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Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy

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Abstract The objective of the present study was to monitor response to preoperative chemotherapy with breast MRI in patients with large breast cancer. Fifty-eight women in whom core biopsy had confirmed the presence of breast carcinoma underwent breast MRI prior to beginning chemotherapy and before surgical excision. In 24 cases patients underwent one or two additional examinations during chemotherapy to monitor their progress. Breast MRI included both T2-weighted spin-echo sequences and T1-weighted gradient-echo sequences before and 1, 2, 3, and 8 min after bolus injection of gadolinium-DTPA. Tumor size and the dynamic contrast medium uptake patterns of the respective carcinomas were evaluated and compared with the final histology findings. Based on their MR tomographic findings (change in tumor size and intensity of contrast media uptake), patients were assigned to groups with non-response (NR), partial response (PR), and complete response (CR). Based on MR tomographic findings, there were 12 patients in the NR group, 34 in the PR group, and 12 in the CR group. In NR group contrast medium uptake tended to increase or show no more than minimal decrease. Diagnostic accuracy for assigning patients to the NR group was 83.3% and to the PR group 82.4%. In patients whose tumors showed only slight response to chemotherapy, breast MRI proved very reliable in determining the size of the lesions. In patients whose tumors displayed significant response and in the CR group, the size of the residual tumor was underestimated in 8 of 12 cases. In 66.7% of patients in the CR group histology revealed residual tumor masses in areas up to 5 cm in diameter. During chemotherapy, intensity of contrast medium uptake decreased in 88.2% of patients with PR and in all patients with CR. Reliable determination of response was possible within 6 weeks following the initiation of chemotherapy. Breast MRI is suitable as a monitoring method. The determination of residual tumor size is unreliable in carcinomas exhibiting significant response to chemotherapy which may lead to false-negative results. The method may be employed for monitoring response to chemotherapy after 6 weeks.

Keywords Breast neoplasms · MR imaging · Therapy

Introduction

The rationale of neo-adjuvant chemotherapy in cases of extensive breast carcinomas is to achieve downstaging of patients' malignancies. Studies have shown that this modality not only permits breast-conserving surgical therapy in many cases but also improves patients' prognosis [1, 2]. The purpose of therapy monitoring is to determine

whether and to what degree the tumor responds to chemotherapy. In addition, in cases of no or only partial response, the method should reliably visualize the size and location of the residual tumor in order to better plan the subsequent surgical therapy. Conventional modalities include palpation, diagnostic ultrasound, and mammography; reliable determination of tumor characteristics is problematic with all of these methods [3, 4, 5, 6]. The role of MRI in therapy monitoring of primary breast neoplasms has been addressed in only a few studies with small patient collectives [7, 8, 9, 10, 11, 12, 13].

The objective of the present study was to evaluate MR tomographic capabilities on a larger patient collective, taking into consideration the following questions: (a) MRI furnishes reliable information with regard to the degree of patients' response to therapy; (b) whether a reliable visualization of residual tumor is possible; and (c) beginning at which point after the initiation of chemotherapy does breast MRI for therapy monitoring becomes useful.

Materials and methods

A total of 63 patients (average age 51.4 years, age range 27–72 years), whose extensive mammary carcinomas were confirmed by core biopsy, were originally recruited for this study. Indications for neo-adjuvant chemotherapy included tumor size (at least stage T2), position, and/or histologic grading. During the study, 5 patients had to be excluded due to discovery of extensive disease metastasis. These patients did not undergo subsequent surgery. Their data are not included in the following evaluation.

Immediately prior to the first cycle of chemotherapy and then after the conclusion of chemotherapy, patients underwent breast MRI. The interval from breast MRI to surgery was 0–78 days (average 18.2 days). Neo-adjuvant chemotherapy in all patients consisted of three to five cycles of either a combination of anthracyclines and taxanes (epirubicine, 90 mg/m^2 or 60 mg/m^2 and paclitaxel 175–200 mg/m^2) or of anthracyclines and cyclophosphamide (600 mg/m^2) at intervals of 3–4 weeks. All patients were informed of the character of the study and gave their written consent.

Breast MRI for therapy monitoring was performed during the individual chemotherapy cycles in 24 patients, 14 of whom underwent one additional MR tomographic examination of the breast and 10 two examinations.

Breast MRI

Breast MRI was performed using a Magnetom Vision unit (Siemens, Erlangen, Germany) with a field strength of 1.5 T.

After informed consent had been obtained and contraindications excluded, patients were placed in the unit in prone position in order to minimize respiration artifacts. Examination of the breast was performed using commercially available bilateral breast surface coils.

Firstly, fast spin-echo (SE) T2-weighted images in axial projection were acquired [TE 90 ms, TR 5376 ms, 2 acquisitions, field of view (FOV) 350 mm, matrix 252×256, slice thickness 4 mm, acquisition time 6:32 min]. For the T1-weighted sequence and for the dynamic measurements, a gradient-recalled-echo (GRE) sequence [fast low-angle shot (FLASH) 3D, TE 5 ms, TR 11.8 ms, flip angle 30°] was utilized, first native, then at 1, 2, 3, and 8 min after intravenous application of 0.15 mmol/kg body weight of Gd-DTPA-injection (Magnevist, Schering, Berlin, Germany). Data acquisition began immediately upon starting injection. This 3D sequence was performed with 32 partitions, corresponding to an effective slice thickness of 4 mm. An FOV of 350 mm was selected. The measurement time of this sequence was 1 min.

The injection of contrast medium took place via a cubital vein (disposable catheter, 20 G) using the MR injector XD 7000 (Ulrich, Ulm, Germany) with a flow rate of 3 ml/sec. The injector is constructed of non-magnetic materials and works with air pressure. Injection is followed automatically by flushing with physiologic saline solution. Acquisition of data in the dynamic contrast medium series was begun immediately upon starting the injection.

All 192 slice images acquired (32 individual T2-weighted images, 160 individual T1-weighted images) were documented. Qualitative contrast medium uptake was evaluated using subtraction images, produced by subtracting the individual images of the native sequence from the images acquired at the same respective slice positions 3 min after contrast medium application. When a focal abnormal contrast medium uptake was detected on subtracted images, the increase in signal intensity over time ("mean curve") was calculated. For evaluation of the findings, dynamic measurements were used which yielded reproducible results after repeated measurements. The computer software programs required for the subtraction images and signal intensity/time curves are included in the standard software program of the Magnetom Vision. For the colored presentations of the pathologic findings, a software program developed in our own department was used. The investigational technique fulfilled the recommendations of the German Society for Radiology [14].

Morphologic criteria suggestive of malignancy on the T1-weighted images included the presence of skin thickening and contour irregularity (spiculated margins). On T2-weighted images the signal intensity of the tumor was compared with that of surrounding glandular tissue.

For comparison with data reported in the literature, the dynamic contrast medium behavior of the lesions was investigated [15, 16, 17, 18, 19]. The increase in signal intensity in percent during the first and second minutes after contrast medium application and at the maximum achieved intensity were compared with the native value for the lesion. An increase in signal intensity of more than 100% during the first 2 min and a signal intensity similar to the peak signal in the third and eighth minute ("plateau") or a minimal decrease in the late images ("washout") were determined to be suspicious for malignancy.

The MR tomographic findings were evaluated in consensus by two experienced examiners (A.R., H.-J.B.).

The size of the primary tumor was determined on the basis of pre-therapeutic MR tomographic findings, for which the largest measured diameter was used. Multifocal lesions were documented. In cases of extensive multifocal disease, the diameter of the entire affected breast volume was determined and defined as the tumor size.

Based on the findings of breast MRI obtained immediately prior to surgery, patients were classed according to the degree of documented size reduction into groups with no response (NR), partial response (PR), or complete response (CR). For this classification, MR images prior to chemotherapy were compared with those following chemotherapy. NR was defined as no measurable change in tumor size in postcontrast MR images following chemotherapy, and PR in cases with measurable tumor size reduction. CR was defined as a lack of contrast medium uptake in postcontrast MR images and a missing demarcation of tumor nodules in precontrast images following chemotherapy.

In those cases in which additional MR tomographic examinations were performed during chemotherapy for therapy monitoring, measurements of tumor size were also taken.

The contrast medium dynamics of the respective tumors in all available breast MR images were determined and the individual groups compared.

The findings were compared with the final histology results. In particular, correlation was sought between the individual tumor type or the type of chemotherapy and the results of breast MRI.

The specificity, positive predictive value, negative predictive value, and/or the accuracy including confidence intervals were calculated for the individual groups.

Results

Based on the respective MR tomographic findings, 12 patients were assigned to the non-response (NR) group, 34 to the partial-response (PR) group, and 12 to the complete response (CR) group. A definite correlation between the cytostatic regimen or histologic tumor type and patients' response to therapy could not be demonstrated. The MR tomographic diagnosis were based on the pre- and postcontrast T1-weighted images. The T2-weigthted images did not lead to relevant results.

Non-responders

Non-responders included 9 patients with invasive ductal carcinoma, two with lobular carcinomas, and one with mucous carcinoma. In 3 cases ductal carcinomas were multifocal. One patient with a lobular carcinoma also exhibited an additional invasive lobular carcinoma of the contralateral breast. The histologically determined tumor size (in multifocal carcinomas, the total tumor volume) ranged from 1.5 to 8.0 cm (average 4.7 cm) and, with the exception of 2 cases, corresponded to the findings of breast MRI obtained either prior to chemotherapy or immediately prior to surgery (Fig. 1). In 2 patients, MR tomographic findings overestimated tumor size. In these cases, tumor diameters both prior to chemotherapy and prior to surgery were determined to be 5.0 and 7.0 cm, respectively. At histologic examination, they were, in fact, only 2.0 and 3.5 cm in diameter, respectively. This resulted in the patients' incorrect assignment to the NR group, although, in reality, there had been a partial response to chemotherapy. The interval between the last MR tomographic examination and surgery was 13 and 16 days, respectively. No additional chemotherapy cycle was interposed in this period. Because the average interval in the other patients between last breast MRI and surgery was even longer (19.6 days, range 0–33 days), findings in these two cases were considered false positive; thus, 10 patients were correctly assigned to the NR group, whereas two others were false positive and were assigned to the NR group instead of the PR group. The calculated positive predictive value and accuracy stand at 83.3% (CI 51.6–97.9%).

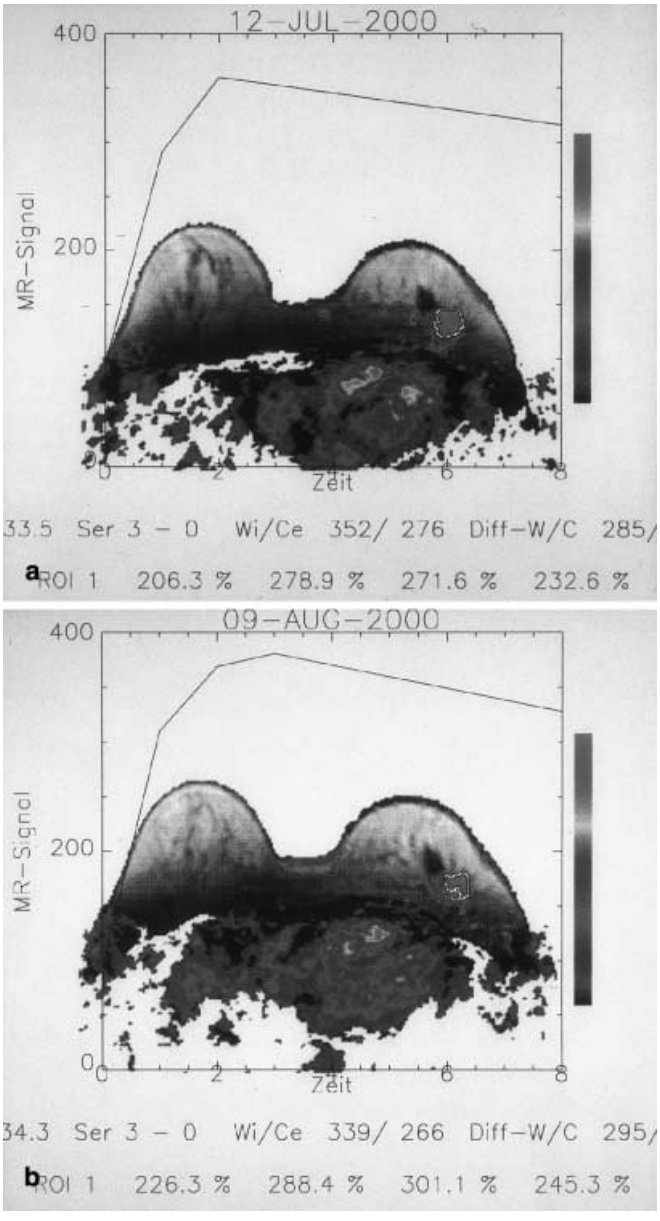

Fig. 1 **a** A 60-year-old patient with invasive ductal carcinoma of the left breast: breast MRI findings prior to neo-adjuvant chemotherapy show typical contrast medium dynamics. There was a maximum increase in signal intensity of 278.9%. **b** The same patient as in **a**. The breast MRI subsequent to chemotherapy shows neither tumor regression nor any noticeable changes in contrast medium dynamics. The patient was therefore assigned to the non-responder group. The MRM findings were confirmed at histology

Patients with partial response

In the group with MR tomographic findings of partial response (PR; *n*=34), histologic examination revealed invasive ductal carcinomas in 27 patients, invasive lobular carcinomas in 4 patients, and 1 case each of mucous carcinoma, ductulolobular carcinoma, and ductal carcinoma

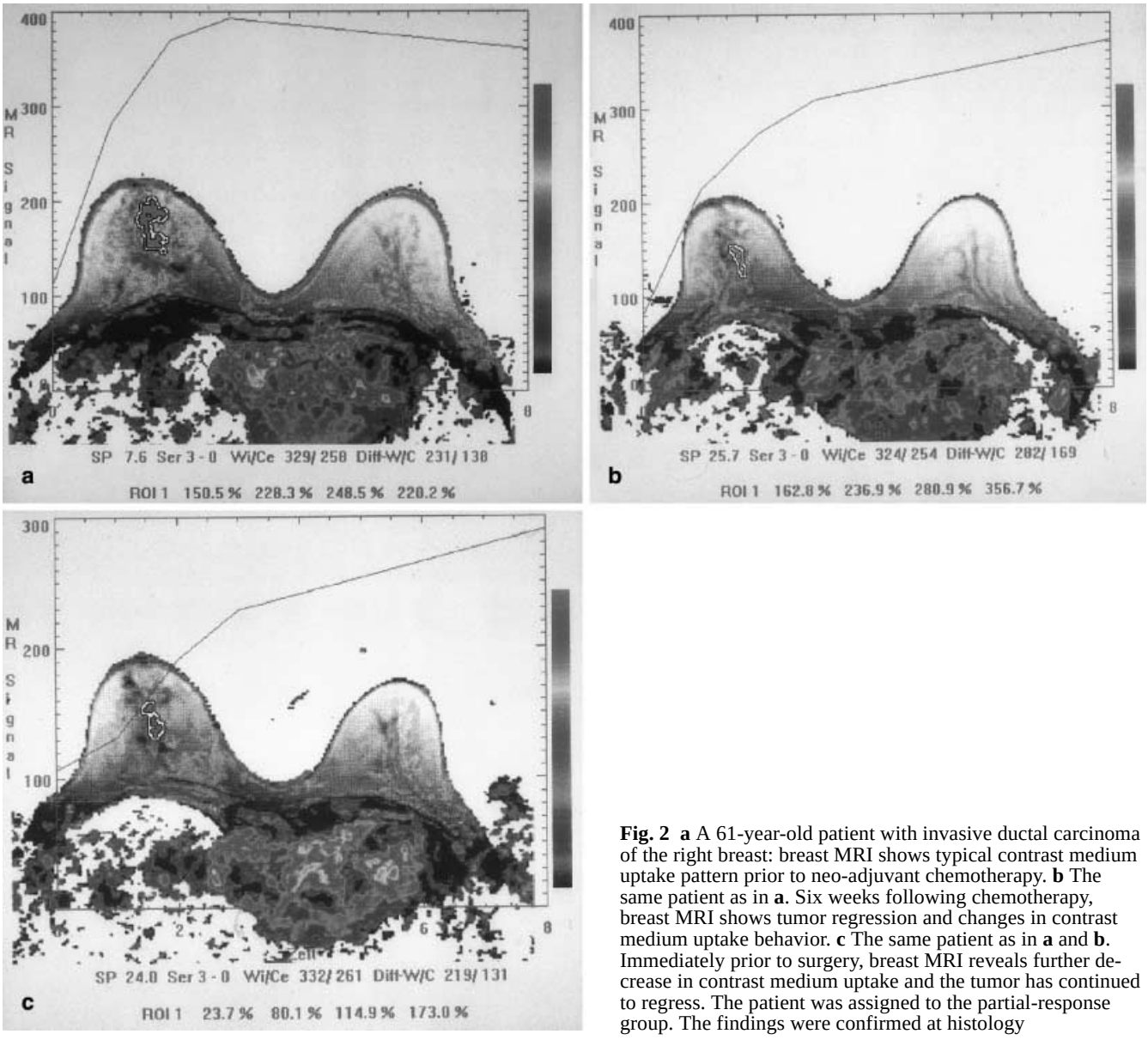

Fig. 2 **a** A 61-year-old patient with invasive ductal carcinoma of the right breast: breast MRI shows typical contrast medium uptake pattern prior to neo-adjuvant chemotherapy. **b** The same patient as in **a**. Six weeks following chemotherapy, breast MRI shows tumor regression and changes in contrast medium uptake behavior. **c** The same patient as in **a** and **b**. Immediately prior to surgery, breast MRI reveals further decrease in contrast medium uptake and the tumor has continued to regress. The patient was assigned to the partial-response group. The findings were confirmed at histology

in situ. Three of the ductal carcinomas were bifocal, whereas eight of the ductal and two of the lobular carcinomas were multifocal. Tumor size at the time of final surgery following completed chemotherapy ranged from 0.0 to 10.0 cm (average 2.8 cm). In only 5 patients did the tumor size measured at breast MRI agree with the findings of histology (Fig. 2). In 19 patients, breast MRI overestimated the actual tumor size by 0.2–3.0 cm (average 1.1 cm). The interval between patients' last MR tomographic examination in surgery averaged 19.7 days (range 1–78 days). In two of these patients histologic examination performed 15 and 40 days, respectively, after breast MRI failed to reveal malignant cells. Tumor sizes as determined by breast MRI had been 0.3 and 2.5 cm, respectively. Based on histology, both of these patients should have been assigned to the CR group; hence, MR tomographic findings in both cases were considered false positive. In 10 other patients (29.4%), tumor size was underestimated by 0.3–4.0 cm (average 1.8 cm). Histologically, these tumors included seven invasive ductal and three invasive lobular carcinomas. Of note is the fact that the size of the three lobular carcinomas was significantly underestimated (range 2.5–4.0 cm, average 3.3 cm). Histology revealed that four of these ten carcinomas had shown no response to chemotherapy and should therefore have been included in the NR group, re-

sulting in four false-negative MR tomographic findings. In 24 of 34 cases, there was only slight reduction in size (<2 cm), whereas in the remaining 10 cases, the size reduction due to chemotherapy was more pronounced. Of carcinomas showing minimal response to chemotherapy, only a small proportion (5 of 24 cases, 20.8%) were underestimated by breast MRI with regard to their size reduction. Among tumors that underwent significant size reduction as a result of chemotherapy, breast MRI underestimated the size of the residual tumor in 50% of cases.

In summary, right classification as PR was done in 28 cases.

Considering the four false-negative and two false-positive findings, breast MRI's specificity stood at 93.3% (CI 79.8–99.3%), its negative predictive value at 87.5% (CI 71.8–96.6%) and its accuracy at 82.4% (CI 68.1–94.9%).

Patients with complete response

In 12 patients, breast MRI following completion of chemotherapy failed to reveal any evidence of residual tumor. Two of these carcinomas were visualized as multifocal lesions at pre-therapy breast MRI. In 1 patient, breast MRI returned findings suggestive of bilateral lesions: This diagnosis was subsequently confirmed by core biopsy. Findings of pre-chemotherapy biopsies included 7 invasive ductal carcinomas, 3 invasive lobular carcinomas, 1 ductolobular, and 1 undifferentiated carcinoma. Results of the post-surgical histologic examination in 4 patients with pre-operatively confirmed invasive ductal carcinomas revealed no residual tumor, thus confirming the findings of breast MRI. In three other patients (one invasive lobular carcinoma, one ductolobular carcinoma, and one ductal carcinoma), post-operative histology revealed residual disseminated tumor in volumes of 3.0, 4.0, and 5.0 cm, respectively. In the remaining 5 patients, histology found areas of active residual tumor 1.0–2.1 cm in diameter (Fig. 3). Histologic types included one undifferentiated carcinoma, two invasive lobular carcinomas, and two invasive ductal carcinomas. In one of these patients with invasive lobular carcinoma, the involved area was still 5.1 cm in diameter. In summary, right classification as CR (no residual tumor in histology) was done in 4 of 12 cases. The resulting rate of false-negative findings at breast MRI thus stood at 66.6%, with a corresponding negative predictive value of 33.3% (CI 9.9–65.1%). Excluding those cases in which only disseminated residual tumor was present, the negative predictive value stands at 58.3% (CI 27.7–84.8%).

In summary, evaluation of data from the total collective of 58 patients with regard to determination using breast MRI of the qualitative response to therapy shows a specificity of 96.3% (CI 88.1–98.6%), a negative predictive value of 92.9% (CI 83.3–98.1%), and a diagnostic accuracy of 89.7% (78.8–96.1%). When the degree of patients' response is quantified (assignment to groups NR, PR, or CR), we see a sensitivity of only 41.7% (CI 28.6–55.1%), due primarily to the incorrect assignment of patients to the CR group. Based on these data, the specificity of the method was calculated at 88.9% (CI 76.7–95.0%), the positive predictive value at 71.4%

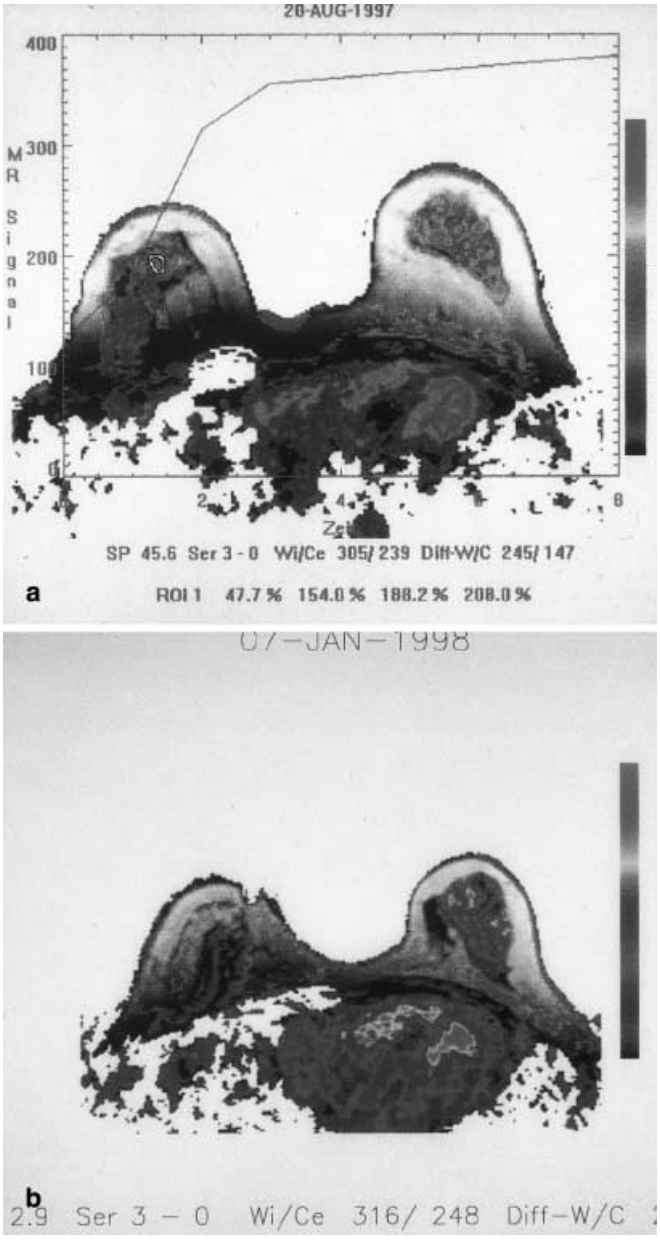

Fig. 3 **a** A 56-year-old patient with invasive lobular carcinoma of the right breast: initial breast MRI findings prior to neo-adjuvant chemotherapy. **b** The same patient as in **a**. Immediately prior to surgery, there is no longer recognizable tumor at breast MRI; hence, the patient was assigned to the complete-response group. Histology revealed an invasive lobular carcinoma 2.1 cm in diameter

Table 1 Qualitative and quantitative evaluation of response with breast MRI (all findings have a histologic correlation. *rn* right negative; *rp* right positive; *fn* false negative; *fp* false positive; *NPV* negative predictive value; *PPV* positive predictive value; *NR* non-response; *PR* partial response; *CR* complete response

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Response yes/no (*n*=58)	–	96.3	92.9	–	89.7
Assessment: NR/PR/CR (*n*=58)	41.7	88.9	72.7	71.4	72.4
NR (*n*=12; 10 rp,2 fp)	100	0	0	83.3	83.3
PR (*n*=34, 28 rn, 4 fn, 2fp)	0	93.3	87.5	0	82.4
CR (*n*=12, 4 rn, 8 fn)	0	100	33.3/58.3	0	33.3

(CI 57.3–81.9%), the negative predictive value at 72.7% (CI 59.1–83.3%), and the diagnostic accuracy at 72.4% (CI 59.1–83.3%; Table 1).

Contrast medium dynamics

Additional MR tomographic examinations were performed during chemotherapy in 24 patients. Fourteen patients underwent one additional MR tomographic examination between the individual chemotherapy cycles, whereas 10 other patients underwent two extra examinations. Six of these patients belonged to the NR group, 16 to the PR group, and 2 to the CR group.

Non-responders

In 8 of 12 carcinomas (66.7%), there was increased contrast medium uptake following chemotherapy. Comparing the maximum values for signal intensity before chemotherapy and after completion of the last chemotherapy cycle, there was an increase in signal intensity ranging from +3.6 to +69.3% (average: +36.1%) after therapy. In the remaining five tumors, there was a percent decrease of –15.2 to –6.6% (average –9.8%). When the data for all 12 of these patients were considered together, the average increase was +17.0% (range –15.2 to +69.3%).

Patients with partial response

Contrast medium uptake decreased in 30 of 34 patients (88.2%) during chemotherapy. The maximum percent increase in signal intensity declined by an average –28.5% (range –74.4 to 6.3%) in the group of patients with PR. In the subcollective of 4 patients with increased contrast medium uptake during chemotherapy, the corresponding value was +12.6% (range +5.1 to +23.5%). It is of note that all four tumors exhibiting increased contrast medium uptake underwent only minor size reduction in comparison with the other carcinomas in this group. The decrease in signal intensity did not correlate with the degree of response to chemotherapy.

MRM monitoring of chemotherapy

In the non-responders, there was a change in contrast medium uptake dynamics as early as 3–6 weeks (average 5.6 weeks) following the initiation of chemotherapy, i.e. as early as after the first chemotherapy cycle. In five of six tumors, there was an increase in maximum signal intensity of +0.9 to +49.9% (average +18.7%). Signal intensities continued to increase during the course of chemotherapy at subsequent MR tomographic examinations. In the sixth patient, there was a decrease in signal intensity of –9.1% 6 weeks after beginning chemotherapy. Signal intensities remained constant at subsequent examinations.

In patients belonging to the PR or CR groups, 11 of 18 patients exhibited a decrease in signal intensities of –65.2 to –10.7% (average –28.2%) 3–8 weeks (average 5.9 weeks) after beginning chemotherapy. Contrast medium uptake in all of these tumors continued to decline during patients' subsequent clinical course (Fig. 2). In the remaining seven7 patients, there was an initial increase in signal intensity of +0.6 to +73.1% (average +12.0%) 2–5 weeks (average 3.1 weeks) after beginning chemotherapy. Subsequent examinations, however, showed a decrease in contrast medium uptake.

Discussion

Because of the continuing refinement in surgical techniques, breast-conserving surgery is successful in approximately 70% of all mammary carcinomas. The goal of neo-adjuvant chemotherapy is the pre-operative size reduction of lesions so that even those patients with primary large mammary carcinomas may profit from these new techniques. It has been recently shown that the proportion of breast-conserving procedures can be increased by the use of neo-adjuvant chemotherapy. For example, Minckwitz et al. report an increase from 36 to 59% [1, 2]. Neo-adjuvant chemotherapy also offers the possibility of testing the effectiveness of cytostatic substances in vivo and of modifying the regimen in cases of non-response. In general, this would appear to improve patients' prognosis [1, 2].

The rationale behind therapy monitoring is to evaluate patients' response to treatment. In cases of marked size decrease, the tumor bed can be adequately marked so that it can be re-identified during subsequent surgery. Monitoring should also permit reliable evaluation of the residual tumor in order to plan the most appropriate surgical technique [3]. This should also be of benefit in optimizing the final cosmetic result [1].

These clinical demands are only partially satisfied by conventional methods such as palpation, mammography, and ultrasound. In addition, a review of the literature reveals contradictory statements regarding the individual techniques [1, 4, 5, 6, 21, 22]. All three methods may over- or underestimate residual tumor size and the findings of the individual methods may not correlate with one another [1, 4, 5, 6, 20, 21, 22]. In a study by Herrada et al., patients' final histology results correlated with the findings of palpation in only 47% of cases, with those of ultrasound in 66.3%, and with those of conventional mammography in 49.4% [22].

The evaluation of complete response is not reliably possible with any of the conventional methods [1, 3, 5, 22]. Histologic findings of complete response correlate with palpation, ultrasound, or mammography in only 13–25% of cases [1, 5, 22]. In a study by Mumtaz et al., all patients in whom clinical criteria indicated complete response were found at histology to have residual tumor up to 6.5 cm in diameter [23]. Because the increasing application of breast-conserving surgery and autologous reconstructions makes exact pre-operative planning crucial, the unreliability of conventional diagnostic procedures in evaluating therapy response are unsatisfactory.

Publications discussing breast MRI's role as a method for monitoring patients' response to breast MRI have only recently appeared in the international literature [7, 8, 9, 10, 11, 12, 13]. The earliest study was published by Gilles et al. in 1994 [7]. Based on a collective of 25 patients, these authors showed that breast MRI visualizes residual tumor tissue after chemotherapy [7]. In a study by Abraham et al., findings of breast MRI and histology regarding residual tumor correlated in 97% of the 39 patients studied [8]; thus, breast MRI proved superior to conventional methods with regard to this question [8].

The findings of the present study confirm on the basis of a larger patient collective the results of our previous work [10]. We can state, in principle, that breast MRI has the potential for use as a method for therapy monitoring because MRI permits evaluation of qualitative response to therapy. This was possible in the present study with a specificity of 96.3% and a negative predictive value of 89.7%.

In addition, the present study investigated whether breast MRI also permits a correct quantitative evaluation of residual tumor. Based on breast MRI findings, patients were assigned to the NR, PR, and CR groups and their breast MRI data were compared with those of post-surgical histology.

The MR tomographic identification of non-responders was relatively reliable. However, two patients were incorrectly assigned to the NR group on the basis of MR tomographic findings, although histology showed that there had been a partial response to therapy; thus, the positive predictive value stands at 83.3%. Because there was an interval of 13 and 16 days, respectively, between breast MRI and surgery in these patients, it is possible, in principle, that these tumors underwent regression during this interval. On the other hand, it is possible that there was a real overestimating of the extent of tumor in these 2 cases, the possible explanation(s) for which are not explained by patients' histology.

In addition, tumor regression was diagnosed in two other patients in our collective, although histology demonstrated that they should correctly have been classified as non-responders. One possible explanation may relate to changes in vascularity occurring in response to chemotherapy which appear as a size reduction at breast MRI. To date, no corresponding experiences have been published in the literature.

In patients with partial response, the reliability of MR tomographic determination of residual tumor appears to depend on the degree to which the tumor responds to chemotherapy. Size determination was most reliable in those tumors with only moderate response to chemotherapy.

The greater the degree to which a tumor responded to chemotherapy, the more unreliable was the size determination of the residual tumor with breast MRI. These issues were not addressed in previous studies [7, 8, 9, 11, 12, 13]. In 55.9% of the PR group, breast MRI overestimated residual tumor size by an average 1.1 cm. As in the two cases in the NR group mentioned above, there was no readily available histologic explanation for this phenomenon. Potential over-estimations of the extent of tumor, however, have also been reported for the conventional diagnostic methods [1, 4, 6, 20, 21].

The MR tomographic determination of complete response proved particularly problematic. The proportion of false-negative findings in our collective stood at 66.7%. This means that, in two-thirds of patients in whom breast MRI failed to visualize the presence of tumor, histology returned evidence of residual tumor. These tumors consisted not only of disseminated areas of malignant tissue but also of invasive tumor nodules up to 1 cm in diameter in volumes of residual tumor up to 5.1 cm in diameter. Hence, MR tomographic capability for correctly diagnosing complete response would appear to be severely restricted.

We found lobular carcinomas in 16.7% in the NR group, in 11.7% in the PR group, and in 25% in the CR group. The residual tumor was underestimated in 7 of 9 patients with lobular carcinomas in the whole study population. An explanation for these results may be the fact that the contrast medium uptake of lobular carcinomas leads more frequently to false-negative results than in

carcinomas with other histologic type. This phenomenon may be increased by chemotherapy.

Similar erroneous MR tomographic findings were reported both in previous studies and in our own previous work [7, 8, 9, 10]. Still unclear are the actual consequences of such false-negative findings. Gilles and coworkers are of the opinion that the failure to visualize small residual tumors does not represent a relevant disadvantage for the method because the absence of macroscopically visualized residual tumor with volumes in excess of 1 cm^3 is associated with a positive effect on patients' rate of recurrence and overall survival [7]. Whether this optimistic appraisal can be maintained in the future is questionable. Firstly, the lack of tumor visualization with diagnostic imaging methods makes it impossible to set an excisional volume for the surgeon, with the resulting possibility that the remaining tumor may not be excised in its entirety. This may also make histological evaluation of the pathological margins difficult. A recent publication by Park et al. has shown that the recurrence rate and patients' prognosis correlates with their pathologic margin status [24]. As a consequence, it seems advisable to determine the extent of the tumor region as precisely as possible. The failure of breast MRI to visualize residual malignant tissue or its underestimation of the size of the residual tumor may therefore have a potentially negative impact on these patients' prognosis.

Careful observation of changes in contrast medium uptake patterns may be very useful in evaluating patients' response to therapy. As already discussed in our previous paper, contrast medium uptake in the NR group tends to increase during chemotherapy or decrease only slightly, whereas in both the PR and CR groups, one observes a progressing decline in contrast medium uptake patterns [10]. Changes in contrast medium dynamics associated with chemotherapy have also been reported by other authors [9, 11, 12, 13]. There was, however, a certain degree of overlapping in the present study in the individual findings returned for non- and partial responders, so that a correlation between the change in contrast medium uptake and patients' degree of response to chemotherapy cannot necessarily be assumed. In the subcollective of 24 patients, in whom MR tomographic examinations obtained during chemotherapy provided added data for therapy monitoring, MR tomographic findings were quite reliable for determination of whether a given tumor was responding to chemotherapy. These findings underscore the suitability of breast MRI for therapy monitoring in patients receiving chemotherapy [10, 11]. It appears important, however, that therapy monitoring start no earlier than the sixth week following initiation of chemotherapy. From this point, response to chemotherapy was reliably evaluated in all patients of this subcollective. In our patients, this was immediately prior to beginning the second chemotherapy cycle. If the MR tomographic examination was performed at an earlier time, however, there were findings of increased contrast medium uptake, even in partial responders. This phenomenon has not, to date, been discussed in the literature.

If these results are confirmed, MR tomographic findings may be useful in identifying non-responders who may then profit from a prompt modification of their neoadjuvant chemotherapeutic regimen. In the PR and CR groups, it may be possible to use MR tomographic data for the placement of clips to assure a reliable intra-operative identification of the tumor bed.

Thus, while breast MRI is subject to certain limitations with regard to a quantitative evaluation of the degree of patients' response to therapy, it remains, with a specificity of 88.9%, a good method for therapy monitoring.

At our present state of knowledge, it appears that factors such as tumor vascularization and permeability of the vascular wall are responsible for the contrast medium dynamics visualized by breast MRI [10, 11]. Cytostatic agents affect both of these factors; hence, the observed changes in contrast medium dynamics may be easily explained. Assuming that tumor angiogenesis has an immediate effect on the response to neo-adjuvant chemotherapy and that the degree of tumor response correlates with patients' prognoses, one could conceivably expect a correlation between the observed changes in contrast medium dynamics and the prognosis [25]. No studies published to date have addressed this issue. Furthermore, MR tomographic findings exert no relevant influence on the therapeutic management of the individual patient.

Whether positron emission tomography (PET) scanning may prove a more satisfactory solution to the problems discussed above remains to be seen. Because of the known changes in glucose uptake occurring in tumors during chemotherapy, it is conceivable that PET scanning may also prove capable of providing data regarding therapy response [26, 27]. Whether the method can reliably determine the size of the residual tumor remains unanswered.

In conclusion, breast MRI is suitable in principle for monitoring the progress of neo-adjuvant chemotherapy. The method is highly reliable for identification of carcinomas in non-responders and in those with only partial response to chemotherapy and for determining the size of such lesions. Breast MRI tends to underestimate the size of tumors that respond well to chemotherapy. More problematic are those instances in which breast MRI fails to identify tumors; thus, even extensive areas of residual tumor may escape detection with the method.

In non-responders, there is either an increase or only slight decrease in contrast medium uptake during chemotherapy. In partial and complete responders, however, contrast medium uptake declines continuously. Beginning in the sixth week following initiation of chemotherapy, findings of breast MRI may reliably indicate a possible response of the tumor to treatment. Whether these changes in contrast medium dynamics correlate with these patients' prognoses must be investigated in further studies.

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