Review

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Navigating the Uncertainty of B3 Breast Lesions: Diagnostic Challenges and Evolving Management Strategies

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Abstract: B3 breast lesions, classified as lesions of uncertain malignant potential, present a significant diagnostic and therapeutic challenge due to their heterogeneous nature and variable risk of progression to malignancy. These lesions, which include atypical ductal hyperplasia (ADH), papillary lesions (PL), flat epithelial atypia (FEA), radial scar (RS), lobular neoplasia (LN), and phyllodes tumors (PT), occupy a "grey zone" between benign and malignant pathologies, making their management complex and often controversial. This article explores the diagnostic difficulties associated with B3 lesions, focusing on the limitations of current imaging techniques, including mammography, ultrasound, and magnetic resonance imaging (MRI), as well as the challenges in histopathological interpretation. Core needle biopsy (CNB) and vacuum-assisted biopsy (VAB) are widely used for diagnosis, but both methods have inherent limitations, including sampling errors and the inability to determine malignancy in some cases definitively. The therapeutic approach to B3 lesions is nuanced, with treatment decisions strongly influenced by factors such as lesion size, radiological findings, histopathological characteristics, and patient factors. While some lesions can be safely monitored with watchful waiting, others may require vacuum-assisted excision (VAE) or surgical excision to rule out malignancy. The decision-making process is further complicated by the discordance between the BIRADS score and biopsy results, as well as the presence of additional risk factors, such as microcalcifications. This review provides an in-depth analysis of the current diagnostic challenges and treatment strategies for B3 lesions, emphasizing the importance of a multidisciplinary approach to management. By synthesizing the most recent research, the article aims to provide clinicians with a clearer understanding of the complexities involved in diagnosing and treating B3 breast lesions while highlighting areas for future research, such as Artificial Intelligence and Genomics, to improve diagnostic accuracy and patient outcomes.

Keywords: B3 breast lesions; diagnosis; imaging techniques; biopsy methods; breast surgery

1. Introduction

Breast cancer is the most frequently diagnosed and the second leading cause of oncological mortality in women. The treatment of breast cancer involves a comprehensive, multidisciplinary strategy, including surgical oncology, radiotherapy, and medical oncology, which, together with the implementation of screening programs, have been correlated with a decline in breast cancer-related deaths. Radiological screening for breast cancer often leads to a biopsy to obtain a diagnosis. Imaging assessments, typically mammography, breast ultrasound, or both, are employed to identify the lesions requiring biopsy and plan the biopsy technique and procedure. Abnormalities detected on imaging are classified based on their probability of malignancy according to the Breast Imaging-

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Reporting and Data System (BI-RADS). A histological diagnosis can be achieved through either CNB or VAB. Biopsy findings can be categorized into five categories: B1 (normal breast tissue or inadequate sample), B2 (benign lesion), B3 (uncertain malignant potential), B4 (high suspicion for malignancy), and B5 (malignant lesion).

The B3 category, whose incidence varies between 3% and 21% with higher rates in the screening-age population [1,2], consists of atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), classical lobular neoplasia (LN), papillary lesions (PL), radial scar (RS) and benign/borderline phyllodes tumors (PT) and other miscellaneous entities such as fibroepithelial lesion (FEL), mucocele-like lesions, and apocrine adenosis.

Because they occupy a "grey zone" between benign and malignant conditions, their diagnosis and management can be complex and often controversial. Diagnostic evaluation of B3 lesions is particularly challenging. Imaging techniques such as mammography, ultrasound, and MRI provide valuable information but are often insufficient to distinguish benign from malignant lesions. Biopsy, including CNB and VAB, is essential but has limitations, such as sampling errors and difficulty accurately assessing malignant potential. Discrepancies between biopsy results and imaging findings further complicate decision-making, as apparently benign lesions may exhibit malignant features and vice versa. Furthermore, B3 lesions are often associated with risk factors such as microcalcifications, which complicate imaging interpretation and influence management decisions. This uncertainty, combined with the diverse nature of B3 lesions, highlights the importance of a multidisciplinary approach involving radiologists, pathologists, and surgeons for accurate diagnosis and optimal treatment planning.

Management strategies for B3 lesions are individualized, considering lesion size, radiological findings, histopathological features, and patient risk factors. Some lesions can be safely monitored with watchful waiting, while others may require more invasive interventions such as VAE or surgical excision to rule out malignancy.

In addition to these ongoing challenges, new technologies, such as artificial intelligence (AI), are emerging in breast cancer research. AI shows promise in improving diagnostic accuracy and imaging interpretation. When combined with molecular and genetic profiling, AI could provide proper insights into the malignant potential of B3 lesions, enabling more precise and personalized treatment strategies.

This study aims to summarize, category by category, the various recommendations related to surgical treatment, radiological management, and the upgrade rate specific to each histological subtype, highlighting the need for a multidisciplinary approach and the potential of new tools to improve diagnostic accuracy and patient outcomes.

2. Atypical Ductal Hyperplasia (ADH)

2.1. Radiology and Pathology

ADH is one of the most frequently recognized B3 lesions in breast pathology. It often correlates with grouped microcalcifications, nodules, or atypical densities visible on mammograms. Predominantly, ADH is detected in cases where calcifications appear on mammograms, constituting a significant majority (81.6%), while, in other studies, the prevalence of ADH detected alongside microcalcifications is even higher (86%) (3). The lesion has non-specific characteristics on MRI like a focal non mass area or a small irregular mass. Histologically, ADH is a small, low-grade, clonal intraductal lesion, typically measuring 2 mm in maximum diameter or involving only segments of a terminal ductal-lobular unit.

2.2. Upgrade Rate

Distinguishing ADH from low-grade DCIS relies solely on lesion size, with lesions exceeding 2 mm classified as low-grade DCIS. Since this determination cannot be reliably made through preoperative CNB or VAB, additional lesion sampling becomes necessary via VAE or surgical removal [4].

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Consistently, published literature underscores that the likelihood of ADH upgrading to malignancy is higher with smaller samples, such as those obtained using 14 G cores, compared to VAB specimens. The upgrade rate for ADH ranges from 18% to 87% for 14 G needles, contrasting with 10% to 39% for 11 or 9 G samples, with a combined positive predictive value of 21% from vacuum-assisted sampling. Fundamentally, it's not unexpected that offering a larger tissue sample decreases the chances of missing a diagnosis of DCIS or invasive carcinoma. [5].

Numerous studies have documented an upgrade rate of ADH to malignancy ranging from 5% to 50%. Factors associated with an increased risk of this upgrade include obtaining a smaller amount of biopsy tissue, mainly through CNB, absence of correlation between calcifications in ADH and imaging results, persistence of calcifications after VAB, lesion size exceeding 15mm on imaging, patient age over 50 years, and the presence of multifocal*ity* in the ADH biopsy specimen [4,6].

2.3. Current Indications

The 3rd International Consensus Conference on B3 lesions, as recently published, advocates for open surgical excision following an ADH diagnosis obtained via CNB and also suggests this as the preferred course of action if ADH is diagnosed through VAB. However, in cases of small or focal ADH lesions observed on imaging and after thorough discussion within a multidisciplinary team, a second VAE procedure can also be considered [7]. According to guidelines from the UK National Health Service Breast Screening Programme (NHS BSP) Working Group, secondary VAE is recommended for further detailed assessment of most B3 lesions, regardless of whether they were initially diagnosed via CNB or primary diagnostic VAB [2].

European guidelines established by EUSOMA, EUSOBI, ESSO, and ESP [6] also advocate for surgical excision in cases of ADH diagnosed by CNB or VAB, mainly if the lesion is visible on imaging (evidence/grade I/A). For lesions smaller than 15 mm, image-guided VAE may be considered (evidence/grade III/B). If the lesion diagnosed by CNB or VAB is more significant than 15 mm, surgical excision is recommended (evidence/grade I/A), with VAE being a potential consideration (evidence/grade III/B).

3. Papillary Lesion (PL)

3.1. Radiology and Pathology

PL are commonly seen in radiology as a well-circumscribed nodule with or without cystic features, or as a small lump within an enlarged duct, occasionally exhibiting peripheral vascularization on ultrasound. Mammography may depict normal findings or reveal clustered calcifications in 25% of cases. Single lesions are frequently located in the retroareolar region, whereas multiple lesions are commonly found in the periphery [8]. On MRI, PL typically manifest as circumscribed, solid enhancing lesions; however, they may also exhibit irregular shapes and indistinct margins [9]. These lesions, characterized by benign papillary architecture comprising fibrovascular cores covered by benign luminal epithelium with associated myoepithelium, are typically classified as B3 due to potential intralesional heterogeneity.

3.2. Upgrade Rate

The presence of associated epithelial atypia is the most significant predictor for the upgrade to malignancy, which should be diligently sought and documented. When a PL lacks epithelial atypia, the probability of malignancy in the subsequent excision specimen is low, varying from 9% to 13.2%. On the other hand, when atypia is present, the upgrade rate significantly rises, ranging from 36% to 47.8% (10). Recent studies have reported a median upgrade rate for PL without atypia to DCIS or IC of only 2.3%; in contrast, PL with atypia showed a markedly higher upgrade rate to DCIS or IC, with a median of 26.9% [11,12]. A recent meta-analysis by Zhang et al. [13] identified ten predictors of upgrade, including BI-RADS 4C or 5 classification, the presence of a mass or calcifications on mammography, bloody nipple discharge, radio-pathological mismatch, peripheral lesion site,

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palpable lump, and lesion size over 1 cm. Upgrade rates linked to these factors ranged from 7.3% to 31.1%.

3.3. Current Indications

Retrospective studies suggest that if CNB yields a PL without atypia, VAB is a viable strategy. In contrast, surgical excision is warranted if CNB or VAB yields a papilloma with atypia [14]. European guidelines [6] advocate surgical excision for PL with atypia, while those without atypia can be safely managed with VAB and, if entirely excised, imaging surveillance. The 3rd Consensus Conference [7] focuses solely on pure PL without atypia and equally recommends surgical excision or therapeutic VAE following a CNB-based PL diagnosis.

4. Radial Scar

4.1. Radiology and Pathology

RS usually appears on mammography as a stellate lesion or an area of architectural distortion with a radiolucent core, sometimes accompanied by calcifications. Tomosynthesis aids in identifying RS on mammograms [15]. The appearance can vary on ultrasound, ranging from no distinct correlation to a hypoechoic irregular mass. Moreover, MRI findings may exhibit variability and lack specificity. RS may present without any MRI correlation, displaying no enhancement, or manifest as mass lesions with irregular margins or non-mass enhancement [16]. These imaging features warrant caution, as RS can mimic invasive breast cancer. Histologically, central fibroelastosis is surrounded by compressed glandular structures and cysts, sometimes associated with sclerosing adenosis, benign epithelial hyperplasia, atypia, or malignant changes [17].

4.2. Upgrade Rate

The upgrade rate of RS is strongly dependent on the presence of concurrent atypical epithelial proliferation. Reported data on the upgrade from RS to DCIS or invasive carcinoma vary significantly, ranging from 0% to 40%. [18]. The quantity and size of the biopsy samples also influence the upgrade rate. For instance, Farshid et al. [19], in a systematic review and meta-analysis, demonstrated higher upgrade rates with CNB (5%) compared to VAB (1%). Numerous studies have shown that RS upgrade rates increase in the presence of atypia in the biopsy specimen. Racka et al. [17] reported a 9% rate of malignant progression following surgical removal of RS without atypia on CNB, whereas lesions with atypia had an upgrade rate of 36%. According to the NHSBSP Guidelines, the upgrade rates in cases with atypia were 36%, compared to 10% for those without [2]. Similar findings were observed in other studies, revealing upgrade rates of 28% for RS with atypia compared to 4% without atypia [20]. Additionally, a recent survey by Quinn et al. involving a large patient cohort reported upgrade rates of 9% in RS without atypia versus 33% in RS with atypia [21].

4.3. Current Indications

European guidelines [6] advocate for VAE in RS without atypia identified through CNB and surgical excision in RS presenting with atypia, although VAE could be contemplated. The 3rd International Consensus Conference noted that following the detection of RS without atypia on CNB, in conjunction with imaging size, 58% of the panel supported therapeutic VAE. In instances where the target lesion was entirely excised, most of the panel (82%) preferred radiological follow-up after diagnostic VAB or VAE [7]. The AGO advises against operative excision if the lesion measures less than 5 mm or is nearly completely removed by VAB. Further re-excision is unnecessary if the lesion borders the resection margin [22]. The NHSBSP suggests comprehensive sampling with VAE, and depending on the outcomes, RS without atypia necessitates no further monitoring, with patients reverting to routine mammographic follow-up every 3 years (routine mammographic screening). For RS with atypia, either open excision or annual mammographic follow-up should be considered, contingent upon the decision of the multidisciplinary team [2].

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5. Flat Epithelial Atypia (FEA)

5.1. Radiology and Pathology

FEA is often observed with other suspicious lesions and shares imaging features with both malignant and benign lesions. When observed on mammography, it manifests as clustered calcifications, while on ultrasound, it may manifest as an irregular hypoechoic mass. In MRI scans, FEA might be concealed or manifest as either a mass or a non-mass area exhibiting nonspecific characteristics [23]. Histologically, FEA belongs to the columnar cell lesions spectrum of the breast, which includes columnar cell alteration and hyperplasia, both lacking atypia; however, the presence of atypia classifies it as FEA [24].

5.2. Upgrade Rate

The upgrade rate for FEA remains uncertain. FEA is often associated with ADH, LN, and low-grade DCIS, with the likelihood of progression being closely connected to concurrent proliferative lesions [23]. However, the risk of progressing to carcinoma is minimal for isolated FEA. Wahab et al. [25] conducted the most comprehensive meta-analysis, including 42 studies with 2482 cases, and found an upgrade rate for pure FEA on CNB after surgical excision of 5%. In contrast, Verschuur-Maes et al. [26] reported a 17% upgrade rate in a systematic review. Other recent reviews and meta-analyses have shown that the upgrade rate following surgical excision ranged from 1% to 16% [27,28].

Like other B3 lesions, FEA diagnosed on CNB requires further sampling because detecting coexisting proliferative lesions elevates the upgrade rate. If more than 90% of calcifications have been excised, recent data, including individual trials, advocate therapeutic VAE with radiological monitoring [25,29]. Unfortunately, these studies only analyze cases of microcalcifications and disregard other radiological findings.

5.3. Current Indications

Several international guidelines advocate for a single case discussion or radiological surveillance as the preferred approach upon FEA diagnosis on VAB. Only situations demonstrating pathological-radiological incongruity, mass lesions, or cases with many residual calcifications post-biopsy should undergo surgical excision [30,31]. Age, imaging, additional breast cancer risk factors, lesion size, and correlations with calcification, in addition to the radiological-pathological alignment of FEA, constitute critical elements for informed decision-making [32]. In line with the WHO Working Group, observation could be deemed an acceptable management strategy in cases of pure FEA if radiological-pathological correlation is assessed [24]. The 3rd International Consensus Conference [7] suggests VAE or surgical excision upon FEA detection on CNB and surveillance if over 90% of the target lesion is removed on VAB. According to AGO guidelines, surgery may be avoided in instances of small lesions or nearly complete (>90%) eradication of calcifications [30]. NHS BSP recommends surgery solely in cases of radio-pathological discordance [2]. European guidelines [6] advocate surveillance in cases of pure FEA diagnosed on CNB or VAB concordant with imaging, VAE or surgical excision in instances of FEA with ADH diagnosed on CNB, VAE or surgical excision in cases of FEA with ADH diagnosed on VAB if not all calcifications are removed, or in cases of pathological-radiological incongruity.

6. Lobular Neoplasia (LN)

6.1. Radiology and Pathology

LN is typically not detectable on mammograms and is often an incidental finding during biopsies. It generally presents as a non-palpable, inconspicuous lesion. However, in rare instances, it may be associated with microcalcifications in the mammogram and occasionally as a mass or focal area of non-mass enhancement on MRI [33]. Classical LN appears as a low- to intermediate-grade, uniform, intralobular epithelial proliferation of non-cohesive cells, often with prominent

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intracytoplasmic lumina. It is a B3 lesion deemed a non-obligate precursor to breast cancer, and based on the extent, the WHO classifies it into atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). Non-classical LN (such as pleomorphic, apocrine, or florid LCIS) are considered potential differential diagnoses and are categorized as B5a lesions, which require distinct management due to their higher rate of progression [24].

6.2. Upgrade Rate

ALH and LCIS are lesions that act as risk factors, increasing the relative risk by 8 to 10 times compared to the general population [34]. Reported upgrade rates following an LN diagnosis from breast biopsy show a wide range, from 0% to 50% [35]. Higher upgrade rates, between 13 and 18%, are observed for LN associated with mass lesions or calcifications [36]. The strongest predictor of an upgrade to invasive cancer is a radiological mismatch, such as when a suspicious mass is identified on imaging, but the histopathologic diagnosis from CNB reveals LN. However, the upgrade rate is generally lower when the diagnosis is made through VAB. Moreover, there is evidence of an upgrade of these lesions when there is coexisting or adjacent DCIS and/or invasive carcinoma; if the target imaging lesion is attributed to another histological entity rather than LN, the upgrade rate is notably lower [37]. A recent meta-analysis that included 16 studies meeting the analysis criteria reduced the upgrade rate, ranging from 3.1 to 5.8% [38].

6.3. Current Indications

Several studies indicate that in the event of LN diagnosis on CNB with radiological-pathological concordance, surgical excision may not be necessary as the upgrade rates are below 5% [35]. The TBCRC 20 trial documented a 13.9% incidence of cancer development after 10 years without affecting breast cancer-specific survival in women diagnosed with LCIS who did not undergo further surgery [39]. The 3rd International Consensus Conference [7] recommends VAE as the step in cases of LN diagnosis on CNB. It does not advocate additional intervention if the target lesion is removed through VAB. European guidelines [6] advise performing VAB/VAE if LN diagnosis is obtained via CNB, and surveillance is deemed appropriate if there is a pathological-radiological agreement. Surgical excision is only considered in cases of radiological-pathological discrepancy after CNB/VAB diagnosis; mastectomies are no longer recommended unless additional high-risk factors, such as a significant family history or pathogenic gene mutations, are present. While in the past, most patients with classic LCIS underwent a mastectomy, today, 50-80% of women with LN diagnosis undergo only surgical excision, and mastectomies are performed in only 10-20% of cases [40].

7. Phyllodes Tumors (PT)

7.1. Radiology and Pathology

PT radiologically appears as a well-defined, round, or oval mass without calcifications. On ultrasound, it typically appears as a progressively enlarging fibroadenoma; occasionally, it may display septa indicative of PT, but these are present in only a small percentage of lesions [41]. MRI features of benign phyllodes are similar to fibroadenomas, often with more irregular margins and heterogeneous content. Moreover, MRI has limited predictive value for distinguishing malignant from benign PT [42]. Histologically, PT is classified as a fibroepithelial lesion composed of epithelial and stromal components, including the more common fibroadenoma. It can be challenging to differentiate fibroadenomas from PT using CNB due to the similar histological characteristics. Usually, PTs have a more cellular stroma, stromal overgrowth, fragmentation, and mitoses. Marked atypia of stromal cells is rarely seen in cores, and if present, there are usually other features indicating PT. According to characteristics such as margins, stromal cellularity, mitotic activity, and the ratio of epithelial to stromal components, the WHO [24] categorizes PT into benign, in differential diagnosis with fibroadenomas, borderline, and malignant. Malignant PT are classified as B5 lesions, whereas benign and borderline types are classified as B3.

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7.2. Upgrade Rate

The upgrade rate to breast cancer following a diagnosis of PT on CNB or VAB is relatively rare. In the literature, the management of these lesions often focuses on the upgrade rate referred to the proportion of phyllodes tumors identified in the final histological assessment when a biopsy provided an inconclusive result where "a phyllodes tumor could not be excluded." There is significant variation in these reports; for example, Rakha et al. [17] found that 37% of fibroepithelial lesions identified on biopsy were ultimately diagnosed as phyllodes tumors upon final histological evaluation, but only one out of 52 lesions were malignant.

7.3. Radiology and Pathology

Some guidelines recommend the excision of fibroepithelial lesions over 3 cm in size to rule out PT. In contrast, others consider the growth rate of the lesion as a more helpful criterion for excision. The distinction between benign fibroadenomas and PT can be challenging for radiologists and pathologists, and even though biopsies with larger gauge needles can be considered to achieve this differentiation, surgical excision is the most appropriate solution when a PT cannot be ruled out on biopsy. The 3rd International Consensus Conference [7] recommends excision after CNB diagnosis of PT, and if the diagnosis is obtained on VAB, follow-up is justified if the lesion is radiologically removed.

8. Discussion

B3 breast lesions include a diverse group of pathological conditions with indeterminate malignant potential. These lesions may be linked to more severe conditions like ductal carcinoma in situ (DCIS), pleomorphic lobular carcinoma in situ, or invasive carcinoma (IC). The probability of progression to malignancy differs widely among various types of B3 lesions, with reported upgrade rates ranging from 10% to 35% [1].

Managing B3 lesions poses a significant challenge for clinicians. With the increasing use of preoperative biopsies in everyday practice, there is a growing need for careful decision-making regarding whether to proceed with surgical excision, VAE, or ongoing surveillance.

In recent years, there has been a shift towards minimizing surgical interventions, mainly due to the introduction of percutaneous VAE. This less invasive technique allows for the complete removal of smaller B3 lesions, reducing the need for more extensive surgery. According to the 2018 NHS Breast Screening Multidisciplinary Working Group Guidance (2), most B3 lesions smaller than 20 mm should be managed using VAE. However, in clinical practice, recommendations often still favor surgical excision.

Numerous guidelines have been published concerning treating B3 lesions, each offering slightly different recommendations. The latest European guidelines, developed by EUSOMA, EUSOBI, ESSO, and ESP [6], advocate for a personalized approach based on factors such as atypia, lesion size, biopsy sample size, and patient preferences. Management options may include follow-up, VAE, or surgery, with decisions made within a multidisciplinary context.

The Third Consensus Conference [7] further supports this individualized approach. If a CNB identifies a B3 lesion, the panelists generally advise removal. There is unanimous agreement for lesions with atypical ductal hyperplasia (ADH) and near-unanimous consensus for those with flat epithelial atypia (FEA), lobular neoplasia (LN), papilloma with atypia (PL), phyllodes tumor (PT), and radial scar (RS). VAE is a suitable alternative to open excision in routine clinical practice in selected cases.

8.1. The Role of Artificial Intelligence (AI) and Genomics in B3 Lesions: Defining Future Perspectives

Incorporating AI and genomic analysis into the study of B3 lesions is essential for advancing our understanding and improving patient outcomes. The integration of these tools is poised to significantly enhance the landscape of diagnosis and treatment, facilitating a shift toward more accurate and individualized medical care. AI has been used in breast screening for decades.

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Nowadays, its use has broadly expanded to include supporting screening programs, increasing the detection of early-stage BC, and optimizing the cost-effectiveness of second-level procedures [43–45]. As Barinov et al. assessed, AI could be used as a qualitative integrated tool during the diagnostic pathway to support imaging in clinician's decision-making. Moreover, Mango et. Al demonstrated that the AI software KOIOS decreased inter- and intra-observer variability, improving accuracy in defining BI-RADS categories [46]. Considering the difficulty in finding an univocal approach toward B3 lesions, AI aims to play a transformative role in their management. AI algorithms, particularly those based on deep learning, can analyze mammograms, ultrasound, and MRI scans to detect and classify suspicious lesions more accurately. AI-based predictive models are being developed to stratify the risk of B3 lesions upgrading to malignancy. These models analyze various features from imaging and biopsy data, and they can help radiologists identify subtle features associated with B3 lesions and distinguish between low and high-risk ones [43], potentially offering a non-invasive approach or identifying high-risk cases that may require surgical intervention. So, they can assist clinicians in choosing between conservative management (e.g., surveillance or VAE) and surgical intervention based on risk assessment. These innovations may also lead to more personalized and cost-effective care for patients with B3 lesions. Browne et al. demonstrated that AI algorithms could provide a more reliable evaluation of BIRADS-3 cases: their data showed that many biopsies with this BIRADS could have been avoided [47], reducing costs and avoiding women undergoing unnecessary invasive procedures. Nevertheless, studies highlight that while AI tools are promising, their full potential is realized when used alongside expert clinical judgment, particularly in higher BIRADS cases where human contribution cannot be overridden due to ethical and medical responsibility reasons. [47,48]. It must also be underlined that data in the literature have some limitations; in fact, all existing studies are retrospective and mainly concern lesions with BI-RADS 4 or 5. Furthermore, there are no studies that concern surgical practice in the case of pre-operative B3 diagnosis and underline how AI can influence it. Therefore, new prospective and retrospective data are needed to thoroughly evaluate the integration between AI and surgery in B3 lesions.

Another emerging area of research is the genomic aspect of B3 breast lesions, which focuses on understanding their potential for malignancy. Genomic analysis can support imaging and histopathology to improve diagnosis, risk assessment, and management of these lesions. Identifying cancer-related expression patterns helps distinguish benign B3 lesions from those with malignant potential. High-risk B3 lesions, for example, may exhibit genetic aberration commonly found in low-grade DCIS (deletion of 16q and gain of 1q) [49]. Moreover, aberrant DNA methylation patterns in B3 lesions could indicate early steps toward malignancy [50]. AI has the potential to revolutionize the management of B3 breast lesions by integrating complex genomic datasets with imaging and clinical data. This comprehensive approach can enhance risk assessment, allowing for more precise identification of lesions with a higher likelihood of malignancy. By analyzing genomic profiles alongside traditional imaging techniques, clinicians can gain deeper insights into the biological behavior of these lesions. Such integration enables a more nuanced understanding of individual patient risk factors and lesion characteristics, potentially guiding treatment decisions. For example, AI algorithms could identify patterns within genomic data that signal a higher risk, prompting more aggressive management strategies. Additionally, improved risk stratification could optimize the use of resources, directing monitoring or interventions where they are most needed. Ultimately, leveraging AI's capabilities enhances diagnostic accuracy and paves the way for personalized treatment approaches, improving patient outcomes in the challenging landscape of B3 breast lesions. The integration of genomics and AI could transform B3 lesion management by developing non-invasive predictive models, identifying molecular pathways for chemoprevention in high-risk individuals, and offering clinicians real-time decision-making support. Combining genomic insights with AI's predictive power has great potential to enhance early detection, reduce overtreatment, and personalize care for patients with B3 lesions.

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9. Conclusion

B3 breast lesions, due to their uncertain malignant potential, represent a complex and evolving challenge in clinical practice. Their heterogeneous nature, combined with the limitations of current diagnostic tools, creates a "grey zone" that complicates the diagnosis and management of these lesions. Although valuable, imaging techniques such as mammography, ultrasound, and MRI often fail to provide definitive answers, and biopsy methods such as CNB and VAB have inherent limitations, including sampling errors and indeterminate results.

Resuming the various indications, surgical intervention is strongly recommended for ADH, but for lesions smaller than 15 mm, VAE may be considered. Surgery is indicated for PL with atypia; otherwise, PL without atypia can be safely managed with VABB and, if entirely excised, with imaging surveillance. For RS with atypia, open excision or VAE is indicated depending on lesion size and type of biopsy performed, while for RS without atypia diagnosed on CNB, VAE is displayed or, if diagnosed or completely removed on VABB, only mammographic follow-up. The upgrade rate for pure FEA is low enough to consider surveillance an effective management option, especially if diagnosed on VAB. Only situations demonstrating pathological-radiological discordance, mass lesions, cases with many residual calcifications post-biopsy, or simultaneous presence of ADH in biopsy specimens should undergo VAE or surgical excision. Isolated LN diagnosed on VAB with adequate radiological-pathological correlation may be managed with follow-up alone. At the same time, surgical excision might be advised for classical LN diagnosed on breast biopsy only if an additional B3 lesion is also detected. In case of diagnosis obtained via CNB, some guidelines advise VAB/VAE and do not advocate any additional intervention if the diagnosis is confirmed. Surgical excision is usually recommended for PT diagnosed on biopsy, even if some guidelines consider the growth rate or lesion size over 3 cm as a surgical indication.

Treatment decisions must be carefully tailored to the individual patient, considering factors such as lesion characteristics, radiological findings, histopathological interpretation, and patient risk factors. This nuanced approach to treatment highlights the need for a multidisciplinary strategy involving radiologists, pathologists, and surgeons to ensure optimal patient care.

This article underlines the importance of further research into improving diagnostic accuracy and refining treatment algorithms for B3 lesions. Future advances in artificial intelligence, genomics, imaging technology, biopsy techniques, and a deeper understanding of lesion biology will be crucial to enhancing outcomes and minimizing overtreatment or missed diagnoses. Ultimately, a more standardized and evidence-based approach to B3 lesion management will reduce clinical uncertainty and improve patient care.

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