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Excision modalities and malignancy risk in different lesions of uncertain malignant potential in the breast (B3)

João Diogo Silva Martins

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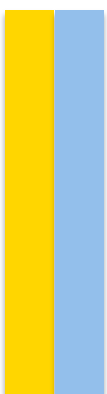

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Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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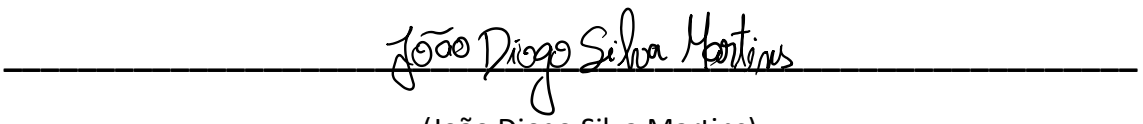

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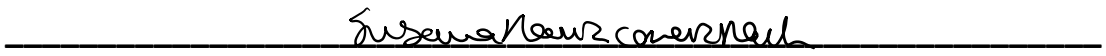

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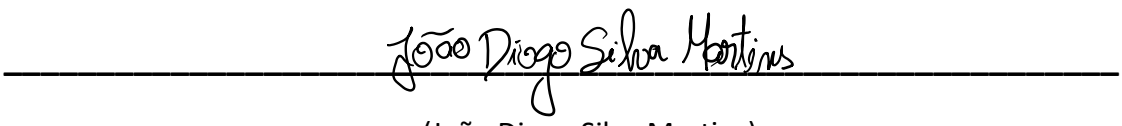
Junho de 2024

Declaration of Scientific Integrity

I, João Diogo Silva Martins, enrolled in the Integrated Master's Program in Medicine at the School of Medicine and Biomedical Sciences of the University of Porto, hereby declare, following the provisions of paragraph a) of article 14 of the Code of Ethical Conduct of the University of Porto, that the content of this dissertation reflects perspectives, research work, and my interpretations at the time of its submission. By submitting this dissertation, I also declare that it contains the results of my research work and contributions that have not been previously submitted to this or any other institution. I further declare that all references to other authors fully comply with the rules of attribution and are referenced in the text by citation and identified in the bibliographic references section. This dissertation does not include any content whose reproduction is protected by copyright laws. I am aware that the practice of plagiarism and self-plagiarism constitutes a form of academic offense.



(João Diogo Silva Martins)

Dedicatória

Dedico este trabalho a todas as mulheres que fizeram de mim o homem que hoje sou.

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À Adriana, à Kika e à Daniela por terem escolhido crescer do meu lado e nunca terem abandonado o barco. À Carolina e à Sofia, pela ajuda, paciência e companheirismo. À Luana e à Mercedes pelas gargalhadas e por até me tolerarem.

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Resumo

Introdução: As lesões mamárias de potencial maligno incerto (B3) fazem parte de um grupo heterogéneo com risco variável de malignidade. Tradicionalmente, têm sido tratadas por excisão cirúrgica, o que pode ser uma estratégia demasiado agressiva uma vez que a maioria recebe um diagnóstico final benigno. Apesar disso, as taxas de subestimação de malignidade no momento do diagnóstico não são negligenciáveis, pelo que é importante encontrar características clínicas, imagiológicas e histológicas que nos ajudem a adotar estratégias de gestão adequadas para cada lesão. O nosso estudo teve como objetivo avaliar o valor preditivo positivo para malignidade em lesões B3 que foram submetidas a excisão, identificando possíveis fatores de risco para malignização e caracterizando as lesões malignas eventualmente diagnosticadas, comparando-as com um subconjunto de doentes que apenas foram submetidos a seguimento clínico e imagiológico.

Métodos: Este estudo retrospetivo analisou uma série de doentes seguidas na Unidade de Mama da Unidade Local de Saúde de Santo António (ULSSA) no contexto de um diagnóstico histológico de lesão B3, entre novembro de 2018 e novembro de 2023. Foram incluídas apenas as doentes sem diagnóstico síncrono de lesão de maior grau histológico.

Resultados: Foram incluídas 51 doentes (idade mediana, 51 anos [IQR=12,0]), 54,9% das quais apresentavam sintomas mamários e 35,6% tinham algum tipo de história familiar de cancro da mama. O diagnóstico mais prevalente no nosso estudo foi o de lesões papilares (PL), em 66,7% dos casos. O tratamento escolhido incluiu uma estratégia de apenas seguimento em 31,4%, excisão cirúrgica em 43,1% e EAV em 23,5%. Das doentes que foram submetidas a excisão da lesão, a taxa de malignidade foi de 8,6% após a excisão, para além de um risco global de 5,4% de transformação maligna durante um período de seguimento de 2 anos. As taxas de malignidade específicas foram de 50,0% para a neoplasia lobular (LN) e 3,8% para as PL. Encontrámos uma correlação estatisticamente significativa entre a modalidade de tratamento escolhida e o risco familiar da doente (p=0,033), a ferramenta de diagnóstico utilizada (p<0,001) e o diagnóstico histológico (p=0,029). Quanto à malignização total, encontrámos como fatores de risco um diagnóstico de LN (p=0,017), a multifocalidade da lesão (p=0,023) e uma categoria BIRADS ≥ 4b aquando do diagnóstico (p=0,019).

Conclusão: A EAV constitui um tratamento seguro e eficaz para lesões B3, capaz de reduzir o número de intervenções cirúrgicas, como confirmado pela baixa taxa de transformação para malignidade após uma EAV neste estudo. Os nossos resultados são consistentes com a literatura atual, confirmando a existência de diferenças no risco de malignidade para os diferentes subtipos de

lesões B3 e ajudando a identificar outros fatores de risco que promovem uma abordagem personalizada na sua gestão. Propomos uma abordagem mais conservadora para o tratamento das PL, enquanto a excisão mais radical parece justificar-se para as LN.

Palavras-chave: Lesão B3; Biópsia assistida por vácuo; Excisão assistida por vácuo; Biópsia com agulha grossa; Risco de malignidade.

Abstract

Introduction: Breast lesions of uncertain malignant potential (B3) are part of a heterogeneous group with variable malignancy risk. Traditionally, they have been managed by surgical excision, but overtreatment is a concern, as the majority have a final benign diagnosis. Despite this, underestimation rates for malignancy at diagnosis are not neglectable, so it is important to find clinical, imaging, and histological features that help us tailor proper management strategies for individual lesions. Our study aimed to evaluate the positive predictive value (PPV) for malignancy in B3 lesions that underwent excision, identifying possible upgrading risk factors and characterizing the malignant lesions eventually diagnosed while comparing them with a subset of patients who only underwent follow-up.

Methods: This retrospective study reviewed a series of patients being followed in the Breast Unit of the Santo António University Hospital (ULSSA) in the context of a histological diagnosis of a B3 lesion, between November 2018 and November 2023. Only patients without a synchronous diagnosis of a higher-grade lesion were included.

Results: This study included 51 patients (median age, 51 [IQR=12.0] years), 54.9% of whom presented with breast symptoms and 35.6% had some type of family history of breast cancer. The most prevalent diagnosis in our study was papillary lesions (PL) at 66.7%. Chosen management included a follow-up-only strategy in 31.4%, an OE in 43.1%, and VAE in 23.5%. Of the patients who underwent lesion excision, the upstage rate for malignancy was 8.6% after excision, in addition to an overall 5.4% risk of upgrade over a 2-year follow-up period. Lesion-specific upgrade rates included 50.0% for lobular neoplasia (LN) and 3.8% for PL. We found statistical significance between the chosen management modality and the patient's family risk for breast cancer ($p=0.033$), used diagnostic tool ($p<0.001$), and histological diagnosis ($p=0.029$). As for total malignancy, we found LN ($p=0.017$), multifocality ($p=0.023$), and BIRADS ≥ 4b at diagnosis ($p=0.019$) as associated risk factors.

Conclusion: VAE offers a safe and effective treatment for B3 lesions, reducing the number of open surgical procedures, as confirmed by the low upgrade to malignancy after a VAE in this study. Our findings are consistent with the current literature by confirming differences in malignancy risk for different B3 subtypes and helping identify other risk factors that promote a case-by-case approach to their management. We propose a more conservative approach to treating PL, whereas more radical excision seems justified for LN.

Keywords: B3 lesion; Vacuum-assisted biopsy; Vacuum-assisted excision; Core needle biopsy; Malignancy risk.

Abbreviations

ADH – Atypical ductal hyperplasia

ALH – Atypical lobular hyperplasia

BMI – Body mass index

BSSM – Bilateral skin-sparing mastectomy

CNB – Core needle biopsy

CSL – Complex sclerosing lesions

DCIS – Ductal carcinoma in situ

FEA – Flat epithelial atypia

G – Gauge

IBC-NST – Invasive breast carcinoma of no special type

LCIS – Lobular carcinoma in situ

LN – Classical lobular neoplasia

MILC – Microinvasive lobular carcinoma

PL – Papillary lesions

PPV – Positive predictive value

PT – Phyllodes tumors

RS – Radial scars

OE – Open excision

VAB – Vacuum-assisted biopsy

VAE – Vacuum-assisted excision

WHO – World Health Organization

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Introduction

Breast cancer is the most frequent cancer among women with an increasing trend of incidence. Mortality rates are however slightly decreasing, even though at an increasingly slower pace, making it the second leading cause of death among women due to oncologic disease at the current moment, having been surpassed by lung cancers.[1] The goal of early breast tumor diagnosis has frequently been accomplished in recent years due to advancements in screening programs and diagnostic techniques. This, along with innovative surgical techniques and targeted biological treatments, has led to an increase in disease-free and overall survival.[2] Much evidence has shown the critical impact that lifestyle and environment, including physical activity, cigarette smoking, obstetric history, and hormone use play in the primary prevention of breast cancer. However, primary prevention measures cannot change every factor linked to the development of this disease. Non-modifiable risk factors include sex, age, genetic mutations, the density of breast tissue, a previous history of breast cancer, and non-cancerous breast diseases such as breast lesions of uncertain malignant potential (B3).[3]

According to the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis, core needle biopsy (CNB) of the breast can be classified into 5 categories or diagnostic groups according to lesion type and risk of malignancy.[4] According to this classification system, most CNB lesions are classified as normal (B1), benign (B2), or malignant (B5), accounting for approximately 85% to 90% of CNB diagnoses[5,6], with the remaining distributed between two borderline categories, that support the accuracy of benign and malignant diagnoses. While a B4 diagnosis means suspicious for malignancy, with studies reporting a positive predictive value (PPV) of core biopsy for carcinoma in these lesions as high as 88%[7], the B3 category, which comprises only a small proportion of the total diagnosis, around 5% to 10% in most series[5–8], has a lower reported PPV for malignancy depending on lesion type, but overall ranging from 10% to 35%[7–18], which highlights its uncertain potential and complex management.

These lesions are part of a heterogeneous group that may yield only benign histology on initial CNB sampling but may also harbor or be adjacent to malignancy. Traditionally, they have been managed by diagnostic surgical excision because of this association and because they can act as a risk factor or precursor of malignancy. However, the majority of B3 lesions show a final benign diagnosis and even when malignancy does develop at these sites, it usually occurs over an extended period with tumors frequently in a good prognostic group with low histological grade and hormone receptor positivity.[19] Despite this, underestimation rates for CNB are not neglectable, so it is important to

find clinical, imaging, and histological features that help us rule out malignancy and tailor proper treatment strategies.

B3 breast lesions are usually identified on imaging as areas of calcification or small masses. They are mostly asymptomatic, though they may also be found in symptomatic women presenting to breast units. There was minimal evidence that B3 lesions found through breast screening have a different upgrade rate than those observed symptomatically, or that the range of lesions is different, despite the lack of data on the presenting routes of B3 lesions and their outcomes.[20] Nevertheless, the widespread implementation of breast cancer screening programs has played a crucial role in the increased detection rate of B3 lesions, leading to breast surgery for a final histopathological diagnosis that is ultimately benign. This represents one of the negative aspects of the mammographic screening system.[16]

Pathologists classify B3 lesions into several subcategories, six of which can be noted as the most relevant.[21] These include: atypical ductal hyperplasia (ADH), characterized by small and low grade intraductal clonal proliferation of epithelial cells; flat epithelial atypia (FEA), identified by an atypical epithelial proliferation of cells without architectural atypia; lobular neoplasia (LN), which includes a wide variety of atypical epithelial proliferation originating from the acinar structures of the breast and can be divided into atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) based on the extent within the terminal ducto-lobular unit (<50% and ≥ 50%, respectively); papillary lesions (PL), characterized as proliferative fibrovascular tissue branches with an overlying layer of epithelial and myoepithelial cells; radial scars (RS) (≤ 1.0 cm) / complex sclerosing lesions (CSL) (> 1.0 cm), which are in fact a continuous of the same histological entity and are indicated by entrapped ducts neighboured by radiating ducts and lobules; and phyllodes tumors (PT) of benign and borderline categories, that can be described as biphasic tumors with a leaf-like architecture, hypercellular stroma, and clef-like epithelial covered spaces.[15] This terminology is based on the World Health Organization (WHO) classification of breast tumors (fifth edition, 2019). Pleomorphic LCIS and florid LCIS are regarded as comparable to DCIS and thus receive a B5 label.

Vacuum-assisted biopsy (VAB) of breast lesions plays an important diagnostic and/or therapeutic role, particularly in benign lesions and B3 lesions, with indications continually expanding. In recent years, advances in knowledge and technology have allowed this procedure to be optimized. The VAB device essentially consists of a needle of a larger caliber than that used in a core biopsy, usually between 7 and 11G instead of 14G, with a suction chamber and rotating cutting blade. The latest VAB devices allow multiple samples to be obtained through one access without reinserting the needle.[22]

The main advantage of VAB devices is the ability to obtain large tissue samples (approximately four grams), comparable to a diagnostic surgical biopsy and in some cases with complete excision of the lesion, thereby optimizing the representativeness of the sample. It can be used for re-evaluation in the event of a core biopsy that is not representative of the lesion on imaging, or to assess possible upgrading in B3 lesions, and carries a lower risk of discordance with the anatomopathological diagnosis in the surgical specimen. The trend to make the treatment for B3 lesions minimally invasive began by using these devices to undertake a vacuum-assisted excision (VAE), of lesions with no atypia, such as radial scars and papillomas.[22] This approach seemed highly appealing, as it would benefit patients and save on healthcare costs by obviating the need for surgery.

The recent "Third International Consensus Conference on lesions of uncertain malignant potential in the breast" reviewed current literature to develop recommendations for surgery or clinical and radiological follow-up. It was recommended that management after a B3 lesion diagnosis should be individually discussed in a multidisciplinary meeting, taking into account the imaging findings pre and post-biopsy of a lesion, the histopathological features at CNB or VAB, the patient's risk factors for an upgrade of the B3 lesion after further diagnosis and life expectancy.[21]

Current recommendations advocate VAE as the preferred assessment method (rather than the option of surgical excision) for certain B3 lesions diagnosed at core biopsy, such as FEA, PL without atypia, RS/CSL, and LN, while due to a higher risk of upgrade into malignancy, OE remains the preferred approach after the diagnosis of ADH. This is also the case for PT because even if the upgrade to malignancy is uncommon after CNB or VAB, the definitive histological diagnosis can best be rendered on OE specimens where completeness of the excision may be assessed.[21]

If a B3 lesion is upgraded to malignancy after a VAE procedure, then therapeutic surgery is required. In contrast, when VAE yields a benign diagnosis, 5 years of annual mammographic surveillance is recommended for lesions associated with epithelial atypia, while lesions without atypia can dismiss any additional surveillance other than routine mammographic screening. This, however, is not a consensual claim, as there remains a lack of evidence regarding the best course of action for these patients.[23]

Our study aimed to clarify the clinical meaning of B3 breast lesions and provide a contribution toward understanding the best approach to their treatment and follow-up. To this end, we investigated the overall and subtype-specific malignancy risks, as well as clinical, radiological, and pathological features of B3 lesions, intending to identify variables that can predict the presence of malignancy, and compare these results between different excision methods and follow-up-only groups.

Methods

This retrospective study reviewed a series of patients being followed in the Breast Unit of the Santo António University Hospital (ULSSA) in the context of a histological diagnosis of a B3 lesion, between November 2018 and November 2023. Only patients without a synchronous diagnosis of a higher-grade lesion were included. This study was approved by the local ethics committee [2023.248(210-DEFI/200-CE)].

Clinical history and examination data such as age, sex, BMI, menopausal status, age at menarche, age at first live birth, number of births, breastfeeding history, smoking history, family history of breast or ovarian cancer, oral contraceptive use, hormonal replacement therapy, personal history of breast disease and symptoms at presentation (palpable lesion, pain, skin changes, breast secretion or none) were retrieved from the hospital records. The family history variable was categorized into a postulated higher-risk subset (history of breast or ovarian cancer in at least three direct family members, at least one below the age of forty or at least one from the male sex)[24], and a postulated low to intermediate-risk subset which includes any other kind of existing family history.

The radiology reports of the imaging exams performed at the time of the diagnosis were evaluated. The collected information included the number of suspect lesions, lesion side, location of the lesion in the breast, size, type of abnormality (microcalcifications, presence of a mass or architectural deformity), and radiological suspicion score according to the Breast Imaging Reporting and Data System (BIRADS). The pathology reports were reviewed to assess the type of core biopsy performed and its histopathological result and compared with the imaging reports to check for correlation. We defined the presence of two or more lesion foci within the same breast quadrant as a multifocal lesion, while the presence of two or more lesion foci in different quadrants or foci separated by more than 50 mm was considered multicentric.[25]

From our access to the medical records, we also collected data on the type of subsequent management after diagnosis (OE, VAE, or follow-up) and analysed the pathology report when an excisional modality was chosen, to correlate with the primary results. An upgrade was reported in the presence of invasive or *in situ* carcinoma of the breast in the final specimens.

The post-excision histopathological results were compared with the primary histopathological results of the biopsy and PPV for the detection of a malignant lesion was calculated. PPV was defined as follows: Number of true positives/(number of true positives + number of false positives)×100.

Finally, we checked for any complications related to diagnostic or treatment procedures and viewed the results of follow-up exams to ensure complete excision was obtained and there was no lesion

recurrence. Recurrence was classified as concordant based on imaging or subsequent histopathological exams, while only the latter confirmed upgrades or different B3 lesions. The BIRADS score of the latest imaging exam available was collected. The risk of recurrence and developing subsequent cancer in the homolateral or contralateral breast according to the type of treatment for the B3 lesion was then estimated.

A descriptive analysis of the patient's clinical, radiological, and pathological characteristics was performed, using number and percentage for categorical variables and median and interquartile range for continuous variables. The Kolmogorov-Smirnov and Shapiro-Wilks tests were used to evaluate normal distribution. For continuous variables, the Independent Samples T-test, One-way ANOVA, Mann-Whitney, and Kruskal-Wallis tests were used according to whether normal distribution was verified and the number of variables being compared. For categorical variables, Pearson's Chi-square test, the Monte Carlo exact test, and Fisher's exact test were used, as appropriate for the data, to assess the association between the patient's characteristics, diagnostic or treatment strategies, and malignant upgrade. Statistical analyses were performed using IBM SPSS 29.0 software for Windows (IBM SPSS, Armonk, NY, USA). The considered statistical significance was $p<0.05$.

Results

This study included 51 patients diagnosed with one or more B3 lesions and no concomitant malignancy, registered from November 2018 to November 2023. All patients were of the female sex and all were still alive as of data retrieval.

Patients were divided into three categories according to their clinical management, with 16 (31.4%) opting for an active surveillance (follow-up only) strategy, while the rest underwent excision of the lesions, either surgically through an open excision (OE) as seen in 22 patients (43.1%) or through VAE as seen in 12 (23.5%). Additionally, 1 patient underwent bilateral skin-sparing mastectomy (BSSM) in the context of multicentric PL associated with LCIS. There was no surgical upgrade of the lesions or any evidence of malignant transformation on the follow-up. However, there were complications related to this treatment modality, as skin flap necrosis occurred following reconstructive surgery. This patient was omitted from the statistical analysis, to avoid creating more variables with no valid cells, but was considered for the descriptive analysis of the total group.

It was determined that most continuous variables did not follow the normal distribution. In the ones that did, such as BMI, age at first live birth, and age at menopause, there was no normal distribution for all management subgroups. For this reason, all data from these variables is presented with median and interquartile ranges.

This group of patients had a median age of 51 years (IQR=12.0) and 21 (44.7%) had a postmenopausal status. Approximately half of the individuals, 28 (54.9%), presented with breast symptoms, 15 (30.0%) had previously known breast pathologies, 1 (2.0%) of which was malignant. A high family risk for breast cancer was identified in 7 women (15.6%), while another 9 (20.0%) also had a positive family history. Only 4 patients (18.2%) were active smokers at the B3 diagnosis, 23 (60.5%) had a positive breastfeeding history and 25 (83.3%) had a positive history for the use of oral contraceptives.

B3 lesions were found in 27 breast biopsies (52.9%) in the left breast, 22 B3 lesions (43.1%) were detected in the right breast, and 2 lesions (3.9%) were bilateral. Most of these lesions were detected in the upper outer quadrant (14 cases; 27.5%), closely followed by the central/retromamillar region (13 cases; 25.5%), where all lesions (100.0%) were subcategorized as intraductal papilloma.

As for the radiological findings, most lesions could be described as nodularity (38 cases; 74.5%), while microcalcifications were found in 9 patients (17.7%), whether isolated or with another associated abnormality. All lesions subcategorized as LN were associated with microcalcifications. An additional 4 lesions (7.8%) were described as distortion on imaging, most of which were

histologically categorized as RS/CSL (3 cases; 75.0%). The most common radiological suspicion level was BIRADS 4a with 26 patients (52.0%) receiving this label at diagnosis, followed by 11 patients (22.0%) with a BIRADS of 4b, and 5 (10.0%) at each BIRADS 3 and 4c categories. Of patients with a BIRADS equal or inferior to 3, 7 (87.5%) were PL and the 1 remaining lesion was diagnosed as FEA. Patients with a PL diagnosis presented most frequently with a 4a BIRADS (22 cases; 66.7%), LN with a 4b BIRADS (3 cases; 75.0%), and RS/CSL with a 4c BIRADS (3 cases; 60.0%).

Most B3 lesions were diagnosed through CNB (34 cases; 66.7%), 16 (31.4%) through VAB, and 1 (2.0%) through OE which was both diagnostic and therapeutic in the context of a lesion suspect of being a PT. Among B3 lesions, PL were the most frequent with 34 cases (66.7%). RS/CSL were found in 5 (9.8%) women, LN in 4 (7.8%), FEA in 3 (5.9%), ADH in 1 (2.0%), PT in 3 (5.9%) and 1 patient (2.0%) had multiple B3 subtypes at diagnosis, in this case both PL and LN. They had a median size of 11.5 mm (IQR=9.0), 8 of them (16.7%) were multifocal, and 3 were multicentric (6.3%). In total, radio-pathological correspondence was positive in 47 patients (92.2%).

Regarding the treatment-related variables, when comparing the final specimen's histological result with the diagnostic biopsy, we found a downgrade in 5 cases (14.3%), meaning the new result was either benign or of normal breast tissue, a concordant result in 24 (68.6%), an upgrade to a malignant lesion in 3 (8.6%) and the detection of a different B3 lesion with no malignancy in another 3 (8.6%). Patients had a median follow-up time of 3 years (IQR=2.1) and in this period, 15 (30.0%) had at least radiological evidence of lesion persistence or recurrence but no upgrade had been reported, 2 (4.0%) had a histopathologically confirmed upgrade to malignancy and in 1 (2.0%), a different B3 lesion (a CSL in this case) was diagnosed during follow-up after prior diagnosis and treatment of another (PL). When this data was retrieved, the most current imaging findings of the patients were categorized as BIRADS 2 in 30 cases (66.7%), BIRADS 3 in 10 (22.2%), 1 (2.2%) in each BIRADS 4a, 4b, and 4c categories, and BIRADS 6 in 2 cases (4.4%).

A full descriptive analysis of the whole study population with all the collected variables can be found in Tables 1 and 2. Table 2 also provides a full breakdown of radiological findings per B3 histologic subgroups.

In Table 1 we additionally report and compare the three management groups in terms of clinical, radiological, and pathological variables. Most notably, we found statistical significance between the patient's family risk for breast cancer and the chosen management modality (p=0.033, Monte Carlo exact test), with OE reporting the highest sum of patients at increased risk, 11 (57.9%), VAE a total of 4 patients (40.0%) and only 1 patient (6.7%) on the follow-up-only group.

The chosen management modality also seems to be related to the used diagnostic tool ($p<0.001$, Monte Carlo exact test). The one patient with a diagnostic and therapeutic OE was excluded from the analysis while determining p. Most patients in the follow-up-only group had a previous VAB (12 cases; 75.0%), while only 4 patients (25.0%) had a CNB and no other medical interventions. Patients that underwent OE had mostly been diagnosed through CNB (17 cases; 77.3%) and 4 (18.2%) had a prior VAB. All 12 patients (100.0%) who underwent VAE had been diagnosed through CNB.

Finally, we found a statistically significant p-value for the histological diagnosis when grouping for management modalities ($p=0.029$, Monte Carlo exact test). All 12 patients (100.0%) who underwent a VAE had a prior diagnosis of a PL. From another perspective, all 3 patients diagnosed with PT underwent OE, all 3 diagnosed with FEA were kept on follow-up, and the only patient diagnosed with ADH was also kept on follow-up after being diagnosed through VAB and their lesion stopped having radiological translation.

Despite the statistical analysis not indicating any other significant differences between management cohorts, it is relevant to mention that radio-pathological concordance was verified in all patients in the follow-up and VAE groups but only in 18 (81.8%) patients treated with OE, meaning that this was the only chosen modality for patients where this condition was not verified. As for diagnostic-treatment concordance, we found that no patients who underwent VAE had an upgrade or different B3 lesion on final histology but these outcomes were each found in 3 (13.6%) patients who had an OE. We found lesion recurrence in each management subgroup, all of which were classified as concordant in the follow-up-only group (8 cases; 53.3%), most of which were concordant in patients who underwent OE (6 cases; 27.3%), and were evenly distributed in the VAE group with 1 patient (8.3%) either having a concordant result, an upgrade or a different B3 lesion. The 1 patient with an upgrade was the only VAE patient who did not avoid surgery. Overall, recurrence was found in 7 cases (31.8%) for the OE cohort and 3 (24.9%) for the VAE cohort.

Patients were also grouped by whether malignancy was or was not found in the final specimen. A statistical analysis was performed, even though this type of upgrade was only detected in 3 patients, and no significantly different characteristics were reported between both groups. We then added the 2 patients where malignancy was found on follow-up to create a “total upgrade” group. Compared to the patients with no upgrade, statistically significant correlations were found between total upgrade and the histological type on the diagnostic biopsy ($p=0.020$, Monte Carlo exact test), the number of lesion foci ($p=0.023$, Monte Carlo exact test), and a BIRADS category of at least 4b at diagnosis ($p=0.019$, Fisher’s exact test). Regarding the correlation between total upgrade and

histological type, we particularly found statistical significance in having an upgrade and being diagnosed with LN (p=0.017, Fisher's exact test).

As aforementioned, final excision histology was malignant in 3 (8.6%) of the patients (2 ductal carcinoma in situ and 1 microinvasive lobular carcinoma). Lesion-specific PPVs were as follows: PL represented the largest subgroup of B3 lesions and had a low malignancy rate, with a PPV of 3.8%. The remaining lesion subtypes had a low incidence in our study group. LN and RS/CSL in the biopsy specimen exhibited an increased malignancy risk in our analysis, with a PPV of 50% and 33.3%, respectively. PT was detected and excised in 3 cases. In all these cases, the initial and final histopathological results matched. None of the identified ADH and FEA lesions in our study group were excised after their first biopsy so PPV could not be determined. The incidence of malignant excisional results and the respective PPVs of the subgroups of B3 lesions are presented in Table III.

When trying to evaluate the risk of developing future breast cancer after a B3 diagnosis we only considered women who had at least a 2-year follow-up period. Of the 34 who met the inclusion criteria for this specific analysis, a total of 2 (5.4%) developed subsequent cancer in the homolateral or contralateral breast in the follow-up period. Despite the small sample size, we found a risk of 4.2% for patients previously diagnosed with PL and 25.0% for patients with LN (Table IV). These patients respectively developed DCIS and invasive breast carcinoma of no special type (IBC-NST) and were both diagnosed and excised through different methods (Table V).

Discussion

Lesions of uncertain malignant potential in the breast (B3) have lately been a theme of particular interest in the medical community, with various new guidelines and consensus meeting reports released in recent years. Our study provides relevant information about the potential risk factors of a malignant upgrade, management modalities, and malignancy risk of each B3 lesion subtype in a small single-center cohort. It also aims to compare its findings with the most current literature, as well as contribute with more data to facilitate the development of lesion-based management.

The upgrade rate of 8.6% in the overall series undergoing excision is slightly below the lower end of the reported range of about 10 to 35%. It is however coincident with the upgrade rate reported in one of the few studies that only accounts for lesions excised through VAE.[19] Potential reasons for this low value in our study population include its distribution among B3 histotypes: While in most studies ADH, the B3 lesion commonly associated with the highest upgrade rates, comprises the most common lesion subgroup[12,14,16,17], in our study, PL were by far the most common, and only 1 case of pure ADH was reported. Another explanation could be that the increased use of VAB and advancements in mammography and ultrasound resolution have recently led to a rise in the detection of lower-grade lesions.[7] A previous study reported a lower incidence of malignancy in diagnostic surgical excision following the initial VAB diagnosis of ADH than after the initial CNB diagnosis.[26] The fact that 31.4% of patients were diagnosed through VAB and less than half were managed with a surgical approach (45.1%), meaning that most did not meet severity criteria such as presenting cellular atypia, may be other contributing factors.

The differentiation into these lesion subtypes can be of great importance for patients. In our study, we found LN in 4 biopsies (7.8%). Of the 2 excised lesions, 1 (50.0%) had an upgrade, meaning LN in this study had the highest risk for an upgrade of all B3 lesions. The tremendous variability of upgrade rates of different studies from 4 to 67%[21] can probably be explained by partially small case numbers or separate evaluation of LN or together with simultaneously present high-risk lesions, such as ADH[27]. A possible reason for such a high upgrade rate in our study could have been a preselection of cases in the multidisciplinary conference since surgical excision was mostly recommended for cases with discrepancies between imaging and histology. Lower malignancy rates of 3–8% refer to larger case numbers[27] or concordance between imaging and pathology[28]. Even though there are other options once a biopsy detects LN, our excision-based approach was deemed appropriate given the high malignancy rate. The fact that most LN were diagnosed incidentally and all were associated with microcalcifications is consistent with the literature. However, this lesion is not considered to

have a typical imaging pattern, and most calcifications on mammograms leading to a diagnosis of LN on VAB occur in the presence of coexisting multiple lesions in the index area.[21]

A future invasive breast cancer has a 4–10% relative risk (1% annual cumulative risk). Invasive cancer usually affects the same breast (60%), but it also increases the risk in the contralateral breast (25%). While young age and concomitant calcification enhance the chance of subsequent malignancy, positive resection margins with classical LN are of no predictive value. Standardizing management approaches for LN poses a challenge due to its dissolute growth pattern. Debated options include OE, lifelong follow-up, and chemoprevention in some countries.[21] In our study, we found that out of 4 LN that were followed for at least 2 years after diagnosis, 1 (25.0%) was upgraded to malignancy. When considering excisional and follow-up upgrades together, LN has a significantly higher risk ($p=0.017$) for an upgrade than all other B3 lesions.

In contrast to other studies, ADH was not the most common B3 lesion in this study. The 1 identified case (2.0%) deviated significantly from larger multicenter studies, where ADH accounted for up to 40% of all B3 lesions.[29] Given this very small sample, it was impossible to determine the PPV for malignancy. The Third International Consensus Conference on lesions of uncertain malignant potential in the breast mentions an upgrade rate of 7.3–57% and calls for reconsideration of the recommendation for excision after biopsy.[21] The fact that ADH is regarded as an indicator lesion and that a differential diagnosis of DCIS and ADH is made solely based on size (ADH is diagnosed if the area of atypia is less than 2 mm) further reinforces this strategy.[21,30] Nevertheless, other options such as imaging follow-up after VAB, when the calcifications in clinical imaging have been completely removed, are being increasingly considered.[21] This was the case for our patient and no lesion recurrence has been detected during follow-up. ADH is a clear majority (81.6%) of B3 lesions found as calcifications on mammography and, sometimes on ultrasound.[21] Imaging reports that microcalcifications were present in this patient, congruently with the literature.

FEA was similarly only found in 3 (5.9%) patients, of which no final histology specimen was obtained, and thus not much can be inferred from our statistical analysis. Although this lesion is often associated with ADH and LN, and older studies showed significantly higher rates of 18.3–34.4% [6, 18], newer studies consider malignancy rates of less than 10% [19, 20]. Surgical excision is unnecessary if the microcalcifications are completely removed with a larger gauge biopsy, so long as radiological follow-up is implemented. This has been the approach at our center, with all these lesions being kept on follow-up-only strategies after mostly being diagnosed through VAB (66.7%). Only instances with radio-pathological discordance, mass lesions, or cases with residual calcifications after biopsy should be treated with OE.[21]

PL were the most frequently diagnosed lesions in our study, with 34 cases (66.7%). After final excision, 1 case was upgraded with an upgrade rate of 3.8%. Pure intraductal PL have a remarkably low upgrade rate of 1–9%, whereas lesions with concomitant atypia have been reported to have a higher upgrade rate of up to 38%.[21] Consequently, radiological surveillance seems appropriate for smaller or completely excised benign PL, or VAE as an alternative to OE. Even though the presence of atypia was not recorded for PL in this study, it is possible to assume that most of the included lesions were pure PL. VAE was used to treat 12 patients and 14 were treated with OE, which reflects the similar relevance of both strategies in this B3 lesion. Radiology-pathology discordance, symptoms (palpable mass or nipple discharge), age 60 years old and older, size 10 mm or larger, peripheral location (>5cm distance from the nipple), concomitant calcifications, and presence of four or more metachronous or concurrent peripheral PL constitute factors that were associated with a higher malignancy risk and should be considered to determine the need for selective surgery.[31] Our study found that out of 24 PL that were followed for at least 2 years after diagnosis, 1 (4.2%) was upgraded to malignancy (DCIS). A recent study that included 139 PL in a follow-up-only strategy found an upgrade rate of 1.4% within 2 years of diagnosis.[32]

In our study, RS/CSL were found to have a risk for upgrade on final histology of 33.3% (1 out of 3 excised lesions). The independent association of this histotype with an increased risk for breast cancer is not consensual among various cohort studies, with some of them justifying the mild risk elevation to a frequent association with other proliferative diseases, while others found an independent association with malignancy.[33,34] Atypia and carcinoma are typically seen at the periphery of the lesion.[34] A recent study on a large patient cohort found an upgrade rate of 9% in RS/CSL without atypia, in contrast to an upgrade rate of 33% in those with atypia.[35] Further studies revealed a low upgrade rate of 0.9–1.6% associated with the increased use of therapeutic VAE after CNB diagnosis of RS without atypia.[21] This is not the case with our study, where VAE was not used and only 2 VABs were performed in 5 diagnosed lesions. We attribute this not to a specific bias towards a more radical approach in these lesions, but to the fact that there were radio-pathological discordances. Metaplastic carcinoma is noted to be a very commonly associated invasive condition[36] but that wasn't the case for the upgrade we reported, which was classified as DCIS. Some researchers have found several risk factors associated with cancer upstaging of RS/CSL, particularly a large radiographic size and the presence of atypical hyperplasia.[34] The average size associated with cancer was reported as 1.4 cm[37], meaning that CSL carry a higher upgrade risk, as did our reported case, with a significant 3.5 cm. We believe that our high PPV for malignancy in this histotype is related to the small sample size and the presence of lesions with associated risk factors.

PT was detected in 3 cases (5.9%), all of which underwent surgical excision. None were upgraded in final histology, leading to an estimated PPV for malignancy of 0%. Clinically, a PT is most often conspicuous by a palpable, fast-growing tumor. Based on distinct characteristics such as mitotic activity, stromal cellularity, borders, and the ratio of epithelial to stromal components, the WHO classification of breast tumors (fifth edition, 2019) divides PT into benign, borderline, and malignant categories. Only the first two are considered as B3 lesions. In our study, 2 PT were benign and 1 was classified as borderline. Regardless of the PT subtype, surgical extirpation or even more radical surgery in the form of a mastectomy must be performed[38], as differentiating PT from benign fibroadenoma poses a great challenge for pathologists in incomplete lesion samples such as the ones from CB. There seems to be an emerging consensus that the growth rate of FA may be the most useful criterion for excision. Although larger sampling such as VAB could be considered in an attempt to distinguish PT from fibroadenomas, and as the upgrade to malignancy is uncommon after this procedure, excision is appropriate for lesions where PT cannot be excluded regardless of size to achieve a correct diagnosis.[15] As the PT in our study were either detected on CB or directly through a surgical biopsy, the chosen surgical approach was in line with current recommendations.

While a substantial portion of our patients seem to have been selected for follow-up-only management, it is important to clarify that most of their lesions were diagnosed through VAB and either complete excision was obtained on follow-up imaging, or asymptomatic lesions with no suspicion criteria remained present. The 4 patients who had a CNB with no other medical interventions had either benign PL that wasn't identifiable on ultrasound for EAV, a clinically stable mass with FEA, a small stromal distortion diagnosed as RS with no atypia or because it was the patient's decision not to be submitted to further interventions.

One of the most important findings of our study was that the overall rate of developing subsequent malignancy during at least 2-year follow-up after diagnosis of B3 lesions that were not upgraded on the final specimen was 5.4%. No malignancy was found before 2 years of follow-up. The 10-year absolute risk of breast cancer is 2.85% in 50-year-old females in the general population.[39] Some recent studies evaluating age-specific 10-year absolute risk, with the goal of risk-stratifying breast cancer screening, indicated a threshold of 6% to define "high-risk" women.[40,41] Our results are however not entirely congruent with this literature. The follow-up malignancy risk below 6% does not provide evidence that all women with a B3 lesion diagnosis should be defined as "high-risk". A tailored approach to surveillance should instead be considered for each lesion subtype and individual lesion's risk factors. In the literature, the three histotypes with a higher risk of future cancer were ADH (13.6%), atypical PLs (9.7%), and LIN (8.8%) and there seems to be consensual that these should not be discharged from clinical and radiological follow-up.[14] Our study did not have a

sufficiently large population of these B3 subtypes to corroborate this claim but the malignization rate of 25% for LN does lead us to consider it high-risk. It has been suggested that high-risk women should undergo an annual mammogram examination with an additional breast MRI, or breast US or contrast-enhanced mammography in the case of contraindication to MRI or if MRI is not readily available, for at least a 5-year follow-up period.[14]

This study tried to identify other risk factors that influence the upgrade of all B3 lesions, from clinical, radiological, and pathological variables, but due to our small sample size, none of the accounted-for factors were statistically significant. In contrast, several studies have underlined that the risk of upgrade to malignancy decreased if lesions were pure, which means lesions were not associated with other anatomopathological findings. Imaging findings classified as BIRADS categories 4b or 4c by radiologists, with a histopathological diagnosis of B3 reported by pathologists, were one of the most important predicting factors for upgrade according to previous studies.[10] Studies on various subgroups of lesions have demonstrated that imaging lesions larger than 6 mm[42] or 10 mm[43] carry a higher probability of upgrade. One study also found that older age was associated with higher odds of malignant upgrade following a B3 diagnosis at VAB[10], while another associated a higher risk for a malignant tumor in older postmenopausal women and patients with ipsilateral breast cancer[18].

When we grouped all patients who had an upgrade either on the final specimen or during follow-up after diagnostic or therapeutic procedures, we found that a BIRADS category at diagnosis of at least 4b, multifocality, and a histological subtype such as LN were significantly associated with the malignancy outcome. This is aligned with the previously mentioned upgrade risk factors.

VAE offers the benefits of being low cost, providing excellent cosmetic results, high patient satisfaction, and avoiding risks of general anesthesia. A focal lesion that is under 15 mm in size will probably be completely removed by VAE, although it is acknowledged that this may not accurately reflect the complete extent of pathological alteration.[19] Reassuringly, there was no association between lesion size and upgrade to malignancy in our study, although this has been previously reported.

Studies have shown that VAE of B3 lesions reduces the number of open surgical procedures.[44] In our study, 12 women were suitable for VAE and underwent the procedure with 11 (91.7%) avoiding further surgery. The number of women avoiding surgery in our series is higher, but this is likely due to a combination of case mix and perhaps a more cautious approach to recommending VAE after the multidisciplinary team discussion.

Still regarding the management of these lesions, primary medical prevention should be offered to those women at increased risk of developing breast cancer, as recommended by the current USA guidelines, UK NICE guidelines, and ESMO guidelines. The majority of B3 lesions, such as ADH and FEA, express estrogen receptors and are therefore sensitive to these antiestrogenic strategies. This is a much more common approach in the context of increased familial risk rather than due to the presence of atypia where the evidence base is less strong due to smaller numbers in trials.[15] As we have noted, familial risk doesn't always outweigh the diagnosis of higher-risk lesions such as ADH and LN. Since the risk of breast cancer development can be roughly halved after 5 years of prophylaxis[45], it is of paramount importance that these studies are also conducted in larger cohorts of women diagnosed with B3 lesions.

Our study has a few limitations – we retrieved information from electronic clinical notes, where several patients had incomplete data, and we did not include a reassessment of the reported findings from pathologists and radiologists. Despite this, all patients were discussed in multidisciplinary team meetings, meaning that exams were reviewed by several specialists. Another limitation of this study is that the risk factors could only be evaluated concerning all B3 lesions due to the small case numbers of the individual B3 subtypes. Thus, general and not subgroup-specific statements can be made on how individual factors increase the upgrade risk for all B3 lesions. As PL were the most identified lesions in our study, it could have been interesting to differentiate the biopsies where atypia was and was not present, to check for this histological criterion's ability to generate different outcomes. A final caveat of this study is that the median follow-up time is currently still short at 3.0 years. Further work is needed to determine the interval and length of mammographic follow-up, as new studies question previous more conservative approaches.[23]

Conclusion

The lack of a thorough understanding of the biological and histological fundaments of B3 lesions results in the challenge of establishing standard criteria for effective patient management. Our findings help shed some light on this issue, as we found a rate of upgrade to breast cancer of 8.6% after excision, in addition to a 5.4% risk of subsequently developing breast cancer either homolaterally or contralaterally during an over 2-year follow-up. The highest risk was associated with LN diagnosis, with up to 50.0% of cases upgraded to BC at excision and 25.0% of women developing BC in subsequent years. Other overall malignancy upgrade risk factors were found such as multifocality and BIRADS ≥ 4b at diagnosis.

Regarding management options, VAE offers a safe and effective pathway for the treatment of B3 lesions, reducing the number of open surgical procedures. This study confirms the validity of this approach as the number of upgrades to malignancy after a VAE is very low. This information can be used to discuss tailored management options with patients and supports the preference for conservative management when the identified risk criteria are absent.

Despite our study group being heavily constituted by lower-grade lesions and having overall lower malignancy rates than reported in most literature, we note that our imaging findings and lesion management strategies for each specific B3 subtype are aligned with the best and most recent evidence available.

A multidisciplinary approach is paramount in the management of all B3 lesions. Team review is also important post-VAE or post-OE to ensure radiological and pathological concordance and to plan follow-up.

Appendix

Table I – Clinical, radiological, and pathological characteristics per management modality

	Follow-up (N=16)	OE (N=22)	VAE (N=12)	Total (N=51)	p-value
Age, median (IQR), years	49.0 (10.0)	51.5 (13.0)	52.5 (9.0)	51.0 (12.0)	0.664[1]
BMI, median (IQR), kg/m^2	28.9 (4.9)	23.3 (12.3)	24.8 (7.7)	26.8 (7.6)	0.548[2]
Smoking, n (%)					1.000[3]
Ex	0	1 (12.5)	0	1 (4.5)	
Yes	1 (16.7)	1(12.5)	2 (25.0)	4 (18.2)	
Personal History of Breast Disease, n (%)					0.631[3]
Benign	6 (37.5)	4 (18.2)	3 (27.3)	14 (28.0)	
Malignant	0	1 (4.5)	0	1 (2.0)	
Family History of Breast Cancer, n (%)					0.033[3]
Low-intermediate risk	0	7 (36.8)	2 (20.0)	9 (20.0)	
High risk	1 (6.7)	4 (21.1)	2 (20.0)	7 (15.6)	
Age at Menarche, median (IQR), years	13.0 (6.0)	13.0 (5.0)	12.5 (3.0)	13.0 (2.0)	0.458[1]
Oral Contraceptive Use, n (%)	9 (81.8)	13 (92.9)	3 (75.0)	25 (83.3)	0.621[3]
Age at First Birth, median (IQR), years	26.0 (14.0)	24.0 (20.0)	26.0 (16.0)	26.0 (9.0)	0.806[2]
Number of Births, median (IQR)	1.0 (1.0)	2.0 (2.0)	1.0 (1.0)	1.0 (1.0)	0.912[1]
Breastfeeding, n (%)	8 (61.5)	11 (61.1)	4 (66.7)	23 (60.5)	1.000[3]
Menopause, n (%)	4 (26.7)	11 (52.4)	6 (60.0)	21 (44.7)	0.203[3]
Age at Menopause, median (IQR), years	50.0 (5.0)	50.0 (6.0)	48.5 (7.0)	50.0 (6.0)	0.861[2]
Hormone Replacement Therapy, n (%)	1 (7.1)	2 (10.5)	0	3 (7.1)	0.798[3]

	Follow-up (N=16)	OE (N=22)	VAE (N=12)	Total (N=51)	p-value
Side of Breast, n (%)					0.083[3]
Left	7 (43.8)	10 (45.5)	10 (83.3)	27 (52.9)	
Right	8 (50.0)	12 (54.5)	2 (16.7)	22 (43.1)	
Bilateral	1 (6.3)	0	0	2 (3.9)	
Location of Lesion in the Breast, n (%)					0.135[3]
Upper outer quadrant	6 (37.5)	6 (27.3)	2 (16.7)	14 (27.5)	
Lower outer quadrant	2 (12.5)	2 (9.1)	2 (16.7)	6 (11.8)	
Lower inner quadrant	2 (12.5)	0	0	2 (3.9)	
Upper inner quadrant	0	3 (13.6)	1 (8.3)	4 (7.8)	
Central/retromamillar	1 (6.3)	9 (40.9)	3 (25.0)	13 (25.5)	
More than one quadrant	1 (6.3)	1 (4.5)	0	3 (5.9)	
Between quadrants	4 (25.0)	1 (4.5)	4 (33.3)	9 (17.6)	
Symptoms, n (%)					0.117[3]
Screening detection	9 (56.3)	8 (36.4)	6 (50.0)	23 (45.1)	
Pain	2 (12.5)	0	0	2 (3.9)	
Nipple Discharge	4 (25.0)	7 (31.8)	5 (41.7)	16 (31.4)	
Palpable Mass	1 (6.3)	7 (31.8)	1 (8.3)	10 (19.6)	
BIRADS, n (%)					0.639[3]
0	0	0	1 (8.3)	1 (2.0)	
2	0	1 (4.8)	1 (8.3)	2 (4.0)	
3	2 (12.5)	2 (9.5)	1 (8.3)	5 (10.0)	
4a	8 (50.0)	10 (47.6)	7 (58.3)	26 (52.0)	
4b	5 (31.3)	4 (19.0)	2 (16.7)	11 (22.0)	
4c	1 (6.3)	4 (19.0)	0	5 (10.0)	
Diagnostic Modality, n (%)*					<0.001[3]
CNB	4 (25.0)	17 (77.3)	12 (100.0)	34 (66.7)	
VAB	12 (75.0)	4 (18.2)	0	16 (31.4)	
OE	0	1 (4.5)	0	1 (2.0)	

	Follow-up (N=16)	OE (N=22)	VAE (N=12)	Total (N=51)	p-value
Foci, n (%)					0.871[3]
Multifocal	2 (14.3)	4 (19.0)	2 (16.7)	8 (16.7)	
Multicentric	1 (7.1)	0	1 (8.3)	3 (6.3)	
Lesion Size, median (IQR), mm	8.0 (14.0)	12.5 (95.0)	7.5 (16.0)	11.5 (9.0)	0.067[1]
Histology, n (%)					0.029[3]
PL	8 (50.0)	14 (63.6)	12 (100.0)	34 (66.7)	
RS/CSL	2 (12.5)	3 (13.6)	0	5 (9.8)	
LN	2 (12.5)	2 (9.1)	0	4 (7.8)	
FEA	3(18.8)	0	0	3 (5.9)	
ADH	1 (6.3)	0	0	1 (2.0)	
PT	0	3 (13.6)	0	3 (5.9)	
Multiple B3	0	0	0	1 (2.0)	
Radio-pathological Concordance, n (%)	16 (100.0)	18 (81.8)	12 (100.0)	47 (92.2)	0.079[3]
Diagnostic-treatment Concordance, n (%)					0.175[3]
Downgrade	-	2 (9.1)	3 (25.0)	5 (14.3)	
Concordant	-	14 (63.6)	9 (75.0)	24 (68.6)	
Upgrade	-	3 (13.6)	0	3 (8.6)	
Other B3	-	3 (13.6)	0	3 (8.6)	
Recurrence, n (%)					0.097[3]
Concordant	8 (53.3)	6 (27.3)	1 (8.3)	15 (30.0)	
Upgrade	0	1 (4.5)	1 (8.3)	2 (4.0)	
Other B3	0	0	1 (8.3)	1 (2.0)	

	Follow-up (N=16)	OE (N=22)	VAE (N=12)	Total (N=51)	p-value
Current BIRADS, n (%)					0.277[3]
2	13 (86.7)	11 (57.9)	6 (54.5)	30 (66.7)	
3	1 (6.7)	6 (31.6)	3 (27.3)	10 (22.2)	
4a	1 (6.7)	0	0	1 (2.2)	
4b	0	0	1 (9.1)	1 (2.2)	
4c	0	1 (5.3)	0	1 (2.2)	
6	0	1 (5.3)	1 (9.1)	2 (4.4)	
Follow-up Time, median (IQR), years	2.9 (2.0)	3.1 (2.5)	2.8 (4.8)	3.0 (2.1)	0.772[1]

Note: Categorical variables were described as absolute frequency and percentage. Quantitative data is depicted as median with interquartile ranges (IQR).

Abbreviations: ADH, Atypical ductal hyperplasia; BMI, Body mass index; CNB, Core needle biopsy; CSL, Complex sclerosing lesions; FEA, Flat epithelial atypia; IQR, Interquartile range; LN, Classical lobular neoplasia; mm, millimetre; PL, Papillary lesions; PT, Phyllodes tumors; RS, Radial scars; OE, Open excision; VAB, Vacuum-assisted biopsy; VAE, Vacuum-assisted excision

[1]Kruskal-Wallis test

[2]One-way ANOVA

[3]Monte Carlo exact test

*Only CNB and VAB cases were considered while determining the p-value.

Table II – Detected radiological lesions according to B3 lesion subgroups

Lesion	Nodularity, n (%)	Microcalfications, n (%)	Distortion, n (%)	Nodularity + Microcalcifications, n (%)	Distortion + Microcalcifications, n (%)
PL	31 (91.2)	0	1 (2.9)	2 (5.9)	0
RS/CSL	2 (40.0)	0	3 (60.0)	0	0
LN	0	2 (50.0)	0	1 (25.0)	1 (25.0)
FEA	1 (33.3)	1 (33.3)	0	1 (33.3)	0
ADH	0	0	0	1 (100.0)	0
PT	3 (100.0)	0	0	0	0
Multiple B3	1 (100.0)	0	0	0	0
Total	**38 (74.5)**	**3 (5.9)**	**4 (7.8)**	**5 (9.8)**	**1 (2.0)**

Abbreviations: ADH, Atypical ductal hyperplasia; CSL, Complex sclerosing lesions; FEA, Flat epithelial atypia; LN, Classical lobular neoplasia; PL, Papillary lesions; PT, Phyllodes tumors; RS, Radial scars

Table III – Positive predictive value (PPV) for malignancy of excised lesions

Lesion	Cases with excision histology, n (%)	Upgraded cases and PPV for malignancy, n (%)
PL	26 (74.3)	1 (3.8)
RS/CSL	3 (8.6)	1 (33.3)
LN	2 (5.7)	1 (50.0)
FEA	0	-
ADH	0	-
PT	3 (8.6)	0
Multiple B3	1 (2.9)	0
Total	**35 (100.0)**	**3 (8.6)**

Abbreviations: ADH, Atypical ductal hyperplasia; CSL, Complex sclerosing lesions; FEA, Flat epithelial atypia; LN, Classical lobular neoplasia; PL, Papillary lesions; PT, Phyllodes tumors; RS, Radial scars

Table IV – Upgraded cases in patients with over 2 years of follow-up per B3 lesion subtype

Lesion	Cases with over 2 years of follow-up, n (%)	Upgraded cases, n (%)
PL	24 (64.9)	1 (4.2)
RS/CSL	3 (8.1)	0
LN	4 (10.8)	1 (25.0)
FEA	2 (5.4)	0
ADH	1 (2.7)	0
PT	2 (5.4)	0
Multiple B3	1 (2.7)	0
Total	**37 (100.0)**	**2 (5.4)**

Abbreviations: ADH, Atypical ductal hyperplasia; CSL, Complex sclerosing lesions; FEA, Flat epithelial atypia; LN, Classical lobular neoplasia; PL, Papillary lesions; PT, Phyllodes tumors; RS, Radial scars

Table V – Characteristics of excision and follow-up upgraded cases

Lesion	Size, mm	Foci	Diagnostic Modality	Excision Modality	Excision Upgrade	Follow-up Upgrade
LN	12	Multifocal	CNB	OE	MILC	-
PL	13	Multifocal	CNB	OE	DCIS	-
CSL	35	Unifocal	CNB	OE	DCIS	-
LN	-	Multifocal	VAB	OE	-	IBC-NST
PL	20	Multicentric	CNB	VAE	-	DCIS

Abbreviations: CSL, Complex sclerosing lesions; CNB, Core needle biopsy; DCIS, Ductal carcinoma in situ; IBC-NST, Invasive breast carcinoma of no special type; LN, Classical lobular neoplasia; MILC, Microinvasive lobular carcinoma; OE, Open excision; PL, Papillary lesions; VAB, Vacuum-assisted biopsy; VAE, Vacuum-assisted excision

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49. doi:10.3322/caac.21820

2. Peintinger F. National breast screening programs across Europe. *Breast Care*. 2019;14(6):354-358. doi:10.1159/000503715

3. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—An updated review. *Cancers (Basel)*. 2021;13(17). doi:10.3390/cancers13174287

4. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition - Summary document. *Annals of Oncology*. 2008;19(4):614-622. doi:10.1093/annonc/mdm481

5. Andreu FJ, Sáez A, Sentís M, et al. Breast core biopsy reporting categories-An internal validation in a series of 3054 consecutive lesions. *Breast*. 2007;16(1):94-101. doi:10.1016/j.breast.2006.06.009

6. Pinder SE, Shaaban A, Deb R, et al. NHS Breast Screening multidisciplinary working group guidelines for the diagnosis and management of breast lesions of uncertain malignant potential on core biopsy (B3 lesions). *Clin Radiol*. 2018;73(8):682-692. doi:10.1016/j.crad.2018.04.004

7. Rakha EA, Ho BC, Naik V, et al. Outcome of breast lesions diagnosed as lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4) on needle core biopsy, including detailed review of epithelial atypia. *Histopathology*. 2011;58(4):626-632. doi:10.1111/j.1365-2559.2011.03786.x

8. Griffiths R, Kaur C, Alarcon L, Szollosi Z. Three-year Trends in Diagnosis of B3 Breast Lesions and Their Upgrade Rates to Malignant Lesions. *Clin Breast Cancer*. 2020;20(3):e353-e357. doi:10.1016/j.clbc.2019.12.009

9. De Beça FF, Rasteiro C, Correia A, Costa S, Amendoeira I. Improved malignancy prediction by B3 breast lesions subclassification. *Ann Diagn Pathol*. 2013;17(5):434-436. doi:10.1016/J.ANNDIAGPATH.2013.05.003

10. Mariscotti G, Durando M, Ruggirello I, et al. Lesions of uncertain malignant potential of the breast (B3) on vacuum-assisted biopsy for microcalcifications: Predictors of malignancy. *Eur J Radiol*. 2020;130. doi:10.1016/j.ejrad.2020.109194

11. Rakha EA, Lee AHS, Jenkins JA, Murphy AE, Hamilton LJ, Ellis IO. Characterization and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. *Int J Cancer*. 2011;129(6):1417-1424. doi:10.1002/IJC.25801

12. Lucioni M, Rossi C, Lomoro P, et al. Positive predictive value for malignancy of uncertain malignant potential (B3) breast lesions diagnosed on vacuum-assisted biopsy (VAB): is surgical excision still recommended? *Eur Radiol*. 2021;31(2):920-927. doi:10.1007/S00330-020-07161-5

13. Forester ND, Lowes S, Mitchell E, Twiddy M. High risk (B3) breast lesions: What is the incidence of malignancy for individual lesion subtypes? A systematic review and meta-analysis. *European Journal of Surgical Oncology*. 2019;45(4):519-527. doi:10.1016/J.EJSO.2018.12.008

14. Bellini C, Nori Cucchiari J, Di Naro F, et al. Breast Lesions of Uncertain Malignant Potential (B3) and the Risk of Breast Cancer Development: A Long-Term Follow-Up Study. *Cancers (Basel)*. 2023;15(13). doi:10.3390/cancers15133521

15. Rubio IT, Wyld L, Marotti L, et al. European guidelines for the diagnosis, treatment and follow-up of breast lesions with uncertain malignant potential (B3 lesions) developed jointly by EUSOMA, EUSOBI, ESP (BWG) and ESSO. *European Journal of Surgical Oncology*. 2024;50(1). doi:10.1016/j.ejso.2023.107292

16. Hoffmann O, Stamatis GA, Bittner AK, et al. B3-lesions of the breast and cancer risk - an analysis of mammography screening patients. *Mol Clin Oncol*. 2016;4(5):705-708. doi:10.3892/mco.2016.790

17. Richter-Ehrenstein C, Maak K, Röger S, Ehrenstein T. Lesions of "uncertain malignant potential" in the breast (B3) identified with mammography screening. *BMC Cancer*. 2018;18(1). doi:10.1186/s12885-018-4742-6

18. Mohrmann S, Maier-Bode A, Dietzel F, et al. Malignancy Rate and Malignancy Risk Assessment in Different Lesions of Uncertain Malignant Potential in the Breast (B3 Lesions): An Analysis of 192 Cases from a Single Institution. *Breast Care*. 2022;17(2):159-165. doi:10.1159/000517109

19. Giannotti E, James JJ, Chen Y, et al. Effectiveness of percutaneous vacuum-assisted excision (VAE) of breast lesions of uncertain malignant potential (B3 lesions) as an alternative to open surgical biopsy. *Eur Radiol*. 2021;31(12):9540-9547. doi:10.1007/S00330-021-08060-Z/TABLES/2

20. MacLean GM, Courtney SP, Umeh H, Sanjeev S, McCormick C, Smith BM. Is mode of presentation of B3 breast core biopsies (screen-detected or symptomatic) a distinguishing factor in the final histopathologic result or risk of diagnosis of malignancy? *World J Surg*. 2013;37(11):2607-2612. doi:10.1007/s00268-013-2191-6

21. Elfgen C, Leo C, Kubik-Huch RA, et al. Third International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). *Virchows Archiv*. 2023;483(1):5-20. doi:10.1007/s00428-023-03566-x

22. Bennett IC. The Changing Role of Vacuum-assisted Biopsy of the Breast: A New Prototype of Minimally Invasive Breast Surgery. *Clin Breast Cancer*. 2017;17(5):323-325. doi:10.1016/j.clbc.2017.03.001

23. Hennessy G, Boland MR, Bambrick M, et al. Value of Long-term Follow-up in Surgically Excised Lesions of Uncertain Malignant Potential in the Breast – Is 5 Years Necessary? *Clin Breast Cancer*. 2022;22(7):699-704. doi:10.1016/j.clbc.2022.05.009

24. Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Familiäres mamma- und ovarialkarzinom: Neue gene, neue therapien, neue konzepte. *Dtsch Arztebl*. 2011;108(19):323-330. doi:10.3238/arztebl.2011.0323

25. Oh J. Multifocal or Multicentric Breast Cancer: Understanding Its Impact on Management and Treatment Outcomes. In: Hayat, M.A. (eds) Methods of Cancer Diagnosis, Therapy and Prognosis. Methods of Cancer Diagnosis, Therapy and Prognosis, vol 1. Springer, Dordrecht. 2008; doi:10.1007/978-1-4020-8369-3_40

26. Sohn V, Arthurs Z, Herbert G, et al. Atypical ductal hyperplasia: Improved accuracy with the 11-gauge vacuum-assisted versus the 14-gauge core biopsy needle. *Ann Surg Oncol*. 2007;14(9):2497-2501. doi:10.1245/s10434-007-9454-0

27. Nagi CS, O'Donnell JE, Tismenetsky M, Bleiweiss IJ, Jaffer SM. Lobular neoplasia on core needle biopsy does not require excision. *Cancer*. 2008;112(10):2152-2158. doi:10.1002/cncr.23415

28. Zhao C, Desouki MM, Florea A, Mohammed K, Li X, Dabbs D. Pathologic findings of follow-up surgical excision for lobular neoplasia on breast core biopsy performed for calcification. *Am J Clin Pathol*. 2012;138(1):72-78. doi:10.1309/AJCPYG48TUTFIBMR

29. Bianchi S, Caini S, Renne G, et al. Positive predictive value for malignancy on surgical excision of breast lesions of uncertain malignant potential (B3) diagnosed by stereotactic vacuum-assisted needle core biopsy (VANCB): A large multi-institutional study in Italy. *Breast*. 2011;20(3):264-270. doi:10.1016/j.breast.2010.12.003

30. Pinder SE, Ellis IO. Ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) - Current definitions and classification. *Breast Cancer Research*. 2003;5(5):254-257. doi:10.1186/bcr623

31. Lee SJ, Wahab RA, Sobel LD, et al. Analysis of 612 benign papillomas diagnosed at core biopsy: Rate of upgrade to malignancy, factors associated with upgrade, and a proposal for selective surgical excision. *American Journal of Roentgenology*. 2021;217(6):1299-1312. doi:10.2214/AJR.21.25832

32. Jee Y, Bakht A, Burner JM, Coldren DL, Howard-McNatt M, Chiba A. Intraductal Papilloma on Breast Biopsy: Upstaging Rate and Implications for Practice Guidelines. *American Surgeon*. 2022;88(7):1467-1470. doi:10.1177/00031348221082276

33. Kabat GC, Jones JG, Olson N, et al. A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer. *Cancer Causes and Control*. 2010;21(6):821-828. doi:10.1007/s10552-010-9508-7

34. Jacobs TW, Byrne C, Colditz G, et al. Radial scars in benign breast-biopsy specimens and the risk of breast cancer. *N Engl J Med*. 1999;340(6):430–436. doi:10.1056/NEJM199902113400604

35. Quinn EM, Dunne E, Flanagan F, et al. Radial scars and complex sclerosing lesions on core needle biopsy of the breast: upgrade rates and long-term outcomes. *Breast Cancer Res Treat*. 2020;183(3):677-682. doi:10.1007/s10549-020-05806-z

36. Denley H, Pinder SE, Tan PH, et al. Metaplastic carcinoma of the breast arising within complex sclerosing lesion: a report of five cases. *Histopathology*. 2000;36(3):203–209. doi:10.1046/j.1365-2559.2000.00849.x

37. Morgan C, Shah ZA, Hamilton R, et al. The Radial Scar of the Breast Diagnosed at Core Needle Biopsy. *Baylor University Medical Center Proceedings*. 2012;25(1):3-5. doi:10.1080/08998280.2012.11928768

38. Ditsatham C, Chongruksut W. Phyllodes tumor of the breast: Diagnosis,management and outcome during a 10-year experience. *Cancer Manag Res*. 2019;11:7805-7811. doi:10.2147/CMAR.S215039

39. Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer A Life-Table Model. *JAMA Oncol*. 2018;4(11):1504-1510. doi:10.1001/jamaoncol.2018.1901

40. Forester ND, Lowes S, Mitchell E, Twiddy M. High risk (B3) breast lesions: What is the incidence of malignancy for individual lesion subtypes? A systematic review and meta-analysis. *European Journal of Surgical Oncology*. 2019;45(4):519-527. doi:10.1016/j.ejso.2018.12.008

41. Schiaffino S, Calabrese M, Melani EF, et al. Upgrade rate of percutaneously diagnosed pure atypical ductal hyperplasia: Systematic review and meta-analysis of 6458 lesions. *Radiology*. 2020;294(1):76-86. doi:10.1148/radiol.2019190748

42. Forgeard C, Benchaib M, Guerin N, et al. Is surgical biopsy mandatory in case of atypical ductal hyperplasia on 11-gauge core needle biopsy? a retrospective study of 300 patients. *Am J Surg*. 2008;196(3):339-345. doi:10.1016/j.amjsurg.2007.07.038

43. Hodorowicz-Zaniewska D, Brzuszkiewicz K, Szpor J, et al. Clinical predictors of malignancy in patients diagnosed with atypical ductal hyperplasia on vacuum-assisted core needle biopsy. *Wideochirurgia I Inne Techniki Maloinwazyjne*. 2018;13(2):184-191. doi:10.5114/wiitm.2018.73528

44. Strachan C, Horgan K, Millican-Slater RA, Shaaban AM, Sharma N. Outcome of a new patient pathway for managing B3 breast lesions by vacuum-assisted biopsy: time to change current UK practice? *J Clin Pathol*. 2016;69(3):248–254. doi:10.1136/jclinpath

45. Fisher B, Costantino JP, Lawrence Wickerham D, et al. Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90(18):1371–88. doi:10.1093/jnci/90.18.1371

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