Management of flat epithelial atypia on breast core biopsy may be individualized based on correlation with imaging studies

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Flat epithelial atypia of the breast commonly co-exists with atypical ductal hyperplasia, lobular neoplasia, and indolent forms of invasive carcinomas such as tubular carcinoma. Most patients with pure flat epithelial atypia on core biopsy undergo surgical excision to evaluate for carcinoma in the adjacent breast tissue. Studies to date have reported varying upgrade rates with most recommending follow-up excision. These studies have often lacked detailed radiographic correlation, central review by breast pathologists and information regarding the biology of the carcinomas identified upon excision. In this study, we report the frequency of upgrade to invasive carcinoma or ductal carcinoma *in situ* in excision specimens following a diagnosis of pure flat epithelial atypia on core biopsy. Radiographic correlation is performed for each case and grade/receptor status of detected carcinomas is reported. Seventy-three (73) core biopsies containing pure flat epithelial atypia were identified from our files, meeting inclusion criteria for the study. In the subsequent excision biopsies, five (7%) cases contained invasive carcinoma or ductal carcinoma *in situ* and seventeen (23%) contained atypical ductal hyperplasia or lobular neoplasia. All of the ductal carcinoma *in situ* cases with estrogen receptor results were estrogen receptor positive and intermediate grade. The invasive tumors were small (pT1a) hormone receptor-positive, HER2-negative, low-grade invasive ductal or tubular carcinomas with negative sentinel lymph-node biopsies. No upgrades were identified in the 14 patients who had all of their calcifications removed by the stereotactic core biopsy. Our rate of upgrade to carcinoma, once cases with discordant imaging are excluded, is at the lower end of the range reported in the literature. Given the low upgrade rate and indolent nature of the carcinomas associated with flat epithelial atypia, case management may be individualized based on clinical and radiographic findings. Excision may not be necessary for patients without remaining calcifications following core biopsy.

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Columnar cell lesions of the breast are common findings in core biopsies performed to evaluate mammographically indeterminate calcifications. Columnar cell lesions with nuclear atypia are classified as flat epithelial atypia by the World Health Organization (WHO).^{1,2} The management of

flat epithelial atypia diagnosed on core biopsy remains controversial.³ However, many patients with flat epithelial atypia are offered local excision to evaluate the possibility of a co-existing carcinoma. In a recent meta-analysis of flat epithelial atypia core biopsy studies, carcinoma was present in excisional biopsies in 13–67% of cases.⁴

Columnar cell lesions and flat epithelial atypia have been recognized for many years and called by many different names.⁵ Columnar cell lesions have been referred to as ‘blunt duct adenosis’,^{6–8} ‘hyperplastic enlarged lobular units’,⁹ ‘columnar alteration with prominent apical snouts and secretions’,¹⁰ and ‘enlarged lobular units with columnar alteration’.¹¹ Flat epithelial atypia has been referred

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to as 'clinging carcinoma, monomorphic type',¹² ductal intraepithelial neoplasia,¹³ and columnar cell change or columnar cell hyperplasia with atypia.¹⁴ The current WHO classification recognizes three diagnostic categories: columnar cell change, columnar cell hyperplasia, and flat epithelial atypia.² In this classification, columnar cell change and columnar cell hyperplasia with atypia are classified as flat epithelial atypia.

Several lines of evidence suggest a potential relationship between flat epithelial atypia and breast neoplasia.¹⁵ Columnar cell lesions and flat epithelial atypia are often co-localized with other patterns of atypia such as atypical ductal hyperplasia and atypical lobular hyperplasia^{16,17} and low-grade *in situ* and invasive carcinomas.¹⁸ Molecular studies have shown similar genetic alterations in flat epithelial atypia, atypical hyperplasia, and low-grade carcinoma in the same tissue section, suggesting that flat epithelial atypia may be a non-obligate precursor in a low-grade breast neoplasia pathway.^{19,20} In long-term follow-up studies of open biopsies, the risk associated with columnar cell lesions and flat epithelial atypia alone appears to be lower than the risk associated with atypical ductal or atypical lobular hyperplasia.^{16,17}

In a prior series from our institution, we reported a series of 31 cases from 1998 to 2003, with available follow-up excisions, 4 (12.9%) of which contained carcinoma.²¹ That study predated the WHO classification of flat epithelial atypia,¹ and we now report the frequency of carcinoma in excision specimens after a diagnosis of flat epithelial atypia on core biopsy for a subsequent 9-year period (2004–2013).

Materials and methods

The study was approved the Institutional Review Board of Carolinas Medical Center. Breast core biopsies with a diagnosis of flat epithelial atypia from 1 January 2004 to 15 October 2013 were retrieved from the Anatomic Pathology information system (CoPath). For all core biopsies, the presence and type of co-existing atypical ductal hyperplasia or atypical lobular hyperplasia or carcinoma was recorded. Cases with co-existing atypical ductal hyperplasia or atypical lobular hyperplasia or carcinoma and cases without an excision pathology report in CoPath were excluded from further study. Cases with atypical ductal hyperplasia or atypical lobular hyperplasia, carcinoma *in situ*, or invasive carcinoma in ipsilateral core biopsies performed concurrently or within 4 months of the core biopsy with flat epithelial atypia were also excluded. All study cases were reviewed by dedicated breast pathologists (CAL and BCC) to confirm the diagnosis of pure flat epithelial atypia using WHO criteria. These criteria include enlarged terminal duct lobular units, often with 3–5 cell layers, with proliferation of cells showing low-grade monomorphic cytology, increased nuclear/cytoplasmic ratios, and

loss of polarity (Figure 1). Multiple levels were examined in all cases. From 2009 through completion of the study period, a cutting protocol obtaining six (6) H&E levels ~150–250 microns apart were routinely examined for each stereotactic core biopsy. Before that change, the diagnostic pathologist requested additional levels (usually three) in all cases in which a 'stand alone' diagnosis of flat epithelial atypia was entertained. At least six levels were examined in the final study group (73 core biopsies with flat epithelial atypia alone).

All available surgical pathology reports for excisions following a core biopsy diagnosis of flat epithelial atypia alone were reviewed. Excision specimens with ductal carcinoma *in situ* or invasive carcinoma were also reviewed by breast pathologists (BCC and CAL) to confirm diagnosis. Three patients had two sites with flat epithelial atypia alone on core biopsy, and each core biopsy site was individually correlated with an excision specimen. The presence and location of calcifications was included in the pathology reports for the core biopsies and the excision specimens. It was not routine practice to submit the entire surgical specimen for large excisions (>15–20 blocks) following a core biopsy diagnosis of atypia. Cases were thoroughly sampled to include the prior biopsy site region and any remaining calcifications within the specimen through correlation with localization needle, biopsy clip(s), and calcifications identified on accompanying specimen image or Faxitron image in our gross room.

The indication for core biopsy, BIRADS score, percentage of calcifications removed, and concordance with histology were recorded by dedicated breast radiologists. Cases were excluded from the study when the overall imaging findings were interpreted by the breast radiologist as discordant with the pathologic diagnosis of flat epithelial atypia. This includes one case with MRI findings of multiple areas of clumped segmental enhancement highly suspicious for ductal carcinoma *in situ*. As the primary objective of this study was to establish the rate of upgrade to carcinoma, only cases with concordant imaging and carcinoma (invasive ductal or lobular carcinoma or ductal carcinoma *in situ* on excision) were regarded as pathologically upgraded. The presence of other risk-associated histologic findings including atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma *in situ* was also recorded. The vacuum-assisted stereotactic core biopsies were performed with nine gauge ATEC or EVIVA devices. The ultrasound core biopsies were performed with a 14-gauge BARD reusable spring-loaded device, and the vacuum-assisted MRI-guided core biopsies were performed with a 9-gauge ATEC device.

Results

A total of 22 707 breast core biopsies were performed during the study period with a mean and median of

Figure 1 Representative images illustrating the criteria used for the diagnosis of flat epithelial atypia (**a** and **b**, at $\times 200$ and $\times 400$ magnification, respectively) and tubular carcinoma (**c**, at $\times 200$ magnification).

2305 and 2219 per year, respectively. Two hundred-ten (210) core biopsies from 201 patients were identified as containing flat epithelial atypia (Table 1). Two (2) cases were ultrasound core biopsies, 5 were MRI-guided, and the remaining 203 were stereotactic core biopsies for calcifications. Radiology data were incomplete for three cases, none of which were upgraded. One of the mammograms preceding core biopsy was BIRADS 3 and the remaining cases BIRADS 4. In 116 biopsies, a higher risk form of atypia or carcinoma was present: 60 (29%) contained atypical ductal hyperplasia, 19 (9%) atypical lobular hyperplasia, 9 (4%) atypical ductal hyperplasia and atypical lobular hyperplasia,

14 (7%) ductal carcinoma *in situ*, 2 (1%) lobular carcinoma *in situ*, and 12 (6%) invasive carcinoma. In the cores with invasive carcinoma, eight were tubular carcinomas (or tubular features), three were low- or intermediate-grade invasive ductal carcinoma, no special type (grades 4/9, 5/9, 6/9), and one was microinvasion (less than 1 mm) associated ductal carcinoma *in situ*. These cases were excluded from further analysis.

Flat epithelial atypia was the most advanced lesion in 94 (45%) core biopsies from 90 patients with a median age at the time of core biopsy of 47 (range 33–71). Fifty (50) patients were premenopausal, 24 were postmenopausal (or had undergone

Table 1 Flat epithelial atypia and co-existing lesions on core biopsy

<i>Total</i>	<i>FEA only</i>	<i>ADH</i>	<i>ALH</i>	<i>ADH & ALH</i>	<i>LCIS</i>	<i>DCIS</i>	<i>Invasive</i>
210	94 (45%) ^a	60 (29%)	19 (9%)	9 (4%)	2 (1%)	14 (7%)	12 (6%)

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma *in situ*; FEA, flat epithelial atypia; Invasive, invasive carcinoma; LCIS, lobular carcinoma *in situ*.

Two hundred-ten (210) core biopsies with flat epithelial atypia from 201 patients were identified from 2004 to 2013. Of those, 116 contained a higher risk form of atypia or carcinoma and were excluded from further analysis. In the cores with invasive carcinoma, 8 were tubular carcinomas (or tubular features), 3 were low- or intermediate-grade invasive ductal carcinoma, no special type (grades 4/9, 5/9, 6/9), and 1 was microinvasion (less than 1 mm) associated DCIS.

^aPercentages rounded to nearest integer.

Table 2 Excision after flat epithelial atypia alone on core biopsy

<i>Total</i>	<i>No atypia</i>	<i>FEA</i>	<i>ADH</i>	<i>ALH</i>	<i>DCIS</i>	<i>Invasive</i>
73	20 (27%) ^a	31 (42%)	14 (19%)	3 (4%)	3 (4%)	2 (3%)

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma *in situ*; FEA, flat epithelial atypia; Invasive, invasive carcinoma.

Of the 94 core biopsies with flat epithelial atypia alone, 21 were excluded from further study. The overall rate of upgrade to carcinoma for the remaining 73 core biopsies was 7% (5/73). Ductal carcinoma *in situ* and a low-grade invasive ductal carcinoma, no special type, were present in 3 (4%) and 2 (3%) excision specimens, respectively. Seventeen excision specimens (23%) contained another, higher risk pattern of atypia (atypical ductal or atypical lobular hyperplasia).

^aPercentages rounded to nearest integer.

Table 3 Flat epithelial atypia alone on core biopsy with carcinoma on excision

<i>Diagnosis</i>	<i>Size (mm)</i>	<i>Grade</i>	<i>Estrogen receptor</i>	<i>BIRADS</i>	<i>Indication</i>	<i>Calcs removed</i>
IDC (NST)	3	1	Positive	4	10 mm calcs	<25%
IDC (tubular)	3	1	Positive	4	6 mm calcs	>75%
DCIS	8	2	Positive	4	12 mm calcs	>75%
DCIS	52	2	NR	4	40 mm calcs	<25%
DCIS	38	2	Positive	4	23 mm density	N/A

Abbreviations: Calcs, calcifications; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; NST, no special type.

Of the five cases upgraded to carcinoma, two were invasive carcinomas measuring 3 mm each and three were intermediate-grade ductal carcinoma *in situ*. The two cases of ductal carcinoma *in situ* with available estrogen receptor immunohistochemistry results were estrogen receptor positive.

hysterectomy), 3 were peri-menopausal, and menopausal status was unknown/unrecorded from 13 patients. Seventeen (17) patients had a first-degree relative with a history of breast cancer, 14 patients had a second- or third-degree relative with breast cancer, and 41 patients had no family history of breast cancer. Family history was unknown/unrecorded for 18 patients. Six (6) patients had a personal history of prior invasive carcinoma or ductal carcinoma *in situ* and 5 patients had a prior diagnosis of atypia (3 atypical lobular hyperplasia and 2 flat epithelial atypia).

Of the 94 core biopsies with flat epithelial atypia alone, 21 were excluded from further study due to excision pathology reports being unavailable for 12 cases, an ipsilateral core biopsy containing a more advanced lesion in 8 cases, and one case with discordant imaging findings. On retrospective review for this study, the discordant case was

classified as a BIRADS-5 imaging study that would have required open biopsy regardless of the core biopsy findings. The overall rate of upgrade to carcinoma for the remaining 73 core biopsies that comprised the final study group was 7% (5/73) (Table 2). Ductal carcinoma *in situ* and a low-grade invasive ductal carcinoma, no special type, were present in 3 (4%) and 2 (3%) excision specimens, respectively. The most common finding on excision was FEA alone (43%). Fifty-one (70%) specimens contained either flat epithelial atypia or no atypia and seventeen (23%) contained another, higher risk pattern of atypia (atypical ductal or atypical lobular hyperplasia). None of the 14 cases with all of the calcifications removed by the stereotactic core biopsy was upgraded to carcinoma.

The features of the cases upgraded to carcinoma are summarized in Table 3. The two invasive carcinomas measured 3 mm each and were positive

Table 4 Selected studies: flat epithelial atypia alone on core biopsy with excision

	Core biopsies	Excisions	Carcinoma (%)	DCIS	Invasive	Recommendation
Lavoue <i>et al</i> ³⁸	60	60	8 (13%) ^a	6	2	Excision
Guerra-Wallace <i>et al</i> ²¹	39	31	4 (13%)	3	1	Excision
Bianchi <i>et al</i> ²⁷	190	190	18 (10%)	NR	NR	Excision
Chivukula <i>et al</i> ³³	39	35	5 (14%)	3	2	Excision
Noske <i>et al</i> ³⁹	43	30	2 (7%)	2	0	Excision
Senetta <i>et al</i> ⁴⁰	41	36	0 (0%)	0	0	Case by case
Ceugnart <i>et al</i> ⁴¹	63	52	2 (4%)	2	0	Case by case
Biggar <i>et al</i> ⁴²	51	51	3 (6%)	2	1	Excision
Khoumais <i>et al</i> ⁴³	104	94	10 (11%)	5	5	Excision
Uzoaru <i>et al</i> ⁴⁴	145	95	3 (3%)	1	2	Case by case
Peres <i>et al</i> ⁴⁵	128	95	9 (10%)	5	4	Excision
Villa <i>et al</i> ⁴⁶	142	121	7 (6%)	NR	NR	Case by case
This study	94	73	5 (7%)	3	2	Case by case
Total	1139	963	76 (8%)	32	19	

Abbreviations: DCIS, ductal carcinoma *in situ*; Invasive, invasive carcinoma; NR, not reported.

Comparison of upgrade rates in selected studies of flat epithelial atypia on core biopsy (adapted from Verschuur-Maes *et al*⁴ to include studies with 30 or more excisions and to include studies from 2010 to 2013).

^aPercentages rounded to nearest integer.

for estrogen receptor and negative for HER-2 gene amplification or protein overexpression. Subsequent axillary sentinel lymph-node biopsies from both patients were negative for tumor. The three cases upgraded to ductal carcinoma *in situ* were all intermediate nuclear grade (2/3) and measured 8, 38, and 52 mm. In the case with 52 mm of ductal carcinoma *in situ*, less than 25% of calcifications were removed at the time of core biopsy. The two cases of ductal carcinoma *in situ* with available estrogen receptor immunohistochemistry results were estrogen receptor positive. One of the patients upgraded to ductal carcinoma *in situ* had a first-degree relative with a history of breast cancer. None of the other patients upgraded to carcinoma had a family history of breast cancer. The indication for biopsy in the case with 38 mm of ductal carcinoma *in situ* was an asymmetric density. Calcifications were the indication for the core biopsies in all of the other upgraded cases.

Discussion

This is one of the larger retrospective series of core biopsies with flat epithelial atypia alone from a single institution. In a recent meta-analysis of 22 studies published between 1990 and 2010, the frequency of finding carcinoma in an excision performed for flat epithelial atypia on a core ranged from 13 to 67%.⁴ Determining a clinically relevant upgrade rate requires correlation of radiology and pathology findings to exclude discordant cases. However, the radiology-pathology correlation data are either missing or incomplete in many studies.⁴ Studies that have included radiology-pathology correlation for core biopsy cases with papillomas^{22,23} and lobular neoplasia^{24–26} tend to report lower upgrade rates and may argue against mandatory excision for these diagnoses on core biopsy. Similarly, our overall upgrade rate of

7% for cases with careful correlation is lower than the majority of published studies with 30 or more excisions (Table 4) and closer to the 9.5% reported by Bianchi *et al*²⁷ in a series of 589 cases from multiple hospitals in Italy. Another recent study of 24 cases showed an upgrade rate of 3.2%.²⁸ Piubello *et al*²⁹ and Noel *et al*³⁰ reported no cases with carcinoma on excision in two smaller series in which only the patients with residual suspicious calcifications underwent surgical biopsy for flat epithelial atypia. It must also be noted that all but one of the pre-core biopsy imaging studies in our series were BIRADS-4. All of the cases reported by Noel *et al*³⁰ and all but two of the cases reported by Piubello *et al*²⁹ were BIRADS-3.

The limitations of this study include potential interobserver variability in the diagnosis of flat epithelial atypia among pathologists,³¹ a change in our microtomy protocol during the study period, the potential for sampling error in excisions that were not entirely submitted for histologic examination, and the variability in the needle gauge used for core biopsy. With the exception of the studies by Kunju and Kleer³² and Chivukula *et al*,³³ the data on the histologic sampling of the core biopsies with flat epithelial atypia are limited, and many studies are based on the routine examination of three (3) H&E levels at potentially varying depths in the tissue block. The data on gross sampling of excision specimens are similarly limited. In our practice, we may not entirely submit large lumpectomies for atypical hyperplasias and flat epithelial atypia diagnosed on core biopsy, but the entire biopsy site and all adjacent breast tissue are submitted.

The primary goal in the clinical management of patients with epithelial atypia of the breast arguably should be risk reduction rather than detection of other potential cancer precursors or small, indolent tumors. But, two different categories of risk must be considered. In the pre-core biopsy and pre-mammo-

graphic eras, the risk associated with atypical ductal hyperplasia and atypical lobular hyperplasia defined in long-term follow-up studies was defined as the relative risk (or odds ratio) of the patient developing a subsequent carcinoma (in either breast), usually 10–15 years after an open biopsy.^{34,35} As percutaneous breast core biopsy became more routine, the risk of finding carcinoma in tissue surrounding the core biopsy site became a more immediate concern. For patients with a core biopsy diagnosis of flat epithelial atypia, referral to a surgeon and the decision to excise an area of flat epithelial atypia are more likely based on the risk of finding carcinoma in adjacent tissue, rather the long-term relative risk of developing a carcinoma in the future in either breast. However, to the best of our knowledge there have been no prospective trials randomizing patients with flat epithelial atypia or any other pattern of atypia to excision vs close observation. Although the rate of upgrade to carcinoma in our series is quite low, the 23% of excision specimens with atypical ductal hyperplasia or atypical lobular hyperplasia in this study could have implications for risk stratification and decisions about chemoprevention.

The invasive carcinomas detected in this study were small, low grade, and hormone receptor positive. Two of the three cases upgraded to ductal carcinoma *in situ* with available hormone receptor results were estrogen receptor positive and none was high grade. The detection of these tumors may represent examples of overdiagnosis.^{36,37} And, if these patients had undergone surveillance rather than surgery, the clinically relevant tumors could likely have been identified at a later date at a point at which they would still be curable. In the two cases with 38 and 52 mm of ductal carcinoma *in situ*, less than 50% of the mammographic abnormalities were removed by core biopsy. None of the 14 cases with all of the calcifications removed by the stereotactic core biopsy was upgraded to carcinoma. These findings suggest that radiographic correlation may help in stratifying risk for upgrade. Patients with complete removal of targeted calcifications at biopsy may choose to undergo close surveillance rather than excision due to the very low risk of upgrading to carcinoma. In contrast, it seems prudent to offer excision to patients with a core biopsy diagnosis of flat epithelial atypia with limited sampling of the radiographic target or discordant imaging findings, similar to what has been proposed for solitary papillomas and lobular neoplasia diagnosed on core biopsy.^{24–26}

Most studies evaluating the upgrade rates of flat epithelial atypia on core biopsy have not reported the characteristics of the carcinoma upgrades identified on excision. As this study demonstrates, flat epithelial atypia is associated with other forms of low-grade atypia and low-grade estrogen receptor-positive carcinomas. The carcinomas found on excision in this study were pT1a, low-grade estrogen

receptor-positive invasive carcinomas or estrogen receptor-positive ductal carcinoma *in situ*. In an era of increasing recognition of overdiagnosis and over-treatment of breast lesions detected by screening mammography, the clinical value of detecting the upgrades in these patients could be challenged.^{36,37}

Disclosure/conflict of interest

The authors declare no conflict of interest.

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