The effectiveness of breast MRI in invasive lobular carcinoma

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Table of contents

Introduction

1

Ritse M. Mann

Partly after:
The effectiveness of MRI in the assessment of invasive lobular carcinoma of the breast
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Diagnosis of Breast cancer

Breast cancer is a major health issue in the Netherlands, even though mortality has been reduced by approximately 23.5% due to the national bi-annual mammography screening program in all women between 50 and 75 years of age [1] and improvements in therapy. The incidence of breast cancer has gradually increased at an estimated rate of 1.2% per year [2].

Breast cancer accounts for nearly one third of newly detected malignancies in women (32,8%) and is still the cause of death for almost 5% of all women who annually die (4.7% 2008) [2,3]. Trends in breast cancer incidence rate and breast cancer mortality are depicted in figure 1. Consequently, optimization of diagnosis and treatment to further reduce the mortality and morbidity of breast cancer is essential.

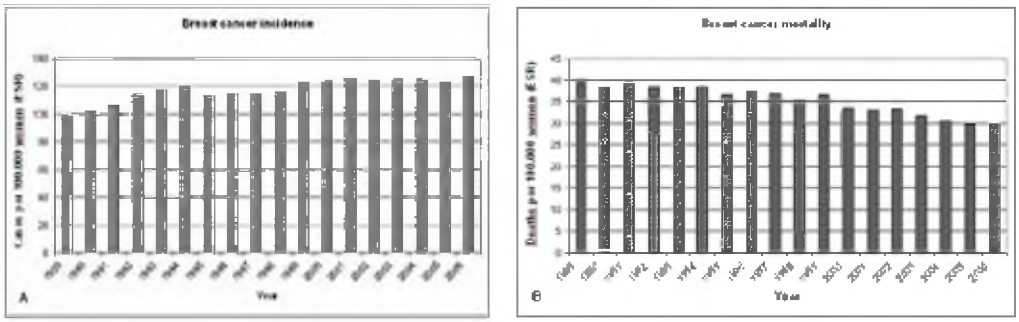

Fig 1: *Trends in breast cancer incidence (A) and breast cancer mortality (B) as provided by the Dutch National Cancer Registration. Reported rates are European Standardized Rates (ESR)*

Currently, detection of breast cancer leans on three supporting pillars. The first is physical examination, either by the patient herself, the general practitioner or a dedicated surgeon. Although physical examination is known to be a very insensitive technique [4,5], a large proportion of tumors is first detected by palpation [6,7]. Mammography is the second and probably most important pillar of breast cancer detection due to its value in mass screening [1,4,8], even though sensitivity is only about 70% [9]. Ultrasound, the third pillar, has currently little value in screening for breast cancer, due to the fact that it is very operator dependent and time consuming [10]. Nevertheless the technique is invaluable in the evaluation and assessment of palpable breast lesions as it can clearly differentiate cystic from solid lesions. Moreover, ultrasound guided biopsy is the easiest way of obtaining histologic material from solid lesions, which is indicated in virtually all lesions that are not typically benign.

Nevertheless, diagnosis consists of more than just detecting a cancer. According to Merriam Websters dictionary, diagnosis is "1 a : the art or act of identifying a disease from its signs and symptoms b : the decision reached by diagnosis". In more medical terms, the 1b explanation translates to staging, because virtually all treatment protocols define the optimal treatment

procedure by the actual disease stage. Consequently, adequate treatment of any disease can only start after a good and complete diagnosis. Basically, knowing what you treat determines how you treat it, or: if your diagnosis is insufficient, so will your treatment be.

Unfortunately, this simple approach raises two major problems:

1) It is unclear how much you need to know to provide optimal treatment
2) It is unclear how to deal with new information when treatment protocols are based upon less than perfect staging

Mammography and ultrasound in tumor staging:
Current staging in breast cancer is based upon the same pillars as tumor detection: clinical examination, mammography and ultrasound [11]. This is historically determined; there is no evidence available that these techniques are the best staging methods. However, many studies have shown that mammography and ultrasound are both better in assessment of the size of malignancies than clinical examination. Until recently this approach was thus accepted as the standard of care.

Breast MRI

In 1971 Raymond Damadian showed that relaxation in NMR experiments differed between normal and malignant tissue [12]. This basic knowledge made the prospect of imaging magnetic relaxation of tissues worthwhile. The first magnetic resonance images were produced by Paul Lauterbur in 1972. He showed that using magnetic gradients it was possible to locate the origin of a radio signal emitted by nuclear spins within an excited body [13]. From here onwards, the field of magnetic resonance imaging has rapidly grown. Image quality, tissue differentiation and imaging speed have largely improved over the years.

The first in vivo MR imaging study of the breasts has been reported by Ross in 1982 [14]. This study, as well as subsequent work from El Yousef and colleagues [15-19], showed the potential of breast MRI to detect breast lesions. However, image contrasts between normal tissue and malignant lesions were poor and hence only large lesions were detected. In general, the sensitivity of breast MRI at this time was comparable to that of mammography at a much higher expense.

The value of breast MRI changed radically when gadolinium containing contrast agents were for the first time administered to detect breast cancer (fig 2) [20]. These contrast agents (at first only Gd-DTPA, later also several other gadolinium chelates such as Gd-DOTA, that was used for most patients in the studies described in this thesis) are diamagnetic and shorten the T1 relaxation time of surrounding tissue [21]. This results in enhancement at T1-weighted images. Contrast agents are given as a bolus and remain mainly intravascular. Diffusion to

the extravascular extracellular space (the contrast agent does not cross the cell membranes) occurs only slowly due to the tight endothelial lining of capillaries [22,23]. In tumors over 2 mm, however, diffusion of nutrients is no longer sufficient to support growth [24], and vascular growth factors are up-regulated. Consequently, new vessels are formed in and around the tumor. The quality of these new vessels is much poorer than that of normal vessels. They are wide, tortuous and the endothelial lining of the vessel wall is often defect, hence these vessels are leaky. In other words, contrast agents can exit the capillaries easier, and rapidly accumulate in the extravascular extracellular space. Based on this physiological principle, most tumors over 2 mm in size enhance on T1-weighted imaging, and in practice, most do.

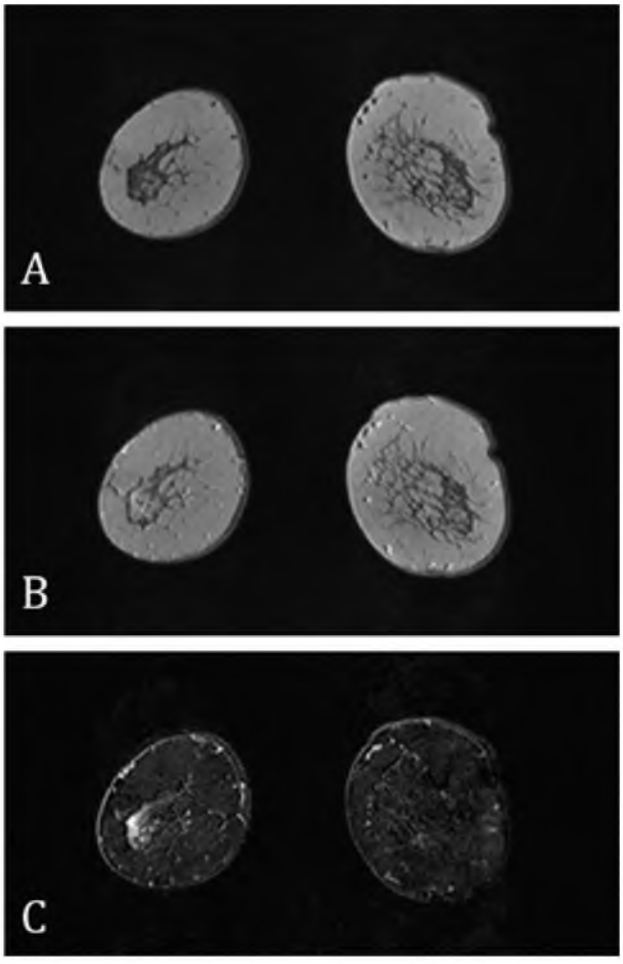

Fig 2: *Coronal T1 weighted breast MRI of both breasts. In the left breast a 3.6 cm ILC is present. The tumor is hardly visible without contrast (A), but clearly enhances after contrast administration (B), although differentiation from fatty tissue is still difficult without unenhanced images. Subtraction of the unenhanced MRI from the contrast enhanced MRI nulls the fat signal and clearly shows the enhancing tumor (C).*

Since 1986, many studies have evaluated breast MRI in different cohorts of women. The results are similar in all studies. Sensitivity for malignant breast lesions is higher than with mammography, ultrasound, and clinical examination. A recent meta-analysis estimated the overall sensitivity to be 90% [25].

A minor drawback is, that other entities that result in leaky microvasculature, will also enhance. Among these most notably inflammation and fibroadenoma [26]. The latter is a benign and very common breast lesion, that may resemble carcinoma. Consequently, specificity of MRI is only 72%. This implies, that histological confirmation of all MRI detected lesions is required.

Breast MRI in preoperative staging

The high sensitivity of breast MRI when used in a screening setting results in an increased detection of cancers. However, MRI screening is currently only indicated in high risk patients, as it has not been tested in other populations [27,28].

MRI is therefore often performed in patients with known primary tumors to accurately stage the tumor. However, the value of MRI in this setting is heavily disputed because all studies currently performed have regarded breast MRI solely as a diagnostic modality.
Different from studies of therapeutic agents that require a systematic review of randomized controlled trials, the highest quality of evidence for diagnostic tests (according to the center for evidence based medicine in Oxford (CEBM)) is reached by a systematic review of validated cohort studies with a good reference standard [29]. The main reason for the difference is that it is well possible to subject a patient to multiple diagnostic tests (with or without results blinded to the other test) and hence perform a matched cohort analysis, whereas it is impossible to subject the same patient to different treatment regimes.
Unfortunately this is conflicting with the levels of evidence for diagnostic tests as proposed by Fryback and Thornbury [31-33]. They describe six levels of evidence ordered in an one-way hierarchical model (fig 3). Evidence of efficacy at a certain level of the model implies efficacy of all lower levels, but does not imply anything about higher levels. Using the quality criteria for diagnostic studies of the CEBM, only evidence up to the fourth level can be generated.

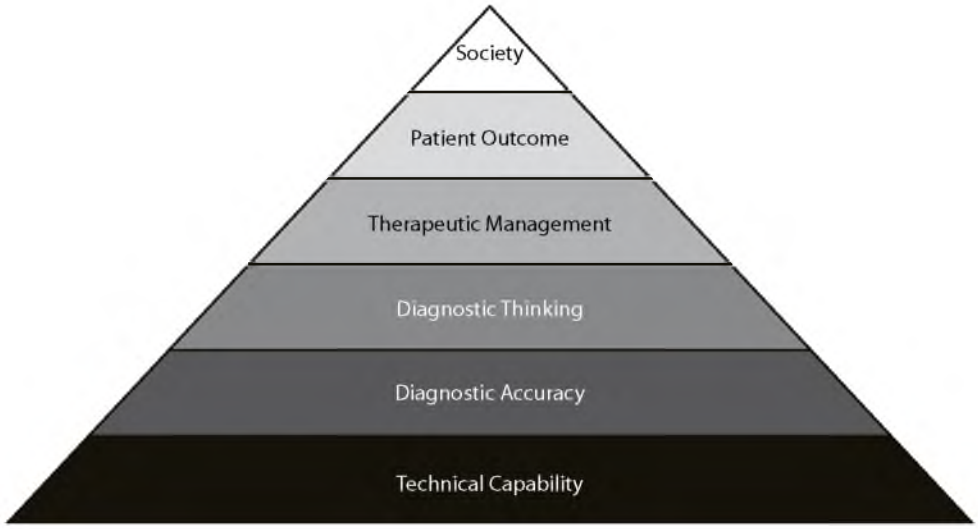

Fig 3: *One-way hierarchical model of the levels of evidence of diagnostic tests, according to Fryback and Thornbury. Evidence of improvement at one level implies positive results at all lower levels, but does not imply anything about hierarchically higher levels.*

At the bottom of the model in diagnostic radiology is the technical capability to obtain adequate images, which is mainly the domain of physicists. It goes without saying that breast MRI (especially at 1.5T) has met these demands, even though new developments continue to be tested. The second level describes diagnostic accuracy and is an area that includes most radiological studies. At this level the sensitivity and specificity of the modalities are tested and weighted. In the preoperative setting, this does no longer regard the actual tumor detection (the presence of the tumor is already established), but instead includes the staging capabilities of the various imaging modalities. Hence, the quality of predicting the pathological size of the tumor, and the detection of additional lesions in the affected breast are major endpoints. Once again, many well-documented studies have shown that breast MRI is better in tumor size estimation and detection of additional lesions than either mammography and ultrasound [34]. The third and fourth level of evidence are highly connected and describe the impact of a diagnostic test on, respectively, diagnostic thinking and therapeutic management of a patient. Since breast MR often detects more extensive cancer spread, its effects at the third and fourth level are predictable: a surgeon who initially thought that his/her patient had a small breast cancer, suddenly realizes that the tumor burden is much larger (3rd level), consequently the proposed therapy shifts from local excision to a wider local excision or even mastectomy (4th level). These effects at the 4th level have been well studied and a recent meta-analysis showed that breast MRI revealed significant additional information in 16% of patients (3rd level), which resulted in a conversion to more extensive surgery in 11.3% of patients, including 8.1% change from local excision to mastectomy [34].
Actually, it is possible that in preoperative staging the 3rd and 4th level are more connected

than they should be. Sometimes it may be useful to know that additional tumor foci are present without altering surgical treatment. Already in the 70s, when breast conserving therapy was investigated as replacement for mastectomy, it was known that in many patients tumor was left in situ. The high rate of local recurrence without radiotherapy and, consequently, the need of radiotherapy in all patients after breast conserving surgery are also mere acknowledgements of the fact that surgery in many patients is debulking rather than curative. On the other hand, local recurrence rates after breast conserving therapy (6-10%) are still higher than recurrence rates after radical mastectomy, though this appears not to affect overall survival.
The rather dogmatic resection of the visible tumor load on mammography is proven effective, but there is still room for improvement. Nevertheless, it is by no means sure that MRI detected additional tumor foci also need to be resected when curation can also be expected from radiotherapy and chemotherapy.

Consequently, the fifth level of diagnostic evidence includes patient outcome. The quality of the diagnostic test is no longer rated in relation to the quality of another diagnostic test, but instead it is regarded as part of the therapy. In the evaluation of diagnostic modalities patient outcome is generally neglected. Vice versa, most therapeutic trials start only after diagnosis is established and neglect the fact that the modalities used to come to a diagnosis are serious contributors to the eventual outcomes [35]. Level 5 evidence is only sparsely available for diagnostic modalities because validated cohort studies evaluating diagnostic modalities are, as stated before, unable to provide this kind of evidence. Instead, modalities that have already proven their value at the 4th level and thus substantially influence therapeutic management should be assessed as new therapeutic options. They consequently should be tested in randomized controlled trials. Although this is understandable from a methodological point of view, serious ethical objections to such study designs arise when new diagnostic modalities have been shown to be substantially better than conventional diagnostic modalities. This seriously limits evaluation of diagnostic tests in patient outcome.
In preoperative staging of breast cancer with MRI the principal outcome parameters to be tested are mortality and disease related morbidity (local and distant recurrence). However, since these are long term outcome parameters and the effect of better staging is probably small in respect to the effect of radiotherapy and adjuvant chemotherapy, studies with large numbers of patients need to be performed. For practical purposes, the rate of incomplete tumor resection may be chosen as a surrogate short term outcome parameter. The rationale for this outcome parameter is easy to understand: regardless of the value of the detection of additional distant lesions on MRI, incomplete tumor excision is followed by re-excision. Tumor extension of the index lesion is more accurately measured using MRI. Therefore, it should be easier to excise the tumor completely at the first attempt and hence less re-excisions will be necessary. Such a study basically tests the capability of radiologists and surgeons to transfer the knowledge of preoperative acquired imaging to the operating room.

In order to test the value of preoperative breast MRI at the 5th level, we designed the PREOP study. The goal of this study was to investigate whether or not the performance of preoperative MRI could reduce the rate of re-excisions necessary for initial incomplete surgery. Moreover the study would allow long term follow-up of the cohorts to observe differences in recurrence and survival. First, the performance of preoperative MRI was defined to be an experimental modality. Patients with breast cancer who were to undergo primary surgical resection were randomized to preoperative MRI or no preoperative MRI. Nevertheless, according to the study design, all patients underwent preoperative MRI, but the images were only interpreted and reported in 50% randomly selected patients. The MR images in the remaining 50% of patients were not interpreted, but saved outside of the PACS system for retrospective comparison of the cohorts at the end of the study.

The study was approved by the ethical committee of the UMC St Radboud and all patients provided informed consent. However, patients in whom staging with conventional methods was inconclusive (virtually all patients with more than 50% fibroglandular tissue at mammography and virtually all patients with tumors over 2 cm at mammography), were offered preoperative MRI outside of the study protocol, due to ethical objections within the multidisciplinary treatment team. Moreover, large international studies [36] showed that preoperative MRI detected additional tumors in the contralateral breast in 3.1- 19% of patients that are not treated if not reported [36-39]. This latter finding subsequently resulted in the Eusobi (European Society of Breast Imaging) recommendation to perform preoperative breast MRI in all patients [27]. Consequently, due to serious ethical and methodological objections of the performer (R.M. Mann) and the principal investigator (C. Boetes), both authors of the Eusobi guideline, the PREOP study was stopped after accrual of only 8 patients.

Nowadays, some evidence has become available that shows that the transfer of knowledge from the preoperative MRI to the operation room is more difficult than expected. In a study by Pengel et al. overall no significant reduction in the rate of tumor positive surgical margins was observed (MRI -19,4%, MRI + 13,8%, p=0.17). Nevertheless, they did observe a reduction in the rate of tumor positive surgical margins from 8,1% to 1,6% in the subgroup of invasive ductal carcinomas (p=0.02), and consequently preoperative MRI may prevent some re-excisions in this population [40]. However, in a similar study by Bleicher et al. no effect of preoperative MRI was noted except for a higher rate of mastectomies in the MRI+ group. This group was thus truly unable to use the MRI information to the benefit of the patient [41]. Studies evaluating the long term outcomes after implementation of preoperative MRI are equally sparse. The two available studies show conflicting results: While Fischer et al. documented both a reduction in local recurrence and a reduction in metachronous contralateral breast cancers, Solin et al. did not detect any differences [42,43].

It may not be surprising that, since efficacy of preoperative breast MRI has not been shown at the fifth level, and in fact has hardly been investigated, no studies have yet assessed level number 6, the societal level. This is the cost-effectiveness of the diagnostic test from a societal viewpoint, the top of the pyramid.

Despite the fact that many small studies investigated breast MRI at the lower levels of the hierarchical pyramid of Fryback and Thornbury, structured reviews of the available data, providing higher quality evidence according to the CEBM, were lacking at the time of initiation of this thesis. Moreover, evidence for the value of preoperative breast MRI at higher levels of the pyramid is not available. Consequently, it is essential to further increase the level and quality of evidence for the performance of breast MRI.

Invasive lobular carcinoma

Invasive lobular carcinoma (ILC) is the second most common form of breast cancer reported in 5-20% of patients. Its relative frequency has been increasing in the last decades. This is probably related to the increased use of complete hormone replacement therapy in perimenopausal women [44,45]. The reduced use of this therapy in recent years may already have resulted in a small decrease of the incidence of ILC [46]. ILC derives its name from the old assumption that the tumor arises from the lobules of the glandular tissue [47], whereas the more common form of breast cancer, invasive ductal carcinoma (IDC), arises from the milk ducts. Since most breast cancers, including IDC and ILC, have been shown to arise from the terminal ductal lobular units, these common breast cancers are somewhat inappropriately named [48,49].
The main difference between IDC and ILC is their growth pattern with ILC tending to grow more diffusely. The 'classic type' lobular carcinoma consists of relatively small, uniform cells that grow in a loosely cohesive fashion, forming lines of cells infiltrating the healthy tissue – so called Indian files (fig 4). Often formation of webs around healthy ducts referred to as targetoid growth is reported. Moreover, skip lesions i.e. areas of tumor separated from the index lesion by normal breast tissue are more common than in IDC [50,51]. Moreover synchronous and metachronous contralateral carcinomas are more often observed in ILC compared to IDC [52].
The genetic basis for these differences is probably due to a mutation in the E-cadherin gene (CDH1). E-cadherin is strongly related to cell-cell cohesion and affects morphology and motility of cells. Hence a lack of E-cadherin expression may be the cause for the disjointed growth of ILC [50,51,53]. Apart from the lack of E-cadherin expression, biologically classic ILC resembles low grade IDC. Similarly, the more aggressive subtype pleiomorphic invasive lobular carcinoma resembles high grade IDC.

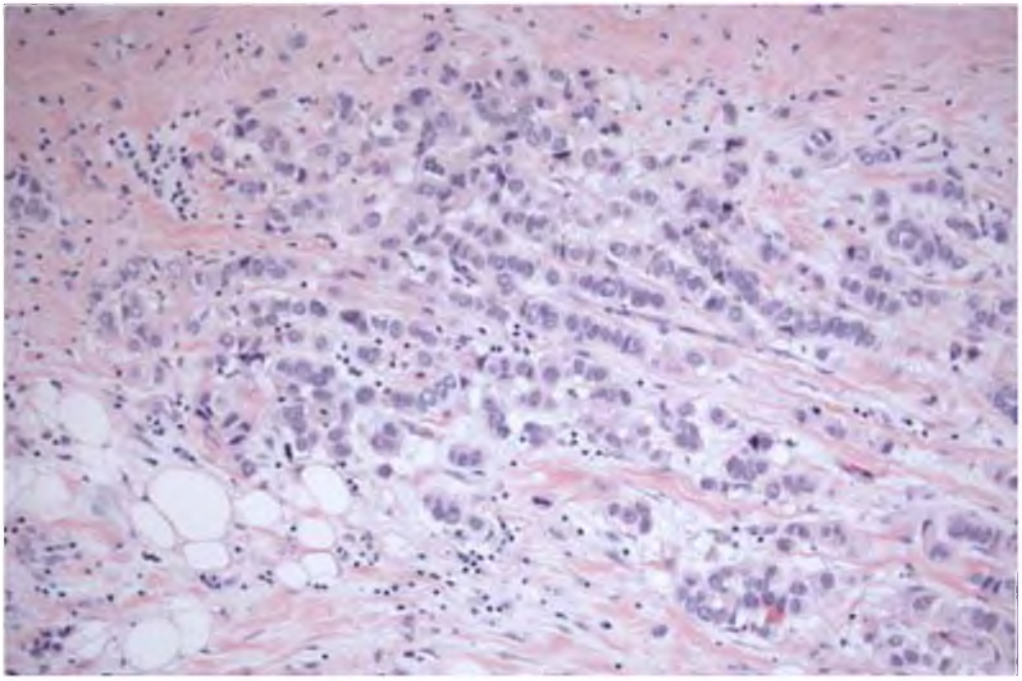

Fig 4: *Ten times enlarged HE-stain of an ILC. Note the relative uniformity and the linear arrangement of the small round cancer cells. (Courtesy of Dr. P. Bult, RUNMC, Department of pathology)*

There are only a few other documented differences between IDC and ILC. ILC are generally larger at detection than IDC and are more often estrogen and progesterone receptor positive.

Furthermore, ILC metastasizes to locations that are extremely rare for IDC, such as the gastro-intestinal tract, the retroperitoneum, the gynecological organs and the leptomeninges (fig 5, fig 6) [54,55]. However, the most common metastatic sites for ILC are the lungs, the liver and bones (fig 6, fig 7).
Outcomes are not very different with a 5 year disease free survival of 85.7 vs. 83.5% for ILC and IDC respectively [52]. Some studies suggest even a slightly better outcome for ILC than IDC, regardless of the often larger size of ILC at diagnosis [56,57]. Currently, there are no differences in treatment based on the histopathological differentiation between IDC and ILC [11].

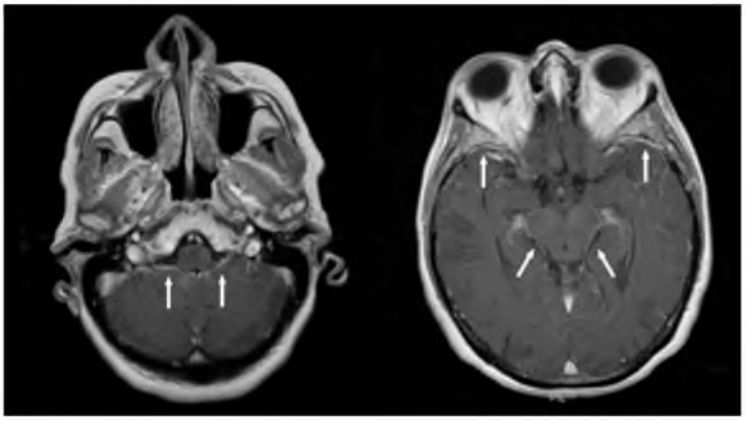

Fig 5: *Axial T1 weighted MRI images of the brain after intravenous administration of 15 ml Gd-DOTA in a 62 year old patient 5 years after detection and treatment of a pT2N3a ILC, who presented with nausea, vomiting and confusion. Note the diffuse leptomeningeal enhancement (arrows), which was later shown to be meningeal carcinomatosis (diffuse ILC metastasis) by lumbar puncture.*

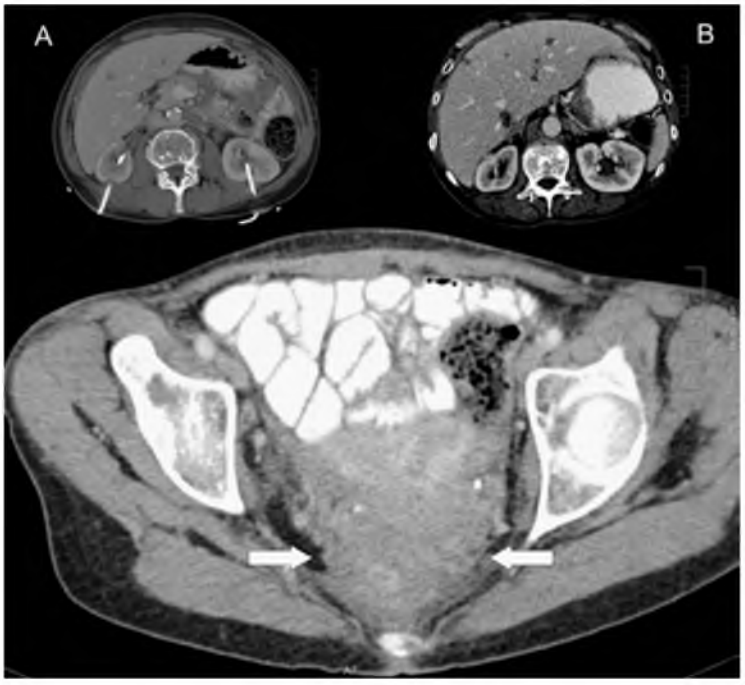

Fig 6: *Postcontrast axial CT images of a 59 year old woman, 3 years after detection and treatment of a pT3N2a ILC, who presented with bilateral hydronephrosis, caused by a large irregular retroperitoneal mass (arrows) obstructing both ureters. Histology was obtained, showing diffuse metastasis of ILC. The hydronephrosis was treated with bilateral nefrostomy (inset A). Also note the multiple hypodense liver metastases and sclerotic metastases in the vertebral bodies (inset A and B).*

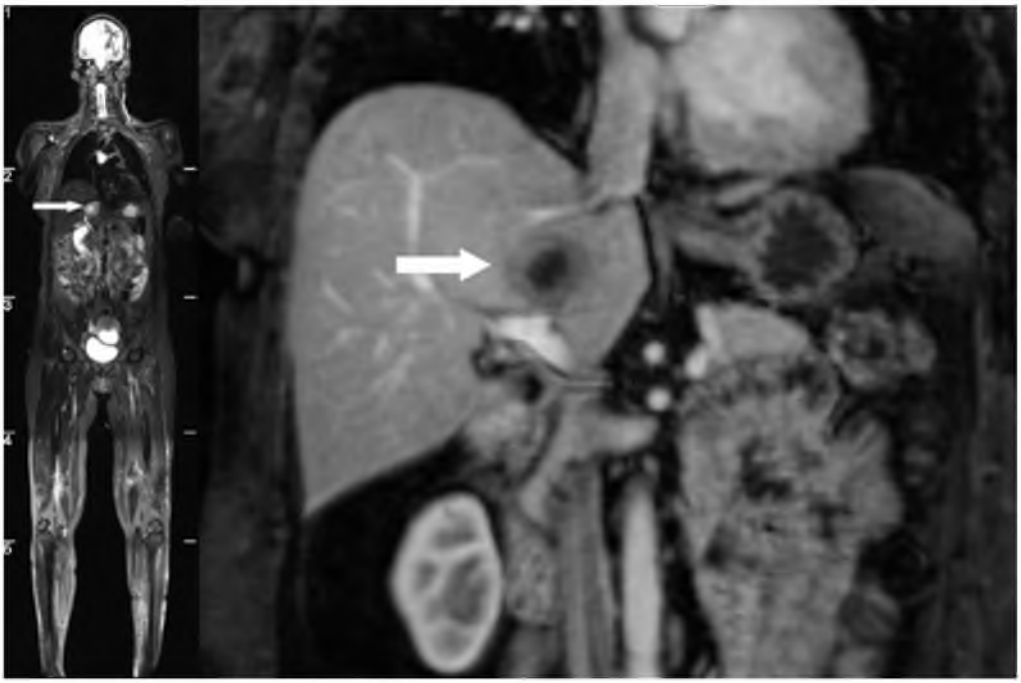

Fig 7: *Images of a 47 year old woman, presenting with a T4 ILC. She underwent whole body MRI to screen for distant metastases. The whole body STIR acquisition (left) and the post contrast (15 ml Gd-DOTA) T1 weighted VIBE acquisition (right) show a large metastasis central in the liver, with central necrosis. The patient underwent neoadjuvant chemotherapy, to which she responded very well, 6 months later the liver metastasis was no longer visible and the primary tumor was surgically removed.*

The thesis

Despite the relative small differences between IDC and ILC, ILC presents a major diagnostic challenge. The tumors are, due to their diffuse growth pattern, more difficult to detect than IDC. The diffuse infiltrative growth pattern is also the most likely explanation for why ILC tends to be larger than IDC. Moreover, the growth pattern of ILC makes mammography and ultrasound unreliable at staging, thus causing high rates of tumor re-excision and leading to a common preference by both patients and surgeons to perform mastectomy. Fortunately, studies have shown, mastectomy rates for ILC are decreasing [58,59].

Since breast MRI has shown to be better at tumor staging compared to conventional tumor staging using clinical examination, mammography and ultrasound, the use of MRI may be especially valuable in the preoperative staging of the subgroup of patients with ILC. However, whether staging with MRI is beneficial for patients with ILC is still unknown.

The principal goal of this thesis is to increase the quality and level of scientific evidence regarding the use of breast MRI in patients with ILC in order to provide a general recommendation for the use of breast MRI in these patients. This recommendation should be supported by high quality evidence up to level 4 and at least some level 5 evidence, because nowadays the use of new diagnostic modalities can no longer be recommended or disencouraged without taking patient outcomes into account. To reach this goal, we defined sub goals as listed below:

- Summarize and qualify the available evidence for breast MRI in ILC up to the fourth level
- Detect the gaps in the available evidence for breast MRI in ILC up to the fourth level
- Fill the gaps in the available evidence for breast MRI in ILC up to the fourth level
- Evaluate the performance of preoperative breast MRI in patients with ILC at the fifth level
- Define a standard for performance of high quality breast MRI in general

The final recommendation is provided in the general discussion and conclusions (Chapter 10). This recommendation is based on all available evidence currently present and although it leans heavily on the other works in this thesis, it does not neglect the valuable contributions of other investigators prior to or during the period I have been working on this thesis. Consequently, I hope to provide a recommendation that can be considered as "state of art", rather than a more limited conclusion of the results of this thesis only, which are in itself just pieces of the puzzle.

Outline of the thesis

In *Chapter 2* the differences between invasive ductal and invasive lobular cancer are discussed in depth from a radiological point of view.

Chapter 3 discusses the evidence to support the use of preoperative MRI in ILC at the start of the present work. It provides a global overview that should be regarded as an introduction to the subject.

In the systematic review in *Chapter 4*, the available evidence for the performance of MRI in patients with ILC is structured and analyzed. We used meta-analytic techniques to increase the scientific value whenever possible and tried to identify the gaps in the currently available evidence.

Chapter 5 is a sidestep that explains the use of very rapid imaging and subsequent analysis to obtain quantitative enhancement parameters, that cannot be derived from more conventional imaging with a high spatial resolution and a relative poor temporal resolution.

Some of these rapid techniques, as well as conventional imaging and CAD applications are subsequently used in *Chapter 6* to evaluate the actual differences between IDC and ILC on MR imaging, since no studies actually compared the two types of cancer directly.

In *Chapter 7* the correlation between MR measured tumor size and size at histopathology was re-addressed, on one hand because the available data were too sparse and too heterogeneous to allow meta-analysis, on the other hand because we tried to identify a cause for the sometimes observed overestimation of tumor size on breast MRI.

These results culminated in *Chapter 8* in a study to the only thing that really matters, namely whether the patient actually benefits from preoperative imaging with MRI in case of ILC. For reasons explained above, the rate of re-excisions and the rate of mastectomies were addressed in a retrospective cohort study stratified by the use of preoperative MRI.

Chapter 9 provides guidelines for the use of breast MRI. Technical demands are described and indications are discussed. Although partly based on the results of above mentioned studies, the guideline was printed before some of the studies above appeared in press, hence statements on the use of preoperative MRI in patients with ILC are still rather conservative.

In the general discussion and conclusions presented in *Chapter10*, the current evidence for the use of preoperative breast MRI in ILC is revisited, a general advice is formulated and shortcomings are discussed. *Chapter 11* provides a Dutch translation of these findings. A short note also addresses the general role of breast MRI in the near future; in *Appendix 1* a specific feature of breast MRI in the future is discussed in more detail.

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Differences between invasive ductal carcinoma and invasive lobular carcinoma of the breast

2

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Differences in incidence

Invasive ductal carcinoma (IDC) is by far the most common type of malignant breast lesions. Various authors report the fraction of IDC between 70 and 90% of all breast cancers [1,2]. The second most common form, invasive lobular carcinoma (ILC) is therefore much less prevalent and is reported to constitute between 5 and 20% of all breast cancers. However, incidence rates of ILC have been increasing over the past decade, possibly due to the extensive use of complete hormone replacement therapy (CHRT). This is nowadays well recognized and the use of CHRT has decreased, but the effect on the incidence of ILC is not (yet) visible [2]. Other types of breast cancer, e.g. medullary carcinoma, tubular carcinoma or mucinous carcinoma, are even more rare and will not be further considered in this article.

Pathologic differences

The terms 'ductal' and 'lobular' are used to describe the behaviour and growth pattern of the tumor. Although, one would expect a ductal carcinoma to arise in the ductuli of the breast and a lobular carcinoma in the lobules, most tumors arise at the terminal ductal-lobular unit [3] and 'ductal' and 'lobular' are thus not indicators of the site of origin.

The pathologic features of IDC are highly variable. This is mainly the result of the fact that IDC is a diagnosis 'by exclusion'. In other words, a breast tumor is called IDC when no specific histologic features that would classify it as a specific type of breast cancer are present [4]. A typical IDC grows as a mass and produces a strong desmoplastic reaction in the surrounding tissue. Macroscopic examination of the pathology specimen shows a gray-white mass, sometimes as hard as rock, due to the extensive desmoplastic reaction of the surrounding tissue [5]. Invasive ductal carcinomas that consist of tumor cells only, with little or no desmoplastic reaction, are tan and much softer. Microscopic histopathology in these tumors is also highly variable and different histopathologic features can be present in a single case. Often necrosis is present, which can be extensive. The appearance of the cells ranges from almost normal epithelial breast cells to severe pleiomorphism and nuclear atypia and mitotic activity ranges from normal to marked. Ductal carcinoma in situ (DCIS) is often found in and around IDC, and is frequently regarded as the precursor lesion of the invasive carcinoma [6]. Although, in some cases DCIS is the prominent feature of the lesion with only minimal invasive components, in other lesions DCIS may be completely absent.

The distinguishing feature between IDC and ILC lesions is the typical growth pattern of ILC. Although some ILC have an appearance very similar to the classic pattern of IDC at gross pathology, often no evident mass can be seen and the specimen will only have an odd rubbery consistency while even in other ILC no macroscopic abnormality can be found [4].

Microscopically, the classic form of ILC is characterized by uniform, small round cells with small regular nuclei with only little mitotic activity that invade the stroma in a single-file pattern around the ducts. This is known as Indian filing and is probably the main reason for the fact

that these tumours are often much larger than initially appreciated. The infiltration of the surrounding tissue in these tumors often cause (almost) no desmoplastic stromal reaction.
Cohesion of the cells in ILC is often very loose due to the typical loss of the adhesion molecule E-Cadherin. This is also one of the most prominent differences between ILC and IDC, because in the latter this molecule is (in varying degrees) present [7]. Apart from the classic form, several variants of ILC are recognized: some are characterized by a different growth behaviour, while others have a similar growth behaviour but a different cellular appearance. In some ILC several variants are present and these are consequently designated as 'mixed' [4].
As in earlier series in the literature only the classic form of ILC was recognized, the currently reported increase in the incidence rates may also be partly contributed to the recognition of the variant types of ILC [4]. Both IDC and ILC lesions are pathologically very heterogeneous entities. Histologic grading is performed for both types of cancer. Tumor grade is usually lower (i.e. more benign) for ILC than for IDC lesions; also the mitotic activity index (MAI) is usually lower for ILC than for IDC lesions. Furthermore, the biological characteristics between the two groups are different and usually more benign in ILC. Invasive lobular carcinomas more often express estrogen and progesterone receptors and more often exhibit a normal expression of p53 and HER-2/Neu [1].

Diagnostic differences

The patient presentation is generally slightly different between patients presenting with ILC and patients presenting with IDC. Patients presenting with IDC have a mean age of around 60 years. Patients presenting with an ILC are generally a little older [1,8,9]. Invasive ductal carcinomas are generally smaller at the time of presentation than ILC, especially the fraction of patients presenting with a tumor larger than 5 centimeter is much larger in patients presenting with ILC. Furthermore, ILC are more often multifocal or even multicentric than IDC and many studies also report a higher incidence of contralateral carcinoma than in IDC [10,11] although numbers are ranging from 3 to 30%. However, even though the tumors are usually larger, the frequency of tumor positive axillary lymph nodes in patients with ILC is only slightly higher [1,8,9,11].
Patients with IDC usually present themselves with a palpable mass or an abnormal mammogram. The mass is often well palpable due to the common fibrotic reaction. Invasive ductal carcinoma on mammography is usually seen as a mass that is either spicular or ill-defined although roughly circumscribed masses do also occur, especially in patients carrying a BRCA mutation. Asymmetric opacity or architectural distortion is present in only 10-15 % of patients [12]. Microcalcifications are present in 30-50% of IDC's and are caused by necrosis and debris [12]. Lesion opacity of IDC is usually higher than that of normal fibroglandular breast tissue (Fig 1).

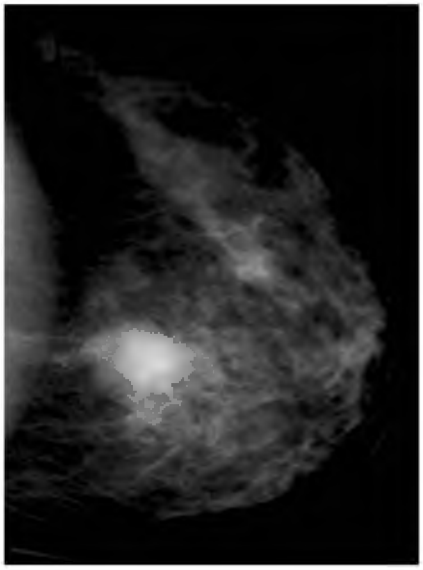

Fig 1: *Cranio-caudal mammogram of the left breast. There is a large hyperdens mass, with an irregular border visible in the medial part of the breast. Lesion density and conformation are typical for the presence of a large IDC.*

Patients with ILC present with similar features. However, due to the more diffuse growth pattern of these tumors, palpation is often more difficult and it is often very difficult to palpate the margins of the abnormality. The mammographic abnormalities are often also much more subtle than with IDC, approximately 50% is seen as a distinct spicular mass, whereas the only signs of malignancy are architectural distortion or asymmetric opacity in 40-60% [12,13]. Most studies confirm that microcalcifications are not typically present in ILC and when present they are usually caused by surrounding DCIS or sclerosing adenosis and not by the ILC [12,14]. Furthermore the opacity of the lesions is often equal to or lower than the opacity of the surrounding fibroglandular tissue, making them even more difficult to observe. Commonly, ILC are only visible on one mammographic view, usually the cranio-caudal (CC) view.
In both IDC and ILC the sensitivity of mammography is largely dependent on breast density. However sensitivity for ILC is due to the more subtle changes usually lower than for IDC and has been reported to be as low as 34% [15]. The actual sensitivity for ILC is probably between 80 and 90% and only slightly lower than the sensitivity for IDC, but up to 30% of findings are classified as equivocal (BI-RADS 3) [13,16]. Invasive lobular carcinomas are hence overrepresented in studies of false negative mammograms [17]. False negative imaging of ILC occurs in 8-21% of cases (Fig 2).

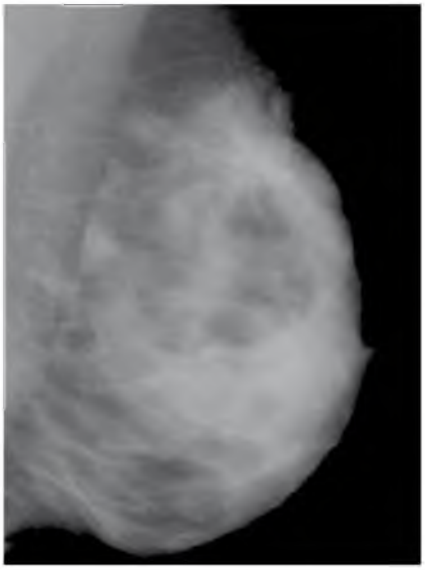

Fig 2: *Medio-lateral oblique mammogram of the left breast. Architectural distortion is visible in the upper part of the breast. Note the absence of a well defined mass and the relative equal opacity of the lesion compared to the normal fibroglandular tissue in the lower part of the breast. This lesion proved to be ILC at histopathology.*

Estimation of the size of breast cancer is very difficult with mammography and underestimation of lesion extent is common. The size of IDC is more correctly measured than the size of ILC [18,19].

With ultrasound, both IDC and ILC are readily detected [15]. Detection of IDC is only marginally better than sensitivity for ILC, although early reports of the sensitivity of ultrasound in cases of ILC are as low as 68% [20], newer transducers perform much better and a sensitivity of up to 98% has been reported [21]. Both IDC and ILC are classically characterized by hypoechoic lesions with an irregular, poor-defined margin and posterior shadowing. However, high grade IDC have a well-defined margin in 11% and posterior shadowing is only present in 30% of cases [22]. Invasive lobular carcinomas are much more likely than IDC to be hyperechoic and are much less often taller than wide [23]. Larger ILC, that have a distinctive infiltrative pattern, are harder to recognize and sometimes shadowing only may be the sole recognizable feature [21]. In many instances ultrasound is only used to obtain a histologic specimen by means of ultrasound guided biopsy. The technique can also be used for size estimation. Several authors report better results than with mammography [20,24], while others found mammographic size estimation more accurate [19,25]. All authors, however, show that ultrasound underestimates tumor size, more so with larger tumor size.

Magnetic resonance is by far the most sensitive modality for the evaluation of breast lesions. It has a very high sensitivity overall [26,27] and various small studies have shown that this also holds true for ILC [25,28]. Approximately 85% of all IDC present as a mass. The margin is usually

spiculated or irregular, often, due to central necrosis, enhancement is more prominent at the border of the lesion and internal enhancement is heterogenous. The presence of an extensive intra ductal component can be seen as ductal enhancement. Only 60% of all ILC are presented as a mass. Architectural distortion and especially asymmetric segmental, regional or diffuse enhancement may be signs of ILC. Furthermore some lobular lesions present with multiple small foci of enhancement [29]. Additional lesions, unobserved by other imaging modalities, are commonly found in both IDC and ILC [30]. However, the incidence of unobserved additional lesions is much higher in ILC patients (30-40%) [31]. Furthermore, unexpected contralateral carcinomas are more commonly found in patients with ILC than in patients with IDC.

The basic principle of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) of the breast is that contrast exits the neovascular capillaries in the tumor easier than normal vessels. These 'leaky' vessels are produced in response to vascular growth factors produced by the tumor in periods of hypoxia, especially vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), is held responsible for the neovascular proliferation. Due to the nature of ILC, which grows in single strands along pre-existing ductuli, these tumors are generally less hypoxic than IDC and consequently require less neovascularisation. Moreover, VEGF expression in lobular carcinoma is not as high as in ductal carcinoma and although mean vascular density is not very different between the two types of breast cancer, vascular neogenesis may be governed by other mechanisms in ILC than in IDC, causing less 'leaky' vessels [32].

This results in a different enhancement pattern in ILC than in IDC. The classic pattern of malignancy, with rapid increase of signal intensity followed by early wash out of the contrast and hence decrease of the signal that is often observed in IDC is frequently not present in ILC [33]. Instead, slow enhancement, with no apparent wash-out can be present and ILC can thus easily be regarded as enhancing fibroglandular tissue on DCE-MRI. This is also the cause of most described false negative MRI evaluations in cases of ILC (Fig 3, Fig4).

Size estimation of breast lesions with MRI is accurate. Various authors mention pearson's correlation coefficients between 0.8 and 0.9 for measurement of ILC [25,34], while size estimation for IDC is generally even more accurate [19]. However, overestimation of lesion size, generally due to the presence of DCIS, LCIS or sclerosing adenosis, occurs in up to 10% of cases, while underestimation of lesion size occurs in equal proportion [25].

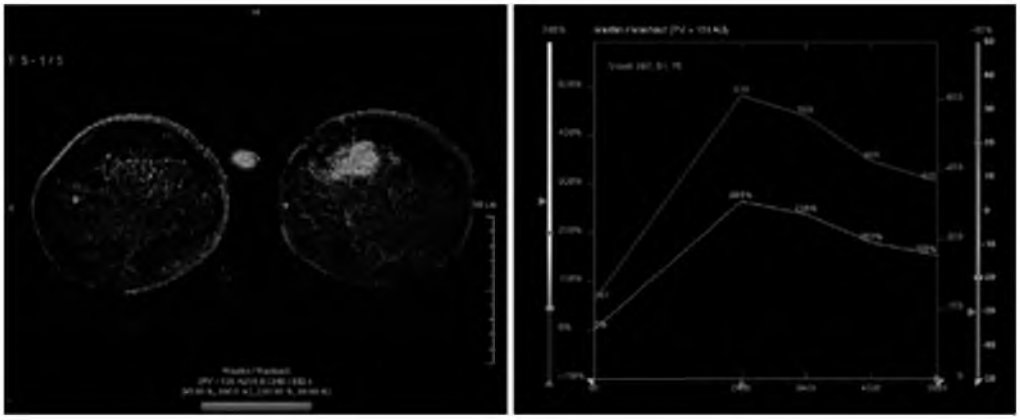

Fig 3: *Subtracted MRI image. In the left breast a large IDC is present with strong enhancement and typical early wash-out of contrast (curves respectively present percentages (lower curve) and arbitrary units (upper curve)), indicative of the malignant nature of the lesion.*

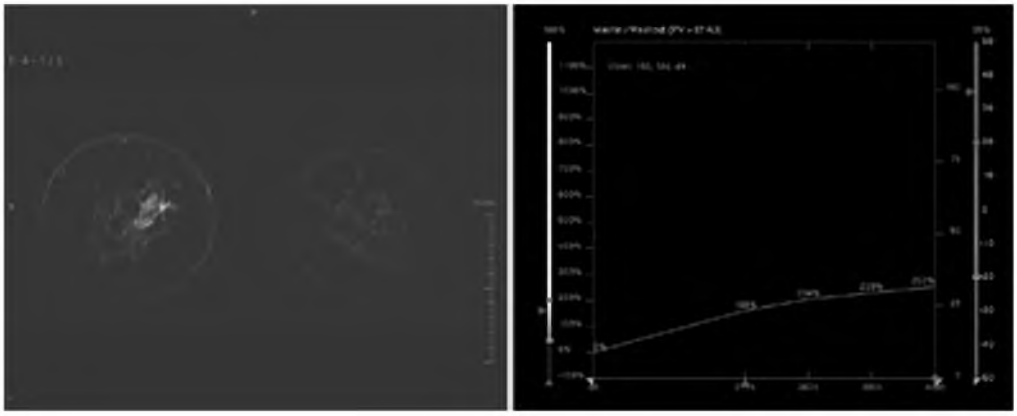

Fig 4: *Subtracted MRI image. In the right breast subtle asymmetric regional enhancement is seen. The patient presented with a palpable abnormality of the breast. Histology showed ILC.*

Differences in treatment

The difficulties in size estimation of ILC with conventional imaging initially resulted in a more aggressive treatment of ILC than IDC. Even with equal sizes, mastectomy was more often performed in IDC than in ILC. However, breast conserving therapy (BCT) has become increasingly accepted for ILC as well [35]. Nevertheless, the chance of positive margins, especially in series where no MRI is performed is higher for ILC than for IDC and conversion to mastectomy after initial BCT is much more common in ILC than in IDC [36,37].

Radiotherapy after initial BCT is essential in both IDC and ILC. The occurrence of recurrent disease is even more reduced in patients with ILC than in patients IDC and is more or less equal for both types of tumor after 10 years [38].
Patients with ILC that are treated with neoadjuvant chemotherapy are less likely to respond to treatment [39] and are less likely to achieve a complete pathological response (i.e. no evidence of tumor in the pathological specimen after surgery) than patients with IDC. However, recurrence free and overall survival are higher for patients with ILC. In patients with ILC the prognostic consequence of pCR is thus not as strong as it is in patients with IDC [40].

Differences in prognosis

The metastatic pattern of IDC and ILC is somewhat different. While both tumors metastasize to bone, lung, pleura and liver, metastases to the gynaecological organs, the gastro-intestinal space, the retro-peritoneal space and the leptomeningen are much more common in patients with ILC [11,41].
Long term prognosis for operated ILC and IDC is very similar, even after BCT for early stage disease [42]. Several studies indicate that the recurrence free survival and overall survival for ILC is slightly better than for IDC, although most do not show histologic type to be an independent prognostic factor. The risk of mortality is however lower for patients presenting with ILC [8].

Conclusion

Invasive ductal and lobular carcinoma differ in their pathological origin, this causes differences in presentation and diagnosis as well as in treatment and prognosis. In general lobular carcinoma's are more difficult to detect and size estimation is harder, making adequate staging and treatment more difficult. MRI is very helpful in adequately assessing ILC.

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Use of Contrast-enhanced Magnetic Resonance Imaging for Detecting Invasive Lobular Carcinoma

3

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Introduction

Invasive lobular carcinoma of the breast (ILC) presents a well recognised diagnostic problem. The incidence, clinical presentation and the pathological findings f this disease will be discussed briefly. The mammographic and ultrasound findings are shown and the use of contrast enhanced magnetic resonance imaging in this disease is presented against this background.

Incidence

Invasive lobular carcinoma is the second most common form of malignancy of the breast. Between 10 and 15 % of all malignancies of the breast are ILC. A recent report on its incidence, based on the documentation of 190458 women with breast cancer in the SEER database (The Surveillance, Epidemiology, and End Results data from the American National Cancer Institute), showed that the proportion of ILC steadily increased from 9.5% to 15.6% between 1987 and 1999. This might be due to the increase in use of combined estrogen and progesterone replacement therapy (CHRT) for prevention of menopausal complaints in this period. It has been shown that CHRT increases the risk on ILC 2 to 4-fold, while it has only little impact on the risk of the most common form of breast cancer, invasive ductal carcinoma (IDC). Although this knowledge has led to the decreased use of CHRT, its effects on the proportion of ILC are not yet visible [1].

Presentation

Patients presenting with an ILC are generally older than those presenting with an IDC. Patients often present with a palpable mass or apparent changes of the breast, others may show a mammographic abnormality consisting of a mass or an architectural distortion. However, findings at palpation or mammography can be very subtle and ILC is easily missed. The tumors are generally slightly larger in patients with ILC than in patients with IDC and the chance of ILC presenting as a tumor larger than 5 cm is 50% greater than the chance of IDC presenting as such (14% vs. 9%) [2,3]. However, axillary lymph nodes are not more often positive.

Invasive lobular carcinomas are characterised by multifocality and multicentricity in the ipsilateral breast and are more often bilateral than other types of invasive breast cancer (15%), although data on the amount of contralateral breast cancer vary widely [2,4].

Metastatic spread of ILC is different from that in IDC. Metastases to lungs, liver, and brain are more common in IDC, while ILC metastases are also found in bone marrow, the leptomeningen, the peritoneal cavity, the retroperitoneal space, and the gynaecologic organs [5,6]. Tumor characteristics of ILC are generally more benign than those of IDC, receptor status of the estrogen and progesterone receptors is more often positive and p53, Her-2/Neu and epidermal growth factor expression is more often normal. However, disease free and overall survival are

not significantly different from IDC, and are mostly dependent upon tumor stage and age at diagnosis [2].

Pathology

Pathology of ILC may mimic an IDC, showing a firm gray-white mass. However, no visible mass may be present and although the breast tissue may have a rubbery consistency there may also be no visible or palpable evidence of malignancy without microscopic examination [7]. Histopathologically, the classic form of ILC is characterised by small round cells, that are relatively uniform. The cells are only loosely cohesive due to a typical loss of expression of the adhesion molecule E-cadherin [8]. They invade the surrounding stroma in a single file pattern (Indian filing), resulting in linear strands along the ductuli. Some cause hardly any desmoplastic stromal reaction. These features make them difficult to observe [9].
Other forms of ILC are the solid form where the tumor cells grow in confluent sheets, and the alveolar form where tumor cells grow in groups of 20 or more cells connected by delicate fibrovascular tissue. Some other variants have been described, including a tubulolobular variant where small tubules with rounded contours are formed concurrent with the classic appearance, a pleiomorphic variant where the tumor cells are generally larger and show more nuclear variation but grow in the typical (classic) pattern and a signet ring cell variant with a prominent portion of cells with a signet ring appearance caused by large intracytoplasmatic lumina [10].
A mixed type is described when no single form comprises > 80% to 85% of the lesion.
The classic form is present in 30-77% of patients, most others have either a solid form lesion nor a mixed type. Furthermore, low grade ductal carcinoma in situ (DCIS) is often present around ILCs [7]. However, the pathological diagnosis of ILC is difficult and poorly reproducible. Specialised breast pathologists are better able to reproduce such a diagnosis, but even then reproducibility of the diagnosis is no more than moderate with kappa- scores between 0.4 and 0.6. Furthermore, 3% of all breast malignancies have both features of ILC and IDC and cannot readily be assigned to either [11].

Mammography

The specific growth pattern of ILC hampers the value of mammography. Sensitivity is reported between 50% and 85%. Up to 25% of mammograms is reported to be normal or of low suspicion. The false-negative rate for ILC is higher than for any other type of invasive breast cancer [12,13]. Its appearance on mammograms is variable. Approximately 60% of lesions are reported as a mass, most are spiculated others are ill-defined and some are even reported as well-defined masses (fig 1). Architectural distortion is seen in 20% to 30% of cases (fig 2), asymmetric density of the breast in 10-15% and no tumor is seen in 5% of cases. Other findings include skin retraction, nipple retraction and cutaneous thickening of the skin. In 10% of patients

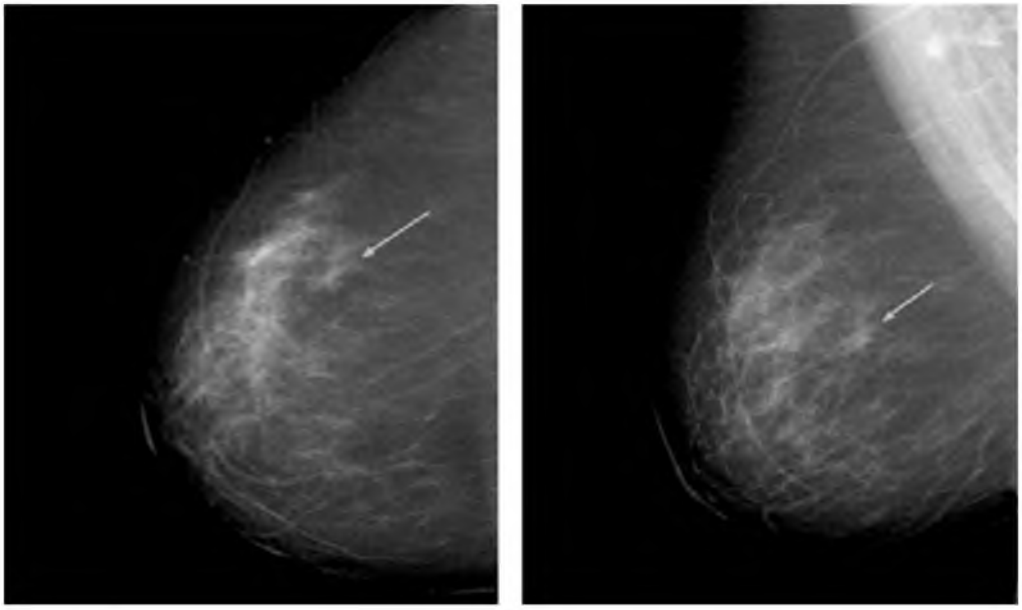

Fig 1: *ILC presenting as small mass on CC and MLO mammograms of a right breast (arrows)*

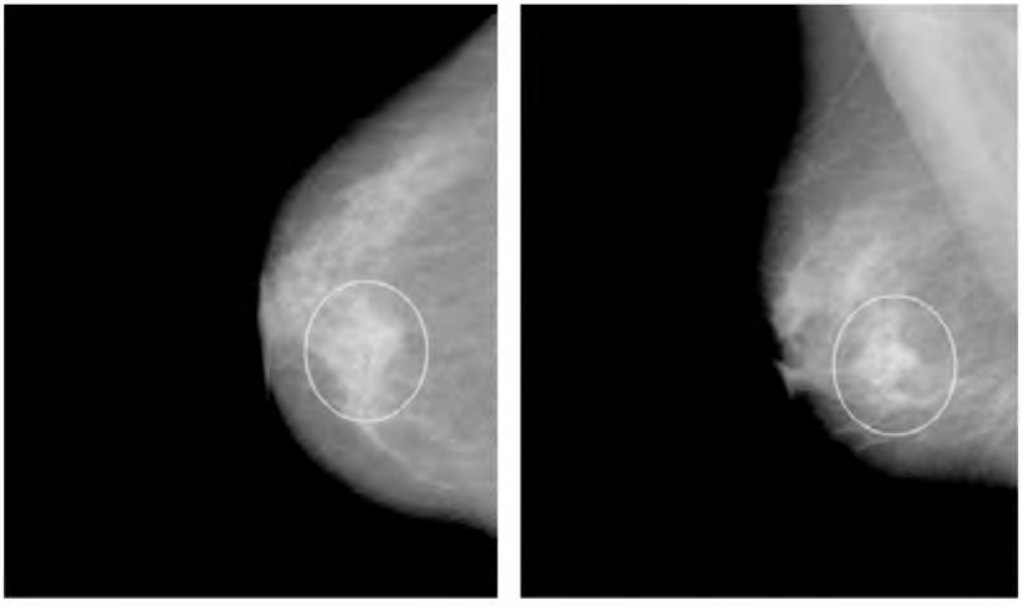

Fig 2: *An area of architectural distortion retromammilair in a right breast (circles), representing a large ILC. Size determination is very difficult.*

microcalcifications are found, although these are not always associated with the ILC but may occur in surrounding ductal carcinoma in situ (DCIS) or sclerosing adenosis [14]. A difficulty is that detectable ILCs on mammography are of a relatively low radiographic opacity, similar to or even less opaque than normal fibroglandular breast tissue. Many visible lesions are thus reported as benign. Furthermore, ILC is often visible in only one radiologic view, usually cranio-caudal [14-16]. Size determination with mammography is difficult. The size of > 50% of all ILCs is underestimated, therefore mammography is unable to accurately measure the extent of ILC [16,17].

Ultrasound

Early reports on the use of ultrasound in ILC mention low sensitivity, comparable to the sensitivity of mammography. However, more recently high resolution ultrasonography has been reported to yield a much higher sensitivity, up to 98% [15].
Invasive lobular carcinoma appears most commonly as hypoechoic masses with or without shadowing in 58% and 27%, respectively. Larger ILC may have a distinctive infiltrative pattern, which is harder to recognize and sometimes shadowing only may be the sole recognizable feature. A significant advantage of imaging with ultrasound is the possibility of easy acquisition of histologic material by an ultrasound guided biopsy. The correlation of pathological size and size measured with ultrasound is however poor. Several authors mention Pearson's correlation coefficients between 0.19 and 0.67. The size is, as with mammography, usually underestimated [17-20].

Goal of MRI in the Assessment of Invasive Lobular Carcinoma

Mammography is characterized by its rather poor sensitivity and inability to accurately measure the size of an ILC not an appropriate modality for the assessment of ILC. Ultrasound seems to have a high sensitivity and provides an easy way to obtain histologic confirmation of the diagnosis. However, ultrasound is unable to provide an accurate assessment of tumor size. The typical growth pattern of ILC makes radical surgery difficult and the secondary mastectomy rate is generally higher than for IDC [13]. Accurate assessment of tumor size is thus the most important feature that should be provided by MRI. Furthermore, its sensitivity should at least equal that of ultrasound.

Magnetic Resonance Imaging

Magnetic resonance imaging of the breasts is generally performed with a dedicated double breast coil in at least a 1.0 T MRI device. Images are obtained in a 3D matrix prior to and after

the administration of a gadolinium based contrast agent. This contrast agent is administered intravenously and leaves the plasma through the new formed "leaky" vessels within, and surrounding the tumor. Standard pulse sequences are aimed at the visualization of contrast and are therefore T1 weighted. Morphologic features are either examined on high resolution subtraction images generated from pre- and post-contrast FLASH-series (Fast Low Angle SHot), or on series that are fat-saturated or are generated by selective excitation of non fat-bound protons only as is the case in the RODEO (ROtating Delivery of Excitation Off-resonance) pulse sequence. Several large prospective studies have shown that MRI has a high sensitivity of around 95% and is more accurate in the determination of disease extent than ultrasound and mammography [21-23]. However, these studies did not explicitly state the value of MRI in cases of ILC. Other authors have, however, presented specific results for ILC in smaller retrospective studies. Direct comparison with ultrasound shows that MRI has a higher sensitivity, although the sensitivity of ultrasound in these studies was not nearly equal to the earlier mentioned results [17,24]. In 40% of patients MRI is able to show more extensive tumor burden [25] and Pearson's correlation coefficient with pathologic size has been reported to be between 0.81 and 0.97 [17,19,20]. Tumor size estimation has been shown to be accurate in 75% of cases, over and underestimation occurs in equal proportions.

The pattern of the lesion on MRI correlates well with pathology and is characterized by either a solitary mass with irregular margins in 30% (fig 3) or by multiple small enhancing foci (60%) with or without enhancing strands between these foci (fig 4), corresponding to clusters of tumor cells connected by single strand invasion or by normal tissue; sometimes only enhancing strands are visible [26]. The standard practice of imaging both breasts at once reveals contralateral breast tumors in a number of cases.

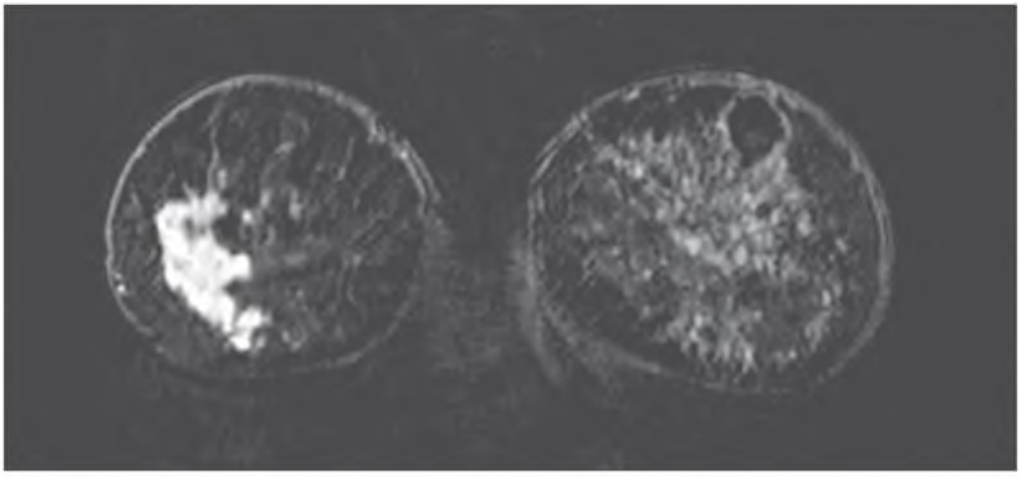

Fig 3: *A large mass on a subtracted high resolution MR image in a right breast representing a very large ILC, note the long spiculae at the superior margins of the tumour suggesting linear spread along the ductuli.*

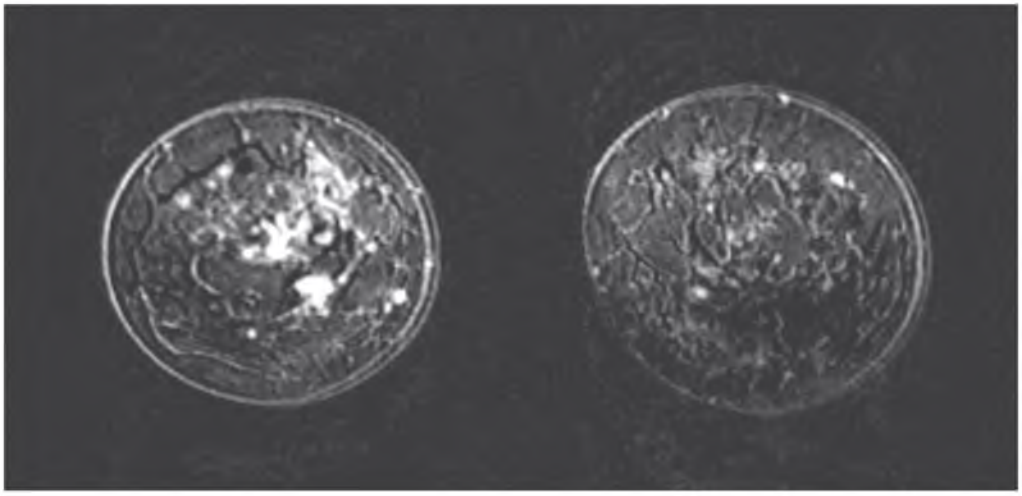

Fig 4: *Multiple small enhancing foci on a subtracted high resolution MR image in the right breast, representing a large multicentric ILC in the right breast.*

Dynamic Sequences in Breast Magnetic Resonance Imaging

Standard breast MRI consists mainly of T1 weighted imaging with a high spatial resolution prior to and after an intravenously administered unspecific extracellular gadolinium based contrast-agent. Contrast enhancement is the principal parameter that determines the visibility of any breast lesion in breast MRI. Typically, exchange of contrast from the intravascular space to the extravascular extracellular space and vice versa is much faster in malignant than in benign lesions. This results in different kinetic profiles for different types of lesions, and even distinct differences between the different histological types of breast cancer. A typical malignant pattern shows rapid early enhancement followed by rapid wash-out of the contrast agent. Some researchers use rapid pulse sequences immediately after the administration of the contrast agent to document the outflow of the contrast agent from the tumor vessels. These "dynamic" acquisitions provide information on the contrast enhancement profile and hence on tumor vasculature. As they document the rather fast transition of contrast agent from the plasma to the extravascular extracellular space a temporal resolution of only several seconds is needed. Consequently spatial resolution is diminished in these sequences.

These contrast enhancement kinetics are mainly dependent on the expression of vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF). This factor is a cytokine that stimulates neovascularization by increasing the microvascular permeability for plasma proteins. This is more important than the vascular density within the tumor [27]. Quantitative and qualitative analyses of the contrast enhancement profile for ILC are however less specific as in IDC. Enhancement is often only marginally faster than in healthy tissue and atypical slow enhancement and absence of wash-out may occur (fig 5). This is probably due to

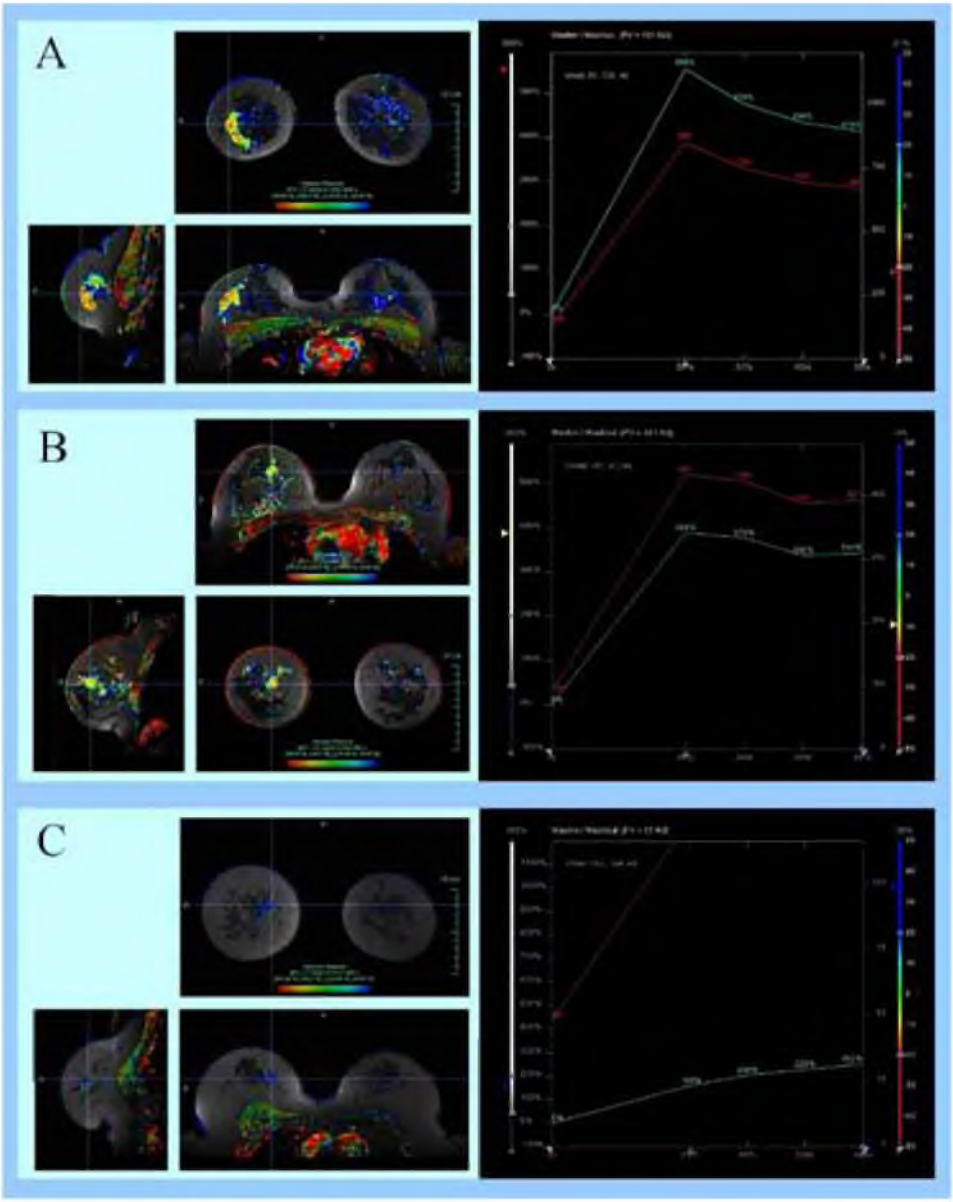

Fig 5: *The dynamic profile of three different ILC. The colours within the tumour represent relative enhancement. Relative enhancement increases as colours change from blue trough green and yellow to red. Tumour A is a very large ILC with a typical malignant enhancement pattern and a dynamic curve showing rapid initial enhancement and subsequent wash-out of the contrast agent. Tumour B shows a less malignant pattern with a plateau phase in the dynamic curve after initial rapid enhancement. Tumour C shows no rapid enhancement and no subsequent wash-out. Although the tumour is readily visible on MRI it may thus be reported as enancing breast tissue because the typical malignant pattern is absent.*

the specific growth pattern of ILC, which does not need extensive neovascularization and thus produces only few leaky vessels [26,28,29]. Furthermore, expression of VEGF is less extensive in lobular carcinoma than in ductal carcinoma even though the vascular density is not really different. This might be reflected in the substantial lower and less specific enhancement profiles found for invasive lobular carcinoma [30].

False-Negative Imaging on Magnetic Resonance Imaging

Even though sensitivity of contrast enhanced MRI for ILC is high, various authors reported false negative findings. This might be due to the difficulties described above, regarding enhancement profiles for ILC. There may be no apparent enhancement at all or enhancement is attributed to normal glandular tissue and the absence of a contrast enhancement profile suggestive of malignancy leads to a false benign classification. [20,31]. Especially ILC growing in a single file pattern without a discrete mass are easily missed. Furthermore, microscopic disease after excision biopsy may be missed [25].

Conclusion

Magnetic resonance imaging has several advantages over mammography and ultrasound in the assessment of ILC. The sensitivity of contrast enhanced MRI is much higher than the sensitivity of mammography and although sonography has been shown to have a high sensitivity, comparative studies favour MRI. Magnetic resonance imaging is better capable of accurate assessment of tumor size than any other imaging modality, even though substantial under or over-estimation still may occur. Magnetic resonance imaging often detects a more extensive tumor burden and may detect unsuspected contra-lateral lesions. However, findings are often subtle and a typical malign enhancement profile may be absent, therefore false negative findings still do occur. In cases of ILC where breast conserving therapy is proposed, contrast enhanced MRI of both breasts appears mandatory.

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MRI compared to conventional diagnostic work-up in the detection and evaluation of invsive lobular carcinoma of the breast – A review of existing literature

4

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Abstract

Purpose

The clinical diagnosis and management of invasive lobular carcinoma of the breast (ILC) presents difficulties. Magnetic resonance imaging (MRI) has been proposed as the imaging modality of choice for the evaluation of ILC. Small studies addressing different aspects of MRI in ILC have been presented but no large series to date. To address the usefulness of MRI in the work-up of ILC, we performed a review of the currently published literature.

Materials and Methods

We performed a literature search using the query "lobular AND (MRI OR MR OR MRT OR magnetic)" in the Cochrane library, Pubmed and scholar.google.com, to retrieve all articles that dealt with the use of MRI in patients with ILC. We addressed sensitivity, morphologic appearance, correlation with pathology, detection of additional lesions, and impact of MRI on surgery as different endpoints. Whenever possible we performed meta-analysis of the pooled data.

Results

Sensitivity is 93.3% and equal to overall sensitivity of MRI for malignancy in the breast. Morphologic appearance is highly heterogeneous and probably heavily influenced by interreader variability. Correlation with pathology ranges from 0.81 to 0.97; overestimation of lesion size occurs but is rare. In 32% of patients, additional ipsilateral lesions are detected and in 7% contralateral lesions are only detected by MRI. Consequently, MRI induces change in surgical management in 28.3% of cases.

Conclusion

This analysis indicates MRI to be valuable in the work-up of ILC. It provides additional knowledge that cannot be obtained by conventional imaging modalities which can be helpful in patient treatment.

Introduction

Invasive lobular carcinoma (ILC) is the second most common histologic type of breast carcinoma after invasive ductal carcinoma (IDC). In most series ILC constitutes between 5 and 15% of all breast cancers, whereas IDC constitutes between 70 and 90% of all breast cancers [1-5]. Probably due to the use of complete hormone replacement therapy (CHRT) the lobular breast cancer component has continuously increased over the past decade from 9.5% in 1987 to 15.6% in 1999 [3].

Patients are, according to most series, a little older than patients presenting with IDC, especially the fraction of patients presenting with ILC younger than 40 is smaller [1,5,6]. Furthermore, the mean tumor size of ILC is slightly larger than in patients with IDC and patient presentation with a tumor larger than 5 cm occurs more often in cases of ILC [1,5,7].

Histopathologically, ILC are clearly defined: Invasive lobular carcinomas are constituted from small, relatively uniform cells, very similar to normal endothelial cells. Characteristically, these cells are only loosely cohesive and infiltrate the stroma in single cell file strands along ductuli. This growth pattern, present in 30-77% of cases [8], is also known as "Indian filing". It is probably caused by a typical loss of the adhesion molecule E-cadherin. Often there is very little desmoplastic stromal reaction [8,9]. The biological characteristics of ILC are usually less alarming than those of IDC: more tumors contain estrogen receptors (ER) and progesterone receptors (PR), while expression of Her2/Neu and p53 are more often normal and axillary lymph nodes are not more often positive, even though ILC are overall larger in size than IDC [1,7].

Probably due to the diffuse infiltrative growth pattern, ILC is frequently missed on mammography [5]. Detection is also compromised because ILC often has a density less than or equal to normal fibroglandular breast tissue on mammography [5,10].

For correct treatment of ILC, adequate staging is important. Both mammography and ultrasound tend to underestimate lesion size and are therefore not optimal for staging purposes [5,11]. This may in part be the reason that higher failure rates of breast conserving therapy (BCT) in ILC than in IDC are reported [2,11,12]. Various authors therefore propose magnetic resonance imaging (MRI) as the modality of choice for the evaluation of ILC. Several small studies addressing the different aspects of the use of MRI in ILC have been presented, but no large series to date. Therefore many questions regarding the use of MRI in ILC remain unanswered.

- The sensitivity of MRI for breast lesions is approximately 95-98%, however, whether this holds true for ILC as well is not clear [13].
- The morphologic aspects of ILC are not yet well defined, nor is the dynamic behavior of contrast agents in these tumors clearly documented.
- Moreover, whether the MRI findings are similar to pathologic findings and can thus be used for accurate staging still needs to be established.
- Finally, the impact of MRI on surgical treatment of ILC should be evaluated.

To answer these questions we performed a thorough review of the existing literature regarding the use of MRI in case of ILC and performed meta-analysis whenever possible. We subsequently

reviewed the literature on other imaging modalities for this indication in order to evaluate the use of MRI from a clinical perspective.

Materials and Methods

Search strategy

We performed a literature search for articles that specifically dealt with the use of MRI in patients with histologic proof of ILC published before the 1st of April 2006. The Cochrane Library, MEDLINE and the in-progress citations as provided by PubMed were searched using the query: "lobular AND (MR OR MRI OR MRT OR magnetic)". These databases were further searched using the "Related Articles" function in PubMed. The same query was used to browse the web using scholar.google.com.

Furthermore, the references of all retrieved articles were mannually searched for relevant cross-references. Articles in all languages were accepted. All retrieved articles were then compared and from overlapping series of patients only the most recent publication was accepted.

Many different search terms were used for literature review of other imaging modalities. However, only Pubmed was used as search engine.

Endpoints

The study was thus undertaken to answer the following four questions.

1. What is the sensitivity of MRI for ILC?
2. What are the visual characteristics of ILC on MRI?
3. Are the findings on MRI equal to the findings at pathology?
4. What is the impact of MRI on surgical management of ILC?

Whenever studies allowed direct comparison between MRI and other imaging modalities, these modalities were also analyzed. Sensitivity was defined as the number of lesions visible on MRI divided by the total number of ILC detected at pathology. We regarded morphology, dynamic curve analysis of contrast behavior, and quantitative dynamic analysis of contrast behavior as three different aspects of tumor appearance and these were thus analyzed separately. A principal distinction between mass-like and non-mass-like lesions was made in the analysis of morphology. Based on the BIRADS lexicon [14], we defined architectural distortion, regional, segmental, ductal, multifocal or diffuse enhancement, and multiple enhancing foci as descriptors of non-mass lesions. Nodular or focal enhancement, well-defined, round, irregular or spiculated masses, and dominant masses with small enhancing foci were defined as descriptors of mass-like lesions. Correlation between the findings on MRI and pathology was evaluated for relative tumor size (unifocal versus multifocal disease and single quadrant versus multicentric disease) and absolute tumor size. The impact on surgical management was derived from all changes implemented, based solely on MRI findings. The numbers of correct and incorrect changes were tabulated.

Eligibility Criteria

All studies that presented a series of at least 10 patients with histologic proof of pure ILC, with or without concurrent DCIS and / or LCIS, were considered eligible. A quality analysis of the study had to be possible, otherwise no abstracts were accepted. Patients with mixed carcinomas of ILC and IDC were excluded. Studies that presented data on both ILC and mixed carcinomas had to allow extraction of the relevant data for ILC only. Every study considered eligible according to these eligibility criteria was then evaluated for all the study endpoints. Specific eligibility criteria for the various considered endpoints are described below.

Detection:

Studies had to be based on a pathology database and all subsequent patients with ILC who underwent a MRI had to be included. The total number of ILC confirmed at pathology had to be clearly stated as well as the number of lesions found with MRI.

Morphology:

Studies describing the appearance of ILC visible on MRI were eligible. Separation between mass and non-mass like lesions had to be possible.

Dynamic curve analysis of contrast behavior:

Studies that described the enhancement versus time curve were eligible. However, as time to peak and shape of the final phase of the enhancement curve were our main endpoints, these had to be described.

Quantitative analysis of contrast behavior:

Studies performing quantitative analysis of the contrast-enhancement parameters were eligible.

Relative correlation with pathology:

Studies presenting data on the unifocal versus multifocal correlation or single quadrant involvement versus multicentric involvement were eligible.

Absolute correlation with pathology:

Studies comparing sizes measured on MRI with those measured at pathology and presenting a correlation coefficient or sufficient raw data to calculate such a value were eligible.

Detection of additional lesions:

Any study describing additional lesions apart from the index lesion detected by MRI only with subsequent acquisition of histologic proof of malignancy was considered eligible. Lesions in the ipsilateral breast and the contralateral breast were evaluated separately.

Impact on surgical treatment:

Studies mentioning all changes in surgical strategy based on MRI findings were eligible.

Statistics

The quality of all included studies was assessed using the QUADAS tool [15]. The latter is a list of 14 items created for quality assessment of studies to diagnostic accuracy. Although not all the included studies specifically evaluate diagnostic accuracy, this tool was judged to be the most appropriate available. Data of all the studies were collected according to the inclusion and exclusion criteria. When at least five studies presented the same type of data or at least 100 patients were included in a smaller series of studies with similar data, we considered

meta-analysis and heterogeneity analysis was performed. Dichotomous data with a binomial distribution (e.g. sensitivity) were transformed to the log odds scale because this scale has a normal distribution and is a good approximation to the exact binomial distribution. A disadvantage of this transformation, however, is that the confidence intervals are a little wider and values in the middle of the distribution (e.g. sensitivity closer to 50%) are more heavily weighted in meta-analysis than values close to the upper or lower level. Pearson's correlation coefficient was transformed to Fisher's Z for the same reason [16].

We calculated Cochran's Q coefficient and the I^2-statistic to assess heterogeneity. Cochran's Q is a form of the χ^2 test and provides information about the applicability of pooling the data. The I^2-statistic provides a quantitative measure of the amount of heterogeneity and has an upper limit of 100%. Values of the I^2-statistic of 25%, 50% and 75% can be interpreted as low, moderate and high heterogeneity, respectively [17]. Meta-analysis of the data using a random effects model was performed when the Q-coefficient showed no significant heterogeneity ($p>0.05$).

In cases where meta-analysis was feasible, the estimate and the 95% CL are expressed. When meta-analysis was not feasible due to severe heterogeneity, only the range of values found in the different studies is mentioned. All calculations were performed using R version 2.3.1 (The R project for Statistical Computing, www.r-project.org) and the meta package (G. Schwarzer, cran.r-project.org).

Results

Studies

We identified 21 separate studies that dealt with MRI and ILC [18-38]. We further identified 4 studies that did not deal specifically with ILC and MRI. However, they did present their data in such a fashion that relevant information for ILC only could be extracted for at least 10 patients [39-42]. Four studies were case-reports and were dropped from the cohort [20,21,29,37]. The study by Bazocchi et al. [18] was excluded because only eight patients underwent MRI. Leung et al. [27] and Newstead et al. [42]only published their findings in abstract form and were consequently excluded. Table 1 gives an overview of the included studies and their characteristics, including the QUADAS score.

The applied scan protocols in the included studies are diverse. In general, most studies presented herein used a 1.5T MRI scanner, although some authors had at least some of their included patients scanned using 1.0T machines [33,34,40]. Most protocols were based on T1 weighted images made with either a normal FLASH 3D sequence or a FLASH 3D sequence with fat-suppression [19,20,23,24,26,31,33-36,38,40,41] or a RODEO sequence with water selective excitation [25,30,32]. A number of authors also used T2 weighted sequences [22,23,31,38,40,41]. Other differences in scan protocols involve the voxel sizes and temporal resolution. Some authors emphasize high spatial resolution [32,39] while others prefer high temporal resolution [26] and yet again others performed both types of sequences in succession [30,38]. Furthermore, single breast coils [30,32,36,41,43] and double breast coils (all others) were used and sometimes

compression was applied to the imaged breast [31,36,39]. In most reported studies the scanning protocols evolved over time and are thus not identical for all imaged patients.

Table 1: *Characteristics of the included studies*

Author	Pub. Year	Study type	N	Age mean	Age min.	Age max.	Field	Scan seq.	Uni/ Bilat	Com Pres-sion	Mean size	Quadas Score
Rodenko GN [32]	1996	1	20	60	38	84	2	1	1	0	X	11
Sittek H [34]	1998	1	23	X	X	X	1	2	2	0	X	11
Weinstein SP [36]	2001	1	17	53	32	69	2	2	1	1	1,7	12
Kim SJ [41]	2001	1	12	54[a]	24[a]	88[a]	2	2	1	0	2,1[a]	12
Trecate G [35]	2001	1	28	X	32	81	2	2	2	0	X	9
Francis A [24]	2001	2	22	X	X	X	2	2	2	0	3,7	12
Qayyum A [30]	2002	1	13	55	46	84	2	1	1	0	X	11
Munot K [28]	2002	1	20	61	39	78	2	3	2	0	X	11
Yeh ED [38]	2003	1	19	59	42	79	2	2	2	0	4,1	11
Kneeshaw PJ [26]	2003	1	21	57	43	72	2	2	1	0	X	11
Quan ML [31]	2003	1	62	53	X	X	2	2	3	1	X	10
Bedrosian I [39]	2003	1	24	53[a]	X	X	2	0	0	1	X	10
Schelfout K [33]	2004	1	26	57	41	74	3	2	2	0	X	11
Diekmann F [22]	2004	1	17	X	X	X	0	0	0	0	X	10
Boetes C [19]	2004	1	34	55	35	78	2	2	2	0	4,9	10
Berg WA [40]	2004	2	29	X	X	X	3	2	2	0	X	13
Kepple J [25]	2005	1	29	62	51	67	2	1	3	0	X	9
Fabre Demard N [23]	2005	1	34	X	X	X	2	2	2	0	X	11

Pub. Year – Year of publication of the original article
Study type – 1 = retrospective cohort study, 2 = prospective cohort study
N – Number of patients included
Age mean – mean age of all included patients, X = not mentioned
Age min., Age max. – Age of respective youngest and eldest patient included in the study, respectively
Field – Strength of magnetic field, 0 = unknown, 1 = 1T, 2 = 1.5T, 3 = both 1T and 1.5T
Scan seq. – Type of scan sequence used, 0 = unknown, 1 = RODEO, 2 = FLASH 3D, 3 = other
Uni/Bilat – Unilateral or bilateral imaging of the breast, 0 = unknown, 1 = unilateral, 2 = bilateral, 3 = both unilateral and bilateral depending on the patient
Compression – Compression applied to the breast, 0 = No, 1 = Yes
Mean size – Mean size of the lesions in centimeters, X = not mentioned
Quadas score – Number of items valid on QUADAS scorings list
[a] Valid for whole study population only, not for subpopulation of patients with ILC

Lesion detection

Eight studies provided sufficient data to calculate sensitivity of MRI for ILC [19,23,24,26,28,33,34,40]. Sensitivity ranged from 83% to 100%. Cochran's Q was 6.48 (p=0.49), I^2 was 0%, indicating homogeneous studies and hence data pooling could be performed. Mean sensitivity was 93.3% (95% CI 88% - 96%). Only the studies by Francis et al. [24] and Berg et al. [40] provided prospective data and are therefore able to show sensitivity in clinical practice. They showed a sensitivity of 95% and 97%, respectively, and were statistically not different from the retrospective studies (2-sided T-test, p=0.78). Seven of these studies also provided data on mammography (Q 31.79 (p<0.001), I^2 = 81%), six on ultrasound (Q 10.92 (p=0.05), I^2 = 54%) and five on clinical examination (Q 29.63 (p<0.001), I^2 = 87%). Sensitivity of ultrasound could also be computed through meta-analysis and was 83% (95% CI 71 - 91%), although moderate heterogeneity was present. The provided data for mammography and clinical examination were too heterogeneous for meta-analysis and ranged from 34 - 91% and 28%-94%, respectively. Figure 1 shows the results of each independent study and the overall results.

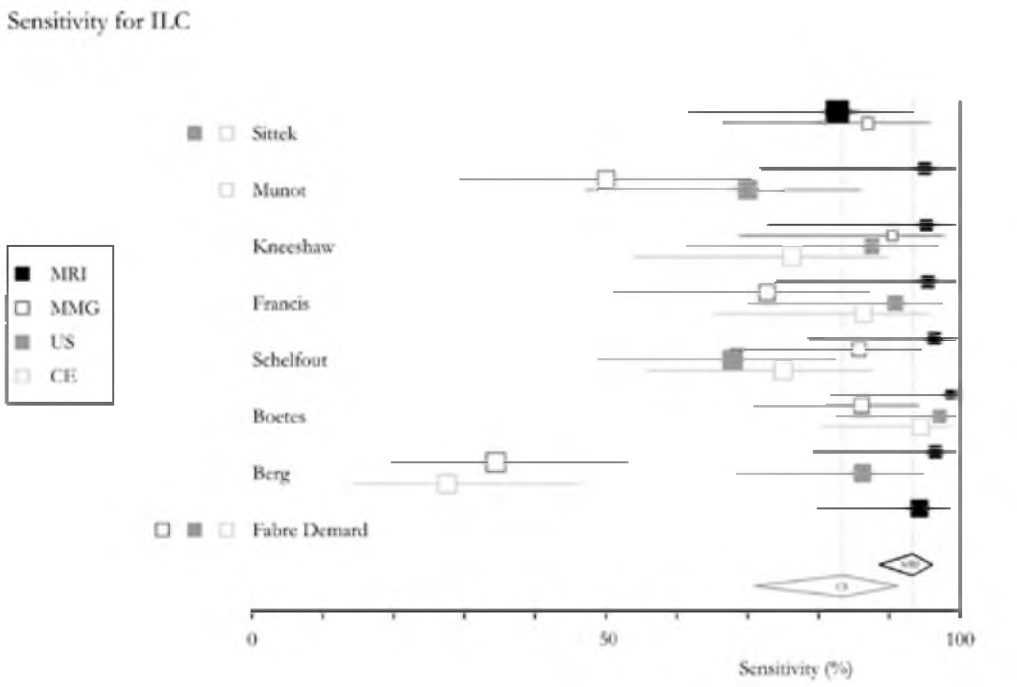

Fig 1: *Forestplot of the sensitivity of the respective modalities for ILC (MMG = mammography, US = ultrasound, CE = clinical examination), the horizontal lines represent 95% confidence intervals. Modalities presented on the right of the authors name have not been tested in the appropriate study. The diamonds at the bottom represent the pooled estimates and their 95% confidence intervals for MRI and US respectively. Because mammography and clinical examination were too heterogeneous for meta-analysis no pooled estimate is presented for these modalities.*

Morphology

Seven studies described lesion morphology on static MRI images [23,30,32,33,36,38,41]. However, Kim et al. [41] studied morphologic appearances of masses only and therefore did not include non-mass-like lesions. Information provided by their study is therefore only used to evaluate the appearance of masses and not for the principal distinction between mass and non-mass lesions. The terminology used in the literature to describe the lesions is highly variable. Only Yeh et al. [38] consistently used the terminology of the BIRADS lexicon [14]. The six eligible studies that presented data on morphologic appearance described a total of 133 tumors. However, results are highly variable. The incidence of a mass-like lesion ranged from 31 – 95% (Q 16.44 ($p<0.01$), I^2 = 70%). Table 2 shows the appearance of ILC on MRI for all individual studies.

Table 2: *Morphologic appearance of ILC on MRI*

Author	Number of Tumors	Non-Mass-like	Mass-Like
Rodenko GN [32]	20	1 (5)	19 (95)
Weinstein SP [36]	18	8 (44)	10 (56)
Qayyum A [30]	13	9 (69)	4 (31)
Yeh ED [38]	20	11 (55)	9 (45)
Schelfout K [33]	27	6 (22)	21 (78)
Fabre Demard N [23]	35	11 (31)	24 (69)

Numbers between parenthesis represent percentages.

Fabre Demard et al. [23] did not specify the lesions beyond the description "mass-like". Other authors used many different terms to further describe lesions. In the study presented by Rodenko et al. [32], 5 pre-defined shapes were used, but they described all 19 mass-like lesions as spicular enhancing masses. In the other studies most lesions are described as spiculated masses as well. Schelfout et al. [33] recognized a dominant mass with multiple enhancing foci in eight cases and Yeh et al. [38] described even a round focal mass. In the 12 mass-like cases described by Kim et al. [41] 10 had an irregular shape and 8 were spiculated. Therefore, among the 76 masses, a total of 65 tumors were described as an irregular or spiculated mass. This appears to be the most common type of mass-like presentation in ILC.

Kinetics

Only two studies reported on the dynamic curve appearance of ILC [34,35]. The most apparent similarity between findings was that maximum enhancement is often delayed and wash-out is present in only a minority of lesions. Sittek et al. [34] reported that maximum enhancement was not reached before two minutes after contrast administration. Trecate et al [35] noted that a classic pattern of rapid signal increase was only present in 4 of 12 pure ILC, whereas a delayed pattern was observed in the other 8 cases.

Two other studies reported on quantitative contrast behavior analysis in ILC [30,38]. Qayyum et al. [30] reported on a parameter called K21, analogue to the K^{trans} parameter as described by Tofts et al [44]. Yeh et al. [38] evaluated the extraction flow product (EF), which is a similar analogue but respects the possibility that contrast leakage from the vessels is limited by flow instead of being limited by the permeability surface area product. Both studies did not, however, include sufficient patients to produce meaningful results, other than a high variability in the values of these parameters and the presence in some tumors of enhancement very much like enhancement in normal breast tissue. It was noted that K21 values appeared to be an order of magnitude less in ILC than in IDC lesions.

Correlation

Several authors evaluated correlation of the MRI findings with pathology [19,24-26,28,32,33,40]. Three studies compared unifocality and multifocality between MRI and pathology [26,32,33] (table 3). Overall 5 of 67 cases (7%) were regarded as multifocal, whereas they appeared unifocal at pathology and, vice versa, two cases (3%) in one study appeared unifocal at MRI, but were multifocal according to pathology.

Table 3: *Relative correlation of unifocality versus multifocality for MRI versus pathology*

Author	Number of patients	UF MRI	UF PATH	MF MRI	MF PATH	Over-estimated	Under-estimated
Rodenko GN [32]	20	9	11	11	9	2	1
Kneeshaw PJ [26]	21	9	10	12	11	1	0
Schelfout K [33]	26	14	17	12	10	2	1
Total	67					5	2

UF = unifocal, MF = multifocal, PATH = pathology
Overestimated = Disease was classified as multifocal on MRI, but was unifocal on pathology.
Underestimated = Disease was classified as unifocal on MRI, but was multifocal on pathology.

Overestimation of multifocality based on mammography in 63 patients from these studies occurred in two patients (3%), whereas underestimation occurred 25 times (40 %) and the lesion was not visible on mammography in another four patients (6%).

Two of these studies further analyzed single quadrant versus multicentric involvement of the affected breast [32,33] (table 4). In the study by Rodenko et al. [32] two cases of single quadrant disease were erroneously classified as multicentric on MRI.

Table 4: *Relative correlation of single quadrant versus multicentric involvement for MRI versus pathology*

Author	Number of patients	SQ MRI	SQ PATH	MC MRI	MC PATH	Over-estimated	Under-estimated
Rodenko GN [32]	20	9	11	11	9	2	0
Schelfout K [33]	26	21	21	5	5	0	0
Total	46					2	0

SQ = single quadrant, MC = multicentric, PATH = pathology.

Overestimated = Multicentric involvement was seen on MRI, but involvement of only one quadrant was shown on pathology.

Underestimated = Involvement of only one quadrant was seen on MRI, but on pathology multicentric involvement was shown.

Mammography in 42 of these patients resulted in overestimation of disease extent in one patient and underestimation in 15. Again, no lesion was visible in four patients.
Berg et al. [40] further showed a series of 12 patients that underwent MRI. Correct size estimation was performed in seven patients. In one patient an additional focus was missed and in four patients overestimation occurred due to foci of LCIS.

Absolute correlation of MRI and pathologic size measurement was performed by six authors [19,24-26,28,32]. Rodenko et al. [32] found a Kappa coefficient of 0.77, which represents substantial agreement. The other authors presented Pearson's correlation coefficients ranging from 0.81 to 0.97 (Q 10.90 ($p = 0.03$), $I^2 = 63\%$). Correlation coefficients for other modalities were substantially more variable. Presented correlation coefficients in table 5 are optimized by excluding cases where no abnormalities were seen from the calculations.

Table 5: *Correlation of tumor size measured by various modalities compared to pathology*

	MRI			MMG			US			CE		
Author	N	PCC	K	N	PCC	K	N	PCC	K	N	PCC	K
Rodenko GN [32]	20		0.773	15		-.081						
Munot K [28]	20	0.97		10	0.66		14	0.67				
Kneeshaw PJ [26]	21	0.86		21	0.93[a]		21	0.93[a]		21	0.47	
Francis A [24]	22	0.87		16	0.79		20	0.56		19	0.89	
Boetes C [19]	36	0.81		36	0.34		36	0.24				
Kepple J [25]	33	0.88					9	0.71				

MMG = mammography, US = ultrasound, CE = clinical examination,
N= number of lesions visible on the appropriate modality,
PCC= Pearson's Correlation Coefficient, K = Kappa Value.
[a] Kneeshaw et al. did not provide a correlation coefficient for either MMG or US, but only one for the combined modalities.

Boetes et al. [19] applied a correctness measure of 1.0 cm to their data and found that MRI underestimated disease extent in five of 36 tumors and overestimated extent in four cases by more than 1.0 cm. The data provided by Francis et al. [24] allow a similar calculation. Underestimation occurred in six of 22 cases and overestimation occurred in one.

Additional lesions

Five studies focused on the detection of concurrent additional lesions in the affected breast apart from the index lesion only visible by MRI [22,23,31,33,36]. In 44 of 146 patients, additional malignant lesions were found (Q 7.20 ($p = 0.13$), $I^2 = 44$ %). Additional malignant findings only visible on MRI were present in 32% of cases (95% CI 22 – 44%). The results of the individual studies are presented in table 6.

Table 6: *Additional malignant findings in the ipsilateral breast by MRI*

Author	Number of Patients	Number of additional findings
Weinstein SP [36]	18	7
Quan ML [31]	51	11
Schelfout K [33]	26	9
Diekmann F [22]	17	9
Fabre Demard N [23]	34	8
Total	146	44
Meta-analysis	100%	32%

Eight studies, presented in table 7, reported on findings in the contralateral breast [19,22-25,28,31,40]. In 12 of 206 patients, unexpected contralateral cancer was discovered exclusively by MRI (Q 2.28 ($p = 0.94$), $I^2 = 0\%$). Cases where contralateral cancer was also visible on mammography and/or ultrasound are excluded. Contralateral carcinoma only visible by MRI was present in 7% of patients. (95% CI 4 - 12%)

Table 7: *Additional findings in the contralateral breast by MRI*

Author	Number of Patients	Number of contralateral findings
Francis A [24]	22	0
Munot K [28]	20	2
Quan ML [31]	53	5
Diekmann F [22]	17	1
Boetes C [19]	34	2
Berg WA [40]	15	0
Kepple J [25]	14	0
Fabre Demard N [23]	34	2
Total	206	12
Meta-analysis	100%	7%

Effect on surgical treatment

Six studies explicitly stated the effect of MRI on the surgical treatment of their patients [23,26,28,31,32,39]. In 160 patients with ILC, a total of 44 changes in surgical management occurred (Q 7.90 (p = 0.16), I2 = 37%). Overall, MRI changed the surgical management in 28.3% of cases (95% CI 20 – 39%). In 24 cases breast-conserving therapy was changed to mastectomy. In nine cases a wider local excision was performed. In the remaining 11 cases the type of change was not further described. Forty-one of 44 changes in surgical management were retrospectively judged necessary based on pathologic findings (Q 1.24 (p = 0.94), I^2 = 0%). Therefore, 88 % of all changes were correct (95% CI 75 – 95%). In three cases the change in management was retrospectively judged unnecessary based on pathology. The data of the individual studies are presented in table 8.

Table 8: *Changes in surgical management based solely on MRI findings*

Author	Number of patients	Number of Changes	Correct Changes	Incorrect Changes	Correct wider excision	Incorrect Wider excision	Correct Mastectomy	Incorrect Mastectomy
Rodenko GN [32]	20	8	7	1			7	1
Munot K [28]	20	3	3				3	
Kneeshaw PJ [26]	21	5	5		1		4	
Quan ML [31]	51	11	11		5		6	
Bedrosian I [39]	24	11	9	2	NA	NA	NA	NA
Fabre Demard N [23]	24	6	6		3		3	
Total	160	44	41	3	9		23	1
Number of changes	100%	28.3%						
Correct changes		100%	88%					

NA = not available. Number of changes and Correct changes show the result of meta-analyses.

Rodenko et al. [32] and Kneeshaw et al. [26] both reported one further unnecessary mastectomy based on MRI outcomes. However, these mastectomies would also have been performed based on the mammography findings and are therefore not only due to the MRI. Berg et al. [40] also reported that findings on MRI in 12 patients with ILC would have resulted in two unnecessary mastectomies. However, mastectomies were also indicated according to the ultrasound report. Nonetheless they based their treatment on the mammograms only and therefore these mastectomies were not performed.

Discussion

Studies and quality analysis

We included 18 studies, but the highest number of studies that could be used to answer a specific endpoint was 8 (sensitivity and contra-lateral findings). Strong evidence is therefore lacking and this review is thus a clear call for more substantial research in this area. The overall study quality of all studies is, according to the QUADAS score, reasonably high (lowest score = 9/14). However, this tool does not include the study size in the analysis, which was generally low. The tool places a strong emphasis on the relation of the test to the reference standard (typical for observational studies). In all studies, the reference standard was pathology and therefore always acceptable as gold standard. However, the test results (in this case the MRI reports), were never shielded from the pathologist who performed the pathologic evaluation. In studies that were performed to evaluate the visual characteristics of ILC on MRI a thorough description of the pathological examination was, deservedly so, not included [23,30,32,33,36,38,41]. These studies thus scored a little lower. There are some other drawbacks that must be considered and that are not included in the QUADAS score. Firstly, all but 2 of the included 18 studies were retrospective in nature, and secondly, the applied MRI protocols were largely heterogeneous (see table 1). However, the presented data were extracted from studies that made use of the various standards in MRI of the breast of the last decade and therefore give a reasonable overview of the overall capability of MRI in ILC imaging in this period.

Sensitivity

The sensitivity of physical examination and conventional imaging for ILC of the breast is not optimal. The sensitivity of physical examination for ILC ranges between 65% and 98% [10,45-47], with usually over 50% of patients presenting with palpable abnormalities.

The sensitivity of mammography for ILC (BIRADS 3 or higher) ranges between 81% and 92% in literature [10,45-51]. In a recent study that evaluated intra- and interobserver variability, sensitivity even ranged from 88% to 98% [52], which could be regarded as sufficient. However, ILC often do not appear as a malignant lesion on mammography; approximately 30% is classified as equivocal and sensitivity is then approximately 57-59% [51].

The overall sensitivity of mammography in the current analysis appears lower than findings in the literature on mammography in ILC. However, equivocal findings may have been classified as undetected lesions in some studies resulting in the overall lower results. Nevertheless, the sensitivities of only 34% found by Berg et al [40], and 50% found by Munot et al. [28] are on the lower end of the spectrum. Munot et al. [28] did not state which views constituted their mammograms, while Berg et al. [40] made craniocaudal, mediolateral and spot-compression views on a standard mammography machine, which we regard as common practice. A possible explanation for the poor results in the study by Berg et al. [40] may be that they defined an ILC as a focus of tumor, thereby allowing more tumors to be present in one breast, whereas other authors defined this as multifocal or multicentric tumors and thus as detected when at least one lesion was visible on mammography. In literature, the reported sensitivity of ultrasound for ILC ranges between 68% and 98% [47,53-58].

As this range is comparable to the range found in the present evaluation, we are of the opinion that an overall sensitivity of 83% is accurate. However, application of newer high frequency ultrasound transducers may improve sensitivity. Initial series using 7.5 MHz transducers show sensitivities of 68% [47] and 78% [56], whereas series that used 10-13 MHz transducers report sensitivities up to 98% [57,59].

Contrast-enhanced MRI is nowadays widely accepted as the most sensitive modality for detection of malignancy of the breast. Early reports on overall sensitivity of MRI for breast lesions range from 93% to 100% [13,60-63]. Thus, the sensitivity of MRI found for ILC in the studies presented herein and the overall sensitivity of 93.3% calculated from these studies are not different from those known for malignancy in the breast in general. The relatively low heterogeneity of all studies describing lesion detection as well as detection of additional lesions in the ipsi- and contralateral breast show that the applied MRI technique only has a minor impact on the ability of MRI to detect lesions.

The overall sensitivity could even be increased to 96% (95% CI 92 – 98%) if an early study is excluded from the analysis [34]. This study reported a sensitivity for ILC of only 83%, a discrepancy that may well be explained by the fact that the slice thickness in this study was 4.2 mm, thicker than in any of the other presented studies, which could have had a negative impact on sensitivity. Moreover, 15 of 23 patients in their series were scanned with a FLASH 3D sequence with TR 8.4/TE 3.0, resulting in image acquisition with a phase-shift of water and fat, which might have further decreased their sensitivity, although this was not apparent from their data.

It must be taken into account that the acquired sensitivity in all studies was achieved in cases where prior knowledge of the existence of ILC was present. Mostly because of the retrospective nature of the presented studies, but also because the two prospective studies both included their patients on the basis of histological proof of invasive (lobular) carcinoma by core biopsy. It is therefore not possible to formulate conclusions on the sensitivity of MRI for ILC prior to biopsy. In a large multicenter trial by Bluemke et al. [64] overall sensitivity for invasive cancer prior to biopsy was 91%, thus it might be expected that sensitivity for ILC prior to biopsy is also slightly lower. However, in most cases the indication for MRI is assessment of disease extent because of inconclusive findings at mammography or ultrasound. In conclusion, the sensitivity of MRI for ILC is higher than that achieved by any other modality, in direct comparison and validated by literature, and is equal to the overall sensitivity of MRI for malignant lesions of the breast. Only modern ultrasound examinations seem to have the ability to approach the performance of MRI in the detection of ILC [57].

Morphology

The morphologic appearance of ILC on MRI ranged from 69% non-mass-like lesions to 95% mass like lesions, thereby raising questions concerning the amount of heterogeneity in the description of morphology of lesions by radiologists. In fact, the general agreement on the description of lesion type according to the BI-RADS lexicon is only moderate [14,65]. In the current analysis, this is even further complicated because most authors did not specifically use the BI-RADS lexicon. Additionally, differences in scan techniques may have further affected the

appearance of the lesion. However, in keeping with the above, the classification of lesion type is also highly variable on mammography, where the incidence of mass lesions ranges from 32% to 78% [10,45,46,48,50,51,55].

The vast majority of the mass-like lesions described on MRI are irregular or spicular lesions. The eight patients with a dominant mass surrounded by multiple enhancing foci, as described by Schelfout et al., may present noncontiguous foci of disease without visible spiculae due to the absence of desmoplastic reaction, which is a well-known histopathological presentation [8]. In all series only one round mass was described [38], suggesting this to be a very rare presentation for ILC. This is consistent with findings in mammography by Le Gal et al. [10], who described a round mass in only 2% of all patients where a mass was present (4/174) while the remainder was either classified as a spicular mass (54%) or poorly defined mass (44%).

Mammographic findings would therefore appear to correlate well with MRI findings. However, only one study allows direct comparison [33]: of all lesions visible in this study on both mammography and MRI, 78% (18/23) were classified as mass-like by MRI, while only 48% (11/23) were classified as mass-like by mammography. Six masses on MRI were visible as architectural distortion on mammography and two as asymmetric density. In one case a lesion described as spicular mass on mammography was visible on MRI as multiple enhancing foci with interconnecting enhancing strands.

Non-mass-like ILC in mammography are typically described as architectural distortion or asymmetric density. In some cases microcalcifications are present, although these are often related to concurrent surrounding DCIS, sclerosing adenosis or fibrotic changes and might thus not be related to the presence of ILC [45,51,55]. The descriptors currently used for non-mass-like lesions on MRI are diverse and include various types of abnormal enhancement, such as regional, ductal, segmental and diffuse enhancement. According to Qayyum et al. [30] the morphologic description of ILC on MRI has a good correlation to histopathologic findings. The non-mass-like presentation might specifically occur in cases where ILC grows in the classic pattern with cells arranged in a linear fashion along the ductuli.

It may thus be concluded that the appearance of most ILC on MRI and mammography is similar: most ILC are mass-lesions that have clear malignant properties. However, the more diffuse growing tumors are characterized by areas of unexpected enhancement and are more difficult to recognize. In a number of cases where no clear mass is visible on mammography, a mass-like lesion may be found on MRI [33].

Kinetics

The relatively late contrast enhancement of ILC apparent in all studies presented here and mirrored by the relatively low values of K21 and EFP in the studies by Qayyum et al. [30] and Yeh et al. [38] must be taken into account when evaluating ILC. Standard subtraction images, generated from the pre-contrast and the first or second post-contrast acquisitions may be inconclusive as maximum enhancement is not achieved at this point in time and the lesion is thus not yet clearly visible. In fact, false negative MRI in cases of ILC is usually contributed to inadequate enhancement of the tumor [26,35,66]. The diffuse and often slow tumor growth,

not requiring extensive neovascularization, may partly cause this difficult visualization [1,67,68]. This is also clear from the relatively lower amount of vascular endothelial growth factor (VEGF) found in tumors with a lobular histology, which might also indicate a different signaling pathway in the formation of neovascular vessels in ILC, resulting in more mature and thus less leaky capillaries [69], with consequently diminished or absent contrast enhancement.

Correlation

In the herein presented studies overestimation of lesion extent by mammography is rare, yet underestimation is more rule than exception. This is also confirmed by studies that specifically deal with mammography in cases of ILC. Yeatman et al. [5] showed that mammography underestimated ILC by a mean of 12 mm. Uchiyama et al. [51] reported 56% of all visible ILC on mammography to be underestimated and Veltman et al. [52] showed 35-37% of all ILC to be mammographically understaged. Ultrasound also tends to underestimate tumor size in the studies presented here.

This finding is underlined by Tressara et al. [70] and more recently by Watermann et al. [71], who documented a structural underestimation of 5.4 ± 12.2 mm in cases of ILC versus 1.4 ± 12.0 mm for cases of IDC. This might be partly due to the observation that US tends to underestimate larger tumors more than smaller tumors and low grade tumors more than high grade [70], consistent with the finding that ILC usually presents with slightly larger and less aggressive tumors [1,5,67,72]. The current analysis shows that there is good correlation of tumor size measured on MRI compared to pathology. The various studies presented only moderately heterogeneous results.

In most cases MRI outperforms mammography and ultrasound in the assessment of disease extent. Most tumors are correctly classified as uni- or multifocal and multicentric disease is only seldom overestimated [19,32].

Additional lesions and effect on surgical treatment

Especially important in this analysis is the detection of additional lesions apart from the index lesion in patients with ILC. The co-existence of other invasive malignant lesions apart from the index lesion in the ipsilateral breast in 32% of patients only visualized by MRI is high. Moreover, the detection of contralateral cancer in another 7% of patients by MRI only, seems to make MRI indispensable. These findings are confirmed by the rate of change in treatment of the ipsilateral breast based on MRI. The fact that change in treatment was considered correct, as verified by pathologic findings in the specimen, in 88% of cases shows that ILC is often more extensive than appreciated on conventional imaging.

However, various authors have shown that there is no significant difference in disease free survival (DFS) or overall survival (OS) after breast conserving therapy (BCT) or mastectomy in patients with breast cancer. Although some authors report more local recurrence in patients with ILC after BCT [2,73], most authors showed that there is no difference in DFS or OS after BCT in ILC versus IDC [74,75]. On the other hand, Yeatman et al. [5] reported a higher rate of conversion from lumpectomy to mastectomy in ILC compared to IDC (17.5% vs. 6.9%). More

recently, Molland et al. [68] reported similar findings (37.2% vs. 22.4%). Hussien et al. [2] even reported failure of BCT in patients with ILC in 63% (34/54) of patients, resulting in conversion to mastectomy in 76% of failures (26/34). However, a very recent study by Morrow et al. [76] showed that BCT did not fail more often in patients with ILC when corrected for age and tumor size, although they still observed a trend of more excisions in patients with ILC (OR 1.58 (0.89-2.79), p = 0.12).

To date, there is no evidence suggesting increase in survival for patients with ILC due to the performance of MRI. What is then the added value of MRI? The rate of recurrence 10 years after BCT followed by radiotherapy is between 7 and 18% and is not significantly different from the rate of recurrence in case of IDC [77,78]. However, in view of the MRI-findings (additional malignant lesions in 32% of patients), we can only conclude that in a large number of patients with ILC, surgery is not curative but merely debulking. As recurrence rates are fortunately much lower, we must assume that curative treatment is to be expected from adjuvant therapy. Unfortunately, because there is no possibility to determine which additional findings will respond to adjuvant therapy, the detection of additional lesions on MRI currently still requires a change of treatment when malignancy has been proven by core biopsy. This may further reduce the rate of recurrence in patients with ILC and may even improve survival. However, this requires confirmation in future studies.

Conclusion

MRI has a high sensitivity for ILC, not achieved by other imaging modalities. Therefore MRI is helpful in cases where conventional imaging is inconclusive. Morphology is often mass-like and a typical ILC presents as an irregular or spiculated mass. However, asymmetric enhancement that can be ductal, segmental, regional or diffuse in nature may be the only sign of tumor. MRI measures disease extent with a high reliability. Although underestimation and overestimation of lesion size by MRI still occurs, it is more accurate than size determination by other modalities, indicating often more extensive tumor burden than expected.

The underestimation by other imaging modalities results in more failure of BCT, more re-excisions and more conversion to mastectomy in series where MRI is not used. Magnetic resonance imaging has an effect on surgical management in that when used to assess disease extent, surgical management was changed in 28.3% of which 88% were judged necessary based on pathology. Larger series of patients are required to confirm the findings of this review; especially evaluation of tumor morphology and dynamic profile seems feasible.

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Ultrafast sequences in magnetic resonance imaging of the breast

5

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Pathophysiological basis of contrast enhancement

Contrast enhanced magnetic resonance of tumors is entirely dependent on the fact that malignant growth of more than 1-2 mm cannot occur without vascular supply of metabolites and oxygen [1]. In response to hypoxia tumors thus generate their own vessels in order to be able to grow. This is achieved by releasing various angiogenic factors that promote neovascularisation. Vascular endothelial growth factor (VEGF) is the most well-known of these angiogenic factors but others contribute as well[2]. The vessels thus produced are different from those in normal tissue. They are extremely heterogenous with many distorted and twisting capillaries with fragile walls, there are many arteriovenous shunts and areas of high vascular density are interspaced with hypoxic areas with high angiogenic activity. [3,4] The walls of these capillaries are 'leaky' due to widened inter-endothelial fenestrae and the (partial) absence of a basement membrane. Furthermore, under influence of VEGF vesiculo-vascular organelles, which provide a pathway for macromolecules trough the endothelium, are upregulated in hypoxic situations [4,5].

Typical contrast agents for dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) are gadolinium chelates. They are injected intravenously, usually as a bolus and are cleared by renal excretion. These contrast agents are usually administered in a dose of at least 0.1 mmol/kg, although some reports claim better results with higher doses [6]. Gadolinium based contrast agent shorten the T1 relaxation time of the surrounding tissue and therefore increase the signal that is received from the tissue[7]. These contrast agents have a low molecular weight and 'leaky' vessels allow easy passage into the extravascular space of tumors. They are however unable to enter the cell and remain therefore in the extracellular space. However, due to the motion of protons that pass the cellular membrane, the intracellular compartment is affected by the presence of the contrast agent.
As long as the concentration of the contrast within the vessels is higher than the concentration in the extravascular extracellular space (EES), also known as leakage space, contrast agent will accumulate here and the signal intensity on T1 weighted images will increase [8].
When the intravascular concentration of the gadolinium agent drops due to leakage and renal excretion the contrast agent flows from the extravascular space back into the intravascular space and out of the tumor area, the signal from the tissue therefore decreases.
The enhancing areas that are used for evaluation of the morphology of a lesion are thus the result of the accumulated contrast in the EES. For the assessment of morphology a high spatial resolution is of the utmost importance. This can only be achieved with a low temporal resolution. Slow dynamic acquisitions, usually made with a spoiled gradient echo sequence, every 90 seconds can achieve a high enough spatial resolution to observe morphology and can be used to evaluate contrast influx and wash-out of the contrast. Rapid initial enhancement, especially when larger than 100% and early wash-out of the contrast agent, visible as a downward slope in the signal versus time curve, are suspicious for malignancy [9,10]. Especially the presence of wash out has been shown to be highly specific for malignant lesions.
Several semi-quantitative measures can be derived from this signal versus time curve. Especially

amplitude of the signal peak and time to peak (ttp) have been used to evaluate tumors and to characterize them further. However, correct assessment of these values demands a more rapid acquisition of images than the standard 90 seconds [11].

Ultrafast sequences

Ultrafast sequences in oncologic imaging are designed to document the arrival of contrast within the lesion and the gradual shift of the contrast agent from intravascular to extravascular. They are typically not designed to document the later phase of contrast behaviour and are thus not used for assessment of morphology nor for the detection of wash out [12].
However, ultrafast sequences may be used to document changes that are caused by the pathologic changes in tumor tissue. First of all, the total number of vessels in a tumor may be increased. Furthermore the vessels are usually larger, therefore vascular resistance is less and the contrast may reach tumor tissue earlier than normal tissue, hence start of enhancement (t0) can be assessed [13]. Second, the easier exchange of contrast agent from the vascular to the extravascular space and vice versa can be documented. Third, due to the increased permeability and often diminished vascular and lymphatic drainage of the EES, enlargement of the EES can be assessed [14].
These sequences can be inserted in standard scanning protocols directly after the injection of the contrast bolus. Typical maximum enhancement in breast lesions is not achieved before 90 seconds after injection, thereby allowing a time-frame for evaluation of initial contrast behaviour by ultrafast sequences without compromising the integrity of the scanning protocol.

Typical sequences are rapid spoiled gradient echo sequences (e.g. TurboFLASH) that document the changes in T1 relaxivity and thus signal increase, so called T1 weighted DCE-MRI (T1w DCE-MRI). The sequence we use consists of 22 TurboFLASH acquisitions with a temporal resolution of 3.6 seconds at 1.5 T and of 2.5 seconds at 3T. Sequences that document the susceptibility changes caused by the passing contrast are T2* weighted acquisitions. They demand an even higher temporal resolution because they are used for so-called 'bolus-tracking', i.e. they document the first pass of the contrast agent through the capillary bed within the tumor, as this causes signal voids in T2* maps. This is called T2* weighted DCE-MRI (T2*w DCE-MRI) [15].

Post-processing

The raw images produced by T1w DCE-MRI can be used to determine ttp and amplitude of the signal peak with greater accuracy than slow dynamic acquisitions. The produced data are however highly dependent on the used equipment and patient specific characteristics. This can be overcome by quantitative pharmaco-kinetic analysis, but complex post-processing of the acquired data is then needed. Several additional measurements must be undertaken.

As the changes in T1 relaxivity are non-linearly related to the contrast concentration, knowledge of the native T1 is needed. Furthermore, measurement of contrast enhancement needs to be calibrated against changes in a reference tissue. Usually changes in blood plasma are used for this calibration, the so-called arterial input function (AIF) [16,17]. However, this demands the inclusion of a large vessel in the imaging plane, not typically present in the imaging of the breast. Therefore signal changes in healthy tissue, like the pectoral muscle, may be used as surrogate reference [18].

The distribution of the contrast agent is regulated by the regional blood flow, the blood volume, the vessel shape and size, the permeability of the endothelium, the endothelial surface area and the size of the leakage space. Correct pharmaco-kinetic analysis should take all these factors into account, which is extremely complex [19,20]. Therefore various simplified models have been produced. All these methods make use of curve fitting techniques, changing the parameters in the model to best match the observed intensity versus time curve. The more parameters included, the more the natural situation is approached. However, inclusion of more parameters increases the chance that good curve fitting can be achieved with several settings, thus decreasing the robustness of the model. The simplest of these pharmaco-kinetic models, known as the two compartment model by Tofts, makes use of only two compartments, namely a vascular compartment without volume and the extravascular extracellular space, which is a fraction of the total extravascular space. The contrast transfer constant (K^{trans}), which describes the flow of the contrast agent from the vascular to the extravascular space is derived from this model as well as the relative fraction of the EES (v_e). These two parameters are mathematically related trough the rate constant (k_{ep}), which is inversely related to the ttp but due to the calibration more robust [21].

$$K^{trans} = k_{ep} * v_e$$

More complex models will allow the vascular compartment a relative volume (v_p), thereby decreasing the size of the EES [21,22].
It is common to think of K^{trans} as a measure of vascular permeability and in cases where abundant contrast is present in the vasculature it is indeed limited by the permeability surface area product. However, when flow is limited or the applied contrast concentration is too low to saturate the complete permeability surface, K^{trans} becomes essentially limited by blood flow and may not accurately represent vascular permeability [21].

Subtraction images generated from T2*w DCE-MRI techniques allow insight into the spatial distribution of perfusion in a tumor. Where the signal drops the most, the highest perfusion is present. Mathematic modelling of the data achieved with these sequences can provide quantitative measures of blood flow. This can be performed by fitting the acquired data to an idealised model (gamma-variate fitting) because in practice, due to extravasation of the contrast, the signal does not return to the baseline after the first pass of the contrast agent. Relative

blood volume (rBV), relative blood flow (rBF) and mean transit time (MTT)can be estimated from this model [23,24]. These are also mathematically related according to the central volume theorem equation.

rBV = rBF * MTT

Clinical applications

In the detection of lesions the role of these fast sequences is only limited. The sensitivity for breast lesions on T1 weighted contrast enhanced magnetic resonance images with a high spatial resolution is in the order of 95-100%. Only low grade ductal carcinoma in situ is more difficult to detect due to absence of enhancement, therefore little is to be expected of ultrafast sequences. However, the standard approach of breast MRI is not very specific. Many benign lesions like fibroadenomas enhance as well. Furthermore normal breast tissue may enhance to a certain limit and distinguishing enhancement based only on morphologic interpretation may be difficult.
Evaluation of the signal intensity versus time curve is in these cases essential. Pharmaco-kinetic parameters may also be an easy way to increase specificity. We found that calculation of pharmaco-kinetic parameters of an enhancing lesion in a region of interest (ROI) indicated by inexperienced readers, was equal in predicting malignancy to morphologic analysis combined with analysis of the signal intensity versus time curve by a reader with over 20 years of experience (Veltman, unpublished data). K^{trans} was the most specific of the pharmaco-kinetic parameters.
A signal intensity loss of over 20% in T2*w DCE-MRI also has been shown to have a very high specificity for malignancy and can also be applied in the differentiation between malignant and benign lesions [25,26]. It was even found to be the only significant factor differentiating benign from malignant lesions in breast tumors induced in rats [27]. As these techniques are both based on absolute values in an image, they can be easily integrated in computer assisted diagnosis and will be useful in the future. (Fig 1, fig 2)

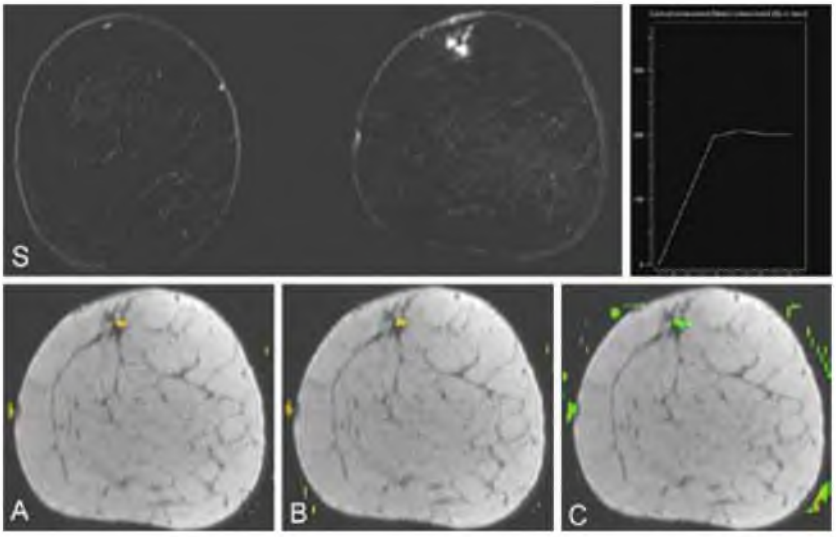

Fig 1: *Subtraction image of both breasts (S). There is a suspicious enhancing lesion in the left breast. The signal intensity versus time curve shows a plateau. Color-coded parametric maps of K^{trans} (A), k_{ep} (B) and v_e (C), projected over T1-weighted images of the affected breast, are not suspicious for malignancy. At pathology the lesion proved to be chronic inflammation.*

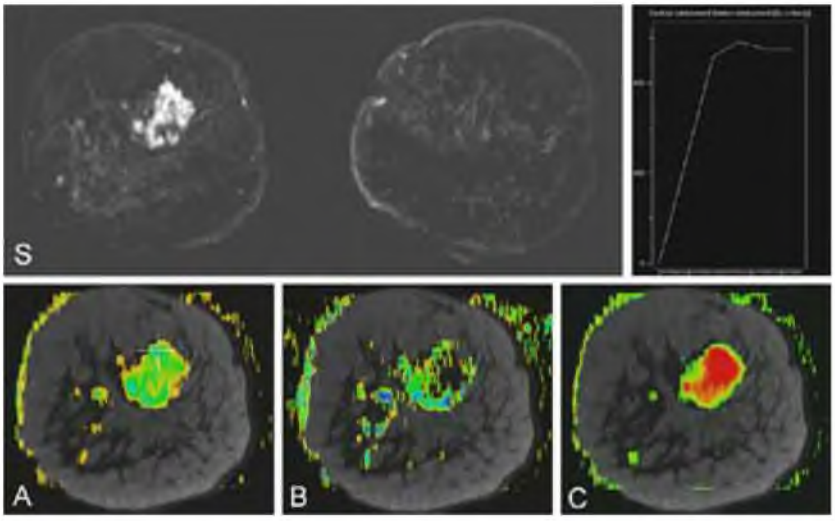

Fig 2: *Subtraction image of both breasts (S). There is suspicious enhancement in the right breast. The signal intensity versus time curve shows rapid initial enhancement followed by a plateau. Color-coded parametric maps of K^{trans} (A), k_{ep} (B) and v_e (C), projected over T1 weighted images of the affected breast are highly suspicious for malignancy. At pathology the lesion proved to be an invasive ductal carcinoma.*

Another field where ultrafast sequences show promising results is the evaluation of malignant lesions that are treated with neoadjuvant chemotherapy (i.e. chemotherapy prior to surgical intervention). As this type of treatment is potentially harmful when the tumor does not respond, close evaluation of tumor response is needed. Furthermore, factors that predict the response prior to the start of treatment are needed.

The latter can be partly achieved by a close evaluation of tumor morphology. A circumscribed mass is usually the best responding tumour. Evaluation of the signal intensity versus time curve is also useful as a higher initial amplitude is associated with a better response. This is also clear in the pharmaco-kinetic analysis as higher K^{trans} values are also closely linked to a better initial response [28,29].

During treatment, decrease in size, or, even better, in tumor volume are the most significant in response evaluation, but responders have a more marked decrease in the amplitude of the peak enhancement than non-responders [28,30]. The signal intensity curve tends to flatten in responders and the tumor becomes more homogenous in its curve distribution [28,31] and the wash-out profile also changes and can be accurately assessed, although the latter is so far not very helpful in the prediction of response [32]. Combination of changes in volume with changes in enhancement ratio increases the specificity of the detection of patients who will achieve a complete pathologic response [33].

Distribution analysis of K^{trans} over a whole tumor decreases in responders and generally increases in non-responders [34,35], but although mean K^{trans} and k_{ep} decrease in responders they generally also decrease in non-responders though not as strong, which hampers the differentiation [29,34,36,37]. In early follow-up MRIs, K^{trans} and k_{ep} were however significant predictors of response and ve increased in eventual non-responders [29]. Changes in median rBF and rBV also correlated significantly with final clinical and pathological response [38].

Dynamic contrast enhanced derived parameters as prognostic factors

The pathophysiological basis of contrast enhancement implies that the process is linked to the biological nature of the tumor. Several authors have tried to correlate the enhancement characteristics and the pharmaco-kinetic parameters of DCE-MRI to known prognostic factors in breast cancer.

The slope of the enhancement curve is associated with microvessel density [39] and it was shown that nodal status of a breast tumor and histological grade were strongly associated with enhancement characteristics [40,41].

Pharmaco-kinetic parameters may therefore be used as non-invasive prognostic parameters, however their independent prognostic value still needs to be assessed.

Conclusion

Ultrafast sequences are designed to document the influx of contrast agent in tumor vessels and the extravasation of the agent directly hereafter. The pharmaco-kinetic parameters that can be derived from these sequences are helpful in the differentiation between malignant and benign breast lesions and in the prediction and monitoring of reponse to neoadjuvant chemotherapy. However, their role in clinical practice still requires further evaluation.

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Comparison of enhancement characteristics between invasive lobular carcinoma and invasive ductal carcinoma

6

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Abstract

Purpose

Invasive lobular carcinoma (ILC) is suggested to enhance less than invasive ductal carcinoma (IDC) on contrast enhanced MRI of the breast. This may impair the diagnostic value of breast MRI in ILC. We compared enhancement characteristics between IDC and ILC to observe the magnitude of these differences.

Materials & Methods

We performed an analysis of enhancement characteristics on biphasic breast MRI in a series of 136 patients (103 IDC, 33 ILC) using an in-house developed application for pharmacokinetic modeling of contrast enhancement and a commercially available CAD-application that evaluated the contrast-enhancement versus time curve.

Results

Pharmacokinetic analysis showed that the most enhancing voxels in IDC had significantly higher Ktrans-values than in ILC ($p < 0.01$). However, no difference in ve-values was noted between groups. Visual assessment of contrast-enhancement versus time curves revealed wash-out curves to be less common in ILC (48% vs 84%). However, when using the CAD-application to assess the most malignant looking curve, the difference was blotted out (76% vs 86%).

Conclusions

ILC enhances slower than IDC, but peak enhancement is not significantly less. The use of a CAD-application may help to determine the most malignant looking contrast-enhancement versus time curve, and hence facilitates lesion classification.

Introduction

Breast cancers are pathologically divided in several histologic types. The most common types are invasive ductal carcinoma (IDC) in approximately 85% and invasive lobular carcinoma (ILC) in 10-20% [1]. IDC is a diagnosis per exclusion, i.e. a tumor is an IDC if no specific subtype can be assigned. ILC on the other hand is a specific histological diagnosis [2,3]; it is a malignancy that is characterized by small, relatively uniform cells that grow in a loosely cohesive fashion due to the loss of the adhesion molecule E-cadherin, and may infiltrate the surrounding tissue in single cell file [4]. There are distinct and well documented differences between IDC and ILC; ILC are generally larger at detection, occur in older patients, show less surrounding fibrosis, are more often estrogen receptor (ER) and progesterone receptor (PR) positive and more often Her2/Neu negative.

The problem with ILC is the lower diagnostic performance of mammography [5-7] and ultrasound [8,9] compared to IDC. This is probably caused by the diffuse growth pattern of some ILC and the lack of sufficient surrounding fibrosis. The sensitivity of mammography for ILC ranges from 35 to 81% [10,11] and the sensitivity of ultrasound for ILC ranges from 68 to 98% (overall approximately 83%, [10]). Moreover, on mammography, ILC presents much more regularly as an asymmetry in the glandular pattern or as architectural distortion than IDC [5,12]. Similarly, on ultrasound ILC are more often associated with hyper- or isoechoic patterns and/or present as architectural distortion than tumors with an invasive ductal histology [9,13]. Consequently, adequate tumor size assessment is compromised, and it has been shown that mammography an ultrasound commonly understage the disease.

The diagnostic performance of breast MR for ILC is much better than the conventional imaging techniques. It is better in size assessment [14-20] and tumor staging and consequently changes the surgical management in 28% of ILC cases [21].
MRI also has become a screening modality for patients at high risk and for evaluation of the contralateral breast of women with proven unilateral breast cancer, hence tumor detection has become an important function of breast MRI. A recent meta-analysis showed that the sensitivity of breast MRI for ILC was 93% and as such not different from the overall sensitivity of MRI for breast cancer in general (90%) [21,22].

However, several studies suggest that ILC enhances later after contrast medium injection [23,24], does not reach similar peak enhancement and does not exhibit early wash-out of the contrast agent [23]. Furthermore, a non-mass like morphology appears to be more common [25,26]. Consequently, terms in the ACR BIRADS MRI lexicon, the standardized reporting tool for breast MRI [27], that have a high positive predictive value for malignancy, such as "irregular mass" and "spiculated margin" may be less commonly applicable [28]. Moreover computer aided diagnosis systems that use enhancement characteristics (all currently available commercial systems) may misdiagnose ILC as a benign lesion.

The aim of this study is to quantify differences in the enhancement patterns of IDC and ILC on breast MRI, using an in-house developed application that has already been shown valuable in the differentiation between benign and malignant breast lesions [29] and a commercially available application dedicated to breast MRI.

Materials and methods

Patients

We searched the clinical database and selected all women with invasive breast cancer who were treated at our hospital between January 2003 and December 2006. In total 327 women were eligible. From this group we selected all women that underwent contrast enhanced breast MRI, which yielded 150 patients. We excluded 13 patients that had a histologic diagnosis that was not pure IDC or pure ILC (with or without accompanying carcinoma in situ) and, furthermore, one patient with an incidentally detected low grade IDC of 7 millimeters because the tumor was, even in retrospect, not visible at breast MRI. The study was thus performed with the imaging data of 136 patients with pathologically assessed invasive breast cancer.

The indication for the performance of breast MRI was highly variable, some were performed as problem solving after inconclusive findings on conventional imaging, others were aimed at preoperative staging and screening of the contralateral breast. Moreover, many patients received a breast MRI due to participation in one of several prospective trials. However, the acquisition protocol in all patients was identical.

Scanning Protocol

In all patients, prior to the investigation, an intravenous canula was placed in the cubital vein for contrast administration. Patients were then placed in the prone position on the scanner table with both breasts hanging free in the coil loops of a dedicated bilateral four channel breast coil (Invivo, Germany). Patients were subsequently entered in the magnet (1.5T Avanto, Siemens, Erlangen, Germany), with the breasts carefully placed at the isocenter. During the investigation the contrast medium was administered at a dose of 0.2 mmol/kg (Dotarem, Guerbet, France), using a powerinjector at a speed of 2.5ml/sec (Medrad, Warrendale, USA).

The scanning protocol was bitemporal in nature, i.e. we performed both relatively high spatial, low temporal and low spatial, relatively high temporal acquisitions. Localizer images and proton density images at low and high temporal resolutions were acquired (used for calibration purposes, see below). This was followed by 1 pre- and 4 post contrast FLASH 3D acquisitions at a high spatial resolution and a relatively low temporal resolution (TR/TE 7.8/4, FA 20, rectangular FOV 340, matrix 256*256, slice thickness 1.3, orientation coronal, AT 90s), interleaved with a consecutive series of 22 turboFLASH acquisitions at a high temporal and low spatial resolution (TR/TE 72/1.54, FA 20, FOV 340, matrix 256 *82, slice thickness 4.5, orientation transversal, AT 4.5s) that was started at the moment of contrast administration and lasted exactly 98 seconds.

Post-processing

The MRI scans of all patients were collected and uploaded to two different dedicated breast MR working stations.

The first workstation was an in-house developed application (MRCAD) that performs pharmacokinetic analysis using the high temporal resolution acquisitions in a Tofts model. The exact mechanism of this modelling approach, which yields the parameters K^{trans} (the volume transfer constant (min-1)), k_{ep} (the rate constant (min-1)), v_e (the relative fraction of the extracellular, extravascular space (%)), t0 (start of enhancement (sec)), and latewash (final slope of the curve (%)), is described in detail elsewhere [29,30], but in short: the observed changes in signal are fitted to a general signal enhancement model. This reduces the acquired data to a standardized exponential curve based on the following five parameters; baseline signal (s0), start of enhancement (t0), time to peak enhancement (ttp), peak enhancement (sp), and wash. Subsequently this reduced signal intensity versus time curve is converted to a tracer concentration (mmol/ml) versus time curve, using the high temporal resolution proton density acquisition and one of the turboFLASH acquisitions to calculate the native T1 of the tissue, and the signal from the peripheral fat to calculate machine gain. This, effectively, converts the signal peak (sp) to a concentration peak (cp).

A standardized model of the plasma profile is used to calculate pharmacokinetic parameters for each voxel as: $v_e = cp_{tumor} / cp_{plasma}$, $t0 = t0_{tumor} - t0_{plasma}$, $k_{ep} = 1 / (ttp_{tumor} - ttp_{plasma})$, latewash = $wash_{tumor} - wash_{plasma}$, and $K^{trans} = v_e * k_{ep}$, were the subscript tumor refers to the observed values in the tumor voxels and the subscript plasma refers to the standardized plasma profile.

This allows the creation of color coded pharmacokinetic maps that can be used as overlays on images with a high spatial resolution on this workstation, but in this study we only used the numerical values per voxel for inter tumor comparison.

All lesions were scored on the MRCAD by a single reader (R.M.). Numerical values per tumor were obtained by drawing a region of interest (ROI) around the whole area where, according to the pathology report, the tumor was located (fig 1). All voxels within this ROI that showed at least 10% change in signal intensity over the observed period, were regarded as part of the tumor. The system automatically produced 10^{th}-percentile and quartile scores for the parameters mentioned above. We analyzed only the distribution of K^{trans} and v_e, which were chosen because of the physiological conditions that are represented by these parameters. K^{trans} is, in situations with sufficient blood flow, proportional to the permeability surface area of the blood vessels within the lesion and hence governs the speed of enhancement, whereas v_e is the relative fraction of the extracellular extravascular space and as such determines the maximum relative enhancement at a given concentration of the contrast medium [31].

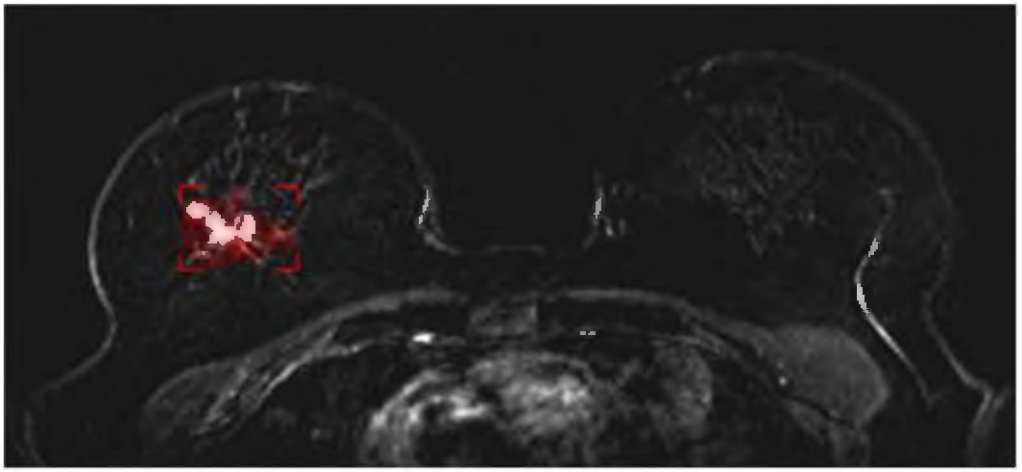

Fig 1: *A wide ROI, consisting of a combination of multiple sphere shaped regions, is drawn around a multifocal and highly irregular tumor using MRCAD.*

The second application is a commercially available package (CADstream v3.1, Confirma, USA). This workstation was only used for the analysis of the high spatial resolution acquisitions.
With the settings used in our hospital, this system generates coronal and sagital subtraction images of the pre-contrast and first post-contrast sequence (early subtraction) which are automatically shown. Furthermore, a coronal pre-contrast T1 acquisition and a maximum intensity projection generated from the early subtraction are shown. CADstream produces a color-coded "angiomap" of the changes in signal intensity over time, using a relative enhancement of 50% as threshold. The applied colors correspond to the enhancement versus time curves as described by Kuhl et al [32]. By choosing the "volumes" option and clicking on a colorized voxel in the tumor, CADstream automatically segments a 3D volume of continuous enhancing voxels. Subsequently, it displays the most malignant looking relative enhancement versus time curve in a 3*3*1 voxel area within the selected volume, and the quantified distribution of kinetic parameters throughout the selected volume (e.g. 10% of voxels in the volume show rapid initial enhancement and wash-out) (fig 2).

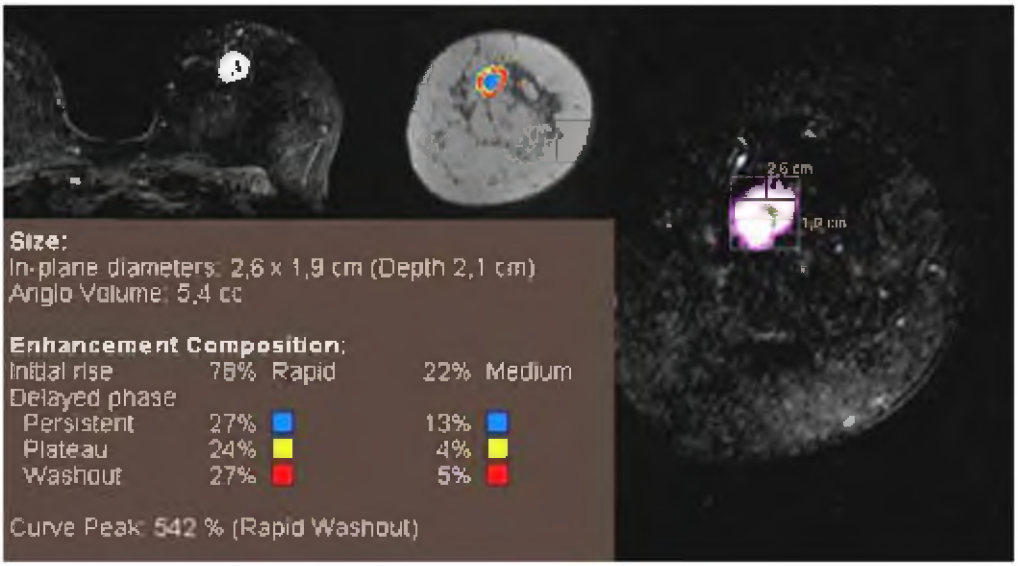

Fig 2: *Auto-segmentation of the dominant focus using CADStream. Note the irregular margin of this mass-like lesion and the presence of rim-enhancement. Under the data-tab CADStream shows the distribution of the relative enhancement curves within the segmented volume.*

All images were evaluated at the CADstream workstation by a different independent reader (C.B.). The reader was aware of the fact that an invasive carcinoma was present and also knew in which breast the lesion was located, but was unaware of the exact location of the tumor within the breast and the final histology of the tumor . The morphologic appearance of all lesions was described according to the BIRADS lexicon. The most malignant looking curve that was representative for the lesion was first obtained by visual assessment.
Subsequently, the lesion, or in case of multifocality, the most dominant focus, was segmented using the "volumes" function. The most malignant curve as detected by the system was noted. The distribution of the enhancement parameters in the volume was also noted.

Pathology

Histopathological characteristics of each tumor were extracted from the pathology report created at the time of treatment.

Statistics

The differences in the description of tumor characteristics between IDC and ILC with a binomial or categorical distribution were evaluated using the chi-square test or Fisher exact test whenever appropriate. Differences in continuous variables were analyzed, using the T-test for unrelated samples.

Results

Pathology

We included 136 patients, 103 with IDC (76%) and 33 with ILC (24%). The mean patient age was 53.5 in the IDC group and 55.8 in the ILC group. In the IDC group 29 patients were treated with a lumpectomy and 74 with a mastectomy, these figures were respectively 11 and 22 in the ILC group. Table 1 shows the overall distribution of the pathologically evaluated parameters. We did not observe differences in the distribution of tumor stages according to the TNM classification between the IDC and the ILC group. Nevertheless, lobular cancers were overall slightly larger than ductal carcinomas, were more often multifocal and/or multicentric, had a different distribution of tumor grade and had an overall lower mitotic activity index (MAI). Typically, IDC were associated with concurrent DCIS. Some DCIS was seen in 60 of 103 cases, and in 39 cases an extensive DCIS component (that is, DCIS more than focal outside the tumor) was present. Only 9 of 33 ILC were associated with some concurrent DCIS and 3 of cases showed extensive DCIS. ILC were, however, usually accompanied by LCIS, which was present in 31 of 33 cases and was extensive in 22. In IDC, LCIS was rare, 21 cases had a small LCIS component and only 2 showed extensive LCIS.

Table 1: *Distribution of the pathologically evaluated parameters*

Characteristic	IDC		ILC		p-value
N	103	(76)	33	(24)	
Mean patient age	53.5		55.7		0.4
Unifocal	63	(61)	13	(39)	0.03
Multifocal/Multicentric	40	(39)	20	(61)	
Size of largest focus (mean (cm))	2.2		3.0		0.05
ER-	16	(15)	1	(3)	0.07
ER+	87	(85)	32	(97)	
PR-	32	(31)	6	(18)	0.15
PR+	71	(69)	27	(82)	
Her2/Neu-[a]	53	(88)	22	(92)	0.70
Her2/Neu+[a]	7	(12)	2	(8)	
Grade I[b]	19	(19)	6	(20)	0.02
Grade II[b]	35	(35)	20	(67)	
Grade III[b]	45	(45)	4	(13)	
MAI (mean)	22.9		7.7		0.03

[a]missing in 52 cases, 43 IDC and 9 ILC, [b]missing in 7 cases, 4 IDC and 3 ILC
ER = Estrogen Receptor expression, PR = Progesteron Receptor expression
MAI = Mitotic Activity Index, Numbers between parenthesis represent percentages

Pharmacokinetic analysis

We did not observe any difference in the distribution of ve, hence the relative fraction of the extravascular extracellular space does not differ between IDC and ILC. However, the distribution of K^{trans} (~permeability surface area) was significantly different between the IDC and ILC groups. The mean K^{trans} was higher in the IDC group than in the ILC group (1.2 vs 0.9 min-1, p=0.01), which was mainly caused by focal areas of much higher K^{trans} in IDC than in ILC. Median K^{trans} values were not significantly different between groups. Increasing percentile scores showed, however, increasing differences between the IDC and ILC groups, as shown in table 2.

In short, the most enhancing voxels per tumor in the IDC group showed a significantly higher permeability surface area than the most enhancing voxels per tumor in the ILC group.

Table 2: *Differences in distribution of the pharmacodynamic parameters between IDC and ILC.*

Parameter	Percentile	IDC	ILC	p-value
Ktrans (min-1)	50	0.97	0.74	0.11
	75	1.86	1.3	0.01
	90	2.8	1.9	<0.001
Ve (%)	50	29	29	0.99
	75	43	42	0.84
	90	56	54	0.74

Kinetic appearance

Visual assessment of the relative enhancement versus time curve revealed that wash-out was more common in the IDC group than the ILC group (87/103 vs 16/33, p<0.01), but this difference was no longer present when evaluating the most malignant curve that was automatically selected by CADstream's "volumes" option (table 3). In other words, in most tumors at least one small area can be detected with a type 3 enhancement curve, regardless of the histological origin.

Maximum relative enhancement was not different between IDC and ILC, nor was the fraction of voxels that showed rapid initial enhancement (at least 100% at the first post-contrast high spatial resolution acquisition) (56 vs 58%, p=0.6).

The distribution of relative enhancement versus time curves in the segmented volumes differed between tumors in the IDC and ILC groups. A type III curve (wash-out) was seen in less than 10% of all segmented voxels in 31/103 IDC and 21/33 ILC (p<0.01). Moreover the fraction of voxels that showed continuous enhancement was also lower in the IDC group than in the ILC group (51% vs 61%, p=0.03).

Table 3: *Results of the evaluation of the most malignant looking curve per tumor by visual assessment and as selected by CADstream. Numbers between parenthesis represent percentages.*

Method		Visual assessed curve				Automatically detected curve			
		IDC		ILC		IDC		ILC	
Curve Type	I) Continuous enhancing	1	(1)	1	(3)	1	(1)	1	(3)
	II) Plateau	15	(15)	16	(48)	13	(13)	7	(21)
	III) Wash-out	87	(84)	16	(48)	89	(86)	25	(76)
p-value		<0.01					0.45		
Maximum Amplitude	(mean (%))	x		x		382		360	
p-value						0.76			

Morphologic appearance

Table 4 shows the distribution of all BIRADS lexicon descriptors for morphology in the evaluated population. We did not observe typical differences in the distribution of morphologic descriptors between IDC and ILC. Most tumors were accompanied by surrounding foci of enhancement and mass-like enhancement was the most common form of presentation for both IDC and ILC. The relative fraction of non-masslike enhancement was higher in the ILC group, but this did not reach statistical significance. Although we allowed the assignment of a tumor to both mass-like and non-mass-like enhancement in case of substantial contribution of both lesion types, only two tumors in the IDC group and two tumors in the ILC group were scored likewise.

Table 4: *Distribution of morphological descriptors according to the BIRADS lexicon. Numbers between parenthesis represent percentages.*

Descriptor	Sub-descriptor	IDC		ILC		p-value
Foci of Enhancement		95	(92)	31	(94)	0.75
Mass-like enhancement		86	(83)	25	(76)	0.32
Shape	Circular	11	(13)	4	(16)	
	Oval	10	(12)	3	(12)	
	Lobular	8	(9)	2	(8)	
	Irregular	57	(66)	16	(64)	
Margin	Smooth	9	(10)	2	(8)	
	Irregular	23	(27)	7	(28)	
	Spiculated	54	(63)	16	(64)	
Internal Enhancement	Homogeneous	6	(7)	3	(12)	
	Heterogeneous NOS	69	(80)	20	(80)	
	Rim Enhancement	10	(12)	2	(8)	
	Enhancing septations	1	(1)	0	(0)	
	Dark septations	0	(0)	0	(0)	
Non-mass like enhancement		19	(18)	10	(30)	0.15
Type	Linear	1	(5)	1	(10)	
	Ductal	0	(0)	0	(0)	
	Segmental	10	(53)	6	(60)	
	Regional	4	(21)	1	(10)	
	Diffuse, Patchy	3	(16)	1	(10)	
	Diffuse, Nonspecific	1	(5)	1	(10)	
Internal Enhancement[a]	Homogeneous	0	(0)	2	(20)	
	Heterogeneous NOS	18	(95)	6	(60)	
	Stippled / Punctate	0	(0)	1	(10)	
	Clumped	0	(0)	0	(0)	

[a]*In 1 IDC and 1 ILC internal enhancement could not be assessed*

Discussion

To our knowledge, this is the first study to directly compare the enhancement characteristics and morphological features of IDC and ILC. However, several other small studies evaluated the appearance of ILC on MRI by itself [14,20,23-26,33-35].

We observed that K^{trans} values were lower in the ILC group than in the IDC group.
Two small studies that performed quantitative pharmacokinetic analysis in ILC did not compare their data to parameter values obtained from IDC and did not include enough patients to produce otherwise statistically meaningful results [33,35]. However, both studies (which respectively evaluated the extraction flow product (EF) and k21, both comparable to K^{trans} in our study) stated that blood vessel permeability in ILC can, in large areas of the tumor, be very similar to blood vessel permeability in normal breast tissue and appeared lower than in IDC, which corresponds well with our data.
The lower K^{trans} values in the ILC group imply that enhancement (especially in the most rapidly enhancing voxels) in the IDC group is faster than in the ILC group (because the permeability of the blood vessels is higher). However, as we did not observe differences in ve (which governs the maximum possible enhancement), peak enhancement does not differ between groups (which is in accordance with our results from the analysis of the high spatial resolution acquisitions) thus the peak is only reached earlier. There is also some histopathological evidence for these differences in the microvasculature between IDC and ILC. Lee et al. showed that the expression of vascular endothelial growth factor (VEGF), a messenger protein that is very important for tumor angiogenesis and increases vascular permeability (it is also known as vascular permeability factor) is higher in IDC than in ILC. Nevertheless, the microvessel density did not differ between these tumor types [36].

We did detect a difference in the appearance of the relative enhancement curves between IDC and ILC when evaluated by visual assessment. This is the most common procedure to assess curve shape in literature [28,32], and is widely used in clinical practice. However, adequate use of the BIRADS lexicon implies the use of the most malignant looking curve in a 3*3*1 voxel area within the tumor for lesion classification [27], therefore, the machine detected most malignant looking curve is probably the most suited to classify lesions as benign or malignant.
The higher permeability in IDC should theoretically lead to steeper wash-out slopes of the relative enhancement versus time curves as contrast also leaves the extravascular extracellular space more easily. However, apart from the 10% signal decrease cut-off point for wash-out, the standard curve classification does not take the slope of the wash-out curve into account. Consequently, the most malignant looking relative enhancement versus time curves of ILC are hardly different from those of IDC when the delay between contrast administration and the post-contrast acquisition is long enough. So far, little research has been undertaken investigating the shape of enhancement curves in ILC [23,24]. Trecate et al. noted in a series of 18 patients with ILC that a type III curve was commonly present, but that this was preceded by a delay before

actual enhancement started in eight patients [24]. Maximum enhancement was consequently reached earlier in IDC than in ILC. Sittek et al. also noted in a series of 23 patients with ILC that a peak contrast enhancement was only reached after approximately 3 minutes [23]. More recently Caramella et al. found a wash-out curve in only 6 of 35 patients, but they did not state how the curve was assessed [14].

Similar to our observations, the most common morphologic pattern of ILC on breast MRI described in literature is an irregular spiculated mass, but the fraction of non-mass like enhancement patterns is highly variable and ranges from 5-69% [20,25,26,33-35]. So far, only one study by Yeh et al., made consistent use of the BIRADS lexicon for the description of lesion morphology [35]. They described an irregular mass-like lesion in 8/19 cases and non mass-like enhancement with a segmental distribution in 5/19 cases, other patterns were less frequently observed. It thus appears that NMLE is indeed (slightly) more common in ILC and may reach statistical significance in larger series. Nevertheless, morphological analysis, even using the rigorous approach of the BI-RADS lexicon is subject to significant interreader variability. For analysis using CADstream an overall kappa-value of 0.41 has been reported, which was similar for ILC (κ =0.40) and IDC (κ =0.42) and is well in-line with earlier reported values in literature[37-39]. Hence, differences between various tumor types can only be appreciated in relation to each other.

This study does not show the potential of breast MRI to detect ILC. It is still retrospective in nature and most tumors were detected by other means. To observe whether MRI is capable of showing ILC undetected by conventional imaging modalities at an earlier stage, a prospective screening trial in a normal population is needed.

In conclusion, ILC enhance slower than IDC but do reach equal peak enhancement. The delay between contrast administration and the post-contrast acquisition should be sufficient to prevent ILC from being misclassified as benign lesions on the basis of continuous enhancement. We recommend a delay of approximately 90 seconds, because in our series this has been shown useful, whereas longer delays may allow more enhancement of normal breast tissue and hence lesions may become obscured. The use of a dedicated workstation that allows automatic detection of the most malignant looking curve may help to assess the most malignant looking curve.
The morphologic features of ILC are only slightly different to those of IDC and can thus be used to describe and classify these lesions. Naturally, the detection of NMLE should initiate work-up. Using these precautions it appears that MRI, as opposed to mammography and ultrasound, is able to detect ILC as well as IDC.

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The value of MRI compared to mammography in the assessment of tumor extent in invasive lobular carcinoma of the breast

7

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Abstract

Aims

Invasive lobular carcinoma of the breast (ILC) is known to be substantially underestimated by mammography, which makes correct planning of treatment difficult. MRI has been proposed as a valuable adjunct to mammography. The purpose of the current study is to evaluate its value, compare it to mammography and assess the possible causes of over- and underestimation of lesion size on MRI.

Method

The mammograms and MRI scans of 67 consecutive patients with ILC were retrieved and re-evaluated. Size measurements were correlated to the sizes extracted from the pathology report.

Results

MRI measurements correlated better to pathologic size ($r=0.85$) than mammographic measurements ($r=0.27$). Underestimation of tumour size was more common on mammography ($p<0.001$); overestimation occurred with equal frequency ($p=0.69$). Overestimation on MRI, caused by non-malignant findings, was attributed to enhancing lobular carcinoma in situ.

Conclusion

MRI is a more accurate modality to determine tumour size in patients with ILC than mammography. The typical underestimation of lesion size by mammography can be prevented with the aid of MRI, without increasing the risk of lesion overestimation.

Introduction

Preoperative extent estimation of breast cancer

In the treatment of breast cancer, there is an increased importance of adequate tumour extent estimation prior to surgery. The main reason is that breast conserving treatment (BCT) has replaced mastectomy as the principal therapy of choice. Local recurrence after BCT and radiotherapy occurs in 3 – 19% of patients and is usually caused by (unrecognized) incomplete resection or multifocality. Theoretically, this can thus be prevented by correct pre-operative assessment of tumour extent [1]. Another reason is the increasing use of neoadjuvant chemotherapy [2]. The decision to treat a patient with neoadjuvant chemotherapy is entirely based on pre-operative tumour size assessment and is advocated for all T3 and T4 tumours [3]. In many studies, however, large resectable T2 breast cancers are also treated with neoadjuvant chemotherapy [1,3]. Additionally, initial tumour size is a strong predictor of subsequent response to chemotherapy (the smaller, the better the response) and the eventual prognosis [4].

A third reason is the upcoming use of non-surgical treatment modalities in the local treatment of breast cancer, such as radiofrequency ablation [5], cryoablation [6] and high-focused ultrasound [7]. These techniques cannot be controlled by pathological examination as no tissue is excised. Their success is, therefore, dependent on perfect size measurement by imaging. This requires imaging modalities that allow robust size measurement of breast cancer.

Extent estimation in invasive lobular carcinoma

Invasive lobular carcinoma of the breast (ILC), the second most common type of invasive breast cancer (present in 10-15%) after invasive ductal carcinoma (IDC), is a diagnostic problem. It is characterized by an insidious growth fashion (present in 33-70% of cases); the stroma is infiltrated in single cell file. Therefore, it is not only more difficult to detect ILC, but also much more difficult to accurately determine the extent of ILC.

Several studies have shown that size measurements in ILC on mammography and ultrasound correlate only moderately with pathological tumour size [8-10]. MRI on the other hand has been more successfully used in adequate tumour size estimation [11-13]. However, the risk of overestimation of lesion size on MRI (and consequently, unnecessary, more invasive treatment) hampers the general acceptance and implementation of this technique in clinical practice [14].

Study objectives

The sample size of the published studies to date is low and does therefore not allow an evaluation of the reasons for under- or overestimation of lesion extent by MRI. The purpose of this study is to evaluate whether size estimation on MRI is indeed superior to mammography in a larger cohort of ILC. Moreover, we elaborate on the causes of under- and overestimation of tumour size and their consequences in patient treatment.

Patients and Methods

We retrospectively searched the pathology and database of all patients surgically treated for breast cancer at our hospital between 1993 and 2005 and reviewed their surgical record. All patients with ILC who were surgically treated and where a MRI was performed in the pre-operative work-up were selected. Patients with other histologic types of invasive cancer and patients with tumours with a mixed histology were excluded. Concurrent ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) were accepted.

Mammography

All collected mammograms up until 1999 were acquired with a Mammomat 3000 (Siemens, Erlangen, Germany). After 1999, the Radiology department converted to digital mammography and all mammograms were made using a Senograph 2000 D or a Senograph DS (GE Healthcare, Wisconsin, USA). In each patient medio-lateral oblique and cranio-caudal views were obtained. An experienced breast radiologist reviewed all mammograms. The radiologist was aware of the patient's condition but unaware of the clinical findings, location of the tumour or size measured at pathology. All lesions were scored from 1 to 5 according to the Breast Imaging Reporting and Data System (BI-RADS) classification. The position of any finding on mammography that would have prompted further evaluation (i.e. BI-RADS 3 or higher) was compared to the location of the tumour at pathology. When the actual tumour was present in the same quadrant of the same breast, the lesion was classified as detected by mammography. The size of the tumour was measured as the largest diameter of the whole tumour in any direction. In case of multifocal disease, besides the size of the whole tumour area, the maximum diameter of the largest focus was also recorded. Spiculae were regarded as desmoplastic stromal reaction, according to the findings by Flanagan et al. [15], and were not included in size measurement.

Ultrasound

We did not review the ultrasound reports, nor the ultrasound images, as we regard ultrasound to be an operator dependent imaging modality that is poorly represented by evaluation of the incidental screenshots taken at the time of evaluation.

MRI

The MRI investigations of all patients were retrieved. Indications for the performance of MRI were clarification of uncertain findings, assessment of tumour extent or participation in one of several prospective studies that were performed at our hospital in the above-mentioned period of time. All MRI were made using a Magnetom Vision or Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany), both at 1.5T. Prior to examination a canula was placed in the cubital vein for contrast administration. The patient was placed in the prone position, with both breast hanging free in a bilateral open breast coil (Machnet, the Netherlands or InVivo, Germany). Localizer images were created, followed by six FLASH 3D acquisitions that were positioned on the localizer (TR/TE 7.8/4 ms, flip angle 20^0, matrix 256*128, rectangular field of view 340

mm, coronal orientation, slice thickness 1.3 mm, acquisition time 98 sec). The contrast agent (Magnevist, Schering, Germany or Dotarem, Guerbet, France) was administered between the first and the second FLASH 3D acquisition (dose of 0.2 mmol/kg) by a power injector (Medrad, Pittsburgh, USA) at a speed of 2.5 ml/sec and flushed with 20 ml of saline. The collected MRI were presented on a DynaCAD (InVivo, Germany) workstation to the same breast radiologist that re-evaluated the mammograms, but separately from mammography. Again, all lesions were located and scored according to the BI-RADS classification.[17] The maximum diameter of the lesion in any plane was recorded as the tumour size on MRI. In case of multifocal disease, both the size of the entire lesion area and the size of the largest focus were measured.

Pathology

Pathologic findings were extracted from the pathology report created at the time of treatment. The location and maximum size of the lesion area were noted, as well as the maximum size of the largest focus in case of multifocal disease.

Statistical methods

Pearson's correlation coefficients were calculated for both mammographic size and MRI size versus pathologic size. In case of multifocal disease, the size of the whole tumour area was used whenever available. When the size of the whole tumour was unavailable or not measurable in any of the three evaluations, the size of the largest focus was used for correlation.

Because the cohort has been acquired over a long period of time, we split the cohort into two sub-cohorts based on date of surgery (1993-1999 and 2000-2005) and also evaluated these sub-cohorts separately. Fisher's Z-test was used to compare correlation coefficients of these sub-cohorts.

Measurements of lesion size on mammography or MRI were considered correct when lesion size was within 1 cm from the pathologic measurement. Lesions were considered underestimated when the measured size was more than 1 cm smaller than pathologic size and overestimated when they were more than 1 cm larger. McNemar's test for related samples was used to test for differences in the amount of cases with overestimation and underestimation between mammography and MRI.

P values smaller than 0.05 were considered significant in all cases.

Specific cut-off sizes

As 3 cm is the cut-off size to initiate treatment with neoadjuvant chemotherapy in our hospital, as is the case in many trials reported in literature, we assessed the accuracy of both mammography and MRI to discriminate between tumours both larger and smaller than 3 cm by receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was used as a measure of accuracy. Logistic regression was used to test whether the combination of mammography and MRI findings would be beneficial in this assessment. We also performed this analysis for lesions larger and smaller than 5 cm as there is a wide consensus that lesions larger than 5 cm should be treated by mastectomy with or without neoadjuvant chemotherapy

and these patients are no longer candidate for BCT.
Subsequently, we analyzed the amount of lesions on both MRI and mammography that appeared smaller than 5 cm but were larger at pathology because this may have clinical implications, whereas underestimation of lesions larger than 5 cm resulting in a size still larger than 5 cm results in the same treatment and has no clinical value.

Results

Patients and lesions

In the investigated period 148 women with ILC were treated. As 78 did not undergo pre-operative MRI, they were excluded. Furthermore, three patients were treated with neoadjuvant chemotherapy and were excluded because the pathological assessment is affected by this therapy. The remaining 67 women were included (age mean/median 55/55 years, range 35-78). In 66 of these patients, an ILC was detected by conventional triple assessment (physical examination, mammography and ultrasound). In the last patient, triple assessment detected an IDC in the left breast, subsequently MRI detected an ILC in the contralateral breast. Only the latter tumour was entered in the study. Two patients had a second, contralateral ILC, in both cases also detected by MRI only. We thus included 69 ILC. Tumour characteristics are presented in table 1.

Table 1: *Tumour (n = 69) characteristics*

Characteristic	N
Palpable	
Yes	55
No	14
Detected on Mammography	
Yes	55
No	13
Detected on MRI	
Yes	69
No	0
Tumour Stage	
T1	17
T2	28
T3	22
T4	2
DCIS present	15
LCIS present	61
Lymph node Stage	
N0	36
N+	33
Final Treatment	
Lumpectomy	20
Mastectomy	49

In one patient no mammography was performed; she had complained of pain during an earlier mammography and refused to undergo this examination. Furthermore, 13 tumours were mammographically occult and 1 was not measurable. The remaining lesions (n = 55) could be measured. On MRI no lesions were occult, and all lesions were measurable (n = 69).

Correlation to pathology

We observed no significant correlation between size measured on mammography and the actual tumour size on pathology. Tumour size measured on MRI was significantly correlated to pathologic size. Figure 1A and 1B show scatter plots of mammographic and MRI lesion size versus pathologic lesion size, respectively. Table 2 gives an overview of the measurements compared to pathology. After division of our cohort in two sub-cohorts (operated prior to, or after January 2000), no significant differences in performance over time for both mammography and MRI were detected (mammography $r = 0.27$ versus $r = 0.31$ ($p = 0.86$), and MRI $r = 0.81$ versus $r = 0.89$ ($p = 0.22$)). Further sub-division of our cohort did not yield any significant results.

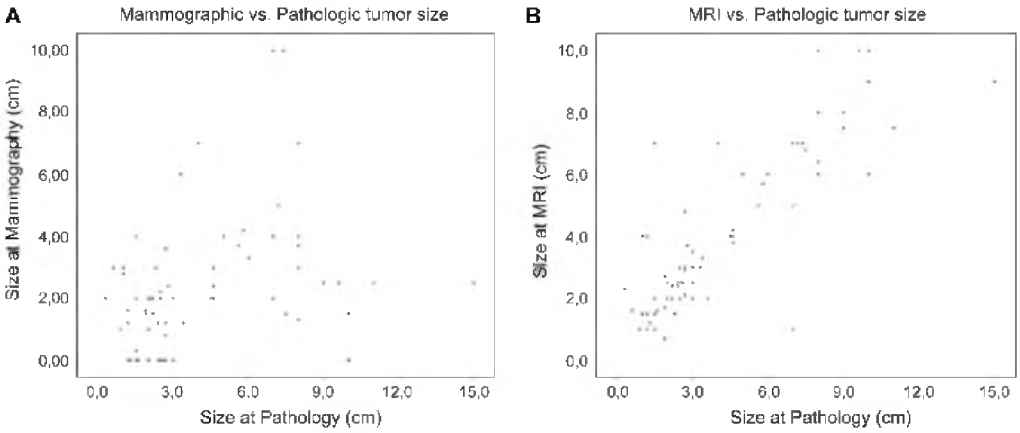

Fig 1: *Scatter plots of tumour sizes as measured on mammography (A) and MRI (B) versus pathologic tumour size.*

Table 2: *Measurement of tumour size on the respective imaging modalities, MRI and MMG (MMG = mammography) compared to pathology (PA). In case of mammography, only detected and measurable lesions are included. NA = Not Applicable*

	MMG	MRI	PA
Mean tumour size (cm)	2.9	4.1	4.3
Median tumour size (cm)	2.4	3.0	2.8
Range (cm)	0.1 – 10	0.7 - 10	0.1 -15
Under-estimated (> 1cm)	29	11	NA
Correct Measurement	20	51	NA
Over-estimated (>1 cm)	5	7	NA
Pearson's Correlation Coefficient	0.27 (p=0.46)	0.85 (p<0.01)	NA

Under- and overestimation of lesion extent

The maximum underestimation on mammography was 13 cm, while maximum overestimation was 4.8 cm. On MRI, maximum underestimation was 6 cm, while maximum overestimation was 5.5 cm.

Underestimation of lesion size occurred significantly more often on mammography ($p < 0.001$) (fig 2, fig3), overestimation, on the other hand, occurred with equal frequency on mammography and MRI ($p = 0.69$). In the five cases where mammography led to overestimation of tumour size, two were attributed to concurrent extensive ductal carcinoma in situ (DCIS) (+3.0 and +2.7 cm, respectively), one case was attributed to sclerosing adenosis (+2.4 cm) and in two cases only

lobular carcinoma in situ (LCIS) was detected at pathologic examination of the specimen (+1.7 and +2.0 cm, respectively).

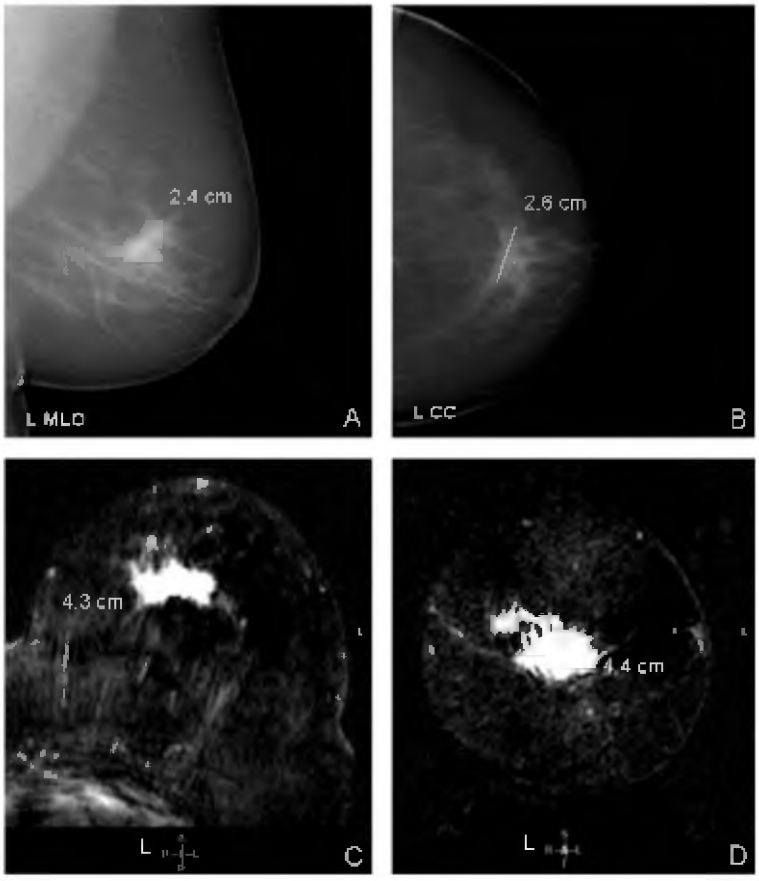

Fig 2: *A and B show the mammogram of a fatty left breast in medio-lateral oblique (MLO) and cranio-caudal (CC) orientation, respectively. Retroareolair, an irregular spiculated mass is observed with a maximum diameter of 2.6 cm. C and D show subtracted MRI images of the same breast in axial and coronal orientation. The irregular, spiculated enhancing lesion measures 4.4 cm. Pathologic examination revealed an unifocal ILC with a maximum diameter of 4.6 cm.*

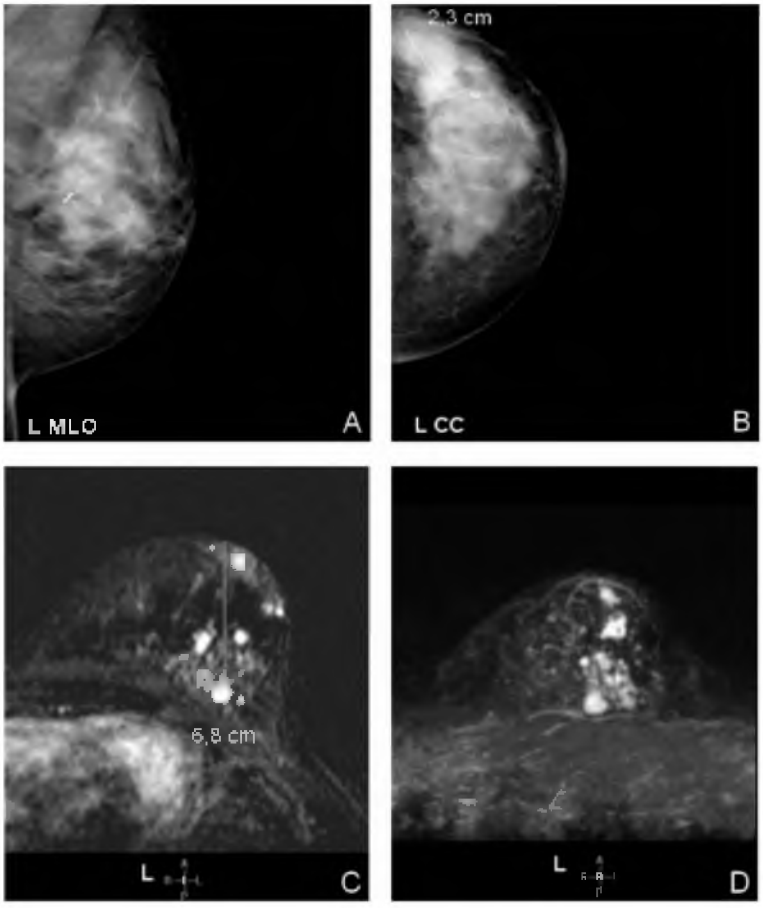

Fig 3: *A and B show the mammogram of a dense left breast in medio-lateral oblique (MLO) and cranio-caudal (CC) orientation, respectively. There is a clip from prior surgery of a benign lesion. Lateral, an irregular mass is observed with a maximum diameter of 2.3 cm. C and D show a subtracted MRI image in axial orientation and a maximum intensity projection (MIP) of the same breast, respectively. MRI reveals multiple enhancing, highly suspicious lesions over an area of 6.8 cm. Histological proof of malignancy was obtained prior to surgery by core biopsy. Pathology after surgery revealed a multifocal ILC over an area of 7.3 cm.*

In seven patients where MRI overestimated the invasive tumour size, two were attributed to concurrent DCIS in and around the tumour (+3.0 and +5.5 cm respectively). In these cases the amount of overestimation correlated well with the extent of DCIS. In one patient the tumour had infiltrated the skin and nipple and overestimation of lesion size (+2.0 cm) was attributed to inflammatory changes. In the remaining four patients, overestimation of tumour size could only be explained by extensive LCIS detected in the specimen (+1.9, +2.1, +2.1 and +3.0 cm, respectively).

In one of these latter patients, the invasive tumour was 2.7 cm and therefore a breast conserving approach would have been possible according to the standards valid at the time of treatment, but a mastectomy was performed. This might have been due to the performance of MRI.

Specific cut-off sizes

MRI was significantly better able to discriminate between tumours larger and smaller than 3 cm (AUC 0.94) than mammography (AUC 0.81) ($p = 0.04$). Figure 4A shows the ROC curves of mammography, MRI and the combination, respectively. Adding mammography to MRI measurements did not significantly increase the AUC (AUC=0.96, $p = 0.42$). Similar results, shown in figure 4B, were observed for the discrimination between tumours larger and smaller than 5 cm (MRI: AUC 0.94, mammography: AUC 0.77) ($p = 0.02$). We observed in total 23 ILC with a pathological size larger than 5 cm, mammographically 19 of these ILC appeared smaller than 5 cm (mean underestimation 5.76 cm), whereas only one appeared smaller than 5 cm on MRI (7 cm tumour, underestimated by 6 cm).

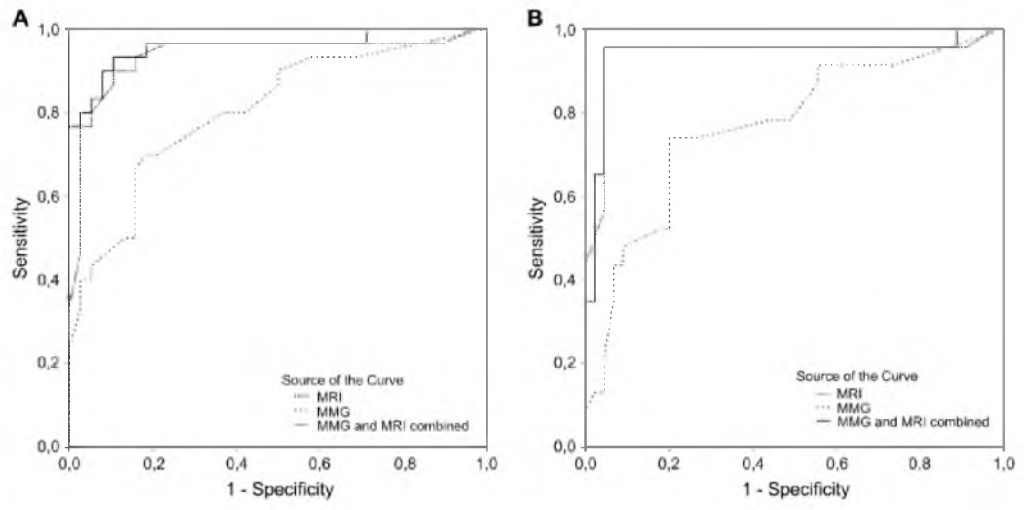

Fig 4: *A: ROC curves for the prediction of pathologic tumour size > 3cm by mammography (MMG) and MRI and the combination of both. B: ROC curves for the prediction of pathologic tumour size > 5 cm.*

Discussion

All ILC evaluated in this study were visible on the MRI. Therefore, MRI has an advantage over mammography, by which only 55 of the tumours were visible. However, false negative results of breast MRI in cases of ILC are reported by other authors. Wurdinger et al. described 5 false negative MRI examinations due to delayed or absent contrast enhancement in a series of 193 invasive carcinomas [17]. Four of these had a lobular histology and the fifth was of tubular origin. The insidious growth fashion of ILC requires less extensive neovascular proliferation. As a consequence, vessels may be more mature and leakage of contrast from the vessels to the extravascular extracellular space, the very reason for enhancement on MRI, can be less pronounced than in other types of breast carcinoma [18], but this does not decrease the value of MRI. Our results clearly show that MRI is by far superior to mammography in the estimation of tumour size. These results are constant over time, we did not observe any statistical differences over the long period of inclusion in this analysis.

Importance of adequate extent estimation in ILC

The importance of adequate tumour size estimation in case of ILC is stressed by the observation that margin status after BCT is more often compromised in ILC than in IDC. As a consequence, re-excision and conversion of BCT to mastectomy are more common for ILC than for IDC [19,20]. The risk is especially increased in ILC larger than 1.5 cm at mammography, and in younger patients [19]. Unfortunately ILC are generally larger than IDC and a size of more than 1.5 cm is common. A further complication is that ILC tend to be more often multifocal and/or multicentric than IDC (14-31%) [21], which is in many cases not observed on mammography or ultrasound [22]. MRI, on the other hand, has been shown to document up to 100% of all cases of multifocality [22]. However, we did not address multifocality as a separate item in this analysis. Instead, we measured, whenever possible, the size of the whole tumour area because this has the most important implications for patient treatment.

Mammography

Our results indicate that size measurement on mammography in cases of ILC is of no value. More than half of all visible lesions are underestimated by more than 1 cm. Furthermore, overestimation of tumour size occurred in another 5 cases. Fortunately, other authors report more positive results of tumour size estimation on mammography in ILC. In a recent study by Heusinger et al. an overall correlation coefficient of 0.70 was reported for ILC. They noted that the accuracy of tumour size estimation on mammography was, apart from histologic type, largely dependent on tumour size itself [23]. Accuracy decreased with increasing tumour size, the size of larger tumours tended to be underestimated, and more so with increasing size. Therefore, it was more difficult to predict mammographically whether or not a tumour was larger than 3 cm than whether a tumour was larger than 2 cm. This finding was even more prominent in ILC than in IDC. Similar results were presented by Dummin et al., who reported a R^2 of 0.73 for size measurements of ILC on mammography compared to pathologic size [24].

This value, however, dropped to 0.21 when only T2 tumours were included in the analysis and eight lobular carcinomas over 3 cm in size were underestimated by a mean of 60%. The lower value of our measurements with mammography can thus be explained by the overall large size of the tumours in this study. This is also apparent from the enormous underestimation in the subgroup of tumours larger than 5 cm. However, we were unable to produce better results with only the (small) subset of T1 tumours in our study.

Another possible explanation for the structural underestimation of tumour size on mammography might be the exclusion of spicules from the tumour size measurement. This method is commonly used in literature [15,24], but some studies indicate that although spicules are usually only a desmoplastic reaction, some may contain tumour cells [25]. Mammographically, these spicules cannot be separated from each other, therefore it has been argued that the spicules should be included in the measurement [25].

MRI

Reported correlation coefficients for tumour size and MRI measurements are, in contrast to mammography and ultrasound, reasonably constant and substantially better. The presented correlation coefficients in literature range from 0.86 to 0.97 and our observation ($r = 0.85$) is thus on the lower edge of this range [12,13,26,27]. Adequate tumour size estimation in case of ILC is therefore achievable with MRI.

Unfortunately, underestimation of tumour size with MRI is still impossible to exclude. We observed 11 cases where the actual tumour size was more than one cm larger than predicted on MRI. In these cases, an attempt for BCT would probably have led to compromised margins and subsequent re-excision. This observation also prohibits the use of non-surgical treatment for ILC. Although not diminishing the significance of MRI underestimation, these cases were in general large lesions (mean 7.57 cm) with a diffuse growth pattern that would not have been eligible to any non-surgical treatment protocol. In all cases, suspicious enhancement was only present in part of the lesion. Furthermore, small satellite lesions surrounding the index lesion may have been excluded from the tumour area, even though these foci are often found in lobular breast cancer [22] and are usually malignant in origin and thus need to be included in tumour sizing [28].

However, the main reason that MRI is not yet widely accepted for tumour extent estimation prior to therapy is not the possibility that MRI may underestimate lesion size but exactly the opposite. MRI may overestimate the actual lesion size and thus result in unnecessary more radical treatment [29,30]. In our study overestimation of lesion size on MRI by more than 1 cm was present in seven cases. In four cases this was probably caused by enhancing LCIS, as this was the only additional histologic finding present in these patients. Although, we can not provide a direct histological correlation for the enhancing area, other authors have also shown that LCIS may enhance on MRI [31].

However, the recent acknowledgement that LCIS still may be a precursor lesion rather than a high-risk lesion for subsequent development of invasive breast cancer may even justify more extensive treatment based on MRI findings [32]. Additional research in this area should be conducted as scientific evidence is lacking.

We could not confirm that MRI measurements led to a more structural overestimation of lesion size than mammography. Therefore, MRI seems a safe way to increase knowledge of tumour extent prior to treatment. Nevertheless, pathological confirmation of additional findings on MRI that might change the intended treatment, prior to surgery, is mandatory because false positive results do occur [28,29].
MRI provides a high accuracy in the discrimination between ILC larger or smaller than 3 and/or 5 cm. Therefore, it can be confidently used to assign patients to adequate surgical treatment and neoadjuvant chemotherapy. Adding mammographic measurements to the MRI measurements did not further increase this accuracy and is thus not useful.

With respect to the above, we believe that MRI should be the imaging modality of choice in case of pathological proof of ILC. Nevertheless, apart from tumour size, size of the breast, expected cosmetic outcome, physical state of the patient, patient history and patient preference should be taken into account with every treatment decision. Any of these factors, alone or combined, may in time be more heavily weighted than tumour size itself.

Conclusion

MRI is the most accurate modality for tumour size estimation in patients with ILC currently widely available. Lesion size is not more often overestimated than with mammography. However, when overestimation occurs due to non-malignant findings, it can usually be attributed to extensive LCIS in and around the tumour. The typical underestimation of lesion size by mammography can be prevented with the aid of MRI. This may be helpful in the reduction of tumour positive margins after BCT and the rightful assignment to neoadjuvant chemotherapy treatment protocols.

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The impact of preoperative breast MRI on the re-excision rate in invasive lobular carcinoma of the breast

8

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Abstract

Purpose

Re-excision rates after breast conserving surgery (BCS) of invasive lobular carcinoma (ILC) are high. Preoperative breast MRI has the potential to reduce re-excision rates, but may lead to an increased rate of mastectomies. Hence, we assessed the influence of preoperative breast MRI on the re-excision rate and the rate of mastectomies.

Methods

We performed a retrospective cohort study of a consecutive series of patients with ILC who presented in one of two dedicated tertiary cancer centers between 1993 and 2005. We assessed the initial type of surgery (BCS or mastectomy), the re-excision rate and the final type of surgery. Patients were stratified into two groups: those who received preoperative MRI (MR+ group) and those who did not (MR- group).

Results

In the MR- group, 27% of the patients underwent a re-excision after initial BCS. In the MR+ group, this rate was significantly lower at 9%. The odds ratio was 3.64 (95% CI: 1.30 – 10.20, p=0.010). There was a trend towards a lower final mastectomy rate in the MR+ group compared to the MR- group (48% vs 59%, p=0.098).

Conclusions

Preoperative MRI in patients with ILC can reduce re-excision rates without increasing the rate of mastectomies.

Introduction

Invasive lobular carcinoma of the breast (ILC) is more prone to incomplete surgical excision and subsequent re-excision than other histological types of breast cancer. Reported re-excision rates in ILC after breast conserving surgery (BCS) range from 29 to 67% [1–5]. In 16–48% of patients with ILC local surgical therapy is still converted to mastectomy after failure of BCS [1,5–10].

Contrast-enhanced magnetic resonance imaging (MRI) of the breast has often been proposed as the solution to failure of obtaining tumor free margins in BCS and subsequent re-excision or conversion to mastectomy. The technique is superior to conventional imaging methods in staging ILC [11–18], which is mainly achieved by improving tumor delineation and detection of additional tumor foci.
Conversely, many studies have shown that preoperative breast MRI changes therapy in 12–33% of patients from BCS to mastectomy [11,13,16,19–22]. Although the changes may be appropriate in 88% of cases according to pathology [23], this percentage is still relatively high compared to local recurrence rates [24]. Nonetheless, large trials have demonstrated that incomplete tumor excision is a risk factor for local recurrence [25]. Hence, the question remains whether MRI is capable of reducing the frequency of incomplete surgery and subsequent need for re-excisions without adverse side effects, such as dramatically increasing the rate of mastectomies [26–28]. This information is essential if MRI is to be implemented in the standard preoperative staging of all patients with ILC.

The aim of this study, therefore, was to assess whether preoperative breast MRI influences the rate of re-excisions and the rate of mastectomies in a large consecutive series of patients with ILC.

Materials and Methods

Ethics

This cohort study was performed according to good clinical practice and the Dutch legal regulations. No approval of the local ethical committees or informed consent was needed for this study. However, patients who participated in earlier prospective clinical trials (approved by the local ethical committees) tailored to different research questions provided informed consent for those studies.

Patients

The pathological and oncological databases of the Radboud University Nijmegen Medical Centre (RUNMC) and the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AVL) were searched and all patients who presented with ILC between January 1993 and

December 2005 at the RUNMC and between January 1999 and December 2005 at the NKI-AVL were included. Both hospitals perform preoperative breast MRI in nearly all patients with ILC since early 2006. Consequently, no patients were included after 2005.
We excluded all patients who: (1) had a history of cancer of any type (n = 32), (2) had prior surgery to the affected breast except for excisional biopsy to establish the diagnosis (n = 15), (3) were initially treated with neoadjuvant chemotherapy or other non-surgical techniques (n = 41), (4) were initially treated in another hospital (n = 378).

Data acquisition

We reviewed the medical, radiological, and pathological records of all patients who met the inclusion criteria. We registered patient characteristics, when the diagnosis was established, time to initial surgery, and type of initial surgery (BCS or mastectomy) [29]. Furthermore, the number and type of repeat operations after initial surgery (due to the detection of involved resection margins at pathological examination in more than two low power fields (10× objective) at microscopy) were recorded. When tumor margins were clear or were only focally involved at microscopy (less than two low power fields) and no re-excision was deemed necessary, the surgical procedure was recorded as being radical (final pathology).
The radiological databases were searched for imaging studies to establish: (1) the type of conventional imaging performed to detect and stage the tumor, (2) whether contrast enhanced breast MRI was performed within 3 months prior to initial surgery, (3) the number of days between tumor detection (either at mammography or clinically), the breast MRI, and final pathology. All patients in whom breast MRI was performed were assumed to have been preoperatively staged with breast MRI.
The pathology databases were reviewed to obtain tumor size and pathological characteristics from the surgical specimens at final pathology. In the case of multifocal lesions the largest diameter of the total area with tumor foci was recorded. If this information was not available, the size of the largest focus was recorded.

Breast MRI

Due to the extensive study period and data acquisition in two cancer centers, the patients were scanned using various MRI systems, various field strengths ranging from 1.0 to 3.0 T and various scan protocols. The spatial resolution of these protocols generally improved over time. However, all patients were scanned in the prone position with the use of a dedicated bilateral breast coil. All protocols included a series of T1 weighted sequences that was repeated at least four times, first prior to the administration of a Gd-containing contrast agent and then several times after intravenous contrast administration at a dose of 0.1 mmol/kg. In all patients, subtraction images were created from the pre and post contrast scans to evaluate tumor morphology and tumor kinetics (internal enhancement and enhancement curve type) according to the BIRADS lexicon [30]. The size of the tumor was measured and reported in three perpendicular planes (coronal, axial, and sagital). The indications for the performance of MRI were diverse and included accepted clinical indications, patient wish and participation in clinical studies that assessed: (1)

the radiologic pathologic correlation of MR-visible tumors, (2) screening of women at high lifetime risk of breast cancer, (3) preoperative staging, and (4) new MRI sequences.

Therapeutic approach

Prior to surgery, the available information for each patient (including clinical examination, mammography in two directions, ultrasound of the affected breast, and breast MRI when available) was discussed in a multidisciplinary meeting of breast cancer specialists (radiologists, pathologists, surgeons, radiation oncologists, and medical oncologists). This team devised the treatment plan in consensus.

Both hospitals applied the policy that MRI findings required pathologic proof of malignancy prior to adaptation of the surgical plan, except if such adaptation was a small extension of a local excision. Proof of malignancy was typically acquired by second look ultrasound or MRI guided (excision) biopsy [29,31].

Statistics

Our primary endpoint was to compare the rate of re-excisions in all patients who underwent preoperative MRI compared with the rate of re-excisions in those who did not undergo preoperative MRI. The rate of initial mastectomies in both groups, the final rate of mastectomies and the time between tumor detection and final pathology were regarded as secondary endpoints.

In addition, we analyzed the rate of re-excisions and the final mastectomy rate in the subset of patients that underwent initial BCS.

All means are expressed as mean ± 1 SD. Binomial comparisons were performed using the chi-square test to check for statistical significance, or a Fisher's exact test whenever appropriate. Continuous variables were compared with the T-test for independent samples. Correlations were assessed with Pearson's correlation coefficient. We calculated odds ratios and 95% confidence intervals for the chance of re-excision with and without preoperative breast MRI for the whole population and for the subset of patients that initially underwent BCS. Calculations were performed using SPSS version 16.0 (SPSS Inc. Chicago, USA). P values smaller than 0.05 were considered significant.

Results

Patient and tumor characteristics

In total, 267 patients met the inclusion criteria. Ninety-nine of these women underwent preoperative MRI (MR+ group), 168 did not (MR– group). Patient groups were comparable, although the mean age of patients in the MR+ group was less. Patient characteristics are described in Table 1.

Table 1: *Characteristics of the patients included in the study.*

	MR – (N = 168)		MR+ (N = 99)		p-value
Age (years)					
Mean	61	± 13	56	± 10	0.001
Median	60		57		
Range	37-89		36-86		
Menopausal State					
Premenopausal	51	(30)	30	(30)	0.880
Postmenopausal	106	(63)	64	(65)	
HRT[a]	11	(7)	5	(5)	
Family History					
Blank	137	(82)	80	(81)	0.578
Positive	31	(18)	18	(18)	
BRCA mutation carier	0	(0)	1	(1)	

[a]*HRT = complete hormone replacement therapy*

The tumors in both groups were equally distributed in size and although the rate of multifocal lesions in the MR+ group was slightly higher, this did not reach statistical significance. Concurrent DCIS was incidentally present in both groups, whereas concurrent LCIS was very common and often extensive. We did not observe any significant difference in hormone receptor expression. Although the Her2/Neu receptor was more often over-expressed in the MR– group, the expression was only assessed in 155 patients and the difference did not reach statistical significance. In Table 2 tumor characteristics are shown.

Table 2: *Pathological characteristics of the included malignancies.*

	MR – (N = 168)		MR+ (N = 99)		p-value
Size (cm)					
Mean	3.4	± 2.8	3.4	± 2.6	0.985
Median	2.3		2.4		
Range	0.1 – 14.0			0.2 -11.0	
Focality					
Unifocal	80	(48)	44	(44)	0.615
Multifocal	88	(52)	55	(56)	
DCIS[a] present					
No	128	(76)	74	(75)	0.849
Limited	28	(17)	17	(17)	
Extensive	9	(5)	7	(7)	
LCIS[b] present					
No	31	(18)	19	(19)	0.994
Limited	57	(34)	34	(34)	
Extensive	78	(46)	46	(46)	
Estrogen receptor expression					
Negative	5	(3)	2	(2)	0.720
Positive	144	(86)	83	(84)	
Missing	19	(11)	14	(14)	
Progesterone receptor expression					
Negative	36	(21)	17	(17)	0.460
Positive	111	(66)	67	(68)	
Missing	21	(13)	15	(15)	
Her2/Neu Expression					
Normal	88	(52)	55	(56)	0.057
Over expressed	11	(7)	1	(1)	
Missing	69	(41)	43	(43)	.

[a]*DCIS = ductal carcinoma in situ*

[b]*LCIS = lobular carcinoma in situ*

Surgery

Initial surgery was radical in 237 of 267 (89%) patients. In total, 30 patients underwent re-excision because of involved margins. Only one of these patients underwent initial mastectomy. This patient underwent an additional resection of residual tumor in the axillary tail. In 4 patients, the re-excision consisted of an extended local excision, in 25 cases the surgical procedure was secondary mastectomy.

The rate of re-excisions was significantly higher in the MR– group (15%) than in the MR+ group

(5%) (P = 0.014), as is shown in Table 3. The odds ratio for re-excision was 3.29 (95% CI 1.22–8.85). In other words, patients in the MR– group were 3.3 times more likely to undergo re-excision than patients in the MR+ group.

Table 3: *Rate of re-excisions and mastectomies in the entire study population.*

	MR – (N = 168)		MR+ (N = 99)		p-value
Re-excisions	25	(15)	5	(5)	0.014
Intial mastectomies	78	(46)	44	(45)	0.753
Final mastectomies	99	(59)	48	(48)	0.098

Numbers between parenthesis represent percentages.

Initial mastectomy was performed in 122 of 267 patients (46%). We did not observe a higher rate of mastectomies in the MR+ group. The final rate of mastectomies was even lower in the MR+ group, though this did not reach statistical significance. Overall, the rate of initial mastectomies declined over the years. We observed a negative correlation coefficient of –0.19 (P = 0.002) between the year of treatment and the rate of initial mastectomies (fig. 1).

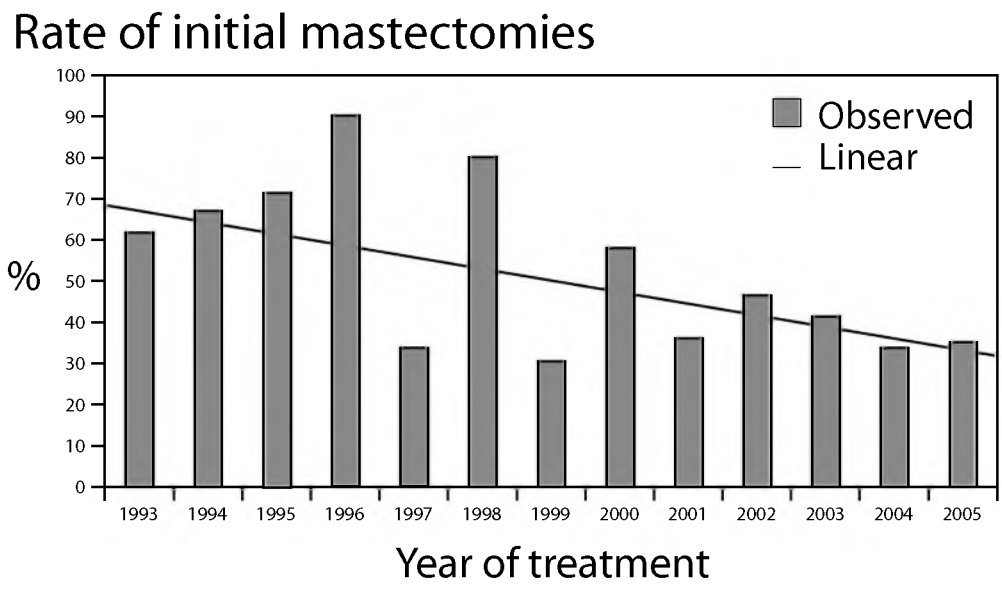

Fig 1: *Rate of patients initially treated with mastectomy by year of inclusion*

Patients initially treated with breast conserving surgery

In the subset of patients who initially underwent BCS after preoperative staging, mean tumor size was lower and multifocality was less common. We did not observe differences in tumor size or rate of multifocality between the MR– and MR+ groups (Table 4). However, the rate of re-excisions was significantly higher in patients in the MR– group, than in patients in the MR+ group (odds ratio 3.64 (95% CI 1.30–10.20)). Consequently, mastectomy as final therapy was much more common in patients who initially underwent BCS but did not undergo preoperative breast MRI (P = 0.010).

Table 4: *Results in the subset of patients that initially underwent BCS.*

	MR –		MR+		p-value
N	90	55			
Mean tumor size (cm)	2.1	± 1.4	2.0	± 1.4	0.724
Multifocal	37	(41)	19	(34)	0.431
Re-excisions	24	(27)	5	(9)	0.010
Final mastectomies	21	(23)	4	(7)	0.013

Numbers between parenthesis represent percentages.

We did not observe differences in tumor characteristics of initially incompletely excised tumors in the two groups. Mean tumor size was 3 cm in both groups, ranging from 0.8 to 7.0 cm in the MR– group, and from 1.0 to 7.6 cm in the MR+ group (P = 0.959). In the MR– group 17 of 25 tumors (68%) were multifocal, while 3 of 5 tumors (60%) in the MR+ group were multifocal (P = 1.000).

Time

The mean time from diagnosis to breast MRI in the MR+ group was 14 (±11) days, ranging from 0 (tumor detected at MRI) to 53 days. The mean time from diagnosis to final pathology in patients in whom initial surgery was successful for 40 (±22) days in the MR– group and 38 (±18) days in the MR+ group (P = 0.436). Hence, no evidence could be found that the time to final pathology was increased by the preoperative MRI.

However, failure to perform radical surgery increased the time to final pathology to 67 (±48) days in the MR– group (P = 0.010) and 81 (±42) in the MR+ group (P = 0.078), respectively.

Overall this led to a slightly longer time to final pathology in the MR– group of 44 (±29) days compared to 40 (±21) days in the MR+ group, although this did not reach statistical significance (P = 0.238).

Discussion

The most essential finding of our study is that preoperative breast MRI in patients with ILC who undergo BCS reduced the rate of surgical re-excision after BCS.
Furthermore, preoperative MRI was not associated with an increased rate of initial mastectomies, the most common objection to preoperative staging of breast cancer with breast MRI. In fact, the final rate of mastectomies was higher in patients who did not have a preoperative breast MRI. Hence, this is the first study that, in terms of outcome, shows benefit of preoperative breast MRI in patients with ILC.

With conventional methods (mammography and ultrasound) adequate staging of ILC is difficult [10,32–34]. The sensitivity is limited and although most lobular carcinomas do eventually present as a mass, ILC is often much larger than anticipated and is often multifocal [10,35].
MRI has proved to tackle many of the difficulties in detection and staging that occur with conventional modalities. With a stable sensitivity of approximately 93%, an accuracy in lesion size estimation of 80% (with an accompanying 10% underestimation of lesion size and 10% overestimation of lesion size) and a good correlation with tumor size at pathology, breast MRI aids in lesion appreciation [11,14,20,23]. Consequently, MRI has been shown to change the therapeutic approach in approximately one-third of patients with ILC [11,16,19,21–23].

Nevertheless, even in ILC, preoperative breast MRI is still disputed, because breast cancer staging with MRI is thought to delay treatment and to result in more aggressive surgery [9,28,29]. Additional lesions detected by breast MRI raise the need for additional work-up.
Since we did not observe a difference in time to final pathology between the MR– group and the MR+ group, it is apparently feasible to perform additional work-up within 40 days on average (the mean time between diagnosis and final pathology in the present study). As long as the waiting time for surgery is longer, preoperative breast MRI will not delay therapy. Re-excision does, however, delay therapy.

The reduction in the re-excision rate is considered to be emotionally important to patients, as it prevents the anxiety that is caused by a second surgical procedure and the increased time to full excision. Moreover, it has been shown that a good cosmetic outcome is reduced by re-excision [36,37]. Finally, re-excision is associated with significant financial costs, which may be reduced by preoperative MRI. However, this requires further study.

In a recent study by Pengel et al. [38], a similar reduced rate of re-excisions due to preoperative breast MRI was shown in a subgroup of patients with IDC. A reduction in the re-excision rate in ILC was not observed but far fewer patients with ILC were included and both focal and extensive involvement of resection margins were regarded as unsuccessful surgery. Moreover, they did not analyse the impact of pre-operative breast MRI on the initial mastectomy rate.

Because studies have shown that the rate of local recurrences is higher in patients who undergo re-excisions than in patients who are initially successfully treated [39,40], our study suggests that preoperative MRI in patients with ILC has the potential to improve local control and therefore survival. However, this negative effect from re-excisions was not evident from other studies [2], and is therefore uncertain.

So far, only two studies have evaluated the impact of preoperative breast MRI on recurrence and survival, none of which evaluated specifically ILC. Unfortunately these studies had contradictory results.
Fischer et al. [41] showed a reduced rate of local recurrences after preoperative MRI, but this study is largely biased due to very different tumor stages between groups. More recently Solin et al. [42] did not observe any differences in local control between patients that did or did not undergo pre-operative MRI. However, they had only a short follow-up period and included many patients in the MR+ group that underwent MRI only after initial surgery.
We agree that the most valid proof of improved outcome is a clear reduction in breast cancer mortality, following a reduction of local recurrence. Such evidence in patients with ILC is still lacking, we neither assessed local recurrence nor survival in this study. However, due to improving overall diagnosis and treatment current recurrence rates have dropped to approximately 0.6–1% per year [43]. Furthermore, ILC is a relatively infrequent breast cancer, so large studies to evaluate the impact of preoperative MRI on recurrence and survival will be acquired over a very long time span. Consequently, surgical approaches and adjuvant therapies will have continued to develop and an effect on outcome using these terms may be difficult to interpret as they are prone to bias.
There are several limitations to our study.

First, the non-randomized and retrospective nature of this study must be taken into account. However, since both the American College of Radiology (ACR) and the European society of breast imaging (Eusobi) currently recommend pre-operative breast MRI for evaluation of the contralateral breast in all women with proven breast cancer [44,45], prospective randomized studies on patients with breast cancer can no longer be deemed ethical.

Second, although mastectomy is more commonly performed for ILC than for IDC due to the typically larger extension of ILC and preference of surgeons and patients, we still observed relatively high rates of initial mastectomies in both groups. This is probably mainly explained by the long time span of the study, since we observed a clear decline of the rate of initial mastectomies over time. The initial mastectomy rate of 35% observed in 2005 is comparable to reported values in literature [6,9].

Third, from the observed similarity in the rates of initial mastectomy between groups it is likely that a selection bias has occurred. Many studies have shown that preoperative MRI changes the surgical approach in 22–44% of patients [11–18], and as mentioned before, in 12–33% of patients

this change is a conversion from BCS to mastectomy [11,13,16,19–22]. Based on few reported findings, this rate of therapy change is balanced by a conversion rate in the opposite direction of approximately 5% [11]. Consequently, a 15–20% higher initial mastectomy rate in the MR+ group would be expected. Since tumor sizes were not different between groups, nor was the rate of multifocality, patients who were unlikely to undergo BCS based on psychological factors, were apparently also less likely to undergo preoperative MRI. We believe this also explains the slight age difference between groups that is also observed in other studies [38,42].

Fourth, all patients were treated in tertiary dedicated cancer centers, generally treating larger and more technically challenging carcinomas. Both centers also had a wide experience in the use of breast MRI which may have improved the outcomes of this study. Since breast MRI is subject to a learning curve for both radiologists and surgeons, our results cannot be directly extrapolated to centers without extensive experience.

Last, breast MRI has also evolved over time. Consequently, the MRI protocols were non-uniform in the study period. Moreover, nowadays spatial resolutions are achievable that were impossible only 5 years ago. Furthermore, the addition of other sequences, such as T2 and diffusion weighted imaging, may further improve pre-operative staging. Our study only evaluated the use of contrast enhanced breast MRI. It is therefore impossible to tell whether or not such advantages may result in further benefit for patients [46,47].

Since we only evaluated ILC, it is not possible to extrapolate our findings to other types of breast cancer. However, we need to discuss the role of preoperative breast MRI in patients who do not qualify for BCS. The main objection that preoperative breast MRI will increase the chance of mastectomy obviously does not hold. Conversely, there is a small chance that preoperative breast MRI will result in BCS due to better delineation of the tumor [11]. Moreover, the indication for screening of the contralateral breast remains valid regardless of the size of the ipsilateral tumor [44,45]. Thus, for optimal therapy and optimal performance of preoperative MRI, it is recommended in all patients with ILC, not only the subset that is eligible for BCS.

In summary, preoperative breast MRI in patients with ILC leads to a reduction of the re-excision rate without increasing the rate of initial mastectomies and is thus directly beneficial for patients with ILC.

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Breast MRI: Guidelines from the European Society of Breast Imaging

9

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Abstract

The aim of breast MRI is to obtain a reliable evaluation of any lesion within the breast. It is currently always used as an adjunct to the standard diagnostic procedures of the breast, i.e., clinical examination, mammography and ultrasound. Whereas the sensitivity of breast MRI is usually very high, specificity —as in all breast imaging modalities— depends on many factors such as reader expertise, use of adequate techniques and composition of the patient cohorts. Since breast MRI will always yield MR-only visible questionable lesions that require an Mrguided intervention for clarification, MRI should only be offered by institutions that can also offer a MRIguided breast biopsy or that are in close contact with a site that can perform this type of biopsy for them. Radiologists involved in breast imaging should ensure that they have a thorough knowledge of the MRI techniques that are necessary for breast imaging, that they know how to evaluate a breast MRI using the ACR BI-RADS MRI lexicon, and most important, when to perform breast MRI. This manuscript provides guidelines on the current best practice for the use of breast MRI, and the methods to be used, from the European Society of Breast Imaging (EUSOBI).

Introduction

The overall aim of breast imaging can be summarized under several general headings. First, it is performed in symptomatic women to exclude breast cancer or other disease that requires immediate treatment. In this respect, it should provide a definitive diagnosis or exclude the presence of a harmful abnormality. Second, in patients with known malignancies, imaging helps in the preoperative staging and subsequent choice of appropriate therapy, either surgical or medical. Third, in patients with known malignancies that are initially treated medically with neoadjuvant chemotherapy, imaging is helpful in the assessment of response to treatment and the evaluation of residual disease afterwards. Fourth, imaging is performed in asymptomatic women to detect breast cancer in its early stages, when it can be better treated, and in this respect imaging increases the prognosis and survival of breast cancer patients. Last, imaging may be used to evaluate foreign bodies within the breast, such as the location of clips and markers or whether breast prostheses are intact. Magnetic resonance imaging of the breast can be used to pursue any of the above-mentioned goals. The aim of this paper is to provide guidelines for the performance and use of breast MRI, with respect to both the technical aspects of this procedure and the current indications.

Technical aspects

Patient handling

MRI of the breast is a study that requires the administration of a gadolinium-containing contrast agent during the study [1, 2]. Early studies have shown that breast MRI without contrast agent is not of diagnostic value [3, 4]. The uptake of contrast medium in breast tissue in premenopausal women is also dependent on the phase of the menstrual cycle. It is essential to perform breast MRI in the correct phase of the cycle as enhancing normal breast tissue may otherwise complicate the interpretation of the study. The optimal time in pre-menopausal women to perform a breast MRI is between the 5th and 12th day after
the start of the menstrual cycle [5–7].

Placement of an intravenous cathether should be done before positioning the patient on the MR table. A long IV line avoids table and patient movement before the injection. The contrast agent should preferably be given by a power injector. It is important to position the patient as comfortably as possible in order to avoid motion artifacts. A dedicated bilateral breast coil is mandatory for this investigation, and the patient should be placed in the prone position with both breasts hanging in the coil loops. The breasts may be supported to further reduce motion artifacts, but should not be compressed.

The position of the breast should be checked before the start of the examination, both breasts must be placed as deeply as possible in the coils with the nipples pointing down. A larger breast coverage is usually obtained by placing both arms at the side of the body and not above the patient's head.

Virtually any MRI scanner can be used to perform contrast-enhanced breast MRI, as long as the system allows image acquisition at a sufficient spatial and temporal resolution (see below). However, scanning protocols need to be adapted to the scanners used, also because the relaxivity of the most commonly used contrast agents decreases at higher field strengths [8, 9]. Breast MRI at low and midfield strength (0.2 T, 0.5 T) depends heavily on parallel imaging to obtain a sufficient resolution. As this further decreases the signal-to-noise ratio (SNR), this is not optimal. In practice, most studies that employed low or midfield scanners did not obtain a sufficient spatial resolution [10, 11]. An increasing field strength (1.5 T, 3 T) allows a higher spatial resolution at a similar temporal resolution and consequently may increase diagnostic confidence [12]. A disadvantage is that, at higher field strengths (e.g. 3 T), inhomogeneity in the B1 field may cause reduced signal in parts of the image and thus less contrast enhancement, which in turn may cause falsenegative image interpretation. Two-dimensional acquisitions are particularly sensitive to this effect and are therefore discouraged at 3 T [13].

Sequences

The conventional breast MRI investigation begins precontrast with either T2- or T1-weighted images. The signal from the body coil can be used to evaluate the position and anatomy of the breasts. Furthermore, both axillae, the supraclavicular fossae, the chest wall and anterior mediastinum can be checked (e.g., for enlarged lymph nodes). However, this is not the purpose of a breast MRI, and this evaluation may also be omitted as there is no evidence of its diagnostic value. Afterwards the signal from the dedicated double breast coil should be used. T2-weighted fast spin echo images can be performed as a start. In the T2-weighted images water-containing lesions or edematous lesions have an intense signal, and in this sequence small cysts and myxoid fibroadenomas are very well identified. In most cases cancer does not yield a high signal on T2-weighted images; thus, these sequences can be useful in the differentiation between benign and malignant lesions. However, as most of these lesions can also be identified on T1-weighted images, there is no evidence as yet of added value of T2-weighted sequences in breast MRI [14, 15].

The most commonly used sequence in breast MRI is a T1-weighted, dynamic contrast enhanced acquisition. The sequence is called 'dynamic' because it is first performed before contrast administration and is repeated multiple times after contrast administration. A T1-weighted 3D or 2D (multi-slice) spoiled gradient echo pulse sequence is obtained before contrast injection and then repeated as rapidly as possible for 5 to 7 min after a rapid intravenous bolus of a Gd-containing contrast agent. A 3D pulse sequence offers a stronger T1 contrast and enables thinner slices than 2D; in turn, a 2D sequence suffers less from motion and pulsation artifacts. Both sequences can be performed with and without fatsuppresion [16, 17].

The choice of the image orientation is important. For bilateral dynamic breast MRI, axial or coronal orientations are most frequently used. Coronal imaging has advantages in that it can reduce heart pulsation artifacts, but it is more susceptible to respirational motion and also to flow artifacts because vessels tend to travel perpendicular to the slice encoding direction.

Although bilateral sagittal imaging is possible today, it requires about double the number of slices required for the other orientations. As this hampers the spatio-temporal resolution, such an orientation is currently not feasible.
The optimal dose of the contrast medium is unknown and also depends on the contrast agent used. In literature, applied doses range roughly from 0.05 to 0.2 mmol/kg. One study showed some benefit of 0.16 mmol/kg gadopentetate dimeglumine over 0.1 mmol/kg [18]. However, a more recent evaluation did not find any improvement in diagnostic accuracy using 0.2 mmol/kg gadobenate dimeglumine over 0.1 mmol/kg of the same agent [19]. Consequently, a dose of 0.1 mmol/kg is probably sufficient.

Peak enhancement in the case of breast cancer occurs within the first 2 min after the injection of contrast medium. Therefore, relatively short data acquisition times, in the order of 60–120 s per volume acquisition, are necessary. This allows sampling of the time course of signal enhancement after contrast injection, which is useful because the highly vascularized tumor of the breast shows a faster contrast uptake than the surrounding tissue. More importantly, it enables a detailed analysis of morphologic details, because only in the very early postcontrast phase, the contrast between the cancer and the adjacent fibroglandular tissue is optimal. Tumors may lose signal (a phenomenon referred to as "wash out") as early as 2–3 min after contrast material injection, whereas the adjacent fibroglandular tissue can still exhibit substantial enhancement, resulting in little contrast between the cancer and the fibroglandular tissue. Long acquisition times will be associated with the risk of not resolving fine details of margins and internal architecture; this could have key importance for the differential diagnosis, and may even run the risk of missing cancers altogether because they are masked by adjacent breast tissue.
A dynamic sequence demands at least three time points to be measured, that is, one before the administration of contrast medium, one approximately 2 min later to capture the peak and one in the late phase to evaluate whether a lesion continues to enhance, shows a plateau or shows early wash-out of the contrast agent (decrease of signal intensity) [20]. It is thus recommended to perform at least two measurements after the contrast medium has been given, but the optimal number of repetitions is unknown. However, the temporal resolution should not compromise the spatial resolution. It was shown that an increase in spatial resolution results in higher diagnostic confidence even when the temporal resolution is slightly sacrificed. [21].
The final spatial resolution of the images depends on different factors, especially the size of the imaging volume, defined by the field of view (FOV), the slice thickness and the acquisition matrix. Breast MRI should be capable of detecting all lesions larger than or equal to 5 mm. Therefore, the voxel size should be under 2.5 mm in any direction. Preferably, the in-plane resolution should be substantially higher as morphologic features needed for lesion characterization, such as margin appearance, can only be evaluated when the resolution is sufficiently high. Therefore, the in-plane resolution should be at least 1 mm–1 , in other words: pixel size (FOV/matrix) should not be greater than 1×1 mm, which requires a matrix of at least 300×300 in a 300-mm FOV.

Assessment of lesion morphology can be performed directly on the enhanced fat-suppressed images. However, as residual fat-signal (hyperintense at T1-weighted images) may cause difficulties in interpretation, the calculation of subtraction images from the pre- and post-contrast series is recommended [22, 23]. Subtraction suppresses the signal from bright fat because fatty tissue hardly enhances. When subtraction is performed, fat suppression in the acquisition is not needed and is even discouraged, because in the large fields of view that are usually required for axial and coronal imaging, homogenous fat suppression is difficult to obtain. This can be problematic since fat and water resonance frequencies are relatively close at 1.5 T—which implies that with less-than-optimal B0 homogeneity across the field of view, water (rather than fat) suppression can occur. Moreover, fat-suppression increases the noise in the image and usually also compromises spatio-temoral resolution.

Evaluation

Use of both detailed morphological information provided by high spatial resolution images and kinetic information (curve type) provided by at least two repetitions of the high spatial resolution sequence represents the latest trend in acquisition protocols and image interpretation to take into account the increasing importance of detailed morphological information without losing identification of washout enhancement curve types [24].

For the diagnostic interpretation the ACR breast imaging reporting and data system (BIRADS) for breast MRI illustrates many of the morphological findings seen on contrast-enhanced breast MRI. It also includes a lexicon that should be used for uniform reporting of the features seen on MRI [25].

Indications for breast MRI

Inconclusive findings in conventional imaging

Patients referred by their general practitioner or through a nationwide screening program to secondary are told that there is a chance that they might have breast cancer. In this situation imaging, with or without biopsy, should exclude the presence of a malignancy sufficiently. The sensitivity of breast MRI for the detection of cancer is the greatest of all imaging techniques [26–28], and when the findings of conventional imaging are inconclusive (i.e., BI-RADS 0), MRI can be used as a problem-solving modality. In general, a negative breast MRI excludes malignancy. Only in case of mammographic microcalcifications, MRI is unable to exclude cancer sufficiently, and the decision to perform biopsy should be based on mammographic findings in this specific situation [29].

Preoperative staging

Breast tumors may be solitary, well-circumscribed masses that are well recognized at mammography and/or sonography. However, tumor size may be underestimated severely by mammography and ultrasound, especially in tumors larger than 2 cm [30, 31]. Tumor size of

invasive carcinomas on MRI correspond in general well to pathologic sizes [32, 33]. Unfortunately, MRI has a tendency to overestimate the size of pure DCIS lesions [34]. Furthermore, in about 25% of the cases, the tumor is multifocal; in other words, there are more invasive tumors in one quadrant. Moreover, multicentricity, which means one or more invasive foci more than 4 cm from the primary tumor, is present in about 20% of all invasive malignancies.

Inadequate size estimation or failure to detect additional foci of disease may thus result in positive resection margins after surgery or early recurrent disease. The sensitivity of breast MRI is, in the setting of preoperative evaluation, close to 100% [26]. MRI is the most reliable imaging technique to measure the tumor size [35, 36], and it detects additional foci of the tumor in the ipsilateral breast in 10–30% of patients [37–45]. Also the presence of an intraductal component (EIC+) can be better evaluated by MRI than with mammography [36, 46–48].

On MRI this may be seen as an area of contrast enhancement with a dendritic configuration close to the primary tumor. However, approximately 20% of the additional foci detected by MRI are benign [43, 49]. Consequently, before large adjustments to the surgical management are effectuated, histological analysis of MR detected additional foci should be performed. Several studies have shown a change in surgical management in about 20% to 30% of all patients undergoing preoperative MRI [26, 37, 39, 49]. Changes were greatest in patients with tumor size greater than 4 cm [50], lobular carcinoma [37] or breast density 4 [49].

However, it is so far unclear whether breast MRI contributes to better control of the disease or survival of all patients with diagnosed breast cancer. Only one study has evaluated such outcomes, and although MRI appears to reduce the incidence of local recurrence (1.2% vs. 6.8%), confounding differences in tumor characteristics between patients treated with and without MRI did occur [51]. The British COMICE trial is a large multicenter trial that randomizes patients between MRI and no-MRI and evaluates the quality of preoperative staging, the differences in outcome, differences in quality of life and costeffectiveness [52]; the first results are expected in 2008. This study and similar ongoing studies may provide better evaluation of staging in the near future.

Synchronous bilateral breast cancer is reported in about 2–3% of all breast cancer patients [53–55], but it is probably more common. Synchronous contralateral lesions are occult on mammography in about 75% of cases. MRI detects otherwise occult lesions in 3–5% of patients that undergo preoperative MRI [56–58]. Some studies show even more alarming results and report MRI-only detected contralateral breast cancer in 19% [59] and 24% [60].

These lesions would probably have presented as metachronous contralateral carcinomas without MRI, as is also clear from the above-mentioned outcome study. The rate of contralateral carcinomas detected at follow-up decreased from 4% without MRI to 1.7% with MRI [51].

Screening of the contralateral breast in patients with proven unilateral breast cancer is thus a valid indication for the performance of preoperative breast MRI. In practice this means that preoperative MRI is recommended in all patients with histologically proven breast cancer, even though the indication for ipsilateral staging of the cancer is still under investigation. Especially in the case of dense breasts, MRI is recommended preoperatively. Furthermore, in patients with histologic evidence of invasive lobular carcinoma, a preoperative MRI is strongly recommended

as these tumors show a more permeative growth pattern and, consequently, are more difficult to measure [32, 61], are more often multifocal or multicentric (additional foci in 32%) [62,63] and are more often complicated by concurrent contralateral carcinomas (occult tumors detected in 7%) [62, 64, 65].

Unknown primary

In the case of a carcinoma of unknown primary, metastases are diagnosed, but a primary tumor site cannot be identified. These metastases may either present in the axillary lymph nodes, the supraclavicular lymph nodes, the bones, the liver, the brain or the lungs. When the mammogram does not show any abnormality, reports in the literature show, in about 50% of the cases, an abnormal MRI [66]. In case of metastatic axillary lymph nodes, MRI is even able to detect a primary breast tumor in 75–85% of patients [67, 68]. MRI thus can subsequently be used to plan the most appropriate treatment as the size of these lesions on MRI is usually concordant with the size at pathology, thus MRI may prevent unnecessary mastectomies or assign patients with large tumors to neoadjuvant protocols.

The evaluation of therapy response in the neoadjuvant chemotherapy setting

Neoadjuvant chemotherapy is the administration of chemotherapy prior to surgical treatment of cancer. Its principal indication is the treatment of unresectable breast cancers, and its goal in this setting is to reduce the tumor to a size that allows resection. However, many studies have shown that the prognosis of breast cancer is equal when chemotherapy precedes or follows after surgery. Because there are some theoretical benefits in the neoadjuvant setting, and tumor response can be closely evaluated with the tumor in situ, neoadjuvant chemotherapy is also the standard of care in large T2 and T3 tumors. MRI has been shown to be superior to evaluate tumor response to neoadjuvant chemotherapy compared to clinical examination, mammography or ultrasound and is thus the imaging investigation of choice.

If neoadjuvant chemotherapy is given to a patient, the first breast MRI should be performed before the start of chemotherapy. A second MRI, for the evaluation of the effect of chemotherapy on the tumor, should be performed when approximately half of the course of chemotherapy has been administered. A third MRI investigation should be performed after the final course of chemotherapy to evaluate the residual disease. In most hospitals four to six cycles of chemotherapy are given in the neoadjuvantsetting.

Response is normally measured using the RECIST criteria [69]. Using these, complete response (CR) is defined as complete vanishing of the tumor, partial response (PR) is defined as decrease of the sum of the longest axes of all individual lesions by more than 30%, progressive disease (PD) is defined as an increase of this sum by more than 25% and the remainder is classified as stable disease (SD). Response to chemotherapy is especially well evaluated in the non-responders (SD, PD) and the good-responder group (CR). The effect of the chemotherapy in partial responders is less well established. Several studies compared the ability of clinical examination, mammography, ultrasound and MRI in the assessment of final response [70–80]. They showed that MRI measurement after therapy correlated best with the pathological findings and was

the best technique for assessing response. Nevertheless, MRI is unable to detect small residual tumor foci that may persist after neoadjuvant chemotherapy. Radiological complete response is thus no proof for pathological complete response (pCR); therefore, resection of the initial tumor bed is still essential in the treatment of these patients [77, 79].

Observation of response during treatment is important as this is the only measure that justifies the applied chemotherapeutic regimen and is the only response evaluation that allows a change in this regime before its completion.

Currently, the performance of MRI halfway during treatment may only change the treatment in clear nonresponders and those with progressive disease as there are no other criteria for early response evaluation. This is due to the fact that size of the tumor often does not immediately decrease. Therefore, the performance of MRI earlier in the treatment (e.g., after the first cycle) as is under investigation in several large trials (such as the ACRIN 6657 trial) is currently not recommended, although in one study complete responders had a change in diameter of at least 45% after the first course of chemotherapy [72]. In another study early change in volume was the most predictive of final response [75]. The value of these MRI investigations first should be established, and criteria for early response need to be defined.

Several other techniques, such as MR spectroscopy [81], diffusion imaging [82] and FDG-PET [83–85] show promise in the (early) evaluation of tumor response to therapy. However, none of these techniques have been tested in large-scale prospective studies and can thus not (yet) be recommended for clinical practice. For a more detailed description of the studies so far performed in the evaluation of response to neoadjuvant chemotherapy, we refer to the review by Tardivon et al. [86].

Imaging of the breast after conservative therapy

MRI may be considered after breast-conserving therapy (BCT) in three instances: first as an evaluation tool for residual disease after positive tumor margins, second as a method of evaluating suspected recurrence by either clinical examination, mammography or ultrasound and third as a screening tool in all patients who undergo BCT.

Unfortunately, early postoperative MRI is hampered by strongly enhancing resection margins in response to the surgical intervention. Therefore, MRI is unable to exclude residual tumor at the biopsy cavity sufficiently, and hence does not change the surgical approach consisting in a larger resection of the tumor bed in the direction where pathological analysis of the surgical specimen showed positive margins [87–89].

Although preoperative staging MRI is to be preferred over MRI after initial surgery, it can be performed when surgical margins are badly involved. In such cases, the first acceptable MRI results are not to be expected sooner than a month after surgery [90]. However, as MRI may reveal more widespread disease throughout the breast remote from the lumpectomy site, it can provide valuable information concerning the decision of wider excision versus mastectomy [91–93]. Morakkabati et al. have shown that postradiation changes occur during and up to 3 months after radiation therapy, but do not reduce the accuracy of MRI to identify residual or recurrent tumor compared to patients without radiation therapy [94].

Most local recurrences after BCT and radiotherapy occur within 5 years after the initial surgery, and the annual risk is estimated at 1–2% per year [95–98]. Early detection and treatment of recurrent disease are important as it may still present without distant metastases. Second primary ipsilateral carcinomas in the treated breast can occur at every site and develop on average 7 years after the first primary tumor [99]. The sensitivity of mammography for recurrent disease in the treated breast is limited, but breast MRI can be a valuable complementary tool as explained earlier. A local recurrence on MRI has the same appearance as a new primary malignancy with strong early enhancement, while a fibrous scar shows either no enhancement or very slow enhancement. In a treated breast, the specificity of breast MRI is higher than in an untreated breast. Different studies have shown that MRI is the most sensitive technique in detecting a local recurrence of the disease [36, 100–104]. When a local recurrence is suspected upon clinical findings or abnormalities on mammography or ultrasound, MRI can be used to exclude local recurrence with a high negative predictive value and thus prevent unnecessary biopsies [93, 103, 104].

Analogous to the situation in preoperative staging, MRI is able to detect multifocality and multicentricity unnoticed by conventional imaging. Naturally, in these cases, the evaluation of the contralateral breast is also important. There is currently not sufficient evidence to recommend or not the screening of patients treated by BCT with MRI.

So far, only one small trial has been performed [101], which showed no difference in sensitivity for recurrence between clinical examination combined with mammography and MRI alone. However, the specificity of MRI was much higher (93% vs. 67%), confirming its value as additional investigation. Moreover, in some patients, it can be impossible to image the primary tumor region by mammography after conservative therapy [105]. In these cases breast MRI is mandatory.

The risk of local recurrence is strongly dependent on the age of the patient at the time of diagnosis [106–109]. Patients over 50 have a risk of approximately 4% after 5 years, but this risk is estimated at 12% after 5 years for patients who were under 45 years of age [108] and at 20% after 5 years for patients under 40 [106]. Although additional boost radiotherapy to the tumor bed can reduce this risk to 10% at 5 years, these patients have a lifetime risk that is probably still greater than 20%, which is equal to the lifetime risk demanded for MRI screening in the general population, as described below.

Therefore, annual MRI screening is an option for all patients under 50 at the time of diagnosis of the first primary carcinoma, but this should first be investigated in larger trials.

MRI screening

The high sensitivity for cancer makes breast MRI a desirable technique for screening purposes. Therefore, many countries have performed screening studies in highrisk populations. The American Cancer Society (ACS) has recently issued guidelines for the performance of MR screening based upon the analysis of six of these studies [110]. As the most important of these studies were all performed in Europe (e.g. the Dutch MRISC study [111], The UK-based MARIBS study [112], the German singlecenter study [113] and the Italian HIBCRIT study [114]), the ACS

recommendations apply mostly to the European situation. The overall sensitivity for breast cancer in these high-risk populations is between 71 and 100% for MRI compared to 16–40% for mammography. The specificity ranges from 81 to 99% for MRI and 93 to 99% for mammography, which is illustrative for the higher detection rate of MR and the (almost two times) higher recall rate that unfortunately complicates MR screening.

There is evidence for the value of annual MR screening in BRCA gene mutation carriers, their first degree, untested relatives and all women with a lifetime risk of 20–25% according to models that depend largely upon family history. Furthermore, MRI screening is advised in patients who received radiation to the chest in their 2nd or 3rd decade (mostly patients with a history of lymphoma) and patients with inherited syndromes, such as LiFraumeni and Cowden syndrome, and their first-degree relatives, although there is no direct evidence for these latter recommendations.

Currently there is not sufficient evidence to recommend MRI or not in women with a lifetimerisk of 15–20%, those with high-risk lesions (LCIS, ALH, ADH) and those with heterogeneously or extremely dense breasts on mammography.

Women with a lifetime risk of less than 15% should currently not be enrolled in MR screening programs. It is still unclear when to start screening. In most highrisk patients, starting at the age of 30 will probably be sufficient. However, in families where the first carcinomas presented at younger ages, the screening needs to start earlier as well. It seems advisable to follow the guidelines for mammography in this aspect and start screening at an age 5 years younger than the youngest relative that presented with cancer. It is also unclear for how long screening with MR should be continued; in older women the breast density decreases significantly, and the added value of MR might thus decrease. However, at every age, the sensitivity for breast cancer of MRI is higher than that of mammography.

Prosthesis imaging

The evaluation of breast implants, which are either placed for breast augmentation or for breast reconstruction after surgery for breast cancer, can be done with MR. This demands specific sequences that are aimed at the visualization of silicone and provide concurrent suppression of the water signal [115–117]. By using these sequences and specific evaluation criteria [116, 117], MRI is the most accurate modality in the evaluation of implant integrity. Its sensitivity for rupture is between 80 and 90%, and its specificity is approximately 90% [117–119], whereas the sensitivity of mammography is approximately 25% [120, 121]. Nevertheless, the indication for breast MRI is less clear than might be expected. Ten years after insertion, approximately 50% of all breast implants are ruptured [117, 118]. It seems therefore advisable to use breast MR only when there are specific complaints that might be caused by leaking prostheses (e.g., local inflammation or the formation of silicone granulomas). MRI may then be used to exclude a ruptured prosthesis as the underlying cause of the complaints, and it may also aid explantation surgery as it documents the presence and extent of silicone leakage better than any other imaging modality.

In patients with prosthesis and prior breast cancer, MRI may be used to evaluate suspected

recurrent disease or as a postoperative screening modality. The presence of the implant does not seem to decrease the sensitivity of breast MR [122, 123].

MR-guided biopsy and lesion localization

It is clear that the increasing list of indications for the performance of breast MR leads to the detection of many lesions that are neither palpable nor visible on conventional imaging techniques. Although most MR-detected lesions can be found (and biopsied) at second-look ultrasound, many can not. This stresses the importance of the possibility of performing MR-guided biopsies and localizations. Any site that performs breast MR examinations should either be able to perform MR-guided interventions in the breast or should be in close contact with a site that can perform these investigations for them. However, the exact description of the involved techniques and the minimal requirements that need to be met when performing these interventions are quite extensive and cannot be described in this paper. A separate guideline describing these interventions will be published soon by Heywang-Kobrunner et al.

Conclusion

Breast MRI is no longer an experimental modality, but has attained a solid position in the diagnosis and workup of (suspected) breast lesions. For adequate performance, some important points should be kept in mind.

- A dedicated bilateral breast coil is mandatory.
- The spatial and temporal resolution must be sufficient.
- AT1-weighted sequence should be obtained for at least three time points, one prior to and two after contrast administration.
- Reporting should be performed by a radiologist with experience in breast MRI, using the ACR BI-RADS MRI Lexicon.
- MRI-guided breast biopsy must be available.

The most important indications currently present are listed below.

- Problem solving in case of inconclusive findings on conventional imaging.
- Screening of the contralateral breast in women with histological evidence of unilateral breast cancer.
- Evaluation of the breasts in case of metastases of an unknown primary carcinoma.
- Evaluation of therapy response in patients treated with neoadjuvant chemotherapy.
- Exclusion of local recurrence after breast-conserving therapy.
- Screening of women with a lifetime risk of 20% or more to develop breast cancer, including mutation carriers.

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General Discussion and Conclusions

10

Ritse M. Mann

Partly after:
The effectiveness of MRI in the assessment of invasive lobular carcinoma of the breast
MRI Clinics of North America, 2010 May;18(2):259-76

Conventional imaging methods in ILC

In the first evaluation of interval cancers after the initiation of breast cancer screening with mammography in the Netherlands, it became clear that ILC was a common pathologic diagnosis in the missed carcinoma group [1]. This was attributed to the diffuse infiltrative pattern of the tumors and the poor desmoplastic reaction of the surrounding tissue [2]. In a later, larger study about a third of the interval carcinomas were of lobular origin. In a recent evaluation that differentiated between 'true' interval carcinomas (fast growing tumors not present at the time of screening) and false-negative screening mammography, 47% of the latter category were tumors with lobular features [3,4]. This may be due to the fact that ILC is more often better visualized on craniocaudal (CC) mammographic images, than mediolateraloblique (MLO) images, while the former are not routinely performed in all screening programs [5,6]. However, even in retrospect 10-20% of ILC is not visible at mammography [6-9].
The hallmark of malignancy on mammography, a spiculated mass, is reported in 28-63% of ILC cases [6,9-13] (fig 1,2). Mammographic findings in the remainder of ILC cases are often subtle. There is no association of ILC with microcalcifications, and the tumors are often isodense to fibroglandular tissue [5,8,10,14,15].

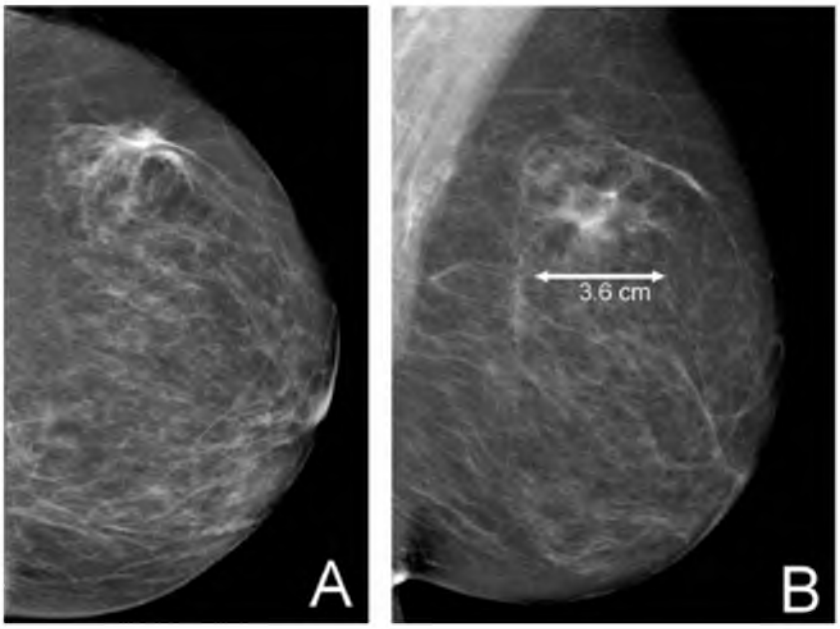

Fig 1: *Mammogram of a 60 year old woman (A: Left breast, CC view, B: Left breast, MLO view) who presented with a palpable mass in the upper outer quadrant of the left breast. There is a hyperdense mass in the upper outer quadrant with an irregular spiculated margin and a maximum diameter of 3.6 cm, which was shown to be a multifocal ILC over an area of 4.2 cm, the largest focus was 2.5 cm.*

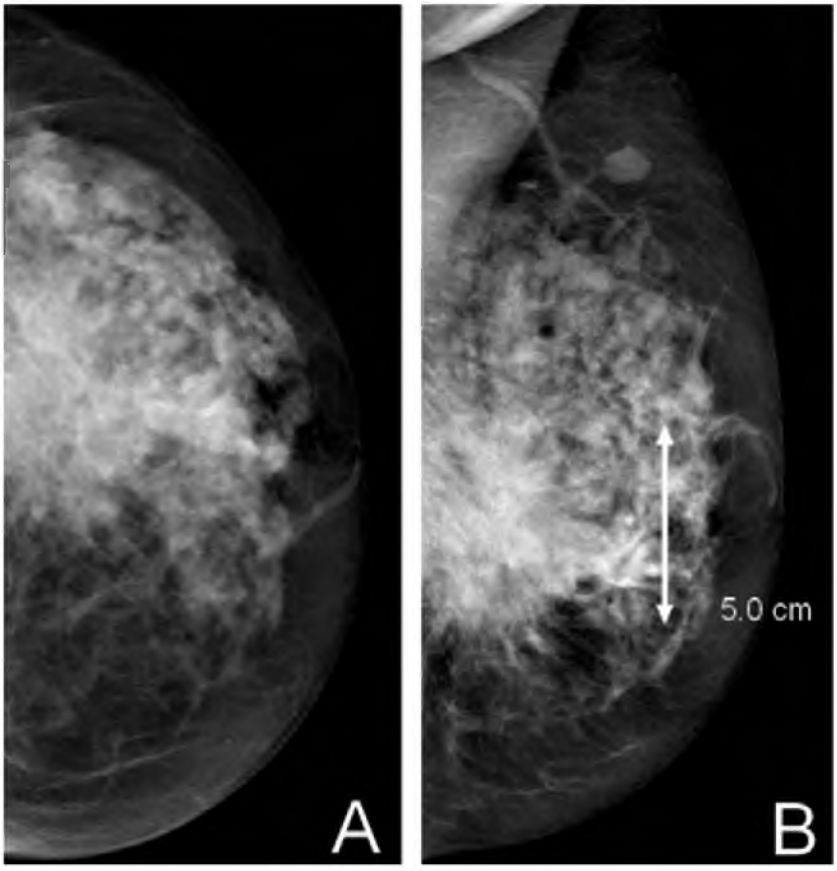

Fig 2: *Mammogram of a 71 year old woman (A: Left breast, CC view, B: Left breast, MLO view) who presented with a palpable lump with skin retraction of the left breast. There is a large architectural distortion in the left breast (at least 5 cm), isointense to the fibroglandular tissue, retracting the whole breast. Histology showed a T4a ILC.*

Common descriptors include: ill-defined mass (7-33%) [6,9,12] architectural distortion (10- 24%) [6,9-12], and asymmetry (4-14%) [6,9]. The wide ranges reported probably reflect interreader variability of the descriptive terminology.

Not surprisingly tumor size estimation with mammography is difficult in ILC. Reported correlation coefficients range widely from 0.2 to 0.8. Small tumors in fatty breasts are quite accurately assessed, but accuracy decreases rapidly with increasing tumor size and increasing density [16-18], resulting in structural underestimation of larger tumors. The vague borders commonly seen in ILC makes assessment of these tumors particularly difficult. This results in measurements with a stronger negative deviation from pathological tumor size when compared with those seen in IDC [6,18]. Consequently, it has been shown that mammography understages over one third of ILCs [19].

Sonography is hardly ever used as a screening modality, hence studies that report on sensitivity

of ultrasound in ILC, report on lesions that have already been detected by other means (either physical examination or mammography).

Nevertheless most ILC are visible at sonography, and reported sensitivities range from 78 to 98% [20-26]. In a recent meta-analysis comparing the sensitivity of ultrasound directly with MRI, the sensitivity of ultrasound was 83%, with a 95% confidence interval ranging from 71-91% [27]. Although one initial study reported difficulties with ultrasound for the detection of ILC under 1 cm in size (only one out of four) [28], later studies using more sophisticated equipment reported sensitivities in the normal range [29,30]. Important to note is that ultrasound sensitivity is also high in lesions that are hardly visible or occult at mammography. Hence there is a complementary value of ultrasound in the detection of ILC in the symptomatic patient [20]. Approximately 60% of ILC lesions exhibit the typical features of malignancy at ultrasound and present as a hypoechoic heterogeneous mass with ill-defined margins and posterior acoustic shadowing [20,21,24] (fig 3). Internal hyperechoic patterns are more commonly seen in ILC than in IDC [21,26] (fig 3D), and some ILC present as areas of focal shadowing without a discrete mass [20,24]. This latter ultrasound pattern may suggest the classic type ILC histology [20].

Regarding tumor size estimation of ILC, ultrasound performs equally to mammography though the spread of reported correlation coefficients is a bit lower, ranging from 0.5 to 0.8 [25,31-33]. Similar to mammography, the quality of the tumor size assessment decreases with increasing size of tumor. This holds particularly true for ILC tumors over 3 cm in size which cannot be accurately assessed with ultrasound [26,32].

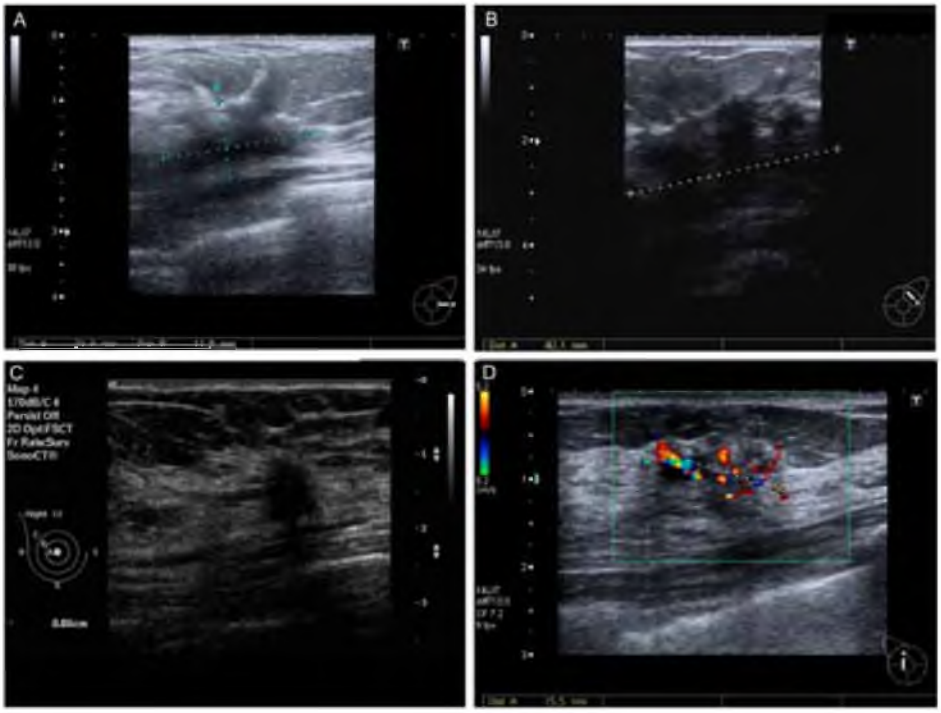

Fig 3: *Ultrasound images of 4 different ILC. The tumors in image A, B and C exhibit typical malignant features, showing hypoechoic irregular spiculated lesions with posterior acoustic shadowing. The tumor in image D was almost isoechoic to normal fibroglandular breast tissue but showed multiple pathologic Doppler signals, due to extensive neovascularisation. The tumor in figure A was over 5 cm at pathology, in B over 8 cm, in C 14 mm and in D 3.2 cm, showing that ultrasound measurements especially in larger tumors are far from accurate.*

Features of ILC on breast MRI

The retrospective sensitivity of breast MRI for ILC is high. In a meta-analysis evaluating studies published until April 2006 describing in total 209 patients, the sensitivity was 93.3% with a 95% confidence interval ranging from 88 to 96%. Leaving out the results of one very early study that scanned patients with an inadequate scan protocol, the sensitivity was even higher at 96% (95% CI 92-98%) [27,34-41]. Since the publication of this meta-analysis, three new studies have appeared in the literature that allowed evaluation of sensitivity [42-44]. The two largest studies both reported a retrospective sensitivity of 100% (in respectively 57 and 69 patients) [43,44]. The third study, that was actually aimed at the evaluation of breast specific gamma imaging for the detection of ILC, reported two false negatives in a series of only 12 patients, resulting in a sensitivity of 83% [42], which can only be explained by bad luck and the low number of patients, as it is far below the earlier reported confidence intervals [27].

Almost all available studies are retrospective in design. Only two studies completely report prospective data and one study is partly prospective [34,37,43]. Francis et al. reported a sensitivity of 95% in 22 ILC, Berg et al. reported a sensitivity of 97% in 29 ILC and Caramella et al. reported a sensitivity of 100% in 35 ILC. Hence, prospective data are well in-line with the results from the retrospective studies.
Nevertheless, all studies evaluated patients that were known to have a carcinoma. Although various authors report ILC that were incidentally detected in MRI examinations performed for other indications, few data are available that report the sensitivity of breast MRI for ILC in a screening situation. In general the sensitivity of breast MRI for breast cancer in screening is lower than in pre-operative staging, though much better than mammography; reported sensitivities range from 77-100% [45]. In the large screening studies too few ILC were detected to produce conclusive results, however, Kriege et al. reported a sensitivity of 100% for MRI in the detection of four ILC, compared to 25% for mammography [46], suggesting an additional value over mammography of screening for ILC with MRI.

For optimal detection of ILC in a screening setting it is essential to know the MR-features of ILC. It is commonly stated that ILC appears more often as non mass-like enhancement and in general enhances less than IDC. At the same time good scientific evidence for these statements is lacking. This is partly due to the fact that the interpretation of breast MRI, even using the rigorous approach of the BI-RADS lexicon, is subject to considerable interreader variability [47-49]. As a direct consequence, the principal distinction between mass-like and non mass-like lesions is a very difficult one to make. Different studies report the incidence of non mass-like enhancement to be between 5 and 69%. Pooling of this data is not possible due to the large heterogeneity in the studies [27].
In the large group of mass-like lesions, about 85% are described as irregular and spiculated. Therefore, an irregular spiculated mass is in fact the most common appearance of ILC on MRI [27,43,50] (fig 4). However, round masses with sharp margins have also been described, that subsequently turned out to be ILC [43,50,51]. Non-mass like enhancement can be either ductal, segmental, regional or diffuse (fig 5).

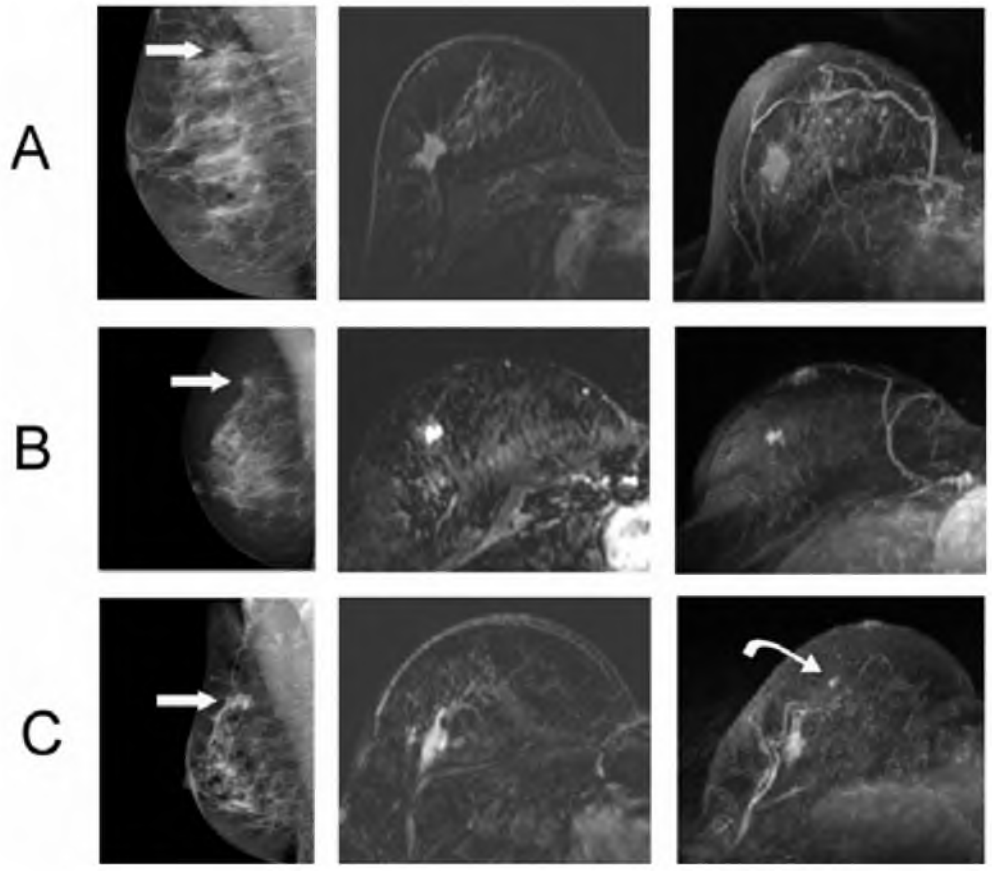

Fig 4: *Three examples (Row A, B and C) of mass-like ILC in the right breast of three different patients at respectively mammography (first column), subtraction MRI (second column) and maximum intensity projection of the MRI (third column). These masses are all irregular and especially the mass in A is heavily spiculated. Note that all masses were also visible at mammography (straight arrows), the additional tumor focus in patient C, more anteriorly located and in these images only visible on the MIP (curved arrow), was only detected at MRI.*

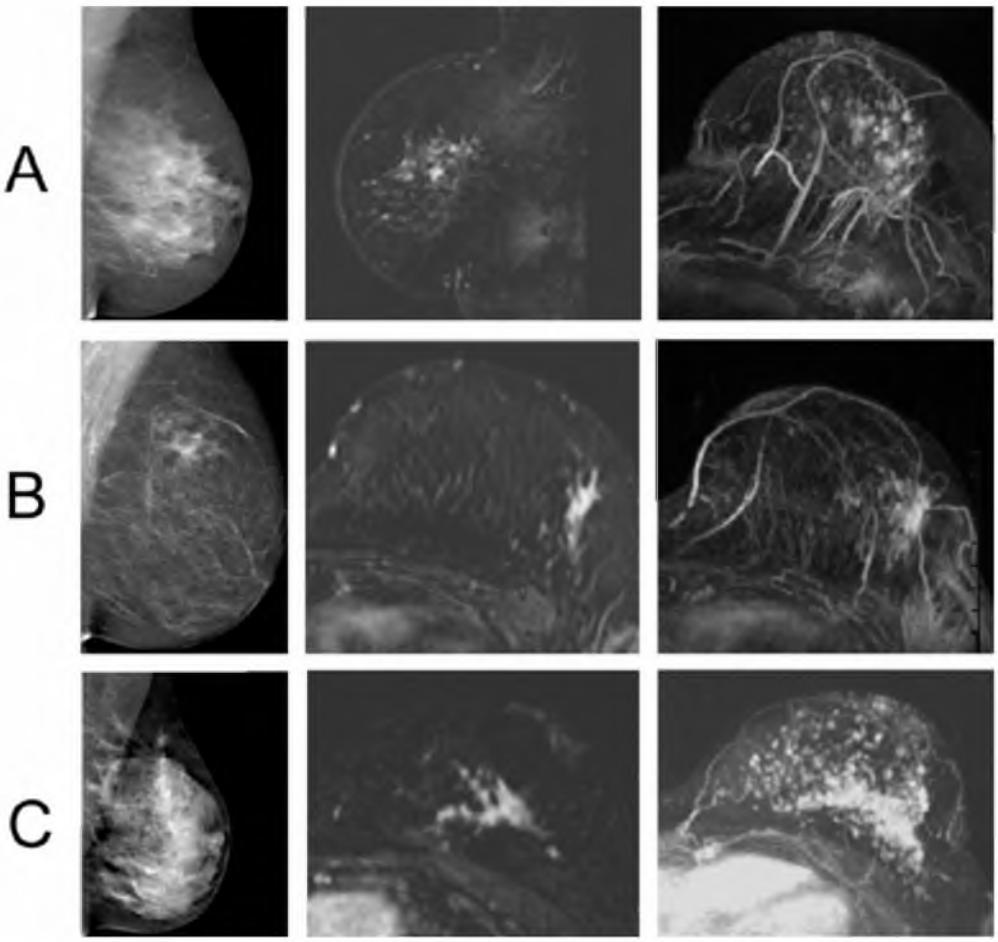

Fig 5: *Three examples (Row A, B and C) of non-mass-like ILC in the left breast of three different patients at respectively mammography (first column), subtraction MRI (second column) and maximum intensity projection of the MRI (third column). The enhancement was respectively regional (A), segmental (B) and diffuse (C). The tumors in A and C were palpable but not seen at mammography, while the tumor in B was mammographically detected, but its multifocal nature was only depicted at MRI.*

Evaluation of the enhancement pattern has less often been described. Sittek et al. and Trecate et al. both noted that peak enhancement was reached relatively late, and wash-out in the late phase of enhancement was uncommon [41,52]. Caramella et al even noted continuous enhancement in the late phase of enhancement (commonly referred to as a type 1 curve) in 37 % of ILC [43]. Two studies that evaluated quantitative enhancement parameters also noted that these values appeared much lower for ILC than in other studies evaluating the same parameters for IDC [51,53].

In the absence of studies that directly compare morphological and kinetic descriptors between IDC and ILC, the magnitude of the differences between the appearances of ILC and IDC cannot be adequately assessed. Such direct comparison studies have been performed and reported upon, but are so far unpublished.

Newstead et al. presented a comparison of 22 ILC to 257 IDC and 83 DCIS lesions at RSNA 2005 [54]. They reported that 55% of ILC presented as a mass, compared to 76% of the IDC and only 16% of DCIS lesions. Time to peak enhancement was twice as long for ILC as for IDC (270 ± 112 s vs. 131 ± 90 s) and enhancement after 68 seconds was consequently lower in ILC than in IDC.

Mann et al. reported at ISMRM 2008 in a comparison of 33 ILC to 103 IDC that 75% of ILC presented as a mass, compared to 84% of IDC [55]. Interreader variability was moderate ($\kappa = 0.41$), comparable to literature values, and similar for ILC and IDC. Peak enhancement was not different between ILC and IDC (360 vs 382%), but at visual assessment wash-out was less common in ILC (48 vs 84%). Using a CAD application, this difference was blotted out, wash-out was detected in 88% of ILC and 94% of IDC, suggesting that CAD applications may be especially helpful in the assessment of ILC (fig 6). This is explained by the observation that the fraction of the lesion that shows wash-out is generally smaller in ILC (<10% of the dominant focus in 64% of ILC vs. 30% of IDC). The results of pharmacokinetic analysis also showed that ILC in general enhance slower than IDC, but not less.

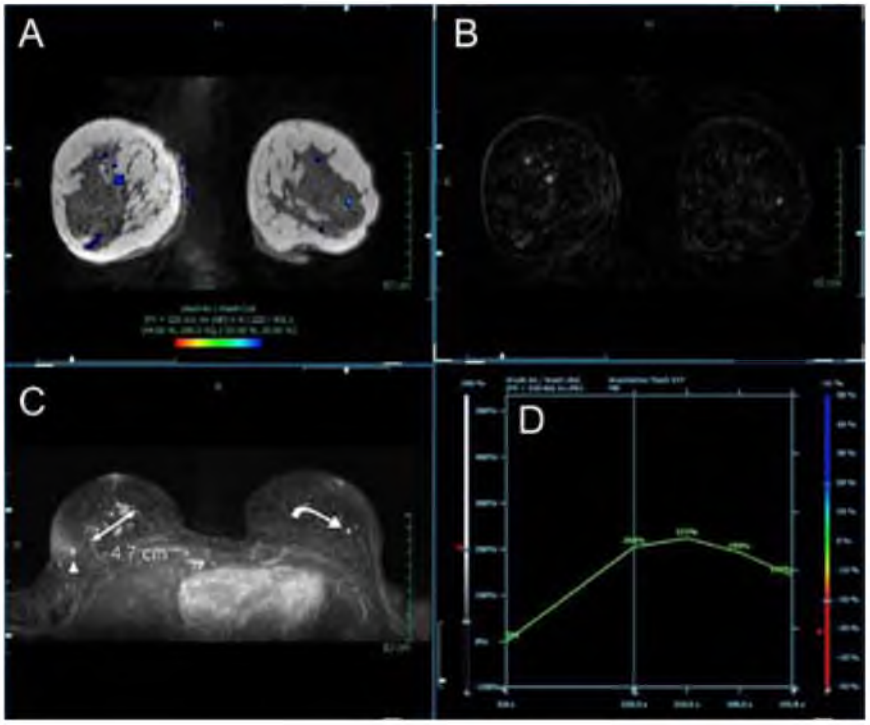

Fig 6: *40 year old woman with strong family history for breast cancer, who presented with nipple discharge. The mammogram showed dense breast tissue with multiple benign calcifications and was thus negative (not shown). Microdochectomy revealed LCIS. MRI was performed, showing a multifocal ILC over an area of 4.7 cm. Although most of the tumor showed continuous enhancement a small area was detected that showed early wash out of the contrast agent. (A: T1w FLASH 3D acquisition with color coded overlay of enhancement, the crosshair is placed at the machine detected spot with most suspicious enhancement curve, B: subtraction image of pre- and postcontrast MRI, C: maximum intensity projection, note the tumor area (double headed arrow), an ipsilateral intramammary lymph node (arrow head) and the biopsy proven fibroadenoma in the contralateral breast (curved arrow), D: machine detected most malignant enhancement curve (corresponding to the crosshair in A)).*

Lastly, Dietzel et al. reported at ECR 2009 on a comparison of 108 ILC to 347 IDC [56]. In their series ILC were more often irregular lesions than IDC (62 vs 55%), though this did not reach statistical significance. An essential finding was, however, that internal necrosis (and hence ring enhancement) was less common in ILC than in IDC (3 vs. 15%) and that perifocal edema was less often observed (30 vs 45%). Moreover they also noted that wash-out was less frequent in ILC than IDC (57 vs. 73%). Both tumor types were nearly always iso- to hypointense compared to glandular breast tissue on T2 weighted imaging.

In summary:

- Almost all ILC are retrospectively visible.
- Most ILC still present as an irregular spiculated mass, but the frequency of non-mass-like enhancement (between 20 and 40%, approximately) is slightly higher than in IDC.
- Ring-enhancement and surrounding edema are less frequently observed.
- Contrast enhancement is slower than in IDC, but not necessarily less, which results in a higher proportion of lesions that do not show a typical wash-out curve.
- CAD applications may help to adequately assess the most malignant curve shape, however, the morphologic appearance is usually that of a suspicious lesion and should not be misinterpreted in the absence of a wash-out curve.

Agreement of MRI findings with pathologic assessment of ILC

Since both mammography and ultrasound findings do not correlate very well with the pathologic assessment of ILC, many studies have focused on the correlation of MR findings with pathology [35,37-40,43,44,57-59]. In general, multifocal disease can be correctly predicted in approximately 80 - 90% of patients. Caramella et al. showed a kappa coefficient of .87 for the detection of multifocal disease compared to pathology [43], which can be translated as excellent inter-reader agreement. This is in comparison to .22 for both mammography and ultrasound, which translates into poor to fair agreement. Nevertheless, both overestimation and underestimation of the number of tumor foci occurs. Overestimation has been attributed to enhancing LCIS [44]. Rodenko et al. noted in a series of 20 patients two cases of single quadrant disease that were interpreted as multicentric disease on MRI. These two cases stress the importance of obtaining histology prior to radical changes to the surgical treatment [59] (fig 7).

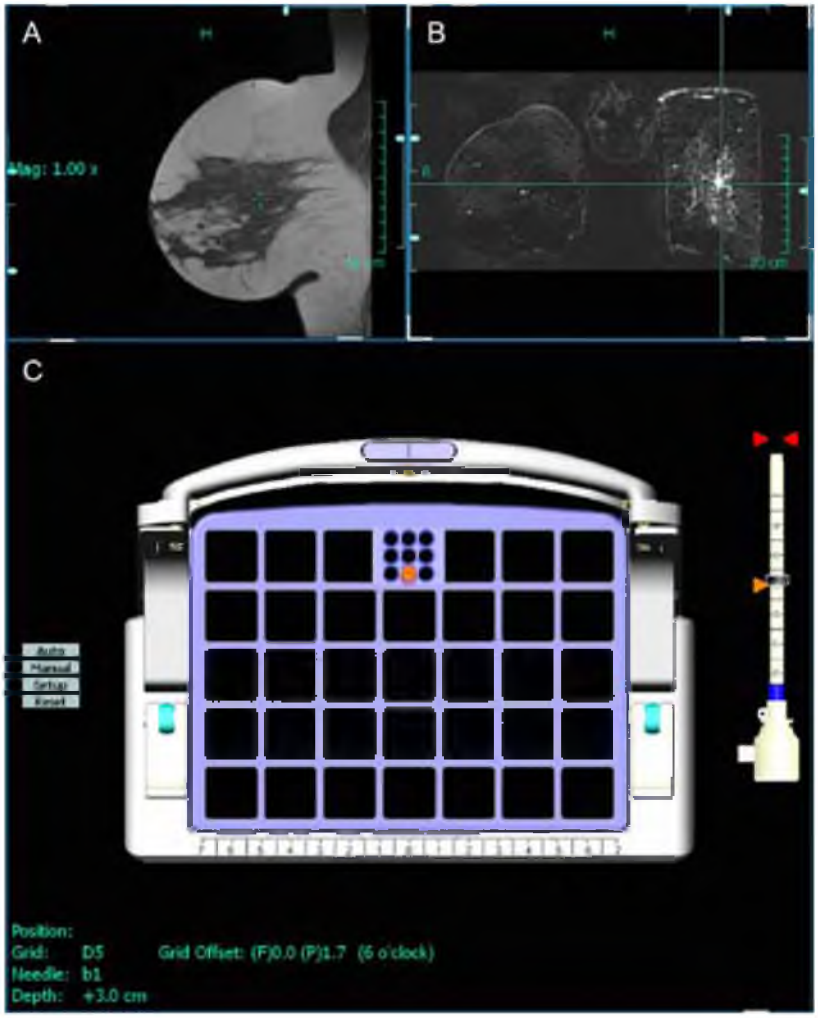

Fig 7: *MRI guided breast biopsy of a multifocal ILC in the left breast, after negative mammography and negative second look ultrasound. A computer program (DynaCAD, Invivo, Orlando, USA) is used to accurately position the needle. In A a native sagital T1 image of the left breast is shown, the needle is currently aimed at the crosshair. In B a subtraction image in the coronal plane of both breasts is shown, which is used to locate the lesion. The lesion is in the center of the crosshair. In C the biopsy grid is shown, it shows where to position the biopsy block (purple block with holes) and in which of the holes to insert the needle (yellow dot) to come closest to the optimal position (red circle). The necessary depth can be read at the bottom of the screen. Using vacuum assisted biopsy, the diagnostic yield is approximately 95%.*

More recently Onesti et al. reported in a series of 10 ILC that 5 tumors were in size overestimated by, an average of 1.2 cm [58]. Nonetheless, most studies report actually good correlation between MRI findings and pathology (table 1, fig 8). Unfortunately, in April 2006 it was not

yet feasible to perform a meta-analysis due to the large variability among the studies [27]. Nowadays, with the publication of the studies by Caramella and Mann, 7 studies have been published that either calculate Pearson's correlation coefficients for tumor size on MRI versus pathology, or present sufficient data to calculate this correlation coefficient [43,44]. Since one of the latter studies is an extension to an earlier published study, there are now six studies, totaling 220 patients, that can be entered in a meta-analysis as listed in table 1.

Table 1: *Reported correlation coefficients of MRI measured sizes with sizes of ILC at pathology.*

Study	N	Pearson's correlation coefficient
Munot et al.	20	0.97
Kneeshaw et al.	21	0.86
Francis et al.	22	0.87
Kepple et al.	33	0.88
Caramella et al	57	0.88
Mann et al.	67	0.85

Applying simple meta-analytical principles to this data yields no longer significant variability ($Q = 9.75$, ($p = 0.084$), $I^2 = 49$ %) and consequently data-pooling can be performed. The estimated correlation coefficient for MRI compared to pathology is 0.89 (95% CI 0.84 – 0.93), which is much better than what can be achieved by mammography or ultrasound, even in the hands of experienced practitioners.

The bad performance of conventional imaging methods is partly explained because MRI detects in many patients tumor foci separate from the index lesion in the ipsilateral breast that were mammographically and sonographically occult. Such additional tumor foci are present in approximately 32% of patients (95% CI 22-44%) and can be both multifocal as well as multicentric [27,36,40,60-62].

In summary:

- In patients with ILC, correlation of MRI findings with pathology is good, yielding a correlation coefficient of 0.89.
- Additional tumor foci, only detected by MRI, are present in 32% of patients with ILC.

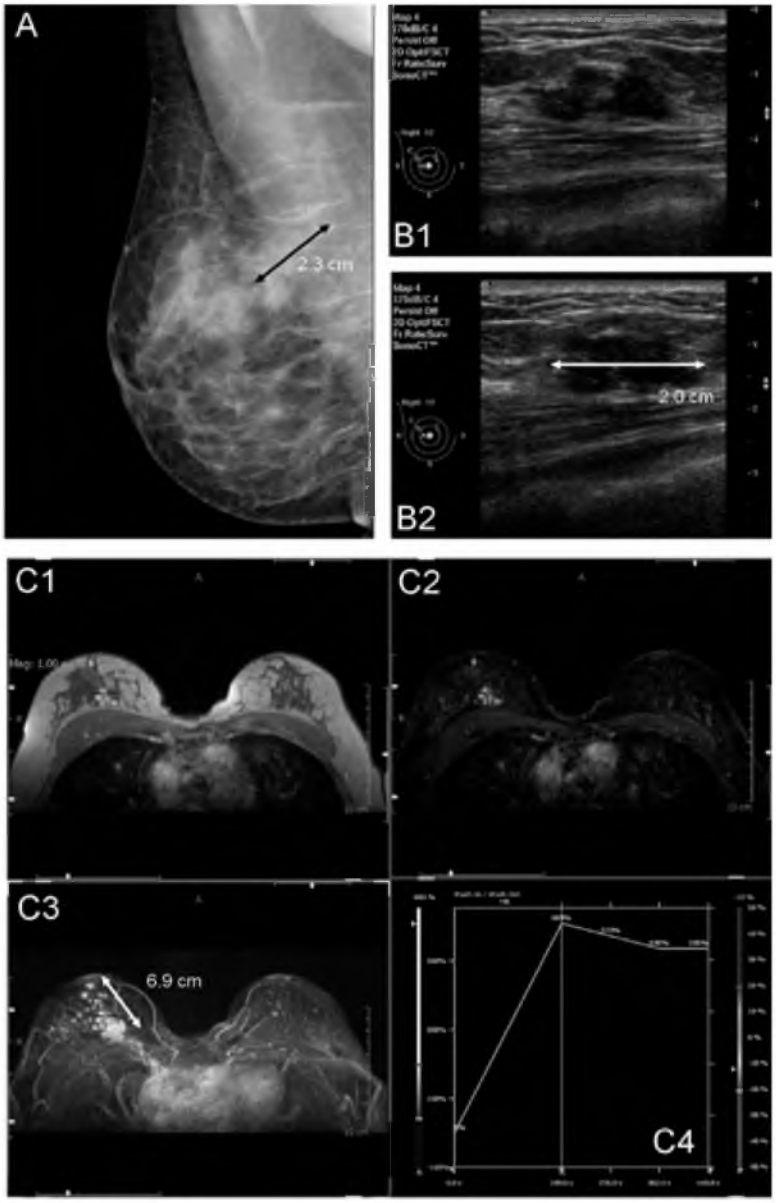

Fig 8: *Images of a 37 year old women, known to be a BRCA2 mutation carier. At mammography (A) an isointense spiculated mass was observed with a maximum diameter of 2.3 cm. At sonography (B) a hypoechoic mass with minimal posterior acoustic shadowing was observed. The maximum diameter of the tumor appeared to be 2.0 cm (B2). The MRI, shown in C (C1: native T1 post contrast acquisition, C2: subtraction image, C3: maximum intensity projection, C4: enhancement versus time curve corresponding with the crosshair in the other images) reveals a multifocal tumor over an area of 6.9 cm. Consequently mastectomy was performed. At pathology, a multicentric ILC was seen over an area of 7.3 cm.*

Consequences for the therapeutic approach of ILC

The good correlation of MRI findings with pathology and the frequent detection of additional tumor foci has a huge impact on the therapeutic approach in patients with ILC. Since the primary treatment for breast cancer, ILC and IDC alike, is usually surgery, the performance of preoperative breast MRI and visualization of additional sites in many patients initiates more extensive surgery. The surgical plan changes in approximately 28% of cases (95% CI 20-39%) [27,36,38,39,59,61]. In 12-33% of patients breast conserving surgery (BCS) followed by radiotherapy is replaced by mastectomy [36,38,39,43,59,61]. Change of therapy in the other direction due to better delineation of the tumor has been reported, but in a substantial smaller percentage of patients (approximately 5%) [43]. Consequently, it has been estimated that overall the primary therapy shifts from breast conserving therapy to mastectomy in 15 to 20% of patients [63]. Furthermore, preoperative MRI is able to stratify some patients to neoadjuvant chemotherapy or vice versa, from chemotherapy to direct surgery, due to better tumor evaluation. Moreover, MRI can also be used to evaluate the effect of neoadjuvant chemotherapy (fig 9).
About 88% (95% CI 75-95%) of changes based on MRI are subsequently deemed correct by pathological confirmation of tumor in the specimen [27].

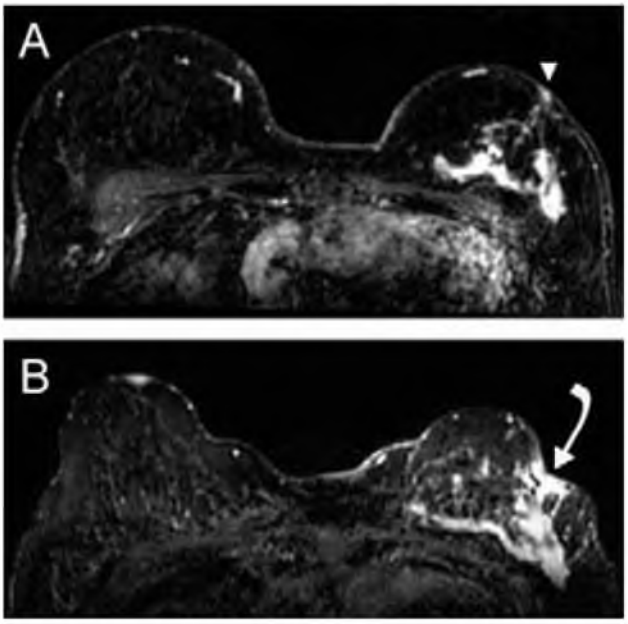

Fig 9: *Two subtraction images of a 47 year old woman, who presented with a T4 ILC in the left breast. Initial assessment with MRI (A) shows a large diffuse growing tumor within the left breast with involvement of the skin (arrowhead). She was initially treated with neoadjuvant chemotherapy. The control MRI (B) unfortunately shows that the tumor did not respond well, but in fact had grown, while the patient became much thinner. Moreover the skin involvement worsened (curved arrow). Consequently salvage mastectomy was performed.*

In summary:

- Preoperative MRI in patients with ILC changes the surgical plan in 28% of cases.
- The primary therapy shifts from breast conserving therapy to mastectomy in approximately 15-20% of patients.
- Based on pathological evaluation of the specimen 88% of changes is correct.

Effect of preoperative breast MRI on outcome in patients with ILC

So far, there is no evidence that suggests an increase in survival for patients with ILC due to the performance of pre-operative MRI. The two studies that have evaluated recurrence and survival as a function of performing pre-operative breast MRI so far have not specifically addressed ILC, nor have they convincingly shown an increased survival for all women with breast cancer [64,65]. The rate of recurrence after BCS followed by radiotherapy is at approximately 0.6-1% per year. This is acceptably low and one can hardly expect this to decrease much further by the addition of MRI in all patients. This implies that at least some of the additional lesions detected by MRI and not surgically excised are adequately treated by radiotherapy and adjuvant chemotherapy. However, reported re-excision rates for ILC in the literature due to failure to radically excise the tumor at the first attempt are unacceptably high, ranging from 29 to 67% [66-70]. Moreover, 16-48% of BCS attempts are still converted to mastectomy after initial unsuccessful surgery [70-75]. These facts are devastating to the mental state of the patient who already has to deal with the fact that she has breast cancer. Moreover, re-excision is detrimental to the cosmetic outcome [76].

It is clear that MRI is the best diagnostic imaging modality currently available for ILC. The question is no longer whether the tumor is correctly depicted, but whether surgeons are able to use this information for the benefit of the patient. The high rate of changes induced by preoperative MRI should assign patients directly to the correct therapy (either BCS or mastectomy), without unnecessarily assigning patients to mastectomy. The surgeon needs to be able to appreciate breast tumors in 3D images rather than on flattened mammography images, requiring training and skill. Moreover, it is necessary to transform the MR image mentally from the prone position in which the patient is scanned to the supine position in which the patient is operated, taking into account the movement of the breast tissue in all directions.
Only recently a retrospective study evaluated the re-excision rate in 267 patients with ILC of which 99 underwent preoperative MRI [63]. Initially,one-hundred-forty-five of these patients underwent BCS, 90 without preoperative MRI and 55 with preoperative MRI. Re-excision was deemed necessary in 24 patients (27%) without preoperative MRI and 5 patients (9%) with preoperative MRI. An odds- ratio for re-excision without preoperative MRI of 3.64 (95% CI 1.30 – 10.20) was calculated. In other words, patients who did not undergo preoperative MRI had a more than 3.5 times higher chance to need a re-excision and, 23% chance of ending with a mastectomy. This is in comparison to only 7% in the group of patients that underwent

preoperative breast MRI and were surgically treated by surgeons used to working with breast MRI. The final rate of mastectomies appeared even lower in the group of patients that underwent MRI (48 vs 59%), though this did not reach statistical significance. Finally, the total treatment time (approximately 42 days) was not dependant on the performance of MRI, but was extended by the need for re-excision.
Currently, there are only two other studies published that evaluated the effect of preoperative MRI on margin status [77,78], none of which specifically addressed ILC. Pengel et al. included 52 patients with ILC of whom half underwent preoperative MRI [78]. Excision was extensively incomplete (and thus requiring re-excision) for 3 of 26 patients (12%) with preoperative MRI and 5 of 26 patients (19%) without preoperative MRI. In this study, the overall reported re-excision rates (much lower than in the previous mentioned study due to the large fraction of IDC) are more than twice as high in the group of patients that did not undergo preoperative MRI (10.6% vs. 5%), but the authors do not report on statistical significance concerning the re-excision rate. The study by Bleicher et al. does not provide sufficient data to extract numbers for ILC, but in general did not detect a reduction in the rate of positive margins, nor in the number of patients that finally underwent mastectomy [77]. Apparently, they were thus unable to use the increased knowledge from MRI for the benefit of the patients, which underlines the need for training and experience, not only of radiologists, but of surgeons as well.

In summary:

- The performance of preoperative MRI may reduce the rate of re-excisions in patients with ILC from 27% to 9%.
- Preoperative MRI in patients with ILC does not increase the final rate of mastectomies.
- Preoperative MRI in patients with ILC does not delay the time to final therapy.
- The success of preoperative MRI is highly dependent on the experience of both radiologists and surgeons with breast MRI.

Evaluation of the contralateral breast with MRI in patients with ILC

Apart from staging of the known cancer, breast MRI in the preoperative setting serves a second purpose that may be even more important. According to Arpino et al. contralateral carcinoma is present in 20.9% of patients with ILC compared to 11.2% of patients with IDC [79]. Overall MRI is estimated to detect in approximately 4% of patients a synchronous contralateral carcinoma that was not detected by any other imaging modality [80]. It may not be surprising that the rate of synchronously detected contralateral breast cancers by MRI in ILC is almost double that seen in IDC and is currently estimated at 7% (95% CI 4-12%) [27,34-37,39,57,60,61,80] (fig 10). This is independent of tumor size and implies the need of preoperative evaluation with MRI in all patients with ILC, not only the subset that initially opts for BCS.
It is essential to realize that the specificity of breast MRI in the screening of the contralateral breast is only about 50% [80]. Histological verification of detected contralateral lesions is thus

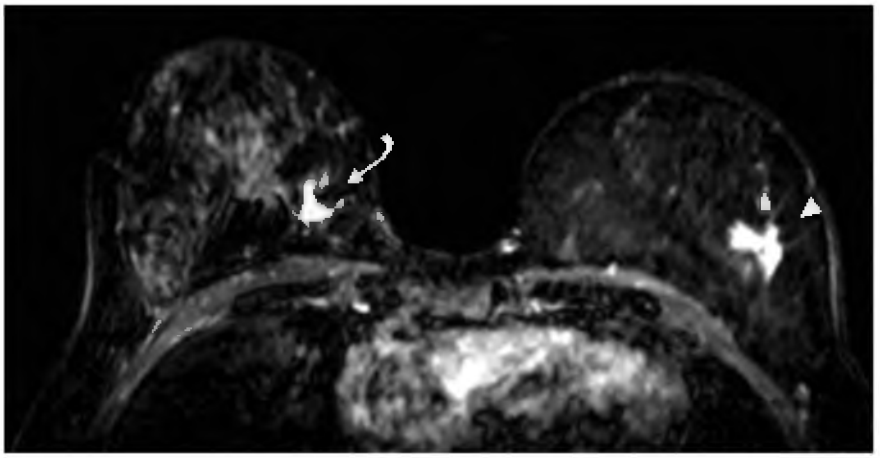

Fig 10: *Subtraction MRI image of both breasts of a 48 year old woman who presented with a palpable lump in the left breast. At mammography and ultrasound (not shown) an ILC of 1.5 cm was detected in the left breast. MRI shows a multifocal tumor in the left breast over an area of 3.4 cm (arrowhead). A second ILC in the right breast is detected (curved arrow) (histologically validated using second look ultrasound).*

essential (as well as verification of any lesion in the ipsilateral breast that would largely change the surgical approach). Second look ultrasound may allow ultrasound guided breast biopsy in approximately 50% of detected lesions [81,82]. MRI guided breast biopsy is a safe, fast, easy and conclusive method to assess the remaining 50%, but easy availability is required [83,84] (fig 7).
The strength, as well as the weakness of MRI in the detection of contralateral carcinomas is that most tumors are identified at an early stage. It is uncertain to what extent these carcinomas influence prognosis in the setting of an already detected ipsilateral carcinoma, and specific data regarding ILC are completely lacking. Contralateral tumors are different from ipsilateral additional detected tumor foci that receive radiotherapy anyway. Most importantly, contralateral tumors remain untreated if undetected. At the same time, adjuvant systemic therapy if given may prevent these tumors from becoming clinically significant. One would expect that the incidence of metachronous contralateral breast carcinoma decreases in patients who underwent preoperative MRI at the time of ipsilateral tumor detection. Unfortunately, the two studies that evaluated this issue report conflicting results. Fischer et al. reported a reduction in the rate of metachronous contralateral carcinoma from 4% to 1.7% due to preoperative MRI, whereas Solin et al. reported an incidence of 6% contralateral carcinoma with and without preoperative MRI [64,65].
Nonetheless, adjuvant therapy alone is generally not considered curative for breast cancer. Since a recent study has shown that early detection of asymptomatic second breast cancer in the ipsilateral breast or the contralateral breast in women with a history of breast cancer increases relative survival by 27 to 47% [85], we can assume that detection of additional contralateral carcinoma by MRI indeed increases survival. The magnitude of this effect remains uncertain.

In summary:

- Preoperative MRI in patients with ILC detects otherwise undetected contralateral carcinoma in 7%
- It is unsure whether preoperative MRI reduces the occurrence of metachronous contralateral carcinomas, there is no evidence available for patients with ILC.
- There is indirect evidence that early detection of contralateral carcinomas improves relative survival.

Current evidence for the performance of breast MRI in ILC, shortcomings and future perspectives

So far, many studies have shown that MRI is able to depict ILC well. MRI has also been shown to correlate better with pathology in the assessment of ILC when compared with other commonly available imaging modalities. Moreover, it significantly affects diagnostic thinking and subsequent therapeutic management.

The notion that preoperative MRI in ILC affects therapeutic management of these tumors is known as level 4 evidence of its value [86]. This, however, does not automatically imply that the performance of preoperative MRI is also good for the patient (known as level 5 evidence). At this level of evidence, the rate of re-excisions is the shortest term outcome parameter that can be evaluated, but also reductions in unwanted side effects of therapy, local recurrence and other metachronous carcinomas can be evaluated. Moreover, the ultimate gain for a patient is increase in survival or even better quality-adjusted life years, which is therefore the principal outcome parameter in many studies.

Only very recently the first studies evaluating outcome parameters after preoperative MRI have been published [63-65,77,78] with only one of these studies specifically addressing ILC [63]. The retrospective study discussed above shows that in experienced hands preoperative breast MRI can reduce the rate of re-excisions in patients with ILC. However, it does not show an effect on tumor recurrence, metachronous contralateral carcinoma or survival, nor does it evaluate cost-effectiveness. Regarding these issues, only indirect evidence is available. Evidence in favor of preoperative breast MRI in patients with ILC at the fifth level is only moderate and further studies are essential. Moreover, the sixth (and highest) level of evidence, which questions whether or not the use of preoperative breast MRI in ILC is beneficial to society and hence is dependent on a cost-effectiveness analysis from a societal viewpoint, has not been addressed.

I am, on the other hand, of the opinion that the currently available evidence in favor of preoperative breast MRI in patients with ILC is substantial. The inherent benefits of breast MRI for patients are large: lowering the chance of incomplete excision and subsequent need for re-excision, and possibly improving survival, while the detrimental effects of preoperative MRI, if adequately performed, are only minor with the possible additional need for biopsy. Consequently, based upon the currently available data, imaging with pre-operative MRI is strongly recommended in all patients with ILC prior to therapy.

Future perspectives of breast MRI, the broader approach

Although the value of preoperative MRI in patients with ILC may be clear, this holds only partly true for other types of breast cancer. In IDC the reported re-excision rates are much lower, and though these can probably also be reduced by preoperative MRI in experienced hands, as shown by Pengel et al. [78], this gain (a reduction from 8 to 2% incomplete excisions) is of a much lesser magnitude than in patients with ILC. The same holds true for the detection of contralateral carcinoma in IDC, since the frequency of MRI detected unexpected contralateral lesions is at 4% only half of the frequency in ILC [80]. Consequently, the possible impact on survival is less. Nevertheless, these numbers are still not insignificant and it will be very difficult to refuse to perform an MRI if a well informed patient requests the investigation.

Moreover, it has been clearly shown that screening with MRI and mammography in patients with a lifetime risk of 15% or more detects more cancers and reduces the frequency of interval carcinomas [45,87,88]. In a recent meta-analysis by Warner et al. it was shown that the addition of mammography in this setting is only very small [89]. Thus, if anything, screening with MRI should be preferred over screening with mammography. This holds particularly true, since it has been shown that MRI is at least as good in the detection of DCIS as mammography and might be even better, which is discussed in more detail in Appendix 1 [90]. Based upon these results and the notion that the lifetime risk of developing breast cancer for the general woman in the Netherlands is at 12-13% only slightly lower than in the tested high risk populations [91], MRI will probably play a major role in breast screening in the near future [92,93].
One of the limiting factors has always been the difficulty of MRI guided breast biopsy. But recently this has become more widely available and nowadays should be accessible to every breast radiologist [83]. When screening is mainly performed by MRI, the discussions about preoperative staging will off course be obsolete, as most tumors will initially be detected and thus staged by MRI.

The most essential drawback to wide implementation of breast MRI in the current medical practice is the still high cost of the examination. It is therefore essential that the prices of MR machines decrease and imaging protocols become standardized and faster, which is still work in progress.

More experimental is the use of breast MRI to assess breast cancer prognosis. The fact that breast MRI is an investigation that leans heavily on physiological principles allows the observation of physiological parameters in every tumor. Because there are many different methods to evaluate these tumors (e.g. contrast enhancement, diffusion, metabolic maps) many different aspects of tumor biology can be assessed. It should therefore be possible to predict tumor behavior and metastatic potential. The big advantage of this approach over standard pathological evaluation is that the entire tumor can be evaluated instead of a random sample. The recently reported

correlation of contrast enhancement and necrosis with so called "triple negative" (i.e. estrogen and progesterone receptor negative and no over expression of Her2/neu) breast cancer is only a first step in this direction [94]. Studies to changes in enhancement pattern, water diffusion and choline spectrum in patients treated with neoadjuvant chemotherapy are a second, already more accepted, example of these possibilities [95-100]. A new dimension, however, is the use of contrast enhancement and diffusion weighted imaging prior to the start of chemotherapy to predict eventual tumor response [101,102], which might allow a more patient selective administration of therapy.

Last, the capability of MRI to accurately assess tumor extension might be used to optimize treatment protocols. Especially the use of radiotherapy, essential to the current practice of breast conserving therapy but in itself a treatment with severe side effects, might be reduced or even abandoned in patients were MRI shows no additional tumor foci [103,104]. Moreover MRI might be used for the guidance of non-surgical treatment of breast cancer, either RFA, cryotherapy, focused ultrasound or vacuum assisted transcutaneous tumor excision [105]. Although it will probably be a long run before such treatment options are seriously considered competitors for surgical therapy.

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Nederlandse samenvatting en integrale vertaling van de algemene discussie en conclusies

11

Ritse M. Mann

Deels naar:
The effectiveness of MRI in the assessment of invasive lobular carcinoma of the breast
MRI Clinics of North America, 2010 May;18(2):259-76

SAMENVATTING

Introductie

Dit proefschrift is gericht op de evaluatie van MRI bij het in beeld brengen van het invasief lobulair carcinoom van de borst (ILC). Het primaire doel van dit proefschrift is het formuleren van een "state of the art" aanbeveling voor het gebruik van MRI bij patiënten met ILC. Deze aanbeveling moet gestoeld zijn op bewijs uit klinische studies en moet ook rekening houden met de gevolgen van het uitvoeren van een MRI voor de patiënten. Het verbeteren van de kwaliteit van het beschikbare bewijs, het aanvullen van het bewijs waar dit incompleet is en het evalueren van de gevolgen van een MRI voor patiënten met ILC werden dan ook als secundaire doelen aangemerkt. Deze samenvatting geeft een globaal beeld van de inhoud van dit proefschrift. Het is geen gedetailleerd overzicht van de gepresenteerde feiten.

Hoewel de samenvatting dus beperkt is in omvang, wordt deze gevolgd door een integrale vertaling van de algemene discussie en conclusies van dit proefschrift (hoofdstuk 10). Deze tekst presenteert de data die op dit gebied momenteel voor handen is, in relatie tot de huidige inzichten voor optimale behandeling van het ILC. De in dit proefschrift beschreven onderzoeken vormen een belangrijk deel van de huidige bewijslast en worden hier daarom uitvoeriger besproken, met name ook in relatie tot de recente bijdragen van andere onderzoekers. U treft hier dan ook vooral mijn overkoepelende conclusies aan. Ik hoop, (voor een ieder die de Engelse taal niet machtig is,) dat na het lezen van dit document de boodschap van het proefschrift toch volkomen duidelijk is.

Globale samenvatting

Hoewel de mortaliteit van borstkanker de laatste decennia licht is afgenomen, is borstkanker nog een van de belangrijkste oncologische doodsoorzaken bij vrouwen in Nederland. De diagnostiek en behandeling van het mammacarcinoom is derhalve nog voor verbetering vatbaar.
Aan de diagnostische kant biedt de mamma MRI mogelijkheden tot een aanzienlijke verbetering. Toch is de rol van mamma MRI in de evaluatie van borstkanker niet duidelijk. Dat mammacarcinomen met MRI goed afgebeeld kunnen worden is helder, maar MRI wordt (nog) niet op grote schaal ingezet voor het screenen van de vrouwelijke populatie. Dus worden de meeste carcinomen niet met MRI gedetecteerd. Het is daarom onzeker of een patiënte daadwerkelijk profiteert van eventuele toegenomen informatie over de grootte en plaats van een carcinoom, zoals MRI die levert.
Omdat de meer standaard beeldvormende technieken voor de analyse van mammacarcinomen, mammografie en echo, vooral bij het ILC niet goed in staat zijn de grootte en uitbreiding van de tumor accuraat vast te stellen lijkt dit een gebied waar mamma MRI bij uitstek een toegevoegde waarde kan hebben.

In hoofdstuk 2 worden de verschillen tussen het ILC en het veel vaker voorkomende invasief ductale carcinoom (IDC) bekeken vanuit een radiologisch oogpunt. De belangrijkste bevinding is dat het ILC een meer diffuse groeiwijze heeft en daardoor minder makkelijk is te onderscheiden van normaal mammaweefsel dan het IDC. Hoofdstuk 3 beschrijft het gebruik van mamma MRI bij ILC op basis van de gegevens die beschikbaar waren bij aanvang van dit proefschrift. Enerzijds bleek dat MRI bij de evaluatie van lobulaire carcinomen een toegevoegde waarde kan hebben, anderzijds dat er veel gebieden zijn waar de beschikbare literatuur geen heldere antwoorden kan geven of waar de resultaten van verschillende studies ver uiteen lopen. Als direct gevolg hiervan is in hoofdstuk 4 getracht de kwaliteit en waarde van de in de literatuur beschikbare data te analyseren door middel van een systematische review van de literatuur en waar mogelijk de data van verschillende studies te combineren met meta-analytische technieken. Hierbij is getracht 4 vragen te beantwoorden, namelijk:

1) Hoeveel procent van de ILC is daadwerkelijk zichtbaar op MRI?
2) Hoe ziet een ILC er eigenlijk uit op MRI?
3) Is datgene wat er op MRI wordt gezien hetzelfde als wat er bij pathologisch onderzoek (PA) wordt gezien?
4) Wat is de invloed van de MRI op het chirurgisch beleid?

Hoewel duidelijk bleek dat verreweg de meeste ILC (93%) goed zichtbaar zijn op MRI, bleek uit deze analyse ook dat er op andere terreinen nog vraagtekens bestonden. Zo was absoluut niet duidelijk hoe een ILC er nu eigenlijk uitziet. In absolute zin doordat verschillende radiologen dezelfde verschijnselen nu eenmaal anders benoemen, maar wellicht belangrijker in relatieve zin omdat nooit vergelijkende studies zijn verricht waarbij de karakteristieken van ILC werden afgezet tegen die van andere typen carcinomen. Daarnaast bleek het niet mogelijk om een eenduidig antwoord te geven op de vraag of de tumorgrootte op MRI goed correspondeert met de grootte bij PA, omdat de resultaten van de studies onderling sterk verschilden. Hierdoor was het niet mogelijk om de resultaten van de verschillende studies te combineren. Wel was duidelijk dat MRI bij een groot aantal patiënten additionele tumor foci ontdekte in de ipsilaterale (32%) en de contralaterale (7%) mamma.
Tot slot bleek ook eenduidig dat MRI een grote impact had op het chirurgisch beleid, dit verandert in 28% van de patiënten. Het bleef echter onduidelijk of de patiënten hier vervolgens ook baat bij hadden.

In hoofdstuk 5 zijn vervolgens een aantal technieken beschreven om de mate van aankleuring van tumoren op MRI te kwantificeren. Dit zou het vergelijken van verschillende onderzoeken, gemaakt op verschillende MRI systemen, mogelijk moeten maken. Bovendien reduceert het de invloed van de beoordelend radioloog op het uiteindelijk resultaat. Een van deze kwantificatie technieken is, samen met de meer conventionele technieken om aankleuring te evalueren, in hoofdstuk 6 ingezet om verschillen in aankleuringspatroon tussen ILC en IDC aan te tonen. Uit deze analyse bleek dat ILC trager aankleurt dan IDC, maar niet noodzakelijkerwijs minder. Daarnaast bleek de conventionele aankleuringsanalyse eenduidiger wanneer gebruik gemaakt

werd van een computerprogramma om de meest verdachte regio binnen een afwijking te lokaliseren. Tot slot waren er geringe verschillen in de morfologische karakteristieken van de twee tumor typen, waarbij ILC zich iets vaker dan IDC presenteert zonder duidelijke massa. Niettemin bleken de verschillen zo gering dat dezelfde terminologie gebruikt kan worden om de kenmerken van beide tumor typen op MRI te beschrijven.

In hoofdstuk 7 is vervolgens ingegaan op de correlatie tussen metingen van de tumor grootte op mammografie, MRI en PA. Hieruit bleek dat er geen significante relatie kon worden vastgesteld tussen de grootte van de tumor op mammografie en de grootte van de tumor bij PA. De correlatie van de tumor grootte op MRI met de tumor grootte bij PA was echter heel goed (r=0.85). Desondanks werd ook op MRI ongeveer 10% van de carcinomen meer dan 1 cm te klein en 10% meer dan 1 cm te groot ingeschat. Een van de oorzaken van het overschatten van tumor grootte is waarschijnlijk de aanwezigheid van aankleurend lobulair carcinoom in situ.

In hoofdstuk 8 is vervolgens gekeken of de betere kennis over de exacte tumor grootte en lokalisatie, die MRI levert ook leidt tot minder operaties. Iedere patiënte moet natuurlijk eenmaal geopereerd worden. Aanvullende operaties zijn nodig als de tumor bij de eerste operatie niet volledig is verwijderd. Het percentage patiënten dat zo'n extra operatie nodig had was in de groep patiënten die geen MRI had gehad 27%. In de groep patiënten die wel een MRI had gehad was dit slechts 9%. Daarbij bleek dat het percentage mastectomieën (= volledige verwijdering van de borst) in de groep patiënten die een MRI hadden gehad niet hoger was dan in de groep patiënten die geen MRI had gehad. Bovendien resulteerde de MRI niet in vertraging van de behandeling. Met andere woorden, een grote groep patiënten had daadwerkelijk baat bij de MRI, zonder dat deze MRI negatieve bijeffecten had.

In hoofdstuk 9 is gepoogd op basis van de beschikbare literatuur en met toevoeging van de opinie van experts op het gebied van de mamma MRI, als de literatuur te kort schoot, te komen tot algemene aanbevelingen voor:

1) De minimale kwaliteitseisen waaraan mamma MRI moet voldoen
2) De indicaties voor het gebruik van mamma MRI

Als kwaliteitseisen zijn geduid:

- Het gebruik van een specifieke mammacoil (een speciale antenne, die de MR signalen uit de borsten opvangt)
- Voldoende hoge ruimtelijke en tijdsresolutie van de MR opname
- T1 gewogen beelden van beide mammae op tenminste 3 tijdspunten in relatie tot de contrast toediening. Eenmaal voor en tweemaal na toediening van intraveneus contrast
- Rapportage door een ervaren radioloog en met gebruik van het BI-RADS lexicon
- Beschikbaarheid van MRI geleide biopsie faciliteiten

Als indicaties zijn geduid:

- Evaluatie van de mammae in geval van niet conclusieve conventionele beeldvorming
- Het screenen van de contralaterale mamma in patiënten met een bewezen carcinoom in een borst
- De evaluatie van de mammae bij patiënten met bewezen metastasen, maar geen bekend primair carcinoom
- De evaluatie van therapie respons in patiënten die initieel met chemotherapie worden behandeld
- Het uitsluiten van een lokaal recidief bij patiënten met in de voorgeschiedenis een borst sparende operatie voor een mammacarcinoom
- De screening van patiënten met een risico om gedurende hun leven een mammacarcinoom te ontwikkelen van 20% of meer

In hoofdstuk 10 tenslotte volgt de algemene discussie, waarvan u op de volgende pagina's een volledige Nederlandse vertaling aantreft.

ALGEMENE DISCUSSIE EN CONCLUSIES

Conventionele beeldvorming bij het invasief lobulair carcinoom

Na de initiatie van borstkankerscreening werd snel duidelijk dat invasieve lobulaire carcinomen (ILC) vaker werden gemist dan andere carcinomen en zich daarom vaker presenteerden als interval carcinomen [1]. Dit werd verklaard door het diffuse infiltratieve groeipatroon van deze tumoren en de slechts zeer beperkte desmoplastische reactie van het normale weefsel [2]. Ongeveer een derde van de interval carcinomen blijkt lobulair van origine en, indien gedifferentieerd wordt tussen werkelijke intervalcarcinomen en fout negatieve screenings mammogrammen, blijkt zelfs dat bij 47% van de fout negatieve mammogrammen, de tumoren een lobulaire groeiwijze hebben [3,4]. Dit kan deels worden verklaard doordat ILC vaak beter zichtbaar zijn op de cranio-caudale mammografie opnamen, terwijl deze in de screening niet standaard verricht worden [5,6]. Niettemin is zelfs retrospectief 10-20% van de ILC niet zichtbaar op een mammogram [6-9].
Het klassieke beeld van een maligniteit op mammografie, een gespiculeerde massa, wordt gerapporteerd in 28-63% van de patiënten met ILC [6,9-13] (fig 1,2). De mammografische bevindingen bij de overige patiënten zijn vaak erg subtiel. ILC zijn niet geassocieerd met microcalcificaties en de densiteit van de tumor is vaak gelijk aan, of zelfs lager dan, die van het omringende klierweefsel [5,8,10,14,15].

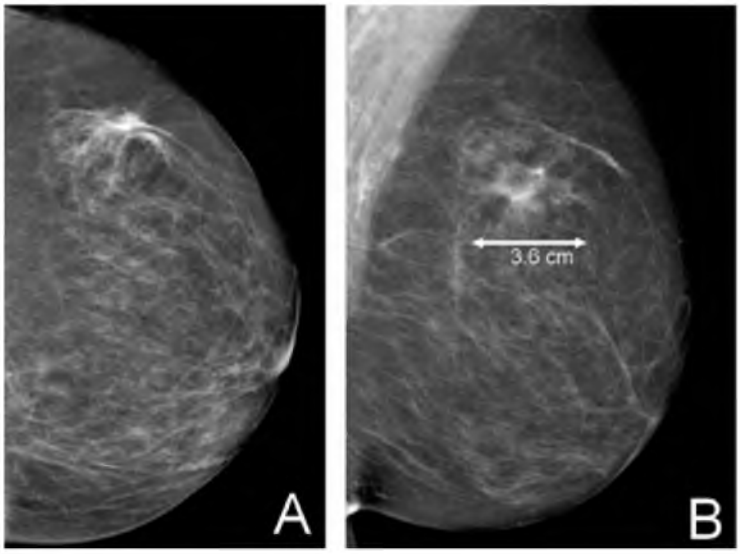

Fig 1: *Mammogram van een 60-jarige vrouw (A: linker mamma, CC opname, B: linker mamma, MLO opname) die zich presenteerde met een palpabele zwelling in het laterale bovenkwadrant van de linker mamma. Er is een hyperdense massa zichtbaar in het laterale bovenkwadrant met een irregulaire gespiculeerde begrenzing en een maximale diameter van 3,6 cm. Bij PA bleek er sprake van een multifocaal ILC over een gebied van 4,2 cm. Het grootste focus was 2,5 cm.*

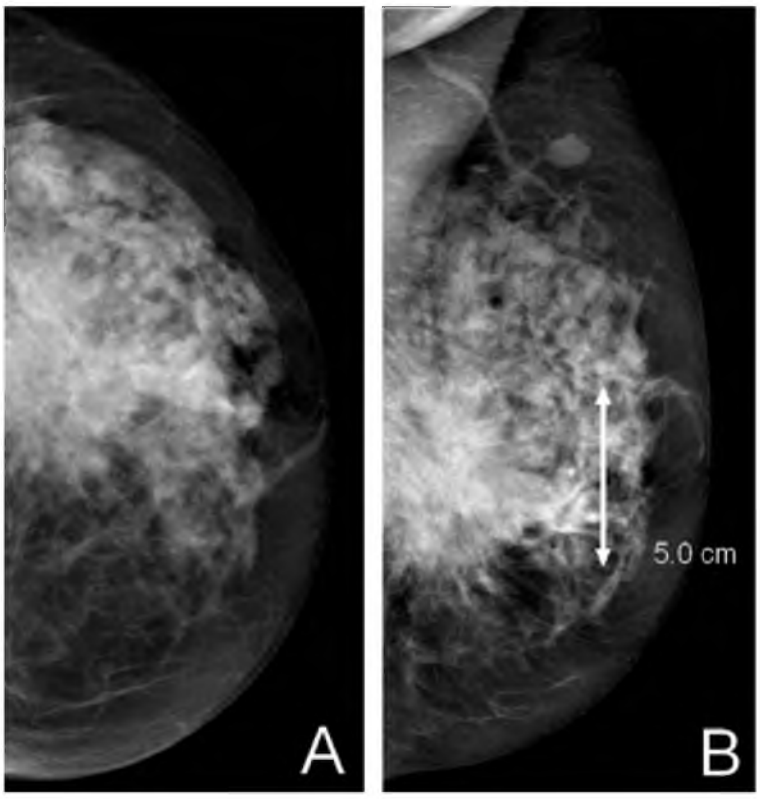

Fig 2: *Mammogram van een 71-jarige vrouw (A: linker mamma, CC opname, B: linker mamma, MLO opname) die zich presenteerde met een palpabele massa en intrekking van de huid. Op het mammogram is een grote architectuurverstoring te zien (tenminste 5 cm), isointens ten opzichte van het normale fibroglandulaire weefsel. De hele mamma is vervormd. Histologie liet een T4a ILC zien.*

Deze tumoren worden onder meer beschreven als: slecht gedefinieerde massa (7-33%) [6,9,12], architectuur verstoring (10- 24%) [6,9-12] of asymmetrie (4-14%) [6,9]. De opvallend wijde marges in het gebruik van de descriptieve terminologie zijn waarschijnlijk het gevolg van de slechts matige overeenstemming tussen verschillende experts.
Zoals verwacht is het slechts zeer beperkt mogelijk om in te schatten hoe groot een ILC is op mammografie. In de literatuur gerapporteerde Pearson's correlatie coëfficiënten variëren van 0.2 tot 0.8. In de praktijk zijn met name kleine tumoren in 'lege' mammae redelijk op maat te schatten. De accuratesse decimeert echter naarmate de tumoren groter en de mammae denser worden. Dit resulteert in een structurele onderschatting van de grootte van grotere tumoren [16-18]. Hoewel ook de grootte van invasief ductale carcinomen (IDC) op mammografie wordt onderschat, resulteren de meestal vage begrenzingen van ILC in een sterkere onderschatting van de tumor grootte dan bij IDC [6,18]. Als gevolg hiervan wordt ongeveer een derde van de ILC op mammografie te laag gestadieerd [19].
Echografie wordt niet gebruikt voor screening, daarom is de sensitiviteit van echo voor ILC

alleen bekend voor laesies, die reeds op een andere wijze zijn gedetecteerd (mammografie of lichamelijk onderzoek). De meeste ILC zijn zichtbaar met echo: de gerapporteerde sensitiviteit varieert tussen de 78 en 98%. [20-26]. In een recente meta-analyse, waarin de sensitiviteit van echografie direct werd vergeleken met de sensitiviteit van MRI, werd voor echo een sensitiviteit van 83% vastgesteld, met een 95% betrouwbaarheidsinterval (BI) van 71-91% [27].
Hoewel een vroege studie problemen rapporteerde met de detectie van kleine ILC (< 1 cm), (slechts een van de vier ILC gedetecteerd) [28], is dit in latere studies gerectificeerd. Deze latere studies rapporteren allen een sensitiviteit voor kleine laesies in de boven beschreven range (71-91%) [29,30]. Essentieel is dat de sensitiviteit van echo ook goed is voor laesies die mammografisch occult zijn, hierdoor kan echo een belangrijke rol spelen in de evaluatie van symptomatische (meestal palpabele) ILC [20]. Ongeveer 60% van de ILC hebben echografisch de klassieke kenmerken van een maligniteit en zien eruit als hypoechoische heterogene massa's met slecht gedefinieerde marges en met een akoestische slagschaduw [20,21,24] (fig 3). Niettemin hebben ILC vaker een intern hyperechogeen patroon dan IDC [21,26] (fig 3D) en sommige ILC presenteren zich als een slagschaduw zonder discrete massa [20,24]. Van dit laatste echopatroon wordt gesteld dat het suggestief is voor een klassiek type ILC (een zeer diffuus groeiende tumor die in lange tumordraden het mammaweefsel infiltreert) [20].

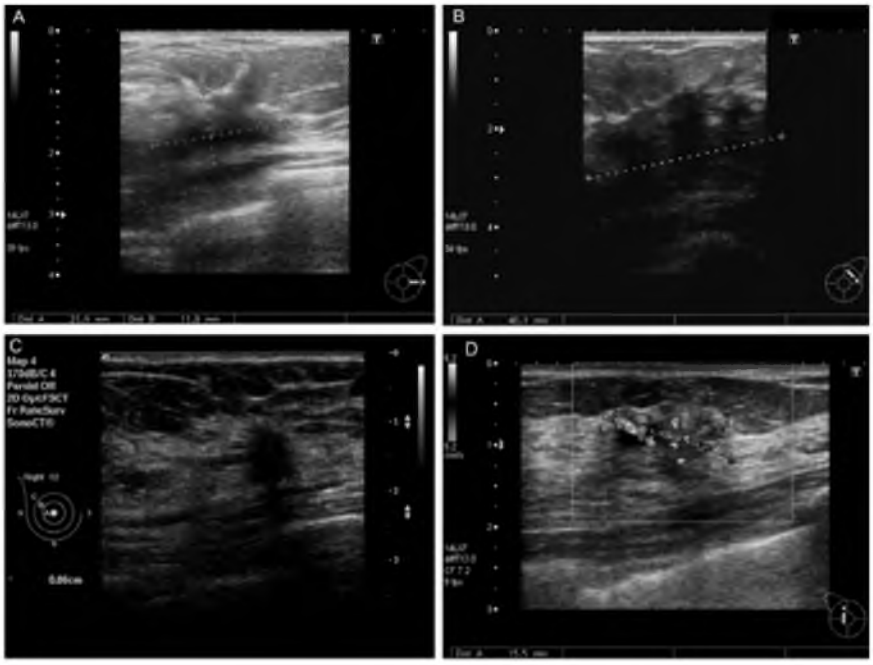

Fig 3: *Echo beelden van 4 verschillende ILC. De tumoren in A, B en C hebben de typische karakteristieken van maligne laesies, d.w.z. een hypoechogene, gespiculeerde massa met posterieur akoestische beschaduwing. De tumor in D is vrijwel isoechogeen ten opzichte van normaal mammaweefsel, maar ter plaatse zijn multipele pathologische Doppler signalen zichtbaar als gevolg van uitgebreide neovascularisatie (zie hoofdstuk 10 voor een afdruk van dit figuur in kleur). Bij pathologie was de*

tumor op A meer dan 5 cm groot , de tumor op B meer dan 8 cm, op C 14 mm en op D 3,2 cm, wat duidelijk aangeeft dat echografische metingen, vooral in grote tumoren ver van accuraat zijn.

Echo is ongeveer even goed in het schatten van de tumorgrootte als mammografie. De range van gerapporteerde correlatiecoëfficiënten is echter iets beperkter en varieert van 0.5 tot 0.8 [25,31-33]. Net als bij mammografie is de accuratesse van de schatting slechter naarmate de tumor groter is, meer nog bij ILC dan bij IDC. De afmetingen van tumoren groter dan 3 cm kunnen niet adequaat worden geschat met behulp van echografie [26,32].

Karakteristieken van ILC op MRI

In een retrospectieve setting is de sensitiviteit van MRI voor ILC hoog. In een meta-analyse die de studies tot april 2006 analyseerde en de sensitiviteit in een totaal van 209 patiënten met ILC beschreef, was 93.3% zichtbaar. Het bijbehorende 95% BI liep van 88 tot 96%. Wanneer de resultaten van een zeer vroege studie, waarin een inadequaat scan protocol was gebruikt worden geschrapt, bleek de sensitiviteit 96% te zijn (95% BI 92-98%) [27,34-41]. Na de publicatie van deze meta-analyse zijn er, voor zover mij bekend, nog drie studies verschenen waarin de sensitiviteit van MRI voor ILC werd bepaald [42-44]. De twee grootste studies rapporteerden beiden een sensitiviteit van 100% (bij respectievelijk 57 en 69 patiënten) [43,44]. De derde studie, die eigenlijk gericht was op de evaluatie van mamaspecifieke gamma-imaging bij het detecteren van ILC, beschreef 2 fout negatieve MRI onderzoeken in een serie van slechts 12 patiënten, resulterend in een sensitiviteit van 83% [42]. Aangezien deze resultaten ver beneden het eerder gemelde 95% BI vallen, kan dit alleen maar worden verklaard door het zeer lage aantal geïncludeerde patiënten [27].

Vrijwel alle studies zijn opgezet als retrospectieve cohortstudies. Slechts twee studies beschrijven prospectief verzamelde cohorten en een studie beschrijft een deels prospectief verzameld cohort [34,37,43]. Francis et al. melden een sensitiviteit van 95% in 22 ILC, Berg et al. melden een sensitiviteit van 97% in 29 ILC and Caramella et al. melden een sensitiviteit van 100% in 35 ILC. De resultaten van de prospectief verzamelde cohorten sluiten dus nauw aan bij die van de retrospectieve cohortstudies.
Niettemin hebben alle studies, zowel de retrospectieve als de prospectieve, alleen patiënten geëvalueerd waarvan al bekend was dat ze een carcinoom hadden. Hoewel verscheidene auteurs gevallen rapporteren van bij toeval met MRI gedetecteerde ILC, zijn er vrijwel geen data beschikbaar over de waarde van MRI voor de detectie van ILC in een screeningssituatie. Globaal is de sensitiviteit van MRI voor carcinomen in een screeningssituatie slechter dan in pre-operatieve stadiering, hoewel MRI voor screening wel veel beter is dan mammografie. De gerapporteerde sensitiviteit varieert van 77% tot 100% [45]. In de grote screeningsstudies bij hoog risico patiënten zijn niet genoeg ILC beschreven om conclusieve uitspraken te doen. Toch rapporteerden Kriege et al. een sensitiviteit van 100% bij de detectie van 4 ILC met behulp

van MRI, terwijl met mammografie slechts een van deze vier tumoren werd gedetecteerd (sensitiviteit 25%) [46]. Dit suggereert dat MRI screening een toegevoegde waarde kan hebben in de vroeg detectie van ILC.

Voor optimale detectie van ILC in een screeningssetting is het essentieel om te weten hoe een ILC er uit ziet op mamma MRI. Er wordt vaak gesteld dat ILC zich vaker dan IDC presenteren als een aankleurende gebied zonder duidelijke massa. Helaas is er opvallend weinig wetenschappelijk bewijs dat deze stelling onderbouwd. Dit is, tenminste deels, het gevolg van het feit dat de beschrijving van laesies op mamma MRI, zelfs met gebruik van de BI-RADS lexicon, last heeft van een sterke inter-reader variatie [47-49]. Een directe consequentie hiervan is dat het simpele onderscheid tussen een massa en een aankleurend gebied zonder massa zeer moeilijk gemaakt kan worden (de ene radioloog zal een afwijkingen een aankleurende massa noemen, terwijl een andere radioloog dezelfde afwijking als aankleurend gebied zonder duidelijke massa kan beschrijven) .
De frequentie van de presentatie van een ILC als aankleurend gebied zonder massa varieert van 5 tot 69%. Het samenvoegen van de data van de verschillende studies is door de heterogeniteit niet mogelijk [27].
In de grote groep ILC die zich wel als een massa presenteert wordt ongeveer 85% beschreven als irregulair en gespiculeerd. Een irregulaire en gespiculeerde massa is dus in feite de meest voorkomende presentatie van een ILC op MRI [27,43,50] (fig 4). Niettemin zijn er zelfs ILC die zich presenteren als ronde massa's met een scherpe rand [43,50,51]. In gevallen van aankleurende gebieden zonder massa, kan de aankleuring beperkt zijn tot het traject van een ductus, maar ook verder uitgebreid zijn tot segmentale, regionale of zelfs diffuse aankleuring (fig 5).

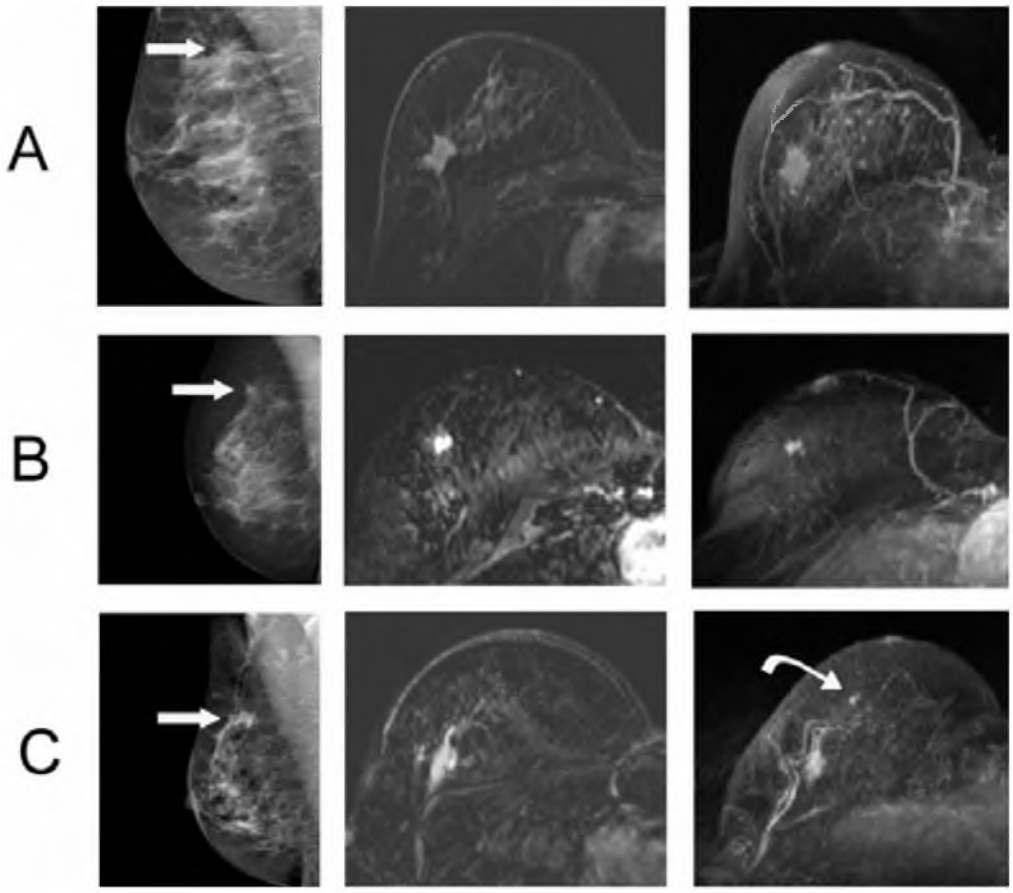

Fig 4: *Drie voorbeelden (Rij A, B en C) van massa vormende ILC in de rechter mamma van drie verschillende patiënten op respectievelijk mammografie (eerste kolom), subtractie MRI (tweede kolom) en maximale intensiteits projectie van de MRI (derde kolom). De massa's zijn allen irregulair en met name de massa bij A is sterk gespiculeerd. Alle massa's waren ook zichtbaar met mammografie (rechte pijlen). Het additionele tumor focus bij patiënt C, meer anterieur gelokaliseerd en op deze plaatjes alleen zichtbaar op de MIP (gebogen pijl) werd echter alleen met MRI gedetecteerd.*

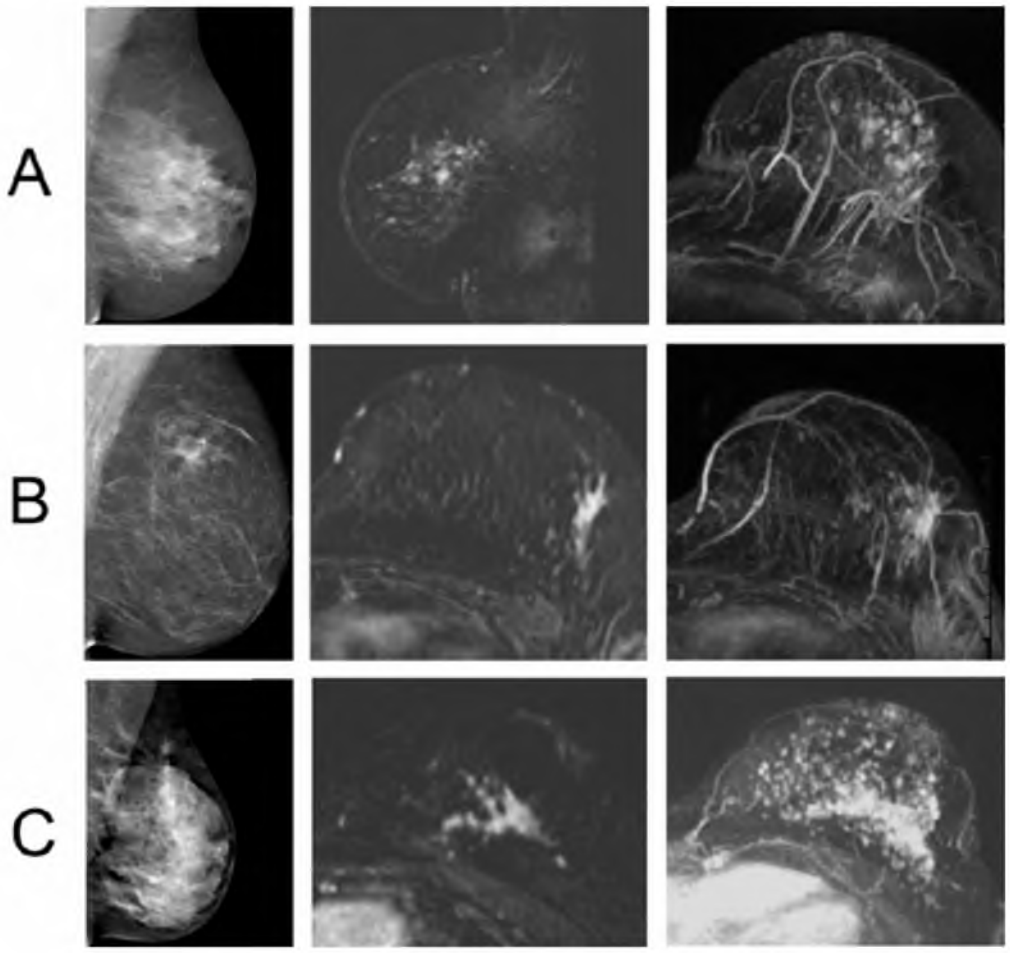

Fig 5: *Drie voorbeelden (Rij A, B en C) van aankleurende gebieden zonder massa in de linker mamma van drie verschillende patienten op respectievelijk mammografie (eerste kolom), subtractive MRI (tweede kolom) en maximale intensiteit projectie van de MRI (derde kolom). De aankleuring was respectievelijk regional (A), segmenteel (B) en diffuus (C). De tumoren bij patienten A en C waren palpable maar mammografisch occult, de tumor in patient B was op mammografie gedetecteerd, maar de multifocale verspreiding was alleen op MRI zichtbaar.*

Het aankleuringspatroon van ILC is minder vaak bestudeerd. Sittek et al. en Trecate et al. beschrijven beiden dat de maximale aankleuring relatief laat werd bereikt en dat het uitwassen van contrast in de late fase van aankleuring minder frequent voorkomt [41,52]. Caramella et al. beschrijven zelfs dat de aankleuringscurve doorstijgt (wat meestal wordt beschreven als een type 1 curve en suggestief is voor een goedaardige laesie) in 37 % van de ILC [43]. Twee studies die gekwantificeerde parameters van contrast aankleuring evalueerden, beschrijven ook dat de geobserveerde waarden in deze studies veel lager lijken dan de waarden die in andere studies worden gerapporteerd met betrekking tot IDC [51,53].

Zonder de aanwezigheid van studies die de morfologie en het aankleuringspatroon van IDC en ILC direct met elkaar vergelijken, kan niet bepaald worden hoeveel ILC en IDC nu werkelijk van elkaar verschillen.

Dit soort studies zijn wel verricht en besproken op verscheidene internationale congressen, maar helaas tot op heden niet gepubliceerd.

Newstead et al. presenteerden een vergelijkende studie over 22 ILC, 257 IDC en 83 DCIS op de RSNA in 2005 [54]. Zij beschreven dat 55% van de ILC zich presenteerden als een massa, vergeleken met 76% van de IDC en slechts 16% van de DCIS. De tijdsduur tot maximale aankleuring van de tumor na contrastinjectie was 2 maal zo lang voor ILC als voor IDC (270 ± 112 s vs. 131 ± 90 s), als direct gevolg hiervan was de aankleuring van de tumor op 68 seconden na contrastinjectie lager in ILC dan in IDC.

Mann et al. presenteerden op de ISMRM 2008 een vergelijkende studie tussen 33 ILC en 103 IDC. Van de ILC presenteerde 75% zich als een massa, terwijl 84% van de IDC zich als massa presenteerde [55]. Er was een matige interreader variabiliteit voor de differentiatie tussen een massa en een aankleurend gebied zonder duidelijke massa (κ = 0.41), vergelijkbaar met in de literatuur gerapporteerde waarden voor interreader variabiliteit van mamma MRI, in het algemeen. Er was geen verschil in de interreader variabiliteit voor ILC en IDC. De maximale aankleuring was niet anders bij ILC dan bij IDC (360 vs 382%), maar bij analyse van de aankleuringscurve zonder gebruik van een computer was de uitwas van contrast (relatief specifiek voor maligniteit) minder vaak zichtbaar in ILC dan in IDC (48 vs 84%). Wanneer wel gebruik werd gemaakt van een computerprogramma om de meest verdachte curve te detecteren, werd dit verschil echter beduidend kleiner. De uitwas van contrast werd op deze manier vastgesteld in 88% van de ILC en 94% van de IDC, wat suggereert dat dergelijke computerprogramma's met name bij ILC een toegevoegde waarde kunnen hebben (fig 6). Dit verschijnsel wordt verklaard doordat bij ILC doorgaans in een kleiner gebied van de tumor dit karakteristieke aankleuringspatroon zichtbaar is (<10% van het dominante focus in 64% van de ILC vs. 30% van de IDC). De resultaten van farmacokinetische analyse lieten ook zien dat ILC over het algemeen langzamer aankleuren, maar niet minder. Dit wordt in meer detail besproken in hoofdstuk 6 van deze thesis.

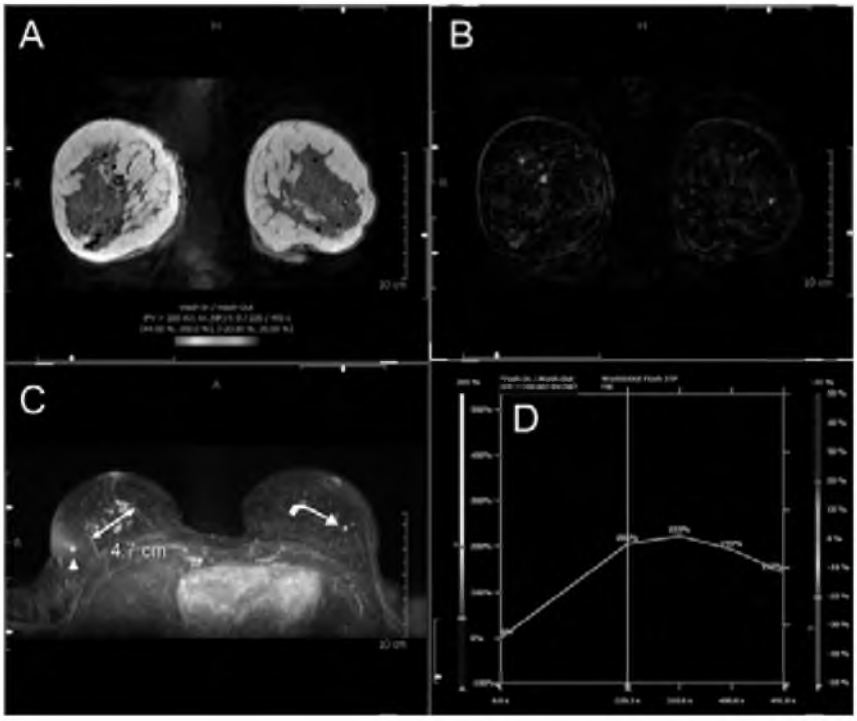

Fig 6: *MRI beelden van een 40-jarige vrouw met een sterke familiar belasting, die zich presenteerde met tepelvloed. Het mammogram liet dens klierweefsel zien met multipele benigne calcificaties en was dus negatief (niet afgebeeld). Microdochectomie liet LCIS zien. Vervolgens is een MRI verricht, waarop een multifocaal ILC over een gebied van 4.7 cm zichtbaar is. Hoewel het grootste deel van de tumor continue aankleuring liet zien, was er toch een klein gebiedje waar het contrast snel uitwaste. (A: T1w FLASH 3D acquisitie met hieroverheen een kleur gecodeerde map van de aankleuring (zie hoofdstuk 10 voor een afdruk van dit figuur in kleur), de cursor is geplaatst op het door het computerprogramma gedetecteerde punt met de meest verdachte aankleuringscurve, B: subtractie beeld van pre- en postcontrast MRI, C: maximale intensiteit projectie, hierop is het tumor gebied (dubbele pijl) duidelijk zichtbaar. Voorts is er een lymfe klier in de rechter mamma zichtbaar (pijlkop) en een fibroadenoom in de contralaterale borst (gebogen pijl). D: door de machine gedetecteerde meest verdachte aankleuringscurve (corresponderend met de cursor in A)).*

Tenslotte rapporteerden Dietzel et al. op de ECR 2009 de resultaten van een vergelijkende studie tussen 108 ILC en 347 IDC [56]. In deze serie waren ILC iets vaker irregulair begrensd dan IDC (62 vs 55%), hoewel dit statistisch niet significant werd bevonden. Belangrijker was dat interne necrose in de tumor (en dus een ringvormig aankleuringspatroon) minder voorkomt bij ILC dan bij IDC (3 vs. 15%) en dat oedeem rondom de tumor minder vaak aanwezig was bij ILC (30 vs 45%). Tenslotte rapporteerden zij ook dat het uitwassen van contrast minder vaak zichtbaar was bij ILC dan bij IDC (57 vs. 73%). Beide tumortypen zijn vrijwel altijd iso- tot hypointens op T2 gewogen MRI afbeeldingen.

Samenvattend:

- Vrijwel alle ILC zijn retrospectief zichtbaar op MRI.
- De meeste ILC presenteren zich als een irregulaire, gespiculeerde massa, maar de frequentie van een aankleurend gebied zonder vorming van een duidelijke massa (tussen de 20 en de 40%) is iets hoger dan bij IDC.
- Ringvormige aankleuring en omgevend oedeem zijn minder vaak aanwezig bij ILC dan bij IDC.
- Contrast aankleuring bij ILC is trager dan bij IDC, maar niet perse minder, wat er toe leidt dat een groter deel van de ILC niet het typische uitwassen van contrast laat zien.
- Computerprogramma's kunnen mogelijk helpen de meest verdachte aankleuringscurves te selecteren. Niettemin is de laesie morfologisch meestal verdacht en deze zou, ook bij afwezigheid van een karakteristiek aankleuringspatroon, niet moeten worden gemist.

Overeenstemming van de MRI bevindingen met pathologische analyse van de specimen bij ILC

Omdat zowel de mammografische als de echografische bevindingen niet geweldig corresponderen met de bevindingen bij pathologische analyse, hebben veel studies zich gericht op de correlatie van MR bevindingen met pathologie [35,37-40,43,44,57-59]. Globaal kan de aanwezigheid van multifocaliteit goed worden voorspeld in 80-90% van de patiënten. Caramella et al. rapporteerden een kappa coëfficiënt van .87 voor de detectie van multifocaliteit in vergelijking met pathologie [43], wat kan worden vertaald als een uitstekende interreader overeenkomst (ter vergelijk: mammografie en echografie scoorden beiden een kappacoëfficiënt van .22 , wat kan worden vertaald als slechte tot matige interreader overeenkomst). Niettemin komen, ook bij MRI, zowel overschatting als onderschatting van het aantal tumor foci voor. Overschatting kan het gevolg zijn van aankleurend LCIS [44]. Rodenko et al. beschreven in een serie van 20 patiënten 2 gevallen van tumoren in 1 kwadrant, die radiologisch waren afgegeven als multicentrische aandoening. Dit onderstreept dat het essentieel is om histologie te verkrijgen van op beeldvorming geobserveerde afwijkingen alvorens het chirurgisch beleid te veranderen [59] (fig 7).

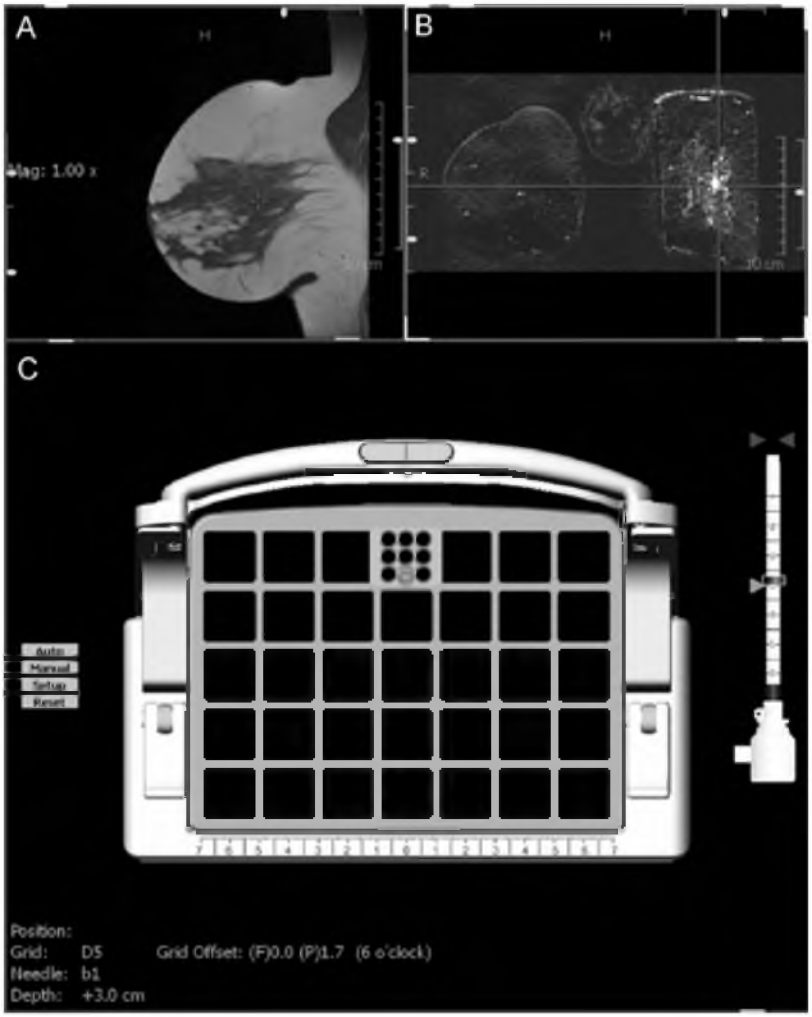

Fig 7: *MRI geleide mamma biopsie van een multifocaal ILC in de linker mamma, na negatieve mammografie en niet geslaagde echografische lokalisatie. Er wordt gebruik gemaakt van een computer programma (DynaCAD, Invivo, Orlando, USA) om de naald accuraat te positioneren. Bij A is een natieve sagitale T1 opname van de linker mamma zichtbaar, de naald is op dit moment gericht op de cursor. Bij B is een coronaal subtractie beeld van beide mammae afgebeeld, waarop de laesie wordt gelokaliseerd. De laesie bevind zich midden tussen de kruisende lijnen. Bij C wordt de biopsie grid afgebeeld. Er is zichtbaar waar het naaldgeleider blokje moet worden gepositioneerd (paarse blokje met rondjes) en welk van de gaten gebruikt moet worden voor de biopsie (gele cirkel) om zo dicht mogelijk bij de optimale biopsie plaats (rode cirkel) te komen (zie hoofdstuk 10 voor een afdruk van dit figuur in kleur). De noodzakelijke biopsie diepte kan worden afgelezen aan de onderzijde van het scherm. Met gebruik van vacuum biopsie is ongeveer 95% van de biopten conclusief*

Recenter beschreven Onesti et al. in een serie van 10 ILC dat 5 tumoren in grootte overschat waren (gemiddeld 1,2 cm) [58]. Het leeuwendeel van de studies beschrijft echter een uitstekende correlatie tussen MRI bevindingen en pathologie (tabel 1, fig 8). In 2006 was het helaas nog niet haalbaar een meta-analyse uit te voeren op de aanwezige data als gevolg van sterke heterogeniteit [27]. Momenteel zijn er, door de publicatie van de studies van Caramella en Mann, 7 studies die Pearson's correlatie coëfficiënten vermelden voor MRI afmetingen versus afmetingen bij pathologie (of voldoende data presenteren om deze te berekenen) [43,44]. Omdat een van de nieuwe studies een extensie is van een eerdere studie zijn er zes studies, met in totaal 220 patiënten die nu voor meta-analyse in aanmerking komen (tabel 1).

Table 1: *Gerapporteerde correlatie coefficienten voor MRI afmetingen versus pathologie afmetingen van ILC.*

Studie	N	Pearson's correlatie coefficient
Munot et al.	20	0.97
Kneeshaw et al.	21	0.86
Francis et al.	22	0.87
Kepple et al.	33	0.88
Caramella et al	57	0.88
Mann et al.	67	0.85

Wanneer nu een meta-analyse wordt uitgevoerd volgens dezelfde principes als in 2006 is er niet langer sprake van significante heterogeniteit ($Q = 9.75$, ($p = 0.084$), $I^2 = 49$ %) en daarom kan deze nu wel uitgevoerd worden. De geschatte correlatie coëfficiënt is 0.89 (95% BI 0.84 – 0.93). Dit is veel beter dan wat er bereikt kan worden met mammografie of echo, zelfs in de handen van ervaren specialisten.
De slechte resultaten die behaald worden met conventionele beeldvormende technieken kunnen, althans deels, verklaard worden doordat met MRI vaak tumor foci worden gedetecteerd op enige afstand van de primaire tumor, die mammografisch en echografisch niet zichtbaar waren. Dit soort additionele tumor foci is aanwezig in ongeveer 32% van de patiënten en deze kunnen zowel multifocaal als multicentrisch zijn gelokaliseerd [27,36,40,60-62].

Samenvattend:

- De overeenstemming van de MRI bevindingen met pathologie is goed. De correlatiecoëfficiënt bedraagt 0.89.
- Additionele tumor foci, welke alleen met MRI worden gedetecteerd, zijn aanwezig in 32% van de patiënten met ILC.

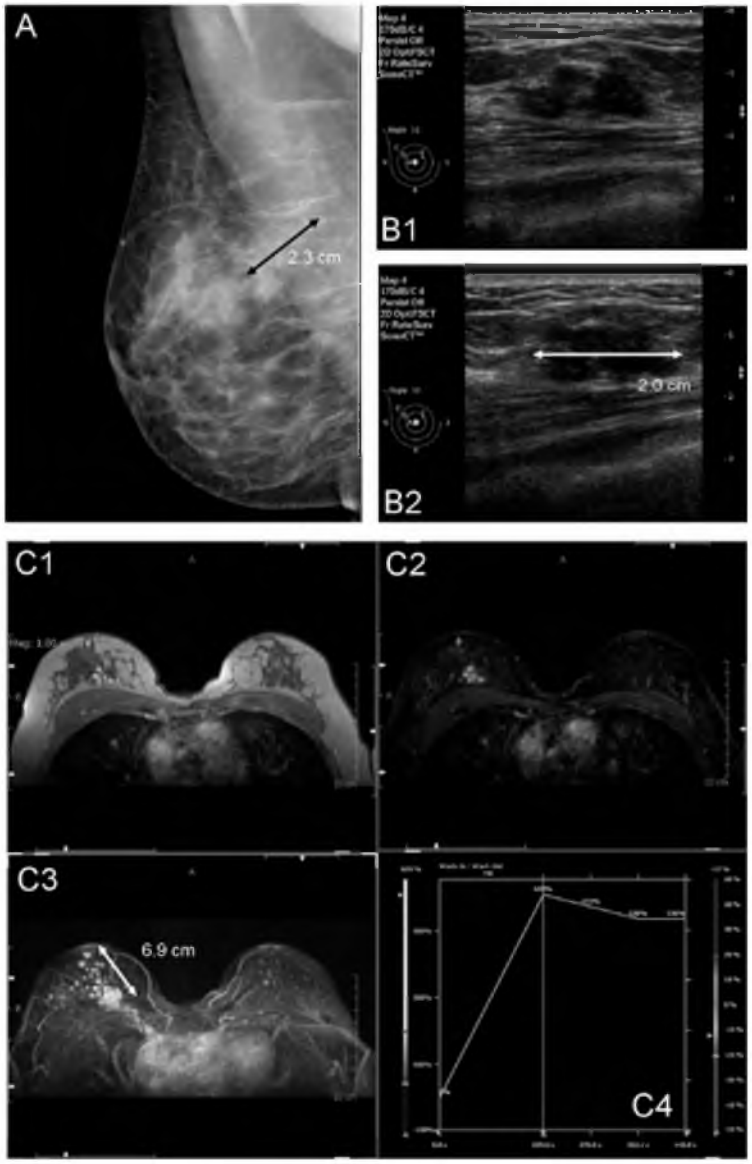

Fig 8: *Beelden van een 37 jarige vrouw, bekend met een BRCA2 mutatie. Op het mammogram (A) is een isointense gespiculeerde massa zichtbaar met een maximale diameter van 2,3 cm. Bij echo (B) is er een hypoechogene massa zichtbaar met zeer geringe posterieure akoestische beschaduwing De maximale tumor diameter bedraagt echografisch 2,0 cm (B2). Op de MRI (C; C1: natieve post contrast T1 acquisitie, C2: subtractie beeld, C3: maximale intensiteit projectie, C4: aankleuring versus tijd curve, corresponderend met de cursor in de andere beelden) blijkt er sprake van een multifocale tumor in een gebied van 6,9 cm. Als gevolg hiervan werd mastectomie verricht. Bij pathologie bleek er sprake van een multifocaal ILC in een gebied van 7,3 cm.*

Consequenties voor de therapeutische benadering van ILC

De goede overeenstemming van MRI bevindingen met pathologie en de goede detectie van additionele tumor foci heeft een enorme impact op het therapeutisch beleid bij patiënten met een ILC. Omdat de primaire therapie bij borstkanker, zowel bij ILC als IDC, meestal chirurgisch is, verandert de therapie vaak in een uitgebreidere operatie. Het chirurgisch beleid verandert in 28% van de patiënten (95% BI 20-39%) [27,36,38,39,59,61]. In 12-33% van de patiënten wordt toch een mastectomie uitgevoerd terwijl initieel een borstsparende operatie was gepland [36,38,39,43,59,61]. Een therapeutische wijziging richting minder uitgebreid opereren komt ook voor als gevolg van betere afgrenzing van de tumor, maar in een substantieel kleiner deel van de patiënten (ongeveer 5%) [43]. Als gevolg hiervan is geschat dat in totaal in 15-20 % van de patiënten als gevolg van de MRI de primaire therapie wijzigt van een borst sparende operatie in een mastectomie [63]. Daarnaast kan preoperatieve MRI patiënten doorverwijzen richting primaire (neoadjuvante) chemotherapie, of juist van chemotherapie toch naar chirurgie, waarbij MRI ook kan worden gebruikt om het effect van de chemotherapie te evalueren (fig 9). Ongeveer 88% (95% BI 75-95%) van de beleidswijzigingen worden achteraf correct geacht na pathologische analyse van het specimen [27].

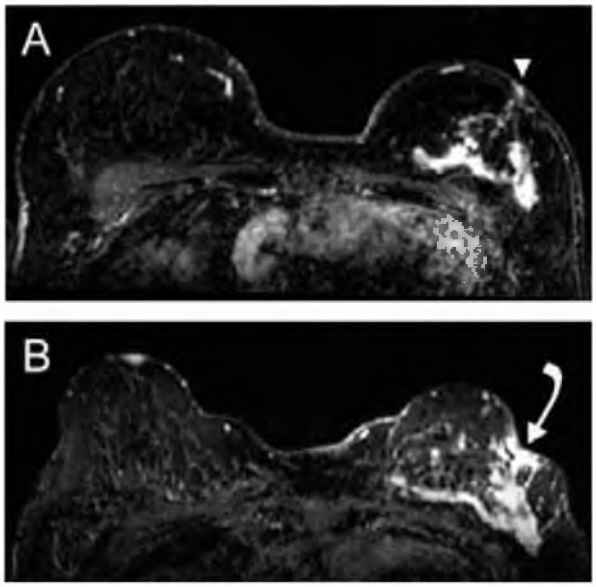

Fig 9: *Twee subtractie beelden van de mammae van een 47 jaar oude vrouw die zich presenteerde met een T4 ILC in de linker mamma. Bij het initiele MRI onderzoek (A) is een grote diffuus groeiende tumor zichtbaar met betrokkenheid van de huid (pijlkop). De patiente werd initieel behandeld met neoadjuvante chemotherapie. Op de controle MRI (B) is helaas zichtbaar dat de tumor hier niet goed op heeft gereageerd, maar in plaats daarvan is gegroeid (terwijl patiente veel dunner is geworden. Verder is ook de ingroie in de huid duidelijk toegenomen (gebogen pijl). Als gevolg van deze bevindingen is een nood mastectomie uitgevoerd.*

Samenvattend:

- Preoperatieve MRI veranderd het chirurgisch beleid in 28% van de patiënten met ILC.
- De primaire therapie wijzigt van een borst sparende operatie in een mastectomie in 15 tot 20% van de patiënten.
- Gebaseerd op pathologische evaluatie van het specimen is 88% van de door MRI geïnduceerde beleidsveranderingen correct.

Het effect van preoperatieve mamma MRI op de uitkomst van de behandeling in patiënten met ILC

Tot dusver is er geen bewijs dat suggereert dat patiënten met ILC die een MRI hebben ondergaan langer blijven leven dan patiënten zonder MRI. De 2 studies die zijn verricht naar het effect van MRI op het voorkomen van recidief en verbetering van de overleving hebben beiden niet specifiek naar ILC gekeken, bovendien konden deze studies niet aantonen dat MRI resulteert in een verbeterde overleving in de hele groep van patiënten met borstkanker [64,65]. De frequentie van recidief na borstsparende therapie en radiotherapie is thans gedaald tot 0.6-1% per jaar. Dit lijkt acceptabel, we kunnen dan ook nauwelijks verwachten dat preoperatieve MRI in alle patiënten dit getal verder doet afnemen. Het impliceert, dat in ieder geval een deel van de additionele laesies, die met MRI worden gedetecteerd, na incomplete chirurgie adequaat worden behandeld met radio- en chemotherapie. Toch zijn de gerapporteerde re-excisie percentages, noodzakelijk na niet radicale tumor excisie, waarbij er meer dan focaal tumor in de snijranden aanwezig is, onacceptabel hoog (29-67%) [66-70]. Daar komt nog eens bij dat 16-48% van de patiënten die initieel borstsparend wordt geopereerd uiteindelijk toch een mastectomie ondergaat omdat de sparende operatie niet radicaal was [70-75].
Deze feiten zijn natuurlijk uiterst pijnlijk voor patiënten, die ook al om moeten gaan met het feit dat ze borstkanker hebben. Bovendien wordt het cosmetisch resultaat slechter na re-excisie dan wanneer de operatie ineens slaagt. [76].

Omdat het duidelijk is dat MRI de beste, momenteel voorhanden zijnde, diagnostische modaliteit is voor de evaluatie van ILC is het niet de vraag of de tumoruitbreiding goed is afgebeeld, maar of de behandelend chirurg in staat is deze informatie te gebruiken voor het optimaal behandelen van de patiënt. Het grote percentage behandelingen dat wordt veranderd naar aanleiding van de MRI is alleen acceptabel als het patiënten direct verwijst naar de optimale therapie (borstsparende chirurgie of mastectomie). Hierbij moeten patiënten die zonder MRI voor een mammasparende operatie in aanmerking waren gekomen naar aanleiding van de MRI niet onnodig een mastectomie ondergaan. Daarvoor moet de chirurg in staat zijn om met de 3D MRI beelden in plaats van de 2D mammografieën te werken. Dit vereist training en kunde. Het is bovendien essentieel om in gedachten het 3D beeld te converteren van de MRI positie, in buikligging met hangende borsten, naar de chirurgische positie in rugligging. Hierbij moet in gedachten rekening gehouden worden met de beweging van het mammaweefsel in alle richtingen.

Pas recent is de eerste studie gepubliceerd waarin re-excisie ratios retrospectief zijn geëvalueerd in 267 patiënten waarvan 99 patiënten een preoperatieve MRI hebben ondergaan [63]. Honderdvijfenveertig patiënten ondergingen primair een borstsparende operatie, 90 zonder preoperatieve MRI en 55 met preoperatieve MRI. Re-excisie was noodzakelijk in 24 patiënten (27%) zonder preoperatieve MRI en in 5 patiënten (9%) met preoperatieve MRI. De oddsratio voor re-excisie zonder preoperatieve MRI is 3.64 (95% BI 1.30 - 10.20). Met andere woorden, dit betekent dat patiënten die geen preoperatieve MRI ondergingen een meer dan 3,5 maal grotere kans hadden een re-excisise te ondergaan (in een populatie waarin zowel radiologen als chirurgen gewend zijn om met MRI te werken). In de groep zonder preoperatieve MRI was de kans om uiteindelijk toch een mastectomie te ondergaan 23%, terwijl dit in de groep patiënten met een preoperatieve MRI slechts in 7% het geval was. Het uiteindelijke percentage patiënten dat een mastectomie onderging was zelfs lager in de groep die wel een preoperatieve MRI onderging dan in de groep die geen preoperatieve MRI had gehad (48 vs 59%), hoewel dit de statistische grens voor significantie niet haalde. Tenslotte bleek dat de totale behandeltijd (ongeveer 42 dagen) niet afhankelijk was van het wel of niet uitvoeren van een preoperatieve MRI, maar wel langer werd wanneer re-excisie noodzakelijk was.
Momenteel zijn er slechts 2 andere studies gepubliceerd die het effect van preoperatieve MRI op het chirurgisch bereiken van schone snijvlakken hebben geëvalueerd [77,78]. Geen van deze studies heeft zich specifiek op ILC gericht. Pengel et al. hebben 52 patiënten met ILC geïncludeerd, waarvan de helft preoperatieve MRI had ondergaan [78]. De snijranden waren meer dan focaal niet vrij (de indicatie voor re-excisie) in 3 van de 26 patiënten (12%) met preoperatieve MRI en 5 van de 26 patiënten (19%) zonder preoperatieve MRI. In deze studie is de totale re-excisie ratio (veel lager dan in de eerder beschreven studie door de grote fractie patiënten met IDC) in de groep patiënten zonder preoperatieve MRI meer dan twee keer zo hoog als in de groep patiënten die wel pre-operatieve MRI ondergingen (10.6% vs. 5%). De auteurs verrichtten echter geen statistische analyse van de re-excisie ratio. Bleicher et al. rapporteren niet voldoende data om gegevens over ILC te extraheren, maar rapporteren over de hele linie geen reductie in het percentage positieve snijranden, noch in het aantal patiënten dat uiteindelijk mastectomie onderging [77]. Blijkbaar was men in deze groep dus niet in staat de toegenomen kennis, verkregen met de MRI, om te zetten in profijt voor de patiënt. Dit maakt de noodzaak voor training en ervaring in het gebruik van MRI, zowel voor radiologen als voor chirurgen extra duidelijk.

Samenvattend:

- Preoperatieve MRI bij patiënten met ILC kan mogelijk het percentage re-excisies reduceren van 27% tot 9%.
- Preoperatieve MRI bij patiënten met ILC leidt niet tot een toename van het uiteindelijke aantal mastectomieën.
- Preoperatieve MRI bij patiënten met ILC verlengt de totale behandelduur niet.
- Het succes van preoperatieve MRI is sterk afhankelijk van de ervaring van zowel radiologen als chirurgen met mamma MRI.

Evaluatie van de contra-laterale mamma met MRI in patiënten met ILC

Naast het stadieren van de bekende tumor heeft preoperatieve mamma MRI een tweede doel, dat mogelijk zelfs belangrijker is. Volgens Arpino et al. is een synchrone tumor in de contralaterale mamma aanwezig in 20.9% van de patiënten met ILC, vergeleken met 11.2% van de patiënten met IDC [79]. In totaal wordt geschat dat preoperatieve MRI in ongeveer 4% van de patiënten een synchrone contralaterale tumor detecteert, die niet zichtbaar is met andere beeldvormende modaliteiten [80]. Het zal niet verbazen, dat het percentage synchrone contralaterale tumoren bij patiënten met ILC, alleen gedetecteerd met MRI, bijna tweemaal zo hoog is als bij patiënten met IDC. Momenteel wordt dit geschat op 7% (95% BI 4-12%) [27,34-37,39,57,60,61,80] (fig 10). Dit is onafhankelijk van de grootte van de ipsilaterale tumor en maakt dus duidelijk dat preoperatieve MRI geïndiceerd is in alle patiënten met ILC, niet alleen de groep die initieel een borstsparende operatie ondergaat.

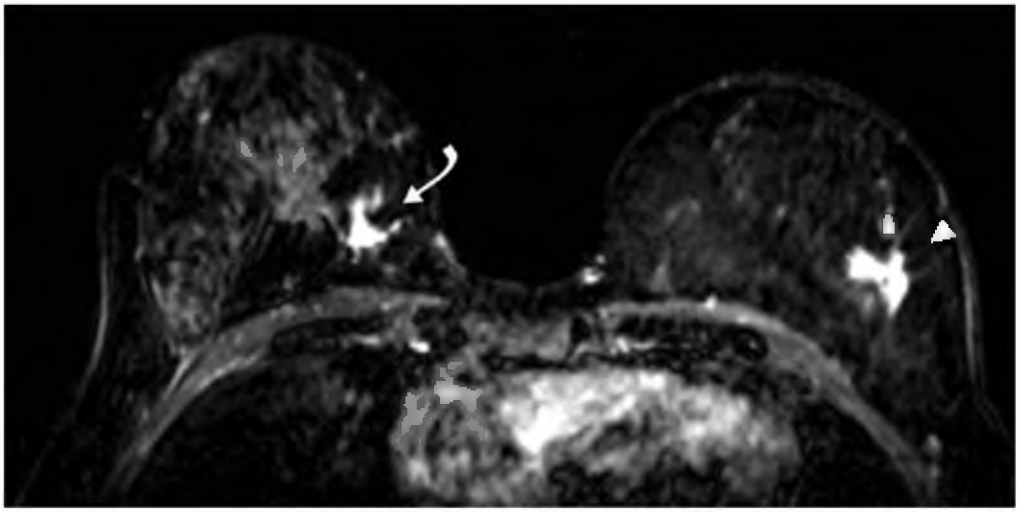

Fig 10: *Subtractie MRI beeld van beide mammae van een 48 jarige vrouw die zich presenteerde met een palpabele zwelling in de linker mamma. Bij mammografie en echo (niet afgebeeld) werd een ILC van maximal 1,5 cm gedetecteerd. Op MRI is een multifocale tumor zichtbaar over een gebied van 3,4 cm (pijlkop). Belangrijker nog is dat de MRI een tweede ILC in de contralaterale mamma laat zien (gebogen pijl), welke middels controle echografie ook histologisch werd bewezen.*

Het is hierbij wel belangrijk dat men zich realiseert dat de specificiteit van MRI bij het screenen van de contralaterale mamma slecht 50% bedraagt [80]. Histologische verificatie van middels MRI gedetecteerde laesies is dus essentieel (net als de verificatie van iedere laesie in de ipsilaterale borst die het chirurgisch beleid sterk zal beïnvloeden). Echo controle kan echogeleide biopsie mogelijk maken in ongeveer 50% van de patiënten [81,82]. MRI geleide biopsie is een veilige, snelle, eenvoudige en conclusieve manier om de rest te evalueren, maar moet wel eenvoudig beschikbaar zijn [83,84] (fig 7).

De kracht en de zwakte van door middel van MRI gedetecteerde contralaterale carcinomen is dat het in de regel kleine tumoren betreft. Het is voor mammacarcinomen in het algemeen onduidelijk in hoeverre deze contralaterale carcinomen de prognose beïnvloeden in de aanwezigheid van een groter ipsilateraal carcinoom en data specifiek voor ILC zijn volledig afwezig. Contralaterale tumoren worden, anders dan additionele ipsilaterale tumor foci die hoe dan ook met radiotherapie worden behandeld, wanneer zij niet worden ontdekt, niet behandeld. Tegelijkertijd kan adjuvante systemische therapie, wanneer dit wordt gegeven, misschien voorkomen dat de contralaterale carcinomen ooit klinisch relevant worden. Men zou verwachten dat de incidentie van metachrone contralaterale tumoren afneemt in patiënten die preoperatieve MRI ondergaan ten tijde van de ipsilaterale tumor detectie. Helaas rapporteren de twee studies over dit onderwerp hebben conflicterende resultaten. Fischer et al. rapporteren een reductie in de frequentie van metachrone contralaterale carcinomen van 4% naar 1.7% als gevolg van preoperatieve MRI, terwijl Solin et al. een incidentie van 6% contralaterale carcinomen rapporteren onafhankelijk van het al dan niet uitvoeren van preoperatieve MRI [64,65].

Niettemin wordt adjuvante systemische therapie alleen over het algemeen niet gezien als een curatieve techniek voor mamma carcinomen. Omdat recent is aangetoond dat vroege detectie van tweede tumoren (zowel ipsilateraal als contralateraal) in het asymptomatische stadium bij vrouwen met een mammacarcinoom in de voorgeschiedenis de relatieve overleving verhoogt met 27 to 47% [85], kunnen we momenteel alleen maar aannemen, dat vroege detectie van contralaterale carcinomen met MRI inderdaad de overleving van patiënten verbetert, hoewel de omvang van dit effect niet duidelijk is.

Samenvattend:

- Preoperatieve MRI detecteert mammografisch occulte carcinomen in de contralaterale borst in 7% van de patiënten met bewezen ipsilateraal ILC.
- Het is niet zeker of preoperatieve MRI het voorkomen van metachrone contralaterale tumoren vermindert. Voor patiënten met ILC is geen data beschikbaar.
- Er is indirect bewijs, dat vroege detectie van contralaterale tumoren leidt tot een relatieve overlevingswinst.

Huidige status van mamma MRI bij patiënten met ILC, tekortkomingen en toekomst perspectieven

Tot dusver hebben meerdere studies laten zien dat MRI goed in staat is om ILC af te beelden en dat de MRI beelden beter correleren met pathologische analyse dan enige andere, momenteel beschikbare, beeldvormende modaliteit. Het uitvoeren van MRI beïnvloedt het diagnostisch denken van de behandelaren en beïnvloedt het daarop volgende therapeutische handelen.
Het feit dat MRI het therapeutisch handelen beïnvloedt staat bekend als nivo 4 bewijs van de waarde [86]. Niettemin betekent dit niet automatisch dat de patiënte er ook beter van wordt, wat bekend staat als nivo 5 bewijs. Op dit vijfde nivo is de reductie in de noodzaak van re-excisies de vroegst mogelijke uitkomstmaat, die kan worden geëvalueerd. Daarnaast vallen ook bijvoorbeeld een reductie van ongewenste neveneffecten van therapie en een reductie in het voorkomen van locale recidieven of metachrone carcinomen in deze categorie. Zelfs de ultieme winst voor de patiënte, namelijk een verbeterde overleving, of beter nog een toename van het aantal 'quality adjusted life years' (levensjaren gecorrigeerd voor kwaliteit), valt in deze categorie. Dit is niet voor niets vaak de primaire uitkomstmaat van goed opgezette studies.
Slechts zeer recent zijn de eerste studies die nivo 5 parameters als een functie van het uitvoeren van preoperatieve MRI analyseren gepubliceerd [63-65,77,78]. Slechts een van deze studies heeft zich specifiek gericht op patiënten met een ILC [63]. Deze retrospectieve studie, waarvan de resultaten in de voorgaande tekst zijn besproken, laat zien dat preoperatieve MRI in handen van een behandelend team met ervaring in het gebruik van MRI het percentage re-excisies kan reduceren. De studie heeft het effect op tumor recidief, het voorkomen van metachrone contralaterale carcinomen of overleving niet geanalyseerd. Ook kosteneffectiviteit van preoperatieve MRI is een nog niet geëvalueerd onderwerp. Voor al deze zaken is slechts indirect bewijs beschikbaar.
In andere woorden, het nivo 5 bewijs voor het uitvoeren van preoperatieve MRI bij alle patiënten met ILC is slechts van gemiddelde kwaliteit en vervolg studies zijn essentieel. Bewijs op het 6e (en hoogste) nivo, dat stelt dat het uitvoeren van preoperatieve MRI in patiënten met een ILC goed is voor de maatschappij als geheel en dus afhankelijk is van een kosteneffectiviteitanalyse vanuit een maatschappelijk oogpunt is volkomen afwezig omdat dit nooit is onderzocht.
Niettemin ben ik van mening dat het momenteel voor handen zijnde bewijs voor het uitvoeren van preoperatieve MRI in patiënten met ILC substantieel is. De consequenties voor patiënten zijn groot. Preoperatieve MRI kan niet alleen de kans op een re-excisie verminderen, maar leidt mogelijk zelfs tot een verbeterde overleving. Aan de andere kant zijn de nadelen van het uitvoeren van preoperatieve MRI bij alle patiënten met ILC, wanneer preoperatieve MRI correct wordt toegepast, beperkt tot de kans op een additionele biopsie. Daarom is, gebaseerd op de momenteel voorhanden zijnde data, het uitvoeren van preoperatieve MRI in alle patiënten met ILC sterk aanbevolen.

Toekomst perspectieven van mamma MRI, een bredere kijk

Hoewel de waarde van preoperatieve MRI in patiënten met ILC duidelijk mag zijn, is dit slechts ten dele waar voor patiënten met andere typen mamma carcinoom. Bij patiënten met een IDC zijn de gerapporteerde re-excisie percentages veel lager en hoewel dit percentage in ervaren handen waarschijnlijk teruggebracht kan worden door het uitvoeren van preoperatieve MRI, zoals gerapporteerd door Pengel et al. die een reductie van 8 naar 2% positieve snijranden liet zien [78], is deze winst van een geheel andere orde van grootte dan bij ILC. Hetzelfde geldt voor de detectie van contralaterale tumoren, de frequentie is met ongeveer 4% slechts de helft van die bij ILC [80]. Als gevolg hiervan is de mogelijke winst in overleving kleiner. Niettemin zijn deze aantallen ook nog altijd te groot om geheel te negeren en het zal daarom ook zeer ingewikkeld zijn om een MRI te weigeren indien een goed geïnformeerde patiënte hierom verzoekt.

Daarnaast is het duidelijk bewezen dat screening met MRI en mammografie bij patiënten met een lifetime risico van 15% of meer, meer carcinomen detecteert en de frequentie van interval carcinomen reduceert [45,87,88]. Uit een recente meta-analyse van Warner et al. blijkt bovendien dat de toegevoegde waarde van mammografie in deze situatie slechts heel beperkt is [89]. Daarom zou feitelijk screening met MRI geprefereerd moeten worden boven screening met mammografie. Omdat recent is gebleken dat MRI minstens even goed is (en misschien zelfs beter) als mammografie in de detectie van DCIS is dit niet langer een argument om mammografie boven MRI te verkiezen. Dit wordt in meer detail bediscussieerd in Appendix 1 [90]. Vanwege deze resultaten en de wetenschap dat het lifetime risico van de gemiddelde Nederlandse vrouw met 12-13% slechts beperkt lager is dan het lifetime risico in de geteste hoogrisico populaties [91], is het logisch om aan te nemen dat MRI in de nabije toekomst van de mammascreening een belangrijke rol zal vervullen [92,93].
Een van de beperkende factoren is altijd de beperkte beschikbaarheid van MRI geleide biopten geweest, maar tegenwoordig is deze techniek veel breder beschikbaar en zou momenteel toegankelijk moeten zijn voor iedere mammaradioloog [83]. Indien de screening vooral wordt uitgevoerd met MRI, dan is de discussie over de zin of onzin van preoperatieve MRI natuurlijk obsoleet. De meeste tumoren zullen dan immers door middel van MRI gedetecteerd worden.

De belangrijkste beperkende factor voor uitgebreide implementatie van mamma MRI in de huidige radiologische praktijk is de nog immer hoge kostprijs van het onderzoek. Het is daarom essentieel dat de kosten van MR-onderzoek omlaag gaan en de scanprotocollen sneller en beter gestandaardiseerd worden. Dit is helaas nog werk in uitvoering.

Een meer experimenteel idee is het gebruik van MRI om de prognose van patiënten met mamma carcinoom te bepalen. Het feit dat mamma MRI een techniek is die zwaar leunt op fysiologische principes maakt het mogelijk om fysiologische parameters in tumor en normaal weefsel te observeren. Omdat er veel verschillende methoden zijn om een tumor te analyseren

(b.v. contrast aankleuring, diffusie, metaboliet kaarten) kunnen verschillende aspecten van de tumor biologie worden geëvalueerd. Het zou daarom mogelijk moeten zijn om het gedrag van de tumor en de potentie om uit te zaaiien te bepalen. Het grote voordeel van deze techniek boven de standaard pathologische analyse is dat de hele tumor geëvalueerd kan worden in plaats van slechts een aselecte steekproef. De recent gerapporteerde correlatie van contrast aankleuring en necrose met het zogenaamde "driemaal negatieve" (oestrogeen receptor negatief, progesteron receptor negatief en Her2/Neu negatief) subtype mammacarcinoom is een eerste stap in deze richting [94]. Studies naar veranderingen in aankleuringspatroon, water diffusie en choline spectrum bij patiënten die worden behandeld met neoadjuvante chemotherapie zijn een tweede, reeds meer geaccepteerd, voorbeeld van deze mogelijkheden [95-100]. Een nieuwe dimensie hierbij is het gebruik van contrast aankleuring en diffusie gewogen MRI om reeds voor de aanvang van therapie de tumor respons te voorspellen [101,102]. Dit zou in de toekomst misschien een beter op de patiënt afgestemde chemotherapeutische behandeling mogelijk kunnen maken.

Ten slotte kan de betere evaluatie van tumor uitbreiding, zoals mogelijk met MRI, ingezet worden voor het optimaliseren van behandelprotocollen. Vooral het gebruik van radiotherapie, essentieel bij de huidige mamma sparende therapie, maar op zich wel een behandeling met (ernstige) bijwerkingen, zou misschien kunnen worden aangepast of zelfs niet verricht hoeven te worden in patiënten waarbij op de MRI geen additionele tumor foci zichtbaar zijn [103,104]. Daarnaast zou MRI gebruikt kunnen worden voor het geleiden van niet-operatieve focale behandelingen van mammacarcinomen, zoals Radio Frequency Ablation (RFA), cryotherapie, laser therapie, gerichte echo of vacuüm excisie van de tumor [105]. Toch zal het waarschijnlijk nog lang duren voor dit soort behandelingen als volwaardige alternatieven voor chirurgie worden gezien.

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Ductal carcinoma in situ and breast MRI

Appendix 1

Carla Boetes
Ritse M. Mann

Lancet. 2007 Aug 11;370(9586):459-60

In today's Lancet, Christiane Kuhl and colleagues present the results of a large prospective assessment of the comparative sensitivity of mammography and MRI for detection of pure ductal carcinoma in situ (DCIS) [1]. It is widely believed that mammography is more sensitive in detecting DCIS than is MRI. However, Kuhl found that the sensitivity of MRI for DCIS is much higher than that of mammography, especially for high-grade lesions, which are thought to be more prone to progress to invasive carcinomas. Almost half of all DCIS lesions are mammographically occult, and high-grade lesions without necrosis are even less likely to be detected. Although these results were unexpected, the pathophysiology of breast cancer provides ample justification for the findings.

Before the spread of screening mammography, about 2% of all detected breast tumours were DCIS, yet autopsy studies have shown that almost 9% of women have undetected DCIS [2]. Since the start of screening mammography, the incidence of DCIS has increased nearly ten-fold, and about 20% of all tumours detected at screening are now pure DCIS. On the basis of circumstantial evidence, almost all invasive carcinomas are believed to begin as DCIS lesions. However, the time course of transition from in-situ to invasive carcinoma is unknown, and whether all DCIS will ultimately evolve to invasive disease is unclear [3,4]. Nevertheless, treatment of DCIS by complete resection, or, when breast-conserving therapy is used, radiotherapy, is deemed appropriate for all DCIS lesions [5].

On mammography, DCIS usually manifests as microcalcifications, which are caused by necrosis and subsequent calcification of debris. These calcifications are usually very small, but need to be bigger than 100 µm for mammographic detection. Only 27% of mammographically detectable DCIS lesions present with soft-tissue changes on mammography [6]. Recently, digital mammography was shown to outperform analogue mammography for the detection of breast cancer. However, in a large study by Pisano and colleagues [7], only 60% of in-situ lesions could be detected by digital mammography. Despite the increase in DCIS detection by mammography, many DCIS do not contain observable calcifications, and will therefore be mammographically occult.

The assumption has been that DCIS cannot be detected by MRI, because MRI does not visualise calcium and cannot be done at a sufficient resolution. Yet contrast-enhanced breast MRI visualises neovascularisation. Normally, the contrast agent is confined to the intravascular space, except in places where the vessel wall is corrupted (eg, by neoplasm). In DCIS, neovascularisation occurs; however, the vessels formed are more mature than vessels in invasive carcinomas. Therefore the typical wash-out patterns, indicative of malignancy, are often absent. Instead, more subtle asymmetric enhancement patterns can be seen (fig 1). In high-grade DCIS, microvessel density is higher and consequently enhancement is stronger, which explains why these lesions are more easily identified on MRI than are low-grade DCIS [8].

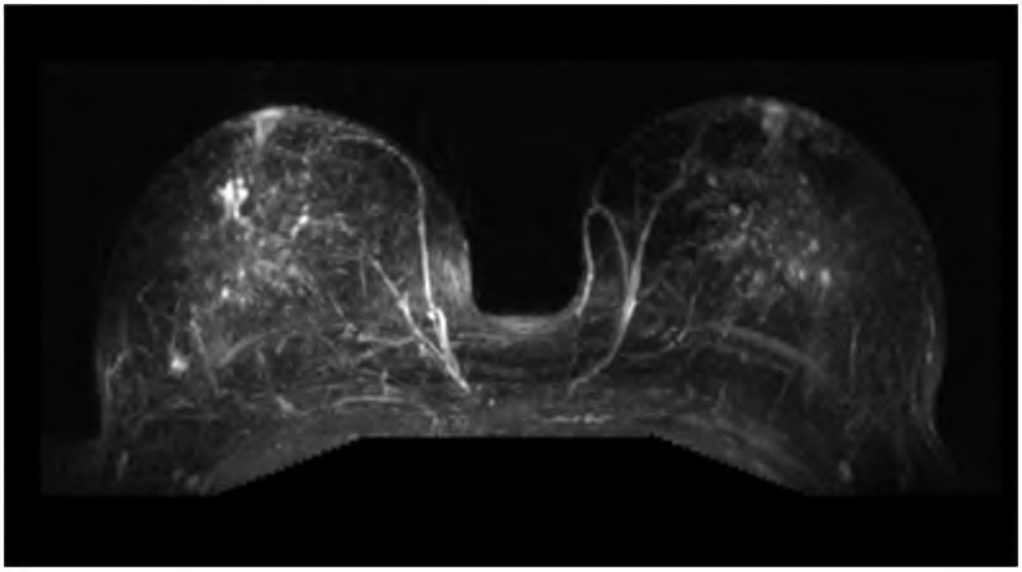

Fig 1: *Maximum intensity projection of subtracted contrast-enhanced breast MRI*
In the right breast, non-mass-like enhancement corresponding to area of grade-2 DCIS is visible.

MRI has a higher sensitivity for DCIS than mammography [9], and about half of contralateral carcinomas detected on MRI are DCIS [10,11]. Kuhl and colleagues' results should therefore be expected theoretically.

That only 20% of tumours detected through screening are pure DCIS is disappointing, when one keeps in mind that most breast tumours probably evolve from DCIS. The observation that MRI detects many DCIS lesions that go unnoticed on mammography implies that some invasive carcinomas can be prevented by timely intervention on the basis of MRI findings. As such, MRI has the potential to increase survival when used to detect breast cancer. However, currently MRI is considered an adjunct to mammography, and all series are biased by the fact that there needs to be an indication before MRI is done. For instance, in Kuhl and colleagues' study, one in eight women had findings that demanded biopsy. These results would not be expected in the general population. Despite the high recall rates, 52% of biopsy specimens in Kuhl's study showed breast cancer, a figure that is also accepted in screening mammography. In MRI screening of high-risk patients [12], MRI also doubled the recall rate but the rate of detected lesions per biopsy did not change—one in three biopsies was positive for cancer.

These findings can only lead to the conclusion that MRI outperforms mammography in tumour detection and diagnosis. MRI should thus no longer be regarded as an adjunct to mammography but as a distinct method to detect breast cancer in its earliest stage. A large multicentre breast-screening trial with MRI in the general population is essential.

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Dankwoord

Appendix 2

Ritse M. Mann

Dit proefschrift had niet kunnen bestaan zonder de hulp van vele zeer gewaardeerde collega's, vrienden en familie. In de volgende alinea's wil ik enkele van hen speciaal bedanken. Niettemin weet ik wel dat vrijwel ieder gesprek dat direct of indirect over de mamma radiologie in het algemeen is gegaan en over de waarde van mamma MRI in het bijzonder, heeft bijgedragen aan de ontwikkeling van de ideeën die in dit proefschrift zijn uitgewerkt. Ik wil dan ook iedereen bedanken met wie ik deze gesprekken heb gevoerd, ongeacht wat u daar als gesprekspartner destijds van heeft gedacht. Voor mij was het bijzonder nuttig.

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Curriculum Vitae

Appendix 3

Ritse M. Mann

Ritse Mann was born on July 24th 1979 in Wageningen, the Netherlands. He graduated from secondary school in 1997 (Pantarijn, Wageningen). Thereafter, he started his medical study at the University Medical Centre Utrecht. During his second year in medicine he also followed medical biology courses and obtained a propedeuse in medical biology in 1999. He finished his master study in 2002 with the study of aortic distensibility using SSFP MRI sequences in healthy volunteers. His internships were concluded with an internship in radiology, during which he also concluded the distensibility study. After his graduation in May 2004, and after a well spent holiday traveling two months through western South America, he started working as a clinical doctor at the emergency room in the Amphia hospital in Oosterhout, which he exchanged 6 months later for a position at the ICU in the Amphia hospital in Breda. In August 2005 he started his research on breast MRI at the radiology department of the Radboud University Medical Centre. He was involved in studies to the many different aspects of breast MRI, but his main focus was on the value of breast MRI in invasive lobular carcinoma of the breast, which culminated in the present thesis. After almost 2,5 years of full time research, he started his residency in radiology in January 2008. Currently he is still working as a resident in radiology, doing breast MR research on the side.

In early 2000 he met his wife, Patricia Poll. They lived together in Utrecht from the end of 2002 and got married on the 27th of May 2006. In November 2007 they moved to Nijmegen, where their first child, a son named Tycho, was born on the 22nd of November 2009.

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