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Pathologic High Risk Lesions, Diagnosis and Management

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Abstract

Percutaneous imaging-guided core needle biopsy (CNB) is a less invasive and less expensive alternative to surgical biopsy for the evaluation of breast lesions. After a CNB the radiologist determine if there is concordance between the pathology, imaging and clinical findings. Patient management after CNB diagnosis of high risk breast lesion varies. Surgical excision is warranted for lesions yielding a CNB diagnosis of ADH; however controversy exists regarding the need for surgical excision after CNB diagnosis of radial scar, papillary lesion, ALH, or LCIS. Repeat CNB or surgical excision is warranted if histologic findings and imaging findings are discordant.

Keywords

Breast; core needle biopsy; high-risk

Introduction

In the era of widespread mammography and image-guided needle biopsies, high risk lesions are often initially encountered as a histologic finding on percutaneous core needle biopsy (CNB). It is important for the clinician to understand which lesions require a surgical excision of the biopsy site to rule out the possibility of an associated malignancy. The high-risk lesions included in this review are: atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), intraductal papilloma, and radial scar.

As minimally invasive diagnostic procedures are now standard it is important to be aware of the limitations of CNB. In examining CNB outcomes, it is critical to assess concordance or discordance between imaging features and the CNB histology. Radiologic-pathologic discordance suggests that the imaging target may not have been accurately sampled.

At stereotactic and US-guided CNB, discordance has been reported in 0% to 6% of all breast CNB; among discordant lesions in the published literature, surgical excision yielded carcinoma in 18% (range, 3%-63%) [1]. In another study at MRI-guided VAB, discordance was reported in 7% of all CNBs, with surgical biopsy yielding carcinoma in 30% [2]. The most common scenario for radiologic-pathologic discordance is a lesion that is evident as calcifications at mammography for which the patient undergoes stereotactic CNB, but no calcifications are identified at specimen radiography. For mass lesions at stereotactic or US-guided CNB or for MRI enhancement at MRI-guided CNB, the recognition of discordance is more challenging because of the lack of a reliable marker to confirm tissue retrieval.

Specifically, specimen radiography, which is valuable to confirm lesion retrieval for calcific lesions, is not useful for masses or for MRI lesions [2, 3]. The issue of radiologic-pathologic discordance is of particular importance when considering appropriate management of lesions that yield a finding of a high risk lesion at CNB.

Atypical Ductal Hyperplasia

The diagnosis of atypical ductal hyperplasia (ADH) is essentially a diagnosis of exclusion, rather than based on positive criteria, and designates a proliferation with many, but not all the features of low grade ductal carcinoma in situ (DCIS). It is usually associated with, or near, suspicious calcifications that are targeted by CNB. ADH comprises a considerable morphologic spectrum that poses a challenge for the pathologist because it may be difficult to distinguish usual duct hyperplasia at one end of the spectrum from low grade DCIS at the other end of the spectrum. This is even more challenging in the limited tissue sample obtained by CNB. ADH is distinguished from low-grade cribriform-type DCIS by using a combination of qualitative and quantitative criteria. The cytologic changes are similar in both ADH and low grade DCIS, but there is less cytological atypia in ADH than in DCIS, and in ADH the residual normal polarized cells are present. Evaluating the extent of the lesion, partial involvement of the terminal duct lobular unit seen in ADH versus complete involvement of > 2 duct spaces seen in DCIS may be helpful in the distinguishing the two lesions. Interobserver variation in the diagnosis of ADH vs low grade DCIS has been reported [4], but following specific diagnostic criteria has been shown to greatly improve diagnostic consistency [5]. Owing to limited sampling associated with CNB, it is not always possible to use quantitative criteria for distinguishing ADH from low-grade DCIS.

When a CNB yields a high risk breast lesion, the decision to recommend surgical excision depends on several factors including the radiologic-pathologic concordance and the risk of an upgraded lesion in the excision specimen. An “upgrade” is defined as a lesion that is classified as benign or atypical on initial CNB, but DCIS or invasive carcinoma is found in the subsequent excision. The rate of upgrade of ADH found in a core biopsy ranges from 15% to 30%, depending on the number and size of the cores. Excision of ADH can yield DCIS or, less often, invasive carcinoma. Investigators have tried to establish criteria that could help determine which patient diagnosed with ADH on CNB does not require excision, but such attempts have been inconclusive. If ADH is present in CNB material, surgical excision of the area should be performed. The excision specimen is usually sampled in its entirety, with special attention to the area adjacent to the biopsy site. If no obvious carcinoma is found in the excision specimen, excision and core biopsy slides should be reviewed together, whenever possible, to ensure that the atypical ductal proliferation is evaluated in its entirety.

Atypical Lobular Hyperplasia and Lobular Carcinoma In Situ

Atypical lobular hyperplasia (ALH) and classic lobular carcinoma in situ (LCIS) are defined by the presence of a neoplastic proliferation of cells exhibiting characteristic cytological features. Lobules involved by LCIS are distended by a monotonous proliferation of small cells that expand the acini and obliterate their lumen. The cells typically show loss of

cohesion caused, by decreased or absent expression of E-cadherin, a plasma membrane cell adhesion molecule. The nuclei are small and uniform, and show only slight membrane irregularity and fine, homogenous chromatin; nucleoli are absent or inconspicuous. Mitoses and necrosis are not typical of classic LCIS, and their identification suggests a non-classic variant of LCIS. ALH and LCIS are composed of similar cellular populations and they are distinguished using quantitative, rather than qualitative, criteria (i.e., the degree to which involved lobules are distended and architecture effaced) therefore, interobserver and even intra observer variability is not infrequent. The term lobular neoplasia (LN) encompasses the spectrum of disease including ALH and LCIS.

LN usually constitutes an incidental microscopic finding and its true incidence in the general population remains unknown. LCIS is associated with a high risk of subsequent invasive carcinoma in either breast, with higher risk for LCIS [6] than for ALH [7]. The classic teaching is that LN is an incidental finding in a biopsy performed for another reason. More recently, there has been increasing recognition that lobular lesions, particularly LCIS, may contain mammographically evident calcifications [8, 9]. Some investigators have suggested that LCIS may be evident as enhancement at MRI, [10, 11]. Lobular lesions generally do not present as masses at mammography or US; therefore, a diagnosis of LN generally does not provide sufficient explanation for a mass on imaging. Furthermore, a diagnosis of LN in a BI-RADS Category 5 lesion is considered a discordant result warranting surgical excision because of the high frequency of cancer at surgical excision in Category 5 lesions [1]

Currently, however, the need to excise a breast target that yields LCIS or ALH as the highest risk lesion at CNB is debated, because some series report significant rates of upgrade ranging from 2 to 25 % [12–14]. The limitations of published series include retrospective design, small numbers, and incomplete or absent information regarding radiologic-pathologic correlation. Only a subset of patients who had lesions that yielded a finding of LN at CNB underwent surgical excision in most series, and the rationale for surgical excision in those patients often is incompletely reported. However, more recent series included only cases of ALH and/or classic LCIS and with careful assessment of radiologic-pathologic correlation, indicate that the upgrade rate at surgical biopsy of LN identified at CNB is very low, just above the 2% threshold routinely used by radiologists to recommend surgical excision.[15, 16].

Rendi and colleagues studied 68 lesions with LN at CNB and prospective surgical excision. One of the lesions that was upgraded had discordant radiologic-pathologic findings. After excluding the discordant case, there were 2 of 67 lesions (3%) that were upgraded at surgical excision. In both lesions, the imaging target was an MRI nonmass-like enhancement, and the upgrade consisted of DCIS [16]. In our series among 72 concordant lesions of LN, the upgrade rate at prospective surgical biopsy was 3%. The concordant lesions with upgrade consisted of minute, low grade carcinomas: a 0.2-cm IDC with associated low grade DCIS in one case, and a 0.2-cm low-grade DCIS in the other.

Similarly, the radiologic-pathologic concordant LN lesions with upgrade in the prospective TBCRC series which evaluated 77 patients with an upgrade rate of 3%, were well differentiated invasive tubular carcinoma and intermediate-grade DCIS. Although there is no

question that low grade carcinomas are malignant, some of these minute lesions may be regarded as “incidental.” If undetected, these small carcinomas likely would have very minimal, if any, impact on patient survival, especially in patients with LN who are subject to close follow-up.

More recent series reporting the presence of concordance for LN lesions on CNB demonstrate that the upgrade rate is low and routine surgical excision may be unnecessary. However, excision is always required if radiologic and pathologic findings are discordant.

Variants of Lobular Carcinoma In Situ

The widespread use of E-cadherin has revealed that a wide range of carcinomas in situ previously regarded as ductal, lack membranous immunoreactivity for E-cadherin consistent with a lobular phenotype. These lesions are recognized lobular proliferations with unusual morphologic features, such as pleomorphic LCIS and LCIS with massive acinar distention, necrosis, and coarse calcifications, and are not part of classic LCIS.

For CNB yielding LCIS with atypical features such as pleomorphic nuclei, necrosis, or massive acinar distension surgical excision is warranted.

Papillary Lesions

Papillary breast lesions are a heterogenous group of lesions that include benign intraductal papilloma, papilloma with atypia and papillary carcinomas.

Intraductal papillomas are benign lesions consisting of arborizing fibrovascular cores lined by epithelium and myoepithelium that arise most often as a solitary lesion in the lactiferous ducts in the central breast, but they can occur peripherally in any quadrant of the breast. They may be detected by palpation or imaging performed for serous or bloody nipple discharge with which they are often associated.

Atypical ductal hyperplasia or ductal carcinoma in situ may involve or arise within a papillary lesion. For pathologist the primary distinction to be made when faced with a papillary lesion on CNB is whether the lesion is associated with atypia. This can be challenging since CNB offers small or fragmented samples, and papillary lesions can be heterogenous. Focal involvement of some papillary lesions by atypia can make the already complex architecture of papillary lesions more difficult to interpret.

There is no consensus regarding management of patients with benign IDP diagnosed on CNB as reported upgrade rates vary from 0% to 9% [17–19]. Some more recent studies have cautiously suggested that patients with a diagnosis of a benign IDP on CNB may be followed if the imaging studies are concordant.

Pareja et al [20] evaluated 171 radiologic-pathologic concordant CNBs diagnosed as IDPs without atypia with subsequent surgical excision and found an upgrade rate of 2.3%. Histology in the surgical excision specimen revealed two invasive lobular carcinomas and two cases of DCIS, measuring 2 mm or less. In only one case did the carcinoma involve the

IDP, the other 3 carcinomas were 8 mm from the IDP suggesting they were incidental findings. The investigators concluded that imaging surveillance for radiologic-pathologic concordant IDPs without atypia is sufficient.

Swapp et al [21] reviewed 77 patients with radiographically concordant IDPs without atypia who underwent surgical excision and no upgrades to carcinoma were found. One hundred women did not undergo surgical excision of the lesion and were followed with imaging. After an average of 36 months of observation (range, 4.8–93.8 months), the 100 patients observed were noted to have clinically and radiologically stable findings.

Those patients with papillary lesions associated with epithelial atypia, or with discordance between imaging and pathology findings, should be referred for consideration of surgical excision. Surgical management after a CNB diagnosis of an image concordant IDP without atypia, however, remains controversial.

Radial Scar

Radial scars (RS) are benign lesions that are composed of a central stellate nidus of dense elastotic collagen surrounded by a corona of epithelial proliferation. RS may appear as architectural distortion or mass lesion on imaging. The characteristic stellate appearance of RS mimics breast cancer on imaging, thus requiring CNB to rule out malignancy. Historically, RS were most often discovered as incidental microscopic findings, but the common use of screening mammography has led to increased imaging detection of these lesions. Multiple reports in the literature show an association of RS with surrounding malignancy in anywhere from 3% to 40% of cases.

The optimal management of a lesion yielding RS without atypia on CNB is controversial. The surgical upgrade to malignant findings ranges from 0% to 10% [22], however some authors of recent series have suggested that surgical excision may not be necessary for all RS found on CNB and radiologic followup without excision may be appropriate. In a series by Donaldson et al [23] no upgrades were identified in 37 pathologic radiologic concordant RS without atypia that were surgically excised. In another series by Miller et al. [24] of 102 benign radial scars on core biopsy, 1% of cases were upgraded to carcinoma. Some authors have suggested more extensive sampling using a 9- or 11-gauge CNB device followed by meticulous radiologic–pathologic correlation and close follow-up could potentially prevent surgery in the majority of radial scar cases without associated atypia on CNB [25]. Conlon et al. [22] reported that one out of 48 cases (2%) of radiologic pathologic concordant RS without atypia was upgraded to carcinoma on excision. The upgraded case was a 2-mm focus of low-grade ductal carcinoma in situ in a background of ADH. In a meta-analysis including their data and 20 published studies of radial scars diagnosed on CNB, the authors found an overall upgrade rate of 7.5% for RS without atypia and an upgrade rate of 26% for RS associated with atypia [22].

If a RS is associated with atypia or the imaging findings are discordant the lesion should undergo surgical excision. Small (<5 mm), incidental RS without atypia may be suitable for short-term follow up. The optimal management of larger RS without atypia is debated.

Referring the patient for a surgical consultation and using a multidisciplinary approach, assessing risk factors, clinical, radiologic, and pathologic findings is prudent.

Conclusion

A CNB that yields a high risk benign breast lesion requires correlation with the imaging and clinical findings to determine concordance. For CNB yielding ADH, IDP with atypia, or RS with atypia, the risk of upgrade to malignancy in the surgical excision is high and these patients should be referred for surgical consultation. For IDPs and RSLs without atypia, observation can be considered in select cases with favorable features and radiologic-pathologic concordance; however, surgical excision is a safe approach with low morbidity. Cases that do not undergo surgical excision must be followed with clinical and imaging surveillance to assure stability. For CNB demonstrating atypical lobular hyperplasia (ALH) or lobular carcinoma in situ (LCIS), observation can be considered if there are no other associated high-risk lesions in the specimen and/or there is another histologic finding that is concordant with the original imaging lesion (i.e., the ALH or LCIS represents an incidental finding); otherwise, surgical excision is a safe approach with low morbidity. ADH, ALH, and LCIS are histologic findings that indicate a significantly increased long-term risk of breast cancer that may affect either breast. Women with these findings should be counseled on risks and benefits of prevention strategies.

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