Image-guided treatment of breast cancer: a patient-centered approach to minimally invasive therapy

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Beeldgestuurde behandeling van borstkanker: een patiëntgerichte benadering van minimaal invasieve therapie

(met een samenvatting in het Nederlands)

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CONTENTS

CHAPTER 1

General introduction and thesis outline

BREAST CANCER

Since ancient times, the breast has been a symbol for femininity, fertility and beauty. Women have always been reluctant in exposing their breasts for examination and considered breast amputation a mutilation. Combined with the aversion of surgeons to harm women by amputating their breast, this is assumed to have hampered breast cancer diagnosis and treatment since ancient times. The first medical record of breast cancer dates from around 1600 B.C. and is most likely a copy of a text written in the Egyptian Pyramid Age in the Old Kingdom (3000-2500 B.C.). In ancient Egypt, breast tumours were cauterised using a "fire drill". In most of the pre-Christian era however, surveillance while invoking the gods for help was the only accepted treatment. Hippocrates (460-377 B.C.) believed that cancer was caused by an excess of black bile (humoral theory). He considered breast cancer a systemic disease that was should not be treated with surgery. In the Roman empire, Celsus (30 B.C. – 38 A.C.) suggested treatment with surgery and cautery for early cancers, advanced breast cancer was considered untreatable. After the fall of the Roman empire, Christianity and Islam hampered medical progress by prohibiting surgical practice. Breast cancer treatment changed during the Renaissance period (14th to 17th century). Science was encouraged; physicians started to study medicine and performed anatomical dissection. Vesalius (1514-1564) vigorously opposed the humoral theory and advised surgical excision of all breast cancers. Throughout the centuries, it became clear that curing breast cancer is possible, albeit against the high price of (mutilating) surgery. The introduction of anaesthesia, antisepsis and microscopy in the 19th century greatly improved breast cancer treatment[1,2].

In the modern world, breast cancer is the most common cancer type in women. Every year approximately 1.7 million women are diagnosed with breast cancer worldwide. It is the leading cause of cancer death in women and in developed countries, breast cancer is the second cause of overall death in women[3,4]. The incidence is increasing in the Netherlands and approximately 14,500 women have been diagnosed with breast cancer in 2015[5]. The increase is mainly due to aging of the population. Dutch women have a life-time risk of 12-13% of being diagnosed with breast cancer[6]. Due to the national screening programme, breast cancer is often diagnosed in an early stage with a good prognosis[7,8].

PROGNOSTIC FACTORS

Prognostic factors are hormone receptor status, tumour stage at diagnosis, breast cancer grade, histologic subtype and patient age. Patients with positive hormone receptors, i.e. oestrogen receptor (ER) and progesterone receptor (PR), have a better prognosis than ER and PR negative tumours[9]. Positive human epidermal receptor growth factor receptor 2 (HER2) status used to be associated with worse prognosis[9,10], but the introduction of targeted drugs such as trastuzumab, has resulted in decreased local recurrence of HER2 positive tumours[11]. High Notthingham tumour grade, i.e. poor differentiation, is an independent prognostic factor for local recurrence[12]. Younger age at diagnosis is considered a risk factor for poor prognosis[13,14]. However, local and regional recurrence rates in young patients have improved over time[11]. Most of these factors are incorporated in risk prediction tools such as Adjuvant! online, which help the clinician to determine whether systemic adjuvant treatment is indicated[15]. Another recently developed risk stratification tool is the MammaPrint®, a 70-gene assay which assesses the risk of distant metastases[16]. The MINDACT study has shown that unnecessary use of chemotherapy can be prevented with the MammaPrint®[17].

THE EVOLVEMENT OF BREAST CANCER TREATMENT

The aim of breast cancer treatment is complete resection of the primary breast tumour, reducing the risk of recurrence, preventing the development of metastases and prevention of premature death. Before breast conserving treatment (BCT) was introduced, breast cancer patients were treated with Halsted radical mastectomy, which implies resection of the pectoral muscle, the breast and all axillary lymph nodes[18]. This mutilating treatment was gradually replaced by modified radical mastectomy in the second half of the 20th century[19]. After its introduction in the '70s, BCT has become a popular treatment for patients with early stage breast cancer, on whom this thesis is focused. BCT consists of lumpectomy followed by whole breast irradiation. Sentinel lymph node biopsy is performed during surgery to assess lymph node metastasis[6].

Overall survival after BCT is similar to survival after mastectomy[20]. In most patients, even those with favourable tumour characteristics, adjuvant treatment with

radiotherapy and/or hormonal therapy reduces the risk of local recurrence[21]. Although very low, the risk of recurrence after BCT remains higher than after mastectomy[20,22,23].

Breast cancer care is shifting towards a more personalized approach. Due to the increasing number and proportion of patients with early-stage breast cancer, it is becoming increasingly clear that some patients are overdiagnosed and consequently overtreated[24,25]. BCT results in unsatisfactory cosmetic outcomes in a non-negligible proportion of patients and surgical complications do occur[26]. These factors resulted in a search for less invasive treatments, which contributed to the development of several minimally invasive treatment options during the last decades.

MINIMALLY INVASIVE TREATMENT OF BREAST CANCER PATIENTS

There are several minimally invasive treatment options for breast cancer. All techniques are aimed at tumour destruction by ablation with either heat, cold or radiation treatment.

The main focus of this thesis is Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) ablation. MR-HIFU ablation is completely non-invasive, as no needle or probe is inserted in the breast. Ultrasound beams are focused in a focal point in the tumour. Due to the high intensity of ultrasound in the focal point, the temperature in the targeted tissue increases rapidly. If a temperature of at least 57-60˚C is reached for a few seconds, protein denaturation occurs, leading to tissue necrosis[27]. The adjacent healthy tissue and the skin remain undamaged because of precise targeting with MRI (magnetic resonance imaging)-guidance.

In 2001, the use of MR-HIFU was reported for the first time for ablation of eleven fibroadenomas[28]. After this study, several small clinical studies on MR-HIFU treatment for invasive cancer followed. Rates of complete ablation varied between 20% and 90%[29-34]. Technical aspects and challenges of MR-HIFU treatment in a research setting have never been described in detail. However, as the reported variation in efficacy implies, room for improvement exists. Possible

causes for the variation in treatment success are technical issues and the lack of structured treatment protocols[35]. Furthermore, the clinical studies performed so far reported MR-HIFU ablation with a single-transducer system, targeting the tumour from anterior direction. The University Medical Center of Utrecht uses a dedicated MR-HIFU breast table, with eight transducers positioned around the breast providing sonications (focal heating cycles) from the sides of the breast. This approach is expected to result in less complications and more complete ablation. The energy density delivered to the skin is lower, as it is divided over eight transducers. Contrary to sonications from anterior, the heart and the lungs are at a further distance in the far-field of the beam path (energy propagation behind the focal point), decreasing the risk of complications[36]. Besides clinical efficacy, an important aspect of introducing a new treatment is cost-effectiveness. Due to its early stage of development, the costs and the potential of MR-HIFU ablation to be cost-effective have not been investigated.

The most frequently used minimally invasive treatment is radiofrequency ablation (RFA). RFA uses a needle electrode, which is inserted in the tumour. An alternating current in the needle probe results in temperature increase in the surrounding tissue. Virtually all RFA treatments are performed under ultrasound guidance[37-39]. A recently proposed minimally invasive treatment is ablative radiotherapy, where a lethal dose of radiotherapy is given to the tumour including a safety margin[40]. Other options are cryoablation[41], microwave ablation[42] and laser interstitial therapy[43].

THE ROLE OF MRI IN MINIMALLY INVASIVE TREATMENT

The role of MRI in minimally invasive treatment of breast cancer is diverse. Firstly, MRI is an important tool for adequate patient selection. Secondly, MRI is used for guidance during MR-HIFU treatment. It provides accurate anatomic details of the tumour and surrounding tissue, enabling precise treatment planning and delivery. Additionally, MRI provides real-time temperature maps[44]. Monitoring the temperature in the breast during HIFU treatments improves the chance of successful treatment by indicating whether sufficient temperatures have been reached or a resonication is required. Finally, MRI is used for treatment evaluation. Residual disease may be detected by contrast-enhanced MRI[32]. However, more research proving the reliability of MRI in detecting residual disease is warranted.

PATIENT SELECTION FOR MINIMALLY INVASIVE TREATMENT

During surgery, an intended safety margin of 1 cm of healthy tissue around the tumour is removed to increase the chance of complete resection. The resection margins are assessed for the presence of tumour cells. Several trials have shown that tumour-positive resection margins are a risk factor for local recurrence[45]. In case of positive margins, patients undergo re-excision or a radiotherapy boost[46]. With minimally invasive treatment the tumour is not surgically excised, but destructed within the breast. As such, histopathological assessment of treatment margins cannot be performed and incomplete treatment cannot be detected. Therefore, only patients in whom complete treatment with clear margins is likely should be subjected to minimally invasive treatment. Furthermore, patients with other contra-indications for minimally invasive treatment, such as an increased risk of complications, are considered ineligible.

A number of factors are associated with an increased risk of positive resection margins or may pose complication risks for minimally invasive treatment. Presence of extensive intraductal component (EIC), extending beyond the tumour border or applied safety margin, increases the risk of irradical treatment[47]. Large or multifocal tumours may be harder to treat with minimally invasive techniques due to proximity of the tumour border to the skin, which is a risk factor for damage to the overlying skin[31]. Large or multifocal tumours also require more thermal energy to treat, resulting in long treatment durations with associated costs for some techniques, patient discomfort and complication risk. Invasive lobular carcinoma is associated with positive resection margins due to underestimation of disease extent on imaging and may therefore not be suitable for minimally invasive treatment[48].

Because no surgical excision specimen is available after minimally invasive treatment, the factors determining the need for adjuvant treatment need to be assessed prior to treatment. The indication for adjuvant systemic therapy is determined using prognostic factors, which largely overlap with risk factors for incomplete resection. The presence of axillary lymph node metastasis, receptor status, tumour size, differentiation grade and age determine whether a patient will receive adjuvant systemic treatment or not[6].

The size of the tumour, the distance to the skin and pectoral muscle and the position in the breast can be accurately determined with magnetic resonance imaging (MRI). Besides, MRI frequently detects additional lesions that are occult on conventional imaging, possibly resulting in ineligibility for minimally invasive treatment[49,50]. Core needle biopsy (CNB) is currently already used to diagnose breast cancer and has a very high sensitivity and specificity for detection of malignancy[51]. Histologic subtype and receptor status can be accurately assessed on CNB[52,53], but CNB-based evaluation of histologic grade is challenging. The concordance between grading on CNB and surgical excision specimen is not perfect. The presence of DCIS can also be determined on CNB, possibly more accurately when combined with MRI. However, imaging protocols and image interpretation should be optimised to improve the moderate specificity of MRI[54]. The sentinel node biopsy can be performed prior to minimally invasive treatment and if a positive lymph node is detected, the patient may be referred for surgical removal of the primary tumour and may not be eligible for minimally invasive treatment.

OUTLINE OF THIS THESIS

In this thesis, challenges associated with the clinical introduction of minimally invasive breast cancer treatment are discussed. The thesis consists of two parts.

Part I - Minimally invasive treatment of breast cancer patients
The first part describes out clinical experience with minimally invasive treatments.

In **Chapter 2** the first clinical experience with MR-HIFU ablation of breast cancer using a dedicated MR-HIFU breast platform (Sonalleve-based prototype, Philips Healthcare, Vantaa, Finland) is described. The main focus of this chapter is assessment of the safety and feasibility of MR-HIFU ablation. Currently, most clinical studies with minimally invasive treatments are performed according to treat-and-resect protocols. In **Chapter 3** the histopathology of breast cancer after MR-HIFU ablation and RFA is evaluated and compared. The costs of MR-HIFU treatment and its ability to be as cost-effective as surgical treatment are evaluated in **Chapter 4**.

Part II - Patient selection for minimally invasive treatment

The key to successful minimally invasive treatment is adequate patient selection, on which the second part is focused.

MRI plays an import role in minimally invasive treatments. The clinical indications for MR imaging prior to surgical treatment are discussed in **Chapter 5**. The ability of MRI to predict the presence of extensive DCIS is evaluated in **Chapter 6**. Patients with extensive DCIS are at higher risk of incomplete resection due to undetected malignant tissue surrounding the tumour. These patients are consequently also at higher risk of residual disease after minimally invasive treatments and should be referred for surgical resection instead. The concordance of tumour grade on CNB and surgical excision specimen is evaluated in **Chapter 7**. Tumour grade is another important prognostic factor and accurate assessment of grade is crucial for setting the indication for adjuvant systemic treatment. In **Chapter 8,** patient preferences for minimally invasive and conventional surgical treatments are evaluated. Patient selection for minimally invasive treatments is based on patient preference as well. Some patients may have a strong preference for surgical resection of their tumours, while others might feel more comfortable with less invasive treatments.

The findings of this thesis are summarized and discussed in **Chapter 9**.

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PART I

Minimally invasive treatment of breast cancer patients

CHAPTER 2

First clinical experience with a dedicated MRI-guided high-intensity focused ultrasound system for breast cancer ablation

European Radiology 2016

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ABSTRACT

Objectives

To assess the safety and feasibility of MRI-guided high-intensity focused ultrasound (MR-HIFU) tumor ablation in breast cancer patients using a dedicated breast platform.

Methods

Patients with early-stage invasive breast cancer underwent partial tumor ablation prior to surgical resection. MR-HIFU ablation was performed using proton resonance frequency shift MR thermometry and an MR-HIFU system specifically designed for breast tumour ablation. The presence and extent of tumour necrosis was assessed by histopathological analysis of the surgical specimen. Pearson correlation coefficients were calculated to assess the relationship between sonication parameters, temperature increase and size of tumour necrosis at histopathology.

Results

Ten female patients underwent MR-HIFU treatment. No skin redness or burns were observed in any of the patients. No correlation was found between the applied energy and the temperature increase. In six patients, tumour necrosis was observed with a maximum diameter of 3-11 mm. In these patients, the number of targeted locations was equal to the number of areas with tumour necrosis. A good correlation was found between the applied energy and the size of the tumour necrosis at histopathology (Pearson=0.76, p=0.002).

Conclusions

Our results show that MR-HIFU ablation with the dedicated breast system is safe and results in histopathologically proven tumour necrosis.

Key points

- MR-HIFU ablation with the dedicated breast system is safe and feasible
- In none of the patients was skin redness or burns were observed
- No correlation was found between the applied energy and the temperature increase
- The correlation between applied energy and size of tumour necrosis was good

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide[1]. The disease is currently frequently diagnosed at an early stage because of mammographic screening programs and improved awareness[2]. Over the past decades, breast cancer treatment has evolved towards less invasive local treatment. Breast-conserving therapy (BCT), i.e., lumpectomy with additional radiotherapy, is currently standard-of-care in patients with early-stage breast cancer and has shown equal survival rates compared to radical mastectomy[3,4]. A range of minimally invasive techniques holds promise for replacing lumpectomy by local breast tumour ablation, for example cryoablation, radiofrequency ablation or microwave ablation. All these techniques, however, require percutaneous insertion of a probe into the breast tumour[5-7]. High-intensity focused ultrasound (HIFU) is a completely noninvasive technique that can be used for thermal ablation in a target volume deep within the body [8]. Imaging during minimally invasive treatment is crucial to localize the target area and monitor the treatment procedure. Magnetic resonance imaging (MRI) offers excellent anatomical imaging for treatment planning by defining the target volume and organs at risk, is able to provide real-time temperature monitoring during therapy, and allows direct evaluation of treatment results[9-11]. In 2001, Huber et al.[12] described the first MRI-guided HIFU (MR-HIFU) treatment in a breast cancer patient. Subsequently several groups reported on MR-HIFU ablation of malignant breast tumours prior to surgical resection[13-16]. Overall, authors concluded that MR-HIFU ablation of breast cancer was technically feasible. Complete tumour necrosis, however, was achieved in only 20-50% of patients, whereas complete tumour ablation has to be ensured before surgical resection can be omitted. Optimizing these results is necessary for MR-HIFU treatment to be considered as a clinically attractive alternative to surgery for local breast tumour control.

In this study, we report the first experiences on tumour ablation in breast cancer patients using an MR-HIFU breast platform specifically designed for breast tumor ablation[17]. In previous studies, treatments were performed using MR-HIFU systems with a single transducer targeting the breast from anterior using a point-by-point ablation method[13,15]. In contrast, with our dedicated platform, the breast is targeted laterally, consequently reducing the risk of unintended heating of the heart and lungs. In addition, the wide transducer aperture decreases the local energy density on the skin during ablation. Furthermore, a volumetric ablation

approach is used, resulting in larger and more homogeneous ablation volumes and a reduction in treatment duration[18,19]. The aim of the current study was to assess the safety and feasibility of tumour ablation in breast cancer patients using the dedicated breast platform.

MATERIALS AND METHODS

Patients

The study protocol was approved by the institutional review board of the University Medical Center Utrecht and written informed consent was obtained from all patients. Patients were recruited in the Diakonessenhuis Utrecht and included in the University Medical Center Utrecht between September 2012 and June 2014. Inclusion criteria were: women aged > 18 years; World Health Organization (WHO) performance status ≤ 2; body weight ≤ 80 kilo; clinically staged T1-2, histopathologically proven invasive breast cancer. Exclusion criteria were: neoadjuvant systemic therapy; contraindications for MRI; macro-calcifications; scar tissue or surgical clips in the direct path of the ultrasound beams.

All patients underwent an MRI examination on a 3-T clinical MR scanner (Achieva, Philips Healthcare, Best, The Netherlands) to assess whether the following additional inclusion criteria were met: maximum tumour diameter ≥ 1.0 cm; tumour location within the reach of the HIFU transducers with the patient in prone position; distance from skin and pectoral muscle to the centre of the target ≥ 1.0 cm.

Dedicated MR-HIFU breast platform

MR-HIFU ablation was performed using a dedicated MR-HIFU breast platform (Sonalleve-based prototype, Philips Healthcare, Vantaa, Finland) which was integrated into a 1.5-T MR scanner (Achieva, Philips Healthcare, Best, The Netherlands). During MR-HIFU treatment, patients were placed in prone position on the HIFU table top with the targeted breast in the water-filled breast cup surrounded by the eight separate 32-element transducers distributed over a 270° circular arc. The specifications of the system have been previously described in more detail[17]. In addition, Deckers et al.[20] recently published a performance analysis of the breast platform.

MR-HIFU treatment

Procedural sedation

Patients were under procedural sedation during MR-HIFU treatment. A team of procedural sedation and analgesia specialists monitored the cardiorespiratory functions and administered sedative agents and analgesics intravenously. In the first two patients, procedural sedation was maintained using continuous propofol infusion and an additional opioid analgesic prior to each sonication. Due to undesired patient motion and variations in the breathing pattern during these first two treatments, a combination of propofol and esketamine was used during all other treatments.

MR imaging

Figure 1 shows a schematic overview of the procedures and MR pulse sequences used during treatment. Treatment planning was performed based on the localization of the breast tumour on dynamic contrast-enhanced (DCE) MR imaging (dynamic scan time 78.3 s; TR/TE 6.6/3.2 ms; flip angle 10°; turbo-factor=36; acquisition voxel size 1.12 x 1.12 x 2.0 mm^3; 140 slices; matrix size 304 x 180; SPIR fat suppression). One dynamic was acquired before and four dynamics were acquired directly after injection of a gadolinium-based contrast agent (GBCA) (0.1 ml gadobutrol/kg body weight (Gadovist, Bayer Schering Pharma AG, Berlin, Germany)). Because of the potential hazard of heating a GBCA inside the body, a waiting time of 30 minutes was maintained between contrast injection and the first sonication. Before each sonication, a short T1-weighted scan was performed, which was visually compared to T1-weighted images acquired at the beginning of the treatment procedure to confirm accurate patient positioning.

During sonications, subtraction-based PRFS (proton resonance frequency shift) MR thermometry using an echo planar imaging (EPI) pulse sequence was performed with the following parameters: TR/TE 70/30 ms; flip angle 20°; EPI-factor 23; acquisition voxel size 1.67 x 1.67 x 5.0 mm^3; 4 slices; matrix size 96 x 92; composite RF pulse fat suppression. Four planes were monitored with a temporal resolution of 2.25 s: a coronal and sagittal slice through the focal point, a coronal near-field slice positioned 9.5 mm anterior to the focal point, and a far-field slice manually positioned at the pectoral muscle. A look-up-table (LUT)-based correction method was used to correct errors in the MR temperature maps caused by respiration-induced magnetic field disturbances[20,21]. Relative temperature

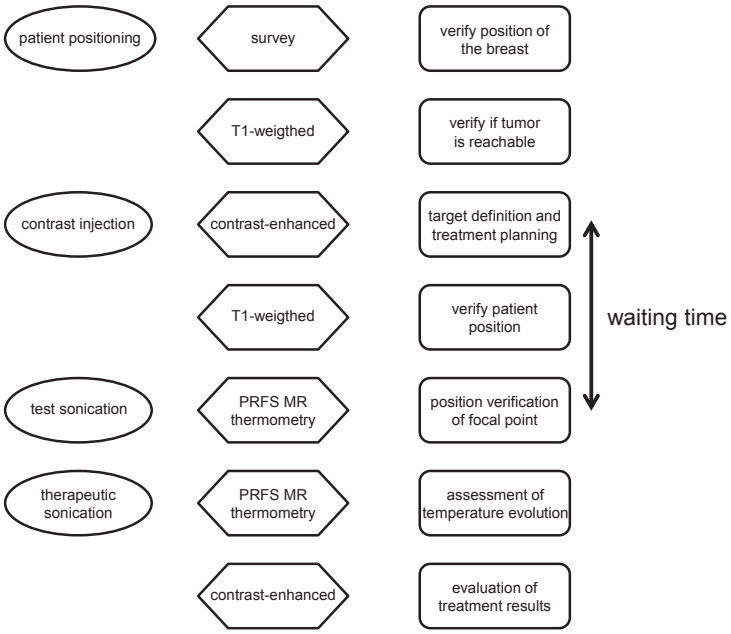

Figure 1 A schematic overview of procedures during MRI-guided high-intensity focused ultrasound (MR-HIFU) treatment

maps were calculated on the fly and overlaid onto T1-weighted, fat-suppressed magnitude images of the thermometry sequence. In patients three to ten, 160 mg/L $MnCl_2{\cdot}4H_2O$ was added to the water in the breast cup to shorten its T2 signal and prevent ghosting artefacts during MR thermometry due to possible subtle motion of the water in the breast cup. The same DCE-MR scan that was used for treatment planning was repeated directly after MR-HIFU ablation for treatment evaluation.

High-intensity focused ultrasound ablation

In this first study with the MR-HIFU breast platform, partial tumour ablation was performed to be able to analyse the location and size of separate sonications and to assess the relationship between different sonication parameters and the size of tumour necrosis at histopathology. Low energy test sonications were performed prior to therapeutic sonications to verify the focal spot position. A correction was performed in case of spatial misalignment. Test sonications were 3-mm treatment cells with low (20-40 W) acoustic power. Therapeutic sonications were performed using a volumetric ablation technique with concentric circular trajectories of

increasing size[18]. The resulting treatment cells, i.e. the differently sized ablation volumes, had an ellipsoidal shape with nominal diameters of 3 x 2 x 2 mm^3 or 6 x 4 x 4 mm^3 (size of the volume bound by the iso-intensity surface at -6 dB of the peak value in the centre) and a sonication duration of 20 and 24.5 s, respectively. The applied acoustic power during therapeutic sonications varied between 50 and 100 W with a frequency of 1.45 MHz. Multiple sonications were allowed at one or more locations within tumours. Each sonication was followed by a period of cooling. Sonications were aborted when temperatures ≥ 80 ˚C were observed in the MR temperature maps. Note that such apparent temperature elevations are not necessarily real, since the occurrence of artefacts (due to breathing or patient motion) may corrupt temperature measurements and lead to erroneous observation of excessive temperatures.

After MR-HIFU treatment

After MR-HIFU treatment, patients were admitted to a clinical ward for a minimum of 3 h to ensure stable hemodynamic function. Surgery was performed within 48 h and 10 days after MR-HIFU treatment. Clinical management of the axilla was performed according to standard clinical guidelines by a sentinel lymph node biopsy (SLNB) or axillary lymph node dissection. After surgical resection, tissue was submerged in formalin. The excised tissue containing the tumour was dissected into slices of approximately 5 mm. Microscopic sections of 4 µm were cut and stained with haematoxylin and eosin (H&E) for histological analysis.

Safety and feasibility

After MR-HIFU treatment, the skin of the treated breast was evaluated by a physician for the presence of skin burns or redness. Patients were asked to report pain scores according to the numerical rating scale, with a score of 0 (no pain) to 10 (worst pain imaginable)[22]. Monitoring of adverse events was done until surgery. A radiologist compared the DCE-MRI before and after MR-HIFU ablation to assess the presence of non-perfused volumes (NPVs) after ablation. For each sonication, the maximum temperature was reported based on the median temperature evolution in nine pixels in the centre of mass of the heating at the end of sonications. In addition, the maximum diameter of the area that reached a temperature higher than 55 ˚C was reported. All analyses were done for the coronal MR thermometry slice using software developed in Matlab (Mathworks, Natick, Massachusetts, USA).

For all performed sonications, the relationship between the duration and power of sonications and the temperature increase from baseline temperature as measured by MR thermometry was assessed using simple linear regression analyses. In addition, the correlation between duration, applied powers, temperature increase and the size of tumour necrosis at histopathology was investigated for each sonicated location. A Pearson correlation coefficient (r) < 0.25 was considered to indicate a trivial correlation, between 0.25 and 0.5 a low correlation, between 0.51 and 0.75 a medium correlation, and > 0.76 a high correlation. A p-value ≤ 0.05 was considered to be significant.

A dedicated breast pathologist evaluated the presence and the size of the areas with tumour necrosis, which were manually delineated using Aperio ImageScope (Leica Microsystems, Rijswijk, The Netherlands).

RESULTS

Patients

Seventeen patients were initially enrolled in the study. In five patients, an additional lesion was detected at pre-treatment MRI. Two of these patients were excluded due to logistical reasons because of additional diagnostic work-up, and three patients withdrew from the study themselves. In addition, two patients withdrew from the study because of fear of an epileptic insult during MR-HIFU treatment (n=1) and claustrophobia (n=1). Finally, ten patients underwent MR-HIFU treatment. Table 1 lists the demographic data of these patients.

MR-HIFU treatment

The overall duration of MR-HIFU treatment was on average 145 minutes. The actual sonication time was 1.7 minutes (Table 2). An overview of the performed sonications per individual patient is provided in Table 3. In the first and third patient, only one therapeutic sonication was performed. These were both aborted in an early phase due to the erroneous measurement of excessive temperatures caused by patient motion or a change in the breathing pattern. In the second patient, three of four therapeutic sonications were prematurely aborted (at 60.8%, 90.2%, and 98.5% of the full sonication length) for the same reasons. In patients four to ten, 23 of 24 (95.8%) therapeutic sonications were fully executed.

Table 1 Baseline characteristics of breast cancer patients who underwent MR-HIFU treatment.

Patients	**n (%)**
Number of patients	10
Age in years, mean ± SD	54.8 ± 12.5
Treated tumors	
Tumours in right breast	6 (60.0)
Tumour location	
Upper outer quadrant	3 (30.0)
Lower outer quadrant	5 (50.0)
Upper inner quadrant	2 (20.0)
Lower inner quadrant	0 (0.0)
Interval between HIFU and surgery	
Time in days, mean ± SD	5.0 ± 2.2
Type of surgery	
Lumpectomy	8 (80.0)
Mastectomy	1 (10.0)
No surgery	1 (10.0)
Axilla	
Sentinel lymph node procedure	8 (80.0)
Axillary dissection	1 (10.0)
No axillary procedure	1 (10.0)
Pathology	
Tumour size in mm, mean ± SD	20.0 ± 5.6*
Type carcinoma	
Invasive ductal carcinoma	8 (80.0)
Invasive lobular carcinoma	2 (20.0)

*Analysed without the patient who refused surgery

Table 2 Time distribution of MRI-guided high-intensity focused ultrasound (MR-HIFU) treatment

Stage of procedure	**Time in minutes, mean ± SD (range)**
Positioning on treatment table (including MR imaging until contrast injection)	25 ± 10 (5-39)
Pre-treatment imaging from contrast injection to the first (test) sonication	59 ± 27 (32-106)
Treatment time (from first to last sonication)	46 ± 17 (12-75)
Post-treatment imaging after the last sonication	14 ± 3 (7-19)
Overall procedure time	145 ± 29 (96-210)
Overall sonication time	1.7 ± 0.8 (0.3-2.6)

Safety

No skin redness or burns were observed in any of the patients. Patient seven developed three small white lumps with a maximum diameter of 0.5 -1.5 cm on the skin of the treated breast in the days after MR-HIFU treatment. Histopathological analysis of a biopsy from one of these lumps showed no signs of abnormal tissue. Over time, the lumps resolved without intervention. Other minor adverse events were nausea and vomiting (in two patients) in the hours after treatment, probably related to the administered anaesthetics. After MR-HIFU treatment, eight patients reported no pain. The other two patients reported a pain score of 4 and 5, respectively.

Treatment results

No visual differences were observed between contrast-enhanced MRI before and after MR-HIFU ablation. In patients in whom valid thermometry data were acquired (n=7), the average maximum temperature of therapeutic sonications was 51.4 ± 5.7 °C (range 40.4 - 61.4 °C). Figure 2 shows an example of MR thermometry images during a sonication.

For the 33 of 47 performed sonications with adequate MR thermometry data, no relationship was found between the duration or applied power of the sonications and the temperature increase. In addition, no correlation was found between the product of duration and power (i.e. the applied energy) and the temperature increase (Figure 3). In particular between different patients, the acoustic powers required to achieve a certain increase in temperature varied considerably. For example, the maximum temperature in patient four was about 59 ˚C during 50-W sonications, whereas the maximum temperature in patient eight remained below 55 °C during three 80-W sonications. Within an individual patient, the peak temperature was more dependent on the applied acoustic power, e.g. for increasing powers, higher maximum temperatures were observed.

The maximum diameter of the area with a temperature > 55 °C varied between 3 and 15 mm. In patient six, no temperatures above 55 °C were observed on the coronal MR thermometry slice. In contrast, a maximum temperature of 58.5 °C was measured during the second 70-W sonication in the sagittal slice. In patient nine, a mild temperature increase about 1 cm anterior of the focal point was measured, whereas no temperature data were acquired in the actual focal point.

Table 3 An overview of the sonications, size, power, duration of sonications, maximum temperature and size of the area(s) that reached a temperature higher than 55 °C for all patients

Patient	Sonication	Size (mm)	Power (W)	Duration (s)	Max temp (˚C)	Temp > 55 °C (mm)
1	1 (test)	3	30	8.5*	NA#	NA#
	2	6	100	8.6*		
2	1 (test)	3	30	16.1*	NA#	NA#
	2	3	70	19.7*		
	3 (test)	3	30	12.3*		
	4	6	60	14.9*		
	5	6	50	24.6		
	6	6	70	22.1*		
3	1 (test)	3	40	12.9*	56.1	10 x 7
	2	6	70	16.8*	52.6	3 x 3
4	1 (test)	3	40	20.2	55.7	5 x 5
	2	6	50	24.6	59.0	3 x 2
	3	6	50	24.6	58.3	7 x 5
	4	6	50	24.6	59.1	5 x 3
5	1 (test)	3	40	20.0	NA^	NA^
	2 (test)	3	40	20.0	NA^	NA^
	3 (test)	3	40	20.0	55.7	8 x 7
	4 (test)	3	30	20.0	51.1	No
	5	6	50	24.5	61.4	15 x 12
	6	6	60	23.2*	57.9	12 x 10
	7	6	50	24.5	56.4	8 x 7
6	1 (test)	3	30	20.1	45.8	No
	2	6	50	24.6	49.4	No
	3	6	60	24.6	50.3	No
	4	6	70	24.6	52.7	No
	5	6	70	24.6	51.6	No
7	1 (test)	3	30	20.1	NA&	NA&
	2	3	50	20.1		
	3	6	70	24.6		
	4	6	90	24.6		
8	1 (test)	3	30	20.1	43.9	No
	2	6	60	24.6	48.0	No
	3	6	80	24.6	46.8	No
	4	6	60	24.6	49.1	No
	5	6	80	24.6	48.8	7 x 5
	6	6	80	24.6	51.9	5 x 2
9	1 (test)	3	40	20.1	43.2	no
	2	6	60	24.6	42.5	no
	3	6	80	24.6	42.7	no
	4	6	80	24.6	40.4	no
	5 (test)	3	40	20.1	42.7	no
	6	6	80	24.6	46.7	no
10	1 (test)	3	30	20.1	45.5	no
	2 (test)	3	40	20.1	46.6	no
	3 (test)	3	40	20.1	44.0	no
	4	6	80	24.6	54.4	no
	5	6	80	24.6	51.7	7 x 7

NA not available

* Sonication was prematurely terminated due to an incorrect excessive heating abort

The quality of the thermometry data was too low for any valid temperature estimates

^ During the first two sonications, the fat signal was not suppressed during RPFS thermometry. No valid thermometry data were acquired

& Sonications were mainly located in the adipose tissue anterior of the tumour and no valid thermometry data were acquired

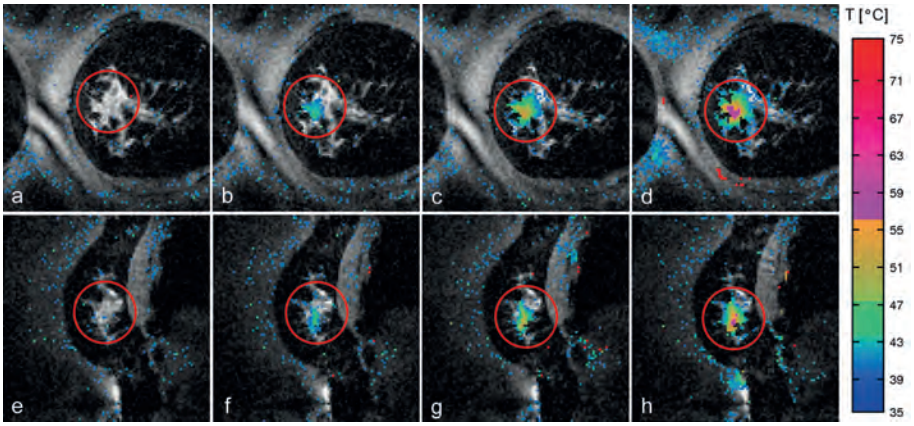

Figure 2 Magnitude images (grey scale) overlaid with MR thermometry data (colour-coded) during the seventh sonication in patient five; a 50-W sonication with a duration of 24.5 s. The maximum temperature reached during this sonication was 56.4 ˚C. Figures **a-d** and **e-h** show the coronal and sagittal images through the focal point, respectively, which were acquired with a temporal resolution of 2.25 s.

Histopathology

In six of ten patients, tumour necrosis was observed after MR-HIFU ablation by the presence of tissue coagulation and leakage of erythrocytes at H&E staining (Figure 4). The maximum diameter of tumour necrosis varied from 3 to 11 mm (Table 4). Patient four refused to undergo surgery. In patients one, seven, and nine, no tumour necrosis was observed. In patient one, only one therapeutic sonication was performed, which was aborted shortly after its initiation. In patient seven, the sonications were mainly located in the adipose tissue anterior to the tumour because the tumour eventually turned out to be just outside the range of the transducers. No necrosis was observed inside the tumour, however, fat cell necrosis was observed in the adipose tissue anterior to the tumour. Also in patient nine, the focal point was located outside the tumour, which was caused by an incorrect misalignment correction after the test sonication.

Sonications were performed at 19 different locations: one to four different locations per patient. In the six patients with tumour necrosis, the number of targeted locations was equal to the number of areas with tumour necrosis at histopathology. In these patients, sonications were performed at 13 different locations, corresponding to 13 different areas of tumour necrosis

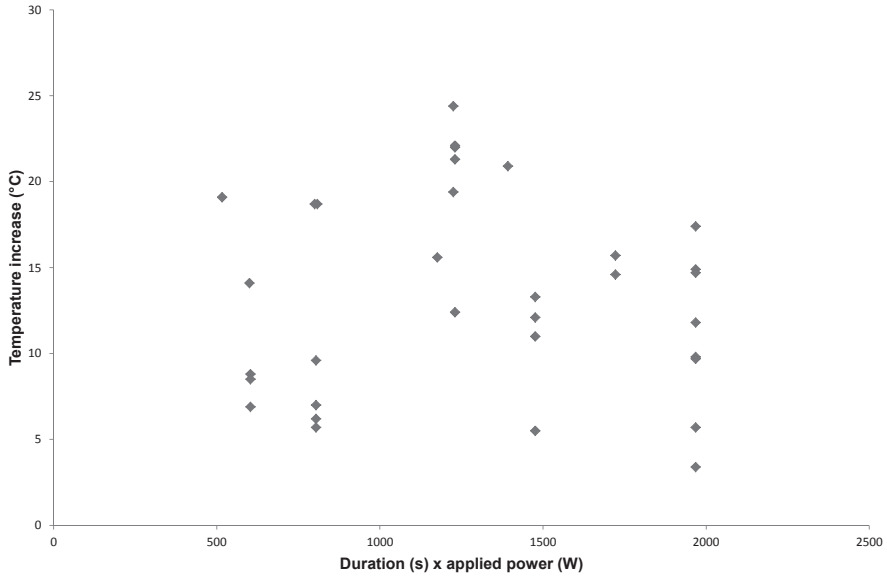

Figure 3 Product of the duration (in seconds) and the applied power (in Watts) of the performed sonications (i.e. the applied energy) versus the increase in temperature (in °C) as measured with MR thermometry

Table 4 An overview of the sonications, locations and tumour necrosis for all patients

Patient	Sonication	Location	Tumour necrosis (mm)
1	1-2	1.1	No
2	1-2	2.1	3 x 1
	3-6	2.2	7 x 3
3	1	3.1	5 x 2
	2	3.2	6 x 4*
4	1-4	4.1	NA[$]
5	1-3	5.1	7 x 6
	4-7[#]	5.2	10 x 5
6	1-5	6.1	11 x 7[§]
7	1-4	7.1	No^
8	1-3	8.1	8 x 3
	4	8.2	4 x 3
	5	8.3	9 x 5
	6	8.4	7 x 4
9	1-3	9.1	No
	4	9.2	No
	5-6	9.3	No
10	1-4	10.1	9 x 4
	5	10.2	7 x 3

* The thermal damage is for the major part present in the glandular tissue outside the tumour due to movement of the patient after the test sonication
[$] No pathology results available
[#] Treatment cells were positioned next to each other and not exactly at the same location
[§] Two other small areas of tumour necrosis were observed
^ No necrosis was observed inside the tumour; however, fat cell necrosis was observed in the adipose tissue surrounding the tumour

Correlation between sonication parameters and the size of tumour necrosis at histopathology

For these analyses, patients four (no histopathology available), seven and nine (sonications located in adipose tissue) were excluded, yielding 14 different locations. A medium correlation was found between the duration of sonications (r=0.73, p=0.003) and the applied acoustic power (r=0.62, p=0.019), and the size of tumour necrosis at histopathology (r=0.76, p=0.002, Figure 5). For 11 locations, adequate MR thermometry data were available. No relationship was found between the temperature increase and the size of tumour necrosis at histopathology. Furthermore, no correlation was found between the size of the area with a temperature higher than 55 °C and the size of tumour necrosis at histopathology. The product of the duration and the temperature increase and the size of tumour necrosis showed a median correlation (r=0.74, p=0.01).

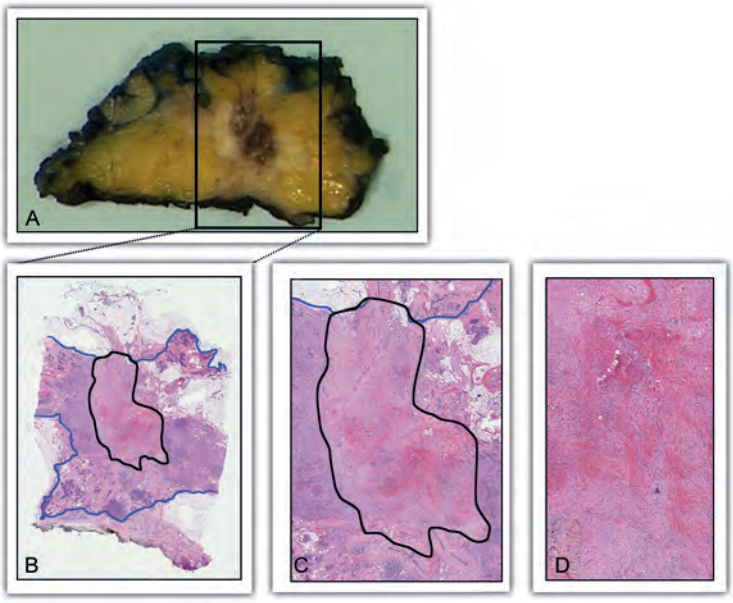

Figure 4 Macroscopic (**a**) and microscopic pictures (**b–d**) of the surgical specimen of the fifth patient. **a**. The yellow tissue is adipose tissue and the white tissue is the tumour tissue. The redbrown area inside the tumour indicates the presence of a haemorrhagic area which is caused by MRI-guided high-intensity focused ultrasound (MRHIFU) ablation. **b–d.** Haematoxylin and eosin (H&E) stainings with increasing magnification. The blue line delineates the invasive tumour which is surrounded by normal fibroglandular tissue and adipose tissue. The area of tumour necrosis is encircled by a black line

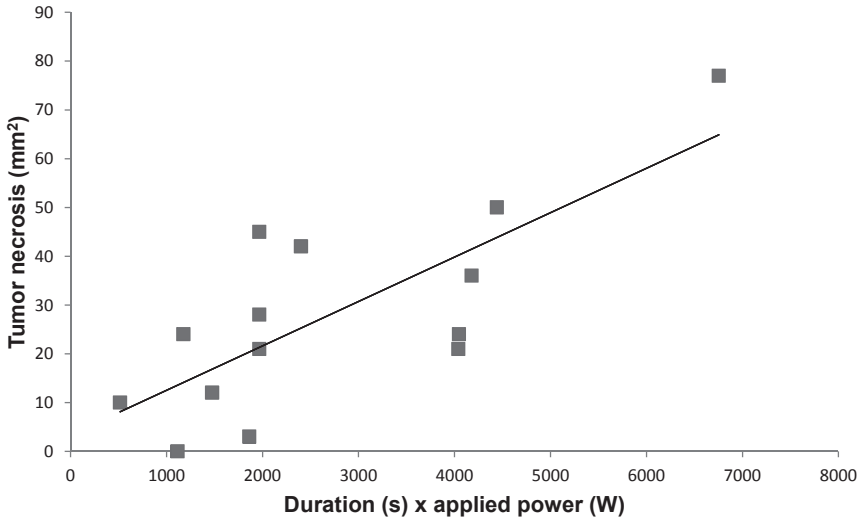

Figure 5 Product of the duration (in seconds) and the applied power (in Watts) of the performed sonications (i.e. the applied energy) versus the size of tumour necrosis (in mm2) at histopathology

DISCUSSION

Our results show that MR-HIFU ablation in breast cancer patients with the dedicated breast system is safe and feasible. In none of the patients was skin redness or burns observed. A good correlation was found between the product of duration and power of sonications (i.e. the applied energy) and the size of tumour necrosis at histopathology ($r=0.76$, $p=0.002$). Furthermore, in patients with tumour necrosis at histopathology, the number of targeted locations was equal to the number of areas with tumour necrosis.

No relationship was found between the applied energy and the increase in temperature. Particularly between different patients, we observed that the acoustic powers required to achieve a certain increase in temperature varied considerably. This may be explained by differences in tumour perfusion and patient characteristics, for example breast size and the ratio between glandular and adipose tissue. Another factor influencing the extent of temperature increase is the distance between tumour and ultrasound transducers. In our system, the circular arc of transducers covers 270°. If the targeted area is close to the 'open' part of the arc of transducers, higher powers may be needed to achieve the same

increase in temperature. Lastly, the measured temperatures are largely dependent on the position of the MR thermometry slices. During certain treatments (e.g., patients six and nine), the measured temperature increase was not as high as one would expect based on other treatments (e.g., patients four and five). This was caused by an incorrect misalignment correction after the test sonication due to the limited experience of the operator, whereby the MR thermometry slice was not positioned exactly through the focal point during the therapeutic sonications.

No relationship was found between the temperature increase and the size of tumour necrosis or the size of the area with a temperature higher than 55 °C and the size of tumour necrosis at histopathology. This may be explained by the reasons given before. A medium correlation was found between the product of the duration of sonications and the temperature increase, and the size of tumour necrosis at histopathology. This result, however, has to be considered carefully because it is a very simplified estimation of the complicated relationship between time and temperature[23]. Unfortunately, we were not able to calculate the exact thermal dose with our data. Another limitation of our analyses is that pathology specimens were not reconstructed in 3D. This means that the maximum diameter used as the outcome measure for the size of tumour necrosis is only an estimate of the whole area of tumour necrosis.

This study was designed to investigate the safety and feasibility of the dedicated MR-HIFU breast platform. Therefore, we chose to allow patients with tumours between 3 and 5 cm in size to participate in this study. Patients with large T2 tumours, however, are generally not appropriate candidates for treatment with minimally invasive ablation techniques such as HIFU[17,24]. In addition, the partial ablation design of our study is different to that of previous studies. In our opinion, this design is more suitable for investigating safety, e.g. through the possibility of analysing the location and size of separate sonications. In addition, the relationship between different sonication parameters and the size of tumour necrosis at histopathology could be analysed for all different locations. Finally, the partial ablation approach allowed us to compare viable versus ablated tumour tissue at histopathology and the non-ablated tumour tissue could be used for the decision about adjuvant treatments.

One of the shortcomings of MR-HIFU ablation in general is the long duration of the procedure[25]. In our study, the overall procedure time was on average 145 min, while the actual sonication time was only 1.7 min. The most time-consuming aspects of the treatment procedure were the waiting time after contrast injection,

filling of the LUT before every sonication and the delays caused by the need to find a proper navigator signal for MR thermometry. In future studies, the ratio between the actual sonication time and the overall procedure time will have to be changed. We chose to treat patients under procedural sedation because of the long duration of treatment in an uncomfortable position. In addition, a regular breathing pattern is preferable for LUT-based corrected MR thermometry. In the first two patients, no valid thermometry data were acquired due to artefacts caused by patient motion and changes in the breathing pattern. Consequently, most sonications were prematurely aborted automatically for safety reasons. From patient three onwards, the sedation regime was changed to esketamine, a sedative agent with minimal impact on the respiration. In addition, the sedation specialists gained more experience and gradually increased the dose of analgesics. In patients four to ten, no patient motion or changes in the breathing pattern were observed anymore and almost all therapeutic sonications could be fully executed. An additional problem during the first two treatments was the occurrence of ghosting artefacts during MR thermometry, and consequently $MnCl_2{\cdot}4H_2O$ was added to the water in the breast cup. Thereafter, no such artefacts were observed anymore.

In our study, we did not observe NPVs immediately after MR-HIFU ablation. In other lesions, for example in benign uterine fibroids, it is known that the observed NPV directly after treatment is related to necrosis[19,26]. Our results indicate that contrary to other lesions, malignant breast tumorUs may show slow enhancement directly after MR-HIFU ablation even when there is no evidence for residual tumour at histopathology. This is in agreement with findings reported by previous groups[27] and may be caused by leakage of contrast into the interstitial space after tumour ablation. In addition, we ablated only a small region within a large tumour and no high-temporal resolution DCE-MRI was performed.

In conclusion, we report our first experiences with MR-HIFU ablation of breast cancer using a dedicated breast platform, concluding that MR-HIFU ablation is safe and results in histopathologically proven tumour necrosis.

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CHAPTER 3

Histopathology of breast cancer after magnetic resonance-guided high-intensity focused ultrasound and radiofrequency ablation

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ABSTRACT

Aims

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) ablation and radiofrequency ablation (RFA) are being researched as possible substitutes for surgery in breast cancer patients. The histopathological appearance of ablated tissue has not been studied in great detail. This study aimed to compare histopathological features of breast cancer after MR-HIFU ablation and RFA.

Methods and results

MR-HIFU ablation and RFA were performed *in-* and *ex-vivo.* Tumours in six mastectomy specimens were partially ablated with RFA or MR-HIFU. *In-vivo* MR-HIFU ablation was performed 3-6 days before excision; RFA was performed in the operation room. Tissue was fixed in formalin and processed to haematoxylin and eosin (H&E) and cytokeratin 8 (CK-8) stained slides. Morphology and cell viability were assessed. *Ex-vivo* ablation resulted in clear morphologic changes after RFA versus subtle differences after MR-HIFU. CK-8 staining was decreased or absent. H&E tended to underestimate the size of thermal damage. *In-vivo* MR-HIFU resulted in necrotic-like changes. Surprisingly, some ablated lesions were CK-8 positive. Histopathology after *in-vivo* RFA resembled *ex-vivo* RFA, with hyper-eosinophilic stroma and elongated nuclei. Lesion borders were sharp after MR-HIFU and indistinct after RFA.

Conclusion

Histopathological differences between MR-HIFU-ablated tissue and RF-ablated tissue were demonstrated. CK-8 was more reliable for cell viability assessment than H&E when used directly after ablation, while H&E was more reliable in ablated tissue left *in situ* for a few days. Our results contribute to improved understanding of histopathological features in breast cancer lesions treated with minimally invasive ablative techniques.

INTRODUCTION

The trend towards local breast cancer treatment with minimally invasive approaches has resulted in the introduction of magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation and radiofrequency ablation (RFA) as possible substitutes for surgical excision. Minimally invasive treatments are potentially suitable for patients with early stage small breast cancers and are expected to improve cosmetic outcome and have a lower risk of surgical complications[1,2].

MR-HIFU is a completely non-invasive technique. Absorption of focused ultrasound waves by tissue induces short-term temperature increases above 55 °C within a sharply demarcated area, so that surrounding tissues and the skin remain undamaged[3-5]. The first MR-HIFU breast cancer treatment was reported in 2001 by Huber et al.[6]. In the subsequent decade, several small clinical trials have been conducted, mostly using a treat-and-resect protocol[7-12]. For RFA, a needle-electrode is inserted to deliver an alternating current that generates ionic agitation, localized frictional tissue heating and cell death[13]. This technique was first introduced for breast cancer treatment in 1999 by Jeffrey et al.[14]. Clinical experience with RFA is slightly more extensive than with MR-HIFU ablation, but still limited[15-26]. Treat-and-resect studies have proved that both techniques achieve complete ablation of breast cancers.

Reliable cell viability assessment is crucial for determining treatment efficacy. In most MR-HIFU studies haematoxylin and eosin (H&E) staining is considered reliable for detecting thermal damage[7,8]. However, an MR-HIFU study in *ex-vivo* human breast tissue suggested that cytokeratin (CK-8) immunohistochemistry can also be used for the assessment of treatment effect[27]. In most RFA studies reduced nicotinamide adenine dinucleotide (NADH) diaphorase staining is used, requiring frozen material with associated poor morphology[15-26,28]. CK-8 staining can be used as a reliable alternative on paraffin sections of RFA lesions as well[29-31].

Our institution has gained experience in the performance and assessment of both RFA[29,30] and MR-HIFU ablation[32]. The aim of this study was to assess histopathological features of cancerous breast tissue ablated with MR-HIFU and RFA using H&E and CK-8 staining.

METHODS

Ex-vivo procedures

Patients

Ex-vivo ablation procedures were performed in fresh mastectomy specimens of six consecutive women with histopathologically proven invasive breast cancer. Directly following mastectomy, MR-HIFU and RF ablation were performed in three breasts each. All procedures were aimed at partial ablation. The study protocol was approved by the Institutional Review Board of the University Medical Center Utrecht (Utrecht, The Netherlands), and all patients signed informed consent.

MR-HIFU ablation

For a detailed description of the MR-HIFU breast system (Philips Healthcare, Vantaa, Finland) see Merckel et al.[32,33] and Deckers et al.[34]. The mastectomy specimens were placed on the HIFU breast table, surrounded by water to facilitate acoustic coupling and supported by cling film. One or two areas within the MR-visible tumour were heated to at least 60 °C for approximately 25 s, for which an acoustic power of 60 W or more was used.

RFA

For a detailed description the RFA system (CelonProSurge 150-T20, Olympus Winter&Ibe GmbH, Hamburg, Germany) see Waaijer et al.[29]. A 5-mm incision was made in the preserved skin of the mastectomy specimens and a breast radiologist inserted the RFA probes under ultrasound guidance. The probe was inserted at the tumour border to achieve partial ablation. The correct placement was confirmed in three directions and RFA was performed under continuous ultrasound monitoring. The generator was set to supply a maximum power output of 15 W and a total energy of 9.0 kJ was administered. The power control unit also stopped delivering radiofrequency energy if steep impedance increase occurred at short time intervals (a 'break' or 'roll-off').

In-vivo procedures

Patients

In the present study, we used the histologic material acquired previously by Merckel at al.[32] and Waaijer et al.[29]. Briefly, 10 patients with histopathologically proven invasive breast cancer of at least 1.0 cm in diameter underwent MR-HIFU ablation. In the RFA study, 15 women with core needle biopsy-proven invasive breast cancer, less than 2.0 cm in diameter on ultrasound (US), underwent RFA.

MR-HIFU ablation

During MR-HIFU treatments, patients were positioned in prone position with the affected breast placed in the breast cup of the MR-HIFU breast system. Partial tumour ablation was performed. Patients were treated under deep sedation. A variable number of sonications ranging from two to seven were performed, divided over one to four locations within the tumours. Powers up to 90 W were used, depending on whether the temperature in the targeted tissue reached at least 60 °C. Three to 6 days after MR-HIFU treatment, patients underwent either mastectomy or local excision. Only mild side effects were reported and consisted of nausea and vomiting in two patients, self-limiting skin lesions in one patient and pain in two patients. No long-term side effects were reported[32,34].

RFA

RFA was performed in the operating room, under sterile conditions and under general anaesthesia. The *in-vivo* RFA procedures were similar to the *ex-vivo* procedures except for insertion of the probe, which was positioned in the centre of the tumour in order to achieve complete ablation. A sterile ice pack was placed on the skin during the RFA procedures to prevent skin burns. After reaching 9.0 kJ or after the power control unit stopped delivering energy because of steep impedance increase, puncture track coagulation was performed at 15 W while deactivating the resistance control. Immediately after RFA, patients underwent mastectomy or local excision. The probe was not correctly positioned in one patient, causing a pneumothorax. No other side effects occurred. In three patients RFA resulted in partial ablation and the histopathological material of two of these patients (40% and 60% ablation) was retrieved for this study to enable comparison with the partially ablated specimens of patients treated with MR-HIFU ablation[29].

Histopathology

After both *ex-vivo* ablation procedures, excised specimens were directly submitted to the pathology department and lamellated into slices of approximately 5 mm and fixed in formalin. The tumour was located, 5-mm tumour slices were taken and routinely embedded in paraffin, and 3-4-µm sections were cut from the paraffin blocks and stained with H&E. All levels containing thermal damage (based on H&E slides) or, in case of doubt, all sections containing tumour were additionally stained immunohistochemically with a monoclonal antibody to CK-8 (CAM5.2, Becton & Dickinson, Erembodegem-Aalst, Belgium). Staining was first developed in 3-3'-diaminobenzidine tetrachloride after application of the peroxidase-labelled streptavidin-biotin (LSAB) kit (Dako Cytomation, Glostrup, Denmark) and subsequently counterstained with Mayer's haematoxylin. CK-8 staining of viable tissue results in a brown cytoplasmic staining pattern, while damaged tissue lacks staining[27].

After *in-vivo* MR-HIFU ablation the tumour remained *in situ* for three to six days. The resected specimens were cut into 5-mm slices, and after formalin fixation microscopic sections of 4 µm were H&E stained for routine histopathological evaluation. If thermal damage was suspected, one level was also stained with CK-8.

After *in-vivo* RFA, the specimens were submitted fresh to pathology where sectioning of the specimen was performed. Formalin-fixed tissue was used for routine histopathological evaluation using conventional H&E staining. CK-8 staining was performed on all 4-µm slides of all blocks containing tumour.

Evaluation and analysis

Pathological variables evaluated included morphology of viable and damaged invasive tumour cells, size of transition zones (area between lethally damaged and viable tissue) and the appearance of CK-8 stained viable and damaged tissue. The pathologic effects were assessed by one experienced breast pathologist (P.v.D.) with 15 years expertise in the assessment of minimally invasive ablative treatments.

RESULTS

Ex-vivo ablations

MR-HIFU ablation

On H&E stained sections, thermally damaged areas showed mild changes compared to viable tumour tissue. Tumour cells in ablated areas were slightly discohesive, and nuclei seemed more compact. In contrast to H&E stained slides, CK-8 stained tissue showed remarkable changes. In thermally damaged areas, CK-8 staining intensity was decreased substantially and more focal in the cytoplasm than in viable areas with bright diffuse cytoplasmic staining. The transition zone between viable and damaged tissue was very narrow, consisting of only a few cells (Figure 1 and Table 1).

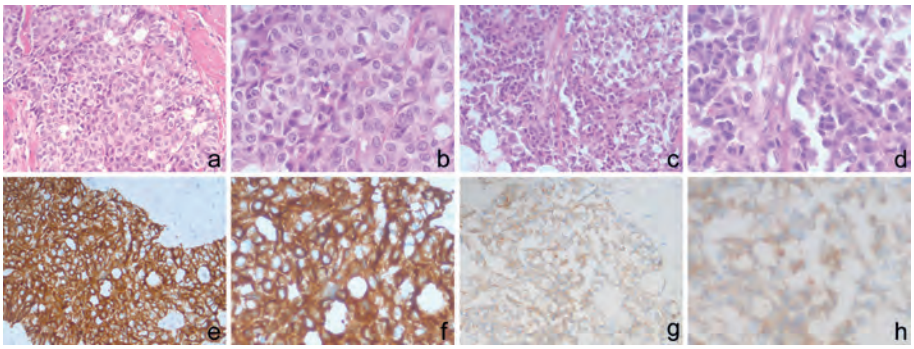

Figure 1 Comparison of viable and damaged tissue after *ex-vivo* magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation in a mastectomy specimen. **a.** Viable tumour tissue, haematoxylin and eosin (H&E) staining. **b.** Viable tumour tissue, H&E staining. **c.** Ablated part [based on cytokeratin-8 (CK-8) staining) of same tumour as **a** and **b** (H&E), lacking clear changes at this magnification. **d.** Ablated tumour (H&E. At higher magnification, slightly discohesive tumour cells and denser nuclei are seen. **e.** CK-8 stained slice of same area as **a. f.** CK-8 stained slice of same area as **b. g.** CK-8 stained slice of same area as **c**. Almost complete loss of CK-8 staining when compared to **e** indicating lethal damage. **h.** CK-8 staining of same area as **d**. Almost complete loss of CK-8 staining, residual staining is less intense and more spotty than in viable tissue as shown in **f**.

RFA

Thermal lesions caused by RFA ablation were characterized by marked deformations, which increased gradually towards the probe insertion spot. In the most damaged areas hyper-eosinophilic stroma and stretched and elongated nuclei were seen. Unlike MR-HIFU-induced changes with a brisk transition between viable and damaged cells, no distinct border between viable and lethally damaged tissue was

seen pointing to a much more gradual transition. This was also illustrated by CK-8 staining, which showed three different zones classified as viable, subviable and lethally damaged (Figure 2 and Table 1), with decreasing staining intensity from bright to absent. In some cases, tissue appeared viable on H&E staining while CK-8 was (partially) negative, indicating a larger thermally damaged area than expected after assessment of H&E staining slides.

In-vivo ablations

MR-HIFU ablation

Tumour tissue ablated by MR-HIFU was characterized by evident necrotic-like changes. Some hyper-eosinophilic stroma was observed. Nuclei were smaller with condensed chromatin, while in some cells only nuclear debris was found. Cytoplasm was partially retracted and tumour cells were discohesive, and ablated areas were infiltrated by erythrocytes. Influx of inflammatory cells was seen in the ablated tissue, as is seen usually in necrotic tissue. The ablated areas were clearly demarcated and the borders could be identified easily on H&E-stained sections. CK-8-stained slides, however, still showed cytokeratin expression in some parts

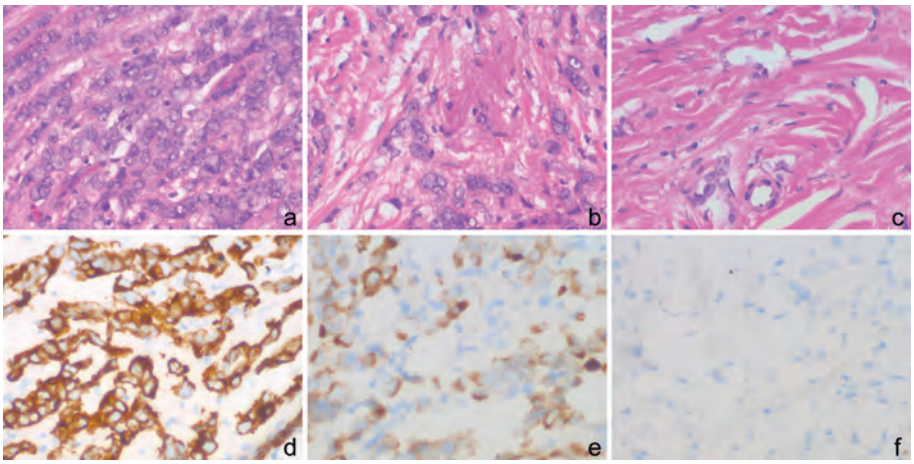

Figure 2 Breast cancer tissue after *ex-vivo* radiofrequency ablation (RFA), showing a gradual increase of the amount of damage towards the probe insertion. **a.** Viable tumour tissue, haematoxylin and eosin (H&E) stained. **b.** Subviable tumour tissue with some deformation of nuclei and hyper-eosinophilic stroma. **c.** Severely damaged tumour tissue with pronounced hyperintense eosinophilic stroma and elongated nuclei. **d.** Cytokeratin-8 (CK-8) stained viable tumour, corresponding to the area of **a**. Cells were clearly positive for CK-8. **e.** Subviable tumour tissue, the same area as **b**. A different pattern and reduced intensity of CK-8 staining is seen when compared to **a**. **f.** Complete absence of CK-8 staining in area corresponding to **c**, which is considered lethally damaged.

of MR-HIFU ablated areas, which was more diffuse and less pronounced at cell borders (Figures 3 and 4 and Table 1). In some cases fibrotic areas developed in the ablation zones.

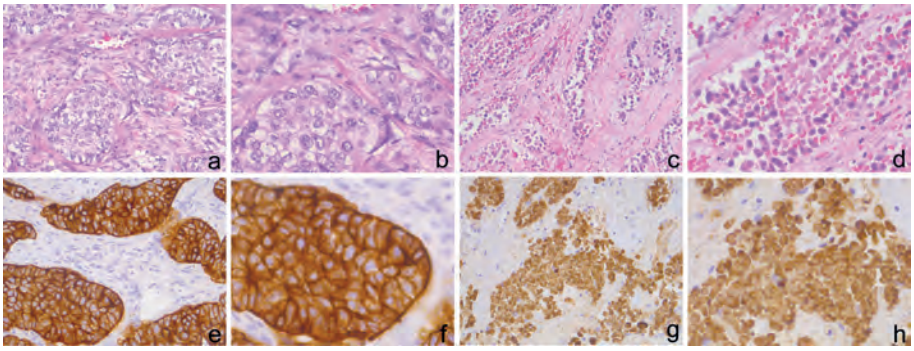

Figure 3 Comparison between viable cancerous breast tissue and tumour tissue ablated in-vivo with magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation. **a.** Viable breast cancer, haematoxylin and eosin (H&E) staining. **b.** Viable breast cancer, H&E staining. **c.** Thermally damaged area of same tumour as **a** and **b**. Necrotic-like changes were clearly visible. **d.** Thermally damaged tumour. Evident changes compared to **b** were seen. Nuclei were smaller with condensed chromatin, in some cells only nuclear debris was found. Cytoplasm was partially retracted and tumour cells were discohesive, infiltrated with erythrocytes. **e.** Cytokeratin-8 (CK-8) stained viable tumour tissue. **f.** CK-8 stained viable tumour tissue, cytoplasmic staining, with increased intensity at tumour borders. **g.** Thermally damaged area with retained CK-8 staining. **h.** Thermally damaged area with retained CK-8 staining. Cells were stained more diffusely than viable cells. The morphology of tumour cells was clearly changed when compared to **f**, but CK-8 staining did not seem to indicate cell death reliably.

RFA

Histopathological findings after *in-vivo* RFA ablation closely resembled findings after *ex-vivo* ablation. *In-vivo* effects, however, were more pronounced than effects of the *ex-vivo* experiments. The H&E stained slides showed clear demarcation of the probe insertion with distinct stromal eosinophilia. CK-8 staining showed identical features to the *ex-vivo* experiments (Figures 5 and 6 and Table 1).

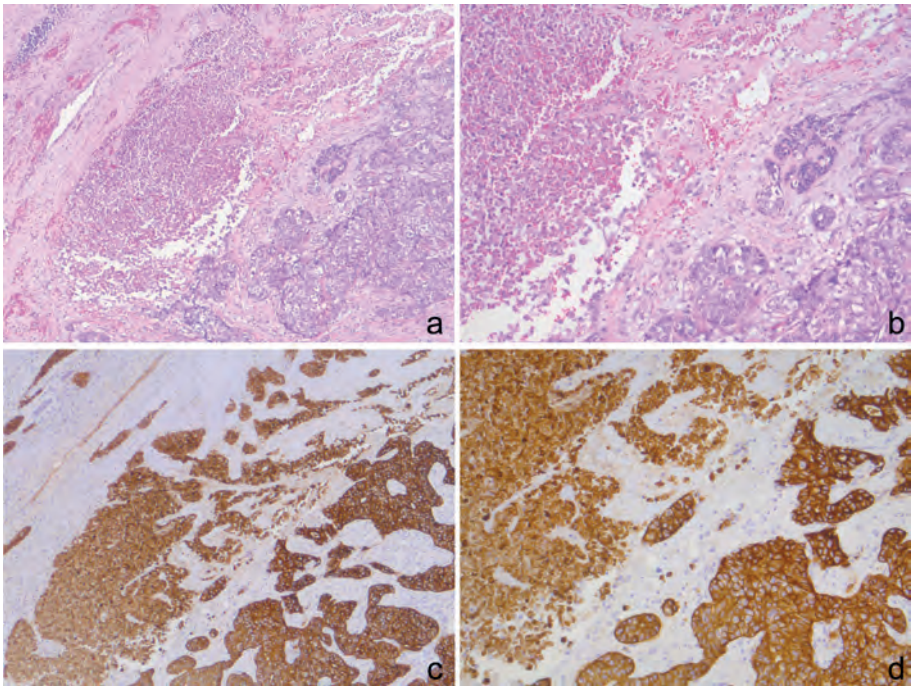

Figure 4 Breast cancer tissue after in-vivo magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation; the patient underwent surgery after 6 days post-MR-HIFU ablation. **a.** Breast cancer tissue containing demarcation of ablated area [haematoxylin and eosin (H&E)]. **b.** Same area as in **a**, showing necrotic-like changes in left upper part of the image and viable tissue in the right lower part. The transition zone is very narrow. **c.** The Cytokeratin-8 (CK-8) stained area is the same as in **a;** no clear loss of staining can be identified. **d.** CK-8 staining of same slide as **b**. A change in cell morphology is seen in the upper left part of the image, but the intensity of CK-8 staining is hardly decreased in the damaged tumour area.

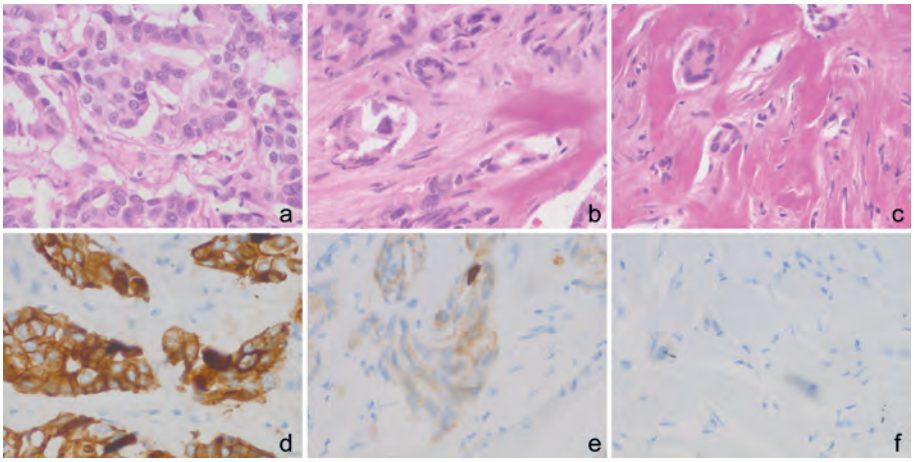

Figure 5 *In-vivo* partial (40%) radiofrequency ablation (RFA) performed directly before surgical excision. No major differences with ex-vivo RFA were seen. **a.** Viable tumour tissue [haematoxylin and eosin (H&E)]. **b.** Subviable tumour tissue (H&E staining) with partial deformation of nuclei and some hyper-eosinophilc stroma. **c.** Lethally damaged breast cancer with severe deformation of all nuclei and pronounced hyperintense eosinophilic stroma (H&E staining). **d.** Cytokeratin-8 (CK-8) staining of same area as **a**. **e.** Subviable tumour tissue, the same as **b**. Remarkable reduction of CK-8 staining. **f.** Lethally damaged tumour tissue, same area as in **c**. Total absence of CK-8 staining.

Table 1 Summary of histopathological similarities and differences after in- and ex-vivo MR-HIFU and RFA

		MR-HIFU	RFA
Ex-vivo	H&E	No pronounced changes, tissue seems viable	Severe deformations, wide transition zone
	CK-8	Loss of staining with small transition zone	Gradual loss of staining from periphery to probe insertion
In-vivo	H&E	Necrotic-like changes with small transition zones	Severe deformations, wide transition zone
	CK-8	CK-8 positive staining in morphologically damaged cells	Gradual loss of staining from periphery to probe insertion

CK-8 Cytokeratin-8; *H&E* haematoxylin and eosin; *MR-HIFU* magnetic resonance-guided high-intensity focused ultrasound; *RFA* radiofrequency ablation

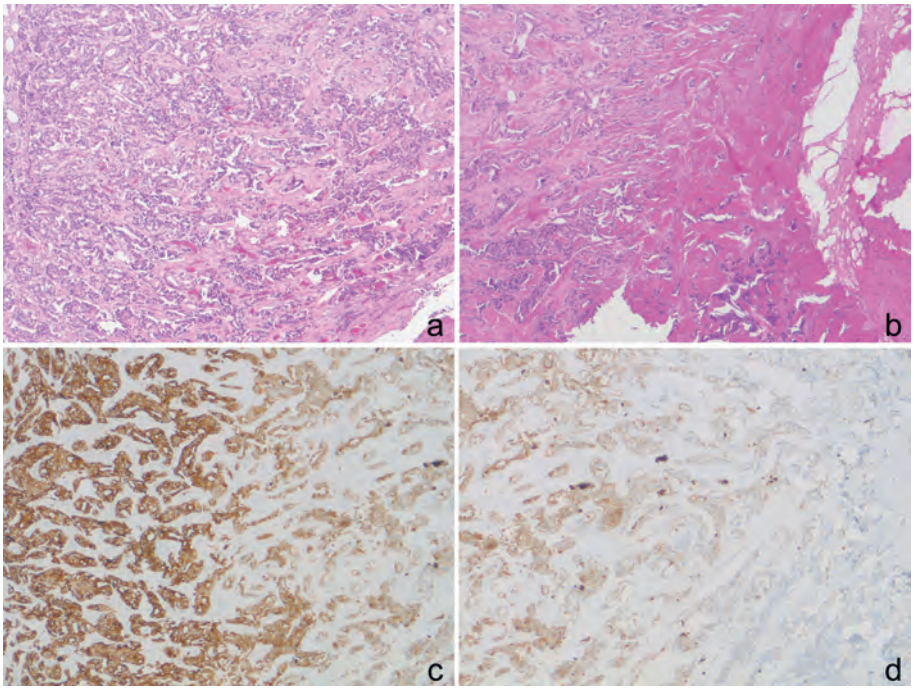

Figure 6 Partial (40%) radiofrequency ablation (RFA) performed prior to surgical excision, which resulted in severe damage with a gradual transition towards viable tumour tissue. Again, no pronounced differences with *ex-vivo* RFA were found. **a.** Transition between viable and subviable tumour tissue [haematoxylin and eosin (H&E)]. **b.** Transition between subviable and lethally damaged tissue (H&E). At the right side evident deformations and hyper-eosinophilic stroma were induced around the probe insertion. **c.** Cytokeratin-8 (CK-8) staining of the same area as **a**. Staining evidently decreased towards the right side of the figure. **d.** Same area as **b**, with minimal CK-8 stained tissue gradually disappearing towards the right side of the figure.

DISCUSSION

This study describes the histopathological similarities and differences in breast cancer tissue ablated with ex- and in-vivo MR-HIFU and RF ablation. Ex-vivo ablation with both techniques resulted in a loss of CK-8 staining, indicating non-viability. H&E staining, however, showed clear morphological changes after RFA and only very subtle differences after MR-HIFU ablation. In-vivo MR-HIFU resulted in necrotic-like, haemorrhagic and fibrotic changes and hyperchromatic nuclei or nuclear debris after 3-6 days. CK-8 staining remained positive in some in-vivo MR-HIFU lesions. Histopathological findings after in-vivo RFA corresponded well with findings after ex-vivo RFA, with hyper-eosinophilic stroma and elongated nuclei. Demarcation of MR-HIFU lesions was very sharp while lesions border after RFA were more indistinct.

The differences between tissue appearance after ex- and in-vivo MR-HIFU ablation are caused presumably by the 3-6 days during which the treated tumour was left in situ after in-vivo ablation. Ex-vivo MR-HIFU with immediate tissue processing resulted in very subtle morphological changes, which may remain undetected at routine histopathological examination. CK-8 staining was, however, reduced in these regions, pointing to apoptosis[35,36]. Wu et al. performed ultrasound-guided HIFU ablation of breast cancer in 23 patients followed by surgery after 7-14 days[37]. In the peripheral region of ablated tissue necrotic changes were seen, as in our *in-vivo* study and other studies[6,9,38]. Tumour cells centrally in the ablated area were described as appearing viable on H&E staining. However, electron microscopy showed that these seemingly viable cells were damaged irreversibly and lethally, illustrated further by absence of NADH diaphorase staining in both the central and peripheral areas. This phenomenon was called heat fixation. CK-8 is an epithelium-specific intermediate filament involved in maintaining the cytoskeleton of glandular tissue. CK-8 is cleaved early in the apoptosis cascade[35,39]. Hence, tissue exposed to high and rapid temperature increase resulting in apoptosis lacks CK-8 staining, even if it may seem undamaged on H&E stained slides[40]. We found heat fixation only in *ex-vivo* ablated tissue and not in the tissue resected after 3-6 days. We hypothesize that our *in-vivo* ablated lesions were too small (6 mm) to maintain a centre containing heat-fixated cells. Instead, the entire lesions became necrotic, comparable to the peripheral region of the ablated tumours described by Wu et al.[37]. Similar findings were reported by Bloom et al. after laser ablation[40]. Conversely, the *in-vivo* MR-HIFU ablation in our study sometimes resulted in (persistent) low level of CK-8 staining in morphologically clearly ablated tumour areas. Hence, CK-8 may be a less reliable indicator for cell viability when used several days after MR-HIFU, and light microscopy at high magnification is possibly overriding.

The similarities between *ex-vivo* and *in-vivo* RFA are attributed to the similar short period between RFA and tissue processing: *in-vivo* RFA in the operation room shortly before resection and *ex-vivo* RFA directly after resection. Changes were slightly less pronounced after *ex-vivo* RFA, due probably to placement of the probe at the border of the tumour aiming for partial ablation. Earashi et al. showed that the thermal damage observed after RFA may increase over time[15]. They compared histopathological findings of tumours treated with RFA followed by immediate resection to those resected after a mean of 91 days. The latter group had remarkably more degenerative changes. Hence, the damage after RFA in our series might have been underestimated due to immediate surgical resection. In

some cases, H&E staining showed less extensive damage than CK-8, confirming that H&E staining alone is not sufficient for assessment of the treatment effect and may also be misled by heat fixation. Our findings are in agreement with previous studies[15,17,31].

Several differences were found between MR-HIFU and RF ablated breast cancer tissue. RFA uses insertion of a needle probe, resulting in most heat accumulation close to the tip of the needle. Consequently, the centre of the ablated area was most damaged and the thermal effects decreased gradually at increasing distance from the probe. Transition between thermally damaged and viable areas after MR-HIFU ablation was much more abrupt due to sharp temperature gradients and short durations of heating, which resulted in limited heat diffusion into the surrounding tissue. The RF-ablated tissue could be subdivided grossly in three zones: most damaged, subviable and viable zones. Some CK-8 staining was seen in the subviable zone and nuclei seemed less hyperchromatic and stretched. Whether all cells in this area are non-viable is uncertain. However, after *ex-vivo* MR-HIFU ablation we found similar morphologic changes. CK-8 staining was not totally absent, and H&E staining did not show remarkable changes. When assessing MR-HIFU lesions several days after treatment, the ablated areas seemed totally necrotic. These findings indicate that the subviable zone probably becomes necrotic over time. The severe central deformations seen after RFA were not visible after MR-HIFU ablation, due probably to differences in maximum temperature: 60 °C for approximately 20 seconds for MR-HIFU, whereas treatment times of 10 minutes at 100 °C during RFA have been reported[29]. The hyper-eosinophilic areas and elongated nuclei after RFA may be caused by these high temperatures, and were therefore not observed after MR-HIFU ablated tumours.

If minimally invasive treatments were implemented as primary treatment without surgery, no excision specimens would be available. Hence, prognostic factors should be assessed prior to treatment. Assessment of histological type, hormone receptor status and human epidermal growth factor receptor 2 (HER2) status is reasonably reliable on core needle biopsy[41-43]. Tumour grade assessment might be more challenging on core biopsies, but previous studies mitigate these concerns, as the agreement between grading on core needle biopsy and excision specimen is within the range of grading agreement between pathologists on resection specimens and discrepancies have few consequences[44-47]. Furthermore, tumour size can be assessed reliably on magnetic resonance imaging (MRI)[48].

The optimal follow-up strategy after ablative therapy is an important issue, which should be investigated in future studies. A small minority of breast tumours does not express CK-8[49,50], and in these tumours CK-8 can obviously not be used to assess cell viability. These cases can be identified in advance by CK-8 staining on the diagnostic core needle biopsy. Other methods can be used to assess apoptosis, for example terminal deoxynucleotidyl transferase biotin dUTP nick and labeling (TUNEL), which is based on the cleavage of DNA later in the apoptotic process[36,39]. Additionally, contrast-enhanced MRI may be a suitable modality for follow-up[10].

MR-HIFU ablation and RFA are promising techniques. Especially in patients with breast cancer diagnosed at an early stage, we expect these techniques to have benefits over surgical treatment. However, the minimally invasive treatments should be optimized first. Not enough evidence exists on whether or not the success rate of MR-HIFU and RFA are comparable to those of surgery. Obtaining more and better evidence is challenging, as very successful treatment options are already available currently for this patient population. If MR-HIFU ablation and RFA and surgery would prove to equally successful, we expect these minimally invasive treatments to become well used in a selected group of patients in the future.

In conclusion, we have demonstrated similarities and differences in breast cancer tissue ablated by MR-HIFU and RFA. Underestimation of tissue damage during assessment of H&E staining slides was seen after both ablation techniques. This was attributed to heat fixation. CK-8 was a reliable marker for tissue damage when used directly after ablation and seemed more reliable than H&E staining. However, ablated tissue left *in situ* for a few days was partially CK-8 positive and H&E was more reliable. Transition zones were large after RFA and very small in MR-HIFU lesions. Our results contribute to improved understanding of the histopathological appearance of breast cancer lesions treated with ablation techniques.

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CHAPTER 4

Early health technology assessment of magnetic resonance-guided high intensity focused ultrasound ablation for the treatment of early-stage breast cancer

Submitted

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ABSTRACT

Background

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) ablation is in development for minimally invasive treatment of breast cancer. Cost-effectiveness has not been assessed yet. An early health technology assessment was performed to estimate costs of MR-HIFU ablation, compared to breast conserving treatment (BCT).

Methods

An MR-HIFU treatment model using the dedicated MR-HIFU breast system (Sonalleve, Philips Healthcare) was developed. Input parameters (treatment steps and duration) were based on the analysis of questionnaire data from an expert panel. MR-HIFU experts assessed face validity of the model and data collected by questionnaires were compared to published data of an MR-HIFU breast feasibility study. Treatment costs for tumours of 1 to 3 cm were calculated.

Results

The model structure was considered of acceptable face validity by consulted experts, and questionnaire data and published data were comparable. Costs of MR-HIFU ablation were higher than BCT costs. MR-HIFU best-case scenario costs exceeded BCT costs with approximately €1000. Cooling times and breathing correction contributed most to treatment costs.

Conclusion

MR-HIFU ablation is currently not a cost-effective alternative for BCT. MR-HIFU experience is limited, increasing uncertainty of estimations. The potential for cost-effectiveness increases if future research reduces treatment durations and might substantiate equal or improved results.

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide and its incidence is increasing[1,2]. As a result of national screening programmes, most breast cancers are detected at an early stage[3]. Early stage breast cancer is usually treated with breast conserving therapy (BCT), which consists of lumpectomy combined with radiotherapy, followed by systemic therapy in patients deemed at high risk of metastases[4]. The overall prognosis after BCT is good, i.e. survival is similar to more radical mastectomy[5]. However, any surgical treatment always bears a risk of impaired cosmetic results and complications[6-8].

Currently, a shift towards non-surgical and less invasive treatment has been observed in several clinical trials, assessing the feasibility and efficacy of minimally invasive therapies[9-12]. One of these novel treatments is Magnetic Resonance guided High Intensity Focused Ultrasound ablation (MR-HIFU)[13]. Using focused ultrasound beams with a high frequency MRI-integrated HIFU systems heating breast tumours to lethal temperatures, and inducing coagulation necrosis. Possible advantages of MR-HIFU ablation are a lower risk of complications such as infection and haemorrhage and the possibility to offer the treatment in an outpatient setting without general anaesthesia. MRI-guidance is used for tumour visualization and temperature measurement during the procedures[13-15]. Initial clinical MR-HIFU studies report the treatment of approximately 122 malignant breast tumours, of which 77 were excised afterwards to assess histopathological response. The percentage of complete tumour ablation in these small feasibility studies varies from 16.7% to 90%[16-25].

Besides effectiveness, potential cost-effectiveness is a relevant aspect of introducing a new technique. MR-HIFU ablation will only have the potential to become a primary treatment in the future if its cost-effectiveness is acceptable compared to surgical treatment. Because its costs have not been assessed yet, the purpose of the current study was early health technology assessment. While assuming equal effectiveness of MR-HIFU and BCT, costs for treatment using MR-HIFU ablation compared to BCT were estimated. Additionally, the influence of several treatment-related features on these costs was assessed.

METHODS

A decision tree model was developed to evaluate the additional costs of MR-HIFU ablation as a replacement of BCT for the treatment of early-stage breast cancer and to what extend these costs are influenced by several treatment-related features. Equal effectiveness of MR-HIFU ablation and BCT was assumed for these analyses, because of the limited amount of clinical data of MR-HIFU treatments[26,27]. Model input data were collected in a systematic way. Where possible, parameter estimates were based on literature. For parameters that were not available in literature, a survey among experts was performed. MR-HIFU experts assessed face validity of the model. In addition, The model input was validated by comparison of treatment duration estimates to a recent publication on the feasibility and safety of MR-HIFU ablation[28].

BCT and MR-HIFU scenarios

BCT was compared with MR-HIFU ablation. For BCT, treatment consisted of surgery with sentinel lymph node procedure, hospital admission, histopathological examination of excision specimen and adjuvant treatment in most cases. MR-HIFU treatment comprised a pre-treatment MRI scan, separate pre-treatment sentinel lymph node procedure, MR-HIFU ablation in day care setting and adjuvant treatment in most cases. Follow-up was not taken into account in this early health technology assessment (HTA).

Patients

MR-HIFU ablation was considered most suitable for patients with early stage breast cancer with a maximum diameter of three centimetres with no malignant foci at a larger distance than 1 cm from the tumour edge[29]. Additional exclusion criteria for MR-HIFU ablation were: ductal carcinoma in situ (DCIS) and lobular histological type, as both increased the risk of incomplete resection and ablation[30,31], the presence of axillary lymph node metastases and all contra-indications for MRI. Furthermore, patients could be excluded from MR-HIFU treatment due to the following factors assessed on pre-treatment MRI: tumour not reachable for the ultrasound beam, or distance from tumour to skin or pectoral muscle < 1 cm[28].

Model

A model comprising the MR-HIFU treatment as performed with the dedicated MR-HIFU breast system (Sonalleve-based prototype, Philips Healthcare, Vantaa, Finland) was developed[32]. The model distinguished four separate phases: patient positioning on the MR-HIFU system, test phase (establishment of the exact treatment focus and treatment planning), therapeutic phase (the actual tumour ablation) and post-treatment phase (figure 1).

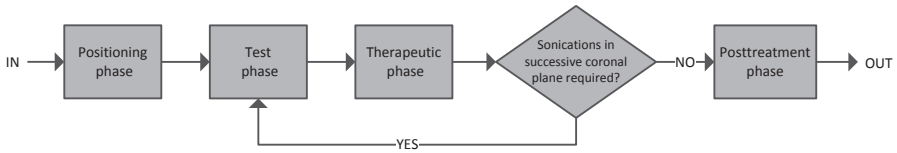

Figure 1 Overview of the four phases of MR-HIFU treatment

In the positioning phase, the patient was positioned on the HIFU table, which was then placed in the MR scanner, and tumour reachability for the HIFU beams was checked. Next, sedation analgesia was administered and target definition was performed based on MR images. In the test phase the respiratory breathing pattern was tracked to correct for breathing artefacts during proton resonance frequency shift (PRFS) thermometry[15]. Additionally, in the test phase the exact location of the focal point was checked and adjusted if necessary. In the therapeutic phase sonications with a higher power than used in the test phase were applied. Using PRFS thermometry maps, the temperature rise in the targeted tissue was followed to ensure that ablative temperatures were reached. Test sonications were applied again after switching to the next treatment slice. In the post-treatment phase contrast-enhanced MRI was performed to evaluate treatment results and sedation analgesia was ceased. The patient was admitted to a clinical ward for observation during the next three hours. Modelling was performed in MATLAB (R2014a). The conceptual model was tested for face validity with MR-HIFU experts involved in the MR-HIFU ablation feasibility and safety study performed with the aforementioned HIFU breast system[28].

Model input data

For an overview of the model input parameters, see Table 1. To estimate the yearly number of early stage breast cancer (stage I and stage II tumours (≤ 3 cm in diameter)) patients, data from the Netherlands Comprehensive Cancer

Organisation were used[33]. Several parameters concerned duration of treatment steps and probability of events related to treatment, e.g. repositioning a patient. These were based on a questionnaire filled in a by a team of (inter) national experts (physicians involved in breast cancer treatment, physicists, technicians and physicians with MR-HIFU experience). Durations were estimated by seven experts, probabilities by four of those seven experts.

To estimate the time that was needed for MR-HIFU treatment, a simplified tumour model was assumed with sphere-shaped tumours with a diameter of 1, 2 or 3 cm. A safety margin of 0.5 cm was added to the tumour size, resulting in spheres with a diameter of 2, 3 or 4 cm. The treatment cells of the HIFU device were considered cylindrically shaped with a diameter of 3, 6, 9 or 12 mm in the coronal plane and a height of 2, 4, 6 or 8 in the sagittal plane respectively. These are the approximate values provided by the dedicated MR-HIFU system[28,32]. The number of sonications required for tumours of different diameters was approximated by assuming cylindrical shaped treatment cells covering a sphere shaped tumour. The number of sonications varied with the height and diameter of treatment cells, as follows: treatment cells with a diameter of 9 mm and height of 6 mm resulted in 17 sonications for tumours of 1 cm, 50 sonications for tumours of 2 cm and 110 sonications for tumours of 3 cm. Treatment cells with a diameter of 12 mm and height of 8 mm resulted in 9, 25, and 50 sonications respectively.

Cost data

The average costs of BCT of the aforementioned patient population were based on a database comprising 1,345 breast cancer patients[34]. Hereby a weighting to the amount of women undergoing lumpectomy with or without adjuvant therapy, i.e. systemic therapy (hormonal therapy and chemotherapy) and radiotherapy, was done[35-37]. To estimate the costs for using the MR scanner and HIFU device, tariffs for MR procedures that were comparable in complexity, such as brain and heart MR imaging were used as a proxy[38]. Costs for the sentinel node procedure and contrast enhanced MRI were based on their tariffs [39]. Depreciation and maintenance costs of devices were incorporated in these tariffs. Costs of the additional MR-HIFU treatment components, e.g. sedation costs, were based on hospital specific rates. Costs of personnel present during the procedures was based on estimates of time needed multiplied by hourly costs, based on the guidance of the National Health Care Institute (Dutch: *Zorginstituut Nederland*)[40]. Costs of follow-up were not taken into account. Costs were indexed to 2014 by using consumer price index numbers[41]

Table 1 Duration of treatment steps and probability of events for clinically applied MR-HIFU breast cancer treatments as predicted by experts compared to data from the MR-HIFU feasibility study

Treatment phase	Parameter	Experts				Faesibility study[28]
		Unit	Median	Min	Max	Median
Positioning	Time patient verification	min	15	10	25	11.5
	Time verification reachability	min	15	7	20	14.5
	Time target definition	min	8	5	15	n/a
	Chance of repositioning	-	0.30	0.10	0.75	n/a
Test	Time to place navigator	min	2	1	10	1
	Time MRI scan	min	2.5	1	15	2.5
	Time for treatment planning	min	2	1	5	n/a
	Time to fill LUT	min	2.75	0	5	n/a
	Test sonication and check focal point	min	3	1	5	4
	Chance of adjustment focal point per coronal plane	-	0.55	0.20	0.90	n/a
Therapeutic	Time therapeutic phase	min	0.50	0.25	0.75	n/a
	Cooling time after each sonication	min	3.5	1	10	n/a
	Chance of abortion per coronal plane	-	0,10	0,05	0,20	n/a
	Chance of resonication per coronal plane	-	0.20	0.10	0.30	n/a
Post-treatment	Time clinical ward	min	240	120	300	n/a
	Chance of omplications	-	0.015	0.01	0.03	n/a

na: not available

Analysis

The costs of MR-HIFU ablation were based on the MR-HIFU submodel. The lowest and median estimates of time needed obtained with expert questionnaires were used to calculate the most optimistic ('best case') and less optimistic ('median case') MR-HIFU treatment scenarios. MR-HIFU treatment costs for tumour sizes of 1, 2 and 3 cm were calculated. This was done for treatment cells of 9 x 6 mm and 12 x 8 mm. These costs were compared to the average BCT costs. Tornado diagrams were constructed to describe the sensitivity of costs to parameter estimates.

RESULTS

Patients

Taking all possible exclusion criteria for MR-HIFU treatment into account, the proportion of patients eligible for MR-HIFU treatment was 11.9% of all patients diagnosed with breast cancer (Table 2)[31,42-52].

Table 2 Proportion of patient eligible for MR-HIFU treatment

Inclusion criteria	Proportion (%)
Tumour ≤ 3 cm	78.6
No lymph node metastasis	65.0
No lobular subtype	90.2
No EIC	84.6
No previous surgery	91.3
No renal insufficiency	97.3
Not multifocal	82.0
No BRCA mutation	97.4
Tumour reachable	66.3
Distance to skin ≥ 1 cm	65.0
Eligible patients*	**11.9**

EIC: extensive intraductal component
* i.e. all of the inclusion criteria present

Model

The structure of the model was considered of acceptable face validity by experts consulted. Model input parameters on analogous variables derived from actually observed data were comparable to the answers obtained through the questionnaires[28]. The duration and chances of occurrence of the different MR-HIFU treatment steps, compared to the data observed in the feasibility study, is shown in Table 1.

Costs of MR-HIFU ablation and BCT

The costs of MR-HIFU ablation for best and median case scenarios and two different cell sizes and the costs of BCT for tumours of 1, 2 or 3 cm are displayed in Table 3. The larger the treatment cell, the lower the MR-HIFU costs and the shorter the procedure time. For all variants, the costs of MR-HIFU ablation were higher than the costs of BCT. When using treatment cells size of 12 x 8 mm, the best case scenario costs of MR-HIFU ablation approached those of BCT.

Table 3 Costs of MR-HIFU ablation for best and median case scenarios compared to costs of BCT

	MR-HIFU ablation								BCT
	Median case				Best case				
	Treatment cell size (mm)				Treatment cell size (mm)				
	6 x 9		12 x 8		6 x 9		12 x 8		
Tumour size (mm)	Costs (€1000)	Time (h)	Costs (€1000)	Time (h)	Costs (€1000)	Time (h)	Costs (€1000)	Time (h)	Costs (€1000)
10	11.5	4.4	10.0	2.8	8.5	1.1	8.2	0.8	7.1
20	15.5	8.8	12.5	5.4	9.1	1.9	8.6	1.3	8.1
30	23.3	17.4	15.5	8.8	10.5	3.4	9.1	1.9	8.1

Factors influencing treatment costs

Factors contributing most to the total treatment costs were: cooling time after each sonication, and time required for breathing correction. For 9 x 6 mm treatment cells the average sensitivity for cooling time over all tumour sizes was 64.6 ± 10.3%, for the breathing correction this was 28 ± 2.7%. For treatment cells of 12 x 8 mm this was 59.3 ± 10.8% and 29.1 ± 1.6% respectively. Changes in these two parameters had larger impact on the cost estimations of treatments with smaller treatment cells than with larger treatment cells. The sensitivity of each model input parameter on model output is shown in Table 4 in tornado diagrams. The sensitivity values for both 9 x 6 mm and 12 x 8 mm treatment cells are presented in respectively Figure 2 and 3.

Table 4 Variance (%) of uncertainties in tornado diagrams. A safety margin of 0.5 cm is added to the tumour size.

	Tumour size (mm)*	**10**		**20**		**30**					
	Treatment cell size (mm)	**9x6**	**12x8**	**9x6**	**12x8**	**9x6**	**12x8**	**9x6**		**12x8**	
Treatment phase	**Parameter**							**Mean**	**sd**	**Mean**	**sd**
Positioning	Time patient positioning	0.5	1.6	0.1	0.3	0.0	0.1	0.2	0.3	0.7	0.8
	Time verification reachability	0.4	1.2	0.1	0.2	0.0	0.1	0.2	0.2	0.5	0.6
	Time target definition	0.1	0.4	0.0	0.1	0.0	0.0	0.0	0.1	0.2	0.2
	Chance of repositioning	0.5	1.6	0.1	0.3	0.0	0.1	0.2	0.3	0.7	0.8
Test	Time MR scan	7.7	8.9	1.2	4.1	0.5	1.2	3.1	4.0	4.7	3.9
	Time to place navigator	3.2	3.7	0.5	1.7	0.2	0.5	1.3	1.7	2.0	1.6
	Time to perform treatment planning per coronal plane	0.6	0.7	0.1	0.3	0.0	0.1	0.2	0.3	0.4	0.3
	Time to fill LUT	31.0	30.2	27.2	29.8	25.9	27.2	28.0	2.7	29.1	1.6
	Time to perform test sonications and verify focal point	1.5	1.7	0.2	0.8	0.1	0.2	0.6	0.8	0.9	0.8
	Chance of readjustment focal point	0.6	0.7	0.1	0.3	0.0	0.1	0.2	0.3	0.4	0.3
Therapeutic	Time to perform therapeutic sonication	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.0	0.2	0.1
	Cooling time after each sonication	52.8	47.8	69.2	60.9	71.8	69.2	64.6	10.3	59.3	10.8
	Chance of resonication per coronal plane	0.8	0.7	1.1	1.0	1.1	1.1	1.0	0.2	0.9	0.2
Post treatment	Time clinical ward	0.2	0.5	0.0	0.1	0.0	0.0	0.1	0.1	0.2	0.3

Sensitivity (variance) was calculated by calculation of the swing square relatively to the total swing square. Hereby, the swing is the range of cost values for a given uncertainty.
* A safety margin of 0.5 cm was added to the tumour size.

Figure 2 Tornado diagrams presenting sensitivity to parameter values of the difference in treatment costs for tumours of 10, 20 and 30 mm with an added safety margin of 5 mm assuming treatment cells of 9 x 6 mm

Figure 3 Tornado diagrams for tumours of 10, 20 and 30 mm with an added safety margin of 5 mm assuming treatment cells of 12 x 8 mm

DISCUSSION

To our knowledge, this is the first study on the potential cost-effectiveness of MR-HIFU ablation of breast cancer. This early health technology assessment suggests that MR-HIFU ablation was more expensive than BCT. When larger treatment cells were assumed, the potential for MR-HIFU ablation to have comparable costs increased. The duration of certain treatment steps including cooling time after each sonication and the time needed to apply breathing correction, had most impact on MR-HIFU costs. Importantly, the analyses were performed under the assumption that MR-HIFU ablation and BCT are equally effective.

Due to the limited amount of MR-HIFU treatment data, the clinical effectiveness and the effect on quality of life and cosmetic outcome is still scarce. Therefore, the effectiveness of MR-HIFU ablation was considered equal to BCT. However, if MR-HIFU treatment would be optimized and surgical excision would be omitted in the future, surgical complications and breast deformation might occur less frequently. This is expected to have a favourable effect on quality of life and cosmetic outcome. Even if MR-HIFU ablation would be slightly less effective than BCT, some patients might still prefer MR-HIFU because of its favourable effect on cosmetic outcome or reduced risk of complications. Especially elderly patients with more comorbidities and shorter life expectancy may be interested in MR-HIFU ablation. Quality of life measures are usually incorporated in health technology assessments as well, and hence better treatment associated utility scores would increase the potential for MR-HIFU to become cost-effective[53].

Our results indicate that in order to improve the cost-effectiveness of MR-HIFU ablation treatment time should be reduced. The currently used cooling times are applied to guarantee safety. If more clinical experience with MR-HIFU ablation is gained, shorter cooling times may possibly appear equally safe. Being able to measure the temperature in the surrounding (adipose) tissue in the breast may contribute by providing real time temperature measurements during cooling. Possible methods for thermometry in adipose tissue are T2-weighted thermometry[54,55] or a hybrid method for thermometry in fat and adipose tissue at the same time[56,57]. Implementation of these techniques will become possible in the near future. The time needed for breathing correction could be improved by using sedation that results in a more regular breathing pattern, or even obviates the need for breathing correction. Furthermore, the parameters of breathing correction could be made more flexible enabling sonications to start after a shorter

period. To what extend this is possible should be clinically investigated first and is not expected in the near future.

Strong points of this study are that it provided the first data on the potential cost-effectiveness of MR-HIFU ablation and that MR-HIFU experts validated the applied treatment models. Due to the lack of empirical treatment data, other sources for model input were needed. Estimations of experts are the most accurate option in this case. Furthermore, the duration of several treatment elements was validated with the published MR-HIFU breast study in which the dedicated MR-HIFU breast system was used[28].

Some limitations of the present study should also be acknowledged. First, MR-HIFU treatment duration may have been overestimated as a result of the lack of experience. As mentioned before, cooling times may be unnecessarily prolonged. Besides, no experience with total tumour ablation exists yet, possibly affecting some estimations. Second, treatment cells were assumed to be cylindrical shaped to enable calculations of the number of sonications required per tumour. The MR-HIFU breast system provides treatment cells with the shape of an oblate ellipse. This difference in shape may have affected the results. Third, the costs of BCT may have been overestimated, as this cost estimate also comprised patients with lobular carcinoma and positive axillary lymph nodes. However, patients with a tumour of the lobular subtype are considered ineligible for MR-HIFU treatment, as lobular breast cancer has a higher risk of incomplete resection and is consequently more expensive to treat. The same applies for patients with positive axillary lymph nodes. Fourth, our estimations were based on the dedicated MR-HIFU breast system used in our centre (Sonalleve-based prototype, Philips Healthcare, Vantaa, Finland). Other MR-HIFU systems exist and it is unclear if our results would be generalizable to these systems.

Still we tentatively conclude that MR-HIFU ablation currently is not a cost-effective alternative to BCT. The costs of MR-HIFU ablation are mostly affected by the long duration of certain treatment components, i.e. cooling time after sonications and the time needed to apply breathing correction. Furthermore, costs were influenced by the size of treatment cell used and decreased with larger treatment cell size. Being an early HTA analysis, the study had to be based on several assumptions and estimations, because the experience of MR-HIFU ablation is still quite limited. Therefore, our results may give important directions for future development of MR-HIFU ablation. Especially cooling time in between sonications and accurate breathing correction take relatively long and thus appear relevant targets for further innovation.

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PART II

Patient selection for minimally invasive treatment

CHAPTER 5

Current clinical indications for magnetic resonance imaging of the breast

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ABSTRACT

Magnetic resonance imaging (MRI) is increasingly used in breast cancer patients. MRI has a high sensitivity compared to mammography and ultrasound. The specificity is moderate leading to an increased risk of false-positive findings. Currently, a beneficial effect of breast MRI has been established in some patient groups and is debated in the general breast cancer population. The diagnostic ability of MRI and its role in various groups of breast cancer patients are discussed in this review.

INTRODUCTION

Magnetic Resonance Imaging (MRI) has a sensitivity exceeding 90% for detecting breast lesions and is superior in measuring lesion size compared to mammography and ultrasound[1,2]. Breast MRI is therefore increasingly used for screening and in the preoperative- and neoadjuvant setting[3,4]. Since the last century, breast-conserving therapy (BCT) is the standard of care for patients with early stage breast cancer. Although survival rates of BCT and mastectomy are comparable, recurrence rates are still lower after mastectomy[5-7]. The accurate assessment of lesion size by MRI is considered beneficial for treatment planning in patients with uncertain tumour size who are potential candidates for BCT. Furthermore, in the current era of upcoming minimal invasive techniques, exact measurement of lesion size is increasingly important[8].

Despite the increased detection rate of breast lesions on MRI[9,10], existing evidence is contradictive as to whether MRI improves clinical outcome in the general breast cancer population[11,12]. The moderate specificity of MRI (around 70%[13]) might contribute to these findings. MRI may even cause an increased rate of unnecessary biopsies or extensive surgery, if used in the general breast cancer population[14,15]. Emerging evidence shows that certain subgroups of patients may benefit from MRI, for example, high-risk patients[16]. This is illustrated by the guidelines of the American Cancer Society (ACS), European Society of Breast Imaging (EUSOBI), European Society of Breast Cancer Specialists (EUSOMA), and American College of Radiology (ACR) that provide recommendations for the use of breast MRI[4,17-19]. In this review, the most important indications for MRI are discussed to clarify which patients should undergo MR imaging. Additionally, the degree of literature consensus for the use of MRI in these subgroups of patients is assessed.

DIAGNOSTIC PERFORMANCE OF MRI

Detection of lesions

Hrung et al.[20] performed a meta-analysis of 16 studies published between 1994 and 1997. The overall sensitivity of MRI for detecting breast cancer was 95% with a specificity of 67%. A meta-analysis performed by Peters et al.[13], comprising 44 studies, reported an overall sensitivity of breast MRI of 90%. The overall specificity was 72%, indicating that 28% of the detected lesions were false-positive findings.

This article mainly focused on small, nonpalpable, early stage breast cancer, explaining the somewhat lower sensitivity compared to the meta-analysis of Hrung et al.[20].

MRI has proven valuable in detecting the index lesion and possibly in detecting additional lesions in breast cancer patients. Houssami et al.[10] published a meta-analysis to assess the diagnostic performance of MRI for detecting multifocal and multicentric disease not visible on conventional imaging. They included 19 studies and found a prevalence of ipsilateral additional foci in 16% of 2,610 women. Histopathology confirmed malignancy in 66% of these lesions. A meta-analysis of 50 papers of Plana et al.[21] corroborates these findings. The prevalence of additional lesions in the ipsilateral breast was 20% and the positive predictive value (PPV) of breast MRI was 66.8%. Plana et al. also reported the diagnostic accuracy of MRI for identifying additional lesions in the contralateral breast. The overall prevalence of contralateral disease was 5.5% with a PPV of 36.6%. A meta-analysis of 22 studies solely focusing on the detection of contralateral disease by Brennan et al.[9] reported an estimated PPV of 47.5%. MRI detected contralateral lesions in 9.3% of women, resulting in a true detection rate of 4.1%.

Establishing lesion size

Lesion size is an important factor for determining the possibility of BCT and the need for systemic therapy. Therefore, accurate lesion assessment is of utmost importance for breast cancer patients. Blair et al. found no significant differences between MRI measurements and pathologic tumour size in 115 women, proving that MRI is highly accurate in assessing disease extent. Tumour size determined on MR images correlated better with pathologic assessment in high-grade tumours (Spearman correlation coefficient 0.76) than in low-grade tumours (Spearman correlation coefficient 0.45)[22]. Grimsby et al. also evaluated the concordance of lesions size measurement between MRI and histopathology. A difference between MRI and histopathology measurements of 0.5 cm was considered concordant and was found in 53% (100 patients). MRI overestimated lesion size in 33% (62 tumours), of which 47 tumours were overestimated by more than 1 cm. Underestimation of MRI occurred in 28 tumours (15%), of which 15 were underestimated by more than 1 cm. Pathologic concordance was more frequently found in smaller lesions, that is, 69% in lesions smaller than 2 cm, 46% in lesions between 2 and 5 cm and 31% in tumours larger than 5 cm[1]. Another retrospective study with 121 patients by Gruber et al.[2] found that MRI findings and histological findings

were not significantly different with a mean overestimation of 2 mm. Schmitz et al. assessed the concordance of MRI and histology in 62 patients with invasive breast cancer who underwent BCT. The mean difference of size measurements was 1.3 mm. MRI overestimated lesion size in 33% (20 tumours) and correctly measured or underestimated lesion size in 67% (41 tumours)[23]. In a group of 23 patients, histopathologic tumour extent was compared to MR imaging and mammography. The Spearman correlation coefficient of mammography with histological size was 0.20, which was not significant (p=0.39). Size measurements of MRI were more accurate with a correlation coefficient of 0.65 (p<0.01). MRI underestimated disease extent in 22% (5/23 patients) and overestimated in 30% (7/23 patients), for mammography this was reported in a majority of 62% (13 of 21 available mammographic examinations) and 9.5% (two cases), respectively. Here, a difference of 10 mm or less was considered concordant[24]. Shin et al. assessed the accuracy of MRI and ultrasound in determining lesion size in 821 patients. MRI was superior to ultrasound in measuring the size of both carcinoma in situ and invasive carcinoma. For invasive lesions without carcinoma in situ the measured differences with histopathology were neither significant for MRI (p=0.29), and nor for ultrasound (p=0.078). For invasive cancer with carcinoma in situ, the differences were not significant for MRI (p=0.064), but significant for ultrasound (p<0.0001)[25].

In some patients conventional imaging is inconclusive in assessing tumour extent[26]. Deurloo et al. showed in which patients MRI is more likely to be complementary to conventional imaging. MRI scans of 165 patients were analyzed and considered of additional value when a difference in tumour size of at least 10 mm was measured, which occurred in 23% (39 patients). This was significantly associated with age (<58 years) and irregular borders on mammography and a discrepancy between lesion size on mammography and ultrasound[16]. A study by Pengel et al.[26] corroborates these findings. MRI was found to have no complementary value in patients who have comparable tumour size on mammography and ultrasound. Yau et al. reported that MRI leads to 21% (42 out of 204) additional findings when used as a 'problem-solving tool'. After biopsy, 14 cancers were detected. Only in three of these patients, biopsy would not have been performed based on conventional imaging. Furthermore, MRI was false negative in one patient. In five patients, unnecessary biopsies were performed. These data do not clarify the role of MRI[27]. Moderate consensus exists as to whether MRI should be used as a problem-solving tool in all patients with inconclusive findings on conventional imaging[18,19].

The aforementioned studies indicate that MRI outperforms mammography and ultrasound in determining lesion size. Especially in patients in whom discrepancy between lesion size on ultrasound and mammography is found, MRI may be used as an additional tool in the diagnostic work-up.

IN WHICH PATIENTS SHOULD WE PERFORM BREAST MRI?

Since the introduction of breast MRI, clinical evidence has consistently shown that MRI has a high sensitivity for the detection of invasive breast cancer[10,13,20]. However, two randomized clinical trials reported that pre-operative MRI for work-up of breast cancer patients did not result in reduced re-excision rates. The Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial included 1,623 breast cancer patients, randomly allocated to MRI and no-MRI groups[15] In the Mammography of Nonpalpable Breast Tumours (MONET) study, 418 patients were randomized to either undergoing MRI or only conventional imaging. In this trial, only patients with nonpalpable breast lesions were included[14]. Additionally, evidence from retrospective studies shows no clear advantage of MRI with regard to long-term clinical outcome[28,29]. Existing literature suggests that selected groups of breast cancer patients might benefit from MRI[4,16-19,26,30,31]. An overview of most important evidence subdivided in current MRI-indications with the degree of consensus between different studies is given in Table 1.

Invasive lobular cancer

Invasive lobular cancer (ILC) is more often multifocal and multicentric than invasive ductal carcinoma and has a diffuse growth pattern[32,33]. Therefore, disease extent of ILC is more likely to be underestimated on conventional imaging methods and requires MR imaging according to the EUSOMA guideline[19]. Several studies were performed to assess the impact of the diagnostic ability of MRI in ILC patients. Mann et al. evaluated diagnostic utility of MRI in 67 ILC patients. They found a significant correlation between MRI measurements and histopathologically determined tumour size (correlation coefficient 0.85, $p<0.01$), as opposed to mammography, which did not correlate to histology (correlation coefficient 0.27, $p=0.46$). MRI underestimated lesion size significantly less frequently than mammography (11 vs. 29 patients, $p<0.001$), while lesion size overestimation occurred in a comparable number of patients (7 vs. 5)[34]. The same group performed a meta-analysis aiming to

compare MRI to the conventional diagnostic work-up of ILC patients. MRI detected additional ipsilateral lesions that were occult on mammography and ultrasound in 32% of cases. The proportion of contralateral cancer detected only by MRI was 7%. These findings resulted in a change in surgical management in 28.3% of patients. Retrospectively, 88% of these alterations were appropriate changes based on pathologic assessment, resulting in an overall sensitivity for MRI of 93.3%[35]. Heil et al. reported comparable findings. In 23 of 92 patients (25%), the surgical approach was changed after MR imaging. Alterations were appropriate in 20 of these patients ($p<0.0001$). Three patients received unnecessary extensive therapy due to false positive MRI findings[36]. In a study consisting of 1,928 ILC patients of whom 396 underwent preoperative breast MRI, the reoperation rate was significantly lower in patients who underwent MRI (OR 0.59, 95% CI 0.40-0.86). However, the odds of undergoing an initial mastectomy were also significantly higher in the MRI group (OR 1.48, 95% CI 1.10-2.00), the number of final mastectomies was comparable, suggesting that the increased initial number of mastectomies was appropriate[37]. In a meta-analysis of Houssami et al, lower re-excision rates were reported in ILC patients who underwent MRI; 10.9% versus 18% without MRI (OR 0.56, $p=0.031$). However, with 31.1%, the initial rate of mastectomies in the MRI group was also higher. Only 24.9% underwent initial mastectomy in the no-MRI groups (OR 2.12, $p=0.008$). The overall mastectomy rate was slightly higher, 43.0% versus 40.2% (OR 1.64, $p=0.034$)[38]. Mann et al. retrospectively assessed an MRI group of 99 patients and a no-MRI group of 168 ILC patients. Significantly fewer patients in the MRI group underwent a re-operation, 5% versus 15% in the no-MRI group (OR 3.29, $p=0.014$). The rate of initial mastectomies did not significantly differ between both groups[30].

Considering the aforementioned literature, the consensus for performing preoperative breast MRI in ILC patients is high. MRI assesses disease extent more accurately than conventional imaging methods, leading to fewer re-excisions without an increase of the mastectomy rate. Therefore, MR imaging of ILC patients is strongly recommended. However, there should be awareness that additional suspicious lesions detected by MRI should be histologically confirmed considering the relatively high number of false-positive findings of MRI.

High-risk women

The American Cancer Society recommends annual MRI screening in high-risk women. Women considered having a high breast cancer risk are BRCA1 or BRCA2

gene mutation carriers, first-degree relatives of BRCA gene mutation carriers, women with a life-time risk of developing breast cancer of 20-25% or higher (based on family history), patients who underwent radiotherapy of the chest before the age of 30 years and women with syndromes caused by mutations in the TP53 and PTEN genes[4]. Likewise, the EUSOBI, ACR and EUSOMA advise adopting a similar protocol in women with a high breast cancer risk[17-19]. Additionally, various subgroups with different breast cancer risks and thus different MRI indications have been defined. Both the ACS and EUSOBI guidelines state that currently insufficient evidence exists to recommend or discourage MRI screening in patients with a 15-20% lifetime risk of breast cancer. Similarly, MR screening of women with lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH), dense breasts or a personal history of breast cancer is not clearly indicated. Whether or not these patients should be screened, may be determined based on doctor and patient preference[4,18]. The EOSOMA considers the breast cancer risk in patients with a lifetime risk of 15-20%, LCIS, ALH, ADH and dense breasts too low to recommend MRI screening[19]. Patients with a lifetime risk of less than 15% should not be enrolled in annual screening programs according to the ACS and EUSOBI, as the added value of MRI screening is not supported by existing literature[4,18].

There is no consensus on when to start the MRI screening program in high-risk patients. Currently, it is advised to start at an age 5 years younger than a relative who first presented with breast cancer. In other patients, starting at the age of 30 years is deemed sufficient. It is also unclear at what age MRI screening can be ceased. Breast density decreases with age, making mammography a more useful screening method in older patients. Nevertheless, the sensitivity of MRI remains higher than that of mammography at every age[4,18,19]. These recommendations for MRI screening are based on available literature and expert consensus. Most evidence is derived from prospective observational cohort studies[39-49]. The sensitivity of MRI for detecting invasive breast cancer ranges from 71% to 100%, which is substantially higher than the sensitivity of mammography (25-58.8%). The specificity was 79-98.4% versus 91-99.8%, respectively. Besides a higher sensitivity, MRI has the ability to detect smaller tumours than mammography[39], leading to early detection of breast cancer, which enables timely treatment. Additionally, patients with a high risk of breast cancer are at an increased risk of 44-55% of presenting with multifocal and multicentric disease at the time of being diagnosed with breast cancer, compared to patients without an increased breast cancer

risk[40,47]. Furthermore, disease onset occurs at younger age when breast density is higher, which impairs the diagnostic accuracy of conventional imaging methods[39].

In spite of the unavailability of data on outcome and survival, MRI seems beneficial in high-risk patients and should therefore be used for screening. Consensus in existing evidence is high, especially for high-risk patients with a lifetime risk higher than 20%.

Neoadjuvant chemotherapy

MR imaging is recommended in patients receiving neoadjuvant chemotherapy (NAC). MRI is able to accurately assess treatment response and assist in determining the appropriate surgical therapy. MRI should be performed before the start of NAC and after completion of the treatment. Since MRI is unable to detect very small residual tumour foci, even patients with complete radiological response have to undergo surgery[17-19]. The EUSOBI recommends to perform MR imaging after the first half of NAC administrations as well, to facilitate a change of therapy in non-responders[18]. Marinovich et al. performed a meta-analysis to evaluate the ability of MRI to determine residual tumour size after NAC, 19 studies containing data of 958 patients were included. The mean difference between MRI-measured size and tumour size determined by pathology was +0.1 cm and 95% of measured differences ranged from -4.2 to 4.4 cm. MRI performed better than mammography, which overestimated residual tumour size by 0.4 cm. Ultrasound measurements were within the same range as MRI measurements[50]. Another meta-analysis reported the utility of MRI for determining complete pathologic response. Forty-four studies with 2,949 patients in total were included. Median sensitivity and specificity for differentiation of complete pathologic response and residual tumour were 92% and 60% respectively. Mammography was significantly less accurate in detecting residual disease[51]. The ACRIN 6657 trial assessed the accuracy of MRI in determining residual tumour size before the start of NAC, after one cycle, between two subsequent regimens and before surgery in 216 patients. MRI was superior to physical examination at all time points[52]. Chen et al. found that tumour type (IDC or ILC), tumour morphology (mass or non-mass like enhancement), HER-2 status combined with estrogen and progesterone receptor status were significantly associated with accuracy after multivariable analysis[53]. Loo et al. analysed the influence of tumour characteristics in 188 patients. They reported that MRI is most accurate in triple-negative or HER2-postitive tumours and less accurate in ER-positive and HER2-negative tumours[54]. Two potential future roles of MRI in the

neoadjuvant setting are currently under investigation. First, MRI may be useful in the early prediction of treatment response after one or two cycles of NAC[52,55]. Second, MRI is potentially able to predict overall and disease-free survival[19]. MRI is not yet used for these indications in the clinical setting.

Table 1 Indications for breast MRI with references and literature consensus

Indication	References	Study type	MRI*	Consensus
Invasive lobular carcinoma	Fortune-Greeley et al. 2014[37]	Retrospective cohort	+	High
	Heil et al. 2012 [36]	Retrospective cohort	+	
	Houssami et al. 2013[38]	Meta-analysis	±	
	Mann et al. 2008[35]	Meta-analysis	+	
	Mann et al. 2010[30]	Retrospective cohort	+	
High-risk	Berg et al. 2012[49]	Prospective cohort	±	High
	Kriege et al. 2004[39]	Prospective cohort	+	
	Kuhl et al. 2005[40]	Prospective cohort	+	
	Kuhl et al. 2010[44]	Prospective cohort	+	
	Leach et al. 2005[41]	Prospective cohort	+	
	Lehman et al. 2005[42]	Prospective cohort	+	
	Lehman et al. 2007[45]	Prospective cohort	+	
	Lord et al. 2007[31]	Systematic review	±	
	Sardanelli et al. 2007[46]	Prospective cohort	+	
	Sardanelli et al. 2011[47]	Prospective cohort	+	
	Warner et al. 2004[43]	Prospective cohort	±	
	Weinstein et al. 2009[48]	Prospective cohort	+	
Neoadjuvant chemotherapy	Marinovich et al. 2013[50]	Meta-analysis	±	High
	Marinovich et al. 2013[51]	Meta-analysis	+	
	Hylton et al. 2012[52]	Prospective cohort	+	
Occult primary	De Bresser et al. 2010[56]	Meta-analysis	+	High
	Lu et al. 2011[57]	Retrospective cohort	+	
Equivocal findings on conventional imaging	Deurloo et al. 2006[16]	Prospective cohort	+	Moderate
	Pengel et al. 2014[26]	Prospective cohort	+	
	Yau et al. 2011[27]	Retrospective cohort	-	
None (general breast cancer population)	Brennan et al. 2009[9]	Meta-analysis	±	Low
	Fischer et al. 2004[12]	Retrospective cohort	+	
	Houssami et al. 2008[10]	Meta-analysis	±	
	Houssami et al. 2014[28]	Meta-analysis	-	
	Hwang et al. 2009[29]	Retrospective cohort	±	
	Parsyan et al. 2013[58]	Systematic review	-	
	Pediconi et al.2012[59]	Prospective	+	
	Peters et al. 2011[14]	Randomized trial	-	
	Plana et al. 2012[21]	Meta-analysis	±	
	Solin et al. 2008[11]	Retrospective cohort	-	
	Turnbull et al. 2010[15]	Randomized trial	-	

* Indicates whether MRI should be performed in the mentioned patient group, according to the authors. ±: Role of MRI is uncertain, +: MRI should be performed, -: MRI should not be performed.

MRI has proven to be useful for measuring residual tumour size and determining complete pathologic response after NAC and is superior to other diagnostic modalities. Considering two meta-analyses that provide evidence with the highest level of confidence, consensus to perform MRI in the neoadjuvant setting is high[50,51].

Occult primary

MRI is useful in identifying the primary tumour in patients with malignant axillary or supraclavicular lymphadenopathy or with distant metastases, without a visible index lesion on conventional imaging[60]. Because of its high sensitivity, MRI might detect the mammographically occult breast cancer and have an important role in avoiding unnecessary extensive surgical treatment. In both the American and European guidelines, breast MRI is therefore recommended in case of lymphadenopathy or metastatic disease of unknown origin with negative conventional breast examinations[17-19]. In a meta-analysis with eight retrospective studies, De Bresser et al. showed that MRI visualizes breast lesions in 36-86% (mean 72%) of 204 patients with occult primary cancer. The mean sensitivity of MRI for detecting the primary tumour was 90% (range 85-100%). However, the specificity of MRI was low (31%, range 25-55%) again indicating the need for histologic confirmation of all MRI detected lesions. MRI followed by biopsy enabled BCT instead of mastectomy in approximately one-third of patients[56].

DISCUSSION AND CONCLUSIONS

We have provided an overview of the recent literature on the diagnostic ability and the most important clinical indications for breast MRI. MR imaging has a high sensitivity with moderate specificity and is superior in assessing disease extent compared to conventional imaging. For almost all aforementioned indications: that is, ILC[35,38], high-risk patients[31,43,44,49], neoadjuvant chemotherapy[50,51] and occult primary tumours[56,57], consensus in the literature is high. MR imaging is recommended for determining disease extent and ruling out contralateral disease in these patients. The evidence for patients with inconclusive findings on conventional imaging is less clear, resulting in moderate consensus[16,26,27]. Whether or not MRI should be performed in these patients, may be determined per case.

In general, increased lesion detection and the risk of overtreatment due to MRI should be taken into consideration when ordering an MRI scan.

Currently, the role of MRI is established in selected patient groups. In the future, the role of MRI might be extended to accelerated partial breast irradiation (APBI)[61-63] and minimal and non-invasive treatments (e.g. radiofrequency ablation, high intensity focused ultrasound and cryotherapy)[8,64]. The ability to precisely determine disease extent, makes MRI an excellent tool for patient selection for both APBI and minimal invasive treatments. Furthermore, MRI is a useful method to plan and guide minimal invasive therapies. At last, MRI can be used for evaluation of treatment results and follow-up. Clinical experience with these treatment modalities is still limited, but holds promise for the future.

Performing breast MRI in the general breast cancer population has not been proven to be advantageous or cost-effective, which is supported by the low consensus in the literature[14,15,28,58]. Currently, MR imaging is not recommended for patients without any of the aforementioned indications. However, due to the lack of randomized clinical trials, the impact of breast MRI on long-term outcome has not been established with certainty. Improvement of the local recurrence rate and survival are the most important factors in determining a possible beneficial impact of MRI. Therefore, we recommend performing MRI in this group only in the research setting. An example is the Alliance phase III trial on the effect of preoperative breast MRI in patients eligible for BCT. Since the measured effect will be small due to already favourable outcomes after BCT, a large study population is required to prove potential impact of MRI. The trials should be standardized with regard to scan protocols and image assessment (BIRADS classification). In summary, MRI should only be performed in patients with established clinical indications or in the research setting.

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CHAPTER 6

Prediction model for extensive ductal carcinoma in situ around early-stage invasive breast cancer

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ABSTRACT

Objectives

Ductal carcinoma in situ (DCIS) is a risk factor for incomplete resection of breast cancer. Especially extensive DCIS (E-DCIS) or extensive intraductal component often results in positive resection margins. Detecting DCIS around breast cancer prior to treatment may therefore alter surgery. The purpose of this study was to develop a prediction model for E-DCIS around early-stage invasive breast cancer, using clinicohistopathological and dynamic contrast-enhanced magnetic resonance imaging (MRI) features.

Materials and Methods

Dynamic contrast-enhanced MRI and local excision were performed in 322 patients with 326 ductal carcinomas. Tumours were segmented from DCE-MRI, followed by 3-dimensional extension of the margins with 10 mm. Amount of fibroglandular tissue (FGT) and enhancement features in these extended margins were automatically extracted from the MRI scans. Clinicohistopathological features were also obtained. Principal component analysis and multivariable logistic regression were used to develop a prediction model for E-DCIS. Discrimination and calibration were assessed and bootstrapping was applied for internal validation.

Results

Extensive DCIS occurred in 48 (14.7%) of 326 tumours. Incomplete resection occurred in 56.3% of these E-DCIS-positive versus 9.0% of E-DCIS-negative tumours ($p<0.001$). Five components with eigenvalue exceeding 1 were identified; 2 were significantly associated with E-DCIS. The first, positively associated, component expressed early and overall enhancement in the 10-mm tissue margin surrounding the MRI-visible tumour. The second, positively associated, component expressed human epidermal growth factor receptor 2 (HER2) and amount of FGT around the MRI-visible tumour. The area under the curve value was 0.79 (0.76 after bootstrapping).

Conclusions

Human epidermal growth factor receptor 2 status, early and overall enhancement in the 10-mm margin around the MRI-visible tumour and amount of FGT in the 10 mm around the MRI-visible tumour were associated with E-DCIS.

INTRODUCTION

Breast cancer is increasingly diagnosed at an early stage, which is the result of improved imaging techniques and screening programmes[1-3]. Because of the increasing incidence of early-stage breast cancer, breast-conserving therapy is the most preferred treatment. The presence of ductal carcinoma in situ (DCIS) increases the risk of positive resection margins[4,5]. Positive margins for either invasive carcinoma or DCIS are associated with an increased risk of local or distant recurrence[6-9]. Re-excision is often required in case of positive resection margins, deforming the breast, increasing the risk of complications and leading to patients' anxiety[10].

Kinetic analysis of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) features enables discrimination of benign and malignant lesions[11,12]. The sensitivity of DCE-MRI for detecting DCIS is higher than the sensitivity of conventional imaging modalities, and DCE-MRI is superior in assessing the extent of DCIS[13,14](Jansen 2011). However, the specificity of MRI for detecting DCIS and invasive cancer is low to moderate[15]. Performing DCE-MRI before surgery in patients diagnosed with DCIS has not been proven to beneficially influence outcome so far. Apparently, patients with DCIS are still at risk of incomplete surgery due to undetected disease. Conversely, MRI may result in increased mastectomy rates due to uncertainty about the relevance of unexpected findings[16]. Despite the ability of DCE-MRI to detect DCIS, different imaging protocols or combining MRI findings with other tumour characteristics seem necessary to improve preoperative detection of DCIS components.

Knowing the risk of positive resection margins due to the presence of DCIS around the primary tumour may guide surgical treatment in the future. For example, during surgical resection, the margin width can be increased to prevent re-excision. Especially, patients with extensive DCIS (E-DCIS) around the tumour are important to identify because their tumours are frequently associated with malignant tissue beyond the intended surgical margin of 10 mm from the tumour border[17,18]. Using DCE-MRI to predict the presence of DCIS in the tissue surrounding invasive ductal carcinoma has, to our knowledge, not been done so far. We hypothesize that computer-extracted features derived from DCE-MRI may improve the detection of DCIS surrounding invasive breast cancers. The purpose of this study is to use patient and tumour characteristics and computer-extracted DCE-MRI features for optimal prediction of the presence of E-DCIS surrounding early-stage invasive breast cancer.

MATERIALS AND METHODS

Patients

A subset of 322 patients with 326 pathologically proven invasive ductal carcinomas was selected from the prospective Multimodality Analysis and Radiological Guidance in Breast-Conserving therapy (MARGINS) study. Patients were consecutively included between 2000 and 2008. The ethics committee of the Netherlands Cancer Institute (Amsterdam, the Netherlands) approved the MARGINS study and all participants signed informed consent. The aim of the MARGINS study was to assess whether adding preoperative MRI to conventional imaging improves the accuracy of staging and localisation of breast cancer. Included patients were diagnosed with invasive breast cancer for which breast-conserving surgery was indicated based on physical examination, mammography and ultrasound (US). The largest tumour diameter on US was recorded. Breast cancer was confirmed by fine-needle aspiration cytology and/or core needle biopsy. All patients underwent additional preoperative contrast-enhanced MRI[19,20]. Patients who received neoadjuvant chemotherapy were excluded as this may change tumour characteristics. Patients who underwent mastectomy due to additional findings on MRI were excluded because this implies wider margins than local excision. Age was obtained from the moment of breast cancer diagnosis.

MRI acquisition

Patients underwent MRI with a 1.5 T scanner (Magnetom, Siemens Medical Systems, Erlangen, Germany). Patients were positioned in prone position, and images were acquired using a double-breast array coil (CP Breast Array, 4 channels; Siemens). Both noncontrast and contrast-enhanced MRI scans were performed. Contrast-enhanced scans were generated after intravenous injection with the gadolinium-based contrast agent gadoteridol (Prohance, Bracco-Byk Gulden, Konstanz, Germany) at 0.1 mmol/kg body weight. Five consecutive scans with intervals of 90 s were performed, 1 before and 4 after contrast administration. The imaging parameters were as follows: 3-dimensional coronal T1-weighted sequence; repetition time, 8.1 ms; echo time, 4.0 ms; isotropic voxels of 1.35 x 1.35 x 1.35 mm^3, without fat suppression.

Extraction of MRI features

Tumours were automatically segmented from MRI scans, and a dedicated breast radiologist established the largest tumour diameter after measuring diameter in 3 orthogonal directions. Volumetric tumour segmentation was performed automatically as previously reported by Alderliesten et al.[21]. Tumour margins were automatically extended with 10 mm in 3-dimensional. First, the breast region was segmented to prevent inclusion of pectoral muscle, skin and air outside the breast in the extended margins[22]. The amount of fibroglandular tissue (FGT) in the extended margins was calculated as the ratio of the volume of FGT over total volume in the extended margin. The FGT was automatically segmented using previously reported methodology by Klifa et al.[23]. Early, late and overall enhancement in these extended margins were derived from subtraction images, which were calculated per FGT-voxel and averaged (Figures 1 and 2)[24]. Early enhancement was defined as the percentage signal increase between precontrast and first postcontrast scan, 100% x $(S_1 - S_0)/S_0$, late enhancement between the late postcontrast and first postcontrast scan, 100% x $(S_2 - S_1)/S_1$, and overall enhancement between the precontrast and the late postcontrast scan, 100% x $(S_2 - S_0)/S_0$. S_0 denotes the image intensity in the precontrast image, S_1 in the first postcontrast image and S_2 in the last postcontrast scan. Signal enhancement ratio (SER) was defined as the ratio between early and overall enhancement, 100% x $(S_1 - S_0)/(S_2 - S_0)$[25]. The median SER values of the FGT voxels were used in the analysis to prevent impact of noise.

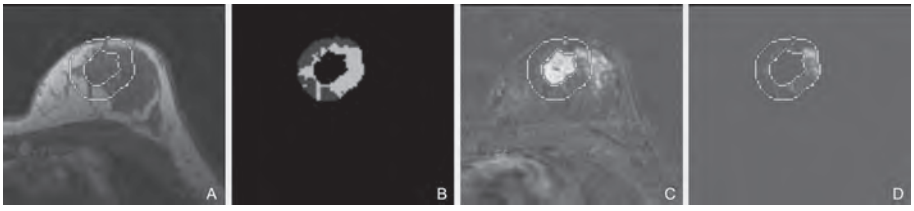

Figure 1 Axial MRI slices through invasive ductal carcinoma with surrounding E-DCIS in left breast. **A.** Precontrast T1-weighted non–fat-suppressed image, inner white line indicates tumor border and outer white line indicates automatically extended margin of 10 mm. **B**. Segmentation of 10-mm margin into FGT (white) and adipose tissue (gray). The proportion of FGT is high. **C.** Subtraction of the first postcontrast scan minus the precontrast scan. **D**. The relative signal increase between the precontrast and first postcontrast scan in the 10-mm extended margin around the MRI-visible lesion.

Breast cancer treatment and histopathologic analysis

Patients underwent wide local excision, with intended tumour-free margins of at least 1 cm. The applied surgical technique was adopted from Aspegren et al.[26], who described wide local excisions extending from skin to basal fascia. Margin

status (positive vs. negative), estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Nottingham histologic grade[27], and presence and amount of DCIS around the invasive tumour were assessed. Positive margins were defined as tumour present in the edge of the excision specimen, either focally (less than 2 low-power fields) or extensively (in 2 or more low-power fields). More than 10% staining of tumour cells resulted in positive ER and PR status. HER2 receptor was considered positive when immunohistochemistry was scored at least 3 and in situ hybridization showed gene amplification. The extent of DCIS in the surrounding breast tissue was estimated as none, minimal, moderate or extensive by an experienced breast pathologist. Extensive DCIS was defined as prominent DCIS within the confines of the invasive tumour (typically occupying at least 25% of the tumour) and DCIS in the grossly normal adjacent breast tissue, or lesions composed primarily of DCIS with one or more foci of invasive carcinoma[18]. The amount of DCIS was considered minimal if DCIS was present in up to 5 ducts and moderate if the amount was beyond the amount of minimal DCIS but not sufficient to meet the criteria for E-DCIS. Extensive DCIS was the primary end point of this study. The presence of E-DCIS was scored dichotomously, yes (extensive DCIS) versus no (none, minimal or moderate DCIS).

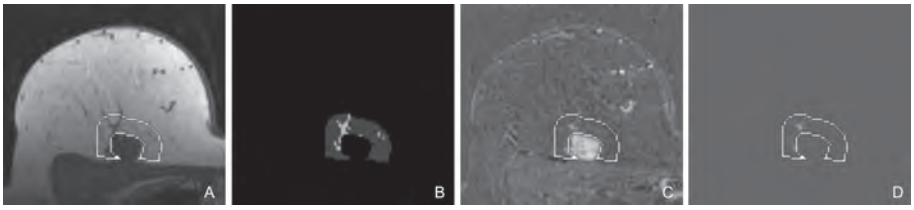

Figure 2 Axial MRI slices through invasive ductal carcinoma without surrounding E-DCIS in the right breast. **A**. Precontrast T1-weighted non–fat-suppressed image, inner white line indicates tumor border and outer white line indicates automatically extended margin of 10 mm. Note that the pectoral muscle is automatically segmented as well and omitted from the extended margin. **B.** Segmentation of 10-mmmargin into FGT (white) and adipose tissue (gray). The proportion of adipose tissue is high and the proportion of FGT is low. **C**. Subtraction of the first postcontrast scan minus the precontrast scan. **D.** The relative signal increase between the precontrast and first postcontrast scan in the 10-mm extended margin around the MRI-visible lesion.

Statistical analysis

For continuous variables, mean (SD) or median (interquartile range) was calculated. Categorical variables were displayed as numbers with percentages. Associations between variables and the presence of E-DCIS in the tumour margin were assessed with independent *t* tests (continuous normally distributed variables), Mann-Whitney *U* tests (continuous abnormally distributed variables), or

Fisher exact tests (categorical variables). Normality was tested with Q-Q plots and Kolmogorov-Smirnov tests. Single imputation was performed for missing data, using the expectation-maximization method[28]. Less than 5% of data was missing, so this method was suitable for our dataset.

Principal component analysis (PCA) with varimax rotation was performed to determine factor loadings and to cluster variables in components. PCA results in completely independent components[29]. The components resemble a cluster of features that have shared variance, so that they are independent from the other tested features. Principal component analysis instead of multivariable analysis of the original variables was used to prevent overfitting of the prediction model. Only variables known before surgical treatment were included in the PCA to reflect the typical pretreatment workflow. The MRI variables included in the PCA were: tumour size measured on MRI and amount of FGT, early, late and overall enhancement and SER in the 10-mm margin surrounding the tumour. Included patient characteristics and variables derived from conventional imaging were age, ER status, PR status, HER2 status, suspicious calcifications and difference between largest tumour diameter on MRI and on US. Components with eigenvalue larger than 1.0 were selected and labelled, variables with relatively high factor loadings were identified. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy test was performed to assess the amount of common variance in the dataset. A value of more than 0.5 is considered sufficient for PCA. Bartlett test was performed as well to assess whether data were independent or not[30].

Individual factor scores for the selected components were calculated and stored. These factor scores were used as covariates to assess the association with E-DCIS using multivariable logistic regression in order to develop a prediction model[31]. The multivariable logistic regression was performed to test which components (or clusters of data) were associated with having E-DCIS. A receiver operating characteristic curve was generated. The area under the curve (AUC) was calculated to assess the discriminative ability of the prediction model. Calibration was assessed with the Hosmer-Lemeshow test and a calibration plot. Bootstrapping with 1000 iterations was used for internal validation and applied to the multivariable model. The shrinkage factor was used to calculate the final AUC value[32]. No external validation was performed. A 2-sided p-value of less than 0.05 was assumed statistically significant in all analyses. SPSS (IBM SPSS Statistics, version 20.0; Armonk, NY) was used for PCA. Multivariable logistic regression and bootstrapping were performed with R statistics (version 3.1.1, Vienna, Austria).

RESULTS

Patient characteristics

The mean (SD) age of included subjects was 57.9 (9.7) years (range 32 - 84). Extensive DCIS was detected in 48 tumours (14.7%; Table 1). In this group, positive resection margins occurred significantly more often than in the group without DCIS around the tumour, 27 (56.3%) of 48 versus 25 (9.0%) of 278 (p<0.001). Univariable analysis showed that tumours surrounded by E-DCIS occurred in slightly younger patients, were less frequently PR-positive, more frequently triple positive, larger on MRI, surrounded by denser breast tissue, showed more early enhancement, and were less frequently of low histologic grade.

Table 1 Patient characteristics and association with extensive ductal carcinoma in situ around the invasive tumour

Characteristics	All (n=326)	E-DCIS - (n=278)	E-DCIS + (n=48)	P-value
Age (y)	57.9 ±9.7	58.5 ±9.5	54.8 ±10.0	0.015
Right side	161 (49.4%)	137 (49.3%)	24 (50.0%)	1.000
Tumour size US (mm)	14.0 (10.0-19.0)*	14.0 (10.0- 18.3)	16.0 (10.6-20.8)	0.123
Tumour size MRI (mm)	17.0 (12.8-22.0)*	16.0 (12.0-22.0)	19.0 (15.0-25.0)	0.029
Difference size MRI-US	2.0 (0.0-5.0)*	2.0 (0.0-5.0)	3.0 (0.0-6.6)	0.544
Suspicious calcifications	55 (16.9%)	42 (15.1%)	13 (27.1%)	0.058
ER positive	273 (83.7%)	237 (85.3%)	36 (75.0%)	0.090
PR positive	204 (62.6%)	182 (65.5%)	22 (45.8%)	0.015
HER2 positive	48 (14.7%)	26 (9.4%)	22 (45.8%)	<0.001
Triple negative	36 (11.0%)	32 (11.5%)	4 (8.3%)	0.626
Triple positive	20 (6.1%)	12 (4.3%)	8 (16.7%)	0.004
Amount of FGT	31.96 ±14.98	31.15 ±15.18	36.65 ±12.94	0.019
Early enhancement	23.31 (15.92-32.88)*	22.55 (15.54-31.50)	27.13 (19.09-41.63)	0.021
Late enhancement	15.41 ±9.87	15.27 ±9.93	16.23 ±9.58	0.535
Overall enhancement	40.81 (29.27-54.81)*	40.65 (28.40-52.77)	42.21 (33.93-66.73)	0.055
SER	50.54 ±20.21	50.28 ±20.35	52.07 ±19.54	0.517
Positive margin	52 (16.0%)	25 (9.0%)	27 (56.3%)	<0.001
Positive SLNB	86 (26.4%)	73 (26.3%)	13 (27.1%)	0.861
≥4 pos. lymph nodes	15 (4.6%)	13 (4.7%)	2 (4.2%)	1.000
Histologic grade 1	105 (32.2%)	97 (34.9%)	8 (16.7%)	0.012
Histologic grade 3	92 (28.2)	76 (27.3%)	16 (33.3%)	0.390

E-DCIS extensive ductal carcinoma in situ, *US* ultrasound, *MRI* magnetic resonance imaging, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *FGT* fibroglandular tissue, *SER* signal enhancement ratio, *SLNB* sentinel lymph node biopsy.
Characteristics are displayed as mean (SD).
* Abnormally distributed variables are displayed as median and interquartile range.

Principal component analysis

The PCA resulted in 5 components with eigenvalues larger than 1 (Table 2). The cumulative explained variance of these factors was 73.03%. The calculated Kaiser-Meyer-Olkin value was 0.468 and Barlett test was significant (p<0.001). Component 1 was represented by early and overall enhancement and was named enhancement 1. Component 2 was correlated with the other 2 enhancement features (late enhancement and SER) and was called enhancement 2. Component 3 was correlated with largest tumour diameter established on MRI and the difference between largest diameter on MRI and US (tumour size). ER and PR status were represented in component 4 (ER/PR status). Amount of FGT combined with HER2 status was represented in component 5 (FGT/HER2). Hence, each component (or cluster of features) contains a part of the data.

Table 2 Factor loadings of principal component analysis with varimax rotation

Variables	Components				
	Enhancement 1	**Enhancement 2**	**Tumour size**	**ER/PR status**	**FGT /HER2**
Early enhancement	.872	-.325	.104	-.189	-.049
Overall enhancement	.926	.197	.096	-.156	-.117
Late enhancement	.499	.786	.047	-.056	-.126
SER	.249	-.909	-.036	-.039	-.048
Tumour diameter MRI	.152	.092	.849	-.082	.167
Diff. size MRI-US	-.093	-.066	.890	.044	-.010
ER status	-.154	.023	-.020	.855	-.098
PR status	-.009	.011	-.013	.853	-.140
HER2 status	.030	-.193	.055	-.137	.762
Amount of FGT	.279	.440	-.192	.114	.519
Age	-.583	-.107	.172	-.118	-.307
Susp. calcifications	-.091	.096	.168	-.170	.471
Eigenvalue	2.41	1.85	1.64	1.61	1.30
Explained variance	20.10%	15.44%	13.63%	13.39%	10.48%
Cumulative variance	20.10%	35.53%	49.16%	62.55%	73.03%

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MRI* Magnetic resonance imaging, *US* ultrasound, *SER* signal enhancement ratio

Prediction model

According to the multivariable logistic regression model, Enhancement 1 (odds ratio (OR) 1.51 (95%-CI 1.09-2.10), p=0.013) and FGT/HER2 (OR 2.38 (95%-CI 1.75-3.23) p<0.001) were positively and significantly associated with E-DCIS. Factor loadings of both early enhancement and overall enhancement were positive,

indicating that the risk of E-DCIS increases with increasing early and overall enhancement. Because of positive factor loadings, patients with dense breast tissue around the MRI visible tumour and a positive HER2 receptor are at increased risk of E-DCIS (Table 3). The logistic regression model yielded an ROC curve with an AUC of 0.79 (95%-CI 0.72 - 0.85) (figure 3). The Hosmer-Lemeshow test was not significant (p = 0.907), indicating a good fit of the model, which was graphically supported by the calibration plot (figure 4). Bootstrapping resulted in a final AUC-value of 0.76 (shrinkage factor 0.89).

Table 3 Outcome of multivariable logistic regression of 5 components as predictors for extensive ductal carcinoma in situ

Component	OR	95%-CI	P-value
Enhancement 1	1.51	1.09-2.10	0.013
Enhancement 2	0.97	0.69-1.35	0.835
Tumour size	1.33	0.98-1.79	0.068
ER/PR status	0.82	0.61-1.12	0.209
FGT/HER2	2.38	1.75-3.23	<0.001

OR odds ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *FGT* fibroglandular tissue, *HER2* human epidermal growth factor receptor 2

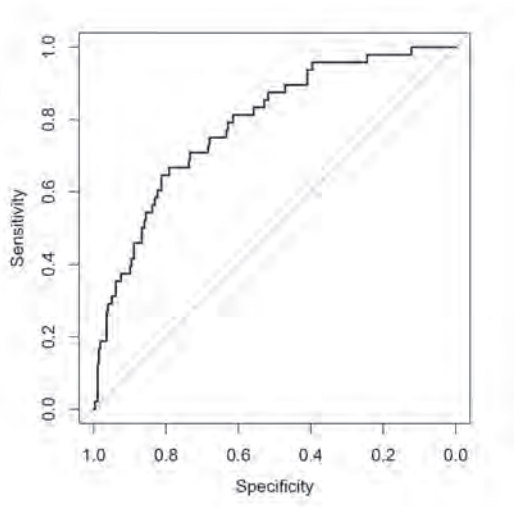

Figure 3 Apparent receiver operating characteristic curve of the prediction model based on the 5 components with eigenvalue larger than 1.0 yielded by principal component analysis. The area under the curve is 0.79 (95%-CI 0.72 - 0.85).

DISCUSSION

Being able to anticipate E-DCIS may improve the rate of incomplete resections. The reported model is a first initiative to predict the occurrence of E-DCIS around invasive breast cancer by combining MRI features with clinical and histopathological features. If the presence of E-DCIS is likely, appropriate steps may be taken. In case of breast carcinoma of limited extent (BCLE; ie, tumours with no malignant tissue at or beyond 10 mm from the edge of the tumour[17]), excision of the primary tumour with a 10-mm margin followed by radiotherapy may be sufficient. In case of non-BCLE, excision could be performed with wider margins. Thus, knowing the risk of E-DCIS prior to treatment may be used to guide surgical treatment in the future. However, combining a preoperative prediction model with margin assessment during surgery would be the most optimal strategy. If only preoperative information is used, removing too much tissue is a potential risk that should be prevented. For example frozen section analysis of the resection bed[33], intra-operative touch preparation cytology[34], or optical coherence tomography[35] are techniques to assess the presence of residual disease during surgery. Conversely, the use of intraoperative margin assessment only without the ability to warn surgeons beforehand about presence of subclinical disease may result in multiple resections that are more difficult to interpret by pathologists.

Enhancement measured at 2 different time points after contrast injection was associated with E-DCIS. Our findings are congruent with previous research, which indicated that E-DCIS is detectable by contrast-enhanced MRI[14,36,37]. Previous work also suggested that MRI is more accurate than mammography in determining the size of DCIS lesions[38]. In addition, increased parenchymal SER was related to local recurrence in patients with DCIS by Kim et al.,[39] suggesting that parenchymal enhancement indeed implies worse surgical outcome. We related enhancement around the MRI-visible tumour combined with patient- and tumour characteristics to the presence of E-DICS. This novel, combined approach resulted in an improved ability to pre-operatively detect E-DICS.

Extensive DCIS or extensive intraductal component (EIC) has been related to HER2 status in previous research as well. Somerville et al.[40] demonstrated that the prevalence of HER2 positivity is significantly higher in IDC with an EIC than without an EIC. HER2 expression is more common in DCIS lesions, which also corroborates our findings[41,42]. Harada et al. assessed whether receptor status in patients diagnosed with DCIS was associated with presence of invasive disease. Their

conclusion was that invasive carcinoma occurred more frequently in patients with HER2-positive DCIS, confirming our results that HER2 was found more frequently in patients with E-DCIS surrounding invasive carcinomas[43]. Furthermore, HER2 positivity (in absence of anti-HER2 therapy) and E-DCIS are both associated with worse clinical outcome[18,44], possibly explaining their relationship in our database.

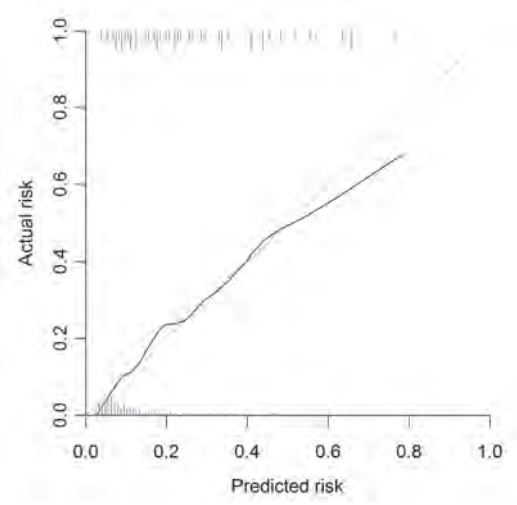

Figure 4 Apparent calibration curve showing the predicted risk of extensive ductal carcinoma in situ plotted against the actual risk. The grey bars represent distribution of predicted risk of women with (actual risk = 1.0) and without (actual risk = 0.0) extensive ductal carcinoma in situ.

Patients with E-DCIS were found to have an increased amount of FGT around the MRI visible tumour. Ductal carcinoma in situ originates from epithelial cells from ducts in the breast. The malignant cells accumulate within the ducts and lobules. Hence, DCIS may resemble FGT on MRI. This is confirmed on conventional imaging by Faverly et al.,[17] who showed that non-BCLE was positively associated with calcifications or larger amount of FGT outside the tumour border on mammography. We did not find a significant association between E-DCIS and suspicious calcifications in our dataset. Furthermore, large amount of FGT is a risk factor for locoregional recurrence, suggesting that FGT surrounding the excised tumours is more likely to contain malignant disease than adipose tissue [45].

Univariable analysis was performed to assess if relevant differences between groups with and without E-DICS existed. The analyses showed that tumours surrounded by E-DCIS occurred in slightly younger patients, were less frequently PR positive, more frequently triple positive, larger on MRI, surrounded by denser

breast tissue, showed more early enhancement, and were less frequently of low histologic grade. Most of the significant differences between the 2 groups were not considered clinically relevant and would not change the clinical workflow. However, these findings demonstrate the higher rate of high-risk features in the E-DCIS positive group.

A number of limitations of this study should be considered. First, we used receptor status as determined on excision specimens. The purpose of this study was to develop a prediction model containing variables that are known prior to surgery. In our data set, breast cancer was typically diagnosed with fine-needle aspiration cytology rather than core needle biopsy. Hence, receptor status was actually established on excision specimens. Nonetheless, breast cancer diagnosis is more often performed using core needle biopsy, which allows reliable assessment of receptor status[46]. Consequently, we used post-operative receptor status as if it were known prior to surgery. This may have resulted in slightly more accurate assessment of receptor status, because the risk of misclassification due to undersampling in heterogeneous tumours with core needle biopsy was avoided. Second, the analysed rim of tissue of 10 mm in diameter extending from the invasive tumour may have been too small, as non-BCLE particularly consists of malignant tissue outside this area. Additional tumour foci frequently occur at larger distances from the primary tumour as well[17]. The reason for assessment of 10 mm was that it corresponds to typical intended surgical margins.

The developed model has a reasonable discriminative ability and is promising for risk stratification for E-DCIS and positive excision margins. We made a first attempt to incorporate both computer-derived features and clinical and histopathological features into 1 model. Several improvements for clinical use are possible. The presence of (E-)DCIS outside the tumour is associated with finding an intraductal component on core needle biopsy. Hence, adding the presence of DCIS on core needle biopsy to the model may further increase the discriminative ability of the model[47]. As fine-needle aspiration cytology was used in many included MARGIN patients, we could not add this variable to our analyses. Additional MRI techniques such as diffusion-weighted imaging (DWI) could also be tested for their ability to detect disease components. Thus far, this technique has been used to discriminate between DCIS, invasive tumour and benign lesions, such that a contrast agent may potentially even be omitted[48,49]. However, the spatial resolution of DWI is currently still limited and may be improved by, for example, high-resolution DWI[50] or MRI scanners with higher field strength.

In conclusion, we proposed a prediction model for E-DCIS around early-stage invasive breast cancer. The model considers HER2 status, early enhancement, overall enhancement and amount of FGT in a 10-mm rim around the MRI-visible lesion. Because the model is based only on pre-treatment variables, it may be suitable for surgical planning.

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CHAPTER 7

Concordance of histologic grade of breast cancer between core needle biopsy and surgical excision specimen; a systematic review and meta-analysis

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ABSTRACT

Background

With the increasing use of neoadjuvant chemotherapy and minimally invasive ablative therapy in breast cancer, pretreatment assessment of tumour grade on core needle biopsy (CNB) is increasingly needed. However, grading on CNB is possibly less accurate than grading based on the surgical excision specimen. A systematic review and meta-analysis of the literature was conducted to derive a reliable estimate of the agreement in grading between CNB and subsequent surgical excision.

Methods

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria, Embase, PubMed and the Cochrane Library were searched. Pooled proportions of agreement in grading between CNB and excision specimen, Cohen's κ and percentages of overestimation and underestimation were calculated. Random-effects models were applied because of substantial heterogeneity, assessed by (I^2 test). Determinants of the level of agreement in grading were explored with meta-regression.

Results

Thirty-four articles were included in the systematic review (6029 patients) and 33 in the meta-analysis (4980 patients). Pooled agreement and κ were 71.1% (95%CI 68.8-73.3%) and 0.54 (95%CI 0.5-0.58) respectively. Underestimation and overestimation occurred in 19.1% (95%CI 17.1-21.3%) and 9.3% (95%CI 7.7-11.4%) respectively. Meta-regression showed associations between agreement of histologic type (positive association) and proportion of patients with oestrogen receptor-positive disease (negative association) and grade agreement.

Conclusion

Grading on CNB corresponds moderately with grading based on excision specimen, with underestimation in about one in five patients. Incorrect CNB tumour grading has limited clinical implications, as multiple factors influence decision-making for adjuvant systemic therapy.

INTRODUCTION

Histologic grade is an independent prognostic factor for survival in patients with breast cancer and is incorporated in several risk stratification tools[1,2], including the Nottingham Prognostic Index and Adjuvant Online[3]. Histologic grade is one of the main determinants of the need for adjuvant systemic therapy[4]. Without the use of tumour grading in determining the indication for systemic therapy, more tumours are identified as high risk. Therefore, omitting grade assessment would result in an overuse of adjuvant systemic therapy[2].

Profiling cellular characteristics of breast cancer, such as receptor status and tumour grade, is needed increasingly before surgical treatment. The indications for neoadjuvant treatment are widening, leading to an increased number of patients receiving neoadjuvant chemotherapy. Neoadjuvant treatment may change tumour characteristics or even lead to complete remission, thereby impairing tumour profiling on the excision specimen[5-7]. Furthermore, a number of minimally invasive ablative therapies, for example high-intensity focused ultrasound treatment, radiofrequency ablation and cryoablation, are increasingly being offered to patients in clinical or research settings[8-12]. As no surgical excision specimen is obtained afterwards, all information for assessing the indication for adjuvant (systemic) therapy in these patients needs to be obtained before the ablative treatment.

Breast cancer is generally diagnosed by core needle biopsy (CNB)[13], which has a high diagnostic accuracy[14,15]. Histological subtype[16-21], hormone receptor status and human epidermal growth factor receptor (HER2) status can be assessed reasonably well on CNB[22,23], whereas grading on biopsy is more challenging. The concordance of tumour grade classification on CNB and surgical excision has been assessed in several studies, with varying concordance rates[18,24-26]. A systematic review and meta-analysis of the literature was conducted to derive a reliable estimate of the concordance of grading between CNB and the subsequent surgical excision specimen.

METHODS

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria[27]. The review protocol was registered in PROSPERO International prospective register of systematic reviews (identifier CRD42015015858)[28].

Search strategy

A search was conducted in PubMed/MEDLINE, Embase and the Cochrane Library electronic databases. Search terms included synonyms for 'breast', 'core needle biopsy', 'histologic grade' and 'surgery', which were combined and searched in title and abstract (*appendix 1*). No search limits were used. Articles were selected according to predetermined inclusion and exclusion criteria. Cross-referencing was done to retrieve additional articles by manually searching reference lists of included articles and by searching articles citing the included studies. The systematic search included papers published until July 16, 2015.

Study selection

Studies were eligible if they reported the assessment of histologic grade using the Nottingham grading system on both CNB and surgical excision specimen from patients with breast cancer, and if the percentage agreement was either provided or could be calculated from available data. Exclusion criteria were: conference abstracts, review articles, biopsy techniques other than CNB, study size of ten patients or fewer, surgical excision not performed, CNB not performed, neoadjuvant chemotherapy in the entire study population and only benign lesions in the study population. Potentially relevant papers were preselected by screening title and abstract of all references yielded by the systematic search. The full text of selected abstracts was evaluated to decide which articles were fulfilling all selection criteria for inclusion in the analyses. One author reviewed full text and included eligible articles. In the event of questionable eligibility, studies were also reviewed by a second author.

Data extraction and quality assessment

The Nottingham grading system is a modification of the Bloom & Richardson grading method. Three morphologic features (degree of nuclear pleomorphism, percentage of tubule formation and mitotic count) are separately given a score

of 1, 2 or 3. Grade is derived by adding these scores. Low grade (1) is allocated to tumours with a total score of 3-5, intermediate grade (2) to those with a score of 6 or 7 points, and high grade (3) to tumours scoring 8 or 9 points. The modification was developed to improve the reproducibility and consistency of grading[29,30].

The primary outcome of this study was the concordance of tumour grade between CNB and surgical excision in terms of percentage agreement and Cohen's κ. Secondary outcomes were underestimation and overestimation of tumour grade by CNB, agreement per grade and agreement per grade component. The number of grade 1, 2 and 3 tumours, as assessed both on biopsy and on the surgical excision specimen, were extracted from the articles. If reported, data on the assessment of (one of the) grade components (tubular formation, nuclear pleomorphism and mitotic rate) on both CNB and surgical excision specimen was also extracted. Additionally, population characteristics such as age, tumour size, histological subtypes, hormone receptor status, type of biopsy guidance, and number and size of biopsies were collected.

All selected full-text articles were appraised critically according to the revised Tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)[31]. Risk of bias was assessed as high, low or unclear for four domains: patient selection, index test, reference standard and flow and timing. Concerns regarding applicability were also assessed for the first three domains. The results were displayed graphically[31].

Authors were contacted for supplementary data if information was missing. One author provided extra information on grading of both biopsy and excision specimen[26]. Discrepancies between numbers reported in text and in tables were found in some articles[19,32-35]. When this occurred, values from tables were used for the analyses. Two reviewers independently performed critical appraisal and data extraction. Disagreement was resolved by discussion and consensus or otherwise by consulting a third independent reviewer.

Statistical analysis

Percentage agreement was calculated by dividing the number of correctly assessed grades on CNB by the total number of tumours in which tumour grade was determined. If percentage agreement was reported without sample size, the article was included only in the systematic review. Contingency tables were composed containing the number of grade 1, 2 and 3 tumours as assessed on both CNB and the surgical excision specimen. Cohen's κ, underestimation, overestimation and agreement per grade were computed from these tables.

Study-specific estimates and pooled estimates of percentage agreement and κ values, with 95% confidence intervals, were displayed in forest plots. Underestimation and overestimation of tumour grade by CNB, agreement per grade and agreement per grade component were analysed and represented in a similar way. The κ statistic represents interobserver agreement beyond chance. A κ value of less than zero is considered poor, 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 almost perfect agreement[36,37].

The I^2 statistic was used to explore the amount of heterogeneity across studies. I^2 indicates the degree of variance that can be attributed to heterogeneity rather than chance. I^2 values of 25%, 50% and 75% indicate low, moderate and high heterogeneity respectively[38]. Substantial heterogeneity was assumed to be present if I^2 values exceeded 30%, and random-effects models were applied to obtain pooled estimates[39]. Percentage agreement values were logit-transformed before pooling. κ values were transformed by the Fisher z-transformation before pooling to correct for the ceiling effect of kappa[40-42]. Publication bias was assessed visually by generating funnel plots[43].

Univariable meta-regression was used to explore determinants of level of agreement between CNB and surgical excision on study level[44,45]. Year of publication, study size, proportion of patients with grade 1, 2 and 3, proportion of oestrogen receptor (ER), progesterone receptor (PR) and HER2 positivity, agreement of ER, PR and HER2 on CNB and excision, mean or median number of cores, and the percentage agreement of histological type between CNB and surgical excision were evaluated. All analyses were performed using R statistics (version x64 3.1.1) after installation of the metaphor package (version 1.9-5)[46]. $P<0.050$ was considered statistically significant in all analyses.

RESULTS

Study selection

The search identified 1638 papers, of which 1317 remained after removing duplicates (*Figure 1*). Title and abstract screening resulted in 56 eligible abstracts. After full-text screening, 23 articles were excluded. Most ineligible abstracts (19) were conference abstracts, one reported only one of the grade components, one reported grade only in discordant cases and one did not report histological grade. No full text was available for one abstract. One additional reference was found

by cross-referencing[47]. Finally, 34 articles were included in the systematic review, including 6029 patients with breast cancer. Thirty-three studies including 4980 patients were eligible for inclusion in the meta- analysis.

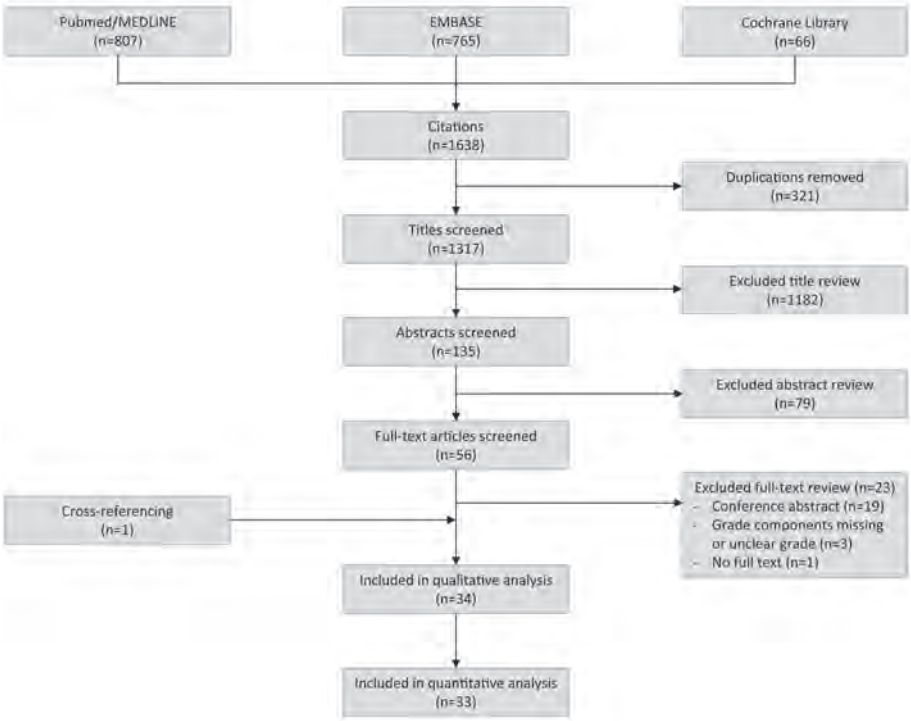

Figure 1 Flow chart of systematic search.

Study description and quality assessment

Quality appraisal is displayed in *Figure 2*, which shows an overview of the proportions of studies with a low, high or unclear risk of bias for four different domains, and low, high or unclear risk of applicability concerns for three domains. Risk of bias was most frequently high in patient selection, namely in approximately one-third of studies. For all four domains, the risk of bias was unclear in at least 30% of studies. Applicability concerns were low in the majority of studies. The funnel plot based on percentage agreement analysis showed no indication of publication bias (data not shown).

Nineteen studies[16,18,21,25,26,33-35,48-58] were retrospective, seven[17,19,20,24,59-61] were prospective and the study design was not reported for the remaining eight studies[15,32,47,62-66] (*Table S1*, supporting information). Study size varied from 17 to

486 patients. The mean or median age of patients with breast cancer ranged between 44.2 and 65 years. The number of cores, which was reported in 25 studies[15,16,18-21,24-26,32-34,49,50,52,55-57,59-62,64-66], varied from one to 25 per lesion or patient. Needle diameter used for biopsies was 14 G in most studies and varied from 10 to 18 G. The proportion of patients with grade 1 tumours on surgical excision varied form 4% to 50%. Grade 2 was found in 33-58% of patients, and the proportion of grade 3 ranged from 13% to 57%[16-21,24-26,35,47-51,53-62,64,66]. Most tumours were invasive ductal carcinomas (IDCs)[15-21,24,26,32,35,47-51,53,55-63,65,66] and eight authors[15,24,34,49,56-58,65] included only patients with IDC. The smallest proportion of patients with IDC was 60%[32].

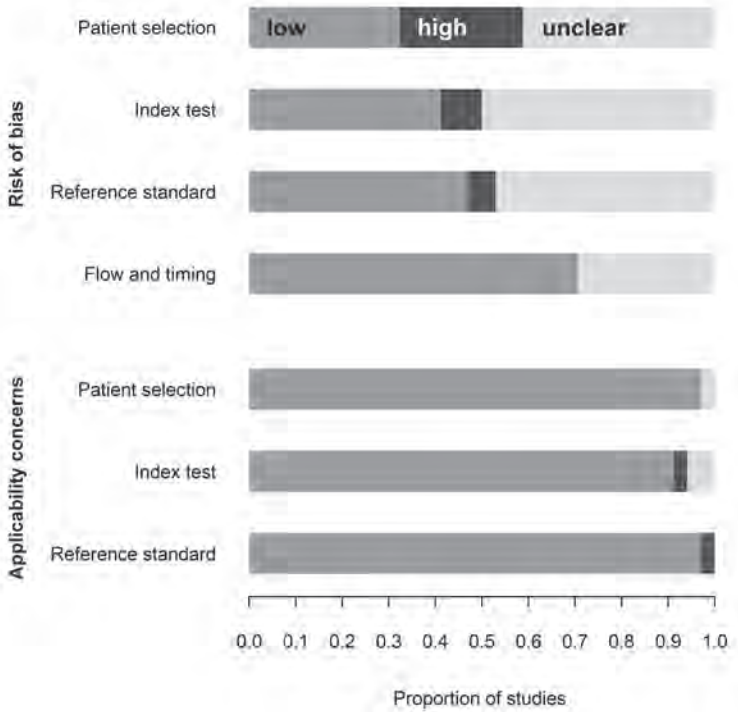

Figure 2 Quality appraisal of included articles. risk of bias and applicability concerns

Concordance in overall grade

Percentage agreement of tumour grade on CNB and surgical excision ranged from 59.3% to 94%. The pooled percentage agreement was 71.1% (95%-CI 68.9-73.3%) (*Figure 3*)[15-21,24-26,32-35,47-51,53-66]. A preliminary analysis of percentage agreement resulted in an I^2 value of 61.9% (95%-CI 38-81.2%, p<0.001), indicating moderate

to high inter-study heterogeneity. Hence, a random-effects pooled estimate of percentage agreement was calculated. Random-effects models were used for all analyses after I^2 calculation. Extracted or computed Cohen's κ varied from 0.35 to 0.91[16-21,24-26,32,35,47,49-51,53-62,64,66]. The pooled estimate of Cohen's κ was 0.54 (95%-CI 0.50-0.58), indicating moderate agreement (*Figure 4*)[16-21,24-26,35,47,49-51,53-62,64,66].

Of the 33 studies included in the meta-analysis of percentage agreement, 27[16-21,24-26,35,47-51,53-62,64,66] provided exact (absolute) numbers per grade and were used to calculate underestimation and overestimation and agreement per grade (*Table 1*). Underestimation of grading by CNB occurred in 19.1% of patients, while overestimation occurred in only 9.3%. The pooled percentage agreement of CNB and excision specimen per grade was similar for grade 1 and grade 2 tumours, 75.7% and 75.9% respectively. Agreement was substantially lower in grade 3 tumours (57.9%). Overall, underestimation by one grade was most common and occurred in 883 (19.7%) of 4485 patients. Overestimation by one grade occurred in 393 patients (8.8%). Underestimation and overestimation by two grades occurred in 23 (0.5%) and eight (0.2%) patients respectively. CNB categorized 1158 tumours as grade 1, of which 796 (68.7%) were also grade 1 on excision, 2401 as grade 2, of which 1584 (66.0%) were similarly graded on excision, and 952 as grade 3, of 798 which (83.8%) were assigned the same grade excision[16-21,24-26,35,47,49-51,53-62,64,66].

Concordance in grade components

Agreement of grade components between CNB and surgical excision was reported in approximately half of studies. Fourteen studies reported nuclear pleomorphism scores [15,16,18,25,26,32-34,49,55,56,58,60,64]. Underestimation occurred more frequently than overestimation (17.4% versus 10.0%), but this was only based on eight studies [16,25,26,49,55,56,60,64]. Tubule formation scores were reported in 12 studies [15,16,18,26,32-34,49,55,58,60,64], which was more frequently overestimated (13.0%) than underestimated (9.2%) [16,26,49,55,60,64]. Agreement of mitotic count, which was provided by 13 studies [15,16,18,26,32-34,49,55,58,60,61,64], was lower than pooled agreement of tubular formation and nuclear pleomorphism (62.4%). This is particularly indicated by a pooled κ of 0.36 [16,18,26,32,49,55,58,60,64]. The majority of discordant cases of mitotic count was underestimated (29.9%) [16,26,32,34,49,55,60,61,64].

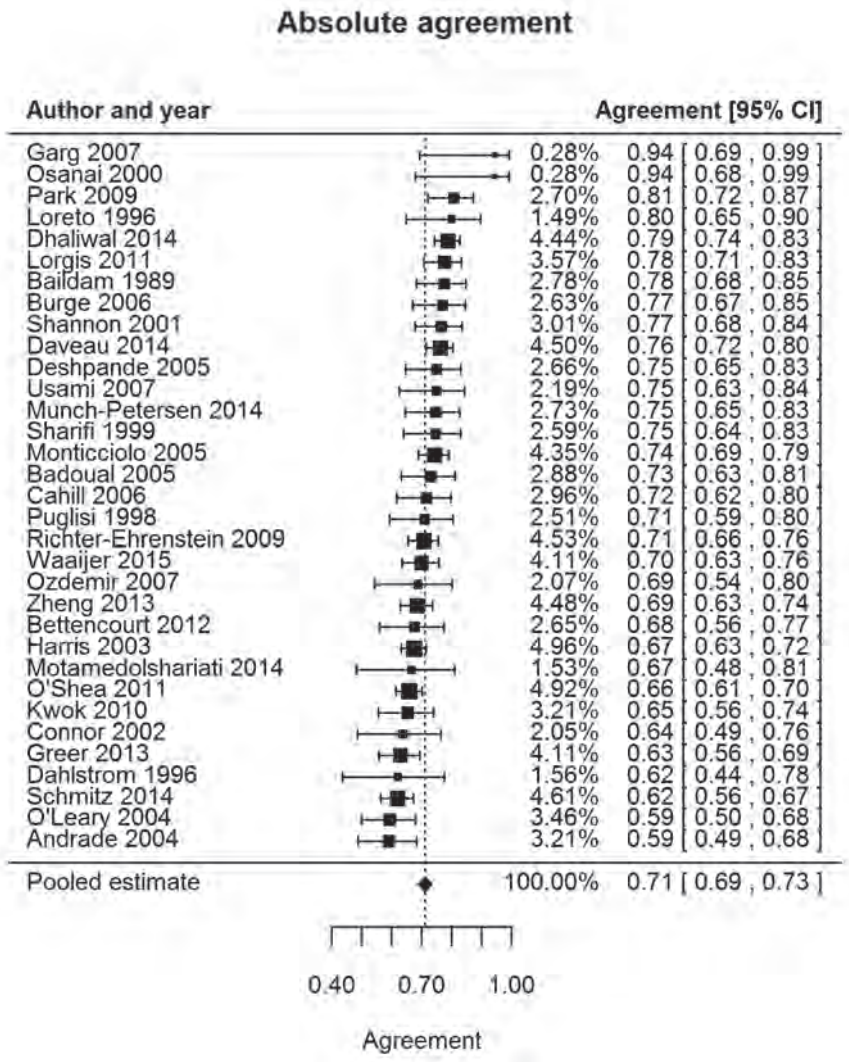

Figure 3 Forest plot of percentage agreement of grade between core needle biopsy and surgical excision, with study-specific and pooled estimates. Values in parentheses are 95& confidence intervals

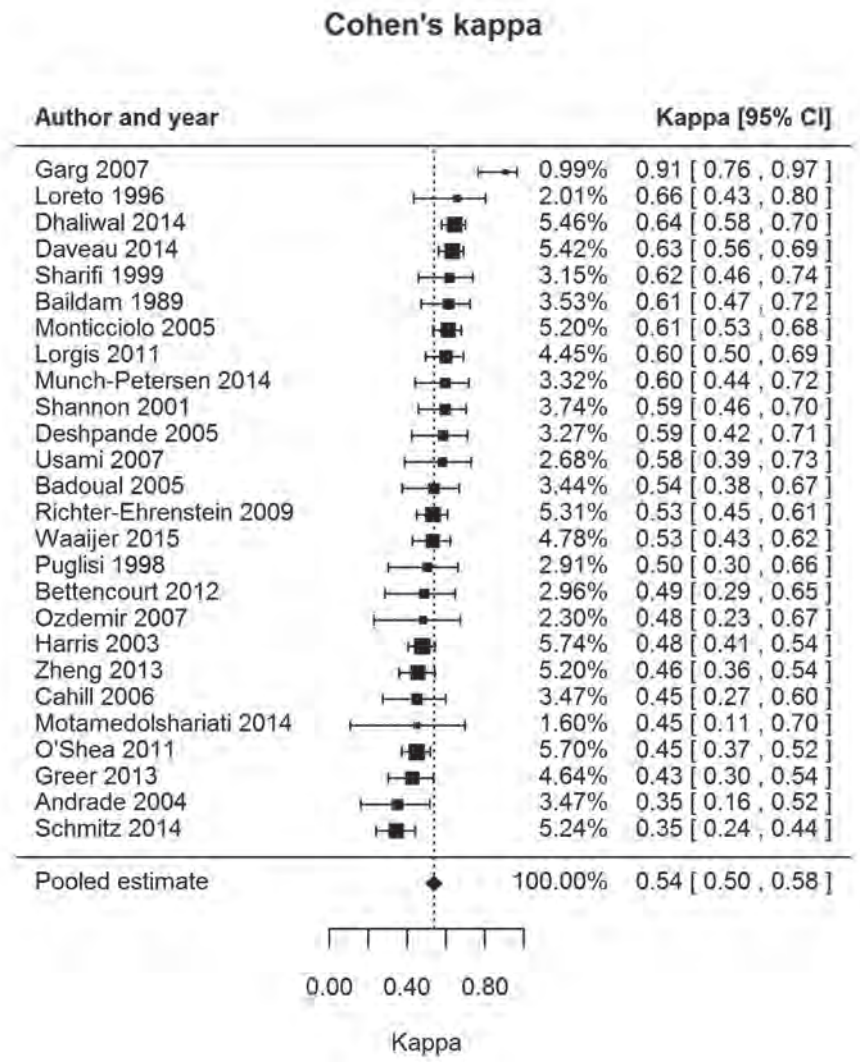

Figure 4 Forest plot displaying study-specific Cohen's κ values of tumour grade assessed on core needle biopsy and surgical excision, with pooled estimate. Values in parentheses are 95% confidence intervals.

Association between concordance in grade and clinicopathological variables

Meta-regression showed that the percentage agreement on tumour type at study level was significantly and positively associated with grade percentage agreement ($p<0.001$)[15-21,24,33,34,47,48,50,54-56,59-63,65] and Cohen's κ ($p=0.044$)[16-21,24,47,50,54-56,59-62]. The proportion of ER-positive cancers in study populations was significantly and

negatively associated with grade agreement between CNB and surgical excision (p=0.042)[16,17,19,20,26,34,35,48,53,56,58,59,61,62,66], but not with Cohen's κ (p=0.205)[16,17,19,20,26,35,53,56,58,59,61,62,66]. None of the other tested variables were significantly associated with variation in relationship between CNB and surgical excision.

Table 1 Pooled estimates

	No. of studies	Agreement (%)		No. of studies	Cohen's κ	
Grade						
Agreement	33	71.1%	68.8-73.3%	26	0.54	0.50-0.58
Agreement gr. 1	27	75.7%	71.9-79.2%	NA	NA	
Agreement gr. 2	27	75.9%	71.4-79.9%	NA	NA	
Agreement gr. 3	27	57.9%	51.9-63.6%	NA	NA	
Underestimation	27	19.1%	17.1-21.3%	NA	NA	
Overestimation	27	9.3%	7.7-11.4%	NA	NA	
Mitotic count						
Agreement	13	62.4%	57.0-67.6%	9	0.36	0.29-0.41
Underestimation	9	29.9%	21.1-40.5%	NA	NA	
Overestimation	8	6.8%	3.0-14.7%	NA	NA	
Nuclear pleomorphism						
Agreement	14	70.2%	65.7-74.3%	9	0.47	0.40-0.54
Underestimation	8	17.4%	13.4-22.4%	NA	NA	
Overestimation	8	10.0%	7.5%-13.3%	NA	NA	
Tubule formation						
Agreement	12	74.5%	68.7-79.5%	7	0.53	0.46-0.59
Underestimation	6	9.2%	7.0-12.1%	NA	NA	
Overestimation	6	13.0%	11.1-15.1%	NA	NA	

Values in parentheses are 95% ccnfidence intervals..
NA not available.

DISCUSSION

This systemic review and meta-analysis has shown that CNB provides the same tumour grade as surgical excision in 71.1% (95%-CI 68.8-73.3%) of women with breast cancer. This corresponds to a pooled κ of 0.54 (95%-CI 0.5-0.58), which indicates moderate agreement beyond chance. Underestimation occurred substantially more frequently than overestimation (19.1% versus 9.3%). The level of agreement was lower for grade 3 than for grade 1 or 2 tumours. At the same time, tumours that were assessed as grade 3 on CNB were most frequently confirmed by surgical excision, whereas grades 1 and 2 on CNB were less often graded similarly.

Of the three grade components, mitotic count had the lowest agreement with surgical excision, whereas tubule formation showed most agreement.

The main reason for discordance of tumour grade between CNB and surgical excision is probably undersampling by CNB. The amount of tissue obtained is limited and tumours are sampled randomly with CNB. The most representative tumour areas may be missed, especially in heterogeneous, larger tumours, with regional differences in grade[57-59]. Additionally, morphological preservation of biopsied tissue is often suboptimal, because it contains crush artefacts due to needle sampling. Mitotic count was concordant in only 62.4% of patients and underestimation was seen in almost one-third of cases (29.9%). This can be attributed to the method of assessment of mitotic count, which requires assessment of 2 mm^2, corresponding to 10 high-power fields[30]. However, according to Dhaliwal and colleagues, fewer than 10 high-power fields were available in only 6% of biopsied tumours. This was contradicted by di Loreto and co-workers[61], who reported that none of biopsies provided 10 high-power fields. An extrapolation or modification has to be made to enable mitotic count assessment on CNB. O'Shea et al.[64] proposed a modification that uses a reduced threshold for mitotic scores in CNB. The agreement of grade between CNB and excision increased from 65% to 72% when this method was applied. Dhaliwal and colleagues[51] applied a similar modification, but did not find an improved percentage agreement for grade. Furthermore, the conditions before and during grade assessment, such as cold ischaemic time, fixation and temperature, differ between CNB and excision specimens[67-69], probably affecting agreement.

Surgical excision is considered the standard for tumour grade assessment. However, numerous studies have shown that reproducibility between pathologists with regard to tumour grading is far from excellent[70,71]. Longacre and co-workers[72] reported the percentage agreement and κ values for grading of 35 slides by 13 pathologists. The percentage agreement for grade 1, 2 and 3 tumours ranged from 61.4% to 87.8%, with κ values of 0.4-0.7. Similar results were found by Meyer et al.[73], who reported moderate interobserver agreement in five trials with seven pathologists, with κ values values between 0.5 and 0.59. A study in 93 excision specimens, which were distributed over seven pathology departments, resulted in moderate intercentre agreement (κ value 0.54)[74]. The possible consequences of underestimation or overestimation of tumour grade on surgical specimens are unknown and therefore not taken into account in daily clinical practice.

Tumour grading on core biopsy has always been considered inferior to grading on surgical excision specimens owing to the limited amount of tissue, undersampling and differences in tissue handling and processing between CNB and surgical excision specimen. Tumour grading on biopsy is not performed for this reason In numerous centres. The present meta-analysis shows that tumour grading on core biopsy is potentially not inferior to tumour grading on the surgical excision specimen. However, surgical excision is considered the reference standard for grade assessment. As described above, the accuracy of tumour grading on excision specimen is moderate.

Incorrect tumour grading may have clinical implications, such as omitting or administering adjuvant systemic therapy erroneously. However, the indication for adjuvant systemic therapy is decided by several factors, including age, lymph node status, tumour size and receptor status. Waaijer and colleagues[58] demonstrated 30.0% grading disagreement, which would result in undertreatment in only 1.5% of patients (3 of 199) and overtreatment in only 3.5% (7 of 199). Daveau and co-workers[49] also analysed the changes in recommended adjuvant treatment owing to grade disagreement. CNB would have given the wrong recommendation regarding the type (hormone or chemotherapy) of adjuvant systemic therapy In seven (2.3%) of 299 patients. Schmitz et al.[53] evaluated the influence of disagreement of tumour grade between CNB and surgical excision on the indication for systemic therapy based on Adjuvant! Online. When combined with other prognostic factors including sentinel lymph node status, CNB-based prediction of indication for systemic therapy led to correct treatment in nine of ten patients. As demonstrated by these analyses, discordant cases usually differ by only one grade, which probably indeed limits the clinical consequences.

A remarkable finding is that the level of agreement in grading between CNB and surgery was significantly associated with the level of agreement in assessment of histologic type between CNB and surgery; this is probably because tumours with similar histologic type in CNB and resection are less heterogeneous lesions that allow assessment of grade and type with higher concordance. Another explanation may be the experience and training of pathologists. The technique of processing and staining of tissue may also influence the comparability of tissue obtained by CNB and surgery, affecting the likelihood to adequately assess tumour grade and type[32,59,63]. In addition, the proportion of ER-positive tumours was associated negatively with grade agreement. This association was not significant

when κ values were used as outcome variable. A plausible histopathological explanation could not be identified in the existing literature.

The main limitation of this systematic review and meta-analysis is the moderate quality of included studies. The retrospective design of the majority of studies might have led to an increased risk of bias, mainly owing to patient selection. Blinding of the pathologist(s) participating in the studies was not reported in a number of articles. Furthermore, in several studies tumour grade was not determined (mostly on CNB) in every patient for unclear reasons, and data on which of the tumours were graded was lacking. A number of studies[18,32,64] excluded patients in whom fewer than 10 high-power fields were available, possibly also resulting in selection bias. Additionally, studies reported their data in different ways; for example, only percentage agreement per grade was reported, and not the number of underestimations and overestimations. As a result, the various analyses included different numbers of patients.

Considerable heterogeneity between studies was found, for which several reasons can be identified. First, the number and size of cores obtained by biopsies varied considerably; the number of cores was not, however, associated with level of agreement in meta-regression. Several studies used different sizes of core without specifying which size was used in which patient, whereas others used only one core size. Therefore, the influence of core size could not be assessed both between and within studies. Second, ultrasound or stereotactic image guidance is usually used for CNB. Some studies[16,21,65] performed only ultrasound-guided biopsies of mostly masses. Others[15,24,52] included all patients with radiologic abnormalities, including less easily detectable or non-palpable abnormalities, possibly increasing the risk of undersampling. Daveau and colleagues[49] demonstrated that grade concordance is higher in tumours biopsied under ultrasound guidance. The proportion of grade 3 tumours differed between studies. As high-grade tumours are least often diagnosed correctly by CNB, this may have influenced agreement. Tumour stage might also influence grade agreement, as larger tumours are more heterogeneous and therefore prone to undersampling[49,58]. Finally, one study[59] assessed grade, tumour type and receptor status per core instead of per sampled tumour, making their results less comparable with other included studies.

A percentage agreement of 71.1% is suspected to be a slight overestimation. Patients in whom fewer than 10 high-power fields were available were often not included[15,18,21,24,57,62]. Hence, determination of mitotic count in these studies was not constrained by the amount of tissue and thus more reliable. In routine clinical

care, however, grade needs to be assessed in every patient, including those with limited amounts of tissue. Besides, in these analyses, non-graded tumours on either CNB or the excision specimen were not taken into account to enable, inter alia, calculation of κ values. Furthermore, pretreatment grade assessment is required for patients who receive neoadjuvant chemotherapy, as this may achieve complete pathological response[75]. Histological grade may even be used to select patients for neoadjuvant chemotherapy[5]. Patients who received neoadjuvant chemotherapy were excluded from most of the studies included in this review. Patients who have an indication for neoadjuvant chemotherapy usually have larger tumours than those scheduled for primary surgery, with more risk of undersampling of crucial tumour regions[49,58]. Consequently, if patients with high-stage breast cancer had been included, the agreement between CNB and surgical excision would have been expected to be lower.

Modest agreement of grade may be considered insufficient by some. Systemic therapy is administered to decrease the risk of metastases[3,4,76], and the indication is based mostly on age, tumour size, lymph node status, receptor status and grade. To decrease the risk of overtreatment and undertreatment, other risk stratification tools, such as multigene arrays, may be used in support of clinical decision-making. The MammaPrint® (Agendia, Amsterdam, The Netherlands) assesses 70 different genes to determine whether patients have a high or low risk of future distant metastases. Oncotype DX® (Genomic Health, Redwood City, California, USA) is based on 21 genes and provides a score that is indicative of recurrence risk. Combining prognostic factors assessed on CNB with those from a multigene assay might enable reliable risk profiling and subsequent therapeutic decision-making, if these gene arrays will prove to have a high predictive value and high concordance between CNB and surgical excision specimen.

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APPENDIX 1

Search syntax

breast OR breasts OR mamma OR mammae

AND

biopsy OR biopsies OR core OR CNB

AND

surgery OR surgeries OR surgical OR operation OR operations OR excision OR excisions OR excised OR resection OR resections OR resected

AND

grade OR grading OR differentiation

Table S1 Characteristics of included studies

First author and year	No. of tumours	No. of tumours	Age		Tumour size on excision (mm)		Image guidance	No. of biopsies	
			Mean / median	Range/ SD	Mean / median	Range		Mean/ median	Range/ SD
Andrade 2004[18]	120	120	-	-	35.1	10-181	US	-	3-5
Badoual 2005[16]	110	110	-	-	-	-	US	1.2	1-5
Baildam 1989[17]	130	130	60	33-84	32/27	-	ST	-	-
Bettencourt 2012[62]	103	103	-	-	-	-	US/ST	-	4-6
Burge 2006[48]	87	87	58	31-82	-	-	-	-	-
Cahill 2006[19]	95	95	60.7	39-82	-	-	US	4	3-5
Connor 2002[63]	44	44	64	-	17	-	ST/US	-	-
Dahlstrom 1996[15]	52	52	58.9	41-85	-	-	ST	5	-
Daveau 2014[49]	350	350	-	-	-	-	US/ST/ none	3	1-11
Deshpande 2005[50]	105	105	62	35-84	-	-	US	>3/>5	-
Dhaliwal 2014[51]	359	359	61	11.3	14	10-20	-	-	-
Garg 2007[24]	26	26	47.2	30-78	-	-	US	-	2-3
Greer 2013[59]	165	165	-	-	-	-	-	4.6	1-25
Harris 2003[60]	500	500	-	-		-	-	2 or 10	-
Kwok 2010[32]	155	155	61	35-88	15	2.5-60	US/ST/ none	2	1-5
Loreto 1996[61]	41	41	59.3	33-89	-	-	US	1.8	1-3
Lorgis 2011[35]	175	175	61	31-91	-	-	-	-	-
Monticciolo 2005[25]	341	341	65	22-93	15	-	US/ST	5	1-21
Motamedolshariati 2014[20]	30	30	51	32-88	37.3	10-130	US/none	>3	-
Munch-Petersen 2014[26]	89	89	65	34-85	16	2-100	-	3	2-14
O'Leary 2004[33]	113	113	-	-	-	-	-	2/3	1-7
Osanai 2000[65]	31	31	44.2	16-70	22.5	7-45	US	1	-
O'Shea 2011[64]	449	449	-	-	-	-	US	-	1-2
Ough 2011[52]	209	209	64/65	27-95	-	-	US/ST	-	4-6
Ozdemir 2007[21]	85	85	48.2	18-80	18.6	6-60	US	3.4	3-5
Park 2009[34]	104	104	50	9.9	-	-	US	5.1	0.9
Puglisi 1998[66]	75	75	60.3	13.2	<20	-	ST/US	2.8	1-9
Richter-Ehrenstein 2009[47]	502	502	-	-	-	-	ST/US	-	-
Schmitz 2014[53]	366	366	62	34-89	-	-	US	-	-
Shannon 2001[54]	-	-	-	-	-	-	-	-	-
Sharifi 1999[55]	79	79	-	-	-	1-100	ST/US	-	5-7/3-7
Usami 2007[56]	120	120	55.3	29-80	-	-	ST/US	7.7	1-17
Waaijer 2015[77]	213	213	60	11.3	15	2-81	US	-	-
Zheng 2013[57]	300	300	60.9/62	28-91	14.9/12.5	3-80	US	>4	-

US Ultrasound *ST* stereotactic *IDC* invasive ductal carcinoma *ILC* invasive lobular carcinoma *IDLC* invasive ductal/lobular carcinoma *Muc* mucinous

* No. of samples instead of tumours

** Some studies report histology of total number of carcinomas, others report only histologic type of tumours with grade assessment

Needle diameter (G)	Histological subtype (%)**					Grade on excision specimen (%)			Absolute agreement	
	IDC	ILC	IDLC	Muc	Other	1	2	3	N	%
14	64.2	7.5	-	6.7	21.7	43.2	36.8	20.0	56	58.9
14/16/18	80.9	11.8	3.6	1.8	1.8	29.0	52.7	18.3	68	73.1
-	86.2	10	-	2.3	1.5	12.2	54.1	33.7	76	77.6
14	65.0	8.7	-	-	26.2	19.7	49.3	31.0	48	67.6
14	79.3	14.9	1.1	2.3	2.3	36.8	33.3	29.9	67	77.0
18	89.5	10.5	-	-	-	4.2	38.9	56.8	68	71.6
11/14	79.5	13.6	6.8	-	-	-	-	-	28	63.6
14	68.6	15.7	-	-	15.7	-	-	-	18	62.1
11/14/16	100	-	-	-	-	25.4	42.3	32.3	267	76.3
-	83.8	12.4	3.8	-	-	32.1	48.8	19.0	63	75.0
-	83.3	5.6	-	-	11.1	22.3	51.0	26.7	283	78.8
18	76.9	15.4	-	3.8	3.8	50.0	33.3	16.7	17	94.4
10/14	79.0	14.6	5.9	-	0.5	23.0	42.4	34.6	120	62.8
14	64.9	5.4	5.0	1.1	23.6	13.4	40.9	45.7	328	67.5
14	60.4	10.9	20.8	2.0	5.9	-	-	-	66	65.3
18	92.7	7.3	-	-	-	50.0	32.5	17.5	32	80.0
-	89.7	10.3	-	-	-	29.4	50.0	20.6	132	77.6
11/14	-	-	-	-	-	30.2	38.9	30.9	214	74.3
16	83.3	13.3	-	-	3.3	23.3	56.7	20.0	20	66.7
-	87.6	12.4	-	-	-	37.9	49.4	12.6	65	74.7
-	-	-	-	-	-	-	-	-	67	59.3
16	100	-	-	-	-	-	-	-	16	94.1
-	-	-	-	-	-	15.4	44.8	39.9	296	65.9
8-11/14/16	-	-	-	-	-	-	-	-	-	63.0
14	77.0	3.3	4.9	1.6	13.1	18.8	52.1	29.2	33	68.8
14	-	-	-	-	-	-	-	-	84	80.8
14/16	89.3	4.0	6.7	-	-	47.8	39.1	13.0	49	71.0
11/14	62.6	12.2	9	-	16.3	23.2	49.2	27.6	223	70.8
-	79	15.7	-	-	5.3	37.3	48.7	14.0	186	62.0
14/16	-	-	-	-	-	10.8	45.0	44.1	85	76.6
14	73.4	7.6	16.5	-	2.5	29.1	38.0	32.9	59	74.7
11/16	62.5	6.3	-	2.7	28.6	21.7	58.3	20.0	45	75.0
-	100	-	-	-	-	30.0	42.7	27.2	149	70.0
14	100	-	-	-	-	11.9	51.0	37.1	196	68.5

CHAPTER 8

Patient preferences for minimally invasive and open locoregional treatment for early-stage breast cancer

Submitted

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ABSTRACT

Purpose

Non- or minimally invasive treatments are being developed as alternatives to surgery for early stage breast cancer patients. Patients' preferences with regard to these new treatments have not been investigated. The aim of this study is to assess preferences of breast cancer patients and healthy women regarding these new techniques, compared to conventional surgical treatments.

Methods

Six hypothetical breast cancer treatment-outcome scenarios were developed; i.e. three standard surgical scenarios (mastectomy, mastectomy with immediate implant reconstruction, breast conserving therapy (BCT)) and three minimally/non-invasive scenarios (radiofrequency ablation (RFA), magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation, ablative single boost radiotherapy). Participants rated treatment-outcome scenarios by visual analogue scale (VAS) and time trade-off (TTO). Friedman and post-hoc Wilcoxon signed-rank tests were used to test whether scores were significantly different from BCT.

Results

Seventy-one breast cancer patients and 50 healthy volunteers participated. Overall, BCT was rated highest in terms of VAS (0.80) and TTO (0.90) scores. After stratification, BCT ranked highest in most subgroups, with the exception of healthy individuals, where the highest score was given to ablative boost (VAS 0.80, TTO 0.88). Mastectomy with immediate reconstruction was least preferred in most subgroups.

Conclusions

This study showed no significant preference for minimally invasive treatment for breast cancer. Using hypothetical scenarios, breast cancer survivors attributed highest scores to BCT, while healthy volunteers showed a slight preference for minimal invasive treatments.

INTRODUCTION

Most breast cancers are diagnosed at an early stage[1], and the incidence of early breast cancer is increasing due to improved imaging techniques and screening programs[2-4]. Most patients with early-stage breast cancer are treated with breast conserving surgery, which is equally effective as mastectomy if combined with whole breast radiotherapy[5-8].

Surgery may impair cosmetic outcome, requires hospitalization and induces pain, haemorrhage and infection in a non-negligible proportion of patients[9-13]. Non- or minimally invasive treatments such as Radiofrequency Ablation (RFA), Magnetic Resonance-guided High-Intensity Focused Ultrasound (MR-HIFU) ablation and single dose ablative radiotherapy are being developed as alternatives to breast surgery[14,15]. MR-HIFU ablation is a non-invasive treatment, which uses focused ultrasound beams to induce lethal temperatures in the targeted cancerous tissue[16,17]. RFA uses a needle electrode, which is inserted in the tumor and generates an alternating current resulting in ablative temperatures[18]. With ablative radiotherapy, a high-dose (lethal) radiation boost is given to the tumor[15]. All three minimally invasive strategies are in an early phase of development and generally performed in research settings.

Until now, it is unknown whether a demand for these innovations exists from a patient's perspective, and if so, which women would prefer to undergo these minimally invasive treatments[19]. The aim of this study was to assess the preferences of breast cancer patients and healthy women regarding new minimally invasive treatment techniques, compared to conventional surgical treatments.

METHODS

The present study includes women with breast cancer who completed breast cancer treatment more than 12 months ago, and healthy women over 40 years without a history of breast cancer. Patients were recruited from the Utrecht Cohort for Multiple BREast cancer intervention studies and Long-term evAluation (UMBRELLA) at the department of Radiation Oncology of the University Medical Center Utrecht (The Netherlands). In the context of UMBRELLA, all patients signed informed consent to receive invitations for future studies on breast cancer. Healthy volunteers were friends or relatives of the participating breast cancer patients.

Patients and healthy volunteers were recruited by telephone. The current study was exempted from review by the Institutional Review Board.

Treatment-outcome scenarios

Treatment-outcome scenarios were developed based on literature, clinical expertise and input of a breast cancer survivor, a nurse practitioner specialized in breast cancer care, a breast surgeon, a medical oncologist, a radiation oncologist, a plastic surgery resident and several clinical researchers involved in the three minimal invasive treatments performed in our center. The treatment-outcome descriptions were piloted in a pilot study including five breast cancer patients and five healthy volunteers. Their comments were used to improve the questionnaires.

Six treatment-outcome scenarios were developed:

1) Mastectomy with sentinel lymph node biopsy (SLNB) ('Mastectomy');
2) Mastectomy followed by direct implant-based reconstruction and SLNB ('Mast-reconstruction');
3) Breast conserving therapy, consisting of lumpectomy with SLNB and whole breast radiotherapy ('BCT');
4) RFA preceded by SLNB and followed by whole breast radiotherapy ('RFA');
5) MR-HIFU ablation preceded by SLNB followed by whole breast radiotherapy ('MR-HIFU');
6) Ablative tumor radiotherapy (single dose) preceded by SLNB ('Ablative boost').

We asked all patients to hypothesize being diagnosed with early stage breast cancer, for which the six hypothetical treatment scenarios were described. For each scenario, we explained all procedures and interventions, including need for sedation or anaesthesia and in case of surgery, the size of the incision. Clinical consequences of the treatments were described, e.g. the duration of hospital stay, level of pain, risk of complications and follow-up schemes. Prognosis of the different treatment scenarios was expressed as 5-year risk of local recurrence and 10-year mortality risk. For 67 participants, we described a worse prognosis after RFA, MR-HIFU and Ablative boost compared to surgery (5-year risk of local recurrence of 5% versus 2% and 10-year mortality 3% versus 2% respectively). For 54 participants, we described equal prognoses for all scenarios (5-year risk of local recurrence of 2% and 10-year mortality of 2%).

Data collection

Patients filled out questionnaires that they received by mail, and provided information on baseline characteristics and self-assessed health (EQ-5D-5L score[20]). Participants rated each treatment-outcome scenario on a continuous scale from 0 to 100 (visual analogue scale (VAS)). A score of 0 represented the worst imaginable health state and 100 perfect health. Additionally, patients rated the scenarios according to the time trade off (TTO) method, Here, patients indicated how many years in perfect health were comparable to 10 years after the described scenarios[21]. Participants were asked to take both the hypothetical treatment experience and expected outcome into account. After explaining these utility measures with two examples, participants completed a warm-up task. They were asked to rate VAS and TTO for two scenarios describing a minor cut in a finger and a cerebrovascular accident resulting in hemiplegia and disabled speech and writing skills. Answers were used to estimate the participants' understanding of the questioning method.

Statistical analyses

Proportions (discrete variables) and medians with interquartile range or means with standard deviation (continuous variables) were calculated for baseline characteristics and VAS and TTO scores. Normality was assessed with Kolmogorov-Smirnov test. Spearman correlation coefficient was used to assess the correlation between VAS and TTO scores. We used Friedman tests for repeated measures in order to compare VAS and TTO scores between treatment scenarios. If a significant difference between the six ratings was found, we compared BCT to all other five scenarios using post-hoc Wilcoxon signed-rank tests, to evaluate which scenario scored differently from BCT. As this resulted in five tests per group, we corrected for multiple testing by reducing the significance level to $p<0.01$.

Stratified analyses were performed to evaluate whether preferences differed according to history of breast cancer, marital status, age, educational level, employment status, children, baseline VAS score, and stage. We also tested patient preferences using worse versus similar hypothetical prognosis.

Table 1 Baseline characteristics of breast cancer patients and healthy volunteers

	Breast cancer patients (n=71)	**Healthy volunteers (n=50)**
Age	60.1 ± 9.4	56.1 ± 9.4
Marital status		
Single	10 (14.1%)	8 (16.3%)
Living together	6 (8.5%)	5 (10.2%)
Married	48 (67.6%)	30 (61.2%)
Divorced	4 (5.6%)	4 (8.2%)
Widow	3 (4.2%)	2 (4.1%)
Education [a]		
Low [b]	22 (31.0%)	8 (16.3%)
Moderate-high [c]	22 (31.0%)	16 (32.7%)
High [d]	27 (38.0%)	25 (51.0%)
Employment		
Full time	9 (12.7%)	12 (24.5%)
Part time	23 (32.4%)	26 (53.1%)
Unemployed	39 (54.9%)	11 (22.4%)
Children		
0	10 (14.1%)	11 (22.4%)
1	7 (9.9%)	5 (10.2%)
2	35 (49.3%)	21 (42.9%)
≥ 3	19 (26.7%)	12 (24.5%)
TNM stage		
0	16 (22.5%)	NA
I	30 (42.3%)	
II	20 (28.2%)	
III	4 (5.6%)	
IV	1 (1.4%)	
EQ-5D-5L questionnaire		
VAS	0.80 (0.75-0.90)	0.90 (0.80-0.95)
Mobility*	1.43 ± 0.75	1.15 ± 0.46
Self-care*	1.03 ± 0.17	1.06 ± 0.25
Usual activities*	1.44 ± 0.67	1.13 ± 0.44
Pain/discomfort**	1.70 ± 0.79	1.50 ± 0.58
Anxiety/depression**	1.33 ± 0.56	1.19 ± 0.57

VAS visual analogue scale, *NA* not applicable
* 1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, 5: unable
** 1: no(t), 2: slight(ly), 3: moderate(ly), 4: severe(ly), 5: extreme(ly)
[a] Based on the Dutch educational system.
[b] Only primary school or low pre-vocational/secondary general education
[c] Secondary vocational/higher general/pre-university education
[d] Higher vocational education/university

RESULTS

Of the 173 women invited by phone, 169 (97.7%) agreed to participate. The questionnaires were returned by 121 (70%) women (70%). Seventy-one women (59%) had a history of breast cancer (Table 1). Patients were older than healthy volunteers (60.1 vs 56.1 years) and more women with a history of breast cancer were unemployed (54.9% vs. 22.4%). Baseline median VAS scores were lower for breast cancer patients (0.80 vs. 0.90). Most breast cancers were diagnosed in early stages (70.5% stage I and II) or as DCIS (22.5%).TTO and VAS scores were strongly correlated (Spearman correlation coefficient 0.63, $p<0.001$). TTO scores were higher than VAS scores (median 0.90 versus 0.80 respectively).

Overall, BCT was ranked highest and Mast-reconstruction had the lowest VAS score, while the lowest TTO score was given to Ablative boost. However, these differences were small. Post-hoc tests indicated that BCT scored significantly higher than all other scenarios (Table 2 and 3).

Breast cancer patients generally gave higher scores than healthy volunteers. Breast cancer patients preferred BCT to all other treatments. For healthy volunteers, Ablative boost received the highest score, but only in terms of VAS score. The post-hoc test, however, did not indicate a significant difference between the VAS scores of Ablative boost and BCT (Table 2 and 3). This indicates that healthy volunteers gave the highest scores to Ablative boost, but did not significantly prefer Ablative boost over BCT.

BCT remained higher than Mastectomy, Mast-reconstruction and RFA scores, regardless of hypothetical prognosis according to VAS scores. When using scenarios with worse prognosis after minimally invasive treatments, TTO scores were higher for standard treatment (i.e. BCT and Mastectomy). This difference disappeared in scenarios assuming similar prognoses.

BCT was the overall preferred scenario in most subgroups, with some exceptions. In women without children, women with low education level and in breast cancer patients with stage II - IV disease, no preferences for a certain treatment scenario were found in terms of VAS. In terms of TTO scores, younger women, women with a partner, employed women and women with a higher baseline VAS did not report significantly higher scores. Mast-reconstruction was scored significantly lower than BCT in most subgroups (Table 2 and 3).

Table 2 Median visual analogue scale scores and interquartile ranges stratified by baseline characteristics

	Strata	n	BCT	vs	Mastectomy	Mast-reconstr.	RFA	MR-HIFU	Ablative boost	P
All		121	**0.80[§] (0.75-0.90)**		0.80*[§] (0.70-0.88)	0.70* (0.60-0.85)	0.80* (0.65-0.90)	0.80* (0.70-0.90)	0.80* (0.70-0.90)	<0.001
Breast cancer history	Yes	71	**0.90 (0.80-0.90)**		0.80* (0.70-0.90)	0.70* (0.60-0.85)	0.80* (0.65-0.90)	0.80* (0.70-0.90)	0.77* (0.70-0.85)	<0.001
	No	50	0.75 (0.65-0.90)		0.70 (0.60-0.80)	0.73 (0.64-0.85)	0.78 (0.65-0.89)	0.80 (0.70-0.89)	0.80 (0.70-0.90)	0.020
Prognosis after min.-invasive treatments	Similar	54	**0.80 (0.75-0.90)**		0.80* (0.70-0.86)	0.73* (0.60-0.88)	0.80* (0.69-0.90)	0.80 (0.70-0.90)	0.80 (0.69-0.90)	0.001
	Worse	67	**0.80 (0.70-0.90)**		0.80* (0.70-0.90)	0.70* (0.60-0.80)	0.78* (0.65-0.90)	0.78 (0.70-0.90)	0.80 (0.70-0.85)	0.001
Age	< 55 y	50	**0.80 (0.75-0.90)**		0.80* (0.70-0.87)	0.80 (0.70-0.88)	0.80 (0.70-0.90)	0.80 (0.70-0.90)	0.80 (0.74-0.90)	0.017
	≥ 55 y	69	**0.80 (0.73-0.90)**		0.75* (0.60-0.90)	0.70* (0.60-0.80)	0.75* (0.60-0.90)	0.80* (0.70-0.90)	0.70* (0.60-0.84)	<0.001
Marital status	No partner	31	**0.80 (0.70-0.90)**		0.75 (0.70-0.80)	0.70* (0.60-0.85)	0.72* (0.60-0.80)	0.80 (0.70-0.85)	0.80 (0.70-0.90)	0.020
	With partner	89	**0.80 (0.75-0.90)**		0.80* (0.70-0.90)	0.70* (0.63-0.85)	0.80* (0.68-0.90)	0.80* (0.70-0.90)	0.80* (0.70-0.85)	<0.001
Education	Low	30	0.80 (0.70-0.90)		0.80 (0.60-0.86)	0.70 (0.60-0.81)	0.80 (0.60-0.90)	0.75 (0.60-0.90)	0.78 (0.58-0.86)	NS
	High	90	**0.81 (0.75-0.90)**		0.80* (0.70-0.90)	0.75* (0.65-0.85)	0.79* (0.65-0.90)	0.80* (0.70-0.90)	0.80* (0.70-0.89)	<0.001
Employment	No	50	0.80 (0.74-0.90)		0.80* (0.60-0.90)	0.70* (0.60-0.80)	0.70* (0.54-0.83)	0.73* (0.61-0.86)	0.70* (0.58-0.80)	<0.001
	Yes	70	0.80 (0.75-0.90)		0.80* (0.70-0.84)	0.79* (0.70-0.85)	0.80 (0.70-0.90)	0.80 (0.70-0.90)	0.80 (0.72-0.90)	0.002
Children	None	21	0.90 (0.75-0.90)		0.75 (0.70-0.85)	0.80 (0.70-0.88)	0.80 (0.60-0.89)	0.82 (0.70-0.90)	0.85 (0.70-0.90)	NS
	≥ 1	99	**0.80 (0.75-0.90)**		0.80* (0.70-0.90)	0.70* (0.60-0.82)	0.78* (0.65-0.90)	0.78* (0.70-0.90)	0.75* (0.70-0.85)	<0.001
Baseline VAS	< 0.85	56	**0.80 (0.75-0.90)**		0.73* (0.66-0.85)	0.70* (0.60-0.85)	0.74* (0.60-0.85)	0.75* (0.70-0.90)	0.74* (0.70-0.85)	0.001
	≥ 0.85	63	**0.80 (0.70-0.90)**		0.80* (0.70-0.90)	0.70* (0.65-0.82)	0.80 (0.70-0.90)	0.80 (0.70-0.90)	0.80 (0.70-0.90)	0.002
TNM stage	0/I	47	**0.90 (0.80-0.91)**		0.80* (0.70-0.90)	0.70* (0.60-0.80)	0.80* (0.70-0.90)	0.77* (0.70-0.90)	0.70* (0.64-0.80)	<0.001
	II/III/IV	25	0.80 (0.80-0.93)		0.80 (0.70-0.90)	0.80 (0.70-0.89)	0.80 (0.60-0.90)	0.80 (0.68-0.95)	0.80 (0.70-0.95)	NS

NS not significant

* Indicates statistically significant difference between BCT and indicated treatment-outcome scenario (p-value < 0.01 after correction for multiple testing)

Bold visual analogue (VAS) scores indicate preferred treatment-outcome scenario per group (if Friedman test indicated significant difference between treatment-outcome scenarios).

[§] In some cases, the Friedman test indicated significant differences between treatment-outcome scenarios, while median scores and even interquartile ranges (IQRs) were similar. More patients may have given higher VAS scores, resulting in a significant difference, whereas this is not apparent from the displayed median and IQR

DISCUSSION

Patients and healthy women have no pronounced preference for minimally invasive or non-invasive treatments over standard breast cancer treatment. Overall, breast cancer patients give the highest score to the BCT scenario, while women without a history of breast cancer indicated a slight preference for minimally invasive ablative boost radiotherapy.

BCT was the overall preferred scenario. Several explanations for this preference exist. Most breast cancer patients underwent BCT. These patients are likely to have given higher scores to the scenario that they are familiar with. This phenomenon, i.e. recalibration of perception of QoL may result in patients experiencing their health state similar or better after treatment than before. Neuman et al. described this phenomenon in rectal cancer patients with a temporary stoma[22], who reported their QoL to be equal to that of the general population. Others have also reported that QoL of breast cancer patients decreased directly after surgery but returned to pre-surgical values[23,24]. In this study, breast cancer patients even gave higher VAS and TTO scores than healthy women. A second reason for preference of BCT is that breast cancer patients may experience a feeling of security when their tumor is completely removed. Resection margins can be assessed after surgery and patients are sure that no malignant tissue is left. In case of minimally invasive treatments, it is less certain whether the tumor is completely removed. Third, patients who underwent BCT may not find that minimal invasive therapies have added value if they experienced no complications and are satisfied with the cosmetic outcome.

Healthy individuals favoured minimal invasive treatment suggesting they believe these treatments to be less burdensome. This is relevant information, as these women represent future breast cancer patients. However, it is unsure whether this slight preference would translate in an actual choice for minimally invasive treatment, should these women develop breast cancer.

Mastectomy with immediate implant-based reconstruction was rated significantly lower than BCT in breast cancer patients and in virtually all subgroups (not in healthy volunteers). This is consistent with a study by Rowland et al.[25], who compared BCT, mastectomy and mastectomy with reconstruction and assessed the impact on psychosocial wellbeing. Patients who underwent BCT reported least problems with body image and sexual attractiveness compared to women who underwent mastectomy or mastectomy with reconstruction. Mastectomy

with reconstruction did not result in a significantly better body image than mastectomy. However, it should be acknowledged that patients undergoing mastectomy with reconstruction are generally higher risk patients, which may affect their body image.

Expected prognosis (i.e. similar versus higher risk of recurrence or death after minimally invasive treatment) did not clearly affect treatment preference. Probably, participants attributed more value to the procedure itself and were less concerned about a slightly poorer outcome.

Participants over 55 years had a stronger preference for BCT than younger patients. Apparently, they were more open to innovative or new treatment possibilities. Another reason might be that a higher number of older patients had breast cancer (67%) and that the younger group consisted of only 50% of breast cancer patients. A preference for minimally invasive treatments was not found in both subgroups, probably because the patient group of ≥55 years was also relatively young. Older patients of e.g. >70 years may be more interested in minimally invasive treatments, as they often have more comorbidities making surgery a less attractive treatment. This could not be proven in this study due to overall relatively young participants (average <60 years). Being unemployed seemed to result in lower utility scores in general and employed patients did not have a strong treatment preference. Again, the unemployed group contained more breast cancer patients, which may be an explanation for this finding.

TTO scores were overall higher than VAS scores, which is a known phenomenon[26]. In some analyses, TTO and VAS scores gave different results. I.e. the influence of prognosis, age and marital status was different for VAS and TTO scores. Some participants may not feel that treatment-outcome scenarios justified a shorter life expectance when traded for a perfect QoL, and gave all health states a TTO score of 1.

Our study suffers from several limitations. The treatment-outcome scenarios did not consider adjuvant systemic treatment. Comparison between the local treatments was pursued in this study, so description of the (side) effects of systemic therapy was not performed, with the aim to avoid complexity of the treatment-outcome scenarios. It was assumed that the effect of adding systemic therapy would be equal for each treatment-outcome scenario and would only result in more elaborate descriptions that take more time to read for participants. Some participants were unable to adequately fill out the questionnaires, or filled them out incompletely. These patients or healthy volunteers had to be excluded,

possibly introducing selection in favour of well-educated women. Additionally, the described heath states were hypothetical. For some women, it may be hard to imagine what they would experience if this actually occurred to them.

In conclusion, this is the first study assessing patients' hypothetical preferences for minimally invasive versus standard treatment scenarios of early stage breast cancer. We did not find an obvious preference for minimally invasive treatments. Breast cancer patients preferred standard treatments, while healthy women had a slight preference for minimal invasive treatments. This study may be useful to guide future development and innovation of breast cancer therapies.

Table 3 Median time trade off scores and interquartile ranges stratified by baseline characteristics.

	Strata	n	BCT	vs	Mastectomy	Mast-reconstr.	RFA	MR-HIFU	Ablative boost	P
All		121	**0.90[§] (0.80-0.98)**		0.90*[§] (0.80-0.95)	0.85* (0.75-0.95)	0.85* (0.70-0.98)	0.85* (0.70-0.97)	0.85* (0.68-0.97)	0.013
Breast cancer history	Yes	71	**0.95 (0.90-1,00)**		0.90* (0.80-0.95)	0.90* (0.75-0.95)	0.90* (0.70-0.98)	0.88* (0.70-0.98)	0.85* (0.69-0.97)	0.003
	No	50	0.83 (0.80-0.95)		0.80 (0.80-0.95)	0.85 (0.70-0.95)	0.80 (0.64-0.96)	0.85 (0.70-0.95)	0.88 (0.66-0.97)	NS
Prognosis after min.-invasive treatments	Similar	54	0.90 (0.80-0.97)		0.90 (0.76-0.95)	0.86 (0.73-0.95)	0.90 (0.69-0.98)	0.88 (0.70-0.98)	0.90 (0.65-0.98)	NS
	Worse	67	**0.90 (0.80-0.98)**		0.90 (0.80-0.95)	0.85* (0.75-0.95)	0.85* (0.70-0.95)	0.85* (0.70-0.95)	0.85* (0.70-0.95)	0.036
Age	< 55 y	50	0.90 (0.80-0.95)		0.90 (0.80-0.95)	0.90 (0.82-0.95)	0.90 (0.79-0.98)	0.90 (0.80-0.97)	0.90 (0.84-0.98)	NS
	≥ 55 y	69	0.90 (0.80-1.00)		0.85* (0.71-0.95)	0.80* (0.68-0.96)	0.80* (0.61-0.98)	0.85* (0.70-0.97)	0.78* (0.60-0.95)	0.001
Marital status	No partner	31	**0.90 (0.80-0.98)**		0.80 (0.70-0.90)	0.80* (0.65-0.90)	0.80* (0.60-0.98)	0.85 (0.60-0.99)	0.85 (0.70-0.97)	0.037
	With partner	89	0.90 (0.80-0.98)		0.90 (0.80-0.95)	0.90 (0.75-0.95)	0.90 (0.70-0.98)	0.86 (0.70-0.96)	0.85 (0.65-0.97)	NS
Education	Low	30	0.90 (0.80-0.95)		0.85 (0.70-0.95)	0.80 (0.69-0.95)	0.87 (0.63-0.96)	0.87 (0.59-0.96)	0.80 (0.54-0.94)	NS
	High	90	**0.90 (0.80-0.98)**		0.90 (0.80-0.95)	0.88* (0.75-0.95)	0.85* (0.70-0.98)	0.85* (0.70-0.97)	0.85* (0.70-0.97)	0.015
Employment	No	50	**0.90 (0.80-1.00)**		0.87 (0.75-0.98)	0.80* (0.69-0.98)	0.75* (0.60-0.96)	0.78* (0.69-0.96)	0.70* (0.50-0.90)	<0.001
	Yes	70	0.90 (0.80-0.95)		0.90 (0.80-0.95)	0.90 (0.79-0.95)	0.90 (0.79-0.98)	0.90 (0.80-0.97)	0.90 (0.78-0.98)	NS
Children	None	21	0.85 (0.80-0.97)		0.80 (0.79-0.93)	0.85 (0.68-0.95)	0.80 (0.60-0.97)	0.85 (0.68-0.97)	0.90 (0.67-0.98)	NS
	≥ 1	99	**0.90 (0.80-0.98)**		0.90* (0.80-0.95)	0.90* (0.75-0.95)	0.85* (0.70-0.98)	0.85* (0.70-0.97)	0.85* (0.66-0.97)	0.039
Baseline VAS	< 0.85	56	**0.90 (0.80-0.98)**		0.90* (0.75-0.95)	0.90* (0.70-0.96)	0.83* (0.64-0.98)	0.85* (0.62-0.97)	0.82* (0.61-0.97)	0.019
	≥ 0.85	63	0.90 (0.80-0.98)		0.90 (0.80-0.95)	0.85 (0.75-0.90)	0.85 (0.70-0.97)	0.85 (0.70-0.97)	0.90 (0.70-0.97)	NS
TNM stage	0/I	47	**0.95 (0.90-1.00)**		0.90* (0.80-1.00)	0.85* (0.75-0.98)	0.85* (0.70-1.00)	0.85* (0.70-1.00)	0.80* (0.63-0.98)	<0.001
	II/III/IV	25	0.90 (0.83-0.95)		0.90 (0.81-0.95)	0.90 (0.80-0.95)	0.90 (0.73-0.95)	0.90 (0.80-0.97)	0.90 (0.70-0.96)	NS

NS: not significant

* Indicates statistically significant difference between BCT and indicated treatment-outcome scenario (p-value < 0.01 after correction for multiple testing)

Bold time trade off (TTO) scores indicate preferred treatment-outcome scenario per group (if Friedman test indicated significant difference between treatment-outcome scenarios).

[§] In some cases, the Friedman test indicated significant differences between treatment-outcome scenarios, while median scores and even interquartile ranges (IQRs) were similar. More patients may have given higher TTO scores, resulting in a significant difference, whereas this is not apparent from the displayed median and IQR.

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CHAPTER 9

Summary and general discussion

This thesis describes a first step of minimally invasive treatment application in breast cancer patients and focuses on patient selection for these therapies. Development and technical optimisation of minimally invasive treatments is just as important as accurate patient selection.

In **Part I**, studies regarding of the use of minimally invasive treatments in a research setting are described. The results of magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) ablation with a dedicated breast system are presented first. Because more clinical studies will be required to assess its efficacy, reliable outcome assessment in the research setting remains important. The histopathological appearance of ablated tissue with MR-HIFU and radiofrequency ablation (RFA) was evaluated as a guideline for pathologists involved in minimally invasive treatment studies. The clinical introduction of a new treatment relies on efficacy, but also on cost-effectiveness. The costs of MR-HIFU ablation were compared with costs of conventional breast-conserving treatment (BCT) using data from the clinical MR-HIFU study combined with model- and expert-based estimations.

Several aspects of patient selection are described in **Part II**. In previous research, treatment results of minimally invasive therapies, including MR-HIFU ablation and RFA, were promising, but far from perfect[1-4]. Based on these studies it was concluded that technical issues still needed to be solved and even more importantly, patient selection should improve[5]. Therefore, this thesis aimed at pre-treatment assessment of several factors influencing treatment results. Additionally, the value of pre-treatment breast magnetic resonance imaging (MRI) in breast cancer was evaluated, emphasising the increasingly important role of MRI in breast cancer care. The increasing number of treatment possibilities and patient desire for shared decision making indicate that patient selection should not only be based on characteristics of their cancers, but also on patient preferences. Therefore, the preference of patients for different treatment options was assessed.

PART I - MINIMALLY INVASIVE TREATMENT OF BREAST CANCER PATIENTS

MR-HIFU ablation

The first clinical experience using the dedicated MR-HIFU breast system is presented in **Chapter 2**. The purpose of this study was to assess the safety and feasibility of MR-HIFU ablation. Ten patients underwent partial tumour ablation and surgical resection two to ten days later. Partial tumour ablation was performed to enable analysis of the size and location of the separate sonications. Furthermore, viable tumour tissue was still available for histopathological examination after surgery so that tumour grade and receptor status could be determined. Treatments were performed under deep sedation with propofol and Esketamine. This study showed that MR-HIFU ablation is feasible. However, in some patients sonications were aborted prematurely due to patient motion or a changed breathing pattern resulting in unreliable thermometry. Tissue necrosis was found in six patients. In two of the four patients without necrosis in the tumour, fat cell necrosis in proximity of the tumour was found. In one patient this pointed to incorrect focal point adjustment after the test sonication and in the other patient the tumour was not reachable for the HIFU beams because of proximity to the pectoral muscle. In one patient the only performed sonication was aborted too early to result in necrosis due to patient movement. One patient unfortunately refused to undergo surgery. Only minor adverse events occurred; in one patient three small white lumps appeared on the skin after treatment and resolved without intervention, two patients experienced nausea and vomiting and two patients experienced pain. No major adverse events occurred. Only a few sonications were performed in all patients. Therefore, this study does not guarantee safety of MR-HIFU ablation when aiming for total tumour ablation. More sonications would have to be performed, possibly increasing the risk of overheating. A drawback of MR-HIFU ablation was the long duration of the procedure, on the average 145 minutes. However, the actual sonication time was only 1.7 minutes, indicating that optimising imaging protocols is most likely to result in shorter treatment durations. For example, the method used to correct for breathing artefacts (look-up table-based) was time consuming[6]. Treatment results were evaluated with contrast-enhanced MRI. Necrotic tissue is non-perfused and therefore expected to be visible as non-enhancing tissue on contrast enhanced MRI. However, this was not observed. Directly after ablation, contrast material may leak into the interstitial

space, mimicking contrast enhancement. This is corroborated in a previous study[2]. Another reason may be that no high spatial resolution MRI was performed and the used treatment cells were small. Although a large amount of information was obtained during the first MR-HIFU breast study, many aspects of MR-HIFU ablation need to be optimised before MR-HIFU ablation can become a treatment possibility for breast cancer patients. More experience with MR-HIFU ablation is required to obtain information about optimal treatment parameters, to optimise imaging during the procedures and to improve the workflow.

Histopathology after ablation

In **Chapter 3** the histopathological changes in tumour tissue following ablation with MR-HIFU ablation and RFA were evaluated and compared. Partial tumour ablation as performed in **Chapter 2** allowed for within patient comparison of histopathological differences between ablated and viable tumour tissue. In the RFA study of Waaijer et al. some tumours were partially ablated as well[7]. The tissue obtained in these studies was used for the analyses. In addition, MR-HIFU ablation and RFA were performed ex vivo in fresh mastectomy specimens. Tissue was both stained with haematoxylin and eosin (H&E) for evaluation of morphology and cytokeratin-8 (CK-8) for evaluation of viability. The ex vivo ablations resulted in severe tissue deformations after RFA, while only mild changes were visible after MR-HIFU ablation. The very subtle changes after ex vivo MR-HIFU ablation can be explained by heat fixation, which occurs in tissues exposed to rapid and high and enough temperature increase to induce apoptosis but not to completely deform the tissue. The tissue appears morphologically undamaged, while CK-8 staining is already absent, meaning that the apoptosis cascade is initiated[8]. CK-8 staining was absent or decreased after ex vivo ablation with both RFA and MR-HIFU, indicating apoptosis. The in vivo results were similar to the ex vivo findings for RFA. More changes with necrotic-appearing tumour cells were seen after in vivo compared to ex vivo MR-HIFU ablation. Remarkably, these necrotic cells did not lack CK-8 staining. These differences are probably due to time. After in vivo MR-HIFU ablation, surgical excision was performed after three to six days. In vivo RFA was performed in the operation room just prior to surgical excision. The transition zone between damaged and viable tissue was large after RFA and small after MR-HIFU ablation, due to differences in technique. After RFA, some areas of the tumour are heated to higher temperatures resulting in direct tissue deformations. The findings of this study contribute to improvement of result evaluation in clinical trials on minimally

invasive treatment and can be considered a guideline for pathologists involved in ablative treatments.

Cost-effectiveness of MR-HIFU ablation

If minimally invasive treatments were to replace surgical treatment, its results in terms of tumour treatment or patient satisfaction should be equal or better than surgical treatment. Another important aspect for introducing new treatments is cost-effectiveness. In **Chapter 4** an early health technology assessment was performed to evaluate the costs of MR-HIFU ablation in comparison with BCT. As the clinical experience with MR-HIFU ablation is very limited, models were developed to estimate the treatment costs of MR-HIFU ablation for different tumour sizes. The effect of several treatment related features on these costs was quantified. Because no real data exists on the efficacy of MR-HIFU ablation, its efficacy was considered equal to BCT. Model input consisted of data from literature, questionnaires answered by MR-HIFU users and data from the aforementioned MR-HIFU ablation study. The costs of MR-HIFU ablation were higher than the costs of BCT. However, when using the largest available treatment cells and considering the most favourable treatment parameters, the difference between the two treatments is approximately €1000, which may be considered acceptable if MR-HIFU ablation has benefits over BCT, such as a better cosmetic outcome and less complications. The factors that had most effect on costs were the time required for breathing correction and the cooling time after each sonication that is considered necessary to guarantee safety. The latter could therefore be decreased, when safety of shorter cooling times could be proven. In general, using the MRI scanner is costly, meaning that the longer the treatment duration is, disregarding for which reason, the more a treatment would cost. One should bear in mind that the results of this study are estimations. This early health technology assessment is a first step in analysing the costs of MR-HIFU ablation, but should be verified if more clinical data is available. Cost-effectiveness of MR-HIFU ablation is not demonstrated, nor can be excluded.

PART II - PATIENT SELECTION FOR MINIMALLY INVASIVE TREATMENT

Pre-treatment breast MRI

Whether breast MRI should be performed prior to surgical treatment in breast cancer patients has been a matter of debate since breast MRI became available. Breast MRI has a sensitivity of at least 90%. However, the specificity of breast MRI is approximately 70%, and breast MRI often results in false-positive findings[9,10]. Because of its high sensitivity, MRI is useful for detecting additional lesions in patients with breast cancer[11,12]. Furthermore, MRI is as accurate as histopathology in measuring tumour size[13]. However, pre-operative MRI has never been proven to reduce re-excision rates or to improve long-term outcome in the breast cancer population eligible for BCT[14,15]. Trials with long enough follow-up to prove or rule out benefit of breast MRI on overall survival are currently not available. **Chapter 5** presents which patients are likely to benefit from pre-operative MRI. The amount of consensus in the literature was used to determine for which patients MRI is beneficial. The diffuse growth pattern of invasive lobular cancer results in underestimation of lesion size on conventional imaging and an increased risk of positive resection margins[16]. In these patients, the use of pre-operative breast MRI has been associated with a lower risk of re-excision[17]. Invasive lobular cancer was therefore considered an important indication for MR imaging. There was moderate consensus in literature about whether MRI should be performed in patients in whom conventional imaging with mammography and ultrasound is inconclusive about tumour extent. Besides these current clinical indications, breast MRI may be suitable as a patient selection tool in minimally invasive treatment studies. The superiority of MRI in assessing tumour size, shape and location makes MRI the modality of choice for assessing eligibility. Moreover, MRI is most accurate in establishing size of smaller tumours, which is the population eligible for minimally invasive treatments[18].

Another purpose of pre-treatment MRI may be detection of the presence of an extensive intraductal component (EIC) or extensive ductal carcinoma in situ (E-DCIS), which is a risk factor for incomplete resection and considered a contra-indication for minimally invasive treatment. The risk of leaving malignant tissue untreated is increased, because DCIS is not always detected by MRI[19]. Therefore, histopathological margin assessment is desired in patients with E-DCIS. With

minimally invasive treatments, the presence of E-DCIS should ideally be assessed prior to treatment so that patients can be referred for surgery instead. In **Chapter 6** a prediction model for E-DICS is described. A margin of 1 cm around the tumour was automatically segmented on MR images. After MR imaging, patients underwent wide local excision. Positive resection margins were significantly more frequently found in patients with E-DCIS. Early and overall enhancement in the tumour margin and a positive human epidermal growth factor receptor 2 (HER2) status and higher amount of fibroglandular tissue around the tumour were associated with presence of E-DCIS. Besides patient selection for minimally invasive treatment, the prediction model may be useful for guidance of surgical therapy. Especially in case of low predicted risk of E-DCIS, local excision with an intended margin of 1 cm would be sufficient. If the risk of E-DCIS is high, excision with wider margins could be performed. However, the predictive value is not high enough to completely rely on the model. Additional techniques such as intraoperative margin assessment could be added to prevent unnecessary wide excisions[20].

Tumour grading on biopsy

Without a surgical excision specimen after minimally invasive treatment, most tumour characteristics required for assessment of the indication for adjuvant treatment have to be assessed on core needle biopsy (CNB). In **Chapter 7** the concordance between tumour grading on CNB and on excision specimen was assessed in a meta-analysis. In 71.1% of cancers tumour grade assessed on CNB was concordant with that of the surgical excision specimen. Underestimation by CNB occurred in 19.1%. Overestimation occurred less frequently (9.3%). The most probable explanation of incorrect grade assessment on CNB is undersampling. Due to tumour heterogeneity, tumour grade may differ within tumours. With CNB, only a limited amount of tissue is obtained[21]. In case of minimally invasive therapy, only tumour grade assessed on CBN will be available. Even though there is substantial discordance between grading on CNB and excision specimen, it is similar to the inter-observer agreement between pathologists assessing grade on surgical excision specimens[22,23]. In the studies included in this meta-analysis, disagreement between pathologists was obviously present as well. Both tumour grade assessed on the biopsies and on the excision specimen they were compared to must have been affected by this inevitable problem. As a result, the real extent of disagreement between tumour grade assessed on CNB and excision specimen can not exactly be measured and varies with the accuracy of pathologists. Adjuvant

systemic therapy is determined by more factors besides tumour grade, such as receptor status and tumour size. As a result, clinical consequences of incorrect tumour grading, e.g. erroneously omitting systemic therapy, do not occur as often as the actual disagreement according to a small number of studies ,Waaijer et al. showed that incorrect tumour grading results in undertreatment in only 1.5% and overtreatment in 3.5%[24]. Schmitz et al. showed that disagreement on the indication for systemic therapy exists in a higher proportion (11% of patients) if all factors that determine the indication for systemic therapy are assessed on CNB[25]. Postma et al. showed that the current discordance between pathologists may affect the indication for systemic treatment in 5%[22]. Meaning that in 5% of patients systemic therapy is currently wrongly administered or omitted. In conclusion, the number of patients who would possibly be harmed by only assessing the indication for systemic therapy on CNB is not negligible, but probably comparable to the current clinical situation. Larger studies are required to determine how many patients would be under- or overtreated if only CNB is used and if this would be considered acceptable. Besides, other risk stratification tools may be added for the assessment of the indication for adjuvant therapy, for example multigene arrays such as MammaPrint®. The MINDACT study has proven that MammaPrint® is able to prevent overtreatment with chemotherapy in patients who would currently undergo chemotherapy based on biological and clinical factors[26].

Patient preferences

The minimally invasive treatments described in this thesis are still in an early phase of development, which was initiated by doctors and the health care industry. An important issue is whether patients are actually interested in undergoing these treatments. If so, which patients are most interested? These questions preferably would have been answered before minimally invasive treatments were introduced. In **Chapter 8**, both breast cancer patients and healthy volunteers were asked to value six hypothetical treatment-outcome scenarios using visual analogue scale (VAS) and time trade off (TTO). Treatment, clinical sequelae and prognosis were described for mastectomy, mastectomy with direct implant-based reconstruction, BCT, RFA[7], MR-HIFU ablation **(Chapter 2)** and single dose ablative radiotherapy[27]. BCT was the most preferred treatment option for breast cancer patients. This may partly be explained by the fact that former breast cancer patients prefer BCT because they are familiar with this treatment. The participants without a history of breast cancer were more interested in minimally invasive treatments. In this study, it

became clear that women have different opinions and perspectives, emphasising the importance of an active role in their treatment choice. Offering patients the possibility to be involved in decision-making increases their knowledge and gives them the idea that their opinion influences their treatment[28]. Besides, physicians are not accurate in predicting the choice of patients, emphasising the importance of an active role of patients[29,30]. Hence, the opinion of the patient is one of the most important selection criteria.

CONCLUSIONS AND FUTURE PERSPECTIVES

The MR-HIFU breast study indicated that partial ablation of breast cancer is feasible and safe. An important benefit of the treatment is non-invasiveness. This study was the first step in the development of MR-HIFU ablation, the next step is assessment of the efficacy of the treatment. A second MR-HIFU breast study has therefore been developed and approved by the medical ethical committee of the University Medical Center of Utrecht in January 2015. The purpose of the second MR-HIFU study is total tumour ablation. Treatment outcome will be assessed on MRI and histopathology. Tumour grade and receptor status will be assessed on CNB prior to treatment. MRI will be used to measure tumour size and exclude additional disease. Because MR-HIFU ablation is not expected to alter lymph drainage in the breast, the sentinel lymph node procedure will be performed during surgery. In future studies without resection, lymph node status will be assessed in a separate sentinel lymph node procedure. Another possibility may be lymph node assessment on 3 or 7 tesla (T) MRI with dedicated imaging protocols, such as T2-weighted imaging and diffusion weighted imaging (DWI)[31,32]. MRI may also be a reliable option for the detection of residual disease, if performed at least one week after MR-HIFU treatment. A thin rim of delayed enhancement around the ablated area on subtraction images has been suggested to indicate complete ablation. This rim enhancement indicates formation of fibrotic tissue around the ablated area. Irregular or nodular early enhancement may indicate residual disease[2,33]. The appearance of ablated tissue on MRI will be further assessed in the second MR-HIFU breast study. Patient recruitment for the second MR-HIFU breast study has not been successful so far, which indicates how hard innovation is when an excellent treatment possibility already exists. Another possible application for MR-HIFU is local drug delivery. Thermo-sensitive liposomes containing a cytostatic

drug are intravenously administered while hyperthermia is generated by MR-HIFU in the tumour area, resulting in release of the chemotherapeutic agent[34,35]. This method may be used in a neoadjuvant setting. The most important improvement to be made is reducing the MR-HIFU treatment duration. Prolonged treatment duration results in patient discomfort and higher treatment costs. Furthermore, the currently used thermometry method is only possible in aqueous tissues such as glandular tissue. Thermometry is difficult in fatty breasts with a small tumour. In addition, real-time temperature measurement close to the skin is not possible because of the subcutaneous adipose tissue. Being able to perform thermometry in the adipose tissue may reduce the treatment duration because shorter cooling times after each sonication may be applied if the actual temperature outside the treatment region can be monitored. Possibilities to do so are T2-weighted thermometry[36,37] or a hybrid method to provide thermometry in fat and adipose tissue at the same time[38,39]. Both H&E and CK-8 staining are required for adequate evaluation of the treatment results and will be used during the second MR-HIFU breast study. Cost-effectiveness of MR-HIFU ablation was not proven. However, substantial data required for cost-effectiveness assessment was lacking and had to be estimated, which probably influenced the results. In the future, effect on quality of life should be incorporated. The VAS and TTO scores obtained in the patient preference study could be useful in future analysis. Real data on treatment efficacy and effect on quality of life is currently most required for the further development of MR-HIFU ablation and other minimally invasive treatment options.

Patients considered most eligible for minimally invasive treatment are patients with early-stage and low-risk breast cancer of the ductal subtype without surrounding DCIS. The risk of incomplete treatment should be as low as possible, because positive treatment margins increase the risk of local recurrence[40]. No surgical excision specimen is available after minimally invasive treatment, all parameters on which the indication for adjuvant therapy is based consequently have to be assessed on CNB and MRI before treatment. If eligibility or the indication for adjuvant therapy cannot be determined with certainty, a patient should be excluded for minimally invasive treatment. The studies presented in this thesis were performed to evaluate or improve pre-treatment assessment of tumour grade, presence of E-DCIS and patient preferences. Tumour grade assessment on CNB corresponds moderately with excision specimens. However, the risk of under- or overtreatment due to incorrect grading is probably limited. Nevertheless,

some physicians advocate using additional tools for grade assessment. DWI and spectroscopy on high field strength MRI (7T) may be associated with tumour grade and may increase the accuracy of assessing the indication for adjuvant chemotherapy[41]. Furthermore, MammaPrint® is likely to be added for indication assessment of adjuvant chemotherapy in the future due to the positive results recently reported in the MINDACT study[26].. MRI can reliably be used to assess tumour size and may also be useful in the detection of E-DCIS in combination with certain tumour characteristics. Patients with E-DCIS should be identified because the risk of incomplete treatment is increased and evaluation of resection margins is desired. The developed model for prediction of E-DCIS could be improved by adding the presence of DCIS on the diagnostic CNB. Furthermore, adding high-resolution DWI to pre-operative MRI protocols may improve the detection of E-DCIS, because high-resolution images of a targeted area can be obtained[42]. Treatment preference of the patient is important and indicates whether minimally invasive treatments are in demand. Patients who already underwent BCT would prefer this treatment to minimally invasive treatments, while healthy women had a preference for minimally invasive treatments. Other selection criteria may be age or comorbidities. Elderly patients with comorbidities may be physically unable to undergo surgery.

Whether minimally invasive treatments will be successful in the future depends on many factors. First and foremost, patients should be willing to undergo these treatments. However, when clinical data is lacking, it is hard for patients to decide if they do. Clinical trials on minimally invasive treatments are hard to perform and require a lot of patience from the researcher. These treatment options are often not technically optimized enough to prove satisfying efficacy in an early phase of development, because more data is required to be able to optimize the treatment. This data will not be obtained if patients and researchers do not believe in the treatment, for example due to a disappointing initial efficacy or side effects. Besides, minimally invasive treatments compete with a very reliable and well-established treatment option, BCT. On the other hand, even less than 60 years ago, BCT was also not considered a treatment option yet and all breast cancer patients had no other choice than to undergo a treatment now considered very mutilating.

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CHAPTER 10

Nederlandse samenvatting

Beeldgestuurde behandeling van borstkanker: een patiëntgerichte benadering van minimaal invasieve therapie

Borstkanker is de meest voorkomende kankersoort bij vrouwen en elk jaar worden wereldwijd ongeveer 1,7 miljoen vrouwen geconfronteerd met de diagnose borstkanker[1,2]. De ziekte komt steeds vaker voor en in Nederland wordt jaarlijks bij 14.500 vrouwen borstkanker ontdekt. Nederlandse vrouwen hebben 12 tot 13% kans om ooit borstkanker te krijgen. De toename wordt met name veroorzaakt doordat de bevolking steeds ouder wordt[3,4]. Door het nationale screeningsprogramma wordt borstkanker steeds vaker ontdekt in een vroeg stadium, als het nog een goede prognose heeft[5,6].

De prognose van borstkanker wordt beïnvloed door meerdere factoren, zoals hormoonreceptor status, borstkanker stadium ten tijde van de diagnose, histologisch type, tumorgraad en de leeftijd van de patiënt[7-12]. Het merendeel van deze factoren wordt gebruikt om vast te stellen of de patiënt een hoog risico heeft op metastasen en of systemische behandeling dus noodzakelijk is.

Het doel van de behandeling van borstkanker is het volledig verwijderen van de tumor, om het risico op recidief en metastasen op afstand zo klein mogelijk te maken. Momenteel wordt mammasparende behandeling (MST) het meest gebruikt bij vroeg-stadium borstkanker. Dit proefschrift is gericht op deze patiëntenpopulatie. MST behandeling bestaat uit partiële resectie van de borst en adjuvante radiotherapie en in sommige gevallen adjuvante chemo- en/of hormoontherapie. Tijdens de operatie wordt ook een schildwachtklierprocedure uitgevoerd[4].

De behandeling van borstkanker wordt steeds meer aangepast aan de individuele patiënt. Met andere woorden, er is een verandering gaande in de borstkankerzorg richting een meer patiëntgerichte benadering. Omdat het aantal patiënten met vroeg-stadium borstkanker toeneemt, wordt het steeds duidelijker dat sommige patiënten mogelijk worden overbehandeld[13,14]. Het cosmetisch resultaat van MST is suboptimaal bij een niet-verwaarloosbaar aantal patiënten. Daarnaast komen chirurgische complicaties, zoals bloedingen of infecties, regelmatig voor[15]. Om deze redenen zijn tijdens de afgelopen jaren meerdere minimaal invasieve behandeltechnieken ontwikkeld.

Dit proefschrift beschrijft de eerste stap in de toepassing van minimaal invasieve behandelingen bij borstkankerpatiënten en richt zich op patiëntenselectie voor deze therapieën. De ontwikkeling en technische optimalisatie van minimaal invasieve behandelingen is namelijk net zo noodzakelijk als goede patiëntenselectie.

In **Deel I** worden studies beschreven waarin minimaal invasieve behandelingen worden toegepast. Eerst worden de resultaten van ablatie met magnetic resonance-geleide hoog intensiteit gefocust ultrageluid (MR-HIFU) gepresenteerd. Daarna worden de effecten van ablatie met MR-HIFU en radiofrequente ablatie (RFA) op borstkankerweefsel beschreven. De resultaten van deze studie kunnen worden beschouwd als een leidraad voor pathologen die meewerken aan onderzoek met minimaal invasieve behandelingen. Klinische introductie van een nieuwe behandeling vindt alleen plaats als de effectiviteit van die behandeling goed is, maar hangt ook af van de kosteneffectiviteit van die behandeling. Daarom worden de kosten van MR-HIFU ablatie vergeleken met die van MST.

Een aantal aspecten van patiëntenselectie wordt beschreven in **Deel II**. Eerdere studies laten veelbelovende resultaten van minimaal invasieve behandelingen zoals MR-HIFU ablatie en RFA zien, maar deze resultaten zijn verre van perfect[16-19]. Uit deze studies werd geconcludeerd dat technische problemen moeten worden opgelost, maar dat het verbeteren van patiëntenselectie minstens net zo belangrijk is[20]. Dit proefschrift richt zich daarom op het voorafgaand aan de behandeling detecteren van factoren die de behandelresultaten en dus de geschiktheid van patiënten voor minimaal invasieve behandelingen beïnvloeden. Daarnaast wordt de waarde van magnetic resonance imaging (MRI) voorafgaand aan borstkankerbehandeling geëvalueerd. De rol van MRI wordt namelijk steeds groter in de borstkankerzorg. Het toenemend aantal behandelmogelijkheden voor borstkanker en de wens van patiënten om meer betrokken te zijn bij hun therapiekeuze geeft aan dat de behandeling niet alleen moet worden gebaseerd op het type borstkanker, maar ook op de voorkeur van de patiënt zelf. Daarom zijn tot slot de voorkeuren van patiënten voor verschillende behandelopties onderzocht in dit proefschrift.

DEEL I – MINIMAAL INVASIEVE BEHANDELING VAN BORSTKANKERPATIËNTEN

MR-HIFU ablatie

In **Hoofdstuk 2** wordt de eerste klinische ervaring met een MR-HIFU systeem beschreven dat speciaal is ontwikkeld voor de behandeling van borstkanker. Het doel van deze studie was om te evalueren of MR-HIFU ablatie haalbaar en veilig is. Tien patiënten ondergingen ablatie van een gedeelte van hun tumor en werden twee tot tien dagen later geopereerd. De behandelingen werden uitgevoerd onder diepe sedatie. De studie liet ten eerste zien dat MR-HIFU behandeling haalbaar is. Wel werden enkele sonicaties vroegtijdig afgebroken omdat de patiënt bewoog of het ademhalingspatroon veranderde, waardoor de thermometrie onbetrouwbaar - en dus onveilig – werd. Het beoogde therapie effect van MR-HIFU ablatie, necrose van tumorweefsel, werd bij zes patiënten bereikt. Deze studie toonde ten tweede aan dat MR-HIFU ablatie veilig is. Er zijn alleen milde en geen ernstige complicaties opgetreden. Omdat er maar een paar sonicaties per patiënt zijn uitgevoerd, bewijst deze studie echter niet dat MR-HIFU ablatie veilig is voor volledige tumor ablatie. Daarvoor zouden meer sonicaties moeten worden uitgevoerd, wat het risico op oververhitting verhoogt. Een nadeel van MR-HIFU ablatie is de lange duur van de behandeling; gemiddeld 145 minuten. Hiervan werden slechts 1,7 minuten besteed aan het verhitten van tumorweefsel met sonicaties. Dit betekent dat optimalisatie van behandelprotocollen nodig is om de behandeltijd te verkorten. De behandelresultaten werden ook geëvalueerd met contrast-MRI. In (geableerd) necrotisch weefsel is geen perfusie aanwezig. Naar verwachting resulteert dit in een niet-aankleurend gebied op contrast-MRI, maar dit was niet het geval. Mogelijk lekte het contrastmiddel in het interstitium direct na behandeling, wat hetzelfde imponeert als aankleuring. Dit werd bevestigd in een eerdere studie[18]. Een andere reden zou kunnen zijn dat de spatiële resolutie van de gebruikte MRI te laag was. De behandeling werd uitgevoerd met kleine behandelcellen waardoor deze mogelijk niet zichtbaar waren op MRI. Ondanks de grote hoeveelheid informatie die de eerste MR-HIFU studie heeft opgeleverd, moeten nog veel aspecten van MR-HIFU behandeling worden geoptimaliseerd voordat MR-HIFU ablatie een behandeloptie wordt. Er is meer ervaring nodig met MR-HIFU ablatie om informatie te verkrijgen over de optimale behandelparameters, de beeldvorming tijdens de procedure te optimaliseren en de workflow te verbeteren.

Histopathologie na ablatie

In **Hoofdstuk 3** worden de histopathologische veranderingen in borstkankerweefsel na MR-HIFU ablatie en RFA geëvalueerd en vergeleken. Gedeeltelijke ablatie, zoals wordt beschreven in **Hoofdstuk 2**, zorgde ervoor dat histopathologische verschillen tussen geableerd en levend tumor weefsel binnen patiënten konden worden vergeleken. In de RFA studie van Waaijer et al. zijn ook enkele tumoren gedeeltelijk geableerd[21]. Het weefsel dat werd verkregen in deze studie werd gebruikt voor de analyses. Daarnaast werd MR-HIFU ablatie en RFA ex vivo uitgevoerd in zes verse mastectomie preparaten. De ex vivo ablaties resulteerden in duidelijke veranderingen in het weefsel na RFA, terwijl na MR-HIFU ablatie alleen subtiele veranderingen zichtbaar waren. De minimale veranderingen na MR-HIFU ablatie kunnen worden verklaard door hittefixatie. Dit houdt in dat weefsel wordt blootgesteld aan voldoende temperatuurstijging om de apoptosecascasde te activeren, maar niet te leiden tot deformatie van het weefsel. Morfologisch ziet het weefsel er dan intact uit, terwijl viabiliteitskleuringen (cytokeratine-8 (CK-8)) schade aantonen[22]. De in vivo resultaten voor RFA waren nagenoeg gelijk aan de ex vivo resultaten. Na in vivo MR-HIFU ablatie werden opvallend genoeg meer verschillen gevonden. De tumorcellen hadden een necrotisch aspect, terwijl ze wel CK-8 positief waren. Waarschijnlijk zijn deze verschillen ontstaan doordat resectie van in vivo MR-HIFU geableerd weefsel plaats vond na drie tot zes dagen, terwijl dit voor RFA direct na de ablatie gebeurde. De overgangszone tussen levend en geableerd weefsel was smal na MR-HIFU ablatie en breed na RFA, doordat RFA de tumor van binnenuit verhit en MR-HIFU achtereenvolgens meerdere kleine gebieden ableert. Bovendien gebruikt RFA veel hogere temperaturen dan MR-HIFU ablatie, wat leidde tot meer weefseldeformatie. De resultaten van deze studie dragen bij aan betere evaluatie van de resultaten van klinische studies met minimaal invasieve behandelingen en kunnen worden beschouwd als een richtlijn voor pathologen die betrokken zijn bij deze studies.

Kosteneffectiviteit van MR-HIFU ablatie

Minimaal invasieve behandelingen kunnen alleen de huidige chirurgische behandelingen vervangen als de behandelresultaten en de kwaliteit van leven minimaal even goed zijn als na chirurgie. Een ander belangrijk aspect voor de introductie van nieuwe behandelingen is kosteneffectiviteit. In **Hoofdstuk 4** werd een vroege health technology assessment uitgevoerd om de kosten van

MR-HIFU ablatie en MST te vergelijken. Omdat er nog te weinig bekend is over de effectiviteit van MR-HIFU ablatie, werd voor deze studie aangenomen dat de effectiviteit van MR-HIFU ablatie en MST hetzelfde is. Door middel van modellen werden de kosten van MR-HIFU ablatie uitgerekend. De input voor deze modellen was gebaseerd op de literatuur, resultaten van de eerste MR-HIFU ablatie studie en vragenlijsten ingevuld door MR-HIFU experts. De kosten van MR-HIFU ablatie zijn hoger dan die van MST. Als de grootst mogelijke behandelcel werd gebruikt in combinatie met de meest optimistische behandelparameters, was het verschil tussen MR-HIFU ablatie en MST ongeveer €1000. Dit zou acceptabel kunnen zijn als MR-HIFU ablatie duidelijke voordelen zou hebben ten opzichte van MST, bijvoorbeeld een beter cosmetisch resultaat of minder complicaties. De kosten werden met name beïnvloed door de tijd die nodig was voor de correctie van ademhalingsartefacten en de afkoeltijd na de sonicaties. De kosten zouden significant lager worden als dit beperkt kan worden, als bijvoorbeeld wordt aangetoond dat kortere afkoeltijden ook veilig zijn. Het is belangrijk om te realiseren dat de resultaten van deze studie schattingen zijn. Deze vroege health technology assessment is de eerste stap in het analyseren van de kosten van MR-HIFU ablatie, maar moet worden bevestigd met toekomstige klinische data. Kosteneffectiviteit met MR-HIFU ablatie is daarom hiermee niet aangetoond, maar ook niet uitgesloten.

DEEL II – PATIËNTENSELECTIE VOOR MINIMAAL INVASIEVE BEHANDELING

Preoperatieve MRI bij borstkanker

Al sinds MRI beschikbaar is, wordt er gediscussieerd over of borstkankerpatiënten een MRI zouden moeten ondergaan voorafgaand aan hun behandeling. MRI heeft een sensitiviteit van minimaal 90% voor de detectie van borstkanker. Daar staat tegenover dat de specificiteit slechts ongeveer 70% is, waardoor MRI vaak leidt tot vals-positieve bevindingen[23,24]. Door de hoge sensitiviteit is MRI bruikbaar voor het vaststellen van additionele laesies in patiënten bij wie borstkanker is gediagnosticeerd[25,26]. Daarnaast is MRI net zo precies als de patholoog voor het vaststellen van de tumorgrootte[27]. Desondanks is het nooit bewezen dat preoperatieve MRI het aantal reëxcisies vermindert of de lange-termijn prognose verbetert in de borstkankerpopulatie die geschikt is voor MST[28,29]. Er bestaan

momenteel geen studies waarin de follow-up lang genoeg is om mogelijke positieve effecten van MRI op overleving aan te tonen. In **Hoofdstuk 5** wordt beschreven welke patiënten waarschijnlijk wel profiteren van preoperatieve MRI. De mate van consensus in de literatuur werd gebruikt om vast te stellen voor welke patiënten MRI bijdragend is. Het diffuse groeipatroon van invasieve lobulaire carcinomen leidt tot onderschatting van de tumorgrootte met conventioneel beeldvormend onderzoek en dus een verhoogd risico op positieve snijvlakken[30]. Omdat preoperatieve MRI in deze patiënten geassocieerd is met een lager risico op reëxcisie, wordt invasieve lobulaire kanker beschouwd als een duidelijke indicatie voor preoperatieve MRI[31]. De consensus over of MRI noodzakelijk is bij patiënten waarbij conventionele beeldvorming middels mammografie en echo inconclusief is over tumorgrootte is matig. Naast de huidige klinische indicaties voor MRI, zou MRI ook gebruikt kunnen worden als een modaliteit voor patiëntenselectie voor minimaal invasieve behandelingen, omdat MRI superieur is in het vaststellen van tumorgrootte, vorm en locatie. Bovendien is MRI het meest nauwkeurig in het vaststellen van de grootte van kleine tumoren, die juist geschikt zijn voor minimaal invasieve behandeling[32].

Preoperatieve MRI kan mogelijk ook bijdragen aan het vaststellen van ductaal carcinoom in situ (DCIS) en met name uitgebreide (extensive) DCIS (E-DCIS), dat een risicofactor is voor onvolledige resectie en wordt beschouwd als een contra-indicatie voor minimaal invasieve behandeling. Het risico om maligne weefsel onbehandeld te laten is verhoogd, omdat DCIS niet altijd wordt gedetecteerd met MRI[33]. Daarom is histopathologische evaluatie van de snijvlakken nodig bij patiënten met E-DCIS. In **Hoofdstuk 6** wordt een model voor het voorspellen van de aanwezigheid van E-DCIS beschreven. Een marge van 1 cm rondom de tumor werd automatisch gesegmenteerd op MRI beelden. Daarna ondergingen patiënten ruime lokale excisie. Positieve snijranden werden significant vaker gevonden in patiënten met E-DCIS. Vroege en totale aankleuring in de tumormarge, positieve human epidermal growth factor receptor 2 (HER2) en veel fibroglandulair weefsel rondom de tumor waren geassocieerd met E-DCIS. Naast patiëntenselectie voor minimaal invasieve behandelingen, kan dit model ook nuttig zijn voor het sturen van chirurgische behandeling. Als het voorspelde risico op E-DCIS laag is, zou lokale excisie met een marge van 1 cm genoeg zijn. Indien het risico op E-DCIS hoog is, kan excisie met grotere marges worden uitgevoerd. De voorspellende waarde is overigens niet hoog genoeg om volledig op dit model te vertrouwen.

Andere technieken zoals evaluatie van snijranden tijdens de operatie zouden kunnen worden gebruikt om onnodig ruime excisies te voorkomen[34].

Bepaling van tumorgraad op biopt

Aangezien er na minimaal invasieve behandeling geen operatieweefsel beschikbaar is, moeten de tumoreigenschappen die nodig zijn om de indicatie voor adjuvante systemische behandeling te stellen worden bepaald op biopten. In **Hoofdstuk 7** wordt in een meta-analyse onderzocht hoe vaak tumorgraad, vastgesteld op het biopt, overeenkomt met het operatieweefsel. In 71,1% van de borstkankers komt de tumorgraad op biopten en operatieweefsel overeen. Onderschatting met het biopt gebeurde in 19,1% van de patiënten. Overschatting kwam minder vaak voor (9,3%). De meest waarschijnlijke oorzaak voor het verschil in tumorgraad tussen biopten en operatieweefsel is dat niet alle gebieden van de tumor worden gesampled met biopten, wat in een heterogene tumor tot met name onderschatting kan leiden[35]. Ondanks het feit dat de discordantie tussen het biopt en operatieweefsel significant is, is deze niet veel groter dan de inter-observer variabiliteit tussen pathologen die tumorgraad bepalen op operatieweefsel[36,37]. In de studies in deze meta-analyse was de discordantie tussen pathologen vanzelfsprekend ook aanwezig. Het vaststellen van zowel tumorgraad op de biopten als op het operatieweefsel waar deze mee werden vergeleken, werden hierdoor onvermijdelijk beïnvloed. Hierdoor kan de discrepantie tussen tumorgraad bepaald op het biopt en operatieweefsel niet met zekerheid worden vastgesteld. Bovendien is deze afhankelijk van de nauwkeurigheid van pathologen. Adjuvante behandeling wordt door meer factoren dan alleen tumorgraad bepaald, bijvoorbeeld receptor status en tumorgrootte. Hierdoor zijn de klinische consequenties van het verkeerd vaststellen van tumorgraad, zoals het onterecht weglaten van adjuvante chemotherapie, beperkt. Waaijer et al. hebben beschreven dat foutieve gradering in slechts 1,5% tot onderbehandeling en in 3,5% tot overbehandeling leidt[38]. Schmitz et al. toonden aan dat de indicatie voor systemische therapie niet juist wordt gesteld in 11%, als ook alle andere factoren die deze indicatie bepalen worden vastgesteld op het biopt[39]. Postma et al. hebben aangetoond dat de huidige discordantie tussen pathologen mogelijk leidt tot het verkeerd stellen van de indicatie voor systemische therapie in 5% van de gevallen[36]. Dit betekent dat in 5% van alle borstkankerpatiënten momenteel ten onrechte wel of geen systemische therapie wordt gegeven. Concluderend is het aantal patiënten dat benadeeld zou kunnen worden door het bepalen van

de indicatie voor systemische therapie op enkel het biopt niet verwaarloosbaar, maar wel vergelijkbaar met de huidige klinische situatie. Grotere studies zijn nodig om vast te stellen hoeveel patiënten zouden worden onder- of overbehandeld als alleen het biopt wordt gebruikt en of dit acceptabel is. Andere technieken om de indicatie voor systemische therapie vast te stellen zouden ook kunnen worden gebruikt, bijvoorbeeld de MammaPrint®. De MINDACT studie heeft bewezen dat de MammaPrint® in staat is om overbehandeling met chemotherapie te voorkomen bij patiënten die momenteel chemotherapie zouden krijgen[40].

Patiëntvoorkeuren

Minimaal invasieve borstkankerbehandelingen zijn nog in een vroege fase van ontwikkeling, die is geïnitieerd door artsen en de industrie. Of patiënten eigenlijk wel geïnteresseerd zijn in deze behandelmogelijkheden, is een belangrijke kwestie. Zo ja, welke patiënten hebben het meeste interesse? Deze vragen hadden het beste kunnen worden gesteld voordat minimaal invasieve behandelingen werden geïntroduceerd. In **Hoofdstuk 8** werd zowel aan borstkankerpatiënten als gezonde vrijwilligers gevraagd om zes hypothetische scenario's te beoordelen waarin behandelingen met klinische gevolgen en prognose werden beschreven. De scenario's werden beoordeeld middels de visueel analoge schaal (VAS) en time trade-off (TTO). De zes scenario's waren mastectomie, mastectomie met directe reconstructie met implantaten, MST, RFA[21], MR-HIFU ablatie (**Hoofdstuk 2**) en single-dose ablatieve radiotherapie[41]. Borstkankerpatiënten hadden het vaakst de voorkeur voor MST. Een van de redenen hiervoor zou kunnen zijn dat deze patiënten bekend zijn met deze behandeling en hier goede ervaringen mee hebben. Gezonde vrijwilligers waren meer geïnteresseerd in minimaal invasieve behandelingen. Deze studie heeft laten zien dat vrouwen verschillende opvattingen en perspectieven hebben, wat het belang van een actieve rol in hun behandelkeuze benadrukt. Als patiënten de mogelijkheid krijgen om mee te beslissen in hun eigen behandelkeuze, neemt hun kennis toe en hebben ze de indruk dat hun mening hun behandeling beïnvloedt[42]. Bovendien zijn artsen niet goed in het voorspellen van de voorkeur van de patiënt, wat het belang van een actieve rol van de patiënt nog meer benadrukt[43,44]. De mening van de patiënt is dus een van de belangrijkste selectiecriteria.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Uit de MR-HIFU borst studie bleek dat partiële ablatie van borstkanker haalbaar en veilig is. Een belangrijk voordeel van MR-HIFU is dat het non-invasief is. Deze studie was de eerste stap in de ontwikkeling van MR-HIFU ablatie en de volgende stap is het evalueren van de effectiviteit van de behandeling. Daarom is de tweede MR-HIFU studie opgezet en goedgekeurd door de medische ethische toetsingscommissie van het UMC Utrecht in januari 2015. Het doel van de tweede studie is het volledig ableren van mammatumoren. Het behandelresultaat zal worden beoordeeld met MRI en histopathologie. Tumorgraad en receptor status worden bepaald op het biopt, voorafgaand aan de behandeling. MRI wordt gebruikt om de tumorgrootte en de afwezigheid van andere laesies vast te stellen. Omdat er geen aanwijzingen zijn dat MR-HIFU ablatie de lymfedrainage van de borst verandert, zal de schildwachtklierprocedure gewoon tijdens de operatie worden uitgevoerd. In toekomstige (studie)behandelingen waarbij geen resectie zal worden uitgevoerd, is het nodig om de schildwachtklierprocedure voorafgaand aan de MR-HIFU behandeling uit te voeren. Een andere mogelijkheid zou evaluatie van de lymfeklieren met behulp van 3 of 7 tesla (T) MRI scans zijn, met specifiek op de lymfeklieren gerichte protocollen, zoals T2-gewogen beeldvorming en diffusion weighted imaging (DWI)[45,46]. MRI is mogelijk ook betrouwbaar voor het detecteren van resttumor, als het wordt uitgevoerd na minimaal een week na de MR-HIFU behandeling. Een dunne aankleurende rand rond het geableerde gebied op subtractiebeelden is mogelijk bewijzend voor volledige ablatie. Deze rand geeft aan dat fibrotisch weefsel wordt gevormd rondom het geableerde gebied. Irregulaire of nodulaire aankleuring zou resttumor kunnen betekenen[18,47]. De histopathologie van geableerd weefsel zal verder worden geëvalueerd in de tweede MR-HIFU borst studie. De inclusie van patiënten is nog niet succesvol geweest tot nu toe, wat aangeeft hoe moeizaam innovatie is als er al een uitstekende behandelmogelijkheid bestaat. MR-HIFU zou ook kunnen worden gebruikt voor hyperthermie bij local drug delivery. Warmtegevoelige liposomen die een cytostaticum bevatten worden intraveneus toegediend, terwijl MR-HIFU hyperthermie genereert in het gebied van de tumor. Dit resulteert in het lokaal vrijkomen van het chemotherapeuticum uit de liposomen[48,49]. Deze methode zou in de neoadjuvante setting kunnen worden gebruikt. De behandelduur van MR-HIFU is een van de belangrijkste aspecten die verbetering behoeft. Langdurige behandelingen zijn oncomfortabel voor de patiënt en

zorgen voor hoge behandelkosten. Bovendien is de huidige methode die wordt gebruikt voor thermometrie alleen mogelijk in weefsel dat veel water bevat, bijvoorbeeld klierweefsel. Thermometrie is dus moeilijk toepasbaar in borsten met veel vetweefsel en een kleine tumor. Daar komt bij dat thermometrie dus ook niet mogelijk is in het subcutane vetweefsel. Als dit wel te realiseren zou zijn, zouden kortere afkoeltijden na iedere sonicatie misschien mogelijk zijn en zou de behandelduur af kunnen nemen. Momenteel worden lange afkoeltijden in acht genomen, omdat het niet bekend is hoe hoog de temperatuur wordt en hoe lang het duurt voordat het subcutane vetweefsel is afgekoeld. Mogelijke opties hiervoor zijn T2-gewogen thermometrie[50,51] of een hybride methode die thermometrie in waterhoudend weefsel en vetweefsel tegelijk mogelijk maakt[52,53]. Het is duidelijk geworden dat H&E kleuring en CK-8 kleuring beide nodig zijn voor het evalueren van de behandelresultaten. Deze zullen dan ook beide worden gebruikt in de tweede MR-HIFU studie. Kosteneffectiviteit van MR-HIFU ablatie is niet aangetoond in dit proefschrift. Belangrijke informatie die nodig was voor het uitvoeren van een kosteneffectiviteitsanalyse was niet beschikbaar en moest worden geschat, wat mogelijk de resultaten heeft beïnvloed. In de toekomst moet ook de kwaliteit van leven in acht worden genomen bij de analyses. De VAS en TTO scores die werden verkregen in de studie over patiëntvoorkeuren mogelijk bruikbaar in toekomstige analyses. Meer informatie over de effectiviteit en het effect op de kwaliteit van leven is momenteel het meest noodzakelijk voor de verdere ontwikkeling van MR-HIFU ablatie en andere minimaal invasieve behandelingen.

Patiënten die vroeg-stadium, laag-risico borstkanker van het ductale type zonder DCIS hebben, worden beschouwd als meest geschikte kandidaten voor minimaal invasieve behandelingen. Het risico op incomplete behandeling moet zo laag mogelijk zijn, omdat positieve snijvlakken het risico op recidief verhogen[54]. Er is geen operatieweefsel beschikbaar na minimaal invasieve behandeling, dus alle tumorkarakteristieken waar de indicatie voor adjuvante therapie op wordt gebaseerd, moeten voorafgaand aan de behandeling worden bepaald op het biopt en MRI. Als de indicatie voor adjuvante therapie niet met zekerheid kan worden vastgesteld, zou de patiënt geëxcludeerd moeten worden voor minimaal invasieve behandeling. De studies in dit proefschrift zijn bedoeld om de beoordeling van tumorgraad, aanwezigheid van E-DCIS en patiëntenvoorkeuren voorafgaand aan de behandeling te evalueren en te optimaliseren. Tumorgraad gebaseerd op het biopt komt redelijk overeen met tumorgraad bepaald op het operatieweefsel. Toch

is het risico op onder- of overbehandeling door incorrecte gradering waarschijnlijk beperkt. Om het risico nog verder te beperken, zouden enkele aanvullende technieken kunnen worden gebruikt. DWI en spectroscopie op MRI met een hoge veldsterkte (7T) zijn mogelijk geassocieerd met tumorgraad en zouden de nauwkeurigheid van het bepalen van de indicatie voor adjuvante chemotherapie kunnen verbeteren[55]. Daarnaast wordt de MammaPrint® waarschijnlijk toegevoegd aan de indicatiestelling voor adjuvante therapie door de recent aangekondigde positieve resultaten van de MINDACT studie[40]. MRI is betrouwbaar voor het bepalen van de tumorgrootte en zou ook gebruikt kunnen worden voor de detectie van E-DCIS in combinatie met bepaalde tumorkarakteristieken. Het is belangrijk om vast te stellen dat patiënten E-DCIS hebben, aangezien dit het risico op incomplete behandeling vergroot en evaluatie van de snijvlakken dus nodig is. Het ontwikkelde model voor het voorspellen van E-DCIS zou verbeterd kunnen worden door de aanwezigheid van DCIS in het biopt toe te voegen. Daarnaast zou de toevoeging van hoge resolutie DWI aan de preoperatieve MRI protocollen de detectie van E-DCIS kunnen verbeteren, aangezien hierbij beelden met hoge resolutie van een geselecteerd gebied worden gemaakt[56]. De behandelvoorkeur van de patiënt is belangrijk en geeft een indicatie van de vraag naar minimaal invasieve behandelingen. Patiënten die zelf al MST hebben ondergaan verkiezen deze behandeling boven minimaal invasieve behandelingen, terwijl gezonde vrijwilligers een voorkeur voor minimaal invasieve behandeling hadden. Leeftijd of comorbiditeiten zouden andere selectiecriteria kunnen zijn. Oudere patiënten met comorbiditeiten zijn soms niet in staat om een operatie te ondergaan.

Of minimaal invasieve behandelingen in de toekomst succesvol zullen zijn, hangt af van veel factoren. Ten eerste moeten patiënten bereid zijn om deze behandelingen te ondergaan. Echter, omdat klinische data momenteel ontbreken, is het moeilijk voor patiënten om dit te beslissen. Klinische studies waarin minimaal invasieve behandelingen worden onderzocht zijn moeilijk om uit te voeren en vragen veel geduld van de onderzoeker. De behandelopties zijn vaak nog onvoldoende technisch geoptimaliseerd om voldoende effectiviteit aan te tonen als de behandeling nog in een vroege fase van ontwikkeling is, terwijl juist deze data nodig zijn om de behandeling te optimaliseren. Deze gegevens zullen niet worden verkregen als patiënten en behandelaars niet geloven in de behandeling, bijvoorbeeld door tegenvallende initiële effectiviteit of bijwerkingen. Bovendien concurreren minimaal invasieve behandelingen met de zeer betrouwbare en

bewezen behandeloptie MST. Aan de andere kant werd MST minder dan 60 jaar geleden nog niet gezien als behandeloptie en alle borstkankerpatiënten hadden geen andere keuze dan een therapie te ondergaan die nu als zeer mutilerend wordt beschouwd.

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CHAPTER 11

List of publications

Curriculum vitae

Acknowledgements
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LIST OF PUBLICATIONS

SCIENTIFIC PUBLICATIONS

Knuttel FM, Menezes GL, van Diest PJ, Witkamp AJ, van den Bosch MA, Verkooijen HM, *Meta-analysis of the concordance of histological grade of breast cancer between core needle biopsy and surgical excision specimen.* Br J Surg. 2016 Mar 15

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CURRICULUM VITAE

Floor Knuttel was born on the 21th of May 1987 in Berkel-Enschot (Brabant), the Netherlands. She received her high school degree in 2005 at the Johan van Oldenbarneveltgymnasium in Amersfoort. Early during high school, she had realized that she wanted to become a doctor. After her high school graduation, she moved to Utrecht and started medical school at the University of Utrecht. During medical school, she completed a facultative internship in paediatrics at Yeditepe Unversity hospital in Istanbul, Turkey. She also made a five-month trip to South-America. After her graduation in 2012, Floor moved to Amsterdam and started working as a PhD student at the Radiology department of the University Medical Center Utrecht, initially under supervision of prof. dr. M.A.A.J. van den Bosch. Later, dr. H.M. Verkooijen and dr. K.G.A. Gilhuijs started supervising her as well. She also completed the Master of Epidemiology for postgraduates at the University of Utrecht. In December 2015, Floor started her Radiology residency in the Academic Medical Hospital in Amsterdam under supervision of dr. A.M. Spijkerboer and dr. R.J. Bennink.

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