Clinical Science

Management of patients diagnosed with atypical ductal hyperplasia by vacuum-assisted core biopsy: a prospective assessment of the guidelines used at our institution

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Abstract

BACKGROUND: Because of underestimation, surgical excision is recommended for atypical ductal hyperplasia diagnosed on directional vacuum-assisted biopsies. The following guidelines have been established according to our retrospective study published in 2008: excision for lesions ≥21 mm, follow-up for lesions <6 mm with complete removal of microcalcifications, and follow-up or excision for 6 to 21-mm lesions with respectively less or ≥2 atypical ductal hyperplasia foci.

METHODS AND RESULTS: These guidelines were assessed in a prospective series of 124 patients with a median follow-up of 30 months. Conformity rate was 92%. Upgrading was 28% (15 of 53 patients) for confirmed surgery and absent for surgery performed beyond the scope of guidelines. For the patients with benign result at surgery (n = 38) or just followed (n = 61), 3 cancers occurred in either breast at 1 to 3 years.

CONCLUSIONS: These convenient guidelines can safely spare surgery for a subset of patients. However, annual mammographic follow-up is recommended since the risk of subsequent cancer remains high for both breasts.

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With the common use of breast core-needle biopsy (CNB) and the recent assessment of the directional vacuum-assisted biopsy (DVAB) technique,1 up to 15% of breast biopsies performed for isolated mammographic calcifications highlight an atypical ductal hyperplasia (ADH) diagnosis. ADH is a proliferative lesion which is a marker of an increased risk of developing breast cancer and is histopathologically defined as either (1) an hyperplastic lesion with some cytological features of low-grade ductal carcinoma in situ (DCIS) that does not fill the entire duct; or (2) a lesion with classic cytological and architectural features of low-grade DCIS measuring <2 to 3 mm.2–4 Patients with ADH on surgical breast biopsy are 4 to 5 times more at risk than the general population of subsequently developing breast cancer.2 After diagnosis of ADH on CNB, a surgical excision is currently recommended.
because of the risk of upstaging to DCIS or invasive cancer on the definitive evaluation of the excised specimen.\textsuperscript{5–14} Many studies focused on this underestimation rate, with a prevalence of upstaging ranging from 11% to 68% after CNB.\textsuperscript{5,6,10,11,15–21} Some of them tried to highlight predictive factors of underestimation, but decision criteria whether to excise or not differ according to the authors\textsuperscript{1,6,8,17,21–25} and none of them have been prospectively assessed. Up to now, no clear guidelines for the management of patients diagnosed with ADH on DVAB have been ascertained.

To identify a subset of patients who could safely be spared surgery, a previous retrospective study was conducted at our institution on a series of 300 patients diagnosed with pure ADH on 11-gauge DVAB between February 1999 and May 2005.\textsuperscript{26} Valuable features were identified to classify patients at diagnosis based on the 3 following criteria: size of the lesion on mammograms, complete removal of microcalcifications by DVAB, and extent of ADH within ducts and/or lobules on CNB defined as “ADH foci.”\textsuperscript{17} This analysis led us to a proposal for the management of patients with ADH, shown in Fig. 1.

This study aims to prospectively assess the relevance of these guidelines which have been used at our institution for ADH management since June 2007.

Patients and Methods

ADH diagnosis and study database

From June 2007 to June 2012, 2,030 consecutive 10-gauge DVABs (Vacora or Sonorex: Bard, France) were performed at the Centre Léon Bérard as part of a breast cancer screening program, with 127 cases of pure ADH diagnosed. All DVABs were performed for mammographic microcalcifications by well-trained radiologists and were obtained with a prone-dedicated stereotactic device (Lorad Multicare Platinum, Hologic Inc, Danbury, CT). Only isolated microcalcifications were included since the underestimation rate could be higher on patients having either a palpable mass or another mammographic lesion.\textsuperscript{18,27} Patients for whom ADH was associated with other histopathological borderline lesions (such as papilloma, radial scar, mucocele-like lesion, or atypical columnar cell metaplasia) were excluded from the study because they might increase underestimation.\textsuperscript{14,19} Before biopsy, the mammogram findings classified according to the Breast Imaging-Reporting And Data System (BI-RADS)\textsuperscript{28} were reviewed by the same radiologist. The size of each microcalcification cluster (lesion size in millimeter) was recorded. A metallic marker was left in the targeted area after the biopsy and both the right position of the marker and the complete or partial removal of calcifications were assessed. A radiography of the core samples was systematically performed to confirm the presence of microcalcifications. The diagnosis of ADH as the most aggressive lesion was made by 2 pathologists specialized in breast pathology, according to established criteria as defined by Page et al and Tavassoli and Norris.\textsuperscript{2–4} The extent of ADH within ducts, as described by Ely et al,\textsuperscript{17} was assessed by the same pathologists. Therapeutic decision was taken by a multidisciplinary team, according to the guidelines previously described. In case of surgical management, a preoperative needle localization and an intraoperative specimen radiography were performed to confirm correct excision. Pathological diagnoses on excision were classified as benign (ADH or other benign lesions) or malignant (DCIS, in situ pleomorphic lobular carcinoma, or invasive carcinoma). In all cases, the presence of a prior biopsy site was confirmed. Demographical data (age, side affected), lesion size on mammograms, number of cores removed, ADH extension within ducts (foci), complete removal of microcalcifications, final therapeutic decision, and definitive diagnosis on surgical specimen were prospectively entered in our database. Three patients with a lesion size missing were excluded from the analysis since the conformity to guidelines of the final therapeutic decision could not be evaluated without this criterion. The following analysis was thus carried out on a series of 124 patients with assessable conformity to guidelines. Patients have given their informed consent, and approval was obtained from the review board of the Centre Léon Bérard.

Follow-up

Outcome and follow-up after ADH diagnosis, including clinical, mammographic, and histopathological data when a

![Figure 1](image-url)
further biopsy was performed, were prospectively entered in a database. We tried to be as close as possible to the current recommendations consisting of bilateral mammograms and clinical examinations within 12 months after DV AB and every year from then, independently of the patient management (surgery or abstention).26 Patients for whom no news had been recorded for more than a year were systematically called and proposed a phone interview to know the follow-up performed since ADH diagnosis: dates of breast medical examinations (MEs) and results (clinical examinations, mammograms), possible CNBs, and surgery. Malignant events were considered when a histological diagnosis of DCIS, in situ pleomorphic lobular carcinoma, or invasive carcinoma was made during the follow-up.

Statistical analysis

Analyses were conducted using the R software package.29 Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation if normally distributed and using median and range otherwise. The cumulative probability of a malignant event was estimated by the Kaplan–Meier product-limit method and the Greenwood’s formulas were used to calculate its variance and a 95% confidence interval (CI).30,31 Standardized incidence ratios for breast cancer (SIRs, the observed number of events divided by the expected number of events) and 95% CIs were calculated on the assumption that the observed number of events followed a Poisson distribution. Expected numbers of breast cancer were computed using incidence rates by age estimated from the French population in 2005.32 The assessment of the follow-up compliance to the current recommendations was performed by estimating a conformity rate at 1 to 4 years after ADH diagnosis or surgery. The mean delay between 2 MEs was estimated by a random effect model, taking into account the nonindependence of repeated MEs for each patient, in modeling a latent “patient effect.” All tests were 2-sided and considered statistically significant if $P \leq .05$.

Results

Baseline characteristics and conformity to guidelines

The management decision and baseline characteristics for the 124 patients (validation series, this study) are shown in Table 1, which also includes for comparison the corresponding figures from the retrospective series used for guidelines.26 There was no statistical difference for mean age at diagnosis and median lesion size in both series, but we observed more patients in the validation series with $>2$ ADH foci (45% compared to 28% in the...
retrospective series, \( P < .001 \) and also slightly fewer patients having experienced a complete removal of microcalcifications (47% compared to 60%, \( P = .026 \)). Accordingly, the management decisions were not equally distributed in the validation and retrospective series (more surgical excisions in the validation series, 49% compared to 40%, \( P < .001 \)). Unsurprisingly, conformity to guidelines was better in the validation series (92% compared to 78%, \( P < .001 \)), even if 8 inadequate surgical excisions and 2 inadequate abstentions occurred.

**Management and outcomes**

The validation series was prospectively analyzed with a median follow-up of 30 months (range: 5 to 55 months). Fig. 2 illustrates the outcome and follow-up of the validation series with emphasis on the management of patients according to the guidelines. Overall, 61 patients underwent a surgery and 63 did not, with no statistical difference in their follow-up (log-rank test, \( P = .93 \)). Among the 53 patients who underwent a surgical excision in accordance with the guidelines, 15 had a malignant lesion, with a median time to surgery of 58 days after diagnosis (range: 14 to 480 days). Thus, the upstaging rate of conformed surgery was 28% (15/53) in agreement with the rate of 37% (28/75) obtained from the retrospective series (Fisher’s exact test, \( P = .34 \)). Among the remaining 38 patients with a benign lesion at surgery, 1 invasive ductal carcinoma in the contralateral breast was diagnosed within the 1st year of follow-up. No malignant event was recorded in this group thereafter. Thus, the probability of a malignant event at 2 years in this group was estimated at 3.3% (95% CI: 0% to 9.5%). Among

![Figure 2](image)

**Figure 2** The management and follow-up of a prospective series of 124 patients with ADH (this study).
the 8 patients who underwent an inadequate surgical excision, all the histological diagnoses were benign and no malignant lesion was found in their follow-up (6 patients with follow-up).

Among the 61 patients in the abstention group in accordance with the guidelines, 1 patient developed an invasive ductal carcinoma in the contralateral breast 2 years after ADH diagnosis on DVAB, with a probability of a malignant event at 2 years estimated at 2.3% (95% CI: 0% to 6.7%). Another patient developed a malignant event at 3 years in the same breast, but on a different quadrant. Thus, the probability of a malignant event at 3 years for the abstention group in accordance with the guidelines was estimated at 8.1% (95% CI: 0% to 19.1%). Finally, regarding the 2 patients who should have undergone surgery in accordance with the guidelines, 1 patient was lost to follow-up after ADH diagnosis. For the other patient, later clinical examinations and mammograms did not show any alteration.

When considering together the 33 patients followed after a confirmed surgery with a benign result and the 55 patients followed in the abstention group according to guidelines, the probabilities of a malignant event at 1, 2, and 3 years were 1.3% (95% CI: 0% to 3.7%), 2.8% (95% CI: 0% to 6.5%), and 6.1% (95% CI: 0% to 13.3%), respectively. In comparison with the French population incidence rate of breast cancer, the 3 malignant events observed in the follow-up of these patients corresponded to a SIR of 2.73 (95% CI: .56 to 7.98).

Follow-up compliance

At study endpoint, 106/124 patients (85.5%) had experienced at least 1 ME by mammogram and clinical examination (3 had refused, 8 had been lost after diagnosis or surgery, and 7 had been diagnosed too recently).

Among them, 65 (61%) patients had had their 1st ME within 12 months after ADH diagnosis on DVAB or surgery, 90 (85%) patients within 18 months, and 98 (92%) patients within 24 months. More details about the number of ME per women and the conformity level with the current recommendations are given in Table 2. Among the 49/106 women who had been diagnosed for >3 years, 25 had been examined by mammograms and clinical examination at least one time every year, corresponding to a conformity rate with the current recommendations of 51% (95% CI: 37% to 64%). Interestingly, the 2 malignant events that occurred at 2 and 3 years after diagnosis (abstention group) were detected during the 3rd ME, indicating that the malignant evolution was detected in its early stage. The mean delay between 2 MEs was then assessed on the subset of 82 patients who had had at least 2 MEs, by fitting a random effect model which could take into account the nonindependence of the repeated MEs within patient. The mean delay between 2 MEs was estimated at 11.7 months, with a standard deviation for the patient random effect equal to 2.24 months. Accordingly, 95% of patients had an ME in average every 7.4 months (the most frequently followed patients) to every 16.1 months (the least frequently followed patients). Finally, the management decision at ADH diagnosis (surgery or abstention) was included as a covariate in the model to test the difference in the delay between the successive MEs according to the management decision, but no statistical difference could be displayed ($P = .65$).

Comments

The overall rate of ADH found in DVAB performed for isolated microcalcifications in this study was 6.3%, which is similar to the literature, ranging from 2% to 15%.1,7,9,11,12,16,22,27,33,34 When ADH is diagnosed on

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**Table 2**  
Follow-up by medical examinations of our prospective series, according to the time elapsed from ADH diagnosis or surgery ($n = 106$)

<table>
<thead>
<tr>
<th>Number of medical examination(s) per women</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 examinations</td>
<td>41</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1 examination</td>
<td>58</td>
<td>53</td>
<td>28</td>
<td>23</td>
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<tr>
<td>2 examinations</td>
<td>6</td>
<td>33</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>3 examinations</td>
<td>1</td>
<td>11</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>4 examinations</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Conformity with the current recommendations

| Conformed surveillance                     | 65     | 40      | 25      | 6       |
| Not conformed surveillance                 | 41     | 47      | 24      | 8       |
| Unassessable conformity because of study endpoint | 0     | 19      | 57      | 92      |

| Conformity rate (%) (95% CI)               | 61 (52–70) | 46 (36–56) | 51 (37–64) | 43 (21–67) |

*Current recommendations consist in bilateral mammograms and clinical examinations within 12 months after DVAB and every year from then, independently of the patient management (surgery or abstention)15.

ADH = atypical ductal hyperplasia; CI = confidence interval; DVAB = directional vacuum-assisted biopsy.
CNB, the necessity of excision is still recommended because of the risk of upstaging (ie, DCIS or invasive carcinoma on definitive specimen). This risk varies from 11% to 68% after automated CNB in initial studies, on account of a poor interobserver reproducibility in the classification of radiological and histological lesions, the variety of techniques, and the patient selection bias. More recent studies report lower underestimation rates, from 0% to 38%, using larger needles and/or DVAB. A review by Jackman et al suggested a lower risk of upstaging for 11-gauge DVAB (19%) compared with 14-gauge DVAB (24%), probably resulting from more extensive tissue sampling and a greater likelihood of complete removal of microcalcifications. Eby et al and Lourenço et al did not find any significant difference either in the frequency of ADH or in the underestimation rate using 11- or 9-gauge DVAB. Jackman et al noted that obtaining more cores also decreases the risks of discordance of histologic findings at surgical biopsy and recommended to get >10 samples per lesion. Others did not find significant correlation between number of cores and underestimation rate, but they all confirm that a minimal number of tissue sampling is needed for an accurate diagnosis. For these reasons, this study was performed using 10-gauge DVAB with at least 10 cores per lesion (mean number of cores: 15.5, range: 10 to 29).

Over the past few years, several authors attempted to highlight predictive factors of underestimation such as pure micropapillary pattern of ADH, extent of ADH on CNB, large lesion size, incomplete removal of microcalcifications, or age ≥50 years. The goal was to identify a subset of “low-risk” patients who could safely be spared surgery, resulting in significant medico-economic savings. However, the risk of malignancy remained above the widely accepted 2% in any group and systematic surgical excision was recommended. In an external multicenter study, Bendifallah et al assessed a scoring system which is used to predict malignancy (Ko’s score) and concluded that it was not sufficiently accurate to safely define a subset of patients who would be eligible for follow-up. This nomogram includes at least 5 parameters: size of microcalcifications and extent of ADH within ducts with different cutoff values from what has been published before, and also complete removal of microcalcifications, palpability of the lesion, and age at diagnosis. Indeed, this nomogram deals with an heterogeneous population with both palpable and nonpalpable lesions, which makes it poorly reproducible and difficult to use in clinical practice.

Ely et al were the first to take into account the extent of ADH on CNB using the terminology of “ADH foci”: involvement of 1 large duct or 1 terminal duct–lobular unit by ADH represents a single focus, involvement of 1 duct and 1 terminal duct–lobular unit represents 2 foci, and so on. In 47 cases of 11- and 14-gauge CNB, the authors demonstrated that all patients with ≤2 foci of ADH did not have a worse lesion on excision, whereas 74% of patients with >2 foci upgraded to carcinoma. These results were corroborated by Sneige et al in a series of 42 DVABs (11- and 14-gauge) with an underestimation rate of 21.4% for patients with >2 ADH foci. Wagoner et al in a larger series of 123 CNB (mainly 11-gauge) found an overall upgrade rate of 7% and 39%, respectively, for cases with ≤2 ADH foci and >2 ADH foci. More recently, similar results were observed by Allison et al in a series of 97 DVABs (upgrading rate: 11% with ≤2 ADH foci, and 28% with >2 ADH foci). These 2 larger series compare well with our retrospective study in which the upgrade rate was 11% with ≤2 ADH foci and 33% with >2 ADH foci. Since the pathologists come from different institutions, these results suggest that the criteria used for measuring the extent of ADH by the number of foci in DVAB might be reproducible, and the method can be used by all pathologists provided they follow the same rules. The discrepancy with 0% upgrade rate (≤2 ADH foci) in the series of Ely et al and Sneige et al compared to the more recent series might be due to the use of both 11- and 14-gauge needles and to a smaller sample size. Indeed, in the 3 larger series even focal ADH can upgrade, with an underestimation rate higher than 2%, which suggests that this feature alone is not sufficient nor acceptable to avoid surgical excision.

The new entity described by Allison et al as “ADH suspicious for Ductal Carcinoma In Situ (DCIS)” might be an interesting parameter to assess, since the upgrade in this group is 48%, compared to 20.6% in all cases, with an odds ratio of 7.4 (P = .0003). Moreover, the upgrade rate increases from 8% to 33% in patients with ≤2 ADH foci when the ADH was also “suspicious for DCIS”, suggesting that this qualitative feature may be more discerning in predicting upgrade than a quantitative criterion alone. However, this qualitative criterion has been used in only 1 institution to date. We tried to use it in our previous work but found it to be subjective and poorly reproducible. Similarly, Adrales et al mentioned “marked atypia” as a predictor of malignancy at excision, but the histologic criteria for “marked atypia” were not precisely defined by the authors, making this feature difficult to use in other studies. Wagoner et al managed to identify a low-risk group of upstaging using 2 criteria (ADH confined to 1 or 2 foci and no residual calcifications after biopsy) that could predict a benign result on excision in all cases (0 malignant results out of 25 patients) with a specificity of 100%. However, a recent study by Kohr et al suggested conflicting results with an upgrade rate that still occurred in 12% of cases when there were 1 to 2 ADH foci and all calcifications had been removed. But neither of the 2 groups considered the lesion size criterion in their analysis. According to our previous work, we combined the quantitative criterion “number of foci” with other parameters considered in the literature as independent risk factors of upstaging, such as the size of the lesion and the incomplete removal of calcifications by DVAB. Testing these 3 parameters in a multivariate analysis led us to propose the guidelines previously described.

To our knowledge, this is the first study prospectively assessing the management of patients diagnosed with ADH.
on DVAB according to 3 main criteria obtained from our previous work: size of the lesion, extent of ADH within ducts, and complete/incomplete removal of microcalcifications. We followed our guidelines in 92% of the ADH diagnoses, which is satisfactory and suggests that it might be a reproducible and easily applicable method. Outcome and follow-up of patients from the prospective series seem to validate our actual guidelines, with a reliable and safe patient management. Indeed, patients who underwent adequate surgery had a high underestimation rate (28%), suggesting that surgical excision could not have been safely avoided. In contrast, the patients with a nonconformed surgery had a high underestimation rate (28%), which does not indicate underestimation of malignancy by DVAB. This result argues against the systematic excision of these patients. One patient among the benign surgery group also had a malignant event in the contralateral breast 1 year after surgery. In spite of the poor precision because of the limited number of malignant recurrences that could be prospectively observed, the SIR calculated for these patients suggested that both abstention and benign surgery groups might represent a subgroup with an increased risk of developing breast cancer in both breasts as suggested by Page2,4 and Tavassoli.3 However, since the 95% CI of the SIRs included 1, we cannot reject the hypothesis that this apparent over risk could simply result from small sample fluctuations. A more important series of patients and a longer follow-up are necessary to increase the precision of these risk estimates. Regarding the mammographic follow-up, it should be noted that the strict recommended follow-up (bilateral mammograms and clinical examinations within 12 months after DVAB and every year thereafter) was respected only in 51% of cases at 3 years after ADH diagnosis or surgery, and can probably be improved at our institution. Villa et al22 and others14,34 suggested that all patients who could possibly be managed conservatively had to undergo a strict mammographic follow-up every 3 or 6 months, then once a year, since they remain “high–risk” patients. However, the 2 malignant events that occurred in our series of 61 patients without surgical excision were only detected at the 3rd ME, 2 and 3 years after the initial diagnosis. Accordingly, mammographic examinations before 12 months might be useless in the absence of a clear clinical suspicion.

Our results corroborate that surgical excision is needed when the risk of malignancy is >2% because of possible upgrading. Conversely, when the risk of malignancy is <2%, excision is no longer beneficial because ADH, whatever its location, is in itself associated with a high risk of breast cancer which occurs anywhere in either breast. Indeed, in our series, further malignant events occurred in the contralateral breast 2 times out of 3 and >1 year after ADH diagnosis. Consequently, patients with ADH should undergo a specific follow-up on both breasts without joining general breast screening programs. A mammogram 1 year after ADH diagnosis and each year thereafter seems reasonable.

Conclusions

Combining determination of the extent of ADH, size of the lesion, and complete/partial removal of calcifications can successfully predict upgrading at excision. We confirm with this prospective study that our proposal for the management of ADH patients on DVAB is an applicable method to identify “low-risk patients” who can safely be spared surgical excision. However, an external review of our guidelines is necessary and further studies in other centers might increase their relevance. Nevertheless, our series indicates that all patients diagnosed with ADH on DVAB should undergo a specific follow-up, independently of their management (surgery or abstention), because the increased risk of developing breast cancer on both breasts does not decline over time.

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References


