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Title:

HISTOLOGY AFTER LUMPECTOMY IN WOMEN WITH EPITHELIAL ATYPIA ON STEREOTACTIC VACUUM ASSISTED BREAST BIOPSY.

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ABSTRACT

Background: Large-core needle biopsy of the breast (LCNB) and vacuum-assisted breast biopsy (VABB) are widely used as alternatives to open surgical biopsy (OSB) for initial diagnosis of mammographic abnormalities. Between 18% and 80% of cases in which such specimens show atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH) are found to be malignant at surgery.

Design: From 1999 to 2005, 68 women with mammographic abnormalities were sampled by stereotactic VABB and presented atypical epithelial hyperplasia. Immunohistochemical staining with anti-cytokeratin 5/6 and anti-E-cadherin antibodies was performed. All women underwent a lumpectomy. Clinical, radiological or histological factors predictive of the risk of finding malignancy at surgery were sought.

Results: VABB initially showed 28 cases of ADH, 32 cases of ALH, one case of flat epithelial atypia, five cases of mixed atypia, and two cases of Lobular Carcinoma In Situ (LCIS). After slide review with immunohistochemical staining, two cases of ADH were reclassified as simple hyperplasia and two cases of ALH were reclassified as mixed atypia. Seven lesions (10.3%) that appeared to be benign on VABB were found to be malignant on OSB (Ductal Carcinoma In Situ (DCIS) in six cases and invasive ductal carcinoma in one case). ADH was the only predictive factor of malignancy on OSB ($p=0.04$ versus ALH).

Conclusion: ADH diagnosed by vacuum-assisted breast biopsy frequently corresponds to cancer on open surgical biopsy. Surgical excision of all breast lesions containing atypical hyperplasia on percutaneous biopsy can be recommended.

Key words: vacuum assisted breast biopsy; atypical epithelial hyperplasia; atypical ductal hyperplasia; atypical lobular hyperplasia; breast cancer; immunohistochemistry

INTRODUCTION

Small, asymptomatic breast tumours are increasingly detected through widespread use of screening. This has led to a corresponding increase in the frequency of percutaneous biopsy and the detection of atypical epithelial hyperplasia (AEH) raising the issue on its management.

Despite the use of vacuum-assisted breast biopsy (VABB), which is now preferred to large-core needle biopsy (LCNB) for subclinical lesions and especially for microcalcifications, there is still a high risk that lesions containing AEH will turn out to be malignant on surgical excision [1-4]. Indeed, there is no clear consensus on reliable clinical, radiological and histological criteria for predicting malignancy when percutaneous biopsy reveals AEH [5-6].

Therefore, in this descriptive study, we sought clinical, radiological or histological factors predictive of the risk of cancer in an homogeneous and continuous series of women who underwent surgical excision for atypical epithelial hyperplasia on vacuum-assisted percutaneous breast biopsy.

PATIENTS AND METHODS.

This study involved 68 patients diagnosed with atypical epithelial hyperplasia of the breast on vacuum-assisted biopsy (Mammotome®) in the Department of Anatomo-Pathology of Tenon Hospital, Paris, France, between July 1999 and June 2005. All patients underwent stereotactic biopsy in one of two units of radiology (Tenon Hospital Unit of Radiology or Duroc Radiology Center) and all patients underwent surgical excision within weeks after Mammotome biopsy (MMT). AEH comprised atypical ductal hyperplasia, atypic lobular hyperplasia, mixed hyperplasia (ductal and lobular), flat epithelial atypia, and lobular carcinoma in situ.

We excluded patients who had synchronous malignant lesions in the same breast and patients who had sonographically assisted Mammotome biopsy.

Radiological procedure.

One patient had radiological opacity, while the remainder had microcalcifications. The BI-RADS classification of the American College of Radiology (ACR) was used to classify the radiological findings. MMT biopsies were done with a vacuum device equipped with an 8-, 10- or 11-gauge needle under stereotactic control on a dedicated table. Each patient had one to four 360° probe rotations at each procedure (mean 2.2), and an average of 14.3 biopsy fragments were recovered. The fragments were routinely X-rayed to detect microcalcifications, and a metallic clip was inserted in the breast when the abnormality was completely removed.

The patients' sociodemographic, clinical and radiological characteristics are shown in table 1.

The following clinical and radiological parameters were analyzed as possible predictors of malignancy on open surgical biopsy: age, family history of breast cancer (first- or second-degree relative), personal history of benign or malignant breast disease, menopausal status, hormone

replacement therapy, radiological lesion type, radiological lesion size, ACR classification, number of probe rotations, number of fragments collected, partial/total excision of the radiological abnormality, radiological microcalcification on the Mammotome specimen(s), and residual calcifications on post-biopsy mammography.

Histology

The histological technique was fully standardized and the results recorded. The Mammotome fragments were included in paraffin, separately for each procedure and all together, with three levels of analysis for each block. New slices were prepared when calcifications that were visible on radiological studies of the biopsy specimens were not confirmed by histology. Histological examination of the surgical specimens was also fully standardized, with inclusion of the whole specimen. All Mammotome slides were blindly reviewed by a single pathologist, and were also subjected to immunohistochemical staining for cytokeratin 5/6 and E-cadherin.

The histological criteria of Page and Rogers and those of Tavassoli were used to diagnose atypical epithelial hyperplasia [7,8] while Schnitt's criteria were used for flat epithelial atypia [9].

The following histological aspects were analyzed: calcifications, size of the abnormality based on HES staining of all slides with atypical lesions (foci of hyperplasia defined by Ely et al.) [10]. A "focus" is defined as the terminal ductulo-lobular unit, and the reported number of foci corresponds to foci bearing hyperplasia.

Immunohistochemistry (IHC).

Tissues were immediately fixed in formalin (10%) and then processed as paraffin blocks. Four-micron-thick sections of formalin-fixed paraffin embedded tissues were deparaffinized in xylene and rehydrated through a graded series of ethanol solutions. Sections were immunostained using the Ventana Nexes automated immunohistochemistry system (Ventana

Medical Systems, Tucson, Arizona). Antigen retrieval was performed by heating tissue sections in 0.01 M citrate buffer pH 6 in a pressure cooker for 20 minutes. Tissue sections were then incubated for 60 minutes with an anti-cytokeratin 5/6 antibody (DakoCytomation®, Trappes France, clone D5/16B4, dilution 1:50) or an anti-E-cadherin antibody (Zymed® CliniSciences®, Montrouge, France, clone 4A2C7, dilution 1:100). Positive controls consisted of myoepithelial cells in normal ducts and lobules for CK 5/6, and normal ductal cells for E-cadherin.

Surgical procedure.

All patients underwent surgical excision (lumpectomy) that was performed after radiological location of the lesions in 98.5% of cases.

The following parameters were recorded: time between MMT and surgical excision; preoperative wire localization or another radiological technique; radiographic detection of calcifications or a clip in the surgical specimen; histology of the surgical specimen; and presence of the biopsy scar on histological examination.

Statistical analysis

We used the Chi-square test for categorical variables and the Kruskal-Wallis or Mann-Whitney test for continuous variables. P values below 0.05 were considered significant.

RESULTS

Mammotome biopsy showed atypical epithelial hyperplasia in 8.1% of patients during the study period.

The biopsy specimens corresponded to ACR grade 3, 4 and 5 in 20.6%, 77.9% and 1.5% of cases, respectively. All women with ACR grade 3 lesions had a personal history of AEH or breast cancer, or family history of breast cancer. The mean size of the radiological abnormality was 9.5 mm (range 2 – 60 mm). The radiological abnormality was fully removed by Mammotome biopsy in 26 cases (39%).

The histological results of MMT and after IHC are shown in table 2. In eight cases IHC was not possible, because the entire MMT specimen had been used for initial histology (complementary search for calcifications). Two patients with an initial diagnosis of ductal atypical epithelial hyperplasia were reclassified after IHC as having simple hyperplasia. Two patients with ALH had mixed hyperplasia. Therefore, IHC contributed to reclassify 4 of 60 (6.6%) AEH on HES. The histological results for the surgical specimens were as followed: 19 patients (28%) had a benign disease, 21 (30.8%) ALH, 10 (14.6%) ADH, 6 (8.8%) mixed hyperplasia (ADH and ALH), 2 (3%) lobular carcinoma in situ (LCIS), 3 (4.5%) flat epithelial atypia (FEA), 6 (8.8%) ductal carcinoma in situ (DCIS) and 1 patient (1.5%) had invasive ductal carcinoma.

MMT was considered to have given false-negative results when it showed ductal or lobular atypical hyperplasia whereas open surgical biopsy showed ductal carcinoma in situ (DCIS) or invasive ductal or lobular carcinoma. The overall false-negative rate was 10.3% (7/68 patients) (table 3).

Among the eight variables tested for their capacity to predict false-negative Mammotome results (see above), with IHC, only the histological subtype on MMT was significant: atypical ductal hyperplasia on MMT was significantly associated with the risk of discovering malignancy on open surgical biopsy ($p = 0.04$).

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DISCUSSION

The present study has demonstrated that the sole predictive factor of malignant lesions in women with AEH on core biopsy was the presence of ADH. Moreover, immunohistochemistry seems to be a useful tool to increase the accuracy of histology, taking into account the poor interobserver variability in the diagnosis of atypical epithelial hyperplasia. The diagnostic agreement for these lesions based on morphological analysis is improved by the addition of immunohistochemical markers.

Despite the significant rate of false-negative results of percutaneous biopsy in published series, the need for surgical excision of all atypical epithelial hyperplasia is controversial [11-13]. In our experience, 7 of the 66 (10.6%) women with AEH on core biopsy had DCIS or invasive lesion on lumpectomy.

Several risk factors to predict malignant lesions at surgical excision

Several parameters with different weight being given to risk factors such as the personal or family history, the size of the radiological abnormality, the histological size of the lesion, and complete or incomplete extinction of the radiological signal after biopsy have been advocated to predict malignant lesions. We identified only one factor predictive of the risk of false-negative biopsy, namely the ductal histological subtype of atypical epithelial hyperplasia. In contrast, age, a personal or family history of breast disease, the size of the radiological lesion, the ACR classification and the size of the histological lesion (number of foci involved) were not predictive of the risk of under-diagnosis. These findings are in keeping with the natural history of breast cancer. The relations between precancerous lesions and in situ or invasive carcinoma of the breast are still not fully understood, despite advances in epidemiology, genetics and molecular biology [14]. Now, ALH and LCIS are grouped together under the term “lobular neoplasia” and

pleomorphic form with comedo-type necrosis seems to be of particular aggressive significance [15]. This specific subtype is thought to be a precancerous lesion and no longer a mere risk indicator.

Ely et al. found that the risk of misdiagnosis depended not on the size of the radiological abnormality but rather on the size of the histological abnormality [10]. The diagnosis was always correct when there were no more than two foci of atypical ductal hyperplasia, while the false-negative rate was 87% when four or more foci were present. In our series, the number of foci did not differ significantly between patients who had correct and incorrect biopsy-based diagnoses. Some authors consider that necrosis, nuclear polymorphism and cellular markers of apoptosis are evocative of cancer [16]. Others have reported an increased risk of false-negative biopsy when a micro papillary aspect is found [10]. There are currently no validated cytological or biological criteria for determining whether or not AEH of the breast corresponds to malignancy and for predicting biological behaviour of these lesions.

Importance of the accuracy of the percutaneous radiological sampling

Some authors report finding no signs of malignancy at surgery when microcalcifications are totally removed by biopsy [17]. Moreover, optimal diagnostic performance with the Mammotome technique seems to require more than 12 fragments, although obtaining a large number of fragments does not eliminate the risk of misdiagnosis [18]. Jackman et al. reported a false-negative rate of more than 11% in patients with a personal history of a benign or malignant breast tumour, fewer than 11 biopsy fragments, an abnormality measuring more than 10 mm, or incomplete excision of the abnormality [19]. Adrales et al. obtained a sensitivity of 100% and a specificity of 76% for malignancy by combining the history personal, the family history, and the degree of hyperplasia [12]. Liberman et al. found a false-negative rate of less than 2% when more than 95% of the microcalcification was removed by means of 11-G vacuum-assisted biopsy with

more than 14 fragments [20]. These criteria were not predictive of the correct diagnosis in our series. Moreover, among the 26 patients with AEH who had complete excision of the radiological abnormality at biopsy, three patients (11.5%) were found to have cancer at surgery. Mammotome-based diagnosis of atypical epithelial hyperplasia of the breast in fact corresponds to carcinoma in situ or invasive cancer at surgery in 10% to 75% of cases, depending on the percutaneous biopsy technique (large-needle or vacuum-assisted) and the number of samples [3]. Vacuum-assisted biopsy is more reliable than large-core needle biopsy in this setting, as it yields a larger volume of breast tissue. Indeed, the false-negative rate is between 33% and 87% with large-core needle biopsy and between 7% and 35% with vacuum-assisted biopsy (Mammotome) [21].

Atypical ductal hyperplasia tends to develop at the periphery of DCIS, and it is therefore important to obtain a representative biopsy sample. In addition, extinction of the radiological signal after percutaneous biopsy, which occurs in 58% to 93% of cases when the radiological abnormality measures less than 5 mm, corresponds to complete excision on histological examination in only 6% to 18% of cases [22]. After percutaneous biopsy, it is important to ensure that the clinical, radiological and histological findings are coherent. Conflicts should be resolved by a second biopsy or by surgical excision. When AEH is found on an initial percutaneous biopsy, repeat biopsy is done in 15% to 56% of cases, depending on the series [23], while the cancer detection rate is higher than on the initial sample.

Considerations about Immunohistochemistry and lobular neoplasia (LIN)

We studied a homogenous population of 68 women. Their management was identical, and slides were analysed with immunohistochemical studies of cytokeratin 5-6 and E-cadherin expression. IHC can confirm the ductal or lobular nature of epithelial hyperplasia and distinguish between simple and atypical forms. This is useful for diagnosing atypical epithelial hyperplasia, especially given the high interobserver variability [24].

Lobular neoplasia, which is revealed by microcalcification in at least one-third of cases, is less frequent than ADH in biopsy and surgical series [15-25]. The behaviour of lobular neoplasia (LN) is less well documented than that of ADH. The risk of invasive cancer of the breast is about 10 to 20% between 15 and 20 years following the diagnosis of LN [26]. In our experience, no malignant lesion was found on lumpectomy when ALH was diagnosed by HES and IHC. Recent data achieved from the Nurse's Health Study suggest that the risk of developing a breast cancer is greater among premenopausal women with ALH (OR, 7.3) than among premenopausal women with ADH (OR, 2.72) whereas the risk seems to be similar for menopausal women with ALH or ADH [27].

Most studies of ALH diagnosed by biopsy have been small and retrospective, introducing the risk of a selection bias. In Liberman et al. series, patients who had a more severe lesion on the surgical specimen than on initial biopsy had another lesion associated with ALH, namely a radial scar or ADH [28]. Other authors have found that it is the association with a breast nodule or mass that is the most important predictor of misdiagnosis [29]. Overall, the risk of misdiagnosis seems to be higher for microcalcification than for opacities or masses [3,30]. We found that patients with a biopsy diagnosis of ALH and who had cancer at surgery in fact had mixed lesions combining ALH and ADH when using IHC. The coexistence of lobular and ductal atypical hyperplasia has also been linked to the risk of finding cancer at surgery by other authors and this risk seems to be greater when both lobules and ducts are involved compared to ADH or ALH.

Limitations of the study.

Several limitations of the present study have to be underlined. Firstly, the sample size that could explain the absence of predictive factor. However, AEH has a relative low incidence. Secondly, about 10% of percutaneous biopsies gave false-negative results in this series contrasting with previous reports with higher false-negative rate. This relatively low rate could be due to

several factors, including the use of stereotactic biopsy, a large number of biopsy fragments per patient (14.3 on average), a total excision of the radiological abnormality in nearly 40% of cases.

No systematic breast MRI was performed to detect small invasive lesion but its indication in this specific setting remains controversial. The place of MRI, as an alternative to surgical excision, is currently being assessed, especially for women with a positive family history and *BRCA1* or 2 mutations. Finally, indication of a chemoprevention for these patients is unclear even if the NSABP-17 trial showed a 56% reduction in the risk of breast cancer when these selected women received tamoxifen prophylaxis.

CONCLUSION

Percutaneous biopsy-based diagnosis of atypical epithelial hyperplasia of the breast poses a dilemma, between the need to avoid unnecessary surgical excision, and the need for specific treatment of in situ or invasive cancer.

Our homogenous series of women with AEH on VABB who all underwent lumpectomy, in which biopsy-based diagnosis was optimized by immunohistochemistry, identified only the ductal subtype as a risk factor for false-negative diagnosis of malignancy at surgery. Underestimation of these lesions investigated by MMT was higher than the threshold rate of 2% accepted by American Radiologist for performing surgical excision. Patients with ADH, whether isolated or associated with ALH, seem to represent a subgroup at high risk. Larger studies are required to characterize the biological behaviour and the natural history of atypical hyperplasia and better define patient management.

“Conflict of interest statement – We declare that we have no conflict of interest”.

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REFERENCES.

1. Jackman R.J., Nowels K.W., Rodriguez-Soto J. et al. (1999) Stereotactic, automated, large-core needle biopsy of nonpalpable breast lesions : false-negative and histologic underestimation rates after long-term follow-up. **Radiology** 210:799-805.
2. Dahlstrom JE, Sutton S, Jain S. (1996) Histological precision of stereotactic core biopsy in diagnosis of malignant and premalignant breast lesions. **Histopathology** 28: 537-41.
3. Darling ML, Smith DN, Lester SC et al. (2000) Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large core needle breast biopsy: results of surgical excision. **Am J Roentgenol** 175: 1341-6.
4. Moore MM, Hargett CW, Hanks JB et al. (1997) Association of breast cancer with the finding of atypical ductal hyperplasia at core breast biopsy. **Ann Surg** 225: 726-31.
5. Tavassoli FA. (2001) Ductal intraepithelial neoplasia of the breast. **Virchows Arch** 438: 221-7.
6. Van de Vijver M, Peterse H. (2003) The diagnosis and management of preinvasive breast disease. Pathological diagnosis – problems with existing classifications. **Breast Cancer Res** 5: 269-15.
7. Page DL, Rogers LW. (1992) Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. **Hum Pathol** 23: 1095-7.
8. Tavassoli FA, Norris HJ. (1990) A comparison of the results of long-term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. **Cancer** 65: 518-29.
9. Schnitt SJ, Vincent-Salomon A. (2003) Columnar cell lesions of the breast. **Adv Anat Pathol** 10: 113-24.
10. Ely K.A., Carter B.A., Jensen R.A. et al. (2001) Core biopsy of the breast with atypical ductal hyperplasia. **Am J Surg Pathol** 25: 1017-1021.
11. Bedei L., Falcini F., Sanna P.A. et al. (2006) Atypical ductal hyperplasia of the breast : the controversial management of a borderline lesion : experience of 47 cases diagnosed at vacuum-assisted biopsy. **Breast** 15: 196-202
12. Adrales G., Turk P., Wallace T. et al. (2000) Is surgical excision necessary for atypical ductal hyperplasia of the breast diagnosed by mammotome ? **Am J Surg Pathol** 180: 313-315.
13. Hartmann L., Sellers T., Frost M. et al. (2005) Benign breast disease and the risk of breast cancer. **N Engl J Med** 353: 229-237.
14. Arpino G, Laucirica R, Elledge RM. (2005) Premalignant and in situ breast disease: biology and clinical implications. **Annals Int Med** 143: 446-57.
15. Tavassoli FA, Boeckler W, Lakhani SR. (2003) Lobular neoplasia. World Health Organization classification of tumours. Pathology and genetics of the breast and female

genital organs. **IARC Press**, Lyon.

16. Ioffe OB, Berg WA, Silverberg SG et al. (1998) Mammographic-histopathologic correlation of large-core needle biopsies of the breast. **Mod Pathol** 11: 721-7.

17. Liberman L., Kaplan J., Morris E. et al. (2002) To excise or to sample the mammographic target: what is the goal of stereotactic 11-gauge vacuum-assisted breast biopsy ? **Am J Roentgenol** 179: 679-683.

18. Lomoshitz FM, Helbich TH, Rudas M et al. (2004) Stereotactic 11-gauge vacuum-assisted breast biopsy: influence of number of specimens on diagnostic accuracy. **Radiology** 232: 897-903.

19. Jackman R. J., Birdwell R.L., Ikeda D.M. (2002) Atypical ductal hyperplasia : can some lesions be defined as probably benign after stereotactic 11-gauge vacuum-assisted biopsy, eliminating the recommendation for surgical excision ? **Radiology** 224: 799-805.

20. Liberman L, Smolkin JH, Dershaw DD et al. (1998) Calcification retrieval at 11-gauge, stereotactic, directional, vacuum-assisted breast biopsy. **Radiology** 208: 251-60.

21. Cangiarella J, Waisman J, Symmans WF et al. (2001) Mammotome core biopsy for mammary microcalcification. Analysis of 160 biopsies from 142 women with surgical and radiological follow-up. **Cancer** 91: 173-7.

22. Kettritz U., Rotter K., Schreer I. et al. (2004) Stereotatic vacuum-assisted breast biopsy in 2874 patients. **Cancer** 100: 245-251.

23. Philpotts LE, Shaheen NA, Carter D et al. (1999) Comparison of rebiopsy rates after stereotactic core needle biopsy of the breast with 11-gauge vacuum suction probe versus 14-gauge needle and automatic gun. **Am J Roentgenol** 172: 683-7.

24. Lacroix-Triki M, Mery E, Voigt JJ et al. (2003) Value of cytokeratin 5/6 immunostaining using D5/16 B4 antibody in the spectrum of proliferative intraepithelial lesions of the breast. A comparative study with 34betaE12 antibody. **Virchows Arch** 442: 548-54.

25. Burak W.E., Owens K., Tighe M. et al. (2000) Vacuum-assisted stereotatic breast biopsy. **Arch Surg** 135: 700-703.

26. Page DL, Schuyler PA, Dupont WD et al. (2003) Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk : a retrospective cohort study. **Lancet** 361: 125-9.

27. Collins LC, Baer HJ, Tamimi RM et al. (2007) Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia. Results from the Nurses' Health Study. **Cancer** 109: 180-7.

28. Liberman L, Sama M, Susnik B et al. (1999) Lobular carcinoma in situ at breast biopsy : surgical biopsy findings. **Am J Roentgenol** 173: 291-9.

29. Middleton LP, Grant S, Stephens T et al. (2003) Lobular carcinoma in situ diagnosed by core needle biopsy: when should it be excised ? **Mod Pathol** 16: 120-9.

30. Shah V.I., Raju U., Chitale D. et al. (2003) False-negative core needle biopsies of the breast. **Cancer** 97: 1824-1831.

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Table 1 : Sociodemographic, clinical and radiological characteristics of the 66 patients with AEH on core biopsy (Mammotome) after haematoxylin eosin safran (HES) and immunohistochemistry (IHC) staining.

Characteristic		AEH on HES and IHC 66 patients
Age		52.2 ± 9.1 (27 – 73)
Menopausal Status	yes	37
	no	29
Family history of breast cancer	yes	22
	no	44
HRT	yes	14/37
	no	23/37
Microcalcifications		65
Opacity		1
ACR	3	13
	4	52
	5	1
Mean size of radiological abnormality (mm)		9.2 [2-60]
Needle caliber	8	2
	10	10
	11	54
Number of MMT probe rotations	1	12
	2	31
	3	21
	4	2
Total number of fragment biopsies		14.3 ± 4.7
Interval from MMT to surgery (weeks)		9.2 ± 8.8
Total excision of the radiological signal		26/66
Pre-operative wire location		65/66
MMT scar seen on surgical specimen		64/66

HRT = Hormonal Replacement Therapy; ACR = American College of Radiology; MMT = Mammotome;

Table 2: VABB (Mammotome) findings, before and after slide review and IHC.

Histological type	N patients without IHC	N patients after slide review and IHC
ALH	32	30
ADH	28	26
Mixed= ALH+ADH	5	7
LCIS	2	2
FEA	1	1
Simple hyperplasia	0	2
Total	68	68

ALH = atypical lobular hiperplasia; ADH = atypical ductal hiperplasia; LCIS = lobular carcinoma in situ ; FEA = flat epitelial atypia.

Table 3: Detailed histological findings in patients with false-negative VABB results.

Patient	Vacuum Assisted Breast Biopsy diagnosis		Surgical diagnosis
	Initial	After review and IHC	
1	ADH	ADH	DCIS + LCIS + ADH
2	ADH	ADH	DCIS
3	ALH	ALH + ADH	DCIS + ADH
4	ADH	ADH	DCIS + ADH
5	ADH	ADH	InvDC + ALH
6	ADH + FEA	ADH	DCIS + ADH
7	ALH	ALH + ADH	DCIS + ALH + ADH

ALH = atypical lobular hiperplasia; ADH = atypical ductal hiperplasia; LCIS = lobular carcinoma in situ; FEA = flat epithelial atypia; DCIS = ductal carcinoma in situ; InvDC = invasive ductal carcinoma.