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# Breast tumor characteristics of *BRCA1* and *BRCA2* gene mutation carriers on MRI

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**Abstract** The appearance of malignant lesions in *BRCA1* and *BRCA2* mutation carriers (BRCA-MCs) on mammography and magnetic resonance imaging (MRI) was evaluated. Thus, 29 BRCA-MCs with breast cancer were retrospectively evaluated and the results compared with an age, tumor size and tumor type matched control group of 29 sporadic breast cancer cases. Detection rates on both modalities were evaluated. Tumors were analyzed on morphology, density (mammography), enhancement pattern and kinetics (MRI). Overall detection was significantly better with MRI than with mammography (55/58 vs 44/57, $P$=0.021). On mammography, lesions in the BRCA-MC group were significantly more described as rounded (12//19 vs 3/13, $P$=0.036) and with sharp margins (9/19 vs 1/13, $P$=0.024). On MRI lesions in the BRCA-MC group were significantly more described as rounded (16/27 vs 7/28, $P$=0.010), with sharp margins (20/27 vs 7/28, $P$<0.001) and with rim enhancement (7/27 vs 1/28, $P$=0.025). No significant difference was found for enhancement kinetics ($P$=0.667). Malignant lesions in BRCA-MC frequently have morphological characteristics commonly seen in benign lesions, like a rounded shape or sharp margins. This applies for both mammography and MRI. However the possibility of MRI to evaluate the enhancement pattern and kinetics enables the detection of characteristics suggestive for a malignancy.

**Keywords** Breast · MRI · Mammography · BRCA1 · BRCA2

## Introduction

BRCA1 and BRCA2 are the most well known gene mutations responsible for an increased risk for developing breast cancer. A BRCA1 or BRCA2 mutation carrier (BRCA-MC) has approximately a 3% risk of getting breast cancer before the age of 30. This risk increases to almost 50% when she reaches the age of 50 and becomes 50–80% at the age of 70 [1, 2]. To reduce this risk, these women can choose between bilateral prophylactic mastectomy [3], oophorectomy [4] or chemoprevention [5]. In breast cancer, close surveillance contributes to a more favorable stage of disease at detection and may reduce the rate of death from breast cancer [6, 7].

In the surveillance or general screening for breast cancer, mammography still plays a prominent role. However, due to the young age and thus in most cases dense breast tissue, the sensitivity for mammography is moderate. False-negative rates of up to 62% have been reported for mammography in screening gene mutation carriers [8, 9]. A malignant lesion in the breast is mammographically best detected if it presents itself as an ill-defined or spiculated

mass, a group of microcalcifications or as an architectural distortion. A smoothly outlined well-defined mass detected on mammography has a chance of less than 1% of being malignant [10, 11]. Tilanus et al. [12] and Kaas et al. [13, 14] have evaluated the mammographic appearance of breast cancer in BRCA-MC. Tilanus and coworkers found the mammographic appearance suspicious for a malignancy in only 38% of the gene carriers in comparison with 71% in a control group. "Prominent pushing margins" caused by a continuous front of tumor cells not separated by connective tissue were described in the BRCA-MC group as the main reason for a false-negative evaluation of mammograms [12]. Kaas and coworkers concluded in their study of 31 breast cancer cases in BRCA-MCs that all mammographically detected lesions should be further evaluated by ultrasound and biopsy regardless of their appearance [13]. Well-defined mammographic tumors correlated in 83% with histologic circumscribed tumor margins in BRCA1-MCs [14].

For women with an increased risk for developing breast cancer magnetic resonance imaging (MRI) should be included for close surveillance [15, 16]. The superior sensitivity of MRI (81%) for the detection of breast cancer in these women compared with mammography (40%) has been proven in literature [17]. However the classification of a lesion detected on MR as benign or malignant still remains a challenge. Morphological and dynamic features are important in breast MRI interpretation. Focal masses with smooth borders are associated with a high negative predictive value for malignancy [17]. An irregular lesion contour, inhomogeneous enhancement pattern and rim enhancement have been reported as features indicating malignancy [18]. The dynamic evaluation is often based on the enhancement characteristics 2–7 min after the injection of a paramagnetic contrast agent. In this approach, the decrease of signal intensity, often referred to as a type 3 curve or washout, is highly predictive for breast cancer, with a likelihood of malignancy of 87% [19]. Until now the appearance of breast malignancies in BRCA-MCs has only been investigated for mammography. In this study we analyzed the MRI characteristics of BRCA-MC-associated tumors compared with sporadic cases of breast cancer.

## Materials and methods

All available (35) BRCA-MCs with a biopsy-proven malignancy, imaged with MRI for screening [9] or preoperative evaluation in the period from July 2000 until November 2006, were included in the study: 23 BRCA1 carriers and 12 BRCA2 carriers. In order to compare tumor characteristics with sporadic cases of breast cancer an age, tumor type and tumor size matched control group was composed from 206 consecutive sporadic breast cancer cases imaged with MRI in the period from November 2001 until January 2007. All BRCA-MC cases were age matched within 5 years with sporadic breast cancer cases. Cases were also matched for tumor type (IDC, ILC or DCIS) and pathological tumor size. For size matching, the BRCA-MC cases were matched to the closest tumor size in the sporadic cases available, with a limit for the maximum size difference of 0.5 cm for tumors smaller than 1 cm, 1-cm difference for tumors up to 5 cm and 1.5-cm difference for tumors larger than 5 cm. BRCA-MC cases that could not be matched following these criteria were excluded.

Mammograms were obtained in the mediolateral oblique and craniocaudal direction on a digital mammographic unit (Senograph 2000 D or a Senograph DS, GE Healthcare, Wis., USA). Detection, density of the lesion compared with breast tissue, lesion morphology, and size were scored. In the morphologic assessment, lesion type was classified as either a mass, a calcifications or as an architectural distortion. Lesion shape was described as rounded, lobulated or irregular and lesion margins as sharp, vague or spiculated. The size of the tumor was measured by determining the longest axis through the displayed lesion. Spiculae surrounding a solid lesion were interpreted as desmoplastic reaction and not included in the measurement.

MRI investigations were performed on a 1.5-Tesla system with a double breast coil (Magnetom Vision, Sonata or Symphony, Siemens, Erlangen, Germany). In the scanning, we used a coronally orientated three-dimensional fast low-angle shot (FLASH 3D) with the following parameters: TE 4 ms, TR 8.1 ms, FA 20°, FOV 360 mm, TA 96 s, image resolution 1.5 mm × 1.5 mm × 1.5 mm for all patients scanned prior to June 2004 and TE 4 ms, TR 7.5 ms, FA 8°, FOV 320 mm, TA 87 s, image resolution 1.3 mm × 1.3 mm × 1.3 mm for all patients scanned after June 2004.

Prior to the MR examination, an intravenous catheter was inserted. All patients were placed in the prone position, with the breasts in the double breast coil and positioned at the isocenter of the magnet. After localizer images were obtained in three directions and a precontrast FLASH 3D series was recorded, 0.1 mmol/kg bodyweight gadolinium chelate (Magnevist, Schering, Germany or Dotarem, Guerbet, The Netherlands) was administered using a power injector (Spectris, Medrad, USA) at 2.5 ml/s followed by a 15-ml saline flush at the same injection rate. Thereafter, five post contrast FLASH 3D series were recorded.

All MRI examinations were retrospectively evaluated on a dedicated breast MRI workstation (Dynacad, Invivo, USA) scoring lesion detection, size, morphology and enhancement kinetics. Maximum intensity projections, coronal images and axial reconstructions of both the T1 weighted and subtracted images and time-intensity curves were displayed. The morphologic assessment included lesion shape, margin appearance and enhancement pattern. Lesion shape was classified as being rounded, lobulated or irregular. Margins were described as sharp, vague or

spiculated. The enhancement pattern of a lesion was classified as homogeneous, heterogeneous or rim enhanced. Lesion enhancement kinetics were evaluated according to the criteria described by Kuhl et al. [19]. Type 1 shows persistent enhancement and is highly suggestive for a benign lesion. Type 2 shows a plateau after initial increased enhancement, where the maximum signal intensity is reached approximately 2–3 min after contrast injection and remains constant. This type of curve is seen in both benign and malignant lesions. In a type 3 curve, the peak enhancement is reached in the early postcontrast phase, and this is followed by a decrease of signal intensity (wash-out). The latter curve is strongly suggestive for a malignant lesion. The dynamic curves were evaluated based on a single voxel or by selecting a region of interest within the lesion, the workstation allowed the readers to use both methods. Because of the possible bias in this retrospective study, a BI-RADS classification [20] could not be scored objectively and was therefore not included in the evaluation.

All studies were evaluated retrospectively by two radiologists in conference and consensus. BRCA-MCs and controls were mixed during the evaluation. Except from the knowledge of a malignancy being present, the radiologists were blinded to any other clinical information. Mammography and MRI images were evaluated in separate sessions. From the histopathology reports, the tumor type, size and mitotic activity index (MAI) were recorded. The study was approved by the institutional review board; since the study was performed retrospectively, informed consent was not required according to the review board.

In the statistical evaluation, differences in patient and tumor characteristics between the BRCA-MC and control group were analyzed using an independent sample *t*-test if variables were continuous and normally distributed. For categorical variables, the Pearson chi-square test was used and we used Fisher's exact test when any of the expected values was less than five. Pearson's correlation coefficients were calculated for both mammographic size and MRI size versus pathologic size. All statistical analyses were performed using SPSS statistical software (version 12.0.1). *P* values<0.05 were considered to indicate statistical significance.

## Results

Six BRCA-MC cases could not be matched according to the criteria defined; these cases were excluded from the study. Four BRCA-MCs were excluded because no match could be found based on patient's age; the other two were excluded because no match could be found based on tumor size.

The mean age and tumor size of the excluded cases were, respectively, 33 years (range 27–36, median 35, SD 3.4 years) and 1.4 cm (range 0.6–2.8 cm, median 1.1 cm, SD 0.8 cm). A total of 29 BRCA-MC cases were included for this study. In the BRCA-MC group, five women were symptomatic (17%); 21 women were symptomatic in the control group (83%).

Mean age in the BRCA-MC group was 42 years (range 32–68 years, median 40 years, SD 8.0 years); this was 44 (range 37–64 years, median 43 years, SD 5.6 years) for the control group. The mean pathological tumor size was 2.0 cm (range 0.4–7.0 cm, median 1.4 cm, SD 1.5 cm) in the BRCA-MC group and 2.3 cm (range 0.6–7.0 cm, median 1.9 cm, SD 1.7 cm) in the control group. No significant difference was found for patient age (*P=0.289*) or maximal pathological tumor size (*P=0.371*).

The mean tumor size on mammography was 2.1 cm (range 0.5–7.0 cm, median 1.5 cm, SD 1.49 cm). The mean tumor size on MRI was 2.4 cm (range 0.6–7.1 cm, median 1.8 cm, SD 1.75 cm).

There was a significant correlation between imaging measurements and pathological measurements; 0.664 ($P<0.001$) for mammographic measurements and 0.808 ($P<0.001$) for MRI measurements.

In both the BRCA-MC and control groups, 23 cases were based on invasive ductal carcinoma (IDC), two cases on invasive lobular carcinoma (ILC), one case on ductal carcinoma in situ grade 1 (DCIS1) and three cases on ductal carcinoma in situ grade 2 (DCIS2). In the BRCA-MC group, a mean MAI of 33.0 (range 6–100, median 27, SD 27.1) was found, compared with 17.5 (range 1–60, median 14, SD 15.9) in the control group. The difference in MAI between the BRCA-MC and control groups was found to be significant ($P=0.044$).

In the control group, one patient refused to undergo mammography because of implants. Overall mammography detected 44 of 57 lesions and MRI detected 55 of 58 lesions. Therefore, the overall detection is significantly better with MRI than with mammography ($P=0.021$).

Mammography detected 22 (76%) lesions in the BRCA-MC group and 22 (79%) in the control group. No significant difference was found ($P=0.807$). All lesions missed on mammography in the BRCA-MC were IDC. In the control group, five cases of IDC and one case of ILC were missed. Mammographic lesion characteristics are presented in Table 1. Lesions in the BRCA-MC group were significantly more described as rounded (12//19 vs 3/13, $P=0.036$) and were more often described to have sharp margins (9/19 vs 1/13, $P=0.024$). Lesions in the control group were significantly more described as irregular (10/13 vs 6/19, $P=0.029$). From the six BRCA-MCs that were excluded, only three lesions were detected on mammography. In two cases a mass was detected and in one case calcifications. Both these masses were described as rounded with sharp margins.

On MRI, 27 lesions (93%) were detected in the BRCA-MC group, 28 (97%) in the control group. No significant difference was found ($P=0.553$). The lesions missed in the BRCA-MC group were both cases of DCIS, one case of

**Table 1** Mammographic lesion characteristics for both groups

| | | BRCA-MC group | Control group | *P* value |
|---|---|---|---|---|
| Lesions detected | | *n*=22 | *n*=22 | |
| Lesion type | Mass | 19 | 13 | 0.042 |
| | Arch. distortion | 1 | 4 | 0.345 |
| | Calcification | 2 | 5 | 0.216 |
| Lesion density[a] | Hyperdense | 8 | 1 | 0.050 |
| | Isodense | 11 | 12 | 0.050 |
| Lesion morphology[a] | Rounded | 12 | 3 | 0.036 |
| | Lobulated | 1 | – | 1.000 |
| | Irregular | 6 | 10 | 0.029 |
| Lesion margins[a] | Sharp | 9 | 1 | 0.024 |
| | Vague | 8 | 8 | 0.473 |
| | Spiculated | 2 | 4 | 0.194 |

[a]Lesion density, morphology and margins of mass-like lesions only

DCIS1, seen on mammography as an architectural distortion, and one case on DCIS2, seen on mammography as a mass. The lesion missed in the control group was based on DCIS2, seen on mammography as calcifications. Their was no significant difference found for the detection of breast cancer between mammography and MRI within the BRCA-MC ($P$=0.18) or the control group ($P$=0.13). Morphological and dynamic MR characteristics are presented in Table 2. Lesions in the BRCA-MC group were significantly more often described as rounded (16/27 vs 7/28, $P$=0.010), with sharp margins (20/27 vs 7/28, $P$< 0.001) and to show rim enhancement (7/27 vs 1/28, $P$= 0.025). Lesions in the control group were significantly more often described as irregular (18/28 vs 8/27, $P$=0.010), with vague margins (15/28 vs 6/27, $P$=0.017) and with a heterogeneous enhancement pattern (22/28 vs 12/27, $P$= 0.009). No significant difference between the two groups was found for enhancement kinetics ($P$=0.667). From the six BRCA-MCs that were excluded, five were detected on MRI. Four of these lesions were described as rounded, one as irregular. The delineation was described as sharp in four and as vague in one of these cases. The enhancement pattern was described as homogeneous in two, heterogeneous in one and as rim-enhancement in two of these cases. All five cases showed a type 3 curve.

## Discussion

In this study, the overall false-negative rate for mammography was significantly higher compared with MRI. Although it is expected that the sensitivity for MRI in both the control group and the BRCA-MC is higher compared with mammography, no significant difference was found in this study within the two groups. This is probably due to the relatively small numbers of cases in this study. Kaas et al. [13] described in their mammographic study on *BRCA1* and *BRCA2* mutation carriers a

**Table 2** MRI lesion characteristics for both groups

| | | BRCA-MC group | Control group | *P* value |
|---|---|---|---|---|
| Lesions detected | | *n*=27 | *n*=28 | |
| Lesion morphology | Rounded | 16 | 7 | 0.010 |
| | Lobulated | 3 | 3 | 1.000 |
| | Irregular | 8 | 18 | 0.010 |
| Lesion margins | Sharp | 20 | 7 | <0.001 |
| | Vague | 6 | 15 | 0.017 |
| | Spiculated | 1 | 6 | 0.049 |
| Enhancement pattern | Homogeneous | 8 | 5 | 0.304 |
| | Heterogeneous | 12 | 22 | 0.009 |
| | Rim | 7 | 1 | 0.025 |
| Enhancement kinetics | Type 1 | 1 | 2 | 1.000 |
| | Type 2 | 4 | 6 | 0.525 |
| | Type 3 | 22 | 20 | 0.380 |

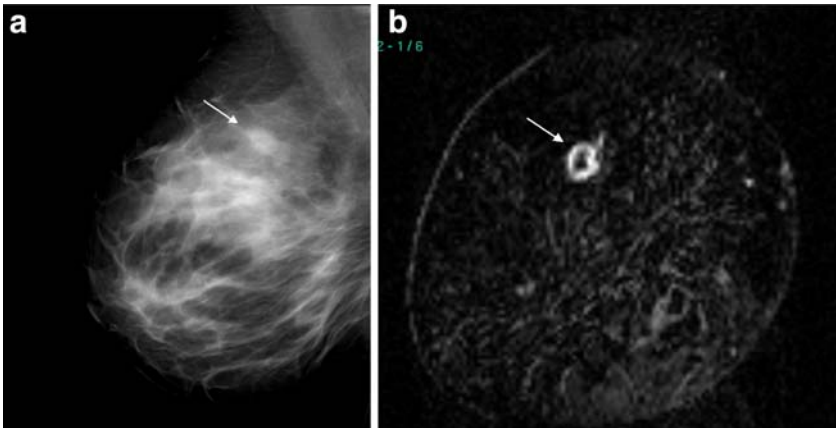


**Fig. 1** **a** An MLO mammogram from the right breast of a 42-year-old *BRCA1*-mutation carrier. **b** A coronal subtraction MR image of the same breast. An 11-mm sharply delineated rounded lesion is present on the mammogram projecting over the upper quadrants (*arrow*). On MRI, the same lesion was detected (*arrow*) with rim-enhancement. The rim-enhancement makes this lesion morphologically suspect malignant. Ultrasound guided core biopsy proved this lesion to be an invasive duct carcinoma

sensitivity of 64% for the detection of a tumor in the original reports. In this study, 76% of the lesions were visible on mammography. Since this was a retrospective study and the radiologist was aware of the fact that a tumor was present at the time of the evaluation, no conclusion can be drawn from the difference in detection between both studies.

On mammography, the mass like lesions detected in the BRCA-MC group were significantly more often described as rounded. Also, lesions were found to differ in margin appearance; tumor margins in the BRCA-MC group were significantly more often described as sharp. A smooth, nonspiculated mass has previously been described by Tilanus et al. [12] as a reason for a false-negative mammographic evaluation in BRCA-MC. Thus, although Sickles et al. [21] described that nonpalpable, circumscribed, noncalcified breast masses (probably benign) should be managed with periodic mammographic surveillance regardless of lesion size and patient age, and Sardanelli et al. [22] published that both the well-defined margins and the rounded shape are more often associated with benign lesions, these findings are not applicable to the BRCA-MCs studied in this or other studies on this subject. Tilanus et al. [12] stated that any mammographic mass in BRCA-MCs must be regarded with suspicion. A similar conclusion was published by Kaas et al. [13]. An additional evaluation using ultrasound and biopsy of all lesions detected in BRCA-MC is mandatory, regardless of their morphological appearance. In their study of 28 BRCA-MCs, Hamilton et al. [23] also described the appearance of breast tumors on ultrasound. On ultrasound, 53% of the tumors were classified as either benign or indeterminate, making a biopsy of any detected mass inevitable. We are also of the opinion that any solid lesion detected in BRCA-MCs should be evaluated by a biopsy.

In the screening of women with an increased risk for developing breast cancer, more tumors are detected by MRI compared with mammography [8, 9]. In this study, all

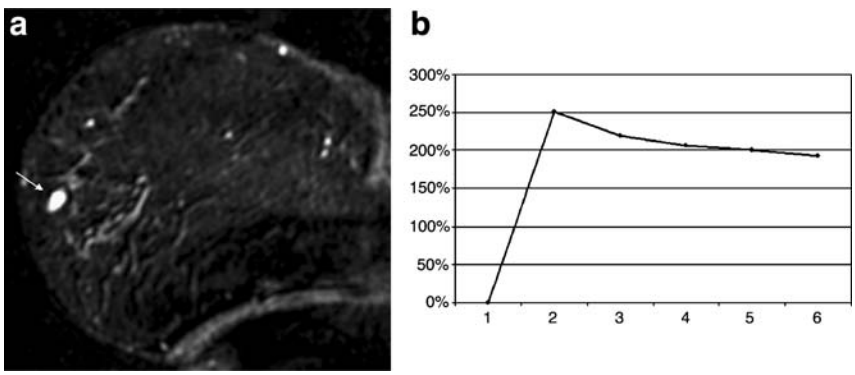


**Fig. 2** **a** A coronal subtraction MR image from the right breast of a 49-year-old *BRCA1*-mutation carrier. Lateral located in the right breast, a sharply delineated rounded, homogeneous enhancing lesion is visible with a longest diameter of 9 mm (*arrow*). **b** The relative enhancement versus time curve. The type 3 curve seen for this lesion was the only characteristic indicating a possible malignancy. Pathology proved this lesion to be an invasive duct carcinoma

lesions missed on MRI were cases of DCIS. MRI is known to have a lower sensitivity in detecting DCIS compared with invasive carcinomas [24], especially in low-grade DCIS. The low or intermediate contrast uptake that is often observed in pure DCIS and the absence of a type 3 curve can result in a false-negative evaluation [24]. Kriege et al. [9] found in the screening of 1,909 women with an increased risk for developing breast cancer, including 358 carriers of germ-line mutations, that MRI missed five cases of DCIS that were detected on mammography, with six noninvasive tumors detected in total in the study. However, Kuhl et al. [25] reported MRI to be more sensitive for DCIS compared with mammography in a prospective study of women with an increased risk for developing breast cancer. Although MRI proved to be more sensitive for the detection of DCIS compared with mammography, not all cases of DCIS were detected by either modality. Therefore, at this point both modalities are still needed in the screening of women with an increased risk for developing breast cancer.

Similar to mammography, on MRI a significantly higher number of lesions were described as rounded and with sharp margins in the BRCA-MC group. Furthermore, the number of lesions with 'rim-enhancement' was found to be significantly higher in the BRCA-MC group. The presence of this enhancement pattern has been associated with malignant lesions [26, 27]. Because MRI enables the radiologist to evaluate the enhancement pattern of the lesion, where mammography does not, these lesions will become more suspectedly malignant, even though other morphologic features are more often seen in benign lesions. The association of rim-enhancement (Fig. 1) with central necrosis or insufficient microvessel growth can be an indicator for the growth rate of tumors. Jimenez and coworkers have described centrally necrotizing carcinomas to have an accelerated clinical course and early systemic metastasis [28]. An accelerated growth rate can be associated with a high MAI. In this study, the MAI was found to be significantly different between both groups. This is in agreement with Tilanus et al. [12], who also found the mitotic count to be significantly higher in tumors found in gene mutation carriers. The higher rate of sharp tumor margins and rim-enhancement may thus be explained by the more aggressive nature of tumors in BRCA-MCs. Several authors have implied that, due to the rapid growth rate of tumors in gene mutation carriers, the screening frequency should be adjusted [13, 29]. Komenaka et al. [29] suggest a higher screening frequency in carriers because of the high number of interval cancers found in their group. Half of these interval malignancies were already positive for lymph-node involvement. The 13 carriers in their study were screened with mammography. Mammography in carriers is not sensitive, particularly because the women are young and thus more often have dense breasts [30, 31]. The use of MRI in screening has already been a step forward since MRI can detect smaller tumors, often occult for mammography, that are less likely to have progressed into lymph-node involvement [9].

Rounded, homogeneous enhancing lesions found on MRI are in general not considered suspicious. A homogeneous enhancement pattern, found in nine BRCA-MCs, does not contribute to the malignant nature of these lesions. Therefore, enhancement kinetics are of value. In this study, the dynamic analysis showed in both the BRCA-MC and the control groups a type 3 curve in, respectively, 82% and 71% of the cases. As described by Kuhl et al. [19], a type 3 enhancement curve is highly indicative for malignancy. Using this characteristic, even rounded, sharply delineated, homogeneous enhancing lesions become suspect malignant (Fig. 2).

Despite all the findings discussed in this study, it remains questionable if the characterization of a lesion detected on either mammography or MRI in BRCA-MCs is even necessary. As the chance for these women to develop breast cancer is significantly increased, almost any detected lesion will in practice be classified as suspect malignant until proven otherwise. Sardanelli et al. [17] found a positive predictive value for MR in women with an increased risk of only 53% due to a high number of false positives. As stated previously for mammographically detected lesions, additional evaluation by core biopsy is the only definitive classification for lesions detected in this group of women. In the case of MRI screening in high risk women, short-term follow-up, target ultrasound or MRI-guided biopsies are therefore often indicated [32]. What the best strategy in this group of women will be, also in terms of cost effectiveness, needs to be further studied.

We conclude that in BRCA-MC malignant lesions frequently have morphological characteristics that are commonly seen in benign lesions, like a rounded morphology or a sharp delineation. This applies for both mammography and MRI. However, the possibility of MRI to evaluate the enhancement pattern and enhancement kinetics of lesions enables the radiologist to detect characteristics suggestive for a malignancy.

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