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Upgrade rate to malignancy of uncertain malignant potential breast lesions (B3 lesions) diagnosed on vacuum-assisted biopsy (VAB) in screen detected microcalcifications: Analysis of 366 cases from a single institution

Bianchi Simonetta [a], Caini Saverio [b,*], Vezzosi Vania [a], Orzalesi Lorenzo [c], Piovesan Luisa [a], Mantellini Paola [d], Ambrogetti Daniela [d]

[a] Division of Pathological Anatomy, Department of Health Sciences, University of Florence, Florence, Italy
[b] Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[c] Division of Breast Surgery, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[d] Breast Cancer Screening Branch, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

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ABSTRACT

Purpose: We retrospectively investigated clinical, radiological, and pathological features of B3 lesions associated with the risk of subsequent upgrade to malignancy. *Methods*: We included consecutive vacuum-assisted biopsies (VABs) performed during 2011–2020 on suspicious microcalcifications not associated with other radiological signs diagnosed as B3 lesions and followed by surgical excision (SE) with definitive histological examination. Multiple logistic regression models were fitted to identify independent predictors of malignancy. *Results*: Out of the 366 B3 lesions included, 56 (15.3 %, 95 % CI 11.8–19.4 %) had upgraded to malignancy at SE: of these, 42/366 (11.5 %, 95 % CI 8.4–15.2 %) and 14/366 (3.8 %, 95 % CI 2.1–6.3 %) were in situ and invasive carcinoma, respectively. At univariate analysis, variables positively associated with upgrade to malignancy were age $\geq$ 60 years ($p = 0.008$), mixed morphology ($p = 0.018$), scattered distribution ($p = 0{,}001$), extension of microcalcifications $>$ 10 mm ($p = 0.001$), and mixed B3 lesion ($p = 0.017$). Among B3 subtypes, the highest rates of upgrade were observed for AIDEP, LCIS/LIN2, FEA + AIDEP, FEA + LCIS/LIN2, and FEA + AIDEP + LCIS/LIN2 (24.6 %, 21.4 %, 25.3 %, 20.0 % and 40.0 % respectively), while FEA and ALH/LIN1 had a lower rates of upgrade (7.5 % and 3.7 %, respectively). Multiple logistic regression analysis confirmed as risk factors older age ($p = 0.029$), larger extension ($p = 0.001$) and mixed morphology ($p = 0.007$) of microcalcifications, AIDEP ($p = 0.011$) among pure B3 lesions, and FEA + AIDEP ($p = 0.001$) and FEA + AIDEP + LCIS/LIN2 ($p = 0.037$) among mixed B3 lesions. *Conclusions*: Based on our findings, vacuum-assisted excision is reasonable as definitive management for FEA and ALH/LIN1, while SE should remain the mainstay of treatment for AIDEP and LCIS/LIN2, whose upgrade rates are too high to safely recommend VAE.

1. Introduction

The widespread implementation of mammographic breast cancer screening programmes and the introduction of more sensitive radiological techniques such as digital mammography in the last decades have led to the detection of a growing number of non-palpable breast abnormalities, particularly microcalcifications. The non-operative diagnostic procedure, i.e. percutaneous core biopsy (CB), in case of microcalcifications is usually performed by vacuum-assisted biopsy (VAB) which has proved to be more efficient than conventional 14 gauge needle CB in obtaining larger volume of tissue with a higher number of accurate preoperative histological diagnosis [1,2].

Abbreviations: AIDEP, atypical intraductal epithelial proliferation; ALH, atypical lobular hyperplasia; BIRADS, Breast Imaging Reporting & Data System; CB, core biopsy; CI, confidence intervals; FEA, flat epithelial atypia; LCIS, lobular carcinoma in situ; LIN, lobular intraepithelial neoplasia; NHSBSP, National Health Service Breast Screening Programme; OR, odds ratio; PL, papillary lesion; RS, radial scar; SE, surgical excision; VAE, vacuum-assisted excision; VAB, vacuum-assisted biopsy; WHO, World Health Organization.

* Corresponding author at: Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Via Cosimo il Vecchio 2, 50139, Florence, Italy.
E-mail address: s.caini@ispro.toscana.it (C. Saverio).

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Although most breast lesions on non-operative diagnostic procedure can be histologically classified according to the European guidelines [3] as either normal/uninterpretable (B1) or benign (B2) on one hand, or suspicious or malignant (B4 and B5 respectively) on the other hand, some lesions cannot fit in these categories having clear-cut indications (no vs. indication to further treatment, respectively) and are reported as B3 lesions, defined as "benign but of uncertain malignant potential" as they can be associated with the contemporaneous presence of in situ or invasive carcinoma [3].

The B3 category encompasses a group of breast lesions characterized by heterogeneous histological features, including: (1) flat epithelial atypia (FEA); (2) atypical intraductal epithelial proliferation (AIDEP); (3) lobular intraepithelial neoplasia (LIN), which can further categorized into atypical lobular hyperplasia (ALH/LIN1) and classic lobular carcinoma in situ (LCIS/LIN2); (4) radial scar (RS) or complex sclerosing lesion; (5) papillary lesion (PL); and (6) other entities including phyllodes tumor and rare lesions (e.g. mucocele-like lesions, atypical apocrine adenosis, and others) [3,4].

The prevalence of B3 lesions ranges between 5 % and 10 % in CBs case series published so far [5–7]. B3 lesions should not be overlooked as a malignancy may be present at the same time and at the same site where percutaneous CB has been performed, which risks going unnoticed if not adequately investigated. This association with synchronous malignancy is the main reason for recommending further examination of each B3 lesion, whether seemingly coincidental or interpreted as the cause or radiological abnormality [5].

Underestimation rates in the literature vary widely: the NHS Breast Screening Working Group, based on a review in UK practice, estimates that the risk of malignancy associated with a B3 lesion can range from < 2 % to around 40 % [4]. B3 lesions still represent a clinical dilemma as the only means of ruling out an associated or adjacent malignancy is to perform a histological examination of the entire lesion. Thus, when a B3 lesion is found at a CB, further evaluation is warranted to exclude a diagnosis of coexisting invasive or non-invasive carcinoma [4]. Classically, surgical excision (SE) was recommended for all B3 lesions to establish an accurate definitive histological diagnosis, while in recent years a percutaneous vacuum-assisted excision (VAE) has been proposed as a viable therapeutic approach (alternative to SE) in a subgroup of B3 lesions [5–7]. Most international guidelines advise that all B3 lesions should be discussed at multidisciplinary team meeting on a case-by-case basis taking into account the lesion size, presence/absence of atypia, pre- and post-biopsy radiological findings, and radio-histological correlation, in order to guide the patient to consider SE or VAE [5]. The aim of VAE is to obtain a complete excision of the lesion identified on imaging in order to either rule out, or upgrade to, a diagnosis of malignancy. When a B3 lesion is upgraded to malignancy on VAE, a therapeutic SE is then required to assess the full extent of the disease and margin status.

As the definitive histological diagnosis on complete excision is considered to be the "gold standard" in evaluating the final outcome, i.e. overall and type-specific upgrade rate of B3 lesions, it is of interest to assess the diagnostic performance of B3 lesions for breast malignancy. Here, we examined a large single-institution retrospective series of consecutive B3 lesions diagnosed on VAB within the frame of a general population-based breast screening program, with a mammographic pattern represented by microcalcifications alone, with the aim of describing the distribution of B3 lesion subtypes and quantify their upgrade rate to malignancy at SE. Moreover, we aimed to evaluate the clinical, radiological, and pathological features of B3 lesions diagnosed on VAB targeting screen-detected microcalcifications alone, in order to provide further evidence concerning the predictors of associated malignancy in definitive histological diagnosis.

1.1. Materials and Methods

This retrospective, observational, single-centre study was approved by the local Ethics Committee that waived the need for informed patient consent.

All consecutive VABs of suspicious (Breast Imaging Reporting & Data System - BIRADS grade 3 and 4) mammographic microcalcifications alone performed under stereotactic X-ray guidance at the Institute for Cancer Research, Prevention, and Clinical Network (ISPRO), Florence, Italy, during 2011–2020 were collected. From the initial dataset we first selected all cases with a B3 lesion diagnosis at VAB. In order to be eligible for inclusion in the present study, a B3 lesion also had to:

- be performed on microcalcifications not associated with other radiological abnormalities at conventional or digital mammography;
- be followed by SE with a definitive histological diagnosis; and
- have available clinical (age at diagnosis), radiological (morphology, distribution and extension of microcalcifications, presence or absence of residual microcalcifications post VAB mammography, needle gauge number of cores), and histological data (pure or mixed B3 lesion, sub-type of B3 lesion).

Biopsies were performed under stereotactic guidance using a VAB system (Mammotome, Ethicon Endo-Surgery, Breast Care, Norderstedt, Germany) using 8- to 11- gauge needles. A median of 12 cores (range 6–18) were collected during each biopsy procedure depending on the operator's personal choice, the extension of target lesion, and the woman's compliance to the procedure.

A post-biopsy radiological examination of the cores was performed in order to assess the correct sampling and confirm the presence of microcalcifications on cores. Cores with and without microcalcifications were subsequently placed into separate containers with 10 % formalin and sent to pathology laboratory. At the end of all VAB procedures, a non-magnetic clip marker was placed in the biopsy site. Finally, a post-VAB mammography was always performed to check the correct position of the clip and evaluate the presence or absence of residual microcalcifications.

1.2. Histological examination

Samples with and without microcalcifications were embedded in different paraffin blocks and processed according to standard protocols. As part of our routine protocol, each paraffin block was examined at a minimum of two levels and sections were stained with H&E. In case of absence of microcalcifications on histology, additional histological sections were examined. Whenever the histological classification into one of the five B categories was uncertain, additional H&E levels and/or immunohistochemistry were obtained. Histological examination of VABs and surgical specimens was performed at the Unit of Pathological Histology and Molecular Diagnostic of Careggi University Hospital, Florence, Italy.

VAB were histologically classified in double reading by two dedicated breast pathologists (having > 30 or > 10 years of experience in breast pathology) according to the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis in B1-B5 categories [3]. In cases of discordant histological diagnosis on VAB, consensus was reached through case-based discussion.

Histological lesions classified as B3 category were: (a) atypical intraductal epithelial proliferation; (b) flat epithelial atypia; (c) lobular intraepithelial neoplasia; and (d) a miscellaneous lesions referred to as "other lesions" which included mucocele-like lesions, papillary lesions, and radial scar. B3 category was defined as pure or mixed when only one or, respectively, two or more types of histological lesion were present on VAB. Moreover, all cases originally diagnosed as LIN were reviewed by the study pathologists and reclassified into atypical lobular hyperplasia or classic lobular carcinoma in situ according to the World Health Organization (WHO) [8].

All B3 cases, discussed in a multidisciplinary team that included radiologists, pathologists and surgeons, were sent to SE for a definitive

histological diagnosis.

1.3. Study variables and statistical analysis

The primary outcome variable was the rate of upgrade to malignancy of B3 lesions. B3 lesions were considered as upgraded if malignancy (i.e. any of ductal carcinoma in situ, pleomorphic lobular carcinoma in situ, or invasive carcinoma) was found at histological examination of surgical specimen.

We calculated the proportion of B3 lesions that upgraded to malignancy according to patient's age, type of microcalcifications (morphology, distribution, and extension), presence or absence of microcalcifications at post-VAB mammography, B3 lesion type (pure vs. mixed) and sub-type (separately for pure and mixed lesions), and characteristics of VAB procedure (needle gauge, number of cores), and tested for differences of proportions across categories by using the Fisher's exact test. We then fitted binary and multivariable logistic regression models to identify the variables independently associated with the odds of upgrading to malignancy, and calculated the predictive parameters (sensitivity, specificity, positive and negative predictive values, and overall accuracy) of the variables that resulted significantly associated with the odds of upgrade in multivariable analyses. Finally, we calculated the area under the ROC curve for the final multivariable logistic regression model, which is an estimate of the joint, overall ability of the variables included in the models to discriminate between B3 lesions that upgraded vs. did not upgrade to malignancy.

2. Results

Over the study timeframe, a total of 2,838 VAB procedures on microcalcifications alone were performed in women invited to mammography screening in the Florence area, 397 of which (14.0 % 95 % CI 12.7–15.3 %) resulted in a B3 lesion. Of these, 25 were excluded for not undergoing SE and 6 were lost to follow-up.

Out of the 366 B3 lesions that were included in the present analysis, 56 (15.3 %, 95 % CI 11.8–19.4 %) were found to have upgraded to malignancy at the subsequent SE: of these, 42/366 (11.5 %, 95 % CI 8.4–15.2 %) were in situ carcinoma (40 DCIS and 2 pleomorphic LCIS), and 14/366 (3.8 %, 95 % CI 2.1–6.3 %) were invasive carcinoma. In the remaining not-upgraded 310 B3 cases, a non-malignant atypical epithelial lesion was confirmed on SE in 179 cases (57.7 %, 95 % CI 52.0–63.3 %), while only a benign lesion was found in 131 cases (42.3 %, 95 % CI 36.7–48.0 %) meaning that B3 lesion was completely removed by VAB even in presence of residual microcalcifications at post VAB mammography.

The distribution of clinical, radiological, and histological characteristics differed between patients with B3 lesions that upgraded vs. did not upgrade to malignancy at SE (Table 1). The characteristics significantly associated with an increased odds of upgrade at univariate analysis were a patient's age $\geq$ 60 years (odds ratio (OR) 2.23, 95 % confidence intervals (CI) 1.24–4.02, p-value 0.008), a mixed morphology of microcalcifications (OR 3.97, 95 % CI 1.26–12.46, p-value 0.018, compared to punctate, fine, uniform morphology, taken as referent), a scattered distribution of microcalcifications (OR 2.93, 95 % CI 1.55–5.55, p-value 0.001; referent: single cluster), an extension of microcalcifications > 10 mm (vs. $\leq$ 10 mm; OR 2.81, 95 % CI 1.54–5.14, p-value 0.001), the presence of residual microcalcifications (OR 2.64, 95 % CI 1.27–5.48, p-value 0.009), and the B3 lesion type being mixed instead of pure (OR 2.01, 95 % CI 1.13–3.58, p-value 0.017). The needle gauge and the number of cores were not significantly associated with the odds of upgrade in univariate analysis.

The role of the B3 type of lesion in determining the risk of upgrade

Table 1
Variables associated with the probability of upgrade to malignancy of B3 lesions diagnosed on VAB for microcalcifications.

	Upgrade (N = 56)	No upgrade (N = 310)	p-value [(a)]	Binary logistic regression		
				OR	95 % CI	p-value
Age at VAB						
<60 years	32 (12.2 %)	232 (87.9 %)		1.00		
≥60 years	24 (23.5 %)	78 (76.5 %)	0.009	2.23	(1.24–4.02)	0.008
Morphology of microcalcifications						
punctuate, fine, uniform	10 (12.8 %)	68 (87.2 %)		1.00		
granular	24 (15.9 %)	127 (84.1 %)		1.29	(0.58–2.84)	0.536
linear / branching	3 (21.4 %)	11 (78.6 %)		1.85	(0.44–7.82)	0.400
powdery	12 (11.5 %)	92 (88.5 %)		0.89	(0.36–2.17)	0.793
mixed	7 (36.8 %)	12 (63.2 %)	0.082	3.97	(1.26–12.46)	0.018
Distribution of microcalcifications						
single cluster	20 (9.8 %)	185 (90.2 %)		1.00		
multiple clusters	10 (19.2 %)	42 (80.8 %)		2.20	(0.96–5.05)	0.062
scattered	26 (24.1 %)	82 (75.9 %)	0.002	2.93	(1.55–5.55)	0.001
Extension of microcalcifications						
≤10 mm	18 (9.2 %)	177 (90.8 %)		1.00		
>10 mm	38 (22.2 %)	133 (77.8 %)	0.001	2.81	(1.54–5.14)	0.001
Residual microcalcifications post VAB mammography						
present	41 (19.6 %)	168 (80.4 %)		1.00		
absent	10 (8.5 %)	108 (91.5 %)	0.07	2.64	(1.27–5.48)	0.009
Type of B3 lesion						
pure lesions	29 (12.0 %)	212 (88.0 %)				
mixed lesions	27 (21.6 %)	98 (78.4 %)	0.021	2.01	(1.13–3.58)	0.017
Needle gauge						
11G	46 (17.1 %)	223 (82.9 %)		1.00		
10G	8 (11.6 %)	61 (88.4 %)		0.64	(0.28–1.42)	0.269
8G	1 (7.7 %)	12 (92.3 %)		0.40	(0.05–3.18)	0.390
14G	1 (10 %)	9 (90 %)	0.676	0.54	(0.07–4.36)	0.562
Number of cores						
<12	18 (17 %)	88 (83 %)		1.00		
12	29 (14.7 %)	168 (85.3 %)		0.84	(0.44–1.60)	0.604
>12	9 (15 %)	51 (85 %)	0.848	0.86	(0.36–2.06)	0.740

The numbers do not always sum up to 366 because of missing values in some variables (n = 1 for Distribution of microcalcifications; n = 9 for Residual calcifications; n = 5 for Needle gauge; and n = 3 for Number of cores).
[(a)] p-values are calculated using the exact Fisher's test.

was studied with more detail in Table 2. The most frequent types of pure and mixed lesion were FEA (n = 129, accounting for 35.2 % of total lesions and 53.5 % of pure lesions) and FEA + AIDEP (n = 91, 24.9 % of total and 72.8 % of mixed lesions), respectively: these were taken as referent to which the other pure and mixed lesion types were compared. Among pure lesions, a significantly increased odds of upgrade was observed, in univariate analysis, only for AIDEP (n = 61; OR 4.35, 95 % CI 1.78–10.63, p-value 0.001), unlike LIN (n = 41), either of LIN subtypes (ALH/LIN1, n = 27, and LCIS/LIN2, n = 14) considered separately, and other pure B3 lesions (n = 10). Among mixed lesions, neither FEA + LIN (n = 21) nor FEA + AIDEP + LIN (n = 13) lesions carried a significantly increased odds of upgrade compared to FEA + AIDEP, and the same held true for any of their subtypes (Table 2). In general, the proportion of upgrade to malignancy equalled or exceeded 20 % for AIDEP (24.6 %), LCIS/LIN2 (21.4 %), FEA + AIDEP (25.3 %), FEA + LCIS/LIN2 (20.0 %), and FEA + AIDEP + LCIS/LIN2 (40.0 %, although based on only 5 cases).

Table 3 shows the outputs of the multivariable logistic regression and quantifies the predictive performance of all the variables included in the model. The characteristics that were retained were a patient's age at VAB ≥ 60 years (mOR 2.11, 95 % CI 1.08–4.13, p-value 0.029), having microcalcifications > 10 mm in extension (mOR 3.12, 95 % CI 1.64–5.94, p-value 0.001) and with a mixed morphology (mOR 4.63, 95 % CI 1.53–14.03), and having AIDEP (mOR 3.50, 95 % CI 1.33–9.18, p-value 0.011), FEA + AIDEP (mOR 4.15, 95 % CI 1.76–9.80, p-value 0.001) or FEA + AIDEP + LCIS/LIN2 (mOR 8.59, 95 % CI 1.14–64.72, p-value 0.037) lesions.

In terms of the ability to predict the upgrade to malignancy, the largest sensitivity (0.68) was shown by an extension of microcalcifications > 10 mm, while having a mixed morphology as well as several B3 lesion types and subtypes had specificity > 0.95. Unsurprisingly given the relatively low proportion of B3 lesions that upgraded to malignancy, the positive and negative predictive values were low (<0.40) and, respectively, high (>0.80) for all features (Table 3). The overall accuracy ranged from a low of 0.59 for the extension of microcalcifications > 10 mm, to above 0.80 for having a mixed morphology and some B3 lesions subtypes.

Selected characteristics of B3 lesions that upgraded to in situ carcinoma (n = 42) were shown in Table 4. The most common lesion type were FEA + AIDEP (n = 20), AIDEP (n = 11), and FEA (n = 7). The nuclear grade among DCIS (n = 40) was G1 in twenty-four cases (60 %), G22 in 10 cases (25 %) and G3 in six cases (15 %). For B3 lesions that upgraded to invasive carcinoma (n = 14), the histotypes were NST (n = 6), tubular and lobular (n = 3 each), and cribriform and ductal + lobular (n = 1 each), and the histological grade was G1 and G2 in 11 (78.6 %) and 3 (21.4 %) cases, respectively (Table 5).

Table 2
Association between type of B3 lesion (pure and mixed lesions) and the probability of upgrade to malignancy.

Type of B3 lesion at VAB	Upgrade (N = 56)	No upgrade (N = 310)	p-value [a]	Binary logistic regression		
				OR	95 % CI	p-value
Pure lesions						
FEA	9 (7.0 %)	120 (93.0 %)		1.00		
AIDEP	15 (24.6 %)	46 (75.4 %)		4.35	1.78–10.63	0.001
LIN [b]	4 (9.8 %)	37 (90.2 %)		1.44	0.042–4.95	0.561
LIN1/ ALH	*1 (3.7 %)*	*26 (96.3 %)*		*0.51*	*0.06–4.25*	*0.535*
LIN2/ LCIS	*3 (21.4 %)*	*11 (78.6 %)*		*3.64*	*0.86–15.43*	*0.080*
Other pure B3 lesions [c]	1 (10.0 %)	9 (90.0 %)	0.008	1.48	0.17–13.03	0.723
Mixed lesions						
FEA + AIDEP	23 (25.3 %)	68 (74.7 %)		1.00		
FEA + LIN	2 (9.5 %)	19 (90.5 %)		0.31	0.07–1.44	0.135
FEA + ALH/ LIN	*0 (0.0 %)*	*11 (100.0 %)*		–	–	–
FEA + LCIS/ LIN2	*2 (20.0 %)*	*8 (80.0 %)*		*0.74*	*0.15–3.73*	*0.715*
FEA + AIDEP + LIN	2 (15.4 %)	11 (84.6 %)		0.54	0.11–2.61	0.441
FEA + AIDEP + ALH/LIN1	*0 (0.0 %)*	*8 (100.0 %)*		–	–	–
FEA + AIDEP + LCIS/LIN2	*2 (40.0 %)*	*3 (60.0 %)*	0.269	*1.97*	*0.31–12.54*	*0.472*

[a] p-values are calculated using the exact Fisher's test.
[b] The OR for the comparison of LCIS7LIN2 to ALH/LIN1 (ref) is 7.09 (95% CI 0.48–386.12), p-value 0.070.
[c] Include: papillary lesions (n = 4), mucocele-like lesions (n = 5), and radial scar (n = 1).

3. Discussion

To the best of our knowledge, this is one of the largest single-institution series to date concerning VAB performed on microcalcifications alone (i.e. with no other radiological signs in addition to microcalcifications) identified within the frame of a population-based mammographic screening program and having a description of the outcomes on subsequent SE. In recent years, the clinical management of B3 lesions has been discussed in several guidelines such as those issued by the American Society of Breast Surgeons [9], the UK NHSBSP (National Health Service Breast Screening Programme) [4], and the 2nd and 3rd International Consensus Conferences [6,7], yet no general agreement has been reached because of the large variability in the rates of upgrade to malignancy in the different case series reported in the literature. The clinical management of B3 lesions is still a matter of debate, and neither SE nor VAE has been established as a reliable guide for the management of B3 lesions. SE is generally recommended in the USA [9], while European guidelines tend to favour VAE, albeit with discrepancies between NHSBSP recommendations [4] and those from the 2nd and 3rd International Consensus Conferences [6,7]. In general, it is essential that the management of B3 lesions takes on a multidisciplinary approach with close communication between all team members (particularly between pathologists and radiologists) and aims at assessing the individual risk of each patient and their suitability for either SE or VAE [4,10].

Our results, in agreement with previously published data [11–14], demonstrated that age ≥ 60 years, mixed morphology, extension > 10 mm of microcalcifications, and any of AIDEP, FEA + AIDEP and FEA + AIDEP + LCIS/LIN2 B3 lesion types are independently associated with increased probability of upgrade to malignancy. The overall upgrade rate to malignancy in our series was 15.3 %, comparable to previous series reported in literature [13,14,2], and reasonably close to the average pooled estimates reported in recent *meta*-analyses (i.e. 17–19 %) [15,16]. Concerning the type of associated malignancy at SE, most cases in our series were either low grade in situ or invasive carcinomas (42.8 % and 19.7 % nuclear grade G1 DCIS and histological grade G1 invasive carcinoma, respectively), similar to figures in Lucioni et al. [17]. Of note, nearly all B3 lesions (pure or mixed) in our series were characterized by either cytological atypia (FEA) or cyto-architectural atypia (AIDEP and LIN). The significantly increased risk of upgrade of mixed (vs. pure) lesions was in fair accordance with our previous large multi-institutional study in Italy [18]. Instead, needle gauge size and number of cores do not appear to correlate with malignancy upgrade

Table 3
Characteristics associated with the probability of upgrade to malignancy in multiple logistic regression analysis, and associated parameters of predictive performance (sensitivity, specificity, positive and negative predictive values, and overall accuracy).

		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	Multiple logistic regression		
							OR	95 % CI	p-value
Age at VAB	≥60 years	0.43	0.75	0.24	0.88	0.70	2.11	1.08–4.13	0.029
Extension of microcalcifications	>10 mm	0.68	0.57	0.22	0.91	0.59	3.12	1.64–5.94	0.001
Morphology of microcalcifications	mixed	0.12	0.96	0.37	0.86	0.83	4.63	1.53–14.03	0.007
Type of B3 lesion	FEA	0.16	0.61	0.07	0.80	0.54	1.00		
	AIDEP	0.27	0.85	0.25	0.87	0.76	3.50	1.33–9.18	0.011
	LIN	0.07	0.88	0.10	0.84	0.76	1.08	0.30–3.87	0.902
	ALH/LIN1	*0.02*	*0.92*	*0.04*	*0.84*	*0.78*	*0.34*	*0.04–2.88*	*0.320*
	LCIS/LIN2	*0.05*	*0.96*	*0.21*	*0.85*	*0.83*	*3.41*	*0.77–15.06*	*0.106*
	Other pure lesions	0.02	0.97	0.10	0.85	0.83	1.96	0.21–18.51	0.559
	FEA + AIDEP	0.41	0.78	0.25	0.88	0.72	4.15	1.76–9.80	0.001
	FEA + LIN	0.04	0.94	0.10	0.84	0.80	1.28	0.24–6.70	0.772
	FEA + ALH/LIN1	*0.00*	*0.96*	*0.00*	*0.84*	*0.82*	–	–	–
	FEA + LCIS/LIN2	*0.04*	*0.97*	*0.20*	*0.85*	*0.83*	*2.47*	*0.42–14.66*	*0.319*
	FEA + AIDEP + LIN	0.04	0.96	0.15	0.85	0.82	2.23	0.041–12.26	0.356
	FEA + AIDEP + ALH/LIN1	*0.00*	*0.97*	*0.00*	*0.84*	*0.83*	–	–	–
	FEA + AIDEP + LCIS/LIN2	*0.04*	*0.99*	*0.40*	*0.85*	*0.84*	*8.59*	*1.14–64.72*	*0.037*

rate and, according to other authors [19,20], should not drive clinical decision making. A complete removal of microcalcifications was obtained by VAB in 36 % of cases, which did not significantly affect the rate of upgrade to malignancy in multivariable analysis. In general, our findings suggest that there may be considerable differences in the upgrade rate to malignancy depending on the B3 lesion type, and in what follows we will delve in more detail into these aspects.

3.1. AIDEP

AIDEP had the highest rate of upgrade to malignancy among pure lesions in our series (24.6 %, of which 18.0 % in situ and 6.6 % invasive carcinoma). This falls within the broad range (1–53 %), and fairly close to the pooled average value (22 %), estimated in recent systematic *meta*-analyses [15,16]. Thus, we corroborate the notion that AIDEP represents a significant risk factor for upgrade among B3 pure lesions. A risk of underestimation > 5 % for invasive carcinoma and > 10 % for in situ carcinoma supports the recommendation that patients with AIDEP should undergo SE as stated by the 2nd and 3rd International Consensus Conferences [6,7] and ASBS recommendation [9]. For completeness, it is to be noted that some discrepancies exist between American and European recommendations [6,7] on one side, and NHSBSP recommendations [4] on the other side, regarding the management of AIDEP. In fact, the latter suggests a more conservative approach, whereby in cases of AIDEP (pure lesion), a VAE should be performed as first approach, while a diagnostic SE is recommended in case additional atypia is found following assessment with VAE [4].

3.2. LIN

LIN is usually an incidental finding as it is only rarely associated with mammographically-detected microcalcifications. In our study, the overall upgrade rate to malignancy of LIN was 9.8 %, which falls in the broad range (6–33 %, with pooled average equalling 16 %) reported in a recent *meta*-analysis [16]. Upon splitting the LIN category into ALH/LIN1 and LCIS/LIN2, we observed that the upgrade rate differed largely between them. This result could open different management strategies: considering their low upgrade rate (3.7 %), ALH/LIN1 could be approached by means of VAE, while the much higher upgrade rate of LCIS/LIN2 (21.4 %, of which 7.1 % and 14.3 % for invasive and in situ carcinoma, respectively), close to that of AIDEP, supports the recommendation that these patients should undergo SE [13,21]. If the lower rate of upgrade to malignancy of ALH/LIN1 compared to LCIS/LIN2 [15,21–24] is confirmed in larger series, the differentiation of LIN lesions into ALH/LIN1 and LCIS/LIN2 could be highly relevant for patients management.

3.2.1. FEA, pure lesion

FEA was the most represented category among pure B3 lesions and had a very low rate of upgrade to malignancy (7 %), unlike AIDEP and LCIS/LIN2. Thirteen studies reported in the Cullinane's review showed that the overall upgrade rate to malignancy was 9 % and the pooled PPV value of VAB in the setting of FEA was 7 %, in perfect agreement with our results.

In consideration of the low underestimation rate, 1.5 % and 5.5 % for invasive carcinoma and in situ carcinoma, respectively, we consider acceptable, in cases of FEA, a complete excision of microcalcifications by VAE according to the recommendations from the NHSBSP and the 2nd and 3rd International Consensus Conferences on B3 lesions [4,6,7]. On the contrary, the ABSB recommendations [9] suggest, in case of pure FEA, observation with clinical and imaging follow-up.

3.2.2. FEA, associated with other B3 lesions

While often occurring as pure lesion, FEA was associated with other atypical epithelial B3 lesions such as AIDEP (36 %), LIN (8 %), or both AIDEP and LIN (5 %) (while representing the main lesion) in a large proportion of cases (125/254, 49 %), similarly to what we found in a previous study of our study group [18].

In mixed lesions, the association of FEA with AIDEP is the most frequently observed and upgrade rate to malignancy of their joint occurrence is significantly higher than for pure FEA lesions. In fact, 25.3 % (23/91) of FEA + AIDEP cases showed an upgrade to malignancy at SE (3.3 % to invasive carcinoma and 22 % to in situ carcinoma), very similar to the upgrade rate of pure AIDEP observed in our series.

Much less often was FEA + LIN observed (21/254, 8 %), which had an upgrade rate of 9.5 %, fairly comparable to pure LIN. After reclassifying LIN into ALH/LIN1 and LCIS/LIN2, we found an upgrade rate of 0 % and, respectively, 20 % (2 cases of which 1 case of pleomorphic LCIS and 1 cases of tubular carcinoma). While acknowledging the limitation represented by the very small number of cases, it is interesting to note that the upgrade rate of FEA + LCIS/LIN2 is very close to that of pure LCIS/LIN2.

Table 4
Details of B3 lesions that upgraded to in situ carcinoma (DCIS or pleomorphic LCIS/LIN3).

Type of B3 lesion	Morphology of microcalcifications	Distribution of microcalcifications	Extension of microcalcifications mm	Microcalcifications present in VAB	Needle gauge	Number of cores	Histotype and nuclear grade
AIDEP	granular	scattered	30	+	11G	>12	DCIS, G1
AIDEP	granular	multiple clusters	55	+	11G	12	DCIS, G2
AIDEP	granular	scattered	20	+	11G	12	DCIS, G3
AIDEP	powdery	scattered	20	+	11G	<12	DCIS, G2
AIDEP	granular	single cluster	14	+	11G	<12	DCIS, G2
AIDEP	powdery	single cluster	4	+	11G	12	DCIS, G2
AIDEP	linear or branching	single cluster	5	+	11G	<12	DCIS, G2
AIDEP	granular	multiple clusters	35	+	11G	<12	DCIS, G3
AIDEP	granular	multiple clusters	12	+	11G	<12	DCIS, G3
AIDEP	granular	single cluster	5	+	10G	12	DCIS, G2
AIDEP	granular	scattered	30	+	10G	12	DCIS, G3
FEA	granular	single cluster	4	+	11G	12	DCIS, G2
FEA	granular	multiple clusters	20	+	11G	12	DCIS, G2
FEA	powdery	multiple clusters	16	+	10G	12	DCIS, G1
FEA	punctate	scattered	20	+	11G	12	DCIS, G2
FEA	mixed	single cluster	10	+	11G	12	DCIS, G1
FEA	punctate	multiple clusters	30	+	11G	>12	DCIS, G2
FEA	punctate	scattered	12	+	11G	12	DCIS, G2
LCIS/LIN2	punctate	scattered	30	+	10G	<12	DCIS, G3
LCIS/LIN2	granular	scattered	20	+	11G	>12	Pleomorphic LCIS/ LIN3
Mucocele-like lesion	granular	single cluster	5	+	11G	12	DCIS, G2
FEA + AIDEP	punctate	single cluster	10	+	11G	>12	DCIS, G2
FEA + AIDEP	powdery	single cluster	8	+	11G	>12	DCIS, G3
FEA + AIDEP	granular	single cluster	10	+	10G	12	DCIS, G2
FEA + AIDEP	granular	multiple clusters	15	+	11G	12	DCIS, G2
FEA + AIDEP	powdery	scattered	20	+	11G	12	DCIS, G1
FEA + AIDEP	punctate	single cluster	5	+	11G	12	DCIS, G2
FEA + AIDEP	powdery	scattered	100	+	11G	12	DCIS, G2
FEA + AIDEP	mixed	scattered	20	+	8G	<12	DCIS, G1
FEA + AIDEP	granular	scattered	20	+	11G	<12	DCIS, G2
FEA + AIDEP	mixed	scattered	30	+	11G	12	DCIS, G2
FEA + AIDEP	mixed	scattered	30	+	10G	12	DCIS, G1
FEA + AIDEP	mixed	scattered	100	+	11G	<12	DCIS, G1
FEA + AIDEP	powdery	single cluster	5	+	11G	<12	DCIS, G2
FEA + AIDEP	granular	scattered	35	+	11G	12	DCIS, G1
FEA + AIDEP	punctate	single cluster	12	+	11G	>12	DCIS, G1
FEA + AIDEP	linear/branching	scattered	30	+	11G	>12	DCIS, G2
FEA + AIDEP	powdery	multiple clusters	20	+	11G	<12	DCIS, G2
FEA + AIDEP	granular	scattered	60	+	11G	12	DCIS, G1
FEA + AIDEP	punctate	single cluster	7	+	11G	12	DCIS, G2
FEA + AIDEP	mixed	multiple clusters	10	+	11G	<12	DCIS, G2
FEA + LCIS/ LIN2	powdery	single cluster	13	+	11G	12	Pleomorphic LCIS/ LIN3

Table 5
Details of B3 lesions that upgraded to invasive carcinoma.

Type of B3 lesion	Morphology of microcalcifications	Distribution of microcalcifications	Extension of microcalcifications, mm	Microcalcifications present in VAB	Needle gauge	Number of cores	Histotype and histological grading
AIDEP	granular	single cluster	8	+	11G	12	NST, G2
AIDEP	powdery	scattered	40	+	11G	>12	Cribriform, G1
AIDEP	multiple/other	scattered	50	+	11G	12	NST, G1
AIDEP	granular	single cluster	10	+	11G	<12	NST, G2
FEA	powdery	scattered	15	+	11G	12	Tubular, G1
FEA	punctate	single cluster	5	+	11G	<12	Lobular, G1
ALH/LIN1	powdery	scattered	40	+	11G	<12	NST, G2
LCIS/LIN2	granular	single cluster	4	+	11G	<12	Ductal and lobular, G1
FEA + AIDEP	granular	scattered	35	+	10G	<12	NST, G1
FEA + AIDEP	punctate	multiple clusters	30	+	11G	12	Tubular, G1
FEA + AIDEP	linear/branching	scattered	35	+	10G	12	NST, G1
FEA + AIDEP + LCIS/ LIN2	granular	scattered	50	+	11G	<12	Lobular, G1
FEA + LCIS/ LIN2	granular	scattered	20	+	11G	12	Tubular, G1
FEA + AIDEP + LCIS/ LIN2	granular	single cluster	6	+	11G	12	Lobular, G1

Finally, in 5 % (13/254) of our cases we found FEA + AIDEP + LIN, resulting in an underestimation rate of malignancy of 15.4 % (2/13). Upon splitting LIN into ALH/LIN1 and LCIS/LIN2, we noted that the only two cases of upgrade to malignancy (both to G1 invasive lobular carcinoma) were found in the association of FEA + AIDEP + LCIS/LIN2.

3.3. Strengths and limitations

As already stated, our series is the largest of its kind to date that gathered data from a population-based breast cancer screening program and studied the factors associated with the risk of upgrade to malignancy following SE. Our study also presents limitations that it is important to acknowledge. An important weakness of our study lies in its retrospective design: the study reflects data collected from routine practice without re-assessment of mammography or pathology, only cases originally diagnosed as LIN at VAB were reviewed and reclassified by two dedicated breast pathologists in ALH/LIN 1 and LCIS/LIN2. Also, the number of some specific pure or mixed B3 lesions is limited and our results must be considered as suggestive, warranting confirmation in larger series. Finally, compared to the observation period of our investigation (2011–2020), there is a generally increasing propensity towards radiological follow-up (instead of surgical excision) of B3 lesions, especially for some subtypes: the findings of our study should therefore be interpreted in the light of these changes in patients management.

4. Conclusion

In conclusion, our study shows an overall upgrade rate to malignancy of 15.3 % of B3 lesions diagnosed on VAB and targeting microcalcifications alone, with older age, mixed morphology, and larger extension of microcalcifications as independent risk factors for higher upgrade to malignancy. According to our results, and in line with a recent *meta*-analysis suggesting that it is reasonable to perform VAE as definitive management for B3 lesion subtypes having upgrade rates < 5 % for invasive carcinoma and < 10 % for in situ carcinoma [25], we conclude that VAE could be safely performed for FEA, ALH/LIN1, and FEA + ALH/LIN while SE should remain the mainstay of treatment for AIDEP (as a pure lesion or presenting together with other lesion types) and LCIS/LIN2, whose upgrade rates are too high to recommend VAE [16,26].

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6. Declaration of generative artificial intelligence in scientific writing

During the preparation of this work, the authors did not use any generative artificial intelligence (AI) and AI-assisted technologies.

7. Ethics

This study was approved by the local Ethics Committee that waived the need for informed patient consent.

CRediT authorship contribution statement

Bianchi Simonetta: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Caini Saverio:** . **Vezzosi Vania:** . **Orzalesi Lorenzo:** . **Piovesan Luisa:** . **Mantellini Paola:** . **Ambrogetti Daniela:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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