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Importance of the preoperative evaluation of multifocal and multicentric breast cancer with magnetic resonance imaging in women with dense parenchyma

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ABSTRACT

Background. The presence and detection of multifocal and multicentric disease significantly increases the risk of recurrence and changes the best therapeutic approach in patients with breast cancer. Mammography has low sensitivity to detect multiple malignant foci in patients with dense breast parenchyma. We prospectively evaluated Magnetic Resonance Imaging (MRI) as part of preoperative assessment. **Material and methods.** Women with clinical and radiological suspicion of breast cancer and dense breast parenchyma (> 75% dense tissue) were included. All patients underwent mammography, ultrasonogram and MRI prior to surgery. Surgical specimens were used for the detection of multifocal and multicentric disease. Patients who required neoadjuvant chemotherapy or radiotherapy were excluded. **Results.** Nineteen patients were evaluated. Histological diagnosis was confirmed in 14 patients, multifocal and multicentric disease was found in five and two patients, respectively. Sensitivity and accuracy to detect multiple malignant foci were 42 and 64%, respectively, for mammography plus ultrasound and 100 and 92% for MRI ($p < 0.05$). **Conclusions.** MRI is more sensible and has a better accuracy than mammography plus ultrasound to detect both multicentric and multifocal breast cancer in women with dense breast parenchyma. MRI can improve preoperative assessment of breast cancer in this group of patients.

Key words. Breast cancer. Dense mammary parenchyma. Magnetic resonance. Mastography. Ultrasonogram. Preoperative stage. Multifocality. Multicentricity.

Importancia de la evaluación preoperatoria de cáncer de mama multifocal y multicéntrico con Imagen de Resonancia Magnética en mujeres con parénquima denso

RESUMEN

Introducción. *La presencia y detección de enfermedad multifocal y multicéntrica incrementa el riesgo de recurrencia y cambia el abordaje terapéutico en pacientes con cáncer de mama. La mastografía posee una baja sensibilidad para la detección de múltiples focos malignos en mujeres con parénquima mamario denso. Evaluamos de manera prospectiva la utilidad de la Imagen por Resonancia Magnética (IRM) como parte de la valoración preoperatoria en este tipo de pacientes.* ***Material y métodos.*** *Se incluyeron mujeres con sospecha clínica y radiológica de malignidad con mamas extremadamente densas (> 75% tejido denso). A todas las pacientes se les realizó mamografía, ultrasonido e IRM antes de la cirugía. Se analizaron las piezas quirúrgicas completas para la detección de enfermedad multifocal y multicéntrica. Se excluyeron a aquellas pacientes que requirieron quimioterapia o radioterapia neoadyuvante.* ***Resultados.*** *Se evaluaron 19 pacientes. Se confirmó el diagnóstico histopatológico de cáncer en 14 pacientes; se encontró enfermedad multifocal en cinco y multicéntrica en dos. La sensibilidad y exactitud para detectar focos malignos fue de 42% y 64% para mastografía más ultrasonido, mientras que para IRM fue de 100% y 92% respectivamente ($p < 0.05$).* ***Conclusiones.*** *La IRM es más sensible y tiene una mayor exactitud que la mastografía más ultrasonido para detectar tanto multicentricidad como multifocalidad en mujeres con cáncer de mama y parénquima mamario denso. La IRM mejora la valoración preoperatoria del cáncer de mama en este tipo de pacientes.*

Palabras clave. *Cáncer de mama. Parénquima mamario denso. Resonancia magnética. Mastografía. Ultrasonido. Estadio preoperatorio. Multifocal. Multicéntrica.*

INTRODUCTION

Breast cancer is a major public health concern worldwide and is by far the most frequent cancer in women (23% of all malignant disease), with an estimated 1.15 million new cases in 2002, ranking second when both genders are considered as a whole.[1,2] Surveillance by both mammography and clinical breast examination have resulted in an early diagnosis of breast cancer and an increase in conservative surgical approaches.

Multiple malignant foci in the breast occur with a frequency between 14 and 47%. Excluding the presence of multifocal (one quadrant) or multicentric (two or more quadrants) disease is important to decide the best therapeutic approach. Distance between malignant foci can also be used to define multifocality (< 5 cm) or multicentricity (> 5 cm).[3] Relapses after conservative surgery are frequent due to undetected malignant foci.[4,5] Moreover, multiple tumors in breast cancer are associated to increased nodal involvement as compared with similar staged unifocal disease. In addition, the sum of the dimensions of multifocal tumors can reclassify these patients as having an advanced stage.[6]

Screening mammography remains as the most important tool to reduce breast cancer mortality. Mammography can often detect clinically occult, early-stage breast cancer that is amenable to successful treatment. However, mammography is not a perfect test and has lower sensitivity in patients with dense breasts.[7,8] Additionally, a high percentage of dense tissue is associated with an increased risk of breast cancer and multiple malignant foci.[9] Factors associated with an increased percentage of density (which represents the amount of breast parenchyma in mammography) are nuliparity in both premenopausal and postmenopausal women, late age at first pregnancy, younger age, low body mass index and the use of hormone replacement therapy.[10]

Magnetic resonance imaging (MRI) has been shown to depict breast cancers that are occult to other forms of detection, including mammography.[11] Because of its ability to image dense breasts, MRI has a high potential for screening high-risk cases such as BRCA-positive patients.[10-12] Added to standard imaging methods in cases of highly suspicious findings, breast MRI has shown to result in a change of treatment in many cases due to the assessment of further lesions in the contralateral breast or the assessment of multicentricity and multifocality.[11-13] In a diagnostic setting, MRI is virtually uninfluenced by breast density, but the specificity is variable and it can be associated with false-positive findings that require unnecessary biopsies and follow-up examinations that are extensive and costly.[14] We conducted a prospective study to evaluate the utility of MRI for the detection of multifocal or multicentric disease in women with extremely dense breast parenchyma with clinical and radiological suspicion of cancer.

MATERIAL AND METHODS

Patients and imaging schedule

We conducted a prospective study between January and December 2005, of patients with percutaneously proven unilateral breast cancer and dense breast parenchyma treated at the Instituto Nacional de Cancerologia de Mexico to evaluate multifocal and multicentric disease by magnetic resonance imaging. All patients met the following criteria: tumor evidence by physical examination, mammography and/or ultrasonogram suggestive of cancer; mammography with extremely dense breast parenchyma according to the American College of Radiology Breast Imaging Reporting and Data System (BIRADS) 4 (> 75% of dense tissue);[15] being considered for surgical treatment, and having a breast MRI before undergoing tru-cut percutaneous biopsy performed by the same doctor, with subsequent pathologic follow-ups available. Both USG and MRI were performed by the same team of radiologists (S.O.M, Y.V.N and T.F.C.). A total of 19 patients were studied. Five patients were excluded due to lack of malignancy in the surgical specimen or candidacy to neoadyuvant chemotherapy due to evidence of locally advanced disease (tumors > 5 cm, lymph node involvement by physical examination, skin infiltration and inflammatory tumors, as well as candidates to surgery who needed neoadyuvant chemotherapy to reduce the size of the tumor).

Breast MRI technique

Breast MRI examinations were made independent to the stage in the hormonal cycle. They were performed with a 1.5-T magnet (Signa; General Electric Medical Systems, Milwaukee, WI) using a surface breast coil. The localizing sequence was followed by sagital fat-suppressed T2-weighted sequence (TR/TE, 4000/85). T1-weighted three-dimensional, fat-suppressed fast spoiled gradient-echo (17/2.4; flip angle, 35º; bandwidth, 31.25 MHz) sequence was then performed before and three times after the bolus IV injection of 0.1 mmol/L of gadopentetate dimeglumi-

ne (Magnevist; Berlex, Wayne, NJ) per kilogram of body weight. Image acquisition started immediately after contrast material injection and a saline bolus. Images were obtained sagitally with an interval per volumetric acquisition of less than 2-3 minutes each. Section thickness was 2-3 mm without gap using a matrix of 256 x 192 and a field of view of 18-22 cm. Frequency was guided in an anterior-posterior direction. After examination, unenhanced images were subtracted from the first contrast-enhanced images on a pixel-by-pixel basis.

Breast MRI interpretation

MRI examinations were interpreted in conjunction with clinical data as well as previous and concurrent breast imaging studies including mammograms and ultrasonograms. Results of mammography and ultrasound studies were scored in a standardized way, according to the BI-RADS classification in a blinded fashion by two different radiologists (S.O.M. and Y.V.N.) and MRI (T.F.C. and S.O.M) members of the medical staff of our institution, a reference cancer center in the country.

MRI-detected lesions referred primarily for biopsy included masses with spiculated or irregular margins, irregular shape, heterogeneous or rim enhancement and non-mass lesions showing linear or segmental enhancement. Other lesions were referred for biopsy at the discretion of the interpreting radiologist in conjunction with clinical history and other imaging studies. Tiny (≤ 1 mm) foci of enhancement or diffuse stippled enhancement generally did not prompt biopsy. Classification was based primarily on lesion morphology; however, kinetic features were visually assessed on the three enhanced image acquisitions, with quantitative kinetic curves generated in specific cases at the request of the interpreting radiologist. In all cases with a total of three enhanced T1-weighted images available, visual analysis of the time course of enhancement in these three images were performed and categorized in accordance with lexicon terminology as "progressive" (increasing signal intensity throughout the dynamic period), "plateau" (stabilized enhancement without change in signal intensity between the initial and subsequent enhanced images), or "washout" (abrupt decline in signal intensity after the initial enhanced images) (Table 1).

Histological analysis

Diagnosis of malignant tumors was based on the results of histological examination. A blinded pathologist (V.M.C) reviewed all surgical specimens. Histopathological variables not available during the tumor biopsy examination were required to complement the study. WHO classification criteria was used to typify the tumors, and histological grading was performed according to the Scarff-Bloom-Richardsson (SBR) score.[16] Tumors obtained previous to therapy, were graded according to the Black nuclear grading system (Grade 1, well differentiated; Grade 2, moderately differentiated; and Grade 3, poorly differentiated). Distance between malignant foci was also used to define multifocality (< 5 cm) or multicentricity (> 5 cm).[3]

Immunohistochemical staining for estrogen receptors (ER), progesterone receptors (PgR), HER-2 and Ki-67, was performed on section of formalin-fixed paraffin-embedded tissue from incisional biopsies and

Table 1. Terms and definitions.

Category	Term
Lesion type:	
Mass	Focal, mass, non-mass
Margin	Smooth, irregular, spiculated
Shape	Round, oval, lobular, irregular
Enhancement	Homogeneous, heterogeneous, rim, dark internal septations, enhanced internal septations, central enhancement
Non-mass:	
Type	Linear/ductal, linear/non-specific, segmental, regional, multiple, diffuse
If linear/ductal	Smooth, irregular, clumped
Otherwise	Homogeneous, heterogeneous, stippled, clumped, septal/dendritic
Visual kinetic pattern	Progressive, plateau, washout
Final assessment	Benign, probably benign, suspicious, highly suggestive of malignancy

subsequent surgical specimens mounted on poly-L lysine slides. For the evaluation of ER and PgR, the Allred semi-quantitative scoring system was used to assess the proportion and intensity of stained cells.[17] Expression of Her2-neu was scored as the percentage of cells with membranous staining, and intensity of signal. Staining was considered negative when < 10% of cells had a weak, incomplete membranous staining; weakly positive or borderline when 10-30% of cells were with weak membranous staining; and strongly positive expression was defined as > 30% of cells with strong membranous staining. Tumors scored 3+ were classified as positive.[18]

Table 2. Clinical and pathological characteristics of the patients.

Characteristic	Values	N
Age, years (Median ± SD)	48 (± 2.9)	14
Family history (%)	50%	7/14
Menopause (%)	71%	10/14
Site:		
UEQ	50%	7/14
UIQ	35%	5/14
IEQ	14.3%	2/14
IIQ	0	
Range (Median ± SD)	2.2 (±0.2)	14
Positive ganglia	21.4%	3/14
Stage:		
I	28.6%	4/14
II	64.3%	9/14
III	7.1%	1/14
Treatment:		
Mastectomy	42.9%	6/14
Quadrantectomy	57.1%	8/14
Range by pathology	2.5 (±0.23)	14
Histologic type:		
Ductal	85.7%	12/14
Lobular	14.3%	2/14
Tumor grade:		
I	21.4%	3/14
II	35.7%	5/14
III	42.9%	6/14
Estrogen receptor:		
Negative	50%	7/14
Positive	50%	7/14
Progesterone receptor:		
Negative	50%	7/14
Positive	50%	7/14
Multifocality	35.7%	5/14
Multicentricity	14.3%	2/14

UEQ: Upper External Quadrant. UIQ: Upper Internal Quadrant. IEQ: Inferior External Quadrant. IIQ: Inferior Internal Quadrant. SD: Standard Deviation.

Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means, medians and standard deviations (error) and categorical variables as proportions with 95% confidence intervals. Sensitivity, specificity, positive and negative predictive values, as well as accuracy and 95% confidence intervals for the detection of multifocality or multicentricity by mammogram/ultrasound and MRI was determined by the Epidat 3.0 software. Comparisons between clinical and radiological variables with the presence of multifocality or multicentricity in the histopathological report were performed using Fisher's exact test. Statistical significance was determined as $p < 0.05$ with a two-tailored test. SPSS software package version 10 (SPSS Inc., Chicago, IL) was employed to analyze the data.

RESULTS

A total of 19 patients with clinical suspicion of breast cancer were initially included in our study. Five patients were excluded due to absence of malignancy (BIRADS 2 by MRI) or the requirement of neoadjuvant chemo or radiotherapy. Clinical and pathological characteristics are shown in table 2. Median age was 48 ± 2.9 years. Only 29% (4/14) of patients were in premenopausal state and 50% (7/14) of the patients had a positive family history of breast cancer. Median major diameters of clinically and pathologically evaluated tumors were of 2.2 and 2.5 cm, respectively. Pre-surgical evaluation showed that 28.6% of patients were in stage I, 64.4% stage II and 7.1% stage III. Multifocal disease was obser-

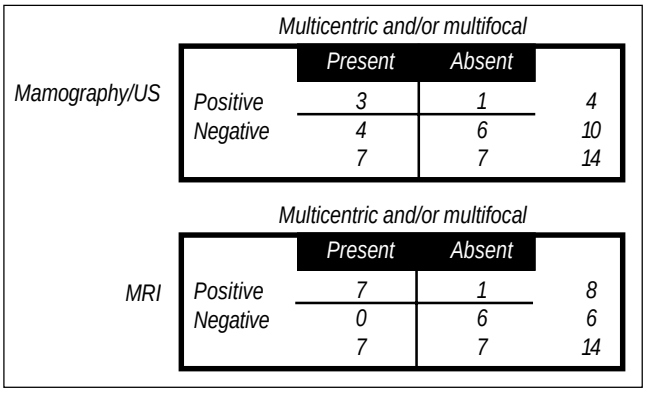

Figure 1. Detected foci of multifocal and multicentric breast cancer by mammography/ultrasound and RMI. Pathologic analysis of biopsy was used to confirm diagnosis.

Table 3. Mastographic and ultrasonographic characteristics.

Characteristic	Percentage	N
Mammography		
• Asymmetry	100%	14/14
• Undetermined margins	78.6%	11/14
• Architectural distortion	71.4%	10/14
• Suspicious calcifications	64.3%	9/14
• Thickening of the skin or adjacent tissue	64.3%	9/14
• Range, size of tumor (Median ± SD)	2.3 (± 0.18)	
• Positive ganglia	64.3%	9/14
Ultrasound		
• Undetermined margins	78.6%	11/14
• Heterogeneous	78.6%	11/14
• Vascularity	78.6%	11/14
• Thickening of the skin or adjacent tissue	71.4%	10/14
• Positive ganglia	64.3%	9/14
• Multicentricity/Multifocality	28.6%	4/14
Mammography/Ultrasound		
• BiRADS 4 (%)	14.3	2/14
• BiRADS 5 (%)	85.7	12/14

SD: Standard Deviation.

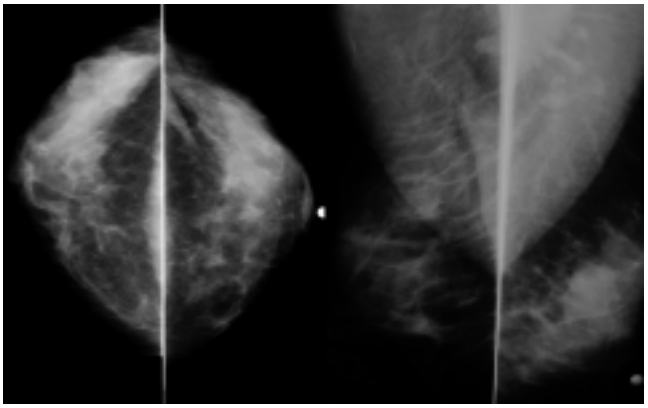

Figure 2. Mammograms showing a marked increase in density, a focal irregular density on the right side.

ved in 50%. Conservative surgery was performed in 57.1% (8/14) and radical mastectomy in 42.9% (6/14). No statistically significant differences between the clinicopathological characteristics and the presence of unifocal and multifocal/multicentric tumors were found.

Mammography and ultrasound missed a total of 11 malignant foci compared with a total of one malignant foci missed on MRI (Figure 1). This foci was a ductal carcinoma for which the mastographic image darkened with the rest of the parenchyma and in the ultrasonographic image it lost its intrinsic vascularity and more than 20% of its margins with the rest of the parenchyma. Median diameters of missed malignant foci were 25 to 50 mm (Table 3), assessed by MRI. No second look ultrasonography was made for any of the lesions.

Contrast-enhanced MRI detected all forms of breast carcinoma consistently. Fat-suppressed three-dimensional and enhancement imaging methods demonstrated previously unidentified lesions in women with mammographically dense breasts (Figures 2-4) (Table 4). The sum of diameters of all foci detected

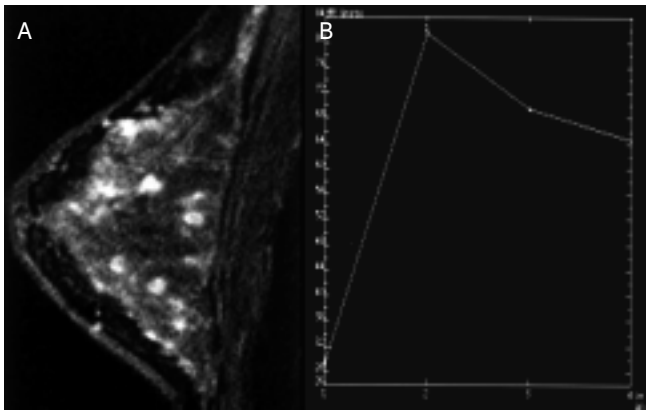

Figure 4. A. Sagital fat-suppressed contrast-enhanced 3D fast SPGR MR image (9.2/2.1) of the right breast showing multifocal areas of enhancement, suggestive of carcinoma. B. Followed by a strong washout.

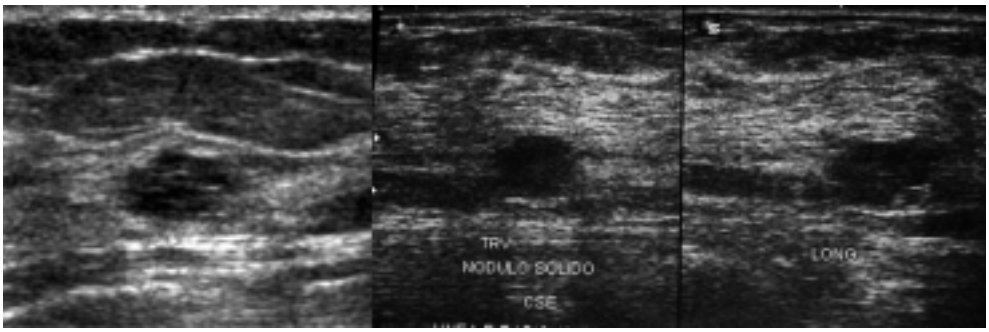

Figure 3. US image revealing corresponding hypoechoic solid masses, in the upper quadrant on the right breast.

Table 4. Characteristics of the patients in the breast-MRI.

Characteristics	MRI	N
Lesion type		
Regular	14.3%	2/14
Irregular	85.7%	12/14
Margins		
Regular	21.4%	3/14
Spiculate	35.7%	5/14
Irregular	50%	7/14
Enhancement		
Ring-like	7.1%	1/14
Homogeneous	14.3%	2/14
Heterogeneous	64.3%	9/14
Central	14.3%	2/14
Enhanced internal septations	64.3%	9/14
Without enhanced internal septations	35.7%	5/14
Visual kinetic pattern		
Progressive	0%	0/14
Plateau	21.4%	3/14
Wash out	78.6%	11/14
Multicentricity/ Multifocality	71.4%	10/14
Median of the greater diameter of the tumor size of the malignant foci (unifocal) identified in Mammography/Ultrasound	2 ± 0.21	14
Median of the diameter of all malignant foci	3.5 ± 0.6	14

MRI: Magnetic Resonance Imaging.

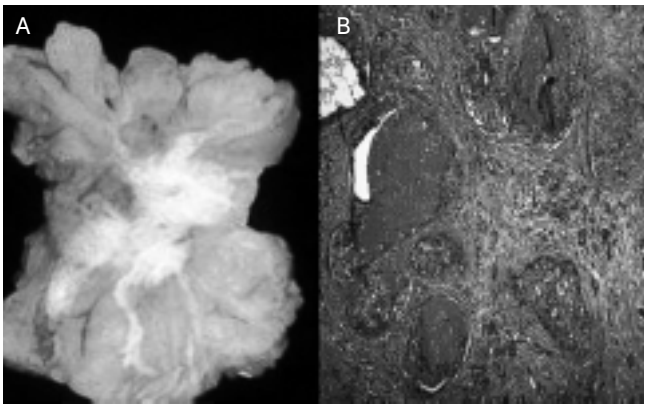

Figure 5. A. Macroscopic specimen shows multiple foci. B. Microscopic analysis of the isolated spicule showing heavy reactive fibrosis and tumor infiltration.

by MRI was significantly greater than that of tumors detected by mammography and ultrasound and later measured by MRI (3.5 ± 0.6 *vs.* 2 ± 0.21, $p < 0.05$). However, no biopsy was taken with the MR image as a guide, and no association was established between the lesions observed by MRI only and their location or histologic type; the characteristics described were merely multifocality and multicentricity (Figure 5).

Table 5 summarizes the diagnostic estimates for multifocal/multicentric tumors of both tests performed showing that MRI has greater sensitivity and better accuracy than mammography/ultrasound (100 *vs.* 42.9% $p < 0.05$ and 92.8 *vs.* 64.3% $p < 0.05$, respectively). Specificity was similar (85.7 *vs.* 85.7%, NS) between both tests.

DISCUSSION

MRI is a relatively recent diagnostic tool for breast cancer. Its role in the management of this pathology is still evolving. We conducted a prospective study comparing MRI *vs.* mammography and ultrasound for the detection of multifocal and multicentric disease, including only women with dense breast parenchyma, with clinical and radiological suspicion of cancer. Multifocal disease was suggested in three out of seven cases on mammography and ultrasound, with only one false-positive examination. MRI is known to detect multifocal and multicentric lesions that are occult on mammography.[19] Our results concur with those previously reported but the specificity that we found is higher for ultrasonography and mastography, in addition, there are no significant differences between the two maybe due to the fact that we studied patients with clinical and radiological suspicion of disease. Sardanelli reported a sensitivity of 66% for mammography and 81% for MRI to detect foci of multifocal, multicentric breast cancer in dense breasts,[19] whereas Van Goethem reported 20 patients with multifocal carcinoma, where

Table 5. Characteristics of mastography/ultrasound and MRI for multifocal and multicentric lesions.

Characteristics	Mammography/ US (IC 95%)	MRI (IC 95%)	P
Sensitivity	42.9 (35.5- 50.2)	100.0(92.9 -100.0)	< 0.05
Specificity	85.7 (78.4-93.01)	85.7 (78.4-93.0)	SN
Positive predictive value	75.0 (62.2-87.7)	87.5 (81.1-93.9)	SN
Negative predictive value	60.0 (54.8-65.18)	100.0 (91.6-100.0)	< 0.05
Accuracy	64.3 (60.6-68.0)	92.8 (89 2-96.5)	< 0.05

MRI: Magnetic Resonance Imaging. US: Ultrasound.

mammography detected the lesions in 35%, ultrasound in 30% and MRI in 100% with a false-positive rate of 12.5, 14 and 23% respectively.[20]

Women with one area of proven breast cancer may harbor additional sites of cancer in the ipsilateral breast. Pathologic analyses of mastectomy specimens have shown sites of cancer other than the index lesion in 20-63% of tumors ≥ 2.5 cm and of these, 19-67% are invasive. Other series report that about 20-47% of mastectomy specimens show additional malignant foci in quadrants other than that of the index tumor.[19] The characterization of these lesions and an accurate staging are of great relevance to plan the therapeutic approach of breast cancer;[31] mainly with the increasing worldwide tendency for conservative surgery and neoadjuvant chemotherapy.[21] This is even more relevant in women with dense parenchyma and breast cancer, in whom mammography and ultrasound have the lowest sensitivity for detecting this pathology.[7] Saarenmaa found in a study with 557 patients that the sensitivity of mammography and ultrasound was inversely related to age and directly related with fattiness of the breast.[9] Besides, detection of multifocal and multicentric tumors in breast cancer does not only have implications when it comes to surgical planning, but also regarding the risk of recurrence and the presence of positive ganglia.[21] In 848 women, 11.1% had multifocal breast cancer, 52.1% had involvement of axillary's ganglia, whereas only 37.5% of the women with unifocal disease presented it. The sum of the dimensions of multifocal tumors, can reclassify the patients' disease into a more advanced stage.[21] We found that the greater diameter of the lesions identified by mammography and ultrasound was significantly minor than the median of multifocal tumors detected by MRI. This may deny patients the opportunity of neoadyuvant therapy if contribution of the smaller foci to the incidence of positive ganglia and survival is ignored.[22] These results show that MRI is significantly more sensitive than mammography for the detection of multiple malignant foci in scattered fibroglandular or heterogeneously and extremely dense breasts. Mammography misses more invasive and larger cancer foci than MRI.[23] The real clinical significance of malignant foci detected solely on MRI is still a matter for debate and further studies about its significance alone are required.[8] One of the limitations found in this study is that even though the surgical specimens had 5 cm margins free of disease, the breast was not evaluated in its totality. If combined with radiation therapy, breast-conserving surgery gives survival rates that are not significantly different from those obtained with mastectomy.[24,25] Randomized studies comparing the outcome of patients undergoing pretreatment MRI with a control group are needed to define the effects of a more precise evaluation of the extent of disease on relapse and survival rates and quality of life.[26-29] The detection of multiple malignant foci could identify patients who could benefit of a non-conservative surgical approach or neoadjuvant chemotherapy.[30]

CONCLUSION

MRI is more accurate in assessing multicentricity or multifocality in women with dense breast parenchyma, without an increase in false-positive tests. MRI represents a better preoperative study tool in this group of patients.

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