Breast Magnetic Resonance Imaging: State of the art and clinical applications

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Abstract  Breast magnetic resonance imaging is a modality that is being progressively integrated into the breast radiologist’s daily clinical practice. There is consensus on the minimal technical requirements that a breast MR exam should have in order to attain diagnostic quality. Diagnostic criteria are mainly based on the American College of Radiology’s BI-RADS magnetic resonance imaging categories. Breast cancer staging is a main clinical application, but it is not universally accepted. Other applications are: response evaluation in patients treated with chemotherapy, screening in high-risk patients, cancer of unknown origin, assessment of a possible relapse and breast implant evaluation.

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Resonancia magnética de mama: estado actual y aplicación clínica

Resumen  La RM es una técnica de imagen que se ha ido incorporando paulatinamente a la práctica clínica diaria del radiólogo de mama. Hay consenso en que deben cumplirse una serie de requerimientos técnicos mínimos para conseguir un estudio de calidad diagnóstica y los criterios diagnósticos se basan fundamentalmente en las categorías BI-RADS del ACR (American College of Radiology). La estadificación del cáncer de mama es una de sus principales aplicaciones clínicas, aunque no está exenta de polémica. Otras aplicaciones donde se ha validado la técnica son la evaluación de respuesta al tratamiento, el cribado en pacientes de alto riesgo, el estudio del cáncer de mama oculto, el estudio de una sospecha de recidiva y la valoración de las prótesis de mama.

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Breast magnetic resonance imaging: technical requirements

Integration of MR imaging into the radiologist’s diagnostic arsenal implies the understanding of a number of practical and technical requirements in order to maximize the morphological and functional information provided by this modality.\(^1\)\(^2\)

**Hardware: magnets and coils**

When selecting a MR unit and other components, two opposite requirements converge: spatial and temporal resolution. Breast MR is technically demanding and benefits from advanced imaging strategies (parallel imaging), powerful gradients (> 20 mT/m) and high field (> 1 T). Dedicated breast surface coils should be used. Multielement coils provide better signal-to-noise ratio and the possibility of parallel imaging.

**Patient positioning, field of view and anatomical coverage**

Breast MR imaging is performed with the patient in prone position and the arms along the body in order to increase anatomical coverage of the coil. Fields of view (FOV) of 280-320 mm with a 512 \(\times\) 256 or 512 \(\times\) 512 mm matrix (depending on the section plane) are normally used. Anatomical coverage in the direction of the section thickness must include from the supraclavicular region to the inframammary fold. MR studies must be bilateral.

**Choice of section plane: sagittal, axial or coronal**

The sagittal plane is probably the most natural but is not the plane of choice. Its technical advantage is the relatively small FOV required, which improves spatial resolution in any matrix (without detriment to the acquisition time). The only drawback is the high number of sections needed to cover both breasts. Accordingly, the sagittal plane has been used only for single-breast imaging. Bilateral sagittal protocols based on parallel imaging (VIBRANT) have been recently developed.

Most widespread dynamic protocols use the axial or coronal planes. The coronal plane has the advantage that images may be acquired with a 50-60% rectangular FOV, which results in a reduction of the acquisition time. However, this plane requires a higher number of sections in the AP direction than the axial plane (cranio-caudal). Nonetheless, both planes are perfectly valid.

It is essential to orient the phase-encoding direction to minimize motion artifacts. For sagittal imaging, this means orienting the direction head-to-feet and left-to-right for the axial plane. For coronal imaging this means orienting head-to-feet, so that a rectangular FOV can be used reducing acquisition time.

**Basic sequences**

**Precontrast T2-weighted sequences**

Precontrast T2-weighted sequences allow us to identify cysts due to their T2 values significantly higher than the rest of the gland structures. In addition, these sequences allow evaluation of the signal intensity of solid lesions (except mucinous carcinoma and myxoid fibroadenoma, both hyperintense, whereas most breast tumors are hypointense), lymph node regions and post-treatment changes (fat necrosis, hematoma and seroma). TR (repetition time) and TE (echo time) values are \(> 2\) s and \(> 80\) ms, respectively, and the optimum sequence is fast spin-echo (FSE).

STIR (short TI inversion recovery) sequences are an alternative to T2 FSE sequences when we want to suppress signals from fat and do not require the field homogeneity needed in fat-suppressed T2 sequences.

**T1-weighted dynamic 3D gradient-echo sequences**

3D sequences have a higher signal-to-noise ratio than 2D sequences because signals are acquired from a volume and not from a plane (more signal collected from every data acquisition). 3D sequences require shorter TR and maintain acquisition times short enough as to maintain the required temporal resolution. Some protocols recommend the acquisition of these sequences with fat suppression in order to minimize motion artifacts, but taking into account that extremely homogeneous fields are required. An alternative to fat suppression is image subtraction that along with a mild compression of the breasts prevents motion artifacts.

Perfusion, diffusion and spectroscopy sequences have not been yet validated on a grand scale and must be considered diagnostic adjuncts and not substitutes to the basic sequences.

**Temporal resolution**

The enhancement peak of malignant lesions usually appears between 1-3 min after contrast injection. For this reason, the required temporal resolution must be less than 120 seconds. Continuous acquisition of temporal sequences of 60-90 seconds during a total acquisition time of 6 min is enough to determine the enhancement curve shape and the enhancement pattern (continuous, plateau or early washout).

**Spatial resolution**

As with mammography and ultrasound, the second requisite for the diagnosis of breast cancer with MR is spatial resolution. Some of the most important diagnostic criteria for the differential diagnosis are based on lesion morphology: margins and internal architecture. In breast MR, any increase in spatial resolution (an increase in the size of the acquisition matrix) is associated with an increase in acquisition time. We recommend setting the time per dynamic acquisition to 60-120 seconds and investing all remaining capacity into spatial resolution. The largest imaging matrix achievable in this acquisition window should be used: a true (non-interpolated) acquisition matrix of 512 \(\times\) 512 for bilateral axial or coronal sequences (with a FOV of 320-350 mm). These specifications should translate into an pixel size of 0.5 \(\times\) 0.5 to 0.8 \(\times\) 0.8 mm (isotropic spatial resolution) in the XY plane and a section thickness of 1-3 mm (Z plane).
Contrast administration

The majority of groups use a dose of 0.1 mmol/kg although the accepted dose ranges between 0.1 and 0.2 mmol/kg. Doses greater than 0.1 mmol/kg have not been proven to improve detection. The contrast agent is injected intravenously before placing the patient into the magnet. Patient must not be moved during the injection. An injector at a rate of 3 ml/s followed by a 20 ml saline flush should be used. Acquisition of the first post-contrast sequence starts after the injection (during the saline flush). For protocols of 1-2 min temporal resolution, there is no need to wait between the injection and the start of the postcontrast series. Ideally, the same injection protocol should always be followed. One should, however, keep in mind that some factors modify the enhancement rate of the lesions (patient age, heart rate, ejection fraction, overall circulation time).

Image post-processing

The purpose of MRI post-processing is to provide the radiologist with additional data to interpret the MR study. Image post-processing should include:

1) Image subtraction (subtraction of the first or second post-contrast sequence from the precontrast sequence).
2) Maximum intensity projections (MIP).
3) Reconstruction of the subtracted images in orthogonal planes (multplanar reconstructions or MPR) and in planes following breast lobules.
4) Creation of time-enhancement curves for suspicious lesions (kinetic study)

If a CAD (computer-aided diagnosis) software or dedicated software for parametric image analysis is available, parametric image maps or enhancement maps with color coding may be created according to the parameters set (maximum velocity, washout, enhancement > 100 %, washout > 10 %, etc.).

Pathophysiological aspects

In premenopausal women, fibroglandular tissue is sensitive to estrogens that exert a histamine-like effect that modifies vasodilatation and capillary permeability. Enhancement peak in this group appears in the first and fourth weeks of the menstrual cycle. This enhancement pattern is usually bilateral and early washout is rare (normally there is an early but continuous enhancement pattern). Nonetheless, in order to reduce the risk of false positives and mask a breast cancer, the examination should be performed during the second week of the menstrual cycle (on day 6-14). Other subgroup includes breastfeeding patients and women on HRT, in whom the contrast uptake pattern can also give rise to false positives. In case of HRT, MRI should be performed 4 weeks after discontinuation of treatment.

Breast MR: basic semiology

Angiogenesis

Angiogenesis in malignant tumors is a disorganized and chaotic process. Certain morphological and functional features in the tumor bed permit the distinction between malignant and benign processes and facilitate tumor detection by imaging techniques:

- spatial heterogeneity and chaotic structure
- fragile vessels with high permeability to macromolecules
- arterio-venous shunting, vascular tortuosity and vasodilatation
- heterogeneity of vascular density

Most breast MR studies use T1-weighted gradient-echo sequences to monitor contrast uptake effects. Increased signal intensity is not directly attributable to contrast per se but depends on a number of physiological and physical factors: tissue perfusion, capillary permeability to contrast, extracellular space volume for contrast diffusion, baseline T1 relaxation time of the tissue, dose of contrast and type of sequence. In these methods, contrast is not visualized, but the changes in adjacent tissues (plasma and extravascular-extracellular space) caused by the contrast.

Diagnostic criteria in breast MR imaging

There is general agreement on the most relevant diagnostic criteria, but disagreement exists regarding their particular influence. The most widespread classifications are the Fischer and the American College of Radiology (ACR) classifications 3-5 that show common diagnostic criteria, have been validated 6,7 and together they integrate morphological and dynamic criteria for lesion analysis. The ACR classification has the advantage of correlating with the BI-RADS classification for mammography and ultrasound and is the most widely used, in contrast, emphasizes less on dynamic features. Although both classifications share the morphological criteria, the Fischer classification quantifies better the dynamic features, although perhaps overrating their relevance in its final score. The Fischer classification proposes a scoring system based on the semiology and may be useful for those who start working with MR images and in the assessment of response to chemotherapy.

The first studies on dynamic criteria emphasized the importance of the early phase in the differentiation between benign and malignant lesions, but now a large number of authors give more emphasis to the postinitial and late phases, considering the washout a reliable criterion of malignancy. Breast tumors show contrast enhancement (except isolated cases of lobular carcinoma and low grade DCIS), but it is also true that many benign lesions enhance. These facts prove that dynamic data should not be used as the sole diagnostic criterion, but they should be integrated with the so-called morphological criteria in order to increase specificity of lesion characterization.
**Fischer’s diagnostic criteria**

The diagnostic criteria defined by Fischer and Baum are shown in tables 1-3.

**BI-RADS criteria**

BI-RADS descriptors are shown in table 4 and diagnostic categories are similar to those used in ultrasound or mammography (BI-RADS 0 to 6).

**BI-RADS differential diagnosis (fig. 1)**

The characterization of a lesion always starts with the morphological analysis. Kinetic analysis is performed subsequently, after identification of the lesions and their probability of malignancy. The morphological analysis helps us to determine whether the lesion is a nodule or a non-nodular enhancement. This determination is essential, since different descriptors are applied depending on the type of lesion. Any isolated lesion less than 5 mm in diameter is considered a “focus”.

Differential diagnosis of nodules comes down to benign and malignant lesions. We define their morphology, borders and, lastly, their internal architecture after contrast enhancement. Malignant lesions (infiltrative breast tumors) generally show irregular and stellate morphology, ill-defined or spiculated borders and heterogeneous or rim enhancement (fig. 2).

As for non-nodular enhancements (fig. 3) differential diagnosis is between DCIS and fibrocystic changes/normal glandular tissue. Initially, the distribution of the lesions is assessed and subsequently their enhancement pattern. Malignant lesions with non-nodular enhancement (DCIS) usually appear as an isolated focus of hyperenhancement or as an area of regional, segmental or linear/dendritic enhancement. Regional or segmental enhancement generally shows a multinodular or cobblestone-like morphology (fig. 4).

Kinetic analysis is performed after the morphological study (fig. 5) and focuses basically on those lesions with significantly increased signal intensity on the first postcontrast image. Malignant lesions usually show early and intense enhancement. In the postinitial portion of the curve, these lesions show plateau (30% of cases) or

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**Table 1** Morphological and kinetic criteria in the Fischer classification.

<table>
<thead>
<tr>
<th>Score</th>
<th>Shape</th>
<th>Border</th>
<th>Enhancement pattern</th>
<th>Initial enhancement</th>
<th>Postinitial enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Round, oval</td>
<td>Well defined</td>
<td>Homogenous</td>
<td>&lt; 50%</td>
<td>&gt; 10%</td>
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<tr>
<td>1</td>
<td>Dendritic, irregular</td>
<td>Ill defined</td>
<td>Heterogeneous</td>
<td>50-100%</td>
<td>from +10 to −10%</td>
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<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>Rim</td>
<td>&gt; 100%</td>
<td>&lt; −10%</td>
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</table>

Source: Fischer. 3

**Table 2** Formulas for the calculation of the initial and postinitial enhancements.

Initial enhancement $= (IS_{max \ 1-3 \ min}) - (IS_{pre-contrast})/IS_{pre-contrast}$

Postinitial enhancement $= [(IS_{6 \ min}) - (IS_{max \ 1-3 \ min})/IS_{max \ 1-3 \ min}] \times 100 \ (%)$

Continuous enhancement: postinitial enhancement $< 10 \%$

Plateau: postinitial enhancement from +10% to −10%

Washout: postinitial enhancement $< −10 \%$

IS: signal intensity.

**Table 3** Assignment of categories according to the scores of the Fischer classification.

<table>
<thead>
<tr>
<th>BI-RADS MR Group</th>
<th>Points</th>
<th>Diagnostic value</th>
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<tbody>
<tr>
<td>I</td>
<td>0-1</td>
<td>Benign</td>
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<tr>
<td>II</td>
<td>2</td>
<td>Probably benign</td>
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<tr>
<td>III</td>
<td>3</td>
<td>Probably benign</td>
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<td>IV</td>
<td>4-5</td>
<td>Suspicious</td>
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<td>V</td>
<td>6-8</td>
<td>Highly suggestive of malignancy</td>
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Source: Fischer. 3.
washout enhancement (60% of cases), although these changes are less conspicuous than the intense enhancement observed during the first phase of the curve.

The signal intensity (SI) of the nodular lesions is analyzed in T2 sequences and compared to that of the fibroglandular tissue (hyper, iso or hypointense). Malignant lesions are more likely to have iso- or hypointense signal compared to the SI of the parenchyma. Exceptions to this are mucinous or medullary tumors (and the rare presence of central tumor necrosis). Myxoid fibroadenomas and intramammary lymph nodes are usually hyperintense. Fibroadenomas with low glandular content are usually hypointense but, unlike cancer, do not enhance.

**Clinical applications for breast MR imaging**

Some of the applications for breast MR imaging are well established (presented in this article), whereas others are controversial (breast cancer staging) or less universally accepted (study of microcalifications, breast secretion, premalignant lesions, residual tumor in patients who have undergone surgery, non-conclusive

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<table>
<thead>
<tr>
<th>Table 4</th>
<th>BI-RADS diagnostic criteria with their corresponding descriptors.</th>
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<tr>
<td><strong>Categories of hyperenhancing lesions</strong></td>
<td><strong>Descriptors</strong></td>
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<tr>
<td>Focus (diameter ≤ 5 mm)</td>
<td>Nodule (tridimensional space occupying lesion)</td>
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<td>Border or rim</td>
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<td>Non-nodular enhancement (without mass effect on the glandular parenchyma)</td>
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<td>Associated findings</td>
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<td>Semiquantitative kinetic assessment (fig. 2)</td>
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findings in mammography and ultrasound) and are not included in the present update.\textsuperscript{3,10}

**Breast cancer staging**

Once the cancer is diagnosed, the following step is to assess its size and to do so knowledge of the clinical significance of imaging findings for staging is essential. Depending on the tumor size, its growth pattern and distribution, the patient will undergo neoadjuvant chemotherapy, breast conserving surgery or mastectomy. The findings to be analyzed are: size, presence of multifocal lesions (including the multifocal variants (fig. 6) of extension to the nipple-areola complex or the

Figure 1  Semiological analysis according to the BI-RADS RM criteria. FQ = Fibrocystic. NAC = Nipple-areola complex.

Figure 2  Algorithm for the management of nodules and foci.
extensive intraductal component) and presence of multicentric and contralateral lesions. The final report will show whether there are additional lesions that need to be reassessed with ultrasound or to undergo MR imaging-guided biopsy. Potential changes in therapeutic planning resulting from the MR findings should be agreed by a multidisciplinary team.

It is obvious that MR is more sensitive in the detection of additional tumor burden than conventional imaging.\textsuperscript{11,12} Acceptance of the technique in the staging context, once its diagnostic performance is proven, implies verifying the impact on the treatment of the patient and on the re-excision and relapse rates.

**Change in therapeutic approach**

The impact of MR findings of additional disease measured in terms of change in therapeutic approach shows a correct change of treatment rate of 5-30\% and an incorrect change of treatment rate of 0.5-11\%. Previously published meta-analyses\textsuperscript{13-15} show the complexity of the analysis of the treatment change due to the large number of variables involved. A rate of 16.6\% of change in the surgical management due to MR findings was reported by Houssami.\textsuperscript{15}

**Re-excision rates**

Despite the lack of randomised studies proving the superiority of MR imaging (results of the COMICE study show a re-excision rate of 19\% for both MR-staged and non MR-staged women),\textsuperscript{16} some authors point out that MR staging results in lower re-excision rates. Grobmyer et al\textsuperscript{17} reported rates of 10\% in a retrospective series of 79 patients and compared these rates with a series of patients from their institution with a re-excision rate of 20\%. A recently published case-control study that assesses the impact on re-excision rates\textsuperscript{18} showed no significant differences between patients staged with MR (13.8\%) and non staged with MR (19.4\%); however, when stratified to tumor type, incompletely excised infiltrating ductal carcinoma was significantly associated with absence of MR staging.
Relapse rates
The study by Fischer analyzes the long-term impact of preoperative MR staging on the relapse and contralateral disease rates, but there are some objections regarding the scientific methodology used to assess the impact on the relapse, since the non-MR assessed group showed criteria of worse prognosis. However, this methodological bias does not affect the higher rate of contralateral disease found in patients non-staged with MR (4%) in comparison with the lower number of contralateral tumors found in the MR group (1.7%), which makes his conclusion perfectly valid.

Monitoring of the response to treatment
The main benefit of neo-adjuvant or primary chemotherapy (PCT) is to reduce the tumor size allowing conserving surgery with free margins. Moreover, PCT theoretically provides an early treatment of the circulating cells with metastatic potential and allows "in vivo" assessment of tumor chemosensitivity. The last decade has seen a rise in the role of MR imaging for the evaluation of the response due to the consistently better histopathologic correlation offered by this modality in comparison with conventional methods. This is largely due to the fact that RM assesses the morphology as well as the function, overcoming the limitations imposed by fibrosis and post-treatment necrosis on mammography, ultrasound and palpation. Previous studies in patients treated with PCT show that the correlation between MR and final histological results ranges between 0.71 and 0.90.

In these patients, MR studies are performed prior to and half-way through the chemotherapy (after the 3rd or 4th cycles) and directly prior to surgery (fig. 7 and 8). The parameters to be assessed are:
- Quantitative: changes in tumor diameter or size throughout the treatment. The RECIST or UICC criteria are normally used for assessment: major partial response (> 50%), minor partial response (< 50%), complete or no response.
- Qualitative: concentric shrinking or fragmentation related to the possibility of achieving free margins in conserving surgery (higher for concentric response).

The major limitation of MR in this context is the infra- and overestimation rates of residual disease (6-25%). Spectroscopy and diffusion imaging show encouraging results, even offering prognostic value.

Diagnosis of tumor relapse
Relapses are uncommon during the first 18 months after treatment and, in most cases, appear in the surgical bed during the first 5 years. Annual risk of relapse has been reported to occur in 1-2%. There is consensus on the superiority of MR to differentiate relapse from post-surgery and post-radiotherapy changes, in comparison with mammography and ultrasound. RM is the imaging modality with the highest sensitivity and negative predictive values for the detection of relapse, avoiding unnecessary biopsies and reducing patient anxiety. Nonetheless, we need to keep in mind that
the surgical scar usually enhances during the first six months and that inflammatory changes of fat necrosis may result in false positives31 (fig. 9).

Likewise, the studies should begin 18 months after the end of radiotherapy. Tumor relapse shows similar semiology on MR than the primary tumor (early enhancement and subsequent washout), while enhancing surgical scar usually shows progressive enhancement and absence of washout. Diagnosis of fat necrosis may be reached without performing a biopsy, through the analysis of T1 gradient-echo and T2 FSE sequences. Characteristically, fat necrosis shows a central area of fat tissue that appears hyperintense on T1 gradient-echo and hyper- or hypointense on T2-weighted sequences.31

Screening of high-risk patients

Family history of breast cancer is one of the most important risk factors for this disease. It has been reported that hereditary familial factors represent between 10-15% of cases.

Figure 6 Multifocal breast cancer. MIP image (a) shows the index tumor of 22 mm located in the left superior quadrant of the right breast and a second enhancing focus of 4 mm (arrow), 35 mm apart, oriented toward the areola, which was reassessed with ultrasound. Ultrasound (b) helped identify the lesion, and guided the biopsy and clip placement. Biopsy was positive for malignancy. The mammogram (c) shows the clip and the correlation between the MR and mammographic findings. Prior to surgery, a radiotracer (ROLL o Radio-guided Occult Lesion Localization) was injected into the clip area (visible on ultrasound) and subsequently the clip was seen within the excised surgical specimen (marked with an intramuscular needle for the pathologist). This MR finding implied a wider conserving surgery.

Figure 7 Fragmented major partial response. Staging breast MR imaging in a patient with extensive DCIS. The second image (post-treatment MR performed prior to surgery) shows residual disease in the shape of scattered small foci of enhancement that occupy the same area as that seen on the pre-treatment image. The tumor volume/breast volume ratio made possible conserving surgery and the patient was able to conserve the breast, but the surgical specimen included the whole area initially involved.
Since the late 1990s, MR imaging is part of the intensive screening of high-risk women and, in the last ten years, several prospective non-randomized studies have been carried out to analyze the results of MR screening. The results of the multicentre studies with the largest number of patients show that MR has a sensitivity two times higher than mammography. Both the combined analysis of five prospective studies by Sardanelli (3571 patients) and the review of 11 studies by Warner show similar results: sensitivity was 81% for MR, 40% for mammography in the study by Sardanelli; and 77% and 39% respectively, in the study by Warner. The interval cancer rate was <10% in all the studies and almost all breast cancers occur in genetic mutation carriers.

Breast cancer in BRCA 1 and BRCA 2 mutation carriers show special clinical, pathological and radiological characteristics: they are apparently benign tumors (with well-defined borders) and appear in very young patients, with a doubling time much shorter (40-50 days) than non-carrier patients (80 days). Triple-negative is the most prevalent molecular phenotype, with worse prognosis. Mammography is of less value in these patients, since this group has dense and more radiosensitive breasts than general population.

Study of occult primary breast cancer
Occult primary breast cancer accounts for less than 1% of all breast cancers. It may present as a metastatic axillary lymphadenopathy or as disseminated disease. When conventional modalities fail to detect the breast tumor, a mastectomy is indicated; however, in one third of the patients no tumor will be found in the surgical specimen. Another option is whole breast radiotherapy, but this treatment has been associated with high relapse rates. MR is emerging as the technique of choice in this clinical context for two reasons: its high sensitivity in the detection of breast cancer and its capability to avoid mastectomies when the extension of the disease allows conserving treatment.

Evaluation of patients with breast implants
There are two different settings for the use of MR in women with breast implants: assessment of breast implant rupture and cancer detection when the implants impair correct visualization of breast tissue. As for the first indication, a meta-analysis including 18 published studies reported an overall sensitivity and specificity of 78% and 91%, respectively, for MR evaluation of
breast rupture. The authors reported that the high predictive value of MR justifies its use in symptomatic women. Other studies confirm these data and recommend the use of unenhanced MR in symptomatic patients. However, in asymptomatic patients the use of MR as a screening tool is not justified. Breast ultrasound and MR may be useful in the detection of cancer when the implants impair mammographic visualization of the glandular tissue.

Conclusion

MR imaging is a powerful diagnostic tool as long as it is used in conjunction with the information provided by mammography and ultrasound. This represents a challenge to knowledge due to its technical peculiarities and the high prevalence of breast cancer in the general population. The spectrum of its clinical applications is constantly expanding and it is expected that MR will become a standard technique in all the Departments of Radiology in the near future.

Conflict of interest

The author declares no conflict of interest.

References


