

Research Article

Pure Calcifications of Category BIRADS 4 and 5 - Importance of Supplementary Quality-Assured HR breast MRI

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Submitted: 01 February, 2025**Accepted:** 17 February, 2025**Published:** 21 February, 2025**ISSN:** 2641-7685**Copyright**

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Abstract

Indication: The value of a supplementary HR breast MRI prior to percutaneous biopsy of suspicious pure microcalcifications is evaluated.

Patients: In 95 patients with pure microcalcifications in the BIRADS 4 or 5 category in the mammogram, a HR breast MRI was also performed. All findings were clarified histologically. The results of the MRI were compared with the histological results.

Results: In the total collective, 59 malignant findings were found, 42 of which were DCIS and 17 invasive carcinomas (NOS 1.5, ILC 1, MUC 1). The remaining 36 biopsies showed histological benign findings. The false positive rate for mammography was 38% and for MRI 1.5%. The MRI showed true-negative findings in 79% of cases. In these cases, a percutaneous biopsy could have been omitted. False-negative findings were present on MRI in 21% (7/33). These were exclusively intraductal carcinomas ranging in size from 0.4mm to 40mm, with an average of 9.1mm. An unremarkable MRI ruled out an invasive carcinoma. A relevant underestimation of findings was found in 16% of X-ray-guided biopsies and in 10% of MR-guided vacuum biopsies.

Conclusions: The use of HR breast MRI in the presence of suspicious pure microcalcifications allows a reduction in unnecessary biopsies in almost 80% of cases without overlooking an invasive carcinoma. However, small intraductal carcinomas can be missed.

INTRODUCTION

The domain of mammography and X-ray-based imaging examination procedures is the detection of intramammary calcifications and focal findings, densification and architectural defects in the more lipomatous remodelled breast (density type ACR A and ACR B). The detection of microcalcifications, which can be an expression of a malignant tumour, is independent of the density type of the breast in this context. A distinction can be made between calcifications that are associated with a malignant lesion. These are primarily endotumoural calcifications and/or peritumoural calcifications, which can be an indication of an EIC (extensive intraductal component). Pure calcifications are understood to be calcifications, which are not associated with any other findings. However, calcifications can also be associated with benign changes (e.g. scar, fibroadenoma, papilloma, adenosis).

For unclear findings in the MX-BIRADS 4 or 5 category, percutaneous biopsy with removal of representative tissue cylinders is the method of choice for obtaining histological findings and a definitive diagnosis according to the guidelines [1]. In corresponding collectives, this

procedure usually reveals around 50% malignant, but also around 50% benign lesions [2]. In the study presented here, we question whether, in the presence of suspicious microcalcifications, quality-assured, high-resolution breast MRI can provide useful additional information in order to reduce the number of unnecessary biopsies or, if necessary, to modify the percutaneous biopsy procedure.

METHODOLOGY

Patients were included in the study if they were asymptomatic and showed pure microcalcifications in the BIRADS 4 or 5 category on diagnostic mammography [3]. Cases with additional abnormalities, i.e. focal findings, asymmetry, architectural disorder were excluded. All patients underwent a high-quality HR breast MRI prior to clarification of the calcifications in the form of a percutaneous biopsy, as indicated by the guidelines.

Digital mammography has been performed with two different digital full-field mammography systems: (a) Senographe 2000D (GE Healthcare, Milwaukee, WI, USA) 2010-2019, and (b) 3Dimensions (Hologic, Berlin, Germany) 2019-2024. Mammograms from outside

facilities were not included. Concerning the morphology, the density type and the BIRADS categorisations of the mammograms were monitor re-evaluated from the original data.

All MRI-examinations were performed in the own institute on different systems: (a) 1.5Tesla whole-body scanner Signa HDX (GE Healthcare, Milwaukee, WI, USA) by using a dedicated open 4-channel-breast surface coil (MRI Device, Knaresborough, NY, USA) 2010-2019. (b) 1.5Tesla whole-body scanner Altea (Fa. Siemens, Erlangen, Germany) by using a dedicated open 7-channel-breast surface coil (Noras, Hoechberg, Germany), and (c) 3.0Tesla whole-body scanner Lumina (Siemens, Erlangen, Germany) by using a dedicated open 7-channel-breast surface coil (Noras, Hoechberg, Germany) 2019-2024. All systems had an integrated device for the fixation of both breasts in cranio-caudal orientation (Noras, Hoechberg, Germany). The MRI examination included a fat-saturated T2 weighted IR-sequence. Subsequently, a 3D T1 weighted gradient-echo-sequence was performed repetitively once before and 2 times after administration of contrast material of a defined dosage of 5ml Gd-DO3A-butrol regardless of body weight (Gadobutrol, 1molar, Bayer Company, Leverkusen, Germany). All diagnostic contrast-enhanced breast MRI were performed in high-resolution technology. This currently includes a matrix of 512 x 512 (2010-2019), 672 x 672 (2019-2023), and 1024 x 1024 pixels (MIO breast MRI 2024). The 3:24 min). The total measurement time was at least 8:27 min. Image post-processing included the subtraction of both measurements after contrast agent administration minus the pre-contrast sequence and the preparation of Maximum Intensity Projections (MIP) of the T2 images and the subtraction series.

Percutaneous biopsies were performed with several technologies: (a) stereotactic biopsy using MultiCare Platinum (Lorad, actual Hologic, Berlin, Germany), (b) tomosynthesis- guided biopsy using Affirm® Breast Biopsy system (Hologic, Berlin, Germany), (c) CT- guided biopsy using Cone-Beam-Breast CT (Koning Corp, CBCT 1000, NY, USA), and MR- guided biopsy using 1.5T scanner Altea (Siemens, Erlangen, Germany). In all cases, vacuum core biopsy systems (i.e. ATEC®, 9 gauge, Hologic, Berlin, Germany) were used, and 4-12 specimens were sampled, depending on positive detection of microcalcifications.

In 2 cases of very extensive calcifications, the probatory clarification of findings was carried out in the form of a quadrant-spanning US-supported punch biopsy with the Bard® Magnum® Biopsy System, 16 gauge, 5-10 specimens, for cost reasons. The evaluation included the histological evaluation of the biopsy collective, the results of the MRI

in comparison to the histological findings and the question of the underestimation of findings for the different biopsy techniques.

RESULTS

The analysis included 95 patients with suspicious pure microcalcifications in the MX BIRADS 4 or 5 categories. The average age was 57.8 years (range 36-81 years). The average mammographic density was 3.4.

Histological Findings after Percutaneous Biopsy

For the entire collective, 31 benign findings of histological category B2 (adenosis 18, FA 5, fatty tissue necrosis 1, fibrosis 2, haematoma 1, scar 3, inflammation 1) and 6 findings with unclear biological potential B3 (ADH 3, papilloma 2, radial scar 1) were found in the punch biopsies. In the remaining 58 cases, the histology of the punch cylinders showed a malignant finding, of which 53 cases were DCIS (11 x grading 1, 26 x grading 2, 16 x grading 3) and 5 cases were invasive carcinoma.

MR Findings

All patients underwent a quality-assured HR breast MRI prior to histological clarification of the calcifications. The breast MRI showed an average BPE of 1.3, and an average arteficial score of 1.2. It showed unremarkable findings in 33 cases. Here, the percutaneous biopsy was stereotactic (n = 27), tomosynthesis- (n = 5) or CT-guided (n = 1). The specimen mammography revealed positive calcification in all cases. Histology of the removed tissue cylinders confirmed benign findings in 26 cases (MRI true negative 26/33; 78.8%) and showed an intraductal carcinoma in the remaining 7 cases (MRI false negative 7/33; 21.2%). The size of the DCIS not detectable by MRI ranged from 0.4mm to 40mm, with a mean of 9.1mm (Table 1, Figure1).

In 62 cases, the MRI showed abnormal findings matching the mammographically detectable calcifications. These were 40 x pure NML, 8 x a focus with surrounding NML and 14 x a focal finding with surrounding NML. The clarification of the 40 findings that presented exclusively as NML on MRI was performed stereotactically (n = 18), tomosynthesis- (n = 1) and CT-guided (n = 4), US-guided

Table 1: False-negative findings in HR breast MRI.

Age	BPE	MR Artefact	Biopsy	Histology	Grading	Size (mm)
73	a	1	stereo	DCIS	1	5
67	a	2	stereo	DCIS	2	0,5
66	a	1	stereo	DCIS	2	0,4
44	a	1	stereo	DCIS	2	8
52	c	1	stereo	DCIS	2	40
58	c	1	stereo	DCIS	2	5
58	a	1	stereo	DCIS	3	5

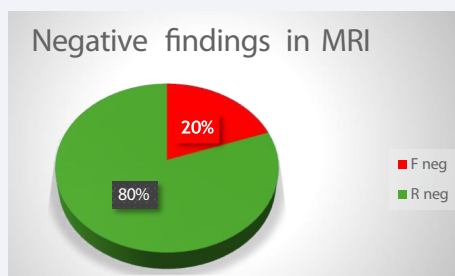


Figure 1 False-negative and true-negative findings in HR breast MRI.

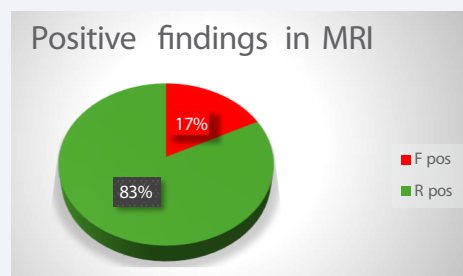


Figure 2 False-positive and true-positive findings in HR breast MRI.

(n = 1), primary open (n = 2) or MR-guided (n = 14). Histologically, 8 of these 40 patients (20.0%) showed benign findings after percutaneous biopsy (3 x adenosis, 1 x fibroadenoma, 1 x inflammation as B2 lesion as well as a papilloma, a radial scar and an ADH as B3 lesion). In the remaining 32 cases (80%), the percutaneous biopsy revealed histological findings of B5a (7 x DCIS grading 1, 14 x DCIS grading 2, 11 x DCIS grading 3). The ADH and the radial scar were surgically excised. This resulted in DCIS grading 1 and confirmation of the radial scar without malignancy (Figure 2).

The 22 calcifications that showed a focus or a focal finding on MRI in addition to the NML were biopsied stereotactically (n = 10), tomosynthesis-guided (n = 3), CT-guided (n = 1), US-guided (n = 1) or MR-guided (n = 7). Histologically, 3 of these 22 patients (13.6%) showed benign findings after percutaneous biopsy (2 x adenosis as B2 lesion and one ADH as B3 lesion). The size of the ADH was 4 mm. It was not re-operated. In the remaining 19 cases (86.4%), the percutaneous biopsy revealed 4 x DCIS grading 1, 7 x DCIS grading 2, 4 x DCIS grading 3 and 4 x an invasive carcinoma). In this group, the 4 invasive carcinomas already histologically confirmed after percutaneous biopsy and a further 9 invasive carcinomas, all with histologically verified EIC, were found after surgery (Table 2).

Histological Findings after OP

A total of 62 patients underwent surgery: of the 6 B3 findings obtained by percutaneous biopsy, two underwent ADH surgery. In one case, a DCIS was found in the surgical specimen. The radial scar was surgically confirmed without evidence of an associated carcinoma. There were a total of 3 benign findings after surgery (ADH, radial scar, FA). The fibroadenoma was operated on at the patient's request. The histological examination of the surgical specimen revealed malignant findings in 60 cases, including 42 DCIS and 17 invasive carcinomas (NOS 15, ILC 1, MUC 1), in all of which an additional EIC was described histologically. In 33 patients with benign findings in the percutaneous biopsy,

no surgical intervention was performed. In 27 cases, there was a follow-up period of at least 2 years without the occurrence of carcinoma after the intervention. In 4 cases there was no follow-up data. In 3 cases, the percutaneous biopsy was performed within the last 2 years.

Underestimation

With regard to the question of underestimation of the final histological findings, a distinction was made between X-ray and MR-guided procedures in the evaluation of the methods used to guide the vacuum biopsy. The US-guided punch biopsies were excluded from this analysis as they involved very large DCIS or IDC areas (55mm, 50mm). There was no underestimation of findings here. The 2 patients who underwent primary surgery were also excluded due to their particular individual constellation. The tumour size here was 50mm and 60mm.

This ultimately resulted in 71 X-ray-guided interventions (stereotactic 56, tomosynthesis-guided 9, CT-guided 6) and 21 MRI-guided vacuum biopsies. In the group of X-ray-guided vacuum biopsies, the malignant findings were exclusively intraductal carcinomas, with the exception of one invasive tumour. With regard to the final histology, 11 of 71 cases (15.5 %) in this group were underestimated (stereotactic 9, tomosynthesis 1, CT-guided 1). Instead of DCIS, the surgical specimen revealed an invasive carcinoma with an average size of 7.5 mm (range 4 mm - 13 mm). In one case of ADH in the stereotactically obtained biopsy specimen, the final histology revealed DCIS grading 1.

In the MR-guided biopsies, the histological work-up revealed 3 invasive carcinomas, 12 DCIS and 6 benign findings. In one case of a patient with a high grade DCIS, the histology after surgery revealed an invasive carcinoma, NOS pT1b 6mm with EIC. In another patient with DCIS grade 2, the final histology revealed an NOS pT1a 2mm with EIC (10%). In all other cases, the histologies of biopsy and surgical specimen matched.

Table 2: Underestimation of the final histology (invasive carcinoma) in the histological processing of the specimens after percutaneous biopsy.

Age	BPE	MR Artefact	MRI	Biopsy	Specimen Diagnosis	Final Diagnosis	Final size (mm)
42	a	1	Focus + NML	MR	DCIS 3	NOS + EIC	6
68	a	1	Focus + NML	stereo	DCIS 2	NOS + EIC	4
75	a	1	Mass + NML	tomo	DCIS 2	NOS + EIC	15
53	a	1	Mass + NML	stereo	DCIS 1	NOS + EIC	5
69	a	1	Mass + NML	stereo	DCIS 1	NOS + EIC	6
48	a	2	Mass + NML	stereo	DCIS 2	NOS + EIC	9
64	a	1	Mass + NML	stereo	DCIS 2	NOS + EIC	8
56	a	MOCO 1	Mass + NML	stereo	DCIS 2	NOS + EIC	5
55	b	1	NML	CT	DCIS 1	NOS + EIC	7
54	a	1	NML	stereo	DCIS 2	NOS + EIC	5
36	a	1	NML	MR	DCIS 2	NOS + EIC	2
64	a	2	NML	stereo	DCIS 1	NOS + EIC	5
63	a	1	Mass + NML	stereo	DCIS 2	NOS + EIC	13

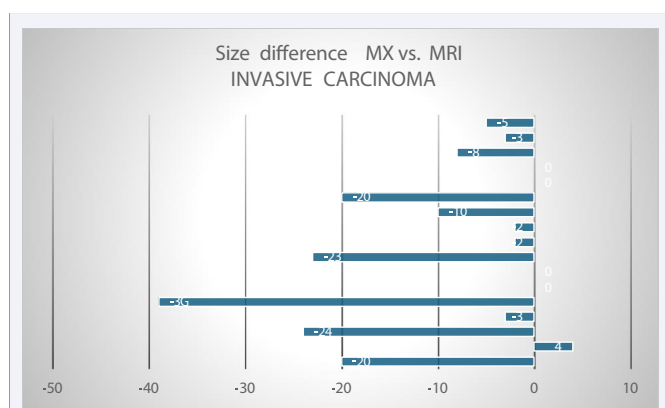


Table 3 Invasive carcinomas. Comparison of the size of microcalcifications in mammography compared to the extent of enhancement in MRI. Data in millimetres. Minus values indicate a larger extension for MRI.

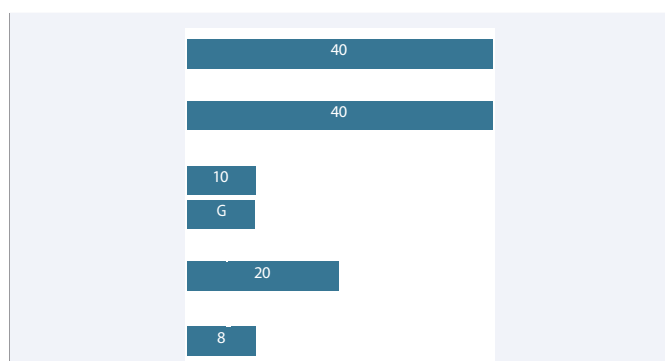


Table 4 Benign findings. Comparison of the size of microcalcifications in mammography compared to the extent of enhancement in MRI. Data in millimetres. Minus values indicate a larger extension for MRI.

Size Comparison between MX and MRI

The comparison of the extent of the calcifications in the mammogram and the conspicuous multiple enhancements in the MRI shows that in 12 out of 17 cases (70.6%) of invasive tumours, the MRI revealed a larger finding (Table 3)(Figure 3,4). In the group of benign tumours, this rate was only 4 out of 32 (12.5%) (Table 4).

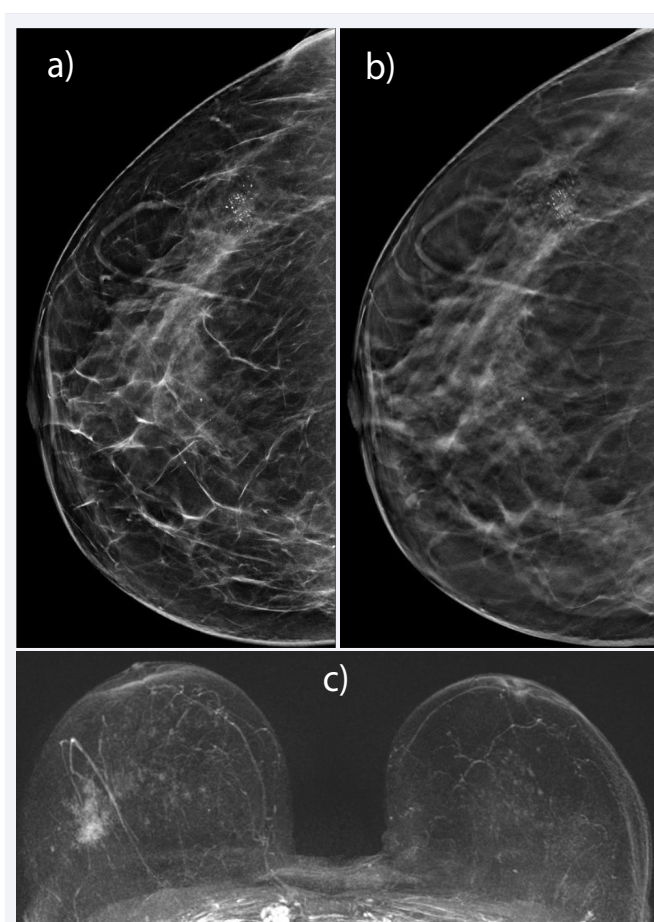


Figure 3 Mucinous breast cancer. 63y patient. Cluster of pleomorphic microcalcifications in the right breast, extend 17mm. Digital mammography in CC projection (a), tomosynthesis (b). Enhancing lesion with surrounding non-mass-like enhancement on MRI, extend 37mm. MIP (c). Histology: Mucinous cancer pT1b with EIC.

Analysis of Calcification Morphology

With regard to the comparison of the morphology of the microcalcifications, there were no diagnostically relevant differences for invasive carcinomas, DCIS and benign findings (Table 5).

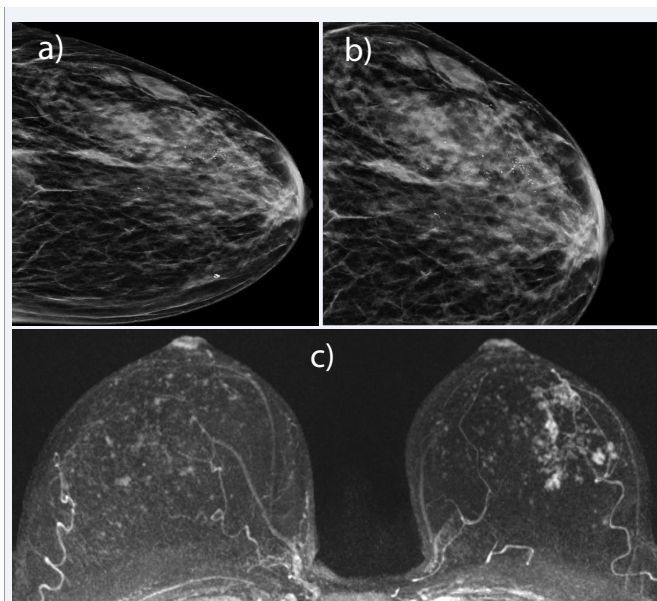


Figure 3 High grade DCIS
71y patient. Segmental pleomorphic microcalcifications in the left breast, extend 55mm. Digital mammography in CC projection (a), zooming (b). Enhancing segmental enhancement, partly non-mass-like enhancement, partly with focus configuration on MRI, extend 55mm. MIP (c). Histology: DCIS, grading 3.

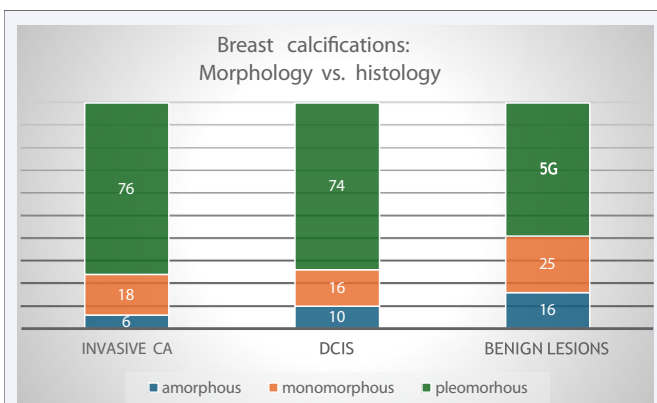


Table 5 Comparison of calcification morphology with detection of invasive carcinomas, DCIS and benign findings (in per cent).

DISCUSSION

X-ray mammography is the only examination method that can reliably detect microcalcifications in the breast, regardless of the type of density. In recent decades, this has justified the widespread use of this examination method as part of screening programmes, even with high tissue density. However, only around 50% of intraductal carcinomas are accompanied by conspicuous microcalcifications. In the group of invasive carcinomas, this rate is around 30%. Microcalcifications often represent an unspecific finding, which can be an indication of malignancy, but can also occur in combination with benign findings. The study presented here also shows that

morphological criteria of intramammary calcifications do not allow sufficient differentiation between benign and malignant tumours. Ultimately, only percutaneous biopsy with radiographically guided biopsy procedures remains to reliably clarify calcification-associated findings [1]. On the basis of large biopsy numbers, older studies indicate a rate of malignant tumours in the clarification of microcalcifications of around 35% [4]. In current reports from screening, this rate is around 50% [2]. Mammography has undergone constant technical and methodological development in recent decades. Digital mammography, tomosynthesis and breast CT should be mentioned in this context [5]. However, this has not significantly changed the reliability of the assessment of microcalcifications.

In contrast to mammography, the detection of breast cancer in contrast-enhanced breast MRI, which does not allow the visualisation of fine calcifications, is based on the visualisation of tumour angiogenesis. However, initial efforts to reduce the rate of unnecessary percutaneous calcification biopsies through the use of MRI failed due to the low spatial resolution of the procedure at the time [6,7]. With the further development of breast MRI, it has been shown that breast MRI is clearly superior to all other imaging techniques not only for the detection of invasive tumours, but also for the detection of intraductal carcinomas [8]. This applies in particular to the more aggressive high-grade DCIS types, while this phenomenon is less pronounced in the less aggressive low-grade DCIS. The background for the accumulation of contrast medium in DCIS is primarily leakage and arterio-venous shunts [9].

In the meantime, MRI has undergone further technical and methodological developments, making it the examination method of choice for women with dense breast structures [6,10,11]. EUSOBI therefore recommends it as the method of choice for women with extremely dense mammary glands and as a stand-alone procedure if the findings are unremarkable [12]. However, this requires a high methodological and technical quality [13]. In this respect, the question is justified as to what extent X-ray mammography should continue to be used as a first-line method for early detection in women with dense breast structures, as it derives its predominant value from the detection of microcalcifications. It must also be questioned whether this makes sense from a radiation point of view, as MRI offers a better alternative without the use of ionised radiation.

The evaluation presented shows that the use of high-quality HR breast MRI can reduce the rate of unnecessary percutaneous biopsies for the clarification of microcalcifications by almost 80%. Li et al. report identical results for microcalcifications in the BIRADS

4 category [14]. In addition to the costs for biopsy and histopathological processing of the biopsy specimens, this would mean an immense reduction in invasive procedures in the area of the female breast. It is worth analysing the overlooking of intraductal carcinomas associated with this procedure in more detail:

- In one case, it was a 5mm DCIS grading 1. It should be noted here that the majority of low-grade DCIS will not leave the milk duct for the rest of their lives and will become an invasive carcinoma. A follow-up of such findings is completely sufficient without changing the risk for the patient.
- In two cases with DCIS grading 2, tumour extensions of 0.4mm and 0.5mm were present. In view of the small size, a follow-up would also be completely sufficient for the patient in the corresponding constellation without any change in risk.
- In two further cases with DCIS grading 2, a relatively high BPE (density type MR ACR c) was primarily present, so that the informative value of the MRI - particularly for the smallest structures - is naturally limited. The recommendation here is to perform a mandatory percutaneous biopsy of the calcifications for density type MR ACR c or d.
- Two further cases remain, one with DCIS grading 2 (8mm) and one with DCIS grading 3 (5mm), in which no conspicuous enhancement matching the microcalcifications could be detected despite the optimal quality of the MRI. Possible causes for this include angiogenesis that has not yet taken place, no or a small number of leaks and shunts, partial volume effects or close topographical proximity to vascular structures.

In a review of DCIS, Erbas et al. state that between 14-53% of intraductal carcinomas may progress to invasive cancer over a period of 10 or more years. The reported prevalence of undiagnosed DCIS in autopsy studies, of approximately 9%, has been used to suggest a larger reservoir of DCIS may exist in the population [15].

Furthermore, advantages are described when MRI is used in the case of microcalcifications, as a considerable number of malignant lesions without mammographically visible MCs were revealed in MRI [16,17]. The MIPA study also showed that although the rate of primary (indicated) mastectomies increased slightly (20% vs. 11%) when MRI was used preoperatively for pure microcalcifications, the rate of re-operations was reduced from 22% to 10% compared to the group without MRI [18]. This proves that

MRI is better at mapping the extent of microcalcification-associated carcinomas than mammography.

In addition to the advantages of MRI, however, the study presented also shows that in the presence of pure microcalcifications, clarification of the findings using X-ray-guided biopsy procedures leads to an underestimation of the overall findings in 16% of cases. In the targeted clarification of calcifications, the EI component surrounding the tumour and not the index tumour per se is obviously hit more frequently. In these cases, a second surgical intervention for lymphadenectomy is subsequently necessary.

SUMMARY

- An unremarkable HR breast MRI excludes invasive breast carcinoma. This applies to density type 1 and artefact level 1 in the MRI.
- In the presence of pure microcalcifications in the BIRADS 4 or 5 category, HR breast MRI allows a reduction in unnecessary percutaneous biopsies in 76% of cases. However, missing small intraductal carcinomas must be accepted.
- A difference in size between enhancement on MRI and calcifications on mammography and the additional presence of a focus or centre in association with an NML tend to indicate the presence of an invasive carcinoma. In this case, the calcifications are more likely to be a correlate of the presence of EIC.
- In the presence of a focus or foci associated with NML, an MR-guided biopsy appears to be more representative for the detection of possible invasive tumour components than a radiographically guided intervention.

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