PATHOLOGICA 2025;117:178-198;
DOI: 10.32074/1591-951X-1113

Guidelines

Consensus document on preoperative diagnostic procedures in breast lesions

Stefano Marletta[1,2], Isabella Castellano[3], Francesca Caumo[4], Carmen Criscitiello[5], Patrizia Frittelli[6], Donatella Santini[7], Daniela Terribile[8], Daniela Bernardi[9,10], Marina Bortul[11], Massimo Calabrese[12], Giuseppe Catanuto[13], Maria Grazia Cattani[14], Leopoldo Costarelli[15], Giulia D'Amati[16], Nicola Fusco[17,18], Oreste Gentilini[19], Moira Ragazzi[20,21], Gianni Saguatti[22], Alfredo Santinelli[23], Cristian Scatena[24,25], Grazia Sciancalepore[26], Francesca Pietribiasi[27], Anna Sapino[28,29], Antonio Rizzo[1]

[1] Division of Pathology, Humanitas Istituto Clinico Catanese, Catania, Italy; [2] Department of Diagnostics and Public Health, Section of Pathology, University of Verona, Italy; [3] Department of Medical Sciences, University of Turin, Italy; [4] Veneto Institute of Oncology (IOV) IRCCS, Padua, Italy; [5] Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan, Italy; [6] UOC Chirurgia senologica, Ospedale Isola Tiberina Gemelli Isola, Rome, Italy; [7] Department of Pathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy; [8] Division of Breast Surgery, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; [9] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (Milan), Italy; [10] Breast Imaging and Screening Unit, Department of Radiology, IRCCS Humanitas Research Hospital, Milan, Italy; [11] SSD Breast Unit, ASUGI Units, Trieste, Italy; [12] IRCCS Hospital Policlinico San Martino, Genoa, Italy; [13] Humanitas University Istituto Clinico Catanese, Catania, Italy; [14] Unit of Anatomic Pathology, AUSL Bologna, Ospedale Bellaria, Bologna, Italy; [15] Department of Pathology, San Giovanni-Addolorata Hospital, Rome, Italy; [16] Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Italy; [17] Division of Pathology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [18] Department of Oncology and Hemato-Oncology, University of Milan, Italy; [19] Università Vita-Salute San Raffaele, Milano, Italy; IRCCS Ospedale San Raffaele, Milano, Italy; [20] Pathology Unit, Azienda USL-IRCCS di Reggio Emilia, Italy; [21] Department of Medical and Surgical Sciences for Children and Adults University of Modena and Reggio Emilia, Modena, Italy; [22] UO Senologia, Ospedale Bellaria, AUSL Bologna, Italy; [23] UOC Anatomia Patologica, Azienda Sanitaria Territoriale di Pesaro-Urbino, Pesaro, Italy; [24] Division of Pathology, Department of Translational Research & New Technologies in Medicine & Surgery, University of Pisa, Pisa, Italy; [25] Department of Oncology, Pisa University Hospital, Pisa, Italy; [26] ASO "S. Croce e Carle", Cuneo, Italy; [27] Division of Pathology, Santa Croce Hospital, Moncalieri, Turin, Italy; [28] Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy; [29] Department of Medical Sciences, University of Turin, Italy

Received: October 9, 2024
Accepted: October 10, 2024

Correspondence
Antonio Rizzo
E-mail: antonio.rizzo@humanitascatania.it

How to cite this article: Marletta S, Castellano I, Caumo F, et al. Consensus document on preoperative diagnostic procedures in breast lesions. Pathologica 2025;117:178-198; https://doi.org/10.32074/1591-951X-1113

Summary
Currently, percutaneous sampling via core needle or vacuum-assisted biopsy is the primary choice to guide the management of patients with clinical or screen-detected breast lesions. Preoperative biopsies allow physicians to get pathological diagnoses as well as key prognostic and predictive data about the nature of the investigated process. Namely, adequate biopsy sampling is crucial for assigning lesions to one diagnostic category (B1-B5). Similarly, evaluating morphological (histotype, vascular invasion, necrosis, etc.) and immunohistochemical/molecular features (ER, PR, Ki-67, and HER2) is the key to address the most effective therapies, especially in the neoadjuvant setting. The multidisciplinary team should always discuss the results of percutaneous biopsies, whose global integration with clinical and radiological findings will drive the adoption of specific treatment options, particularly for uncertain (B3) and suspicious/malignant (B4-B5) lesions.
In the present work, we report a comprehensive overview of breast percutaneous biopsy techniques, diagnostic categories, and multidisciplinary management based on widely acknowledged evidence of good clinical practice.

Key words: preoperative biopsy, breast cancer, consensus, multidisciplinary management

Introduction

Preoperative percutaneous biopsy is the diagnostic method of choice for the evaluation of a screen-detected or clinically evident breast lesion. This technique, which forms a critical part of the diagnostic triad (clinical,

imaging, and histology), allows for precise therapeutic planning ideally in a single operative procedure [1].
A preoperative histological diagnosis allows for:

- Diagnosing the lesion, often eliminating the need for surgical intervention in most benign cases.
- Tailoring therapeutic measures for each patient, by determining whether a carcinoma is in situ or invasive and providing information on the histotype and grade of the neoplasm.
- Formulating key prognostic and predictive indicators (such as receptor status, proliferation index, and HER-2) before surgery, which are essential parameters in cases of primary systemic therapy.

The preoperative histological diagnosis should always be reviewed by a multidisciplinary team, which must confirm its representativeness by correlating clinical and radiological data. In cases of discrepancy, for example, when a histologic diagnosis of a benign lesion is rendered despite a suspicious radiological picture, the radiologist may recommend repeating the biopsy, possibly using a larger needle, to ensure a comprehensive preoperative diagnosis for the multidisciplinary meeting. Excisional biopsy should be reserved to selected cases, following a careful discussion by a multidisciplinary team.

Diagnostic preoperative sampling techniques:

The use of fine-needle aspiration cytology is currently limited to the aspiration of simple cysts and axillary lymph nodes [2]. Regarding the procedure of core needle biopsy - CNB - the currently employed sampling techniques are as follows:
1) **Preoperative percutaneous CNB**: this procedure utilizes automatic or semi-automatic devices under ultrasound guidance or, less commonly, stereotactic guidance. It involves the use needles with diameters ranging from 12 to 14 G, with 14 G being the most commonly recommended size. CNB is considered the procedure of choice for preoperative diagnosis, even in cases of palpable lesions, with sampling primarily performed under ultrasound guidance. For lesions where neoadjuvant therapy is anticipated, it is advisable to extensively sample the lesion with at least 4-6 cores from different areas of the neoplasm[3] (Fig. 1).

2) **Vacuum-assissted biopsy (VAB)**: this technique is performed using vacuum-assisted devices, either under stereotactic or ultrasound guidance, employing larger needles. Specifically, 11, 10, and 9 G needles are used for first-line diagnostic VAB, while 7-8 G needles are used for second-line VAB (performed after an inconclusive result from the initial VAB and/or for excisional purposes).
The use of VAB, which provides larger tissue volumes, is strongly recommended for non-palpable mammographically suspicious lesions without ultrasound correlation. VAB is also indicated as a second-line method to improve diagnostic accuracy if CNB did not provide a definitive diagnosis [1]. An elective indication for VAB includes clusters of radiologically dubious/suspicious microcalcifications (BIRADS: 4) [2]. VAB is also used for evaluating distortions or asymmetries that are difficult to visualize on ultrasound (Fig. 2).
As a second-line method, VAB can also be useful for excisional purposes (VAE: vacuum assisted excisional biopsy) in case of specific B3 lesions, such as papillary, radial scar, etc (see below)[4].
With the introduction of tomosynthesis, it is now the possible to perform biopsy sampling under tomosynthesis guidance (tomosynthesis-assisted VAB), allowing for even more accurate and rapid sampling.
For lesions identified using contrast-enhanced methods, such as magnetic resonance imaging (MRI) and/

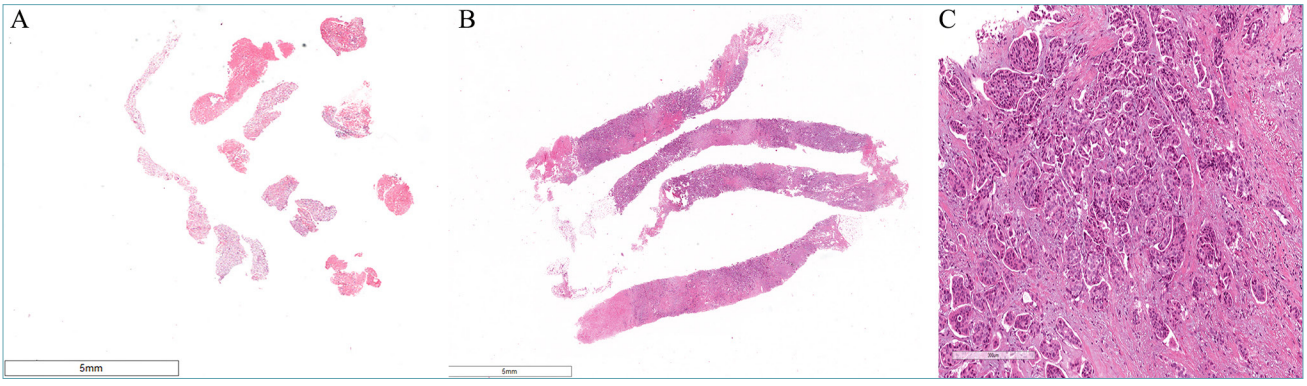

Figure 1. Biopting sampling fragments, providing material poorly representative for biomarkers evaluation (A) Low-power microphotograph of another core-needle biopsy, collecting four highly cellular representative cores, suitable for biomarker evaluation (B). Higher magnification reveals a micropapillary invasive breast carcinoma (C).

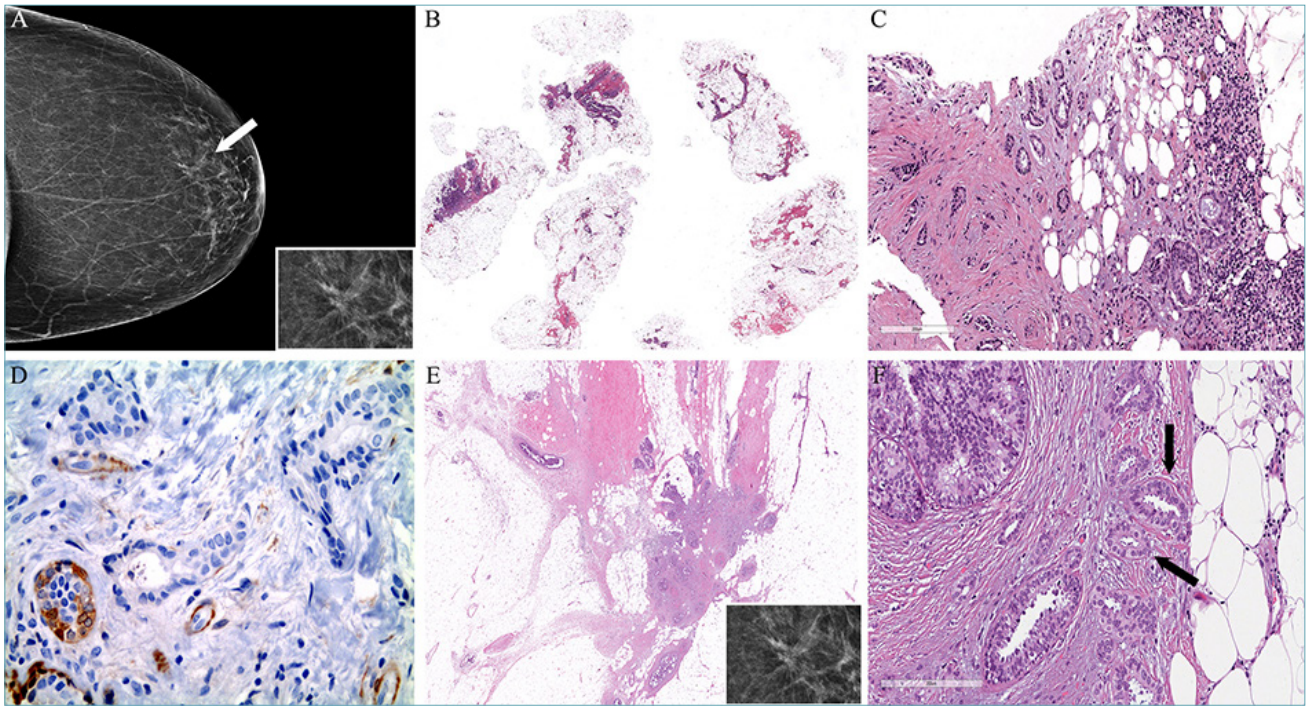

Figure 2. Mammogram showing an architectural distortion, seen as focal spiculated retraction on detailed viewing, classified by the radiologist as BI-RADS 4B (A). Histological examination of the VAB sampled area (B) revealed foci of desmoplastic stroma (C) embedding angulated glandular structures staining negative for the myoepithelial marker calponin (D), consistent with tubular carcinoma. The preoperative diagnosis was then confirmed at surgical resection: in this latter, a fibrosclerotic area with finger-like margins recalling mammographic findings was observed (B, E), enclosing malignant well-differentiated glands with intraluminal apical snouts (arrow) (F).

or contrast-enhanced mammography (CEM), but not identifiable on second-look mammography or ultrasound, VAB guided by contrast-enhanced methods is recommended [1].

The VAB procedure:

The VAB procedure involves using a biopsy probe that is positioned in the breast after administering local anesthesia. The probe is guided by ultrasound, mammography (in stereotactic or tomosynthesis mode), and/or CEM. Once the biopsy probe is placed near or within the lesion to be sampled, is connected to a suction system that creates negative pressure. This allows breast tissue to be aspirated into the sampling chamber. Inside the probe, a rotating blade resects the tissue, which is then collected in a retrieval basket. The probe remains inside the breast and can be rotated up to a 360° angle to obtain additional samples. For optimal lesion sampling, it is recommended to perform 6 to 24 biopsies, with an average of 12. These biopsies are typically taken at specific topographical coordinates, ideally corresponding to the quadrants of a clock: on average, 6 biopsies at even hours and 6 at odd hours.

The advantages of this method include obtaining a large tissue volume for histological examination and the ability to rapidly evacuate any hematoma at the biopsy site due to the negative pressure approach. Larger-gauge needles allow for the collection of up to 400 mg of breast tissue per individual specimen. It is possible to obtain up to 2 g of tissue (using five specimens with a 7 G needle or twelve specimens with a 10 G needle) [5]. After the sampling procedure, it is recommended to leave a metallic clip at the biopsy site.

Processing and preparation of material from breast CNBs and VABs:

For accurate interpretation of material obtained through breast biopsy, the pathology laboratory must receive the following:

a) the accompanying request form (Supplementary material) should include the patient's demographic information, topographical data related to the biopsy site (laterality and quadrant), relevant clinical details (e.g., diabetes, pregnancy, etc.), and the pathological history, including any previous breast interventions. Additionally, the imaging description related to the biopsy should be provided. The radiological classifi-

cation category according to BI-RADS should always be accompanied by information about the lesion's size and characteristics (e.g., nodule, distortion, microcalcifications). The technique used for lesion localization, the number of obtained tissue fragments (cores), and the presence of microcalcifications within them should also be specified.

b) In cases where microcalcifications are present, the biopsy cores should be radiographed and then immediately put in fixative to ensure proper evaluation of immunophenotypic and molecular parameters (specific guidelines for fixation are provided below). To assess the adequacy of the material concerning the mammographically identified lesion, it is helpful to have radiographic images of the biopsy cores. In Breast Units that use digital mammography, the pathologist should be able to view the radiographic images of the cores on a high-quality monitor [6]. If microcalcifications seen in the radiographic images are not evident in the histological preparations, considering the risk of microcalcifications dislodging during sectioning, the corresponding tissue blocks should be radiographed to confirm their presence and then subjected to serial sections.

c) **Breast needle biopsy fragments** should be placed in containers labeled with topographical coordinates corresponding to the biopsy site, and promptly sent to the pathology laboratory. It is recommended that each container holds a maximum of 4 fragments for CNBs and 2 fragments for VABs. It is important that the radiologist separates the fragments containing microcalcifications from those that do not at the time of collection [1]. Optimal fixation in 10% buffered formalin is crucial for high-quality histological preparations. For biomarker evaluation, a minimum fixation time of 6 hours and a maximum of 48-72 hours are recommended [7]. After processing, proper embedding in paraffin and adequate sectioning using hematoxylin and eosin (H&E) staining are essential. For CNBs performed on breast nodules, a single H&E section may be sufficient, while for each VAB tissue block, at least three H&E sections at three different levels, separated by 40 µm, should be prepared. In some laboratories, additional unstained sections are cut during CNB preparation for potential immunohistochemical evaluations and biomarker determination.

Preoperative histological diagnosis: reporting methods

The proposed referral system used in preoperative diagnostics follows the European Guidelines, which involve adopting five diagnostic categories [8]. These categories do not replace the histopathological description of the lesion but are intended to assist in multidisciplinary discussions regarding specific therapeutic decisions for each patient [9]. When requesting a histological examination, the radiologist is required to provide not only relevant anamnestic information but also to assign a level of suspicion to the lesion using the BI-RADS diagnostic categories. Each category is associated with a predictive value based on both clinical and morphological characteristics. The multidisciplinary team, typically involving the radiologist and pathologist, is responsible for integrating and comparing different categories (clinical, radiological, and histological) to verify the consistency between radiological suspicion and histological findings. In more complex cases, the multidisciplinary consultation may also include the surgeon. To achieve a definitive diagnosis of a screen-detected lesion, typically no more than two core needle biopsy procedures should be performed in succession [1]. In screen-detected lesions, except in cases where CNB is contraindicated, the use of intraoperative diagnosis on frozen sections should be avoided [10].

The classification system based on the five diagnostic categories offers the advantage of precise and easily reproducible standardization. It is straightforward for clinicians to interpret and facilitates multidisciplinary evaluation. However, it has limitations, as it groups different preoperative biopsy techniques together. While CNB is as a sampling technique, VAB can also be used for excision, especially of small lesions. When a VAB excision follows the diagnosis obtained from CNB specimens, the use of the diagnostic categories may be omitted [11]. Consensus documents and guidelines emphasize the importance of highlighting the characteristics of the diagnostic tool during multidisciplinary discussions [4,12].

The literature reports an excellent correlation between the five diagnostic categories used in CNB reporting and the definitive histology [13]. Numerous studies also demonstrate excellent interobserver diagnostic agreement [14]. Similar to screen-detected lesions, the EUSOMA guidelines for breast units recommend dual-signature reporting for breast biopsies [10].

Diagnostic categories

B1: Normal/inadequate tissue. This category includes:

1) Fragments composed solely of fibrous and/or adipose tissue.

2) Fragments composed of normal breast tissue (glandular lobules and stromal tissue) without appreciable histological lesions.

3) Fragments composed of breast tissue in which,

despite serial sampling, the microcalcifications that prompted the biopsy are not histologically evident.
It is essential that a B1 diagnosis is accompanied by a detailed description of the material examined along with comments on the importance of integrating histological data with clinical and radiological information. When sampling a hamartoma or lipoma, the biopsy may reveal only normal breast tissue or adipose tissue, which corresponds to the identified lesion. Faint architectural distortions may histologically correspond to a modest increase in stromal fibrous tissue. The presence of minute microcalcifications in involuted lobules is frequently observed histologically. However, since mammography cannot detect microcalcifications smaller than 100 µm in diameter, it is crucial for the pathologist to describe the size and location of the microcalcifications identified histologically.
In this diagnostic category, only a **multidisciplinary evaluation** can determine the representativeness of the histological findings in relation to the radiologically identified lesion.

B2: Benign lesion. This category encompasses a wide range of benign breast lesions, including fibroadenomas, sclerosing adenosis, florid epitheliosis, and steatonecrosis. In some cases, it may be challenging to determine whether the histologically identified lesion, such as cystic disease, is accurately representative of the lesion described radiologically [15].

B3: Lesion of uncertain malignant potential. This category includes two groups of lesions:
1) Morphologically benign lesions that, due to the fragmentary nature of the sample and the heterogeneity of morphological appearance, pose interpretative challenges. Examples include papillary lesions, focal scleroelastotic lesions, infiltrative epitheliosis, phyllodes tumors, and mucocele-like lesions.
2) Lesions with an increased risk of neoplastic progression (NP), such as lobular intraepithelial neoplasia (LIN), flat epithelial atypia (FEA), and atypical intraductal epithelial proliferations.
B3 lesions represent a highly heterogeneous diagnostic category, with variable risk levels associated with individual lesions. The clinical significance varies depending on whether the diagnostic evaluation is performed using 14 G CNB or 8 G VAB [4]. It is important to note that the frequency of this diagnostic category varies based on the type of lesion biopsied. It is higher (up to 15%) in clusters of microcalcifications identified in screen-detected lesions and lower in nodular lesions [16].
The positive predictive value (PPV) for B3 lesions is generally around 20% [17], with significant differences among various lesion types (see Table I, modified from Rubio et al.[12]). The risk of developing invasive breast cancer following a B3 diagnosis increases over time (10 years: 3.8% and 3.7%; 15 years: 8.9% and 8.6%; 25 years: 30.5% and 26.2%, for ipsilateral and contralateral breasts, respectively) [18].

Table I. Summary of rates of upgrade to malignancy of commonest B3 lesions (modified from Rubio et al.) [12].

B3 lesion	Total upgrade to malignancy	Upgrade to DCIS	Upgrade to invasive
ADH	0-50% (22%)	20%	5%
ALH	12%	9%	2%
cLCIS	22%	15%	7%
FEA	0-5%	1%	2%
RS/CSL	1-10%	1-5%	1%
PL	< 10%	5%	2%

Abbreviations: ADH: atypical ductal hyperplasia, ALH: atypical lobular hyperplasia, cLIS: classic lobular carcinoma in situ, FEA: flat epithelial atypia, RS/CSL: radial scar/complex sclerosing lesion, PL: papillary lesion.

Table II. Clinical management of B3 lesions (modified from Rageth et al.) [4].

B3 lesion	Diagnosed on CNB	Diagnosed on VAB
ADH	Surgical resection	VAE if < 15 mm (surgery is preferred for wider lesions)
FEA	VAE	Follow-up if completely removed
LN*	Surgical resection or VAE if radiologically detectable	Surgical resection or follow-up if completely removed
PL#	VAE	VAE
PT	Surgical resection with negative margins	Follow-up if completely removed benign PT
RS/CSL	VAE if radiologically detectable	Follow-up if completely removed

Abbreviations: CNB: core needle biopsy, VAB: vacuum-assisted biopsy, ADH: atypical ductal hyperplasia, VAE: vacuum-assisted excision, FEA: flat epithelial atypia, LN: lobular neoplasia, PL: papillary lesion, PT: phyllodes tumor, RS: radial scar, CSL: complex sclerosing lesion.
* LN cases with florid/pleomorphic features, large in size, or displaying necrotic foci are labelled as B5.
# PLs and RSs with atypia are regarded as either FEA or ADH/AIDEP according to the atypia degree.

The following paragraphs detail the most common lesions falling into the B3 category, with clinical their management summarized in Table II.

1) **Atypical ductal hyperplasia (ADH) / atypical ductal epithelial proliferation (AIDEP)** [19,20].
Radiological features: when diagnosed incidentally, ADH/AIDEP often lacks specific imaging characteristics. On mammography, these lesions typically appear as clusters of microcalcifications and less frequently as masses or asymmetric densities. On ultrasound, they present as nodular formations or hypoechoic areas with irregular margins. In MRI and CEM, ADH/AIDEP also lacks specific features, often manifesting as non-mass-like enhancements [21,22]. Depending on the identification method, biopsies can be performed using either CNBs or VABs under ultrasound guidance, mammography (stereotaxic or tomosynthesis), or, less commonly, MRI guidance.
Histological criteria: ADH is defined as a clonal proliferation that is morphologically similar to low-grade ductal carcinoma in situ (DCIS) but involves only a part of the ducts or, if continuous, limited to fewer than two ductal spaces measures less than 2 mm [23]. AIDEP is a technical term recommended by European guidelines to describe ADH on CNB or VAB when sampling limitations prevent precise assessment of the extent of atypical proliferation [24,25] (Figs. 3C and 3D).
Upgrade to malignancy: the risk of upgrading to in situ or invasive cancer in cases of ADH diagnosed via needle biopsy during surgery varies between 5% and 50%. This risk is higher when there is discordance between imaging findings and histopathological results, as well as in cases with nodular lesions or extensive and multifocal microcalcifications. Considering all these factors, the overall rate of ADH upgrading to

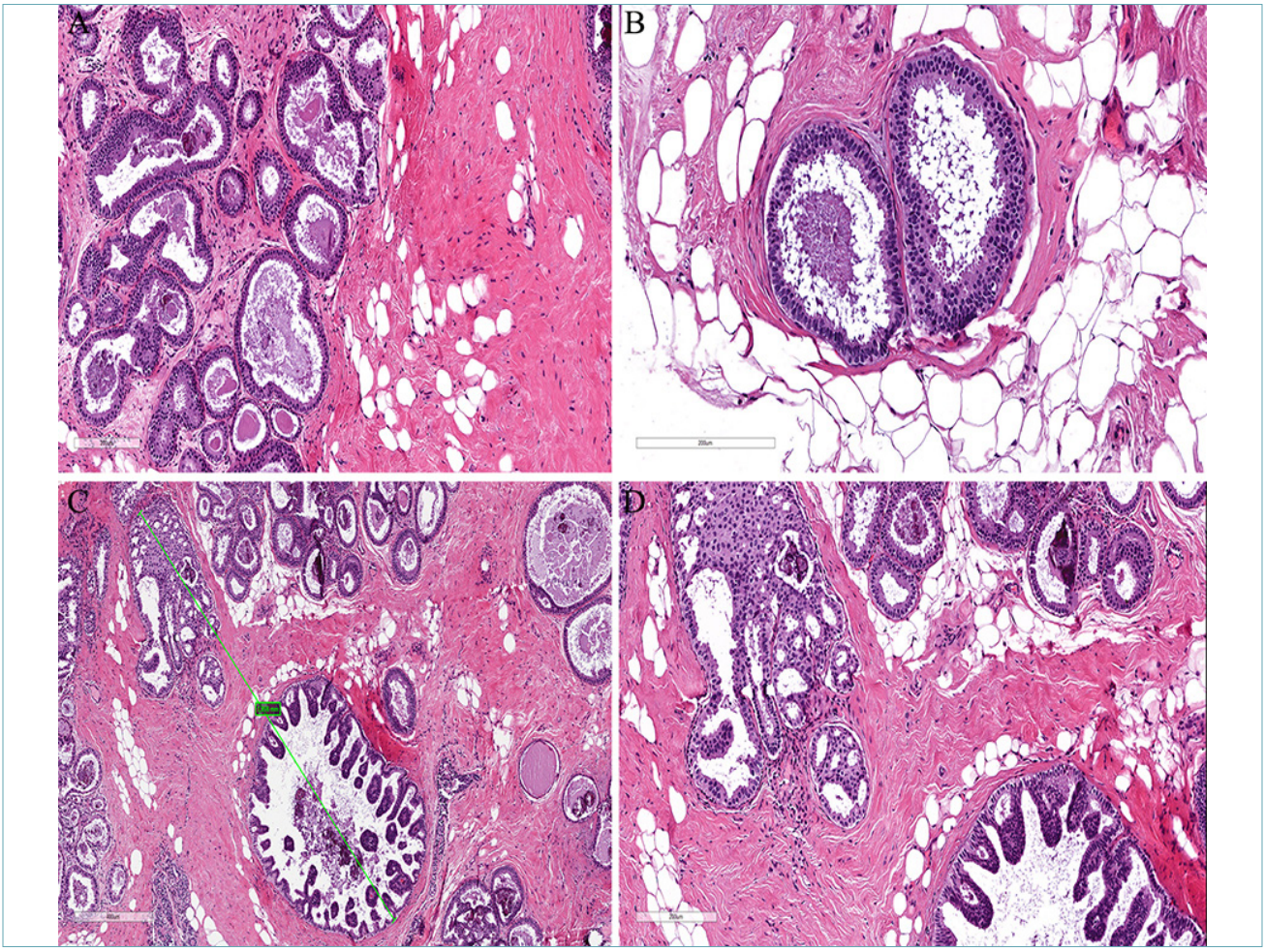

Figure 3. VAB examples of FEA (A, B) showing ductal structures lined by multiple layers of monomorphic roundish cells with apical snouts and monomorphic low-grade atypia. Low (C) and medium-power (D) pictures from another case, revealing, close to FEA foci, a glandular proliferation with architectural growth pattern (solid, cribriform, and micropapillary) and atypia equal to low-grade DCIS. Such a lesion was technically diagnosed as AIDEP/ADH on CNB due to its size (< 2 mm) as sampling limitations prevented precise assessment of its extent.

malignant tumors (in situ or invasive) is approximately 22%, which justifies surgical excision for diagnostic purposes [12].

VAB/VAE vs. surgery: based on this evidence, the recently published 3rd International Consensus Conference on B3 lesions confirms the recommendation for surgical excision following a diagnosis of ADH obtained via both CNB and VAB [26]. However, controversy remains regarding the possibility of avoiding surgery by managing these lesions with vacuum-assisted excisional biopsy (VAE). Guidelines issued by the National Health Service Breast Screening Program (NHS BSP) in the United Kingdom suggest performing a second-line VAE as a diagnostic approach for most B3 lesions (including ADH, classic LN, radial scar, FEA, and mucocele-like lesions with or without epithelial atypia) diagnosed via CNB or VAB. As long as complete lesion excision is achieved post-procedure and there is no evidence of malignancy on VAE, these patients are considered suitable for annual mammographic surveillance [12].

- *Indications for VAE in ADH Cases*: based on evidence-based data, VAE may be considered under the following conditions:

· Preliminary multidisciplinary discussion.

· Patient age (the risk of upgrading reduces with an increase of the patient's age).

· Radiological lesion size (< 15 mm).

· Absence of any residual radiological lesion after the CNB or VAB procedure.

- *Contraindications for VAE in ADH Cases*: evidence-based data suggest that VAE is contraindicated in the following situations:

· Nodular lesions.

· Presence of extensive microcalcifications (> 15 mm) and/or multifocal calcifications.

· History of previous breast cancer.

· Discordance between imaging findings and histological results.

NOTE: the decision to proceed with VAE should consider not only evidence-based data but also national/local resources (availability of VAE procedures and necessary follow-up) and the involvement of competent personnel.

Recommendations (Table II):

1. For ADH diagnosed via CNB or VAB in a visible imaging lesion, surgical excision is the preferred option. VAE can be considered for excisional purposes if the lesion size is less than 15 mm (evidence/grade III/B) in specific situations, but only after multidisciplinary discussion.
2. ADH diagnosed via CNB or VAB and with a size greater than 15 mm should undergo surgical excision (evidence/grade I/A).

2) **FEA**

Radiological features: FEA is a lesion typically associated with grouped amorphous calcifications on mammography; less frequently, it is identified on ultrasound as a hypoechoic mass with irregular or lobulated margins [27].

Histological criteria: FEA is characterized by ducts lined with one or more layers of atypical cells, with round, monomorphic nuclei and visible nucleoli, similar to those seen in low-grade DCIS. The cells often exhibit apical snouts (Figs. 3A and 3B). Roman bridges and micropapillary formations are typically absent. The lobules are distended but maintain their shape, and the involved ducts are often dilated and contain secretions where calcifications deposit.

Upgrade to malignancy: for pure FEA, the risk of local recurrence and upgrade to carcinoma is low. Based on the largest published meta-analysis, the risk of upgrade is estimated to be less than 5%: 1% for invasive forms and 2% for DCIS. Overall, the reported risk in the literature ranges from 1% to 16% and appears to be influenced by the frequent association with foci of ADH [28].

Recommendations: if FEA is diagnosed on CNB, VAB or VAE is indicated. After VAB, if the mammographic lesion is small and the microcalcifications have been removed, follow-up is justified (Tab. II).

3) **Lobular neoplasia (ln) / classic lobular carcinoma in situ / intraepithelial lobular neoplasia (LIN1 and LIN2)**

Radiological features: the diagnosis of classic lobular neoplasia/intraepithelial lobular neoplasia is predominantly an incidental pathological finding as it is generally occult. When associated with mammographic findings, it is mostly represented by calcifications and/or masses; in these cases, the literature reports an association with pleomorphic variants and a higher upgrade rate to surgery (up to 18%). When detected on MRI or CEM, it appears nonspecific, often manifesting as foci or non-mass-like enhancement areas [29,30].

Histological criteria: classic LN is characterized by an intralobular proliferation composed of monomorphic cells of small to medium size, loosely cohesive, resulting in acinar expansion (more than 8 cells). Lobular neoplasia includes atypical lobular hyperplasia (ALH, LIN1) and classic lobular carcinoma in situ (LCIS; LIN2). According to the WHO the differential diagnosis between these two lesions is based on the extent of involvement of terminal duct-lobular units (TDLUs) (less than 50% for ALH and more than 50% for LCIS, respectively) [31,32]. Classic LN is pri-

marily an incidental finding during CNBs performed for mammographically identified lesions (Fig. 4); it is rare for classic LN to be the sole lesion encountered in screen-detected biopsies. Classic LN should be differentiated from non-classic LCIS variants (LIN3, florid LCIS and pleomorphic LCIS). When LCIS cells involve large acini or ducts (more than 40-50 cells in the largest diameter of an acinus and/or minimal stroma between acini), the diagnosis of florid LCIS should be considered, and the lesion is classified as B5a. When the intralobular proliferation consists of markedly enlarged atypical cells (more than 4 times the size of a lymphocyte) similar to those seen in high-grade DCIS, sometimes with apocrine changes and frequently associated with comedo necrosis and intraluminal microcalcifications, the neoplasia should be considered as pleomorphic LCIS and classified as B5a [33].

Upgrade to malignancy: recent studies on classic LN occasionally detected in biopsies have shown a low incidence of malignancy (1-4%) on subsequent excisional biopsy. The likelihood of understaging is higher (13-18%) when classic LN is the target lesion of the CNB and even higher in the presence of masses or microcalcifications with radiopathological discordance [34-36]. Factors favoring surgical excision in the case of a biopsy diagnosis of classic LN include the presence of another associated B3 lesion, the presence of another mammographically visible lesion, and any lesion with imaging-histology discordance. Unlike classic LN, 25-40% of cases with pleomorphic LCIS present foci of infiltrating lobular carcinoma on surgical excision [4,37-39].

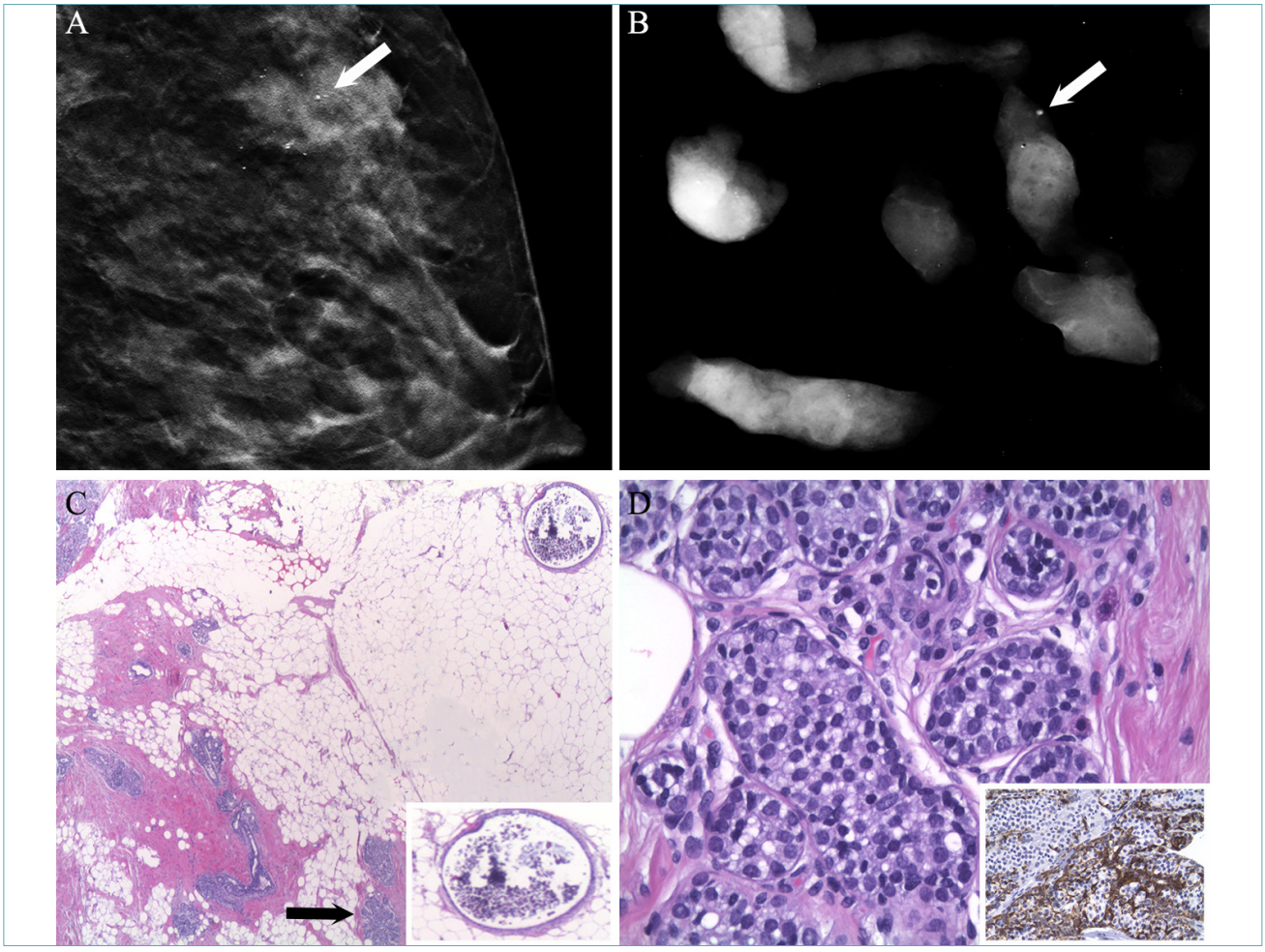

Figure 4. Mammogram showing an asymmetric area of increased density with sparse microcalcifications (arrow, classified by radiologist as BI-RADS 4B) (A). Microcalcifications were confirmed by radiography of the VAB cores (arrow).(B). At microscopic examination, adjacent to an intraluminal dystrophic calcification (inset) (C), an incidental acinar proliferation (arrow) consistent with classic LN/classic lobular carcinoma in situ was identified (D). The inset underscores E-cadherin negativity of the classic LN cells.

Recommendations:
1. When classic LN is diagnosed on VAE, follow-up may be appropriate in case of concordance with imaging and no residual lesions are present. Radiological follow-up can include an MRI at 6 months, considering radiological density and family history.
2. When classic LN does not show concordance with imaging, surgical excision after VAE is indicated. Radiological follow-up can include performing an MRI. Morphological variants of lobular neoplasia (LIN3, pleomorphic LCIS, and florid LCIS) should be classified as B5 and referred for surgical excision (Tab. II).

4) **Phyllodes tumor (PTs)**
Radiological features: on mammography, PTs typically appear as nonspecific lesions of varying sizes, with oval or lobulated shapes, generally well-circumscribed, and with clear margins. The ultrasound characteristics are not specific and resemble those of a fibroadenoma, although the echotexture can often be heterogeneous with single or multiple cystic areas. On MRI, PTs manifest as nodular lesions with well-defined margins, although they can be polypoid and show variable and nonspecific enhancement kinetics [40]. Biopsy is generally performed under ultrasound guidance using CNB or VAB.
Histological criteria: PT is a fibroepithelial lesion characterized by stromal hypercellularity, an intracanalicular growth pattern, and stromal fronds lined by epithelium that protrudes into cystic spaces giving a leaf-like appearance. Although 85% of cases are benign, PTs can exhibit borderline clinical behavior (15%) or even malignancy (10%), with a risk of distant metastasis. This distinction requires evaluation of certain histological aspects (stromal cellularity, degree of atypia, presence of stromal overgrowth, expansive margins, heterologous components), and accurate assessment can only be made on a surgical specimen.

Recommendations: if the diagnosis of PT is based on CNB, surgical excision with clear margins is indicated. If benign PT is incidentally found on VAB and imaging is negative, follow-up may be considered. In other cases, histological evaluation of the entire lesion with negative margins is recommended. It's important to note that recent literature revisions suggest a low recurrence rate after surgical excision for benign PTs [41]. Occasionally, not all criteria for a preoperative diagnosis of PT are met on biopsy. In such cases, a microscopic description of the observed pattern, such as "fibroepithelial lesion with increased stromal cellularity, absence of mitoses and/or necrotic areas, and cellular atypia/B3," can be considered.

5) **Papillary lesions (PLs)**
Radiological features: the diagnosis of PLs can be incidental or arise in the presence of clinical symptoms, such as secretion, and variable mammographic findings. Mammography may be negative or reveal findings such as dilated ducts, and nodular opacities typically with well-defined margins, sometimes associated with calcifications. Solitary PLs are often found in the retroareolar or central location, while multiple lesions are typically scattered throughout a quadrant. Ultrasound usually shows a well-defined nodule with or without cystic components or a small mass within a dilated duct. On MRI, PLs can appear as single or multiple masses with clear margins, but they can also be irregular and show intense contrast enhancement, often associated with dilated ducts. Differentiating between benign lesions and those with atypia or malignancy can be challenging [42]. Depending on the mode of lesion identification, CNB or VAB can be performed under ultrasound, mammography (stereotactic or with tomosynthesis), or less frequently, MRI guidance.
Histological criteria: PLs are a heterogeneous group of lesions that mostly fall into category B3 (Fig. 5). On imaging, intraductal papillomas vary in size and presentation, from cystic lesions to calcified masses. As indicated by the WHO 2019 classification, they can be classified as follows:
a) Papillomas (if smaller than 2 mm and completely excised on biopsy, they can be classified as B2).
b) PLs with atypia (AIDEP/ADH and/or classic LN, falling into category B3).
c) PLs associated with DCIS (falling into category B5).
Intraductal PLs with marked sclerosing proliferative aspects (also known as ductal adenoma) fall into category B3.
Upgrade to malignancy: the presence of ADH is a strong predictor of upgrading to either in situ or invasive carcinoma. The risk of upgrade is less than 10% in the absence of atypia or ADH and increases to 27-36% in PL with ADH.

Recommendations: a PL visible on imaging can undergo VAE. In the presence of atypia, subsequent surgical excision is recommended. In the absence of atypia, follow-up may be appropriate if the lesion is completely removed. If the PL cannot be completely excised with VAE, surgical excision is necessary (Tab. II).

6) **Focal scleroelastotic/radial scar (RS)/complex sclerosing lesion (CSL)**
Radiological features: RS is typically identified on mammography and tomosynthesis as an area of architectural distortion or a stellate lesion with a radiolu-

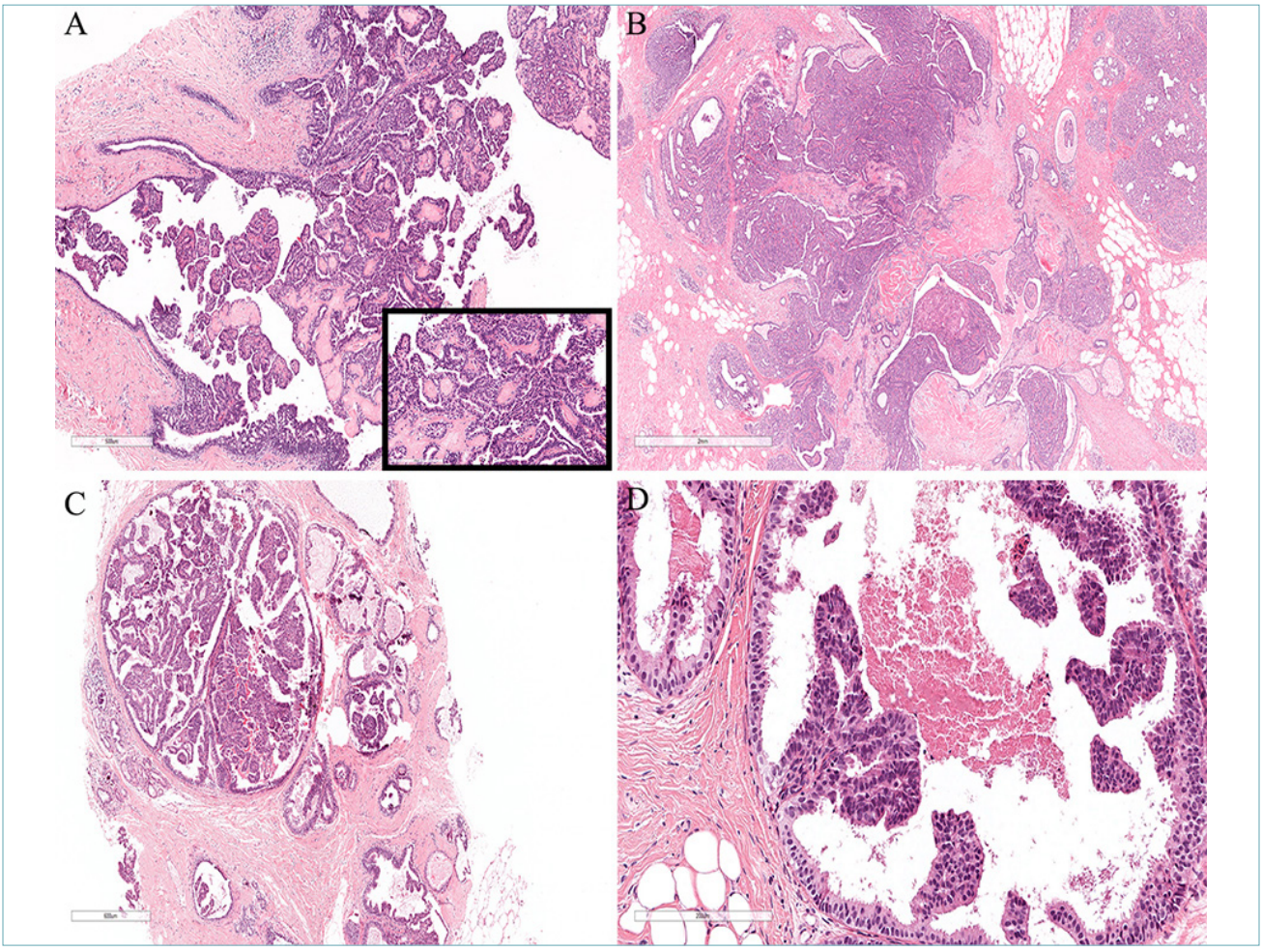

Figure 5. Biopsy sample of a papillary proliferation displaying fibrovascular structures enriched in stroma (A) lined by epithelial cells with no evidence of atypia (inset). The definitive diagnosis of benign papillary lesion was established on the surgical specimen, supported by the distribution of basal markers IHC staining (not shown) (B). Another biopsy sample showing ductal spaces filled with an epithelial-rich proliferation (C) made up of atypical cells covering thin fibrovascular cores (D). The morphological findings were consistent with a papillary DCIS, further supported by p63 and cytokeratin 14 staining (not shown).

cent center, sometimes associated with calcifications. The appearance of this lesion on ultrasound and even MRI is quite variable and often non-specific [43]. Depending on the mode of lesion identification, CNB or VAB can be performed under ultrasound, mammography (stereotactic or with tomosynthesis), or less frequently, MRI guidance.

Histological criteria: RS is morphologically characterized by a central fibroelastotic core that entraps distorted glandular structures, which may lose their myoepithelium, and by cystic or hyperplastic glandular structures at the periphery. It is essential to exclude the presence of atypia (AIDEP/ADH and/or classic lobular neoplasia/LN). Factors influencing therapeutic decisions in RS without atypia are primarily related to lesion size (greater than 1 cm).

Recommendations: if RS is visible on imaging and has dimensions less than 1-1.5 cm, it can undergo VAE followed by subsequent follow-up (Tab. II). In the presence of atypia, surgical excision is indicated.

7) **Mucocele-like lesions (MLs)**

Radiological features: MLs appear on mammography as nodular opacities with a benign appearance, sometimes accompanied by coarse calcifications. On ultrasound, they appear as nodular formations with well-defined margins and heterogeneous echotexture,

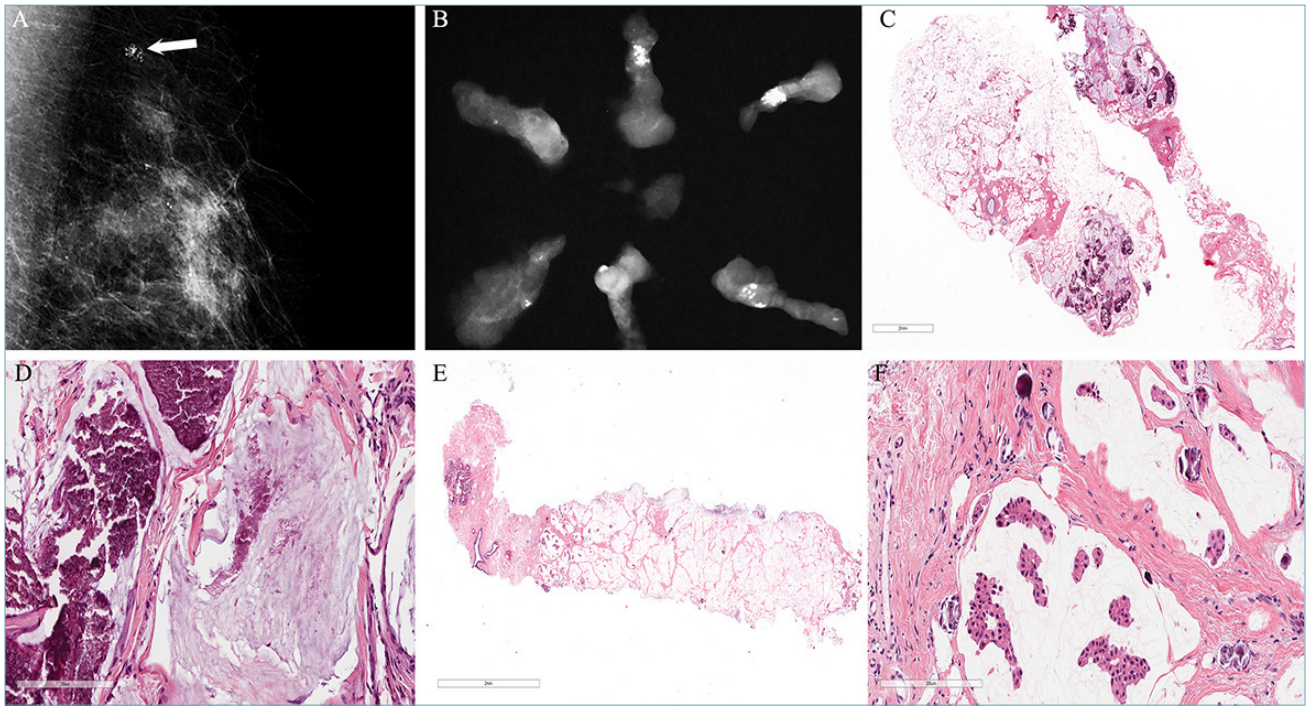

Figure 6. Mammogram showing sparse microcalcifications and a clusterof coarse heterogeneous calcifications (arrow), classified by the radiologist as BI RADS 4B (A), with the cluster excised by VAB procedure (B). Focal-shaped accumulations of mucin with abundant calcifications (C) in absence of epithelial cells (D), characteristic of a mucocele-like lesion, were noticed at the histological exam of bioptic material. Low (E) and high-power (F) microphotographs from another bioptic case displaying a malignant invasive mucinous carcinoma, characterized by aggregates of carcinomatous cells floating within mucin, associated with scattered peri- and intratumoral psammoma-like calcifications.

with or without calcifications (Fig. 6A). Radiologically, differential diagnosis can be challenging, and a biopsy is necessary for confirmation [44]. Biopsy is generally performed under ultrasound guidance using CNB or VAB (Fig. 6B).

Histological criteria and upgrade to malignancy: MLs are histologically characterized by extravasation of acellular mucus into the breast stroma, usually near a ruptured duct. They can be associated with mucinous carcinoma (Figs. 6C-6F). The risk of upgrade is low (less than 2% in pure ML) and is related to the presence of atypical lesions in the surrounding parenchyma (FEA, ADH, or classic LN).

Recommendations: if the diagnosis is based on CNB and no atypia is evident [45-47], VAE can be considered. In the presence of atypia, surgical excision is indicated.

8) **Rare lesions**

Published guidelines [15] recommend classifying rare lesions as category B3 when identified via CNB or when not completely excised by VAB. These include adenomyoepithelioma, microglandular adenosis, spindle cell lesions such as fibromatosis, and some vascular lesions with ambiguous interpretations (Fig. 7). Surgical excision is suggested for such lesions.

Management of B3 lesions

The preoperative diagnosis of B3 lesions always requires multidisciplinary discussion, as not all B3 lesions necessitate surgical intervention. In general, following the recommendations from the second and third European Consensus Conferences [4,26], English guidelines [1] and EUSOMA [12], very small lesions (≤ 2 TDLU) that are completely removed using VAB techniques (with adequate radiological post-biopsy assessment) do not require surgery if there is complete concordance between radiological and histological data, along with verification of clinical and patient history. In addition to the suspicion grade expressed in BI-RADS, it is crucial to evaluate residual microcalcifications on post-biopsy mammography, especially after VAB [48]. Notably, after a B3 diagnosis based on

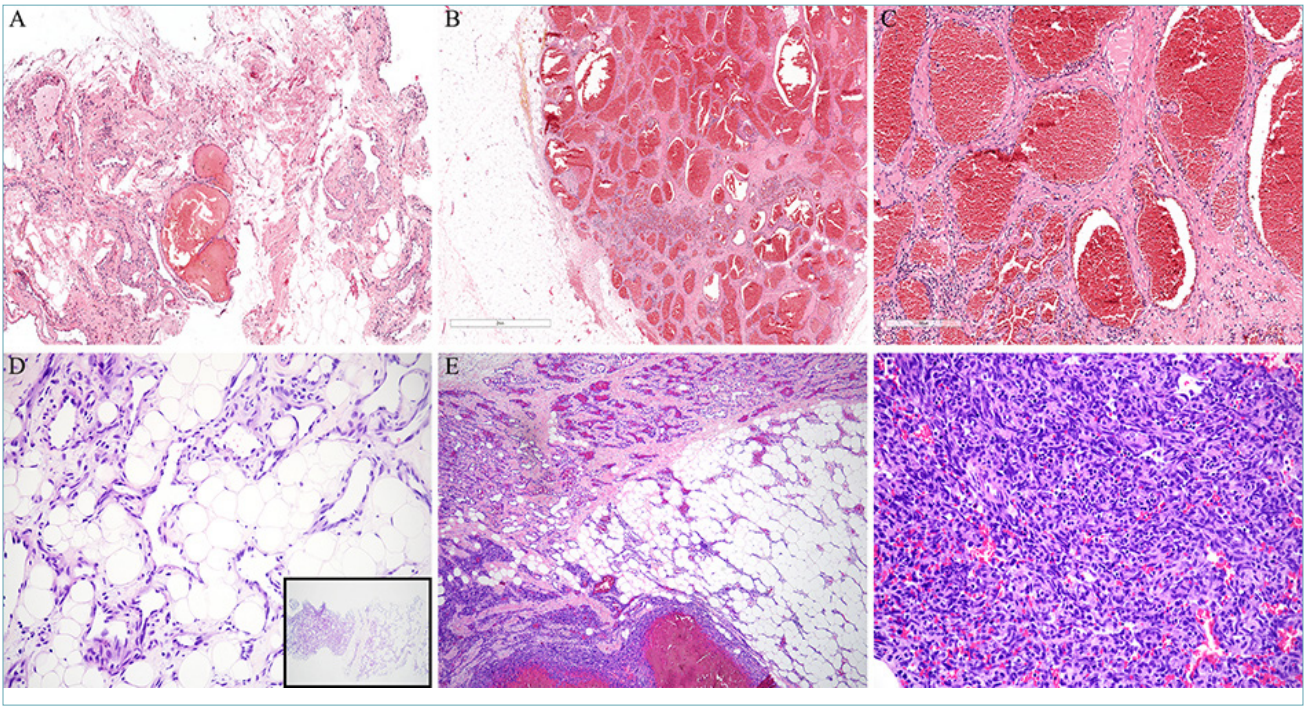

Figure 7. Biopsy fragments of a vascular lesion lined by flat cells without cytological atypia (A), which was later diagnosed as capillary hemangioma on surgical resection (B, C). Although such morphological findings were suggestive of a benign disease, it was prudentially placed into the B3 category due to the difficulty of assessment of cytologycal atypia in vascular channels and of the relationship with the adjacent adipose tissue. Histological features (inset) of another vascular lesion: despite otherwise bland cytological atypia, the suspicion of its malignant nature was raised by the direct infiltration of the surrounding adipose tissue (D). Histological images from the corresponding surgical specimen (E, F), showing, adjacent to well-differentiated areas, highly cellular foci made up of spindle cells with severe cytological atypia (F). Such morphological findings were consistent with the definitive diagnosis of angiosarcoma.

material obtained via CNB or 11 G VAB, introducing a second-line VAE with an 8-7 gauge needle allows for a diagnostic definition of B2 or B5 in a significant percentage of cases, thereby reducing the number of B3 lesions requiring surgical intervention [1,49]. In cases of VAE with radiological confirmation of target excision, adding a diagnostic category is not recommended, as VAE is considered equivalent to surgical excision in these selected cases [1].

The radiologist performing the biopsy should leave a non-magnetic clip as a marker, especially when the lesion is completely excised or minimally visible. Additionally, orthogonal mammography views should be obtained preoperatively to assess any residual microcalcifications and ensure proper clip placement or detect any dislocation, which should be appropriately highlighted and discussed before surgery [48]. Regarding follow-up for patients after a B3 diagnosis, Senonetwork recommendations [50] suggest that, in most cases, involving "intermediate-risk" women (to be verified through family and personal history), annual follow-up for at least 10 years is appropriate [48].

The importance of a multidisciplinary and "patient-centered" approach for B3 lesions has been emphasized by recent European guidelines [12], to avoid understaging and to assess the long-term risk. Validated communication tools (decision aids) should be developed for use during diagnostic, preoperative, and follow-up phases. Furthermore, it is essential to explain that even in cases of upgrade to B5 diagnosis, the risk of being in a life-threatening condition is minimal [51].

B4: Suspicious Lesion. This category includes cases where there is a strong suspicion of malignancy (PPV equal to or greater than 80%). However, a definitive diagnosis of neoplasia cannot be made due to either the small amount of material available for examination (e.g., single atypical glands at the edge of a specimen) or the presence of artifact-related tissue changes (e.g., crushing, poor fixation, hemorrhagic

infiltration) that hinder accurate morphological interpretation. English guidelines also recommend using the B4 category in specific situations, such as when minute suspicious neoplastic foci are present for invasive carcinoma, and immunohistochemical evaluation or receptor determination is not feasible [15]. A preoperative B4 diagnosis requires further histological investigation (repeat biopsy via VAB or diagnostic excision biopsy). However, except in the case of a B4 diagnosis of PT, it should not be a direct indication for definitive surgical intervention.

B5: Malignant neoplastic lesion. This diagnostic category unequivocally indicates malignant lesions. It includes various forms of DCIS and invasive carcinoma, as well as less common neoplasms like malignant PTs, sarcomas, lymphomas, and metastatic tumors. Specifically, in VABs, it is recommended to specify the number of fragments containing neoplastic tissue and measure the maximum dimension (in millimeters) of the neoplasia.

The UK guidelines [15] further distinguish the B5 category into B5a, B5b, and B5c for carcinomas. B5a includes DCIS with its three differentiation grades [23] and pleomorphic LCIS. To note, florid LCIS is still classified as B4 by the Royal College of Pathology guidelines [7]. Encapsulated papillary carcinoma and solid-papillary carcinoma, in the absence of invasive features, should also be included in this category because biopsy alone cannot definitively establish the infiltrative nature of the lesion. In approximately 20% of cases with a preoperative diagnosis of carcinoma in situ, the definitive histological examination reveals contiguous infiltrating components alongside the in situ lesion [52].

The B5b category encompasses not only infiltrating carcinomas, but also less common infiltrating neoplasms such as malignant PTs, sarcomas, lymphomas, and metastatic tumors (Fig. 8). It is important to take into account that, according to the European guidelines, non-epithelial neoplasms could be also categorized under the proposed B5d category [8]. Preoperative histological diagnosis allows for the determination of infiltration foci in most cases, specifying the histotype and differentiation grade of the neoplasia. For lymphomas and sarcomas, the use of immunohistochemical markers enables precise characterization.

The B5c category refers to rare cases where it is not possible to definitively distinguish whether a carcinoma is in situ or infiltrating based on the biopsy material. This category is used when the biopsy contains only carcinoma with minimal surrounding stroma or when rare atypical cells are present in the stroma within the context of overlapping inflammation or artifact-related changes, making it unclear whether stromal infiltration is present.

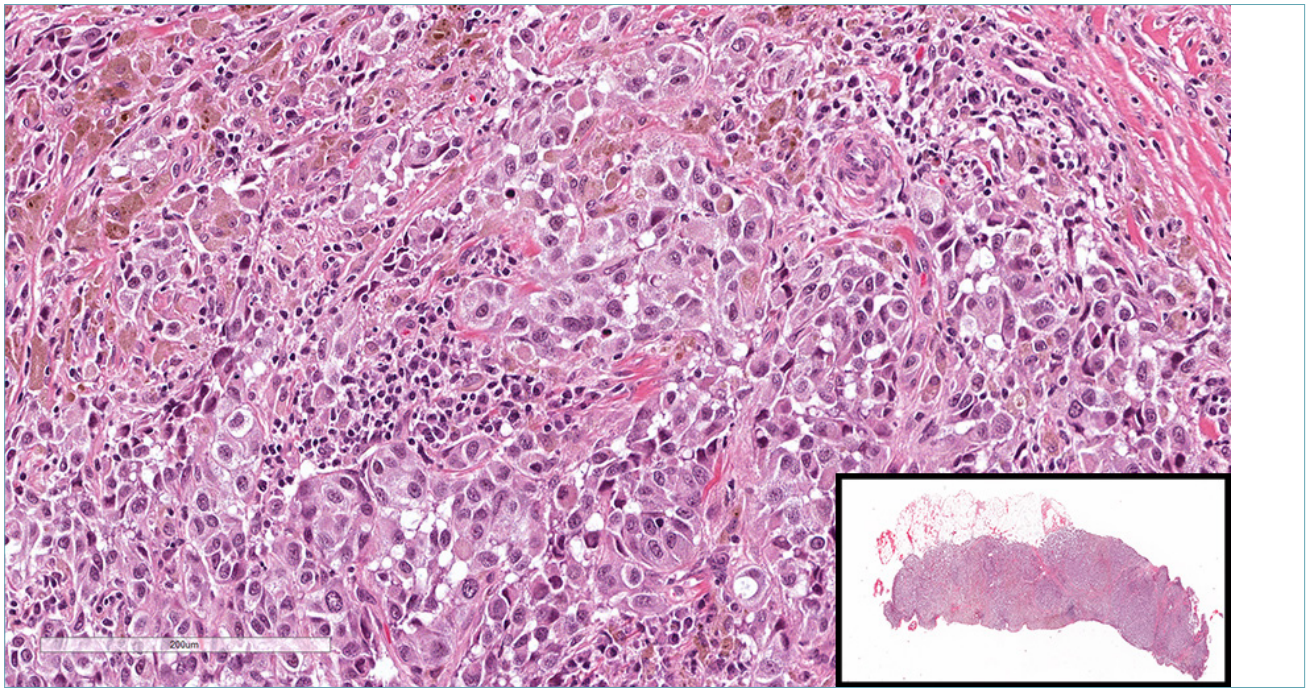

Figure 8. Densely cellular cores (inset) made up of atypical epithelioid cells associated with melanin pigment, consistent with metastatic malignant melanoma. The neoplastic cells stained positive for Melan-A and HMB45 (not shown).

Prognostic and predictive factors in breast invasive carcinoma

In invasive carcinomas, it is generally possible to state the predominant histotype and differentiation grade. High quality studies report the highest inter-observer agreement for certain histotypes (e.g. mucinous, lobular) and lower agreement for others (i.e. medullary, mixed) [53]. Identifying the lobular histotype, potentially using immunohistochemical markers such as E-cadherin and/or p120, is particularly important. This identification can indicate the need for preoperative MRI, which aids in assessing the potential multifocality of the lesion and subsequently planning the most appropriate therapeutic approach (mastectomy vs. conservative surgery) [54].

A definitive diagnosis of microinvasive carcinoma cannot be made preoperatively as it requires evaluating the entire neoplasia. However, it is crucial to report the presence of stromal microinvasion foci (individual neoplastic cells infiltrating the stroma; infiltration less than 1 mm) in the preoperative diagnosis. This information can guide multidisciplinary decisions regarding sentinel lymph node biopsy. In cases with stromal microinvasion foci, serial sectioning of the tissue block and immunohistochemical staining for cytokeratins are recommended to rule larger invasive foci.

Precise concordance between the grade of infiltrating carcinoma in the preoperative biopsy and the definitive histological examination is achieved in approximately 70% of cases [55,56]. Among the three parameters in the Elston-Ellis score (tubule and gland formation, nuclear pleomorphism, and mitotic count) [57], nuclear grade is the most reliable in the preoperative setting. However, variations may occur, particularly concerning the mitotic count, which can lead to underestimation (typically by one level; e.g., G2 vs. G3) compared to the definitive histological examination [15]. This information should be communicated to the multidisciplinary team as specifying the grade of the neoplasia is crucial for therapeutic decisions regarding neoadjuvant chemotherapy (NAC). (UK guidelines - level of evidence B: invasive tumor grade is a prognostic and predictive factor for therapy response) [15]

Currently, preoperative reporting recommends evaluating intratumoral stromal lymphocytic infiltrates, known as tumor-infiltrating lymphocytes (TILs) [58]. This assessment is particularly significant for triple-negative or HER-2-positive carcinomas undergoing NAC [59]. TIL quantification in CNBs should be conducted at 20-40x magnification using a 10x eyepiece. Thanks to consensus scoring guidelines, the reported concordance in preoperative TIL evaluation is good (63%) [60]. Additionally, preoperative reports should specify the presence of vascular invasion when it is unequivocal [9].

CNB material is suitable for evaluation of biomarkers, which is pivotal for patients likely to receive NAC (Level of evidence IA - Steroid receptor status predicts response to endocrine therapies; Level of evidence IA - Overexpression of HER2 predicts response to HER2 targeted treatments) [61]. For reporting hormone receptors and HER2 expression, adherence to the ASCO CAP guidelines is recommended [62-64]. As for Ki-67, while numerous studies support its prognostic value, clinical validation has proven challenging, especially in defining a useful cutoff and dealing with high inter-observer variability. However, both high and low values of this marker have demonstrated reproducibility and clinical relevance [65]. According to the latest update from the International Ki-67 Working Group (IKWG), Ki-67 has predictive clinical utility in hormone-positive and HER2-negative carcinomas, with cutoffs of ≤ 5% and ≥ 30% [66].The IKWG study suggests that to minimize inter-observer variability for evaluating Ki-67 biopsy material should be used which involves calculating the average score across four high-power fields, each containing approximately 100 cells, after a rapid assessment of the entire section [67]. In this view, automated digital image analysis systems show promising results but require further standardization and clinical validation.

Given the heterogeneity of breast carcinoma, the assessment of immunohistochemical markers is most informative when the neoplastic tissue is well-represented in the biopsy material. Thus, it is advisable to repeat the evaluation of biomarkers during the definitive histological examination, either entirely or partially, if the quantity of neoplastic tissue in the preoperative diagnosis is limited or if there is any discrepancy between the preoperative histological appearance and the definitive findings. Specifically, if the biomarker profile has already been investigated on CNB material, it is recommended to reassess it in the operative specimen in the following cases:

1) morphologically different/heterogeneous tumors/different grade (G) from that observed in the biopsy;
2) previous NAC;
3) limited invasive component in biopsies;
4) unusual HER2 scoring or biological profiles: (i.e. IHC/ISH);
5) Equivocal HER2 (IHC 2 +) scoring negative for amplification;
6) Ki-67[68]: luminal tumors with HER2 negative scoring.

Namely, due to the likelihood of discordant profiles between biopsies and surgical specimens, it is advisable to repeat Ki-67 testing in the following cases: G2, divergent morphological features and/or grading between the primary tumor and synchronous axillary lymph node

metastases in preoperative biopsies, tumors ≥ pT1c;
7) Expression of estrogen receptors (ER) < 30% and progesterone receptors (PR) less than 20% in preoperative biopsies;
8) HER2 score 0 in preoperative biopsies;
9) Large tumors (greater than 3 cm).

Multiple tumors

All suspicious foci for invasive tumors should undergo CNB sampling (early breast cancer: ESMO Clinical Practice Guidelines 2019 - Level of evidence I A) [69]. If CNB is not feasible, it is crucial to identify which tumor was biopsied and to place a non-magnetic marker in the biopsied site. It is recommended to perform the biomarker profile on all biopsied invasive tumors, particularly if they have different grading, histotypes, or display high-grade features (G3) [70]. Additionally, when synchronous metastatic lymph nodes exhibit morphology, histotype, or grading differences compared to the breast neoplasia, evaluating prognostic factors at both sites may be useful, especially in determining eligibility for neoadjuvant treatment [71-75] (Fig. 9).

Specific requirements for preoperative diagnosis of cases eligible to NAC

Pathologists must be provided with complete and detailed clinical information, including the location and dimensions of the lesion(s), along with copies of imaging reports (mammography, ultrasound, MRI). It is recommended to sample at least one core per centimeter of the tumor. For lesions larger than 2 cm, biopsies should be taken from different areas of the tumor. Ideally, 5-6 diagnostic cores should be obtained using a 14 G needle. If only one diagnostic fragment is available, consider repeating the CNB. The tissue fragments should be immediately fixed in buffered neutral formalin for no less than 6 hours and no more than 72 hours.
The preoperative histological report, particularly before neoadjuvant chemotherapy or primary systemic therapy, should include the following information:
1) number of diagnostic fragments;
2) histotype:
3) histological grade (Elston-Ellis or nuclear grade);
4) cellularity, expressed as the percentage of invasive

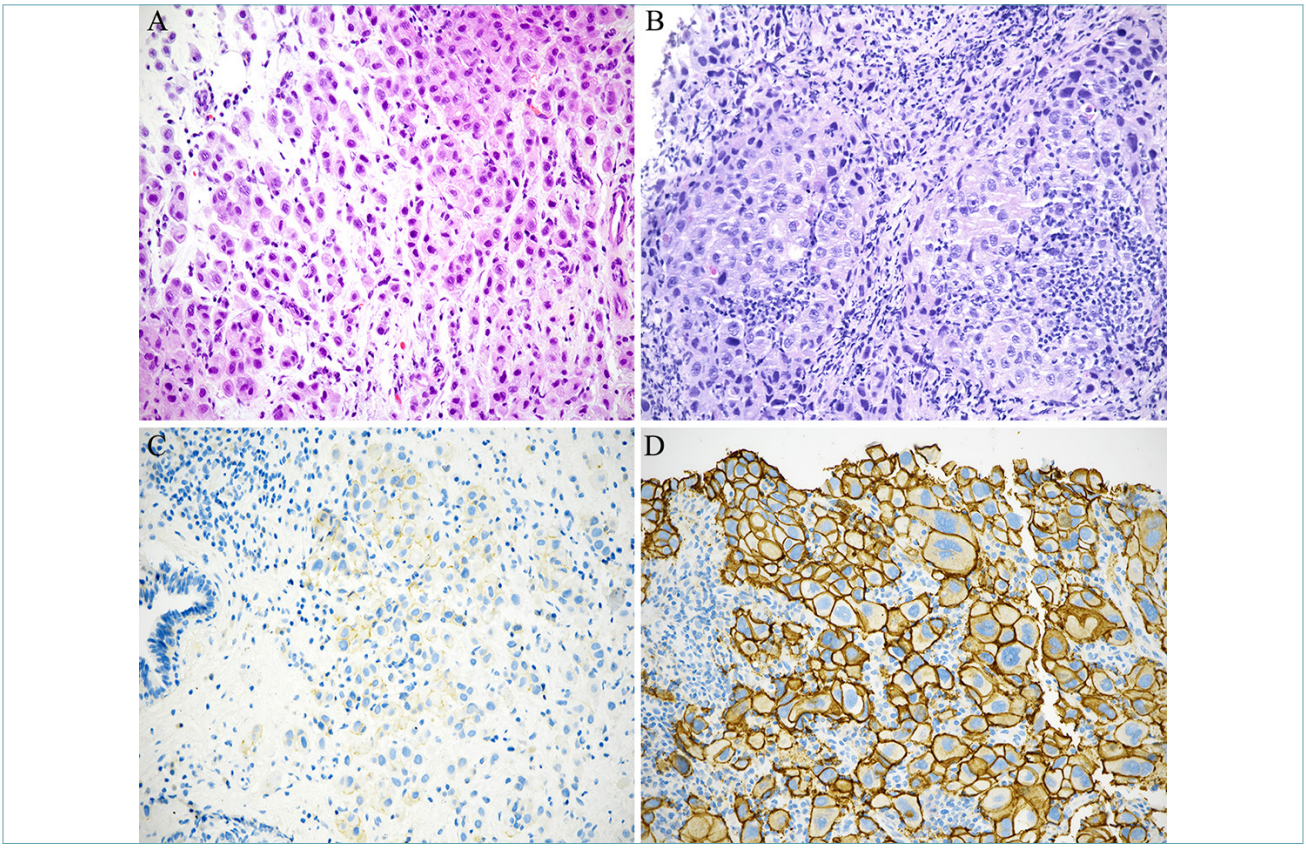

Figure 9. Biomarker discordance between primary breast tumor and axillary lymph nodal metastasis: H&E sections displaying an invasive lobular carcinoma with histiocytoid features in the primary tumor (A), compared to no-special type morphology in the nodal localization (B). Immunohistochemically, the neoplastic cells from the primary tumor revealed faint and incomplete membranous HER2 staining (score 1 +) (C), opposite to strong and complete expression (score 3 +) within the nodal metastasis (D).

carcinoma area within the tumor bed;
5) presence or absence of vascular invasion, when assessable;
6) presence or absence of tumor necrosis;
7) presence or absence of in situ carcinoma;
8) TILs, expressed as a percentage relative to the total stromal cells within the tumor (especially for TN and HER2+ carcinomas);
9) expression of ER, PgR, Ki-67, and HER2*;
10) for skin biopsies, note any epidermal infiltration, ulceration, or dermal vascular invasion.
**Regarding HER2 reporting, provide not only the score (0, 1+, 2+, 3+) but also the percentage of positive cells, positivity pattern, intensity (mild, moderate, intense), and specifics of the test used (clone, platform)* [64].

To ensure the reliability and reproducibility of preoperative diagnostics, adherence to regional, national, and/or international quality programs is essential [1,10].

Lymph node sampling is recommended by several guidelines (ASCO, NCCN, etc.). It is important to note that while fine-needle aspiration cytology (FNA) remains reliable for detecting malignant cells in suspicious axillary lymph nodes [23], it is now advisable to also perform biopsy histological sampling of these nodes. Published evidence highlights that ultrasound-guided CNB achieves higher sensitivity rates compared to FNA (88% vs 73-74% respectively), with comparable specificity [76,77]. These findings have significant clinical and therapeutic implications, especially for patients with small HER2-positive and triple-negative tumors in the neoadjuvant setting. For example, HER2-positive tumors measuring less than 15 mm with negative nodes may undergo upfront surgery followed by adjuvant chemotherapy with paclitaxel and trastuzumab, thereby avoiding the side effects of anthracycline-based regimens [78]. Conversely, patients with preoperatively positive lymph nodes are recommended to receive neoadjuvant chemotherapy combined with trastuzumab/pertuzumab, and in cases of residual disease, they may receive adjuvant TDM1 therapy. Similarly, patients diagnosed with triple-negative tumors with nodal metastases are currently treated with pembrolizumab as neoadjuvant immunotherapy, but they could proceed directly to upfront surgery if they have small tumors with negative axillary lymph nodes [61]. In addition, it is important to clinically validate emerging pathological data indicating a 5-10% discordance in biomarkers profile between primary breast tumors and synchronous core-biopsied axillary nodal metastases, as this discrepancy may have further prognostic and therapeutic implications [75].

Regardless of the lymph node biopsy technique used, it is advisable to place a clip inside the pathological lymph node. For patients initially diagnosed as cN+ (clinically positive lymph nodes) who convert to cN0 (clinically negative lymph nodes) after primary systemic therapy, evidence suggests that identifying and removing the biopsied lymph node can significantly reduce the false-negative rate (FNR) to well below 10%. This threshold is based on historical studies on sentinel lymph nodes, such as the B32 and Veronesi studies in the early-stage setting. However, retrieving the lymph node marked with a clip can be technically challenging or require specialized devices. Specifically, the targeted axillary dissection (TAD) technique reduces the FNR to 4.2% with a near 100% identification rate [79]. Alternatively, using a dual identification method (radiometabolic tracer and vital dye) and removing at least three lymph nodes can effectively reduce the FNR to below 10% [80]. More recently, the SenTa study, a prospective registry involving 50 centers, demonstrated an 86.9% success rate for TAD with a false-negative rate of 4.3% [81]. These findings underscore the utility of TAD and align with a recent Italian retrospective series, which found approximately 25% of clipped lymph nodes did not correspond to sentinel nodes [82].

Turn-around time

Recent evidence confirms the importance of timely management, emphasizing that treatment should start within 8 weeks from diagnosis [83]. For triple-negative neoplasms, it is particularly advisable to begin treatment within 4-6 weeks. Consideration should also be given to alternative pathways for managing particularly aggressive neoplasms, as well as for more indolent types, such as tubular carcinoma or grade 1 carcinomas.

Diagnostic challenges and pitfalls in preoperative assessment

- Lesion fragmentation: access to imaging of the lesion, proper handling of biopsy material, and multidisciplinary collaboration are essential.
- Complex lesions: preoperative evaluation of complex proliferative breast lesions may require immunohistochemical techniques and serial sectioning of the material.
- Partial assessment: partial sampling of a lesion can lead to underestimation. For example, approximately 20% of in situ carcinomas associated with microcalcifications reveal infiltrative foci upon definitive surgical intervention.

Difficulties in interpretation related to specific morphological findings

Low-grade epithelial atypia: mild atypia in the terminal ductal-lobular epithelium is common in CNBs. It is crucial not to overestimate minimal atypia, as it represents usual ductal hyperplasia (UDH) or apocrine metaplasia (classified as B2). Atypia at risk of progression, such as ADH, is a clonal proliferation that overexpresses ER and shows concurrent loss of basal immunomarkers (CK 5, CK 5/6, and CK 14). These immunohistochemical markers are valuable for distinguishing ADH from UDH in routine diagnostics.

Apocrine atypia and apocrine DCIS: apocrine atypia, especially when associated with sclerosing lesions, can be challenging to interpret on CNB. Large nuclei with prominent nucleoli may be overestimated and misinterpreted as DCIS. Pure apocrine DCIS is relatively rare. In such cases, features like periductal fibrosis, lymphocytic infiltrate, mitoses, and comedonecrosis can assist in accurate diagnostic interpretation.

Pseudolactational cystic changes: Hypersecretory pseudolactational cystic changes can persist beyond lactation or pregnancy, even into the postmenopausal period. Recognizing the lobular pattern, cytoplasmic vacuoles, and typical hobnail architecture is crucial to correctly classify the lesion (Fig. 10).

Microglandular adenosis: in microglandular adenosis, myoepithelial cells are not visible. The tubules have a round profile, patent lumen and are composed of cells with clear cytoplasm. Immunohistochemically, these cells show positivity for S100 protein and cathepsin-D but are negative for EMA, ER, PR, and HER-2.

Stromal proliferations and spindle cell lesions: spindle cell proliferations can pose diagnostic challenges in CNBs. Specifically, scar-related changes

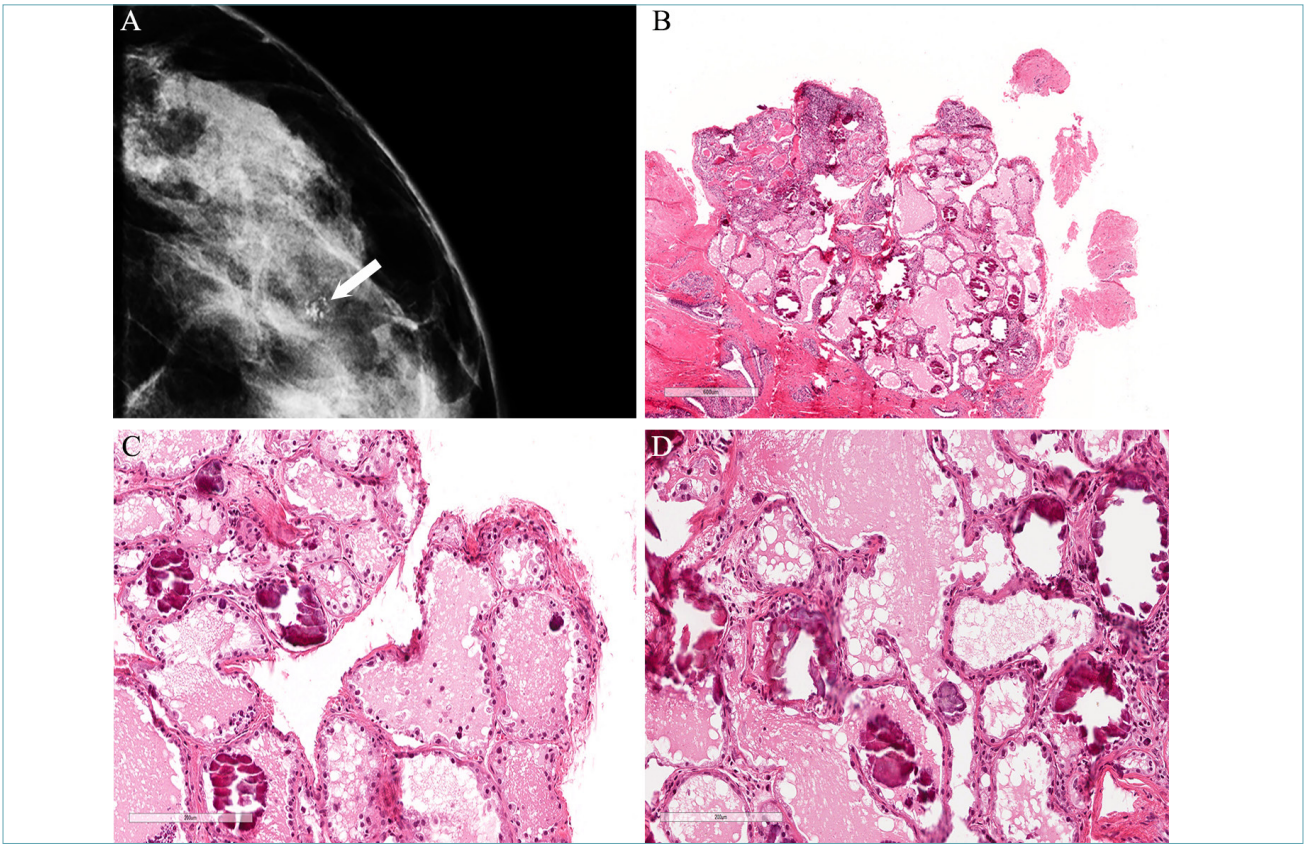

Figure 10. Mammogram showing a single cluster of coarse heterogeneous microcalcifications (arrow, BI-RADS 4B) (A) undergoing VAB. Low (B) and high-power magnification (C, D) histological pictures depicting dilatated ductal structures filled with eosinophilic secretion and microcalcifications lined by a single layer of foamy epithelial cells without cytological atypia and a hobnail appearance. Such morphological features were consistent with pseudolactational cystic changes.

may exhibit cytological atypia. Similarly, distinguishing between myofibroblastoma, fibromatosis, and metaplastic or spindle cell carcinomas can be complex.

Post-radiation changes: radiation therapy can induce cytological changes in ductal epithelium and histiocytic cells, such as anisonucleosis and regressive atypia, which may mimic neoplastic cells.

Peculiar scenarios potentially occurring in definitive histological examinations following preoperative biopsy.

Complete preoperative resection of the lesion. In small lesions, there may be no neoplastic residue in the definitive histology. In such cases, the biological characterization must rely on preoperative biopsy material.

Alterations in residual tissue. Scar tissue exhibiting regressive changes and chronic histiocytic giant cell inflammation, often seen following a previous biopsy, is now commonly observed in definitive histology. These findings indicate the successful excision of the preoperatively targeted area and should be described in the pathology report.

Epithelial cell displacement along the needle tract and in regional lymph nodes.
Diagnostic procedures involving needle insertion into the lesion can result in the artifactually displacement of epithelial cells. Recognizing these displaced cells is crucial, especially when evaluating sentinel lymph node or assessing potential microinvasive foci. In cases where there is an absence of myoepithelium within granulation tissue that contains hemosiderin deposits and/or reparative fibrosis, this should be reported as pseudoinfiltration.

Dimension assessment of the neoplastic lesion undergoing preoperative biopsy. When evaluating the size of a neoplastic lesion based solely on the residual tumor after biopsy, there is a risk of underestimating the T stage, as highlighted by the AJCC, 8th edition (2018). To avoid this, the overall lesion size should be determined using a combination of imaging, macroscopic evaluation, and histological section measurements. For the "T" parameter evaluation, the AJCC, 8th edition (2018) recommends using the largest tumor size measured either from biopsy material or definitive surgical specimens, provided that imaging does not indicate a larger tumor size.

Conflicts of interest statement

The authors have nothing to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution

Conceptualization: SM and AR. Methodology: SM and AR. Formal analysis and investigation: SM and AR. Writing — original draft preparation: SM, NF, and AR. Writing — review and editing: IC, FC, CC, PF, DS, DT, DB, MB, MC, GC, MGC, LC, GDA, NF, OG, MR, GS, AS, CS, GSc, FP, and ASap. Supervision: AR.

References

1 Public Health England. Clinical guidance for breast cancer screening assessment (NHSBSP Publication No 49). London; 2016. Available at: https://www.gov.uk/government/publications/breast-screening-clinical-guidelines-for-screening-management.

2 Schünemann HJ, Lerda D, Quinn C, et al. Breast Cancer Screening and Diagnosis: A Synopsis of the European Breast Guidelines. Ann. Intern. Med. 2020;172:46-56. https://doi.org/10.7326/M19-2125.

3 Tamaki K, Sasano H, Ishida T, et al. Comparison of core needle biopsy (CNB) and surgical specimens for accurate preoperative evaluation of ER, PgR and HER2 status of breast cancer patients. Cancer Sci. 2010;101:2074-2079. https://doi.org/10.1111/j.1349-7006.2010.01630.x.

4 Rageth CJ, O'Flynn EAM, Pinker K, et al. Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast Cancer Res. Treat. 2019;174:279-296. https://doi.org/10.1007/s10549-018-05071-1.

5 Sharma N, Cornford E, Cheung S, et al. The impact of vacuum-assisted excision in the management of indeterminate B3 lesions in the NHS Breast Screening Programme in England. Clin. Radiol. 2021;76:470.e23-470.e29. https://doi.org/10.1016/j.crad.2021.01.021.

6 Writing Group of the National Quality Assurance Coordinating Group for Breast Screening Pathology. Guidance. Breast screening: quality assurance guidelines for breast pathology services. 2020. Available at: https://www.gov.uk/government/publications/breast-screening-quality-assurance-guidelines-for-breast-pathology-services/breast-screening-quality-assurance-guidelines-for-screening-pathology-services#regional-delivery-of-breast-pathology-quality-and-quality. Accessed April 25, 2024.

7 Ellis IO, Carder P, Hales S, et al. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer.; 2016. Available at: https://www.rcpath.org/uploads/assets/7763be1c-d330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16.pdf.

8 Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis.; 2006. Available at: papers://7fb3a579-17eb-4f3e-967a-87b6e77fe28f/Paper/p1630.

9 Bilous M. Breast core needle biopsy: issues and controversies. Mod. Pathol. 2010;23 Suppl 2:S36-45. https://doi.org/10.1038/modpathol.2010.34.

10 Biganzoli L, Cardoso F, Beishon M, et al. The requirements of a specialist breast centre. The Breast 2020;51:65-84. https://doi.org/https://doi.org/10.1016/j.breast.2020.02.003.

[11] Lee AH, Anderson N, Carder P, et al. Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening. London; 2021. Available at: www.rcpath.org.

[12] 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. Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. 2024;50:107292. https://doi.org/10.1016/j.ejso.2023.107292.

[13] Collins LC, Connolly JL, Page DL, et al. Diagnostic agreement in the evaluation of image-guided breast core needle biopsies: results from a randomized clinical trial. Am. J. Surg. Pathol. 2004;28:126-131. https://doi.org/10.1097/00000478-200401000-00015.

[14] Trocchi P, Holzhausen H-J, Löning T, et al. Intraobserver Agreement on Histopathologic Evaluations of Core Breast Biopsies. Breast J. 2017;23:215-219. https://doi.org/10.1111/tbj.12708.

[15] Lee AH, Anderson N, Carder P, et al. Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening. London; 2021.

[16] Rakha EA, Lee AHS, Jenkins JA, et al. 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;129:1417-1424. https://doi.org/10.1002/ijc.25801.

[17] 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;20:264-270. https://doi.org/10.1016/j.breast.2010.12.003.

[18] Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. J. Clin. Oncol. 2005;23:5534-5541. https://doi.org/10.1200/JCO.2005.04.038.

[19] Commission E, Consumers D-G for H and, Karsa L, et al. European guidelines for quality assurance in breast cancer screening and diagnosis - Fourth edition, supplements. (Karsa L, Holland R, Broeders M, et al., eds.). Publications Office; 2013. https://doi.org/doi/10.2772/13196.

[20] Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis.; 2006.

[21] Brem RF. Management of Breast Atypical Ductal Hyperplasia: Now and the Future. Radiology 2020;294:87-88. https://doi.org/10.1148/radiol.2019192192.

[22] 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;294:76-86. https://doi.org/10.1148/radiol.2019190748.

[23] WHO Classification of Tumours Editorial Board. WHO Classification of Tumours. Breast tumours. 5th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2019.

[24] Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann. Oncol. 2008;19:614-622. https://doi.org/10.1093/annonc/mdm481.

[25] von Karsa L, Arrossi S. Development and implementation of guidelines for quality assurance in breast cancer screening: the European experience. Salud Publica Mex. 2013;55:318-328. https://doi.org/10.21149/spm.v55i3.7215.

[26] 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 Arch. 2023;483:5-20. https://doi.org/10.1007/s00428-023-03566-x.

[27] Solorzano S, Mesurolle B, Omeroglu A, et al. Flat epithelial atypia of the breast: pathological-radiological correlation. AJR. Am. J. Roentgenol. 2011;197:740-746. https://doi.org/10.2214/AJR.10.5265.

[28] Wahab RA, Lee S-J, Mulligan ME, et al. Upgrade Rate of Pure Flat Epithelial Atypia Diagnosed at Core Needle Biopsy: A Systematic Review and Meta-Analysis. Radiol. Imaging Cancer 2021;3:e200116. https://doi.org/10.1148/rycan.2021200116.

[29] Berg WA, Mrose HE, Ioffe OB. Atypical lobular hyperplasia or lobular carcinoma in situ at core-needle breast biopsy. Radiology 2001;218:503-509. https://doi.org/10.1148/radiology.218.2.r01fe32503.

[30] Hartmann LC, Degnim AC, Santen RJ, et al. Atypical hyperplasia of the breast--risk assessment and management options. N. Engl. J. Med. 2015;372:78-89. https://doi.org/10.1056/NEJMsr1407164.

[31] Tavassoli FA, Devilee P, International Agency for Research on Cancer, et al. Pathology and genetics of tumours of the breast and female genital organs. In: World Health Organisation Classification of Tumours. Lyon, France: International Agency for Research on Cancer; 2003:432.

[32] Tavassoli FA. Lobular neoplasia: evolution of its significance and morphologic spectrum. Int. J. Surg. Pathol. 2010;18:174S-177S. https://doi.org/10.1177/1066896910370879.

[33] Calhoun BC, Collins LC. Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. Histopathology 2016;68:138-151. https://doi.org/10.1111/his.12852.

[34] Szynglarewicz B, Kasprzak P, Hałoń A, et al. Lobular carcinoma in situ of the breast - correlation between minimally invasive biopsy and final pathology. Arch. Med. Sci. 2017;13:617-623. https://doi.org/10.5114/aoms.2016.61815.

[35] Muller KE, Roberts E, Zhao L, et al. Isolated Atypical Lobular Hyperplasia Diagnosed on Breast Biopsy: Low Upgrade Rate on Subsequent Excision With Long-Term Follow-up. Arch. Pathol. Lab. Med. 2018;142:391-395. https://doi.org/10.5858/arpa.2017-0155-OA.

[36] Susnik B, Day D, Abeln E, et al. Surgical Outcomes of Lobular Neoplasia Diagnosed in Core Biopsy: Prospective Study of 316 Cases. Clin. Breast Cancer 2016;16:507-513. https://doi.org/10.1016/j.clbc.2016.06.003.

[37] Sullivan ME, Khan SA, Sullu Y, et al. Lobular carcinoma in situ variants in breast cores: potential for misdiagnosis, upgrade rates at surgical excision, and practical implications. Arch. Pathol. Lab. Med. 2010;134:1024-1028. https://doi.org/10.5858/2009-0300-OA.1.

[38] Flanagan MR, Rendi MH, Calhoun KE, et al. Pleomorphic Lobular Carcinoma In Situ: Radiologic-Pathologic Features and Clinical Management. Ann. Surg. Oncol. 2015;22:4263-4269. https://doi.org/10.1245/s10434-015-4552-x.

[39] Fasola CE, Chen JJ, Jensen KC, et al. Characteristics and clinical outcomes of pleomorphic lobular carcinoma in situ of the breast. Breast J. 2018;24:66-69. https://doi.org/10.1111/tbj.12843.

[40] Plaza MJ, Swintelski C, Yaziji H, et al. Phyllodes tumor: review of key imaging characteristics. Breast Dis. 2015;35:79-86. https://doi.org/10.3233/BD-150399.

[41] Lerwill MF, Lee AHS, Tan PH. Fibroepithelial tumours of the breast-a review. Virchows Arch. 2022;480:45-63. https://doi.org/10.1007/s00428-021-03175-6.

[42] Eiada R, Chong J, Kulkarni S, et al. Papillary lesions of the breast: MRI, ultrasound, and mammographic appearances. AJR. Am. J. Roentgenol. 2012;198:264-271. https://doi.org/10.2214/AJR.11.7922.

[43] Cohen MA, Newell MS. Radial Scars of the Breast Encountered at Core Biopsy: Review of Histologic, Imaging, and Management

Considerations. AJR. Am. J. Roentgenol. 2017;209:1168-1177. https://doi.org/10.2214/AJR.17.18156.

[44] Dang BQ, Miles B, Young P, et al. Mucocele-Like Lesion of the Breast. Cureus 2023;15:e37829. https://doi.org/10.7759/cureus.37829.

[45] Rakha EA, Shaaban AM, Haider SA, et al. Outcome of pure mucocele-like lesions diagnosed on breast core biopsy. Histopathology 2013;62:894-898. https://doi.org/10.1111/his.12081.

[46] Gibreel WO, Boughey JC. Mucocele-Like Lesions of the Breast: Rate of Upstaging and Cancer Development. Ann. Surg. Oncol. 2016;23:3838-3842. https://doi.org/10.1245/s10434-016-5352-7.

[47] Meares AL, Frank RD, Degnim AC, et al. Mucocele-like lesions of the breast: a clinical outcome and histologic analysis of 102 cases. Hum. Pathol. 2016;49:33-38. https://doi.org/10.1016/j.humpath.2015.10.004.

[48] Bucchi L, Belli P, Benelli E, et al. Recommendations for breast imaging follow-up of women with a previous history of breast cancer: position paper from the Italian Group for Mammography Screening (GISMa) and the Italian College of Breast Radiologists (ICBR) by SIRM. Radiol. Med. 2016;121:891-896. https://doi.org/10.1007/s11547-016-0676-8.

[49] Strachan C, Horgan K, Millican-Slater RA, et al. 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;69:248-254. https://doi.org/10.1136/jclinpath-2015-203018.

[50] Senonetwork. Raccomandazioni Senonetwork Di Buona Pratica Clinica - Lesioni B3.; 2020. Available at: https://www.senonetwork.it/it/raccomandazioni/1-3798-1-#.

[51] Wong SM, King T, Boileau J-F, et al. Population-Based Analysis of Breast Cancer Incidence and Survival Outcomes in Women Diagnosed with Lobular Carcinoma In Situ. Ann. Surg. Oncol. 2017;24:2509-2517. https://doi.org/10.1245/s10434-017-5867-6.

[52] Lee CH, Carter D, Philpotts LE, et al. Ductal carcinoma in situ diagnosed with stereotactic core needle biopsy: can invasion be predicted? Radiology 2000;217:466-470. https://doi.org/10.1148/radiology.217.2.r00nv08466.

[53] Ellis IO, Coleman D, Wells C, et al. Impact of a national external quality assessment scheme for breast pathology in the UK. J. Clin. Pathol. 2006;59:138-145. https://doi.org/10.1136/jcp.2004.025551.

[54] El Sharouni M-A, Postma EL, Menezes GLG, et al. High Prevalence of MRI-Detected Contralateral and Ipsilateral Malignant Findings in Patients With Invasive Ductolobular Breast Cancer: Impact on Surgical Management. Clin. Breast Cancer 2016;16:269-275. https://doi.org/10.1016/j.clbc.2015.10.002.

[55] Harris GC, Denley HE, Pinder SE, et al. Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. Am. J. Surg. Pathol. 2003;27:11-15. https://doi.org/10.1097/00000478-200301000-00002.

[56] Rakha EA, Ellis IO. An overview of assessment of prognostic and predictive factors in breast cancer needle core biopsy specimens. J. Clin. Pathol. 2007;60:1300-1306. https://doi.org/10.1136/jcp.2006.045377.

[57] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403-410. https://doi.org/10.1111/j.1365-2559.1991.tb00229.x.

[58] Salgado R, Denkert C, Demaria S, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann. Oncol. 2015;26:259-271. https://doi.org/10.1093/annonc/mdu450.

[59] Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann. Oncol. 2019;30:1541-1557. https://doi.org/10.1093/annonc/mdz235.

[60] Khoury T, Peng X, Yan L, et al. Tumor-Infiltrating Lymphocytes in Breast Cancer: Evaluating Interobserver Variability, Heterogeneity, and Fidelity of Scoring Core Biopsies. Am. J. Clin. Pathol. 2018;150:441-450. https://doi.org/10.1093/ajcp/aqy069.

[61] Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann. Oncol. 2024;35:159-182. https://doi.org/10.1016/j.annonc.2023.11.016.

[62] Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J. Clin. Oncol. 2020;38:1346-1366. https://doi.org/10.1200/JCO.19.02309.

[63] Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J. Clin. Oncol. 2018;36:2105-2122. https://doi.org/10.1200/JCO.2018.77.8738.

[64] Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. J. Clin. Oncol. 2023;41:3867-3872. https://doi.org/10.1200/JCO.22.02864.

[65] Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). Eur. J. Cancer 2017;75:284-298. https://doi.org/10.1016/j.ejca.2017.01.017.

[66] Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group. J. Natl. Cancer Inst. 2021;113:808-819. https://doi.org/10.1093/jnci/djaa201.

[67] Leung SCY, Nielsen TO, Zabaglo L, et al. Analytical validation of a standardized scoring protocol for Ki67: phase 3 of an international multicenter collaboration. NPJ Breast Cancer 2016;2:16014. https://doi.org/10.1038/npjbcancer.2016.14.

[68] Ahn S, Lee J, Cho M-S, et al. Evaluation of Ki-67 Index in Core Needle Biopsies and Matched Breast Cancer Surgical Specimens. Arch. Pathol. Lab. Med. 2018;142:364-368. https://doi.org/10.5858/arpa.2017-0014-OA.

[69] Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann. Oncol. 2019;30:1194-1220. https://doi.org/10.1093/annonc/mdz173.

[70] Scatena C, Lemmi E, Cremonini A, et al. Heterogeneity of ER, PgR, HER2 and Ki67 in multifocal/multicentric breast cancer with a single histotype and same grade: implications for pathologists and oncologists from a large multi-institutional series. In: 14th European Breast Cancer Conference. Milan; 2024. https://doi.org/10.1016/j.ejca.2024.113619.

[71] Santinelli A, Pisa E, Stramazzotti D, et al. HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. Int. J. Cancer 2008;122:999-1004. https://doi.org/10.1002/ijc.23051.

[72] Kinoe H, Yamanouchi K, Kuba S, et al. Discordance of hormone receptor, human epidermal growth factor receptor-2, and Ki-67 between primary breast cancer and synchronous axillary lymph node metastasis. J. BUON. 2018;23:60-66.

[73] Zhao S, Xu L, Liu W, et al. Comparison of the expression of prognostic biomarkers between primary tumor and axillary lymph node metastases in breast cancer. Int. J. Clin. Exp. Pathol. 2015;8:5744-5748.

[74] Xi X, Huang X-W, Yuan H-Z, et al. Biomarker heterogeneity between primary breast cancer and synchronous axillary lymph node

metastases. Oncol. Lett. 2020;20:273. https://doi.org/10.3892/ol.2020.12136.

[75] Marletta S, Giorlandino A, Cavallo E, et al. Discordance of Biomarker Expression Profile between Primary Breast Cancer and Synchronous Axillary Lymph Node Metastasis in Preoperative Core Needle Biopsy. Diagnostics (Basel, Switzerland) 2024;14. https://doi.org/10.3390/diagnostics14030259.

[76] Balasubramanian I, Fleming CA, Corrigan MA, et al. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br. J. Surg. 2018;105:1244-1253. https://doi.org/10.1002/bjs.10920.

[77] Xu Q, Wang J, Wang J, et al. The effectiveness of ultrasound-guided core needle biopsy in detecting lymph node metastases in the axilla in patients with breast cancer: systematic review and meta-analysis. Clinics (Sao Paulo). 2023;78:100207. https://doi.org/10.1016/j.clinsp.2023.100207.

[78] Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N. Engl. J. Med. 2015;372:134-141. https://doi.org/10.1056/NEJMoa1406281.

[79] Caudle AS, Yang WT, Krishnamurthy S, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J. Clin. Oncol. 2016;34:1072-1078. https://doi.org/10.1200/JCO.2015.64.0094.

[80] Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet. Oncol. 2013;14:609-618. https://doi.org/10.1016/S1470-2045(13)70166-9.

[81] Kuemmel S, Heil J, Rueland A, et al. A Prospective, Multicenter Registry Study to Evaluate the Clinical Feasibility of Targeted Axillary Dissection (TAD) in Node-positive Breast Cancer Patients. Ann. Surg. 2022;276:e553-e562. https://doi.org/10.1097/SLA.0000000000004572.

[82] Costarelli L, Arienzo F, Broglia L, et al. Clipping a Positive Lymph Node Improves Accuracy of Nodal Staging After Neoadjuvant Chemotherapy for Breast Cancer Patients, but Does It Drive Management Changes? Ann. Surg. Oncol. 2024;31:3186-3193. https://doi.org/10.1245/s10434-024-15052-y.

[83] Wiener AA, Hanlon BM, Schumacher JR, et al. Reexamining Time From Breast Cancer Diagnosis to Primary Breast Surgery. JAMA Surg. 2023;158:485-492. https://doi.org/10.1001/jamasurg.2022.8388.