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Our Radiological Experience on B3 Lesions: Correlation Between Mammographic and MRI Findings With Histologic Definitive Result

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Abstract

Lesions suspected for breast cancer are always sampled by biopsy before management decisions are made. The result is classified basing on histologic characteristics, ranging from B1 to B5. The B3 class represents benign lesions with a possible, but not always predictable, risk of increased malignancy. Currently, every single B3 case has to be discussed in a multi-disciplinary team. Specific mammography and magnetic resonance findings can reduce the rate of surgeries on benign lesions and better evaluate the malignancy rate of B3 lesions.

Introduction: The purpose of this study was to evaluate mammographic and magnetic resonance imaging (MRI) features in B3 lesions. **Patients and Methods:** From 2011 to 2018, 139 patients with histologically proven B3 lesions who underwent mammography or/and MRI, were retrospectively reviewed. B3 lesions were classified in: atypical ductal hyperplasia (ADH), lobular neoplasia (LN), papillary lesion (PL), radial scar (RS), flat epithelial atypia (FEA), phyllodes tumor (PT), or mesenchymal lesion. Imaging features evaluated were: the presence of microcalcifications, mass and architectural distortions on mammograms and type of margins (circumscribed, irregular, spiculate), enhancement (mass-like, non-mass-like), size ($\leq$ 15 mm, $>$ 15 mm), and kinetics curves (I, II, III) on MRI. The definitive histologic results confirmed benign lesion or were upgraded to malignancy, and the positive predictive value was calculated. **Results:** Histologic classification of B3 lesions counted 45 (32.37%) ADH, 12 (8.63%) LN, 25 (17.99%) PL, 5 (3.61%) RS, 31 (22.31%) FEA, 20 (14.39%) PT, and 1 (0.70%) mesenchymal lesion. One hundred seven patients had mammography, and 38 had MRI. In 90 (65%) cases, the histologic diagnosis confirmed B3, in 15 (11%) cases, benign lesion, and in 34 (24%) cases, malignancies were found, with best positive predictive value for mesenchymal tumor (1), ADH (0.36), and FEA (0.4). Significant correlations comparing core needle biopsy groups and microcalcifications (P = .016) and presence of mass (P = .002) and comparing definitive histology with the presence of mass (P = .023), were found. Regarding MRI, the morphology correlated with core needle biopsy groups (P = .038); morphology (P = .024), dimension (P = .040), and kinetic curve (P = .005) correlated with malignancy. **Conclusions:** The B3 category includes different entities, with various risk of malignancy; their heterogeneity is associated with specific mammographic and MRI features, although further confirmations are needed.

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Introduction

In the past years, diagnosis and treatment improvements led to a significant decrease of breast cancer mortality rates. However, breast cancer still remains the most common cancer in the world, second only to lung cancer for cancer-related deaths. Screening and early diagnosis have an essential role in detecting tumors that would have otherwise been neglected, with the result of fewer invasive surgery practices and lower recurrence rates.[1]

Although imaging techniques have a limited role in characterizing suspect findings, mammography, ultrasound, and magnetic

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resonance imaging (MRI) can detect tumors, assess their location, and differentiate between benign and malignant lesions. The literature has reported an increase in diagnosis of suspicious findings with a score higher than 4 on the Breast Imaging Reporting and Data System (BI-RADS) scale, which needs histologic analysis.[2] The consequence is a higher bioptic procedures rate.

Core needle biopsy (CNB) is a reliable histologic analysis sampling technique, with a higher sensibility and specificity than fine needle aspiration cytology. It is relatively quick, not invasive, and cost-effective. Histologic samples can provide information on tumor type, grade, and biological factors, useful to surgeons and oncologists.[3,4] According to the B-code, biopsy results are classified into 5 main categories, where 1 is normal breast tissue, 2 is a benign lesion, 3 is a borderline lesion of uncertain malignant potential, 4 is suspicious, and 5 is malignant lesion (B5a, in situ; B5b, invasive; B5c, not otherwise assessable).[5]

Findings with a B3 score are harder to study: they represent benign lesions with a possible, but not always predictable, risk of increased malignancy. Although the sample to be characterized is bigger and more easily available in open biopsy, in CNB, sampling and targeting errors are more common: if the mass is difficult to sample with CNB, and the mass tissue itself is of heterogenous nature, the biopsy sample may not be representative of the mass (ie, decreasing the specificity). Some of the B3 lesions may be not-obligated precursors to malignancy, or simply associated with a higher risk of developing breast cancer. Furthermore, the B3 score is a group composed of findings with heterogenous histologic features and corresponding different potentials of malignancy.[6]

B3 lesions represent only a small part of all biopsy samples (~5%). Because most of these lesions are asymptomatic and usually detected after screening, their detection rate has increased, with a corresponding increase in surgeries.[7] B3 lesions include, in decreasing order of risk: atypical ductal hyperplasia (ADH); lobular neoplasia (LIN) including lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH); radial sclerosing lesions (RSL); papillary lesions (PL); flat epithelial atypia (FEA); fibroepithelial lesions; and others. Currently, there are no guidelines to determine how to eventually treat these lesions.[8] Surgical treatment of B3 lesions may lead to dismissal of an otherwise treatable higher grade lesion, whereas treating all of them leads to overtreatment. Right now, every single B3 case has to be discussed in a multi-disciplinary team: there is no decisive solution, and each patient is different from one another.

The aim of our study is to establish if there are predictive imaging features (analyzing mammography and MRI) for B3 lesion characterization, to reduce the rate of benign lesion surgeries and better evaluate the malignancy rate of different mammography and MRI-detected and biopsy-proven B3 lesions. A secondary aim is to evaluate which imaging technique has a better predictive value.

Materials and Methods

Patients

Institutional review board approval was obtained for this retrospective study, which was performed in a large university referral hospital for breast disease.

We retrospectively reviewed 986 CNBs that were carried out from January 2011 to September 2018 at our institution.

Inclusion criteria were a histologically diagnosed B3 lesion and mammography and/or MRI examination. All patients were interviewed about their hormonal status and possible hormonal therapy, breast cancer familiarity, menopausal state, and number of pregnancies. One hundred thirty-nine patients were included in this study, with only 1 lesion each, for a total of 139 lesions. All patients provided written informed consent.

CNB and Histologic Classification

Before each sampling, patients were administered 10 cc of mepivacaine. Ultrasound-guided CNB was performed by using a semiautomatic biopsy gun or a vacuum-assisted biopsy device. A 16- or 14-gauge needle was used, depending on the device and the size of the lesion. Each CNB sample was stored in formalin solution, sent for histopathologic examination to our institution, and classified according to the National Health Service B-code. B3 lesions were also classified as ADH, LN, PL, RS, FEA, PT, or mesenchymal lesion.

Imaging: Mammography and MRI Protocol

All mammographies were performed on a low dose Digital Mammograph (Inspiration-Siemens). Each mammogram was reviewed by 2 radiologists with 30 (C.d.F.) and 7 years (D.S.) of experience and was evaluated for the presence of microcalcifications, masses, and architectural distortions. Microcalcifications were classified under the American College of Radiology criteria detailed in the latest edition of the Breast Imaging Reporting and Data System (BI-RADS) Atlas. Regarding the morphology, microcalcifications were classified as benign (skin, vascular, popcorn-like, round, rod-like, dystrophic, rim, milk of calcium, suture), suspicious (amorphous, coarse heterogeneous), or high-risk (pleomorphic, fine linear, or branching). Regarding the distribution, microcalcifications were classified as diffuse, regional, grouped, linear, or segmental.

All MRI examinations were performed on a 3T magnet (Discovery 750; GE Healthcare, Milwaukee, WI) using a dedicated 8-channel breast coil (8US TORSOPA) with the patient in the prone position. After localizer sequences taken in 3 orthogonal planes, the following sequences were acquired: (1) Axial T2-weighted single shot fast spin echo sequence using a modified Dixon technique (IDEAL) for intravoxel fat-water separation (TR/TE 3500-5200/120-135 ms, matrix 352 × 224, FoV 370 × 370, NEX 1, slice thickness 3.5 mm). (2) Axial single shot fat suppressed echo-planar diffusion weighted sequence (TR/TE 2700/58 ms, matrix 100 × 120, FOV 360 × 360, NEX 6, slice thickness 5 mm) with diffusion-sensitizing gradient applied along the x, y, z axes and with a b-value of 0 and 1000 s/mm^2. (3) Axial T1-weighted 3D dynamic gradient echo fat suppressed sequence (VIBRANT) (TR/TE 6.6/4.3 ms, flip angle 10°, matrix512 × 256, NEX 1, slice thickness 2.4 mm), before and 5 times after contrast administration.

Contrast medium, gadobenate-dimeglumine (Multihance; Bracco Imaging, Milan, Italy), was administered in a concentration of 0.2 mmol/kg injected through a 20 G intravenous cannula at the rate of 2 mL/s using an automatic injector and followed by infusion of 15 mL saline solution at the same speed. Subtracted images were automatically derived from DCE-MRI.

The detected lesions were classified according to the following MRI features: margins, classified as circumscribed (regular or

lobulated), irregular, speculate, or blurred edges; type of enhancement after contrast administration, grouped as mass-like lesions or non−mass-like lesions (ductal, segmental, regional); size, divided into ≤ 15 mm or > 15 mm; and kinetics curves, type I, II, or III.

Histopathologic Diagnosis

All patients underwent subsequent surgical excision performed by lumpectomy, quadrantectomy, or mastectomy. The excision samples were examined by our institution's pathologists, and the histology was analyzed. The results were classified as confirmed benign lesion or lesion upgraded to ductal carcinoma (in situ [DCIS] or invasive [IDC]), to lobular carcinoma (in situ [LCIS] or invasive [ILC]), to medullary carcinoma or to other type of neoplasia.

Statistical Analysis

The number of biopsy B3 results were compared with the results obtained after surgical excision using the χ^2-test according to Pearson. The correlation between the histologic results before (at CNB) and after the excision (definitive surgery) were evaluated using the Pearson correlation test. The Kruskal-Wallis H test was used to evaluate the non-parametric analysis between CNB results and definitive histologic results divided into 2 subgroups (tumor and non-tumor). Statistical comparison between histologic results (CNB and definitive surgery) and imaging analysis was carried out using the Kruskal-Wallis H test. Statistical significance was set at $P < .05$. SPSS Statistics V20.0 was used for the statistical analysis.

Results

Pre-surgical Histologic Results

All 139 patients were female, aged between 17 and 86 years old (average, 51.13 years old). Forty-eight (34.53%) patients had familiarity for breast cancer, of which 3 patients had more than 2 affected family members, 45 (32.37%) underwent hormone therapy in the past, 56 (40.29%) had 1 or more pregnancies and 63 (45.32%) were in menopause.

Histologic classification of B3 lesions counted 45 (32.37%) ADH lesions, 12 (8.63%) LN, 25 (17.99%) PL, 5 (3.61%) RS, 31 (22.31%) FEA, 20 (14.39%) PT, and 1 (0.70%) mesenchymal lesion.

Regarding imaging, 107 patients had a mammography examination, and 38 patients had an MRI exam (6 patients had both the exams).

Post-surgical Histologic Results and Positive Predictive Value (PPV)

In 90 (65%) cases, the histologic diagnosis of B3 was confirmed, whereas in 15 (11%) cases, a histologic benign lesion was found. In 34 (24%) cases, the histologic examination of the surgically excised lesion detected the presence of malignant pathology; in particular, DCIS or IDC were found in 28 cases (13 of DCIS and 15 of IDC), LCIS or ILC were found in 2 cases (1 of LCIS and 1 of ILC), 1 medullary carcinoma, and sarcoma or angiosarcoma were observed in 3 cases.

Among the B3 lesions, the biopsy results found out only 1 mesenchymal lesion, and it was associated with mesenchymal tumor also in final histologic analysis (PPV of 1). ADH proved to be the most conspicuous subgroup. Nevertheless, ADH and FEA showed the higher malignancy correlation, after mesenchymal lesion, with a PPV of 0.36 and 0.4, respectively. Also PL and LN diagnosed by biopsy showed an increased risk of malignancy, with a PPV of 0.32 and 0.25, respectively. RS and PT revealed only a modest increase in risk of degeneration (PPV of 0.2 and 0.1, respectively). Regarding the risk of malignancy, a significant correlation between the specific B3 subgroup and the definitive histologic result was demonstrated ($P = .010$), and a significant difference was also observed among various B3 lesion subgroups ($P = .011$) (Figure 1).

The incidence of malignant neoplasms in the definitive histologic analysis and the respective PPVs of the B3 groups are shown in Table 1.

Imaging: Mammography

The B3 lesions show different abnormalities on mammography.

Microcalcifications were detected in 49 (46%) of 107 cases. Microcalcifications showed benign morphology in 25 cases, intermediate morphology in 14, and high-risk morphology in 10 cases. Regarding the distribution, the microcalcifications were grouped in clusters in 16 cases, were linear in 7 cases, and were widespread in 9 cases, and they had regional and segmental distribution in 9 and 8 cases, respectively.

A mass opacity was present in 43 (40%) patients, whereas a distortion of the normal parenchymal architecture was identified in 18 (17%) patients.

LN and FEA, primarily, and RS and ADH, secondarily, were more frequently associated with the presence of microcalcifications. PT and PL frequently showed the presence of a mass, and the mass was present also in the only case of mesenchymal lesion. Parenchymal distortion was associated with ADH and RS. Details of the findings of the mammogram are shown in Table 2.

A significant correlation was found comparing mammographic features with the histologic results of preoperative CNB in the case of microcalcifications ($P = .016$) and the presence of mass ($P = .002$) but not for parenchymal distortion ($P = .388$) (Figure 2A).

There were no significant correlations with the risk of malignancy comparing the presence of microcalcification and parenchymal distortion with the definitive result of the histopathologic examination on excised lesions ($P = .234$ and $P = .182$, respectively), but a significant difference was observed for presence of a mass ($P = .023$) with a higher rate of malignancy for the presence of a mammographic mass (Figure 2B).

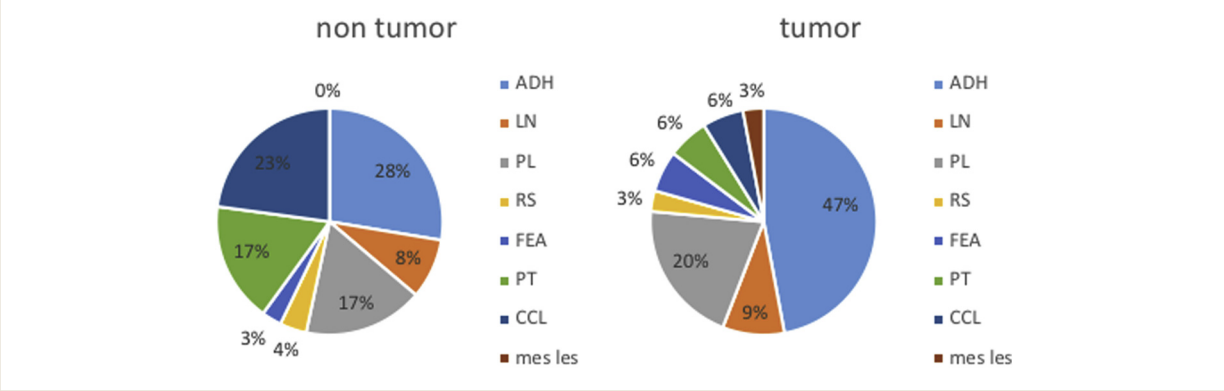
Imaging: MRI

Among 38 performed MRIs, only 1 case of ADH, confirmed by the definitive histologic examination, presented a totally negative exam. MRI was able to detect B3 lesions in all the remaining 37 cases (97% sensitivity).

All the exams were analyzed by evaluating the pre- and post-contrast sequences. A nodular enhancement was detected in 26 (70%) lesions, whereas a non−mass-like enhancement was detected in the remaining 11 (30%) cases. Of these, a ductal enhancement was shown in 1 case, segmental enhancement in 7 cases, and a regional enhancement in 3 cases.

Most lesions presented with irregular margins (18 cases; 49%); regular margins were detected in 8 (22%) cases, spiculate margins in 3 (8%), and blurred margins in 7 (19%). Only 1 (2%) lesion showed lobulated margins.

Figure 1 The Charts Show the Percentage of B3 Lesion Subgroups for the 2 Groups of the Definitive Histologic Analysis (Tumor Group and Non-tumor Group)



Abbreviations: ADH = atypical ductal hyperplasia; FEA = flat epithelial atypia; LN = lobular neoplasia; Mes les = mesenchymal lesion; PL = papillary lesion; PT = phylloid tumor; RS = radial scar.

On MRI examination, 21 lesions had a diameter less or equal to 15 mm, and 16 lesions had a diameter more than 15 mm.

Regarding enhancement kinetics, the intensity/time curves were type I in 12 (32.5%) cases, type II in 13 (35%) cases, and type III in 12 (32.5%) cases.

Analyzing MRI features among different B3 lesion groups, we documented that all B3 lesion groups were more frequently associated with irregular, speculated, or blurred edges. PT and mesenchymal lesions are associated in all cases with mass-like morphology. Also, FEA and PL occurred predominantly as mass-like lesions (83% of lesions in both cases), whereas ADH appeared as mass formation in 5 (45%) cases and as a non−mass-like lesion with segmental or regional morphology in the remaining 6 (55%) cases. The larger lesions were PT and the mesenchymal lesion. Regarding kinetics curves, type III was more frequent for the mesenchymal lesion (100%) and PL (42%), whereas the majority of the other lesions were associated with curve I or II. Details of B3 classes MRI features are shown in Table 3.

Comparing the various MRI findings with the different classes of B3 lesions diagnosed by biopsy, only the morphology was significantly associated with the risk of malignancy ($P = .038$), with a higher prevalence in mass-like lesions. No significant discriminative difference was observed for the other MRI features ($P = .570$ for the margins, $P = .313$ for the dimensions, and $P = .161$ for the kinetics curves).

By comparing the MRI findings with the final postoperative histologic examination, the morphology, the dimension, and the kinetic curve of the lesions were significantly correlated with the risk of carcinoma, with a P value of .024, .040, and .005, respectively. In particular, the malignant lesions more frequently showed a non−mass-like rather than a mass-like enhancement, a larger diameter, and type III intensity/time curves. Regarding the lesion margins, no relevant differences were observed between benign and malignant lesions ($P = .468$). All these findings are summarized in Figure 3A-D.

Discussion

B3 is a histologic class that represents a heterogeneous group of breast lesions.[7] The diagnosis of B3 lesions has increased over the

Table 1 Incidence of Malignant Neoplasms in the Definitive Histologic Analysis and the Respective PPVs of the B3 Subgroups

	B3	IDC	DCIS	ILC	LCIS	Medullary Carcinoma	Other Malign Lesions	Benign Lesions	Total (%)	PPV %
CNB										
ADH	26	9	7	0	0	0	0	3	45 (32.37)	36
LN	9	0	2	1	0	0	0	0	12 (8.63)	25
PL	17	4	2	0	0	1	0	1	25 (17.99)	32
RS	3	1	0	0	0	0	0	1	5 (3.6)	20
FEA	23	1	2	0	1	0	0	4	31 (22.3)	40
PT	12	0	0	0	0	0	2	6	20 (14.39)	10
Mes les	0	0	0	0	0	0	1	0	1 (0.72)	100
Total	90	15	13	1	1	1	3	15	139	

Abbreviations: ADH = atypical ductal hyperplasia; CNB = core needle biopsy; DCIS = ductal carcinoma in situ; FEA = flat epithelial atypia; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; LN = lobular neoplasia; Mes les = mesenchymal lesion; PL = papillary lesion; PPV = positive predictive value; PT = phylloid tumor; RS = radial scar.

Table 2 Mammographic Feature Frequencies for Each B3 Subgroup

	Micro, n (%)	Mass, n (%)	Distortion, n (%)
CNB			
ADH	17 (45)	13 (34)	10 (26)
LN	9 (82)	1 (9)	0
PL	4 (27)	10 (67)	1 (6)
RS	2 (50)	1 (25)	1 (25)
FEA	15 (56)	7 (26)	5 (18)
PT	2 (17)	10 (83)	1 (8)
Mes les	0	1 (100)	0
Total	49	43	18

Abbreviations: ADH = atypical ductal hyperplasia; CNB = core needle biopsy; FEA = flat epithelial atypia; LN = lobular neoplasia; Mes les = mesenchymal lesion; PL = papillary lesion; PT = phylloid tumor; RS = radial scar.

years from the diffusion of intensive screening programs and an early diagnosis of breast pathologies. In some cases, B3 lesions may potentially evolve into malignant alterations, especially, according to our results, in the case of ADH, less frequently in the case of PL or FEA, and rarely in the case of PT, RS, and CLL.

Currently, the management of B3 lesions is not standardized, but it widely varies among the different structures.[8] Despite CNB having a high sensitivity and being associated with a low false-negative rate, the presence of malignant proliferations in the context of B3 lesions may be underestimated.[9,10] Nevertheless, numerous studies demonstrate the possibility of a malignant evolution.[8,11] In our study, 34 (24%) of 139 lesions classified as B3 on preoperative histologic examination proved to be malignant on the definitive histologic analysis. In many cases, the underestimation of the biopsy may be owing to the caliber of the needle used or to specific lesion characteristics.[12] For all these reasons, the need to excise B3 lesions is evident, although most of them (76% in our study) will be benign or will confirm B3 histologic class.

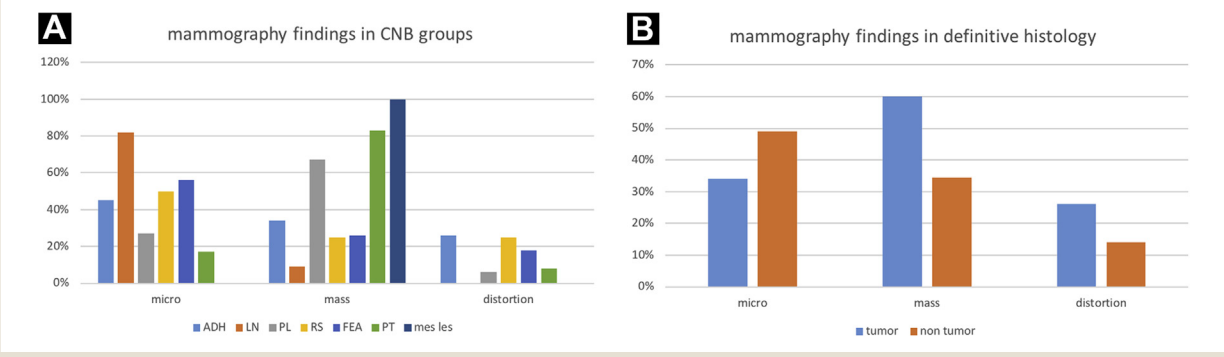
Among B3 subgroups, the most conspicuous was represented by ADH, which showed a malignant degeneration in 36% of cases, in agreement with other studies that report malignancy values ranging between 32% and 59% for ADH lesions diagnosed by mammographic screening.[13-16] However, the definitive diagnosis of ADH cannot be determined by biopsy. For this reason, the European Working Group for Breast Screening Pathology recommends the use of the term "atypical epithelial proliferation of a ductal type" (AEPDT) instead of "atypical ductal hyperplasia" (ADH) for cases diagnosed by biopsy.[17] At the same time, dimension is the main criterion for distinguishing ADH from low-grade DCIS. This indicated the reason to remove an ADH/AEPDT.

In our study, the 2 B3 groups more frequently associated with the possibility of malignant evolution were mesenchymal lesion (100% of all cases) followed by FEA (40% of cases). Nevertheless, we found only 1 mesenchymal lesion at CNB impacting on this percentage. On the other hand, our results, under which FEA lesions should require surgical excision for their association with malignancy, are consistent with the findings of previous studies,[18,19] even considering that FEA is an unifying term proposed by the World Health Organization Working Group on the Pathology and Genetics of Tumors of the Breast[20] also for columnar cell lesions with low-grade cytologic atypia.

LN is also associated in literature with a high upgrade rate (average of 26.7% in a range of 13.1%-44%), and with ADH, LCIS is considered as a continuum of LN. In our study, we found an upgrade rate to malignancy of 25% (3 of 12 cases, of which 2 cases were upgraded to DCIS and 1 case to ILC). At present, relatively few absolute reported cases of either ALH or LCIS with surgical follow-up are cited in the B3 biopsy literature. Crystal et al noted only 4 cases of LN upgraded among 8 cases (3 cases to DCIS and 1 to invasive carcinoma); Strigel et al[21] described 2 cases upgraded to DCIS and LCIS, and Rauch et al[22] reported 1 of 6 cases of LCIS and 9 of 12 cases of ALH upgraded to ILC at surgery.

In the case of RS, some research would justify a more conservative approach. Crystal et al did not detect any malignant degeneration associated with this type of B3 lesion.[18] In our study, only 1 of the 5 diagnosed RS showed malignancy (20% of cases), halfway between the results of Heller et al (high levels of upgrade to the final histologic diagnosis in the case of RS)[23] and those of the Richter-Ehrenstein group (upgrade in 16.6% of cases).[19] Therefore,

Figure 2 Mammographic Findings for the 2 Groups of Definitive Histologic Analysis. The Reported Value Are Expressed in Percentage Relative to the 23 Tumors and 84 Non-tumors Lesions



Abbreviations: ADH = atypical ductal hyperplasia; FEA = flat epithelial atypia; LN = lobular neoplasia; Mes les = mesenchymal lesion; PL = papillary lesion; PT = phylloid tumor; RS = radial scar.

Table 3 For Each B3 Subgroup, All MRI Feature Frequencies Analyzed Were Reported

A, Margins, Classified as Circumscribed (Regular or Lobulated), Irregular, or Spiculate

	Regular, n (%)	Lobulated, n (%)	Spiculated, n (%)	Irregular, n (%)	Blurred Edges, n (%)
CNB					
ADH	1 (10%)	0	3 (30%)	5 (50%)	1 (10%)
PL	3 (25%)	0	0	5 (42%)	4 (33%)
RS	1 (33%)	0	0	2 (66%)	0
FEA	1 (17%)	1 (17%)	0	2 (33%)	2 (33%)
PT	2 (40%)	0	0	3 (60%)	0
Mes les	0	0	0	1 (100%)	0
Total	8	1	3	18	7

B, Type of Enhancement After Contrast Administration, Grouped as Mass-like Lesions or Non–mass-like Lesions (Ductal, Segmental, Regional)

	Ductal, n (%)	Segmental, n (%)	Regional, n (%)	Mass, n (%)
CNB				
ADH	0	4 (40)	2 (20)	4 (40)
PL	0	1 (8.5)	1 (8.5)	10 (83)
RS	1 (33)	1 (33)	0	1 (33)
FEA	0	1 (17)	0	5 (83)
PT	0	0	0	5 (100)
Mes les	0	0	0	1 (100)
Total	1	7	3	26

C, Size, Divided Into ≤15 mm or >15 mm

	≤15 mm, n (%)	>15 mm, n (%)
CNB		
ADH	6 (55)	5 (45)
PL	9 (75)	3 (25)
RS	2 (67)	1 (33)
FEA	4 (67)	2 (33)
PT	1 (20)	4 (80)
Mes les	0	1 (100)
Total	22	16

D, Kinetics Curves, Type I, II, or III

	Curve 1, n (%)	Curve 2, n (%)	Curve 3, n (%)
CNB			
ADH	3 (30)	4 (40)	3 (30)
PL	1 (8)	6 (50)	5 (42)
RS	2 (67)	1 (33)	0
FEA	2 (33)	2 (33)	2 (33)
PT	4 (80)	0	1 (20)
Mes les	0	0	1 (100)
Total	12	13	12

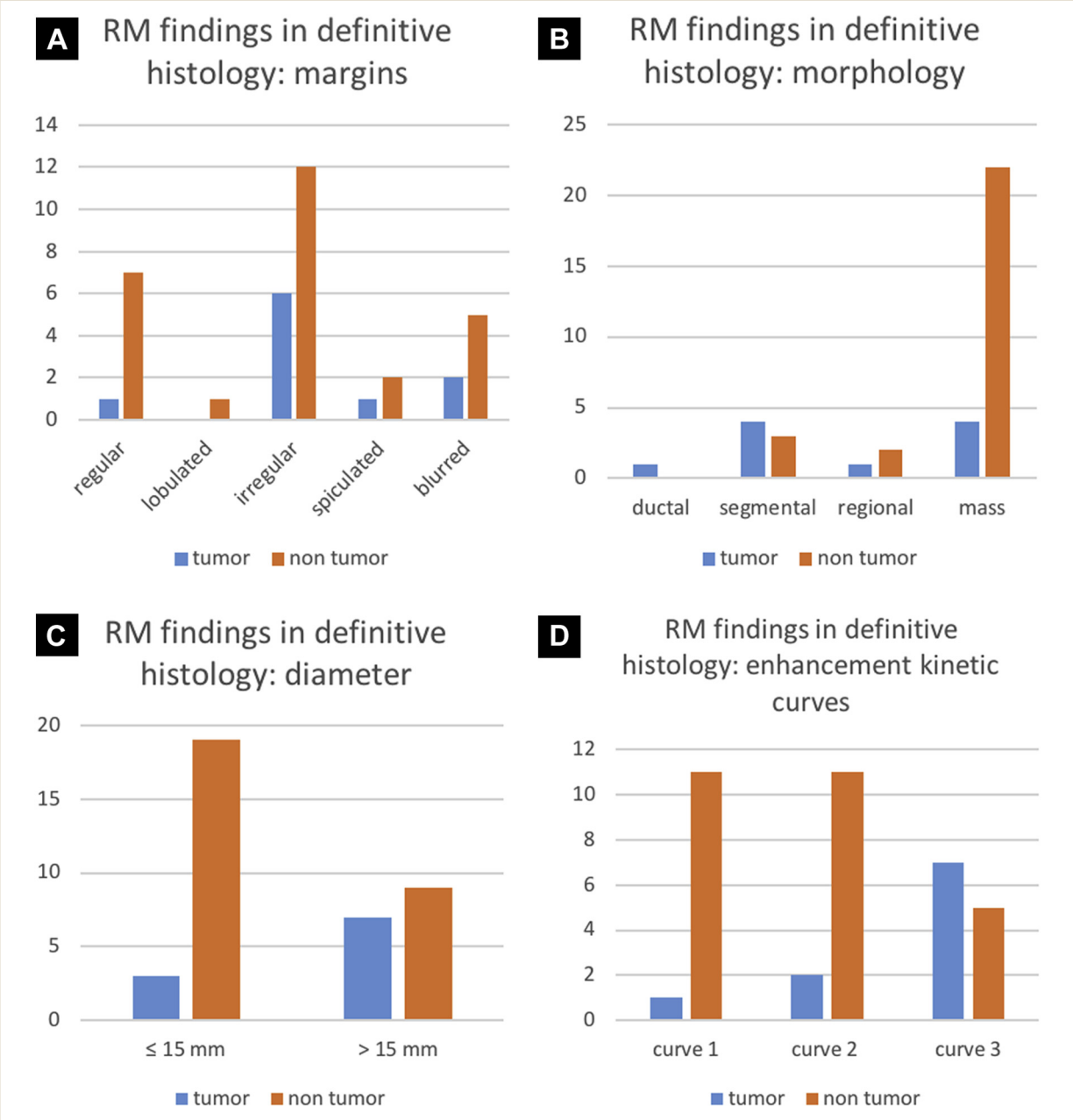
Abbreviations: ADH = atypical ductal hyperplasia; CNB = core needle biopsy; FEA = flat epithelial atypia; LN = lobular neoplasia; Mes les = mesenchymal lesion; PL = papillary lesion; PT = phylloid tumor; RS = radial scar.

further large-scale studies are needed for a more precise characterization of this type of lesion.

Regarding PL, previous studies showed conflicting results. In some cases, no malignant neoplasms were observed at the definitive histologic analysis[18]; in others, a modest risk was found.[19,24] Our results show the presence of malignant proliferations in 18% of PL.

Finally, our study found no risk of malignancy associated with PT. In their review, Abdulcadir et al found 5 cases of PT (13%) confirmed as malignant at final histologic examination.[25] However, PT are principally differentiated from fibradenomas on the basis of increased stromal cellularity, and not only on CNB. The degree of stromal cellularity between benign or borderline PT and cellular

Figure 3 Magnetic Resonance Features Are Reported for the 2 Groups of Definitive Histologic Analyses. Margins (A), Morphology (B), Diameter (C), and Enhancement Kinetic Curve (D)



Abbreviation: RM = magnetic resonance imaging.

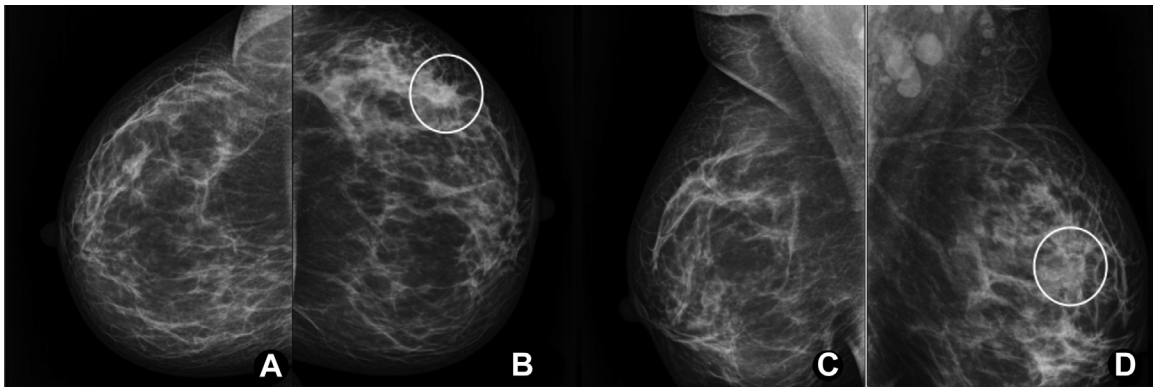
fibradenomas may not be considerably different, but the diagnosis can be difficult also in surgical specimens, justifying surgical removal. In our series, both of the sarcomas identified at definitive histology corresponded to PT lesions at CNB, supporting the need to recur to surgical excision.

Our results are in line with other studies, which do not observe significant differences between the risk of malignancy and the various B3 subgroups, although excluding mesenchymal lesions for its statistical influence, FEA and ADH are more often associated with increased risk, confirming their remarkable heterogeneity and malignant potential compared with the other B3 classes.[19,26]

In our research, mammography was not able to potentially discriminate malignant from benign lesions, in accordance with the results from Hoffmann et al.[26]

In our study, microcalcifications were present in 46% of patients who had mammography, and were more often associated with LN, FEA, RS, and ADH. These results are the same as those reported by Hoffmann et al, who found microcalcifications in 56% of B3 lesions,

Figure 4 C.S., a 52-Year-old Woman With Evidence of Mass Opacity Associated With Gland Distortion and Pleomorphic Microcalcifications, Localized at the External Upper Quadrant of Left Breast. The Patient Underwent Core Needle Biopsy With B3 Result (Atypical Ductal Hyperplasia). Post-surgical Definitive Histologic Examination Showed a Grade 2 Invasive Ductal Carcinoma (Estrogen Receptor, 90%; Progesterone Receptor, 65%; Ki67, 7%; Human Epidermal Growth Factor Receptor 2, 3+)



predominantly associated with LN, FEA, and ADH.[26] In 16% of cases, our data showed the presence of malignant proliferations in association with microcalcifications, in contrast with the study of Rakha et al, who found an adverse outcome in about the 40% of B3 lesions associated with microcalcifications.[27] However, the extreme variability in B3 lesion groups associated with microcalcifications depends on the high heterogeneity of the 2 largest groups, ADH and FEA. FEA frequently present with microcalcifications on breast mammography, often low suspicion, and they are an increasingly common finding in non-operative breast core samples. Even more, columnar alteration, a subgroup of the FEA class, was reported in 42% of 100 consecutive biopsy specifications for microcalcifications in one of the early seminal papers[25] on these lesions, most of which correspond to non-malignant lesions.[28]

These factors could contribute to variate their upgrade rate.

The presence of mass at mammography was present in the single case of mesenchymal lesion, and among other lesions, was more often correlated with PT and PL. This data is also in agreement with the results reported by Hoffmann et al.[19] By comparison with the definitive histologic examination, we have detected malignancy in 60% of cases, a percentage definitely higher compared with that of Rakha et al (22%)[27] (Figure 4).

Parenchymal distortion was present in 18 lesions, more often associated with ADH and RS. Of these, 6 lesions underwent a

Figure 5 D.M.L., a 40-Year-old Woman. Post-contrast T1 Weighted Fat-suppressed 3D Gradient-echo Magnetic Resonance Image (A) and Maximum Intensity Projection Reconstruction (B) Show the Presence of a Nodule at the Confluence of External Quadrants of Left Breast, of About 11 × 10 mm and Other Small Closed Foci of Contrast Enhancement, Characterized by Rapid but Progressive Enhancement With a Plateau Phase (Curve SI/T Type II), Diagnosed as B3 Lesion at Core Needle Biopsy, and Confirmed as Papillary Lesion at Post-lumpectomy Histologic Analysis

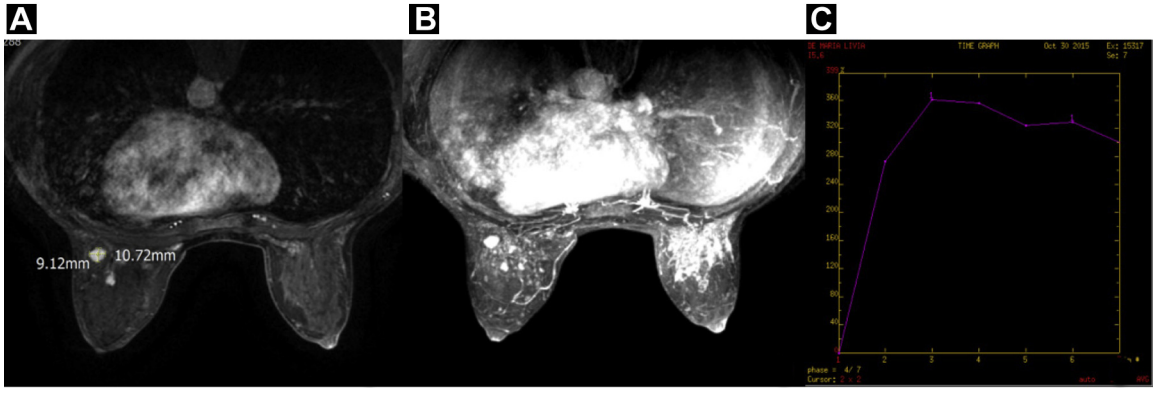
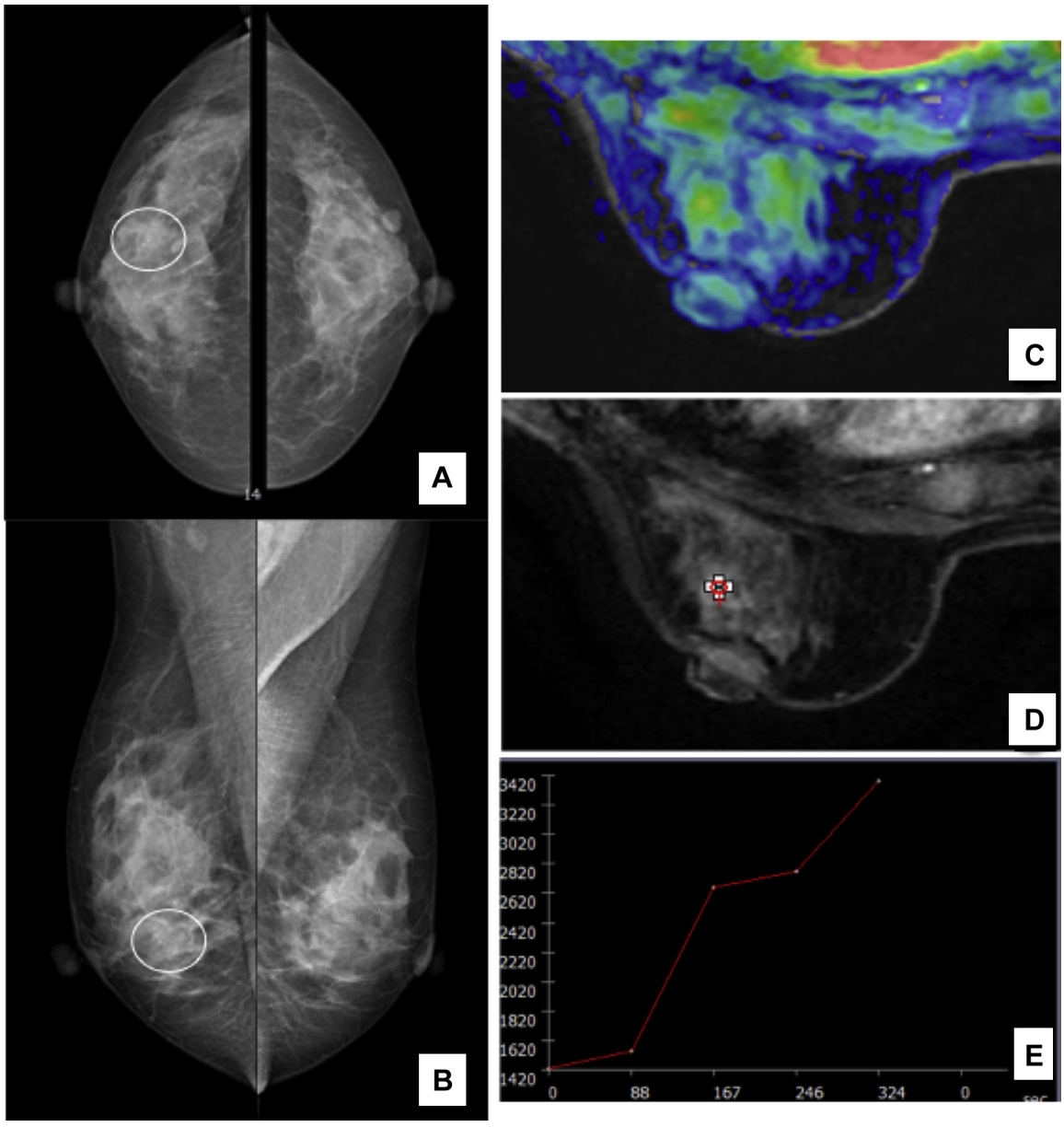


Figure 6 T.E., a 49-Year-old Woman With Family History of Breast Cancer and Identification of a Cluster of Punctate Microcalcifications in the External Peri-nipple Area of Right Breast at Screening Mammogram (A and B). The Patient Underwent Core Needle Biopsy With B3 Result (Atypical Ductal Hyperplasia). A Magnetic Resonance Imaging Examination Was Performed With Evidence of a Small Linear Area of Contrast Enhancement at T1-weighted Fat-suppressed 3D Gradient-echo With Blurred Edges (C and D) and Curve SI/T Type I (E). Grade 3 Ductal Invasive Carcinoma (Estrogen Receptor, 90%; Progesterone Receptor, 70%; Ki67, 50%; Human Epidermal Growth Factor Receptor 2, 2+) Was Found at Definitive Surgery

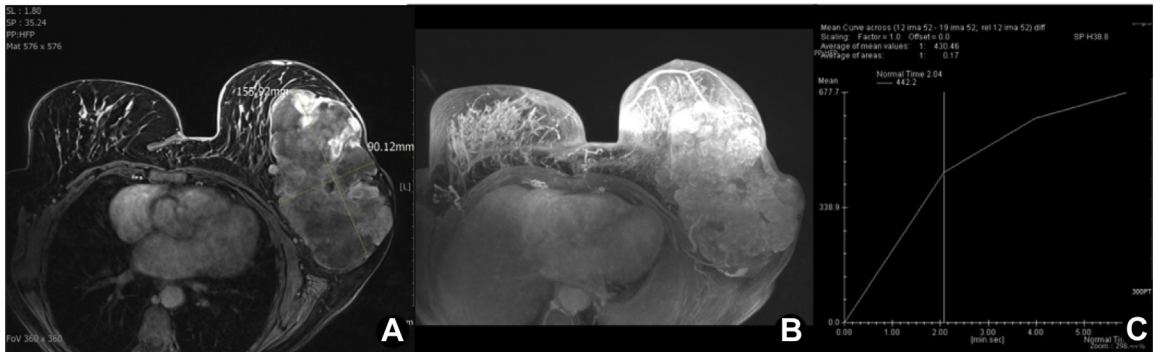


diagnostic upgrade (33% of the total). Our result differs in part from that of Hoffmann and colleagues, who detected the presence of parenchymal distortion at mammography only in 3 (3%) B3 out of 104 lesions, none of which proved to be malignant.[26]

Regarding MRI examination, Heller et al found no predictive features of malignancy,[23] whereas Linda et al pointed out the high negative predictive value of this methodology (98.2%) in predicting the unfavorable evolution of lesions. They concluded that in case of absent or modest enhancement, the possibility of malignancy, and therefore surgical procedures, should be substantially excluded.[29] Our study is consistent with these results, having shown a correlation between cancer and MRI features such as enhancement kinetics, morphology, and lesion dimensions.

The upgrade was more often associated with non–mass-like lesions, described as ductal, segmental, or regional enhancements. This result contrasts with some previous studies, which found a

Figure 7 C.G.M., a 66-Year-old Woman, With an Expanding Mass at External Quadrants of Left Breast, With Lobulated Margins and Without Infiltrative Behavior, of 155 × 90 mm, Well-evident at Axial Post-contrast T1 Weighted Fat-suppressed 3D Gradient-Echo Magnetic Resonance Image (A) and Maximum Intensity Projection Reconstruction (B), Characterized by Slow and Progressive Enhancement (Curve SI/T type I) (C), Diagnosed as B3 Lesion at Core Needle Biopsy (Phylloid Tumor). A Low-grade Stromal Tumor Was Found at Post-surgical Histology



significant correlation between malignancy and mass-like lesions, with a lower risk in case of non−mass-like lesions.[21] This discrepancy is probably owing to the fact that, in these studies, the widespread type of enhancement, characteristically indicative of benignity, was considered as mass-like lesions, but was not found in our work. Additionally, it is well known that the morphology of RS and PL is more often mass-like than that of ADH, which is typically characterized by ductal or focal enhancement. In our series, PL and CCL were predominantly associated with mass lesions (Figure 5), whereas FEA and PT were associated with non−mass-like lesions. As shown for mammography, ADH presented the largest variety of presentation for MRI features as well (Figure 6).

Another analyzed MRI feature that contrasts with our results is the size of the lesion: in the study by Preibsch et al, a greater probability of benignity was shown in the case of local extension greater than 20 mm ($P = .045$).[24] Our data showed a greater risk of malignancy for lesions greater than 15 mm, which can also be explained by the fact that larger dimensions were more often associated with non−mass-like lesions (average of 23 mm) rather than mass-like lesions (average of 15.5 mm). The largest lesions were represented by the mesenchymal lesion and PT lesions, and it is interesting to note that these 3 lesions revealed cases of sarcoma, angiosarcoma, and a case of stromal tumor at definitive surgery (Figure 7).

The contrast enhancement kinetic curve depended on the malignancy of the lesions, with a type III curve more often associated with upgraded B3. In particular, the mesenchymal lesion, 42% of PL, and 40% of FEA revealed a malignancy at definitive surgery, presenting a type III curve. These results are in line with well-known literature.[24,30]

As far as the type of margins, in our study, there are no significant correlations with the probability of unfavorable evolution, although the irregularity of the same can be indicative of greater invasiveness, in line with what was found in the previous work by Heller et al.[23]

Regarding the lesions misinterpreted at MRI, the only case of negative MRI involved a lesion in a very dense breast with elevated background enhancement initially diagnosed as ADH at CNB, which revealed a low-grade DCIS.

This study has some limitations. First of all was the limited number of patients (for a total of 139 lesions) and the variability of the lesions, which could impact on conclusions and significance of the results. Furthermore, it is a retrospective study, which does not allow to fully reproduce the variables that have influenced the management of individual cases. There is a partial overlap between patients who had mammographies and MRI examination, and different samples for the 2 imaging evaluation methods.

However, in conclusion, our study confirms that the B3 category includes different entities, each with a different risk of malignant evolution, confirming their heterogeneity and malignant potential. These lesions presented characteristics that can be partially superimposed on benign diseases or early stages of carcinomas at imaging as well.

Regarding the ability of the different methodologies to detect the malignant potential, our study highlighted important differences between mammography and MRI.

B3 are associated with specific mammographic and MRI features in our study; nevertheless, mammography showed important limits, such as not being able to detect characteristics significantly correlated with an unfavorable outcome, in accordance with the literature. The same cannot be said for MRI, which is associated with conflicting results in various studies.

Therefore, the management of these cases should be discussed within a multidisciplinary team, to determine whether the biopsy is representative of the lesion or not and to determine the histology of the same. The choice is not simple: deciding not to intervene could lead to the risk of neglecting a more advanced disease (DCIS or IDC), whereas the excision could represent an overtreatment in the case of benign lesions.

Given the increasing incidence of such lesions in recent years, the absence of a standard of treatment and the presence in literature of conflicting results on the actual role of imaging in these cases, meta-analysis and further large-scale studies are necessary to reach more significant results.

Clinical Practice Points

- Breast B3 lesions are a heterogeneous group of lesions, more often benign, but with a possible and not always predictable risk of increased malignancy. Currently, there are no guidelines on how to treat these lesions. The greatest difficulty is to identify and correctly categorize all the lesions for the best treatment option. Surgical treatment could be reserved for high-risk malignancy lesions to avoid an overtreatment in other cases.
- B3 lesions are associated with specific mammographic and MRI findings. Our study highlighted the ability of these different methodologies to detect the malignant potential.
- The possibility of predicting the behavior of B3 lesions and identifying their possible evolution would impact on patient management and prognosis, avoiding undertreatment for advanced disease (DCIS or IDC) on the one hand and overtreatment and excision in the case of benign lesions on the other hand.

Disclosure

The authors have stated that they have no conflicts of interest.

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