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FULL PAPER

Role of MRI in the staging of breast cancer patients: does histological type and molecular subtype matter?

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Objective: To assess the role of MRI in the pre-operative staging of patients with different histological types and molecular subtypes of breast cancer, by the assessment of the dimensions of the main tumour and identification of multifocal and/or multicentric disease.

Methods: The study included 160 females diagnosed with breast cancer who underwent breast MRI for pre-operative staging. The size of the primary tumour evaluated by MRI was compared with the pathology (gold standard) using the Pearson's correlation coefficient (r). The presence of multifocal and/or multicentric disease was also evaluated.

Results: The mean age of patients was 52.6 years (range 30–81 years). Correlation between the largest dimension of the main tumour measured by MRI and pathology was worse for non-special type/invasive ductal carcinoma than for other histological types and was better for

luminal A and triple-negative than for luminal B and Her-2 molecular subtypes. Multifocal and/or multicentric disease was present in 48 patients (30.0%), and it was more common in breast carcinomas classified as Her-2 molecular subtype. There was no statistically significant difference in the frequency of multifocal and/or multicentric tumours identified only by MRI in relation to histological type or molecular subtype.

Conclusion: The results of this retrospective study demonstrated that histological types and molecular subtypes might influence the MRI assessment of breast cancers, especially in the evaluation of tumour size.

Advances in knowledge: The real benefit of MRI for treatment planning in patients with breast cancer may be different according to the histological type and molecular subtype.

INTRODUCTION

MRI has been increasingly used in the management of patients with breast cancer. One of the main indications for breast MRI is pre-operative staging, since this method has a high sensitivity in the evaluation of tumour extension and detection of multifocal and multicentric tumours.¹ MRI can identify additional tumour sites in 15–27% of patients in the same breast and 3–10% of patients in the contralateral breast.^{2,3} MRI is especially useful not only in patients with diagnosis of invasive lobular carcinoma, owing to the increased risk of additional sites of disease, but also in females with cancer diagnosis where it is difficult to accurately delineate the extent of disease on standard modalities.

Breast cancer is a heterogeneous disease with many histological types and molecular subtypes that have different response to therapy and prognoses.^{4–7} The main molecular subtypes of invasive breast carcinomas are related to the expression of hormone receptor and Her-2 status.

Tumours with a high expression of hormone receptors are classified as luminal: luminal A subtype is associated with a low proliferation index and accounts for 50–60% of all breast cancers; luminal B subtype is associated with a high expression of proliferation-related genes and accounts for 20% of all breast cancers. Her-2 subtype accounts for 10% of all breast cancers and is characterized by the absence of hormone receptors and high expression of Her-2. Triple-negative subtype accounts for 7–16% of all breast cancers and is characterized by the absence of expression of hormone receptors and Her-2, associated with a high expression of cytokeratin genes of high molecular weight and epithelial growth factor receptor. This subtype is associated with less differentiated invasive carcinomas and accounts for 70% of breast cancers on *BRCA1*-mutated females.^{6–9}

These different types of tumour also have different presentations on imaging studies; however, only few studies^{9,10} have evaluated the use of pre-operative MRI in patients with specific types of breast cancer. For example, the

expression of negative hormone receptors is associated with more aggressive features of breast cancer on MRI, such as peripheral enhancement, washout dynamic curve, greater size and adenopathies.^{11–16}

The purpose of this study was to assess the role of breast MRI for pre-operative staging in patients with breast cancer of different histological types and molecular subtypes, by the assessment of the dimensions of the main tumour and identification of multifocal and/or multicentric disease.

METHODS AND MATERIALS

After approval of the A C Camargo Cancer Center ethics research board, we retrospectively evaluated patients with breast cancer who underwent MRI for pre-operative staging and treatment planning between August 2012 and August 2014. The study excluded patients who underwent MRI at another institution. The main tumour size measured by MRI was compared with the pathology (gold standard). The presence of multifocal and/or multicentric disease and its effect on patient management were also evaluated.

After reviewing the electronic records of these patients, a standard data form was completed including demographic data, personal history of breast cancer, MRI, mammography and ultrasound findings, in addition to histological results of percutaneous biopsy and/or surgery. A radiologist with experience in breast imaging reviewed MR images of all patients included in the study, in order to properly characterize the described lesions. Conventional imaging (mammography and ultrasound) findings, as well as histological data, were obtained from the reports of the institution.

The histology of breast lesions was classified using the “WHO Classification of Breast Tumours” (4th edition)¹⁷ in invasive breast cancer of no special type (NST) [previously known as invasive ductal carcinoma (IDC)], special types of invasive breast carcinoma (*i.e.* invasive lobular carcinoma, tubular carcinoma, mucinous carcinoma and metaplastic carcinomas) and ductal carcinoma *in situ* (DCIS). According to the oestrogen receptor (ER), progesterone receptor (PR) and Her-2 status, which were determined by using the pathological reports obtained from the initial breast biopsy, breast carcinomas were classified into four molecular subtypes, as follows: luminal A (positive for ER and/or PR, with Ki-67 <15%); luminal B (positive for ER and/or PR, with overexpressed Her-2 or Ki-67 ≥15%); Her-2 (negative for ER and PR, with overexpressed Her-2); and triple negative (negative for ER, PR and Her-2 receptors). Multifocal disease was defined as histologically-proven additional sites of malignancy within the same breast quadrant of the main tumour. Multicentric disease was defined as histologically-proven additional sites of malignancy within different quadrants of the ipsilateral breast or in the opposite breast.

MR images were obtained with the patient in the prone position in a 1.5-T scanner (Signa HDxTTM; GE Healthcare, Milwaukee, MA), using a dedicated eight-channel breast coil. Each examination consists of images taken before and after the use of paramagnetic contrast (gadopentetate dimeglumine; Gd-DTPA) in a 20 ml dose and speed infusion of 3 ml s⁻¹. Before contrast administration, a T₁ gradient-echo sequence, three dimensional

(3D) in the axial plane with 2.5-mm-thick slices and a fat-saturated STIR sequence in the sagittal plane of both the breasts, with 4-mm-thick slices are acquired. Five gradient-echo sequences in T₁, 3D, in the axial plane are obtained using fat suppression for dynamic examination. Fat suppression technique was based on selective excitation of the water peak, which gives more uniform suppression of the tissues and improves the contrast of lesions after injection. The first sequence is obtained before contrast injection, the second after 20 s of contrast injection and the other sequentially in the following minutes with a temporal resolution of 60–90 s. Post-processing images subtracting the pre-contrast of post-contrast images are obtained from these dynamic images for better viewing of the highlight areas. The last sequence consists of gradient-echo T₁ images, contrast-enhanced 3D in the sagittal plane, of both the breasts, with 0.1-mm-thick fat-saturation cuts. Main tumour size was measured on the largest diameter in the post-contrast sequence in which the lesion was more evident.

All data were stored in a database for statistical analysis using the software SPSS® v. 20.0 (IBM Corporation, Armonk, NY; formerly SPSS Inc., Chicago, IL). Categorical variables were described as simple and relative frequencies. Numerical variables were described as mean, standard deviation (SD), minimum and maximum. The Pearson's χ^2 test was used to compare categorical variables. The value of the largest dimension measured by MRI was considered to assess the size of the main tumour. The Pearson's correlation coefficient (*r*) was calculated using the pathology as the gold standard. Only patients who had the dimensions of the main tumour described in the pathology report were included for this analysis, and the patients who underwent neoadjuvant chemotherapy were excluded. We considered the results that had the probability of Type I error ≤5% (*p* = 0.05) as statistically significant.

RESULTS

160 females were included, with mean age of 52.2 ± 11.5 years, range 30–81 years. Eight patients (5.0%) had previous breast cancer history. The main tumour appeared on MRI as mass in 121 cases (75.6%) and non-mass enhancement in 39 cases (24.4%).

The most common histological types were NST/IDC (60.6%), invasive lobular carcinoma (13.8%) and DCIS (7.5%). The main tumour presented as non-mass enhancement in 15.5% of NST/IDC and in 38.1% of other histological types. Of the 139 patients submitted to molecular subtype analysis (86.9% of the total), 36 patients (22.5%) were luminal A, 83 patients (51.9%) were luminal B, 8 patients (5.0%) were Her-2 and 12 patients (7.5%) were triple negative. The main tumour presented as non-mass enhancement in 6 (16.7%) luminal A, 15 (18.1%) luminal B, 3 (37.5%) Her-2 and none of triple-negative molecular subtypes.

The largest dimension of the main tumour varied from 7 to 114 mm in MRI (*n* = 160; mean = 38.1 ± 23.5 mm) and from 5 to 100 mm in pathology (*n* = 99; mean = 26.8 ± 20.0 mm). Correlation between the largest dimension of the main tumour measured by MRI and pathology was worse for NST/IDC than for other histological types and was better for luminal A and

triple-negative than for luminal B and Her-2 molecular subtypes (Table 1).

Multifocal and/or multicentric disease was present in 48 patients (30.0%). It was more common in breast carcinomas classified as DCIS or special histological types than NST/IDC, as well as in breast carcinomas classified as Her-2 molecular subtype (Table 2). MRI revealed multifocal and/or multicentric disease that was not identified in conventional studies in 16 out of 48 patients (33.3%). Figure 1 illustrates an example of multifocal breast cancer identified on MRI. There was no statistically significant difference in the frequency of multifocal and/or multicentric tumours identified only by MRI in relation to the histological type or molecular subtype (Table 3).

MRI changed the therapeutic planning in 17 patients (10.6% of the total): in 10 patients, candidates for conservative surgery, mastectomy was performed after MRI; in 6 patients, additional breast resection was performed to remove multifocal and/or multicentric disease identified on MRI; and 1 patient was referred for neoadjuvant chemotherapy after MRI. In six other cases (3.8% of the total), there were additional resections for benign lesions that had been considered suspicious with MRI.

DISCUSSION

Breast cancer subtypes have become essential to estimate prognosis and guide systemic therapy. Breast cancers with different molecular subtypes have different patterns of disease presentation and response to treatment. Thus, it is important to know the imaging features that are associated with each subtype to select patients who may have more benefits from MRI.

Several authors described the importance of breast MRI in the pre-operative staging, since this method is more sensitive than conventional imaging examinations on tumour extension evaluation, especially for DCIS and invasive lobular carcinoma.^{18–20} The results of this study demonstrated that MRI and pathology tumour size were positively correlated in all histological types

and molecular subtypes ($r > 0.650$). The correlation between the tumour size evaluated by MRI and pathology was worse for NST/IDC than for special types of breast cancer and DCIS in our sample. This finding could be associated with the overestimation of tumour size due to the presence of desmoplastic response that usually accompanies NST/IDC. However, other authors have showed different results; for example, Behjatnia et al²¹ found that the size of NST/IDC is measured more accurately than the size of invasive lobular carcinoma on MRI.

It is also known that different molecular subtypes of breast cancer may have different morphological and kinetic features on MRI.^{22,23} In this study, the correlation between the tumour size evaluated by MRI and pathology was stronger for luminal A and triple-negative molecular subtypes. According to Taneja et al,²⁴ luminal B subtype is more associated with architectural distortion than other subtypes and Her-2 subtype presents more commonly as a mass with indistinct outlines. These findings could explain the worse correlation between tumour size evaluated by MRI and pathology in these subtypes in our population. On the other hand, triple-negative subtype is associated with high-grade rapid-growing tumours that present more frequently as a round-oval mass with circumscribed margins.²⁵ Some authors studied the kinetic assessment and found that each molecular subtype may show different kinetic patterns; however, Her-2 subtype is more frequently associated with rapid early contrast uptake and washout pattern.^{22,26}

In addition, MRI has high sensitivity in the detection of multifocal, multicentric and contralateral tumours.^{2,3} In this study, NST/IDC breast carcinomas had less multifocal and/or multicentric disease than other histological types. Besides, one-third of patients with multifocal and/or multicentric disease were identified only on MRI.

Only few studies^{9,10} have evaluated the value of pre-operative MRI on different molecular subtypes. Grimm et al¹⁰ recently evaluated 441 patients with breast cancer submitted to pre-operative breast MRI and found that luminal B and Her-2 molecular

Table 1. Correlation between the largest dimension of the main tumour, in millimetres (mm), measured by pathology and MRI, assessed by the Pearson's correlation coefficient(r)—comparison between the histological type and molecular subtype of breast cancers

Breast cancer type	N	Pathology (mean + SD) (mm)	MRI (mean + SD) (mm)	r	p -value
All cases	99	26.8 ± 20.0	33.2 ± 22.4	0.730	<0.001
Histological type					
NST/IDC	55	23.5 ± 15.3	30.4 ± 23.5	0.679	<0.001
Other	44	31.5 ± 24.3	36.6 ± 22.3	0.794	<0.001
Molecular subtype					
Luminal A	32	27.0 ± 21.9	27.0 ± 17.6	0.866	<0.001
Luminal B	44	27.5 ± 18.5	35.4 ± 24.0	0.651	<0.001
Her-2	4	23.5 ± 11.3	37.5 ± 17.7	0.661	<0.001
Triple negative	7	27.9 ± 20.7	33.9 ± 25.2	0.988	<0.001

IDC, invasive ductal carcinoma; NST, no special type; SD, standard deviation.

Table 2. Correlation between multifocal and/or multicentric tumours, histological type and molecular subtype of breast cancers

Breast cancer type	Multifocal and/or multicentric tumour		
	Yes	No	<i>p</i> -value
Histological type (<i>n</i> = 160)			0.035
NST/IDC	23 (23.7%)	74 (76.3%)	
Others	25 (39.7%)	38 (60.3%)	
Molecular subtype (<i>n</i> = 139)			0.029
Luminal A	14 (38.9%)	22 (61.1%)	
Luminal B	21 (25.3%)	62 (74.7%)	
Her-2	5 (62.5%)	3 (37.5%)	
Triple negative	1 (8.3%)	11 (91.7%)	

IDC, invasive ductal carcinoma; NST, no special type.

subtypes were more likely to have multifocal and/or multicentric disease. In our study, only Her-2 molecular subtype was associated with multifocal and/or multicentric disease. However, there was no statistically significant difference in the rate of multifocal and/or multicentric disease identified only by MRI among histological types and molecular subtypes.

Pre-operative MR evaluation modifies the treatment in up to one-third of patients with breast cancer.^{2,3} In our series, 10.6% of all patients underwent more aggressive surgery to remove multifocal and/or multicentric disease identified only on MRI. However, there is no agreement in the literature regarding the benefit to the patient provided by performing pre-operative MRI. There are no

Figure 1. A patient with invasive breast carcinoma of no special type in the right breast, Her-2 molecular subtype. MRI showed the main tumour in the posterior aspect of the outer quadrants of the right breast as an irregular mass with heterogeneous enhancement (thick arrows), associated with anterior adjacent foci and another irregular mass (thin arrows), not described in conventional methods. (a) Axial 3D maximum intensity projection of post-contrast subtracted images. (b and c) Sagittal high-resolution post-contrast fat-saturated T_1 weighted sequence.

Table 3. Correlation between multifocal and/or multicentric tumours identified only by MRI, histological type and molecular subtype of breast cancers

Breast cancer type	Multifocal and/or multicentric tumour		
	MRI only	Conventional imaging	p-value
Histological type			0.222
NST/IDC	10 (43.5%)	13 (56.5%)	
Others	6 (24.0%)	19 (76.0%)	
Molecular subtype			0.651
Luminal A	7 (50.0%)	7 (50.0%)	
Luminal B	7 (33.3%)	14 (66.7%)	
Her-2	2 (40.0%)	3 (60.0%)	
Triple negative	0 (0.0%)	1 (100.0%)	

IDC, invasive ductal carcinoma; NST, no special type.

controlled prospective studies that have shown reduced recurrences or increased survival in patients with breast cancer who underwent MRI for staging and treatment planning. In addition, some studies raise questions about the number of additional surgeries due to the results of MRI and their impact in terms of morbidity and mortality in the medium and long term.^{27,28}

The results of this study should be considered in the context of its limitations. Because of the retrospective nature of this study, it was not possible to assess molecular subtype of all patients included in the analysis. Owing to the increasing number of patients being submitted to neoadjuvant chemotherapy in our

centre, it was also not possible to assess tumour size in the surgical specimen in such cases. The incidence of Her-2 molecular subtype in our sample was very small, which may impair the analysis of the findings.

In conclusion, the results of this retrospective study demonstrated that histological types and molecular subtypes might influence the MRI assessment of breast cancers, especially in the evaluation of tumour size. Future prospective studies should be conducted to define the real benefit of MRI for treatment planning in patients with breast cancer of different histological types and molecular subtypes.

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