Factors that impact the upgrading of atypical ductal hyperplasia

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PURPOSE
The purpose of this study was to identify the factors that may have an impact on upgrading atypical ductal hyperplasia (ADH) lesions to malignancy.

MATERIALS AND METHODS
Between February 1999 and December 2010, the records of 150 ADH lesions that had been biopsied were retrospectively reviewed. The biopsy types included 11-gauge stereotactic vacuum-assisted biopsy (SVAB) (n=102) and ultrasonography (US)-guided 14-gauge automated biopsy (n=48). The patients were divided into two groups: those who had cancer in the final pathology and those who did not. Variables associated with underestimation of ADH lesions were compared between the groups.

RESULTS
The underestimation rates according to the biopsy types were 41.7% (20/48) for the US-guided 14-gauge automated biopsy and 20.6% (21/102) for the 11-gauge SVAB ($P = 0.007$). The rate of underestimation was significantly higher in lesions greater than 7 mm than it was in smaller lesions, with both US-guided 14-gauge automated biopsy and 11-gauge SVAB ($P = 0.024$ and $P = 0.042$, respectively). The rate of underestimation was significantly higher with the 11-gauge SVAB ($P = 0.025$) in lesions that were suspicious (R4) and highly suggestive of malignancy (R5) than in those that were probably benign (R3).

CONCLUSION
The underestimation rate in ADH lesions was significantly higher with US-guided 14-gauge automated biopsy compared to the 11-gauge SVAB. The underestimation rate was also significantly higher in lesions greater than 7 mm regardless of the biopsy type, and in lesions biopsied using SVAB that were regarded as suspicious (R4) or highly suggestive of malignancy (R5) on imaging.

Atypical ductal hyperplasia (ADH) is a borderline lesion classified between usual ductal hyperplasia and ductal carcinoma in situ (DCIS). It is associated with an increased risk of developing breast cancer and may coexist with DCIS or invasive cancer (IC). ADH is a rare condition, with the frequency of observed cases ranging between 2% to 11% (1, 2). Because of the widespread use of mammographic screening in recent years, the number of lesions with ADH has increased.

The diagnosis of ADH on percutaneous image-guided core needle biopsies is challenging. Image-guided breast biopsies are performed under either stereotactic or ultrasonography (US) guidance. The US-guided core needle biopsy is fast, safe, accurate, and economical (3). More recently, the directional vacuum-assisted method has become available with 8-, 9-, 10-, and 11-gauge needles. The vacuum-assisted devices provide larger core samples than those obtained with the automated guns, potentially enabling more complete sampling of lesions and less chance of sampling error (4–6).

These technical advances in percutaneous needle biopsy have improved the accuracy of diagnosis. However, diagnosis of ADH on percutaneous image-guided core needle biopsies remains challenging, as distinguishing ADH from low-grade DCIS is particularly difficult. Thus, the diagnosis of breast cancer in ADH lesions remains a critical and important problem. The aim of this study was to identify the factors that may have an impact in upgrading ADH lesions to malignancy.

Materials and methods

From February 1999 to December 2010, a total of 9313 percutaneous needle biopsies, including 1480 stereotactic vacuum-assisted biopsies (SVAB) and 7833 US-guided automated biopsies, were performed. All biopsies were performed by two consultant radiologists. The breast biopsy database was retrospectively reviewed. A study sample of 150 breast lesions in which atypia that did not amount to DCIS were identified and included in this report. In line with our Trust's policy, approval by the ethics committee was not required, as this was a retrospective survey and no patients were individually identified.

Biopsy procedures

US-guided 14-gauge automated biopsy

Patients were placed in the supine or oblique supine position, and 14-gauge core biopsies were performed using high-resolution US with a 13-5 MHz linear transducer (Antares, Siemens Medical Systems, Issaquah, Washington, USA). When a lesion that contained microcalcifications was biopsied, the specimen radiographs were obtained to document the presence of calcifications. The median number of specimens per lesion was 3 (range, 1–7).

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Stereotactic vacuum-assisted 11-gauge biopsy

All SVABs were performed on a digital prone table (Fischer Imaging, Denver, Colorado, USA) using 11-gauge vacuum probes (Mammotome, Ethicon Endo-Surgery, Norderstedt, Germany). The target lesion was identified following the scout and two stereotactic images angled 15° to either side of the initial image; after local anesthesia with 10 cc lidocaine, the needle was inserted in the center of the lesion. A second set of stereotactic images was taken to confirm accurate position of the needle. Needle-tip location was modified, if required, to ensure its proximity to the target. If the specimen radiograph showed no calcification in the cores, further sets of biopsies were obtained with further specimen radiography until adequate calcium retrieval was obtained (Fig. 1). In cases where more than one lesion was targeted, a different device was used. The median number of specimens per lesion was 13 (range, 6–35). Of all 1480 SVABs, there was one patient where the postbiopsy hematoma formation required a surgical drainage.

Radiographs of the specimens

For lesions containing microcalcifications, the core specimens were visualized in a digital imaging machine (Faxitron X-ray Corporation, Tucsan, Arizona, USA) having the capability of four levels of magnification. Exposure factors of 16 kV and 10 mAs were used to confirm that the correct lesion was obtained in the specimen. The specimen radiograph was assessed while the patient was still in position. If the specimen radiograph showed no microcalcifications, more sets of biopsies were obtained with further specimen radiography until radiographic correct lesion was demonstrated in the core samples. The tissue specimens were then placed in formalin and processed in the Department of Pathology.

Pathological handling of the specimens

The pathological handling of the specimens was performed in line with the National Health Service Breast Screening Program (NHSBSP) guidelines and the Royal College of Pathologists (RCPath) guidelines (7).

Data collection and analysis

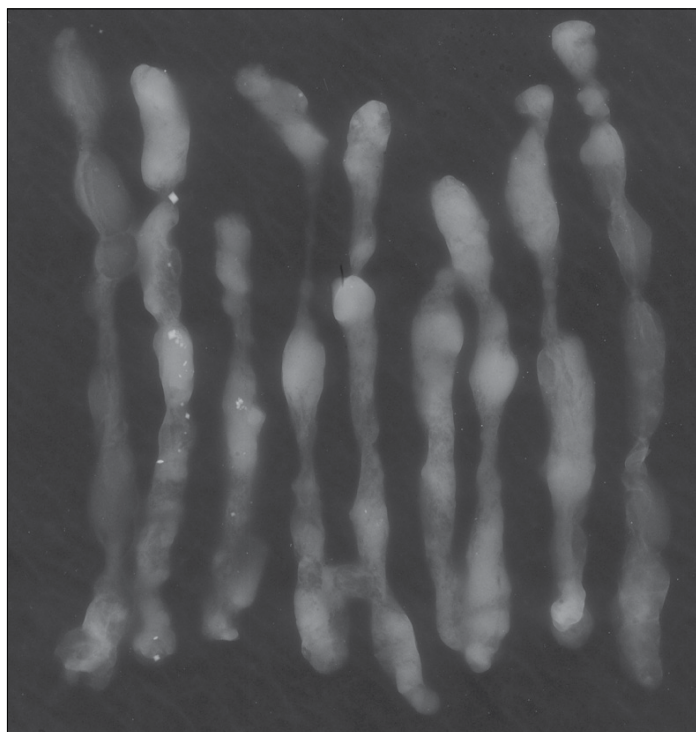The radiological findings were recorded using a coding system from 1

Figure 1. The specimen X-ray shows cores with and without microcalcification.

to 5, according to European guidelines (R1, negative; R2, benign changes; R3, probably benign; R4, suspicious lesion; R5, highly suggestive of malignancy) (8). The diagnosis and code were reported, as described in the NHSBSP and the RCPath guidelines (7). The patients' age, patient type, radiologic code, lesion type, lesion size, number of core specimens obtained, and the biopsy type were recorded.

When surgery was performed, the final histopathological diagnosis was compared with the diagnosis obtained preoperatively at US-guided 14-gauge biopsy or SVAB. The study population was divided in two groups based on the presence or absence of cancer in final pathology at surgery. The cancer in final pathology was defined as underestimate.

Statistical analysis

Statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 13.0, SPSS Inc., Chicago, Illinois, USA). Data are presented as the mean±standard deviation or n (%). One-sample Kolmogorov-Smirnov test was used to evaluate the distribution of data. The differences between the subgroups were analyzed by chi-square or Fisher's exact, student t and

Mann-Whitney U tests. A $P < 0.05$ was considered significant.

Results

The study included 150 lesions with atypia that had been biopsied with US-guided 14-gauge automated biopsy (n=48) or 11-gauge SVAB (n=102).

The underestimation rates according to the biopsy types were 41.7% (20/48) for the US-guided 14-gauge automated biopsy and 20.6% (21/102) for the 11-gauge SVAB ($P = 0.007$). There were significant differences in terms of size of the lesion and the number of core specimens obtained between the 14-gauge automated biopsy and the 11-gauge SVAB ($P < 0.001$ and $P = 0.045$, respectively).

US-guided 14-gauge automated biopsy

A total of 48 lesions were identified from 48 patients whose median age was 59.5 years (range, 39–92 years). These lesions included 36 masses, seven architectural distortions and five masses with microcalcifications. The median number of specimens per lesion was 3 (range, 1–7), and the median diameter of the lesions was 11 mm (range, 4–47 mm). Of the 48 lesions, 45 underwent surgical excision and three were followed up; biopsies showed mild atypia in these three

lesions. The median follow-up was 30 months (range, 24–72 months). Final surgical pathology revealed 20 of the 48 (41.7%) to be cancerous: 17 DCIS and three IC (Table 1).

There were no differences between the groups that received accurate diagnosis and those that were underestimated, in terms of patients' type (P = 0.661), lesion type (P = 0.553), radiological code (P = 0.933), or the number of core specimens obtained (P = 0.092). The rate of underestimation was significantly higher in lesions greater than 7 mm than in smaller lesions (P = 0.024) (Table 2).

Stereotactic vacuum-assisted 11-gauge biopsy

Totally 102 lesions were identified from 102 patients whose median age was 52 years (range, 37–76 years). The lesions included 99 microcalcifications, one mass and two asymmetric densities. The median number of specimens per lesion was 13 (range, 6–35), and the median diameter of the lesions was 9 mm (range, 3–90 mm). Of the 102 lesions, 72 were surgically excised and 30 were followed up. Biopsies showed mild atypia in 17 of these 30 lesions, and mammograms revealed widespread microcalcifications in 10 of them. Two patients did not want to undergo operation for ADH lesions, and one patient had cardiac disease. The median follow-up was 51.5 months (range, 24–120 months). Final surgical pathology showed 21 (20.6%) of the 102 lesions to be cancerous: 11 DCIS and 10 IC (Table 1).

There were no differences between the groups that received accurate diagnosis and those that were underestimated, with respect to patient type (P = 0.966), lesion type (P = 0.112) or the number of core specimens obtained (P = 0.224). The rate of underestimation was significantly higher in lesions greater than 7 mm than in smaller lesions (P = 0.042). The rate of underestimation was also significantly higher with SVAB (P = 0.025) in lesions that were suspicious (R4) and highly suggestive of malignancy (R5) than in those which were regarded as probably benign (R3) on imaging (Table 3).

Discussion

ADH is a proliferative, nonobligate precursor breast lesion and a marker of increased risk for breast carcinoma (9).

Table 1. Comparison of 14-gauge automated biopsy with 11-gauge SVAB

	US-guided 14-gauge automated biopsy	11-gauge SVAB	P
Underestimation rate (n)	20/48	21/102	0.007
Diameter of the lesion (median [range])	11 mm (4–47 mm)	9 mm (3–90 mm)	0.045
Number of specimen per lesion (median [range])	3 (1–7)	13 (6–35)	< 0.001

US, ultrasonography; SVAB, stereotactic vacuum-assisted biopsy.

Table 2. Comparison of accurately diagnosed and underestimated lesions at US-guided 14-gauge automated biopsy

	Accurately diagnosed (n=28)	Underestimated (n=20)	P
Patient type			
Screen	18	16	0.238
Symptomatic	10	4	
R code			
R3	22	15	0.933
R4	4	3	
R5	2	2	
Lesion type			
Mass with calcifications	2	3	0.553
Architectural distortion	5	2	
Mass	21	15	
Diameter of the lesion (mm)			
≤7	11	2	0.024
>7	17	18	
Number of specimen per lesion			
1–3	24	13	0.092
4–7	4	7	

Table 3. Comparison of accurately diagnosed and underestimated lesions at 11-gauge stereotactic vacuum-assisted biopsy

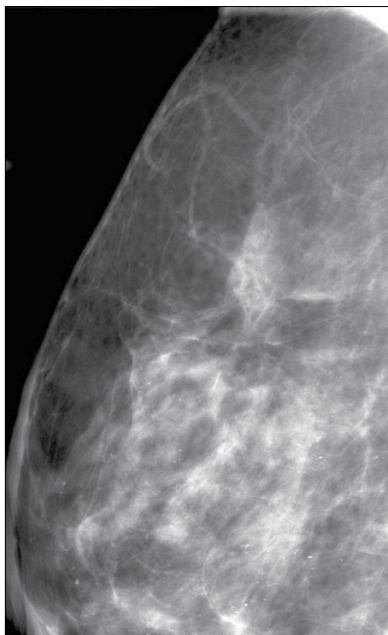|	Accurately diagnosed (n=81)	Underestimated (n=21)	P
Patient type			
Screen	42	11	0.966
Symptomatic	39	10	
R code			
R3	59	10	0.025
R4	20	8	
R5	2	3	
Lesion type			
Microcalcifications	79	20	0.112
Mass	0	1	
Asymmetric density	2	0	
Diameter of the lesion (mm)			
≤7	35	4	0.042
>7	46	17	
Number of specimen per lesion			
6–12	39	7	0.224
13–35	42	14	

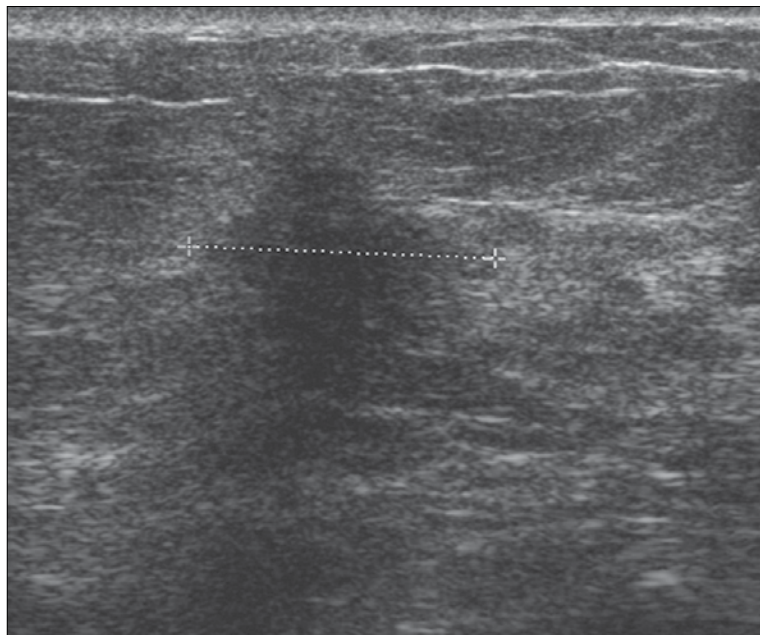**Figure 2.** Craniocaudal mammogram shows widespread microcalcifications.

Figure 3. US shows a mass lesion *(calipers)* with needle biopsy diagnosis of atypical ductal hyperplasia. Surgical excision revealed invasive cancer.

ADH exhibits the partial involvement of two-basement membrane-bound spaces by a cell population similar to noncomedo type DCIS (cribriform). It usually measures 2 to 3 mm in diameter (10). Because ADH may coexist with DCIS, and the distinction between the two is partly quantitative, it is sometimes impossible to distinguish between these two lesions in the limited samples provided by percutaneous image guided core needle biopsy. ADH carries a four to five times higher risk of subsequently developing invasive carcinoma in either breast (11, 12).

According to our unit's policy, patients who are diagnosed with atypia suggesting the possibility of ADH on preoperative core biopsy (US-guided or stereotactic) are offered to undergo a further excisional biopsy. In few cases however, patients with ADH are followed up instead of undergoing surgery. The criteria for follow-up include biopsies showing mild atypia, mammography revealing widespread microcalcifications (Fig. 2), patients with severe co-morbidities, or patients who decline surgery. In total, 33 lesions were followed up with mammography and US.

Percutaneous image-guided core needle biopsy is a well established alternative to surgical biopsy that provides a faster, less invasive, and less expensive method for the histological assessment of breast lesions (13). US-guided automated biopsy is preferable in terms of patient comfort, procedure time, and cost (3). However, the automated biopsy findings for ADH are less reliable because of histologic underestimation of malignancy. The rate of underestimation of ADH has been reported to range from 11% to 65% for 14-gauge automated biopsy (14–20). Technical advances in percutaneous core needle biopsy, such as increasing needle diameter from 14-gauge to 11-gauge and adding a vacuum device, have allowed larger samples of tissue to be obtained (5, 6), substantially improving the accuracy of diagnosis. Despite these improvements, the rate of underestimation for ADH has been reported as 10% to 26% for 11-gauge vacuum-assisted biopsy (VAB) (2, 14, 21–28). In this study, 11-gauge SVAB was associated with a lower rate of underestimation for ADH (20.6%), compared to US-guided 14-gauge automated biopsy (41.7%) ($P = 0.007$).

Youk et al. (19) reported that the rate of underestimation with US-guided 14-gauge core needle biopsy was not significantly higher in lesions measuring over 10 mm than in smaller lesions. Jang et al. (20) reported that the rate of underestimation was significantly higher in lesions over 21 mm than in smaller lesions with US-guided 14-gauge core needle biopsy. In this study, the rate of underestimation was significantly higher in lesions measuring 8 mm or more than it was in smaller lesions with US-guided 14-gauge core needle biopsy ($P = 0.024$) (Fig. 3).

Jackman et al. (16) reported that the risk of underestimation with SVAB increased with the size of the lesion. They also found that the risk of underestimation did not increase with the maximum size of the lesion for ADH, with SVAB (24, 25). Decreased underestimation rates with SVAB were found to be statistically significant if the maximum diameter of the lesion was less than 10 mm (2). In this study, the rate of underestimation was significantly higher in lesions that measured 8 mm or more compared to smaller lesions ($P = 0.042$) (Fig. 4).

Detailed US features according to the Breast Imaging-Reporting and Data System (BI-RADS) were analyzed. Four lesions categorized as BIRADS category 4b or greater were malignant (19). There was no significant difference in the lesion characteristics or the BI-RADS categories at US between the group that was accurately diagnosed and the underestimated group using US-guided 14-gauge core needle biopsy (19). Similarly, in this study, there was no significant difference between the two groups for the radiological code with US-guided 14-gauge core needle biopsy. Further, there was no
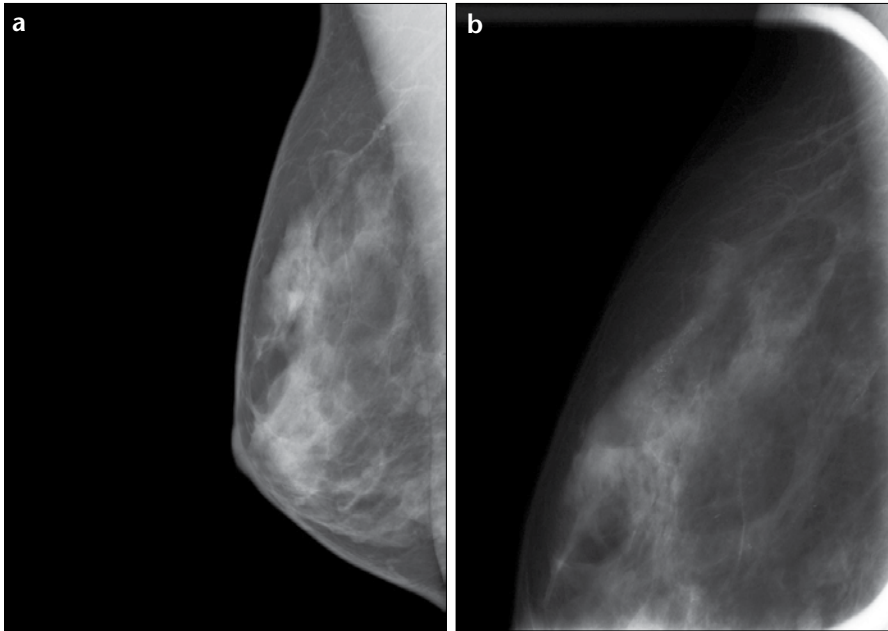
Figure 4. a, b. Right craniocaudal mammogram **(a)** shows microcalcifications with needle biopsy diagnosis of atypical ductal hyperplasia. Right breast magnification view **(b)** shows microcalcifications.

significant difference in the BI-RADS categories between the accurately diagnosed group and the underestimated group with SVAB (2). In this study, however, the rate of underestimation was significantly higher with SVAB (P = 0.025) in lesions that were suspicious (R4) and highly suggestive of malignancy (R5) than in those that were probably benign (R3).

Some investigators reported no association between the number of core specimens obtained for groups that were underestimated with both 14-gauge core needle biopsy (19) and VAB (2, 24, 25). Jackman et al. (16) reported that the underestimation of malignant disease increased with VAB when the number of cores obtained per lesion was 10 or less. However, other authors did not confirm these findings (23, 29). In this study, there was no difference between the group that received an accurate diagnosis and the underestimated group with US-guided 14-gauge core needle biopsy and 11-gauge SVAB in terms of the number of core specimens obtained.

Although Jackman et al. (2) reported higher underestimation rates for VAB of mass lesions than of microcalcifications, Philpotts et al. (24) found a significantly higher underestimation rate for VAB of microcalcifications than of masses. Jang et al. (20) found no difference in terms of the lesion type between the two groups with US-guided core needle biopsy. In this study, there was no difference with respect to lesion type between the group that received an accurate diagnosis and the underestimated group with both US-guided 14-gauge core needle biopsy and SVAB. However, we acknowledge that the number of cases in our study for each lesion type category was not large enough, which may have an influence on statistical power.

In conclusion, the rate of underestimation for ADH lesions was found to be significantly higher with US-guided 14-gauge core needle biopsy than with SVAB. The rate of underestimation was significantly higher in lesions greater than 7 mm than in smaller lesions with US-guided 14-gauge core needle biopsy and SVAB. The rate of underestimation was also significantly higher with SVAB in lesions that were suspicious (R4) and highly suggestive of malignancy (R5) than in those regarded as probably benign (R3) on imaging.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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