs were not observed in cases achieving pCR following PST [15,16]. The TILs international working group has recently encouraged the evaluation of post-treatment TILs in a research setting, especially in the case of pCR [13].

A limitation of the present study is that it was designed as a feasibility study for the novel treatment option of single dose pre-operative PBI and was therefore not powered on finding predictors for treatment response. Furthermore, not all biopsies and resection specimens could be retrieved and evaluated, which decreased the already limited sample size. However, we assume the missing samples were not associated with the pathologic response, because the percentage of responders and non-responders was not different between the entire group of patients, the group of patients with a pre-irradiation sample available, and the group of patients with a post-irradiation sample available. Therefore, the missing samples are presumably at random, and will not affect the interpretation of our results. Nonetheless, a larger number of available slides could have improved the differentiation between responders and non-responders, and we recommend further evaluation of TILs as a biomarker in future larger cohorts. Furthermore, as the pre-irradiation biopsy was performed for diagnostic purposes, only

a single biopsy was taken. Since only the single biopsy could be assessed this could have led to either over- or underestimation of the number of TILs, because no purposeful sampling has been performed [29]. The present study could also have benefitted from additional biopsies of the irradiated tumor, a few weeks following irradiation, to better assess the acute immune response since the acute response has faded at six to eight months after pre-operative PBI. It could be hypothesized that tumors with a more extensive acute cellular immune response have a higher chance of achieving pCR, which might be better assessable at six to eight weeks following irradiation than the currently used six to eight months. These additional biopsies were not performed to avoid imposing this additional burden on participating patients. Other possible biomarkers for the prediction of pathologic response after pre-operative PBI that could be further investigated are MR-imaging, including functional imaging, and circulating tumor DNA [30–32]. With all these possible biomarkers, a large patient cohort will be necessary to differentiate between responders and non-responders, as we expect only subtle differences in these low risk breast cancer patients.

CONCLUSION

TILs could be determined in tumor tissue of low-risk breast cancer patients before and after an ablative dose of pre-operative PBI using IHC staining. In this limited cohort, a statistically significant decrease in TILs was observed following irradiation. No differences in numbers of pre-irradiation TILs between responders and non-responders were observed in this small group of low-risk breast cancer patients.

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6

DYNAMIC CONTRAST-ENHANCED AND DIFFUSION-WEIGHTED MRI FOR RESPONSE EVALUATION AFTER SINGLE-DOSE ABLATIVE NEOADJUVANT PARTIAL BREAST IRRADIATION

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ABSTRACT

Purpose: This study aimed to evaluate changes in dynamic contrast-enhanced (DCE) and diffusion-weighted (DW) MRI acquired before and after single-dose ablative neoadjuvant partial breast irradiation (NA-PBI) and to study the relation between semi-quantitative MRI parameters and both radiologic and pathologic response.

Methods: Analyses were performed on 3.0T DCE and DW-MR images of 36 low-risk breast cancer patients treated with single-dose NA-PBI followed by breast-conserving surgery six or eight months after NA-PBI. MR images were acquired before NA-PBI and one week, two, four, and six months after NA-PBI. Breast radiologists assessed radiologic response in each scan and breast pathologists scored pathologic response after surgery. Patients were grouped to pathologic responders (<10% residual tumor cells) and non-responders (³10% residual tumor cells). Semi-quantitative MRI parameters evaluated were: time-to-enhancement (TTE), 1-minute relative enhancement (RE_{1min}), percentage of enhancing voxels (%EV), distribution of wash-out curve types, and apparent diffusion coefficient (ADC). Parameters were evaluated for all patients together and grouped by radiologic and pathologic response.

Results: In general, the enhancement increased one week after NA-PBI (baseline vs. one week median – TTE: 15s vs. 10s; RE_{1min}: 161% vs. 197%; %EV: 47% vs. 67%) and decreased from two months onwards (six months median – TTE: 25s; RE_{1min}: 86%; %EV: 12%). Median ADC increased from $0.83x10^{-3}$ mm^2/s at baseline to $1.28x10^{-3}$ mm^2/s at six months. TTE, RE_{1min} and %EV showed the most potential to differentiate between radiologic responses, and TTE, RE_{1min} and ADC between pathologic responses.

Conclusion: Semi-quantitative analyses of DCE and DW-MRI showed changes in relative enhancement and ADC one week after NA-PBI, indicating acute inflammation, followed by changes indicating tumor regression from two to six months after radiotherapy. No clear relation between the MRI parameters and both radiologic and pathologic response could be reported in this feasibility study.

INTRODUCTION

Recent studies have investigated hypofractionated neoadjuvant PBI (NA-PBI) for early-stage breast cancer patients with a low risk of local recurrence, aiming to reduce overall treatment time and irradiated volume, and thus treatment-related toxicity[1,2]. In a recent trial on single-dose ablative NA-PBI including thirty-six low-risk breast cancer patients at our department, fifteen patients (42%) showed a pathologic complete response (pCR) and twelve patients (33%) a near pCR. Surgery might be redundant in patients achieving pCR or near pCR following NA-PBI. To accomplish omission of surgery, pathologic response needs to be adequately predicted. In our trial, ten of the fifteen patients with pCR, but also five of the twenty-one patients without pCR, showed a radiologic complete response on magnetic-resonance imaging (MRI) just before BCS. This resulted in a positive predictive value (i.e. probability that radiologic complete response on MRI predicts pCR) of 67% and a negative predictive value (i.e. probability that no radiologic complete response on MRI predicts residual disease) of 76%[3]. Therefore, the qualitative clinical response assessment on MRI was insufficient to predict pathologic response in patients after NA-PBI.

Studies on breast cancer patients treated with neoadjuvant chemotherapy have shown that pathologic response could be predicted using (semi-)quantitative analysis of MRI, though not in low risk breast cancer patients[4–7]. Recently, two studies reporting on response assessment after high dose NA-PBI showed significant changes in quantitative MRI parameters acquired before and one to three weeks after NA-PBI, yet these results were not correlated to pathologic response[8,9]. Mouawad et al. reported a significant change in the kinetic parameter K^{trans} calculated from the dynamic contrast-enhanced (DCE) MRI[9]. Wang et al. reported a dependency between radiation dose and direction of apparent diffusion coefficient (ADC) change calculated from the diffusion-weighted (DW) MRI in a subgroup analysis[8].

The aim of our study was to determine whether MRI parameters change up to six months following single-dose ablative NA-PBI, and whether there is a relationship between MRI parameters and both radiologic and pathologic response.

METHODS

Study population and treatment

The study population consisted of 36 low-risk breast cancer patients participating in a single arm prospective interventional study at the department of Radiation Oncology at the University Medical Center Utrecht, the Netherlands (ClinicalTrials.gov identifier: NCT02316561)[3,10]. The Institutional Review Board approved the trial and all patients gave written informed consent for inclusion. Median age was 65 years (range 51-78 years) and median largest tumor diameter at baseline on MRI was 13 mm (range 5-20 mm). All patients had an ER-positive and HER2-negative tumor.

Patients were treated with single-dose ablative NA-PBI of 20 Gy to the planning target volume (PTV) of the gross tumor volume (GTV), and 15 Gy to the PTV of the clinical target volume (CTV = GTV + 2 cm), with a 3 mm PTV margin for both GTV and CTV. A diagnostic biopsy marker was used for position verification. If no marker had been placed during the diagnostic biopsy or if it was not visible on CBCT, a gold fiducial marker (Visicoil, IBA Dosimetry, Germany) was placed. Patients underwent BCS six months (n =15) or, after an alteration in the study protocol, eight months (n=21) after radiotherapy. Six patients (17%) received additional neoadjuvant endocrine treatment after NA-PBI according to national guidelines[11].

MRI acquisition

Patients underwent 3.0T MRI scans (Ingenia, Philips, The Netherlands) in the prone position using a dedicated 16-channel breast coil before radiotherapy (baseline) and after radiotherapy at one week, two, four, six, and, if applicable, eight months. The scan protocol included a DW-MRI series, a high-temporal-resolution/low-spatial-resolution 3D T1-weighted DCE-MRI series (referred to as "high-temporal"), and a low-temporal-resolution/high-spatial-resolution 3D T1-weighted DCE-MRI series ("high-spatial"). Scan parameters are presented in the supplementary material. The DW-MRI was acquired prior to contrast-injection using single-shot echo planar imaging. ADC maps were reconstructed using the scanner's software. The high-temporal DCE-MRI series consisted of 17 rapid full 3D volumes acquired during the first 90 seconds after contrast-injection (Gadovist, Bayer, injection 0.1 ml/kg at 1 ml/s). The high-spatial DCE-MRI series consisted of six full 3D volumes: the first acquired before contrast-injection and the remaining five acquired in the five minutes directly after the high-temporal DCE series (figure 1). Both DCE series were acquired using a T1-weighted fast field echo sequence (spoiled gradient echo (SPGR)). All sequences were acquired with spectral attenuated inversion recovery (SPAIR) fat suppression.

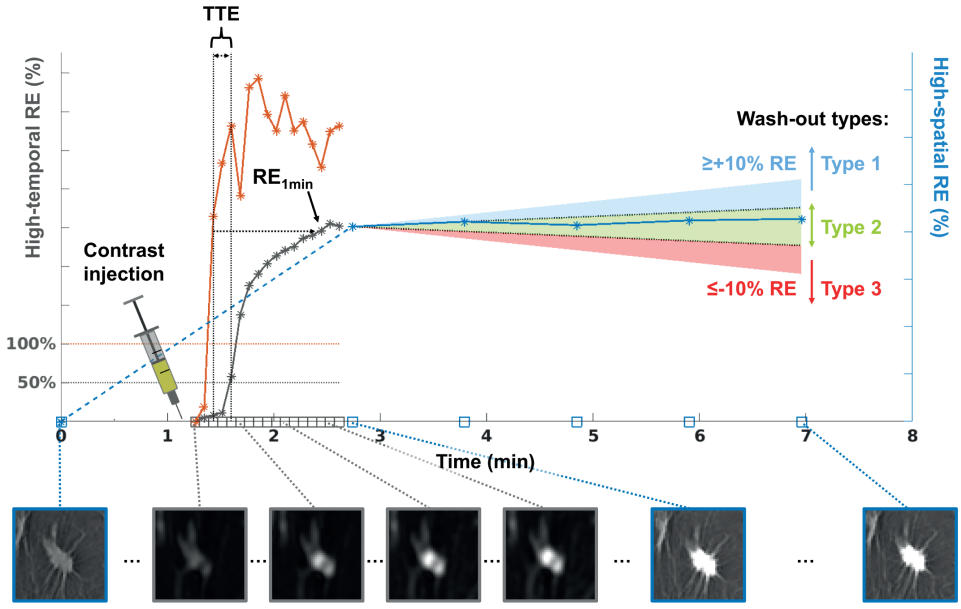


FIGURE 1. Illustration of the high-temporal (grey boxes) and high-spatial (blue boxes) DCE-MRI acquisition showing: median relative enhancement (RE) in aorta ROI (orange) and 90th percentile RE in GTV-ROI in high-temporal (grey) and high-spatial DCE (blue). The vertical dashed lines indicate the onset of aorta enhancement (left) and GTV enhancement (right). Indicated semi-quantitative parameters: time-to-enhancement (TTE), 1-minute relative enhancement (RE_{1min}) and cut-off boundaries (-10% and +10% RE) for voxel-wise wash-out curve type classification.

Clinical response assessment

Expert breast radiologists qualitatively assessed the radiologic response at each scan moment after NA-PBI, according to clinical practice in neoadjuvant systemic treatment, and were blinded to pathologic response. The MR images were scored as radiologic complete response, defined as absence of pathologic contrast enhancement and absence of diffusion restriction, or no radiologic complete response. A radiologic complete response was seen in one patient (3%) at one week, in six patients (17%) at two months, in nine patients (26%) at four months, and in fourteen patients (40%) at six months after NA-PBI[3].

The pathologic response was evaluated on the surgical specimen and was classified as pCR (no residual tumor cells), near pCR (<10% residual tumor cells), partial response (10-50% residual tumor cells), stable disease (>50% residual tumor cells), or no evidence of response, according to EUSOMA criteria[12]. Fifteen of the 36 patients (42%) showed pCR,

twelve (33%) near pCR, seven (19%) partial response, and two (6%) stable disease, while none of the patients had no evidence of response[3]. Patients were grouped to responders (pCR and near pCR) and non-responders (all other patients) for further analysis.

Semi-quantitative response assessment

Tumor delineation and image registration

Two researchers delineated the GTV on the first post-contrast image of the high-spatial DCE baseline MRI (i.e. before NA-PBI) under supervision of a breast radiation oncologist and a breast radiologist. To determine the onset of contrast wash-in in the aorta, a fixed region-of-interest (ROI) was placed in the descending aorta (aorta-ROI) in the high-temporal DCE-MRI at each scan moment.

Rigid registrations were applied to transform the GTV delineation from the baseline MRI to the MRI acquired after NA-PBI (figure 2) and to correct for motion between and within both DCE series[13]. To correct for geometric distortions in the DW series, we performed a deformable registration to register the DW series to the high-spatial DCE series[13,14]. After the registrations, the final GTV-ROIs for semi-quantitative analysis were created by expanding the transferred GTV delineations with a 1-voxel margin to account for delineation and registration inaccuracies.

MR images and registrations were visually assessed. MR images affected by artefacts (e.g. failure of fat suppression, distortion in the GTV region caused by a marker) and MR images to which the GTV delineation could not be correctly transferred were excluded from analysis, as well as DW series that could not be registered correctly to the DCE series.

Semi-quantitative analysis

At each scan moment we computed the following parameters for the GTV-ROI (Figure 1):

In the high-temporal DCE series:

- Time-to-enhancement (TTE): time difference between contrast reaching the aorta and the tumor[15,16]. TTE=t_{tumor}-t_{aorta}, where t_{aorta} is the first time point with ≥100% increase in median relative enhancement (RE) within the aorta-ROI and t_{tumor} the first time point with ≥50% increase in the 90th percentile RE within the GTV-ROI. If the t_{tumor}-threshold was not reached, t_{tumor} was set to the time of the last high-temporal DCE image plus an additional 5 seconds;
- 1-minute relative enhancement (RE_{1min}): the 90th percentile RE value in the GTV-ROI at one minute after enhancement of the aorta[17,18];

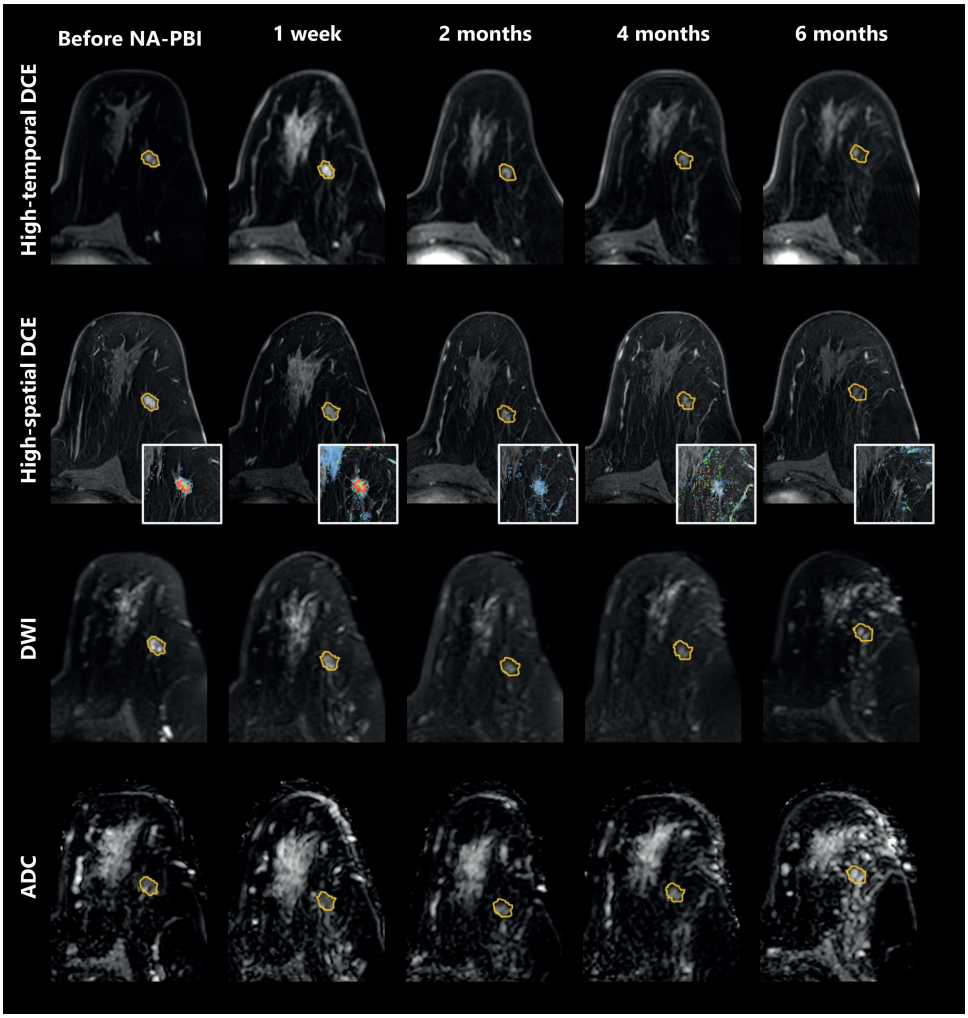


FIGURE 2. Overview of all MR images acquired in a single patient and GTV-ROIs used for analysis (yellow). The high-spatial DCE insets show the wash-out curve types for the voxels >100% relative enhancement: type 1 (blue), type 2 (green), and type 3 (red). This patient had no radiologic complete response at any moment and showed a near pCR (<10% residual tumor cells) after surgery.

In the high-spatial DCE series:

- Percentage of enhancing voxels (%EV): the percentage of voxels in the GTV-ROI with >100% RE at the first post-contrast image[19,20];
- Relative distribution of wash-out curve types for enhancing voxels: determined from the voxel-wise RE difference between first and last post-contrast-injection images, and defined as: type 1 (≥+10% RE) – low probability of malignancy, type 2 (-10% to +10% RE) – intermediate probability of malignancy, and type 3 (≤-10% RE) – high probability of malignancy[4,21,22].

In the DW series:

- Median ADC-value.

For both DCE series the RE was determined as where SI is the signal intensity, t=0 the pre-contrast-injection image, and t>0 the post-contrast-injection images. In the high-spatial DCE series, a Gaussian filter was applied to reduce influence of noise. All semi-quantitative analyses were performed using Matlab[23].

Statistical analysis

Semi-quantitative parameters were analyzed using descriptive statistics (median and interquartile range (IQR)) for the entire cohort, per qualitative radiologic response group, and per pathologic response group, using Rstudio (version 1.1.453[24]). No further statistical tests were performed due to the small number of included patients. We analyzed MR images obtained up to six months following NA-PBI for all 36 patients. The analyses of the eight months MR images of the 21 patients that underwent surgery at eight months following NA-PBI are presented in the supplementary material.

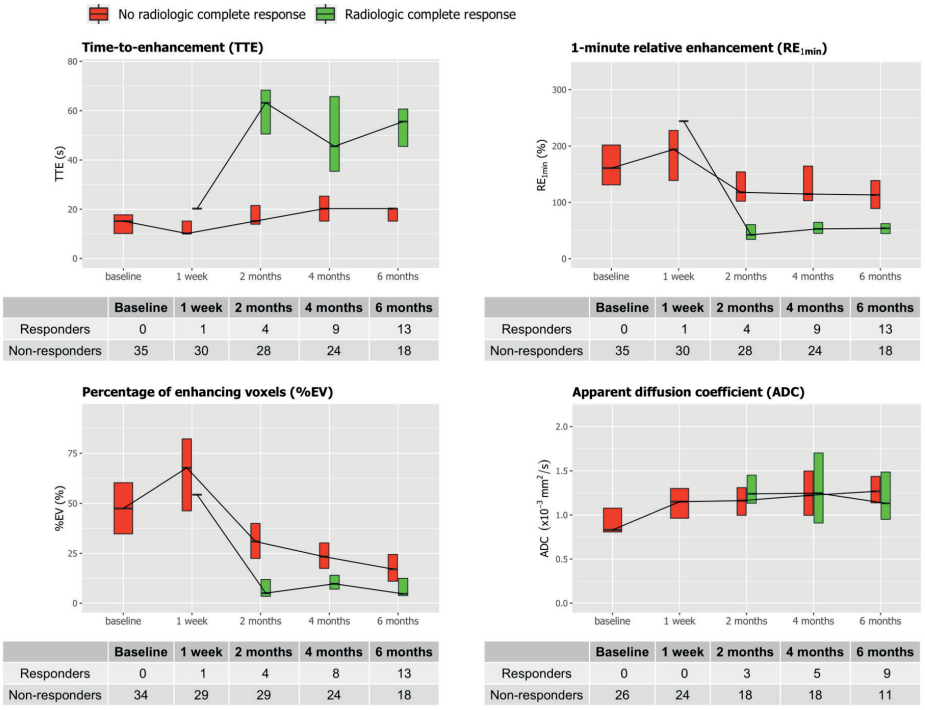
RESULTS

We analyzed 163 high-temporal and 161 high-spatial DCE series and 115 DW series out of a total of 180 scans. Five high-temporal DCE series, seven high-spatial DCE series, and five DW series were not or incorrectly acquired (i.e. no pre-contrast image available, interrupted before end of dynamic series, or incorrectly saved). We excluded the high-temporal and high-spatial DCE series of 12 scan moments in ten patients from analysis because the registration of the delineation could not be performed (n=9) or because fat suppression had failed (n=3). We excluded all DW series of eight patients because the DW series could not be correctly registered to the DCE-MRI. DW series of 20 scan moments in fourteen additional patients were excluded because registration could not be performed (n=17) or fat suppression had failed (n=3).

The median volume for analysis was 1.17 ml (IQR 0.57-1.78) for the high-spatial DCE series, 1.57 ml (IQR 0.86-2.28) for the high-temporal DCE series, and 1.40 ml (IQR 0.72-1.80) for the ADC-analyses.

All patients

Semi-quantitative parameter values calculated from MR images for the entire cohort are shown in table 1. Median TTE decreased from 15 seconds at baseline to 10 seconds at one week following NA-PBI and increased to 25 seconds at later scan moments. Median RE_{1min} showed an increase from 161% at baseline to 197% at one week after NA-PBI followed by a decrease to 86% at six months after NA-PBI. The same pattern was observed for median %EV (47% at baseline, 67% at one week, 12% at six months) and for wash-out_{type1} (22% at baseline, 36% at one week, 9% at six months). A decrease in median wash-out_{type2} and wash-out_{type3} was observed from baseline (11% and 8%, respectively) to six months after radiotherapy (1% and 0%, respectively). The ADC steadily increased from $0.83x10^{-3}$ mm^2/s at baseline to $1.27x10^{-3}$ mm^2/s at six months after radiotherapy.



	Baseline	1 week	2 months	4 months	6 months
Responders	0	1	4	9	13
Non-responders	35	30	28	24	18

	Baseline	1 week	2 months	4 months	6 months
Responders	0	1	4	9	13
Non-responders	35	30	28	24	18

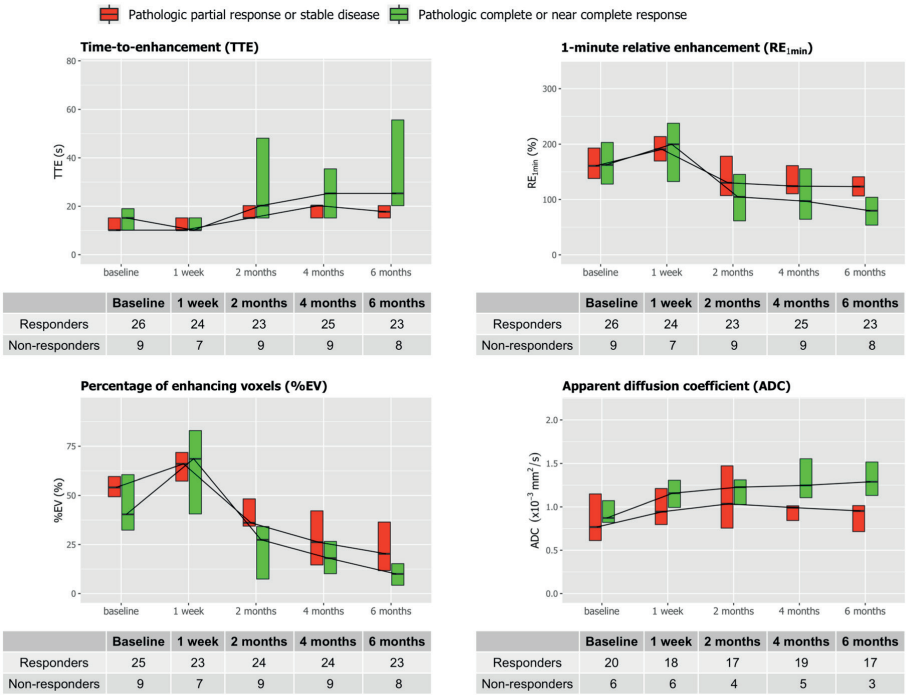
	Baseline	1 week	2 months	4 months	6 months
Responders	0	1	4	8	13
Non-responders	34	29	29	24	18

	Baseline	1 week	2 months	4 months	6 months
Responders	0	0	3	5	9
Non-responders	26	24	18	18	11

FIGURE 3. Median (interquartile range) semi-quantitative parameter values before and following NA-PBI grouped by qualitative radiologic response along with the number of available scans per scan moment.

Grouped by qualitative radiologic response

Analyses of semi-quantitative parameters in relation to radiologists' clinical assessments are depicted in table 2A. Parameters standing out when grouped by qualitative radiologic response are TTE, RE_{1min}, and %EV (figure 3). Median TTE increased from 15 seconds (baseline) to 56 seconds in radiologic complete responders versus 20 seconds in the radiologic non-complete responders (six months). Median RE_{1min} decreased from 161% (baseline) to 54% for the radiologic complete responders versus 113% for the radiologic non-complete responders (six months). Median %EV changed from 46% (baseline) to 5% for radiologic complete responders versus 17% for radiologic non-complete responders (six months). Median ADC-value changed from $0.83x10^{-3}$ mm^2/s (baseline) to $1.13x10^{-3}$ mm^2/s for radiologic complete responders and $1.27x10^{-3}$ mm^2/s for radiologic non-complete responders (six months).



	Baseline	1 week	2 months	4 months	6 months
Responders	26	24	23	25	23
Non-responders	9	7	9	9	8

	Baseline	1 week	2 months	4 months	6 months
Responders	26	24	23	25	23
Non-responders	9	7	9	9	8

	Baseline	1 week	2 months	4 months	6 months
Responders	25	23	24	24	23
Non-responders	9	7	9	9	8

	Baseline	1 week	2 months	4 months	6 months
Responders	20	18	17	19	17
Non-responders	6	6	4	5	3

FIGURE 4. Median (interquartile range) semi-quantitative parameter values before and following NA-PBI grouped by pathologic response along with the number of available scans per scan moment.

Grouped by pathologic response

Analyses of semi-quantitative parameters in relation to pathologic response are depicted in table 2B. The most notable parameters when grouped by pathologic response were TTE, RE_{1min} and ADC-value (figure 4). Median TTE changed from 15 seconds (baseline) to 25 seconds (six months) for pathologic responders and from 10 seconds (baseline) to 18 seconds (six months) for pathologic non-responders. Median RE_{1min} showed a decrease from 162% (baseline) to 80% (six months) for pathologic responders, versus 161% (baseline) to 123% (six months) for pathologic non-responders. Median ADC-value increased from $0.87x10^{-3}$ mm^2/s (baseline) to $1.29x10^{-3}$ mm^2/s (six months) for pathologic responders, versus $0.77x10^{-3}$ mm^2/s (baseline) to $0.95x10^{-3}$ mm^2/s (six months) for pathologic non-responders.

DISCUSSION

In this study, we evaluated the response to single-dose ablative NA-PBI in low-risk breast cancer patients using semi-quantitative analyses of repeated MRI acquired before and up to six months after radiotherapy. In the entire cohort, semi-quantitative analyses at one week after radiotherapy showed an increase in %EV, indicating acute inflammation, and analyses at two to six months after NA-PBI showed a decrease in %EV and voxels with a malignant washout curve, and an increase in ADC-values, indicating tumor response. %EV, TTE, and RE_{1min} appeared to correspond to differences between radiologic complete responders and non-complete responders as qualitatively assessed by breast radiologists. This indicates that semi-quantitative DCE parameters may correctly distinguish the qualitative radiologic response, even though radiologists mostly rely on more qualitative assessment to determine response. TTE and RE_{1min} at six months after NA-PBI and median ADC-value at four months after NA-PBI showed interesting trends for the identification of pathologic response groups. However, differences between the qualitative radiologic response groups and differences between the pathologic response groups were not statistically tested in this small cohort.

The initial increase in relative enhancement observed on MRI acquired at one week after radiotherapy was also observed in two other studies on NA-PBI[8,9]. Wang et al. suggested that this early response could be used as a response biomarker, but Mouawad et al. argued that it demonstrated too much acute inflammatory effects to assess tumor response and proposed to wait at least 2.5 weeks after radiotherapy before performing MRI. Our results at one week after NA-PBI confirmed signs of increased enhancement which most likely indicate radiotherapy-induced acute inflammation[25,26]. Wang et al. reported no changes in ADC one week after radiotherapy in their full group of 15 patients, presumably due to the short time interval between radiotherapy and imaging, though their subgroup analysis showed a relative increase in ADC in the highest dose group (21 Gy). Our results showed a similar increase in ADC-value one week after radiotherapy.

We applied rigid registration for propagation of the GTV delineation between scans acquired at different scan moments. Advantages of this approach are that it ensured use of the same GTV-ROI for analyses at each scan moment, that it was not subject to delineation subjectivity or delineation errors, and that it even allowed us to evaluate MRI parameters in radiologic complete responders. Disadvantages of the approach are that we could not evaluate change in tumor volume over time and that it led to surrounding non-tumor tissue entering the ROI for tumors that reduced in volume. We argue that since this tissue is mainly fatty tissue or healthy glandular breast tissue, it presents

different values for the semi-quantitative parameters than tumor tissue. Another approach for GTV-ROI determination could be to manually adapt the GTV delineation at each scan moment or to use deformable image registration to do this, which would have allowed evaluation of tumor volume change. However, such an approach is less reproducible and prone to delineation errors. Despite the image registrations, we had to exclude a reasonable number of scans. Because these belonged to different patients and were distributed over all scan moments after NA-PBI, this has most likely not influenced interpretation of the results of the semi-quantitative parameters.

In all patients, a marker was introduced for tumor localization. This marker impeded both the DCE and DW-MRI analyses because it lacks MR signal and distorts the homogeneity of the local magnetic field. Because the marker is present at each scan moment and the artefact will appear largely between scans moments, changes in parameters will most likely be due to changes in the tumor tissue. In two patients a marker was inserted between the baseline MRI scan and the first MRI scan acquired after NA-PBI, therefore we delineated the marker artefact and excluded those voxels from the GTV-ROI at each scan moment. As it is necessary to place a fiducial marker for clinical radiologic follow-up, position verification during radiotherapy, and tumor localization during surgery, we recommend to use a marker which causes only small artefacts on MRI, such as a gold fiducial marker or a carbon coated ceramic breast tissue marker[27,28].

A limitation of our study is that it was designed as a feasibility study for single-dose ablative NA-PBI, resulting in too small numbers of patients in the pathologic response groups (27 responders versus 9 non-responders) to statistically test differences in semi-quantitative parameters between the groups. Although it resulted in unevenly sized subgroups, we chose to classify patients with a near pCR as responders, because we expected that differences between pCR and near pCR cannot be macroscopically distinguished in the MR images. Furthermore, it might be safe to omit surgery in patients with near pCR as well.

Another limitation is that our MRI protocol did not include a B0 map, for assessment and correction of distortions and marker artefacts, and a T1 map, for evaluation of quantitative DCE parameters, such as K^{trans} and v_e [29–31] . It has been shown that semi-quantitative analysis of the signal-intensity time curves correlates well with quantitative assessments[18,31,32]. Therefore, we argue that our semi-quantitative approach using available clinical scans is valid.

Ideally, pathologic response can be predicted from MRI scans acquired before or after NA-PBI to select patients with an excellent pathologic response. In those patients, surgery could be omitted after NA-PBI. We believe that TTE and RE_{1min} at six months after NA-PBI, and ADC at least four months after NA-PBI might contribute to this goal.

All other parameters, and TTE, RE_{1min} and ADC at earlier scan moments after NA-PBI, did not indicate differences between the pathologic response groups. This can be valuable information for future studies, and has to be further evaluated in larger cohorts.

CONCLUSION

The evaluation of semi-quantitative parameters derived from DCE-MRI and DW-MRI before and after single-dose ablative NA-PBI showed changes indicating acute inflammation shortly after radiotherapy followed by changes indicating tumor response up to six months after radiotherapy. TTE, $RE1_{min}$, and %EV showed the largest differences between radiologic complete responders and radiologic non-complete responders as assessed according to clinical practice. TTE,RE_{1min}, and ADC-value are the most promising parameters for differentiation between pathologic responders and non-responders.

TABLE 1. Median (interquartile range) semi-quantitative parameter values before and following NA-PBI for the full patient population. The number of assessable scans per time point is presented [in brackets].

Parameter	**Baseline** median (IQR) [n]	**1 week** median (IQR) [n]	**2 months** median (IQR) [n]	**4 months** median (IQR) [n]	**6 months** median (IQR) [n]
High-temporal DCE series					
TTE (s)	15 (10-18) [35]	10 (10-15) [31]	20 (15-27) [32]	20 (15-30) [34]	25 (18-46) [31]
RE_{1min} (%)	161 (131-202) [35]	197 (143-232) [31]	113 (92-150) [32]	108 (73-160) [34]	86 (57-135) [31]
High-spatial DCE series					
%EV	47 (35-60) [34]	67 (48-82) [30]	30 (9-38) [33]	19 (11-28) [33]	12 (5-20) [31]
%-wash-out_{type1}	22 (15-28) [34]	36 (23-45) [30]	26 (9-33) [33]	15 (9-21) [33]	9 (4-14) [31]
%-wash-out_{type2}	11 (8-14) [34]	11 (4-18) [30]	3 (1-5) [33]	2 (1-4) [33]	1 (1-3) [31]
%-wash-out_{type3}	8 (4-16) [34]	6 (1-21) [30]	1 (0-2) [33]	1 (0-2) [33]	0 (0-2) [31]
DW series					
Median ADC (x 10^{-3} mm^2/s)	0.83 (0.81-1.08) [26]	1.15 (0.96-1.30) [24]	1.23 (1.00-1.31) [21]	1.22 (0.97-1.54) [24]	1.27 (1.01-1.49) [20]

Abbreviations: IQR = interquartile range; DCE = dynamic contrast-enhanced; DW = diffusion-weighted; TTE = time-to-enhancement; RE_{1min} = relative enhancement 1-minute after aorta enhancement; %EV = percentage of enhancing voxels; %-wash-out_{typex} = percentage of voxels with wash-out type curve x; ADC = apparent diffusion coefficient

TABLE 2. Median (interquartile range) semi-quantitative parameter values before and following NA-PBI grouped to radiologic response (A) and pathologic response (B). The number of assessable scans per time point is presented [in brackets].

TABLE 2A – grouped to radiologic response

Parameter	**Radiologic complete response**	**Baseline** median (IQR) [n]	**1 week** median (IQR) [n]	**2 months** median (IQR) [n]	**4 months** median (IQR) [n]	**6 months** median (IQR) [n]
High-temporal DCE series						
TTE (s)	Yes	- [0]	20 (20-20) [1]	63 (51-68) [4]	46 (35-66) [9]	56 (46-61) [13]
	No	15 (10-18) [35]	10 (10-15) [30]	15 (14-22) [28]	20 (15-25) [24]	20 (15-20) [18]
RE_{1min} (%)	Yes	- [0]	244 (244-244) [1]	42 (34-60) [4]	53 (45-64) [9]	54 (45-62) [13]
	No	161 (131-202) [35]	194 (139-228) [30]	118 (102-154) [28]	115 (103-164) [24]	113 (89-139) [18]
High-spatial DCE series						
%EV	Yes	- [0]	54 (54-54) [1]	5 (3-12) [4]	10 (7-14) [8]	5 (4-12) [13]
	No	47 (35-60) [34]	68 (46-82) [29]	31 (22-40) [29]	23 (17-30) [24]	17 (11-24) [18]
%-wash-out_{type1}	Yes	- [0]	35 (35-35) [1]	3 (3-10) [4]	7 (5-9) [8]	4 (3-8) [13]
	No	22 (15-28) [34]	38 (23-45) [29]	27 (10-34) [29]	18 (13-24) [24]	11 (9-20) [18]
%-wash-out_{type2}	Yes	- [0]	13 (13-13) [1]	0 (0-0) [4]	1 (1-2) [8]	1 (1-1) [13]
	No	11 (8-14) [34]	11 (4-18) [29]	3 (1-5) [29]	3 (2-5) [24]	3 (1-5) [18]
%-wash-out_{type3}	Yes	- [0]	6 (6-6) [1]	0 (0-1) [4]	1 (0-2) [8]	0 (0-1) [13]
	No	8 (4-16) [34]	7 (1-21) [29]	1 (0-2) [29]	1 (0-2) [24]	1 (0-2) [18]
DW series						
Median ADC (x 10^{-3} mm^2/s)	Yes	- [0]	- [0]	1.24 (1.13-1.45) [3]	1.25 (0.91-1.70) [5]	1.13 (0.95-1.49) [9]
	No	0.83 (0.80-1.08) [26]	1.15 (0.96-1.30) [24]	1.16 (1.00-1.31) [18]	1.22 (1.00-1.50) [18]	1.27 (1.14-1.44) [11]

Abbreviations: IQR = interquartile range; DCE = dynamic contrast-enhanced; DW = diffusion-weighted; TTE = time-to-enhancement; RE_{1min} = relative enhancement 1-minute after aorta enhancement; %EV = percentage of enhancing voxels; %-wash-out_{typex} = percentage of voxels with wash-out type curve x; ADC = apparent diffusion coefficient

TABLE 2B – grouped to pathologic response

Parameter	Pathologic complete or near complete response	Baseline median (IQR) [n]	1 week median (IQR) [n]	2 months median (IQR) [n]	4 months median (IQR) [n]	6 months median (IQR) [n]
High-temporal DCE series						
TTE (s)	Yes	15 (10-19) [26]	10 (10-15) [24]	20 (15-48) [23]	25 (15-35) [25]	25 (20-56) [23]
	No	10 (10-15) [9]	10 (10-15) [7]	15 (15-20) [9]	20 (15-20) [9]	18 (15-20) [8]
RE_{1min} (%)	Yes	162 (128-203) [26]	200 (133-238) [24]	105 (62-145) [23]	97 (64-155) [25]	80 (54-104) [23]
	No	161 (138-193) [9]	191 (170-214) [7]	130 (107-178) [9]	124 (110-161) [9]	123 (106-141) [8]
High-spatial DCE series						
%EV	Yes	40 (32-61) [25]	69 (41-83) [23]	27 (7-34) [24]	18 (10-27) [24]	10 (4-15) [23]
	No	54 (49-60) [9]	66 (57-72) [7]	36 (34-48) [9]	26 (15-42) [9]	20 (12-36) [8]
%-wash-out_{type1}	Yes	21 (12-27) [25]	38 (22-49) [23]	19 (4-28) [24]	14 (7-19) [24]	7 (3-11) [23]
	No	24 (22-37) [9]	35 (26-41) [7]	33 (27-39) [9]	18 (14-36) [9]	14 (10-27) [8]
%-wash-out_{type2}	Yes	10 (7-14) [25]	11 (4-15) [23]	3 (1-5) [24]	2 (1-4) [24]	1 (1-2) [23]
	No	11 (10-16) [9]	19 (13-21) [7]	3 (1-9) [9]	3 (1-5) [9]	3 (2-5) [8]
%-wash-out_{type3}	Yes	8 (3-17) [25]	6 (1-21) [23]	1 (0-2) [24]	1 (0-3) [24]	0 (0-1) [23]
	No	8 (6-13) [9]	15 (6-23) [7]	1 (0-2) [9]	1 (0-2) [9]	1 (0-3) [8]
DW series						
Median ADC (x 10^{-3} mm^2/s	Yes	0.87 (0.82-1.07) [20]	1.16 (0.99-1.31) [18]	1.23 (1.03-1.31) [17]	1.25 (1.11-1.55) [19]	1.29 (1.13-1.52) [17]
	No	0.77 (0.61-1.15) [6]	0.95 (0.80-1.21) [6]	1.04 (0.76-1.47) [4]	0.99 (0.84-1.01) [5]	0.95 (0.72-1.02) [3]

Abbreviations: IQR = interquartile range; DCE = dynamic contrast-enhanced; DW = diffusion-weighted; TTE = time-to-enhancement; RE_{1min} = relative enhancement 1-minute after aorta enhancement; %EV = percentage of enhancing voxels; %-wash-out_{typex} = percentage of voxels with wash-out type curve x; ADC = apparent diffusion coefficient

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7

THREE METHODS FOR EVALUATION OF COSMETIC OUTCOME IN CLINICAL TRIALS AFTER BREAST CONSERVING TREATMENT: INTERRATER AGREEMENT AND RELIABILITY

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ABSTRACT

Purpose: Various methods of cosmetic evaluation following breast cancer treatment are being used in clinical trials, including patient-reported outcome, evaluation by professionals and evaluation through objective software. We compared agreement and reliability between these three evaluation methods in early stage breast cancer patients, to assess whether the methods can be used interchangeably.

Methods: Cosmetic evaluation in 36 breast cancer patients treated with neoadjuvant radiotherapy and breast-conserving surgery was performed at baseline and at 1-year follow-up by patients, by professionals and through objective software (BCCT.core). Patients reported cosmesis on a 5-point Likert scale (very satisfied, satisfied, not unsatisfied, unsatisfied, very unsatisfied), professionals and software used a 4-point scale (excellent, good, fair, poor). Patient-reported unsatisfied and very unsatisfied were combined to create a comparable 4-point scale. Proportions of agreement and reliability (Cohen's kappa) were calculated.

Results: Agreement between patient and professionals was 36% (95%-CI 21%–55%) at baseline and 29% (15%–48%) at 1-year follow-up, between patients and software 41% (25%–59%) and 30% (15%–50%), and between professionals and software 61% (42%–77%) and 59% (41%–75), respectively. At baseline reliability was very poor: kappa of 0.00 (-0.22–0.22) for patients and professionals, -0.09 (-0.33–0.16) for patients and software, and 0.24 (-0.07–0.55) for professionals and software. At 1-year follow-up reliability remained poor: kappa of 0.10 (-0.08–0.27), -0.07 (-0.28–0.13), and 0.10 (-0.13–0.33), respectively.

Conclusion: Agreement between the three evaluation methods was fair to moderate, while reliability was poor. Therefore, the three methods should not be used interchangeably.

INTRODUCTION

The majority of early stage breast cancer patients is treated with breast conserving surgery (BCS) and adjuvant radiotherapy [1]. In evaluating the outcome of breast cancer treatment, the focus of research is shifting from survival rates towards long-term side effects and patient-reported outcomes, such as physical functioning and quality of life [2–5]. Quality of life is associated with the cosmetic outcome of breast cancer treatment [6–9]. Multiple methods to evaluate the cosmetic outcome following BCS are available, and can be categorized into three methods: evaluation by patients, evaluation by professionals, and evaluation through an objective software tool. Examples of the first are the Breast-Q questionnaire and the questionnaire developed by Sneeuw et al. [10,11]. Examples of evaluation by professionals are mostly applied in clinical trials, and can consist of assessment by a professional or can be based on a consensus reached by an expert panel [12,13]. The most commonly used objective tool is the BCCT.core software tool in which digital photographs are assessed through an algorithm [14]. It is unclear whether these methods can be used interchangeably, and whether studies with different cosmetic outcome measurement tools can be compared [8,14–17]. Furthermore, clinical trials often incorporate multiple methods to assess cosmetic outcomes, which potentially poses an unnecessary burden to patients and/or professionals [12,13].

In this study, we evaluated reproducibility in terms of agreement and reliability of three different tools for cosmetic outcome assessment , i.e. a patient questionnaire, a questionnaire for professionals, and the BCCT.core software [11,18,19].

METHODS

Patient selection

Patients participating in the ABLATIVE trial (Clinicaltrials.gov identifier: NCT02316561) were included [20]. Within this trial we included 36 low-risk breast cancer patients who were treated with single-dose neoadjuvant ablative radiotherapy of 20 Gy to the tumor and 15 Gy to breast tissue within 2 cm of the tumor. Eligible were patients with primary non-lobular unifocal breast cancer with a maximum diameter of 30 mm, without lymphatic and distant spread of disease. Patients with an indication for (neo)adjuvant chemotherapy were not eligible. Median age of the patients was 65 years (range 51-78), median tumor diameter on MRI was 13 mm (range 5-20), and median BMI was 26.8 (range 20.7-43.9) (table 1). Six patients received additional adjuvant endocrine treatment. Single-dose radiotherapy was followed by BCS after an interval of six or eight months. The Institutional Review Board of the UMC Utrecht, the Netherlands,

approved the trial and all women had given written informed consent. The primary goal of the ABLATIVE study was to assess the rate of pathologic complete response following neoadjuvant irradiation.

Cosmetic evaluation

Cosmetic outcomes were evaluated independently by patients, by a professional, and through the BCCT.core software. All evaluations were performed at baseline (i.e. prior to breast treatment), and at 1 year following irradiation, which is four or six months following BCS. Patients were asked to fill out the Sneeuw et al. questionnaire, dedicated radiation oncologists or physician assistants filled out a standardized questionnaire during an outpatient visit, and digital photographs were taken on the same day [11,21]. From the questionnaire by Sneeuw et al. the final question on overall cosmesis was used ("How satisfied/unsatisfied are you with the appearance of your treated breast in comparison to your untreated breast?"). One professional filled out the questionnaire per evaluation moment. Digital photographs were analyzed using the BCCT.core software [14]. The outcome of the BCCT.core software is based on asymmetry between the breasts, color, and scar visibility. Patients, professionals and the researcher who analyzed the photographs through the software were blinded to each other's ratings. All were aware of the timing of evaluation; either at baseline or at 1-year follow-up. Patient reported cosmetic outcomes were rated on a 5-point Likert scale, i.e. very satisfied, satisfied, not unsatisfied, unsatisfied, or very unsatisfied. The questionnaire for professional evaluation and the software tool BCCT.core consisted a 4-point Likert scale, i.e. excellent, good, fair, or poor.

Statistical analysis

For the analyses, patient evaluation was transformed to a 4-point Likert scale by combining unsatisfied and very unsatisfied into one category. Consequently, we assumed very satisfied to be equal to excellent, satisfied to be equal to good, not unsatisfied to be equal to fair, and (very) unsatisfied to be equal to poor.

For both the baseline and 1-year follow-up evaluations, the agreement between each pair of the three methods was calculated by dividing the agreeing evaluations by all evaluations. The reliability between each pair of the three methods was evaluated using a weighted Cohen's kappa with linear weights. For both the agreement and reliability a 95% confidence interval (CI) was calculated at baseline and 1-year follow-up. The agreement describes to which extent the different evaluation methods agree on each measure. The reliability describes to which extent patients with different ratings can be distinguished from each other [22]. For the reliability, a negative value of Cohen's kappa

indicates an observed agreement lower than would be expected based on chance. In order for the three methods to be used interchangeably, both the agreement and reliability need to be acceptable. Statistical analyses were performed using R open-source software ('irr' and 'rel' package, version 3.6.0).

RESULTS

At the time of analysis, thirty-five patients reported cosmetic outcome at baseline and 31 at 1-year follow-up. The professional and the software tool assessed cosmesis of 34 and 35 patients at baseline, respectively, and of 36 and 34 patients at 1-year follow-up, respectively.

At baseline and 1-year follow-up, the majority of the ratings by patients, professionals and objective software was excellent or good (Table 1). At baseline, not unsatisfied ratings were reported by two patients (6%), and (very) unsatisfied ratings by two patients (6%) as well, while the corresponding fair and poor were not reported by the professional or software evaluation methods. At 1-year follow-up, nine patients (29%) rated the cosmetic outcome as not unsatisfied, while fair was rated three times by the professional (8%) and twice by the software (6%). Two patients (7%) rated the cosmetic outcome as (very) unsatisfied, while poor was not rated by the professional or the software.

TABLE 1. Patient characteristics at baseline

Median age in years (range)	65 (51-78)
Median BMI in kg/m^2 (range)	26,8 (20,7-43,9)
Median tumor diameter in mm (range)	13 (5-20)
Patients with neoadjuvant endocrine treatment	6 (17%)

Proportions of agreement between patients and professionals were 36% (95%-CI 21% – 55%) at baseline and 29% (95%-CI 15% – 48%) at 1-year follow-up. At baseline and at 1-year follow-up, proportions of agreement between patients and software were 41% (95%-CI 25% – 59%) and 30% (95%-CI 15% – 50%), and between professionals and software 61% (95%-CI 42% – 77%) and 59% (95%-CI 41% – 75%), respectively.

At baseline reliability (Cohen's kappa) was 0.00 (95%-CI -0.22 – 0.22) between patients and professionals, -0.09 (95%-CI -0.33 – 0.16) between patients and software, and 0.24

(95%-CI -0.07 – 0.55) between professionals and software. At 1-year follow-up Cohen's kappa was 0.10 (95%-CI -0.08 – 0.27) for reliability between patients and professionals, -0.07 (95%-CI -0.28 – 0.13) between patients and software, and 0.10 (95%-CI -0.13 – 0.33) between professionals and software.

TABLE 2A. Patient- and professional-reported cosmetic outcomes at baseline

		Patient-reported			
		Very satisfied	**Satisfied**	**Not unsatisfied**	**(Very) unsatisfied**
Professional-reported	Excellent	8	13	0	1
	Good	4	4	2	1
	Fair	0	0	0	0
	Poor	0	0	0	0

TABLE 2B. Patient- and professional-reported cosmetic outcomes at 1-year follow-up

		Patient-reported			
		Very satisfied	**Satisfied**	**Not unsatisfied**	**(Very) unsatisfied**
Professional-reported	Excellent	1	1	0	0
	Good	10	7	8	1
	Fair	0	1	1	1
	Poor	0	0	0	0

TABLE 3A. Patient-reported cosmetic outcome and objective evaluation by BCCT.core at baseline

		Patient-reported			
		Very satisfied	**Satisfied**	**Not unsatisfied**	**(Very) unsatisfied**
BCCT.core	Excellent	4	8	1	1
	Good	8	10	1	1
	Fair	0	0	0	0
	Poor	0	0	0	0

TABLE 3B. Patient-reported cosmetic outcome and objective evaluation by BCCT.core at 1-year follow-up

		Patient-reported			
		Very satisfied	**Satisfied**	**Not unsatisfied**	**(Very) unsatisfied**
BCCT.core	Excellent	3	2	4	0
	Good	7	6	4	2
	Fair	1	1	0	0
	Poor	0	0	0	0

TABLE 4A. Professional-reported cosmetic outcomes and objective evaluation by BCCT.core at baseline

		Professional-reported			
		Excellent	**Good**	**Fair**	**Poor**
BCCT.core	Excellent	11	3	0	0
	Good	10	9	0	0
	Fair	0	0	0	0
	Poor	0	0	0	0

TABLE 4B. Professional-reported cosmetic outcomes and objective evaluation by BCCT.core at 1-year follow-up

		Professional-reported			
		Excellent	**Good**	**Fair**	**Poor**
BCCT.core	Excellent	2	8	1	0
	Good	1	18	2	0
	Fair	0	2	0	0
	Poor	0	0	0	0

DISCUSSION

The agreement between the three evaluation methods, ranging from 29% to 61%, is fair to moderate. The reliability of the methods, ranging between -0.09 and 0.24, is poor. Therefore, the three different methods for evaluation of cosmetic results cannot be used interchangeably, meaning if one of the evaluation methods is missing, the outcomes of the other methods should not be used as a substitute [18,23].

The poor reliability can be partly explained by the skewed data, meaning that the vast majority of all obtained ratings was good (satisfied) or excellent (very satisfied). This results in a very high expected agreement based on chance, and therefore in a rapid decline in reliability with each observed disagreement between the evaluation methods. As most ratings were good (satisfied) or excellent (very satisfied), most disagreements were found between these two ratings. However, as indicated by the poor reliability, the evaluation methods do not agree, or agree less than would be expected based on chance, on which patients have a fair or poor cosmetic outcome. We believe the reported Cohen's kappa's are a proper representation of the reliability between the three evaluation methods, as it has been reported earlier that irradiation followed by BCS showed good cosmetic outcome [24]. Like previous studies on agreement and reliability between different evaluation methods, we also find the highest agreement between professionals and a software tool and lower agreement when patient-reported outcomes are involved [11,17,25]. However, we report lower overall ratings of agreement and reliability. Wadasadawala et al. report a kappa of 0.67 for reliability between professionals and the software tool, and 0.46 for professionals and patients at 18 to 36 months following treatment, compared to 0.10 and 0.10 in our study at 1 year following treatment [25]. Our results are more in line with the study by Sneeuw et al. from 1992, who reported a kappa of 0.07 for reliability between professionals and patients at a mean of 4 years following treatment [11]. Brouwers et al. also report on reliability between the three evaluation methods, and conclude a moderate reliability between patients and professionals, with a kappa of 0.42, fair reliability between patients and a software tool, kappa of 0.26, and fair reliability between professionals and the software tool, kappa of 0.39, at a median of 51 months following treatment. All of these reliabilities are higher than the ones that we report. It should be noted that in all studies mentioned, the outcomes are dichotomized to being either good/satisfactory and poor/unsatisfactory. When having only two outcome categories, both the agreement and reliability is expected to improve.

Merie et al. advocated that a gold standard for the evaluation of cosmetic results should be implemented in clinical trials, to be able to compare between different trials and

to identify treatment variables that affect the final cosmetic result [16]. They proposed the BCCT.core software tool to be used as this gold standard, because it is an objective measurement, with a high reproducibility and reliability. Furthermore, it is rather easy to implement, time-efficient, and more cost-efficient than an expert-panel evaluation. While we agree on the benefits of an objective software tool, it is not able, as the term objective already indicates, to consider the subjective effects of breast cancer treatment on the cosmetic result. Software tools for the evaluation of cosmetic results mostly rely on symmetry, or actually asymmetry, between the breasts. However, the appreciation of the cosmetic result by the patient is more than only (a)symmetry between the breast. Some of the subjective factors that can affect the cosmetic result are firmness, tenderness and pain [8,26]. Furthermore, a patient's view on the breast is different from professionals and photographs, as patients view their breasts mostly from above and not in front of a mirror with their arms raised. The evaluation method that most adequately considers these effects is the evaluation by patients themselves. However, patients also use factors to evaluate the outcome, that both professionals and software tools would deem outside the scope of cosmesis, such as their relationship to the healthcare professionals and the clinical outcome of their treatment in the evaluation of the cosmetic outcome [27].

The International Consortium for Health Outcomes Measurements (ICHOM) Initiative recommends to use a patient questionnaire to assess the cosmetic outcome to acknowledge these more subjective factors [3]. They specifically recommend to use the Breast-Q questionnaire, which uses different questionnaires for the preoperative and postoperative setting [28]. However, no Dutch translation of this questionnaire was available at the time this study was initiated, therefore it was not evaluated. The recommendation by ICHOM is based on the knowledge that patients' perspectives can and should be used to facilitate a shared-decision-making process, which empower patients during their disease and treatment. This also benefits health care providers, as they can adequately inform new patients on the broad range of possible results of a proposed treatment. Professionals' evaluations are more of a proxy for the patient evaluation of cosmetic outcome, as their evaluation will be based on subjective outcomes as found during physical examination or as information provided by the patient [29]. The downside of using several methods for cosmetic evaluation simultaneously within one trial, is the burden for patients and professionals. Posing for photographs for the software tool can be experienced as uncomfortable by patients [30]. Collecting multiple questionnaires for patient-reported outcome measures should be limited to only the necessary data, in order to minimize the burden and time-investment for patients and professionals, as well as the time-investment by the investigators to build the data collection [31].

During our analyses the outcomes were divided into four categories: excellent (very satisfied), good (satisfied), fair (not unsatisfied), and poor((very) unsatisfied). It can be argued that the difference that actually matters should be analyzed using only two categories: excellent/good and fair/poor. The three analyzed evaluation methods all have at least four categories, by combining the four categories into two categories, specific information on the appreciation of the cosmetic result will be deleted. The subtle differences between excellent and good, and between fair and poor, are important as well, and will be ignored by using only two categories. We acknowledge that it is a limitation of this study, that we have combined outcomes for the patient-reported evaluation into one category in this study. However, without this intervention evaluating the reliability and agreement between the three evaluation methods would not be possible. Another limitation of this study is the small sample size of only 36 patients. A larger set of patients would lead to a more precise estimate of the agreement and reliability. In a larger set of patients, a more heterogenous group could be evaluated, with a larger range in age and tumor size, in order to extrapolate the results we report to a larger group of breast cancer patients. Larger tumors, and therefore larger excised volumes, could lead to more poor and fair ratings which might increase the reliability [32].

As we report in this study, the more objective evaluation methods cannot be used interchangeably for the patient-reported cosmetic outcome. Patients' perspectives differ from objective tools, as they incorporate more factors into the appreciation than the evaluation by a professional or (a)symmetry as detected by software programs. Because patients are the ones who will be confronted with the cosmetic outcomes in their daily lives, their appreciation should be evaluated to be able to assess current treatment options, as well as differences between current and new treatment options. Additionally, an objective software tool can be used, however, they should not be used as a substitute in case of missing patient-reported cosmetic outcome, or vice versa. Incomplete agreement between the evaluation methods will continue to exist, as professionals and objective software tools will continue to take different factors into account than patients. Incomplete agreement is not a fundamental problem, but the differences between the tools should be kept in mind during communications with patients and the initiation of research within this field.

We believe that the primary evaluation method for cosmetic outcome that is used in a trial, should depend on the research question. For example, when the focus is on interhospital or international research, as to evaluate differences in cosmetic outcome between hospitals or countries, at least an objective software tool (such as BCCT.core) should be used. The objective tool is less affected by pre-existing differences between patients from different hospitals or different countries, such as the level of physical

activity or socioeconomic status. Cosmetic outcomes as evaluated by patients can be affected by emotional and social circumstances, and are therefore not the preferred method to analyze interhospital or international differences, as these circumstances can differ for patients at different institutes [33]. However, if the focus of a trial is to evaluate the cosmetic outcome of a standard treatment or the effect of a new treatment option on the cosmetic outcome, we believe at least patient-reported outcomes should be incorporated, as recommended by ICHOM.

CONCLUSION

Reproducibility of the three evaluation methods (patient-reported, professional-reported, and software-reported) for cosmetic outcome following breast cancer treatment was poor, reflected by the fair to moderate agreement and poor reliability. Therefore, the three methods should not be used interchangeably.

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8

SUMMARY AND FUTURE PERSPECTIVES

PREAMBLE

Nowadays, the majority of women diagnosed with early stage breast cancer is treated with breast conserving surgery followed by adjuvant breast radiotherapy, either whole breast irradiation or partial breast irradiation. The aim of this thesis wass to further expand the treatment options for low-risk early-stage breast cancer patients by evaluating the effect of single dose neoadjuvant partial breast irradiation. The research discussed in this thesis is only one of the steps that need to be taken before neoadjuvant irradiation for breast cancer patients can be implemented in the standard of clinical care through adaption of the national guidelines. The shift from adjuvant PBI to neoadjuvant PBI for low-risk breast cancer patients fits in the tendency of the past decades of treatment de-escalation. This movement started with the shift from mastectomy to breast conserving surgery and adjuvant whole breast irradiation, and continued with the ongoing shift from conventional to hypofractionated radiotherapy schedules, and from adjuvant whole breast irradiation to adjuvant partial breast irradiation. The introduction of neoadjuvant partial breast irradiation resulted in ultra-hypofractionation and even in single-dose radiotherapy in low-risk breast cancer patients. Other new treatment options for low-risk breast cancer consist of the omission of adjuvant radiotherapy following breast-conserving surgery in patients older than 70 years (currently investigated in the TOP-1 trial), and hypofractionated neoadjuvant PBI, (currently investigated in the PAPBI and PAPBI-2 trial) [1]. The expansion of treatment options for low-risk breast cancer, provides patients with the opportunity to weigh benefits and disadvantages in their treatment choice.

In this thesis the technical and clinical research regarding single dose NA-PBI is discussed, however (long term) effects in comparison to standard treatment, economic effects and impact on workload for healthcare professionals has not been addressed. Obviously, these aspects need to be evaluated as well, in order for this novel treatment option to be implemented in standard clinical practice and reimbursed by healthcare insurance companies.

SUMMARY

In chapter 2 we identified several benefits and challenges of MR-guided radiotherapy for breast cancer patients [2]. The major benefit of MR-guided radiotherapy in the neoadjuvant setting is improved target visualization on MRI compared to the standard planning-CT, which we expect to result in increased sparing of normal tissue and therefore a reduction in treatment-induced toxicity and improvement in patient-

reported outcomes. Furthermore, during MR-guided radiotherapy daily and real-time monitoring of the target volume can lead to online adaptive radiotherapy without the need for an additional planning-CT. The major challenges in MR-guided neoadjuvant PBI are the positioning of the patient within the bore of the MRI-scanner, artefacts near the target volume due to biopsy markers or surgical clips, and geometric inaccuracy.

In chapter 3 the process of reaching consensus on guidelines for the contouring of the target volume in neoadjuvant PBI on MRI was presented [3]. The study was performed in low risk breast cancer patients, resulting in very small gross tumor volumes, ranging from 0.19 cm^3 up to 2.44 cm^3. After adding a margin of 20 mm to the gross tumor volume, while staying within the borders of the ipsilateral breast to create the clinical target volume, only low interobserver variation was observed. The guidelines can be used in target volume definition during research and clinical implementation of MR-guided neoadjuvant PBI.

In chapter 4, we investigated the feasibility of neoadjuvant single-dose PBI in low-risk breast cancer patients [4]. Fifteen women (42%) achieved a pathologic complete response, twelve women (33%) achieved a near pathologic complete response, with less than 10% residual tumor cells, and in none of the women an increase in tumor size was observed. Six women (17%) developed a postoperative wound infection, of which one required a surgical treatment. No deterioration in patient-reported breast symptoms, anxiety, and depression were observed during or following treatment. Following this trial, we concluded single-dose neoadjuvant PBI to be a feasible treatment alternative for low-risk breast cancer patients. This novel treatment approach is therefore a major step in the ongoing trend of treatment de-escalation for low-risk breast cancer patients.

In chapter 5 and 6 we explored response monitoring options for the early identification of patients with an excellent pathologic response following neoadjuvant PBI [5]. In chapter 5 we evaluated the number of three different types of tumor infiltrating lymphocytes (TILs) before and after radiotherapy, using material from the diagnostic biopsy and from the surgical resection, respectively. Each type of TILs is essential in a different step in the anti-tumor response of the immune system. We observed a decrease in all types of TILs following irradiation, but no differences between responders and non-responders at any timepoint. In chapter 6 we analysed semi-quantitative parameters within the tumor area derived from MRI-scans obtained before and at several time points following radiotherapy, and assessed whether these parameters differed between responders and non-responders. We observed an increase in relative enhancement in the tumor on the MRI at one week following radiotherapy, suggesting an acute inflammation response. On MR images obtained at later timepoints, an ongoing decrease in

relative enhancement was observed, suggesting tumor response to radiotherapy. The analysed semi-quantitative parameters derived from MRI seem promising in the future differentiation between responders and non-responders.

In chapter 7 we assessed the agreement and reliability of three different methods for the assessment of cosmetic outcomes following breast cancer treatment. A high reliability would demonstrate that the different methods can be used interchangeably in the assessment of cosmetic outcomes. However, we observed a poor reliability. Therefore, the three methods, patient-reported cosmetic outcome, professional-reported cosmetic outcome, and cosmetic outcome as assessed by an objective software tool, can't be used interchangeably. Since oncological outcomes in the standard treatment of low-risk breast cancer patients are excellent, outcomes such as the cosmetic result are of great importance to evaluate in clinical trials. We would recommend to at least include the patient-reported outcomes.

FUTURE PERSPECTIVES

The blue sky discussed within this chapter consists of options to improve the treatment with neoadjuvant single-dose partial breast irradiation in low-risk breast cancer patients. These improvements aim to increase the rate of patients achieving pathologic complete response and to predict the pathologic response in low-risk breast cancer patients receiving neoadjuvant partial breast irradiation. The biggest benefit of neoadjuvant partial breast irradiation would be achievement of pathologic complete response and being able to predict this excellent response before performing surgery. Accordingly, additional surgery could be omitted [6]. Even for patients without a predicted pathologic complete response, the benefit would be the single-dose treatment, instead of 5 or even 15 fractions of radiotherapy, diminishing the time spent at the hospital and reducing the risk of both acute and late treatment-induced toxicity. There might also be a patient group for whom neoadjuvant single-dose partial breast irradiation leads to less favourable results than the current standard treatment. These patients should be identified beforehand as well, in order for them to receive the most appropriate treatment.

To reach this blue sky several paths can be followed, including paths that have been discussed in the preceding chapters, such as repeated MR-imaging and assessment of tumor infiltrating lymphocytes. Furthermore, there might be options to increase the

chance of achieving pathologic complete response, which will lead to more low-risk breast patients having a bigger benefit from treatment with neo-adjuvant partial breast irradiation.

Treatment

An alteration in the treatment approach of neoadjuvant single-dose partial breast irradiation, aiming to increase the chance of pathologic complete response, could consist of increasing the radiation dose that is administered. In the ABLATIVE trial a dose of 20 Gy was prescribed, after which a pathologic complete response was observed in 42% of patients and only mild toxicity was reported [4]. Two other research groups have performed a trial on neoadjuvant single-dose partial breast irradiation and reported acceptable toxicity as well during a maximum follow-up of 37 months [7,8]. In these two studies, a higher dose was prescribed than in the ABLATIVE trial, up to 21 Gy. However, the goal of these studies was not to achieve a pathologic complete response and surgery was performed shortly after radiotherapy. A higher dose on the target volume, preferably does not lead to an increased dose to the surrounding normal tissue. As the 20 Gy in the ABLATIVE trial and the 21 Gy in the other two studies were administered on a conventional linac, a higher dose than 20 Gy on a conventional linac might be feasible as well, or an MR-linac could be used [9,10]. Benefits of administering radiotherapy on an MR-linac instead of on a conventional linac, are the omission of additional radiation dose through repeated CBCT, the possible avoidance of placing an additional marker for tumor localisation during irradiation and the option of real-time treatment plan adaptation. However, there might be downsides to administering treatment on an MR-linac, and to prescribing a higher dose as well.

Firstly, a higher dose could result in increased toxicity, as the surrounding normal tissue will presumably also receive a higher radiation dose. None of the studies on neoadjuvant partial breast irradiation report on actual long-term toxicity, as only a short follow-up is available. Long-term toxicity, such as breast fibrosis, deterioration of cosmetic results and even cardiac toxicity, occurs at the earliest at 3 months following irradiation, but can occur several years after irradiation as well [11–14]. In order to be able to increase the prescribed dose, it is crucial to first evaluate the long-term toxicity in all patients in the ABLATIVE study, and the other studies on neoadjuvant partial breast irradiation, preferably during 10 years. It is uncertain whether toxicity will decrease with treatment on an MR-linac compared a conventional linac, due to the already low occurrence of toxicity following standard treatment in the first place, but also due to the fact that there is little intrafraction movement in breast tumors [15]. A benefit of the MR-linac compared to a conventional linac is real-time monitoring of the tumor resulting in less

uncertainty of the position of the tumor and therefore in theory smaller margins can be used. However, with little intrafraction motion, the planning target volume margin on a MR-linac is not expected to be substantially smaller than on a conventional linac.

Secondly, a higher dose will lead to a longer treatment time, consisting of both the setup time and the beam-on time. A longer treatment time can be a burden for patients, as they need to be in treatment position, which is supine with the arms raised above the head, the entire time [16]. This can be a painful position, not in the least if a sentinel node procedure has been performed recently, limiting the range of motion of the arm on the operated side. A higher dose will mostly affect the beam-on time, as it will take longer to build up the total prescribed dose, and the setup time, as the position of the patient needs to be verified more often during treatment to ensure irradiation of the target volume. Also, treatment on an MR-linac demands even more time when real-time position monitoring and online plan adaptation are used, which could result in reduction of planning target volume margins thus sparing of the surrounding normal tissues [17]. Another challenge when treating patients on the MR-linac is the limited bore size, causing not all breast cancer patients to be able to fit in the scanner in the standard radiotherapy position. This might be overcome by shifting patients to a prone position, however this could also lead to a reduction in patient comfort, especially with the earlier described extended treatment times. Furthermore, the magnetic field distortion and artefacts caused by markers on MR imaging can complicate the replanning on the MR-linac. By using markers that lead to less distortion and artefacts, or by avoiding the insertion of markers completely this challenge could be handled. Distortion of the magnetic field not caused by markers but by the patient, could be resolved by using correction software or a further adaptation of patient positioning. However, not all inaccuracies can be corrected using these options, which might result in adding an unwanted additional margin to the target volume. Especially for the low-risk breast cancer patients with small tumors, the size of the additional margin greatly influences the total irradiated volume. When marker placement will be completely omitted, visibility of the tumor itself can be improved by an intravenous injection of a gadolinium-based contrast agent during treatment on an MR-linac. However, the effect of irradiation on a target volume that contains contrast agent is unclear. The contrast agent might act as a radiosensitizer resulting in an increased dose [18].

In conclusion, low-risk breast cancer patients treated with neoadjuvant partial breast irradiation are not expected to have major benefits from treatment on an MR-linac compared to a conventional linac. Despite the uncertainties and challenges regarding increasing the radiation dose prescribed during neoadjuvant PBI, if an increased dose does result in a higher rate of pathologic complete response, there might also be patients

who therefore experience less treatment-induced toxicity, as subsequent surgery might be omitted. This trade-off needs to be discussed between physicians and breast cancer patients using the concept of shared decision making. For adequate shared decision making, additional data on the risk of treatment-induced toxicity and the chance of pathologic complete response are crucial.

Response prediction

To be able to omit surgery in case for pathologic responders, the response needs to be estimated prior to surgery. It can be argued that it should be known as soon as possible which patient will benefit from neoadjuvant irradiation and which patient can be best treated with the current standard of breast conserving surgery and adjuvant irradiation. Ideally, response prediction would be performed prior to any treatment during the diagnostic process, so it can be incorporated into the shared decision-making process. If response prediction can't be performed prior to treatment, it would ideally be performed shortly after treatment, in which case patients do not have to wait, possibly anxiously, between radiotherapy and surgery to know their options for further treatment.

In this thesis we appreciate patients as pathologic responders and pathologic non-responders, based on the percentage of residual tumor cells [19]. It can be argued that not only in patients with pathologic complete response, but also in patients with a near pathologic complete response (i.e. less than 10% residual tumor cells) surgery might be redundant. Firstly, because they might achieve pathologic complete response at a longer interval following radiotherapy. And secondly, because the residual tumor cells might not be viable and might not able to do harm to the patient. If both patients with pathologic complete response and near pathologic complete response are appreciated as responders, a larger group of patients could have the major benefit of omission of surgery. It should also be noted that the patients who were appreciated as non-responders show definite signs of response, however, there was still residual tumor left.

In addition to the semiquantitative MRI-parameters and tumor infiltrating lymphocytes that have been studied in this thesis, there are other fields that can be explored to improve prediction of responders and non-responders. As response markers for prediction have been evaluated in other neoadjuvant treatment setting, such as neoadjuvant chemotherapy in more advanced breast cancer patients or neoadjuvant chemoradiation in patients with rectal cancer, these markers can be indicative in our search for predictors [20,21].

The first possible field of interest is the liquid biopsy. Liquid biopsies are blood samples, in which the amount of circulating tumor cells (CTC) or circulating tumor DNA (ctDNA)

can be assessed [22]. CTC and ctDNA are released by the tumor or by metastases of the tumor and can therefore be a representation of the amount of active tumor. ctDNA has been found to be present in 50% of breast cancer patients without metastases [23]. If this percentage is equal for the low-risk breast cancer patients eligible for neoadjuvant single-dose partial breast irradiation, a change in ctDNA following treatment can only be assessed in half of the patients. Nonetheless, baseline ctDNA levels can and should be assessed in all patients, as no detectable ctDNA might also be an important factor in predicting the pathologic response. As the amount of ctDNA is a representation of active tumor load, a decline following treatment is hypothesized to present a response to treatment as there is less active tumor to release cells or DNA [24,25]. Contradictory, a rapid rise in CTC or ctDNA during or shortly after treatment could also indicate tumor response, as a damaged or apoptotic tumor also release cells and DNA through damaged cells [26]. It should be noted that the half-life of ctDNA is assumed to be very short in vivo, less than 1.5 hours, so to assess an increase following treatment due to apoptotic tumor, blood samples should be obtained very rapidly after treatment [27,28].

A second possible field of interest is additional imaging and using quantitative parameters, both at baseline and following treatment, given the promising results of the semi-quantitative parameters presented in this thesis. The additional imaging could, for example, consist of metabolic changes in tumor as assessed on a 7T MRI scanner, or the assessment of enhancement of normal breast tissue which is already being imaged during imaging of the tumor [29,30]. Metabolic changes have been assessed in breast cancer patients treated with neoadjuvant chemotherapy in a small clinical study, however, no conclusions on associations between changes and response could be reported [29]. A decrease in enhancement of the parenchyma of the contralateral breast in breast cancer patients treated with neoadjuvant endocrine therapy was found to be associated with a worse prognosis, compared to an increase in enhancement [30]. The quantitative parameters, in addition to the semi-quantitative parameters, can be obtained from the follow-up imaging with only small adaptation in the scan protocol. These quantitative parameters that can be reived from contrast-enhanced MRI are the transport rate of contrast agent from blood to tissue (Ktrans), and the volume fraction of extravascular-extracellular space in tissue (ve) [31–33]. An important factor when incorporating additional imaging as a potential predictor for pathologic response, is that the tumors within the population of patients treated with neoadjuvant single-dose partial breast irradiation are relatively small. Therefore, the adequate definition of the tumor following treatment is an essential factor in assessing the changes in the tumor. Subtle changes within the tumor could be missed when a region outside the tumor is

analysed as being tumor, and changes in normal breast tissue due to irradiation may mimic tumor response. When a region outside the tumor is the actual region of interest, such as with contralateral parenchymal enhancement, this is not an issue.

To adequately differentiate between responders and non-responders prognostic research into the earlier mentioned options is crucial. Preferably only one test will predict the pathologic response with a large certainty, but presumably multiple tests are necessary to incorporate in a prediction model to increase the certainty of the predicted pathologic response. Furthermore, with each additional test, whether it be a liquid biopsy or additional imaging, the impact on the patient should be kept in mind. If the additional testing negatively influences patient-reported outcomes, this can annulate the possible positive effect of the intended treatment de-escalation.

FINAL REMARKS

The research presented in this thesis aimed to contribute to a new approach for treatment de-escalation in low-risk breast cancer patients. With the expanding number of treatment options, informing patients and their relatives about these options, including the benefits, disadvantages, and the prognosis of each treatment approach, will remain crucial. To be able to give this information to physicians and patients, scientific research is vitally dependent on today's patients who, without self-interest, participate in research that will ultimately benefit future patients.

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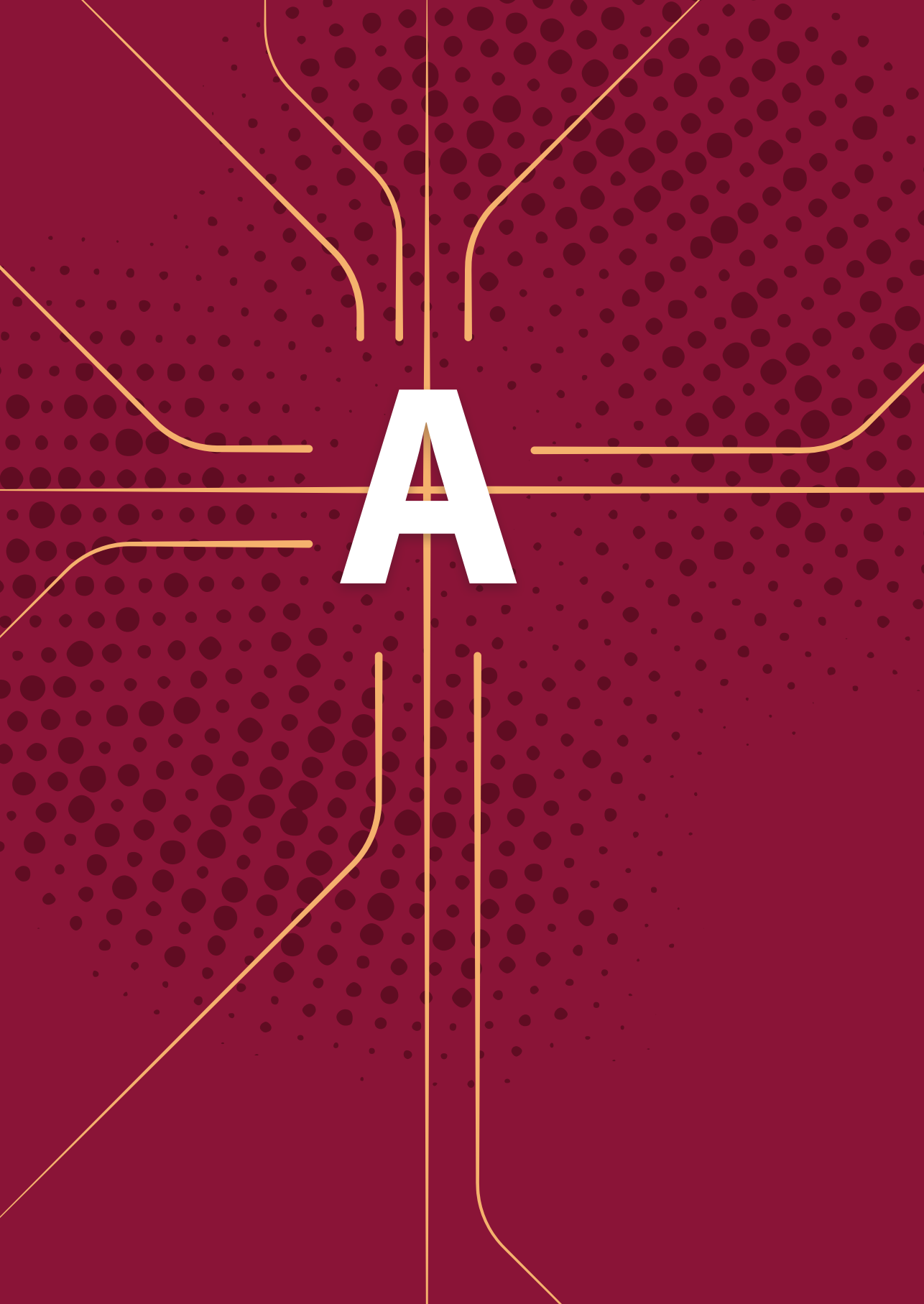
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APPENDICES

NEDERLANDSE SAMENVATTING

Het onderzoek dat in dit proefschrift gepresenteerd wordt heeft tot doel om een nieuwe behandelmethode voor laagrisicoborstkanker te evalueren. Met laagrisicoborstkanker bedoelen we een tumor met een maximale diameter van 2 cm zonder uitzaaiingen of met uitzaaiingen alleen naar de lymfeklieren in de oksel aan dezelfde zijde als de tumor, of een tumor met een maximale diameter van 5 cm zonder uitzaaiingen naar de lymfeklieren. Momenteel worden vrouwen bij wie laagrisicoborstkanker wordt gediagnosticeerd meestal behandeld met een borstsparende operatie gevolgd door bestraling. Tijdens de bestraling wordt een gedeelte van de borst of de gehele borst bestraald in 15 doses, verdeeld over drie weken. Deze combinatie van operatie en bestraling zorgt ervoor dat de relatieve 10-jaars overleving van vrouwen met laagrisicoborstkanker tussen de 83% en 95% ligt. De combinatie van behandelingen kan echter ook tot bijwerkingen leiden, zoals vermoeidheid, pijn, verlittekening van de borst, en een verhoogd risico op hart- en vaatziekten.

De nieuwe behandeloptie die in dit proefschrift besproken wordt bestaat ook uit een combinatie van operatie en bestraling, maar juist in de omgekeerde volgorde; de bestraling vindt voorafgaand aan de operatie plaats. Bestraling voorafgaand aan een operatie wordt neoadjuvante bestraling genoemd. Door neoadjuvant te bestralen, kan de bestraling zeer gericht, op een kleiner doelgebied, en in één enkele dosis worden gegeven, wat mogelijk tot minder bijwerkingen zou kunnen leiden. Ook zou de neoadjuvante bestraling kunnen leiden tot vernietiging van de tumorcellen, waardoor de aanvullende operatie eventueel vermeden zou kunnen worden.

In **hoofdstuk 2** van dit proefschrift wordt magnetic resonance imaging (MRI) geleide radiotherapie voor borstkankerpatiënten besproken. Het hoofdstuk behandelt de voordelen van MRI-geleide radiotherapie voor borstkanker en ook de uitdagingen die er nog zijn tot deze behandelmethode breed toegepast kan worden in de klinische praktijk. Het grote voordeel van MRI-geleide radiotherapie, als het wordt toegepast in de neoadjuvante situatie, is dat de tumor beter afgebeeld kan worden dan met de huidige standaard beeldvorming voor bestraling: computed tomography (CT). In vergelijking met CT-beelden kan een tumor in de borst preciezer worden gezien op MRI-beelden, zeker als daarbij opnames worden gemaakt waarbij de patiënte contrastmiddel toegediend krijgt. Door deze betere afbeelding kan de bestraling gerichter worden gegeven, waarbij er een kleinere veiligheidsmarge rondom de tumor gebruikt kan worden. Zo kan een kleiner volume in de borst bestraald worden indien er gebruik wordt gemaakt van MRI-beelden, wat kan leiden tot minder straling in het omliggende gezonde weefsel. Als gevolg hiervan treden er mogelijk minder bijwerkingen van de

bestraling op en rapporteren patiënten beter uitkomsten (zoals kwaliteit van leven, cosmetische tevredenheid en fysiek functioneren). Een ander voordeel van MRI-geleide radiotherapie is dat een veranderende anatomie, bijvoorbeeld door ademhaling of andere beweging tijdens een bestraling, vrijwel direct kan worden waargenomen op de beelden en het bestralingsplan daarop aangepast kan worden. Ook zo kan er gezorgd worden dat omliggend gezond weefsel minder straling krijgt, en de tumorcellen de juiste dosis straling krijgen. De uitdagingen die in dit hoofdstuk beschreven worden zijn onder andere de houding van patiënten in de MRI-scanner en verstoringen van de MRI-beelden door markers en clips rondom de tumor. Als patiënten op de buik in de MRI-scanner liggen, is er niet altijd voldoende ruimte voor de borst om vrij te hangen, en als patiënten op de rug liggen moeten zij de gehele tijd hun armen boven het hoofd houden. Ook is voor deze houdingen niet bij alle patiënten voldoende ruimte in de MRI-scanner en kan het lang moeten aanhouden van deze houding voor ongemak en pijn zorgen. Zowel markers als clips in de borst zorgen voor artefacten op de MRI-beelden, omdat ze een verstoring van het magnetisch veld veroorzaken. Doordat deze artefacten vlak bij de tumor liggen, zorgen ze voor problemen met het afbeelden van de tumor, wat het lastiger maakt om een bestralingsplan te maken. De markers en clips zijn op dit moment wel noodzakelijk, ze worden door de radioloog of chirurg geplaatst om de tumor te lokaliseren voor een latere operatie of beeldvorming.

In **hoofdstuk 3** wordt beschreven hoe er met een internationale groep van radiotherapeuten en een radioloog overeenstemming is bereikt over het intekenen van borsttumoren op MRI-beelden voor neoadjuvante bestraling. Deze overeenstemming is van belang voor verder onderzoek naar neoadjuvante radiotherapie voor borstkankerpatiënten, omdat dezelfde behandelingen in verschillende onderzoeken ervoor zorgt dat uitkomsten van die onderzoeken mogelijk samen kunnen worden gevoegd en met elkaar kunnen worden vergeleken. Het begin van het uitvoeren van dezelfde behandelingen ligt in overeenstemming over de verschillende type MRI-beelden die gebruikt worden, en wat er op die beelden gedefinieerd wordt als tumor en wat als gezond borstweefsel. Om de overeenstemming te bereiken zijn tien casus van borstkankerpatiënten geselecteerd waarbij in drie sessies de tumoren zijn ingetekend door de radiotherapeuten. Tijdens de eerste sessie werden twee casus ingetekend en werd een conceptrichtlijn opgesteld voor het intekenen van de tumoren, tijdens de tweede sessie werden volgens deze conceptrichtlijn tien casus ingetekend. Na het berekenen en bekijken van de verschillen in intekeningen tussen de radiotherapeuten in de tweede sessie werden de richtlijnen aangepast en werd er een laatste sessie georganiseerd. Hier werden zes casus opnieuw ingetekend, waarna de verschillen in definitie van de tumor opnieuw werden berekend. Er waren kleine variaties tussen de radiotherapeuten in de tumordefinitie, deze verschillen zaten met name in casus met

bloedvaten of markers vlak naast de tumor, met veel aankleuring van het gezonde klierweefsel in de borst, en bij casus waarbij de tumor lange, sprietigere uitlopers had. De uiteindelijke richtlijnen bevelen aan om de tumor in te tekenen op MRI-beelden 1 tot 2 minuten na toediening van contrastmiddel en om markers vlak naast de tumor ook te definiëren als de te bestralen tumor.

In **hoofdstuk 4** van dit proefschrift wordt de behandeling met eenmalige neoadjuvante radiotherapie voor laagrisicoborstkankerpatiënten onderzocht in de klinische praktijk. Hiervoor werden 36 vrouwen behandeld met de eenmalige bestraling en, na een periode van zes tot acht maanden, een borstsparende operatie. Bij deze operatie werd alleen de tumor, of wat nog resteert van de tumor na de bestraling, verwijderd. Vrouwen die meededen aan dit onderzoek hadden kleine tumoren (maximale doorsnede van 3 cm) en waren 50 jaar of ouder. De belangrijkste uitkomst was de mate van respons van de tumor op de bestraling na de zes tot acht maanden. Ook werd er gekeken naar bijwerkingen van de behandeling en werden patiënt-gerapporteerde uitkomsten verzameld. Bij 15 vrouwen (42%) was de tumor geheel verdwenen, bij 12 vrouwen (33%) was er minder dan 10% van de oorspronkelijke tumor aanwezig. Bij de overige 9 vrouwen (25%) was er meer dan 10% van de oorspronkelijke tumor aanwezig, maar was er geen enkele vrouw met groei van de tumor na de bestraling. Bij zes vrouwen (17%) ontstond er een infectie van de wond na de borstsparende operatie, waardoor één van deze vrouwen opnieuw geopereerd moest worden om de infectie te behandelen. Er werd tijdens het onderzoek geen achteruitgang gezien in patiënt-gerapporteerde klachten van de borst, angst- of depressieklachten. De conclusie van dit onderzoek was dat de behandeling met eenmalige neoadjuvante bestraling een haalbaar alternatief is voor de huidige standaard van de adjuvante bestraling. Bovendien zou deze behandeling in de toekomst kunnen leiden tot het weglaten van de aanvullende borstsparende operatie, als er voorspeld kan worden bij welke vrouwen de behandeling leidt tot het geheel verdwijnen van de tumor.

In **hoofdstuk 5 en 6** worden manieren onderzocht om te kunnen voorspellen bij welke vrouwen de tumor geheel verdwijnt na de eenmalige neoadjuvante radiotherapie. Dit hebben we gedaan door te kijken naar het aantal tumor infiltrerende lymfocyten (TILs) voorafgaand aan en na de bestraling, en door een aantal parameters van de MRI-beelden voorafgaand en na de bestraling te bekijken. De TILs en MRI-parameters, en de veranderingen daarin na de bestralingen zouden ons kunnen helpen in het voorspellen bij welke vrouwen de tumor geheel zal verdwijnen na de radiotherapie. De hoeveelheid TILs en de MRI-parameters hebben we bepaald in dezelfde 36 vrouwen met borstkanker die behandeld zijn met eenmalige neoadjuvante radiotherapie, zoals beschreven in hoofdstuk 4 van dit proefschrift.

TILs zijn cellen die door het immuunsysteem worden aangestuurd en een belangrijke taak hebben in de natuurlijke afweer van het lichaam tegen tumorcellen. We hebben in dit onderzoek drie soorten TILs bekeken, die elke een eigen rol hebben in de cascade van de afweer. Van elk van deze TILs hebben we bepaald hoeveel er aanwezig waren in het biopt dat van de tumor was genomen voor de diagnose en in het operatiepreparaat. Van elk van de verschillende soorten TILs werd een afname gezien na de bestraling, er werd echter geen verschil gezien in het aantal aanwezige TILs tussen de vrouwen waarbij de tumor (vrijwel) geheel was verdwenen en waarbij er nog tumor aanwezig was.

MRI-parameters zijn specifieke kenmerken van de tumor die op MRI-scans bepaald kunnen worden, zoals het gedeelte van de tumor dat aankleurt nadat er contrastmiddel is toegediend, hoe lang het duurt voordat de tumor aankleurt nadat er contrastmiddel is toegediend, of de mate van diffusie restrictie. Diffusie restrictie zegt iets over de mate waarin watermoleculen vrij kunnen bewegen. Veel en snelle aankleuring na toediening van contrastmiddel wijst over het algemeen op de aanwezigheid van tumorcellen. In tumoren zit het weefsel dichter op elkaar dan in gezond borstweefsel, waardoor watermoleculen zich in tumoren minder vrij kunnen bewegen dan in gezond borstweefsel. Deze MRI-parameters werden bepaald binnen de regio van de oorspronkelijke tumor, zoals bepaald op de scan voorafgaand aan de bestraling. Deze regio werd overgezet naar de MRI-scans die één week, twee maanden, vier maanden, en zes maanden na de bestraling werden gemaakt. Binnen de hele groep van 36 vrouwen met laagrisicoborstkanker werd er een toename gezien in de aankleuring van de tumor na toediening van contrastmiddel één week na de bestraling, waarna er vanaf twee maanden een afname van de relatieve aankleuring werd gezien. Deze verandering in aankleuring kan worden verklaard door de acute ontstekingsreactie op de bestraling en later door vernietiging van de tumorcellen. Hetzelfde werd gezien bij de andere parameters, zoals het aankleurende gedeelte van de tumor en de diffusie restrictie. We hebben niet onderzocht of er verschillen in deze parameters waren tussen de vrouwen waarbij de tumor (vrijwel) geheel was verdwenen en vrouwen waarbij er nog tumor aanwezig was.

In **hoofdstuk 7** van dit proefschrift worden drie verschillende methodes die het cosmetisch resultaat van behandelingen van de borst evalueren met elkaar vergeleken. Deze drie evaluatiemethodes zijn: een vragenlijst die door de vrouw die behandeling heeft ondergaan zelf invult, een vragenlijst die wordt ingevuld door de behandelend arts, en een programma dat foto's op een objectieve manier beoordeelt. We vonden een lage betrouwbaarheid van de verschillende methodes, wat betekent dat de uitkomsten niet goed overeenkomen, en de uitkomsten dus niet onderling uitwisselbaar zijn. Dit

betekent dat wanneer de beoordeling van het cosmetisch resultaat van de patiënt zelf ontbreekt, daar niet een andere beoordeling van de behandelend arts of van de foto's door een softwareprogramma voor gebuikt kan worden. Dit is van belang voor toekomstig onderzoek waarbij het cosmetische resultaat van borstbehandeling wordt beoordeeld.

Zoals aan het begin van dit hoofdstuk beschreven, zou eenmalige neoadjuvante radiotherapie bij laagrisicoborstkankerpatiënten kunnen leiden tot het achterwege laten van een operatie. De eerste stap hiertoe hebben we gezet door aan te tonen dat deze behandeling bij een groot gedeelte van deze vrouwen leidt tot complete vernietiging van de tumor. Er dient echter nog meer onderzoek uitgevoerd te worden om de behandeling te optimaliseren voordat die in de klinische praktijk aangeboden kan worden. Zo zouden aanpassingen in de behandeling met radiotherapie onderzocht kunnen worden, zoals het toedienen van een hogere dosis, om te zien of dit bij meer vrouwen tot een complete vernietiging van de tumor leidt. Ook kunnen de mogelijkheden voor het voorspellen van de reactie van de tumor op eenmalige neoadjuvante bestraling onderzocht worden, zoals het meten van circulerend tumor DNA en het verrichten van aanvullende MRI-scans. Als de reactie van de tumor op de bestraling voorspeld kan worden, kan namelijk bepaald worden bij welke vrouwen de operatie mogelijk achterwege gelaten kan worden, en ook welke vrouwen minder voordeel van de eenmalige bestraling zullen hebben. Door deze onderzoeken met elkaar te combineren, kan het uiteindelijke doel: het verminderen van bijwerkingen van de behandeling voor vrouwen met borstkanker, bereikt worden.

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Jeanine Else Vasmel was born on December 30, 1989 in Amsterdam as the second daughter to Els Hoogteijling and Henk Vasmel. She grew up in Voorschoten and Stavanger (Norway) with her sister Marlies and her brother Niek. After graduating from the Stedelijk Gymnasium Leiden in 2008, she moved back to Amsterdam to study Medicine at the Vrije Universiteit. During her studies Jeanine has engaged in many extracurricular and social activities.

Jeanine obtained her medical degree in 2005, and immediately started her career as a non-training resident in Surgery at the Flevoziekenhuis in Almere, under supervision of dr. PJM Verbeek. After one year she transferred to the UMC Utrecht where she continued as a non-training resident, under supervision of prof. dr. MR Vriens. At the UMC Utrecht she developed her interest in research which resulted in the thesis you are reading right now. In parallel with her PhD program Jeanine obtained a postgraduate Master of Science degree in Epidemiology, specializing in clinical epidemiology.

In January 2021 she has commenced her training as a radiologist at the Meander Medisch Centrum in Amersfoort under supervision of dr. JJ Florie.

Currently, Jeanine lives with Bram and their daughter Hazel in Utrecht.

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