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Upgrade Rates of B3 Breast Lesions After Surgical Excision: A Retrospective Observational Study from a Public Breast Unit in Greece with a Narrative Review of the Literature

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Abbreviations:

ADH: Atypical Ductal Hyperplasia; AIDEP: Atypical Intraductal Epithelial Proliferation; ALH: Atypical Lobular Hyperplasia; CCL: Columnar Cell Lesions; CFLs: Cellular Fibroepithelial Lesions; CNB: Core Needle Biopsy; CSL: Complex Sclerosing Lesion; DCIS: Ductal Carcinoma in Situ; FEA: Flat Epithelial Atypia; LCIS: Lobular Carcinoma in Situ; LN: Lobular Neoplasia; PLCIS: Pleomorphic Lobular Carcinoma in Situ; PLs: Papillary Lesions; RS: Radial Scar; UDH: Usual Ductal Hyperplasia; VAB: Vacuum Assisted Biopsy; VAE: Vacuum Assisted Excision

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1. Abstract

1.1. Background

Advances in breast imaging have increased the detection of B3 lesions with uncertain malignant potential. Their management remains controversial because of variable upgrade rates to ductal carcinoma in situ (DCIS) or invasive carcinoma. This study evaluated the upgrade rates and management of B3 lesions in a public breast unit.

1.2. Materials and Methods

A retrospective single-centre study was conducted including women diagnosed with B3 lesions on core needle biopsy between September 2019 and September 2024. All patients underwent surgical excision. Clinicopathological characteristics and final histopathological findings were analysed to determine upgrade rates and their association with lesion subtypes.

1.3. Results

Among 8,500 screened women, 50 (0.58%) were diagnosed with B3 lesions. Malignancy was identified in 10 cases (20%) following surgical excision, including 8 cases of DCIS and 2 invasive carcinomas. Atypical ductal hyperplasia (ADH) demonstrated the highest upgrade rate (29.16%). All invasive carcinomas were hormone receptor-positive, HER2-negative, and exhibited a low proliferative index (Ki-67 <10%), consistent with a favourable prognosis.

1.4. Conclusions

B3 lesions demonstrate a clinically significant, subtype-dependent risk of malignancy, with ADH carrying the highest risk of upgrade. In settings without access to minimally invasive excision techniques, surgical excision remains a reliable diagnostic and therapeutic strategy. These findings support a risk-adapted management approach that balances oncologic safety with the avoidance of overtreatment.

2. Introduction

Breast cancer is the most prevalent malignancy in women globally, associated with significant morbidity and mortality with an incidence of approximately 145 cases per 100,000 women and a mortality rate of 33 per 100,000 annually [1]. Notably, one in eight women is expected to develop breast cancer in their lifetime, making it the leading cause of death in women aged 45-55

[1-2]. Incidence rates vary worldwide, being higher in developed nations, likely due to lifestyle differences and better access to screening and early diagnosis [1-2]. The advent of organized mammographic screening and improved imaging technologies has contributed to the earlier detection of breast cancer and subsequent reductions in mortality rates [1]. There has been a rise in the identification of small, suspicious lesions that are often classified as having uncertain malignant potential or designated as B3 lesions following core needle biopsy. These lesions typically require further sampling due to their heterogeneous nature or the associated risk of progression to malignancy, which is estimated to be between 10% and 35% [3]. The B3 lesions category consist of: (a) atypical ductal hyperplasia (ADH), (b) lobular neoplasia (LN) as lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), (c) flat epithelial atypia (FEA) in, (d) radial scar; composite sclerosing lesion (RS/CSL), d) papillary lesions, e) cellular fibroepithelial lesions (CFL) with the main representative being phyllodes tumours (PT), f) mucinous lesions and g) rare breast lesions (Aden myoepithelioma, apocrine adenosis, spindle-cells lesions). These lesions typically manifest as microcalcifications, architectural abnormalities, or small nodules and papillary lesions during breast screenings, particularly in asymptomatic women. Moreover, they exhibit heterogeneity in their histological morphology and biological behaviour, indicating a potential predisposition to future breast carcinoma development [4]. The presence of atypia in a B3 lesion carries a risk of histological upgrading to malignancy at secondary evaluation [5-6]. The most recent studies showed 4.8% upgrading to malignancy without coexisting atypia and 24% when atypia coexisted [5]. When malignant transformation does occur, it typically develops after a prolonged period and most frequently corresponds to tumours belonging to a favourable prognostic category, characterized by low-grade histology and positive hormone receptor status, thus conferring an excellent overall prognosis [2]. Concerns have arisen about the overtreatment of patients due to unnecessary surgical procedures, which could result in heightened healthcare costs and complications. Recent findings suggest that vacuum-assisted excision (VAE) for selected B3 lesions may offer a more effective and less invasive alternative to traditional open surgical excision, maintaining both diagnostic accuracy and oncologic safety [7]. Despite the progress, the decision between monitoring, serial biopsy, or surgical intervention still relies on the B3 subcategory of the lesion, the radiological findings, and the histopathological correlation [8]. Management of B3 category lesions in percutaneous core needle biopsies remains controversial due to high underestimation rates. Identifying clinical, imaging, and histological features that rule out malignancy is vital for patient care. Open excision has traditionally been used for diagnosis; however, many B3 lesions are now considered benign. This shift Favors conservative techniques like vacuum-assisted excision (VAE) and monitoring, with recent European guidelines – EUSOMA, 2024 advocating for tailored approaches based on cancer progression risks. [4]. In addition, the value of a multifactorial approach that integrates imaging data, histological classification, and clinical factors for making informed treatment decisions has been recognized [9].

3. Materials and Methods

A retrospective observational analysis was performed at a public tertiary breast unit between September 2019 and September 2024. Due to the Covid-19 pandemic, during the period 2019-2021, the breast department was not operating, resulting in no samples being collected. During this period, 8,500 women underwent screening mammography. Both the initial biopsies and the final open biopsies were performed at Agios Pavlos Hospital, while the pathological study was carried out in the pathological laboratory of the hospital. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. Due to the retrospective design of the study, written informed consent was not required. Patients were contacted by telephone for follow-up assessment, and verbal consent for participation and use of anonymized clinical data was obtained. Patient management and treatment were not altered in any way for the purposes of this study. According to institutional policy, formal ethics committee approval was not required for this retrospective audit of existing anonymized clinical data.

3.1. Inclusion Criteria

Patients were eligible for inclusion if they were adult women who underwent image-guided CNB at Agios Pavlos Breast Unit between September 2019 and September 2024, with histopathological confirmation of a B3 lesion (including atypical ductal hyperplasia, flat epithelial atypia, lobular neoplasia, papillary lesions, phyllodes tumour, radial scar, or other rare subtypes), followed by complete surgical excision with available final histology results and at least 6 months of post-excision follow-up data. Fifty patients (0.58%) were diagnosed with B3 lesions following image-guided CNB and were included in the study. All biopsies were performed under imaging guidance, with four to five cores obtained per lesion and all patients underwent open surgical excision. Although contemporary guidelines increasingly support VAE for selected B3 lesions, all patients in our cohort underwent open surgical excision because VAE was not available at our institution during the study period.

3.2. Exclusion Criteria

Exclusion criteria comprised patients with prior history of ipsilateral breast malignancy or excision, incomplete surgical management (e.g., no excision within 6 months of CNB or lost to follow-up), direct CNB diagnoses of B5 (malignant) lesions, imaging-pathology discordance without subsequent excision, male patients, pregnant women, or lesions diagnosed via non-CNB methods.

3.3. Statistical Analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages. Upgrade rates were calculated for each B3 lesion subtype. The aim of the study was to

perform a review and analysis of data on the management and treatment of B3 lesions and the presentation of their management in clinical practice in the Breast Department of a public hospital. A study flowchart is presented below (Figure 1).

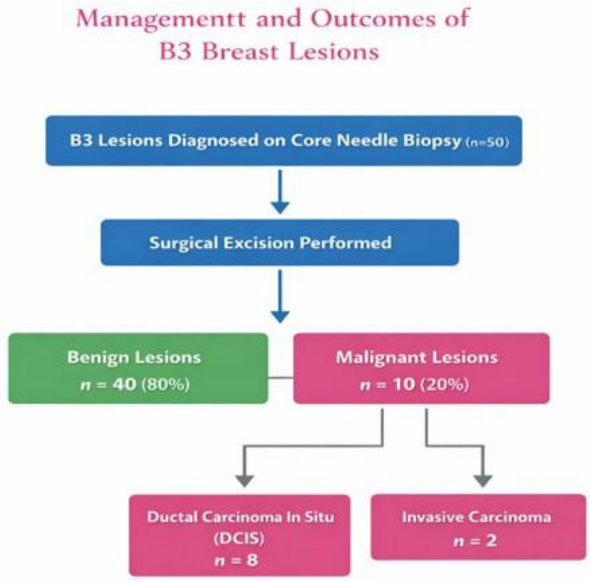

Figure 1: Study flowchart: This diagram illustrates the cohort progression: 8,500 screened women led to 50 B3 diagnoses via CNB, all underwent excision, with 20% upgrading to malignancy (mostly DCIS).

4. Results

During the study period, excluding the period of interruption of breast-unit activity during the COVID-19 pandemic, approximately 8,500 women underwent annual screening at the breast department of Agios Pavlos General Hospital. Our clinical study examined lesions detected during annual screening of 50 women who, after initial core biopsy, were diagnosed with B3 lesions. Under guidance, samples from all patients were collected in the following manner: 1. Preparation of the field using betadine solution and a sterile field 2. Injection of xylocaine at the biopsy needle entry point 3. Incision of the skin using a No. 11 scalpel 4. Placement of the 14G biopsy needle through the skin incision 5. Taking 4-5 tissue samples and placing them in a 1:100 formalin solution 6. Applying pressure to the site for haemostasis.

Histopathological evaluation was performed using haematoxylin eosin staining. In cases demonstrating atypia, immunohistochemistry included cytokeratin 5/6 (CK5/6), E-cadherin, and p63 to exclude invasive components. All patients underwent open surgical excision after CNB diagnosis. When invasion was detected, additional markers including estrogenic receptor (ER), progesterone receptor (PR), HER2, and Ki-67 were assessed. Cases upgraded to malignancy were discussed at a multidisciplinary tumour board and were subsequently enrolled in structured follow-up. Among the 50 patients diagnosed with B3 lesions, surgical excision revealed malignancy in 10 cases, yielding an overall upgrade rate of 20%. Eight cases were upgraded to DCIS and two to invasive carcinoma. Importantly, both invasive carcinomas identified were estrogenic receptor–positive, progesterone receptor–positive, HER2-negative, and exhibited a Ki-67 proliferation index below 10%. These findings are consistent with luminal A like tumours, which are associated with favourable prognosis. All patients entered a structured five-year follow-up program, consisting of ultrasound at six months post-excision and annual mammography with ultrasound thereafter. Patients with invasive carcinoma received appropriate oncologic treatment following tumour board evaluation.

4.1. Patient Characteristics

The study included 50 patients with a histologic diagnosis of a B3 lesion after CNB with a median age of 52 years (range 30-78). All patients after diagnosis of B3 lesion were treated with open resection biopsy, since vacuum-assisted excisions are not available in the public sector. After clinical and imaging examination, 23 patients presented lesions in the form of microcalcifications, 12 in the form of architectural distortion, 9 in the form of papillary lesions, and 6 in the form of small masses. The majority of these lesions were detected by ultrasound or mammography with their characteristics summarized in Table 1.

Histopathological diagnoses after initial assessment of these lesions included atypical intraductal hyperplasia, flat epithelial atypia, papillary lesions, phyllode tumours, lobular neoplasia, and radial scar at the rates shown in the table below.

Majority of lesions were atypical ductal hyperplasia (24), flat epithelial atypia (11) and papillary lesions (9). Smaller number of lesions included, lobular neoplasia (2), radial scar (1), phyllodes tumour (1), Aden myoepithelioma (1) and mucocele like lesion (1).

Table 1: Imaging Findings of B3 Lesions.

Imaging Findings	Absolute Number	Percentage (%)
Microcalcifications	23	46%
Architectural distortion	12	24%
Papillary lesions	9	18%
Small masses	6	12%
Total	**50**	**100%**

4.2. Upgrade to Breast Carcinoma

In 10 of the 50 (20%) B3 lesions after open excisional biopsy, carcinoma (in situ or invasive) was found. Specifically, after secondary evaluation, 8 B3 lesions were upgraded to DCIS, while 2 were upgraded to invasive carcinoma. Five of the 8 B3 lesions that were upgraded to DCIS involved lesions that, after core biopsy, were characterized as atypical intraductal hyperplasia. In addition, 2 of the 24 (8.33%) B3 lesions with atypical intraductal hyperplasia were upgraded to invasive carcinoma. Both carcinomas identified were hormone-receptor positive breast carcinomas with a very good prognosis (high expression of estrogenic and progesterone receptors, cell proliferation index <10%, Her-2 negative). The remaining cases of malignancy development (DCIS) included one papillary lesion, one flat epithelial atypia and one lobular intraepithelial neoplasia as shown in Table 3.

Table 2: Distribution of patients based on histological subtype after initial assessment (core biopsy).

Core biopsy diagnosis	Patient number	Percentage (%)
Atypical ductal hyperplasia	24	48%
Flat epithelial atypia	11	22%
Papillary lesions	9	18%
Lobular neoplasia	2	4%
Phyllodes Tumor	1	2%
Radial Scar	1	2%
Rare lesions	2	4%
Total	**50**	**100%**

Table 3: Upgrade rates according to different subtypes of the B3 lesions in our unit.

B3 Lesion subtype	Upgrade to DCIS	Upgrade to invasive breast carcinoma
Atypical ductal hyperplasia (24)	5 (20.83%)	2 (8.33%)
Flat epithelial atypia (11)	1 (9.1%)	
Papillary lesions (9)	1 (11.1%)	
Lobular neoplasia (2)	1 (50%)	
Phyllodes tumor (1)	0	
Radial scar (1)	0	
Rare lesions (2)	0	

4.3. Follow-up

All patients with B3 lesions were placed on a close monitoring program for the next five years. The first reassessment took place six months after excision with ultrasound, and thereafter annually with mammography and ultrasound. Patients who developed invasive carcinoma were treated accordingly after consultation with the oncology board.

5. Narrative Review of Features and Management of B3 lesions

5.1. Atypical Ductal Hyperplasia (ADH/AIDEP)

Intraductal breast hyperplasia is divided into three categories: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS) [10]. The term atypical ductal hyperplasia (ADH) refers to small foci of epithelial hyperplasia of the ducts, which do not exceed 2 mm in diameter and involve a single duct [11-12]. The distinction between atypical ductal hyperplasia and low-grade ductal carcinoma in situ (DCIS) is based on the size of the lesion collected, with foci larger than 2 mm being classified as low-grade DCIS [10, 12]. ADH is one of the most commonly diagnosed B3 lesions of the breast, a pre-cancerous breast lesion characterized by morphological features similar to DCIS, more limited in extent (<2mm) and partial ductal invasion, found in 12-17% of percutaneous biopsies [11]. Clonal proliferation, overexpression of ER, and loss of basic cytokeratin's differentiate ADH and low-grade DCIS from UDH [10-11]. They usually result from sampling microcalcifications, as they appear as clustered calcifications and less commonly as masses, architectural abnormalities or asymmetric densities on mammography [11]. On ultrasound, ADH may be seen as a mass or as an ill-defined hypoechoic

area, while on magnetic resonance imaging it has a non-specific appearance [10-11]. Image-guided biopsy can be performed using core needle biopsy or vacuum-assisted biopsy for lesions sized <15mm [3]. The distinction between ADH and low-grade DCIS, as previously mentioned, is based solely on the size of the lesion: lesions larger than 2 mm are called low-grade DCIS [11]. Therefore, it is clear that there is always a risk that the sample taken during percutaneous biopsy is part of low-grade DCIS. Women older than 50 years, with microcalcifications or multifocal lesions, or the presence of necrosis have a higher likelihood of being upgraded to DCIS [6]. Probability of upgrade is estimated around 5–50% and increases with CNB/imaging discordance [3]. Consequently, the recommendation for managing these lesions is almost always open biopsy after the initial diagnosis [13]. According to European guidelines and the third international symposium, ADH detected by CNB or VAB should be surgically excised. When available, stereotactic resection with VAE is advised when the lesion is smaller than 15 mm. Surgical resection is the preferred course of treatment for lesions bigger than 15 mm, with VAE serving as a tool for additional sample [3]. In our study, ADH constituted the most frequent B3 subtype and demonstrated the highest upgrade rate, thus reinforcing the established recommendations that ADH diagnosed on core needle biopsy generally warrants surgical excision, particularly when lesion size exceeds 15 mm or when complete removal via vacuum-assisted excision cannot be confidently achieved.

5.2. Lobular Neoplasia (LN)

Lobular neoplasia (LN) includes lesions previously referred to as atypical lobular hyperplasia and lobular carcinoma in situ (LCIS), excluding pleomorphic lobular carcinoma in situ, which is considered analogous to DCIS and is therefore considered a B5a lesion rather than B3 [3]. Variants such as pleomorphic lobular carcinoma in situ (PLCIS) or florid LCIS are referred to in the literature as non-classical lobular neoplasia and are classified as B5a and B4 or B5a lesions respectively [3, 14]. There are many cases where they coexist with classic lobular neoplasia, often complicating the differential diagnosis. LN is found in 0.5-4% of benign lesion biopsies, most commonly in premenopausal women and they appear 85% multifocal and 67% bilateral [9]. Although it was previously believed that the risk of developing invasive carcinoma was the same in both breasts, it has recently been shown that the risk of developing invasive lobular carcinoma is three times higher in the same breast compared to the contralateral breast [3, 15]. Classic lobular neoplasia is designated as a B3 lesion and typically emerges as an incidental finding during biopsies conducted for other reasons, as it lacks clear imaging or clinical indicators of its presence. Mammography rarely detects these lesions, often appearing as amorphous, inconspicuous areas. In rare cases, they may manifest as microcalcifications or, less commonly, as a mass or focal area of non-mass enhancement on MRI [16]. Upgrade rates vary significantly in the literature (0–45%), largely depending on radiologic–pathologic concordance and whether pleomorphic or classic variants are present [3]. More specifically, the rate of progression to any malignancy was 3.1%, generally for lobular neoplasia, 2.5% for atypical lobular hyperplasia (ALH), 5% for lobular carcinoma in situ (LCIS), while the rate of progression to invasive malignancy was 1.3%, 0.4%, and 3.5%, respectively [17]. As for histological characteristics, the neoplastic cells lack, have eccentrically located nuclei, and often contain vacuoles within their cytoplasm. They are divided in: type A (small nuclei with indistinct nucleoli and minimal cytoplasm) or type B (larger nuclei with more distinct nucleoli and cytoplasm), express estrogenic and progesterone receptors (ER, PR +), and are negative for the HER2 marker and for E-cadherin [3, 15]. They are characterized by mild to moderate nuclear atypia (85%) and may coexist with other B3 lesions such as papillomatous lesions, radial scar or fibroadenomas [9]. If, following a CNB, the result is classic LCIS in a lesion visible on imaging, the recommendation is to perform VAB/VAE [3]. Subsequently, when there is agreement between the histological and radiological findings and no residual lesion is present, no further surgery is required, and frequent follow-up is recommended. In cases of discordance, the recommendation is for further surgical excision or VAE [3]. Unilateral or bilateral mastectomy is now recommended in rare cases of patients where other risk factors are present, such as a positive history of malignancy or the presence of mutations in the BRCA 1 or 2 genes [3]. Both florid LCIS and pleomorphic LCIS tend to be unifocal and exhibit a more diffuse distribution compared to classic LCIS, which tends to be multifocal and often bilateral [18]. Overexpression of HER2 makes the former more aggressive compared to classic LCIS, with higher rates of upgrade in the final histological examination. For this reason, when the histological result following CNB shows features of non-classical LCIS, the recommendation is to excise the lesion with healthy margins [18-19].

5.3. Flat Epithelial Atypia (FEA)

Flat epithelial atypia is characterized by replacement of native epithelium by a single or multiple layers of mildly atypical columnar cells [3]. On mammography and FEA imaging, they appear primarily as irregular calcifications, whereas on ultrasound, their appearance bears similarities to ADH and DCIS [20]. Many studies have documented the association between focal epithelial atypia and the presence of concomitant lesions such as ADH, DCIS, invasive carcinoma, and lobular neoplasia [21]. They are found in 1-2% of percutaneous biopsies and are related to increased likelihood of malignant transformation after excision is around 5% according to several studies [11, 22]. Isolated FEA has been associated with relatively low upgrade rates, particularly when completely removed by vacuum-assisted biopsy. However, the risk increases when FEA is associated with additional atypical lesions [22]. The management of flat epithelial atypia remains controversial. In general, the likelihood of pure FEA progressing to invasive carcinoma or malignancy in general is low; however, it increases when there are other coexistent lesions [3, 23]. Specifically, in cases where the lesion, following

a CNB is FEA without the concurrent presence of other lesions, the recommendation of the American College of Surgeons is no longer surgical resection, but close monitoring [3, 21, 23]. When ADH is present in the diagnosis, the recommendation is further resection either by VAE or by surgical intervention [3].

5.4. Radial Scar/ Composite Sclerosing Lesion (RS / CSL)

Radial scar is related to an area of tissue with sclerotic lesions <10mm resembling a scar under the microscope. Lesions >10mm are classified as complex sclerosing lesions [3]. They are found in multiple localizations or unilateral in women 30-60 years old as nonpalpable lesions and 0.03 - 0.8% on percutaneous biopsies [24]. The presence of radial projections complicates the differential diagnosis from carcinoma. Microcalcifications are common [25]. On ultrasound, their appearance varies from a hypoechoic, irregular mass with indistinct borders to a focal area of shadowing without the presence of a mass [3]. Magnetic resonance imaging can be used to rule out underlying invasive malignancy associated with RS/CSL due to its excellent negative predictive value (approximately 99%) [26]. However, it is not capable of distinguishing the presence or absence of atypia. According to the literature, the rate of radial scar upgrading to DCIS or invasive carcinoma ranges from 0 to 40% [3, 25]. The likelihood of histological upgrading to malignancy is closely related to the presence of atypia. In the absence of atypia, the probability of histological upgrading is low (9%) whereas with atypia upgrade rates were 36% [27]. When the diagnosis is made via CNB, the likelihood of malignant transformation is higher, leading to a recommendation for surgical excision of the lesion. In contrast, when a vacuum-assisted biopsy is performed, the risk of upgrade is significantly reduced, resulting in a recommendation for further excision with VAE [3, 25]. Surgical excision is primarily recommended when the radial scar is characterized by atypia; however, even in this case, if it is feasible, VAE is also recommended [3].

5.5. Papillary Lesions (PLs)

Papillary lesions encompass a spectrum ranging from benign intraductal papilloma's, intraductal papilloma with foci of ADH, intraductal papilloma with foci of DCIS, papillary ductal carcinoma in situ, encapsulated papillary carcinoma, solid papillary carcinoma, and invasive papillary carcinoma and are most common in ages between 30 and 50 years [28]. They are divided into papilloma's without atypia, papilloma's with atypia, with DCIS and solitary papillomatous carcinoma (B4/5a) and thus, they can range histologically from B2 to B5a [28]. Depending on location, they are classified as central (under the nipple) or peripheral (usually multiple). They are more commonly found in the centre of the breast than at the periphery [28,29]. Larger lesions may appear as well-defined round or oval soft-tissue opacities with or without microcalcifications. Ultrasound may reveal an intraductal lesion. Often, serous or bloody discharge from the nipple is observed. Peripheral papilloma's are smaller in size, often multiple, and usually asymptomatic [28-29]. Mammography can show normal results or findings like dilated ducts, retrosternal masses, or clustered pleomorphic microcalcifications, indicating increased malignancy risk. Ultrasound typically reveals well-defined nodules or small masses in dilated ducts, with potential internal vascularization noted on Colour Doppler [29]. On MRI, papillary lesions may appear as well-defined masses with marked enhancement or as irregular masses associated with dilated ducts. The presence of multiple papilloma's in the periphery is more likely to be associated with ADH and/or DCIS compared to solitary papilloma's within the duct [30]. In general, papillomatous lesions without atypia are benign or borderline lesions [31]. Histological upgrading rate is around 0-12% [3]. Abnormal unilateral nipple discharge and papillary lesions on imaging (solid-cystic mass or small mass within a dilated duct) suggest the use of VAB for sampling. If subsequent CNB indicates an intraductal papillary lesion without atypia or ADH, VAB or VAE with close patient follow-up is recommended. However, if ADH is present, further surgical excision of the lesion is necessary, especially for large papilloma's or when VAB is not feasible [3, 31].

5.6. Cellular Fibroepithelial Lesions

Cellular fibroepithelial lesions include cellular fibroadenomas (B2) and phyllodes tumours (B3). Differentiation between these entities on core biopsy may be challenging due to sampling limitations. Features such as stromal hyperplasia, cellular fragmentation, increased mitotic count, and marked atypia of the stromal cells suggest the presence of a phyllodes tumour, resulting in the classification of the lesion as a B3 lesion [11]. The differential diagnosis of fibroadenomas from phyllodes tumours is usually difficult with CNB due to overlapping histological features, even when strict histopathological criteria are applied [11]. Imaging-wise, fibroepithelial tumours appear as nonspecific, round or oval, lobulated, well-defined lesions. A radiolucent halo may also be present, particularly in cases of foliate tumours. Phyllodes tumour (PT) is a rare benign tumour (<1% of breast tumours) with rapid growth, usually a palpable-mobile mass which may also cause ulceration of the overlying skin [32]. Imaging typically reveals oval or lobulated masses, occasionally with cystic components. It appears as a high-density mass with irregular borders, usually lobulated/oval, or microcalcifications on mammography [32]. Microcalcifications are observed in approximately 10% of cases [11]. On ultrasound as a submucosal lesion with heterogeneity in the interior [32]. PTs, even when benign, require surgical excision with clear margins due to their potential for local recurrence and, in borderline or malignant forms, metastatic spread. Local recurrence rates are high, commonly reported between 10–17% for benign, 14–25% for borderline, and 23–30% (up to 40% in some studies) for malignant PTs. Distant metastasis is almost exclusive to malignant phyllodes tumours [33-34]. While rare overall, about 9%–27% of malignant forms may develop metastasis, typically via the hematogenous route to the lungs (66%) or bones (28%) [33-34]. PTs necessitate a distinct treatment approach, primarily surgical excision with wide margins, due to their tendency to recur, even

when benign. It is also recommended that fibroepithelial lesions exceeding 3 cm be completely removed to exclude a papillary tumour [11]. However, recent studies suggest that this is not necessary, especially if the result of the CNB or VAB is fibroadenoma regardless of size [35]. It appears that there is now a general consensus that the growth rate of a fibroepithelial lesion may be a more useful criterion for excision than size alone [36]. Nevertheless, in cases where the presence of a phyllodes tumour cannot be ruled out, the recommendation is surgical excision of the tumour [3, 36].

5.7. Mucocele-Like Lesions and Rare Lesions

Mucocele-like lesions are characterized by cystic spaces filled with mucin and may be associated with ADH, DCIS, or mucinous carcinoma [37]. Imaging findings often include hypoechoic lesions, complex cystic lesions or microcalcifications and are not conclusive when it comes to distinguishing them from malignant mucinous carcinomas [37-38]. This distinction is made primarily through immunohistochemical staining. When no epithelial atypia is identified, upgrade rates are low (approximately 2%), and close imaging surveillance may be considered. However, the presence of ADH or DCIS within the lesion significantly increases upgrade risk and necessitates surgical excision. Their management include close follow-up if clear lesion and excision is advised if ADH/DCIS co-exist [3, 37, 39]. Rare B3 entities such as Aden myoepithelioma, micro glandular adenosis, spindle cell lesions, and myofibroblast Oma exhibit variable biological behaviour and usually present as masses. The likelihood of histological upgrading for these lesions has not been determined, as there are insufficient data. Due to limited evidence and unpredictable malignant potential, surgical excision is generally recommended to ensure complete histological evaluation [3, 11].

6. Discussion

B3 breast lesions are lesions of uncertain malignant potential, due to the high probability of their upgrading to cancerous lesions in the final surgical specimen. They fall in a “gray area” between benign and malignant, making diagnosis and treatment complicated. Imaging methods like mammography, ultrasound, and MRI help but are not always enough to differentiate between types [16]. Biopsy methods, including CNBs and VAB, are necessary but also have limitations, such as potential sampling errors. Biopsy results and imaging can differ, complicating decision-making. Management of B3 lesions evolves with advancements in imaging and biopsy techniques, incorporating lesion type, atypia presence, biopsy method, and patient characteristics. The oncology board significantly influences final decisions. Although B3 lesions are typically benign, their uncertain malignant potential necessitates a personalized approach. Our cohort’s 20% upgrade rate aligns with reported rates of 10% to 35% [4-6]. An example of reported upgrade rates of each subtype as presented by Rubio et al. is featured below Table 4.

This variability reflects differences in lesion subtype distribution, sampling adequacy, and criteria for radiologic–pathologic concordance. ADH consistently demonstrates the highest upgrade risk among B3 lesions, with pooled analyses reporting rates between 15% and 30% [6, 11]. Lucioni et al. (2020) found a 28% overall rate of B3 lesion upgrading post-VAB, with ADH at 41%. B3 subtypes with cellular atypia present a notably higher malignancy risk, aligning with our study [40]. Our observed rate of 29.16% further supports the recommendation for surgical excision in most ADH cases, particularly when lesion size exceeds 15 mm or when imaging–pathology discordance is present. Management of B3 lesions is complicated by factors such as microcalcifications, leading to uncertainty in diagnosis and treatment. A multidisciplinary approach is essential for accurate assessment. Individualized management is based on lesion size, imaging results, histopathology, and patient risk factors, with options ranging from careful observation to invasive techniques like VAE or surgical resection to exclude malignancy [16].

In our sample, it was found that B3 lesions have an approximate 20% probability of upgrading to malignancy, aligning with existing literature that reports upgrade rates between 10-35%. Notably, even with invasive malignancy, patient prognosis remains positive due to early detection and favourable biological markers. This was evidenced by cases of atypical intraductal hyperplasia wherein invasive ductal carcinoma was detected post-surgical biopsy, showcasing incipient invasion (<1 cm) by hormone-dependent ductal carcinoma with a low Ki-67 proliferation index (<10%), indicating very good prognosis. Additionally, all 50 women in the study participated in regular annual mammograms and ultrasounds for five years, as literature indicates a significant risk of subsequent ipsilateral or contralateral breast cancer following a B3 lesion diagnosis.

The study reinforces Bellini et al. (2020) findings on 731 women with B3 lesions undergoing surgical or vacuum-assisted excision. After 52.5 months, 9.2% developed breast cancer, with atypical ductal hyperplasia (ADH) showing the highest progression risk 39.8% progressing to carcinoma and 13.6% developing cancer during follow-up. ADH warrants careful management due to significant risks [41]. The current study’s ADH upgrade rate of 29.16% highlights the need for close monitoring of ADH patients and complete lesion resection. Bellini et al. detail B3 subtype distributions linked to imaging findings, particularly microcalcifications, which serve as vital predictors. They validate VAE for diagnosis and treatment, comparing practices between public and specialized centres [41]. B3 lesions must be identified and removed via surgery or VAE per guidelines. Despite increased recommendations for VAE for assessing B3 lesions, many public hospitals lack this system, necessitating surgical excisions for further management when required. This issue highlights the limitations within public healthcare facilities.

The need for more specific guidelines, regarding the proper management of B3 lesions was first met in 2018, when the NHS Breast screening multidisciplinary working group presented a review and guidance on the management of B3 lesions of the breast [11]. VAB is recommended for the thorough examination of most B3 lesions, aiming for extensive sampling. The 2023

conference emphasized that open excision is preferred for ADH lesions, which cannot be reliably differentiated from low-grade DCIS via needle biopsies [6]. Similarly, the third International Consensus Conference suggested that lesions identified by needle biopsy as phyllodes tumours be removed openly, whilst lobular neoplasia, papillary lesions and radial scars can be managed with vacuum-assisted excision. In 2024, EUSOMA, EUSOBI, ESP (BWG), and ESSO collaborated and released the European guidelines for the diagnosis, management, and follow-up of breast lesions with unknown malignant potential a summary of which is presented in Table 5 [3].

The 2024 guidelines emphasize using minimally invasive methods or no intervention to reduce overtreatment, lessen patient discomfort, and lower healthcare costs. The most recent European guidelines were published by EUSOMA in 2024 and focus on personalizing treatment based on histological subtype, imaging and pathological correlation, as well as risk upgrade risk. According to these guidelines, lesions such as papilloma's without atypia, radial scars, and FEA can be treated with VAE and follow-up, while lesions with atypical features, such ADH and LIN, should be referred for surgical excision [3]. A comparison of the guidelines for the management of B3 breast lesions reveals significant differences in both the therapeutic approach and the level of acceptance of less invasive techniques such as VAE. Malignant transformation normally happens over a long period of time [42].

In 2025, Corsi et al. focused on how to apply the EUSOMA (2024) guidelines for managing B3 breast lesions at a breast centre in Italy. Their retrospective study evaluated 354 patients with various B3 findings, including papilloma's, ADH, actinic scars, FEA, lobular neoplasia (LIN/LCIS), and phyllodes neoplasms. Its aim was to assess the adherence of medical procedures to recently introduced EUSOMA guidelines and to investigate the frequency of cancer advancement. It found that 46.3% of cases underwent unnecessary surgical excisions, even though conservative options were available. Only 9.1% of surgeries showed malignancy, and the overall upgrade rate to cancer was around 13%, confirming many lesions are benign. [43]. This study also revealed a notable discrepancy between initial biopsies and final histological findings, with a disagreement rate of 43.2%. Agreement was high for lobular carcinoma in situ (LCIS) at 88%, but low for FEA at 18% and radial scars/sclerosing complexes at 42%. Cancer conversion was noted in both in situ (31 cases) and invasive carcinomas (12 cases), along with four malignant papillary neoplasms. Additionally, the research identified key prognostic factors for malignant progression, including older age, post-menopausal status, larger lesion diameter on imaging, and higher BI-RADS categories (4 and 5) [43]. The compliance with guidelines differed by lesion type; papilloma's had 64% compliance, while LCIS cases only 26%. According to the study, enhancing collaboration among specialists and adhering to EUSOMA guidelines is crucial for reducing unnecessary surgeries and improving patient care quality [43].

The UK national breast screening program emphasizes complete removal documentation and flexibility in clinical decisions, permitting VAE usage for papilloma's and radial scars without atypical features, but recommending surgical excision for suspicious cases or atypical hyperplasia [8]. Depending on the patient's risk profile and the extent of the first excision, multiple approaches are used in the US. As long as total removal and sufficient radio pathological correlation are attained, the American Society of Breast Surgeons is in favour of using VAE for low-risk lesions (such as FEA and non-atypical papilloma's). Conversely, it suggests surgery in cases of atypical findings or inconsistent imaging [44]. We recommend annual bilateral mammography and breast ultrasound for at least 5 years in patients with a history of B3 lesion excision to ensure early breast cancer diagnosis, noting a 9.2% incidence of metachronous carcinoma [4].

The European approach, particularly via EUSOMA, emphasizes personalized treatment and avoiding overtreatment, while France Favors more invasive methods and the U.S. opts for selective observation. Effective implementation requires a multidisciplinary team to assess imaging and histopathology, reducing overtreatment and underdiagnosis. Research on the genetic aspects of B3 breast lesions aims to improve diagnosis and treatment through genomic analysis, aiding in distinguishing benign from malignant potential lesions [16]. AI is set to transform the treatment of B3 breast lesions by combining genomic databases with imaging and clinical data. This integration increases the detection of malignant lesions and risk assessment, providing for a better understanding of individual patient risk factors and lesion features that can be used to guide treatment decisions.

Patients with B3 lesions may benefit greatly from improved early identification, less overtreatment, and more individualized care when genetic insights and AI's predictive capabilities are combined [16]. Future efforts should focus on refining risk stratification models and expanding access to minimally invasive excision techniques to optimize patient outcomes while minimizing overtreatment.

Table 4: Reported Upgrade Rates to Malignancy for the Most Common B3 Lesions (Rubio et al) [3].

B3 Lesion	Overall Upgrade to Malignancy (%)	Upgrade to DCIS (%)	Upgrade to Invasive Carcinoma (%)
ADH – Atypical Ductal Hyperplasia	0–50	20	5
ALH – Atypical Lobular Hyperplasia	12	9	2
cLCIS – Classic Lobular Carcinoma in situ	22	15	7
FEA – Flat Epithelial Atypia	0–5	1	2
RS/CSL – Radial Scar / Complex Sclerosing Lesion	1–10	1–5	1
IDP – Intraductal Papilloma	<10	5	2

Table 5: Summary of Management Recommendations for B3 Lesions According to Current European (EUSOMA) Guidelines, 2024 [3].

B3 Lesion	Diagnosis by CNB or VAB – Recommended Management
ADH – Atypical Ductal Hyperplasia	Open surgical excision when the lesion is radiologically visible. Vacuum-assisted excision (VAE) under imaging guidance may be considered for lesions <15 mm. For lesions >15 mm, open surgical excision is generally recommended, although VAE may be appropriate in selected cases.
FEA – Flat Epithelial Atypia	If histology shows pure FEA without ADH and radiologic–pathologic concordance is confirmed, no further intervention is required. In cases associated with ADH, open surgical excision or VAE is recommended. If vacuum-assisted biopsy (VAB) does not completely remove microcalcifications, further management with open excision or VAE is indicated.
LN – Lobular Neoplasia	VAE is recommended for complete lesion removal in cases of classic lobular carcinoma in situ (LCIS), followed by surveillance when radiologic–pathologic concordance is present. In cases of imaging–pathology discordance, further open excision or VAE is required. Contralateral or bilateral mastectomy is reserved for selected high-risk patients.
PL – Papillary Lesions	Open surgical excision is recommended in cases associated with ADH. Vacuum-assisted biopsy (VAB) is appropriate in the absence of atypia or ADH, provided complete lesion removal is achieved.
RS – Radial Scar / Complex Sclerosing Lesion	In the absence of atypia, further management with VAB is recommended. When atypia is present, open surgical excision or VAE is advised.
Rare lesions (e.g., adenomyoepithelioma, microglandular adenosis, myofibroblastoma, schwannoma, etc.)	Surgical excision only, due to limited available evidence and uncertain malignant potential.

6.1. Limitations

This study is constrained by its retrospective design, single-centre nature, and moderate sample size, which limit statistical power and generalizability. It highlights the necessity of biopsy despite challenges in sampling and malignancy assessment and notes that many public institutions lack a vacuum aspiration system, necessitating surgical excision. Infrastructure enhancements are required for guideline implementation. Nevertheless, the study offers useful real-world data from a public breast hospital, reflecting actual clinical decision-making processes.

7. Conclusions

The implementation of breast screening and advancements in imaging techniques contribute to the early detection of B3 lesions, which are diverse subclinical abnormalities with varying malignant potential. The upgrade rate observed was 20%, with ADH showing the highest risk. Malignancy development typically involves early infiltration by hormone-dependent cancers with favourable prognoses. Therefore, a personalized management approach based on the statistical likelihood of upgrading B3 lesions is essential, as identified tumours were generally early-stage and biologically favourable (high expression of estrogenic and progesterone receptors, cell proliferation index <10%, Her-2 negative).

8. Statement of Ethics

This was a retrospective observational study based on the review of archived clinical and pathological records of patients diagnosed with B3 breast lesions between September 2019 and September 2024 at the Breast Unit of General Hospital of Thessaloniki “Agios Pavlos”. Patient management and treatment were not altered in any way for the purposes of this study. All data were anonymized prior to analysis. According to institutional policy, formal ethics committee approval was not required for this retrospective audit of existing anonymized clinical data. The study was conducted in accordance with the ethical principles of

the Declaration of Helsinki and its later amendments. Patients contacted for follow-up provided verbal consent for the use of their anonymized clinical information for research purposes.

9. Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

10. Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to institutional and patient confidentiality requirements but are available from the corresponding author on reasonable request.

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