The role of second-look ultrasound of BIRADS-3 mammary lesions detected by breast MR imaging

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ABSTRACT

Objective: To asses the value of second-look ultrasound (US) for identifying BIRADS 3 (Breast Imaging Reporting Data System) mammary lesions detected by breast Magnetic Resonance imaging (MRI).
Materials and methods: From April 2008 to May 2009 330 breast MRI were performed of which 60 patients are classified as BIRADS 3. 84 lesions underwent second-look US and percutaneous vacuum biopsy Vacora system US-guided. Statistical analysis: lesions were stratified into two groups: visible on US (Group 1) and not visible on US (Group 2).
  The clinical impact of second-look US was studied in terms of negative predictive value (NPV).
Results: The positive predictive value (PPV) of category 3 BIRADS MRI was found to be 89%. Second look-US results detected lesions in 51% of the MRI enhancing lesions. The second look-US showed a NPV of 97%. The NPV of second look-US was significantly greater than the NPV of MRI BIRADS 3 (97% vs 89%, $p < 0.05$). The logistic regression analysis showed a higher number of malignant lesions in group 1 than in group 2 (7vs 2, OR 3.7, $p < 0.05$).
Conclusions: The second-look US permitted the correct management of subcentimetric MRI BIRADS 3 lesions not visible with conventional imaging tecniques.

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1. Introduction

Breast cancer is the most frequently diagnosed malignant cancer in women. More than 38,000 new breast cancers are diagnosed annually in Italy [1], it is the leading cause of cancer death in women, followed by bronchial carcinoma. According to the projections of the American Cancer Society in 2010, about 39,840 deaths are expected in the U.S. from breast cancer, with a gradual reduction in mortality of 3.2% from 1990 to 2006 in women younger than 50 years old and 2% in those aged over 50 [2]. The reduction in the incidence of mortality is attributable to the combined effect of early diagnosis and more effective treatment.

Non invasive diagnostic imaging of mammary carcinoma includes mammography, ultrasound (US) and magnetic resonance imaging (MRI).

BI-RADS (Breast Imaging Reporting Data System) is a scoring system developed for classifying mammary lesions into 5 classes, where class 1 and 2 conclude the diagnostic procedure (R1-R2

benign lesion) while class 3-4-5 generate either a short-term follow-up strategy (R3 probably benign lesion) or an invasive diagnostic procedure (R4-R5 probably malignant lesion) [3,4].

The increasingly prominent role of MRI in detecting breast lesions not visualized by the traditional imaging system, allowing not only morphological, but functional characterization of the focus of neoangiogenesis [5–8]. However, the main limitations to the technique are the high number of false positive findings and the subsequent management of incidental findings [9–11]

Re-evaluation with US study performed after MRI and targeted at the site where MRI identified the new lesion (second-look US or targeted US) permits characterisation of this lesion or confirmation of MR false positive finding. It contributes to the diagnostic workup in many cases and selects patients for biopsy or lesion localization under MRI guidance.

The aim of this retrospective study is to assess the role of second-look US in evaluating BI-RADS 3 lesions detected on breast MRI.

2. Materials and methods

2.1. Study population

From April 2008 to May 2009, 330 breast MRI were performed (150 patients with suspect cancer lesions visualized by

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Table 1
MR identified lesions included in our study.

Characteristics	n (%)	Dimensions (mm)[a] (mm)
BIRADS 3		
Nodula lesions with regular edges	74 (88)	6 ± 3
Non nodular lesions	10 (12)	7 ± 2

[a] Maximum transversal diameter calculated based on T1- post MR contrast images.

mammography and ultrasound; 50 patients with suspect carcinoma unknown primary (CUP) tumor syndrome, 52 patients with ascertained mammary carcinoma genetic risk, 78 patients for post-surgery follow-up). Of these 330 patients, 275 neoplasia had confirmed by MRI. Of these 275 patients, 88 were treated with neoadjuvant chemotherapy and consequently excluded from the study. Of the remaining 187 patients, 60 with 84 focal enhancement (6 ± 3 mm) classified as BI-RADS 3 and not visualized by the conventional imaging techniques (Table 1) were included in the study. MRI lesions scored as BI-RADS 1, 2, 4, 5 were excluded.

Eight-four incidental lesions classified as BI-RADS 3 included in this study were identified on breast MRI for which further diagnostic investigation with targeted US and percutaneous microbiopsy was recommended. The reference standard was histopathology of image-guided microbiopsy or surgical specimens or clinical and imaging follow-up at 12 months.

Patients with lesions visualized by US second-look underwent percutaneous microbiopsy performed with a vacuum biopsy systems Vacora (Bard Biopsy Systems, Tempe, AZ, USA) US-guided. Patients with lesions not visualized by second-look US underwent percutaneous microbiopsy performed with a vacuum biopsy systems Vacora MRI-guided. Patients with benign lesions on microhistological examination were monitored with MRI examination (average follow-up: 8 months; range: 6 months, 1 year). Patients with malignant lesions on microhistological examination were

surgically treated (excision). Atypical hyperplasia was considered as malignant lesion, while simple hyperplasia was considered as benign.

The study was authorized by the Internal Ethics Committee. All patients attending the study signed an informed consent.

2.2. MRI examination

The study was performed on a 1.5 T (Intera, Philips Healthcare, Best, The Netherlands) between the 7th and 14th days of the menstrual cycle (43 cases) and without temporal limitations in postmenopausal women (12 cases). All the patients underwent MRI exam with SENSE technology. Images were acquired with a dedicated bilateral breast surface coil and the patient in the prone position. MRI images were acquired in the axial planes. The MRI protocol included the following sequences: T1 (TSE) (TR/TE 6.8/3.3 ms; thickness, 3 mm, gap 0; matrix, 512 × 512); T2- TSE (TR/TE 3800/140 ms; thickness, 3 mm, gap 0; matrix, 225 × 512); a short tau inversion recovery frequency(STIR) (TR/TE/TI/4000/42/155 ms; 3.0 mm, gap 0; 320 × 224) and a T1 dynamic frequency (2D) (FFE) (TR/TE 290/4.6 ms; flip angle, 90°; matrix 256 × 512; thickness, 3 mm; 8 dynamics; with 50 s time resolution for each). The T1 dynamic frequencies were acquired after 0.1 mmol/Kg gadolinium bolus injection (gadopentetic acid and dimeglumine salt, Magnevist; Schering, Berlin, Germany) administered at a rate of 2 mL/sec, followed by 20 ml of physiological solution.

2.3. MR images analysis

All studies were analysed independently by two breast radiologists. During the assessment of MRI exams, the images of the conventional exams previously performed were available (mammography, ultrasound). Each observer assessed the enhancement characteristics: shape nodular (assessment of shape: circular, oval, lobulated or irregular; edges assessment: smooth, irregular,
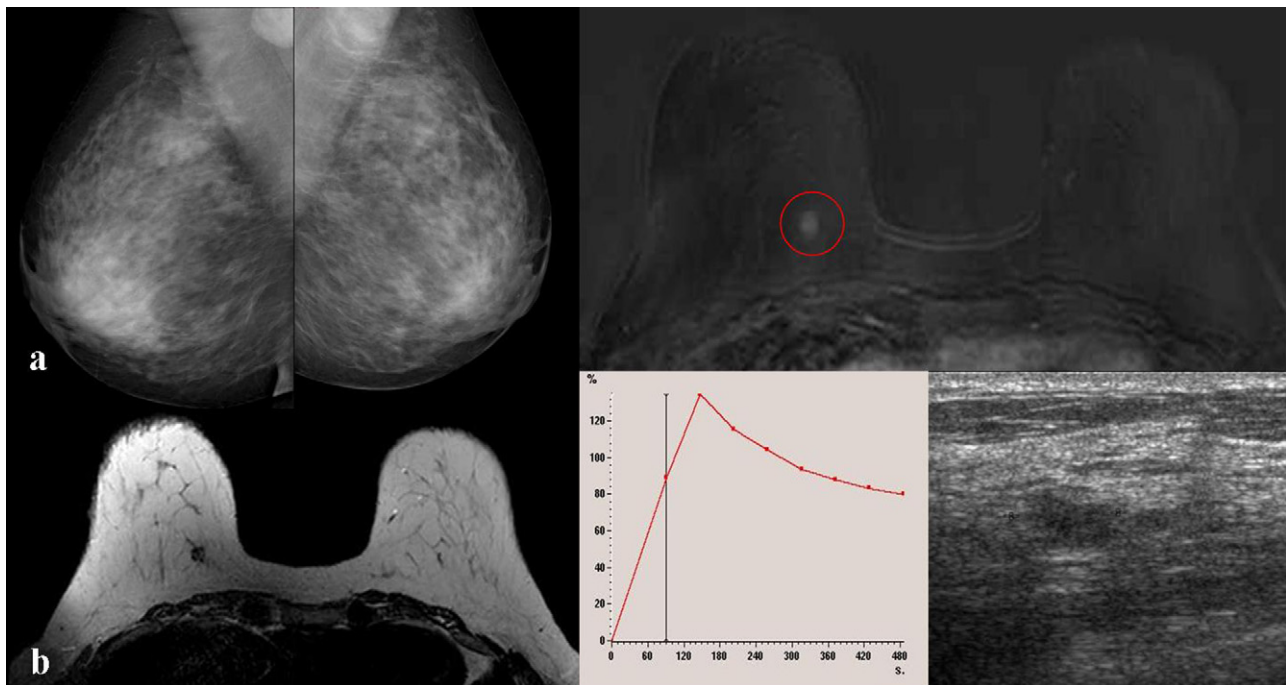

Fig. 1. Mammography (a) performed with oblique projections shows a breast picture with predominant fibroglandular structure, on the right armpit an oval radiopacity is visible (lymph node). MRI (b) shows circular enhancement with irregular edges just next the right breast QII, that exhibits sharp hypointensity in T2 weighted images. The IS/t curve of the right lesion shows a rapid and intense wash-in and wash out. The second look ultrasound (c) confirms a blurred hypoechogenic area on enhancement site (right QII), with irregular edges. The histological exam performed with VAB taking, identified this lesion as infiltrating ductal carcinoma.
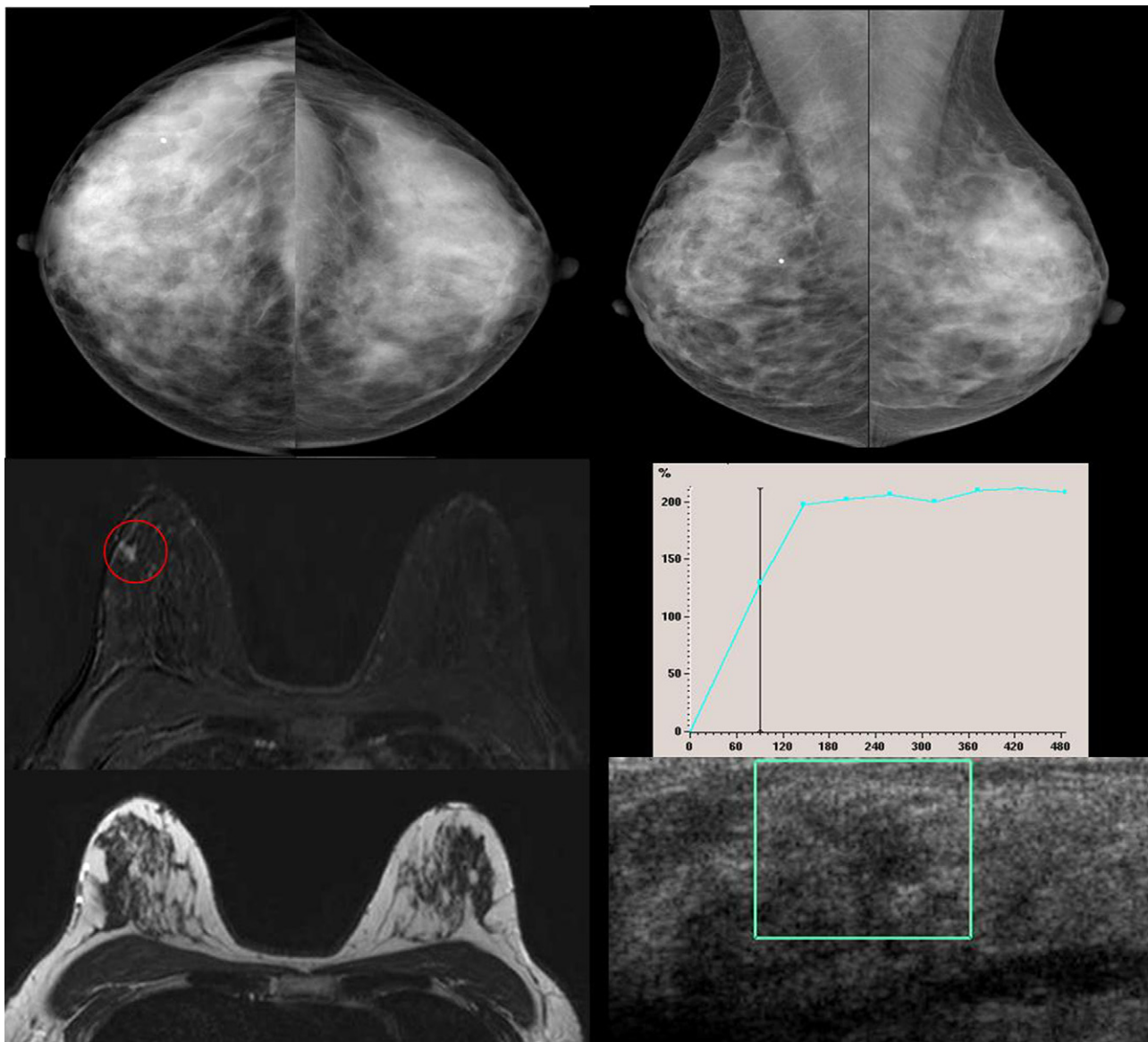
Fig. 2. Mammography (a) shows multiple, scattered microcalcifications with etrogeneous morphology in fibroglandular breasts with asymmetrical parenchyma distribution. MRI(b)shows spiculated-edge enhancement on right QSE not mass-related. The IS/t curve shows a rapid and intense plateau- tending wash-in and wash out tendente al plateau. The second-look ultrasound (c) shows on the site of the MR-highlighted a pseudo-nodular, dishomogeneous, mainly hypoechogenic formation that, on a color-Doppler module examination, does not appear significantly vascularized. The histological exam performed with VAB taking, identified this lesion as carcinoma in situ.

spiculated) or non-nodular (distribution pattern assessment: focal, linear, ductal, segmental, regional, diffuse) and the internal architecture (enhancement distribution: homogeneous, heterogeneous, dot-like). The regions of interests (ROI), were drawn manually around the suspicious lesions and an area adjacent to it in order to evaluate the signal/time intensity ratio (Is/t). The Is/t curves were characterized depending on the presence of persistent enhancement (Type 1), plateau (Type 2) or wash-out (Type 3). Lesions were classified according to BI-RADS criteria, using Fisher score.

2.4. Second-look US

US study was performed by using a 7–15-MHz transducer (ATL HDI 5000, Philips Healthcare, Best, The Netherlands) by dedicated breast radiologist. The targeted US was carried out within 1 week of the MRI examination. To locate the MRI lesions on

US, the distance of the lesion from the skin and nipple were used.

2.5. US Images analysis

The lesions with signs of benignity were allocated to BIRADS 3 group (circular or oval shape, parallel orientation, circumscribed edges, neat interface, no US beam back blocking, no adjacent parenchyma alterations) and were monitored with MRI after 6 months. All the lesions that did not satisfy benignity criteria and did not show at least 3 signs of malignancy (irregular shape, anti parallel orientation, blurred edges, hyperechogenic halo, ultrasound beam acoustic blocking, adjacent parenchyma alterations) were included in BI-RADS 4 group. The lesions showing at least 3 signs of malignancy were assigned to BI-RADS 5 group. The lesions included in BI-RADS 4-5 group underwent with histopathological examination. In the cases in which the MRI lesion had an US
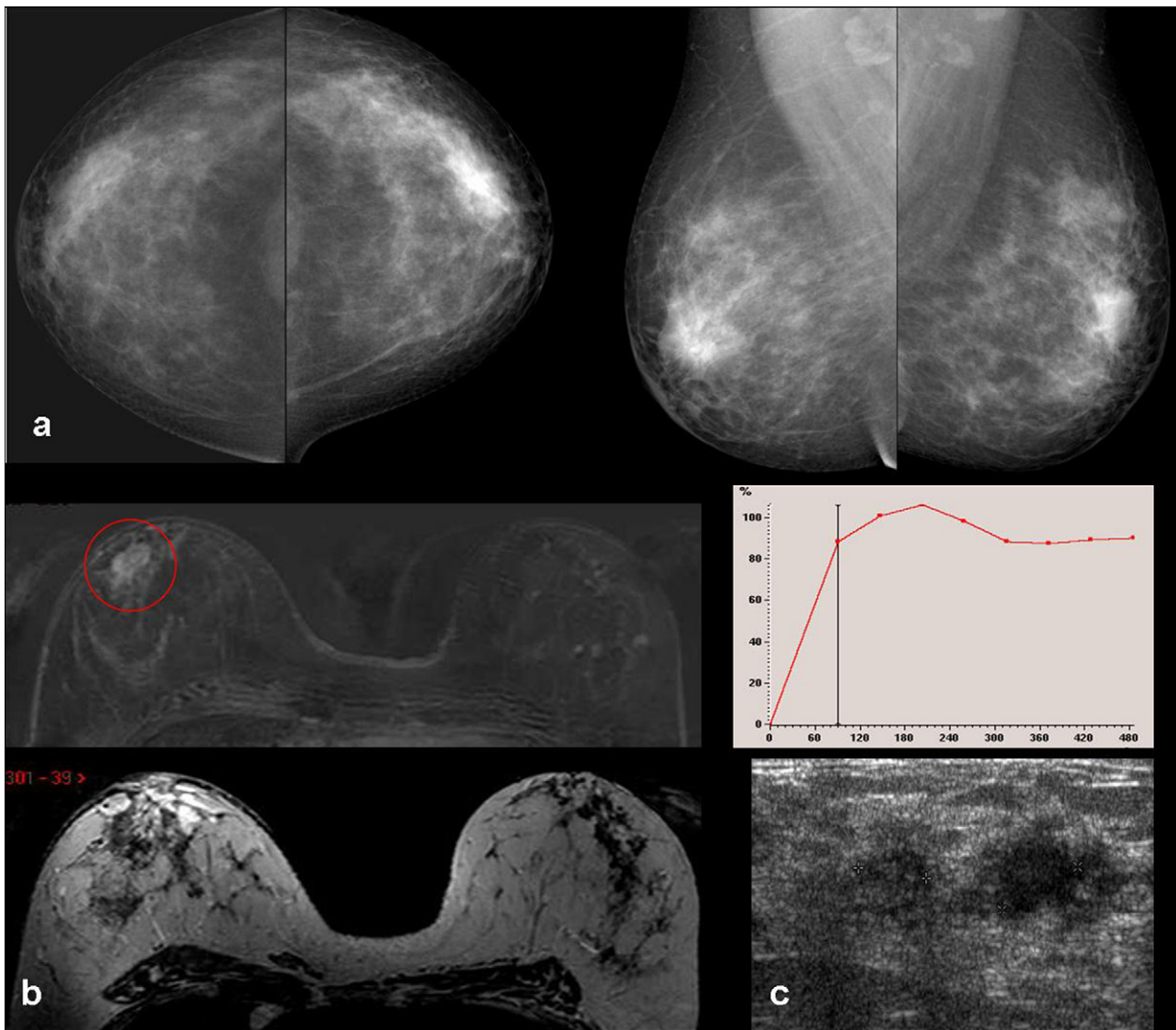
Fig. 3. Mammography (a) shows an area of glandular thickening mainly apparent on the right where irregular edges are visible. MRI(b) shows on right back areola region, a nodular area with dishomogeneous contrast enhancement with irregular edges related with mammographic finding; on the left at least tre nodular enhancement areas are visible on the outer quadrants passage not mass-related. The left IS/*t* curve shows a rapid and intense wash-in and wash out. The second look ultrasound (c) targeted on findings found on the left shows hypoechogenic areas with irregular edges. The histological exam performed with Tru-Cut taking on the right and VAB on the left, identified this lesion as infiltrating ductal bilateral carcinoma.

correlate, the diagnostic workup proceeded if necessary to US-guided biopsy.

2.6. Vacuum assisted biopsy: VAB

Lesions were sampled by vacuum biopsy systems Vacora (Bard Biopsy Systems, Tempe, AZ, USA) MRI-guided for standard histological and immunohistochemical parameters (receptors for estrogen, progesterone and HER-2/neu). The system is equipped with an MRI compatible, disposable coaxial stainless steel introducer needed to guide the amagnetic fine needle up to the area of interest. The needle consists of two stainless steel cannulae with 10 Gauge outer diameter; the inner cannulae includes a window for the sample collection, connected with the aspiration cylinder. The vacuum biopsy systems can be employed as handheld device as well: it allows pressure vacuum generation through an electric engine equipped with a microprocessor [12].

2.7. Statistical analysis

After the second-look US examination, lesions were stratified in two groups: US-visible lesions (Group 1) and US-non visible lesions (Group 2). Through a logistic regression analysis we studied: (i). to what extent the MRI lesion characteristics [enhancement type (nodular or non nodular), dimensions (cut off 5 mm) were correlated to the US visible lesions. (ii) To what extent lesion malignity or benignity (diagnosed with the histological examination) was correlated to the lesions US appearance.

The US visible lesions were classified according to BI-RADS criteria: BI-RADS ECO 2 (benign lesions), BI-RADS-ECO 3 (probably benign lesions), BI-RADS-ECO 4 (probably malignant lesions), BI-RADS-ECO 5 (malignant lesions). The logistic regression analysis was employed to identify the US signs mainly associated with lesion malignity or benignity. Clinical impact of targeted US was assessed by negative predictive value (NPV). The McNemar test was employed to compare the NPV of MRI BIRADS 3 group with the global NPV of second-look US (the number of lesions re-categorized
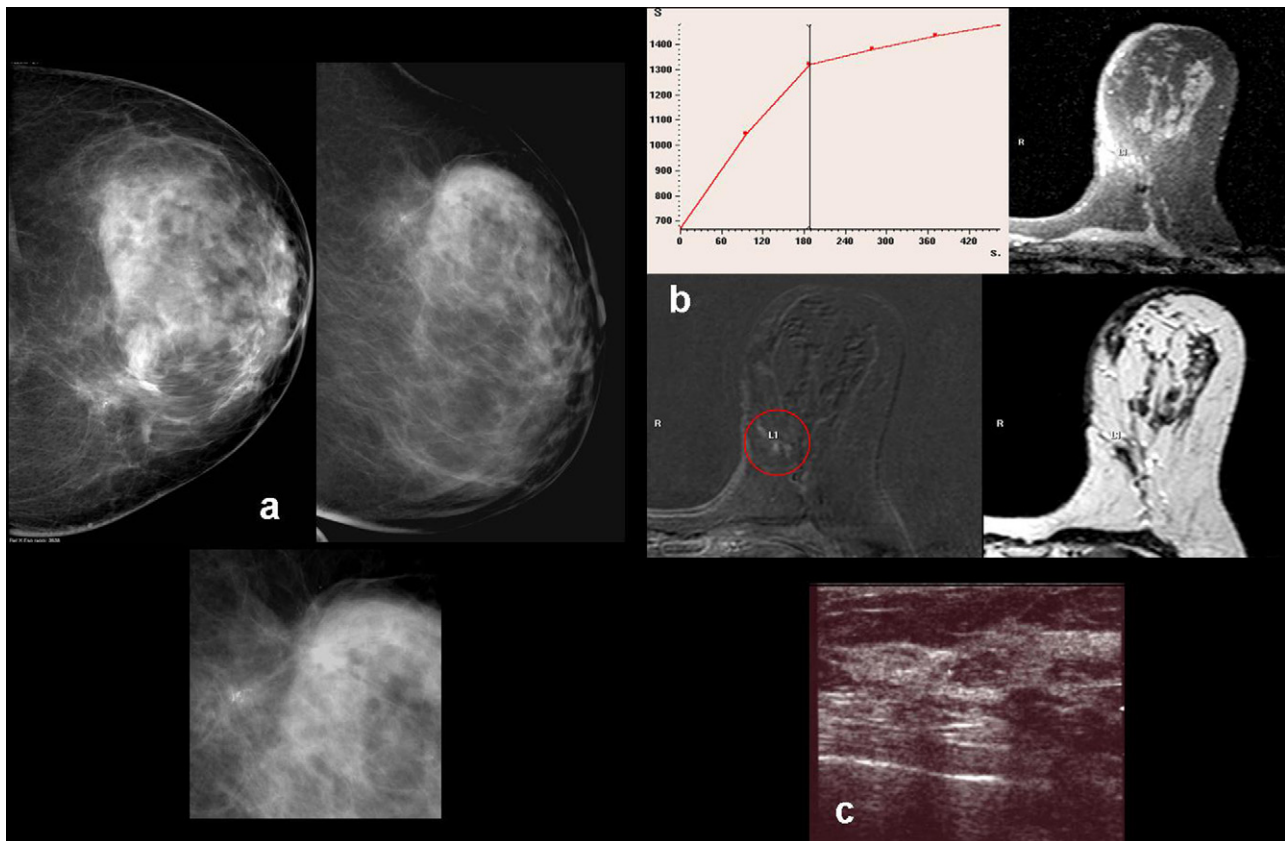
Fig. 4. Mammography (a) shows on the inner quadrants passage area, high-density microcalcifications with irregular morphology that were not visualized during the previous checkup. MRI (b) shows a blurred contrast-enhancement extending with irregularly linear morphology with slow and gradual wash-in. The second-look ultrasound (c) shows hypoechogenic area with blurred edges. The micro-histological exam performed with VAB identify this lesion as simple ductal hyperplasia (FP).

into the different BIRADS groups were added up and the global NPV was compared with NPV of MRI BIRADS 3) The regression analysis was conducted using the "stepwise" procedure, with the backward elimination; the model goodness-of-fit was evaluated with the Hosmer and Lemeshow test. An odds ratio significantly different from 1 was considered as association index. The significance level of the test was $p \leq 0.05$. The statistical analysis was performed with a commercially available software (NCSS 3.7 version, 329 North 1000 East Kaysville, Utah 84037 USA).

3. Results

3.1. MRI BIRADS 3 lesions histological characteristics

Of 84 MRI BI-RADS 3, 9 lesions (10%) were malignant (Figs. 1–3, 5), while 75 (90%) were benign (Fig. 4). All the nodular lesions showed homogeneous enhancement and regular edges. A persistent Is/t curve or a plateau were observed in 43% and 53% cases, respectively. No statistically significant correlation between lesion histology and enhancement or Is/t curve type was found. In our series the MRI BI-RADS 3 category positive predictive value (PPV) amounted to 89%.

3.2. Correlation between MRI characteristics and second-look US

Targeted US detected 51% of MRI enhancing lesions (Group 1). The logistic regression analysis revealed a predominance of nodular lesions in Group 1 (OR 14.1, $p < 0.05$), compared with Group 2 (US non visible lesions) (OR 5.2, $p < 0.05$); No statistically significant

correlation between lesion dimensions and Group 1 or Group 2 (OR 0.95, $p = 0.32$) was found.

3.3. Correlation between histopathological characteristics and second-look US

On 84 VAB, 43 (51%) US-guided biopsies (second-look US visible lesions, group 1) and 41 MRI biopsies (49%) (second-look US non visible lesions, group 2) were carried out.

On average 9 ± 2 bits/lesion were taken. In all cases the taken specimens were considered adequate and diagnostic. The histologic diagnosis on VAB is shown in Table 2. The benign lesions were re-assessed with MRI dynamic examination 1 week after the procedure. In 20% of the cases a residual enhancement was observed, while in the remaining 80% the enhancement was not visible. The

Table 2
The histologic diagnosis on VAB.

	Group 1[a] n(%)	Group 2[b] n (%)
Benign Lesions	**36 (43)**	**39 (46)**
Fibrocystic breast disease	11	12
Adenosis	8	10
Simple Hyperplasia	14	11
Papilloma	3	6
Malignant Lesions	**7 (8)**	**2 (2)**
Infiltrating Ductal Carcinoma	3	0
Ductal carcinoma in	3	1
Atypical Ductal Hyperplasia	1	1

[a] Lesions visible with second look ultrasound.
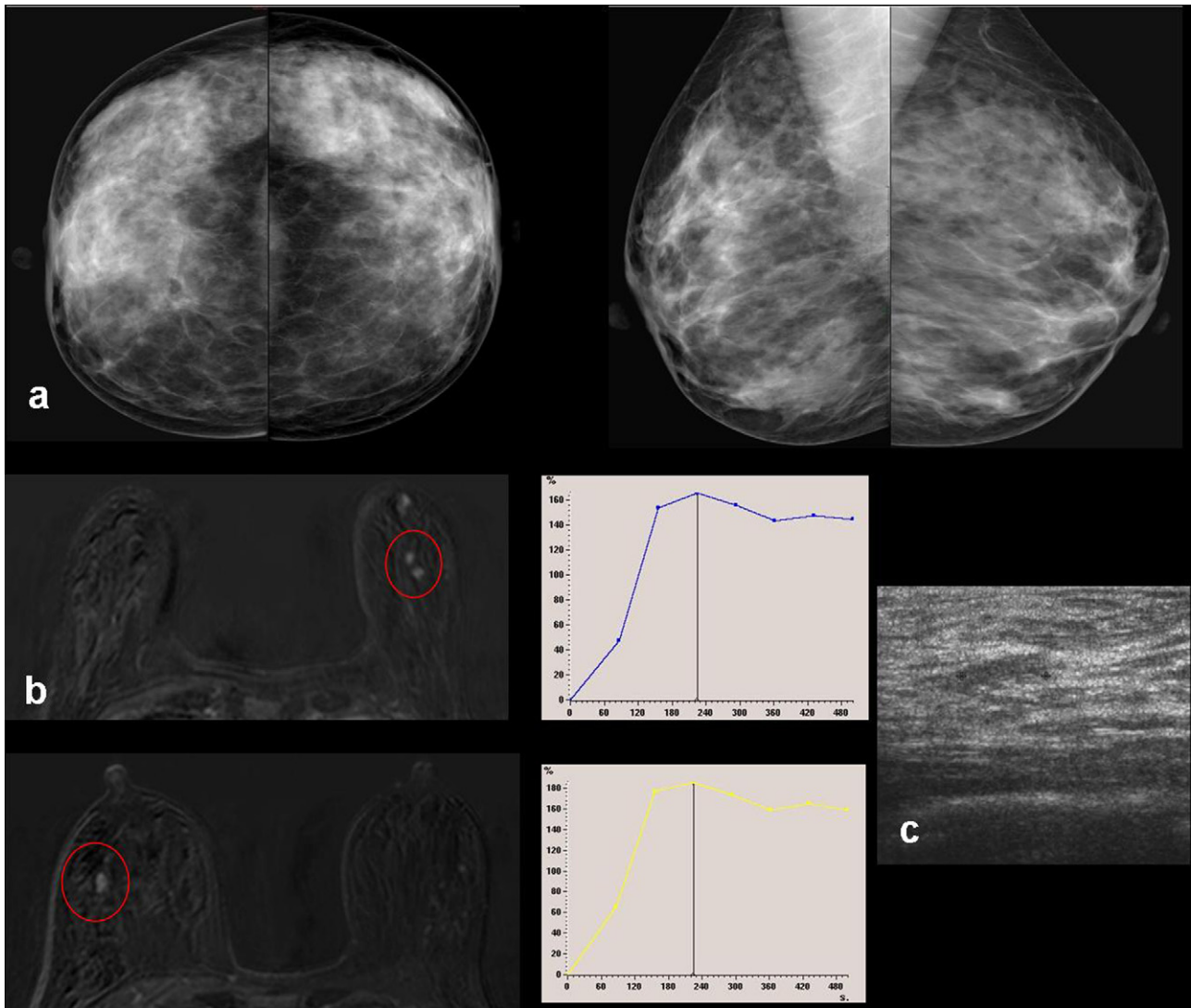[b] Lesions not visible with second look ultrasound.

Fig. 5. Mammography (a) shows a fibro-glandular breast; in the left brast at QSE can see a cluster of microcalcifications with radiopaque nodular areas. MRI (b) shows in the left breast the presence of three areas of finding breast enhancement, in the right breast at the crossing portion are observed two areas of nodular contrast-enhancement and smooth regular margins unrelated to mass. These lesions have a profile curve characterized by rapid wash in and wash out. The second-look ultrasound (c) confirmed in the left at the site of the MRI finding the presence of a multilobulated hypoechoic area with irregular margins. The subsequent histological evaluation, was performed by VAB, demonstrated a infiltrating ductal carcinoma.

logistic regression analysis showed a prominant malignant lesions in Group 1 compared with Group 2 (7 vs 2; OR 3.7, $p < 0.05$).

No significant correlation between lesion dimensions and malignity (OR 1.2, $p > 0.05$) was found. The majority of the cases included in BI-RADS 4 showed a hyperechogenic ecostructure and blurred edges. In these cases only the presence of blurred edges was associated with a malignity diagnosis to a greater extent. (OR 15.4, $p < 0.05$). The majority of cases in BI-RADS 4 with hyperechoic echotexture and ill defined margins were malignant. Only the presence of well defined margins was associated with higt significantly a benign histology (OR 11.3, $p < 0.05$).

The 5 benign lesions classified as BI-RADS 4 showed hypoechogenic echotexture and lobulated edges. No lesion was classified at US as BIRADS 1-2-5.

3.4. Evaluation of the second-look US diagnostic accuracy

Of 7 malignant lesions, 1 lesion as BI-RADS 3 and 6 lesions as BI-RADS 4 were classified at the second-look US. Of 36 benign lesions, 34 were classified as BIRADS 3 and 2 as BIRADS 4 (Table 3). The US

Table 3
Benign and malignant lesions distribution in ultrasound BIRADS categories.

BIRADS	Malignant n (%)	Benign n (%)
3	1 (14)	34 (94)
4	6 (86)	2 (6)

second-look thus showed a 97% NPV. The second-look US NPV was significantly higher than the NPV for MRI BIRADS 3 (97% vs 89%, $p < 0.05$).

4. Discussion

The aim of this retrospective study is to evaluate the diagnostic accuracy of second-look US from the NPV of subcentimetric MRI enhancing lesions. The BIRADS 3 choice was intentional as it is the only group exhibiting similar likelihood for both malignant and benign lesions. Class 1 and 2 lesions (benign lesion) do not require diagnostic work-up, and class 4–5 generate an invasive diagnostic procedure (probably malignant lesion), the group 3

requires a short-term follow-up strategy (probably benign lesion), or an invasive diagnostic procedure to be assessed on a case by case basis, based on images obtained with conventional imaging techniques (mammography, MRI and US) for each patient. The study showed that the MRI BIRADS 3 lesions, visible with US second-look demonstrated nodular enhancement with well defined margins, regular edges and that ultrasound visibility is not correlated to lesion dimensions. Further, the regression analysis highlighted a malignant lesion predominance in the US visible group compared to the US non visible group. The targeted US had a significantly higher NPV than MRI BIRADS 3 (97% vs 89%); the US second-look was more reliable than MRI BIRADS 3 category not only in predicting sub-centimetric lesion benignity but also in directing the radiologist to the most appropriate short-term follow-up.

Regardless of the employed imaging technique (Mammography, Magnetic Resonance or Ultrasound), BIRADS classification was developed to permit close checkups practice (BIRADS 3) as an alternative to invasive diagnostics (BIRADS 4 and BIRADS 5). It is essential to achieve a reliable BIRADS 3, with a high NPV, in order to shorten diagnostic times (or eliminate inappropriate follow-up requests in case of a histological malignant lesion).

The percentage of malignant lesions for MRI BIRADS 3 group in our series (10%) is comparable with the results published by other authors. [13,14]. Tozaki et al. on the contrary, reported NPV values higher than ours [15]. It must be said, however, that the Authors did not report the lesions dimensions in their work. The lesion dimensions affect the perception of the lesion margins and hence its characteristics. Subcentimetric nodular lesions (6 ± 3 mm), included in this study, according to the size of the lesions mentioned in the Laguna's study [19], show hardly characterizable edges, because the irregularities are barely visible and consequently the lesions can be mistakenly classified as smooth edges lesions (BIRADS 3 and not 4). Moreover, the morphology of these lesions, as it has not a morphological equivalent on the T2 weighted sequences, is assessed on enhancement morphology (interface between vascularized area and non vascularized parenchyma, contrary to ultrasound which has the ability to examine the interface between expansive process and adjacent parenchyma) [16]. In our series only 43/84 (51%) lesions were visible with ultrasound second look. This result is comparable with other results found in the literature [17]. We should consider also that the identification with US imaging of a lesion visualized by MRI is not simple from a technical point of view, because of the different positions of the patients between the two exams that can result in localization errors, especially with big-sized breast.

In accordance with other studies, our series showed a predominance of malignant lesions in the group of US visible lesions, while a correlation between lesion US visibility and its dimensions (cut-off 5 mm) was not observed. In our study the NVP of US was 97%, a value notably higher than NPV of MR BIRADS 3 (89%). Our results tally with those reported by other authors, showing a high NVP for US class BIRADS 3 [18].

The US second-look permitted the correct management of subcentimetric MRI BIRADS 3 lesions not visible with conventional imaging tecniques. However, as approximately only 51% of the MRI enhancements are visible on US second-look, a percentage slightly lower than reported in the literature [19]. This is probably because in our study we considered only lesions classified as BIRADS 3.

Also the malignant lesions in the group without US correlate (2%), result in lower percentage compared to malignant lesions visible at second-look US (8%).

In our study, 41 lesions not visible with second look US were subjected to MRI-guided vacuum-assisted biopsy. In the absence of US correlation, the presence of a tumor cannot be ruled out. Then, with this method it is possible to overcome the major limitation present in Laguna's study [19]. But, also in our study, remain the US limitations. Therefore, it is advisable for those patients at high risk of developing mammary carcinoma and in cases of MRI suspicion with no US correlate to have an MRI-guided targeted biopsy or localisation in order to achieve a quick diagnosis.

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