# High risk lesions of the breast: Review of the current diagnostic and management strategies

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Learning objectives

1. Review the various high risk lesions of the breast and spectrum of imaging findings
2. Understand the current status of diagnostic and management challenges through a case based approach
3. Discuss the radiologist's role in evaluation of these lesions
"High risk breast lesions" are described as such because they are in themselves precancerous, they are often found adjacent to cancer and/or they carry an increase in future cancer risk. They include a diverse spectrum of pathologies such as atypical ductal hyperplasia, lobular neoplasia, flat epithelial atypia (FEA), mucocele, papillary lesions and radial scar. This wide range of pathologies is reflected in the varying clinical and imaging spectrum, heterogeneous biological behavior and different risks of malignancy. A landmark study by Dupont and Page categorized benign breast lesions as nonproliferative, proliferative without atypia, or atypical hyperplasia. Of these nonproliferative disease was not associated with increased risk of breast cancer; proliferative disease without atypia had a 1.9-fold increase in risk and atypical hyperplasias were associated with 5.3 fold increased risk of cancer (1).

While the overall incidence is relatively low, the wider use of screening mammography has resulted in increased detection of these lesions. Atypical hyperplasia is detected in 12-17% of biopsy specimens done for microcalcifications detected on mammography; a substantial rise from the pre mammography era where it was detected in only 3.6% of biopsy specimens.

The diagnosis and management of these lesions remains complex. There is potential to prevent progression to invasive disease or detect future disease early with accurate diagnosis, appropriate management and timely surveillance. However, this also brings with it the possibility of over-diagnosis and over-treatment.

Defining the risk that a particular lesion confers for an individual patient is key to striking the right balance between under-treatment and over-treatment. The risks for different pathologies vary, being greater with atypical hyperplasias and LCIS. However, there is yet insufficient data to assess the risk conferred by some of the more recently defined pathologies such as flat epithelial atypia. Furthermore, even within the same category of lesions, the risk to an individual patient can differ. For example, while several studies have found elevated risk associated with atypical ductal hyperplasia (ADH), approximately 80% of women did not develop cancer during the follow up period (1-4). Clinicopathological and molecular features that can predict progression of high-risk lesions to invasive carcinoma in an individual remain to be identified.
Accurate histopathological characterization is the cornerstone of appropriate management and may sometimes be challenging. The initial diagnosis of these lesions is often made on samples obtained by imaging guided biopsies with a potential for sampling errors during biopsy and subsequent processing of the sample. Additionally, differentiating between high risk lesions and their more sinister counterparts may be difficult in some cases. The reported upstage rates of ADH to DCIS and invasive carcinoma range from 11.5% to 62% (3).

This also raises the question of what constitutes an adequate biopsy sample for histopathological evaluation in terms of the type of [core needle biopsy (CNB), often 14G or vacuum assisted biopsy (VAB), typically 9 -11 G], and number of cores; and whether increasing the volume of tissue obtained and reducing potential undersampling could help guide management. Indeed use of vacuum assisted biopsy is associated with reduced upgrades in comparison to core needle biopsies (5). Recent studies have also looked at whether certain lesions sampled by VAB including selected papillomas and radial scars with no atypia or ADH with no residual microcalcifications could be managed conservatively (6). Similarly MRI is also being studied as a potential tool to identify lesions with invasive components and those that can be managed conservatively with the aim of reducing the number of unnecessary surgical excisions.

It is thus understandable that there is considerable disagreement in the literature and amongst physicians involved in breast care regarding the diagnosis and management of these lesions with some advocating excision and others a more conservative approach. Even as research into this complex field evolves, what is clear is the need for a more individualized approach involving a multidisciplinary team (MDT). Radiological-pathological concordance should be sought in all cases and is especially important in cases where a conservative approach is being considered. The radiologist is an important member of the MDT with imaging playing a vital role in a) lesion identification and extent assessment, b) tissue sampling and lesion localization for excision, c) management and d) follow up.

This exhibit reviews the various high risk lesions of the breast and looks at the current status of diagnosis and management of the individual lesions through a case based approach.
Findings and procedure details

ATYPICAL DUCTAL HYPERPLASIA:

CASE 1: Atypical ductal hyperplasia with no upgrade to in-situ or invasive carcinoma

Fig. 1: Two patients with atypical ductal hyperplasia on biopsy and no upgrade on excision. Both had screen-detected clustered indeterminate calcifications on mammograms. Selected mammographic magnification images shows: patient 1 Fig A and B - amorphous and punctate type microcalcifications; and patient 2, Fig C and D - coarse heterogenous type microcalcifications. Vacuum assisted biopsy was performed under stereotactic guidance and both patients subsequently underwent hookwire localization and surgical excision with no in-situ or invasive cancer on excision specimens.

References: DDI, NUHS, Singapore 2015

CASE 2: Atypical ductal hyperplasia on initial biopsy with upgrade to DCIS on excision
Fig. 2: A 42 year old woman was detected on screening mammograms to have a focal cluster of pleomorphic microcalcifications which shows a mixture of amorphous, punctate and linear type calcifications (Fig A and B). Vacuum assisted biopsy was performed and initial HPE showed atypical ductal hyperplasia on a background of columnar cell change with no evidence of in-situ carcinoma. The patient underwent a wide local excision and HPE of the surgical excision specimen showed low nuclear grade DCIS with clear margins (Fig C). The patient was administered localized radiotherapy/APBI and put on tamoxifen.

References: DDI, NUHS, Singapore 2015

Histopathology and definitions:

Atypical Ductal Hyperplasia (ADH) is characterized by increased numbers of uniform, small to medium sized ductal cells with single small nuclei and infrequent mitoses. Involved ducts are filled and distended either partially or completely. Atypical cells can form rosette-like patterns and more complex arrangements with bridging structures and secondary lumens, giving rise to solid, micropapillary or cribriform morphologies (2, 7-9). Intraluminal secretions are produced (7).

ADH forms part of a spectrum from usual duct hyperplasia to low grade DCIS. ADH differs from low-grade DCIS primarily with regard to the extent of the proliferation of the abnormal cell population and also has less cytological atypia (2,9). In ADH atypical cells
are limited to fewer than 3 contiguous spaces and each individual focus of the lesion must measure less than 2mm in maximum diameter (2, 7, 9, 10).

The atypical cell populations show high levels of oestrogen receptor (ER) expression, and low proliferative rates (2, 8). Genetic and molecular alterations are often shared with low-grade DCIS and low-grade ER-positive (luminal type) invasive breast cancers (2). Molecular studies show that the neoplastic proliferations are clonal, with similar and progressive transcriptional and epigenetic alterations in specimens of concurrent atypical hyperplasia, carcinoma in situ, and invasive carcinoma (8), this suggests that ADH is an early, non-obligate precursor lesion in the development pathway of low-grade breast carcinomas (2, 8, 9).

**Epidemiology/ Clinical:**

ADH is being identified increasingly in screening populations. The prevalence in the general population is not known (7). The age range is broad with an average of 48-52 years (9).

**Imaging Features:**

Microcalcifications on mammography are characteristic of ADH (7, 9) ( Fig. 1 on page 26 , Fig. 2 on page 26 ). ADH is a relatively common underlying pathology in biopsies performed for microcalcifications, but rare for biopsies of palpable masses (7).

**Outcomes:**

The significance of ADH relates to upstaging to malignancy at the time of diagnosis and to increased risk of future malignancy

**Histopathologic upgrade:**

Because ADH is distinguished from DCIS on quantitative criteria, CNB sampling limitations create significant risk of upgrade (9). The reported upgrade rate range in the literature is large - 11.5%-62% (7-9). The risk of upgrade is inversely related to the extent of sampling of the indeterminate and suspicious calcifications, and there is evidence that large bore needles and vacuum assisted biopsy decrease the upgrade
rate to DCIS (7, 10). Upgrade risk is low when all mammographic calcifications have been removed, and for lesions smaller than 6 mm when completely removal is documented at post-biopsy imaging (10). Upgrade is more commonly associated with linear, branching, and granular calcifications than with fine round calcifications, and also with micropapillary histology (10).

**Increased risk of future cancer:**

Patients with a previous diagnosis of ADH have a four-to fivefold increased risk for invasive breast cancer in relation to the general population (7-9). Twenty five years after a biopsy that showed atypical hyperplasia, breast cancer (either in situ or invasive) had developed in 27.5-30% of the women in two series (8). The risk is highest in the first 15 years after diagnosis and declines afterwards according to one author (7) but appeared to increase linearly over time according to another paper (8). Younger age at the time of diagnosis of ADH and relatively less involution of background lobular units are associated with greater risk of progression to invasive cancer. Data about the effect of family history on relative risk after ADH is conflicting (8). The risk is highest in the ipsilateral breast (7), but 40% of cancers are contralateral suggesting "field effect" (9). 78% of the cancers were ductal, and 22% lobular or other in one large series (8).

While relative risk of breast cancer development was found to be elevated in all studies, it is noted that approximately 80% of women remained cancer-free during the follow-up period, which often extended beyond 10 years, and this data must also guide counselling and management (2).

**Management:**

Current practice is to proceed to surgical referral with a view to excision on all cases of ADH diagnosis (7-9). Given that most women will not eventually contract breast cancer, there is also a need for prospective studies to determine whether specific clinical and pathologic features can be used to predict sufficiently low probability of malignancy and thus avoid surgery (10).

After treatment routine mammographic screening is recommended for all patients (7). Recent research places relative risk for this group at or above the current standard for MRI screening and further trials are needed to evaluate its role in addition to mammography (8). U.S. Preventive Services Task Force has concluded that there is moderate certainty of a moderate net benefit from the use of tamoxifen or raloxifene chemoprevention in women at an estimated 5-year risk of 3% or greater (8). In current practice,
with minimal data available on this topic and with chemopreventive agents for risk reduction available, **atypical hyperplasia is generally not considered an indication for prophylactic mastectomy** (8).

**FLAT EPITHELIAL ATYPIA:**

**Case 1 : Flat epithelial atypia with in- situ or invasive carcinoma**

![Fig. 3: A 45 year old woman with screen detected localized cluster of amorphous and coarse heterogenous microcalcifications seen on selected mammographic magnification images of the left breast (A ,B, C). Vacuum assisted biopsy was performed under stereotactic guidance and the cluster was deemed to have been completely removed on post biopsy mammogram. Initial HPE showed flat epithelial atypia and the patient subsequently underwent hookwire localization and surgical excision (Fig D). Final HPE confirmed flat epithelial atypia with no evidence of in-situ or invasive carcinoma**

**References:** DDI, NUHS, Singapore 2015

**Case 2 : Flat epithelial atypia with ADH on subsequent excision**
**Fig. 4:** A 53 year old woman with screen detected right breast microcalcifications which were a combination of punctate, amorphous and coarse microcalcifications distributed in a segmental fashion (A, B). Initial vacuum assisted biopsy showed flat epithelial atypia. The patient underwent a wide local excision and HPE of the surgical excision specimen showed extensive flat epithelial atypia with focal atypical ductal hyperplasia and microcalcifications on a background of usual type duct epithelial hyperplasia, columnar cell change and papillomatosis (C). No definite in-situ or invasive carcinoma was seen

**References:** DDI, NUHS, Singapore 2015

**Case 3:** Flat epithelial atypia with DCIS on subsequent excision
Fig. 5: A 51 year old woman was detected to have amorphous microcalcifications in a segmental distribution in her left breast on routine screening mammograms (Fig A,B). Vacuum assisted biopsy was performed and initial HPE showed flat epithelial atypia with fibrocystic changes and no evidence of in-situ or invasive carcinoma. The patient underwent a wide local excision and HPE of the surgical excision specimen showed widespread low nuclear grade DCIS with positive margins and background proliferative breast changes. Invasive carcinoma was not present. The patient subsequently underwent a left mastectomy

References: DDI, NUHS, Singapore 2015

The term 'flat epithelial atypia' (FEA) was first designated 'clinging carcinoma in situ' in 1979 and more recently included in the unifying term of "ductal intraepithelial neoplasia," together with usual ductal hyperplasia, atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS) in 2003. Flat epithelial atypia or flat ductal intraepithelial neoplasia (DIN) 1A is defined by the WHO as a presumably neoplastic intraductal alteration characterized by replacement of native epithelial cells by one single or three to five layers of monotonous mildly atypical cuboidal to columnar cells of a terminal duct lobular unit. FEA is now the commonly used term for columnar cell change/hyperplasia exhibiting mild cytologic atypia which ranges from round, small, monomorphic nuclei, with finely dispersed to slightly marginated chromatin and inconspicuous nucleoli to nuclei which display a greater degree of pleomorphism with clumped chromatin and conspicuous nucleoli. FEA is distinguished from atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) by the absence of
architectural atypia in the form of cribriform spaces, arcades, fronds or well-formed micropapillae.

Flat epithelial atypia most often presents as indeterminate microcalcifications on screening mammography (Fig. 3 on page 27, Fig. 4 on page 28, Fig. 5 on page 29). The microcalcifications are most often amorphous (65%) but may be coarse heterogeneous and fine pleomorphic, thus lacking specific features (11). These microcalcifications were also most often clustered. None of the calcifications display a suspicious ductal-type branching shape. Ultrasound findings which are associated with the cases of flat epithelial atypia are not specific and should not suggest flat epithelial atypia as a provisional diagnosis.

Although FEA has been recognized by pathologists for over 3 decades, the advent of widespread breast cancer screening programs with subsequent increase in the number of biopsies performed for mammogram detected abnormalities has resulted in increased diagnosis. FEA has a high prevalence in core needle biopsies (3.7%-10%) and is frequently associated with ADH, lobular neoplasia, low-grade DCIS (micropapillary and cribriform types) and low-grade invasive tubular or lobular carcinoma. This has prompted close attention to biopsy specimens containing FEA in order to exclude the presence of other pathologies. In cases of extensive flat epithelial atypia, involvement by carcinoma in situ or invasive carcinoma can be focal or patchy, and thus may not be detected unless surgical excision of the entire lesion is performed for histopathologic examination. Studies in which core needle biopsies and vacuum-assisted devices were used showed a wide range of upgrade rates to insitu or invasive carcinoma from as low as 4.2% (12) up to 30%.

This wide range coupled with limited data in literature has resulted in a lack of consensus with regard to optimal management of pure FEA diagnosed at image guided biopsies. Invasive carcinomas have also been shown to develop in up to 14.3% of patients with FEA during a follow-up period of 10 years (13). Therefore, when imaging-guided needle biopsy yields flat epithelial atypia, the current recommendation remains surgical excision followed by ongoing increased risk surveillance. Prospective studies are needed to determine if close follow-up without surgery may be performed for patients with small-sized focal microcalcifications which have been well-sampled with a vacuum-assisted device.

LOBULAR CARCINOMA IN SITU AND ATYPICAL LOBULAR HYPERPLASIA:
Case 1: LCIS on biopsy

![Images showing mammograms and histopathologic examination of breast tissue](image)

**Fig. 6:** A 48 year old woman with screen detected cluster of indeterminate microcalcifications (encircled) right retroareolar breast (spot magnification CC and LM views - A, B). Stereotactic guided vacuum biopsy was done with no residual calcifications. HPE showed breast tissue with some stromal fibrosis, columnar cell change and one focus of lobular carcinoma in-situ located close to expanded lobules with columnar cell change. No invasive carcinoma was identified. Patient was stable at 2 year follow-up with no clinical or mammographic evidence of malignancy. Typical appearances of LCIS on histopathologic (C) examination with a uniform population of cells distending terminal ducts and lobules.

**References:** DDI, NUHS, Singapore 2015

Lobular carcinoma in situ and atypical lobular hyperplasia are sometimes grouped together as 'lobular neoplasia' and classified according to degree of atypia. Although these conditions share common pathological features (2, 7, 9, 14), they are associated with significantly different outcomes (2, 14). **Pathologically, monomorphic cell populations originate in and distend lobular acini and terminal ducts** (7, 9, 14) and also are prone to pagetoid spread between the surface epithelial cells and basement membrane along the duct system (9, 14). **LCIS is generally diagnosed when there is involvement of more than 50% of lobular acini, ALH when less than 50% are involved** (2, 7, 14).
Classical LCIS is **typically estrogen and progesterone receptor positive, HER-2 negative** (2, 14), EGFR-1 negative (14), with low proliferation rates. (2). Expression of E-cadherin, a plasma membrane adhesion molecule is almost always reduced or absent (9, 14). A pleomorphic variant (PLCIS) strongly resembles DCIS histopathologically (7, 14) with nuclear pleomorphism and frequently central acinar necrosis (2). Microcalcifications may be present microscopically (14). In this variant estrogen and progesterone receptors, and HER-2 are positive and proliferation rates medium to high (2, 14). Lobular neoplasia can be found in association with DCIS, IDC, and ILC (7). Recent research has shown that ALH, LCIS are clonal and share mutations with adjacent ILC when it is present. (2, 14).

LCIS is **frequently multifocal, multicentric and can be bilateral in up to 1/3 cases** (2, 10, 14). The true incidence of lobular neoplasia is unknown because it is hardly ever symptomatic (2, 7); it has been reported at **0.8 to 5% of open surgical biopsies and cancer excision (14)** and **0.02% to 3.8% of CNB** (2, 14). Incidence increased by 300% in 1978-1998, this is thought to be due to increased histopathological awareness, increase in vacuum assisted biopsy and screening (7). The mean age for diagnosis has been reported as 44-49 years (10, 14).

**Imaging features:**

Authors have commented that there are "no typical radiological manifestations" (7, 14); imaging findings often relate to accompanying pathology (10). **Calcifications (Fig. 6 on page 30)** can be seen in 21-67% (7) - typically clustered, punctate, dense and <=0.5mm (10); those seen in the PLCIS variant are usually larger and denser (10), and more likely to present mammographically (14). LCIS can also present mammographically as a **mass with calcifications or alone** (10, 14) or as a **distortion** (14). **Sonographically a solid, hypoechoic microlobulated mass has been described** (10).

**Outcome:**

Variations in terminology (lobular neoplasia vs LCIS and ALH), variations in indication for excision (incidental LCIS as against radiologic-pathologic discordance of a mass or calcification) and small numbers in many studies mean that data regarding the risk of pathological **upgrade from core needle to excision biopsy is very inconsistent, and figures from 0-67% are cited in the literature** (10-14). PLCIS has **40-60% association with invasive lobular carcinoma on core biopsy and excision** (14).
Lobular neoplasia can behave as both a non-obligate precursor lesion and/or a marker of ‘field effect’ (9) with regard to future cancer. Like ADH, ALH is associated with at least a 3-4x relative risk of cancer (2, 7, 14), with an ipsilateral:contralateral ratio of 2:1 (2) Bilateral risk for invasive carcinoma of up to 30% is also reported in some series (14). The invasive cancer is more often IDC than ILC (2, 7, 14).

Greater cancer risk is associated with younger age, premenopausal status, relatively less age related lobular involution and multifocality (2) and also with family history (14). Insufficient data exists to assess risk of PLCIS separately (2).

**Management:**

Recommendations vary widely with surgical excision advocated in many papers (10, 14), particularly when there is clinicopathologic discordance, when features of DCIS are present, E-cadherin immunohistochemistry is unclear, suspicious microcalcifications are present histologically (14), or when there is PLCIS (10).

Adjuvant tamoxifen/raloxifene therapy has been advocated with some authors reporting cancer risk reduction from 14.5% to 3.6% (10), but others feeling this is not well supported by data (14).

Surveillance with annual mammogram and clinical examination is a minimum treatment (7), particularly where there is "clear radiologic-pathologic concordance” (9). MRI has not been shown to be beneficial in these cases (7).

**RADIAL SCAR/ COMPLEX SCLEROSING LESIONS:**

Case 1: Radial scar with no upgrade on excision
Fig. 7: A 42 year old female, clinically asymptomatic with distortion detected on screening mammogram in the left upper outer quadrant, confirmed on spot compression views (A,B). US showed an ill-defined irregular hypoechoic mass at 1:00 (C). US guided core needle biopsy was done with five samples obtained with a 14G needle; HPE showed radial scar with no atypia. The patient underwent hookwire localization and surgical excision (D,E). HPE of the surgical excision specimen showed radial scar with columnar cell change and no atypia or invasion.

References: DDI, NUHS, Singapore 2015

Case 2: Radial scar with subsequent excision showing DCIS and LCIS
Fig. 8: 67 year old female with baseline screening mammogram showing architectural distortion and loosely clustered microcalcifications in the left inner central breast, confirmed on subsequent spot CC and LM magnification views (A,B) (arrows). US showed a corresponding irregular hypoechoic lesion with adjacent mild stromal distortion (arrow) at 10:00 (C, D). US guided core needle biopsy and tissue marker placement was done. HPE was reported as "complex sclerosing lesion with focal columnar cell hyperplasia and atypia with microcalcifications present. The patient underwent mammographic guided hookwire localization and wide local excision (E,F). Final HPE showed upgrade with multifocal low grade DCIS and LCIS. Multiple intraductal papillomas were also seen. Patient underwent RT but declined chemoprevention; two subsequent annual mammograms showed no suspicious findings. References: DDI, NUHS, Singapore 2015

Radial scar (RS) /complex sclerosing lesions (CSL) are benign proliferative lesions that are characterised by a fibro-elastic core containing entrapped ducts with an intact myoepithelial layer and ductules radiating outwards to form a stellate pattern. A radial scar > 1 cm in size is termed a complex sclerosing lesion. They are most common in the 40-60 year old age group and are seen in 1.7 - 28% of benign breast specimens (15); presenting either as the dominant lesion or as an incidental microscopic finding in the biopsy specimen. They may co-exist with other benign pathologies such as cysts, sclerosing adenosis, and usual epithelial hyperplasia; or atypical hyperplasias, DCIS and early stage invasive carcinoma. The presence of entrapped glands at the centre of a RS may mimic tubular carcinoma though an intact
myoepithelial layer and immunohistochemical markers can help make the distinction in an adequately sampled lesion.

Clinically patients are usually asymptomatic. These lesions are seen most commonly on mammograms as distortion (Fig. 7 on page 31, Fig. 8 on page 32) or an irregular mass with the classic appearance described as that of a stellate lesion with central lucency and thin radiating spicules and varying appearances in different projections. Microcalcifications (Fig. 8 on page 32) can be seen in up to 50% cases, usually as an associated finding. On ultrasound the lesion may be occult or be seen as architectural distortion, a poorly defined hypoechoic area with shadowing, or as an irregular or spiculated mass (Fig. 7 on page 31, Fig. 8 on page 32). MRI features of RS are variable with some showing non mass like enhancement and others a spiculated mass with distortion.

Upgrade rates vary from 0-24% depending on the presence of atypia in the biopsy sample and whether CNB or VAB has been done; with the lowest risk of upgrade seen on an adequate VAB specimen (at least 12 samples with a 11G needle) that shows no atypia and the highest with a CNB specimen that shows atypia. Studies have indicated a zero or very low upgrade rate with VAB specimens that show no atypia (6), thus indicating a potential for conservative management of these lesions. Additionally, while mammographic and sonographic features cannot predict upgrade to malignancy, MRI has been shown to have very high negative predictive value (97.6%) with some authors recommending close follow up for radial scars with normal MRI findings.

The general consensus is to excise RS with atypia. For lesions without atypia there is role for a conservative approach and close follow up for small lesions, lesions sampled by VAB and lesions with no suspicious imaging findings (7, 9, 10). As RS does not confer an increased risk of breast cancer beyond that associated with proliferative disease, routine age appropriate screening is recommended for benign lesions that have been excised.

**BENIGN PAPILLARY LESIONS:**

Case 1: Multiple papillomas with no upgrade on excision
Fig. 9: 38 year old woman with blood tinged nipple discharge from the left breast. US showed two similar complex cystic intraductal lesions with internal vascularity at retroareolar (A,C) and 2:00 position (B,D). Both underwent US guided core needle biopsy and HPE showed benign intraductal papillomas. Both lesions were later excised with the excision specimen confirming benign intraductal papillomas with no upgrade.

References: DDI, NUHS, Singapore 2015

Case 3: Papilloma with atypia with subsequent upgrade to DCIS
Fig. 10: 49 year old woman with screen detected abnormality right breast. Spot compression CC and MLO views (A, B, encircled) show an irregular indistinctly margined mass in the lower inner breast, confirmed on US as a suspicious hypoechoic irregular mass (arrow, C). US guided core needle biopsy and HPE showed intraductal papilloma with atypical ductal hyperplasia. Hookwire localization and excision was done (D,E) and this showed upgrade to low grade DCIS. No invasive carcinoma was seen.

References: DDI, NUHS, Singapore 2015

Papillary lesions cover a wide spectrum of benign and malignant pathologies. The key feature of a papillary lesion is a fibrovascular stromal core with a lining of epithelial and myoepithelial cells that is attached to the duct wall and projects into the lumen. Benign papillary breast lesions account for less than 10% of benign breast lesions and include benign solitary intraductal papilloma (BSIP), multiple intraductal papilloma (MIP) and papillomas with atypia.

Solitary papillomas arise from a large central duct, are more common in the perimenopausal age group and present with bloody or clear nipple discharge. Multiple papillomas, on the other hand arise from terminal duct lobular unit and are peripheral lesions that primarily affect younger women and present as a palpable mass. Papillomas with atypia contain a neoplastic population of cells; some authors categorize this as atypical ductal hyperplasia (ADH) if the population of such cells is # 3 mm; atypia is more common in multiple papillomas.
Patients with solitary and multiple papillomas without atypia have a 2 and 3 times increased risk of cancer respectively. The presence of atypia increases the risk; solitary and multiple papillomas with atypia have a 5 and 7-fold increase risk of cancer respectively.

Papillomas can have diverse imaging features which often overlap with their malignant counterparts and other breast lesions. Mammographic findings include rounded or ovoid well circumscribed retroareolar masses, sometimes with associated ductal dilatation in a BSIP or peripheral mass/es in MP. Coarse calcifications or microcalcifications may sometimes be seen within the papillomas. On US, the classic presentation is that of a solid mural nodule within a dilated duct. Other features include an intracystic mass (Fig. 9 on page 33), well circumscribed hypoechoic solid mass or just ductal dilatation in a small papilloma. Occasionally papillomas can appear as irregular and ill defined masses on mammograms and ultrasound (Fig. 10 on page 34). Ductography may be useful in select cases and shows an intraluminal filling defect, ductal dilatation, ductal wall irregularity and distortion. MRI findings include a round or ovoid well -circumscribed mass with variable enhancement patterns and ductal dilatation.

Upgrade rates for benign papillomas diagnosed by core - needle biopsy are variable ranging from 6.9%-27.7% for atypia and 3-1 - 20% for malignancy (16); papillomas with atypia can be upgraded to malignancy in 67% cases. Studies have indicated a zero or very low upgrade rate with VAB specimens for benign papillomas (6). Similar to radial scar, MRI has been shown to have very high negative predictive value for malignancy in papilloma (97.4%) (4).

The general consensus is to excise papillomas with atypia. For lesions with no suspicious imaging features and no atypia on a VAB specimen that samples most of the lesion, close follow up can be considered (7, 10).

**MUCOCOELE LIKE LESIONS:**

**Case 1: Mucocele like lesion with no upgrade on excision**
Fig. 11: 27 year old woman with complex cyst on outside screening ultrasound. US (A) showed a horizontal oriented 1.5 cm cystic lesion which contains a small mural nodule in the dependent portion with no vascularity in the left breast 2 o'clock 3 cm from nipple. Ultrasound guided 14G core needle biopsy showed a mucocoele like lesion with some ducts distended with mucin with no evidence of ductal carcinoma in situ or invasive carcinoma. At excision biopsy there were fibrocystic changes and variably cystically-dilated ducts lined by flattened cuboidal epithelium and containing abundant mucin. In addition, large pools of mucin within the stroma containing occasional strips of benign appearing ductal epithelium were present in the intervening breast stroma, giving rise to a pseudo-cystic architecture. The pathologist concluded that the mucin was most like derived from the mucin filled benign ducts identified in the vicinity. Typical histopathological appearance of a mucocele like lesion with mucin filled cysts/dilated spaces (B).

References: DDI, NUHS, Singapore 2015

Case 2: Mucocele like lesion with upgrade to ADH on excision
Fig. 12: 51 year old patient. Screening mammogram showed 10 mm new clustered microcalcifications posterior central right breast confirmed on spot magnification CC and LM views (A, B, encircled). Stereotactic vacuum assisted breast biopsy showed mucocoele-like lesion with cystically dilated ducts filled with mucus, some of which were ruptured with mucus extravasation. One duct showed focal papillary hyperplasia. Microcalcifications were noted. No in situ or invasive malignancy was seen. On excision biopsy one area showed mild expansion by a solid, cribriform or micropapillary proliferation of mildly atypical epithelial cells sufficient for low-grade ductal carcinoma in-situ (DCIS). This was adjacent to the biopsy site. In the remaining breast tissue there were benign changes including stromal fibrosis, cystic change with apocrine metaplasia, columnar cell alteration and hyperplasia, fibroadenomatoid change, sclerosing adenosis, and foci of ductal hyperplasia of usual type. Some lobules showed rounded foci of microcalcification, present either in lumina or in stroma adjacent to acini. Some dilated ducts contained mucinous material or cellular debris were seen. 

References: DDI, NUHS, Singapore 2015

Mucocoele like lesions (MLL) are defined as - "Mucin filled cysts/dilated spaces with areas of stromal mucin extravasation (9, 10, 17)."

The pathogenesis is thought to be excess mucin production and duct obstruction, then rupture and extravasation due to incidental trauma (18). The cysts/spaces are lined with flat/cuboidal epithelium (18). This epithelium can be homogeneously or heterogeneously benign, atypical or malignant (10, 18, 19) and cover a spectrum from fibrocystic change with mucin filled ducts, through ADH, and DCIS to invasive carcinoma (18), in particular, mucinous carcinoma (17, 18).
**Clinical:**

MLL are rare, forming between 0.2 and 0.36% of breast core biopsy specimens (18, 20), benign MLL have been described as making up 0.25 of core needle biopsies in one series (19). Most lesions are clinically occult; in one series 83% cases were screen detected and 17% symptomatic (17). Age distribution is wide - 23-84 years in reported series, but most typically middle age (18-20).

**Imaging findings:**

Calcifications on mammography are the predominant findings (17-20) (Fig. 12 on page 35). Occasionally calcifications are seen within a mammographic mass when imaging-guided needle biopsy yields flat epithelial atypia (20), or a mass is seen without calcification (20). The calcifications in one series were reported most frequently as clustered or new, and less commonly as coarse, linear, granular, pleomorphic, extensive or suspicious (18, 19). On review of the associated pathology specimen, the calcifications are usually seen within the MLL but sometimes lie within adjacent lesions or breast tissue (18, 20).

On ultrasound MLL are seen as masses which can be cystic, solid, complex cystic and/or contain calcifications (18-20) (Fig. 11 on page 35). In one series, however, 23% of MLL were not seen on ultrasound (10). Average/median lesion size is reported at 1-8mm (19, 20).

**Outcome:**

UK guidelines consider mucoceles to be lesions of uncertain malignant potential, B3 (17). The major concern is whether the associated epithelium has been adequately sampled to at the time of the initial core needle biopsy and whether excision will result in significant histological upgrade. Authors also differ as to whether atypia is considered a significant upgrade. Study numbers are often small, and highly variable upgrade rates to malignancy or malignancy/atypia have been reported between 0-43% (17-19).

Where no atypia was seen on core biopsy patients often did not proceed to excision. In cases with excision biopsy correlation there was typically upgrade rate to malignancy (DCIS in all cases) of approximately 4%, and to atypia (typically ADH or FEA) or malignancy (DCIS) of up to 18% (17, 19). Small numbers of women in some studies
were managed conservatively and were followed up for 1-4 years, all of whom were reported to be stable (18-20).

**When atypia was diagnosed** at the time of the initial biopsy then **upgrade, mainly to DCIS but also to invasive cancer was reported in 21-31% of cases**, and a proportion also reconfirmed atypia/ADH (17, 18). Where malignancy was present it was most commonly of mucinous type according to a review of 13 studies (17). One study showed that MLL presenting as a mass were more likely to be upgraded (18), another showed that no radiologic or morphologic features were of predictive value (19). Risk of upgrade was not related to number of cores/sampling technique or whether the MLL had been removed completely during the biopsy (18, 19).

The risk of future malignancy is also not related to the MLL per se but to the associated epithelial proliferation, and malignant potential is felt to be uncertain (9).

**Management:**

The heterogeneity of data and disagreement about the significance of upgrade to atypia lead to conflicting recommendations about management:

**Surgery is recommended by many authors** to avoid sampling error, because of the upgrade rate, to confirm atypia and allow appropriate management, and 'because of the continuum of mucinous DCIS and mucinous carcinoma' (10, 18, 19). The presence of a mass, or non radiologically-pathologically concordant extensive, pleomorphic calcifications were also highlighted as indications for excision (18).

**Surveillance is recommended by other authors if the MLL is entirely benign with no atypia or mass, and when it has been excised or well sampled by vacuum assisted device** (10, 18, 19).

Multidisciplinary review of clinical, radiological and pathological findings is important, any discordance should be investigated further (17).
Fig. 1: Two patients with atypical ductal hyperplasia on biopsy and no upgrade on excision. Both had screen-detected clustered indeterminate calcifications on mammograms. Selected mammographic magnification images shows: patient 1 Fig A and B - amorphous and punctate type microcalcifications; and patient 2, Fig C and D - coarse heterogenous type microcalcifications. Vacuum assisted biopsy was performed under stereotactic guidance and both patients subsequently underwent hookwire localization and surgical excision with no in-situ or invasive cancer on excision specimens.

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Fig. 2: A 42 year old woman was detected on screening mammograms to have a focal cluster of pleomorphic microcalcifications which shows a mixture of amorphous, punctate and linear type calcifications (Fig A and B). Vacuum assisted biopsy was performed and initial HPE showed atypical ductal hyperplasia on a background of columnar cell change with no evidence of in-situ carcinoma. The patient underwent a wide local excision and HPE of the surgical excision specimen showed low nuclear grade DCIS with clear margins (Fig C). The patient was administered localized radiotherapy/APBI and put on tamoxifen.
Fig. 3: A 45 year old woman with screen detected localized cluster of amorphous and coarse heterogenous microcalcifications seen on selected mammographic magnification images of the left breast (A , B , C). Vacuum assisted biopsy was performed under stereotactic guidance and the cluster was deemed to have been completely removed on post biopsy mammogram. Initial HPE showed flat epithelial atypia and the patient subsequently underwent hookwire localization and surgical excision (Fig D) . Final HPE confirmed flat epithelial atypia with no evidence of in-situ or invasive carcinoma

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Fig. 4: A 53 year old woman with screen detected right breast microcalcifications which were a combination of punctate, amorphous and coarse microcalcifications distributed in a segmental fashion (A, B). Initial vacuum assisted biopsy showed flat epithelial atypia. The patient underwent a wide local excision and HPE of the surgical excision specimen showed extensive flat epithelial atypia with focal atypical ductal hyperplasia and microcalcifications on a background of usual type duct epithelial hyperplasia, columnar cell change and papillomatosis (C). No definite in-situ or invasive carcinoma was seen.

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Fig. 5: A 51 year old woman was detected to have amorphous microcalcifications in a segmental distribution in her left breast on routine screening mammograms (Fig A,B). Vacuum assisted biopsy was performed and initial HPE showed flat epithelial atypia with fibrocystic changes and no evidence of in-situ or invasive carcinoma. The patient underwent a wide local excision and HPE of the surgical excision specimen showed widespread low nuclear grade DCIS with positive margins and background proliferative breast changes. Invasive carcinoma was not present. The patient subsequently underwent a left mastectomy

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Fig. 6: A 48 year old woman with screen detected cluster of indeterminate microcalcifications (encircled) right retroareolar breast ( spot magnification CC and LM views - A,B). Stereotactic guided vacuum biopsy was done with no residual calcifications. HPE showed breast tissue with some stromal fibrosis, columnar cell change and one focus of lobular carcinoma in-situ located close to expanded lobules with columnar cell change. No invasive carcinoma was identified. Patient was stable at 2 year follow-up with no clinical or mammographic evidence of malignancy. Typical appearances of LCIS on histopathologic (C) examination with a uniform population of cells distending terminal ducts and lobules

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Fig. 7: A 42 year old female, clinically asymptomatic with distortion detected on screening mammogram in the left upper outer quadrant, confirmed on spot compression views (A,B). US showed an ill-defined irregular hypoechoic mass at 1:00 (C). US guided core needle biopsy was done with five samples obtained with a 14G needle; HPE showed radial scar with no atypia. The patient underwent hookwire localization and surgical excision (D,E). HPE of the surgical excision specimen showed radial scar with columnar cell change and no atypia or invasion.

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Fig. 8: 67 year old female with baseline screening mammogram showing architectural distortion and loosely clustered microcalcifications in the left inner central breast, confirmed on subsequent spot CC and LM magnification views (A,B) (arrows). US showed a corresponding irregular hypoechoic lesion with adjacent mild stromal distortion (arrow) at 10:00 (C, D). US guided core needle biopsy and tissue marker placement was done. HPE was reported as "complex sclerosing lesion with focal columnar cell hyperplasia and atypia with microcalcifications present. The patient underwent mammographic guided hookwire localization and wide local excision (E,F). Final HPE showed upgrade with multifocal low grade DCIS and LCIS. Multiple intraductal papillomas were also seen. Patient underwent RT but declined chemoprevention; two subsequent annual mammograms showed no suspicious findings.
Fig. 9: 38 year old woman with blood tinged nipple discharge from the left breast. US showed two similar complex cystic intraductal lesions with internal vascularity at retroareolar (A,C) and 2:00 position (B,D). Both underwent US guided core needle biopsy and HPE showed benign intraductal papillomas. Both lesions were later excised with the excision specimen confirming benign intraductal papillomas with no upgrade.

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**Fig. 10:** 49 year old woman with screen detected abnormality right breast. Spot compression CC and MLO views (A, B, encircled) show an irregular indistinctly margined mass in the lower inner breast, confirmed on US as a suspicious hypoechoic irregular mass (arrow, C). US guided core needle biopsy and HPE showed intraductal papilloma with atypical ductal hyperplasia. Hookwire localization and excision was done (D,E) and this showed upgrade to low grade DCIS. No invasive carcinoma was seen.

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**Fig. 11:** 27 year old woman with complex cyst on outside screening ultrasound. US (A) showed a horizontal oriented 1.5 cm cystic lesion which contains a small mural nodule at the dependent portion with no vascularity in the left breast 2 o'clock 3 cm from nipple. Ultrasound guided 14G core needle biopsy showed a mucocoele like lesion with some ducts distended with mucin with no evidence of ductal carcinoma in-situ or invasive carcinoma. At excision biopsy there were fibrocystic changes and variably cystically-dilated ducts lined by flattened cuboidal epithelium and containing abundant mucin. In addition, large pools of mucin within the stroma containing occasional strips of benign appearing ductal epithelium were present in the intervening breast stroma, giving rise to a pseudo-cystic architecture. The pathologist concluded that the mucin was most like derived from the mucin filled benign ducts identified in the vicinity. Typical histopathological appearance of a mucocoele like lesion with mucin filled cysts/dilated spaces (B).

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Fig. 12: 51 year old patient. Screening mammogram showed 10 mm new clustered microcalcifications posterior central right breast confirmed on spot magnification CC and LM views (A, B, encircled). Stereotactic vacuum assisted breast biopsy showed mucocoele-like lesion with cystically dilated ducts filled with mucus, some of which were ruptured with mucus extravasation. One duct showed focal papillary hyperplasia. Microcalcifications were noted. No in situ or invasive malignancy was seen. On excision biopsy one area showed mild expansion by a solid, cribriform or micropapillary proliferation of mildly atypical epithelial cells sufficient for low-grade ductal carcinoma-in-situ (DCIS). This was adjacent to the biopsy site. In the remaining breast tissue there were benign changes including stromal fibrosis, cystic change with apocrine metaplasia, columnar cell alteration and hyperplasia, fibroadenomatoid change, sclerosing adenosis, and foci of ductal hyperplasia of usual type. Some lobules showed rounded foci of microcalcification, present either in lumina or in stroma adjacent to acini. Some dilated ducts contained mucinous material or cellular debris were seen.

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Conclusion

This exhibit reviews the current status of diagnosis and management of high risk breast lesions from a radiologist’s perspective

Key points :

• High risk lesions of the breast have different biological behaviours and risks of cancer. These lesions are usually clinically occult and are being diagnosed more frequently with screening. Even so many remain rare, with a lack of evidence regarding their malignant potential and optimal management.

• There is general consensus that atypical ductal hyperplasia should be excised.

• For lesions which are likely to be affected by sampling error (LCIS, radial scars/CSL, papillomas and mucoceles) and those where atypia has been shown on biopsy, excision is frequently advised, however, strict radiologic pathologic correlation showing that small lesions have been completely or largely excised at biopsy may allow conservative management and surveillance, but data from large prospective studies would be needed to validate this approach. Similar considerations also apply to FEA, with data particularly lacking.

• Chemoprevention should be discussed with women with ADH ALH, and LCIS, especially those who are premenopausal at diagnosis.

• All patients who have been diagnosed with high risk lesions should continue to have mammography.

• The role of MRI in these patients is evolving and needs to clarified by further research.
References:


