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Magnetic resonance imaging in the evaluation of axillary lymph nodes in patients with early-stage invasive breast cancer

Ressonância magnética na avaliação de linfonodos axilares em pacientes com câncer de mama invasivo em estágio inicial

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Abstract **Objective:** To evaluate the performance of magnetic resonance imaging (MRI) in detecting axillary metastasis in early-stage invasive breast tumors.

Materials and Methods: This was a retrospective observational study of images and reports from MRI scans performed between 1 January 2000 and 31 December 2019 at our institution. The images were analyzed by a radiologist specializing in breast imaging, who evaluated the presence or absence of signs of metastatic involvement of the axillary lymph nodes, comparing the findings with existing reports and with the results of the pathology evaluation of the sentinel lymph node or other resected lymph nodes.

Results: The sensitivity of MRI for detecting axillary metastasis was poor in our study sample because of the low axillary tumor burden in this group of patients. The overall sensitivity and specificity were 35.0% and 81.2%, respectively. The positive and negative predictive values were 26.9% and 86.3%, respectively.

Conclusion: It seems that MRI has good specificity in the detection of axillary metastases, especially for those considered macrometastases. However, its sensitivity in our study was inferior to that reported in the most recent studies.

Keywords: Magnetic resonance imaging; Lymph nodes; Breast neoplasms; Lymphatic metastasis.

Resumo **Objetivo:** Avaliar o desempenho da ressonância magnética (RM) na detecção de metástase axilar em tumores de mama invasivos em estágio inicial.

Materiais e Métodos: Este é um estudo observacional retrospectivo que analisou imagens e laudos de RM realizadas de 1º de janeiro de 2000 a 31 de dezembro de 2019 em nossa instituição. As imagens foram analisadas por um radiologista especializado em mama, que avaliou a presença ou ausência de sinais de comprometimento metastático dos linfonodos axilares no estudo de RM, os quais foram comparados com os laudos existentes e com os resultados da avaliação anatomopatológica do linfonodo sentinela ou outros linfonodos removidos.

Resultados: A RM mostrou baixa sensibilidade na detecção de metástases axilares, em razão da baixa carga tumoral axilar neste grupo de pacientes. Em termos gerais, a sensibilidade foi 35,0%, a especificidade foi 81,2%, o valor preditivo positivo foi 26,9% e o valor preditivo negativo foi 86,3%.

Conclusão: Nosso estudo demonstrou que a RM apresentou boa especificidade na detecção de metástases axilares, principalmente para as consideradas macrometástases. Por outro lado, a sensibilidade foi inferior aos últimos estudos publicados.

Unitermos: Ressonância magnética; Linfonodos; Neoplasias da mama; Metástase linfática.

INTRODUCTION

In the female population, breast cancer has the highest incidence of any type of tumor, with estimates that at least 1 in 8 women will receive this diagnosis at some point in their lives, and is the leading cause of cancer-related death[1]. It has a wide range of presentations, with varied clinical, morphological, and genetic manifestations[2], which directly influence the response to treatment and therapeutic options[1]. The main imaging method used for breast cancer screening is mammography, and the number of mammograms performed has increased in recent years. Therefore, more than half of breast tumors are now diagnosed in the early stages, allowing the use of treatments that are less aggressive and more individualized[1,2].

Historically, axillary staging in patients with breast cancer has been defined through surgery. However, less invasive methods have increasingly been used to perform axillary staging. One such method is the sentinel lymph node technique, which spares patients from the consequences inherent to a surgical procedure.

In recent years the use of imaging to evaluate axillary lymph nodes has played a prominent role, allowing non-invasive evaluation of the lymph node status[1]. Although axillary assessment has traditionally been performed with ultrasound[2], recent studies have suggested that, in some scenarios, magnetic resonance imaging (MRI) is more effective for this purpose[3,4].

The objective of this study was to evaluate the performance of MRI in axillary staging in patients with early-stage (T1 or T2) breast tumors with clinically negative axillae who were scheduled to undergo upfront surgery.

MATERIALS AND METHODS

This was a retrospective observational study that analyzed MRI scans performed between 1 January 2000 and 31 December 2019 at Hospital Israelita Albert Einstein, in the city of São Paulo, Brazil. We evaluated a sample of consecutive patients with biopsy-proven early-stage (T1 or T2) invasive breast cancer who were scheduled to undergo upfront surgery and underwent preoperative MRI for staging and who subsequently underwent surgery with histopathological evaluation of the lymph nodes.

All MRI examinations were performed according to a standard protocol established for locoregional staging, already adopted at the hospital, in which the sequence analyzed was T1-weighted without fat saturation, including axillary levels I, II and III. Patients were positioned with their arms above their heads, and the axillary and breast MRI examinations were performed at the same time. Axial T1-weighted MRI sequences were acquired as follows: in a 1.5-T scanner (Signa HDxt; GE Healthcare, Milwaukee, WI, USA), with a field of view of 32 × 32 mm, a slice thickness of 2 mm, and a 256 × 256 matrix; in a 3.0-T scanner (Discovery 750W GEM; GE Healthcare), with a field of view of 32 × 32 mm, a slice thickness of 1.8 mm, and a 420 × 420 matrix; and in a 1.5-T scanner (Aera; Siemens Healthineers, Erlangen, Germany), with a field of view of 32 × 32 mm, a slice thickness of 1 mm, and a 340 × 320 matrix. Approximately 0.1 kg/mL of gadobutrol (Gadovist; Bayer Schering Pharma AG, Berlin, Germany) was injected intravenously.

The examinations were analyzed by a radiologist specializing in breast imaging, including MRI, with more than 25 years of experience in evaluating the presence or absence of atypical axillary lymph nodes. The radiologist received information only about the laterality of the underlying disease, without access to the pathology results of the lymph nodes or to the results of previous examinations, such as mammography and ultrasound. Because clinically negative axillae was an inclusion criteria, the radiologist was aware of the clinical stage.

A lymph node was considered positive if it met the following criteria[5]: long-axis diameter > 0.5 cm; cortical thickness > 0.3 cm; eccentric cortical thickening; and absence or compression of the fatty hilum. If only one of those criteria were met, the lymph node was considered pathological.

Bilateral axillary assessment was performed simultaneously, allowing comparison between the number, morphology, and dimensions of the lymph nodes ipsilateral to the cancer and those of the contralateral lymph nodes, in accordance with the symmetry criteria described by Baltzer et al.[6]. When none of those findings were present, the test was classified as negative for signs of metastatic involvement of axillary lymph nodes. The internal mammary chains were not evaluated in this study. The result of the axillary MRI assessment was then compared with the result of the pathology analysis of the sentinel lymph node and of other lymph nodes removed when axillary dissection was indicated during the surgical procedure. In the histopathological analysis, lymph nodes that presented macrometastases or micrometastases were considered positive for neoplastic dissemination, with immunohistochemical confirmation of its mammary origin.

Patients in whom the MRI scan presented technical problems that limited the assessment of the axillary region were excluded, as were those who had undergone neoadjuvant therapy, those with a personal history of treatment for breast cancer in either breast, and those with a history of surgery involving axillary manipulation.

Data were collected from the electronic medical record system and analyzed with the picture archiving and communication system of the institution. The results were verified through statistical analysis, involving the evaluation of sensitivity, specificity, positive predictive value, negative predictive value, false positives, and false negatives.

RESULTS

A total of 119 patients were included in the study: 117 (98.3%) with unilateral disease; and two (1.7%) with bilateral disease. In 96 (80.7%) of the cases, the surgical procedure was performed within the first 30 days after MRI, whereas it was performed between 31 and 60 days after in 20 (16.8%), between 61 and 90 days after in one (0.8%), and more than 91 days after in two (1.7%). The mean age was 54 ± 11 years. The tumor was in the right breast in 43 patients (36.1%), in the left breast in 74 (62.2%), and in both breasts in two (1.7%). Among the 121 tumors evaluated, the most prevalent histological subtype was invasive ductal carcinoma, seen in 94 cases (77.7%), followed by invasive lobular carcinoma, in 17 (14.0%), mixed type, in three (2.5%), and special subtypes, such as metaplastic and mucinous, in seven (5.8%). Positivity for estrogen receptors was identified in 115 tumors (95.8%), whereas only five tumors (4.2%) tested negative. The hormonal profile data were unavailable in one case, and those data were therefore evaluated in a total of 120 tumors. In addition, 110 cases (90.9%) tested positive for progesterone receptors and 10 cases (8.3%) tested negative. We were

unable to obtain the HER2 data in three cases. Among the 118 tumors for which those data were available, 114 (96.6%) were HER2-negative and only four (3.3%) were HER2-positive. Therefore, on the basis of the immunohistochemical classification, most cases (61.3%) were classified as luminal A, followed by luminal B (in 31.9%), whereas four cases (3.4%) were classified as HER2-positive and four other cases (3.4%) were classified as the triple-negative subtype.

In the MRI analysis, 95 cases (78.5%) were considered negative for axillary lymph node metastases, whereas 26 cases (21.5%) presented positive results. Among the 26 cases that showed signs of lymph node involvement on MRI, one atypical lymph node was observed in 20 cases (76.9%); two atypical lymph nodes were observed in five cases (19.2%) and three atypical lymph nodes were observed in only one case (3.8%).

In the histological evaluation of the axillae, 101 cases (83.5%) were negative for lymph node metastases and 20 (16.5%) were positive. Of the 20 cases with axillary metastases in the histopathological analysis, 17 (85%) had one affected lymph node; two (10%) had two affected lymph nodes and one (5%) had three affected lymph nodes. Of those 24 metastatic lymph nodes, 11 (45.8%) had micrometastases and 13 (54.2%) had macrometastases.

When comparing the MRI and pathology results (Table 1), we found that 82 of the 95 cases with negative results on MRI did not present positive lymph nodes in the pathology analysis, which means that 86% of the negative lymph nodes were true-negative results (Figure 1). Of the 26 lymph nodes categorized as positive on MRI, seven were also positive in the pathology analysis, translating to a 26.9% rate of true-positive results (Figure 2). As can be seen in Figure 3, the rate of false-negative results was 13.7%, with 13 lymph nodes being categorized as positive in the pathology analysis among the 95 that were categorized as negative on MRI. Figure 4 shows another example of a true-positive result.

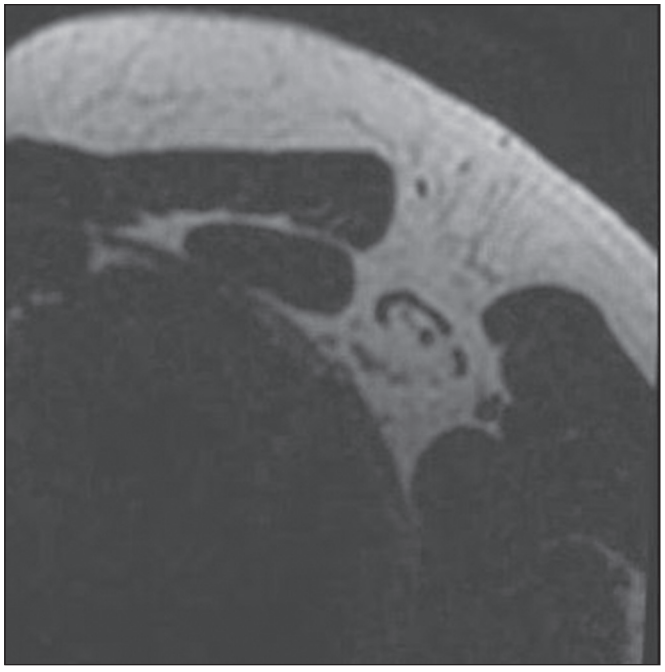

Figure 1. A 41-year-old patient with a 3.3-mm invasive ductal carcinoma that was positive for estrogen and progesterone receptors and negative for HER2, in the left breast. T1-weighted MRI sequence showing normal lymph nodes in the ipsilateral axilla. Two lymph nodes were dissected and were found to be free of metastatic disease, illustrating a true-negative MRI result.

The mean metastasis diameter was 3.9 ± 4.1 mm. The sensitivity of MRI was 35.0% and its specificity was 81.2%, with a predictive positive value of 26.9% and a negative predictive value of 86.3% (Table 1).

DISCUSSION

Axillary staging is an important step in the evaluation of patients with breast cancer[1]. Imaging methods play a fundamental role in this scenario because they allow non-invasive evaluation of the axillary lymph nodes[7].

Ultrasound has traditionally been the method of choice for axillary evaluation because it is a relatively affordable method that is easily accessible and does not use

Table 1—Sensitivity, specificity, positive predictive value, and negative predictive value of MRI for the detection of axillary metastases in patients with early-stage breast tumors.

	Negative n (%)	Positive n (%)	Total n (%)	Kappa 95% CI	Sensitivity (%) 95% CI	Specificity (%) 95% CI	PPV (%) 95% CI	NPV (%) 95% CI
All				0.144	35	81.2	26.9	86.3
Negative for axillary metastases	82 (67.8)	13 (10.7)	95 (78.5)	–0.054; 0.342	15.4; 59.2	72.2; 88.3	11.6; 47.8	77.7; 92.5
Positive for axillary metastases	19 (15.7)	7 (5.8)	26 (21.5)					
Total	101 (83.5)	20 (16.5)	121 (100)					
HER2-negative				0.189	41.2	81.4	28	88.8
Negative for axillary metastases	79 (69.3)	10 (8.8)	89 (78.1)	–0.019; 0.397	18.4; 67.1	72.3; 88.6	12.1; 49.4	80.3; 94.5
Positive for axillary metastases	18 (15.8)	7 (6.1)	25 (21.9)					
Total	97 (85.1)	17 (14.9)	114 (100)					
HER2-positive				–0.600	0	0	0	0
Negative for axillary metastases	0 (0)	3 (75)	3 (75)	–1.686; 0.486	0; 70.8	0; 97.5	0; 97.5	0; 70.8
Positive for axillary metastases	1 (25)	0 (0)	1 (25)					
Total	1 (25)	3 (75)	4 (100)					

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

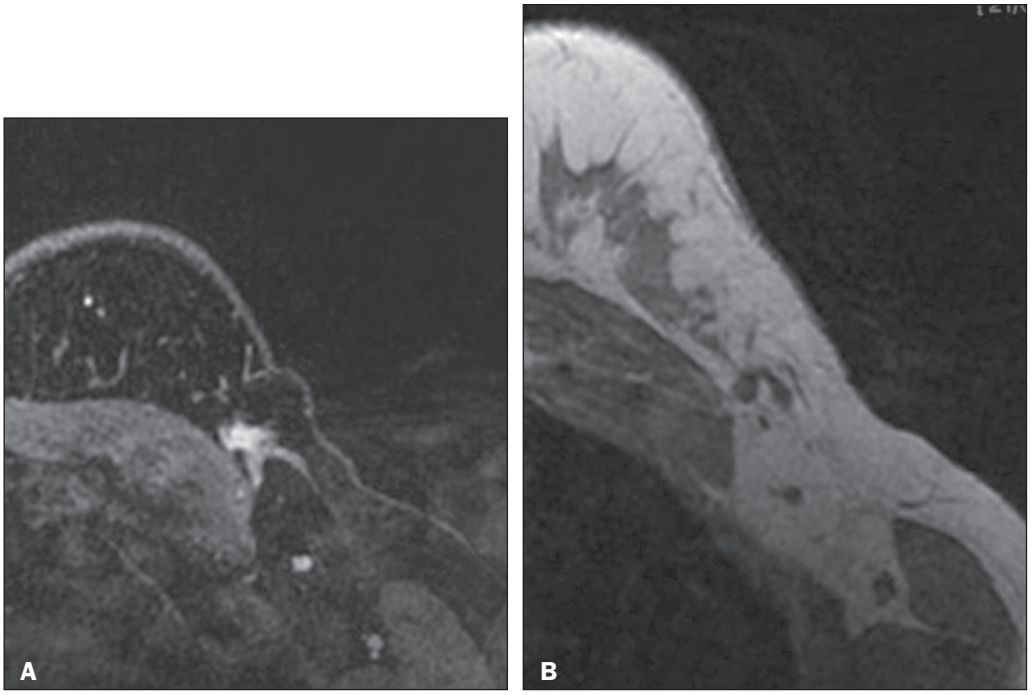

Figure 2. MRI scans of a 55-year-old patient with a 7-mm invasive ductal carcinoma that tested positive for estrogen and progesterone receptors and negative for HER2. **A:** T1-weighted sequence with fat suppression, showing an irregular mass in the left breast. **B:** T1-weighted sequence without fat suppression, showing an ipsilateral axillary lymph node with eccentric cortical thickening, which was classified as atypical. Axillary lymph nodes were dissected and were found to be free of metastatic disease, illustrating a case in which MRI produced a false-positive result.

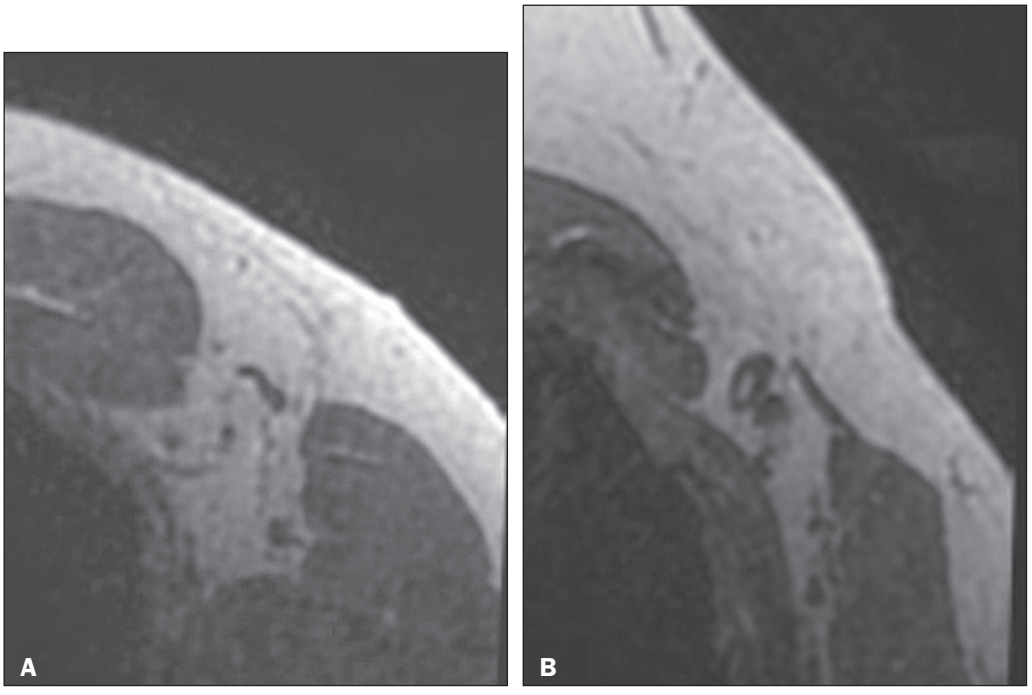

Figure 3. A 54-year-old patient with a 14-mm invasive ductal carcinoma that was negative for estrogen and progesterone receptors and positive for HER2. MRI scans in which the axillary lymph nodes were classified as negative (**A,B**). However, micrometastases were detected in one of the dissected lymph nodes, which illustrates a false-negative case.

ionizing radiation or contrast medium. However, it is an operator-dependent method[8,9]. Because MRI not only allows an adequate evaluation of the axillary lymph nodes but also is not operator-dependent and allows the simultaneous evaluation of both axillae, it has proven to be a very useful method in this evaluation[3,4]. In addition, recent studies have shown that MRI has the potential to detect axillary metastasis through the use of radiomics[10–12]. It is known that the findings observed in lymph nodes affected by metastases result from changes in their normal anatomy due to the presence of tumor cells[1].

The main changes observed in metastatic lymph nodes on imaging examinations are as follows[5]: focal or diffuse cortical thickening (> 3.0 mm); obliteration of the adipose hilum; rounded morphology; and, in more advanced cases, changes in contour and blurring of adjacent tissues. Therefore, the findings are directly related to the tumor burden of metastatic lymph nodes. The greater the axillary tumor burden is, the greater will be the morphological changes observed in the affected lymph nodes. Methods that use metabolic parameters could increase sensitivity in the detection of small axillary metastatic masses.

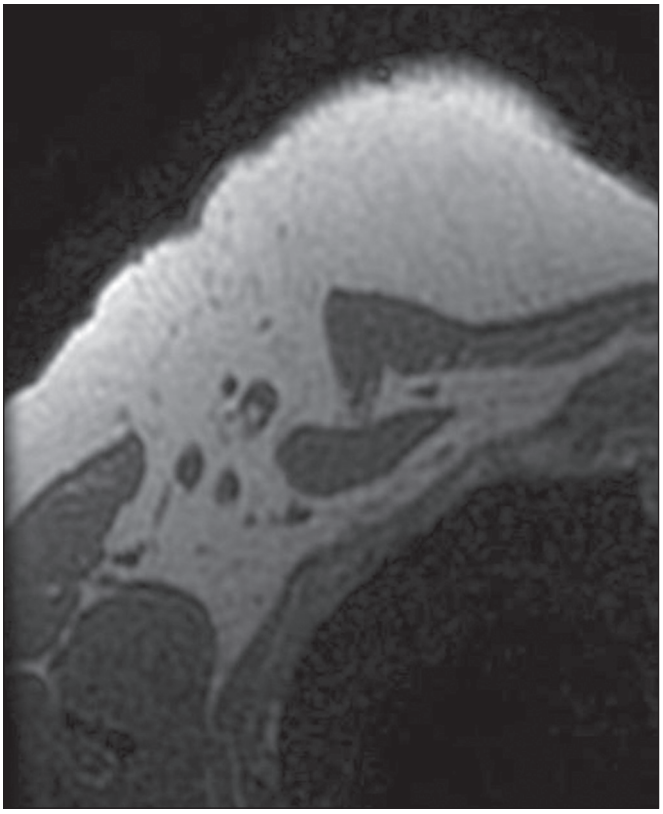

Figure 4. A 70-year-old patient with a 15-mm invasive ductal carcinoma that was positive for estrogen and progesterone receptors. T1-weighted MRI sequences without fat suppression, showing lymph nodes that were classified as positive. In a dissected ipsilateral lymph node, 4-mm macrometastases were detected, providing an example of a true-positive case.

Most patients with early-stage tumors and clinically negative (T1N0) axillae do not have axillary metastases or, if they do, have a low tumor burden. That has been observed in several studies, in which the reported proportion of patients with negative lymph nodes ranged from 68% to 82%[13–17]. That was also observed in the present study, in which the majority (83.5%) of the patients did not have axillary metastases. Of the patients with metastatic axillary lymph nodes, 85% had only one, 10% had two, and 5% had three. Therefore, the axillary tumor burden was low in most cases. Similar numbers were also observed in other studies, in which 68.5–79.6% of patients had no axillary metastases. When metastases were present, they affected only one or two lymph nodes in 63.0–80.6% of cases[14–16].

In our study sample, the mean metastasis diameter was 3.9 mm. Approximately 45.8% of the affected lymph nodes presented only micrometastases (< 2.0 mm in diameter). Among the 54.2% that presented macrometastases, the mean metastasis diameter was 6.8 mm. Micrometastases have been observed in 10.0–31.3% of patients with early-stage tumors and negative axillae[18–20]. Therefore, no major morphological changes in metastatic lymph nodes are expected among patients with early-stage tumors and clinically negative axillae. In the present study, MRI was found to have low sensitivity and specificity for the detection of axillary metastases in this specific group of patients (sensitivity of 35%; specificity of 81.2%). When we considered only cases of micrometastases, the sensitivity of MRI was just 20%. Among the 11 patients with macrometastases, MRI was able to detect those macrometastases in only five (sensitivity of 45.5%).

In agreement with our findings, Abe et al.[21], Kuckelman et al.[22], and van Nijnatten et al.[23] also reported that MRI had low sensitivity (23%, 43%, and 40%, respectively) for detecting axillary metastases in patients with a low axillary tumor burden. Chen et al.[24] also found MRI to have low sensitivity and specificity (63.2% and 68.5%, respectively) for detecting axillary metastasis, with better negative predictive value for HER2-positive and triple-negative tumors. Similar to what we observed in our study, the false-negative results were obtained in cases of low tumor burden.

In our study sample, there was a weak correlation between the number of lymph nodes affected and the number of atypical lymph nodes observed on MRI. Among the 20 patients with metastatic lymph nodes, there were only five in whom there was agreement between the number of positive lymph nodes in the pathology analysis and the number of atypical lymph nodes detected on MRI. We observed 13 cases of false-negative MRI results, among which seven (53.8%) were cases with micrometastases and the six other cases (46.2%) involved lymph nodes with a mean metastasis diameter of 6.4 mm.

Our study has some limitations. The retrospective nature of the study could have introduced a detection bias. In addition, the fact that the MRI examinations were evaluated by only one physician could be viewed as a limitation. However, that physician had more than 25 years of experience in breast radiology.

CONCLUSION

Our findings allow us to conclude that MRI has low sensitivity for detecting axillary metastases in patients with early-stage tumors. That is related to the fact that the axillary tumor burden is low in such patients, who therefore present lymph nodes with few or no changes in their morphology, which is the main parameter evaluated on imaging.

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