Surgical Management of High-Risk Breast Lesions

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KEYWORDS

- High-risk lesion
- Atypical hyperplasia
- Lobular carcinoma in situ
- Percutaneous breast biopsy
- Breast cancer risk
- Papillary lesions
- Radial scar

KEY POINTS

- High-risk breast lesions include 2 large main categories: those lesions that are found on percutaneous biopsy that have a significant risk of demonstrating cancer at excision and lesions that indicate an increased risk of breast cancer over a woman’s lifetime.
- In general, the following lesions identified on percutaneous breast biopsy should be excised: atypical ductal hyperplasia (ADH), flat epithelial atypia, papillary lesions with atypia, and radial scar with atypia.
- For papillary lesions and radial scars 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 percutaneous biopsies 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 (ie, the ALH or LCIS represents an incidental finding); otherwise, 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.
- 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.
INTRODUCTION

The term high-risk lesion of the breast refers to any of a group of histologic abnormalities that confer an increased risk of breast cancer. The surgeon’s role in the clinical management of these lesions is 2-fold and includes issues related to the method of diagnosis as well as strategies for surveillance and risk reduction.

In the era of widespread mammography and image-guided needle biopsies, the surgeon is often presented with a high-risk lesion as a histologic finding on core needle biopsy. In this setting, the key is in understanding which lesions require a surgical excision of the biopsy site to rule out the possibility of an associated malignancy. In the absence of a concurrent malignancy, a high-risk lesion is simply a histologic finding in breast tissue that is associated with an increased risk of breast cancer in the future.

In general, patients who are found to have high-risk lesions are managed long term with surveillance and prevention strategies; but in some circumstances, surgical risk reduction may be considered. In this article, the authors review issues related to the diagnosis of high-risk lesions and recommendations for clinical management.

HIGH-RISK LESIONS: HISTOLOGIC ENTITIES

The classic high-risk breast lesions, lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH), are those that were identified many years ago as being associated with an increased future risk of breast cancer. In the 1970s, it was recognized that a diagnosis of LCIS conferred an increased risk of breast cancer of approximately 1% per year and that this risk was conferred equally to both breasts.1 In 1985, Dupont and Page2 demonstrated that women with either ADH or ALH had an approximate 4-fold increased risk of breast cancer compared with the general population, a level of risk that was approximately one-half of that conferred by a diagnosis of LCIS. With technical advances, the shift to percutaneous core needle biopsy and increased attention to benign histologic findings frequently identified in breast specimens, several additional lesions are now included in the high-risk lesion category, including papillary lesions, radial scar, and flat epithelial atypia (FEA). Each of these is discussed in further detail.

RATIONALE FOR SURGICAL EXCISION OF HIGH-RISK LESIONS

Percutaneous core needle biopsy of breast abnormalities is subject to several limitations. First, the targeted lesion can be inadequately sampled or clearly missed; fortunately, this occurs only infrequently. However, it is common that only a portion of the lesion is removed, introducing the possibility of sampling error3; and the lesions are often fragmented into multiple smaller pieces by the nature of the procedure, which can increase the difficulty in making a definitive histologic diagnosis.4

It is well documented that certain histologic diagnoses, when made on core needle biopsy specimens, will frequently be upgraded to cancer when the remaining biopsy site is surgically excised.5–7 Multiple studies have also shown that the likelihood of upgrading to a diagnosis of cancer is related to the volume of tissue sampled by the needle biopsy, with higher upgrade rates for smaller-gauge biopsy needles (ie, 14G needle vs 11G vacuum-assisted biopsy devices) and larger mammographic lesions.8–10

For all of these reasons, it is important to confirm that there is concordance between the radiologic findings and pathologic findings on the core biopsy and to understand which lesions on the core needle biopsy should be surgically excised. When surgical excision is undertaken, the goal is to remove the biopsy site and the original imaging...
lesion that led to the core needle biopsy to rule out the presence of an associated malignancy.

RADIOLOGIC-PATHOLOGIC CONCORDANCE

Radiologic-pathologic concordance is required in current practices that perform percutaneous needle biopsy, whether the biopsy is guided by palpation or by ultrasound or stereotactic imaging.11,12 The combined assessment of clinical, imaging, and pathologic findings that are all internally consistent is referred to as concordance. As a part of the multidisciplinary team that now characterizes modern breast care, the surgeon must also understand and contribute to the concordance assessment of breast core needle biopsy results.13–16

To assess concordance, the surgeon must review the original diagnostic mammograms demonstrating the abnormality and also the postbiopsy imaging to assess whether the biopsy marker is located at the site of the original lesion. The histologic findings as described by the pathologist are then interpreted in the context of the clinical and imaging findings to determine if they are all in agreement. Ideally, concordance determination is performed with input from the radiologist, pathologist, and surgeon.

Surgical excision is always indicated when the findings are discordant or there is concern that the target lesion was not sampled. A core needle biopsy demonstrating atypia, or a papillary lesion in the presence of a palpable or imaging mass lesion, is a classic situation that should lead to surgical excision. Additional recommendations for surgical excision are discussed for each high-risk lesion.

ATYPICAL HYPERPLASIA (ADH AND ALH)

ADH is an epithelial proliferative lesion of the terminal duct lobular unit that demonstrates both cytologic atypia and architectural changes that are similar to ductal carcinoma in situ (DCIS). In ADH, the size and extent of the lesion is smaller, involving only 1 or 2 ducts and measuring less than 2 mm, so it does not meet the criteria for DCIS.17 Therefore, fragments of tissue from a core biopsy that seem to be ADH would have the same appearance as a small portion of a DCIS lesion. For this reason, sampling error is very relevant in core biopsies demonstrating ADH. Multiple studies of surgical excision of core biopsy sites demonstrating ADH have reported upgrade rates of 10% to 20% Table 1.5,7,10,18–33

Despite common use of large-gauge vacuum-assisted biopsy devices in more recent years, upgrade rates following a core biopsy diagnosis of ADH are still high enough (31% in a recent publication)19 that surgical excision is considered to be the standard of care. Recent studies have attempted to define favorable subgroups with ADH on core needle biopsy that do not require surgical excision, such as cases whereby all or more than 95% of calcifications have been removed and there is no mass lesion; however, caution is advised with this approach because other studies have failed to confirm these findings.34–38

ALH is a proliferative lesion in which the epithelial cells grow in a confluent fashion of monomorphic cytology that distends the acini and enlarges the terminal duct lobular unit. ALH is similar in appearance to LCIS, but distinguished from it by its lesser extent. When ALH is found on percutaneous biopsy and surgically excised, published upgrade rates to cancer vary widely and range from less than 5% to approximately 50%. However, the literature has been limited by the fact that not all cases in the older series underwent excision, introducing the possibility of selection bias, and many series included results from cases that would be considered discordant.27,29–31
a result of this variability, routine surgical excision of ALH on needle biopsy is controversial.

Although surgical excision is a safe approach, it may be unnecessary in most cases because ALH is often an incidental histologic finding in the surrounding breast tissue of the originally targeted lesion that often proves to be benign. Some surgeons routinely excise all cases of ALH on percutaneous biopsy, whereas others excise only cases with higher suspicion caused by other coexisting high-risk lesions or in cases of ALH associated with mass lesions (ie, discordance) or larger areas of calcifications. Recent reports support observation for select cases of ALH as long as all findings are concordant and there are no other high-risk lesions in the core biopsy specimen.27,28,39 In cases of ALH or ADH that are not surgically excised, short-term mammographic follow-up is recommended.

Once a concurrent malignancy has been excluded, women with ADH and ALH should be counseled regarding their increased risk of breast cancer in the future and informed about medical treatment options to reduce their risk (Table 2). Multiple studies have demonstrated the risk of breast cancer to be approximately 4-fold higher than the general population risk, and the risk is conferred to both breasts.2,40–42 In a recent study, the degree of long-term breast cancer risk was associated with the volume of atypia found in the tissue, with risk stratified based on 1, 2, or 3 or more foci of atypia (see Table 2).43 The absolute cumulative risk of breast cancer was approximately 20% at 20 years for the group with atypical hyperplasia, with less risk among those with 1 focus and higher risk among those with 3 or more foci of atypical hyperplasia.43

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<thead>
<tr>
<th>Lesions on Core Biopsy</th>
<th>Upgrade Rate</th>
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<tr>
<td><strong>Lesions on Core Biopsy</strong></td>
<td><strong>Upgrade Rate</strong></td>
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<tr>
<td><strong>ADH</strong></td>
<td><strong>%</strong></td>
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<tr>
<td>ADH</td>
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<td><strong>Papillary lesions</strong></td>
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<td>Papillary lesions</td>
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<td><strong>FEA</strong></td>
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<td>Fea</td>
<td>8</td>
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<td><strong>ALH</strong></td>
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<td>ALH</td>
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<td>22</td>
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<td><strong>LCIS</strong></td>
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<td>LCIS</td>
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In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study of tamoxifen chemoprevention, women with atypical hyperplasia who received tamoxifen for 5 years achieved an 86% reduction in breast cancer incidence.44 More
recently, the Study of Tamoxifen and Raloxifene (STAR) trial demonstrated that raloxifene results in similar risk reduction to tamoxifen with less toxicity.45

FEA

FEA is a recently described columnar cell breast lesion characterized by cytologic atypia. Columnar cell lesions demonstrate epithelium with a columnar appearance oriented perpendicular to the basement membrane of the acini within terminal duct lobular units. In FEA, the epithelial layer is 1 to 2 cell layers with cytologic atypia characterized by round to ovoid nuclei with nucleoli and loss of polarity.

FEA is a rare lesion, occurring in approximately 5% of percutaneous breast biopsies. Because it is rare and characterized only recently, data on upgrade rates to cancer with surgical excision are limited. Existing published reports indicate that cancer is found in approximately 10% to 15% of FEA cases at surgical excision,24–26,46 supporting a recommendation for routine surgical excision.

The Nashville Cohort Study provides the only data regarding the long-term risk of breast cancer in women with FEA, and the sample size is small (only 52 women).47 The study found that women with columnar cell lesions (n = 1261) had a modest increase in breast cancer risk (relative risk, 1.5), yet this risk was not further increased by the presence of FEA. The small number of women with FEA likely limits the accuracy of risk estimation for this subgroup, and further study is needed to define the long-term risk associated with FEA (see Table 2).

PAPILLARY LESIONS

Papillary breast lesions comprise a range of lesions from completely benign findings (intraductal papilloma) to malignant (intraductal papillary carcinoma or invasive papillary carcinoma). These lesions can be difficult to distinguish based on tissue fragments from percutaneous biopsy.48 Another feature of papillary lesions is that they can be heterogeneous, such that the entire lesion requires histologic evaluation to rule out atypical hyperplasia or cancer. When a core biopsy diagnosis of a papillary lesion is followed by surgical excision, upgrade rates to cancer range from 10% to 35% across series.20–23 Papillary lesions without atypia have a lower risk of being upgraded to cancer, leading some to suggest observation rather than excision for selected papillary lesions without atypia, especially if imaging findings confirm that the lesion has been completely removed.49,50 Papillary lesions without atypia are classified as proliferative benign breast lesions; these lesions confer a modest increase in the risk of future breast cancer: approximately 2-fold more than the general population risk (see Table 2).2,40–42

<table>
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<tr>
<th>Histologic Finding</th>
<th>Relative Risk</th>
<th>Absolute Risk</th>
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<tr>
<td>Normal (general population as reference)</td>
<td>1</td>
<td>12% by 80 y of age</td>
</tr>
<tr>
<td>FEA</td>
<td>1.5 (very limited data)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Papillary lesions</td>
<td>~2</td>
<td>~12%–15% at 20 y</td>
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<tr>
<td>Radial scar</td>
<td>~2</td>
<td>~12%–15% at 20 y</td>
</tr>
<tr>
<td>ADH or ALH</td>
<td>~4</td>
<td>~15%–20% at 20 y</td>
</tr>
<tr>
<td>LCIS</td>
<td>~10</td>
<td>~1% per y; ~20%–25% at 20 y</td>
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The long-term risk of breast cancer associated with papillary lesions with atypia is the same as that conferred by ADH or ALH alone, and women should be counseled accordingly.\textsuperscript{51}

**RADIAL SCAR**

A radial scar is a breast lesion that can mimic a malignant breast tumor, presenting with a palpable mass and/or as a spiculated lesion on imaging. A radial scar can also be a purely histologic finding without an imaging or palpable correlate. Histologically, a radial scar appears as a fibroelastotic core with multiple proliferative epithelial breast elements, often with adenosis that can demonstrate areas of trapped epithelium within stroma that can be mistaken for infiltrating epithelial cells and malignancy. If a radial scar is an incidental histologic finding in an otherwise benign breast biopsy, no further treatment is needed; however, when a radial scar is present in a core biopsy specimen, there is a risk for misdiagnosis based on the sometimes limited sampling of the epithelial elements and, until recently, surgical excision was recommended for all mammographically or palpably detected radial scar lesions.

Several factors have now been shown to be associated with a higher risk of upgrading to cancer at surgical excision allowing a more selective approach. If a radial scar demonstrates atypia or was biopsied with a 14G or smaller needle, or less than 12 cores were obtained, the upgrade rates are 8\% to 28\%; these cases should still undergo complete excision. Conversely, radial scars without atypia or those that are sampled with 12 or more cores by an 11G or larger biopsy have reported upgrade rates of 5\% or less and may be suitable for short-term follow-up.\textsuperscript{52,53} Radial scars are also considered to be proliferative benign breast lesions with an approximately 2-fold increased risk of breast cancer (see Table 2).\textsuperscript{2,40,54}

**LCIS**

LCIS is characterized by small, bland-appearing monomorphic cells with small nuclei that fill and distend at least half the acini of a lobular unit.\textsuperscript{55} As stated earlier, ALH has a microscopic pattern similar to LCIS but is generally less extensive. Because the distinction between LCIS and ALH can be subjective, it has been suggested that they both be referred to in a more general category of lobular neoplasia (LN); however, this terminology has not been universally adopted.

The term LCIS was first coined in 1941 by Foote and Stewart\textsuperscript{56} when they observed this lesion in 14 out of 300 cancerous mastectomy specimens. They hypothesized that LCIS represented a direct precursor to invasive lobular carcinoma and recommended mastectomy as treatment. Emerging data throughout the 1970s demonstrated that the risk of breast cancer following a diagnosis of LCIS was lower than expected for a direct precursor lesion and was conferred equally to both breasts.\textsuperscript{1,57,58} These observations, in combination with the fact that the subsequent cancers that developed in women with LCIS were of both the ductal and lobular phenotype, led to the acceptance of LCIS as a marker of increased risk rather than a true precursor.

Compared with the general population, women with LCIS have an 8- to 10-fold increased risk of breast cancer; several studies have demonstrated this risk to be steady over a woman’s lifetime such that the risk is approximately 1\% per year.\textsuperscript{60} In the series with the longest follow-up, the probability of developing carcinoma in situ or invasive cancer by 10 years after the diagnosis of LCIS was 13\%, 26\% after 20 years, and 35\% by 35 years.\textsuperscript{61}

LCIS is typically an incidental finding in a breast biopsy performed for another reason. As such, the true incidence of LCIS in the population has been difficult to
ascertain. Historical series suggest it is present in up to 4% of otherwise benign breast biopsies,\textsuperscript{1,57,58} whereas population-based data reported to Surveillance, Epidemiology, and End Results from 1978 to 1998 demonstrate an incidence of 3.19 per 100 000 women.\textsuperscript{62} In the modern era of widespread screening mammography, it has been suggested that LCIS may be associated with calcifications in 21% to 67% of cases;\textsuperscript{63} LCIS has also been reported to enhance on magnetic resonance imaging,\textsuperscript{64} although these data are limited.

Histologically, LCIS is often multicentric and bilateral.\textsuperscript{1,56–58} A diagnosis of LCIS made by surgical excision does not require further surgical intervention. Similarly, the finding of LCIS in the surrounding breast parenchyma of a lumpectomy specimen containing DCIS or invasive carcinoma does not alter surgical management of the breast primary and does not increase the rate of in-breast recurrence in patients undergoing breast conservation.\textsuperscript{65–67}

The scenario that often results in controversy is the management of LCIS diagnosed on core biopsy. Similar to the data regarding upgrade rates following a core biopsy diagnosis of ALH, a recent pooled analysis of studies published from 1999 to 2008 demonstrates that the upgrade rate at surgical excision for a core biopsy diagnosis of LCIS also varies widely (0%–50%).\textsuperscript{68} Yet these series are limited in that not all patients with LCIS underwent excision and not all cases with radiographic-pathologic discordance were excluded, creating an inherent selection bias and increasing the likelihood of finding an associated malignancy. In addition, in many cases, LCIS or LN were not the only lesions identified in the core biopsy specimen leading to the indication for surgical excision.

More recently, 2 single-institution series have demonstrated that, with careful exclusion of cases with other high-risk lesions on core biopsy (ie, ADH, papilloma, radial scar) and with exclusion of cases with radiographic-pathologic discordance, the actual rate of upstaging to DCIS or invasive cancer is quite low.\textsuperscript{32,33} Rendi and colleagues\textsuperscript{32} reported an upgrade rate of 4% following surgical excision of 68 cases of LN on core biopsy; similarly, Murray and colleagues\textsuperscript{33} reported an upgrade rate of 3% following surgical excision of 72 cases of LN on core biopsy. In both of these series, the cancers identified were small low-grade malignancies. Although both of these series are also retrospective and subject to selection bias, they represent the most careful reviews of this clinical scenario to date and suggest that routine excision is not warranted for all cases of LCIS on core biopsy.

Once a concurrent malignancy has been excluded, women with LCIS should be counseled regarding their increased risk of breast cancer in the future and informed about medical and/or surgical treatment options to reduce their risk. As stated previously in the context of ADH and ALH, prospective randomized data from the NSABP Breast Cancer Prevention Trial (P-1) demonstrated that among high-risk women, tamoxifen decreased the risk of developing invasive breast cancer.\textsuperscript{44} Similarly, the NSABP STAR (P-2) trial demonstrated that raloxifene was just as effective as tamoxifen in reducing the risk of breast cancer in high-risk postmenopausal women.\textsuperscript{45} Women with LCIS were well represented in both of these studies, comprising 6.2% of 13 338 participants in the NSABP P-1 trial and 9.2% of 19 747 participants in the STAR trial. In both subsets, chemoprevention reduced the risk of developing breast cancer by more than 50%.

In parallel with the surgical management of invasive breast cancer, trends in the surgical management of LCIS have been toward conservative management; in current practice, only a minority of women with LCIS will pursue bilateral prophylactic mastectomy. The option of surgical risk reduction is often considered more strongly in the subset of women with LCIS and other risk factors, such as a strong family
history or extremely dense breasts; however, patients considering surgery for risk reduction need to be fully aware of all the risks and benefits of this approach and should be encouraged to consider the impact that prophylactic surgery may have on their quality of life with respect to body image and sexual functioning. They should also be informed that prophylactic mastectomy does not completely eliminate cancer risk. The decision to undergo bilateral prophylactic mastectomy is highly individualized and should not be undertaken without ample time to consider all of the available options for risk management.

SUMMARY

High-risk breast lesions include LCIS, ADH, ALH, FEA, radial scar, and papillary lesions. When these lesions are identified on core needle biopsy, careful radiologic-pathologic concordance is necessary. In general, excision of high-risk lesions is indicated to rule out coexisting malignancy; however, in carefully selected cases, observation with short-term follow-up may be appropriate. Women with LCIS, ADH, and ALH should be counseled about options for breast cancer risk reduction.

REFERENCES


