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BREAST RADIOLOGY

Percutaneous vacuum-assisted excision (VAE) of breast lesions of uncertain malignant potential (B3 lesions): a preliminary single-centre Italian experience

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Abstract

Purpose In recent years vacuum-assisted excision (VAE) has been described as an alternative treatment for some B3 lesions. This study aims to assess the effectiveness of using VAE to manage selected B3 lesions by quantifying the number of B3 lesions undergoing VAE, the malignant upgrade rate, and the complications encountered.

Materials and methods Our department evaluated all B3 lesions diagnosed between January 2019 and October 2021 and treated them with VAE. The data were collected during the initial biopsy and final histology based on VAE image guidance, also considering initial lesions and complications. The exclusion criteria were: B3 lesion of size > 20 mm, presence of a concomitant malignant lesion, lesion < 5.0 mm distant from the skin, nipple or pectoral muscle, phyllodes tumours or indeterminate B3 lesions. Lesions that upgraded to malignancy underwent surgical excision, while benign lesions performed radiological follow-ups.

Results From 416 B3 lesions diagnosed, 67 (16.1%) underwent VAE. VAE was performed under X-ray (50/67) or ultrasound guidance (17/67). Five cases (7.5%) upgraded to a malignant lesion, 2 ADH, 2 LIN and one papillary lesion that underwent surgery. No malignancy or new lesions has occurred at the site of the VAE, with an average radiological follow-up of 14.9 months.

Conclusions VAE could be a safe and effective pathway for managing selected B3 lesions. Lesions initially subjected to CNB with ADH and LN outcome, before undergoing VAE, should perform a VAB for better tissue characterization and management.

Keywords Biopsy · Breast · Breast biopsy · Breast cancer

Introduction

Lesions of uncertain malignant potential (B3) breast lesions are a lesion group characterized by a high heterogeneity that could be associated with ductal carcinoma in situ (DCIS), pleomorphic lobular carcinoma in situ or invasive carcinoma [1]. The probability of being associated with malignant lesions is highly variable among the different types of B3 lesions, with an upgrade rate between 10 and 35% [2, 3]. However, most B3 lesions are shown to be benign on histological diagnosis, and associated malignant lesions are generally in situ or low-grade invasive carcinomas. On the other hand, the incidence of this group of alterations is equal to 3–21% and increasing in published biopsy series, thus affecting a growing number of patients [4]. Until a few years ago, the only possible treatment for B3 lesions was diagnostic

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surgical excision to exclude the presence of associated malignant lesions. Recently, the VAE (Vacuum Assisted Excision) of selected B3 lesions is becoming increasingly widespread since it reduces the need for surgical excision and moves towards more conservative management. The possibility of removing large amounts of tissue, equivalent to those removed during a diagnostic surgical excision with vacuum-assisted devices for percutaneous breast biopsy, reduces the risk of underestimation of associated malignancy and increases diagnostic accuracy and thus obviating the need for surgery [2, 3, 5–7].

VAE (Vacuum Assisted Excision) aims to obtain the same amount of tissue as a diagnostic surgical excision, i.e. 4 g of tissue, using the same Vacuum Assisted Biopsy (VAB) method to remove the entire B3 lesion [8, 9].

Numerous guidances have been published about B3 lesions treatment with VAE, which slightly differ from each other in indications. According to the 2018 NHS Breast Screening Multidisciplinary Working Group Guidance [3], B3 lesions smaller than 20 mm should be managed with VAE. On the other hand, Papillary lesions (PL) with atypia and other indeterminate B3 lesions, i.e. cellular fibroepithelial lesions and myofibroblastoma, need to be excluded. According to the Second International Consensus Conference [2], instead, for atypical ductal hyperplasia (ADH) and phyllodes tumours (PT), surgical excision is recommended, while the other B3 lesions smaller than 25 mm could be excised with VAE. Both guidelines always recommend the discussion of each case at the Breast Multidisciplinary Team Meeting (MDTM). B3 lesions that has been upgraded to malignancy after the VAE must undergo therapeutic surgical excision. Benign lesions, after VAE, can undergo radiological follow-up with different frequencies according to the selected guidance.

Compared to surgical excision, VAE decreases invasiveness and stress in patients, providing adequate aesthetic results and reducing complications and costs [5, 6, 9].

In this setting, our preliminary study aims to evaluate the effectiveness of using VAE to manage selected B3 lesions by quantifying the number of B3 lesions undergoing VAE, the malignancy upgrade rate and the complications encountered.

Materials and methods

This single-centre prospective study received approval from our institutional review board and was conducted according to Good Clinical Practice guidelines.

Enrolment in this study was proposed to all women aged 35–90 years diagnosed with B3 lesions after CNB or VAB performed at our centre between January 2019 and October 2021. The exclusion criteria for VAE were: B3 lesion diagnosed with CNB or VAB of size > 20 mm, presence of a concomitant B5 lesion elsewhere on either breast, lesion < 5.0 mm distant from the skin, nipple or pectoral muscle, phyllodes tumours or indeterminate B3 lesions, i.e. cellular fibroepithelial lesion, myofibroblastoma and patient preference for diagnostic surgery. All cases were discussed at our breast MDTM.

Eligible women willing to provide informed consent entered this study and underwent VAE within one month of the first biopsy, as depicted in the protocol flowchart (Fig. 1).

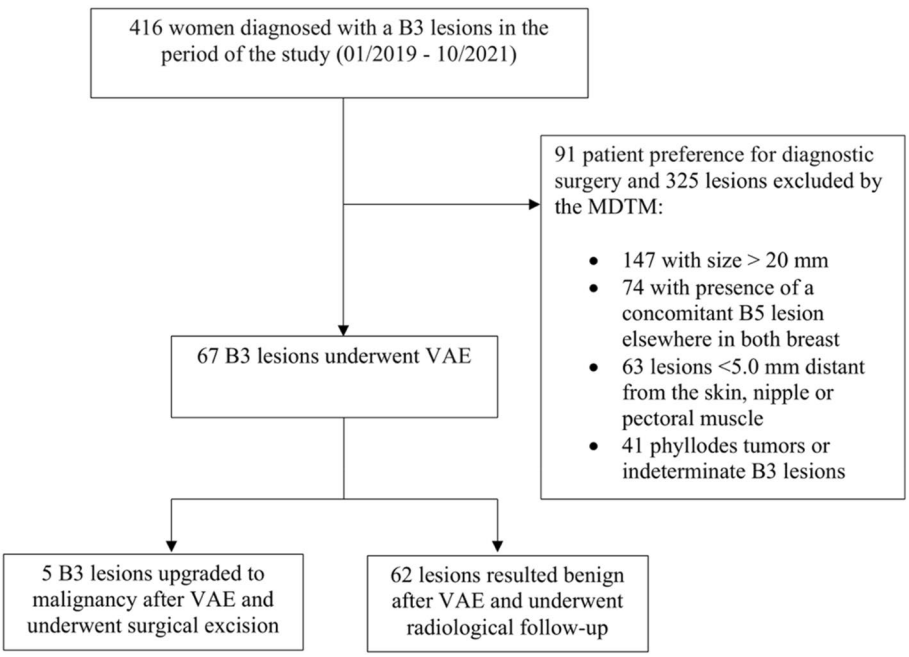

Fig. 1 Flowchart illustrating patient exclusion criteria, the B3 lesions included in the study, management and outcome

The Radiology Information System and Picture Archiving and Communications System (RIS-PACS) was used to collect information. They were related to the type of mammography (MG), Digital Breast Tomosynthesis (DBT) or Ultrasound (US) alteration corresponding to the B3 lesions included in the study, the size of the lesion, the breast density evaluated on DM or US according to the BI-RADS criteria [10] as well as the age and personal history of breast cancer (BC) for each patient. In addition, information regarding the initial biopsy, the VAE and any procedural complications that occurred during the VAE, i.e. bleeding, infection, and severe pain, were also collected from the RIS. The histological results of the initial biopsy, the VAE and any surgery performed (in case of malignancy result of the VAE) were then obtained.

First-line biopsies were performed both as Percutaneous CNB with a semiautomated biopsy gun (Precisa, Hospital Service) with a 14-Gauge, 10-cm-long needle and as DBT-guided VAB using a vacuum-assisted biopsy device (Mammotome revolve; Devicor Medical Products) with an 8-Gauge needle or using a vacuum-assisted biopsy device (Brevera; Hologic) with a 9-Gauge needle [11]. In addition, two pathologists (with more than 25 years of experience in breast pathology) analyzed the samples; they also analyzed the samples obtained with the VAE and surgical specimens.

The VAE procedures were performed with US guidance when the B3 lesion was US-visible or with DBT guidance when the initial B3 lesion was identified with MG or DBT using a vacuum-assisted biopsy device (Mammotome revolve; Devicor Medical Products) with an 8-Gauge needle. A mean of 24 core samples per lesion was obtained (range 20–28 at the operator's discretion according to the samples' quality, intending to achieve 4 g of tissue) [2, 3].

Six radiologists from our department performed the procedures, with 10–30 years of experience in breast radiology.

A radio-opaque marker clip (Mammomark and Mammostar; Devicor Medical Products, Cincinnati, OH) was placed at the end of each biopsy, and VAE was to identify the procedure site.

Therefore, the results of the VAE were followed by an MDTM discussion.

Malignant lesions after VAE underwent surgical excision, while benign lesions, i.e. B3, B2 or B1, underwent radiological follow-up at our department; six months after the VAE, a first examination was performed with mammography, DBT and ultrasound, and then again 12 and 24 months after VAE.

Statistical analysis

Non-parametric tests were used to verify any statistically significant difference between the size of the malignant lesions and the benign ones after VAE. Fisher's exact test and post-hoc analysis were applied to verify whether some characteristics related to the B3 lesions (histological type of B3 lesion, presence of atypia, Dominant Radiological Feature) or related to the patients (age and mammographic density) or the biopsy technique (type of initial biopsy performed, i.e. VAB or CNB) could significantly increase the risk of upgrading after VAE. The risk difference was used to test significance at $p \leq 0.05$. Statistical calculations were performed using the IBM SPSS Statistics (version 23.0) statistical software (SPSS).

Results

From January 2019 to October 2021, our Institute performed 5440 core needle biopsies (CNB) and 1558 VABs. As a result, 416 (5.9%) were classified as B3. From 416 B3 lesions identified with CNB or VAB at our centre from January 2019 to October 2021, 67 (5.9%) were considered eligible for VAE after case discussion at the MDTM. Our study group consisted of 67 women aged 39–86 years, mean age of 53.5 years (standard deviation [SD] 11.1) with 67 B3 lesions identified by CNB or VAB and subjected to VAE with US guidance or with DBT guidance. 74.6% (50/67) of VAE cases were performed under DBT guidance, and 25.4% (17/67) under US guidance. No significant complications related to VAE were observed. Four moderate hematomas at the access site resolved spontaneously during the follow-up, which did not require therapy. 5/67 B3 lesions (7.5%) upgraded to malignancy after VAE; 2 atypical ductal hyperplasia (ADH) lesions, 2 classical lobular neoplasia (LIN) and one papillary lesion (PL). Lesions that upgraded resulted in two cases of DCIS, one G1 and one G2, three cases of invasive carcinoma, one G1 invasive cribriform carcinoma, one G1 invasive lobular carcinoma, and one invasive papillary carcinoma, as described in Table 1. These five patients underwent surgical excision. 62/67 lesions (92.5%) had a benign outcome after VAE, and thus radiological follow-up was performed. Therefore, the upgrade rate of B3 lesions subjected to VAE in our study was equal to 7.5%.

The characteristics of the B3 lesions included in the study are summarized in Table 2. The lesions included 8 ADH, 15 radial scars (RS), 7 PLs, 25 flat epithelial atypia (FEA) and 12 LN.

60 (89.6%) B3 lesions identified with MG and/or DBT were represented by 4 (6.6%) pure parenchymal distortions, 3 (5.0%) distortions with microcalcifications, 37 (61.6%) clusters of pure microcalcifications, 5 (8.3%) opacities with microcalcifications and 11 (18.3) pure opacities. Ten of the initial 60 (16.6%) lesions identified in MG or DBT also had a US equivalent as hypoechoic masses (9/10) or parenchymal distortion (1/10). The 17 (25.4%) B3 lesions identified with US were represented by 16 (94.1%) hypoechoic masses and one (5.9%) parenchymal

Table 1 Characteristics of B3 lesions upgraded to malignancy after VAE and surgical outcome

Patients	Age	Breast density (BI-RADS)[a]	Personal history of breast cancer	Lesion size (mm)	Initial biopsy result	Dominant radiological feature	Presence of atypia	Method of initial biopsy	Method of VAE[b]	VAE result	Type of surgery performed	Histological result after surgery
1	61	C	Yes	10	ADH[c]	Mass	Yes	CNB[e]	US-Guided	Invasive Carcinoma	Mastectomy	2.0 mm, G1, Invasive Cribriform Carcinoma, LuminalA
5	48	C	No	6	LN[d]	Pure Microcalcifications	Yes	VAB[f]	Xray-Guided	DCIS[g]	Wider Excision	4.0 mm, G1, DCIS
9	62	C	No	10	ADH	Mass	Yes	CNB	US-Guided	DCIS	Wider Excision	2.0 mm, G2, DCIS
41	71	C	No	7.5	LN	Mass	Yes	CNB	US-Guided	Invasive Carcinoma	Wider Excision	11 mm, G1, Invasive Lobular Carcinoma, LuminalA
67	86	C	No	13	PL[h]	Mass	Yes	CNB	US-Guided	Invasive Carcinoma	Wider Excision	2.0 mm, G1, Invasive Papillary Carcinoma, LuminalA

[a]BI-RADS, Breast Imaging Reporting and Data Systems; [b]VAE, Vacuum Assisted Breast Excision; [c]ADH, atypical ductal hyperplasia; [d]LN, classical lobular neoplasia;[e]CNB, Core Needle Biopsy; [f]VAB, Vacuum Assisted Biopsy; [g]DCIS, Ductal Carcinoma In Situ; [h]PL, Papillary lesions

Table 2 Characteristics of the patients and radiological and pathological features of the B3 lesions included in the study, with final histological results for each characteristic and risk difference of upgrade post VAE

Patients and B3 lesion characteristics	n	VAE result		*p* value
		Benign (%)	Malignant (%)	
Breast density (BI-RADS[a])				0.0084
A	3	3 (100)	0	
B	25	25 (100)	0	
C	27	22 (81.5)	5 (18.5)	
D	12	12 (100)	0	
Method of initial Biopsy				0.013
CNB[e]	17	13 (76.5)	4 (23.5)	
VAB[f]	50	49 (98)	1 (2)	
Initial Biopsy result				0.0016
B3 with Atypia	52	47 (90.4)	5 (9.6)	
B3 without Atypia	15	15 (100)	0	
Histological type of B3 lesion				0.0252
ADH[c]	8	6 (75)	2 (25)	
LN[d]	12	10 (83.3)	2 (16.7)	
PL[h]	7	6 (85.7)	1 (14.3)	
RS[i]	15	15 (100)	0	
FEA[j]	25	25 (100)	0	
Dominant Radiological Feature				ns
Pure parenchymal distortions	4	4 (100)	0	
Distortions with microcalcifications	3	3 (100)	0	
Clusters of pure microcalcifications	37	36 (97.3)	1 (2.7)	
Opacities with microcalcifications	5	5 (100)	0	
Pure opacities	11	9 (81.8)	2 (18.2)	
Hypoechoic masses	16	12 (75)	4 (25)	
Parenchymal distortion	1	1 (100)	0	
Method of VAE[b]				0.013
US-guided[g]	17	13 (76.5)	4 (23.5)	
DBT-guided[k]	50	49 (98)	1 (2)	
Total	67	62 (92.5)	5 (7.5)	

[a]BI-RADS, Breast Imaging Reporting and Data Systems; [b]VAE, Vacuum Assisted Breast Excision; [c]ADH, atypical ductal hyperplasia; [d]LN, classical lobular neoplasia; [e]CNB, Core Needle Biopsy; [f]VAB, Vacuum Assisted Biopsy; [g]US, Ultrasound; [h]PL, Papillary lesions; [h]RS, Radial Scar; [j]FEA, flat epithelial atypia; [k]DBT, Tomosynthesis

distortion. No MG/DBT and/or US feature was found to be more associated than the others with an increased risk of upgrade.

Lesions' maximum size ranged between 2 and 15 mm (mean = 6.6 mm, SD = 3.0). Lesions that had upgraded after VAE had a larger mean size (9.3 mm vs. 6.35 mm; median 10 mm vs. 5.5 mm) than benign lesions, although this was not statistically significant (*p*: 0.0526). The breast density evaluated on DM or US according to the BI-RADS criteria was type A for 3 (4.5%) patients, B for 25 (37.3%) patients, C for 27 (40.3%) patients and D for 12 (17.9%) patients. Type C density is significantly more associated with the upgrading risk than the other types (5/5; *p*: 0.0084). The 5/67 women (7.5%) who had upgraded to malignancy after VAE also had a significantly higher mean age (65.6 vs. 52.5; *p*: 0.0094) and a higher median age (62 vs. 50) compared to patients with lesions who had not upgraded.

The initial biopsy was performed with a 14-Gauge CNB in 25.4% of women (17/67), with an 8-Gauge or 9-Gauge VAB in 74.6% (50/67). A VAE performed with US guidance, following an initial biopsy performed as CNB, has a significantly higher risk of upgrading than an initial biopsy performed with the VAB technique (*p*: 0.013).

Among the different types of B3 lesions included in the study we found that B3 lesions different from ADH and LIN, i.e. FEA, RS and PL had a lower risk of upgrading to malignancy than these histological types, with a statistically significant difference (*p*: 0.0252). Atypia was present in 52/67 (77.6%) B3 lesions treated with VAE, while 15/67 (22.4%) B3 lesions had no atypia. 5 on 52 (9.6%) lesions with atypia

upgraded to malignancy after VAE while no lesions without atypia upgraded to malignancy. The biopsy results revealed a significant correlation between the presence of atypia and the increased risk of upgrade after VAE in this subgroup of patients (p: 0.0016).

Five lesions upgraded to malignancy after VAE and therefore underwent surgical excision, four had wider excisions, and one was treated with a mastectomy (the latter underwent a mastectomy since she had already had a lumpectomy for an ipsilateral invasive carcinoma four years before the VAE). There was a malignant outcome after VAE in 2 out of 8 cases (25.0%) of ADH, in 2 out of 12 (16.6%) of LN and in 1 out of 7 (14.3%) of PLs.

Sixty-two benign lesions underwent radiological follow-up, performed at six months and then at 12 and 24 months with mammography, DBT and ultrasound, with an average follow-up of 12.6 months. 24/62 (38.7%) patients currently have a 6-month follow-up, 23/62 (37.1%) patients a 12-month follow-up, and 15/62 (24.2%) patients 24-month; the follow-up is still ongoing and will end when all the patients have performed the examination 24 months after VAE. So far, no new lesions or malignancies have been identified at the site of the VAE, and radiological follow-up is currently negative for all patients (Fig. 2).

Discussion

In the past, surgical removal of B3 lesions was the only possible alternative to be offered to patients with this histological diagnosis to exclude the presence of associated malignant lesions. In recent years, as an alternative to diagnostic surgery for some of these B3 lesions, percutaneous removal with large-calibre needles or VAE is becoming more widespread since the risk of upgrading to malignancy is low, especially for certain types of B3 lesions [2, 3, 6, 8, 12]. VAE aims to remove at least 4 g of tissue, the same amount as a diagnostic surgical excision, to allow an accurate histological diagnosis, to adequately exclude the presence of malignant lesions, and thus avoid surgical excision. VAE has recently been introduced into the National Health Service Breast Screening Programme as an alternative to diagnostic surgical excision for selected B3 lesions. In the First and Second International Consensus Conference on lesions of uncertain malignant potential in the breast, VAE is recommended as the preferred therapy for the majority of B3 lesions [2, 3, 13]. The removal procedure of benign breast lesions with VAE is codified and widespread, with several studies published in the literature [14–16]. On the other hand, a few experiences have been published to date on the removal of B3 lesions [5, 6, 17–20].

In our study, VAE proved to be an effective procedure, obviating 14.9% of surgical excisions for selected B3 lesions subjected to VAE, which resulted benign and with an upgrade rate of 7.5%. These results are in line with those published by Giannotti et al. whose upgrade rate was 8.6%, and thanks to VAE, 40.7% of diagnostic surgical excisions were avoided. [5] In the UK's major study published on the subject, 60% of diagnostic surgical excisions for B3 lesions were spared by VAE [20].

There have yet to be national guidelines for managing B3 lesions in Italy, but only a consensus document from the Italian Mammography Screening Group (GISMA) [21]. It could explain the lower number of lesions included in our work, i.e. subjected to VAE, compared to the total of B3 lesions diagnosed during the study with a more significant exclusion of cases by the MDTM and also the lower number of obviated excisional surgical biopsies obtained compared to Giannotti et al. and Strachan et al. [5, 20]. Perretta et al. [18] show a 7.89% upgrade rate on a heterogeneous group of B3 lesions; B3 lesions in Panzironi et al. study did not upgrade to malignancy; however, on a limited number of lesions, all US-detected were subjected to US-guided biopsy [6]. Tennant et al. [17] reported an upgrade rate of 4.7%, including in the study only PSs without atypia and RS. Our study shows that the upgrade probability is significantly higher in ADH and LN lesions than in other histotypes, in line with what has already been published in the literature. A recent meta-analysis reports an overall upgrade rate of 29% for ADH lesions and an upgrade rate of 14%, including patients with apparent complete lesion removal after biopsy. The authors, therefore, recommend surgical excision for managing ADH diagnosed with percutaneous needle biopsy due to high upgrade rates [22]. The second consensus conference also recommends more frequent surveillance for LN lesions. However, treatment with VAE is always recommended over surgical excision since LN has to be considered as both a risk factor and a non-obligate precursor of invasive breast carcinoma and upgrade rates are highly variable (0–60%) in the literature [2, 23]. Type C density in our work is noted to be significantly more associated with upgrade risk than the other types of breast density categories. It may be due to the prevalence of type C density in our population and the qualitative assessment of breast density we performed that could be subject to interobserver variability. Using quantitative density measurement systems, perhaps expanding the population included, could confirm or not this preliminary result.

A review of the literature, though, indicates that the upgrade of B3 lesions is more frequent in calcification (compared to mass or architectural distortion) and in lesions with atypia (compared to those without atypia) [2, 5, 24–26]. This study shows no significant differences in the upgrade rate between the MG/DBT and US features. Instead, we found a significant difference for lesions with atypia compared to those without atypia, as in the work of Giannotti et al. [5]. The average size of the lesions treated with VAE in this work

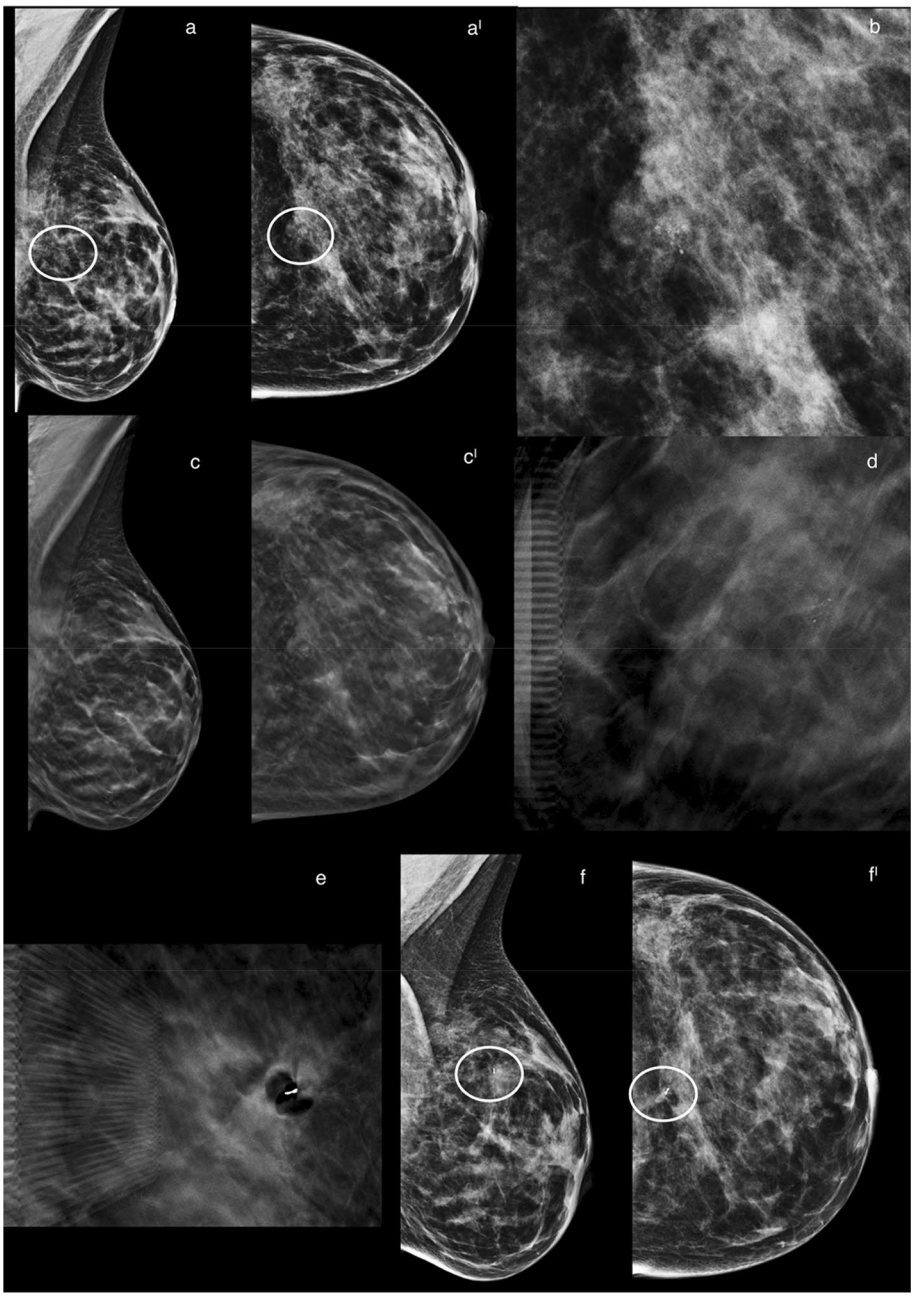

Fig. 2 **a**–**a**$^{\mathbf{I}}$ MG and **c**–**c**$^{\mathbf{I}}$ DBT showed a 6.0 mm cluster of pure microcalcifications in the upper central quadrant of the left breast (white circle); **b** magnification of the cluster; **d** first line DBT-guided VAB resulted FEA; **e** after the MDTM the lesion underwent VAE resulted FEA, a benign result; **f**–**f**$^{\mathbf{I}}$ 24 months MG follow up showed no new lesions or malignancy at the site of the VAE marked with clip (white circle)

was 6.6 mm, in line with international guidance. Several works have demonstrated that the probability of complete excision of a lesion increases if the dimensions are < 2 cm [6, 18, 27]. Lesions that had upgraded after VAE have a larger mean size (9.3 mm vs. 6.35 mm) than benign lesions, although this was not statistically significant (p: 0.0526). It is probably due to the low number of upgraded lesions we had. The probability of upgrading is significantly higher in lesions formerly subjected to CNB than in those initially subjected to VAB. It could be due to the calibre of the needle used for CNB (14-Gauge), which is much smaller than the one used for VAB (8 or 9-Gauge), involving a smaller amount of tissue removed and a greater probability of underestimation as already described in the literature [28–30]. The lesions subjected to initial CNB with ADH and LN outcome, before being subjected to VAE, could perform a VAB for better tissue characterization and management of patients to be directed to surgical excision in case of upgrade or to VAE in case of benign result.

The main advantages of VAE, over excisional surgical biopsy, are the decrease of invasiveness and stress combined with a satisfactory aesthetic result. As demonstrated in previous studies, it is also cost-effective (from 20 to 82% less than a surgical biopsy) [6, 31, 32]. VAE is a

safe procedure as it does not cause major but only mild complications in low percentages of cases, as found in our experience, with only 4/67 (6.0%) cases post-procedural hematomas, which resolved spontaneously during the follow-up. It is also in line with what has been published by Perretta et al. [18] where 17/266 (6.4%) patients reported hematoma at the biopsy site, not requiring aspiration, and 20/266 (7.5%) patients post-procedural pain.

The limitations of this study are related to the low number of patients and lesions included, but above all, the most critical limitation is related to the short follow-up period for most of the patients, which is still ongoing. Indeed, 24/62 (38.7%) patients currently have a 6-month follow-up, 23/62 (37.1%) patients 12 months and 15/62 (24.2%) patients 24 months. Nevertheless, it needs a more extended period to accurately evaluate the presence of new lesions or malignancies at the VAE site, given the low upgrade rate of B3 lesions. However, this was a preliminary study to evaluate the efficacy and safety of VAE in order to conduct a larger-scale study subsequently.

In this preliminary study, the VAE resulted as a safe and effective pathway for managing some selected B3 lesions, reducing the number of diagnostic surgical excisions, in line with the studies already published on the subject. Lesions initially subjected to CNB with ADH and LN outcome, before undergoing VAE, should perform a VAB for better tissue characterization and management. Studies on larger patient populations are recommended to confirm the scientific evidence.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GB, FP, FA. The first draft of the manuscript was written by GB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data and materials support our published claims and comply with field standards.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of AOU Careggi approved this study.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the images in Fig. 2.

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