Value of stereotactic breast core biopsy in patients with atypical ductal hyperplasia

C Tourasse (1), P Sebag (2), JF Dénier (3), N Rouyer (4) and C Donné (3)

Résumé
Valeur des macrobiopsies mammaires sous guidage stéréotaxique en cas de découverte d’une hyperplasie canalaire atypique
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Objectif : Les auteurs, dans une étude rétrospective bi-centrique, analysent le risque de sous-estimation des foyers de microcalcifications explorés par macrobiopsies. Les facteurs radiologiques et anatomopathologiques intervenant dans ce risque sont exposés.

Matériel et méthode : 1 400 lésions (ACR 2 à 5) ont été revues avec analyse de la taille, du pourcentage d’exérèse, du résultat histologique. Trois cent quatre-vingt-un patientes ont été opérées. Une relecture inter-sites d’une partie des lames histologiques a été conduite.

Résultat : Le taux de sous-estimation a été de 5,9 % pour les CCIS et 12,5 % pour les HCA. La majorité des sous-estimations apparaissait sur les foyers supérieurs à 20 mm où le taux d’exérèse chute de 98 % (foyers < 10 mm) à 9 %. La relecture des lames a montré une variabilité de l’interprétation du diagnostic d’HCA qui s’atténue avec l’expérience de l’opérateur. Il n’a jamais été observé de sous-estimation lorsque le nombre de foyers d’HCA était inférieur ou égal à trois. Pour les CCIS le risque de sous-estimation augmente si le nombre de biopsies contenant du CCIS est supérieur à 50 % et si le grade est élevé.

Conclusion : La découverte d’une HCA reste un diagnostic péjoratif justifiant une reprise chirurgicale, mais une bonne pratique des macrobiopsies avec exérèse du foyer couplée à l’analyse des prélèvements par un opérateur expérimenté permet de sélectionner des cas où le risque de sous-estimation est faible et doit faire discuter en concertation une surveillance.


Abstract
Purpose: Based on a dual center retrospective study, the risks of under-diagnosing clusters of microcalcifications on core biopsies are analyzed. Imaging and histopathological factors affecting this risk are explored.

Materials and Methods: A total of 1,400 lesions (ACR BI-RADS 2-5) were reviewed and analyzed for size, degree of excision (%), and histology result. A total of 381 patients underwent surgery. Inter-center review of some histological slides was also performed.

Results: The rate of under-diagnosis was 5.9% for ductal carcinoma in situ (DCIS) and 12.5% for atypical ductal hyperplasia (ADH). Most cases of under-diagnosis involved clusters larger than 20 mm in diameter where the percentage of excision decreased from 98% (clusters <10 mm) to 9%. Review of histological slides showed inter-observer variability that decreased in relation to experience. ADH was never under-diagnosed when 3 or less foci were present. The risk of under-diagnosis for DCIS increased when the number of biopsies containing DCIS was superior to 50% and if the grade was high.

Conclusion: The presence of ADH on biopsy specimens requires surgical biopsy, but optimal core biopsies with cluster removal and histological analysis by an experienced observer allows identification of low risk patients that could undergo close follow-up.

Key words: Vacuum assisted core biopsy. Stereotactic biopsy. Breast pathology. Atypical ductal hyperplasia.

Vacuum assisted core biopsy in the management of breast microcalcifications became available in 1998. This technique is now recognized as a reliable diagnostic tool and an alternative to surgical breast biopsy. During that same period, advances in histological diagnosis of breast lesions have been made, with refinements in characterization of benign and malignant lesions, and introduction of a sub-category of benign lesions defined as borderline lesions. These non-invasive proliferative lesions, either lobular or ductal in origin, are a risk factor for future development of invasive carcinoma or are a precursor to invasive carcinoma (1). The most frequently encountered lesion remains ADH, a precursor of DCIS. The detection of ADH on a core biopsy specimen raises the concern of under-diagnosing DCIS and has traditionally been managed surgically (2). Based on a retrospective review of 1,400 lesions biopsied using vacuum assisted core biopsy, we have evaluated this risk based on lesion size, percentage of lesion excision and histological features.

Materials and methods
In this dual center study, the charts of 1,310 patients seen over a 4-year period

Abbreviations
ADH : Atypical Ductal Hyperplasia
DCIS : Ductal Carcinoma In Situ
ACR : American College of Radiology

were reviewed. A total of 1,400 clusters of microcalcifications (800 for site 1 and 600 for site 2) classified using the ACR BIRADS classification (3) were reviewed. All clusters underwent vacuum assisted core biopsy using the Mammo- tome system (Breast Care, 1, rue Camille Desmoulins TSA 81002 92787, Issy-les-Moulineaux, France) with dedicated table and direct approach for site 1 (Giotto table, IMS Via Sagittario 5, 40037 Pontecchio Marconi Bologne Italy) or a lateral approach for site 2 (Fischer table, Fischer Imaging France 23, square Edouard VII, 75009 Paris). Biopsies were performed using 11G needles for all but 53 patients where an 8G needle was used in order to better match needle size with the radiographic size of the target cluster; the latter clusters were larger than 20 mm and a direct approach was used for biopsy.

The following items were recorded from each chart: initial cluster size, evaluation of calcifications on the sample radiograph, and percentage of cluster excision. The degree of cluster excision was recorded for each cluster: complete excision (100%), near-complete excision (90-99%) or incomplete excision (<90%) with the understanding that an incomplete excision was not indicative of technical failure but merely indicative of the decision by the radiologist to terminate the procedure after removal of a sufficient and representative portion of the cluster.

A total of 381 patients (27%) underwent surgery, and surgical results were available in 309 patients. Histological findings on the surgical specimens were compared to results from the vacuum assisted core biopsy. Not all patients with ADH on vacuum assisted core biopsy underwent surgery. The decision was reached by a multidisciplinary committee on a case-by-case analysis after review of the patient’s age, personal and family risk factors, cluster size and percentage of excision by vacuum assisted core biopsy, and feasibility of patient of follow-up. Patients with borderline lesions who did not have surgery underwent close mammographic follow-up (6 months, 1 year, then yearly). Because differences were noted between both centers in the rate of under-diagnosis of ADH cases, a sample of 37 slides from both sites were reviewed by two pathologists, one from each site.

**Results**

The ACR BIRADS classification for all 1,400 clusters of microcalcifications was as follows: 12 category 2 (0.8%), 321 category 3 (23%), 1,001 category 4 (71.5%) and 66 category 5 (4.7%). Results from vacuum assisted core biopsy showed benign lesions in 904 cases (64.6%), malignant lesions in 373 cases (26.6%) and borderline lesions (ADH, grade I and II LCIS) in 123 cases (8.8%). A total of 276 cases of ductal carcinomas in situ (DCIS), 70 cases of invasive ductal carcinomas (IDC), and 105 cases of ADH were diagnosed. Surgical results were available for 237 cases of DCIS and an associated invasive ductal carcinoma component was present in 14 cases (5.9% rate of under-diagnosis). Seventy-two of 105 patients with ADH underwent surgery, and a DCIS component was present in 9 cases (12.5% rate of under-diagnosis).

The size of the clusters of microcalcifications was distributed as follows: 49.8% ≤10 mm, 20.6% between 10-15 mm, 15% between 15-20 mm and 16.6% >20 mm. These results are summarized in table 1.

Complete or near complete excision of the cluster was achieved for 98% of clusters ≤10 mm, 80% of clusters between 10-15 mm, 60% of clusters between 15-20 mm and 9% of clusters >20 mm.

Under-diagnosis of an invasive component on DCIS was more frequent when higher grade DCIS was present on most biopsy cores (table II).

For the 23 cases of under-diagnosed DCIS on ADH and invasive ductal carcinoma on DCIS, 16 involved clusters >20 mm in size. In one of the centers (site 1), the use of an 8G needle became standard for the last 53 clusters >20 mm in size. This resulted in a reduction of the rate of under-diagnosis from 10.2% to 5.6%.

Itemized comparison of data from both sites reveals that both series of cases were similar with regards to the distribution of BIRADS categories, ratio of benign/malignant lesion, and percentage of DCIS while the number of ADH was discordant with virtually a two-fold difference between the sites (table III). To determine if this discordant result could be the result of a variability in the interpretation of the histological diagnosis of ADH, a review of slides from both sites was undertaken using the following protocol: a total of 57 borderline lesions were selected (13 from site 1 and 24 from site 2), ranging from simple non-atypical ductal hyperplasia to low-grade DCIS, including recent and older charts. Both pathologists, one from each site, were blinded to the diagnosis. Each pathologist reviewed his own slides once and those of his colleague.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Results.</th>
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<tbody>
<tr>
<td>Cluster size</td>
<td>&lt;1 cm</td>
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<tr>
<td>Core biopsy Nbr of lesions</td>
<td>697</td>
</tr>
<tr>
<td>Core biopsy ADH</td>
<td>51</td>
</tr>
<tr>
<td>Core biopsy DCIS</td>
<td>94</td>
</tr>
<tr>
<td>Surgery Under-diagnosis 72/105</td>
<td>3</td>
</tr>
<tr>
<td>Surgery Under-diagnosis DCIS/IDC 237/276</td>
<td>1</td>
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<tr>
<th>Table II</th>
<th>Under-diagnosis of invasive ductal carcinoma in DCIS based on grade and percentage of biopsy containing DCIS.</th>
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<tbody>
<tr>
<td>Histological grade of DCIS</td>
<td>1</td>
</tr>
<tr>
<td>Nbr of patients with &gt;50% of cores harboring DCIS</td>
<td>4</td>
</tr>
<tr>
<td>Nbr of patients with &lt;50% of cores harboring DCIS</td>
<td>8</td>
</tr>
<tr>
<td>Nbr of under-diagnosed cases when the nbr of cores with DCIS is &gt;50%</td>
<td>0</td>
</tr>
<tr>
<td>Nbr of under-diagnosed cases when the nbr of cores with DCIS is &lt;50%</td>
<td>0</td>
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Table III  
Distribution of DCIS and ADH for both sites.

<table>
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<tr>
<th></th>
<th>% DCIS</th>
<th>% ADH</th>
<th>ADH Operated patients</th>
<th>ADH Under-diagnosis</th>
</tr>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; site</td>
<td>21.1</td>
<td>9</td>
<td>81.6</td>
<td>8.6</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; site</td>
<td>17.2</td>
<td>4.8</td>
<td>63.6</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Discussion

A total of 72% of cases were classified as BIRADS category 4, with evidence of malignancy in 26.6% of cases. These results are consistent with reports from the literature (4, 5).

Most malignant lesions corresponded to DCIS, since all lesions corresponded to clusters of microcalcifications. Most biopsied lesions were <10 mm in size (57.3%) with complete or near complete excision of the cluster in 98% of these cases. The percentage of cluster excision decreased with enlarging lesion size, with significant reduction for lesions larger than 20 mm (9%).

The rate of under-diagnosed DCIS in patients with ADH was 12.5% (9/72), a number consistent with reports from the literature (6-9). The absence of detected cancer at follow-up of these patients suggests that our rate of under-diagnosed DCIS in patients with ADH on vacuum assisted core biopsy would probably be lower if these patients had undergone surgery as well.

The concept of under-diagnosis refers to a biopsy result showing a less advanced component of the target lesion. To explain and anticipate this phenomenon, we have reviewed the charts to identify factors that could come into play. Cluster size and percentage of lesion excision at vacuum assisted core biopsy appeared to be important factors. We have observed that the volume of the biopsy sample was important for the accuracy of the histological diagnosis. This is consistent with results published by Darling (10) in 2000 when comparing diagnostic accuracy between 14G and 11G needles. The percentage of lesion excision at vacuum assisted core biopsy is an important factor in the risk of under-diagnosis (11-13). Smaller clusters are amenable to more complete excision with reduced risk of under-diagnosis (clinical case nº 1, fig. 1). On the other hand, the percentage of lesion excision for clusters larger than 20 mm in size is much lower, consistent with reports from the literature (14), with corresponding increase in the risk of under-diagnosis. Our results indicate that the increased excision volume provided by the use of the larger 8G core needle for larger clusters could be valuable to reduce this risk of under-diagnosis (15).

However, we have encountered 2 cases of under-diagnosis for lesions <20 mm in size and complete cluster excision. Additional factors must thus be involved, especially histological criteria. We noticed that the series from both sites were similar with regards to the percentage of cancers, DCIS, and invasive ductal carcinomas, while the percentage of ADH for site 1 was twice that of site 2. This underscores the difficulties and subjective nature of the histological diagnosis of ADH versus simple non-atypical ductal hyperplasia. The subjective nature of this diagnosis is well documented in the literature with marked inter-observer variability for the reproducibility of a diagnosis of ADH (16-18). Our results show an inter-observer variability of 43%, intra-observer variability of 8% at a fixed time and 15.5% over time, demonstrating the difficulty in establishing a histological diagnosis of ADH. The absolute value for inter-observer variability is high but it is, in reality, low because it only relates for each case to 1 or 2 foci identified by a single pathologist with no significant change in clinical patient management. No discordant result between simple non-atypical ductal hyperplasia and DCIS was noted.

Table IV  
Histological results and discordant pathological interpretations of 37 reviewed charts (13 from site 1 and 24 from site 2).

<table>
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<tr>
<th>Observer 1&lt;sup&gt;st&lt;/sup&gt; site</th>
<th>Observer 2&lt;sup&gt;nd&lt;/sup&gt; site</th>
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<tbody>
<tr>
<td>Discordant results at review of own slides</td>
<td>2/13 discordant results: 2 ADH/DCIS</td>
</tr>
<tr>
<td>Discordant results at review of colleague’s slides</td>
<td>11/24 discordant results: 4 ADH/non-ADH, 6 non-ADH/ADH, 1 DCIS/ADH</td>
</tr>
<tr>
<td>Discordant results between 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; review (45 days) of colleague’s slides</td>
<td>3/24 discordant results: 2 non-ADH/ADH, 1 ADH/DCIS</td>
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Fig. 1: Clinical Case n° 1: BIRADS category 4 cluster of microcalcifications, 5 mm in size, completely excised by vacuum assisted core biopsy. Three cores with ADH on the specimen. Surgical tumorectomy. Adenosis with simple ductal hyperplasia on the surgical specimen.

a initial cluster
b excised cluster and clip placement
c specimen radiograph
d focus of atypical cylindrical metaplasia on a core
e surgical specimen
f adenosis next to the post-biopsy granuloma (*), on the tumorectomy specimen.
Fig. 2: Clinical Case n° 2: Multiple small clusters of microcalcifications (BIRADS 4) scattered over a 30 mm region. Excision of a few clusters at vacuum assisted core biopsy; residual clusters on the post biopsy follow-up. Six cores with ADH on the specimen; DCIS on the surgical specimen.

a initial cluster
b specimen radiograph
c post-biopsy follow-up
d focus of ADH on the biopsy specimen
e surgical specimen
f regions of low grade DCIS (→) next to the post-biopsy granuloma (*), on the tumorectomy specimen.
Analysis of histological diagnoses over time for both pathologists showed that interpretations tended to become more homogeneous. This indicates that diagnostic accuracy improves over time with increasing expertise and experience gained from correlation between histological results on vacuum assisted core biopsies and surgical specimens.

When this diagnosis is made, the pathologist must try to estimate its extent because, for cases of ADH/DCIS under-diagnosis, biopsy specimens contained at least 4 foci of ADH (clinical case n° 2, fig. 2). This number is a factor that should be considered since it does not directly correlate to cluster size. It is an independent factor in the risk of under-diagnosing DCIS. This parameter is described by additional authors including Ely and Sneige (17, 18) who consider that the presence of 4 or more foci of ADH is a strong predictive factor of finding a higher-grade lesion on the surgical specimen.

As such, it appears that the risk of under-diagnosis is low if the cluster of microcalcifications is less than 20 mm in size, completely removed at vacuum assisted core biopsy and 3 or less foci of ADH are present. On the other hand, the risk appears high if the cluster is larger than 20 mm in size, and incompletely excised and/or with 4 or more foci of ADH.

With regards to DCIS, the rate of under-diagnosed invasive ductal carcinoma was 5.9% (14/237), which is consistent with numbers published in the literature (12). In one case, the cluster of microcalcifications was less than 10 mm in size, and clusters of invasive lobular carcinoma were present on the surgical specimen, in addition to the DCIS, away from the site of vacuum assisted core biopsy. The patient underwent secondary mastectomy. In reality, this is more a case of incidental associated pathology than a case of under-diagnosed invasive carcinoma. Similar to ADH, most cases of under-diagnosis involved clusters larger than 20 mm in size (70%). This is mainly explained by the following two reasons:

- the discordance between the radiographic and histological size of a lesion increases with radiographic size (8), as supported by the number of mastectomies performed in these patients;
- the percentage of lesion excision that significantly decreases for lesions larger than 20 mm in size.

We have selected 86 cases of DCIS, including 5 cases with under-diagnosis, from our series to study several histological parameters: histological grade and percentage of biopsy cores harboring DCIS (table III). We found that if 50% of cores harbor foci of high-grade DCIS, the risk of under-diagnosing invasive carcinoma is high. On the other hand, the risk is low with low-grade DCIS in less than 50% of cores.

Based on these results, the incidence of under-diagnosis has lead us to obtain multi-targeted cores or use 8G needles in larger clusters. These techniques have shown promising results.

**Conclusion**

This retrospective study confirms that vacuum assisted core biopsy can excise a large volume of breast tissue and that this volume should be adapted to lesion size. Complete excision of the cluster of microcalcifications is an important factor in reducing the risk of under-diagnosis. Also, the use of an 8G needle for clusters larger than 20 mm in size seems to reduce the risk of under-diagnosis by increasing the volume of excised tissue.

The histological diagnosis of ADH remains difficult to make, as demonstrated by the inter-observer variability, and expertise is required to reduce this variability.

The presence of 4 or more foci of ADH is a strong predictive factor of under-diagnosis.

In summary, our results show that the presence of ADH on vacuum assisted core biopsy is a factor of increased risk usually requiring surgical biopsy, but that optimized vacuum assisted core biopsy technique coupled with expert histological interpretation allows selection of a subset of patients with statistically low risk of under-diagnosis where follow-up may be an acceptable alternative.

**References**


