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Significance of "Atypia" Found on Needle Biopsy of the Breast: Correlation with Surgical Outcome

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SIGNIFICANCE OF "ATYPIA" FOUND ON NEEDLE BIOPSY OF THE BREAST: CORRELATION WITH SURGICAL OUTCOME

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SIGNIFICANCE OF "ATYPIA" FOUND ON NEEDLE BIOPSY OF THE BREAST: CORRELATION WITH SURGICAL OUTCOME. Anika Nina Watson, Liane E. Philpotts. Section of Breast Imaging, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT.

Although core needle biopsy has been shown to be effective in diagnosing both benign and malignant mammographically detected lesions in the breast, it has also been shown to underestimate cancer most likely due to sampling error. Since a diagnosis of atypical hyperplasia versus malignancy is based on quantitative factors (which could be affected by an error in sampling), the current recommendation is surgical excision for atypical hyperplasia diagnosed on core biopsy. The purpose of the study was to determine if a subset of patients with atypia diagnosed by core biopsy fit the Breast Imaging Reporting and Data System's (BI-RADS) Category 3, "probably benign," definition of having a less than 2% chance of being carcinoma at subsequent surgical excision when comparing histologic subtype, mammographic findings, core biopsy factors, and clinical factors. For this subset of patients, imaging follow-up, rather than surgical excision could be recommended.

Retrospective searches of the breast imaging and pathology databases from 1992 to August 2005 were performed to identify all cases of 'atypia' found on core biopsy. The data collection and database use were HIPAA-compliant and followed the protocols of the institutional review board. The pathology reports were reviewed to determine the histologic type: atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), mixed, or "other" atypia. The ADHs were further classified as to focal/mild, not otherwise stated (NOS), or marked based on the pathology reports. Follow-up information was obtained to identify cases in which lesions that were initially diagnosed as atypia at the time of core biopsy were later upgraded to malignancy after subsequent surgical excision or mammographic follow-up. The histologic subtype, mammographic findings, core biopsy factors, and clinical factors were compared to lesions which were not upgraded to carcinoma. The results were analyzed with a Chi-square test, with $p < 0.05$ indicative of significant difference.

There were 327 cases of 'atypia' found in the 3898 (8%) core needle biopsies that were performed during the above stated time period. The histologic subtypes were: ADH (75%), ALH (13%), mixed (4%), "other" (7%). There was an overall malignancy rate of 13%. Malignancy was found in 14% of ADH lesions, 5% of ALH, 20% of mixed, and 10% of "other" atypias on excision. The 215 ADH cases were further examined in their histologic subtypes (37% were focal/mild, 42% NOS, and 20% ADH marked). Malignancy was found in 6% focal/mild ADH, 10% NOS ADH, and 40% ADH marked. When comparing all the factors considered, the lowest underestimation rate (3%) was found in patients with focal/mild ADH diagnosed with a vacuum- assisted 11-gauge biopsy needle.

Upgrade rates vary significantly depending on classification of ADH and the type of atypia. While severe forms of atypia (NOS ADH, ADH marked, mixed atypias, and "other" atypias) should continue to receive routine surgical excision, there are selected subsets of patients with whom other management options could possibly be considered. For patients with focal/ mild atypical ductal hyperplasia diagnosed at the time of core biopsy with a vacuum-assisted 11-gauge needle, imaging follow-up (mammography or MRI) could be considered on an individual basis.

ACKNOWLEDGEMENTS

The receiving of a doctorate of medicine degree is the culmination of a dream that began over twenty years ago. It is a dream that has now become a reality due to the help and assistance of so many individuals along the way.

I would like to thank my parents, Percy W. Watson and Dianne Watson-Johnson, who have always been there for me, and also my siblings: Ayanna, Kobie, Mallori, and Megan. There are several individuals in the Yale medical community who have been there to support me during my time at Yale University Medical School. Dr. Woody Lee has been an advisor and mentor who has offered me his wisdom on numerous occasions over the past four years. Dean Nancy Angoff has been there whenever I have had a problem and has seen me grow from a student to a physician. Also, this thesis would not have been possible without the direction, guidance, and support from Dr. Liane Philpotts, my thesis advisor.

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INTRODUCTION

Atypia is an abnormality of a cell, a deviation of the regular form, which may be a precursor to malignancy. However, its significance in the breast is to a great extent dependent upon context. Studies have shown a wide variation in the rate of underestimation of carcinoma at surgical excision. For this reason the continued recommendation has been surgical excision after atypia is diagnosed on core needle biopsy.

A normal duct has two layers, a basally located myoepithelial cell layer with cells that have a dark, compact nuclei and little cytoplasm and a single luminal cell layer (cells have a large nuclei, small nucleoli, and more abundant cytoplasm) (*1*). In epithelial hyperplasia, the lumen becomes filled with a heterogeneous population of cells of various morphologies, including both luminal and myoepithelial cell types as seen in *Figure 1* (*1*). In atypical hyperplasia, there is a specific lesion of either ductal or lobular elements with uniform cells and loss of apical-basal cellular orientation, but not sufficiently abnormal to be diagnosed as either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) (*Figure 2-4*) (*2*).

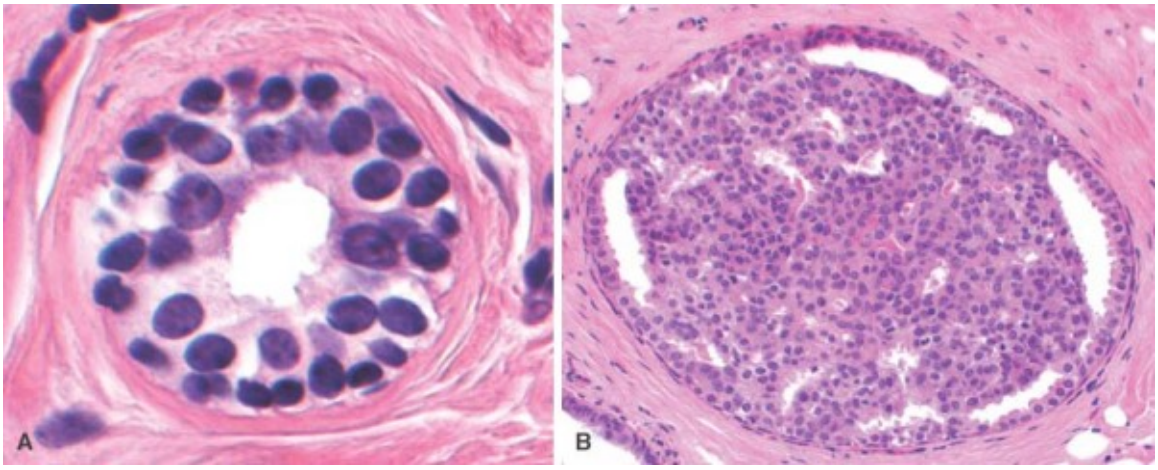

Figure 1: A. *Normal.* A normal duct or acinus has a single basally located myoepithelial cell layer (cells with dark, compact nuclei and scant cytoplasm) and a single luminal cell layer (cells with larger open nuclei, small nucleoli, and more abundant cytoplasm). **B.** *Epithelial hyperplasia.* The lumen is filled with a heterogeneous population of cells of different morphologies, often including both luminal and myoepithelial cell types. Irregular slit-like fenestrations are prominent at the periphery. (*1*)

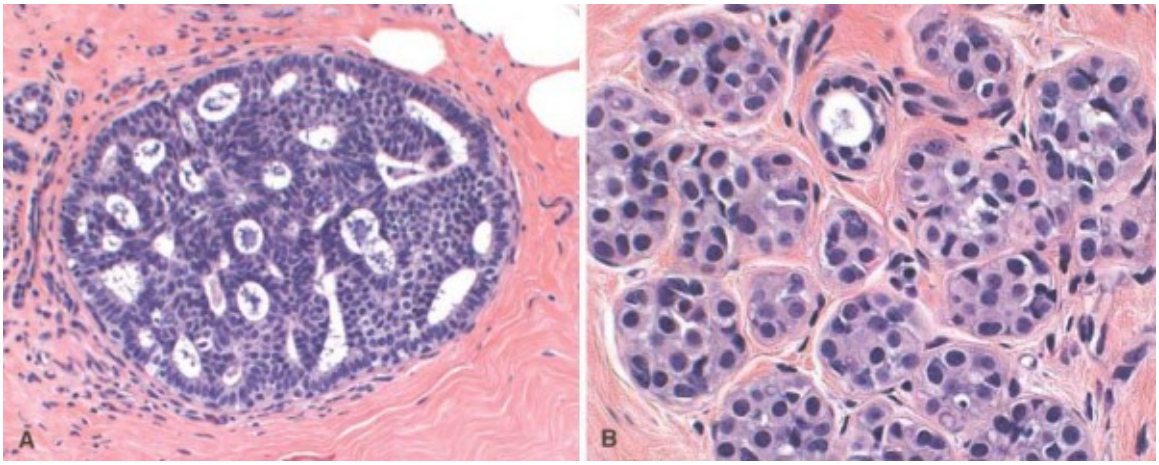

Figure 2: A. *Atypical ductal hyperplasia*. A duct is filled with a mixed population of cells consisting of oriented columnar cells at the periphery and more rounded cells within the central portion. Although some of the spaces are round and regular, the peripheral spaces are irregular and slit-like. These features are highly atypical but fall short of a diagnosis of DCIS. **B.** *Atypical lobular hyperplasia*. A population of monomorphic small, rounded, and loosely cohesive cells partially fills a lobule. Some intracellular lumina can be seen. Although the cells are morphologically identical to the cells of LCIS, the extent of involvement is not sufficient for this diagnosis. *(1*)

Atypical ductal hyperplasia (ADH) has been traditionally considered a histologically borderline lesion that has some but not all of the features of ductal carcinoma in situ. These features may include a uniform population of cells, smooth geometric spaces between cells or micropapillary formations with even cellular placement, hyperchromatic nuclei, or any combination of these three features. Atypical ductal hyperplasia also lacks the extent of involvement required to meet the strict criteria for DCIS (*3-5*). Involvement of a single duct or an aggregate diameter of involvement of less than 2 mm constitutes a diagnosis of ADH, and a more extensive lesion with the same histologic features is labeled DCIS (*5*).

For a diagnosis of LCIS, Page et al. stated that more than half the acini in an involved lobular unit must be filled and distended by the characteristic cells, leaving no central lumina (*6*). A lesion is regarded as atypical lobular hyperplasia (ALH) when it is less well developed, with the acini only partly filled with the characteristic cells and minimal or no distention of the lobule. Therefore, the diagnosis of ADH versus DCIS and ALH versus LCIS relies mainly on quantitative rather than qualitative measures (*Figure 3 & 4*).

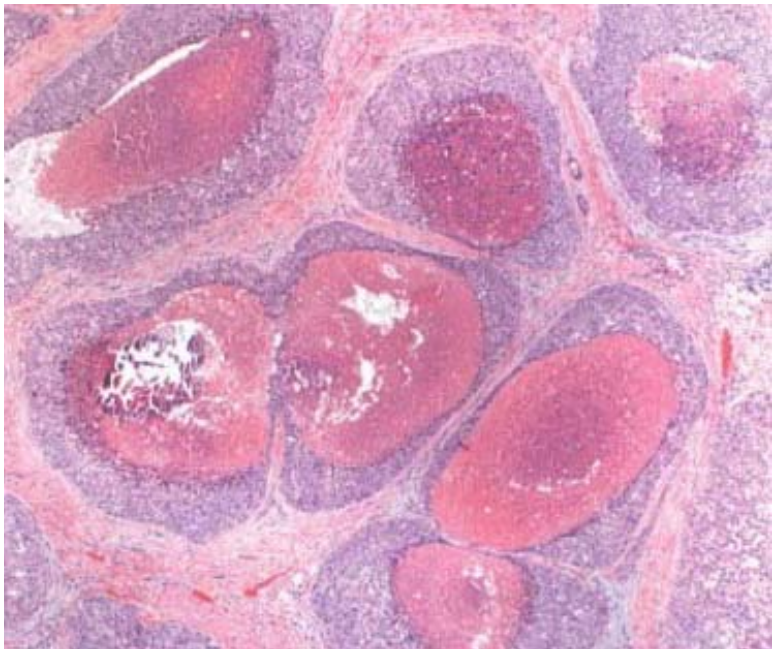

Figure 3: *Ductal carcinoma in situ (Comedo)* fills several adjacent ducts (or completely replaced lobules) and is characterized by large central zones of necrosis with calcified debris. This type of DCIS is most frequently detected as radiologic calcifications. Less commonly, the surrounding desmoplastic response results in an ill-defined palpable mass or a mammographic density. (*1*)

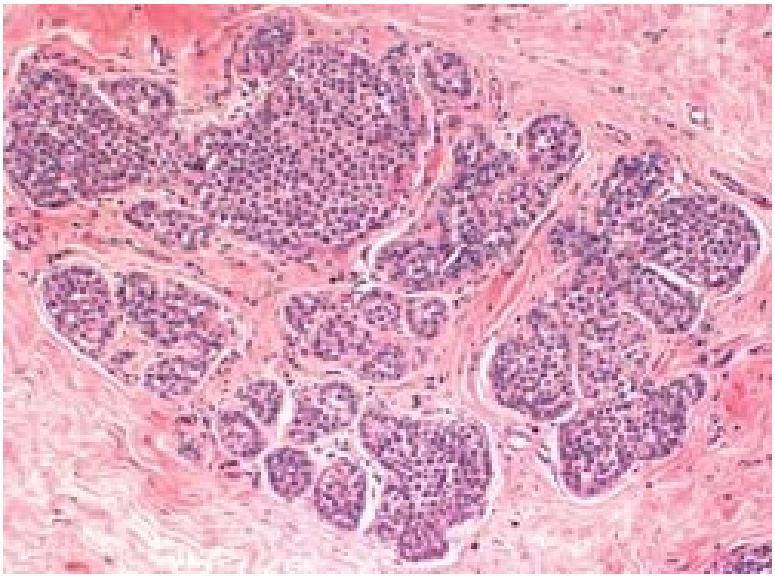

Figure 4: *Lobular carcinoma in situ*. A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized**.** (*1*)

Core needle biopsy is a percutaneous procedure that involves removing small samples of breast tissue using a hollow "core" needle. For palpable lesions, this is accomplished by fixing the lesion with one hand and performing a freehand needle biopsy with the other. In the case of non-palpable lesions, stereotactic mammography or ultrasound image guidance is used. Stereotactic mammography involves using computers to pinpoint the exact location of a breast mass based on mammograms taken from two different angles. The computer coordinates help the physician to guide the needle to the correct area in the breast. With ultrasound, the radiologist will watch the needle on the ultrasound monitor to help guide it to the area of concern. Twelve core needle insertions are typically needed to obtain a sufficient sample of breast tissue with stereotactic guided biopsy, and three to five insertions with ultrasound guided biopsy. Typically, samples approximately 0.75 inches long (approximately 2.0 centimeters) and 0.0625 inches (approximately 0.16 centimeters) in diameter are removed (*7*).

Vacuum-assisted breast biopsy is a minimally invasive procedure that also allows for the removal of multiple tissue samples. It is able to remove approximately twice the amount of breast tissue compared with core needle biopsy while still offering the patient a minimally invasive breast biopsy procedure. However, unlike core needle biopsy, which involves several separate needle insertions to acquire multiple samples, the special biopsy probe used during vacuum-assisted biopsy is inserted only once into the breast through a small incision (*7*).

Both core needle and vacuum-assisted biopsy usually allow for a more accurate assessment of a breast mass than fine needle aspiration because the larger core needle usually removes enough tissue for the pathologist to evaluate abnormal cells in relation to

the surrounding small sample of breast tissue taken in the specimen. Nevertheless, core needle and vacuum-assisted biopsy only remove *samples* of a mass and not the entire area of concern. Therefore, it is possible that a more serious diagnosis may be missed by limited sampling of a lesion. Since the diagnosis of atypical hyperplasia versus carcinoma relies mainly on quantitative measures there is a fear that underestimation of cancer can occur. This is the reason why atypical hyperplasia remains one of the major reasons for re-biopsy after core biopsy.

In the case of ADH (atypical ductal hyperplasia), studies have shown underestimation rates as high as 75%, with a range of 20% - 75% using a 14-gauge automated large-core needle (*8-13*). With the advent and use of the 11-gauge directional vacuum-assisted device the percentage of underestimation has decreased due to improved tissue sampling and more accurate placement of the localizing marker at the biopsy site. However, it has not been sufficient enough to avoid surgical excision following the diagnosis of ADH on core needle biopsy, with upgrade rates from 10% - 27% (*9, 11, 14, 15*).

There is a similar recommendation for ALH (atypical lobular hyperplasia) diagnosed on core biopsy (*16, 17*). There has been difficulty in drawing firm conclusions in the management of ALH. The few studies that have attempted to address the appropriate management of ALH when identified on core needle biopsy are limited by small patient numbers and thus there is the possibility of selection bias with regard to excision in the available studies. Further, a number of them were published only in abstract form and provided only limited methodologic, radiologic, and clinical details (*17*).

Surgical excision thus remains the recommendation for follow-up treatment after a diagnosis of “atypia” on initial biopsy (*18-29*). This recommendation diminishes the benefit of core biopsy. Core biopsy allows for large sampling of the breast lesion and when compared with surgical excision, it is less expensive, easier to perform, and causes no cosmetic breast deformity. Also, it reduces the number of procedures for which the patient is subjected (*30*).

The Breast Imaging Reporting and Data System (BI-RADS) lexicon of the American College of Radiology categorizes mammographically visible lesions (*31*). BI-RADS is the product of a collaborative effort between the National Cancer Institute, the Centers for Disease Control and Prevention, the Food and Drug Administration, the American Medical Association, the American College of Surgeons, and the College of Pathologists. This system is a quality assurance tool designed to standardize mammographic interpretations and facilitate outcome monitoring. Through a medical audit and outcome monitoring, BI-RADS provides important peer review and quality assurance data to improve quality of patient care. BI-RADS classifies lesions into one of six different categories:

Category 0: Need Additional Imaging Evaluation

Category 1: Negative

Category 2: Benign Finding

Category 3: Probably Benign Finding, Short Interval Follow-Up Suggested

Category 4: Suspicious Abnormality, Biopsy Should Be Considered

Category 5: Highly Suggestive of Malignancy, Appropriate Action Should Be Taken

Lesions in category 3 have a frequency of cancer of less than 2%, being categorized as probably benign with the recommendation of a short interval of follow-up (*32*). The recommendation is mammographic follow-up rather than biopsy. To date there have been no clinical, mammographic, or biopsy features alone or used in combination that have been identified that could recognize a subset of patients diagnosed with ADH as having lesions with a less than 2% chance of carcinoma at surgical biopsy (*25*). Most studies that have been performed looking at underestimation rates with ADH diagnosis have not divided it into histologic subclasses based on a quantitative measure of the amount of atypia present.

We performed an institutional review to determine the outcome of atypias (ADH, ALH, mixed, or "other" atypias) found on core biopsies of the breast by comparing histologic subtype, mammographic findings, core biopsy factors, and clinical factors with surgical histology or mammographic follow-up. The goal was to define a potential subset of patients for whom the risk of malignancy is low and surgical excision may not be necessary.

STATEMENT OF PURPOSE

Based on clinical observation there appears to be differences in the underestimation of malignancies for different types of atypia diagnosed on needle biopsy. The purpose of the study was to determine if a subset of patients with atypia diagnosed by needle biopsy fit the Breast Imaging Reporting and Data System's (BI-RADS) Category 3, "probably benign," definition of less than 2% chance of being carcinoma at subsequent surgical excision when comparing histologic subtype, mammographic findings, core biopsy factors, and clinical factors. For this subset of patients, imaging follow-up, rather than surgical excision could be recommended.

MATERIALS AND METHODS

A retrospective search was performed of the diagnostic imaging and pathology databases at our institution from December 1992 to August 2005 for all cases of atypia diagnosed from image-guided biopsy (stereotactic and ultrasound). Each database was searched independently and in combination to identify cases of atypia. The study was approved by the institutional review board, the human investigations committee. Individual patient consent was not required for the project. The study was in line with HIPPA regulations.

Of the 3898 core biopsies, atypia, without associated malignancy, was diagnosed in 327 (8%). Follow-up information was available for 286 (87%) of the 327 cases of atypia identified. Either no follow-up information was available or follow-up was provided at another institution for 41 cases. Patients who did not receive follow-up were excluded from the study, as were those who received their initial diagnosis or surgical excision at another institution. The radiology reports were reviewed to record the recommendations for subsequent management. The core biopsies performed between the years of 1992 to 1996 were done using a 14-gauge core needle biopsy technique. However, beginning in October 1996 most stereotactic biopsies were performed using an 11-gauge vacuum-assisted biopsy device (Mammotone; Biopsy/Ethicon Endo-Surgery, Cincinnati, OH). For ultrasound biopsies, the choice of either the automated or the vacuum-assisted method was at the discretion of the responsible radiologist. The procedures were performed on a dedicated prone table. Until June 1997, the table was a Stereoguide (Lorad Medical Systems, Danbury, CT); from July 1997 through March 1999 the Universal table (United States Surgical, Norwalk, CT) was employed (*14*).

Superficial anesthesia was ensured by means of injection of 1% lidocaine hydrochloride. Deep anesthesia was ensured by using 1% lidocaine hydrochloride (10 mg/mL) with epinephrine (1:100,000; 10 mg/mL epinephrine). Lidocaine hydrochloride with epinephrine was not given in patients with a history of cardiac disease. Tissue was acquired after firing the probe inside the breast, with pre- and post-fire images (stereotactic or ultrasound) documenting probe position within the lesion.

The average number of core specimens obtained per case was 12 for stereotactic guided biopsy and 3-5 specimens for ultrasound guided biopsy. Six breast radiologists were responsible for the procedures during the study period; however, many of the biopsies were performed by fellows and residents under the supervision of the responsible radiologist.

For each case of atypia, the breast imaging and pathology reports were reviewed. The breast imaging reports were reviewed to attain the size of the needle used in the core biopsy, mammographic findings of the lesion, and whether the biopsy was stereo- or ultrasound guided. The pathology reports were reviewed to determine the histologic type: atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), “mixed”, or "other" atypia. “Other” atypias included atypical papillomas, atypia caused from radiation effect, and atypical hyperplasia not classified as either ductal or lobular by the pathologist. The atypical ductal hyperplasias were further classified as to focal/mild, not otherwise stated (NOS), and marked ADH based on the report of the pathologist. Histologic slides of percutaneous biopsy specimens were interpreted at our institution. Before 2000 slides were reviewed primarily by a single pathologist. Biopsies after that

year were reviewed primarily by one of two pathologists. All were experienced in breast pathology.

Patient characteristics were obtained and reviewed including age, parity, personal and family history of breast cancer, which was classified as either *weak*, *intermediate*, or *very strong*. A designation of *weak* was given to those where breast carcinoma was diagnosed in a second-degree relative. A designation of *intermediate* was given to those with a first-degree, post-menopausal relative and *very strong* to those with a pre-menopausal, first-degree relative. Comparison of outcomes in relation to clinical factors (personal or family history) was also performed.

A review of the diagnostic imaging and pathology databases was done to obtain data regarding the follow-up management of the atypical lesions, whether that follow-up was surgical excision or mammography. Subsequent surgical histology or breast imaging reports of mammograms were reviewed. The results of the core needle biopsy were correlated with the ensuing follow-up to identify cases in which cancer was underestimated by core needle biopsy. Underestimated cancers were those in which carcinoma was not diagnosed at the core needle biopsy (i.e., only atypia diagnosed). Accurately diagnosed lesions were defined as those in which the histologic diagnosis from the excisional biopsy was the same as or a lower stage than the diagnosis of the core needle biopsy.

Seven separate analyses were performed to compare the accurately diagnosed and underestimated cases: the entire ADH group, the entire ALH group, the entire Mixed group, the entire “Other” atypias group. The ADH group was then further analyzed according to its sub-classifications: ADH focal/mild, ADH NOS, and ADH marked. The

mammographic features (calcifications, mass, or architectural distortion), patient characteristics, and biopsy technique in all cases were reviewed.

Two-by-two tables were analyzed using the chi-square test. In cases were the expected cells were small, Fisher's exact tests were employed. Statistical significance was set at two tailed alpha < 0.05. Data was analyzed with statistical SAS software for Windows (Version 9.1).

RESULTS

Of the 327 cases of atypia identified, surgical histology or mammographic information was available in 286 (87%) of the cases. Forty-five patients (16%) elected for mammographic follow-up, with a mean average follow-up time of 19 months (range= 1-105 months). Patients undergoing imaging follow-up had no suspicious changes, including 1 patient who had MRI follow-up. The other 240 patients (84%) underwent surgical excision of the lesion.

. From the total of 286 cases there were 191 (67%) who had mammographic features of calcifications, 83 (29%) who had mammographic features of a mass, 8 (3%) who had both calcifications and a mass present, 3 (1%) with architectural distortions, and 1 had both a mass and architectural distortion present. Two hundred and fifteen (75%) patients were found to have atypical ductal hyperplasia (ADH) at core biopsy. There were 37 (13%) cases of atypical lobular hyperplasia (ALH) and 10 (3%) cases classified as "mixed" atypia. The remaining histologic subtypes were "other", of which there were 21 (7%) patients and 3 (1%) with an unknown type of atypia (*see Table A*).

Of the 215 atypical ductal hyperplasia (ADH) cases, 79 (37%) were found to have mild or focal atypia, 93 (43%) cases were classified as 'not otherwise stated' (NOS) ADH, and 43 (20%) patients having marked ADH (*see Table B*).

The majority of core biopsies with atypia were performed with stereotactic guidance (n=266, 93%), with the remaining ones being ultrasound guided (n=20, 7%). In 20% (n=57) of the core biopsies a 14-gauge automated needle was employed, and in 80% (n=228) an 11-gauge vacuum-assisted device was used. There was a single procedure in which an 8-gauge vacuum-assisted device was used.

Selected risk factors for breast cancer were reviewed. These risk factors included a history of carcinoma elsewhere, personal and/or family history of breast carcinoma, history of gynecological cancer, nulliparity, and late child bearing age. Of the 286 women with atypia on core biopsy, 124 (43%) had either a personal or family history of breast cancer, 134 (47%) had no history, and for 28 (10%) patients this information was unavailable.

For the entire group, 38 cases of cancer were diagnosed at excision, for an overall malignancy rate of 13% for all atypias; invasive carcinoma in 9 (24%) and DCIS in 29 (76%). The overall malignancy rate for ADH was 14% (n=31).Malignancy was found in 6% (n=5) of the cases of focal/mild atypical ductal hyperplasia, in 10% (n=9) of the 'not otherwise stated' (NOS) ADH, and 40% (n=17) of the cases of marked ADH. The remaining histologic types examined had underestimation rates as follows, atypical lobular hyperplasia (ALH) was found to have a malignancy of 5% (n=2), 20% (n=2) of the mixed atypia demonstrated malignancy, and 10% (n=2) of the "other" atypias on excision.

Of the 38 cases in which carcinoma was underestimated, 87% (n=33) had calcifications on the initial mammogram, 11% (n=4) presented as a mass, and 3% (n=1) presented a mass and architectural distortion. In 97% (n=37) the biopsy was under stereotactic guidance, with the remainder being under ultrasound guidance (3%, n=1) (*Table C*). An 11-gauge vacuum-assisted device was employed in the majority of the biopsies (n=23, 61%), with a 14-gauge automated needle being used in 39% (n=15) of the procedures. Thus, the 11-gauge vacuum-assisted device had an upgrade rate of 10%, while the 14- gauge automated needle had an upgrade rate of 26% (*see Table D*). Sixteen

(42%) had either a personal or family history of breast cancer, 13 (34%) had no personal or family history, and for 9 (24%) patients this information was unavailable (*see Table E*).

Table A: *Atypia Histologic types:* Percentage upgraded vs. percentage benign after surgical excision

	Positive (+)	**Upgraded (%)**	**Negative (-)**	**Benign (%)**	***p*-value**
ADH **n= 215**	31	14	184	86	*p*=0.3264
ALH **n= 37**	2	5	35	95	*p*=0.1932
Mixed atypia **n= 10**	2	20	8	80	*p*=0.6272
Other atypia **n= 21**	2	10	19	90	*
Unknown atypia **n= 3**	1	33	2	67	*

Positive (+): Lesions upgraded to cancer after surgical excision
Negative (-): Benign lesions
Upgraded (%): Percentage upgraded to cancer after surgical excision
Benign (%): Percentage of benign lesions
***:** *p*-value unable to be calculated

Table B: *Atypical Ductal Hyperplasia (ADH):* Upgrade rate comparing histologic sub-classifications

ADH	**Positive (+)**	**Negative (-)**	**Percentage (%)**
Focal n= 79	5	75	6
NOS n= 93	9	86	10
Marked n= 43	17	26	40

Positive (+): Lesions upgraded to cancer after surgical excision
Negative (-): Benign lesions
Percentage (%): Percentage upgraded to cancer after surgical excision

Table C: Mammographic findings vs. Biopsy factors comparing rates of upgrade

	Total				**Ultrasound guidance**			**Stereotactic guidance**			
	(+)	**(-)**	**(%)**	***p-val***	**(+)**	**(-)**	**(%)**	**(+)**	**(-)**	**(%)**	***p-val***
Calcs n= 191	33	158	17	p=0.005	0	0	0	33	158	17	*p*=0.0113
Masses n= 83	4	79	5	p=0.007	1	19	5	3	60	5	*p*=0.0163
Arch. Dist. n= 3	0	3	0	p=1.0`	0	0	0	0	3	0	*p*=1.0
Mass + Calcs n= 8	0	8	0	p=0.6029	0	0	0	0	8	0	*p*=0.6046
Mass+ A.D. n= 1	1	0	100	p=0.1329	0	0	0	1	0	100	*p*=0.1391

Calcs: Calcifications
Arch. Dist.: Architectural distortion
Mass+ Calcs: Mass + Calcifications
Mass+ A.D.: Mass + Architectural distortion
(+): Upgraded lesion, found to be cancer at time of surgical excision
(-): Benign lesion at time of surgical excision
(%): Percentage upgraded to cancer after surgical excision

Table D: *ADH histologic subtypes:* Comparison of needle size and rate of upgrade

	Positive (+)	**Negative (-)**	**Percentage (%)**	***p*-value**
ADH (f) 14g	3	10	23	*p*=0.0294
ADH (f) 11gV	2	63	3	*p*=0.0366
ADH NOS 14g	4	15	21	*p*=0.0808
ADH NOS 11gV	5	69	7	*p*=0.0808
ADH marked 14g	5	4	56	*p*=0.4448
ADH marked 11gV	12	22	35	*p*=0.4448

14g: Automated 14-gauge biopsy needle
11gV: Vacuum-assisted 11-gauge biopsy needle
Positive (+): Lesions upgraded to cancer after surgical excision
Negative (-): Benign lesions
Percentage (%): Percentage upgraded to cancer after surgical excision

Table E: *Atypia Histologic types:* Upgrade rates compared to personal/ family history of breast cancer

		Positive (+)	**Negative (-)**	**Percentage (%)**	***p*-value**
ADH	Total	31	184	14	
	(+) P/F Hx	13	73	15	p=0.3235
n= 215	(-) P/F Hx	11	95	10	
	Unknown	7	17	29	
ALH	Total	2	35	5	
	(+) P/F Hx	1	17	6	p=1.0
n= 37	(-) P/F Hx	1	15	6	
	Unknown	0	3	0	
Mixed atypia	Total	2	8	20	
	(+) P/F Hx	2	6	25	p=1.0
	(-) P/F Hx	0	2	0	
n= 10	Unknown	0	0	0	
Other atypia	Total	2	19	10	
	(+) P/F Hx	0	11	0	p=0.2143
	(-) P/F Hx	2	8	20	
n= 21	Unknown	0	0	0	
Unknown atypia	Total	1	2	33	
	(+) P/F Hx	0	1	0	*
	(-) P/F Hx	0	0	0	
n= 3	Unknown	1	1	50	

P/F Hx: Personal and/or family history of breast cancer
Positive (+): Lesions upgraded to cancer after surgical excision
Negative (-): Benign lesions
Percentage (%): Percentage upgraded to cancer after surgical excision
***:** *p*-value unable to be calculated

DISCUSSION

Atypias found on core biopsies of the breast constitute a diverse group of processes representing high risk markers, precursor lesions, or frank malignancies (due to sampling errors). The percentage of cases with associated malignancies found on surgical excision is also greatly variable, especially in the case of ADH and ALH. It has been generally accepted that in women with ADH, the risk of breast cancer is increased four-fold (*23*). The situation is more complex with ALH. Historically, lobular carcinoma in situ was considered to represent an indicator of risk for invasive breast cancer rather than a direct precursor lesion. However, accumulating information suggests that lobular carcinoma in situ proliferative lesions are not only indicators of increased risk of breast carcinoma, but indeed precursors of invasive disease (*16, 23, 36*).

The determining factor between a diagnosis of ADH versus DCIS and ALH versus LCIS is based largely upon the size of the lesion. Although ductal carcinoma in situ represents a biologically and morphologically diverse disease, it is characterized by a proliferation of malignant epithelial cells confined within the lumens of the mammary ducts, without evidence of invasion beyond the basement membrane into the adjacent breast stroma (*33*). Atypical ductal hyperplasia has some but not all features of DCIS, with an aggregate diameter of less than two millimeters or involvement of a single duct (*34*). For a diagnosis of LCIS more than half the acini in an involved lobular unit must be filled and distended by the characteristic cells, leaving no central lumina (*35*). When a lesion is less well developed, with the acini only partly filled with the characteristic cells and minimal or no distention of the lobule is it classified as ALH. With atypical lesions

there has been much discussion over recommendations for management of these patients, particularly those diagnosed by core needle biopsy.

Core needle biopsy is widely used in place of surgical biopsy for lesions detected mammographically in the breast. Although it has shown to be effective in diagnosing both benign and malignant lesions, it has also been shown to underestimate cancer most likely due to sampling error. This uncertainty has led to the recommendation for additional surgery. For instance, a patient with ADH at core biopsy will be advised to undergo surgical excision of the lesion for fear it will be upgraded to carcinoma with complete excision. Thus, with a diagnosis of atypia comes the need for an additional procedure, reducing the benefits of core needle biopsy. Therefore, minimizing underestimation or identifying a subset of patient in which underestimation is low would be desirable.

The option of having imaging follow-up rather than surgical excision would also help to reduce the amount of emotional and mental stress that patients undergo. Although core needle biopsy offers decreased morbidity and scarring when compared with surgical breast biopsy it has been reported that patients experience clinically marked levels of anxiety while they undergo breast biopsy, whether it is an open- or core needle biopsy. In fact, levels of anxiety for a breast biopsy have been reported to exceed the anxiety levels for patients who undergo elective surgery, such as cholecystectomy (*37-42*). Many women fear the worst outcome when they undergo breast biopsy (*43*). These feared outcomes include the possibility of disfiguring surgery, radiation treatment, and chemotherapy, as well as the possibility that the disease may be incurable (*44*).

Consequently, having an alternative to surgical excision may help to reduce the level of anxiety a patient may experience.

This study is similar to previous studies in the overall percentage of atypia without associated breast carcinoma diagnosed with core needle biopsy (8%), with an overall upgrade rate of 13%, which is on the lower range of most published values (*18, 45, 46*). However, when analyzing factors, such as histologic subtype, mammographic findings, core biopsy factors, and clinical factors, variables can be isolated that identify subsets of patients for whom underestimation is low.

Although it has been thought that the designation of the degree of atypia in breast hyperplasia is arbitrary, and subject to interobserver variability, it can be clearly seen that when atypia is divided into its histologic subtypes there is a very low malignancy rate for focal atypical ductal hyperplasia, with increasing rates with increased severity of atypia present. Adrales et al. demonstrated that the pathologic characteristics of Mammotome specimens in their study were found to be statistically significantly different between their two excision groups (totaling 62 patients), with 44% of the patients in the malignant group having markedly atypical hyperplasia as compared with only 9% of those with mild or moderate atypia (*18*). O'hea et al. performed 3 sub-classifications: group 1 comprised patients with atypia that did not fully meet the criteria for ADH; group 2 comprised patients with true ADH; and group 3 comprised patients with severe ADH, which was borderline ductal carcinoma in situ. No cancer was found after surgical biopsy in the patients who were in group 1 (mild atypia, not meeting the criteria for ADH) (*28*).

Furthermore, our study demonstrates, in the case of ADH, there can also be an advantage to divisions into different sub-classifications than the above mentioned, with division of mild and moderate (or 'not otherwise stated') into two separate categories. Those patients exhibiting focal atypia have a lower rate of malignancy (6%) than those with atypia that is 'not otherwise stated' (10%) (*see Table B*). Given the low likelihood of malignancy on subsequent excision of cases of both focal/mild ADH (6%) and ALH (5%), mammographic follow-up could possibly be considered rather than routine surgical excision. However, this option would have to be considered on an individual basis.

It is true that the 6% carcinoma underestimation in focal/mild ADH and 5% for ALH is too high for these lesions to be labeled as category 3 in BI-RADS (frequency of cancer should be less than 2%). In category 3, lesions would be categorized as most likely benign with the recommendation of short interval follow-up with the advisement of imaging (mammographic) follow-up rather than surgical biopsy. However, when other confounding factors, such as initial mammographic findings and core biopsy factors, are analyzed along with the histology there could be a subset of patients for which this option could be presented.

Patients whose initial mammography showed microcalcifications and patients whose core biopsy was performed with an automated 14-gauge needle all exhibited a higher rate of upgrade. While only 191 of the 286 (66%) total atypical lesions were calcifications, they comprised 33 of the 38 lesions (86%) that were upgraded to carcinoma after excision. Thus, having an upgrade rate of 17% (p=0.005). This in contrast with atypical lesions that had an initial mammographic presentation of a mass, with an upgrade rate of only 5% (p=0.007) (*see Table C*).

Likewise, previous studies have demonstrated a clear difference in the rates of underestimation when either a 14-gauge or 11-gauge needle is employed. Studies have published underestimation rates as high as 75%, with a range of 20% - 75% using a 14-gauge automated large-core needle (*8-13*). The development of the directional vacuum-assisted biopsy device and the introduction of the 11-gauge needle have allowed improved accuracy in sampling clusters of calcifications and masses (*9, 11, 14, 15*). Although the number of lesions in most series was relatively small, the collective data provided by these investigators indicate a decrease in the rate of histologic underestimation when compared to the 14-gauge automated needle. The 11-gauge directional vacuum-assisted device removes a larger quantity of tissue per sample (96 mg) than the automated 14-gauge needle (17mg) (*47*). Also, calcification retrieval and complete mammographic lesion removal are more likely with the directional vacuum-assisted biopsy device instrument (*48*). The vacuum-assisted biopsy device produces heavier and larger specimens with more contiguous sampling. Liberman et al. demonstrated an increase from 4% complete lesion removal with automated core biopsy to 13% with vacuum- assisted biopsy (*49*). Burbank similarly reported complete lesion removal of 48% of lesions diagnosed by vacuum-assisted device compared with 15% of lesions removed by automated core needle biopsy (*50*).

The data from this study supports previous published findings and is statistically significant in the case of focal/mild ADH. While the overall upgrade rate for focal/mild ADH is 6%, a clear distinction can be made based on the size of the needle employed. The underestimation rate with an automated 14-gauge needle is 23% (p=0.0294), while

the rate with an 11-gauge vacuum-assisted device is only 3% (p=0.0366), close to the 2% marker to fit into the BI-RADS category 3 (*see Table D*).

Other core biopsy factors that were not analyzed in this study that could prove beneficial are the percentage of lesion removed at core biopsy and the number of samples that were taken of the lesions, both important variables in reducing sampling error (*26, 51, 52*). This is supported by Liberman et al. who underlined the importance of complete excision rather than sampling of the mammographic lesion to minimize the risk of underestimation (*53*). For instance, the rate of upgrade could be investigated with complete removal of the lesion along with the division of ADH into histologic subtypes (focal/mild, NOS, and marked ADH). However, to do this it may be necessary to conduct a multi-institutional study in order to obtain study numbers that would be statistically significant.

Along with histologic subtype, mammographic findings, and core biopsy factors, clinical factors can also provide data to aid in the management of post-core biopsy decisions. Clinical factors that could be included are a personal or family history of breast cancer and factors unable investigated in this study such as age, nulliparity, late child bearing age, and use of hormone replacement therapy. Although we were unable to find a statistically significant correlation with positive personal or family history of breast cancer due to small data set and large percentage of patients for whom this information was unknown, previous studies have been able to demonstrate a correlation (*see Table E*). Dupont et al. showed that a positive family history of breast carcinoma, along an initial diagnosis of atypia, demonstrated an increase risk of breast cancer 8 to 10 times above baseline. A personal history of breast cancer shows an up to 14 times greater risk (*23*).

For a patient with focal/mild ADH, biopsied with a vacuum-assisted 11-gauge needle and with no personal or family history of breast cancer imaging follow-up could possibly be presented as an option.

One imaging modality that could in the future prove valuable in the follow-up of patients with atypia is magnetic resonance imaging (MRI). MR imaging is emerging as a valuable adjunct to mammography and ultrasound for the evaluation of the breast. It could prove beneficial in evaluation of cases that remain inconclusive despite mammographic evaluation and core biopsy (*54*). Breast MR imaging has high sensitivity for the detection of breast cancer but suffers from a relatively low specificity. However, research is showing that new automated software could increase specificity without decreasing sensitivity, but further research is still needed (*55*). MR could be incorporated in such that if a patient, originally diagnosed with atypia on core biopsy, has a negative MR in the biopsy area the patient could opt for mammographic, rather than surgical, follow-up. At this present time there is no recommendation as to what intervals of time, after initial core biopsy, MR should be performed.

Obviously the possible consideration of imaging follow-up could only pertain to patients with focal/mild ADH or ALH. Cases of marked ADH (40%) exhibited a high rate of malignancy, with 4 out of 10 being malignant upon surgical excision. “Mixed” atypia also exhibited a high rate of malignancy (20%). For this reason, both histological types (marked ADH and “mixed” atypia) should continue to receive the routine surgical excision. ADH NOS (10%) and “other” atypia (10%) should also likely receive routine surgical excision. An underestimation rate of 10% is sufficiently high that risk benefit ratio would weigh on the side of surgical excision.

Although there was a significant difference in the rate of carcinoma upgrade between focal ADH and more severe atypia, interobserver variability was not assessed and is therefore a limitation of this study. The histologic slides were initially read by one pathologist experienced in breast pathology; however slides reviewed after the year 2000 were read primarily by one of two pathologists. Although there have been some proposed classification schemes for atypical ductal hyperplasia, it is still possible for some variability in pathologists interpretations (*3*). For future studies it would be recommended that the slides only be reviewed by one pathologist experienced in breast pathology. Another option that could be used separately or in conjunction would be to use some type of quantitative factor to objectify the sub-classification such as the number of core samples in which atypia was seen in combination with other features that distinguish florid hyperplasia without atypia versus ADH versus DCIS.

It is interesting to note that while the percentage of cases of atypia has remained stable over the past decade, the upgrade rate has been markedly decreasing. Recently at our institution a retrospective review to identify all cases of atypia diagnosed on core biopsy was performed. The percentage of cases diagnosed with atypia was calculated for the entire group and for each year. A retrospective search of the breast imaging and pathology databases was then performed to correlate surgical pathological results in patients undergoing excision. The underestimation rate of cancer was determined and similarly analyzed for the entire group and per year. The percentage of cases yielding a diagnosis of atypia on core biopsy during the time period was 7% (range 3-10%). The percentage of atypia per year has been fairly stable in the last decade ranging from 8% in 1996 to 5% in 2000 to 8% in 2004. Nonetheless, on excision, the upgrade rate showed a

progressive decrease during the same time. The overall upgrade rate being 13%. This ranged from 38% in 1996 to 9.5% in 2000 to 4.5% in 2005 (*56*). Therefore, this study showed that more patients are undergoing surgical excision to diagnose fewer cancers. It will be interesting to see if this trend is observed at other institutions. How this data will play into the management of patients with atypia has yet to be seen.

Although, a subset of patients with an upgrade rate of less than 2% was unable to be identified when comparing histologic subtype, mammographic findings, core biopsy factors, and clinical factors, this study was able to show that there is significant variation in the upgrade to carcinoma after surgical excision in various subsets of patients. This data may be able to play a role in the management of patients with atypia diagnosed on core needle biopsy, especially when the histologic subtype of atypia is considered with other confounding factors. However, this decision would have to be made on an individual patient basis. More severe atypia (NOS ADH, marked ADH, “mixed” atypia, and “other” atypia) should continue to receive routine surgical excision.

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