Upstaging of Atypical Ductal Hyperplasia After Vacuum-Assisted 11-Gauge Stereotactic Core Needle Biopsy

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Background: Nonpalpable mammographic abnormalities are frequently evaluated by means of a stereotactic core needle biopsy. This technique is a very sensitive indicator of invasive cancer, but is less reliable to discriminate between ductal carcinoma in situ and atypical ductal hyperplasia (ADH). The objective of this study was to determine the correlation of the 11-gauge vacuum-assisted core needle biopsy to open biopsy when a diagnosis of ADH is obtained.

Hypothesis: The use of 11-gauge vacuum-assisted stereotactic core needle biopsy does not conclusively diagnose ADH.

Design: Retrospective analysis.

Setting: University-affiliated teaching hospital.

Patients: Mammographic findings were evaluated with an 11-gauge vacuum-assisted stereotactic core biopsy in 1750 patients. Seventy-seven patients were diagnosed as having ADH; of these, 65 underwent excisional biopsy.

Main Outcome Measures: Pathological upstaging rate.

Results: Of the 65 patients who underwent excisional breast biopsy, 11 (17%) had their condition upstaged to a breast cancer diagnosis. These patients had presented at a later age than those who retained a benign diagnosis after excisional biopsy. The number of cores taken did not correlate with diagnostic accuracy.

Conclusions: Of the 65 patients who underwent open biopsy for ADH in this series, only 83% had an accurate diagnosis. A diagnosis of ADH by stereotactic core needle biopsy should be followed by an open excisional biopsy.

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Histologic findings in 1750 stereotactic core needle biopsy specimens. DCIS indicates ductal carcinoma in situ; ADH, atypical ductal hyperplasia; and LN, lobular neoplasia (includes atypical lobular hyperplasia and lobular carcinoma in situ).

Histologic findings in 65 excisional breast biopsy specimens with a preoperative diagnosis of atypical ductal hyperplasia established by vacuum-assisted 11-gauge stereotactic core needle biopsy. DCIS indicates ductal carcinoma in situ; IDC, invasive ductal carcinoma; and ILC, invasive lobular carcinoma.

Table 1. Characteristics of SCNB With Subsequent Benign or Malignant Excisional Biopsy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>n = 54</td>
<td>n = 11</td>
</tr>
<tr>
<td>Median</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.8 (8.0)</td>
<td>66.0 (13.7)</td>
</tr>
<tr>
<td>Range</td>
<td>40-74</td>
<td>43-81</td>
</tr>
<tr>
<td>P value</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>No. of cores taken</td>
<td>n = 32</td>
<td>n = 6</td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>21.5</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15.7 (8.3)</td>
<td>24.0 (10.2)</td>
</tr>
<tr>
<td>Range</td>
<td>6-36</td>
<td>11-36</td>
</tr>
<tr>
<td>P value</td>
<td>.10</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SCNB, stereotactic core needle biopsy.

During the 5-year period of study, 1750 stereotactic core needle biopsies were performed. Significant pathologic findings were identified in 576 patients (33%) by this technique (Figure 1); there were 188 invasive cancers, 311 cases of DCIS, and 77 cases of ADH. Of the 77 patients with ADH, 65 (84%) proceeded with an open excisional biopsy. The mean age of these 65 patients was 55.9 years (range, 40-81 years). Eleven patients (17%) were diagnosed as having cancer and 54 had benign diagnoses (Figure 2).

The frequency of ADH remained constant between the first and second time periods (4.2% vs 4.8%; P = .56), ruling against a stage migration due to an improvement in technique. Patients who underwent biopsy (n = 65) were comparable in age to those without a biopsy (n = 12); mean ages were 55.9 and 60.9 years, respectively (P = .12). No other sociodemographic information was available on patients who did not undergo biopsy.

Patients whose disease was upstaged during the first 42 months (n = 36) were similar to those whose disease was upstaged later (n = 29). Mean age was 56.6 and 55.0 years, respectively (P = .53). The median number of cores (available for only 38 patients) was also comparable in the 2 patient cohorts (18 and 13, respectively; P = .26). Patients who were missing data on the number of core specimens (n = 27) were similar in age to those who had data (n = 38); mean ages were 57.5 and 54.7 years, respectively (P = .27).

Among all 65 patients, 11 (17%) had a cancer diagnosis. Age was significantly associated with a cancer diagnosis in the total patient group as well as the subgroup of 38 patients (Table 1 and Table 2). Specifically, the odds of a cancer diagnosis increased by 11% to 13% for each 1-year increase in age (see parameter estimates of 1.11 and 1.13 in Table 2). Patients in the later time period cohort were slightly less likely to have a cancer diagnosis than those in the earlier cohort, but these results were statistically nonsignificant. In the subgroup of 38 patients, those with a larger number of core specimens appeared to be more likely to have a cancer...
diagnosis (odds ratio, 6.43; Table 2), but the small sample size resulted in poor precision of this estimate (95% confidence interval, 0.67-61.45).

**COMMENT**

This study identified a 17% risk of upstaging of ADH with an 11-gauge vacuum-assisted stereotactic core device. A series of studies limited to a vacuum-assisted 11-gauge apparatus have a collective rate of 16% of upstaging for a diagnosis of ADH, with 64% of those upstaged cases having a diagnosis of DCIS (Table 3).

The mean age at diagnosis of ADH established by core biopsy is 53.8 years, considerably earlier than the mean age at diagnosis for a malignancy (66 years). Adrales et al15 made a similar observation, with their cohort with benign disease being diagnosed at a mean age of 53 years and patients with cancer diagnosed at age 59 years. Atypical ductal hyperplasia has long been recognized to confer a risk of subsequent breast cancer.19 It is likely that ADH is not only a risk factor for but a precursor to DCIS and invasive cancer, explaining the earlier age incidence of patients with ADH alone as compared with those with ADH and a malignancy. Clearly, not all ADH progresses to malignancy, but, if recognized before a malignancy develops, it should occur on average at an earlier age than in patients with cancer. The range of onset for malignant transformation is broad enough that malignancy cannot be excluded on the basis of age alone. However, this observation supports the notion that a diagnosis of ADH in a woman in her 60s should be aggressively pursued with an excisional biopsy.

Lack of correlation between the number of cores taken and the final diagnosis has also been observed,10,13 suggesting that there are many variables that may affect the number of core specimens obtained. The most obvious variable would be a selection bias of the person performing the test. If the index of suspicion is high, a more aggressive approach might lead to taking more samples than if the suspicion were low. This explanation is supported by this study in that malignant diagnoses had a higher average number of cores retrieved (24.0) than did benign diagnoses (15.7). With a larger sample size for the malignant cohort, this difference might have reached statistical significance (P = .10).

The lack of correlation also may be explained by a variable not addressed in the current study: the size of the mammographic or pathologic entity. Others have shown that size is an important variable in providing an accurate diagnosis.20 Jackman et al20 recognized that, as the maximum mammographic lesion diameter increased, so did the risk of ADH underestimation. Adrales et al15 identified marked atypia and residual calcifications as predictors of additional disease after a core biopsy diagnosis of ADH. The existence of marked atypia suggests an initiated progression to the malignant phenotype, thus prompting a more exhaustive tissue analysis. The presence of residual calcifications or the percentage ablation of microcalcifications has been recognized by others as a risk factor for upstaging and supports the concept that larger lesions have a greater opportunity to harbor an area of malignant transformation that is overlooked by a limited sampling procedure.17

**CONCLUSIONS**

Atypical ductal hyperplasia, when diagnosed by 11-gauge vacuum-assisted core biopsy, leads to an accurate
diagnosis in 83% of patients who go on to have an excisional biopsy. Patients who have additional treatable diagnoses are likely to be older and have coexistent in situ or invasive carcinoma. The core needle sampling procedures should be generous, based on the many observations that correlate larger specimens and complete ablation of mammographic calcifications with greater accuracy. There have been no identifiable factors to date that safely exclude a malignant diagnosis when ADH is discovered with core needle biopsy. Thus, surgical excision remains indicated in this situation.

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REFERENCES


DISCUSSION

Christina Finlayson, MD, Denver, Colo: One of the criticisms of mammography is its false-positive results. Approximately 5% of mammographic biopsies will result in atypical ductal hyperplasia. Whether or not this requires excision is a point of controversy because of our desire to try to decrease the number of invasive procedures that need to be done for these women, and whether it represents a sampling error. When our biopsies were done with a 14-gauge core, we had an incidence of 30% to 50% where there would be a correlation with the additional finding of carcinoma at excisional biopsy. When we were able to increase the size of the core biopsies to 11-gauge with the vacuum-assisted technique, there was hope that we would be able to decrease the number of excisional biopsies that needed to be done because of our ability to more accurately sample the area. This study confirms the problem; there still is a high incidence of associated in situ and invasive carcinomas when ADH is identified on core biopsy.

I have a few questions for Dr Winchester in regard to the study. Some people have looked at other criteria such as mammographic criteria to see if that could be used to decrease the number of excisional biopsies that need to be performed. Were you able to look at either the volume of your cores, the volume that contained ADH in comparison to the volume of the cores, or the complete excision of the mammographic abnormality to show any correlation with the subsequent excisional findings?

I was also interested in how you manage your lobular neoplasias, as they have the same risk of the future development of breast cancer.

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif: I very much enjoyed this paper and agree with the conclusions. I believe it to be timely. Two questions.

Atypical ductal hyperplasia is a difficult diagnosis. Have your pathologists had occasion to go back and look at the 77 ADH diagnoses blinded to see if they would render the same diagnosis again?

Secondly, is there any explanation besides improved sampling with excisional biopsy that there would be upstaging? In other words, is there any other reason besides sample error that would account for the upstaging with excisional biopsy?

David W. Easter, MD, San Diego, Calif: My questions are about volume vs 2-dimensional measurements. How did your pathologist differentiate the volume or true diameter of a lesion vs the 2-dimensional measurements? For example, if I took an apple and sliced it up, I can make that a very long apple.

The second question is, how many times did you go back and excise those patients and find no lesions in the breast?

David S. Robinson, MD, Kansas City, Mo: It is a remarkable paper for 2 reasons: first, the data are well presented, and second, because of the sustained interest of surgeons in image-directed biopsies, a domain shared by both surgeons and radiologists.

I have also questions regarding the pathologists’ readings. You described 2 ways of defining ADH. Do your pathologists use both? With regard to interobserver variability, were
the same pathologists who review the initial core biopsy then reading the excisional biopsies? If not, the upgrading from ADH to DCIS could be accounted for by changing pathologists. Moreover, because the predominant mammographic reasons for a biopsy to ADH and DCIS are new clusters of microcalcifications or an increase in the number of microcalcifications in an existing cluster. Do you think it is important to remove all of the microcalcifications? Can we leave a few and still have an accurate diagnosis of ADH? Finally, in the original abstract, you said that 36 of the 50 patients underwent reexcision. What criteria did you use to select those 36, and, reciprocally, what happened to the 14 patients not reexcised?

Jeffrey Landercasper, MD, LaCrosse, Wis: I agree with the conclusions of the paper. I have 3 questions.
1. Did you make attempts to compare characteristics of the mammographic lesions with a final histologic diagnosis, ie, did the size of the lesion on mammography or the different characteristics of the microcalcifications correlate with the final benign or malignant diagnosis?
2. Did you use ultrasound to study any of these patients preoperatively, and did that help you identify the malignant lesions?
3. Did you mark the area of the original stereotactic biopsy with a radiopaque marker to assure that your subsequent open biopsy removed the correct area to make sure that you are not missing the malignant lesion? Did you do a post–open biopsy mammography to assure that you have removed all the microcalcifications?

James A. Edney, MD, Omaha, Neb: I have a question and a comment. I would ask the authors who performed these stereotactic biopsies, the radiologists or the surgeons? As the “primary care providers” for breast cancer patients, surgeons really need to be intimately involved in the process of stereotactic breast biopsy. Radiologists, in general, have—and I do not mean this in a pejorative sense—a limited understanding of the pathology of breast cancer and oftentimes when confronted with a diagnosis of atypical ductal hyperplasia say, “Well, it is not malignant,” and if they are communicating only with the patient’s primary care provider, the patient may often not be referred for a wider excision or more intense surveillance. As a result, it is very important that surgeons insinuate themselves into this paradigm. In the near future, definitive treatment will be delivered by stereotactic or ultrasound-guided tissue ablation, whether it be by cryotherapy, laser, or radiofrequency ablation. As a result, the surgeon with limited imaging skills will no longer be the “primary care provider” for breast cancer patients. This will be a grave disservice for the patient and the profession.

Howard Silberman, MD, Los Angeles, Calif: I was wondering whether the authors have had any experience with the emerging field of breast MRI [magnetic resonance imaging] in identifying preoperatively this small but significant 17% subset?

Dr Winchester: Thank you for all those excellent questions. I will start with Dr Finlayson’s questions. We did not analyze anything with our mammogram data with regard to predicting the upstaging of ADH, but I think it has been recognized in other published series that the size or extent of ablation does predict a subsequent upstaged diagnosis. With regard to ALH, or atypical lobular hyperplasia, in my review of these 1750 patients, there were 20 patients who had lobular neoplasia, which included LCIS [lobular carcinoma in situ] or ALH, and, in those 20, only 10 had a subsequent excisional biopsy. One of those patients had DCIS. That is characteristic of other reports that usually describe a single-digit series, but have recognized a 10% to 30% incidence of other treatable pathology.

Dr Goodnight, our pathology is reviewed by at least 2 pathologists. In this study, 2 pathologists went back and reviewed our material again. Typically, 4 or 5 pathologists review each breast specimen and, therefore, I believe that our characterization of each diagnosis of ADH is accurate.

Dr Easter, assessing the volume is difficult when you see several areas of discontinuous ADH. The right answer is probably to measure each area individually rather than as a conglomerate. This question raises the difficulty with this diagnostic test that samples an entity that may be very extensive in some situations, making it difficult to render an accurate diagnosis by virtue of a core needle sample. To define DCIS, however, measurements should be done by what is continuous, not discontinuous.

With regard to subsequent pathology identified after excising ADH, most patients actually had benign histologies. Only about 25% had ADH on further excision. Is that because all of the cores had ablated all of the ADH, or because of an initial misinterpretation on the initial core biopsy? It is not clear, but most of these patients, after a broader sampling with excisional biopsy, had benign histology. With regard to definitions of ADH, we employ both definitions in our Department of Pathology as far as distinguishing ADH from DCIS. If it is less than 2 mm, it is a clear-cut indication of ADH; if not all the criteria are met for DCIS, that is the second. So they both need to be addressed to define the entity.

I have already touched upon the pathology questions raised by Dr Goodnight. What should one do with remaining calcifications after this diagnosis is made? Clearly, you should do an excisional biopsy as a first step. What to do after that depends on what is found. If there is extensive ADH on the subsequent excisional biopsy, a postexcisional mammogram is useful and may prompt additional surgery if extensive calcifications remain.

What happened to the 14 patients in the abstract who did not have excision? We do not know. Some may have gone to other institutions, some may not have understood the importance of doing additional testing, but I have no clear answer as far as what everyone did or what is being done about them now. If they were my patients, I would make a strong push to have additional surgery. Again, we made no effort to collect mammographic data, but, as I mentioned before, that is important in other series. The volume of residual or ablated calcifications is probably very important in predicting an upstaged diagnosis.

Ultrasound was used selectively in our patients. That represents another 700 or 800 patients not included in this series, because if ultrasound identifies something seen mammographically, those patients are likely to have a different entity. The incidence of ADH is much lower in patients with solid lesions as compared to those with microcalcifications. Core biopsies are routinely followed by placement of a radiopaque clip, which is important for the subsequent excision if a diagnosis of ADH or malignancy is identified. Postexcisional mammograms are a good idea, particularly for extensive ADH.

Who performs the stereotactic core biopsy in our institution? It is radiologists. We work very closely with them. They understand the importance of this entity and the need for further diagnostic testing if we find ADH. The point is well taken that surgeons should be closely involved, although this is frequently a very contentious area and the interactions may be difficult. I am a strong proponent of surgeons with ultrasound; however, my hospital has had difficulty recognizing the logical extension of what I do as a surgeon.

Breast MRI is an interesting area. We have a research project in progress, but I do not have information regarding correlation of an ADH diagnosis with MRI findings.