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REVIEW ARTICLE

Controversies in Pathology

High-risk and selected benign breast lesions diagnosed on core needle biopsy: Evidence for and against immediate surgical excision

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The vast majority of image-detected breast abnormalities are diagnosed by percutaneous core needle biopsy (CNB) in contemporary practice. For frankly malignant lesions diagnosed by CNB, the standard practice of excision and multimodality therapy have been well-defined. However, for high-risk and selected benign lesions diagnosed by CNB, there is less consensus on optimal patient management and the need for immediate surgical excision. Here we outline the arguments for and against the practice of routine surgical excision of commonly encountered high-risk and selected benign breast lesions diagnosed by CNB. The entities reviewed include atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, intraductal papillomas, and radial scars. The data in the peer-reviewed literature confirm the benefits of a patient-centered, multidisciplinary approach that moves away from the reflexive "yes" or "no" for routine excision for a given pathologic diagnosis.

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INTRODUCTION

Percutaneous core needle biopsy (CNB) under image guidance has been a standard part of the evaluation of nonpalpable breast lesions for over 30 years. Until relatively recently, most patients with high-risk and selected benign lesions diagnosed on CNB underwent immediate surgical excision to exclude an unsampled invasive breast cancer or ductal carcinoma in situ (DCIS) near the CNB site. Upgrade rates in the early CNB literature were as high as 30–50% for many benign and atypical lesions[1]. Some of the variability in upgrade rates may be attributed to variations in the size of the biopsy device, with lower upgrade rates reported for 12-gauge or larger vacuum-assisted biopsies than 14-gauge ultrasound-guided CNB[2]. In addition, upgrades have been variably defined, with some authors classifying high-risk lesions diagnosed after excision of selected benign breast lesions as upgrades[3–6]. In this review, only a diagnosis of invasive carcinoma (any histology) or DCIS after immediate surgical excision is considered an upgrade. In contemporary practice, there is an active debate over whether more recent data provide sufficient evidence to offer selected patients surveillance instead of surgery[1,7]. In the absence of well-accepted consensus guidelines, recommendations for surgery versus observation are not uniform across institutions[8–10]. There are data to suggest that patients who are not referred for surgical consultation are less likely to adhere to follow-up imaging or chemoprevention[11]. However, the overall rates of uptake and adherence to chemoprevention among patients with high-risk lesions are generally low[12,13].

There appears to be an emerging consensus on limiting the role of surgery for non-malignant CNB diagnoses when careful radiologic-pathologic correlation can be confirmed. Radiologic-pathologic correlation involves an assessment of whether the histologic findings in a CNB represent the targeted imaging abnormality and the extent to which the lesion and/or calcifications were removed. A diagnosis of invasive breast cancer or DCIS on excision (the appropriate definition of an upgrade) should not be regarded as a true upgrade if the CNB pathology did not fully account for the imaging findings. Cases with a suspicious, palpable mass, BI-RADS Category 5 imaging and co-existing lesions associated with breast cancer risk also should be excluded when upgrade rates are reported. The upgrade rates in recent studies with larger sample sizes, detailed radiologic-pathologic correlation, and strict criteria for upgrades are much lower than those reported earlier in the CNB era[1,14].

Only a few small prospective studies of CNB with non-malignant lesions have been published and most clinical practice guidelines lack the specificity required for consistent application across different practice environments. Guidelines and consensus statements may include active surveillance as a vaguely defined "option" in "selected" cases without clear, reproducible criteria for the selection of cases for observation[15,16]. As a result, many patients with high-risk and selected benign lesions on CNB undergo immediate surgical excision. This article will review the evidence for and against immediate surgical excision of selected

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Table 1. Key arguments for and against immediate surgical excision of high-risk and selected benign breast lesions diagnosed on core needle biopsy.

For immediate surgical excision	Against immediate surgical excision
The upgrade rates in the literature are variable and have an unacceptably broad range	Upgrade rates are low (i.e., < 5%) in many studies with clear definitions of upgrades and detailed radiological-pathological correlation
Many studies are single-institution, retrospective, and subject to selection bias	Prospective studies, some of which are multi-institutional, have been published recently
Many studies have limited or no follow-up, especially for lesions that were not excised	Several studies with years of follow-up for lesions that were not excised have been published recently
Criteria for selecting patients for nonoperative management vary across institutions and published consensus statements are vague	Criteria from recent, prospective studies could provide a basis for more consistent selection of patients for nonoperative management
Many studies report upgrades in both groups of patients: patients who undergo immediate surgical excision and those who are followed	Studies that document the site of subsequent ipsilateral carcinomas in the nonoperative group report very low rates of malignancy at the index site
Patients who are not referred for surgical consultation have lower rates adherence to imaging and chemoprevention	The rates of uptake and adherence to chemoprevention among patients with high-risk and borderline lesions are generally low
Some patients may be overtreated, but, at this time, the subset of patients who may safely forego immediate surgical excision cannot be reliably identified	Nonoperative management of carefully selected patients mitigates overtreatment; surgery remains an option if concerning clinical or radiological findings develop during follow-up

cases of ADH, pure lobular neoplasia (ALH and classic LCIS), radial scars and benign intraductal papillomas on CNB. The key arguments for and against immediate surgical excision are summarized in Table 1.

ATYPICAL DUCTAL HYPERPLASIA (ADH)

Patients with ADH diagnosed on CNB should undergo immediate surgical excision

Histopathologically, ADH is defined as a monomorphic proliferation of cells with cytologic atypia and architectural complexity that lacks the necessary criteria for DCIS (Fig. 1). There is ample evidence in the literature to support immediate surgical excision of ADH diagnosed on CNB. Upgrade rates for ADH diagnosed on CNB have been reported to be as high as 30% to >50%[17–21]. In an analysis by Lewin et al. of 18 studies including over 3,000 excisions, the upgrade rate for ADH identified on CNB ranged from 13 to 56%, with a mean upgrade rate of 23%[22]. In other studies, some of which explicitly included radiological–pathological correlation, the average upgrade rate was approximately 20%[23–28]. In a recent meta-analysis of 6258 cases, the pooled upgrade rate for ADH was 29% and the upgrade rate specifically for cases with apparent complete removal of the imaging abnormality was 14%[29]. It also has been shown that ADH diagnosed on ultrasound-guided CNB with a 14-gauge device is more likely to be upgraded than 12-gauge or larger vacuum-assisted CNB[18,30]. Upgrades after ADH are more likely to be DCIS than invasive carcinoma and the invasive tumors are more likely to low-grade than high-grade[28]. The historically high upgrade rates for unselected cases of ADH in these and other studies[18,26–28,31] and the fact some upgrades are invasive have contributed to the resistance to offering active surveillance for selected patients with ADH on CNB.

National Comprehensive Cancer Network (NCCN) guidelines (2021) recommend surgical excision when ADH is identified on CNB[16]. Similarly, the American Society of Breast Surgeons (ASBS) Consensus Guidelines state that because of the high risk of upgrade to carcinoma, excisional biopsy should be offered to patients[15]. The ASBS guidelines (2016) note the subtle distinctions between ADH and DCIS is some cases, and that there is a risk of missing malignant lesions when ADH is not excised routinely. The ASBS guidelines also note, however that selected patients with ADH can be safely observed and avoid surgery. In three studies, all ADH cases in which the lesion depicted on the mammogram was completely removed at 11-gauge vacuum-assisted stereotactic biopsy were free of carcinoma at surgical excision[32–34]. However, given the variability of opinion in the literature and the lack of large prospective studies, most cases of ADH should be surgically excised[15].

Recent studies suggest surveillance may be appropriate for selected patients with ADH

Several studies provide evidence for the selection of patients with ADH who may be offered close clinical follow-up with imaging as an alternative to immediate surgical excision[26,35–38]. Surveillance may be a reasonable option in cases with detailed radiologic-pathologic correlation, no more than 2–3 foci of ADH in the CNB, and substantial removal of calcifications (≥ 50% in some studies; ≥ 90% in others) by vacuum-assisted CNB[36,37,39]. Features that still warrant immediate excision include suspicious ultrasound or MRI findings, intermediate-high grade nuclear atypia, and cellular necrosis. With four ongoing clinical trials of active surveillance for DCIS (COMET, LORD, LORIS, LORETTA), the reluctance to offering active surveillance to a carefully defined subset of patients with ADH seems paradoxical. It should be pointed out that limiting the role of immediate surgical excision does not mean a patient would never receive a recommendation for surgery. Surgery would remain an option, especially if there are any significant changes in imaging or clinical findings as the patient is followed. In essence, the change in clinical management could be thought of as retaining the option for "delayed surgery" in selected patients instead of mandatory immediate surgical excision for all patients[40]. Ideally, additional, multi-institutional prospective studies of ADH diagnosed on CNB would be conducted to confirm or further refine the selection of patients for observation[41–43].

ATYPICAL LOBULAR HYPERPLASIA (ALH) AND CLASS LOBULAR CARCINOMA IN SITU (LCIS)

Patients with ALH and classic LCIS diagnosed on CNB should undergo immediate surgical excision

Lewin et al. analyzed 13 retrospective studies with over 900 excisions and showed a wide range of upgrade rates after excisional biopsy for ALH diagnosed on CNB between 0 and 67% with a reported mean of 9%[22,28,44–54]. The upgrade rates for LCIS also showed a broad range, from 5 to 60% with a mean of 18%[22,28,44–54]. Based on the relatively broad range of reported upgrade rates, some authors to recommend caution in the interpretation of the data[55]. Buckley et al. have pointed out that many series of classic LCIS are single-institution, retrospective studies with relatively small sample sizes and limited or no follow-

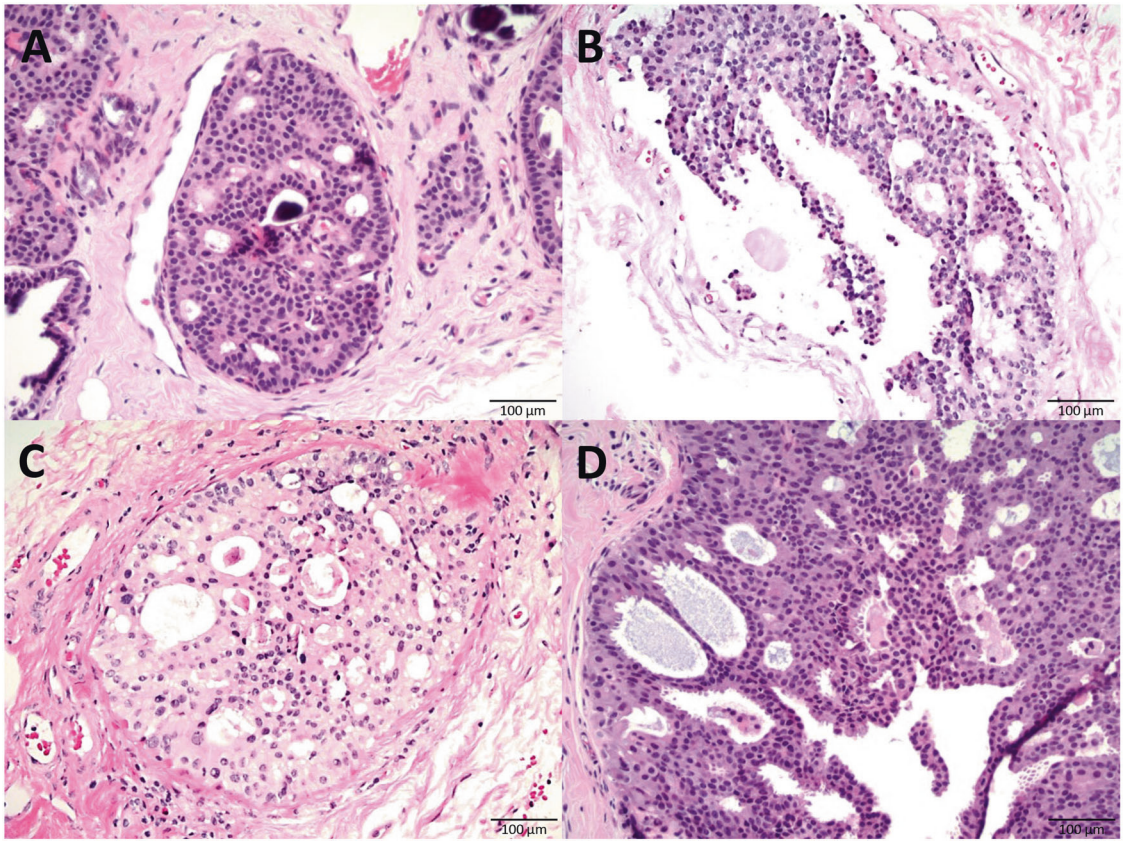

Fig. 1 Atypical Ductal Hyperplasia (ADH). ADH is comprised of a monomorphic proliferation of cells with cytologic atypia and architectural complexity that do not completely fulfill the criteria for a diagnosis of ductal carcinoma in situ (DCIS). Examples are shown in images **A**–**D** (all images H&E at 200X magnification). ADH may present as an area of abnormal calcifications on screening mammography that is amenable to stereotactic-guided core needle biopsy (microcalcifications in images **A** and **C**).

up for patients who do not undergo excision[55]. Without long-term follow-up, these studies may significantly underestimate the rate of development of carcinoma after a CNB diagnosis of LCIS. These potential limitations likely apply to the breast CNB literature in general[56]. The size of the biopsy device also may influence upgrade rates for ALH and classic LCIS, with a higher likelihood of upgrade for 14-gauge CNBs[2].

Middleton et al. evaluated the efficacy of using standard radiologic and histologic criteria to guide the management of patients with classic LCIS and ALH[44]. Surgical excision was recommended for all cases of radiologic-pathologic discordance and was more likely for cases of LCIS rather than ALH, for targeted rather than incidental lesions, in cases with five or fewer cores taken, and for mass lesions. There were upgrades among patients offered immediate surgical excision and those followed with clinical and radiological surveillance. Of the 20 patients with immediate excision, 8 (40%) were upgraded[44]. Nonoperative management was offered to 104 patients, and 5 (5%) were upgraded to malignancy at a subsequent surgical excision[44].

In a study of 8205 14-gauge ultrasound-guided CNB by Ferré et al. there were 20 CNB with lobular neoplasia and the upgrade rate was 25% (5/20)[54], supporting the practice of routine surgical excision of lobular neoplasia. Rendi et al. reported a study of 106 cases of lobular neoplasia diagnosed on CNB with surgical excision follow-up for 93 cases: 25 with lobular neoplasia and ADH and 68 cases with lobular neoplasia alone[50]. There were no upgrades among normal-risk patients who underwent CNB to assess calcifications identified on routine mammographic screening[50]. Patients with any other imaging indication (high-risk screening, determination of extent of disease, follow-up after lumpectomy, evaluation of a clinical finding) or an imaging finding (mass, architectural distortion, MRI enhancement) were found to have a nonzero risk of upgrade at excision[50]. Interestingly, of the 7 total upgraded cases (4 with ADH, 3 with lobular neoplasia alone), 5 underwent biopsy for non-mass enhancement on MRI. The authors recommended surgical excision for lobular neoplasia on CNB for all patients considered high-risk on the basis of personal or family history regardless of whether mammography or MRI is used as the screening modality[50].

Both the ASBS (2016) and NCCN (2021) support surgical excision of LCIS variants diagnosed on CNB[15,16]. Pleomorphic LCIS is a less common, high-grade variant of LCIS[57]. Histopathologically, it differs from classical LCIS in that the cells are higher grade with pleomorphic features when compared to classic LCIS with 2–3X variation in size and expansile central necrosis with calcification may be seen (Fig. 2). Because of the propensity to calcify, pleomorphic LCIS may be identified mammographically and may represent the targeted lesion of the percutaneous CNB rather that an incidental finding. In a series that included 15 cases of pleomorphic LCIS diagnosed on CNB, upgrade rate to malignancy was 27% (4/15)[57]. In another recent study of pleomorphic and florid LCIS, the overall upgrade rate was 19% (6/32)[58]. Of the 6 cases upgraded at excision, 5 were radiologic-pathologic concordant. As a result of the high upgrade rate to DCIS or invasive cancer at surgical excision after diagnosis on CNB, LCIS variants should be treated with complete surgical excision[58–60].

Recent studies suggest surveillance may be appropriate for many patients with ALH and classic LCIS

Several recent studies suggest that upgrade rates are less than 5% in a subset of lobular neoplasia on CNB with no other lesion requiring excision (ADH, papilloma, radial scar) and radiologic-

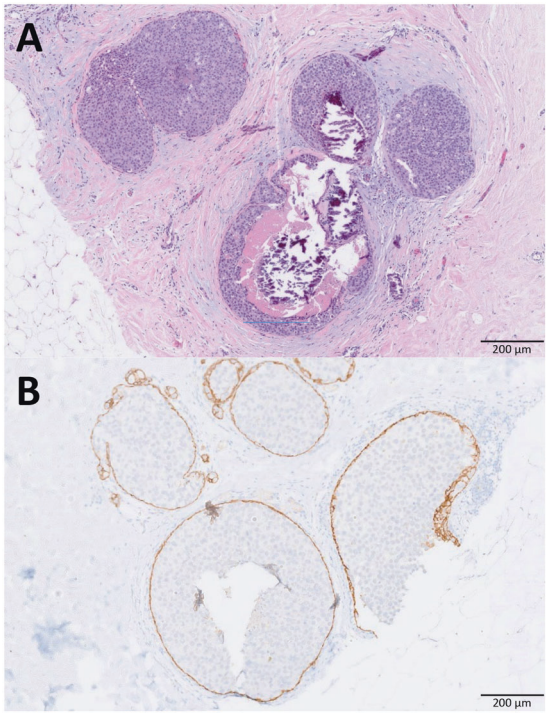

Fig. 2 Pleomorphic Lobular Carcinoma in Situ (LCIS). H&E 100X image **A** and Immunostain for e-cadherin in **B**. H&E shows markedly distended terminal duct lobular units comprised of solid pattern of cells with cytologic atypia that lack cohesion. Central necrosis with calcifications is readily apparent. An immunostain for e-cadherin demonstrates an absence of staining within the proliferation, though staining is retained by the myoepithelial cells surrounding the ducts and lobules. Unlike classic LCIS that is radiographically occult and is an incidental finding on core needle biopsies, pleomorphic LCIS often presents as abnormal calcifications seen on imaging.

pathologic concordance[24,44,61,62]. The upgrade rate for incidental ALH and classical LCIS in cases with radiological-pathological correlation is approximately 3%[28,50–53,63]. The lower upgrade rates for pure lobular neoplasia diagnosed on CNB are consistent with the data from retrospective studies of patients who did not undergo immediate surgery[44,64] and a recent prospective study of classic LCIS (TBCRC 020)[65].

In a study of 104 patients at MD Anderson Cancer Center with classic-type lobular neoplasia (ALH or LCIS) who were followed clinically and radiologically for a mean of 40.8 months (range 5.3–103.2), Middleton et al. reported that 2 (1.9%) developed breast cancer near the CNB site[44]. Similar findings were reported in a prior study from MD Anderson and a series from Mt. Sinai in New York[52,66]. Recommendations for surveillance were based on review at a weekly multidisciplinary conference that included radiology, surgery and pathology. Exclusion criteria included pleomorphic or florid LCIS, coexisting radial scars, and co-existing papillomas[44]. Based on these data, the authors recommend surveillance for patients with ALH or classic LCIS in < 3 terminal duct lobular units (TDLU) in the CNB and radiologic-pathologic correlation[44].

Laws et al. recently reported a study of 80 patients at Brigham and Women's Hospital with radiologically concordant pure ALH or classic LCIS diagnosed on CNB who were offered observation[64]. With a median follow-up of 27 months, none of the patients developed an ipsilateral breast cancer in the same quadrant as the CNB site. The 3-year risk of failure for conservative management was 6.2%. All of the failures were excisions prompted by evolving imaging findings at the CNB site, and the final pathology was benign in all of these cases[64]. These data provide further evidence for the safety of non-surgical management of ALH and classic LCIS.

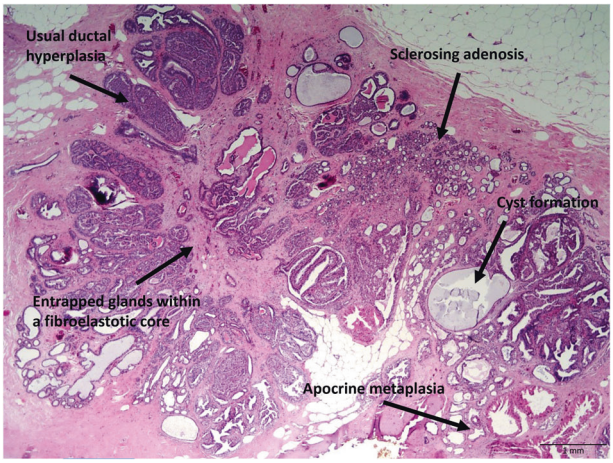

Fig. 3 Low power view of a Radial Scar from a surgical excision, H&E 20X. H&E shows this benign sclerosing lesion with stellate architecture. There is a central fibroelastic core that is characteristic with entrapped benign glands. Epithelial hyperplasia, apocrine metaplasia, sclerosing adenosis and cyst formation may be seen. While the diagnosis is often apparent on surgical excisions, it may be more difficult to recognize on small, fragmented core tissue from a needle biopsy.

The results of a multi-institutional trial for classic-type lobular neoplasia diagnosed on CNB (TBCRC 020) were recently reported[65]. The goal of TBCRC 020 was to determine the upgrade rate after CNB. Cases with a palpable mass, BI-RADS Category 5, prior history or current diagnosis of breast cancer, or co-existing ADH or LCIS variants were excluded[65]. The upgrade rate for classic-type lobular neoplasia was 3% based on local pathology review and 1% by central pathology review[65]. The data from TBCRC 020 provide additional evidence for the safety of delaying surgical excision in carefully selected cases of ALH and classic LCIS.

Classic LCIS and ALH are often incidental findings that are not associated with mammographically detected calcifications. The ASBS (2016) no longer advocates routine excision of classic LCIS and ALH when radiologic-pathologic diagnoses are concordant and no other high-risk lesion requiring excision is present[15]. Specifically, normal risk patients who undergo CNB to assess calcifications found by routine mammographic screening yielding lobular neoplasia alone may not require excisional biopsy[50]. The NCCN continues to recommend surgical excision when multiple foci of ALH or LCIS are present in the CNB, particularly when extensive LCIS is present involving more than 4 TDLUs[16]. In cases of concordant ALH or classic LCIS, patients may be offered observation using shared decision making between the patient and physician as well as planned imaging follow-up[50]. Patients with variants of LCIS (i.e., pleomorphic and florid LCIS) diagnosed on CNB should undergo immediate surgical excision.

RADIAL SCARS WITHOUT ATYPIA

Patients with radial scars diagnosed on CNB should undergo immediate surgical excision

Radial scars are benign sclerosing lesions of the breast characterized by a central fibroelastotic core. Benign glands radiate from the center, and other features such as usual ductal hyperplasia, apocrine metaplasia, and cyst formation are commonly seen (Fig. 3). When diagnosis is made by CNB, the lesion may be somewhat more fragmented making it difficult to appreciate the underlying lesion (Fig. 4). Though radial scars are benign, many studies have shown a significant association with occult

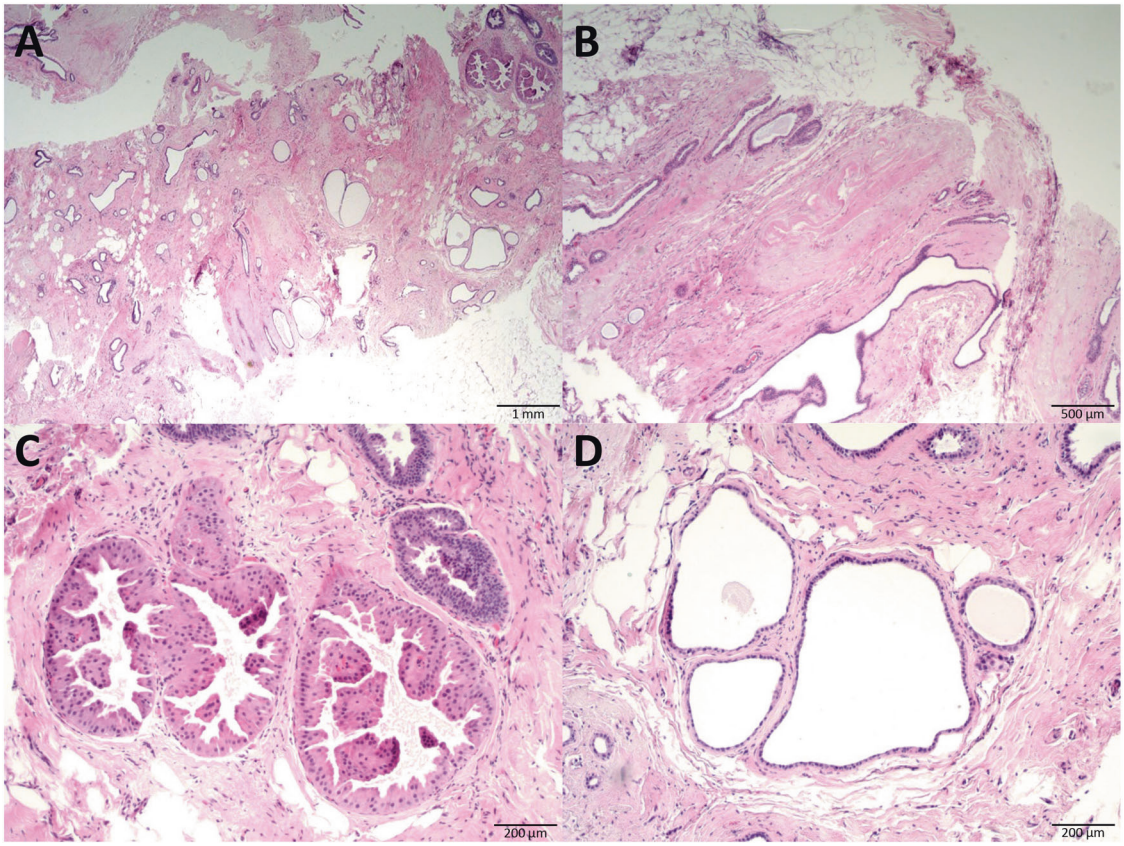

Fig. 4 Images from a Core Needle Biopsy (CNB) of a Radial Scar, all H&E images. 3D Mammography demonstrated an area of architectural distortion that was biopsied using stereotactic guidance. A low power view at 20X magnification is seen in **A**. The fibroelastotic stroma with glandular proliferations radiating from the center are not as apparent in this CNB as the excision from Fig. 3. A 40X view in **B** shows part of a fibroelastotic core. 100X magnification shows an area of apocrine metaplasia in **C** and cystic dilation of glands in **D**. The constellation of findings are consistent with a radial scar in this setting.

synchronous breast cancer[67–69]. Radial scar diagnosed by CNB has become somewhat more prevalent with the widespread use of 3D mammography or tomosynthesis that detects more subtle architectural distortions[70].

When radial scars are diagnosed by core needle biopsy, observed upgrade rates to carcinoma are as high as 16%[28]. In addition, when radial scars are excised, additional high-risk lesions such as ADH and LCIS may be identified in up to 26% of excision specimens[71]. Certainly, the upgrade to frank malignancy changes the management of patients presenting initially with radial scar. But management may also change significantly based up the upgrade to atypia. Patients may be referred to high risk clinics where chemoprevention or increased screening protocols could be initiated. Some authors recommend excision for radial scars > 10 mm in size[72,73]. However, the association of size with likelihood of upgrade has not been consistently observed[74]. In current practice, we still lack a clear consensus on which patients with radial scars may be observed and most patients are still referred for surgical consultation. Given the ease of excision, the potential change in patient management, and risk of carcinoma, patients should be offered surgical excision. Large radial scars and those associated with ADH, ALH, or LCIS should be excised[3].

Recent studies suggest surveillance may be appropriate for many patients with radial scars without atypia

In a recent meta-analysis by Farshid et al. of 3163 radial scars from 49 studies, the overall upgrade rate was ~7% and two-thirds of the upgrades were DCIS[75]. Among radial scars without atypia diagnosed on vacuum-assisted CNB, 1% were upgraded (all DCIS). In contrast, radial scars with atypia diagnosed with a 14-gauge biopsy device had an upgrade rate of 29%[75]. In a recent series of radial scars without atypia, the upgrade rate was 1% (DCIS only) and none of the patients followed with active surveillance developed an ipsilateral breast cancer[76]. Other studies have shown similar results, with no subsequent cancers at the CNB site and a low rate of developing breast cancer at other sites in the same breast[74,77]. Some authors recommend surgical excision of all radial scars based on the possibility of finding additional high-risk lesions that would warrant high-risk follow-up and consideration of chemoprevention (i.e., ADH, ALH, or classic LCIS)[3,4] but uptake and adherence among these patients may be low[12,13].

INTRADUCTAL PAPILLOMAS

Patients with intraductal papillomas diagnosed on CNB should undergo immediate surgical excision

Given the risk of upgrade[5,6,21,78–80] and the potential for significant interobserver variability in the classification of papillary lesions[81], patients should undergo immediate surgical excision to avoid the underestimation of malignancy. In a series of 814 consecutive CNB for screen-detected lesions from 2005 to 2014, Farshid and Gill reported an upgrade rate of 30.8% (32/104) for a combined category representing papillary lesions with and without atypia[21]. The authors noted that, at the time of their publication, the National Health System Breast Screening Program (NHSBSP) Clinical Guidelines for the United Kingdom (2016) recommended complete removal of papillary lesions (either by surgical excision for lesions with epithelial atypia or vacuum-assisted excision for those without atypia)[82]. In a series of 234 CNB from 2001 to 2009, Rizzo et al. reported an upgrade rate of 8.9%

(21/234) for benign papillomas and 2 of the upgrades were invasive[5]. In an international, multicenter study of 188 benign papillomas diagnosed on CNB, Foley et al. reported upgrades to invasive carcinoma or DCIS in 14.4% (27/188)[78]. Glenn et al. reported an upgrade to malignancy in 4.7% (7/146) of papillomas without atypia[6]. Chen et al. reported a lower upgrade rate of 3.7% (8/206) for benign papillomas, and all of the upgraded cases were considered radiologically concordant[83]. Based on the unacceptably broad range of upgrade rates in these and other studies[79,80] and the potential for upgrades in radiologically concordant cases[83], immediate surgical excision is the most appropriate clinical management for papillomas diagnosed on CNB.

Recent studies suggest surveillance may be appropriate for many patients with benign intraductal papillomas

Intraductal papillomas of the breast are common lesions seen in routine practice (Fig. 5). High upgrade rates have been reported for papillary lesions diagnosed on CNB[5,6,21,78–80], but what is most important is the rate of upgrade to invasive carcinoma or DCIS specifically for radiologically concordant papillomas without atypia. Although some studies have shown high interobserver variability in the classification of papillary lesions[81], others have shown substantial or fair agreement among pathologists for benign and atypical papillomas[84,85]. The studies reported by Rizzo et al.[5], Glenn et al.[6], Foley et al.[78] and others[79,80] lack detailed radiologic-pathologic correlation. In the study reported by Chen et al. all of the upgraded cases were reported to be radiologically concordant[83]. However, many of the upgrades were in patients with ≥ 20% lifetime risk of breast cancer and/or a history of atypia or breast cancer[83]. Upgrade rates for papillomas are lower in studies that exclude patients with BI-RADS 5 or discordant imaging, restrict the definition of an upgrade to invasive carcinoma or DCIS, and limit the study population to patients with an average risk of breast cancer[83,86]. Studies with high upgrade rates often lack clear criteria for which patients were referred for surgery versus nonoperative management, raising the possibility selection bias influenced the results. In the series reported by Rizzo et al. surgical excision was performed in ~75% of cases[5]. Of the 100 patients who did not undergo excision, 59 had imaging follow-up (mean of 86 months) that was normal or benign (BI-RADS 1, 2, or 3)[5]. The possibility that patients at the highest risk of upgrade were selected for immediate surgical excision cannot be excluded. Upgrade rates for papillomas also are higher when smaller (i.e., 14-gauge) biopsy devices are used[2].

Several carefully conducted retrospective studies provide support for nonoperative management of benign papillomas. Swapp et al. reported a series of 224 solitary, benign, radiologically concordant intraductal papillomas with no upgrades in the 77 patients who underwent immediate excision[87]. There were no upgrades in a series of incidental benign papillomas measuring < 2 mm ('micropapillomas') reported by Jaffer et al.[88]. In the series reported by Swapp et al., 100 patients were followed with observation and none of them developed breast cancer with a mean follow-up of 36 months[87]. Grimm et al. reported similar findings in a series of 252 benign, radiologically concordant papillomas with at least 2 years of imaging follow-up[89].

Ma et al. recently reported a series of papillomas prospectively evaluated at a biweekly multidisciplinary conference at Emory University[90]. Cases were evaluated in real time for patient care and surveillance was recommended for benign papillomas with radiologic-pathologic correlation and at least 1/3 of the imaging abnormality removed, ≤ 2 foci of ADH adjacent to the papilloma in the CNB ($n = 6$), and ALH involving or adjacent to the papilloma in the CNB ($n = 7$)[90]. In cases of with ADH involving the papilloma or adjacent ADH with intermediate-high grade nuclear atypia suspicious for DCIS in the CNB, patients were referred for surgical excision. With a mean follow up of 18.9 months (range 6.1–42.0 months), the 73 patients who did not have surgery had stable imaging findings and none developed breast cancer[90]. These findings are similar to several retrospective studies of nonoperative management with 3–5 years of clinical and radiological follow-up. In those studies, the rate of development of invasive carcinoma or DCIS in patients who did not undergo immediate surgical excision ranged from 0 to 4%[80,87,91–97].

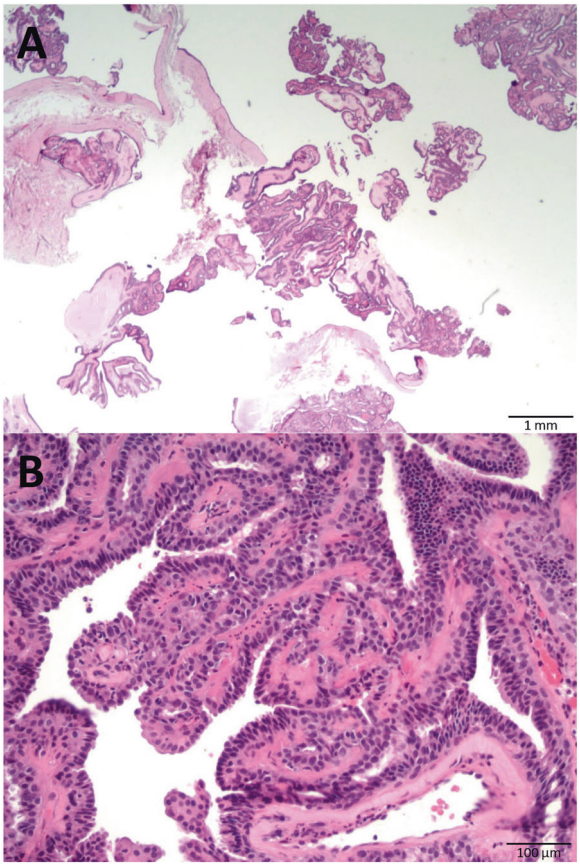

Fig. 5 Images from a Core Needle Biopsy (CNB) of a benign intraductal papilloma. H&E images, 20X magnification in **A** and 200X in **B**. Intraductal papillomas are often quite fragmented when examined on CNB specimens as can be seen in the low power image in **A**. Fragments of the dilated duct surrounding the intraductal papilloma may also be seen. The higher power view in **B** demonstrates an arborizing pattern of papillae with fibrovascular cores. Both an epithelial and myoepithelial cell layer is identified. Intraductal papillomas may become sclerotic, calcify and even infarct.

Results of a multi-institutional trial for papillomas without atypia diagnosed on CNB were recently reported by the TBCRC[98]. The primary endpoint of TBCRC 034 was a pre-defined rule that surgery would not be required if the upgrade rate for benign papillomas diagnosed on CNB was ≤ 3%[98]. Cases with a palpable mass, nipple discharge, BI-RADS 5 category, concurrent or prior history of breast cancer, or co-existing ADH or LCIS variants were excluded[65,98]. The upgrade rate for papillomas without atypia (based on local pathology review) was 1.7% in TBCRC 034, providing further support for the nonoperative management of benign intraductal papillomas[98].

DISCUSSION

The potential for upgrade to malignancy at surgical excision because of the sampling volume limitation of CNB as well as possible targeting inaccuracy remain the principal reasons for immediate surgical management of high-risk and selected benign

lesions of the breast. There is a persistent concern for underestimating malignancy on CNB (i.e., missing a diagnosis of carcinoma) in this patient population. There appears to be an emerging consensus in the current peer-reviewed literature for limiting the role of immediate surgery for many high-risk and selected benign lesions of the breast diagnosed on CNB (Table 1). Prospective data similar to large oncology clinical trials with thousands of patients will not be forthcoming. The few prospective studies that have been published and the most carefully conducted retrospective studies are already guiding clinical practice in many institutions.

One of the key questions in contemporary practice is whether immediate surgical excision avoids underdiagnosis and undertreatment of malignancy or represents overtreatment of patients with non-malignant diagnoses who could be managed with close observation. Another key question is which patients should be offered nonoperative management. Active surveillance could be offered to patients who would have been offered nonoperative management in the TBCRC trials[65,98]. The data from those trials suggest that an upgrade rate of ≤ 3% could be a reasonable threshold for offering surveillance versus surgery. This threshold is similar to the upgrade rate of ≤ 2% for BI-RADS Category 3 lesions which are routinely followed with repeat imaging at 6 months[99].

In addition to the concern for underestimating malignancy, some experts advocate surgery for some benign lesions (e.g., radial scars and papillomas without atypia) based on the possibility of finding additional atypical lesions (i.e., ADH, ALH or classic LCIS) in the excision specimen that would warrant high-risk follow-up and consideration of chemoprevention[3,4]. It should be noted that ADH, ALH, and classic LCIS were present in only 4% of surgical specimens from patients with benign papillomas in TBCRC 034[98]. These data indicate that routine surgical excision would not change the clinical management for the vast majority of patients who match the eligibility criteria for that trial.

Clinical management should be based on a more nuanced approach that incorporates radiologic and pathologic correlation and patient preference. The risk calculation for patients with the same pathologic diagnosis seen on CNB may be quite different. For example, a 40-year-old with 4 cm of suspicious calcifications seen on mammogram with a diagnosis of ADH is very different from an 88-year-old with a small cluster of indeterminate calcifications completely excised by CNB. Pathologic diagnoses on CNB cannot be interpreted in isolation. Clinical and radiologic context are essential. The financial and psychologic cost of surgical excision in comparison with radiologic surveillance must be examined, especially in the context of any anxiety associated with radiological surveillance. If close observation and follow-up is chosen for lesions with a lower likelihood of upgrade, the patient must play an active role in decision making. Finally, if surveillance is chosen, patient compliance with follow-up must be considered[15].

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AUTHOR CONTRIBUTIONS

The Introduction and Discussion were written jointly by the authors. The sections arguing for immediate surgical excision of high-risk and selected benign lesions were written by AH and HG. The sections proposing nonoperative management of selected patients with high-risk and selected benign lesions were written by BC.

COMPETING INTERESTS

Dr. Calhoun is a Member of the Oncology Advisory Board for Luminex Corp. Dr. Gilmore is a Consultant for Agendia, Inc. and a Member of the Digital Pathology Advisory Board for Sectra. Dr. Harbhajanka has no financial relationships to disclose.

ADDITIONAL INFORMATION

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