Sensitivity and Specificity of Unilateral Edema on T2w-TSE Sequences in MR-Mammography Considering 974 Histologically Verified Lesions

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Abstract: The objective of this investigation was to determine the diagnostic value of unilateral edema in differentiating benign from malignant breast disease on T2w-TSE images in MR-Mammography (MRM). All patients from a 10-year period undergoing surgery in the same institution after having received MRM in our department were included in this prospective analysis of previous acquired examinations. To eliminate bias caused by prior procedures, all patients having had biopsy, operation, radiation therapy, or chemotherapy before MRM were excluded. T2w-TSE images were acquired after a dynamic contrast-enhanced series of T1-weighted images in a standardized examination protocol (1.5 T). Edema was defined as a high-signal intensity on T2w-TSE images and it was categorized as absent, perifocal, or diffuse. Examinations were rated by two experienced observers blinded to all procedures and results following MRM. In cases of discordance, the opinion of a third radiologist decided. Statistical testing included Pearson's Chi-squared test and Fisher's exact testing. A total of 1,010 patients with a mean age of 55 years (SD: 11.6 years, range: 16–87 years) with 1,129 histologically verified lesions were included in this investigation. After removing all patients with prior procedures from the patient collective, 974 lesions were left for statistical analysis. Perifocal edema was highly significantly (p < 0.001) associated with malignant disease, leading to a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 33.5%, 93.9%, 89.6, and 57.1%, respectively. Unilateral edema in general showed the following diagnostic parameters: sensitivity 53.0%, specificity 80.5%, PPV 80.9%, and NPV 52.3%. Edema seems to be associated with malignancy in the majority of cases. Especially, specificity and PPV were found to be high. These findings may be helpful in diagnostic decisions on otherwise equivocal cases.

Key Words: breast, edema, MRI, MR-Mammography, sensitivity and specificity

MR-Mammography (MRM) is regarded as the most sensitive method for detection of breast cancer with varying reports on specificity (1–5). The latter may be one reason for the rather slow adoption of the method into clinical routine. A standard examination protocol in MRM includes repetitive measurements of T1-weighted sequences after intravenous application of a contrast agent. Benign and malignant tumors can be differentiated due to vascularization differences (4,6,7). However, there is an overlap of enhancement characteristics between benign and malignant tumors. Several investigators have proposed additional morphologic criteria to be implemented into scoring and description systems to improve diagnostic accuracy. Beside one paper, these approaches do not consider additional information from T2-weighted sequences, that is basically the amount of fluid in the tissue analyzed (8–10). As been described previously, malignant lesions of the breast show a hypointense signal on T2-weighted sequences, possibly attributed to tumor fibrosis in form of a desmoplastic
reaction (11). Moreover, water in the tissue around the lesion may be found using T2-weighted sequences, referred to as edema. This phenomenon is well known in MRI of the brain and also described for soft tissue tumors (12–15). It is described in a book regarding lesion features in MRM (16). Edema is included into a clinical scoring system as an indicator for malignant breast disease and included as an adjunct criterion in the ACR BIRADS lexicon (8,17). However, edema may also occur in benign lesions, e.g., inflammatory changes like post-therapeutic conditions (18).

This prospective blinded analysis of previous acquired examinations was performed to determine the clinical value of edema in MRM. Therefore, the aim of this paper is:

1. to present diagnostic parameters of different types of edema in the breast in a large collective of histologically verified lesions excluding cases with prior diagnostic or therapeutic manipulations; and
2. to identify influences on the prevalence of edema by means of histopathologic correlation with special focus on size, grading, and histopathologic subtype.

**METHODS**

**Patients, Lesions**

A total of 4,847 consecutive MRMs were performed at our institution from December 22, 1994 to March 31, 2004. Indications for the examination were unclear or suspect findings in x-ray Mammography and/or Ultrasound of the breast. Eligible for this investigation were all patients undergoing surgery or biopsy for definite histopathologic diagnosis at the Department of Gynecology at our university after MRM. Thus, 1,040 patients with a mean age of 54.5 years (SD: 13.1 years), showing 1,164 histologically verified lesions were taken into account. To eliminate bias due to therapeutic effects, all patients having had biopsy or open surgery up to 6 months before MRM or any radiation or chemotherapy in their clinical history were excluded. As a result, 974 lesions in 940 patients were left for statistical analysis.

**Imaging**

All MRM examinations were performed on 1.5 T systems by using dedicated bilateral breast coils. Until December 31, 2001, all MRM examinations were performed on a 1.5 T Gyroscan ACS II system from Philips Medical Systems (Philips, Hamburg, Germany). Four MRI scanners were used from January 1, 2002 to March 31, 2004: two Philips Medical Systems magnets (Gyroscan ACS II and Interax- Gyroscan ACS II) and two Siemens Medical Solutions devices (Siemens Healthcare, Erlangen, Germany) (Vision Plus and Magnetom Symphony). All examinations followed a standardized protocol including an axial-orientated dynamic T1-weighted gradient echo sequence after bolus injection (3 mL/second, 20 seconds delay after injection) of contrast agent (Gd-DTPA, Magnevist; Bayer HealthCare, Leverkusen, Germany). In all patients, an axial T2w-TSE sequence without fat saturation was performed in the same orientation. Imaging parameters were as follows for the Philips MRI units: repetition time (TR) 4,000 ms, echo time (TE) 300 ms, slice thickness 4 mm, field of view (FOV) 350 mm, matrix 193 × 256 voxel. A TR of 12,288, TE 259, and a matrix of 256 × 256 voxels were used on the Vision Plus Siemens unit with same FOV and slice thickness. On the Siemens Symphony MRI, a TR of 8,900 ms, TE 207 ms, a slice thickness of 3 mm, and a matrix of 512 × 512 voxels by FOV of 350 mm was used.

**Histopathologic Analysis**

All histopathologic diagnoses were performed at the Department of Pathology of our university. Benign breast lesions were divided into solid benign tumors (fibroadenoma, phylloid tumor, papilloma), inflammatory conditions, and other benign proliferative findings as well as fibrocystic changes. For malignant lesions, the histologic type evaluation was performed according to the World Health Organization (WHO) classification of breast carcinoma.

**Image Analysis**

Two radiologists experienced in MRM (>500 examinations each) visually analyzed the images of all patients in consensus. T2w-TSE images were read in conjunction with the other sequences to identify enhancing lesions. The observers were blinded to surgical and histopathologic results. Surgical and pathologic information was correlated with the radiologists’ evaluation directly after each patient analysis. Maximum size measurements using measurement tools were ordinarily classified according to the T-classification (1 = 1–5 mm, T1a; 2 = 6–10 mm, T1b; 3 = 11–20 mm, T1c; 4 = 21–50 mm, T2; 5 = >50 mm, larger T2). To simplify comparisons, lesions were dichotomized in two groups of small (T1) (1–20 mm) and more advanced (>21 mm) changes.
Definition of Edema

Edema was assessed visually on T2w-TSE images. It was rated positive if a high fluid-like signal intensity not caused by intraductal fluid or cysts was present. The nominal classification scheme was differentiated between:

1. absence of edema;
2. unilateral perifocal edema, defined as a pathologic high T2w signal in the tissue surrounding the lesion analyzed; and
3. unilateral diffuse edema, in form of a diffuse asymmetric unilateral finding of fluid associated to a lesion.

Examples for different types of edema are shown in Figures 1–3.

Statistical Analysis

For statistical analysis, we used two-sided Pearson’s chi-squared test to verify significant differences between the prevalence of edema and the analyzed criteria. Sample sizes <40 were analyzed by Fisher’s exact test. For all tests, p-values <0.05 were regarded as significant. In addition to sensitivity and specificity values, likelihood ratios were calculated according to: sensitivity/(1 − specificity) = positive likelihood ratio (LR+) and (1 − sensitivity)/specificity = negative likelihood ratio (LR−).

For data collection and analysis, Excel 2003 (Microsoft, Redmond, WA) was used. Exact statistical testing and graphs were performed using SPSS 15 for Windows (Statistical Package for Social Sciences, SPSS, Chicago, IL).

RESULTS

Of the 974 MR-mammographically identified lesions in 940 patients included in this study, 594 (61%) were histopathologically defined as malignant and 380 (39%) as benign. Subtype distribution in these groups are given in Tables 1 and 2. The residual patients’ age distribution (55.0 years, SD: 13.3 years) did not differ from the age distribution of the whole patient collective (p > 0.05). Lesion size ranged from 3 to 140 mm with a median size of 3 on the ordinal classification given above (11–20 mm).
Unilateral edema in general was observed in 274 of 974 lesions (28.1%). Perifocal edema was seen in 222 (22.8%) and diffuse unilateral edema in 52 (5.3%) cases (Table 3).

Edema prevalences were found significantly (p < 0.001) higher in malignant compared with benign lesions. Resulting diagnostic parameters are listed in Table 3 with their 95% confidence intervals (CI).

With 5.6% (95% CI: 2.2–9.0%), edema was a rather rare finding in solid benign tumors (two fibroadenomas, two phylloid tumors, and six papillomas). In comparison, fibrocystic disease was more often correlated with edema in 19 of 180 (10.6%, 95% CI: 6.1–15.1%), whereas edema was seen frequently (33.3%, 95% CI: 12.9–53.1%) in inflammatory changes. The increased frequency of edema in inflammatory changes proved to be significantly (p = 0.023 perifocal edema; p = 0.019 diffuse edema) different from other benign subgroups (Table 2).

Moreover, prevalence of diffuse edema was significantly (p = 0.003) higher in nonsolid (fibrocystic disease and inflammation) benign lesions compared with solid (fibroadenoma, phylloid tumor, and papilloma) tumors, whereas the prevalence of perifocal edema was not (0.299).

Edema frequently occurred in invasive ductal cancer with 47.1% (95% CI: 41.4–52.8%) and in all seven cases of inflammatory breast cancer (Table 4). Other malignancies showed edema in 31.6–38.8%. Carcinoma in situ cases showed a lower prevalence of edema (16.5%, 95% CI: 8.6–24.4%). However, edema was significantly more common in CIS compared with benign tumors (p = 0.019 diffuse and p = 0.023 perifocal).

Lesions above 20 mm (T2, T3) in size showed a twofold higher prevalence (p < 0.001) of edema compared with smaller (T1) lesions (Table 4). Size

Table 1. Edema in Benign Subgroups

| Edema                | None (%) | Perifocal (%) | Diffuse (%) | Total (%) |
|----------------------|----------|---------------|-------------|-----------|
| Fibroadenoma         | 97 (98)  | 1 (1)         | 1 (1)       | 99 (100)  |
| Phylloid tumor       | 13 (86.7)| 2 (13.3)      | 0 (0)       | 15 (100)  |
| Papilloma            | 59 (90.8)| 6 (9.2)       | 0 (0)       | 65 (100)  |
| Inflammation         | 14 (66.7)| 4 (19.0)      | 3 (14.3)    | 21 (100)  |
| Fibrocystic Disease  | 161 (89.4)| 10 (5.6)     | 9 (5.0)     | 180 (100) |
| Total                | 344 (90.5)| 23 (6.1)     | 13 (3.4)    | 380 (100) |

Table 2. Edema in Malignant Subgroups

| Edema                  | None (%) | Perifocal (%) | Diffuse (%) | Total (%) |
|------------------------|----------|---------------|-------------|-----------|
| Carcinoma in situ      | 71 (83.5)| 12 (14.1)     | 2 (2.4)     | 85 (100)  |
| Invasive ductal         | 154 (52.9)| 116 (39.9)| 21 (7.2)    | 291 (100) |
| Invasive lobular        | 69 (61.6)| 34 (30.4)     | 9 (8.0)     | 112 (100) |
| Invasive ductal and lobular | 13 (68.4)| 6 (31.6)     | 0 (0)       | 19 (100)  |
| Inflammatory cancer     | 0 (%)    | 4 (57.1)      | 3 (42.9)    | 7 (100)   |
| Other malignancy        | 49 (61.3)| 27 (33.8)     | 4 (5.0)     | 80 (100)  |
| Total                  | 356 (59.9) | 199 (33.5) | 39 (6.6) | 594 (100) |

Table 3. Diagnostic Parameters of Edema

| Edema     | Sensitivity  | Specificity | LR+ | LR− |
|-----------|--------------|-------------|-----|-----|
| Perifocal | 33.5% (199/594) | 93.9% (357/380) | 5.5 | 0.7 |
| Diffuse   | 6.6% (39/594) | 96.6% (367/380) | 1.9 | 1   |
| Total     | 38.3% (238/594) | 88.4% (544/380) | 4.2 | 0.7 |

LR+, positive likelihood ratio; LR−, negative likelihood ratio; CI, 95% confidence interval.

Figure 3. A 72-year-old patient with invasive ductal cancer pT1b G3. Left: subtraction (T1w) image 1 minute after injection of 0.1 mmol Gd-DTPA at 3 mL/second, showing a partly well-differentiated mass lesion with early contrast enhancement. Right: T2w TSE image with a matrix of 512 × 512 showing a perifocal edema (arrow).
differences in benign lesions did not have a statistically significant effect on edema prevalence (p = 0.177 perifocal, p = 0.142 diffuse).

In 41 of 509 invasive tumor cases, no grading could be obtained from the medical records. Edema was more frequently observed in cases with higher grading (G1: 24.1%, 95% CI: 13.1–35.1%; G2: 35.6%, 95% CI: 29.3–41.9%; G3: 60.5%, 53.5–67.5%; Table 4). The differences between G1 and G2 did not prove statistical significance (p = 0.236 perifocal, p = 0.459 diffuse), the higher prevalence of edema in G3 compared with G2 was highly significant (p < 0.001).

### DISCUSSION

**Edema Associated with Breast Lesions: Histopathologic Correlation**

According to our results, the occurrence of edema significantly increased from benign over non-invasive to invasive breast cancer. Regarding these findings, there is a clear association with malignancy not only for perifocal, but also for diffuse unilateral edema. Invasive growth and tumor progression are associated with peritumoral proteolysis and the formation of new vessels (neoangiogenesis) that are characterized by increased vascular permeability due to leaky basilar membranes compared with physiologic vasculature (15,19–27). The resulting transudation from the intravascular to the extracellular space may be a factor contributing to the presence of perifocal edema in MRM. Increased transudation through the vessel wall mediated by inflammatory cytokines is probably as well the explanation for the presence of an edema in inflammatory processes. In our patient collective, inflammatory findings were the only benign changes frequently associated with edema. Neoangiogenesis and tumor growth are closely related to increased levels of proteolytic enzymes, such as metalloproteinases, degrading the extracellular matrix. The majority of these enzymes are provided by stromal cells, such as fibroblasts (19,20,26,28,29). In animal examinations as well as human studies, the presence of fluid accumulation in the form of edema could be seen in settings with an increased activity of metalloproteinases (29,30). Our results suggest an increased proteolytic activity in cases exhibiting edema. Tissue fragmentation and decomposition as a result of proteolytic activity might lead to an increased accumulation of fluid which can be depicted on T2w images. With the design of our investigation based in a clinical setting, no comparisons of pathologic tissue characteristics exceeding routine clinical classifications with edema were possible. Also, interobserver variability of histopathologic results, especially tumor grading, could not be addressed in this study. Further investigations focusing on this issue might determine the given presumption.

Regarding nuclear grading, there was a significant higher prevalence of edema in poorly differentiated carcinomas (G3) compared with well- and intermediate-differentiated tumors (G1 and G2). Higher nuclear grading is associated with a more aggressive growth pattern, increased neoangiogenesis, and higher levels of proteolytic enzymes (23,28,31,32). According to the cited experimental literature and the statements above, a higher level of neoangiogenesis and proteolysis may be assumed in these cases. Furthermore, histologic grade is an independent predictor of both breast cancer-specific survival and disease-free survival (33). Our results suggest a more aggressive tumor growth in lesions with associated edema in clinical MRM. This finding might provide a prognostic value.

Unilateral edema did significantly occur more often in malignant tumors exceeding 2 cm in size, whereas larger benign tumors did not show a significant increase in edema. A higher tumor load is likely to

| Edema | None | Perifocal | Diffuse | Total |
|-------|------|-----------|---------|-------|
| Benign (<=20 mm; %) | 274 (91.9) | 16 (5.4) | 8 (2.7) | 298 (100) |
| Benign (>20 mm; %) | 70 (85.4) | 7 (8.5) | 5 (6.1) | 82 (100) |
| Malignant (<=20 mm; %) | 271 (71.3) | 92 (24.2) | 17 (4.5) | 380 (100) |
| Malignant (>20 mm; %) | 85 (39.7) | 107 (50.0) | 22 (10.3) | 214 (100) |

### Table 5. Edema in Different Gradings of Invasive Malignancies

| Edema | G1 (%) | G2 (%) | G3 (%) | Gx (%) | Total (%) |
|-------|--------|--------|--------|--------|----------|
| None | 44 (75.9) | 145 (64.4) | 73 (39.5) | 23 (56.1) | 285 (56.0) |
| Perifocal | 13 (22.4) | 70 (31.1) | 88 (47.6) | 16 (39.0) | 187 (36.7) |
| Diffuse | 1 (1.7) | 10 (4.4) | 24 (13.0) | 2 (4.9) | 37 (7.3) |
| Total | 58 (100) | 225 (100) | 185 (100) | 41 (100) | 509 (100) |

Table 4. Edema in Benign and Malignant Lesions Depending on Size

| Edema | None | Perifocal | Diffuse | Total |
|-------|------|-----------|---------|-------|
| Benign (<=20 mm; %) | 274 (91.9) | 16 (5.4) | 8 (2.7) | 298 (100) |
| Benign (>20 mm; %) | 70 (85.4) | 7 (8.5) | 5 (6.1) | 82 (100) |
| p-Value | Not significant | Not significant | Not significant | Not significant |
| Malignant (<=20 mm; %) | 271 (71.3) | 92 (24.2) | 17 (4.5) | 380 (100) |
| Malignant (>20 mm; %) | 85 (39.7) | 107 (50.0) | 22 (10.3) | 214 (100) |
| p-Value | <0.001 | <0.001 | Significant | Significant |

### Table 5. Edema in Different Gradings of Invasive Malignancies

| Edema | None (%) | Perifocal (%) | Diffuse (%) | Total (%) |
|-------|----------|---------------|-------------|-----------|
| G1 | 44 (75.9) | 13 (22.4) | 1 (1.7) | 58 (100) |
| G2 | 145 (64.4) | 70 (31.1) | 10 (4.4) | 225 (100) |
| G3 | 73 (39.5) | 88 (47.6) | 24 (13.0) | 185 (100) |
| Gx | 23 (56.1) | 16 (39.0) | 2 (4.9) | 41 (100) |
| Total | 285 (56.0) | 187 (36.7) | 37 (7.3) | 509 (100) |
cause an overall elevated angiogenetic and proteolytic activity. The absence of edema in a number of smaller carcinomas may be due to imaging limitations. A smaller affected volume with only beginning edema may be missed by MRI due to partial volume effects. Renz et al. reported perifocal edema in 70% and diffuse edema in 37% in a cohort of locally advanced tumors (T3 and T4) using a T2w-TSE sequence with a 512 × 512 matrix (34). These results may be due to the selected cohort of locally advanced cancers. Only a controlled comparison of techniques using a different imaging matrix could work out technically caused differences.

**Diagnostic Differentiation Between Benign and Malignant Lesions**

Association of edema with malignancy, especially in a perifocal distribution has been described in various organs (12–14,30,35). According to the literature, the differentiation between benign and malignant breast lesions is mainly based on morphology and semiquantitative measurements of the contrast enhancement characteristics of the lesion itself (2,4,6,7,9). Although there have been suggestions of a diagnostic value using T2-weighted sequences, published results are heterogenous (8,11,36). The current MRI BIRADS classification scheme does not integrate T2w findings, also the frequently used Göttingen score does not (9,10). Malich et al. proposed the use of T2w findings, such as visual signal intensity of the lesion or different types of edema (8). According to our results and in concordance to the findings of Malich et al., edema has a limited sensitivity, but a high specificity. These results implicate the use of edema in a scoring system, as has been demonstrated by Malich et al. The use of scoring systems may be reduced when based on a statistically not representative data base. Fischer et al. found major differences in diagnostic accuracy compared with the initial report of Baum et al. when they compared two scoring systems in the same patient collective (37). To avoid statistical uncertainties, we investigated the prevalence of edema in a large patient collective to obtain representative data and calculated likelihood ratios as well as 95% CI. Edema exhibits a clear signal difference to the surrounding tissue on the T2w-TSE sequence investigated. Although not quantified by statistical means, interobserver variability regarding unilateral edema of the breast was low during consensus rating of both radiologists. In this study, edema was rated as positive or absent in a nominal way. A more sophisticated graduation of edema findings could be more adequate to describe associated pathology. An important issue to mention is therapeutic or diagnostic manipulations prior to MRM. Edema has been described as a typical finding after radiotherapy (18). Before edema findings are interpreted in routine diagnostics, patient history should be considered.

**CONCLUSION**

According to our results, perifocal edema is specifically associated with malignancy and can therefore help to differentiate between benign and malignant breast disease. Furthermore, edema is associated with a higher grading and increased tumor size. These observations may be of prognostic value and should be considered in future investigations. Edema exhibits a clear signal difference to the surrounding tissue. This fact may be useful to quantify the amount of edema in the tissue analyzed. Further study combining several morphologic and dynamic criteria is needed to fully estimate the full value of edema for MRM.

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