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CLINICAL TRIAL

Who may benefit from preoperative breast MRI? A single-center analysis of 1102 consecutive patients with primary breast cancer

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Abstract Several authors question the potential benefit of preoperative magnetic resonance imaging (MRI) against the background of possible overdiagnosis, false-positive findings, and unnecessary resections in patients with newly diagnosed breast cancer. In order to reveal a better selection of patients who should undergo preoperative MRI after histological confirmed breast cancer, the present analysis was implemented. We aimed to evaluate the influence of preoperative breast MRI in patients with newly diagnosed breast cancer to find subgroups of patients that are most likely to benefit from preoperative MRI by the detection of occult malignant foci. A total of 1102 consecutive patients who underwent treatment for primary breast cancer between 2002 and 2013 were retrospectively analyzed. All patients underwent triple assessment by breast ultrasound, mammography, and bilateral breast MRI. MRI findings not seen on conventional imaging that suggested additional malignant disease was found in 344 cases (31.2 %). Histological confirmed malignant foci were found in 223 patients (20.2 %) within the index breast and in 28 patients (2.5 %) in the contralateral breast. The rate of false-negative biopsies was 31 (2.8 %) and 62 (5.6 %), respectively. Premenopausal women ($p = 0.024$), lobular invasive breast cancer ($p = 0.02$) as well as patients with high breast density [American College of Radiology (ACR) 3 + 4; $p = 0.01$] were significantly associated with additional malignant foci in the index breast. Multivariate analysis confirmed lobular histology ($p = 0.041$) as well as the co-factors "premenopausal stage" and "high breast density (ACR 3+4)" ($p = 0.044$) to be independently significant. Previous studies revealed that breast MRI is a reliable tool for predicting tumor extension as well as for the detection of additional ipsilateral and contralateral tumor foci in histological confirmed breast cancer. In the present study, we demonstrate that especially premenopausal patients with high breast density as well as patients with lobular histology seem to profit from preoperative MRI.

Keywords Breast cancer · MRI · Surgery · Preoperative management

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Introduction

Magnetic resonance imaging (MRI) of the breast has been shown to be the most sensitive technique for the detection of breast malignancies [1–3]. Numerous studies confirmed the superiority of breast MRI compared to conventional breast imaging by mammography and sonography, with an emphasis on cancer screening in women with elevated familial breast cancer risk [4–7].

Previous studies revealed that breast MRI is a reliable tool for predicting tumor extension as well as for the detection of

additional ipsilateral and contralateral tumor foci in histological confirmed breast cancer. Current data suggest that MRI is able to detect occult additional tumor foci in up to 37 % of patients [8–10]. This is also true for the contralateral breast, with detection rates of additional lesions in up to 5.5 % that would have been missed in conventional imaging [11, 12]. The detection of additional occult tumor foci may influence the therapeutic strategy by performing wider excisions, mastectomies instead of breast-conserving therapy (BCT) in cases of multicentric disease or excision of lesions in the contralateral breast that would have been overseen in conventional imaging. The goal of the planned surgery in all of these cases is to achieve tumor-free margins (R0) after surgery. It is matter of fact that spread of invasive tumor occurs also in some distance from the index tumor, and remaining tumor cells may develop into recurrent disease with unfavorable prognosis [13–15]. In this context, a meta-analysis by Clarke et al. demonstrated that for every four avoided local recurrences, about one breast cancer death over the next 15 years might be prevented [16]. Thus, precise planning of surgery and accurate removal of tumor foci is of outmost importance.

Nevertheless, the role of routine preoperative MRI in patients with newly diagnosed breast cancer is still under ongoing discussions. The improved sensitivity of preoperative breast MRI compared to conventional imaging by sonography and mammography results in more aggressive surgery [17, 18]. Nevertheless, low recurrence rates may be achieved by conventional imaging today. Some critics emphasize the risk of overdiagnosis, overtherapy, treatment delays, rising costs, and finally the efficiency of adjuvant treatment to devitalize any occult tumor foci [19–21]. Contrarily, data of long-term prospective trials are still missing, answering the question regarding disease-free survival and overall survival, based on MRI detection, in respect of occult tumors in the ipsilateral and contralateral breast. In the plurality of patients, the use of preoperative MRI causes costs without giving further information due to identical results compared to conventional imaging by ultrasound and mammography [1, 9]. Recently, Pengel et al. and Fortune-Greeley et al. stated that the use of preoperative MRI should be selective and only used in patients with a maximum likelihood of additional information [22, 23].

In order to reveal a better selection of patients who should undergo preoperative MRI after histological confirmed breast cancer, the present analysis was implemented. We aimed to evaluate the influence of preoperative breast MRI in patients with newly diagnosed breast cancer in order to find subgroups of patients that are (1) most likely to benefit from preoperative MRI by the detection of occult malignant foci and (2) detect patients with a low probability of differing results on conventional imaging.

Patients and methods

A total of 1102 consecutive patients who underwent treatment for primary invasive breast cancer or DCIS between 2002 and 2013 at the Breast Cancer Center at the University of Bonn Medical Center were retrospectively analyzed. Data on tumor and patient characteristics were obtained from the original histopathologic and clinical reports.

Eligibility criteria

All patients with primary breast cancer, who underwent bilateral MRI of the breast in addition to conventional assessment by clinical breast examination, high-frequency physician performed sonography and bilateral mammography with a minimum of two views, were eligible for this study. All patients underwent surgery after the staging (BCT or mastectomy combined with sentinel lymphonodectomy or conventional axillary lymph node dissection). For all patients, a complete pathological workup was available.

Mammography and sonography

Conventional mammography was performed according to national guidelines. At least two views per breast were obtained. Further views or spot magnification were performed at the discretion of the interpreting radiologist. Films from external institutions were used if their quality was considered adequate and in accordance with national guidelines. Ultrasonography and Doppler ultrasonography studies were performed by either a gynecologist or a radiologist and according to previously reported standards [8]. Mammograms and ultrasound were interpreted in accordance with the guidelines of the American College of Radiology (ACR), and parenchymal density was recorded based on the breast imaging reporting and data system (BIRADS) [24].

Magnetic resonance imaging

Imaging of both entire breasts was performed at the Department of Radiology using a standard dynamic axial contrast-enhanced subtracted breast MRI. All MRI examinations were performed on a 1.5-T system (INTERA; Philips Best, the Netherlands) and reviewed by two radiologists. Breast MRI was performed with a 512,400 imaging matrix before and four times after intravenous injections of 0.1 mmol/kg bodyweight gadopentetate dimenglumine, with a maximum of 20 ml (Magnevist; Schering, Berlin, Germany). MRI diagnosis was documented by use of a five-point scoring system identical to

the mammographic scoring categories of the ACR BIRADS. Further explanation of our MRI procedure and imaging technique has been reported previously [8].

Statistics

Analysis was performed with SPSS 18.0. A p value ≤ 0.05 was considered as statistically significant.

Results

The patient's and tumor characteristics of the current study are summarized in Table 1. The median age at diagnosis was 55 years (range 23–84). Data on the breast density are shown in Table 2. The share of patients with a low dense breast parenchyma (ACR 1 + 2) and high dense breast parenchyma (ACR 3 + 4) was almost the same: 563 (51.1 %) versus 539 (48.9 %).

Table 1 Patient's and tumor characteristics ($n = 1102$)

Characteristics	$n = 1102$	%
Premenopausal	427	38.7
Postmenopausal	675	61.3
Ductal carcinoma in situ (DCIS)	180	16.3
Ductal invasive (NST)	636	57.7
Lobular invasive	157	14.2
Medullary invasive	36	3.3
Tubular invasive	22	2.0
Papillary invasive	7	0.6
Mixed type	64	5.8
pTis	180	16.3
pT1	607	55.1
pT2	245	22.2
pT3	43	3.9
pT4	27	2.5
Nx	242	22.0
pN0	540	49.0
pN1	202	18.3
pN2	74	6.7
pN3	44	4.0
M0	1054	95.6
M1	48	4.4
G1	103	9.3
G2	598	54.3
G3	401	36.4
ER negative	199	18.1
ER positive	903	81.9
PR negative	261	23.7
PR positive	841	76.3
Her2/neu negative	926	84.0
Her2/neu positive	176	16.0

MRI findings not seen on conventional imaging by mammography and sonography were found in 344 cases (31.2 %). In 766 cases (69.5 %), MRI did not result in additional findings compared to conventional imaging. In 8 patients (0.7 %), MRI only findings were present in the index and contralateral breast. In patients with additional findings in MRI, a second look ultrasound was performed. In cases with reproducible findings, biopsies were performed under ultrasound guidance. In all other cases, MR-guided biopsies were performed. Further histological confirmed malignant foci within the index breast were found in 223 patients (20.2 %). In 31 cases (2.8 %), additional biopsies were due to false-positive MRI results and could have been omitted.

In univariate analysis, premenopausal women ($p = 0.024$), lobular invasive histology ($p = 0.02$) as well as patients with high breast density (ACR 3 + 4; $p = 0.01$) were significantly associated with an additional diagnostic yield (Table 3). Multivariate analysis by logistic regression also confirmed lobular histology ($p = 0.041$) as well as the co-factors "premenopausal stage" and "high breast density (ACR 3+4)" ($p = 0.044$) to be independently significant. Factors like age, tumor size, lymph node status, and receptor status had no significant association with a higher rate of MRI-detected lesions.

Contralateral breast cancer was detected by MRI in 28 patients (2.5 %). False-positive MRI results within the contralateral breast were found in 62 cases (5.6 %). Due to the low number of cases and no statistical power, contralateral disease was not the focus of the current study and therefore not included in the further statistical analysis.

Discussion

The role of routine preoperative MRI is still under ongoing discussions due to possible overdiagnosis, false-positive findings and unnecessary resections in patients with newly diagnosed breast cancer. The aim of the present study was to reveal subgroups of patients who should undergo preoperative MRI after histological confirmed breast cancer due to an additional diagnostic yield of this procedure. A total of 1102 patients with newly diagnosed breast cancer have been analyzed. All patients underwent triple assessment by sonography, mammography, and bilateral breast MRI prior to surgery. In 31.2 % ($n = 344$), MRI revealed findings that were not seen in conventional imaging by sonography and mammography. A supposed positive benefit of preoperative MRI due to additional occult foci that would have been overseen in conventional imaging has been found in 223 patients (20.2 %). These findings

Table 2 Breast density in association with menopausal stage ($n = 1102$)

Breast density	$n = 1102$ (%)	Premenopausal $n = 427$ (%)	Postmenopausal $n = 675$ (%)
ACR 1	74 (6.7)	11 (2.6)	63 (9.3)
ACR 2	489 (44.4)	135 (31.6)	354 (52.4)
ACR 3	449 (40.7)	225 (52.7)	224 (33.2)
ACR 4	90 (8.2)	56 (13.1)	34 (5.0)

resulted in more precise treatment planning prior to surgery. These results are in concordance with previous studies [8–10].

Mainly premenopausal women present with more dense fibro-glandular breast tissue compared to postmenopausal women. Thus, radiologic assessment in young patients and women with high breast density (ACR 3 + 4) is challenging by conventional imaging procedures. The superiority of MRI in these patients has been previously demonstrated in several studies [1, 7, 25]. A recent study by Pengel et al. suggests that younger age and high breast density (ACR 3 + 4) are associated with a high likelihood that preoperative MRI does lead to further findings [23]. This was especially true for patients with a discrepancy in tumor diameter at sonography and mammography. In the present analysis, premenopausal stage ($p = 0.024$) and high breast density (ACR 3 + 4; $p = 0.01$) were independent factors and demonstrated an significant association between preoperative MRI and patients with the highest probability of having additional malignant foci in the index breast that resulted in a presumably favorable change of treatment. Multivariate analysis also showed that "premenopausal stage" and "high breast density (ACR 3+4)" are significant co-factors ($p = 0.044$) with a higher chance of additional findings in preoperative MRI.

Imaging of invasive lobular carcinoma is more challenging than other types of breast cancer due to its unique pathologic growth pattern [26]. The present study demonstrated a significant yield of additional malignant findings in patients with lobular invasive histology in univariate analysis ($p = 0.02$) as well as in multivariate analysis ($p = 0.041$). Previous studies with much smaller sets of patients (Pengel et al.: $n = 685$, McGhan et al.: $n = 70$ and Heil et al.: $n = 92$) also described the potential benefit of preoperative MRI in patients with lobular carcinoma [23, 27, 28]. Mann et al. also concluded that preoperative MRI in patients with lobular invasive carcinoma may reduce repeated excision rates without increasing the rate of mastectomies [29]. MRI allows precise treatment planning and accurate removal of tumor foci, which is of outmost importance regarding re-operation rates [30]. Approximately, one-fourth of all patients who undergo initial BCT for breast cancer will have a subsequent follow-up operation with consecutive health care costs and related morbidities [31]. In this context, further studies have to reveal the cost–value ratio of additional preoperative breast MRI compared to the treatment expenses for additional surgery due to imprecise treatment planning.

In the current analysis, 427 women (38.7 %) were premenopausal, 157 patients (14.2 %) had a lobular invasive histology, and in 539 cases (48.9 %) patients had a high density of the breast (ACR 3 + 4). Performing preoperative breast MRI only in patients with the highest probability for a positive change of management, MRI may have been omitted in 351 patients (31.9 %). Limiting preoperative MRI only to patients with the highest benefit of this diagnostic procedure may also result in a reduction of health care costs.

The false-positive rate in the current analysis was only 2.8 % resulting in 31 additional biopsies due to false-positive MRI results. Still, the issue of unnecessary intervention and extensive surgery remains a problem [19, 20]. One reason for a high rate of additional lesions might be indebted to an observer bias, since the radiologist knows the patients' history of histological proven breast cancer and the associated likelihood of additional lesions. Some studies suggest there is a higher false-positive rate if the patient history is known [32, 33]. The false-positive rate might be lowered by involvement of a further (blinded) observer and a strict use of preoperative biopsies in uncertain findings. Nevertheless, we highly recommend to perform preoperative biopsies of every additional finding and not to perform mastectomies or contralateral surgery only after radiologic assessment by MRI.

National and international guidelines as well as the European Society of Breast Cancer Specialists (EUSOMA) recommend the use of preoperative MRI for selected patients with primary breast cancer (multifocal disease, lobular carcinoma, high breast density, large DCIS, and occult primary tumor) [34–38]. Nevertheless, a general consensus is still missing and most critics are waiting for the results of prospective trials. As a result of modern adjuvant oncologic treatment, very low recurrence rates after breast cancer surgery and excellent long-term outcomes may be achieved. Therefore, prospective studies designed to demonstrate a significant difference in progression-free survival or overall survival due to additional preoperative MRI would need extremely large numbers of patients as well as a very long follow-up and may therefore be very difficult to perform [9, 19]. In this context, we

Table 3 Additional diagnostic yield of breast MRI in the index breast ($n = 1102$)

Characteristics	No influence due to similar results ($n = 848$[a])		Additional malignant foci ($n = 223$)		False-positive MRI ($n = 31$)		p value
	n	%	n	%	n	%	
Age							
≤55	421	75.3	126	22.5	12	2.1	0.076
>55	427	78.6	97	17.9	19	3.5	
Menopause							
Premenopausal	317	74.2	102	**23.9**	8	1.9	**0.024**
Postmenopausal	531	78.7	121	17.9	23	3.4	
Morphology							
Non-invasive	141	78.3	36	20.0	3	1.7	0.587
Invasive	707	76.7	187	20.3	28	3.0	
T-stage							
pTis	141	78.3	36	20.0	3	1.7	0.072
pT1	470	77.4	115	18.9	22	3.6	
pT2	188	76.7	51	20.8	6	2.4	
pT3	26	60.5	17	39.5	0	0	
pT4	23	85.2	4	14.8	0	0	
N-stages							
Nx	207	80.9	45	17.6	4	1.6	0.159
N0	398	75.7	107	20.3	21	4.0	
N1	243	75.9	71	22.2	6	1.9	
M-status							
M0	823	77.0	215	0.1	31	2.9	0.54
M1	25	75.8	8	4.2	0	0	
Tumor grades							
G1	84	82.4	15	14.7	3	2.9	0.086
G2	452	75.7	122	20.4	23	3.9	
G3	312	77.4	86	21.3	5	1.2	
Histology							
DCIS	141	78.3	36	20.0	3	1.7	0.54
Non-specific type (NST)	499	78.5	120	18.9	17	2.7	
Lobular invasive	110	70.1	40	25.5	7	4.5	
Mixed type	47	73.4	15	23.4	2	3.1	
Others	51	78.5	12	18.5	2	3.1	
Lobular cancers							
Lobular cancer	110	70.1	40	**25.5**	7	4.5	**0.02**
Non-lobular	738	78.1	183	19.4	24	2.5	
ER							
Negative	163	81.9	33	16.6	3	1.5	0.146
Positive	685	75.9	190	21.0	28	3.1	
PR							
Negative	205	78.5	50	19.2	6	2.3	0.729
Positive	643	76.5	173	20.6	25	3.0	
Her2/neu							
Negative	712	84.0	184	19.9	30	3.2	0.126
Positive	136	16.0	39	22.2	1	0.6	
Breast density (ACR)							
1 + 2	454	80.6	94	16.7	15	2.7	**0.01**
3 + 4	394	73.1	129	**23.9**	16	3.0	

Bold letters indicate significance

[a] Contralateral cases have been included for statistical reasons

recommend to perform prospective trials only in defined subgroup of patients with the highest chance of additional lesions in preoperative MRI. As shown in the present analysis, such a stratified study design would lead to an increased rate of additional malignant findings and is therefore cost effective and feasible within an acceptable time frame. Such studies may also reveal if BCT is feasible in multicentric disease, if small additional foci have only been confirmed by preoperative MRI.

Meanwhile, we need to rely on well-conducted retrospective analyses to define subgroups of patients with the highest chance of a benefit due to preoperative MRI. The current study is one of the largest single-center analysis yet performed on preoperative MRI in primary breast cancer. Here we describe the highest probability of additional information and a consecutive presumably favorable change of management due to preoperative MRI in premenopausal women with high breast density (ACR 3 + 4) as well as patients with lobular invasive histology. As described before, these factors also get support by numerous previous studies. Thus, we recommend that premenopausal stage, lobular invasive carcinoma as well as high breast density (ACR 3 + 4) should be embedded in clearly defined guidelines for the use of preoperative MRI in patients with confirmed primary breast cancer.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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