Imaging features of high-risk lesions and their differential diagnosis on Digital Breast Tomosynthesis - personal experience in clinical setting.

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Learning objectives

Among the many women who undergo annual mammography while receiving care from a primary care professional, the occasional patient is faced with the discovery of suspect or abnormal findings and recommendations for a breast biopsy.

High-risk lesions of the breast are lesions that confer an increased risk of breast cancer, either because of an increased probability of finding cancer associated with percutaneous biopsy findings or because of an increased probability of developing breast cancer over the long term.

Use of Digital Breast Tomosynthesis (DBT) is increasing in clinical practice thanks to its ability to reduce breast tissue overlapping. The ability to provide "slices" through the breast and reduce the noise contributed by the normal breast structures is the major benefit from tomosynthesis. Digital breast tomosynthesis is still a fairly new modification of X-ray mammography, but it provides important improvements.

Goals:

- To describe the classification and to recognize the main distinctive pathologic features of high-risk lesions of the breast on breast imaging.

- To explain the diagnosis and management of high-risk lesions.

- To identify and confidently diagnose high-risk breast lesions on digital breast tomosynthesis (DBT).
Background

INTRODUCTION

The term high-risk lesions or "borderline lesions" of the breast may be used for the following lesions:

1) Precancerous lesions/ Precursor lesions

2) Lesions with uncertain malignant potential (difficult differential diagnosis between benign and malignant lesions)

3) Risk lesions for developing carcinoma on both breast in the future

The management of these lesions is controversial and is often extended to high-risk lesions detected on mammography and ultrasound, with surgical excision usually recommended.

DIAGNOSIS

Digital Breast Tomosynthesis (DBT) is a technology recently applied to breast imaging that uses multiple projection images to reconstruct the breast in thin sections using select reconstruction algorithms. This technique improves detection and characterization of lesions resulting in improved cancer detection, sensitivity and specificity leading to reduced need for additional work up in many cases.

Radiation exposure is equal to or slightly higher than Full Field Digital Mammography (FFDM), however the potential reduction in recall rates may mitigate this factor. Data acquired during the DBT acquisition are then reconstructed into a 2D synthesized images. 3D DBT and synthesized 2D mammograms can improve breast disorders detection rate by reducing tissue overlap and by making architectural distortion more conspicuous.

In theory, using DBT, the radiologist may be more accurate in characterising some breast lesions to reduce the rate of false-positive breast biopsies but it is unknown whether this applies to microcalcifications.

Image guided core-needle biopsy (CNB) has become the procedure of choice to investigate mammographically "suspicious" lesions of the breast and has been shown to be an effective means to rule out cancer alleviating the discomfort of surgery.
In our experience fine-needle aspiration (FNA) or core needle biopsy (CNB) was performed usually under ultrasonographic or stereotactic guidance. Core needle biopsy with vacuum-assisted or automated biopsy devices are used preferably with incorporated larger-gauge needles (9-11 gauge) in order to acquire more tissue samples and decreased the probability of false-negative or false-positive findings. Eventually, in case of small lesions, a radiographic marker was deposited at the biopsy site to identify the area for future follow-up or to guide surgical excision of non-palpable lesions.
CLASSIFICATION OF HIGH-RISK LESIONS

High-risk lesions, such as atypical ductal hyperplasia (ADH), lobular neoplasias (i.e., lobular carcinoma in situ [LCIS] and atypical lobular hyperplasia [ALH]), papillomas, radial scars, mucinous lesions, and flat epithelial atypias are the most frequent high-risk histological diagnoses.

We reviewed mammographic and digital breast tomosynthesis (DBT) abnormalities with histologic findings of our most frequent high-risk breast lesions.

- **ATYPICAL DUCTAL HYPERPLASIA**

  Atypical ductal hyperplasia (ADH) is a proliferative ductal lesion that, when diagnosed by core needle or surgical biopsy, increases a patient's risk of breast cancer approximately fourfold. Distinction between ADH and low grade ductal carcinoma in situ (DCIS) is difficult since there are no definitive morphologic criteria. Lesion size < 2 mm is often considered as an important criterion.

  Calcifications are the most common mammographic manifestation of ADH, cases diagnosed from biopsy of an asymmetry or mass are rare. Detailed assessment of calcification distribution and form are helpful predictors for malignancy.

  In our institution we usually perform stereotactic vacuum-assisted core needle biopsy for calcifications designated as suspicious or highly suggestive of malignancy (BIRADS category 4 or 5). Multiple studies have shown that the improved contrast of digital mammography improves conspicuity of calcifications over film-screen mammography. In our work we also demonstrate the additional conspicuity DBT provides us in the detection of subtle clustered calcifications. Case examples Figure 1 and 2.

- **LOBULAR NEOPLASIAS**

  Is a spectrum of lesions that includes atypical lobular hyperplasia (ALH) also called lobular intraepithelial neoplasia and lobular carcinoma in situ (LCIS).

  **ATYPICAL LOBULAR HYPERPLASIA**

  Is a pre-malignant lesion considered a part of borderline breast disease. ALH represents a proliferation of monomorphic cells which, in distinction to LCIS, occurs in a non-distended lobule or small lobular duct. ALH maintain regular lobular architecture (Figure 3).
ALH is usually asymptomatic and not associated with specific mammographic findings. Frequently associated with columnar cell lesions and flat epithelial atypia; less commonly associated with low grade invasive carcinomas which may have mammographically-detectable calcifications (Figure 4,5), density or mass targeted on biopsy.

**LOBULAR CARCINOMA IN SITU**

LCIS originates in the terminal ductal lobular unit where the malignant cells fill and distend the lobular acini. Unlike Invasive Lobular Carcinoma, they leave the basement membrane intact (Figure 3). LCIS often doesn't cause any signs or symptoms, although some non-specific changes may occur (i.e., a lump, an area of puckered or otherwise unusual skin, a thickened region under the skin, or nipple discharge).

Two forms of lobular carcinoma in situ were associated with calcifications: the classic form with small, uniform cells, and the pleomorphic form with larger cells frequently associated with central necrosis. Because ductal carcinoma in situ and lobular carcinoma in situ share the pathophysiology of necrosis, in some mammographically similar features, radiologists may not be able to distinguish between the two types prospectively.

In our case example (Figure 6), on mammography and DBT, all calcifications were clustered, punctate, high density, and smaller than or equal to 0.5 mm.

**• INTRADUCTAL PAPILLOMA**

Papilloma is a branching epithelial tumor originating from the wall of the milk duct. There are two types of intraductal papillomas, the central and the peripheral type. The central type develops in the large milk ducts near the nipple (solitary intraductal papilloma) and often arises in the period of menopause. It is usually felt as a small lump near the nipple and may cause nipple discharge or bleeding. The peripheral type are often multiple papillomas arising in the ducts farther away from the nipple at the peripheral breasts, and are usually detected in younger women. The peripheral type are associated with a higher risk of malignancy.

Intraductal papillomas are the most common cause of bloody nipple discharge in women age 20-40 and generally do not show up on mammography. Anyway mammography is typically recommended for any patient presenting with abnormal nipple discharge. Some studies have reported that mammography has a low positive predictive value of only 16.7%, and low sensitivity of 59% in the diagnosis of malignant duct pathology associated with nipple discharge. In this case, DBT plays an important role in the detection and characterization of subtle findings that can range from distended retroareolar ducts, a developing asymmetry, architectural distortion, periductal microcalcifications to initial nipple retraction. Case example Figure 7.
RADIAL SCARS

Radial scar (RS) of the breast has been previously described in the literature under several different names such as radial sclerosing lesion, scleroelastotic lesion, indurative mastopathy, nonencapsulated sclerosing lesion, sclerosing papillary proliferation, and, if larger than 1.0 cm, complex sclerosing lesion. RS is a benign breast lesion characterized by a central fibroelastotic core with ducts and lobules radiating outward, giving the lesion its characteristic stellate appearance. In addition, pathologic examination of a radial scar often reveals a diverse array of pathologic findings including typical epithelial hyperplasia, adenosis, papillomatosis, atypical epithelial hyperplasia, ductal carcinoma in situ (DCIS), and early stage invasive carcinomas. Reports in the literature suggest that radial scar is associated with surrounding malignancy in 0-40% of the cases. Although most radial scars are found incidentally at microscopic evaluation of biopsy specimens of another lesion, the widespread use of mammography has led to identification of features characteristic of this lesion.

The mammographic appearance of RS is characterized by an area of architectural distortion and according to the criteria of Tabar and Dean:

- the presence of a central radiolucency
- the presence of radiating long thin spicules
- varying appearance in different projections
- radiolucent linear structures parallel to the spicules
- the absence of a palpable lesion or skin changes.

The relative low density of the centre plays an important role in the differential diagnosis between radial scar and carcinoma, in which the centre tends to be more dense and the translucent area is characteristically absent. On ultrasound, a radial scar, which disturbs the architecture of surrounding breast parenchyma, is often ill-defined round, oval or lobulated lesion with variable internal echoes.

RS detection increased dramatically over the past few years. In our experience, DBT showed up to be better than DM in the detection of RS. This might depend on the planar configuration of RS, which may have varying appearances on orthogonal views. However, the differential diagnosis between RS and malignancy can only be solved by the final histological examination. Case example Figure 8.
Fig. 1: Fine dust-like microcalcifications were found in the retroareolar region of the left breast in a 60 years old woman with recent left nipple retraction. The patient underwent both digital mammography (A) and digital breast tomosynthesis (B). The microcalcifications were classified as suspicious (BI-RADS 4). Surgical approach, lumpectomy, was performed due to insufficient breast compression thickness on stereotactic biopsy. Histology of the surgical specimen consisted of Atypical Ductal Hyperplasia.

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Fig. 2: A 54 years old woman was recalled from the regional screening program due to the presence of subtle coarse heterogeneous (granular) microcalcifications in the central retroareolar region of the right breast. The microcalcifications were classified as suspicious (BI-RADS 4) on both diagnostic modalities (A - Digital mammography, B - Digital breast tomosynthesis). Vacuum assisted biopsy was performed and histology showed Atypical Ductal Hyperplasia.

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Fig. 3

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Fig. 4: A 63 years old woman was recalled from the regional screening program due to the presence of an architectural distortion in the upper quadrants of the right breast. The distortion was classified as suspicious (BI-RADS 4) on both imaging modalities (A - Digital mammography, B - Digital breast tomosynthesis). The patient underwent US guided core needle biopsy (not shown), yielding histology consistent with Atypical Lobular Hyperplasia.
Fig. 5: A 62 years old woman was recalled from the regional screening program due to the presence of subtle microcalcifications associated with tenuous opacity in the upper-outer quadrant of the right breast. The area was classified as suspicious (BI-RADS 4) on both diagnostic modalities (A - Digital mammography, B - Digital breast tomosynthesis). The patient underwent US guided core needle biopsy (not shown), and histology was compatible with Atypical Lobular Hyperplasia.

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Fig. 6: A 41 years old woman, with family history of breast cancer, underwent screening Digital mammography (A) on which subtle microcalcifications in association with architectural distortion was detected in the upper-outer quadrant of the right breast. On Digital breast tomosynthesis (B) the area was classified as highly suspicious for malignancy (BI-RADS 5) for the presence of fine pleomorphic microcalcifications. Core needle biopsy under US guidance (not shown) was performed, and histology was compatible with Lobular Carcinoma in Situ, confirmed at surgery.

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Fig. 7: Clear left nipple discharge in a 63 years old woman was detected during breast compression on regional screening mammography. The patient was recalled and underwent both Digital mammography (A) on which distended retroareolar duct was detected, and Digital breast tomosynthesis (B) which revealed also the presence of periductal microcalcifications in this area. The lesion was then classified as suspicious (BI-RADS 4). The patient underwent US guided core needle biopsy (not shown), yielding histology consistent with Intraductal Papilloma.

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Fig. 8: A 60 years old woman was recalled from regional screening program because of focal asymmetry in the upper-outer quadrant of the left breast. The patient underwent both digital mammography (A) and digital breast tomosynthesis (B) on which the focal asymmetry was classified as "Radial Scar", highly suspicious for malignancy (BI-RADS 5). The patient underwent first US guided core needle biopsy (not shown) yielding histology consistent of fibrosis. Due to imaging-histology discordance, lumpectomy was performed, making histology compatible with Invasive Ductal Carcinoma.

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Conclusion

Much progress has been made these last years in the histological diagnostic, classification and pathogenesis of high-risk lesions. Nevertheless, no consensus exists to date on the management of these lesions. In particular, surgical indications and follow-up modalities remain controversial for each histological type.

In our experience the majority of high-risk breast lesions detected on DM were associated with microcalcifications. The ability to provide "slices" through the breast and reduce the noise contributed by the normal breast structures is the major benefit from tomosynthesis (DBT). We noticed that calcifications of all types are seen as well, or seen with even greater clarity on DBT studies when compared with DM. DBT plays an important role in the detection and characterization of subtle findings that can range from distended retroareolar ducts, a developing asymmetry, architectural distortion and periductal microcalcifications.

Very few reports in the literature have compared DM and DBT for classification of microcalcification clusters. Some authors, like Spangler et al. have outlined that DBT may underestimate BI-RADS cluster classification compared to FFDM (Figure 9). As the information is viewed as slices, the observer may not perceive the clustering of the calcifications.

On the other hand, DBT may have the advantage of avoiding unnecessary biopsies in patients with benign conditions manifest as microcalcifications.
<table>
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<th>Benign Calcification</th>
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Note—Data are no. of cases.

<sup>a</sup>Although calcification was detected, BI-RADS scores were not provided in one malignant and two benign cases, all in digital breast tomosynthesis mode.

**Fig. 9**

Personal information

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