



Positive predictive value for malignancy of uncertain malignant potential (B3) breast lesions diagnosed on vacuum-assisted biopsy (VAB): is surgical excision still recommended?

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Abstract

Purpose Breast lesions classified as of “uncertain malignant potential” represent a heterogeneous group of abnormalities with an increased risk of associated malignancy. Clinical management of B3 lesions diagnosed on vacuum-assisted breast biopsy (VABB) is still challenging: surgical excision is no longer the only available treatment and VABB may be sufficient for therapeutic excision. The aim of the present study is to evaluate the positive predictive value (PPV) for malignancy in B3 lesions that underwent surgical excision, identifying possible upgrading predictive factors and characterizing the malignant lesions eventually diagnosed. These results are compared with a subset of patients with B3 lesions who underwent follow-up.

Methods A total of 1250 VABBs were performed between January 2006 and December 2017 at our center. In total, 150 B3 cases were diagnosed and 68 of them underwent surgical excision. VABB findings were correlated with excision histology. A PPV for malignancy for each B3 subtype was derived.

Results The overall PPV rate was 28%, with the highest upgrade rate for atypical ductal hyperplasia (41%), followed by classical lobular neoplasia (29%) and flat epithelial atypia (11%). Only two cases of carcinoma were detected in the follow-up cohort, both associated with atypical ductal hyperplasia at VABB.

Conclusion Open surgery is recommended in case of atypical ductal hyperplasia while, for other B3 lesions, excision with VABB only may be an acceptable alternative if radio-pathological correlation is assessed, if all microcalcifications have been removed by VABB, and if the lesion lacks high-risk cytological features.

Key Points

- *Surgical treatment is strongly recommended in case of ADH, while the upgrade rate in case of pure FEA, especially following complete microcalcification removal by VABB, may be sufficiently low to advice surveillance as a management strategy.*
- *The use of 11-G- or 8-G-needle VABB, resulting in possible complete diagnostic excision of the lesion, can be an acceptable alternative in case of RS, considering open surgery only for selected high-risk patients.*
- *LN management is more controversial: surgical excision may be recommended following classical LN diagnosis on breast biopsy if an additional B3 lesion is concurrently detected while in the presence of isolated LN with adequate radiological-pathological correlation follow-up alone could be an acceptable option.*

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Keywords Image-guided biopsy · Carcinoma lobular · Breast cancer · Atypical ductal hyperplasia (ADH) · Malignant epithelial neoplasms

Abbreviations

ADH	Atypical ductal hyperplasia
CNB	Core needle biopsy
FEA	Flat epithelial atypia
LN	Classical lobular neoplasia
PL	Papillary lesions
PPV	Positive predictive value
PT	Benign phyllodes tumors
RS	Radial scars
VABB	Vacuum-assisted breast biopsy

Introduction

According to recommendations of the National Coordinating Group for Breast Screening Pathology and the European Communities Working Group on breast screening pathology, all breast biopsies should be classified into five categories: B1, normal; B2, benign; B3, lesion of uncertain malignant potential; B4, suspicious for malignancy; and B5, malignant [1]. Histological diagnosis of a B3 lesion may be obtained by either core needle biopsy (CNB) using a 14-G needle or stereotactic vacuum-assisted breast biopsy (VABB) performed with an 8-G or 11-G needle.

The B3 subgroup consists of lesions that are known to either show biological and pathological heterogeneity or have an increased risk of associated malignancy. This category includes atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), classical lobular neoplasia (LN), papillary lesions (PLs), radial scars (RS), and benign phyllodes tumors (PT) [2].

Although they account for only 5 to 10% of all breast biopsies [3, 4], B3 lesions are often a source of anxiety for the patient due to the lack of a homogeneous approach to the treatment of these lesions. Clinical management of B3 lesions is still challenging even in the breast center multidisciplinary team. Clinical and pathological series dealing with B3 lesions report variable rates of associated malignancy detected in subsequent surgical excision. Moreover, malignancy rates vary according to different histologic subtypes: while ADH and PT are associated with an increased risk for malignancy, other B3 subtypes only seem to carry a sampling risk [5].

Surgical excision may no longer be the only available treatment: VABB allows for removal of larger volumes of tissue than a CNB and may be sufficient for therapeutic excision, which would benefit patients and save on healthcare costs by obviating the need for surgery [6].

The present study aims to evaluate lesions prompting a B3 designation on VABB over a 12-year period in our institution

and to assess the correlation between different morphostructural abnormalities detected in VABB specimens and the positive predictive value (PPV) for malignancy in subsequent surgical excision. Moreover, we aim to identify possible upgrading predictive factors and to compare these results with a control group that underwent follow-up instead of surgical excision.

Materials and methods

Study population

From January 2006 to December 2017, 1250 VABBs were performed at Fondazione IRCSS, Policlinico San Matteo, University of Pavia, using an 11-G and (in the last 5 years, if technically possible) 8-G stereotactic vacuum-assisted instrument (Mammotome™); all patients undergoing CNB were excluded from the first selection and are not included in this study.

Clinical and diagnostic data were collected from patient records, including patient status at presentation (asymptomatic/symptomatic), clinical findings (palpable nodule/nipple discharge), and mammographic findings (BIRADS assessment category).

Clinical, radiological, and surgical data were discussed at a multidisciplinary meeting with breast radiologists, pathologists, and surgeons within the “Breast Centre,” Fondazione IRCSS, Policlinico San Matteo, and further treatment options were discussed.

Sixty-eight (45%) patients out of 150 who were diagnosed with B3 underwent surgery. The choice between surgical excision and follow-up was based on criteria shared by breast radiologists, pathologists, and surgeons. Operative management indications were:

- High-risk radiological features (microcalcifications with suspicious morphology: amorphous, coarse heterogeneous, fine pleomorphic and fine-linear branching)
- High-risk histologic features (e.g., cellular atypia, necrosis, solid architecture, concurrent presence of more than one B3 lesion in the same biopsy)
- Extensive area of microcalcifications
- Residual microcalcifications after VABB
- Discordance between radiological and pathological reports

Patients who underwent surgery were discussed again at the postoperative multidisciplinary meeting.

In presence of small lesions for which complete excision by biopsy alone was likely, and in low-risk cases with clinical, radiological, and pathological concordance, in the absence of residual microcalcifications, close mammographic follow-up was proposed. Sixty-four (43%) patients with B3 lesions were followed up for an average of 4 years (range 1–10 years), while 18 patients were lost at follow-up and were not included in further analysis.

Pathologic assessment

Bioptic samples and sections obtained from surgical specimens were fixed in 10% buffered formalin, embedded in paraffin, and processed according to standard protocol. Multiple slides (3–5 μm) were cut from blocks and stained with hematoxylin and eosin; some unstained slides were saved for potential immunohistochemistry.

Automated formalin-fixed, paraffin-embedded (FFPE) sections immunostainings (Dako Omnis) were performed, employing the streptavidin-biotin peroxidase revelation system (EnVision FLEX). Antibodies against estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), Mib1/Ki67, myoepithelial markers (p63, calponin), E-cadherin, and β -catenin were used. Immunostaining for cytokeratin 5/6 was used in the most complex cases to help in the differential diagnosis between usual and atypical ductal hyperplasia.

All the cases were reviewed by three breast pathologists (M.L., E.B., C.R.), and histopathologic diagnoses were reported according to the criteria of the World Health Organization 2019 [7] and European guidelines for quality assurance in breast cancer screening and diagnosis 2006 [1]. VABB results were categorized according to the B classification.

Since different B3 subtypes may occur simultaneously in one VABB, we have categorized lesions according to the most severe histologic feature. So, a VABB with concomitant ADH and FEA was grouped under ADH.

VABB findings were correlated with subsequent excision histology.

In case of in situ or infiltrating carcinoma on surgical specimens, receptor status, nuclear proliferation index, and expression of HER2 were assessed.

A positive predictive value (PPV) for malignancy was derived for each B3 subtype.

Results

During the study period, 1250 women underwent VABB at our hospital, of whom 150 had a B3 diagnosis (12%). The most frequent lesions on VABB were ADH ($n = 54$, 36%) and FEA ($n = 49$, 33%), followed by LN ($n = 29$, 19%), PL ($n = 13$, 8%), RS ($n = 4$, 3%), and PT ($n = 1$, 1%) (Table 1).

Sixty-eight (45%) patients of 150 who were diagnosed with B3 underwent surgery, with an excision rate of 59% for ADH (32/54), 37% for FEA (18/49), 48% for LN (14/29), 15% for PL (2/13), 25% for RS (1/4), and 100% for PT (1/1) (Table 1).

Final excision histology was benign in 49 (72%) and malignant in 19 (28%) cases. Malignant lesions were detected after VABB diagnosis of FEA in 2 cases only (2/18, 11%), while the PPV for malignancy was higher for ADH (13/32, 41%) and LN (4/14, 29%); PL, PT, and RS were not associated with malignancy in surgical specimens (Table 2).

Invasive breast cancer was observed in 10 cases: following ADH diagnosis in 8 patients, following FEA diagnosis in one patient, and following LN diagnosis in one patient. Nine were invasive carcinoma of no special type (NST), well differentiated (G1) in 6 cases and moderately differentiated (G2) in 3 cases. A single case of well-differentiated (G1) tubulo-lobular carcinoma was found after LN at VABB. The maximum radial extension of the invasive component was 12 mm. In all invasive breast cancers observed, cancer cells were strongly estrogen and progesterone receptors positive, did not express HER2, and had a low proliferation index (range 3–15%). An associated component of in situ carcinoma was found in all invasive cases: ductal carcinoma in situ (DCIS) G1 in 5 cases, DCIS G2 in 4 cases, lobular carcinoma in situ (LCIS) in the case of tubulo-lobular carcinoma (Table 3).

In situ breast cancer was observed in 9 cases: following FEA diagnosis in one patient, following ADH diagnosis in 5 cases, and following LN diagnosis in 3 patients. Low-grade (G1) DCIS was found in 4 cases, intermediate-grade (G2) DCIS was found in 4 cases, and pleomorphic LCIS associated with high-grade (G3) DCIS was found in a single case with a preoperative diagnosis of LIN and FEA. The maximum radial extension of the in situ carcinoma was between 3 and 12 mm. Cancer cells were estrogen and progesterone receptor positive in all cases; nuclear proliferation index was between 3 and 30%. HER2 was negative in 8 cases (8/9, 89%), whereas the remaining case had a 2+ score according to ASCO/CAP guidelines 2013 [8] but FISH showed no amplification of *HER2* (Table 4).

Sixty-four patients of 150 who were diagnosed with B3 (43%) underwent follow-up only, with 31% of patients diagnosed with ADH undergoing follow-up (17/54), 51% for FEA (25/49), 41% for LN (12/29), 54% for PL (7/13), and 75% for RS (3/4) (Table 1). During follow-up, changes in mammographic findings leading to surgical excision were found in only two patients with VABB diagnosis of ADH. Pathological analysis of surgical specimens revealed a malignant lesion in both cases. Intermediate-grade (G2) DCIS was found in one case after 4 years of follow-up and intermediate-grade (G2) invasive carcinoma of no special type was found in the other case after 3 years of follow-up (maximum radial extension of the invasive component: 11 mm). In both cases, cancer cells were strongly estrogen and progesterone receptors

Table 1 VABB database records indicating number of different B3 lesions that underwent surgical excision and those that underwent follow-up only

	Subtypes of B3 lesion on VABB	Cases with surgical excision	Cases with follow-up only
Atypical ductal hyperplasia	54 (36%)	32 (59%)	17 (31%)
Flat epithelial atypia	49 (33%)	18 (37%)	25 (51%)
Classical lobular neoplasia	29 (19%)	14 (48%)	12 (41%)
Papillary lesion	13 (8%)	2 (15%)	7 (54%)
Radial scar	4 (3%)	1 (25%)	3 (75%)
Benign phyllodes tumor	1 (1%)	1 (100%)	0
Total	150	68 (45%)	64 (43%)

positive and did not express HER2 and their nuclear proliferation index was low (10%). Follow-up upgrade rate for ADH was 12% (2/17) (Table 5).

Discussion

Clinical management (surgical excision vs follow-up) of B3 lesions found on breast biopsy is still a matter of debate due to their low but significant risk of associated malignancy not diagnosed with biopsy alone. In our study, the exclusive use of an 11-G and (in the last 5 years, if technically possible) 8-G needle with vacuum-assisted procedure instead of a 14-G needle, providing larger tissue specimens, allowed a more accurate selection and diagnosis of B3 cases, minimizing the risk of undetected DCIS, as showed in literature [8–10].

The choice between surgical excision and follow-up was based on criteria (BIRADS IV, high-risk histologic features such as necrosis and cellular atypia, extensive area of microcalcifications, residual microcalcifications after VABB) shared by breast radiologists, pathologists, and surgeons after careful multidisciplinary evaluation. These criteria, based on clinical practice, were also reported in similar studies: Piubello et al [11] recommend excision in case of ADH; Rakha et al [12] advice surgical excision in case of cellular atypia. The same criteria are reported by Rageth et al in the First and Second International Consensus Conferences

on lesions of uncertain malignant potential in the breast [12–14], both strongly advocating for the surgical excision of ADH when diagnosed on biopsy; for other lesions (FEA, LN, papillary lesions, RS), active surveillance can be recommended in case of complete excision and radiological-pathological concordance. Similarly, Calhoun et al [15] point out that follow-up can be a valid option in case of complete calcification removal with VABB and recommend surgical excision in case of radiological-pathological discordance. Due to the application of these shared criteria, our overall excision rate (45%) was lower compared with that of other studies (Hayes et al 100% [16], Noske et al 66% [17], Rakha et al 100% [12], Mayer et al 100% [18]). Additionally, most of the referenced series only included CNB as the biopsy method of choice, or made no distinction between CNB and VABB in the inclusion criteria; this is likely to result in a higher rate of upgrade in the surgical excision, as CNB is widely accepted to carry a higher risk of underestimation of the lesion grade on the final report, due to a likely undersampling of the lesion.

Still, it is important to point out some limitations of our study, such as the relatively small number of cases (as in most published series of VABB-only retrospectives) and the not-negligible number of patients lost at follow-up ($n = 18$), representing 12% of our entire B3 cohort.

Recently breast MRI has been suggested as a possible imaging modality to distinguish high-risk lesions which require surgery, from those that can be managed with follow-up. In

Table 2 Positive predictive value (PPV) for malignancy for B3 lesions that underwent surgical excision after VABB

	Cases with surgical excision	Upgraded cases and PPV for malignancy (%)
Atypical ductal hyperplasia	32 (47%)	13 (41%)
Flat epithelial atypia	18 (26%)	2 (11%)
Classical lobular neoplasia	14 (21%)	4 (29%)
+ Flat epithelial atypia	3	2 (66%)
Papillary lesion	2 (3%)	0
Radial scar	1 (1.5%)	0
Benign phyllodes tumor	1 (1.5%)	0
Total	68	19 (28%)

Table 3 Invasive cancers observed in patients who underwent surgical excision: morphological characteristics and immunophenotypic profile

VABB diagnosis	Carcinoma type, grade	Size (mm)	In situ associated	Calcifications	ER (%)	PgR (%)	Ki-67 (%)	HER2
ADH	NST, G1	3	DCIS G1	+	90	90	3	0
ADH	NST, G1	4	DCIS G1	+	90	90	5	0
ADH	NST, G1	5	DCIS G1	+	95	60	5	0
ADH	NST, G2	9	DCIS G2	+	95	80	10	0
FEA	NST, G1	8	DCIS G1	+	90	90	<5	0
ADH	NST, G2	7	DCIS G2	+	95	60	15	0
ADH	NST, G1	6	DCIS G2	+	90	90	5	0
ADH	NST, G2	10	DCIS G2	+	85	60	13	0
LN	TLC, G1	12	LCIS	–	85	85	5	0
ADH	NST, G1	3	DCIS G1	+	80	50	3	0

NST, invasive carcinoma of no special type; TLC, tubulo-lobular carcinoma; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2

the absence of suspicious enhancement, the risk of upgrade is low and surgical excision could be avoided; further studies are necessary to confirm this observation [18–21].

In our study, the PPV for malignancy was 28%; this is higher than rates from other series (Hayes et al 16% [16], Noske et al 10% [17], Mayer et al 10% [18]) that include, however, either CNB only or a mixed selection of CNB and VABB. This may reflect the different prevalence of B3 subtypes that underwent surgical excision in our cohort: only 4 patients with PL or RS or PT at preoperative diagnosis (4/68, 6%), 18 patients with FEA (18/68, 26%), 32 patients with ADH (32/68, 47%), and 14 patients with LN (14/68, 21%).

Atypical ductal hyperplasia

ADH was the most represented category and the overall PPV for malignancy in case of ADH in our series was 41%. Published underestimation rates for stereotactic VABB range

from 13 to 33%, while higher values are reported in CNB-only series [17, 18, 22–31]. In our cohort, carcinomas associated with ADH were of low and intermediate histological grade (5 invasive carcinomas of no special type G1, 3 invasive carcinomas of no special type G2, 2 DCIS G1, 3 DCIS G2), with a median maximum radial extension of 6 mm (range 3–12 mm), all strongly estrogen and progesterone receptor positive. Since ADH is cytologically indistinguishable from low-grade DCIS, it is not surprising that this lesion is highly associated with non-invasive and invasive cancer and thus surgical treatment is strongly recommended [14].

Seventeen patients out of 54 (31%) with ADH diagnosis on VABB underwent follow-up only. This percentage seems to be quite high, but each case was discussed during the multidisciplinary meetings and the patients' preferences were taken into account as well, providing that no residual microcalcifications were found after VABB procedure and no other risk factor was highlighted in the pathology report.

Table 4 In situ carcinomas observed in patients who underwent surgical excision: morphological characteristics and immunophenotypic profile

VABB diagnosis	Carcinoma type, grade	Size (mm)	Necrosis	Calcifications	ER (%)	PgR (%)	Ki67 (%)	HER2
ADH	DCIS, G2	12	+	+	90	90	5	1+
LN	DCIS, G1	na	–	–	99	95	5	0
ADH	DCIS, G2	6	+	+	95	95	3	0
LN + FEA	DCIS, G1	2	–	+	95	95	5	0
ADH	DCIS, G1	6	+	+	95	95	5	0
ADH	DCIS, G1	3	–	+	99	99	3	0
ADH	DCIS, G2	4	+	+	95	10	30	2+
LN + FEA	DCIS + PLCIS, G3	na	–	–	95	95	10	1+
FEA	DCIS, G2	12	+	+	90	90	8	0

DCIS, ductal carcinoma in situ; PLCIS, pleomorphic lobular carcinoma in situ; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; na, not available

Table 5 Follow-up-only cohort: average follow-up and upgraded cases

	Cases with follow-up only	Average follow-up (years)	Upgraded cases (%)
Atypical ductal hyperplasia	17 (26%)	5.1	2 (12%)
Flat epithelial atypia	25 (39%)	4.3	0
Classical lobular neoplasia	12 (19%)	2.8	0
Papillary lesion	7 (11%)	2.3	0
Radial scar	3 (5%)	2.7	0
Total	64	4.0	2 (3%)

Only 2/17 (12%) patients from the ADH follow-up group had a long-term upgrade (1 DCIS and 1 invasive breast cancer). Similar rates of long-term upgrade to invasive breast cancer, ranging between 3 and 8% in case of patients on follow-up without surgical treatment after a VABB diagnosis of ADH, were reported by other studies [32, 33].

Besides, the finding that ADH-associated carcinomas are only of low and intermediate histological grade confirms the hypothesis that low-grade and high-grade DCIS represent genetically distinct disorders and that ADH shares many similarities with low-grade DCIS [2].

Flat epithelial atypia

Pure FEA was associated with one case of low-grade invasive carcinoma and one case of DCIS in our study (11% upgrade rate, in line with the reported values in other VABB-only series) [11, 15, 34–42]. Controversy exists in the management of VABB-diagnosed FEA. In a meta-analysis by Verschuur-Maes et al, carcinoma was present in the excisional biopsies of 13–67% of cases of FEA diagnosed on breast biopsy [43]. However, in several of the more recent studies, upgrade rates were lower, ranging from 0 to 21%, particularly when all microcalcifications were removed. According to the WHO Working Group, observation may be an acceptable management strategy in case of pure FEA if radiological-pathological correlation is assessed [2, 43].

Classical lobular neoplasia

Classical LN is usually an incidental finding on breast biopsy because it does not usually form any palpable mass and less than half of classical LN are associated with microcalcifications detected by mammography. The upgrade rate after LN diagnosis on breast biopsy is variable in the literature, ranging from 0 to 50% [2, 44–46]. In our series, the PPV for malignancy after LN was 29%, with one patient having tubulo-lobular carcinoma, 2 having intermediate-grade DCIS, and one having high-grade DCIS combined with pleomorphic LCIS. Interestingly, the upgrade rate increased when LN was associated with

FEA (2/3, 66%), providing evidence of the need for surgical excision after classical LN diagnosis on breast biopsy if an additional B3 lesion is concurrently detected [47].

Papillary lesions

No papillary lesion identified on VABB in this study proved to be malignant on excision. Upgrade rates after surgical excision of benign papilloma diagnosed following breast biopsy vary from 0 to 28% [13]. A recent meta-analysis showed a declining trend in the underestimation rate for benign papillomas on biopsy after 2005, possibly because of better sampling of targeted lesions with the use of larger-gauge needles [48]. Most studies based on the follow-up of VABB-excised PLs without atypia did not report any upgrade to malignancy within at least 2 years of surveillance [49–51]. The exclusive use of VABB in our study can explain the lack of upgrade for PL: in our series, PL excision was reserved only to large, radiologically suspicious lesions. In the absence of other indications for excision, data are becoming increasingly available that support surveillance of radiologically concordant benign papillomas and incidental papillomas of < 2 mm as a safe alternative to surgery [52].

Complex sclerosing lesions/radial scar

Upgrade rate for RS was 0% in our cohort. Studies correlating breast biopsy diagnoses of RS with final pathology after surgery have shown variable results, with upgrade rates ranging from 0 to 40% [51]. Based on correlation between imaging and pathology, RS without atypia following VABB are unlikely to reveal malignancy in the surgical excision specimen if the lesion is less than 6 mm on imaging and the patient is younger than 40 years or older than 60 years [13]. In case of RS, the AGO 2019 [53] guidelines recommend surveillance if the imaging findings have been completely excised at VABB and no atypia was found in the histological examination, while RS with atypia on histology following CNB/VABB should undergo therapeutic open surgical excision [2, 5].

Conclusion

The difficulty in establishing standard criteria for appropriate patient management is a consequence of the incomplete understanding of the biologic and histologic background of B3 lesions. Hence, multidisciplinary discussion is crucial for appropriate management of these patients.

Despite some limitations due to its retrospective design, our study shows that a selected group of patients with B3 lesions could benefit from a more conservative approach. Surgical treatment is strongly recommended in case of ADH, while the upgrade rate in case of pure FEA, especially following complete microcalcification removal by VABB, may be sufficiently low to advise surveillance as a management strategy. The use of 11-G- or 8-G-needle VABB, resulting in possible complete diagnostic excision of the lesion, can be an acceptable alternative in case of RS, considering open surgery only for selected high-risk patients. LN management is more controversial: in our series, the upgrade rate increased when LN was associated with FEA. As a consequence, surgical excision may be recommended following classical LN diagnosis on breast biopsy if an additional B3 lesion is concurrently detected while in the presence of isolated LN with adequate radiological-pathological correlation follow-up alone could be an acceptable option.

Furthermore, non-operative management of B3 lesions may save on healthcare costs. This is not a negligible aspect, as breast cancer is the most common cancer in women, its incidence is rising as life expectancy increases, and B3 category is often the result of evaluation of screen-detected lesions.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was not required because it is a retrospective study.

Methodology
• retrospective

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