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Original article

Prognostic value of contrast-enhanced MR mammography in patients with breast cancer

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Abstract. The objective of this study was to evaluate the prognostic value of contrast-enhanced MR mammography in patients with breast cancer. A total of 190 patients with breast cancer (37 noninvasive carcinomas, 153 invasive carcinomas) underwent dynamic contrast-enhanced MR mammography preoperatively. Using 1.5-T unit, T1-weighted sequences (2D FLASH) were obtained repeatedly one time before and five times after IV administration of 0.1 mmol gadopentetate-dimeglumine per kilogram body weight. The findings on MR imaging were correlated with histopathologically defined prognostic factors (histological type, tumor size, tumor grading, metastasis in lymph nodes). In addition, immunohistochemically defined prognostic factors (c-*erb*B-1,c-*erb*B-2, p53, Ki-67) were correlated with the signal increase on MR mammogram in 40 patients. There was no significant correlation between the findings on MR mammography and the histopathological type of carcinoma, the grading, and the lymphonodular status. Noninvasive carcinomas showed a higher rate of moderate (38%) or low (27%) enhancement on MR imaging than invasive carcinomas (6 and 3%). The results on MR mammography and the results of immunohistochemical stainings did not correlate significantly. Noninvasive carcinomas showed significantly lower enhancement than invasive carcinomas. However, the signal behavior of contrast-enhanced MR mammography is not related to established histopathological prognostic parameters as subtyping, grading, nodal status, and the expression of certain oncogenes/tumor suppressor genes.

Key words: Carcinoma of the breast – MR imaging – Prognostic factors – Histopathology – Immunohistochemistry

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Introduction

Contrast-enhanced MR imaging is being increasingly used as a complementary diagnostic modality in breast imaging of selected patients [1–4]. However, whereas conventional mammography and breast ultrasound demonstrate morphologic changes in cases of breast cancer, MR mammography depicts malignant findings by showing the pathologic vascularization of the carcinoma.

The aim of our study was to evaluate if the visible vascularization of carcinomas in MR mammography allows a prognosis of these tumors. We report on the relationship between results of MR imaging in malignant breast lesions and histopathologically as well as immunohistochemically defined prognostic factors.

Materials and methods

From January 1994 to December 1995, 190 consecutive patients with histopathologically verified breast carcinomas (37 noninvasive carcinomas, 153 invasive carcinomas) underwent contrast-enhanced dynamic MR mammography preoperatively. The MR imaging of the breast was performed on a 1.5-T unit (Magnetom SP 63, and Magnetom Vision, Siemens, Erlangen, Germany) with a dedicated bilateral breast surface coil. The complete breast was imaged six times, one before and five times after intravenous injection of 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany). Sequences were performed one after the other with a delay time of 3 s. The time interval for sequencing was 1.5, 3, 4.5, and 6 min after administration of contrast medium. A two-dimensional fast low-angle shot (FLASH) pulse sequence was used with a repetition time of 336 ms, an echo time of 5 ms, and a flip angle of 90°. This sequence yielded 32 transverse sections of 4-mm section thickness in 1 min, 27 s without gaps. The field of view (FOV) was 320 mm with a matrix of 256 × 256. The postprocessing procedure included the subtraction of the images of the

second measurement after contrast medium injection from the precontrast images. The semiquantitative analysis of the signal-to-time relation was performed with the region of interest (ROI) technique. The ROI (2–5 pixels) was placed in the tumor area with the strongest signal enhancement. The evaluation of images with identical slice positions using the cine mode was also performed during postprocessing in all patients. The initial signal increase of the tumor was evaluated during the first 3 min (the first and second sequencing) after contrast medium administration. Three groups of findings on MR mammography were defined:

1. Strong signal enhancement (initial signal increase > 50 % compared with signal before application of contrast media)
2. Moderate signal enhancement (initial signal increase from 10 to 50 % compared with signal before application of contrast media)
3. Low signal enhancement (initial signal increase < 10 % compared with signal before application of contrast media)

Surgically obtained, formaldehyde-fixed and paraffin-embedded tissue specimens were cut into 2-μm-thick serial sections and stained with hematoxylin and eosin. The evaluation contained:

1. The histopathological type of carcinoma (ductal, lobular, tubular, mucinous, medullary, papillary)
2. The invasion and the size of the tumor correlating to the UICC (pT_{is},pT_1,pT_2,pT_3/pT_4)
3. The tumor grading (G1, G2, G3)
4. The infiltration of axillary lymph nodes (negative/positive)

In addition, we performed different immunohistochemical reactions in 20 cases of noninvasive carcinomas (10 patients with strong enhancement, 10 patients with low enhancement), and another 20 patients with invasive carcinomas (10 patients with strong enhancement typical of malignancy, and 10 patients with moderate or low enhancement). The stainings were performed using formaldehyde-fixed, deparaffinized tissue sections to prove the following prognostic indicators: (a) c-*erb*B-1 [antibody: anti EGF-R1 antibody (Amersham International, U. K.)]; (b) oncogene c-*erb*B-2 (HER-2/neu; antibody: c-neu and 9G6, Oncogene Science, Uniondale, New York); (c) proliferation antigen Ki-67 (antibody: MIB1, Dianova GmbH, Hamburg, Germany); and (d) mutation-associated antigen p53 (antibody: Do-7, Dako, Glostrup, Denmark).

Red product of reaction was shown by APAAP technique in combination with newfuchsin. The immunohistochemical evaluation differentiated three groups: (a) positive staining in less than 1 % of the tumor cells per visual field; (b) positive staining in 1–25 % of the tumor cells per visual field; and (c) positive staining in more than 25 % of the tumor cells per visual field.

The statistical significance was evaluated with the student's *t*-test.

Table 1. Comparison of histopathological type of breast cancer with enhancement on dynamic MR mammography in 190 patients with breast cancer

Histopathological type	Enhancement on MR mammography		
	Strong	Moderate	Low
Ductal (in situ)	15	11	11
Ductal (invasive)	110	10	1
Lobular	12	2	1
Tubular	5	–	–
Mucinous	5	–	1
Medullar	4	–	–
Papillar	2	–	–

Table 2. Comparison of tumor invasion and tumor size, respectively, with enhancement on dynamic MR mammography in 190 patients with breast cancer

Invasion/size	Enhancement on MR mammography		
	Strong	Moderate	Low
Carcinoma in situ	15	11	11
pT1	93	7	3
pT2	29	3	–
pT3/4	16	2	–

Table 3. Comparison of tumor grading with enhancement in dynamic MR mammography in 190 patients with breast cancer

Grading	Enhancement on MR mammography		
	Strong	Moderate	Low
I	15	2	3
II	118	19	11
III	20	2	–

Results

The analysis of the signal behavior in contrast-enhanced MR mammography showed a strong signal enhancement in 153 patients (81 %) with breast cancer. Twenty-three patients (12 %) had a moderate signal increase, and enhancement was low in 14 patients (7 %).

The evaluation of the histopathological type demonstrated 158 cases with ductal (37 ductal carcinoma in situ and 121 invasive), 15 lobular, 5 tubular, 6 mucinous, 4 medullary, and 2 papillary carcinomas. There was no significant correlation between signal enhancement in MR mammography and histopathological type of cancer (Table 1). The rate of moderate or low enhancement was significantly higher in the group of noninvasive carcinomas as compared with the groups of invasive carcinomas ($p < 0.01$). However, there was no correlation between findings in MR mammography and tumor size for invasively growing carcinomas (Table 2). In the same way, tumor grading as well as the infiltration of axillary lymph nodes showed no significant correlation to the results of contrast-enhanced MR mammography (Tables 3, 4).

There was a moderate relationship between signal increase in MR mammography and the immunohis-

Table 4. Comparison of axillary lymph node metastases with enhancement in dynamic MR mammography in 153 patients with invasive breast cancer

Lymph nodes	Enhancement on MR mammography		
	Strong	Moderate	Low
Negative[a]	85	7	1
Positive	54	5	1

[a] Carcinoma in situ not included

Table 5. Comparison of immunohistochemical stainings with enhancement in dynamic MR mammography in 40 patients with breast cancer (10 patients with low signal enhancement, 10 patients with moderate signal enhancement, and 20 patients with strong signal enhancement)

Immunohistology	Enhancement on MR mammography		
	Low	Moderate	Strong
c-erb B-1			
Low	10	9	20
Moderate	0	1	0
Strong	0	0	0
c-erb B-2			
Low	10	10	20
Moderate	0	0	0
Strong	0	0	0
Ki 67			
Low	4	3	8
Moderate	5	4	5
Strong	1	3	7
p 53			
Low	9	10	18
Moderate	0	0	1
Strong	1	0	1

tochemical proof of the proliferation antigen Ki-67, but the correlation was statistically not significant. Neither the finding of the epidermal growth factor c-*erb*B-1, nor the overexpression of the oncogene c-*erb*B-2, demonstrated a correlation. The occurrence of the mutation-associated antigen p53 showed no statistically significant correlation to the signal behavior of breast cancer in MR mammography (Table 5).

Discussion

There is common agreement that different factors allow an estimation of tumor prognosis in patients with breast cancer. The size as well as the invasion of the tumor, the histological type, the grading, and especially the occurrence of metastasis in the axillary lymph nodes are important so-called classic prognostic factors [5, 6]. Noninvasive, intraductal tumor growth, high cell differentiation, and missing lymph node metastases are favorable conditions correlating with good prognosis. There are no reports about the correlation between these classic prognostic factors and the signal enhancement in contrast-enhanced dynamic MR imaging of the breast. Different authors report on a ductal carcinoma in situ which did not show contrast enhancement after administration of contrast medium [7, 8]. The presented study confirms these findings by significantly lower enhancement for noninvasive carcinomas as compared with invasive breast cancer. However, we found no correlation between classic prognostic factors in invasive carcinomas and contrast behavior in dynamic MR mammography. These results refer to the described protocol. They are probably valid also for other MR imaging protocols, although that is not proved in this study.

The number of publications about the value of immunohistochemically defined prognostic factors in breast cancer has increased rapidly in past years [9–12]. Different recently introduced antibodies and oncogenes have received considerable attention.

The family of c-*erb*B receptors is increasingly recognized as an important system that controls normal cell development. Unbalancing of this system frequently causes malignant transformation. The leading aberration is amplification and uncontrolled expression. Currently, the family comprises four related receptors: c-*erb*B-1, c-*erb*B-2, c-*erb*B-3, and c-*erb*B-4. c-*erb*B-1 (epidermal growth factor receptor, EGFR) was found to be an important variable for the clinical prognosis of lymph-node-negative tumors. A relationship between the presence of increased cellular levels of EGFR and short relapse-free intervals and overall survival of breast cancer patients has been demonstrated [9]. For some pre-invasive breast cancers as well as for progressed carcinomas it has been shown that c-*erb*B-2 induces more aggressive tumor behavior. In lymph-node-positive cases, amplification of c-*erb*B-2 is more important for relapse-free interval and survival than many other prognostic factors excluding axillary lymph node status [11, 13]. Considering the therapeutic potential of c-*erb*B-2 (HER-2/neu), it seems that c-*erb*B-2-specific regimes might have considerable therapeutic merits. In analogy to the EGFR system, an inverse relationship between the expression of estrogen and progesterone receptors and the level of c-*erb*B-2 protein has been demonstrated by different authors [14, 15]. A high rate of positive stained cells has been found in DCIS of comedo type, whereas infiltrating ductal carcinoma does not ususally overexpress c-*erb*B-2 [16]. There are controversial opinions about the prognostic value of c-*erb*B-2-encoded protein p185 in breast cancer [17]. Preliminary data indicate that the expression of c-erbB-3 correlates with breast cancer cell differentiation and with a better clinical prognosis [10]. However, the significance of c-*erb*B-3 expression for transformation and tumor progression remains to be elucidated.

Ki-67 antigen, detectable with the monoclonal antibody MIB1, appears to be a reliable marker of cell proliferation [12]. Weikel et al. found good correlation between Ki-67 and tumor grading [18]. They also described a strong correlation between the Ki score and the length of the disease-free period in patients with recurrent tumor [18]. Recent studies suggest that the p53 protein regulates the G_1-S phase transition of the cell cycle. Mutations of these genes are proving to be one of the most frequent genetic changes in a wide variety of

human malignancies [19]. Mutations of p53 and the resulting accumulation of the protein correlates with high proliferation, high histological grade, and absence of estrogen and progesterone receptors [20]. More recent reports suggest that p53 protein overexpression may represent an independant marker of poor prognosis in breast cancer [21].

Different authors have demonstrated the correlation between neovascularization in invasive breast carcinoma and the risk of metastasis [22, 23]. Therefore, the evaluation of tumor angiogenesis may prove valuable in patients with aggressive breast carcinoma [22]. Some authors observed a correlation between tumor angiogenesis and the signal increase in MR imaging of the breast; other authors did not [24, 25]. As the findings in dynamic contrast-enhanced MR mammography are based on tumor angiogenesis, further studies should determine whether they have prognostic significance independent of traditional prognostic parameters determined in this study.

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