Available online at www.annclinlabsci.org

Atypia on Breast Core Needle Biopsies: Reproducibility and Significance

Farbod Darvishian,[1] Baljit Singh,[1] Aylin Simsir,[1] Weimin Ye,[2] and Joan F. Cangiarella[1]
[1]Department of Pathology, New York University Medical Center, New York, New York
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

Abstract. This study analyzes the interobserver variability in interpreting atypia on breast core needle biopsies and in each category of atypia calculates the upgrade risk of carcinoma in the subsequent surgical excision. We identified 51 cases of atypia on breast core needle biopsies performed at our institution from January 2003 to August 2006. The atypia was classified into 4 categories: atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), flat epithelial atypia (FEA), and atypia of undetermined significance (AUS). After a tutorial session, these cases were independently reviewed by four pathologists, whose overall multi-rater kappa value for agreement on different categories of atypia was 0.79 (95% CI, 0.69-0.89), which is within the substantial agreement range. The upgrade risk in each category of atypia was as follows: ADH 20% (p = 0.04); ALH 10% (p = 0.6); FEA 16.6% (p = 0.23), and AUS 100% (p = 0.96). Based on our findings, we conclude that follow-up excision should be performed after a diagnosis of ADH. The upgrade risk did not reach statistical significance in ALH or FEA. Although follow-up excision cannot be strongly recommended in ALH and FEA, it should be considered since the upgrade risk is not negligible. Strict adherence to the diagnostic criteria and tutorial sessions can help pathologists to achieve substantial agreement in interpreting atypia on breast core needle biopsies.

Keywords: breast cancer, breast core needle biopsy, epithelial atypia, surgical pathology quality assurance

Introduction

Breast core needle biopsies (BCNB) with epithelial atypia commonly result in subsequent surgical excision because of the possibility of underestimating a higher grade lesion. The frequency of underestimation varies, depending on the type and extent of atypia [1-23]. Therefore, establishing a diagnosis of atypia and subtyping the atypia are important for risk assessment and evaluating the need for excision. Although the criteria for atypia are well-established, there is inherent subjectivity in interpretation of atypia in BCNB, especially since the evaluation is limited by the small amount of tissue obtained with core biopsy. The diagnosis of atypia is classified into atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and flat epithelial atypia (FEA). Each category harbors a certain risk for upgrade to higher grade lesions, namely ductal carcinoma in situ (DCIS) or invasive carcinoma, in the subsequent excision. In the case of ADH, the upgrade risk ranges from 13 to 48%; it is generally agreed that this finding on BCNB should be followed by definitive surgical excision [1-17]. For ALH and FEA, the need for subsequent excision is more controversial. The upgrade risk in subsequent excision in ALH ranges from 2 to 20% depending on the study [1,14,15,18,19,23]. FEA has not been studied as extensively as ADH and ALH, but judging from the recent literature, it carries an approximate upgrade risk of 14-30% on subsequent breast excisions [1,16,22,23]. Several factors contribute to the wide range of upgrade risk

Address correspondence to Farbod Darvishian, M.D., Department of Pathology, New York University Medical Center, 530 First Avenue (SK7N), New York, NY 10016, USA; tel 212 263 0138; fax 212 263 5509; e-mail farbod.darvishian@nyumc.org.

in the atypical categories, including the needle size [13], extent of atypia (ie, volumetric factor) [24,25], concomitant atypia [19], pathologist's expertise [26], and institutional setting (eg, referral center vs community hospital).

This study had two primary objectives. First, to assess the interobserver variability in interpreting BCNBs performed at our institution using different categories of atypia, and second, to assess the upgrade risk in subsequent breast excisions in each category. In addition, we reviewed the relevant literature.

Materials and Methods

This study was approved by the Institutional Review Board of New York University School of Medicine.

All cases of "atypia" on breast core biopsies diagnosed at New York University Medical Center (NYUMC) from January 2003 to August 2006 were searched. The inquiry criteria for "atypia" included atypical ductal hyperplasia, atypical lobular hyperplasia, columnar cell change with atypia, flat epithelial atypia, cytologic atypia not otherwise specified, and pagetoid spread of atypical cells. Papillary lesions with atypia and consultation cases were excluded.

The selected cases were anonymized and distributed among 4 pathologists for independent review (FD, AS, BS, JFC). These pathologists are either dedicated breast pathologists or have expertise in the practice of breast pathology. We held a tutorial session to review the general criteria for atypia on known cases. After the meeting, we classified the cases into 3 categories of atypia (ie, ADH, ALH and FEA) based on the established criteria [27,28].

Briefly, ADH is defined by its resemblance to DCIS but falls short of fulfilling the criteria for DCIS. ADH is composed of round to cuboidal or polygonal evenly spaced cells with distinct cell borders and round or oval monotonous nuclei. Architecturally, spaces show no swirls or streaming and are round, regular, and smooth. The micropapillae have a narrow base and may form rigid, geometric configuration forming bridges, which lack attenuation. These cytologic and architectural findings should be present in less than two separate spaces or not circumferentially for the diagnosis of ADH [27].

Similarly, ALH is defined by its resemblance to LCIS. ALH is composed of round to cuboidal or polygonal, evenly spaced cells with round, monotonous nuclei in a lobular unit, which is not completely filled, distorted, or distended [27].

FEA is defined by cells with low grade (monomorphic type) atypia lining acini without forming complex architectural patterns. These features should not fulfill the combined architectural and cytologic atypia criteria for diagnosis of ADH or DCIS. Lining cells have nuclei that are typically round, but may be ovoid in some cases. Nucleoli may or may not be prominent. The cells typically lack polarity and are not regularly oriented perpendicular to the basement membrane. These features are usually associated with apical snouts, luminal secretions, and calcifications [28].

A fourth category of non-classifiable atypia of undetermined significance (AUS) was defined as sparse pagetoid spread of atypical cells. A fifth category of "no atypia" was recognized if the findings were deemed not to fulfill the criteria for atypia. If any 2 of the 4 patterns of atypia coexisted (eg, ADH/FEA), this was noted in independent case reviews.

After the initial review, we reviewed the cases in a group session in order to reach a consensus diagnosis. The results of the initial review were used to assess the agreement among the reviewers, using kappa statistics. The consensus diagnosis was analyzed vis-a-vis the final pathologic diagnosis after definitive surgical excision to evaluate the upgrade findings defined by the presence of DCIS and/or invasive carcinoma.

The multi-rater kappa statistic was calculated as described by Fleiss [29] and Landis and Koch [30]. The degree of agreement (kappa value) was categorized as follows: 0 poor; >0-0.2 slight; >0.2-0.4 fair; >0.4-0.6 moderate; >0.6-0.8 substantial; and >0.8-1 almost perfect.

Results

From January 2003 to August 2006, 1648 breast core needle biopsies (BCNB) were reviewed at the Department of Pathology at NYUMC; 915 cases were performed in-house and the remaining 733 were consultation cases. The breakdown of the 915 in-house BCNBs was as follows: invasive ductal carcinoma (n = 93); invasive lobular carcinoma (n =

Table 1. Clinicopathologic features of 49 patients with 51 breast core needle biopsies that showed atypia.

Age (yr; mean & range)	54.2 (31-81)
Laterality	
Left	21 (41%)
Right	30 (59%)
Location	
Upper outer quadrant	33 (65%)
Upper inner quadrant	5 (10%)
Lower outer quadrant	5 (10%)
Lower inner quadrant	4 (8%)
Central	2 (3.5%)
Unknown	2 (3.5%)
Reason for biopsy	
Calcifications	43 (84%)
MRI enhancement	2 (4%)
Mass/nodule	6 (12%)
Upgraded cases	10 (19.6%)
DCIS	6 (11.7%)
IDC	4 (7.9%)

DCIS: Ductal carcinoma in situ
IDC: Invasive ductal carcinoma
MRI: Magnetic resonance imaging

24); invasive mammary carcinoma with mixed ductal and lobular features (n = 16); ductal carcinoma in situ (n = 66); lobular carcinoma in situ (n = 3); fibrocystic change with atypia (n = 67); fibrocystic change without atypia (n = 284); fibroadenoma (n = 126); and others, including papillary lesion, stromal fibrosis, intramammary lymph node, fat necrosis, duct ectasia, mucocele-like lesion, or benign breast tissue with no pathologic abnormality (n = 136). Of the 67 BCNBs with atypia, 16 did not have a subsequent surgical excision and/or were associated with a synchronous ipsilateral malignancy. The remaining 51 BCNBs with a diagnosis of atypia had been performed on 49 patients, whose clinicopathologic features are summarized in Table 1. The time interval between the biopsy and the follow-up excision ranged from 7 days to 75 days (mean = 28 days). The follow-up surgery in all of the study cases consisted of segmental excision. Routinely, all breast tissue was submitted for histologic examination.

After the consensus meeting, we agreed on the classification of atypia in the remaining 51 cases as follows: ADH (n = 20; 40%), ADH/ALH (n = 2; 4%), ADH/FEA (n = 3; 6%), FEA (n = 12; 24%), ALH (n = 10; 20%), and AUS (n = 1; 2%) (Fig. 1). In 2 cases (4%) we did not reach a concensus agreement on the type of atypia; we reclassified 1 case (2%) as negative for atypia.

The multi-rater kappa value for agreement on different categories of atypia was 0.79 (95% CI, 0.69-0.89), which is within the substantial agreement range [30]. The kappa values for agreement on the individual categories of atypia were as follows: ADH = 0.69; ADH/ALH = 0.85; ADH/FEA = 0.82; ALH = 0.78; FEA = 0.85; AUS = 0.65; and no atypia = -0.003.

Overall, there were 10 cases with an upgrade of diagnosis to invasive ductal carcinoma (4 cases) or DCIS (6 cases) after follow-up surgery. The results of upgrades in each category of atypia are listed in Table 2. In summary, upgrade was noted in 4 ADH cases (20%), 1 ALH case (10%), 2 FEA cases (16.6%), 2 ADH/ALH cases (100%), and 1 case of AUS (100%). Among these groups, only the upgrade risk in the ADH category reached statistical significance (p = 0.04).

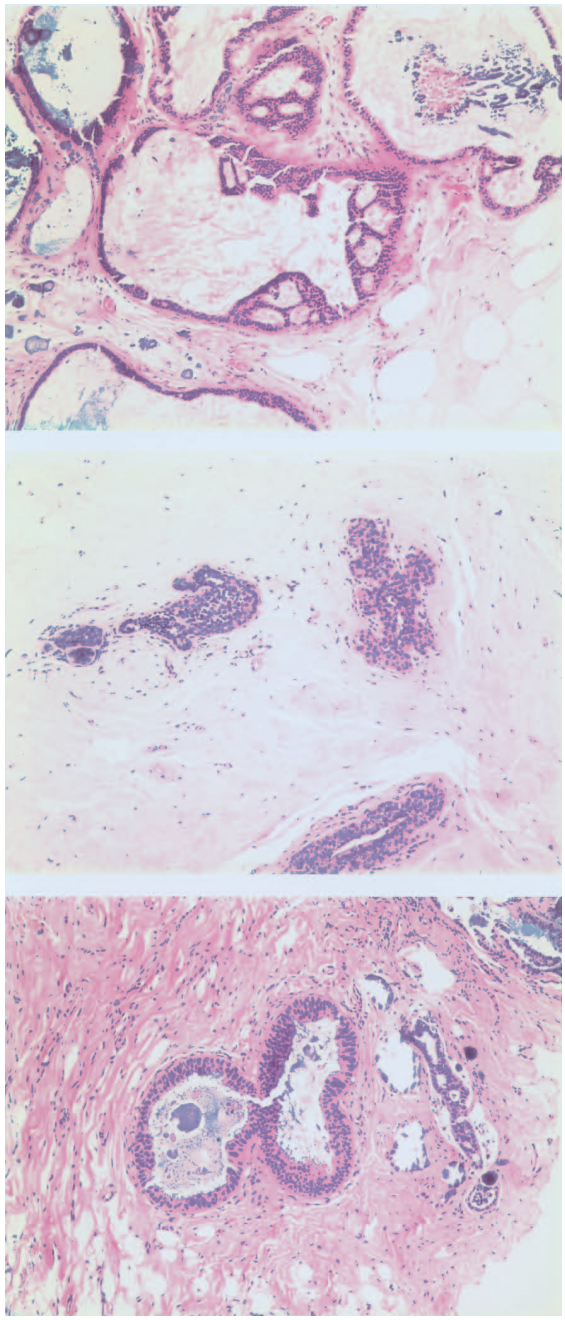

Fig. 1. Top panel: atypical ductal hyperplasia (ADH). Monomorphic ductal cells forming rigid arches and micropapillae in two ducts without circumferential involvement of the ducts. Note the surrounding dilated ducts and the associated microcalcifications. Middle panel: atypical lobular hyperplasia (ALH). A monomorphic population of dyscohesive cells incompletely filling two neighboring lobules without distortion or distension. Bottom panel: flat epithelial atypia (FEA). Relatively monomorphic cells line the dilated ducts in 1 to 3 cell layers with loss of polarity. Note the luminal secretion and the associated microcalcifications.

Table 2. Atypical categories with upgrade on follow-up excision

	Upgrade frequency			
	Invasive ductal carcinoma	DCIS	Total	p value
ADH (n = 20)	1	3	4 (20%)	0.04
ALH (n = 10)	0	1	1 (10%)	0.6
FEA (n = 12)	0	2	2 (16.6%)	0.23
ADH/ALH (n = 2)	2	0	2 (100%)	0.99
ADH/FEA (n = 3)	0	0	0 (0%)	N/A
AUS (n = 1)	1	0	1 (100%)	0.96

ADH: Atypical ductal hyperplasia; ALH: Atypical lobular hyperplasia; FEA: Flat epithelial atypia; AUS: Atypia of undetermined significance; DCIS: Ductal carcinoma in situ.

The reasons for biopsy were reported as microcalcifications in 43 cases (84%), mass or nodule in 6 cases (12%), and magnetic resonance imaging (MRI) enhancement in 2 cases (4%). Of the 6 upgraded DCIS cases, 5 were detected by microcalcifications and 1 by MRI enhancement; of the 4 upgraded invasive ductal carcinoma cases, 2 were detected as a mass or nodule and 2 by microcalcifications.

Discussion

In an attempt to evaluate the reproducibility of interpreting epithelial atypia on BCNBs performed at our institution, we achieved a "substantial" degree of agreement (k = 0.79; 95% CI, 0.69-0.89). The kappa values of the individual categories of atypia ranged from 0.69 in pure ADH to 0.85 in FEA and ADH/ALH. We particularly targeted the less extensively studied FEA, rather than the well-established categories of ADH and ALH, which nevertheless fell in the substantial category of agreement (0.69 and 0.78, respectively). In an earlier publication, Tan et al [31] reported an intraobserver agreement of fair to substantial for the spectrum of columnar cell lesions (k = 0.334-0.669), with the lowest agreement for columnar cell change with atypia or FEA. While agreement was good for the extreme end of the spectrum, ie, DCIS, the authors advised more effort for the diagnosis of columnar cell change with cytologic atypia. With training tutorials and better definition of criteria for FEA, O'Malley et al [28] found excellent agreement on interobserver reproducibility of FEA diagnosed on excisional biopsies with a kappa value of 0.83 (95% CI, 067-094).

Recognition of FEA on BCNBs can be more challenging than on excisional biopsies due to the volumetric effect. Our interobserver reproducibility of 0.85 for FEA demonstrates the role of tutorials and strict adherence to defined criteria in achieving an almost perfect agreement on the diagnosis of this lesion on BCNBs. We did not reach agreement on the subtype of atypia in two cases, neither of which was associated with an upgrade on follow-up excision. In one of these cases, there was relatively monotonous ductal epithelial proliferation populating a few abortive and non-circumferential micropapillae limited to two ducts. These borderline features resulted in splitting of diagnoses into ADH and ductal hyperplasia without atypia. In the second case, there was thickening of a longitudinally-sectioned duct due to an epithelial proliferation, which raised the question of ALH versus a pagetoid spread of low grade ductal carcinoma in situ. While this uncertainty could be readily resolved by immunohistochemical staining using antibody to E-cadherin, we agreed on the presence of atypia, not otherwise specified, in the biopsy slides. We also ruled out atypia in another case due to insufficient criteria. The follow-up excision in this case showed fibrocystic change without atypia. In all 3 aforementioned cases, the paucity of the area of concern (volumetric issue) precluded a definitive assessment of the BCNBs.

The diagnosis of fibrocystic change with atypia was made in 67 (7.3%) of 915 BCNBs performed at our institution (7.3%), which is consistent with 6.3% to 7.14% reported in the literature [11,12]. We selected 51 cases of the 67 with atypia for this study, all of which were followed by surgical excision. Of the 51 cases, 10 cases (19.6%) showed

an upgrade on subsequent excision. Upgrade was noted in 4 cases with pure ADH on BCNBs (20%) and 2 cases with ADH/ALH (100%) although only the former reached statistical significance (see Table 2). Our upgrade in ADH fell in the approximate range of 13-48% reported in the literature [1-17]. The frequency of upgrade when combining cases of pure ADH with ADH and coexisting ALH was 27% (6 of 22), which indicates a slightly higher likelihood of upgrade. In a report by de Mascarel et al [1], coexistence of ADH and ALH, however, did not confer a higher likelihood of upgrade to pure ADH (26% and 36%; respectively). Of the 4 cases of pure ADH with upgrade, the clinical indication for biopsy was mammographic microcalcifications in 2 cases, sonographic mass in 1 case, and MRI enhancement in 1 case. The latter patient had a previous contralateral invasive ductal carcinoma, which placed the patient in an even higher risk category for malignancy than ADH alone. The follow-up excision on this patient demonstrated DCIS. The patient with the sonographic mass had a 0.9-cm hypoechoic mass, which turned out to be an invasive ductal carcinoma on follow-up excision. The diagnosis of ADH in BCNB was therefore deemed an undersampling.

We identified 10 cases of ALH, one of which showed an upgrade to DCIS on follow-up excision (10%). This case came to clinical attention because of mammographic microcalcifications, which were associated with ALH and sclerosing adenosis and not with the subsequent DCIS. In the literature, an upgrade risk of 2-20% for ALH has been reported [1,14,15,18,19,23]. As both ALH and LCIS are considered markers for higher risk of cancer development, in many studies these two lesions have been considered together as lobular neoplasia with a frequency of 0.58% to 0.7% over all BCNBs, with the caveat that LCIS probably carries a higher risk of upgrade than ALH [14,32]. Karabakhtsian et al [20] found 2.4 times higher risk of upgrade for LCIS than for ALH. Cognizant of this spectrum, we excluded LCIS cases as the study was designed to target the atypical category of breast epithelial lesions. Nonetheless, we identified only 3 cases of pure LCIS in addition to the 10 ALH cases, which together comprised 1.4% of all BCNBs. It is debatable whether the diagnosis of ALH or LCIS on BCNB should be followed by surgical excision. While some authors conclude that lobular neoplasia can be managed without follow-up excision, others recommend excision [33-37]. ALH was associated with a 10% risk of upgrade in our study, which is not insignificant; however the lack of statistical significance precluded a definitive conclusion on the need for follow-up excision. Whether followed surgically or by imaging studies, lobular neoplasia on BCNB should be correlated with the radiologic findings and surgical follow-up should be considered if the results are discrepant.

Flat epithelial atypia (FEA) encompasses a constellation of changes, which have been variously called atypical cystic duct, atypical lobules type A, clinging carcinoma, hypersecretory hyperplasia with atypia, small ectatic ducts lined by atypical ductal cells with apical snouts, columnar cell alteration with prominent apical snouts and secretions with atypia, atypical cystic lobules, ductal intraepithelial neoplasia-flat type, and columnar cell hyperplasia with atypia [28]. FEA has been described in association with other markers for higher risk of cancer including LCIS and ADH as well as with low grade DCIS and tubular carcinoma (hence pretubular hyperplasia) [38,39]. Despite the association, the significance of FEA on BCNBs is unclear. The risk of upgrade on the follow-up excision has been variously reported in the range of 14.3-30% [1,16,22,23]. One confounding factor, as stated above, is association of FEA with ADH, which potentially skews the upgrade risk. Kunju and Kleer [16] reported a concomitance rate of 64% for FEA and ADH in their series. Only 23% of their BCNBs had pure FEA. Interestingly, the upgrade risk was 11% in ADH/FEA group and 21% in pure FEA. In our study, 12 of 15 cases with FEA had pure FEA and 3 had concomitant FEA and ADH. None of the cases in the latter group showed an upgrade while 2 of the BCNBs with pure FEA were upgraded to DCIS (16.6%; $p = 0.23$). Both of these cases were detected by mammographic calcifications. Based on the limited studies in the literature including the current study, the upgrade risk in FEA is not negligible although we did not demonstrate statistical significance due to the limited number of cases.

Finally, we identified one case of atypia of undetermined significance, which was associated with invasive ductal carcinoma and DCIS on follow-up excision. Microscopically, this case showed atypical cells in a pagetoid spread in terminal ducts. On ultrasound, there was a 1.3 cm hypoechoic mass. In light of the imaging and pathologic findings, the BCNB was interpreted as undersampling, emphasizing the importance of radiologic-pathologic correlation. Retrospectively, the case should have been interpreted as DCIS.

Recently, immunohistochemical antibodies have been used to aid in the differential diagnosis of atypical epithelial proliferations of breast. One of these is an antibody to high molecular weight cytokeratin (CK5/6 and 34BE12), which is preferentially expressed in usual ductal hyperplasia but not in ADH, DCIS, or LCIS. The other commonly used antibody is against E-cadherin, an epithelial transmembrane protein, whose expression is lost in lobular neoplasia but not in ductal proliferations. Although these tools can be of use in specific circumstances, they appear to have little impact on improving interobserver reproducibility for non-invasive breast lesions [40,41]. Adherence to the defined criteria is still the gold standard for classification of atypical epithelial proliferations.

In summary, the reproducibility of interpretation of atypia on BCNBs was "substantial" (k = 0.79; 95% CI, 0.69-0.89). Follow-up excision is recommended in the ADH category of atypia. Although we cannot strongly recommend excision for FEA and ALH on BCNB due to limited number of cases, we favor considering follow-up excision especially upon radiologic-pathologic discordance.

References

1. de Mascarel I, MacGrogan G, Mathoulin-Pélissier S, Vincent-Salomon A, Soubeyran I, Picot V, Coindre JM, Mauriac L. Epithelial atypia in biopsies performed for microcalcifications: practical considerations about 2,833 serially sectioned surgical biopsies with a long follow-up. Virchows Arch 2007;451:1-10.
2. Margenthaler JA, Duke D, Monsees BS, Barton PT, Clark C, Dietz JR. Correlation between core biopsy and excisional biopsy in breast high-risk lesions. Am J Surg 2006;192:534-537.
3. Harvey JM, Sterrett GF, Frost FA. Atypical ductal hyperplasia and atypia of uncertain significance in core biopsies from mammographically detected lesions: correlation with excision diagnosis. Pathology 2002; 34:410-416.
4. Liberman L, Holland AE, Marjan D, Murray MP, Bartella L, Morris EA, Dershaw DD, Wynn RT. Underestimation of atypical ductal hyperplasia at MRI-guided 9-gauge vacuum-assisted breast biopsy. AJR 2007;188:684-690.
5. Adrales G, Turk P, Wallace T, Bird R, Norton HJ, Greene F. Is surgical excision necessary for atypical ductal hyperplasia of the breast diagnosed by Mammotome? Am J Surg 2000;180:313-315.
6. Houssami N, Ciatto S, Ellis I, Ambrogetti D. Underestimation of malignancy of breast core-needle biopsy: concepts and precise overall and category-specific estimates. Cancer 2007;109:487-495.
7. Moore MM, Hargett CW 3rd, Hanks JB, Fajardo LL, Harvey JA, Frierson HF Jr, Slingluff CL Jr. Association of breast cancer with the finding of atypical ductal hyperplasia at core breast biopsy. Ann Surg 1997;225:726-731.
8. Cangiarella J, Waisman J, Symmans WF, Gross J, Cohen JM, Wu H, Axelrod D. Mammotome core biopsy for mammary microcalcification: analysis of 160 biopsies from 142 women with surgical and radiologic followup. Cancer 2001;91:173-177.
9. Maganini RO, Klem DA, Huston BJ, Bruner ES, Jacobs HK. Upgrade rate of core biopsy-determined atypical ductal hyperplasia by open excisional biopsy. Am J Surg 2001;182:355-358.
10. Rao A, Parker S, Ratzer E, Stephens J, Fenoglio M. Atypical ductal hyperplasia of the breast diagnosed by 11-gauge directional vacuum-assisted biopsy. Am J Surg 2002;184:534-537.
11. Gal-Gombos EC, Esserman LE, Recine MA, Poppiti RJ Jr. Large-needle core biopsy in atypical intraductal epithelial hyperplasia including immunohistochemical expression of high molecular weight cytokeratin. Breast J 2002;8:269-274.
12. Renshaw AA, Cartagena N, Schenkman RH, Derhagopian RP, Gould EW. Atypical ductal hyperplasia in breast core needle biopsies. Correlation of size of the lesion, complete removal of the lesion, and the incidence of carcinoma in follow-up biopsies. Am J Clin Pathol 2001;116:92-96.
13. Darling ML, Smith DN, Lester SC, Kaelin C, Selland DL, Denison CM, DiPiro PJ, Rose DI, Rhei E, Meyer JE. Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large-core needle breast biopsy: results of surgical excision. AJR 2000;175:1341-1346.
14. Yeh IT, Dimitrov D, Otto P, Miller AR, Kahlenberg MS, Cruz A. Pathologic review of atypical hyperplasia identified by image-guided breast needle core biopsy. Correlation with excision specimen. Arch Pathol Lab Med 2003;127:49-54.
15. Dillon MF, McDermott EW, Hill AD, O'Doherty A, O'Higgins N, Quinn CM. Predictive value of breast lesions of "uncertain malignant potential" and "suspicious for malignancy" determined by needle core biopsy. Ann Surg Oncol 2007;14:704-711.

16. Kunju LP, Kleer CG. Significance of flat epithelial atypia on mammotome core needle biopsy: Should it be excised? Hum Pathol 2007;38:35-41.
17. Winchester DJ, Bernstein JR, Jeske JM, Nicholson MH, Hahn EA, Goldschmidt RA, Watkin WG, Sener SF, Bilimoria MB, Barrera E Jr, Winchester DP. Upstaging of atypical ductal hyperplasia after vacuum-assisted 11-gauge stereotactic core needle biopsy. Arch Surg 2003; 138:619-622.
18. Berg WA, Mrose HE, Ioffe OB. Atypical lobular hyperplasia or lobular carcinoma in situ at core-needle breast biopsy. Radiology 2001;218:503-509.
19. Renshaw AA, Derhagopian RP, Martinez P, Gould EW. Lobular neoplasia in breast core needle biopsy specimens is associated with a low risk of ductal carcinoma in situ or invasive carcinoma on subsequent excision. Am J Clin Pathol 2006;126:310-313.
20. Karabakhtsian RG, Johnson R, Sumkin J, Dabbs DJ. The clinical significance of lobular neoplasia on breast core biopsy. Am J Surg Pathol 2007;31:717-723.
21. Cangiarella J, Guth A, Axelrod D, Darvishian F, Singh B, Simsir A, Roses D, Mercado C. Is surgical excision necessary for the management of atypical lobular hyperplasia and lobular carcinoma in situ diagnosed on core needle biopsy?: a report of 38 cases and review of the literature. Arch Pathol Lab Med 2008;132:979-983.
22. Brogi E, Tan LK. Findings on excisional biopsy (EBX) performed after identification of columnar cell change (CCC) of ductal epithelium in breast core biopsy (CBX). Mod Pathol 2002;15:29A–30A [abstract].
23. Martel M, Barron-Rodriguez P, Tolgay Ocal I, Dotto J, Tavassoli FA. Flat DIN 1 (flat epithelial atypia) on core needle biopsy: 63 cases identified retrospectively among 1,751 core biopsies performed over an 8-year period (1992-1999). Virchows Arch 2007;451:883-891.
24. Ely KA, Carter BA, Jensen RA, Simpson JF, Page DL. Core biopsy of the breast with atypical ductal hyperplasia: a probabilistic approach to reporting. Am J Surg Pathol 2001;25:1017-1021.
25. Degnim AC, Visscher DW, Berman HK, Frost MH, Sellers TA, Vierkant RA, Maloney SD, Pankratz VS, de Groen PC, Lingle WL, Ghosh K, Penheiter L, Tlsty T, Melton LJ 3rd, Reynolds CA, Hartmann LC. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol 2007;25:2671-2677.
26. Rosai J. Borderline epithelial lesions of the breast. Am J Surg Pathol 1991;15:209-21.
27. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55:2698-2708.
28. O'Malley FP, Mohsin SK, Badve S, Bose S, Collins LC, Ennis M, Kleer CG, Pinder SE, Schnitt SJ. Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast. Mod Pathol 2006;19:172-179.
29. Fleiss JL. Statistical Methods for Rates and Proportions, 3rd ed, John Wiley & Sons, New York, 2003.
30. Landis JR, Koch GG. Measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
31. Tan PH, Ho BC, Selvarajan S, Yap WM, Hanby A. Pathological diagnosis of columnar cell lesions of the breast: are there issues of reproducibility? J Clin Pathol 2005;58:705-709.
32. Foster MC, Helvie MA, Gregory NE, Rebner M, Nees AV, Paramagul C. Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional biopsy necessary? Radiology 2004;231:813-819.
33. Nagi CS, O'Donnell JE, Tismenetsky M, Bleiweiss IJ, Jaffer SM. Lobular neoplasia on core needle biopsy does not require excision. Cancer 2008;112:2152-2158.
34. Hwang H, Barke LD, Mendelson EB, Susnik B. Atypical lobular hyperplasia and classic lobular carcinoma in situ in core biopsy specimens: routine excision is not necessary. Mod Pathol 2008;21:1208-1216.
35. Pinder SE, Provenzano E, Reis-Filho JS. Lobular in situ neoplasia and columnar cell lesions: diagnosis in breast core biopsies and implications for management. Pathology 2007;39:208-216.
36. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. Arch Pathol Lab Med 2002 ;126:697-701.
37. Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. Am J Surg Pathol 2005;29:534-543.
38. Brandt SM, Young GQ, Hoda SA. The "Rosen triad": tubular carcinoma, lobular carcinoma in situ, and columnar cell lesions. Adv Anat Pathol 2008;15:140-146.
39. Abdel-Fatah TM, Powe DG, Hodi Z, Lee AH, Reis-Filho JS, Ellis IO. High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. Am J Surg Pathol 2007; 31:417-426.
40. MacGrogan G, Arnould L, de Mascarel I, Vincent-Salomon A, Penault-Llorca F, Lacroix-Triki M, Bibeau F, Baranzelli MC, Fridman V, Antoine M, Bécette V, Brouste V, Jacquemier J, Mathoulin-Pélissier S; GEFPICS group. Impact of immunohistochemical markers, CK5/6 and E-cadherin, on diagnostic agreement in non-invasive proliferative breast lesions. Histopathology 2008;52:689-697.
41. Gal-Gombos EC, Esserman LE, Recine MA, Poppiti RJ Jr. Large-needle core biopsy in atypical intraductal epithelial hyperplasia including immunohistochemical expression of high molecular weight cytokeratin: analysis of results of a single institution. Breast J 2002;8:269-274.