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High-Risk Lesions at Minimally Invasive Breast Biopsy: Now What?

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Abstract
Purpose The purpose of this section is to provide a detailed review of high-risk lesions and their associated risk of upgrade at surgical excision in order to guide in management and appropriate risk reduction strategies.
Recent Findings "High-risk" breast lesions refer to an eclectic group of histologic abnormalities associated with an increased risk of breast cancer. Current data show a vast disparity in upgrade rates upon surgical excision for high-risk lesions, which leads to confusing and often conflicting recommendations. There has been suggestion in the media that breast biopsies lead to "over-diagnosis" and unnecessary breast surgeries. However, the goal of breast imagers is to detect early cancers, and in doing so, the recommendation for surgical excision of the appropriate high-risk lesions is necessary.
Summary In managing high-risk lesions we must balance the opportunity to diagnose early, curable breast cancer by recommending surgical excision with prudent and conservative management along with careful radiologic and pathologic correlation.

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Introduction

"High-risk" breast lesions refer to an eclectic group of histologic abnormalities associated with an increased risk of breast cancer. High-risk lesions can be divided into two categories: those found at minimally invasive breast biopsy that have significant risk of upgrade to cancer upon surgical excision and those that indicate an increased risk of breast cancer over a woman's lifetime. This section will focus on the former which include atypical ductal hyperplasia, lobular neoplasia, papillary lesions, radial scar, mucocele-like lesions and flat epithelial atypia, each with varying relative and absolute risks for cancer. The key to management of high-risk lesions is understanding which lesions require surgical excision to best ensure detection of early curable breast cancer.

Percutaneous core needle biopsy is currently the standard of care for evaluation of indeterminate breast lesions. Advantages to this minimally invasive procedure include lower morbidity, lower costs and easier patient recovery as compared to surgical excision [1]. At our institution, nearly 100% of patients have percutaneous biopsies for histologic diagnosis prior to surgical excision. In some practices, up to 30% of breast biopsies may still be performed surgically, although the number of percutaneous breast biopsies continues to increase nationally, while the number of open surgical biopsies decreases [2]. Percutaneous breast biopsies have many advantages, but they have some inherent limitations as well. During core needle biopsies, only a portion of the lesion is sampled, and therefore, there is a risk of under-sampling particularly when the lesion is

heterogeneous. Sampling error has been reported at 0.5–4.5% for stereotactic guided core biopsies [3]. Under-sampling is particularly concerning in high-risk lesions since the portion of the lesion with the highest grade may not be sampled, and therefore, the risk for associated cancer may be underestimated. Furthermore, since high-risk lesions and cancers are often adjacent, an under-sampled lesion may miss the malignant component of the lesion at minimally invasive biopsy.

Numerous studies on high-risk lesions can be found in the medical literature with many reports focused on the upgrades rate of high-risk lesions to cancer upon surgical excision [4–7]. It is important to determine which lesions require surgical excision and which can be followed with imaging. Unfortunately, there is substantial variation in the literature regarding upgrade rates which leads to confusing and often conflicting recommendations. For example, upgrades rates for radial scars have been reported to vary between 0 and 40% [8–10] and between 0 and 11% for papillomas [11, 12•]. The disparity in the data can be attributed to small sample size, lack of randomized prospective studies, predominantly single institutional studies, and interobserver variability among pathologists. High-risk lesions lie along a spectrum of histologic changes within breast tissue and the final diagnosis made by a pathologist can be somewhat subjective. It stands to reason that the type of biopsy device used can impact the upgrade rate. There is an inverse relationship between upgrade rate and amount of tissue acquired. Larger gauge biopsy devices, particularly those with vacuum assistance, result in greater volume of tissue and lower upgrade rates. Nevertheless, there is no device that can assuredly determine that cancer will not be found at subsequent surgical excision of a high-risk lesion diagnosed at percutaneous biopsy. Furthermore, it is not only the biopsy device and amount of tissue acquired that impacts the upgrade rate. A recent study of the upgrade rate of ADH identified with breast MRI demonstrated that a substantially higher upgrade rate occurred than when ADH is found with mammography and sampled with stereotactic biopsy, even when the same type of biopsy device is used [4, 13].

The controversy and dilemmas surrounding the management of high-risk lesions has gained attention in mainstream media as well. Articles like "Breast biopsies leave room for doubt, study finds" as seen in the health section of the New York Times erroneously suggest to the lay person that percutaneous breast biopsies are ineffective and inaccurate [14]. Furthermore, there has been suggestion in the media that breast biopsies lead to "over-diagnosis" and unnecessary breast surgeries [15]. Our goal as breast imagers is to detect early cancers, and in doing so, the recommendation for surgical excision of the appropriate high-risk lesions is necessary. There is a delicate balance between early detection and over-treatment. The purpose of this paper is to provide a detailed understanding of high-risk lesions and their associated risk of upgrade at surgical excision in order to guide in management and appropriate risk reduction strategies.

Atypical Ductal Hyperplasia (ADH)

Atypical ductal hyperplasia (ADH) is the most frequently encountered high-risk lesion, accounting for 2–11% of minimally invasive breast biopsies [16–18]. Histologically, it is defined as proliferation of dysplastic epithelial cells within ductal spaces. ADH fulfills some but not all the features of DCIS either by having all the features of DCIS but involving only one duct or by having all the features of DCIS but measuring less than 2 mm in diameter [19].

ADH most frequently presents as microcalcifications on mammography and when it does should undergo biopsy with stereotactic-guided vacuum-assisted biopsy [20]. Less common presentations include a lobulated mass with no posterior acoustic features on ultrasound and an enhancing mass or non-mass enhancement on MRI [13, 21]. The reported upgrade rate of ADH diagnosed at minimally invasive biopsy upon surgical excision ranges from 10 to 56% [21–23]. Of note is the substantial variability in the upgrade rate. However, it is clear that the use of smaller gauge biopsy devices, without vacuum assistance, results in high upgrade rates, often more than 50%. It is for this reason that vacuum-assisted biopsy probes were developed with the result of improved lesion sampling. In fact, the acquisition of larger tissue samples did result in substantially lower upgrade rates. However, even with an 11-gauge vacuum assistance biopsy probe, the upgrade rate is approximately 20–25% necessitating the recommendation of surgical excision for all ADH diagnosed at minimally invasive biopsy, regardless of the size or type of biopsy device used [22, 24••].

The imaging modality in which ADH is identified also influences the upgrade rate. Recent studies evaluating the upgrade rate of MRI detected breast lesions which underwent biopsy with MRI-guided vacuum assistance demonstrated an upgrade rate 32-38%, higher than that reported for stereotactic biopsy for calcifications identified mammographically [13, 25]. For ADH identified with ultrasound and sampled using a 14-gauge core needle, Mesurolle et al. found an upgrade rate of 27–56% [21, 26•]. However, the upgrade rate decreased to 23% when the ultrasound guided biopsy utilized a vacuum-assisted biopsy device [27], but not enough to reliably exclude cancer, and therefore, surgical excision should be recommended. Surgical excision of biopsy-proven atypical hyperplasia is recommended by NCCN guidelines [28].

What is evident is that there is a complex interaction between the type of lesion, the type of biopsy device, and the imaging modality in which the ADH is identified. Although all these factors influence the upgrade rate of ADH diagnosed at minimally invasive breast biopsy, what is clear is that the finding of ADH warrants a recommendation of surgical excision regardless of the type of imaging or biopsy device used due to the persistent finding of cancer at subsequent surgical excision.

The vast majority of ADH found at minimally invasive breast biopsy is confirmed to be benign at surgical excision. Therefore, it would be a significant step forward if we could determine which ADH is at greater risk of having a malignancy associated with it and which women have ADH that can reliably be determined to not be associated with higher grade lesions and obviate the need for surgical excision in all cases. Such studies, utilizing molecular markers and genomics to identify more "aggressive" ADH are underway such that in the future, it is possible that not all women diagnosed with ADH will need surgery to exclude cancer [29]. However, for now, the findings of ADH at minimally invasive breast biopsy necessitate the recommendation for surgical excision (Figs. 1, 2).

The presence of ADH also indicates an increased risk of developing breast cancer. Degnim et al. demonstrated a relative risk of 3.88 in women with atypia [30]. Additionally, marked elevations in risk were seen with multifocal atypia. With a single focus of atypia, cumulative breast cancer risk was 18% at 25 years of follow-up. Two or more foci of atypia resulted in a cumulative risk of 45% at 25 years with three or more foci of atypia having a cumulative risk of 48% at 25 years. Risk was similar for atypical ductal and atypical lobular hyperplasia. The relative risk was higher for women less than 45 years old. The effect of family history on breast cancer risk in women with atypical hyperplasia is controversial, although Degnim et al. [30] found that family history added no significant risk. The major histologic modifiers of breast cancer risk in women with atypical hyperplasia are the number of separate foci of ADH and degree of involution of the background lobular units. Women with a greater number of separate foci of atypia have a higher risk. Increased degree of involution of background lobular units is associated with lower risk. It is noteworthy that studies have demonstrated that the risk of developing breast cancer in younger women and in women with multiple foci of ADH is greater than the 20–25%, the threshold recommended by the American Cancer Society for annual MRI surveillance [31]. Yet, today, MRI surveillance in this population is not routinely recommended. As more data on the risk of the subsequent development of cancer in women with a diagnosis of ADH demonstrates a risk of cancer greater than 25%, perhaps the use of MRI for surveillance in this population of women should be reconsidered.

Chemoprevention has been studied with tamoxifen and raloxifene in women with a history of ADH. In the NSABP P-1 study of tamoxifen, there was an 86% reduction in breast cancer incidence in women with ADH who received tamoxifen for 5 years [32]. The STAR trial showed that raloxifene has a similar effect on risk reduction with less toxicity [33]. Currently, the recommendation for women

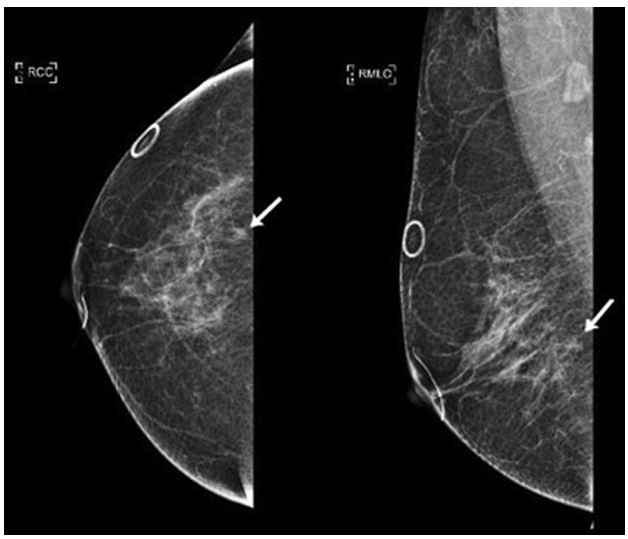

Fig. 1 CC and MLO views of the right breast demonstrate a developing asymmetry in the *right lower outer* quadrant (*arrow*) in a patient with a history of DCIS in the left breast and LCIS in the right breast status post-surgical excision

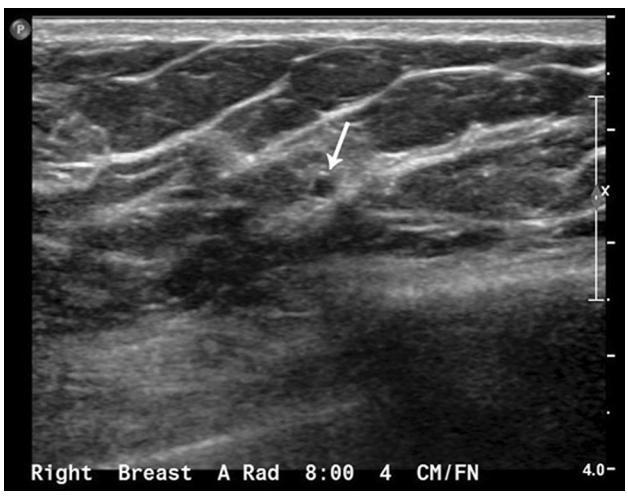

Fig. 2 Ultrasound image of the right breast at the 8:00 axis demonstrates a 0.4 mm oval hypoechoic mass (*arrow*) corresponding to the mammographically demonstrated asymmetry. At 14-gauge core needle biopsy, this was proven to be ADH. Patient was referred for surgical excision and this lesion was upgraded to DCIS at surgical excision

with ADH includes consultation for chemoprevention for risk reduction.

Lobular Neoplasia

Lobular Neoplasia (LN) includes both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). Classic lobular neoplasia is characterized by a monotonous, dyscohesive proliferation of evenly spaced small round cells of low to intermediate nuclear grade that both fill and distend acini of involved lobular units [19]. These are often found incidentally during the workup of an otherwise suspicious breast lesion and are found in less than 2% of percutaneous biopsies [34].

Classically, ALH and LCIS are multicentric and bilateral and are considered a risk factor for developing an invasive cancer within either breast. The risk for developing breast cancer in women with a diagnosis of lobular neoplasia is 4–5 times greater for ALH and 8–10 times greater for LCIS [35]. Since LN is a marker of increased risk surgical removal of the biopsy site yielding ALH or LCIS does not decrease a woman's chance of developing breast cancer at an alternate site in the breast.

The reported upgrades rates for LN vary widely in the literature, ranging from 2 to 25% [5, 7, 36–40]. Similar to the data on ADH, variation in upgrades rates is likely due to small sample sizes, retrospective studies, and pathologist variability. In a multi-institutional study, 32,420 core biopsies from 14 institutions were reviewed [5]; 278/32,420 (0.9%) were found to be lobular neoplasia. Of the surgically excised cases, 23% contained DCIS or invasive cancer, an upgrade rate similar to that reported for ADH. Lewis et al. found a 19% upgrade rate to cancer at surgical excision [36]. Although the management and the need for surgical excision remains controversial, the finding of similar upgrade rates of Lobular Neoplasia and ADH, the latter of which requires surgical excision, suggests the need for surgical follow-up of lobular neoplasia and at our institution all lobular neoplasia is recommended for surgical consultation.

Pleomorphic LCIS is a subtype of LCIS which has been found to have higher upgrade rates at surgical excision. Pleomorphic LCIS is described histologically as dyscohesive cells having more abundant cytoplasm, with larger, more pleomorphic nuclei that may contain nucleoli [19]. It is also frequently associated with central comedo necrosis and calcifications, characteristics that are often considered more typical of DCIS [41, 42]. In a study published in 2015, Flanagan et al. reviewed 23 cases of pleomorphic LCIS, 21 of which went to surgical excision where the upgrade was 52.4%; 7/21 were upgraded to invasive cancer and 4/21 were upgraded to DCIS [43]. Pleomorphic LCIS is also found to recur at a similar rate to low–intermediate grade DCIS when margins status is evaluated [44]. Given that pleomorphic LCIS is considered a more aggressive form of LN with high upgrade rates, it should be surgically removed. There remains debates in the surgical and oncologic literature as to how to manage margin status in these cases [45, 46], with some recommending excision requiring negative margins and some suggesting that negative margins are not necessary [47].

The management of ALH and LCIS, remains controversial and varies significantly across institutions. Options include surgical excision for all biopsy proven LN, close interval imaging follow-up or surgical excision on a case by case basis. Significant sampling error occurs regardless of the biopsy device, number of samples, histologic-radiographic concordance, mammographic appearance, and complete excision of the lesion.

The bottom line is that there is no consensus as to the management of LN found at minimally invasive breast biopsy. Some suggest that only pleomorphic LCIS should be surgically excised as the morphology and molecular features suggest a more aggressive process [42]. Since the upgrade rate of the larger, multi-institutional studies suggest upgrade rates similar to ADH, all LN is excised at our institution. Some suggest surgical excision of only pleomorphic LN while others suggest radiologic pathologic correlation with follow-up of all LN without recommending surgical excision.

Papillary Lesions

Papillary lesions are proliferative lesions defined by the presence of a fibrovascular stalk surrounded by epithelial proliferation with or without myoepithelial cells [48]. The absence of a myoepithelial cell layer in the papillary component indicates papillary carcinoma [49]. Papillomas can present with a palpable lesion or with nipple discharge, and are the most common cause of bloody nipple discharge. Up to 5% of lesions at core needle biopsy are papillary lesions. On mammography, papillary lesions may be seen as multiple masses with or without calcifications or may present as calcifications alone. The ultrasound appearance is typically a solid, homogeneous, intraductal mass [50]. On MR imaging, papillomas are enhancing masses with smooth margins and rapid wash-in and wash-out kinetics [50, 51]. They can be associated with a dilated duct. Papillary lesion can be benign, atypical, or malignant (including DCIS and invasive papillary cancer) [48]. Imaging features do not reliably distinguish benign from malignant papillary lesions (Figs. 3, 4, 5).

There have been multiple studies reporting the upgrade rate of benign papillary lesions at percutaneous biopsy. Several studies from 2004 to 2008 reported an upgrade rates from 0 to 37% for benign papillary lesions at percutaneous core biopsy [52–55]. Destounis et al. found no significant

difference in core needle biopsy versus vacuum-assisted biopsy, with an upgrade rate of 6% [56]. An international multicenter review demonstrated an upgrade rate of 14% for benign papillary lesions and that the overall risk of malignancy was increased with older age and with the presence of atypia in the biopsy specimen [57]. In the same study, the upgrade rate for papillary lesions with atypia was 36%.

Given the high upgrade rate, any papillary lesion with atypical or malignant features should be surgically excised. A study comparing core needle biopsy with vacuum-assisted biopsy demonstrated an upgrade rate of 10.2% for core needle biopsy versus 0% for vacuum-assisted biopsy [58], suggesting that vacuum assistance should be utilized when sampling a suspected intraductal mass. However, additional studies are needed to confirm this finding. If a benign papillary lesion is followed, strict radiologic pathologic correlation is necessary. Micropapillary lesions with complete excision do not require surgical excision but should be followed with radiologic pathologic correlation. Should there be any change in the appearance of the lesion, or growth, then surgical excision is recommended. Alternatively, re-biopsy with vacuum assistance can be considered in select clinical cases. Any papillary lesion that is not completely removed at the time of biopsy should be considered for surgical excision [59]. For benign papillary lesions, these are generally excised, but with vacuum-assisted biopsies and adequate sampling, close imaging follow-up may be sufficient.

Radial Scar

Radial scar, also known as radial sclerosing lesion or complex sclerosing lesion when it is greater than 1 cm in size, is rare, accounting for 0.03–0.09% of breast biopsies [60]. Pathologically, this entity consists of a central fibroelastotic core with outwardly radiating ducts accounting for the stellate or spiculated appearance with central lucency seen mammographically. The most common proliferative components are sclerosing adenosis, duct hyperplasia, and cysts [19]. Surgical excision is generally recommended as radial scars are intrinsic heterogenous, and therefore, even with a benign finding at minimally invasive breast biopsy, the need to exclude cancer in a different portion of the lesion suggests the need for surgical excision.

There is a higher risk of malignancy with larger radial scars, increasing patient age, and the presence of a mass/architectural distortion versus microcalcifications [61]. There are no specific histologic features that correlate with malignancy. The upgrade rate has been reported to range from 0 to 12%. However, the upgrade rate is higher in radial scars when associated with other high-risk lesions. Andacoglu et al. describe a series of 67 radial scars in which 22.4% upgraded to radial scar with atypia and 5.9% were upgraded to carcinoma [62]. The average age of patients whose lesions were upgraded to carcinoma was 64, suggesting a higher association of radial scar and malignancy in postmenopausal patients [62]. In another series of 88 patients with isolated radial scar, the upgrade rate was 1.6% [63], a rate sufficiently low to suggest that careful radiologic–pathologic correlation may be sufficient. Ferreira et al. found an upgrade rate of 19.5% in a series of 113 cases of radial scar with an upgrade rate of 4% for biopsies performed with vacuum assistance and 23.9% for the core needle biopsy group [60]. Leong et al. suggest that surgical excision is not indicated for isolated radial scar, as the upgrade rate to DCIS was 0.6% in a series of 161 patients [64]. As with other high-risk lesions, there is

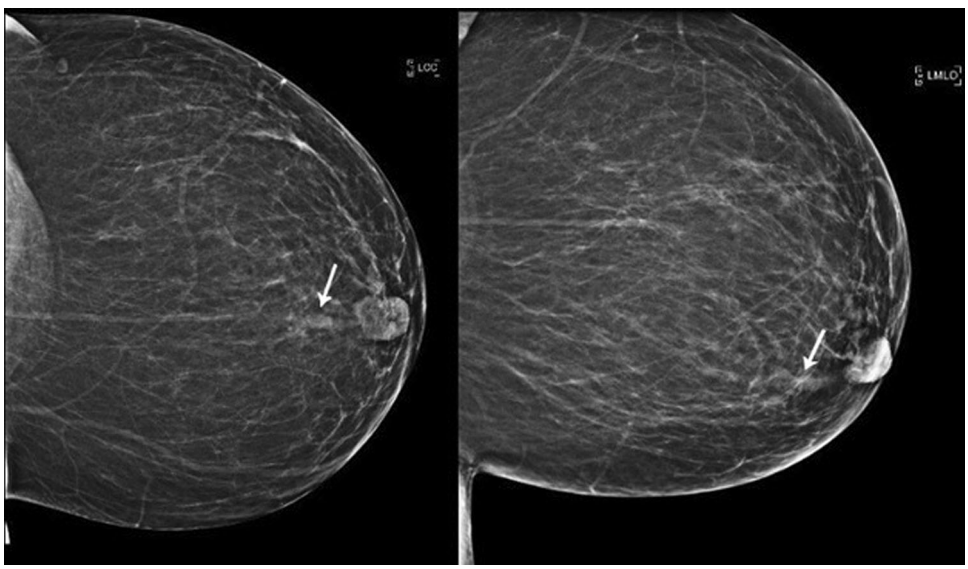

Fig. 3 CC and MLO views of the left breast from a screening mammogram in a 48-year-old female demonstrate an asymmetry in the retroareolar left breast (*arrow*)

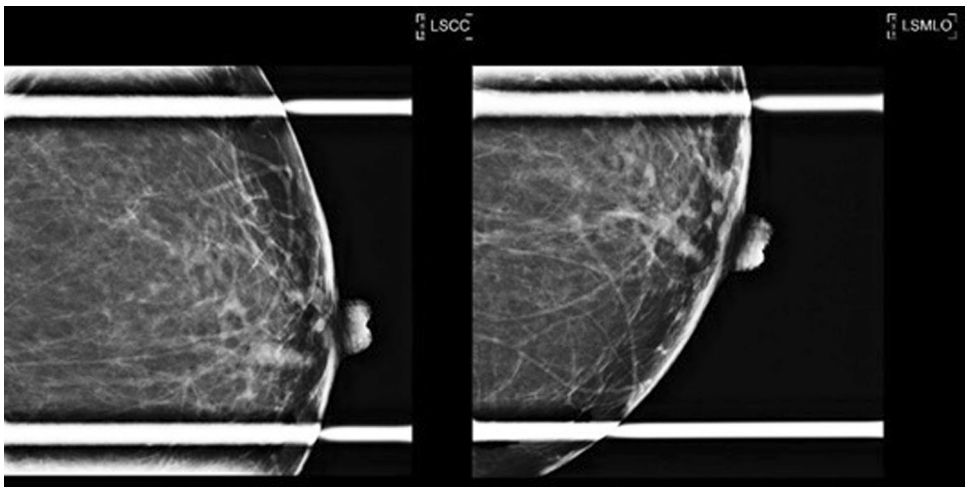

Fig. 4 Spot compression CC and MLO views of the left breast

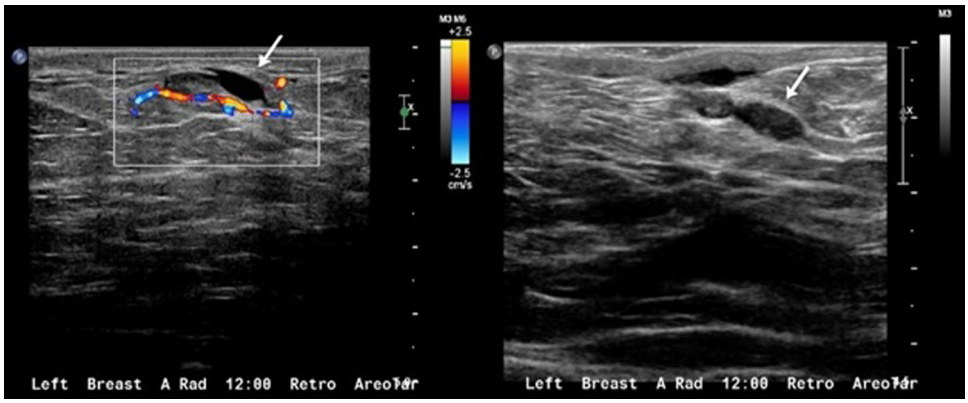

Fig. 5 Grayscale and color Doppler ultrasound images of the left breast demonstrate duct ectasia with an intraluminal mass (*arrow*) which was sampled with a 14-gauge core biopsy needle under ultrasound guidance, yielding intraductal papilloma

substantial variability in upgrade rate. The reported studies are predominantly single institutional studies with a limited cohort, likely the reasons for the differences. However, the management recommendations remain confounding and conflicting and will likely stay as such until larger, multi-institutional studies are available to definitively answer the question as to the management of radial scars at minimally invasive breast biopsy.

Some studies have suggested that radial scar does not confer an increased risk of breast cancer when compared to benign proliferative disease without atypia [65]. Others have suggested that the risk of developing breast cancer following a diagnosis of radial scar moderately increased at 1.3–2.6 [65–67].

In summary, both in situ and invasive cancers, when found in association with radial scar, can be focal or patchy. Therefore, surgical excision should be considered to exclude malignancy when this lesion is found at minimally invasive biopsy due to the upgrade rate. However, if vacuum-assisted biopsy is performed with adequate sampling (at least 12 specimens) or in the case of an isolated radial scar, close imaging follow-up can be performed for surveillance (Fig. 6).

Flat Epithelial Atypia

Flat epithelial atypia (also known as ductal intraepithelial neoplasia grade 1a) is considered a borderline lesion, as it may represent an early stage in the development of low-grade malignancies [68]. It is a newer term used to describe columnar cell change in the terminal duct lobular unit and is associated with low-grade cytologic atypia, lobular neoplasia, low-grade DCIS, and invasive tubular or lobular cancer [69]. It is rare, accounting for 1–5% of minimally invasive breast biopsies [70]. The upgrade rate ranges from 5 to 33%, as there is limited published data. According to Peres et al. [71], the upgrade rate was 15% in 184 cases of FEA that were surgically excised [71]. An analysis of 27 cases of pure FEA demonstrated an upgrade rate of 11% [72]. This study also defined focal versus prominent FEA, where focal FEA involved "fewer than three adjacent acinar spaces within a lobule or adjacent lobules" and prominent FEA "involves widespread acini with FEA and/or a larger confluent focus of FEA." Thirty-three percent of patients in the prominent FEA group were upgraded to malignancy, higher than that found in women with focal FEA [72]. Acott et al. found an upgrade rate of 2.2% for

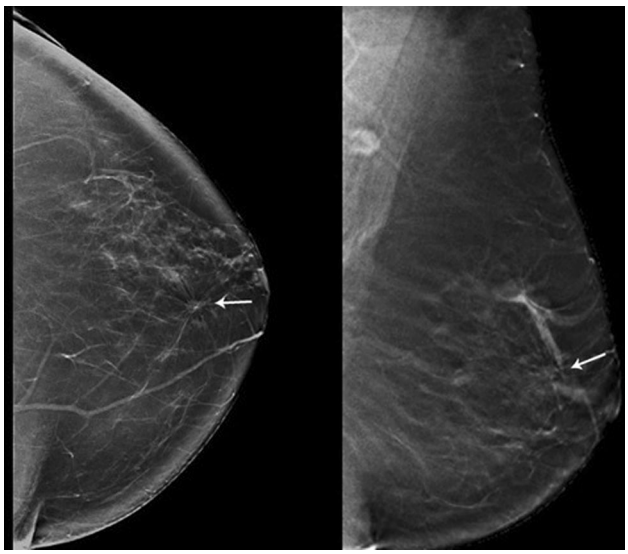

Fig. 6 Radial scar. CC and MLO views of the left breast from a diagnostic mammogram in a 62-year-old female demonstrate a 0.8 cm irregular mass in the upper inner quadrant associated with architectural distortion. At 14-gauge core needle biopsy under ultrasound guidance, this was proven to be a sclerosing lesion with ADH

isolated FEA and 16.1% for FEA associated with ADH [73]. In a study of 103 columnar cell lesions and ADH diagnosed by ultrasound-guided core needle biopsy, Ahn and colleagues showed an upgrade rate of 44.4% for FEA associated with ADH, whereas the isolated FEA upgrade rate was 6% [26].

There are data suggesting that FEA is a high-risk marker for the subsequent development of breast cancer, with 11–14% risk of developing breast cancer in 10 years after diagnosis of FEA [72]. However, additional, multi-institutional studies are needed to further define the increased risk of cancer in women with a diagnosis of FEA.

Currently, at our institution, all cases of FEA at minimally invasive biopsy are referred for surgical consultation. However, there is no consensus on this and the recommendation varies among institutions. Additional multi-institutional studies are needed to develop a consensus on the management of FEA.

Mucocele-Like Lesions

Mucocele-like lesions (MLL) are dilated spaces containing mucin, and associated with mucin in the surrounding parenchyma, are relatively uncommon and include a variety of lesions from benign mucoceles to invasive mucinous (colloid) carcinoma [74]. They frequently present as microcalcifications but may present as a mass or a mass with calcifications [75]. This is a rare pathologic finding, accounting for less than 1% of benign breast biopsy diagnoses [76]. To distinguish a mucocele-like lesion from mucinous carcinoma, there must not be any epithelial cells within the luminal or extravasated mucin [76]. In a series of 23,962 core needle biopsies, 58 (0.2%) were mucocele-like lesions, and in another series of over 4000 breast biopsies, 0.51% were mucocele-like lesions. The upgrade rate for MLLs without atypia is 0% in a number of series [76–78], although in one series 17% (4/23) of MLL without atypia, demonstrated atypia at subsequent surgical excision. In MLL with atypia, the upgrade rate ranges from 8 to 31% [76, 77]. Interestingly, the MLL upgraded at surgical excision presented as masses whereas the MLL presenting as microcalcifications were not associated with malignancy. It is important to remember that the number of MLL in these series is small. What is consistent is that in all these series there were no upgrades to malignancy when core needle biopsy demonstrated MLL without atypia. Nevertheless, without multi-institutional, larger series we cannot definitively recommend management of MLL which are not associated with atypia. However, MLL associated with atypia should undergo surgical excision to exclude the possibility of cancer.

Conclusion

It is noteworthy that the controversy and discussion of whether to surgically excise high-risk lesions found at minimally invasive breast biopsy has been present for over three decades. There are few clear answers. The current recommendation is to excise ADH found at minimally invasive breast biopsy to exclude the possibility of malignancy. The reason a definitive answer is available for ADH is that ADH is the most frequently encountered high-risk breast lesion, and therefore, studies of ADH include greater number of cases than the other high-risk lesions. Nevertheless, even with ADH there remain many questions. Can we use molecular markers and genomics to stratify ADH such that not all women with ADH at minimally invasive breast biopsy would require surgery. There are ongoing studies that address that question specifically, but to date we cannot and therefore all women with ADH require surgical excision. What is becoming increasingly evident is that in young women, in women with multiple foci of ADH and in women whose background parenchymal is not involuted, the risk of subsequent development of cancer in women with ADH is higher than previously thought. In fact, in these women the 10 year risk of developing breast cancer is greater than 20%, which raises the question of whether this population of women warrants annual surveillance with MRI or molecular breast imaging.

It is clear that papillary lesions, radial scars, and MLL that are associated with atypia require surgical excision.

However, the management of these lesions without atypia remains controversial, largely due to the lack of large, multi-institutional studies. Until larger, definitive studies are available, at our institution we recommend excision of radial scars. With papillary lesions, if the entire lesion is excised at minimally invasive biopsy, we follow with close radiologic pathologic correlation. Otherwise, we recommend surgical consultation. MLL without atypia may be followed with close imaging follow-up as a number of studies have demonstrated no upgrade at surgical excision.

The management of lobular neoplasia is confounded by the rarity of the finding at minimally invasive breast biopsy and remains controversial. In our series of over 60,000 minimally invasive breast biopsies, the upgrade rate of lobular neoplasia was 23%, similar to that found for ADH where the recommendation of surgical excision is clear. Therefore, at our institution we recommend surgical excision of all lobular neoplasia. In other institutions, only pleomorphic lobular neoplasia undergoes subsequent surgical excision and in others lobular neoplasia undergoes close radiologic–pathologic correlation.

In managing high lesions, we must balance the opportunity to diagnose early, curable breast cancer by recommending surgical excision with prudent and conservative management along with careful radiologic/pathologic correlation. With the exception of ADH, papillary lesions associated with atypia, MLL associated with atypia, and probably pleomorphic LCIS, we must await larger, multi-institutional studies to help define the definitive management of high-risk breast lesions.

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Compliance with Ethical Guidelines

Conflict of Interest Rachel F. Brem is on the board of directors and holds stock in Dilon Technologies. Anita K. Mehta and Grace M. Thomas each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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