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Atypical ductal hyperplasia: Clinicopathologic factors are not predictive of upgrade after excisional biopsy

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ABSTRACT

Introduction: National Comprehensive Cancer Network (NCCN) guidelines currently recommend excisional biopsy for atypical ductal hyperplasia (ADH) diagnosed on core needle biopsy (CNB) due to the possibility of pathologic upgrade to breast cancer upon excisional biopsy. We aimed to quantify the current rate of upgrade and identify risk factors.

Methods: A retrospective review of women in the Legacy Health Care System with a diagnosis of ADH was performed for 2014 through 2015. Initial pathology and patient factors were reviewed for potential predictors of upgrade.

Results: 91 women with ADH were identified. 84 (92%) underwent excisional biopsy; 16 (19%) were upgraded to breast cancer. Those upgraded were significantly older than non-upgraded patients (64.6 versus 56.7 years, $p < 0.01$), and 15 (94%) had greater than one duct involved by ADH.

Conclusion: The principal clinicopathologic factor associated with upgrade is increasing patient age, however this is not sufficiently predictive. Excisional biopsy in patients diagnosed with ADH on CNB should continue. Further study may provide an avenue for selective excisional biopsy in patients with ADH.

Introduction

Atypical ductal hyperplasia (ADH) is a commonly identified pathologic finding in between 8 and 17% of all breast core needle biopsies (CNB),[1–3] and was first identified by Foote in 1941.[3] When ADH is identified, surgical excision is generally recommended due to the risk of pathologic upgrade to cancer in 7–46% of cases following excisional biopsy.[4–10] With approximately 700,000 breast biopsies performed annually in the United States, the number of surgeries performed for ADH represent a large monetary and time investment.[11] The prospect of identifying women with ADH who might avoid excisional biopsy remains a potentially beneficial yet elusive goal. Recent efforts aimed at risk stratifying patients with a diagnosis of ADH have had limited success, at best stratifying the risk of underlying malignancy to 5% in "low risk" patients.[4,9,10,12] In the present study, we aimed to quantify the rate of pathologic upgrade of ADH in a large private hospital system and identify potential risk factors for upgrade.

Methods

Data were obtained via a query of a prospectively maintained community breast center registry from January 1st, 2014 through December 31st, 2015. The principal inclusion criterion was any diagnosis of ADH following CNB. The sole exclusion criterion was the presence of additional advanced pathologies on CNB apart from ADH, including ductal carcinoma in situs (DCIS), invasive ductal carcinoma (IDC), or invasive lobular carcinoma (ILC). Data points captured included age at diagnosis, breast quadrant location, and method of lesion identification (mammography versus self-exam). Retrospective chart review was used to capture data on additional surgical procedures and pathology results. IRB approval was obtained. All core needle biopsies were performed using a 9-gauge needle, with provider-level variation in the utilization of vacuum-assisted biopsy.

For women who went on to receive excisional biopsy, the final pathologic diagnosis was then compared to initial biopsy results to identify women with pathologic upgrade of their ADH lesion to

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either DCIS or IDC, as well as women who had no residual ADH identified. The original slides of upgraded patients were reviewed by a pathologist for the identification of any pathologic factors that appeared predictive of upstaging or the absence of residual ADH.

The Hughes RiskApps™ standardized risk assessment tool was utilized to determine lifetime risk of breast cancer in all patients who were upgraded. The Hughes tool gives the estimated lifetime risk of breast cancer per the Gail, BRCAPRO, Tyrer-Cuzick v6, Tyrer-Cuzick v7, and Claus Models. When the Hughes risk assessment was not utilized, such as for women who were not upgraded, the Gail model was used to calculate lifetime risk based on patient historical data collected from chart review. The highest value of lifetime risk as estimated in any model was used.

Results

Within the study period, 1603 breast biopsies were performed. Of these, 91 (5.6%) were diagnosed with ADH in the absence of more advanced pathology. 90 were diagnosed via routine mammographic screening, and one via self-breast exam. The mean age at diagnosis was 58.1, with a range of 41–80. Of these women, 84 (92%) went on to receive excisional biopsy, and 16 (19%) were upgraded to a diagnosis of breast cancer. Of these, 3 (19%) were IDC and 13 (81%) to DCIS. 31 (37%) of patients with ADH on CNB showed no residual ADH on excisional biopsy. These data are graphically summarized in Fig. 1.

The average age of upgraded patients was 64.6, with a range of 42–80, and was significantly higher than the non-upgraded patients at 56.7 ($p < 0.01$). The total size of ADH on CNB in upgraded patients ranged from 1 to 7 mm, and there was no correlation between size of ADH and risk of upgrading. Of note, 15 of 16 (94%) upgraded patients had greater than one duct involved by ADH on CNB (range 1–46 ducts). Upon pathologist review of initial CNB slides for upgraded patients, there were no changes to the initial given diagnosis of ADH. Of note, the single patient diagnosed with ADH with a palpable mass was not among those upgraded after excisional biopsy. Data on the presence or absence of residual calcifications following CNB, as well as BIRADS score, were incomplete in the dataset and could not be ascertained by chart review due to inconsistent reporting and an incomplete set of post-CNB images.

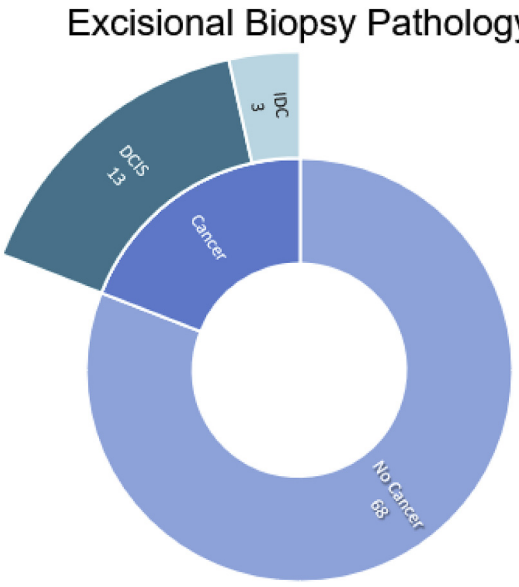

Fig. 1. Excisional biopsy results.

The estimated lifetime breast cancer risk of upgraded patients was 16.2% on average and ranged from 5.6% to 47%. The average lifetime risk for non-upgraded patients was 15.8% and ranged from 6.4% to 49.2%. The average lifetime risk was not significantly different between these two groups ($p = 0.72$).

Of the 7 patients who elected to not undergo excisional biopsy, follow up information was available in 6 and is summarized in Table 1. All six were followed semi-annually to annually with clinical breast exams as well as mammography, breast MRI, or both. Duration of follow up ranged from 45 to 56 months following diagnosis of ADH, with none of these patients developing breast cancer within this time frame.

Discussion

Atypical ductal hyperplasia is a high-risk lesion, and it remains standard practice to recommend an excisional biopsy when ADH is diagnosed due to the risk of pathologic upstaging. Our data confirm that the modern rate of upstaging remains as high at 19%. Nonetheless, the goal of attempting to perform fewer invasive procedures and decrease harms of screening remains laudable. To that end, researchers have attempted to identify clinicopathologic features that could select those at highest risk for upgrade. Potential predictive factors include the presence of residual calcifications, number of ADH foci on CNB, size of atypia, patient age, and lifetime breast cancer risk.

Previous studies have evaluated radiographic features such as the type and number of calcifications seen on mammogram, as well as number of residual calcifications after CNB, to predict eventual pathologic upgrade. One such study by Caplain and colleagues suggested that follow up could be considered for patients with ADH lesions.[13] In our population, imaging records were performed within other health systems and were not available for review in approximately one third of patients. Another one third of patients did not have any comment on imaging regarding residual calcifications. The remaining number of patients with detailed imaging records was insufficient to make any meaningful conclusions. Prior studies have shown that the presence of residual calcifications has not been shown to be predictive of upgrade.[14,15] Youn found that 33% of patients with no residual calcifications were found to have DCIS on excisional biopsy,[14] while Kohr found that the risk of upgrade was similar between those who had all mammographic calcifications removed versus those who did not (17% vs 20%).[15] As such, the presence or absence of residual calcifications should not influence surgical decision making.

The number of foci involved with ADH on CNB as well as the total size of atypia have also been proposed as a tool for predicting upgrade.[12,14,16] Our data found that the number of ducts involved in our upgraded patients was quite variable, ranging from 1 to 46. Upon review by pathology, it was noted that 15 of 16 (94%) upgraded patients had at least two ducts involved by ADH. This may suggest that patients with only one duct involved with ADH are at lower risk of upgrade. This metric is not routinely reported on pathology reports, and it was only possible to review this data point for the upgraded patients, therefore comparisons with non-upgraded patients could not be made. Regarding size of atypia, our results showed that the size of atypia was quite variable, ranging from 1 to 7 mm. Therefore, our data are unable to either support or refute the use of ADH foci, duct involvement, or total ADH size in counselling patients as to their risk of upgrade.

On review of our patients, we did find that patient age was significantly associated with risk of upgrade, with upgraded patients being 9 years older on average than non-upgraded patients. McGhan and colleagues also found that no patients under the age of 50 were upgraded.[1] This could be because the risk of breast cancer

Table 1
Clinical features of patients not undergoing excisional biopsy.

Patient Number	Age	Lifetime Risk of Breast Cancer	Mammography or MRI Surveillance	Months Since ADH Diagnosis	Breast Cancer (Y/N)
1	47	43.8%	Yes	54	N
2	49	23.5%	Yes	45	N
3	64	30.7%	Yes	45	N
4	80	7%	Yes	46	N
5	49	23.5%	Yes	56	N
6	44	42%	Yes	46	N

increases with age, and the pre-test probability of cancer in mammographically suspicious lesions also increases with age. As such, increasing patient age should be a consideration for proceeding with excisional biopsy.

Additionally, we investigated whether women at higher lifetime risk of breast cancer may have higher risk of pathologic upgrade. We previously published on using lifetime risk of breast cancer as a predictive tool to inform screening in women under the age of 50 and found that most diagnosed with breast cancer in this population are not at elevated lifetime risk compared to the general population.[17] The limitations of using lifetime risk as a predictive tool are reflected in the ADH population as well. We found that the lifetime risk for patients upgraded to breast cancer after excisional biopsy was nearly identical to those who were not upgraded at 16%. It should be noted that not all patients had lifetime risk assigned through the Hughes Risk App, and approximately half were retrospectively calculated using the Gail model. This does introduce heterogeneity into how this value was tabulated and is a limitation of the present study. Regardless, it does not appear that lifetime risk can be used to determine risk of upgrade in this patient population.

There was a small group of patients who declined excisional biopsy, and yearly follow up data was available for all but one. Interestingly, none of these patients have developed breast cancer at a median of 46 months after diagnosis. These patients have been followed closely with annual to semi-annual mammograms and MRIs. There may be a group of patients for whom close follow up would be reasonable; future investigations of patients refusing excisional biopsy may be able to identify clinicopathologic factors associated with low risk of future breast cancer diagnosis.

In light of our findings, pathologic factors do not appear to have a significant bearing on the risk of upgrade, with the exception of single duct involvement which may be at lower risk of upgrade. We continue to recommend that all women with ADH diagnosed on CNB be counseled towards excisional biopsy to exclude underlying malignancy. The present findings may also inform case-by-case decisions for observation versus excision in women under 50, as this group was less likely to be upgraded. Further study of this disease process is still needed to further elucidate which patients may be safely observed without surgery.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose. This research project was undertaken without financial assistance of any kind.

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