False-negative MR imaging of malignant breast tumors

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Abstract. In this study we analyze MR-negative malignant lesions of the breast. A total of 204 patients with palpable and/or mammographic lesions were studied. The MR technique consisted of the turbo FLASH and MP-RAGE subtraction techniques. All patients underwent surgical biopsy and/or mastectomy and all specimens were examined by the correlative radiologic-histologic mapping technique. A total of 208 lesions were evaluated; 145 turned out to be malignant and 63 proved to be benign. Six malignant lesions were misinterpreted as benign on MR imaging; thus, suspicious contrast enhancement was present in 96% of the lesions detected by mammography, US, or clinical examination. Especially 4 of the 17 ductal carcinoma in situ (DCIS) lesions were misinterpreted (23.5%). Despite optimal technique, 6 malignant lesions were not identified by MR imaging. The highest prevalence of these MR occult lesions was in the group of DCIS. Although MR imaging has an important role in the evaluation of breast lesions and, primarily, in ruling out malignancy, one should be aware of the fact that false-negative MR findings do occur.

Key words: Breast neoplasms – MR – Contrast enhancement – Gadolinium

Introduction

Mammography has been considered recently the most effective modality for the detection of breast cancer. Its sensitivity is close to 90% [1]. However, with the use of an intravenous gadolinium-containing contrast medium, the sensitivity of MR imaging is superior to mammography [2]. Various authors claim that absence of contrast enhancement practically excludes malignancy [3, 4].

Although the sensitivity of MR imaging is high, normal glandular tissue may also enhance as well as various benign lesions resulting in a specificity of 42% as reported by Heywang et al. [6], and of 61% as reported by Harms and Flamig [4]. Only Kaiser claims a very high specificity of 96.9% [3].

Data pertinent to false-negative results are relatively few [7–9]. In the present study we discuss our 2.5-year experience with MR-negative malignant tumors.

Materials and methods

Histologic results and preoperative imaging findings (mammography, MR imaging) in 204 women subjected to mastectomy or lumpectomy for a malignant or benign lesion of the breast were analyzed. The mean age of the patients was 52.5 years (range 19–81 years). In 4 patients bilateral lesions were present; thus, a total number of 208 lesions were available for analysis.

For the mammographic examination a CGR 600T unit (GE Medical Systems, Milwaukee, Wis.) was used. In addition to the standard oblique and craniocaudal projections, magnification views in both projections were obtained in most cases.

The MR imaging was performed on a Magnetom 63/84 SP4000 (Siemens, Erlangen, Germany) at a field strength of 1.5 T. Gadopentetic dimeriglumine (Magnevist, Schering, Berlin, Germany) was used as contrast medium. A detailed description of the examination technique has been presented elsewhere [10]. Briefly, it consists of a 3D MP-RAGE sequence or 3D FLASH sequence (slice thickness 1.4 mm, 128 slices, 192 x 256 matrix, 300-mm field of view) before and after intravenous injection of a gadolinium-containing contrast medium and a turbo FLASH sequence (slice thickness 10 mm, 63 sequential breast images, 128 x 256 matrix, 350-mm field of view) during the injection of the contrast medium. Informed consent was obtained in all patients.

A certain combination of features of both the turbo FLASH and MP-RAGE/FLASH sequence were used...
for the differentiation of benign and malignant lesions. For the turbo FLASH sequence our main criterion for the diagnosis of a malignant lesion is enhancement within 11.5 s after aortic enhancement. In addition, centripetal enhancement was regarded as a sign of malignancy. Conversely, late enhancement ( > 11.5 s) and centrifugal enhancement were regarded as signs of benignity. On the subtracted MP-RAGE/FLASH sequence images with focal enhancement, and especially with irregular borders, were considered to be suspicious for malignancy. Field enhancement, either diffuse or patchy, was considered equivocal, as this pattern of enhancement may be seen in both benign and malignant lesions [2].

Surgical biopsy and mastectomy specimens were examined pathologically by using a correlative radiologic-histologic mapping technique, described in detail elsewhere [11].

Results

Of a total of 208 lesions, 63 lesions were benign and 145 were malignant on histology. In this series suspicious contrast enhancement was present in 96% of the lesions detected by mammography, US, or clinical examination.

Six malignant lesions were interpreted as benign on MR imaging (Table 1). In these cases no or late enhancement on the turbo FLASH, and either no enhancement at all or enhancement equal to that of the contralateral breast (symmetric enhancement) on the MP-RAGE sequence, was noted. The histologic diagnoses are presented in Table 2. Four cases of ductal carcinoma in situ (DCIS) from a total of 17 were occult on MR imaging. In addition, two invasive cancers were not identified. In one case, biopsy findings showed a mucinous carcinoma of 2 mm with an associated DCIS of 10 mm. The other case was an invasive lobular carcinoma (ILC) of 40 mm.

Discussion

The role of MR imaging in addition to mammography is based on its high sensitivity in tumor detection due to the consistent contrast enhancement of breast cancer. Harms et al. [12] claimed that all types of breast cancer enhance, that enhancement of the tumor is always stronger compared with normal breast tissue, and that lack of enhancement indicates a benign lesion or normal tissue. Even pre-invasive lesions, such as DCIS and lobular carcinoma in situ, showed stronger enhancement than normal glandular tissues in their series [12]. According to Heywang-Köbrunner the absence of contrast enhancement excludes malignancy with a high probability, but due to possible errors MR imaging is not used for differentiation of microcalcifications [13]. Kaiser stated that lack of significant enhancement ( > 500 NU) implies the presence of normal breast tissue [3].

Malignant tumors of the breast often show an increased capillary network with increased permeability, factors which contribute to the earlier and stronger contrast enhancement in breast malignancies [14].

In our series, of 145 histologically confirmed malignant tumors, 6 (4%) could not be recognized on gadolinium-enhanced MR imaging, because no abnormal enhancement was seen (Table 1). Four lesions proved to be a DCIS of which 3 were of the non-comedo (well-differentiated) type (for histologic subclassification of DCIS see [15]) with a diameter of 2.5, 10, and 90 mm, respectively, suggesting that tumor size alone is not responsible of these false-negative results. These three cases did not show increased enhancement on either the turbo FLASH or MP-RAGE, or the FLASH sequence, compared with normal tissue. However, another five cases of non-comedo DCIS did show enhancement within the threshold of 11.5 s on the turbo FLASH sequence with sizes of 10–70 mm in greatest diameter. Overall, only 62.5% of the non-comedo DCIS were recognized in this series.

Another case of MR occult DCIS was histologically a comedo (poorly differentiated) type of 50 mm. In this case the region of interest was very likely out of the chosen level of the turbo FLASH sequence. On the MP-RAGE sequence the lesion enhanced slightly more than the surrounding glandular tissue, but not enough to be considered as suspect for malignancy. Seven other patients with a poorly or intermediately differentiated DCIS did enhance significantly on both the tur-

| Table 1. Clinical and radiologic data in six MR-negative tumors. DCIS ductal carcinoma in situ |
|-----------------|-----------|-----------------|-----------|
| Tumor no. | Age (years) | Palpable | Mammography | US | Pathology |
| 1 | 52 | + | - | - | 2.5-mm non-comedo DCIS |
| 2 | 51 | - | + | - | 100-mm non-comedo DCIS |
| 3 | 65 | - | + | - | 10-mm non-comedo DCIS |
| 4 | 53 | - | + | - | 50-mm comedo DCIS |
| 5 | 54 | + | - | - | 40-mm invasive lobular carcinoma |
| 6 | 53 | - | + | 0 | 2.5-mm mucinous carcinoma with 10-mm non-comedo DCIS component |

| Table 2. Specification of MR-negative tumors according to histology. IDC invasive duct carcinoma; DCIS ductal carcinoma in situ; ILC invasive lobular carcinoma; TUB tubular carcinoma |
|-----------------|-----------|-----------|
| Histology | NR | False-negative |
| IDC | 91 | 1 (1%) |
| DCIS | 17 | 4 (23.5%) |
| ILC | 30 | 1 (3%) |
| MED | 6 | 0 |
| TUB | 2 | 0 |
Fig. 1a, b. A 53-year-old patient underwent a mastectomy of the left breast, 4 years before, for an invasive lobular carcinoma. On physical examination the right breast is firmer now. a Mammography showed a slightly distorted area in the retromamillary region (arrows) and US was normal. b An MR imaging examination showed enhancement on both the turbo FLASH and MP-RAGE sequence, but was interpreted as normal. Histology revealed a 40-mm invasive lobular carcinoma, non-tumor forming, with diffuse spread of tumor cells.

bo FLASH and the 3D MP-RAGE or FLASH sequence.

Guidi et al. suggest that different subtypes of DCIS show different patterns of stromal microvessels, and that especially the comedo DCIS has a diffuse increase in such microvessels [16]. Perhaps this is one of the reasons that the comedo DCIS generally shows more enhancement than the non-comedo type.

Harms et al. [12] reported on 57 patients with 42 malignancies, including all cases of DCIS, all showing significantly more enhancement than the normal tissue; however, the subtype of DCIS was not mentioned.

Gilles et al. also reported on a series of 26 cases of DCIS which all show early enhancement [7]. On the other hand, Greenstein Orel et al. [8] stated that small foci of DCIS are not visible on MR imaging. Heywang-Köbrunner [2] agrees with Allgayer et al. [17] in that MR imaging is not good in differentiating lesions with mammographic microcalcifications because both DCIS and proliferative dysplasia can be associated with microcalcifications and may both show abnormal enhancement.

In the patient with the false-negative MR findings of an invasive lobular carcinoma (ILC), the start of enhancement on the turbo FLASH sequence was not within the limit of 11.5 s, our threshold for malignancy (Fig. 1) [10]. On the 3D MP-RAGE sequence the degree of enhancement was regarded as normal. However, the contralateral breast had already been amputated and thus could not serve as reference. Histology revealed an ILC 40 mm in diameter. This tumor showed a peculiar histologic growth pattern in which tumor cells were diffusely spread through thin fibrous threads between normal fatty areas. Wilhelm et al. [9] also reported on a false-negative case of ILC of 20 mm with diffuse growth pattern. Gilles et al. [7] in a series of 64 breast malignancies described 2 cases of an ILC in which no early contrast enhancement was seen.
Finally, 1 case of invasive duct carcinoma (IDC) turned out to be false-negative (Fig. 2). In this case in a small area of 10 mm coarse granular microcalcifications were seen on the mammogram. Ultrasound was not performed. The unenhanced 3D MP-RAGE images showed a low-signal-intensity area corresponding to the area of microcalcifications on the mammography. On the turbo FLASH sequence an area of vague enhancement starting 18.4 s after the aortic enhancement was seen. Thus, the threshold of 11.5 s was exceeded. On the enhanced MP-RAGE sequence the other parts of both breasts showed signal intensity similar to that of the suspicious area. Histology revealed a 2-mm mucinous carcinoma associated with an area of non-comedo DCIS of 10 mm. This patient had voluminous breasts and the lesion was situated adjacent to the pectoral muscle. As the sensitivity of the coil decreases with increasing distance between the lesion and the coil, the sensitivity for this lesion was perhaps not sufficient in this patient [18].

In conclusion, our retrospective analysis of 145 histologically proven malignant tumors shows that despite optimal technique, not all of these tumors were revealed with MR imaging: 6 cases (4%) did not fulfill our main criterion of early enhancement on the turbo FLASH sequence. On the 3D MP-RAGE/FLASH sequence these lesions did not show any abnormal enhancement either. The highest prevalence of false-negative cases was in the group of DCIS: 23.5% were missed. The non-comedo DCIS cases were especially responsible for these diagnostic failures. In addition, also a case of ILC was missed. Although MR imaging plays an important role in the detection of breast cancers, primarily in high-risk patients, one should be aware of the fact that false-negative MR findings do occur in a small percentage of cases. In all but one of our MR-negative cases was the mammography suspected of showing malignancy. Mammography remains the main diagnostic technique for examination of the breasts. The MR imaging technique is of complementary value in better delineation of tumor size, in detecting additional malignant lesions, and in mammographically difficult, dense breasts [19].

References