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BREAST

Which factors influence MRI-pathology concordance of tumour size measurements in breast cancer?

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Abstract

Objectives To assess MRI-pathology concordance and factors influencing tumour size measurement in breast cancer.

Materials and methods MRI tumour size (greatest diameter in anatomical planes (MRI-In-Plane) and greatest diameter along main tumour axis (MRI-MPR)) of 115 consecutive breast lesions (59 invasive lobular carcinoma, 46 invasive ductal carcinoma, and 10 ductal carcinoma in situ) was retrospectively compared to size measured at histopathology (pT size (Path-TNM) and greatest tumour diameter as relevant for excision (Path-Diameter; reference standard)). Histopathological tumour types, preoperative palpability, surgical management, additional high-risk lesions, and BI-RADS lesion type (mass versus non-mass enhancements) were assessed as possible influencing factors.

Results Systematic errors were most pronounced between MRI-MPR and Path-TNM (7.1 mm, limits of agreement (LoA) [-21.7; 35.9]), and were lowest between MRI-In-Plane and Path-Diameter (0.2 mm, LoA [-19.7; 20.1]). Concordance rate of MRI-In-Plane with Path-Diameter was 86 % (97/113), overestimation 9 % (10/113) and underestimation 5 % (6/113); BI-RADS mass lesions were overestimated in 7 % (6/81) versus 41 % (13/32) for non-mass enhancements. On multivariate analysis only BI-RADS lesion type significantly influenced MRI-pathology concordance ($p<0.001$). 2/59 (3 %) ILC did not enhance.

Conclusion Concordance rate varies according to the execution of MRI and histopathological measurements. Beyond this only non-mass enhancement significantly predicted discordance.

Key Points

- *Execution and scope of MRI and histopathological size measurements influence concordance rate.*
- *Non-mass like enhancement predicts discordance.*
- *Additional high-risk lesions in proximity of tumour do not cause measurement discordance.*
- *Low percentage of ILC do not enhance at all.*

Keywords Breast neoplasms · Magnetic resonance imaging · Pathology clinical · Carcinoma lobular · Carcinoma ductal breast

Abbreviations

IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
DCIS	Ductal carcinoma in situ
LoA	Limits of agreement
MIP	Maximum intensity projection
MRI-In-Plane	Greatest diameter in anatomical planes on MRI
MRI-MPR	Greatest diameter along main tumour axis on MRI
MPR	Multiplanar reconstruction
Path-TNM	pT-stage size according to TNM at histopathology
Path-Diameter	Greatest tumour diameter as relevant for excision at histopathology

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Introduction

Overestimation of tumour size and false positive findings are known problems in the use of routine pre-operative magnetic resonance imaging (MRI) [1, 2]. The exact reasons for overestimation of tumour size by MRI are not fully understood. Some authors [3, 4] found that the presence of high-risk lesions and proliferative disease cause MRI overestimation. Less known is the risk of underestimating tumour size at histological examination due to specimen sectioning in an inadequate tumour axis [1]. Furthermore, MRI tumour extent is a pre-surgical size, which indicates to the surgeon the volume of tissue to be removed, whereas histological tumour size as measured for TNM staging is a measure of tumour load and, therefore, a prognostic indicator [1, 5]. In cases of invasive unifocality, the tumour measured on MRI corresponds to tumour size at pathology. MRI tumour extent may include both invasive and non-invasive components [1]. In contrast to this, the TNM tumour size is defined as the size of the invasive lesions only [5]. In case of multifocality, the TNM tumour stage is defined according to the size of the largest invasive lesion. However, pre-surgical MRI lesion enhancement may include invasive and non-invasive tumours, as well as multifocal invasive tumours interconnected by non-invasive tumours and non-malignant cells.

Invasive lobular carcinoma (ILC) is the second most common histological type of breast carcinoma after invasive ductal carcinoma (IDC). Characteristically, ILCs are only loosely cohesive and infiltrate the stroma in single cell file strands along mammary ducts, producing little desmoplastic response [6–8]. Probably due to the diffuse infiltrative growth pattern, ILC poses problems for diagnosis and assessment of tumour extent in mammography, ultrasound, and histology [8, 9]. Various authors [8, 10–13] have proposed MRI for the preoperative assessment of ILC. Most studies addressing the accuracy of MRI for establishing the tumour extent in ILC are based on a small numbes of women, and report overestimation rates are of up to 34 % [10, 11, 14–18].

The purpose of this retrospective analysis is to evaluate the influence of different MRI and histopathological tumour size measurements, as well as other possible influencing factors (histopathological tumour types, preoperative palpability, surgical management, additional high-risk lesions, and BI-RADS lesion type) on MRI-pathology concordance for measuring tumour extent in breast carcinoma.

Materials and methods

Study design

This study retrospectively analyzed maximum diameter measurements of 115 consecutive biopsy-confirmed malignant breast lesions (59 invasive lobular carcinoma, 46 invasive ductal carcinoma and ten ductal carcinoma in situ) that underwent MRI between January 2007 and February 2011 within 6 weeks (mean 7 days, standard deviation (SD) 7) prior to surgery. All patients did not receive pre-MRI or preoperative systemic therapy. Two out of 59 (3 %) ILC lesions did not enhance after contrast medium application and were excluded for size comparison.

Patients

The local internal review board approved this retrospective study and waived informed consent. The average age of the 109 patients was 58 years (SD 10). We retrieved data from medical records.

MRI and size measurements

All studies were performed on a 1.5 T clinical MR system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany) using a dedicated double breast coil with patients in prone position. Morphologic sequences were fast spin echo in coronal slice orientation and inversion recovery in transversal orientation. A dynamic T1-weighted gradient echo sequence (3D fast low-angle shot sequence; TR=4.32 ms, TE=1.39 ms, FA=12°, matrix size 512×512, FOV 380×380 mm^2, slice thickness 2 mm, middle of k-space 18.6 s; ten successive measurements each of 55 s measurement time; total acquisition time 9 min 11 s; automatic administration of paramagnetic contrast agent (gadopentetate dimeglumine, 0.2 mmol/kg body weight after 55 s; flow rate 2 mL/s followed by injection of a 20 mL saline flush at the same injection speed) was performed. Standard subtraction images and time-resolved transversal maximum intensity projection (MIP) of the subtraction images of both breasts were created. The dynamic MR imaging was followed by a high resolution, transversal fat-suppressed T1-weighted gradient echo sequence.(TR=10.7 ms, TE=2.12 ms, FA=25°, matrix size 512×352, FOV 320×260 mm^2, slice thickness 0.8 mm, acquisition time 3:29 min).

Maximum diameter measurements were assessed by two examiners in accordance. Examiners were blinded for the entire medical record including histopathology findings. MIP images of various view angles were used for orientation of how the tumour lay in three-dimensional space. All post-contrast sequences were reviewed. In most cases the second subtraction after contrast administration was used for size measurement. Cases that showed slow or continuous enhancement were analyzed in the sequence that showed maximum contrast uptake – either on the following subtracted sequences or the high-resolution, fat suppressed sequence. Tumour size was established using the diameter of mass and/or non-mass enhancements.

We performed two different measurements on MRI: (1) MRI-In-Plane and (2) MRI-MPR. MRI-In-Plane was measured in the anatomical planes (transverse, sagittal, and coronal plane), which are oriented relative to the long axis of the body. MRI-MPR is a measurement of the longest axis in three-dimensional space (Fig. 1) established using the manufacturer's multiplanar reconstruction tool. We used MRI-MPR for assessment of possible additional factors influencing MRI-pathology concordance.

Pathology review and size measurements

All histological examinations were performed in-house, according to generally accepted histological standards [19]. Palpable tumours were sliced in the long axis of the tumour. Tumour size was measured at the level of the largest diameter. Specimens with non-palpable tumours or mastectomies were sliced either from the nipple towards the pectoral wall or from medial to lateral and tumour size was measured as the sum of slices containing tumour. We noted two different histopathological tumour sizes: (1) Path-TNM and (2) Path-Diameter. Path-TNM refers to the tumour size used for TNM staging. In multifocal cases this corresponds to the size of the largest invasive focus. Path-Diameter includes all invasive foci, DCIS, and interconnecting non-malignant cells, as would be relevant for surgical excision (Fig. 2). Path-Diameter was established by one pathologist (20 years of experience in breast pathology) and was considered the reference standard for MRI accuracy assessment and evaluation of influencing factors. We followed the pathology codes of the BI-RADS® Fourth edition [20]. Grading for invasive carcinoma was performed according to Elston and Ellis [21] and for DCIS according to the grading part of the Van Nuys classification [22].

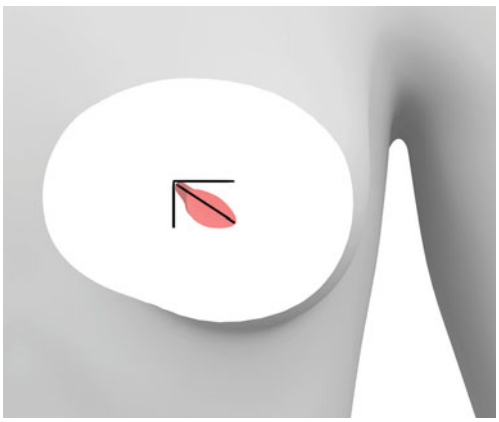

Fig. 1 Comparison between size measurements in anatomical planes and along main tumour axis. The size along the main tumour axis is the largest

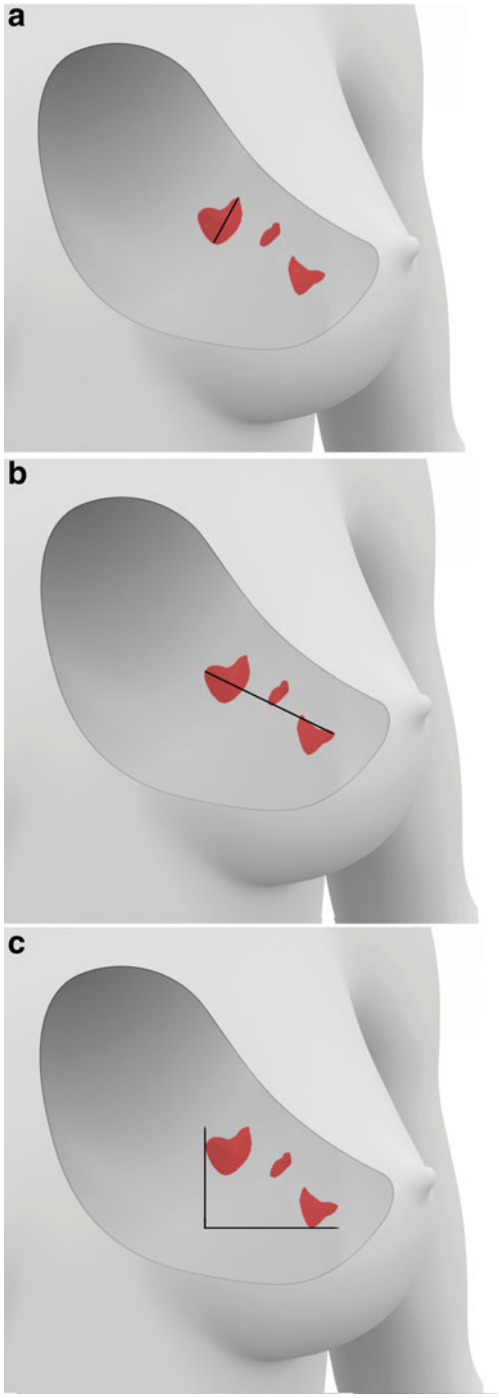

Fig. 2 Histopathological tumour size measurements in case of multifocal lesions. **a**) Path-TNM, **b**) Path.Diameter, **c**) Possible underestimation of Path-Diameter in case tumour is not palpable or is a mastectomy specimen

Surgical management

Standard practice at our institution is to achieve negative margins of at least one millimeter (mm) including invasive and ductal carcinoma in situ components if present. Otherwise, re-excision was performed. The performance of breast-

conserving surgery depended on the expected cosmetic result after surgery, radio-oncological considerations, and patients' wishes, rather than on tumour size per se or the presence of multiple foci.

Statistical analysis

For statistical analysis, the software packages SPSS (SPSS 20, Chicago, USA), Excel 2000 (Microsoft, Redmond, USA) and R (The R Project for Statistical Computing, www.r-project.org, version 3.1.1) were used. For descriptive statistics mean +/- SD was used. Tumour size measurements on imaging within 10 mm of histopathological measurement were considered concordant; otherwise they were termed over- or underestimated. Dependency of concordance and over- and underestimation rates on different factors were analyzed using the generalized Fisher's exact test for r x c tables.

Agreement between measurement techniques and their dependence on influencing factors were illustrated using Bland-Altman plots. The 95 %-Limits of agreement (LoA) between different size measuring techniques were given as the mean difference plus or minus 2 SD. The mean difference estimate is the systematic difference between two measurement methods and the 95 %-LoA gives an interval within which 95 % of the differences will lie inside. To determine factors influencing the accuracy of MRI, a multivariate linear regression analysis was performed with the difference between MRI-MPR and Path-Diameter as the dependent variable. *P*-values less than 0.05 were considered statistically significant.

Results

Tumour size and agreement of different MRI and histopathological methods

The average tumour size on MRI measured by MRI-In-Plane (25.7±20.3 mm) was smaller than MRI-MPR (29.0± 24.0 mm). On histopathology Path-TNM (19.4±14.7 mm) was smaller than Path-Diameter (25.5±23.1 mm).

Systematic differences and LoA of the different MRI and histopathological measurement techniques are listed in Table 1. Systematic errors were most pronounced between MRI-MPR and Path-TNM with an average difference of + 7.1 mm, and least pronounced between MRI-In-Plane compared to Path-Diameter with + 0.2 mm. The largest variation between the methods was observed between MRI-MPR and Path-TNM as indicated by the widest LoA, ranging from -21.7 mm to 35.9 mm. The two MRI measurements achieved the lowest variation with LoA from -8.6 mm to 15.2 mm.

Table 1 Systematic errors and limits of agreement between MRI and histopathological measurements of tumour size in breast cancer

	Mean difference (mm)	Limits of agreement
MRI-MPR vs. MRI-In-Plane	3.3	[-8.6, 15.2]
MRI-MPR vs. Path-Diameter	3.5	[-17.3, 24.3]
MRI-MPR vs. Path-TNM	7.1	[-21.7, 35.9]
MRI-In-Plane vs. Path-Diameter	0.2	[-19.7, 20.1]
MRI-In-Plane vs. Path-TNM	4.2	[-21.2, 29.6]
Path-Diameter vs. Path-TNM	3.2	[-17.8, 24.2]

MRI-pathology concordance

When comparing MRI with Path-Diameter, the rate of discordance in general and of overestimation in particular was higher for MRI-MPR than MRI-In-Plane (Table 2). Upon examination of factors influencing concordance of MRI-MPR with Path-Diameter, a significant difference was found between ILC, IDC and DCIS in terms of MRI-pathology concordance (p=0.048). Size on MRI (based on MRI-MPR) was concordant with Path-Diameter in 49/57 of ILC (86 %), versus 35/46 IDC (76 %), and 5/10 DCIS (50 %). DCIS was underestimated in 2/10 (20 %) and overestimated in 3/10 (30 %) of cases. No significant difference in MRI-pathology concordance could be found between cases that were palpable and cases that were not (p=0.62). Cases undergoing lumpectomy were more often concordant (64/76; 84 %) than cases undergoing mastectomy (25/37; 68 %, p=0.04). There was no significant difference in MRI-pathology concordance between cases according to whether or not negative margins were achieved after first surgery (first successful excision) (p= 0.08). Cases with high-risk lesions were overestimated less frequently (3/37; 8 %) than cases without high-risk lesions (16/76; 21 %). However, these results did not reach statistical significance (p=0.18). A significant difference in MRI-pathology concordance could be found between mass lesions and non-mass enhancements (p<0.001). We found the size of masses on MRI-MPR to be concordant with Path-Diameter in

Table 2 MRI-pathology concordance based on Path-Diameter as reference standard

	MRI-In-Plane		MRI-MPR	
	n=113	%	n=113	%
Overall				
Underestimated	6/113	5	5/113	4
Concordant	97/113	86	89/113	79
Overestimated	10/113	9	19/113	17

74/81 cases (91 %), underestimated in 1/81 cases (1 %) and overestimated in 6/81 cases (7 %), whereas non-mass enhancements were concordant in only 15/32 cases (47 %), underestimated in 4/32 cases (12.5 %) and overestimated in 13/32 cases (41 %). Based on MRI-In-Plane, the overestimation rate of mass lesions was 3/81 (4 %) versus 7/32 (22 %) with non-mass enhancements. On MRI, 43/57 ILC (75 %) enhanced as masses and 14/57 ILC (24.5 %) presented as non-mass enhancements. Of IDC, 35/46 (76 %) enhanced as masses and 11/46 (24 %) were non-mass enhancements. In addition, 3/10 DCIS (30 %) were masses and 7/10 (70 %) were non-mass enhancements. There were 16 multifocal cases (9 ILC, 7 IDC), of which 8 (5 ILC, 3 IDC) presented as single non-mass enhancements on MRI.

Factors influencing tumour size measurement (MRI-MPR versus Path-Diameter)

Bland-Altman plots between MRI-MPR versus Path-Diameter regarding possible influencing factors are shown in Fig. 3. On multivariate analysis only the BI-RADS lesion type (mass versus non-mass enhancements had a significant impact

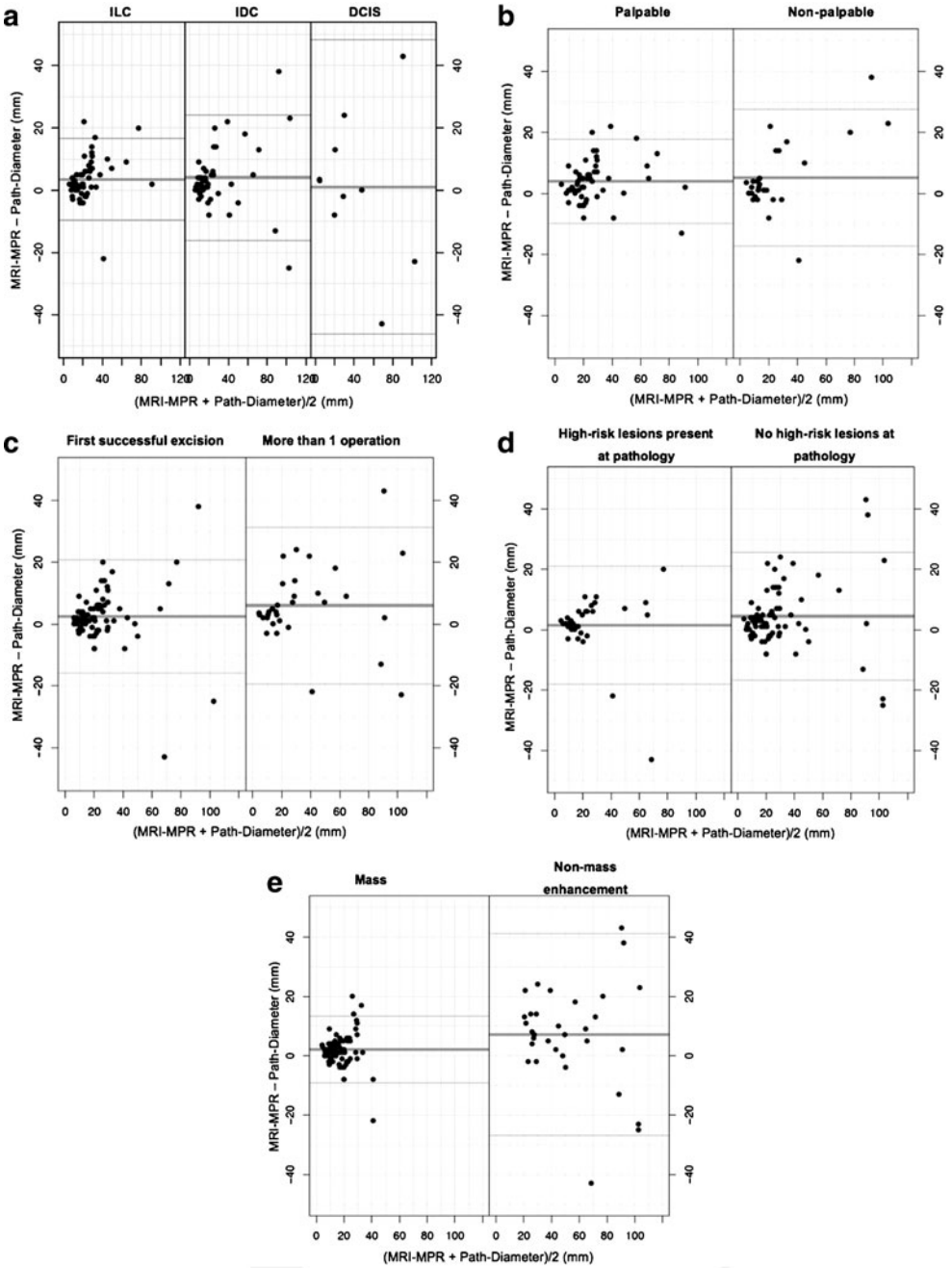

Fig. 3 Bland Altman Plots illustrating the difference between MRI measurement (MRI-MPR) and size at pathology (Path-Diameter), according to **a**) histopathological tumour type, **b**) palpability, **c**) surgical management, **d**) presence of high risk lesions, and **e**) lesion type

Table 3 Multivariate analysis of possible factors influencing MRI-histopathology concordance based on Path-Diameter with MRI-MPR comparison

Factor	Estimate (95 %-CI)	*p*-value
First Successful Excision	−0.37 (−4.53, 3.79)	0.86
Lesion Type		<0.001
Mass	Reference	
Non-mass enhancement	9.41 (5.25, 13.56)	
Lesion palpable	−1.31 (−4.83, 2.21)	0.47
Histopathological type		0.1
ILC	Reference	
IDC	1.61 (−1.87, 5.09)	
DCIS	−6.24 (−13.46, 0.99)	

on MRI-pathology concordance ($p<0.001$) (Table 3). An example of a mass and non-mass enhancement is shown in Figs. 4 and 5.

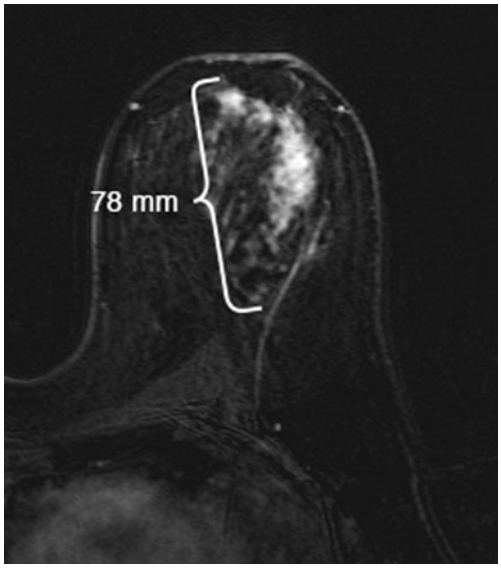

Fig. 5 MRI of non-mass enhancement of a 58-year-old patient with IDC with surrounding DCIS. The non-mass enhancement measures 78 mm along the main tumour axis on MRI (MRI-MPR) and 65 mm along the greatest diameter at histopathology (Path-Diameter)

Discussion

Our results show that MRI-In-Plane had a better concordance rate with Path-Diameter than MRI-MPR, with concordance in 86 %, overestimation in 9 %, and underestimation in 5 % of cases. Comparing MRI-In-Plane with Path-Diameter also showed the smallest systematic error (0.2 mm). On multivariate analysis only the BI-RADS lesion type had a significant influence on MRI-pathology concordance with considerable discordance for cases presenting as non-mass enhancements on MRI ($p<0.001$).

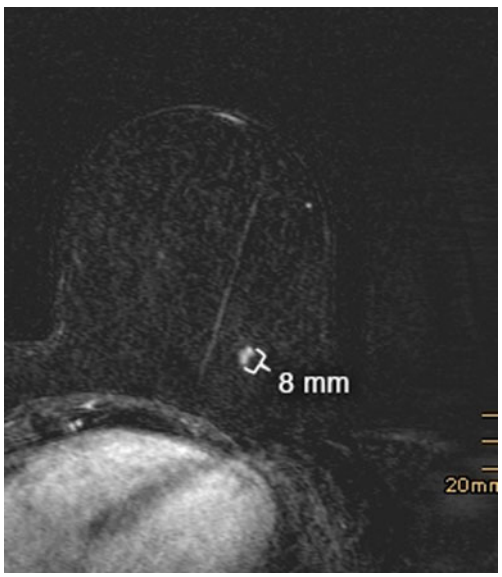

Fig. 4 MRI mass lesion of a 60-year-old patient with ILC. The mass lesion measures 8 mm along the main tumour axis on MRI (MRI-MPR) and 8 mm along the greatest diameter at histopathology (Path-Diameter)

Published results assessing MRI-pathology concordance ranged from an underestimation rate of 0 – 59 % to an overestimation rate of 7 – 70 % [3, 18, 23, 24]. Limits within which measurements on MRI are considered concordant with measurements at pathology vary and range from 0 mm – 20 mm [11, 24–27]. We used a limit of 10 mm to define concordance and Bland Altman plots to measure systematic and random differences. A possible cause of MRI overestimation is the use of Path-TNM for MRI-pathology size comparison [24]. In case of a combined invasive and non-invasive malignant tumour, only the invasive component is considered in Path-TNM [5]. At pathology a lesion is considered multifocal as soon as non-cancerous cells separate the tumours, regardless of the distance between them [9]. Some authors only compared the largest lesion at pathology [24, 28] without taking into consideration that multifocal tumours may present as one non-mass enhancement on MRI. In order to evaluate concordance of MRI with pathology, this non-mass enhancement on MRI must be compared with the diameter through the multifocal tumours at pathology. For this reason, we retrospectively reassessed the greatest tumour diameter on histopathology as relevant for surgical excision in order to evaluate the accuracy of preoperative MRI assessment.

A further reason for MRI-pathology discordance could be an underestimation of the true tumour size at histopathological examination. Various studies have shown that formalin fixation causes shrinkage in specimen and tumour size [29, 30]. The degree of formalin-induced changes in size is organ- and tumour-specific [29]. Krekel et al. found no change of tumour-free margins or tumour shrinkage of breast cancer specimen

following formalin fixation [31]. However, authors have shown that shrinkage affects surrounding tissue and influences tumour margins, rather than tumour size itself [32, 33]. Therefore, underestimation of real tumour size by histopathology due to formalin fixation may be discussed in case the tumour diffusely infiltrates surrounding tissue.

Another possible reason for underestimation at histopathological examination could be that particularly large or non-palpable tumours and mastectomy specimens are sliced along the anatomical organ axis, rather than along the main tumour axis. This might serve as one possible explanation for our results: we found smaller systematic and random errors, as well as better concordance and fewer overestimations when comparing Path-Diameter with MRI-In-Plane rather than with MRI-MPR, as would have been expected a priori. Tot et al. [1, 34–36] use large-format histopathology. They found this method to allow correct documentation of size, distribution, extent and surgical margins of the tumour(s), while providing the most detailed analysis of the subgross morphology of breast carcinoma [35, 36]. They recommend the use of preoperative MRI for plane selection of specimen [1].

In order to determine reasons for discordance beyond different measurement techniques we analyzed factors that may have influenced agreement. We examined histopathological tumour type, preoperative palpability, type and number of surgical procedures performed, the presence of additional high-risk lesions in close proximity, and the BI-RADS lesion type as possible sources of error. Our results show that only the lesion type (mass versus non-mass enhancements) had a significant impact on MRI-pathology concordance ($p<0.001$).

Onesti et al. and Grimsby et al. found that the histopathological tumour type had no significant influence on MRI-pathology concordance ($p=0.29$ and $p=0.38$, respectively) [4, 25]. However, other authors have shown DCIS to have a significant influence on agreement [37]. Although we did not find histopathological tumour type to significantly influence MRI-pathology concordance, we noted that DCIS appeared more difficult than invasive carcinoma in this regard.

Determining the size of a tumour at pathology may be difficult in cases in which re-excisions were performed [1]. The size of the tumour is measured in sequence and the diameter is established as the sum of the sizes of the resected tumours [37–39]. In our study, radiologic-pathologic discordance of MRI was slightly higher in cases where more than one surgical procedure was performed, although this difference did not reach statistical significance ($p=0.08$).

Mann et al. attributed overestimation of ILC by MRI to enhancing lobular carcinoma in situ surrounding or in close proximity to the tumour [3]. Grimbsy et al. studied the surrounding of IDC lesions overestimated by MRI [4]. They found DCIS, satellite lesions, lymphovascular invasion, proliferative breast tissue, and benign findings to be a possible source of overestimation by MRI. We did not find a significant difference in the presence of high-risk lesions, proliferative breast tissue, or benign findings between overestimated lesions and lesions that were measured concordant with size at pathology ($p=0.18$). A recent systematic review found that no studies to date have shown specific characteristics for presentation of high-risk lesions on MRI [40].

We found considerable rates of overestimation (41 %, based on MRI-MPR and Path-Diameter comparison) and underestimation (12.5 %) for breast tumours with non-mass enhancements. Mann et al. confirm these results, showing that under- and overestimations were more likely in non-mass enhancements, rather than in masses (22 % versus 15 % and 33 % versus 5 %, respectively; $p=0.02$) [41]. Tot acknowledges that it is difficult to measure the size of diffuse tumours, as they lack a distinct tumour body [9]. Therefore, perhaps the reason that non-mass enhancements are associated with radiologic-pathologic discordance is not only that measurement on MRI is difficult, but that the same tumours are difficult to measure at pathology.

Two out of 59 ILC did not enhance at all. This is in accordance with other studies [42, 43]. Otherwise, underestimation rate of this study population was low with 5/113 (4 %) for MRI-MPR. The underestimated lesions were one ILC and otherwise either IDC with low grade DCIS or pure low grade DCIS. Tot et al. [1] found low-grade in situ lesions, micropapillary DCIS, and ILC to be the most frequent causes for radiologic-pathologic discordance. In these situations a radiological multi-modality approach is of particular interest.

Study limitations

The high proportion of ILC relative to IDC and DCIS of this retrospective study is a result of the German S3-guideline [44], which recommends preoperative MRI solely for ILC. Therefore, the IDC and DCIS cases were selected cases to undergo pre-operative MRI. Inter- and intraobserver-variabilities must be considered for MRI and histopathologic diameter measurements [45, 46].

Conclusion

We found that concordance rate varies according to the execution and scope of MRI and histopathological size measurements. On examining further possible factors that influence concordance, we only found non-mass enhancements to significantly predict discordance.

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One of the authors has significant statistical expertise. Institutional Review Board approval: waived requirement for IRB approval and informed consent because retrospective study and anonymity was ensured.

Written informed consent was waived by the Institutional Review Board. The manuscript contains parts of the thesis work of cand. med. Daniela Berg (second author)

Methodology: retrospective, case-control study, performed at one institution.

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