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Atypical Ductal Hyperplasia on Percutaneous Breast Biopsy: Scoring System to Identify the Lowest Risk for Upgrade

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ABSTRACT

Background: NCCN guidelines recommend surgical excision for patients with atypical ductal hyperplasia (ADH) on percutaneous biopsy. Improved imaging and biopsy techniques have lower contemporary upgrade rates, challenging standard practice. We sought to identify low-risk features of ADH to define patients who may benefit from active monitoring over surgical excision.

Methods: A retrospective analysis identified 87 stereotactic biopsies diagnosing ADH undergoing surgical excision at a single institution from 01/2008 to 10/2015. Imaging was reviewed for lesion size and residual calcifications. Biopsy slides were reviewed for ADH features. Categorical variables were analyzed using Chi-square and Fisher's exact tests; continuous variables with T- and Wilcoxon tests. Logistic regression model was used to determine the association between the number of low-risk features present and odds of upgrade.

Results: Upgrade was identified in 13 cases (14.9%; 11 ductal carcinoma in situ and 2 invasive breast cancer). Low-risk imaging features included imaging size <1cm (P=0.004) and >50% removed by biopsy (P=0.03). The only significant low-risk pathologic feature was the lack of micropapillary features (P=0.10). Focal ADH (1-2 foci, P=0.12) was felt to be clinically significant. Those with the lowest risk of upgrade (0%) had all 4 low-risk features (n=17, 20%). When comparing biopsies that differed by one low-risk feature, the biopsy with one less low-risk feature present had 129% increase in odds of upgrade (exact OR=2.29, 95% CI 1.35, 4.15, P=0.001).

Conclusion: Overall upgrade rate was low in this contemporary cohort. Patients at lowest risk for upgrade had all 4 low-risk features and could be safely offered active monitoring over surgical excision.

INTRODUCTION

Breast cancer is the second most common cancer among women in the United States, with more than 280,000 cases of invasive breast cancer (IBC) and ductal carcinoma in situ (DCIS) predicted to be diagnosed in 2021.[1] This translates into nearly 1 in 8 women in the United States being diagnosed with breast cancer over the course of her lifetime. There are multiple risk factors associated with the development of breast cancer, including family history and lifetime exposure to estrogen, as well as a personal history of a

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biopsy with atypical hyperplasia. Atypical hyperplasia carries a 4-fold increase in future breast cancer risk.[2]

Atypical ductal hyperplasia (ADH) is a high-risk breast lesion. Calcifications are the most common radiologic finding associated with ADH.[3] However, the lesion could be identified incidentally (not with the targeted calcifications) or in association with other lesions such as a radial sclerosing lesion or intraductal papilloma (not pure).[4,5] Microscopically, ADH is a proliferative lesion that fulfills some but not all the criteria for low grade DCIS. Pathologists evaluate several quantitative and qualitative parameters to accurately diagnosis this lesion. The most recent World Health Organization (WHO) Classification of Breast Tumors endorses the traditional quantitative criteria of Page and Tavassoli requiring at least 2 fully involved duct cross sections and ≤0.2cm in size.[6]

Standard of care for an abnormal breast imaging finding is percutaneous image-guided core needle biopsy, with or without vacuum assistance (VAB).[7] More than 1 million breast biopsies are performed for women with an abnormal imaging finding each year, 10-15% of which yield a finding of atypical hyperplasia.[2] When these women undergo surgical excision for ADH identified on percutaneous biopsy, the upgrade rate to underlying malignancy ranges in the literature anywhere from 4% to 54%.[3,8–11] NCCN guidelines continue to recommend surgical excision for patients with ADH on percutaneous biopsy due to this high risk of upgrade to DCIS or IBC.[12] However, as imaging and biopsy techniques have improved over the last decade, the need for routine excision of all ADH has been called into question.[13,14]

Multiple studies have been performed in an attempt to stratify which patients have the lowest risk of underlying malignancy and may therefore avoid surgical excision.[8,9,13,15–20] Attention has been focused on a combination of specific pathologic and radiographic features of ADH. However, no criteria have been consistently able to accurately predict the rate of upgrade in patients with ADH on core needle biopsy. Therefore, the purpose of this study was to calculate our institutional upgrade rate in a contemporary cohort of patients diagnosed with ADH on percutaneous biopsy, and determine if specific pathologic and radiographic features could result in defining a group at the lowest risk of upgrade to underlying DCIS or IBC.

METHODS

Study population

This study is an IRB-approved, HIPAA compliant retrospective chart review from a single institution. A patient list was generated from a query of breast imaging reports for the keyword "atypical ductal hyperplasia". All consecutive female patients≥18 years of age with a diagnosed of ADH on stereotactic biopsy from January 2008 to October 2015 were identified. A total of 600 percutaneous needle biopsies resulted in a diagnosis of ADH during this study period. This study was designed to specifically examine patients with ADH diagnosed on stereotactic biopsy, as screen detected calcifications were expected to yield the lowest risk of upgrade, when compared to masses biopsied via ultrasound guidance or magnetic resonance imaging (MRI) mass enhancement. Therefore, all patients undergoing ultrasound-guided or MRI-guided biopsies with ADH were excluded (n=460). Because of the need to have surgical pathology to accurately define surgical upgrade rate, cases were excluded if they did not undergo surgical excision or if excision was performed at another institution (n=19). Cases were also excluded if there was a concurrent ipsilateral malignancy, for the concern that upgrade rate may be higher in those circumstances (n=25). Cases with a concurrent contralateral breast cancer were allowed, as this has not been historically identified as a risk factor for upgrade. Finally, as ADH upgrade rate has been known to be higher when ADH is associated with another lesion such as a papilloma or radial sclerosing lesion, all cases where ADH was associated with another entity (not pure) were excluded (n=9) (Figure 1).

Imaging Analysis

Patient demographics, clinical presentation, personal history of breast cancer, or family history of breast cancer were obtained from the medical record. All patients underwent stereotactic biopsy for their imaging abnormality with multiple cores using 9g needle with vacuum assistance (VAB). All core biopsy specimens underwent specimen radiograph to document removal of the target, and all patients had post-biopsy mammogram to document clip placement and assessment of the extent to which the target was removed by the biopsy. All breast imaging, with the exception of one case where the images were unavailable, was re-reviewed by 1 of 4 breast-specific radiologists (OW, MI, MR, JG). Imaging presentation and indications for biopsy (calcifications v. mass-/asymmetry/distortion) was documented, as well as the number of cores obtained, lesion size on mammogram, mammographic breast density, and the estimated percentage of the lesion removed by biopsy.

Pathology Analysis

All biopsy slides, with the exception of one case where the slides were unavailable, were re-reviewed by 1 of 2 dedicated breast pathologists (FF, OT). ADH was identified as associated with targeted histologic calcifications or as incidental. The number of foci of ADH were documented as focal (1-2) or

extensive (≥3), and attention was directed to the presence or absence of individual cell necrosis or micropapillary features (Figure 2). The pathology report from surgical excision was also reviewed to determine final diagnosis. ADH upgrade was defined as the presence of DCIS or IBC at the biopsy site on surgical excision. The patient chart was also reviewed for additional percutaneous biopsies or surgeries diagnosing a subsequent breast cancer at least 6 months after the excision of ADH to determine future cancer risk.

Statistical Analysis

Radiographic and pathologic associations were investigated at the biopsy level, as there were two patients with bilateral ADH and two patients who underwent percutaneous biopsy in the same breast followed by surgical excision twice during the study period. Categorical variables, including demographic, radiologic, and pathologic characteristics were summarized using frequencies and percentages. Continuous variables were summarized using means and standard deviations. Chi-square and Fisher's exact tests were used to test for associations between upgrade and categorical demographic, clinical, radiologic, and pathologic characteristics. T-tests and Wilcoxon-Mann-Whitney tests were used to test for associations between upgrade and continuous variables. An exact logistic regression model was used to examine the association between the odds of upgrade and the number of low-risk features present, where the number of features was treated as a continuous predictor variable. All analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC), and a P-value of <0.10 was used to determine statistical significance.

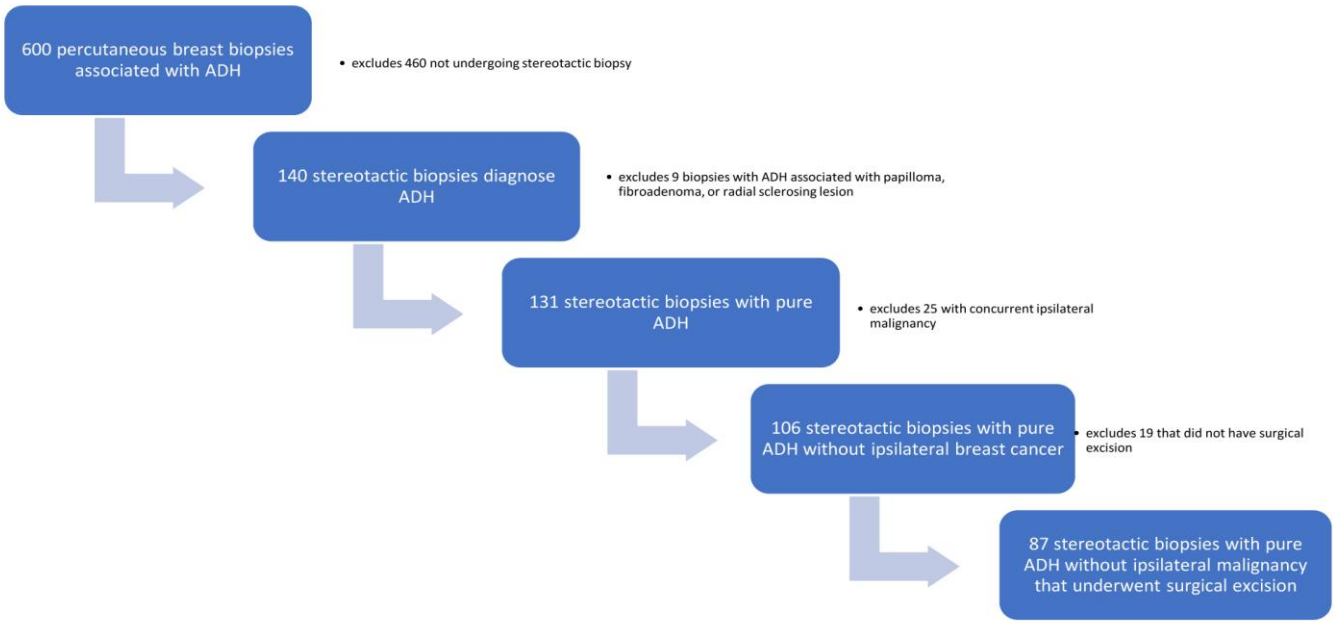

Figure 1. Flow chart of patient selection with ADH during the study period

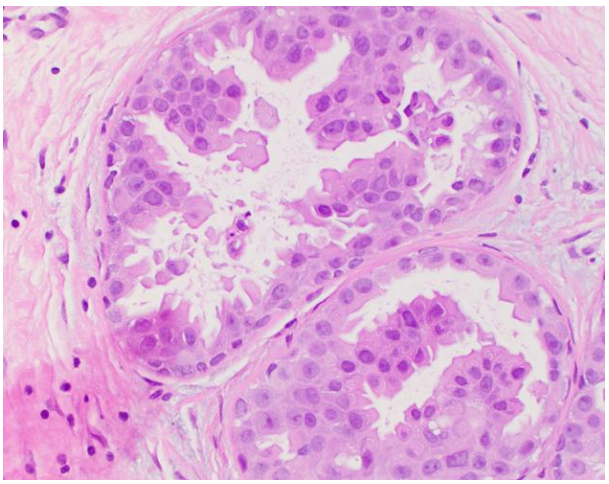

Figure 2. ADH with micropapillary pattern (H&E, x400). The intraductal epithelial proliferation is composed of club-shaped bulbous papillary tufts without fibrovascular cores. Epithelial cells appear to have a monomorphic population. The features are not sufficient for a diagnosis of ductal carcinoma in-situ but appropriate for an interpretation of ADH.

RESULTS.

In total, 83 patients underwent 87 stereotactic biopsies during this study period with the diagnosis of pure ADH, meeting all inclusion criteria for the study (Table 1).

The majority of biopsies were performed in Caucasian, non-Hispanic women (80.5%) at a mean age of 56 years (standard deviation (SD) 10.6). A number of women had a family history of breast cancer (47%) and 19.5% had a personal history of breast cancer, which included 9 with concurrent contralateral breast cancer at the time of ADH diagnosis. Patient demographics and personal history or family history of breast cancer were not statistically associated with an upgrade at surgical excision (Table 2).

Upon review of the radiologic characteristics, the vast majority had calcifications as the indication for biopsy (92%), as expected, with this study being limited to those undergoing stereotactic biopsy for diagnosis. Multiple core specimens were obtained during stereotactic biopsy with a significant majority of cases having > 6 cores removed (94%). The median size of the lesion was smaller for lesions that did not upgrade to malignancy (0.8 v. 2.0cm, P=0.004, Figure 3).

Table 1. Patient and Tumor Factors at the Biopsy-Level. DCIS: ductal carcinoma in situ; DCIS-M: microinvasive ductal carcinoma in situ; IBC: invasive breast cancer

Characteristics	N=87 stereotactic biopsies
Age (year) at diagnosis; mean (SD)	56 (10.6)
Race/Ethnicity	
Caucasian/Non-Hispanic	70 (80.5%)
African American	11 (12.6%)
Hispanic	4 (4.6%)
Asian	2 (2.3%)
Side of biopsy	
Left	37 (42.5%)
Right	50 (57.5%)
No. of lesions upgraded	13 (14.9%)
DCIS/DCIS-M	11 (84.6%)
IBC	2 (15.4%)

Table 2. Univariate analysis of factors associated with upgrade at biopsy level

Variable	Upgrade (n=13)	No upgrade (n=74)	P-value
Age (mean, SD, year)	55.8 (9.8)	56.4 (14.6)	0.90
Personal history of breast cancer	1 (7.7%)	16 (21.6%)	0.45
Family history of breast cancer	4 (30.8%)	35 (47.3%)	0.23
Breast density			
A	1 (7.7%)	6 (8.1%)	0.62
B	8 (61.5%)	35 (47.3%)	
C	4 (30.8%)	33 (44.6%)	
Radiologic presentation			
Calcifications	13 (100%)	67 (90.5%)	1.00
Mass/asymmetry/distortion	0	7 (9.5%)	
Imaging size (cm, median, IQR)[a]	2.0 (1.0,5.1)	0.8 (0.6,1.2)	0.004*
No. cores removed			
≤6	0	5 (6.8%)	1.00
>6	13 (100%)	69 (93.2%)	
Percent of lesion removed by biopsy			
≤50%	6 (46.2%)	13 (17.6%)	0.03*
>50%	7 (53.9%)	61 (82.4%)	
ADH associated with target calcifications	12 (92.3%)	54 (73%)	0.18
Individual cell necrosis[b]	3 (23.1%)	11 (14.9%)	0.40
Micropapillary features[b]	6 (46.2%)	19 (25.7%)	0.10*
Extent of ADH			
1-2 foci (focal)	2 (15.4%)	29 (39.2%)	0.12
≥3 foci (extensive)	11 (84.6%)	45 (60.8%)	

[a]one case with images not available for review, [b]one case with biopsy slides not available for review

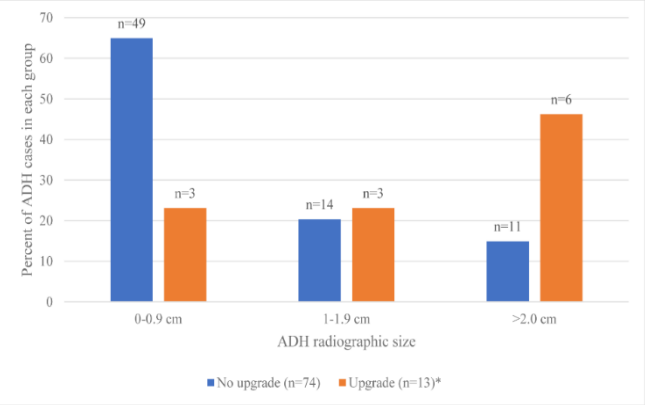

Figure 3. ADH size on imaging by upgrade status
*one case with images unavailable to review for imaging size

Table 3. Summary data for low-risk ADH features and upgrade

No of Low risk Features	No upgrade (n=74)	Upgrade (n=13)	Rate of No upgrade
0	4 (5.4%)	5 (38.5%)	0.44
1	7 (9.5%)	1 (7.7%)	0.88
2	19 (25.7%)	4 (30.8%)	0.83
3	27 (36.5%)	3 (23.1%)	0.90
4	17 (23%)	0	1.00

Following the biopsy, an assessment was performed for the amount of the imaging target that was removed by the percutaneous biopsy and 78% of lesions had >50% of the targeted lesion removed by the stereotactic biopsy, which was also significantly associated with lower upgrade risk (P=0.03). Breast density and the number of cores removed were not statistically associated with an upgrade at surgical excision (Table 2).

Upon review of the pathologic characteristics, the presence of micropapillary features was significantly associated with upgrade to IBC or DCIS (P=0.10). Additional pathologic features of ADH such as individual cell necrosis (P=0.40) and the number of ADH foci or extent of disease (P=0.12) did not reach statistical significance for association with an upgrade to underlying malignancy. Slides were also reviewed to determine if ADH was associated with the radiographic targeted calcifications for biopsy or if it was an incidental finding by the association of calcifications with ADH, which also did not reach statistical significance (P=0.18).

Thirteen cases of ADH (14.9%) upgraded to either DCIS (n=11) or IBC (n=2) on final pathology. Of the 11 cases of DCIS, 10 were nuclear grade I or II and were hormone-receptor positive (91%) and the remaining case of DCIS was hormone-receptor negative and associated with microinvasion. The lowest rate of upgrade was in those who had an imaging abnormality <1cm with >50% removed by the stereotactic biopsy and had <3 foci of ADH without associated with micropapillary features. While this accounted for a small number of patients in this cohort (n=17, 20%), none of these patients upgraded to an underlying malignancy (0%). When fewer than all 4 low-risk features are present, the odds of upgrade increased (Table 3).

The loss of one low-risk feature is associated with a 129% increase in the odds of upgrade (OR=2.29, 95% CI 1.35, 4.15). Leave-one-out cross-validation was used to assess model validity, which resulted in an area under the cross-validation ROC curve of 0.761.

Because ADH is a known risk factor for the development of subsequent breast cancer, all patient charts were reviewed for a diagnosis of subsequent breast cancer after surgical excision of ADH. Of the 74 who did not upgrade to DCIS or IBC at the time of ADH excision, 9 (12%) were diagnosed with a subsequent cancer during follow-up (4 DCIS and 5 IDC), 7 in the ipsilateral breast and 2 in the contralateral breast. The median follow-up of these 74 patients was 71.3 months (IQR 53.3, 100.9) with a median time to subsequent cancer diagnosis of 18 months (IQR 13.5-55).

DISCUSSION

Percutaneous image-guided biopsy has greatly reduced the need for open excisional biopsy in obtaining a diagnosis for a mammographic abnormality. ADH is present in a significant proportion of core biopsy specimens. Following a diagnosis of ADH, it is currently recommended that excisional biopsy follow to rule out underlying malignancy.[12] The reasons for this include significant inter- and intraobserver variation among pathologists when diagnosing ADH,[21] histologic similarities between ADH and DCIS, and the potential for under sampling of the lesion due to a relatively small sample size obtained by percutaneous biopsy, particularly when the imaging target is large.

In this study of pre-selected patients with mammographic abnormality followed by stereotactic biopsy identifying pure ADH, we demonstrated an upgrade rate at surgical excision of 14.9%, which is at the lower end of the historically quoted range, though still too high to recommend observation to all patients with ADH on stereotactic biopsy. We further attempted to identify low-risk features that when present could reassure a low likelihood of upstaging of ADH to DCIS or invasive breast cancer. We found in our population that age, personal or family history of breast cancer, breast density, and the number of cores removed were

not associated with risk of upgrade. Though none of these features reached statistical significance, pathologic features such as ADH which were not associated with the target calcifications (incidental) or focal ADH (limited to 1-2 foci) had lower risk of upgrade. Features that were significantly identified as low-risk for upgrade included lesions smaller than 1cm, >50% of the lesion removed by stereotactic biopsy, and if ADH was not associated with micropapillary features.

The literature has been varied as to what patient demographic, radiologic, and pathologic findings have been associated with a higher risk of an upgrade at the time of surgical excision, emphasizing the importance of understanding one's patient population and radiologic and pathologic resources. Jensen *et al*. were one of the first to describe micropapillary features and extent of ADH to be associated with a higher rate of upgrade,[8] both of which we were found to be associated with upgrade in our study. Similar to other studies, we found the percentage of the lesion removed and the size of the lesion to also be a risk of upgrade upon excision.[9,13,16,17] Patient demographic features such as age at diagnosis of ADH and family history of breast cancer as risk factors,[18,20] were not reproducible in our study.

There have been no randomized controlled trials to determine the need for surgical excision of ADH, though an amendment for AFT-25 COMET does now include severely atypical ductal hyperplasia bordering on DCIS in randomization. Meanwhile, those of us who manage breast cancer continue to push the edge of where we are comfortable de-escalating surgical intervention and have targeted DCIS. There are currently several trials actively enrolling, one in the US (AFT-25 COMET, NCT02926911),[22] and two in Europe (LORD NCT02492607,[23] in the Netherlands and Belgium, LORIS in the UK),[24] attempting to identify which patients with DCIS can be offered active monitoring over excision. In addition, there is one registry trial in Japan (JCOG 1505 LORETTA) treating women with endocrine therapy alone without excision of DCIS.[25] However, separating ADH from low-risk DCIS can be controversial and arbitrary, fraught with interobserver variability and lacking biological validation.[26] Some accept Tavassoli's definition of DCIS being $\geq$2mm,[27] regardless of the number of involved ducts and others prefer Page's original proposal that DCIS must include at least two fully involved duct cross-sections.[28] In our patients population, when ADH upgraded to malignancy, the majority (n=10, 77%) met criteria for low-risk DCIS, acceptable for randomization or observation in the above mentioned trials (grade I-II and hormone-receptor positive). Though not yet standard of care, if COMET concludes a low rate of progression to IBC when surgical excision is omitted for low risk DCIS, and this becomes accepted as standard of care, only 3 of the 87 biopsies with ADH (3.4%) would have benefited from surgical excision and identification of the more aggressive underlying malignancy.

Our study has several limitations, including the retrospective nature of this analysis and the relatively small sample size. Also, there is potential for selection bias in that all of our patients had to undergo surgical excision to be included in the analysis. There were multiple patients during this time period that were excluded because it was determined they did not need surgical excision or the patient declined excision. One patient who did upgrade did not have biopsy slides or imaging available for re-review, which may have limited the strength of our findings. However, the strengths of this study included the contemporary time frame of our study, the re-interpretation of all available patients' imaging and biopsy slides by breast-specific radiologists and pathologists for the above detailed characteristics, and the extensive length of follow-up.

CONCLUSION

In summary, we were able to conclude that for patients with ADH identified on stereotactic biopsy, the overall risk of upgrade to underlying malignancy is lower than historically quoted, though may still be too high to offer active monitoring to all. With careful radiologic and pathologic correlation, patients with the lowest risk for upgrade to DCIS or IBC may safely omit surgical excision. Our study was able to demonstrate that the lowest risk for upgrade in our patient population are those with an imaging target of <1cm in size, >50% of the lesion removed by the percutaneous biopsy, 1-2 foci of ADH, and the absence of micropapillary features. Further application of these low-risk criteria in a prospective manner will be necessary, including the management of ADH identified by other imaging modalities. The oncologic safety of surgical de-escalation and offering active surveillance for ADH will also be necessary to establish in future studies.

ETHICAL CONSIDERATION

This study was IRB approved by the University of Kansas Health System. Informed consent was waived for this retrospective review. There is no conflict of interest.

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