Controversial Breast Entities

Pseudoangiomatous Stromal Hyperplasia (PASH)

Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign proliferation of mesenchymal elements in the breast. Histologically, clusters of spindle cells form cleft-like spaces, resembling ectatic vessels, and can sometimes mimic a low-grade angiosarcoma. PASH has not been shown to signify an increased risk of subsequently developing breast cancer (1).

Imaging findings are variable. PASH can appear as an oval or round, non-calcified mass with circumscribed margins that resembles a fibroadenoma. Mammographically, it can also appear as a focal asymmetry or a developing asymmetry. It may be noted incidentally on imaging or PASH may also present as a palpable mass, sometimes one that is enlarging rapidly.

PASH is associated with hormone exposure, including oral contraceptive use, and is also seen in peri- and post-menopausal women on HRT (2).

Management:

- Per the American Society of Breast Surgeons consensus guidelines, the recommended management of PASH is clinical follow-up.
- Per review of the radiology literature, the following management considerations have been outlined (2,5):
    - If PASH is incidentally found in a CNB specimen, management should be as per the dominant lesion. No additional intervention is necessary or required.
    - When PASH is identified as a mass on imaging or is the targeted lesion on biopsy, surgical excision should be considered for large size (>3 cm).
    - Excision should be performed in a mass that shows progressive growth or is rapidly enlarging, and in all cases with radiologic-pathologic discordance or suspicious features on imaging.
    - Recurrence after excision has been reported to occur in 5-22% of cases.

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Flat Epithelial Atypia (FEA)

Flat epithelial atypia (FEA) is defined by the World Health Organization as a flat proliferation composed of one to several layers of cells which lack polarity and display low-grade cytological atypia (1,2,4). The cells usually have abundant pale and eosinophilic cytoplasm, and the involved terminal duct lobular units tend to be enlarged, with dilated smooth acini and inspissated and calcified secretions. Along with low-grade atypia, the diagnosis of FEA requires the absence of architectural complexity. When complex patterns, such as focal trabecular, Roman arches, or micropapillae are present, the diagnosis of atypical duct hyperplasia should be used instead (4). FEA seems to be associated with a very slight (1-2x) increased breast cancer risk (2).

FEA usually presents as microcalcifications on mammograms. It may also present as mammographic architectural distortions, or masses and non-mass findings on ultrasound (8).

FEA is found in approximately 5% of breast core needle biopsies (7,3). However, of note, a study by Samples et al concluded that there was substantial interobserver variability (~17 to 52% agreement) among pathologists in the diagnosis of FEA (5). In the literature, FEA has been shown to have an upgrade rate ranging from 0-21% (7,3). Studies with higher upgrade rates also included FEA with associated proliferative lesions with atypia. In cases of biopsies with pure concordant FEA, and where cases of the biopsy target being a mass or symptomatic were excluded, upgrade rates have been shown to be 2-3%.

Management:

- Per the American Society of Breast Surgeons consensus guidelines, the recommended management of pure FEA is observation with clinical and imaging follow-up. Excision is recommended for cases of FEA with concomitant ADH.
- Per review of the literature, the following management considerations have also been outlined:
    - Observation may be considered:
        - in cases of pure imaging concordant FEA diagnosed after percutaneous biopsy (needle size of 11 gauge or larger)
        - In cases where little or no residual calcifications are seen on post-biopsy imaging
        - Where FEA is incidental or minimal in the biopsy specimen
    - Excision should be considered:
        - in cases where there is imaging discordance
        - In cases where FEA presented as a mass or the biopsied target was symptomatic to the patient
        - In cases where FEA is associated with ADH or another high-risk lesion.
        - In patients with a history of breast cancer where FEA is the prominent or dominant lesion.

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Radial Scar/Complex Sclerosing Lesion

Radial scars are benign proliferative lesions characterized by a central focus of fibroelastic stroma with epithelial elements in the stroma and radiating spokes of ducts and lobules (1, 5). These ducts and lobules often demonstrate a variety of proliferative changes, including duct hyperplasia, sclerosing adenosis, and cysts (5). The distortion of the entrapped glands and the stellate appearance of radial scars can mimic cancer on diagnostic imaging and histology. The term radial scar usually refers to lesions smaller than 1 cm. If larger than 1 cm, the term complex sclerosing lesion is utilized.

Radial scars commonly present as architectural distortion on mammography, which is more frequently detected with digital breast tomosynthesis compared to 2D imaging (1,2). Radial scars can also present as calcifications or may be associated with calcifications mammographically. When seen on ultrasound, radial scars look like irregular hypoechoic masses. The MRI appearance is variable and ranges from not being visible to irregular enhancing masses or non-mass enhancement. There are no imaging characteristics that reliably distinguish radial scar from malignancy in any modality (5).

There is no evidence that radial scars evolve over time into malignancies, i.e. they are not considered premalignant lesions. Radial scars, however, frequently coexist with other proliferative lesions, including atypia, and do coexist with cancers at a frequency higher than one would expect simply from chance alone (5). The upgrade rate of radial scars may be related to the coexistence of other proliferative lesions and/or sampling error given that the associated lesions are frequently eccentric and peripherally located.

The upgrade rate of radial scars in the literature is variable and ranges from 0- 43% (4,5). In general, later publications with the use of larger-gauge vacuum-assisted sampling devices and more cores have shown significantly lower upgrade rates. For example, a recent meta-analysis with over 3000 radial scars diagnosed on core needle biopsy showed an upgrade rate of 7% (3). This further decreased to 1% when looking at radial scars without atypia diagnosed with 8-11 gauge needles (3). Features associated with increased upgrade risk included older age, postmenopausal status, the finding of architectural distortion or mass (rather than calcifications), the target abnormality being palpable, the presence of atypia, and small biopsy gauge (1, 2,4,6).

Management:

- Per the American Society of Breast Surgeons consensus guidelines, excision is recommended for radial scars/complex sclerosing lesions. Small, adequately sampled CSLs may be observed.
- Per review of the literature, the following management considerations have also been outlined:
    - Small (<1 cm) lesions sampled via a large gauge vacuum-assisted biopsy device with no associated atypia may reasonably undergo observation in appropriate patients (average risk, rad-path concordant, biopsy target of calcifications, or is incidental/the non-primary abnormality on biopsy).
    - It may be challenging to assess changes in radial scars presenting as architectural distortion if imaging surveillance is elected rather than excision. MRI may be helpful for triage.
    - When doubt about sufficient sampling exists, surgical excision seems the best and safest approach.

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Papilloma

Breast lesions of papillary origin comprise less than 10% of benign lesions and less than 2% of breast cancers (2). The practice of excising benign papillary lesions (also called central or solitary papillomas) without evidence of atypia is overall quite controversial and a consensus has not been reached. Benign papillomas are the most commonly diagnosed papillary lesions. Multiple benign papillomas (5 or more) is defined as papillomatosis.

Papillary lesions on mammogram commonly present as masses that may be associated with calcifications. On ultrasounds, papillary lesions can appear as complex cystic/solid masses or homogeneous solid masses. Suspicious features would include an echogenic halo, taller-than-wide orientation, echogenic halo or posterior acoustic enhancement that is associated with calcifications (1).

Management of benign papillary lesions remains controversial. Traditionally, they were all excised but recent studies have proposed that surgical intervention is not necessary in the absence of atypia and if there is no imaging discordance. Some of the features that have supported close observation are women less than 55 years of age and mass size less than 1 cm. When an excisional biopsy is not performed, a follow-up with mammography and ultrasound every 6 months for 2 years and annually after that has been recommended [33].

The incidence of invasive carcinoma following excision is 2% or less in the ipsilateral breast, 2% or less in the contralateral breast and 0.3% for bilateral neoplasms. These data support the decision of not performing extensive surgery after benign papillomas have been diagnosed by excisional biopsy (6).

“The event-free survival of papillomas without atypia has been reported at 96%, compared with 77% for papillomas with atypia. This confirms that findings of atypia are associated with a higher risk of recurrence or developing upgraded lesions in a long-term follow-up” (1).

The American Society of Breast Surgeons guidelines currently recommend that papillary lesions be either excised or undergo clinical/imaging follow up. More specifically, excision is recommended for palpable lesions and those associated with atypia. The consensus document also states “Given significant disagreement seen in retrospective data in the literature, small, incidental benign papillary lesions with imaging concordance may be offered close clinical follow-up” (5).

Table 1. Papillary breast lesion classification.

Benign papillary lesions	
1. Intraductal papilloma (solitary)	
2. Intraductal papillomatosis	
Atypical papillary lesions	
1. Intraductal papilloma with atypical hyperplasia	
2. Papilloma with DCIS	
Malignant papillary lesions	
Noninvasive:	Invasive:
1. Papillary ductal carcinoma *in situ*	1. Invasive papillary carcinoma
2. Encapsulated papillary carcinoma	2. Invasive micropapillary carcinoma
3. Solid papillary carcinoma	

DCIS: Ductal carcinoma *in situ*.

Table 2. Pearls in papillary breast lesions.

PBL	Nature of proliferating epithelial cells	Imaging clues	Prognosis and aggressiveness	Pathology tips
Benign papillomas	Hyperplastic	Central lesions with round or oval shape and circumscribed margins associated to dilated ducts	Potential of 0–16% for malignant transformation	– Present myoepithelial cells in papillae and periphery – Intraductal proliferation of epithelial and myoepithelial cells within fibrovascular stalks giving a frond-like appearance
Atypical papillary lesions	Mix of hyperplastic and neoplastic	– Similar to benign papillomas – Circumscribed masses or clusters of calcifications	High risk of carcinoma (25–30%)	– Few or no myoepithelial cells – Papilloma with ADH: area of atypia is <3 mm – Intraductal papilloma with DCIS: area of atypia es >3 mm
Papillary ductal carcinoma *in situ*	Neoplastic	– Peripherally located – Multicentric disease	– Associated with extensive disease. – Low risk of invasion	– Coexists with other variants of DCIS – Absent myoepithelial cells in the papillae but surrounded by a peripheral layer – Dilated ducts with protuberances that form arches
Encapsulated papillary carcinoma	–Neoplastic	– Solitary, centrally located – Typically well defined cystic mass	– High risk of local recurrence – Low risk of invasion	– Absent myoepithelial cells in the papillae and frequently absent in the periphery – Rounded tumor and thick fibrous capsule – Positive for estrogen and progesterone receptors and negative for HER2
Solid papillary carcinoma	Neoplastic	– 95% are unilateral – Typically solid – Central round well defined nodules – Often multinodular involving peripheral areas	– Metastases are rare – Good prognosis – Low risk of invasion	– Absent myoepithelial cells in the papillae and frequently absent in the periphery – Well circumscribed, soft masses with positive hormone receptors and negative for HER2 – Low proliferation index – Cells frequently show neuroendocrine and mucinous differentiation – Spindle cell morphology

				– Spindle cell morphology
Invasive micropapillary carcinoma	Neoplastic	– Associated with high rate of lymph node metastases – High density masses with spiculated margins	Aggressive form	– Absent myoepithelial cells in the papillae and periphery – Morula-like epithelial group of cells WITHOUT fibrovascular cores floating in mucinous material.
Invasive papillary carcinoma	Neoplastic	Round oval circumscribed masses with no metastatic disease	Good prognosis	– Absent myoepithelial cells in the papillae and periphery – Papillary morphology in >90% of the invasive tumor – Papillae with fibrovascular cores.

ADH: Atypical ductal hyperplasia; DCIS: Ductal carcinoma *in situ*.

Executive summary

Benign papillary lesions

- A total of 70–85% of all papillary breast lesions.
- They can be central (most common) or peripheral.
- Usually in woman between 35–55 years.
- Most common cause of nipple discharge.
- Ultrasound characteristics: round or oval shape with circumscribed margins that can be associated with dilated ducts.
- MRI characteristics: round, oval or lobulates masses with type 2 or 3 time intensity curves.
- These lesions have potential for malignant transformation ranging from 0–16%.
- Management is controversial and some authors have proposed follow-up when the patient is less than 55 years and the lesion is less than 1 cm.

Atypical papillary lesions

- Papillomas with few or no myoepithelial cells.
- Imaging characteristics are similar to benign papillomas.
- Management is always excision due to high risk of carcinoma.

Papillary carcinoma

- Can be invasive or noninvasive.
- Defined by the absence of myoepithelial cells.
- Papillary ductal carcinoma *in situ* is a noninvasive type of cancer and should not be confused with papilloma with ductal carcinoma *in situ*. It can show pleomorphic or amorphous calcifications. They have peripheral location and are usually multifocal.
- Encapsulated papillary carcinoma is noninvasive papillary carcinoma and it is frequently solitary and centrally located. Ultrasound is the modality of choice and may appear as a mixed type of lesion with cystic and solid components.
- Solid papillary carcinoma is noninvasive and these are usually unilateral and centrally located. Can show as a high density, rounded or oval well circumscribed mass.
- Invasive carcinomas include invasive papillary carcinoma and invasive micropapillary carcinoma (IMPC). Invasive papillary carcinoma usually presents as a round, oval or lobulated mass whereas IMPC has spiculated margins and can be associated with microcalcifications. IMPC usually has axillary lymph node metastases which confers a worse prognosis.

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Atypical Ductal Hyperplasia

Upgrade rates in the literature of ADH to either DCIS or an invasive breast cancer widely vary from 0-85%, but are often over 20% (1,2)

One of the largest meta-analyses studies performed to date on ADH upgrade rates by Schiaffino, et al in a study titled "*Upgrade Rate of Percutaneously Diagnosed Pure Atypical Ductal Hyperplasia: Systematic Review and Meta-Analysis of 6458 Lesions*" published in Radiology in 2020.

In this meta-analysis, Schiaffino et al investigated "both patient and imaging characteristics in an attempt to stratify cases that might not require surgical excision. If risk stratification could definitively identify even a small percentage of patients with ADH who would not require surgical excision, it would be a significant contribution. Yet once again, neither the patient characteristics nor the type of biopsy device used, nor the imaging modality used to identify the lesion, demonstrated upgrade rates sufficiently low to obviate surgery. The investigators conclude that "surgical excision is recommended for all patients with ADH found at minimally invasive breast biopsy."(1)

"Multiple studies have attempted to identify features for stratifying high-risk lesions and determining who might safely be followed up with imaging. Factors investigated include patient characteristics, such as a family or personal history of breast cancer, or previous diagnosis of ADH. In addition, studies have demonstrated that the upgrade rate varies with the imaging modality that depicted the lesion and the type of biopsy device used, with higher upgrade rates for MRI-detected as compared with mammography-detected lesions and lower upgrade rates with larger, vacuum-assisted biopsy devices. Other studies have evaluated whether high-risk breast lesions in which the biopsy removed the entirety of the visible lesion cor-relate with pathologic removal, obviating subsequent surgical excision. It does not. Even if the entirety of the lesion is removed based on imaging, ADH must still proceed to surgical excision due to the significant upgrade rate. Studies to stratify patients with ADH have been ongoing for more than 2 decades.We have not been able to identify any factor with a sufficiently low upgrade rate to obviate surgery."(1)

Management:

- The American Society of Breast Surgeons position statement recommends surgical excision of ADH, with an exception made for a "small volume ADH if completely excised on CNB may be observed based on risk factor assessment and multidisciplinary input"(2).

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Lobular Neoplasia (ALH/LCIS)

- LCIS is a noninvasive lesion that arises from the lobules and the terminal ducts of the breast. The histologic features differ between classic and nonclassic forms of LCIS. Management is impacted by pathologic detection of classic vs. non-classic forms of LCIS.

- Classic LCIS that has rad-path concordance has a low upgrade rate of less than 3%, and therefore can be managed with “can be observed with clinical and imaging follow-up based on risk assessment and multidisciplinary input” (1).

- Non-classic LCIS is known as Pleomorphic LCIS and Florid LCIS. “Surgical excision is recommended for any nonclassic LCIS (ie, pleomorphic LCIS, florid LCIS) diagnosed on CNB or any LCIS with radiologic-pathologic discordance” (1,2).

- Histology of Classic LCIS: Classic LCIS is characterized by a solid proliferation of small cells, with small, uniform, round-to-oval nuclei and variably distinct cell borders. The cells typically show cytologic dyshesion. The cytoplasm is clear to lightly eosinophilic; occasionally, the cells contain intracytoplasmic vacuoles that may be large enough to produce signet ring cell forms. Rarely, cases are difficult to classify as either ductal carcinoma in situ (DCIS) or LCIS, as there is some cytologic overlap in the features of low-nuclear-grade DCIS with a solid growth pattern and LCIS (1).

- Histology of Pleomorphic (non-classic) LCIS: Pleomorphic LCIS, originally described in 1996, consists of larger cells that demonstrate marked nuclear pleomorphism but otherwise demonstrate the same characteristics of cytologic dyshesion and intracytoplasmic vacuoles as classic LCIS. Pleomorphic LCIS often demonstrates central necrosis and calcifications, which are otherwise rarely seen with LCIS but are more commonly associated with DCIS.
Recognition of the pleomorphic lobular phenotype is critical because the nuclear features, necrosis, and calcifications can make the differentiation from DCIS challenging. Furthermore, pleomorphic LCIS can be associated with an infiltrating pleomorphic lobular carcinoma, in which the infiltrating tumor cells have the same morphologic appearance as the in situ component (1).

- Histology of Florid (non-classic) LCIS: Florid LCIS is characterized by marked distension of the involved ducts and lobules, typically by the cells of classic LCIS, such that the lesion becomes mass forming. Often there is central (or comedo-pattern) necrosis within the involved spaces, which may calcify. Florid LCIS may present as an image-detected mass or as microcalcifications. When diagnosed on core needle biopsy (CNB), excision is indicated (1,2).

- Excision of LCIS is also recommended for any rad-path discordant findings (1,2).

- “ALH and classic LCIS are histologically differentiated by the quantification of acini involvement within a lobular unit. ALH is defined as less than 50% of acini distended by neoplastic cells and LCIS as more than 50% of acini distended by neoplastic cells” (3)

- Incidental ALH on core needle biopsy has a less than 3% risk of upgrade.

Thus, incidental, radiologic-pathologically concordant ALH diagnosed on CNB no longer requires excision, provided excision is not indicated for the targeted lesion. Examples of this scenario include if the radiologic target is a well-circumscribed mass and pathology shows a fibroadenoma with adjacent ALH, or if the radiologic target comprises microcalcifications and the pathology shows calcifications associated with apocrine cysts and adjacent incidental ALH. Localized excisional breast biopsy is recommended for discordant lesions" (1).

- "Whether or not patients with ALH and LCIS on core biopsy specimens require surgical excision is a matter of controversy. Several recent studies suggest that when a core-biopsy based diagnosis of lobular neoplasia is made, and no other lesions requiring excision (ADH, papilloma, radial scar) are present, and radiological–pathological concordance is present, upgrade rates are less than 5%. As a result, we no longer advocate routine excision of ALH or LCIS when the radiological and pathological diagnoses are concordant, and no other lesions requiring excision are present.

A number of non-classical LCIS variants, including pleomorphic, with necrosis, signet ring, or apocrine, exist. These lesions tend to have high-grade cytology and an unfavorable biomarker profile.28 Current evidence suggests these lesions, and pleomorphic LCIS, in particular, should be treated with complete surgical excision, similar to DCIS." (2).

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Summary of Management Recommendations

Lesion	Recommendation	Exception/Notes
Pseudoangiomatous Stromal Hyperplasia	If presents as mass or is the target lesion in biopsy: clinical/ imaging follow-up If incidental: manage based on dominant or target lesion in biopsy specimen	Surgical consultation/excision if: -large size (>3 cm) -progressive growth or rapidly enlarging mass -suspicious features on imaging
Flat Epithelial Atypia	Clinical and imaging follow up should be considered: -in cases of pure, imaging concordant FEA -with little or no residual calcifications post-biopsy -where FEA is incidental or minimal Surgical excision is recommended in cases of FEA with ADH or in discordant cases.	Surgical consultation should also be considered if: - FEA presented as a mass or the biopsied target was symptomatic to the patient -FEA is associated with another high risk-lesion -In patients with a history of breast cancer with FEA being the prominent/dominant lesion in the biopsy specimen.
Radial scar/complex sclerosing lesion	Surgical excision	Observation may be considered for: -Small (<1 cm) lesions -Sampled via large gauge VAB device -No associated atypia -Average risk patient -Biopsy target of calcifications -RS/CSL is incidental/the non-primary abnormality on biopsy.
Papilloma	Benign papillary lesions can either be surgically removed or undergo imaging surveillance for up to a 2 year period after histopathological diagnosis.	Excision should be considered if the mass is palpable/symptomatic, if there is any atypia, or if there is imaging-pathology discordance
ALH/LCIS	Excise or observation with clinical and imaging follow up	Excision is necessary if pathology is discordant, limited sampling, or other high risk lesion is present
ADH	Surgical excision	Observation may be performed in cases of small volume ADH if completely excised on CNB based on risk factor assessment and multidisciplinary input.