Magnetic resonance imaging of breast cancer: factors affecting the accuracy of lesion sizing

Poster No.: C-0609
Congress: ECR 2014
Type: Scientific Exhibit
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Keywords: Cancer, Diagnostic procedure, MR, Breast
DOI: 10.1594/ecr2014/C-0609

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Aims and objectives

A precise preoperative assessment of tumor extension with imaging techniques plays a central role in breast surgery, and the choice of breast conserving treatment significantly depends on the relationship between tumor-to-breast size [1]. Magnetic resonance imaging (MRI) has been shown to be more accurate than ultrasound and mammography in estimating the local extension of both invasive breast cancer and ductal carcinoma in situ (DCIS) [2, 3]. Since achieving negative margins at initial surgery decreases the chance of tumor recurrence, MRI is employed in the preoperative surgical planning to evaluate the local extent of the disease and to assess the presence of synchronous tumors. The potential for under- or overestimation of tumor size on MR images has been investigated in different previous studies, which yielded mixed results [4-9]. In the more recent works [8, 9], there is evidence that lesion size can influence the accuracy of MRI measurements. In a retrospective study on 77 patients, Onesti et al. [8] compared the preoperative tumor size measured on MR images to the tumor size at final pathology. Stratifying their patient cohort according to the MRI tumor size (#2.0 cm and >2.0 cm), the Authors found a greater difference between the two measurements (i.e. MRI/pathology difference) in the group of lesions larger than 2.0 cm.

Grimsby et al. [9] investigated on 190 patients the correlation between MRI and pathology tumor sizing, finding concordance within 0.5 cm in 53% of cases, while MRI overestimated 33% and underestimated 15% of tumors. Among tumors overestimated by MRI, 65% had additional significant findings in the breast tissue around the main lesion: satellite lesions, DCIS, and/or lymphovascular invasion, but tumor histology was not found to be a source of discordance between MRI and pathology tumor sizing. The aim of our study was to re-assess on a large number of lesions the hypothesis that histological subtype may influence the discrepancy between MRI and pathology measurements. The second objective was to verify if the discrepancy between MRI and pathology tumor sizing is more affected by tumor dimensions or histological subtype.
Methods and materials

This was a retrospective, single-center, institutional review board approved study within a breast surgery specialty practice. All women who had a newly diagnosed, biopsy-proven, primary breast cancer with a positive MRI before surgical treatment were identified by performing a search in our single-institution radiology database from January 2007 to December 2012. Different data were collected for all patients, including age, tumor size on both MRI and final pathology, histological characteristics of the tumor, type of surgical intervention (i.e. lumpectomy, quadrantectomy or mastectomy), and the presence of neoadjuvant chemotherapy. Patients who received neoadjuvant chemotherapy before surgery were excluded, since it has been previously demonstrated that this factor is a source of discordance between preoperative MRI tumor sizing and final pathology measurements [9]. To compare cancer sizing by MRI with pathology, only the largest diameter of lesion size was used. Patients without a clear and precise measurement of the largest diameter of the lesion size in the postoperative pathology report were excluded.

Pathology

Histopathological reports of all enrolled patients were retrieved from our institutional pathology database and carefully reviewed. Patients with bilateral, multifocal and multicentric lesions were identified. The presence of two or more foci of cancer within the same breast quadrant was defined as multifocal disease, while the presence of two or more foci of cancer in different quadrants of the same breast was defined as multicentric disease. Tumors were classified according to five histological subgroups, including invasive ductal carcinoma (IDC), invasive ductal carcinoma with extensive intraductal component (EIC), invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS) and other histological types (mixed IDC/ILC, mucinous, papillary, medullary, tubular and apocrine breast carcinoma). The second subgroup, represented by EIC, was defined, according to Berg et al. [10], as ductal carcinoma with an invasive component, where at least 25% of the tumor was DCIS with or without additional discrete foci of DCIS outside the main tumor mass. Consistent with the common practice of the Pathology Service of our Institution, all surgical specimens were received with orientation and examined in fresh state. Specimens were cut into 5-mm thick levels along their longest axis (i.e. 5-mm slicing technique), according to Egan et al. [11]. Formalin fixation happened only after the cut sections of each specimen were obtained. In this way, tissue shrinkage and the potential change in size of tumors did not occur as a result of specimen fixation prior to cut. The measurements were then calculated by multiplying number of levels showing cancer by the thickness of each level. In situ components were included in the analysis. The largest dimension of tumor size was used as reference standard. In the case of multifocal disease, the final pathology size was obtained by summing the major microscopic dimension of different tumor foci within the same breast quadrant. On the
other hand, in the case of multicentric disease, different tumor foci were considered and measured as separate lesions.

**Magnetic Resonance Imaging technique**

Written informed consent was obtained from all patients before MRI. Breast MRI examinations were performed on a 1.5 T MRI scanner (Avanto, Siemens, Erlangen, Germany) with the patient in the prone position in a dedicated phased-array breast coil, using the following MRI protocol:

- T2-weighted Turbo Inversion Recovery Magnitude (TIRM) axial sequence (Repetition Time 8950.00 ms, Echo Time 87.00 ms, matrix size 380×384, elliptical filter, slice thickness 4.00 mm, interval 0.00 mm, distance factor 25%, overlapping 1 mm, FOV read 340 mm, FOV phase 100%, flip angle 120°, voxel size 0.9×0.9×1.6 mm)
- T1-weighted 3D fat-suppressed FLASH (fast low-angle shot pulse sequence) imaging of both breasts in the axial plane (Repetition Time 3.99 ms, Echo Time 1.36 ms, flip angle 12°, single acquisition of signal, rectangular FOV 32-36 cm, matrix size 400×400, slice thickness 1.6 mm, interval 0.00 mm). Contrast enhanced dynamic breast MRI was performed with the acquisition of one pre-contrast 3D FLASH sequence and 5 sequences during the intravenous injection of paramagnetic contrast medium (0.1 mmol/kg of gadobenate dimeglumine [Gd-BOPTA]). Imaging volumes were acquired at 1, 2, 3, 4 and 5 minutes after injection. Contrast medium speed injection was standardized at 3 ml/sec and followed by injection of a 20 ml saline flush at same flow rate.

The overall acquisition time of the MRI protocol was 17-20 min. It is well known that increased enhancement after biopsy can make it difficult to differentiate breast lesions from surrounding parenchyma [12]. On the other hand, what should be the best time interval for performing MRI after a biopsy procedure remains unclear, and no previous work has given a precise response to this question. On the use of MRI in assessing residual disease after positive tumor margins in breast-conserving surgery, EUSOBI (European Society of Breast Imaging) suggests to respect a time interval of one month between surgery and diagnostic MRI [13], since post-surgical inflammatory edema can artificially increase lesion’s size. In the case of VABB, which can be considered quite an invasive procedure, we routinely respect this time interval of one month.

**Interpretation of MRI examinations**

All breast MRI examinations were reviewed in consensus on a dedicated workstation by two radiologists (AG and TM) with 8 and 20 years of experience in the field of breast diseases, who had access to previous imaging records of each patient.
The dynamic sequence was examined with subtraction and maximum intensity projection (MIP) techniques. Time-enhancement kinetic curves were generated to assist in the interpretation. Cancer extension on MR images was defined in the early phase of dynamic studies as well-enhanced areas, including linear or clumped enhanced areas, according to Kuroki et al. [6]. The greatest dimension of tumor size was measured by means of an electronic digital caliper and compared with the microscopic size (Figs. 1-2).

**Statistical analysis**

Categorical data were expressed as number and percentage, while continuous data as mean and standard deviation (SD). The normal distribution of MRI and pathology measurements was assessed by means of the D’Agostino-Pearson test [14] in each histological subgroup. Since some datasets (e.g. MRI and/or pathology tumor size in the different histological subgroups) did not follow the normal distribution, non-parametric tests were used instead of parametric ones.

Concordance between MRI and pathology was defined as a difference ≤5 mm.

The degree of relationship between two independent variables was determined using the Spearman’s rank correlation. Spearman’s rho values were interpreted as follows:

- for values of rho of 0.9 to 1, the correlation is very strong;
- for values of rho between 0.7 and 0.89, correlation is strong;
- for values of rho between 0.5 and 0.69, correlation is moderate;
- for values of rho between 0.3 and 0.49, correlation is moderate to low;
- for values of rho between 0.16 and 0.29, correlation is weak to low;
- for values of rho below 0.16, correlation is too low to be meaningful.

Mann-Whitney test was used to assess the difference between the medians of two independent groups. Kruskal-Wallis test was used to verify the presence of a statistically significant difference between the medians of more than two different groups. After a positive Kruskal-Wallis test (p-value <0.05), a post-hoc analysis was conducted performing pairwise comparison of subgroups. The number of lesions under- and overestimated by MRI was calculated, as well as the mean value of under- and overestimation ± SD. Bland-Altman analysis was used to determine to what extent the MRI tumor size correlated with the histopathological tumor size. In addition, the absolute difference between MRI and pathology measurements was calculated, and the presence (or absence) of MRI-pathology discordance (i.e. an MRI-pathology difference >5 mm) was put as dichotomous dependent variable in a multivariate logistic regression model, using the histological subgroup of lesions and the pathology size as independent variables.
Images for this section:

**Fig. 1:** Transverse T1-weighted 3D FLASH subtraction MR image (A) shows an irregular-shaped periareolar lesion in the left breast, with a largest diameter of 80.12 mm. (B) shows the surgical specimen. The histopathologic section (hematoxylin and eosin, 10x, (C) reveals an invasive ductal carcinoma not otherwise specified with high grade of nuclear polymorphism, low grade of differentiation (Nottingham grading: G3), and no appreciable intraductal spread (DCIS component <25%). It was ER (estrogen-receptor) negative, and Ki-67 positive (proliferative activity: 42%).

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**Fig. 2:** Transverse T1-weighted 3D FLASH subtraction MR image (A) shows a lobulated lesion in the outer quadrants of the right breast, with a largest diameter of 26.49 mm. (B) shows the surgical specimen. The histopathologic section (hematoxylin and eosin, 20x, (C) reveals an invasive lobular carcinoma with the typical pattern of linear growth.
It is characterized by high grade of nuclear polymorphism, low grade of differentiation (Nottingham grading: G3), negativity for ER (estrogen receptors), and positivity for Ki-67 (proliferative activity: 15%).

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Results

A total of 186 women (mean age 52.25±10.63) were included for a total of 221 lesions. This discrepancy was due to 4 patients with bilateral tumors, 30 (16.1%) patients with multicentric disease and 1 patient with a peculiar bifocal disease. This latter patient had two lesions in the same breast quadrant with different histology (i.e. IDC and invasive mucinous carcinoma), which were separately considered and measured. Sixty-three patients (33.9%) had multifocal disease. Fifteen women were excluded from an initial cohort of 201 patients, since they received neoadjuvant chemotherapy before surgery. A total of 190 surgical procedures were performed on 186 patients: this discrepancy was due to 4 patients with bilateral breast cancer who underwent bilateral mastectomy (each surgical procedure was separately considered). Surgical interventions consisted of 89/190 (46.8%) mastectomies, 59/190 (31.1%) quadrantectomies, and 42/190 (22.1%) lumpectomies. Tumor histology was as follows: 112 IDC (50.68%); 23 EIC (10.41%); 31 ILC (14.03%); 30 DCIS (13.57%); other histological types included 12 mixed IDC/ILC (5.43%), 7 mucinous (3.17%), 3 papillary (1.36%), one medullary (0.45%), one tubular (0.45%) and one apocrine carcinoma (0.45%).

All lesions underwent biopsy prior to MRI, but only for 101 women (a total of 101 tumors) it was possible to retrieve precise information about the method of preoperative biopsy (vacuum assisted breast biopsy - VABB -, core biopsy, fine-needle aspiration cytology - FNAC -). For the remaining patients this information was not accessible in a retrospective setting, since they were referred to our breast surgery specialty practice from other centers, and data regarding their biopsy procedure were not present in our institutional database. A total of 49 patients underwent FNAC prior to MRI, 32 underwent VABB, and in the remaining 20, a core biopsy procedure was performed.

The mean size of tumors at pathology was 24.8±19.4 mm, while at MRI it was 29.7±20 mm (two-tailed probability with the Kruskall-Wallis test, p<0.05), with a global significant overestimation of MRI. The overall correlation between pathology and MRI measurements was strong (Spearman's rho=0.792, 95%CI for rho 0.737 to 0.837, p<0.05) (Fig. 3). MRI-pathology concordance within 5 mm was found in 111/221 cases (50.2%). Perfect concordance (MRI-pathology difference= 0) between MRI and breast cancer size at pathology was found in only 13/221 cases (5.9%). MRI overestimated the size of 81/221 tumors (36.7 %) with a mean value of overestimation of 16.8±12.9 mm. MRI underestimated the size of 29/221 tumors (13.1%) with a mean value of underestimation of -14.2±7.1 mm.

**Effect of tumor dimension on the difference between MRI and pathology measurements**

All the 221 tumors were stratified into 2 groups on the basis of their MRI size, according to Onesti et al. [8] (Group A consisting of 98 tumors #20 mm and Group B consisting of 123 tumors >20 mm), and Bland-Altman statistics were performed in each group to
assess the mean MRI-pathology difference and the corresponding limits of agreement (Fig. 4). The mean MRI-pathology difference was higher in Group B (6.6) than in Group A (1.7), and the limits of agreement were wider in Group B (lower limit -21 [95%CI -25.4 to -16.7]; upper limit 34.3 [30 to 38.7]) than in Group A (lower limit -8.1 [95%CI -9.9 to -6.4]; upper limit 11.6 [95%CI 9.9 to 13.3]).

The 81/221 tumors overestimated by MRI were then stratified into 2 groups according to their MRI size (Group 1 consisting of 16 tumors #20 mm and Group 2 consisting of 65 tumors >20 mm), and the mean value of overestimation was calculated in each group: it resulted to be significantly higher in Group 2 than in Group 1 (Group 1= 9±2.5; Group 2= 18.7±13.7; p<0.05 with the Mann-Whitney test for independent samples).

**Effect of histology of tumors on the correlation between pathology and MRI measurements**

The correlation between pathology and MRI was separately tested for each histological subgroup: IDC (rho=0.864, 95%CI for rho 0.808 to 0.904, p<0.05), EIC (rho= 0.642, 95%CI for rho 0.312 to 0.833, p<0.05), ILC (rho= 0.856, 95%CI for rho 0.719 to 0.928, p<0.05), DCIS (rho= 0.56, 95%CI for rho 0.250 to 0.766, p<0.05), other histological types (rho= 0.612, 95%CI for rho 0.286 to 0.811, p<0.05). The best correlation was found for IDC (rho= 0.864), and the worst for the DCIS subgroup (rho= 0.56). The 221 lesions were further divided according to their histological type. The Kruskal-Wallis test demonstrated a significant difference of overestimation among the five histological subgroups (p<0.05) (Fig. 5). Results of the post-hoc analysis showed that the median overestimation in the EIC group was significantly higher than that of the IDC group, while the median overestimation in DCIS group was higher than that of all the other histological groups, excluding EIC.

**Multivariate logistic regression**

The absolute difference between MRI and pathology measurements was calculated, and the presence of a difference >5 mm was put as dichotomous dependent variable in a multivariate logistic regression model, using the histological subgroup of lesions and the pathology size as independent variables. Results of the multivariate logistic regression with stepwise inclusion method are shown in Table 1. In our study, tumor dimension at MRI and two peculiar histological types (EIC and DCIS) are factors that significantly influence the discrepancy between MRI and pathology measurements of tumor size. In particular, DCIS histology was the independent factor more significantly associated with an MRI/pathology difference #5 mm (p= 0.0005, odds ratio= 6.03), while the influence of tumor dimension was less significant (p= 0.0073, odds ratio= 1.02).
**Fig. 3:** The scatter diagram graphically shows the relation between tumor size measured on MR images (MRI, horizontal axis) and microscopic measurement of the greatest dimension of tumor size at final pathology (pathology, vertical axis). The MRI/pathology correlation, tested by the Spearman's rank correlation, was strong ($\rho=0.792$, $p<0.05$).

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Fig. 4: Bland-Altman plots for Group 1 (lesions #20 mm) (A) and Group 2 (lesions >20 mm) (B). The graphs display a scatter diagram of the differences plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. The mean difference between MRI and pathology sizing is greater for Group 1 than for Group 2.

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**Fig. 5:** Box-and-whisker plot showing how the median value of MRI/pathology difference in tumor sizing varies among the different histological subgroups. The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points. An outside value is defined as a value that is larger than the upper quartile plus 1.5 times the interquartile range (inner fences), while a far out value is defined as a value that is larger than the upper quartile plus 3 times the interquartile range (outer fences). These values are plotted using a different marker in the warning color. The median value of the absolute MRI/pathology difference was significantly higher in the histological groups B and D. Legend: A= IDC; B= EIC; C= ILC; D= DCIS; E= other histological types.

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Table 1: Multivariate logistic regression. A variable was removed from the model if its associated significance level was greater than the p-value of 0.1 (variables not included in the model: ILC, other tumors). The Wald criterion demonstrated that tumor size at pathology, EIC and DCIS histological subgroups made a significant contribution to prediction of the dependent variable, which was defined as a difference between MRI and microscopic sizing of lesions #5 mm. DCIS histology was the strongest significant predictor (p<0.0005). When tumor histology is DCIS, the odds ratio is 6 times larger.

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Conclusion

MRI is often used, in addition to conventional imaging, for the preoperative assessment of breast cancer size to determine the optimal surgical strategy. Recent studies have suggested that MRI is superior to mammography in determining invasive tumor size, depicting multifocality, as well as evaluating the intraductal component. In the present study, breast cancer size at histopathology has been used as reference standard, and compared to the MRI measurements performed by two breast radiologists working in consensus. The most recent works comparing MRI and pathology in the assessment of size and local extension of breast cancer confirmed a trend of overestimation by MRI [8, 9]. In their work, Onesti et al. [8] found that MRI significantly overestimated mean tumor size (p<0.05), proposing that this result was primarily due to tumors measuring >20 mm at MRI. Also Grimsby et al. [9] suggested that discordance between MRI and pathology tumor sizing is strongly affected by tumor size at MRI. In addition, they found that other factors, including patient age, multifocal disease, and histological type, do not seem to influence MRI-pathology discordance. However, the Authors did not perform a multivariate or logistic regression analysis. In the present study, we aimed to assess, on a relatively large number of primary breast carcinomas (i.e. 221 lesions), what is the best predictor of MRI-pathology discordance between tumor size and histology. Both EIC and DCIS lesions were well represented in our study cohort (10.41% and 13.57%, respectively), thus allowing us to assess the influence of an "in situ" component on the accuracy of MRI measurements. We found that MRI overestimated the size of 81/221 tumors (36.7%); this figure of overestimation is similar to those reported by Onesti et al. [8] (i.e. 35%) and by Grimsby et al. [9] (i.e. 33%), since they defined concordance between measurements as a difference within 5 mm, with a method similar to ours. Kuroki et al. cited a 93.5% concordance using a limit of ±15 mm, which could represent a substantial discordance in the clinical setting [6]. In our study, the mean overestimation was larger in the group of tumors >20 mm (p<0.05), thus underscoring the importance of lesion's size in determining the accuracy of MRI measurements. Interestingly, in a recent work [15], the Authors found that the mean difference in sizing between MRI and histology was only 2 mm, which corresponded to a non-significant size overestimation by MRI. Grimsby et al. [9] found that, among patients with tumor size overestimated by MRI, 65% had satellite lesions, DCIS, and/or lymphovascular invasion in tissue surrounding the main tumor. This observation encouraged us to consider tumors with an extensive intraductal component (EIC) as a distinct histological group, according to Berg et al. [10]. There is a robust evidence that two major limitations of breast MRI are a significant rate of false positives [16-21], and a trend of overestimation of lesion's size by MRI [8, 9]. In previous studies [6, 20], lesions with "non-mass-like" enhancement were identified as a challenging subgroup causing a high proportion of false-positive diagnoses at diagnostic breast MRI. To this regard, MR-directed "second-look" ultrasound may help in avoiding false positives and is a useful tool for decision making as part of the diagnostic workup. Nevertheless, a successful MRI-ultrasound correlation is neither easy nor immediate [22-24]. We found that DCIS histology is the strongest independent predictor of discrepancy between MRI
and pathology sizing of breast tumors, and this may be due to different factors. DCIS lesions have been found to exhibit "non-mass-like" enhancement at a high rate, ranging between 69% and 90% in previous studies [25-28]. Despite we did not systematically consider lesion shape and morphology in our analysis, we can reasonably hypothesize that also this feature may have contributed to the MRI overestimation of DCIS lesions (Figs. 6-7). Another plausible explanation for MRI overestimation may be the background contrast enhancement of breast parenchyma adjacent to DCIS foci, which may become more evident due to benign proliferation (i.e. adenosis, fibrocystic changes), presence of high-risk lesions (i.e. atypical ductal hyperplasia), granulation tissue or foci of liponecrosis [29]. A limitation of our study is related to the potentially problematic nature of determining an accurate pathology size for DCIS lesions [30]. However, the standardized, accurate system of specimen analysis, which is routinely performed by our Pathology Service, may have reduced this source of bias. In addition, the microscopic measurement has been shown to be more accurate than tumor sizing on gross specimens [30].

In conclusion, the results of our study suggest that DCIS histology is a factor independently and strongly associated to discordance between MRI and pathology sizing of breast cancer. Lesion size can also influence the accuracy of MRI measurements, but to a lesser extent.
Fig. 6: Transverse T1-weighted 3D FLASH subtraction MR image (A) shows a lesion with a largest diameter of 20 mm in the outer quadrants of the left breast, characterized by "non-mass-like" enhancement. (B) shows the surgical specimen. The histopathologic section (hematoxylin and eosin, 10x, (C) reveals a pure DCIS. In the case of this relatively small lesion, MRI-pathology difference was 10 mm, which corresponded to 50% of the MRI size of the tumor.

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Fig. 7: Transverse T1-weighted 3D FLASH subtraction MR image (A) shows a huge lesion with a largest diameter of 105 mm in the outer quadrants of the right breast, characterized by "non-mass-like" enhancement. (B) demonstrates the surgical specimen. The histopathologic section (hematoxylin and eosin, 20x, (C) reveals a pure DCIS. This case was characterized by an important MRI-pathology difference of 45 mm.

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