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Preoperative MRI and surgical management in patients with nonpalpable breast cancer: The MONET – Randomised controlled trial

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SUMMARY

Background: We evaluated whether performing contrast-enhanced breast MRI in addition to mammography and/or ultrasound in patients with nonpalpable suspicious breast lesions improves breast cancer management.

Methods: The MONET – study (MR mammography of nonpalpable breast tumours) is a randomised controlled trial in patients with a nonpalpable BIRADS 3–5 lesion. Patients were randomly assigned to receive routine medical care, including mammography, ultrasound and lesion sampling by large core needle biopsy or additional MRI preceding biopsy. Patients with cancer were referred for surgery. Primary end-point was the rate of additional surgical procedures (re-excisions and conversion to mastectomy) in patients with a nonpalpable breast cancer.

Findings: Four hundred and eighteen patients were randomised, 207 patients were allocated to MRI, and 211 patients to the control group. In the MRI group 74 patients had 83 malignant lesions, compared to 75 patients with 80 malignant lesions in the control group. The primary breast conserving surgery (BCS) rate was similar in both groups; 68% in the MRI group versus 66% in the control group. The number of re-excisions performed because of positive resection margins after primary BCS was increased in the MRI group; 18/53 (34%) patients in the MRI group versus 6/50 (12%) in the control group ($p = 0.008$). The number of conversions to mastectomy did not differ significantly between groups. Overall, the rate of an additional surgical intervention (BCS and mastectomy combined)

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after initial breast conserving surgery was 24/53 (45%) in the MRI group versus 14/50 (28%) in the control group ($p = 0.069$).

Interpretation: Addition of MRI to routine clinical care in patients with nonpalpable breast cancer was paradoxically associated with an increased re-excision rate. Breast MRI should not be used routinely for preoperative work-up of patients with nonpalpable breast cancer.

1. Introduction

Since the 1970s, breast conserving therapy (BCT), i.e. local excision followed by breast irradiation, has replaced mastectomy as the treatment method of choice in women with early stage breast cancer.[1] Although BCT has excellent 5-year survival rates, a substantial number of patients (20–49%) have tumour positive resection margins after breast conserving surgery (BCS) and require a re-excision or a conversion to mastectomy.[2–4] When less invasive surgery is performed, accurate preoperative imaging is considered to be important in order to accurately assess tumour size in 3 dimensions and detect additional foci of disease other than the proven index cancer (multifocal and/or multicentric disease). Many studies have shown that tumour extent is more accurately determined by means of Magnetic Resonance Imaging (MRI) compared to mammography and ultrasound.[5–8] Furthermore, the results of a meta-analysis show that MRI detects 16% (interquartile range 11–24%) additional cancers in patients with known breast cancer.[9] It has been suggested that preoperative MRI may improve surgical planning, leading to a reduction of re-excision rate and conversions towards mastectomy. This has resulted in the increasing use of preoperative Breast MRI in patients with early stage breast cancer scheduled for BCT.[5–9]

To date only one randomised controlled trial assessed the effect of preoperative Breast MRI on surgical management. The COMICE trial investigated the clinical efficacy of preoperative Breast MRI in 1623 primary breast cancer patients. Patients were randomised to triple assessment only ($n = 807$) or combination of Breast MRI and triple assessment ($n = 816$). In this trial, the addition of Breast MRI to conventional triple assessment was not associated with a reduction in re-operation rate (re-excisions and mastectomies), which was 19% in both groups. They concluded that pre-operative Breast MRI might be superfluous in this patient population.[10]

The impact of Breast MRI for work-up of patients with nonpalpable breast lesions has not been assessed yet. As a result of screening and technical improvements in mammography and other imaging techniques such as Breast MRI, the number of small, early stage breast carcinomas and *in situ* carcinomas has increased substantially.[11–14] The problem of nonpalpable breast cancer is that it cannot be visualised or palpated by the surgeon during excision. As a consequence, in approximately 30% - 40% of the patients a breast amputation is planned as an initial surgical procedure.[14] In 25–50% of all patients initially treated with BCS more than one surgical intervention (re-excision or amputation) is required to remove all tumourous tissue.[12]

We conducted a randomised controlled trial to assess the clinical efficacy of dynamic contrast-enhanced Breast MRI in women diagnosed with a nonpalpable breast lesion, with the effect of Breast MRI on the number of additional surgical procedures (re-excisions and conversions to mastectomy) in these patients as its primary end-point.

2. Materials and methods

2.1. Design

The MONET (MR mammography Of Nonpalpable Brast *Tu*mours) study is a randomised controlled trial (NCT00302120) in which patients with nonpalpable suspicious breast lesions (BIRADS category 3, 4 or 5) detected on mammography or breast ultrasound, who are referred for histological analysis of the lesion, are eligible for the study. Patients were recruited from three large community teaching hospitals and one university hospital. Exclusion criteria were palpable lesions, age below 18 years, breast surgery or radiation therapy less than nine months prior to inclusion, pregnancy or lactation, obesity (>130 kg), claustrophobia, inability to maintain prone position for one hour, or other general contra-indications for MRI (e.g. pacemaker, other metal implants). Written informed consent was obtained from all patients and the study was approved by the ethical boards of the participating hospitals. After informed consent was obtained, patients were randomised to the control group who received care as usual, or to the MRI group who underwent an MRI scan of the breast in addition to the usual care. Randomisation was performed by an independent trial centre and stratified by hospital. The design of the study has been described in detail elsewhere. Trial registration number: NCT00302120. [15]

2.2. Control group

Patients in the control group received routine medical care, including mammography, ultrasound and lesion sampling by ultrasound-guided or stereotactic large core needle biopsy (LCNB). A minimum of four 14–16 Gauge biopsy specimens per lesion were taken and histopathological analysis of the lesion was performed. Patients with a benign biopsy result were discharged from clinical follow-up. Patients with cancer (*in situ* carcinoma or invasive carcinoma) were referred for surgery. Depending on the size of the tumour, the size of the breast and patient's preference, breast conserving surgery (BCS) followed by whole breast irradiation or a mastectomy was scheduled. According to our national guidelines needle-wire localisation was performed on the non-palpable breast

cancer prior to BCS. In patients with invasive breast carcinoma, a sentinel node biopsy was performed during surgical excision of the tumour.

2.3. MRI group

All MR imaging was performed at the university hospital. Bilateral dynamic contrast enhanced (DCE) Breast MRI was performed on a 3 Tesla clinical MRI scanner (Achieva, Phillips Healthcare, Best, the Netherlands) prior to LCNB of the suspicious nonpalpable breast lesion. Patients were placed prone on a dedicated phased-array bilateral breast coil (MRI devices, Würzburg, Germany). The scan protocol will include a transverse high-resolution T1-weighted fast gradient echo fat-suppressed series (TE/TR 1.7/4.5 ms; inversion delay SPAIR 130 ms; flip angle 10°; FOV 340×340 mm^2, acquired voxel size $0.66 \times 0.66 \times 1.6$ mm^3, reconstructed voxel size $0.66 \times 0.66 \times 0.80$ mm^3) and a transverse T2-weighted fat suppressed spin echo series (TE/TR 120/9022 msec; inversion delay SPAIR 125 ms; flip angle 90°; FOV 340×340 mm^2, acquired voxel size $1.01 \times 1.31 \times 2.0$ mm^3, reconstructed voxel size $0.66 \times 0.66 \times 2.00$ mm^3). Both series will be used to study the morphology of the lesion. A diffusion-weighted fat-suppressed series (TE/TR 61/5000 msec; inversion delay SPAIR 70 ms; flip angle 90°; FOV 320×320 mm^2; acquired voxel size $2.22 \times 2.52 \times 4.00$ mm^3, reconstructed voxel size $1.33 \times 1.33 \times 4.00$ mm^3; *b*-values 0, 150, 499 and 1500 s/mm^2) will be acquired to assess the cellularity of the lesion. Finally, dynamic contrast-enhanced fat-suppressed T1-weighted gradient echo images (TE/TR 1.3/3.4 ms; flip angle 10°; FOV 320×320 mm^2, acquired voxel size $0.91 \times 0.91 \times 2.00$ mm^3, reconstructed voxel size $0.83 \times 0.83 \times 1.00$ mm^3; dynamic scan duration 60 s) will be acquired before and immediately after the administration of 0.1 mmol/kg Gadolinium-DTPA (Magnevist, Schering, Germany) to study the contrast enhancement of the lesions and herewith the perfusion of the lesion. All patients will receive this scan-package with a total scan duration of less than 30 minutes (Fig. 1a and b).[15] The images were interpreted by breast radiologists with five or more years of experience in Breast MRI, using a Picture Achieving and Communications System (Phillips Healthcare, Best, The Netherlands). Classification of the lesions was based on lesion morphology, enhancement pattern and enhancement kinetics (persistent, plateau, or washout) according to the BI-RADS MRI classification system as proposed by the American college of Radiology.[16] Additionally, the suspicious non-palpable lesion detected with conventional imaging (mammography, and/or ultrasound) at inclusion was coded as 'detectable' or 'non-detectable' on MRI. Lesions visible on MRI only were reported as well. All patients underwent stereotactic or ultrasound-guided LCNB of the suspicious nonpalpable breast lesion. In case additional lesions were detected on MRI, a second-look ultrasound was performed and the lesion was sampled by ultrasound or by MRI guidance. MR images were discussed with the surgeon preoperatively in a multidisciplinary meeting. Surgery was performed by an experienced breast surgeon with five or more years of experience in breast surgery. Surgical excision was performed in all cases by guidance of conventional imaging techniques (mammography and ultrasound) in combination with the MRI findings.

2.4. Study end-points en statistics

Patient baseline characteristics on age, height, weight, parity, history of breast cancer were retrieved from questionnaires. Data on mammographical findings, MRI findings, large core needle biopsy (LCNB), surgical interventions and histopathological results were prospectively collected during 1 year of follow-up after the LCNB. The primary outcome was the proportion of patients undergoing repeat operation (re-excision or mastectomy) due to positive margins after the first surgical procedure. The number and type of surgical procedures in patients in the MRI group was compared to the number of procedures in the control group.

The statistical power of the study was calculated for a potential reduction of the number of surgical procedures as primary end-point. Based on the data of previous studies on nonpalpable breast cancers, we expect that 23% of the patients would require more than one surgical procedure to remove all tumourous tissue. We expected that DCE Breast MRI would reduce this rate to 11% due to the detection of multifocal and multicentric disease and better 3D depiction of the tumour. The MONET trial was powered at 90% to detect this 12% reduction as significant ($p < 0.05$, two-sided), which required 250 women in the control group and 250 in the MRI group. For each patient the number of days between inclusion and LCNB, the number of days between inclusion and the first surgical procedure and the number of days between inclusion and complete tumour removal was assessed and compared between the MRI group and control group (Mann–Whitney test). The number of primary mastectomies, the number of re-excisions and conversions to mastectomy after primary breast conserving surgery (BCS) were compared between both groups (Chi-square). To compare the diagnostic performance of MRI (in combination with mammography and ultrasound) and LCNB, a two-by-two table was constructed. The positive predictive value was calculated by dividing the number of correctly identified positives by the total number of positive Breast MRI's. The negative predictive value was calculated by dividing the number of correctly identified negatives by the total number of negative MRI's. In all analyses, a p-value < 0.05 was considered statistically significant. The data were analysed using SPSS version 15.0.

3. Results

Of the 626 patients that were eligible for inclusion, 463 patients were included in the study (participation rate 74%). After randomisation 45 patients were excluded (24 in the MRI group; 21 in the control group). Reasons for non-participation and exclusion after randomisation are listed in Table 1. The mean duration between randomisation and completion of follow-up for all patients was 41 months (range 27–61 months) upon completion, the results of 418 patients were available for analysis. A total of 207 patients ($n = 225$ mammographic lesions) was randomly allocated to the MRI group and 211 patients ($n = 231$ mammographic lesions) to the control group. Baseline characteristics of the patients were comparable between both groups and is presented in Table 2.

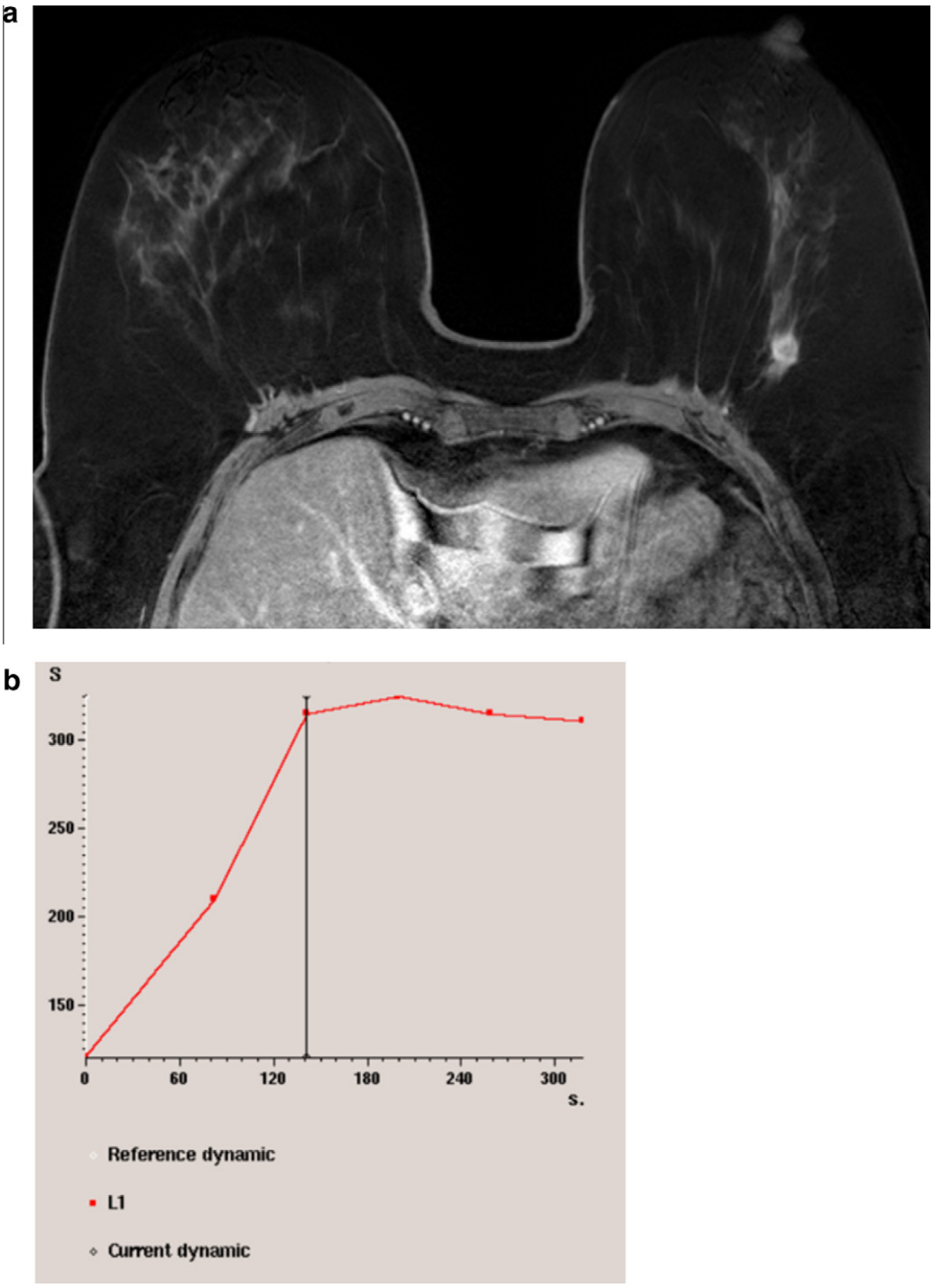

Fig. 1 – (a) and (b) 3T bilateral fat-suppressed dynamic contrast-enhanced MRI shows an irregular enhancing mass with suspicious enhancement kinetics (rapid initial wash-in, followed by a plateau) in the left breast of a patient. This lesion was classified as a BI-RADS V lesion.

Of all lesions detected by mammography in the MRI group ($n = 225$), 105 lesions were detected on MR images as well (47%). The 120 lesions that were not detected on MRI included 96 benign lesions (6 fibroadenoma, 57 fibrocystic change, 1 papiloma, 16 hyperplasia/adenosis, 1 LCIS, 3 metaplasia, 3 inflammatory changes, 9 other benign lesions), 21 *in situ* carcinomas (8 well-differentiated DCIS, 13 non well-differentiated DCIS), 2 DCIS lesions with micro-invasive disease and 1 invasive lobular carcinoma. MRI detected 11 additional suspicious breast lesions that were occult on mammography. In 5 lesions tissue sampling was performed with a second look ultrasound-guided biopsy, and in 6 lesions a MRI-guided biopsy was performed. 2/11 of the suspicious MRI-only breast lesions were proven to be malignant (DCIS in the contralateral breast

Table 1 – Reasons for non-participation and exclusion.

Reasons for non-participation	Number of patients
Contra-indication for MRI	63
Personal/logistical reasons/ fear of delay in diagnosis	100
Reasons for exclusion	
MRI required for clinical reasons	4
Technical problems with MRI	3
Contra-indication for MRI	7
Personal/logistical reasons	8
No histological analysis of the lesion	20
Unknown	3

in both cases). An overview of the included patients and corresponding histopathological lesion diagnosis are presented in Fig. 2.

In the MRI group, 74 patients had 83 malignant lesions (41 DCIS, 42 invasive carcinomas) compared to 75 patients with 80 malignant lesions in the control group (41 DCIS, 39 invasive carcinomas). Mean lesion in the MRI group a total of 78 surgical procedures were initially performed; 51 BCS and 23 mastectomies for ipsilateral cancer. Additionally, 2 BCS and 2 mastectomies were performed for the treatment of contralateral cancer. This resulted in a primary BCS rate of 53/78 (68%), and a primary mastectomy rate of 25/78 (32%) in the MRI group. In the control group 76 surgical procedures were initially performed; 49 BCS and 26 mastectomies for ipsilateral cancer, and 1 BCS performed for treatment of contralateral disease. This resulted in a primary BCS rate of 50/76 (66%), and a primary mastectomy rate of 26/76 (34%) in the control group. The number and type of initial surgical procedures were comparable between both groups ($p = 0.776$) (Fig. 3).

Table 2 – Patients baseline characteristics.

Characteristic	MRI group $n = 207$ (225 mammographical lesions)	Control group $n = 211$ (231 mammographical lesions)
Age (yrs)	Mean: 55.1 [sd: 9.5]	Mean: 56.1 [sd: 9.6]
Body Mass Index (kg/m^2)	Mean: 25.5 [sd: 3.8]	Mean: 25.6 [sd: 4.6]
Nulliparity	35 (17%)	36 (17%)
Breast cancer history (yes)	13 (6%)	21 (10%)
BI-RADS classification		
BIRADS 3	91 (40%)	87 (38%)
BIRADS 4	118 (53%)	120 (52%)
BIRADS 5	14 (6%)	22 (9%)
Unclear	2 (1%)	2 (1%)
Lesion characterisation		
Microcalcifications only	136 (60%)	134 (58%)
Microcalcifications and density	14 (6%)	14 (6%)
Density	67 (30%)	80 (35%)
Other	8 (4%)	3 (1%)
Lesion size (mm)	Median: 15.0 [interquartile range: 10.4–17.3]	Median: 15.1 [interquartile range: 11.5–18.7]
Number of days between inclusion and LCNB	Median: 7.0 [interquartile range: 4–9]	Median: 3.0 [interquartile range: 1–7]
Number of days between inclusion and first surgical procedure	Median: 36.0 [interquartile range: 28–47]	Median: 31.5 [interquartile range: 24–48]

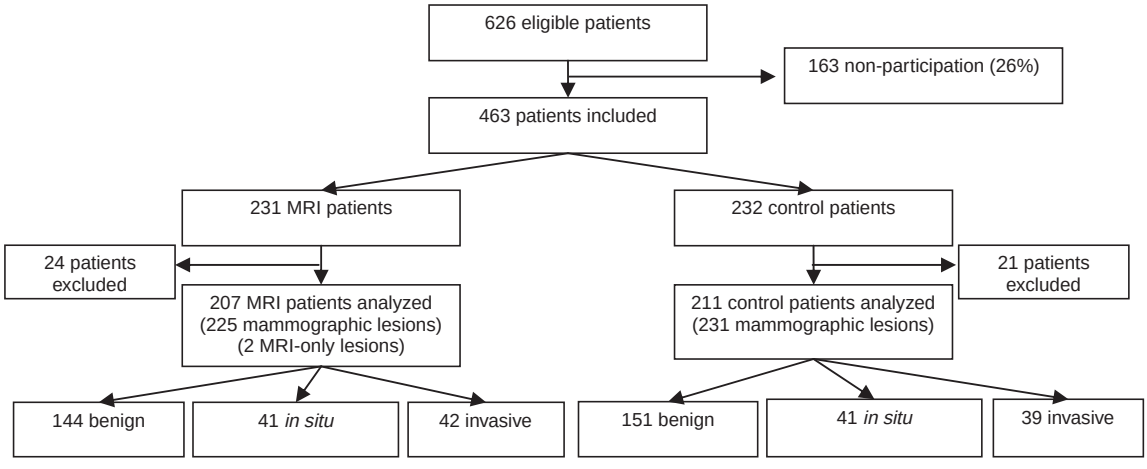

Fig. 2 – flow chart of eligible and included patients.

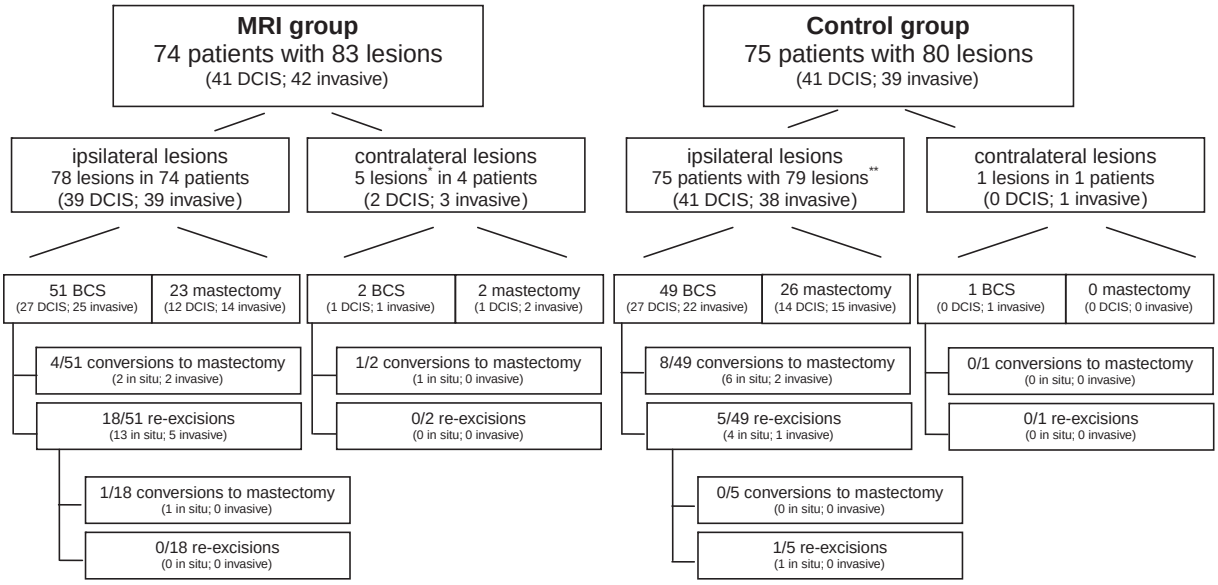

Fig. 3 – Summary of surgical procedures in MRI group and control group specified for in situ carcinomas and invasive carcinomas. *, two lesions were MRI-only lesions. **, one patient (with 1 invasive lesion) did not undergo surgery due to metastasized renal cancer.

The number of re-excisions performed because of tumour positive resection margins after primary breast conserving surgery was higher in the MRI group; 18/53 (34%) re-excisions in the MRI group, compared with 6/50 (12%) re-excisions in the control group ($p = 0.008$). The number of conversions to mastectomy after primary BCS was lower in the MRI group than in the control group, 6/53 (11%) versus 8/50 (14%), respectively, but did not reach statistical significance ($p = 0.489$). Overall, the rate of an additional surgical intervention (BCS and mastectomy combined) after initial breast conserving surgery was 24/53 (45%) in the MRI group versus 14/50 (28%) in the control group ($p = 0.069$). The median number of days between inclusion and complete tumour removal was 42.5 days in the MRI group and 40 days in the control group ($p = 0.11$). The surgical procedures performed in both groups are described in more detail in Fig. 2, specified for DCIS and invasive carcinomas.

4. Discussion

Our results showed that breast MRI in addition to routine medical care (mammography, ultrasound and lesion sampling by large-core needle biopsy) in patients with nonpalpable breast tumours did not reduce the number of surgical procedures in cancer patients. In fact, the number of re-excisions due to positive tumour margins after initial breast conserving surgery was increased in the MRI-group, i.e. 34% versus 12% in the control group. The number of conversions to mastectomy after BCS did not significantly differ between both groups. The increased re-excision rate in the MRI-group contradicts the theory that the use of Breast MRI in clinical practice may improve surgical planning, leading to a reduction of re-excision rate and conversions towards mastectomy.

In the past decades several nonrandomised retrospective studies have demonstrated that MRI increases the detection of tumour foci around the primary index lesion (multifocal or multicentric disease), not identified on conventional imaging.[17–27] A recent meta-analysis of these studies has shown that preoperative MRI detects MRI-only foci that turned out to be cancer in up to 16% (range 1–28%) within the affected breast.[28] The variability in the prevalence of MRI-only foci is likely to be the result of differences in used MRI technology. The impact of increased detection rate of additional disease foci with MRI on clinical outcome was not studied. So far, only one study prospectively assessed the value of MRI in clinical practice (The COMICE trial). In this study 1623 breast cancer patients (proven after triple assessment) were randomised for MRI (yes/no) prior to surgery. They reported that addition of MRI to conventional triple assessment was not significantly associated with reduced operation rate. In the MRI group 153/816 (19%) needed reoperation, compared to 156/807 (19%) in the control group. They concluded that MRI might be unnecessary in this population of patients.[10] Additionally, two large observational studies reported that MRI was not associated with a significant reduction in positive margins after local excision. Pengel et al. found positive margins in 22/159 (14%) of the MRI patients versus 35/180 (19%) in the control group.[29] Whereas, Bleicher, et al. reported positive margins in 11/51 (22%) of the MRI patients versus 33/239 (14%) in the control group. Furthermore, for women with a preoperative MRI mastectomy was the initial surgery in 28% of the women compared with 20% for women who did not undergo MRI.[30] These findings are further supported by a recent meta-analysis of non-randomised studies assessing the clinical value of pre-operative Breast MRI. Pooled estimates of the impact of MRI on surgical management, defined as change in surgery due to MRI-detection, showed that 11.3% (95% CI 6.8–18.3) had more extensive surgery (mastectomy or increased lumpectomy size) than initially planned. The meta-analysis concluded that preoperative MRI in breast cancer patients may increase the number of unnecessary surgical procedures.[28]

The study population of the COMICE trial differed from ours due to the fact that they included only patients with biopsy proven breast cancer, and performed the Breast MRI examination after biopsy. Most of their patients presented with palpable breast tumours and were suitable for triple assessment. For the present study, we decided to focus solely on patients with nonpalpable breast tumours because these may be considered the most challenging to remove in one attempt since these lesions cannot be seen or palpated during surgery. Moreover, the number of nonpalpable lesions is increasing due to the widespread introduction of screening programs. Our results indicate that MRI does not reduce the number of reoperations in these patients. The increased re-excision rate in the MRI group is difficult to explain, taking into account that the baseline characteristics (tumour size, type, location and surgical institute) were comparable between both groups.

In an attempt to clarify this controversy, we analysed the volumes of the excision specimens of the initial breast conserving procedure and found that the median excision volume in the MRI group was 69.1 cm^3 versus 90.2 cm^3 in the control group. When the MRI group was divided in those patients with a MRI positive finding (suspicious lesion was detected on MRI and conventional imaging) the median excision volume was 84.8 cm^3, whereas when no lesion was detected on MRI (suspicious lesion only visible on conventional imaging) the median excision volume was 40.3 cm^3. As a consequence the number of reoperations was the highest in patients that had negative MRI findings (11/17 patients), and the majority of these patients presented with DCIS as the histopathological diagnosis (10/11 = 91%). This implies that patients with DCIS which could not be reproduced on MRI were treated with smaller lumpectomy specimens during the initial BCS procedure, resulting in an increased rate of tumour positive resection margins. We propose that additional routine Breast MRI in patients with nonpalpable breast cancers may be counter-productive: non-visualisation of a lesion on the MRI paradoxically mislead the surgeon into removing a smaller lump than indicated.

A potential limitation of our study is the fact that, although patients included in this study are a representative sample of the national screening population, we had a relative high percentage of lesions consisting of microcalcifications only, i.e. 60% versus the 25% described in the literature. This could perhaps be explained by the fact that we selected purely patients with nonpalpable lesions, which resulted as a consequence in a high proportion of DCIS patients, who presented with microcalcifications only. Another important issue is the fact that we performed Breast MRI at 3T. It is known that at higher field strength B0 and B1 inhomogeneities can cause significant problems. This could particularly be the case in Breast MRI as the breast is partly surrounded by air which has a substantially different suscepitibility than breast tissue. When we first performed Breast MRI at 3 Tesla, before the start of the MONET study, there were indeed substantial problems, especially homogeneous fat suppression was difficult to achieve in the breast. However, over time, the quality of the shimming protocols was increased and we were able to obtain homogeneous B0 and adequate suppression of the fat signal using SPAIR – which was indeed referred to as fat suppression rather than SPAIR in reference number 15. We did not start the MONET study before we could acquire high quality images with adequate suppression of the fat signal (Fig. 1a and b). Furthermore another recently performed study compared the diagnostic accuracy of Breast MRI at 1.5 with 3T in 37 women with 53 lesions and showed that the image quality was slightly higher on 3T compared to 1.5T and they observed no signal variation throughout the field of view at 3T.[31] Other recent studies reported also high diagnostic accuracy of Breast MRI at 3T.[32,33] In agreement with these studies we believe that the image quality of our 3T Breast MRI examinations is state-of-the-art, and at least comparable to image quality obtained at 1.5T systems.

Another important issue is the difficulty to effectively incorporate the MR images during surgery. In our study MR images were presented and discussed with the surgeon preoperatively in a multidisciplinary meeting, but perhaps they should have been made digitally available during surgery in the operation room.

In conclusion, our results indicate that the addition of MRI to the usual care in patients with nonpalpable breast cancer does not reduce the number of surgical procedures. Paradoxically, MRI appears to be associated with a significantly increased re-excision rate. Hence, Breast MRI, should not be considered during work-up of these patients.

Conflict of Interest

None declared.

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