



Joan Cangiarella MD

**Vice Chairman Department of Pathology
New York University School of Medicine**

“Diagnostic and Management issues in the interpretation of radiologic guided core needle biopsies”

Diagnostic and management issues for the pathologist in the interpretation of radiologic guided core needle biopsies

Joan Cangiarella, MD
Vice-Chair, Department of Pathology
NYU School of Medicine

Key Points

● **Large needle core biopsy is a safe and cost-effective method for the diagnosis of palpable and nonpalpable mammary lesions.**

● **The triple test is the key to success: the clinical findings must correlate with the radiologic and pathologic findings, there must be confidence that the lesion being biopsied was sampled and that the pathologic results are concordant with the imaging findings.**

Discordance between the clinical, radiologic or pathologic findings warrants excision.

● **A multidisciplinary approach is the key to the success of a core biopsy program.**

● **Some breast lesions pose management dilemmas following breast core biopsy.**

Over the past two decades there has been a remarkable growth in the use of percutaneous core biopsy for the diagnosis of breast lesions. While this technique has proven to be accurate, safe and cost-effective there still remains categories of mammary lesions for which the diagnosis by core is diagnostically challenging or where the management guidelines for certain diagnoses on core remains controversial. This handout focuses on the challenges in the interpretation and management of lesions diagnosed by percutaneous core biopsy.

Mammary lesions to be discussed

- I. Atypical ductal hyperplasia
- II. Papillary lesions
- III. Atypical lobular hyperplasia and lobular carcinoma in situ
- IV. Fibroadenoma versus phyllodes tumors
- V. Radial scar

Atypical ductal hyperplasia (ADH)

Pathologic findings

Atypical ductal hyperplasia is a proliferative lesion of breast epithelium that fulfills some but not all of the criteria of the low grade, non-comedo type of ductal carcinoma in situ. Atypical ductal hyperplasia shows partial involvement of a basement membrane bound space by cells similar to those seen in low grade, non-comedo DCIS. The cells are evenly spaced, and uniform with regular oval to rounded nuclei, pale cytoplasm and distinct intercellular borders. Cytologic monotony and uniformity are characteristically

described features. In ADH (as compared to DCIS) there is usually a second (nonatypical) cell population that consists of columnar, polarized cells immediately above the basement membrane (Page). In ADH (as opposed to florid hyperplasia) the bothersome cell population usually has hyperchromatic nuclei (Page). In ADH, the worrisome cell population must be a bar crossing an entire space or a population of at least 6-7 cells across (Page). The cells may be arranged in an architectural pattern similar to intraductal hyperplasia or in a pattern seen in DCIS such as the cribriform, micropapillary or papillary types. The number and size of the ducts involved is important. Page et al required that these changes be present within two or more spaces to qualify as DCIS. Tavassoli et al. added a size requirement: ADH must be limited to a diameter that does not exceed 2mm. The upper limit for an ADH diagnosis would be the most minimal lesions recognized as low grade DCIS, mainly of the cribriform type. When in doubt between a diagnosis of DCIS and ADH, most recommend that a diagnosis of ADH be given. The lower limit for a diagnosis of ADH would be florid epithelial hyperplasia with even placement of cells and focal areas of cellular uniformity.

Radiographic findings

The rate of ADH in mammographically detected breast lesions ranges from 2.4-9.8% (Harvey JM et al). Microcalcification is the most common mammographic presentation of ADH (Helvie MA et al). Architectural distortion, masses and focal asymmetry are less commonly noted (Hoang JK et al.). Studies have examined whether more precise classification of microcalcification may enable some patients who have ADH on percutaneous core biopsy to avoid surgery (Hoang JK et al.) and found that microcalcification with higher rates of malignancy at surgical excision were granular in form and segmental or linear branching in distribution as contrasted to the fine rounded calcification seen in benign cases.

Risk assessment

ADH is associated with a risk of 4-5 times the general population for the development of breast carcinoma. Some genetic evidence (Shackney SE et al.) suggests that ADH may be a precursor to the development of mammary cancer.

Percutaneous core biopsy

When atypical ductal hyperplasia is encountered on a core biopsy the first concern is whether the histologic finding of ADH is representative of the target lesion. Atypical ductal hyperplasia is found in 2% to 15% (mean 5%) of cases of percutaneous core biopsies (Table 1). Surgical excision is the recommended management as a significant number of cases diagnosed as ADH on core biopsy will be upgraded or show ductal carcinoma in-situ (DCIS) or invasive carcinoma after excision. The reported upgrade rates are dependent on the technique (spring loaded (automated) core biopsy or directional vacuum assisted core biopsy (DVAB)) and the gauge of the needle used. The use of larger diameter needles (lower gauge) and vacuum assistance has allowed large samples to be obtained and in many studies lowered the upgrade rate (Table 1). Underestimation rates are 10-27% for 11 gauge VABC and 19-56% for 14 gauge large core biopsy (Table 1). Most cases of carcinoma found at excision are DCIS with invasive carcinoma seen in approximately 30% of cases.

Several studies have attempted to review pathologic and radiologic findings to determine criteria that may allow some patients with ADH on percutaneous core biopsy to avoid excision. Some studies have shown that when foci of ADH are found in only one or two ducts, upgrade rates drop to zero and thus excision may not be necessary (Ely KA et al, Sneige N et al.). However, other studies have seen upgrade rates of 12.5% when focal ADH is seen (Eby PR et al.).

Table 1: Underestimation rates for diagnosis of carcinoma (either DCIS or invasive carcinoma) for cases diagnosed as ADH on percutaneous core biopsy

Author	Total number of cores	# cores with ADH (%)	Biopsy needle (size, type)	# cases with excisional bx follow-up	# cases with DCIS or invasive CA(%) at surgical excision
Liberman1995	264	25(9%)	14 g automated	21	11 (52%)
Jackman 1994	450	19(4%)	14 g automated	16	9 (56%)
Jackman1997	1400	55(3.9%)	14g automated	54	26 (48%)
Renshaw	3026	216 (7%)	11g or 14g automated	95	13 (14%)
Darling	3873	148 (4%)	14g automated	25	11 (44%)
			14g DVAB	28	11 (39%)
			11g DVAB	86	16 (19%)
Ko	4493	102 (2%)	14g automated or 11g VABC	74	34 (45.9%)
Sneige	824	61 (7%)	11g or 14g DVAB	42	3 (7%)
Eby	391	58 (15%)	11g DVAB	49	10 (20%)
	600	83 (14%)	9g DVAB	74	16 (22%)
Liberman 1998	112	10 (8.9%)	11g DVAB	10	1 (10%)
Meyer	1032	18 (2%)	14 g automated or 14g DVAB	18	10(56%)
Brem	422	20 (5%)	11g DVAB	16	4 (25%)
Philpotts	753	26 (3%)	11g DVAB	26	6 (23%)
Adrales	1081	90 (8%)	11g DVAB	62	9 (15%)
Cangiarella	160	9 (6%)	11 g DVAB	8	2 (25%)
Lai	673	19 (3%)	11g DVAB	12	2 (17%)
Jackman 2002	1964	131(7%)	11g DVAB	104	22 (21%)
Pandelidis	1341	37 (3%)	11g DVAB	35	5 (14%)
Winchester	1750	77 (4%)	11g DVAB	65	11 (17%)
Sohn	4579	88 (2%)	11g DVAB	78	14 (17%)
Forgeard	2214	300(14%)	11g DVAB	116	29 (25%)
Burak	851	46 (5%)	11g DVAB	46	6 (13%)
Plantade	2130	135(6%)	11g DVAB	37	10 (27%)
Travade	633	62 (10%)	11g DVAB	31	6 (19%)
Maganini	1553	44 (2.8%)	11g VABC	32	4 (13%)
Liberman 2007	237	15 (6%)	9 g DVAB	13	5 (38%)
TOTALS	36806	1894(5%)		1273	306 (24%)

Follow-up studies in patients with ADH

Three studies, all from France have followed patients with ADH on percutaneous core biopsy (Plantade et al., Forgeard et al., and Travade et al.) and spared surgery in approximately 65% of patients.

Plantade et al: factors that led to surgery were personal or family hx of cancer, lesion size greater than 10mm, presence of ADH on the last cores removed, or concomitant atypical lobular hyperplasia on core. In a follow-up period of 29 months, 2 invasive pleomorphic lobular carcinomas were missed.

Travade et al: patients with complete removal of the lesion by DVAB or older than 70 years of age with no other risk factors did not undergo surgery. A follow-up period of 35.5 months revealed no missed lesions.

Forgeard et al: 184 patients of 300 patients diagnosed with ADH on DVAB were followed with follow-up data available in 135. Four developed carcinoma (Table 2).

Table 2: Clinical and pathologic findings in 4 patients who developed carcinoma at followup (Forgeard et al).

Lesion size	Core Biopsy	Time to recurrence	Excision dx
Unknown	<2 foci ADH	5 years	DCIS, Intermediate grade
13 mm	<2 foci ADH	5 years	DCIS, intermediate grade
30 mm	>2 foci ADH	3 years	DCIS, low grade
4 mm	>2 foci ADH	1 year	Invasive ductal carcinoma

All three DCIS cases developed at least 3 years after a diagnosis of ADH which may be related to ADH as a risk factor rather than underestimation. The invasive carcinoma occurred in a different location of the breast. This study concluded that excision was not necessary for a diagnosis of ADH on DAVB if lesions were less than 10 mm, if all of the calcifications were removed by DVAB and if less than or only 2 foci of ADH was noted on DVAB.

Predictors of underestimation in ADH diagnosed at percutaneous core biopsy

Others studies have shown that predictors of underestimation of ADH on percutaneous core biopsy include: personal history of breast cancer (Jackman Rad 2002, Sneige N et al), the presence of a palpable mass or a mass seen on ultrasound (Jacobs TW et al, Liberman L et al. Radiology 1997), incomplete removal of the lesion with DVAB (Jackman 2002, Sneige, Adrales, Renshaw), large lesion size (Jackman 2002, Renshaw AA), low number of cores (Plantade, Jackman RJ et al. Radiology 1997) and ADH within at least 3 foci (Sneige, Adrales, Jacobs TW, Ely KA). One study showed that palpable lesions, microcalcification on mammography, size on imaging of greater than 15 mm and age of older than 50 years were independent predictors of malignancy whereas focal ADH was a negative predictor (Ko E et al.). While some studies suggest that taking more cores per lesion leads to lower underestimation rates (Jackman RJ et al. Radiology

1994) especially in calcified lesions where five to eight cores have been recommended, others show no change in underestimation rates (Brem et al, Winchester et al).

Inter and intra-observer variability in the diagnosis of ADH

Inter and intra-observer variability in the diagnosis of ADH is widely recognized (Rakovitch E et al., Schnitt SJ et al., Elston CW et al.) Studies have shown inconsistency among pathologists particularly in discriminating hyperplasia from ADH and ADH from low grade DCIS. Rosai asked 5 experienced pathologists to evaluate 17 proliferative breast lesions using the diagnostic criteria they used in everyday practice. In this study, there was not a single case in which all 5 pathologists agreed and in one-third of cases, the diagnosis spanned from hyperplasia without atypia to carcinoma in situ (Rosai J) Schnitt et al. studied interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria (Schnitt SJ et al.) In this study he instructed 6 pathologists to use the diagnostic criteria of Page and provided them with a written summary of the criterion and a set of teaching slides with the representative lesions and asked them to classify 24 proliferative breast lesions. This study showed better concordance, with all six pathologists agreeing in 58% of cases and four or more agreeing in 92% of cases. However in 33% of cases there was disagreement with at least one pathologist disagreeing between a diagnosis of ADH and a diagnosis of DCIS. In 1999, an analysis of the consistency among which pathologists from 12 different European countries classify and diagnose breast lesions was undertaken (Sloane JP et al). In this study, the kappa statistic for a diagnosis of ADH was .27. In benign cases, an ADH diagnosis was rendered in a mean of 23% of the cases (range 15-32%) In DCIS cases, an ADH diagnosis was rendered in a mean of 18% of the cases (range 9-42%). In this study, the most difficult problem among pathologists was classifying ADH and intraductal proliferations. Giardina et al confirmed this observation by studying the interobserver reproducibility in the diagnosis of breast lesions in which 12 pathologists evaluated a set of 88 slides. The diagnostic agreement was high in cases of invasive carcinoma and benign lesions but low in atypical cases (mean kappa, 0.25).

The level of interobserver agreement between general and expert pathologists was also low in a study that assessed diagnosis of large-core needle biopsies (Verkooijen HM et al.) In this study only 24% of the large-core needle biopsies with an expert diagnosis of atypia were diagnosed as such by the general pathologists.

Immunohistochemistry

Overexpression of the cell-cycle associated protein cyclin D1 messenger RNA has been noted more frequently in DCIS than non-malignant conditions and amplification of its encoding gene CCND1 has been identified in DCIS at a higher frequency than in ADH. One report studied the immunohistochemical staining patterns for cyclin D1 and Ki-67 in core biopsies and counted a proliferation index by measuring the percentage of positive nuclei in at least 500 nuclei in the same duct space involved by ADH. They found by using a cutoff of 25% for cyclin D1 and 2% for Ki-67 the sensitivity for the presence of DCIS on excision was 100% for both cyclin D1 and Ki-67 and the specificity was 75% and 69% respectively (Hameed O et al.)

Cytokeratin 5/6 (basal cell cyokeratin) and 34betaE12 (high molecular weight cyokeratin) has been shown to have some utility in distinguishing benign intraductal proliferations from ADH and DCIS. Otterbach et al. showed positivity in luminal epithelial cells for CK5/6 in the majority of ductal hyperplasias (88%) but negativity in atypical ductal hyperplasias (92%). Apocrine metaplasia and columnar alterations also show a negative reaction. High molecular weight cyokeratin (34betaE12) shows no expression or weak expression in most cases of ADH and DCIS but is strongly expressed in florid hyperplasia (Monfar F et al.).

Key Points

- **The pathologic diagnosis of ADH on core biopsy is difficult due to an inability to distinguish this lesion from low grade DCIS on a limited sample obtained by core and the high degree of interobserver variability in the diagnosis of ADH.**

- **The finding of ADH on core biopsy warrants surgical excision as the underestimation rate of carcinoma at surgical excision is 24% (mean) (Table 1).**

Papillary lesions

Pathologic findings

Papillary lesions represent a spectrum of breast lesions ranging from benign papillomas to atypical papillomas to intraductal papillary carcinoma and invasive papillary carcinoma. Papillomas occur in the major or minor lactiferous ducts of the breast. Papillomas are often easily recognized by pathologists due to their fibrovascular core, myoepithelial cell layer and an outer layer composed of cuboidal or columnar cells. Most benign papillomas are seen in women aged 30-50 years and are smaller than 1 cm in size. Some contain foci of atypia and thus are called atypical papillomas.

Difficulties arise in the categorization of papillary lesions as benign, atypical or malignant. Some papillomas have epithelial proliferations that fulfill the cytologic and architectural features of ADH or DCIS. Atypical papillomas have marked nuclear atypia, hyperchromatic nuclei, cribriform pattern and a monotonous cell population. DCIS involving a papilloma is usually low grade, and of the solid, cribriform or micropapillary type. Myoepithelial cells are reduced or absent in the foci of DCIS and ADH. Distinguishing a papilloma with ADH from one with DCIS can be challenging. Page et al classifies a lesion as a papilloma with DCIS when it has the architectural and cytologic features of non-comedo type DCIS and measures >3 mm in size. Lesions less than or equal to 3 mm in size are classified as atypical papillomas. Tavassoli classified carcinoma arising in a papilloma when the atypical cell population involves at least 33% but less than 90% of the lesion.

Papillary ductal carcinoma in situ shows papillae that are more delicate and less fibrotic than papillomas (Collins LC et al.). The epithelium is usually composed of cells with a uniform appearance. The epithelium may have one to several layers of columnar cells with degrees of stratification or a proliferation of uniform cells in solid, cribriform or micropapillary growth patterns. Some cases of papillary DCIS have a dimorphic cell population with cells with abundant pale cytoplasm located in a basal location.

Radiographic Findings

Papillomas are single in approximately 50% and present with nipple discharge in about 30%. Papillomas can present radiographically as an architectural distortion, a density or a mass with or without associated microcalcification. Mammography and sonography has not been shown to clearly discriminate benign from malignant papillary lesions (Ashkenazi). On sonography, echo pattern and margins of the mass were shown to be a distinguishing feature of benign and malignant papillary lesions. Benign papillary lesions were mainly homogeneous and either iso, hypo or hyperechoic. Malignant lesions were mixed hyper and hypoechoic or of complex cystic echogenicity. Most malignant papillary lesions are not well circumscribed whereas about half of the benign lesions are well-circumscribed (Shin HJ). Puglisi et al. (Puglisi F et al.) compared the level of radiographic suspicion in papillary lesions with the diagnosis at surgical excision. In this study, 14% of the lesions characterized as no or low radiologic suspicion were carcinoma at excision. However, when the radiologic suspicion was moderate or high, carcinoma was noted in 88% of the cases.

Risk assessment

Papillomas with atypia have been shown to have an increased risk of the development of invasive breast cancer. Page et al. (Cancer 1996) showed that women with papillomas containing areas of atypical hyperplasia have a similar or a greater risk of breast cancer than others with atypical hyperplasia within the parenchyma of the breast. They also noted that the risk of development is largely local, in the region of the original papilloma supporting the recommendation of excision of all atypical papillomas. Multiple papillomas, in contrast to solitary papillomas are more likely to be associated with breast cancer.

Percutaneous core biopsy

Papillary lesions are uncommonly encountered on percutaneous core biopsy (0.01% to 8.1% of all core biopsies). While the accepted recommendation for atypical papillary lesions and papillary carcinoma diagnosed on percutaneous core biopsy is excision the management of benign papillary lesions diagnosed by percutaneous core biopsy remains controversial. A summary of papillary lesions diagnosed by percutaneous core biopsy with surgical biopsy followup is presented in Table 3. The range of carcinoma found after biopsy of a benign papillary lesion is wide (from 0-29%, Table 3). Some studies recommend excision of all papillary lesions diagnosed at percutaneous biopsy as malignancy is noted in a significant number (Bernik SF et al.). Others recommend excision when atypia is present however others suggest radiologic followup when a benign papillary lesion without atypia or suspicious radiographic features is identified on percutaneous core biopsy. Some studies have shown that only cases with radiologic-pathologic discordance require biopsy (Ko E et al., Renshaw AA et al.) however since in many cases mammography and sonography cannot distinguish between benign and malignant papillary lesions this can be difficult.

Reasons to excise percutaneously diagnosed papillomas include difficulties in pathologic interpretation, sampling errors in papillomas that may contain foci of atypia or carcinoma

and the premalignant potential of these lesions. There can be difficulty in distinguishing benign, atypical and malignant papillary lesions on percutaneous core biopsy due to fragmentation of papillary lesions on core biopsy. The small sampling of a papillary lesion by core biopsy may miss malignancy within or adjacent to the lesion. Papillary malignancies can have large areas of benign papilloma and benign papillomas can infarct leading to cytologic atypia, necrosis and mitotic figures that can cause confusion with carcinoma. One study showed that among papillomas with ADH, ADH occupies less than 25% of the papilloma and thus sampling is a concern (Page DL et al. Cancer 1996).

Lower gauge core biopsy (larger needles) does not help in the assessment of papillary lesions (Lieberman L et al. Am J Roentgenol 2006, Jackman RJ et al.). Arora et al (Arora N) found that older patient age was a significant predictor of malignancy.

Table 3. Underestimation rates for diagnosis of carcinoma (DCIS or invasive) at excision in atypical and benign papillomas diagnosed at percutaneous core biopsy

Author	# pap lesions	#atypical on PCB	# atypical with CA at excision/total number excised	#benign on PCB	#benign with CA at excision/total number excised
Bernik	122	16	7/16(44%)	47	4/47 (9%)
Tseng	41	9	5/7(71%)	28	7/24 (29%)
Skandarajah	80			80	15/80(19%)
Syndor	94	15	9/15(60%)	48	3/23 (13%)
Shin	124	16	1/16 (6%)	86	12/86 (14%)
Rizzo	372	36	5/23 (22%)	288	9/101(9%)
Kil	76	9	3/9 (33%)	67	3/67(4.5%)
Arora	154	66	20/66 (30%)	18	0/18 (0%)
Ashkenazi	43	18	12/18(67%)	20	4/20(20%)
Ko	76	18	8/17 (47%)	43	1/19(5%)
Shah	129	10	3/10(30%)	49	1/40(3%)
Agoff	51	26	12/25(48%)	25	0/11(0%)
Mercado 2001	36	6	0/6(0%)	12	1/6 (17%)
Renshaw	62	20	14/20(70%)	18	0/18 (0%)
Lieberman 1999	34	10	3/10 (30%)	7	0/7 (0%)
Lieberman 2006	50			50	5/25 (20%)
Puglisi	51			29	2/29(7%)
Rajendiran	105	10	2/10 (20%)	27	2/27(7%)
Rosen EL	57	10	3/10(30%)	27	0/4 (0%)
Irfan	6			6	0/3(0%)
Ivan	50	8	5/8(63%)	30	0/6(0%)
Bazzocchi	33	3	2/3(66%)	26	0/26(0%)
Mercado 2006	43			43	2/36(5.5%)
Philpotts	22			16	1/6 (6%)
Iofee	37	4	3/3(100%)	28	2/8(25%)
TOTALS	1948	310	117/292(40%)	1118	74/737(10%)

Includes only papillary lesions diagnosed by core biopsy

Immunohistochemistry

CK5/6, p63 and calponin have been shown to be useful in classifying papillary lesions. CK 5/6 can be helpful in distinguishing benign papillomas from atypical papillomas as the atypical cell proliferation lacks expression of high molecular weight cytokeratin. Immunohistochemical stains for calponin and p63 highlights myoepithelial cells and has been shown to be helpful in distinguishing benign papillomas from intraductal papillary carcinomas. One study that utilized calponin, p63 and high molecular weight cytokeratin (CK5/6) allowed an increase in the negative predictive value and in the overall accuracy

of diagnosis of papillary lesions on core biopsy (Shah VI et al.). Observer variability in reporting of core biopsies from papillary lesions has shown to be reduced with the use of immunohistochemistry for CK5/6, calponin and p63 in one study, where the overall agreement in diagnosis was only 44% on the basis of H and E staining but improved to 91% with the addition of CK5/6, calponin and p63 (Douglas-Jones A et al.).

Key Points

- **Difficulties arise in the categorization of papillary lesions as benign, atypical or malignant on core due to fragmentation of cores and sampling errors due to the presence of focal atypia.**

- **Atypical papillary lesions and papillary carcinoma on core biopsy warrants excision. The management of benign papillomas on core biopsy is more controversial. Most studies recommend excision as the underestimation rate for carcinoma at excision is 10% (mean) (Table 3).**

Atypical lobular hyperplasia (ALH) and Lobular Carcinoma in situ (LCIS)

Pathologic findings

For a diagnosis of LCIS there is distension of the lobule involved with loss of cellular cohesion and cells with clear cytoplasm, round to oval nuclei and a lack of hyperchromasia. Page suggests 50% involvement of the lobular unit while Rosen suggests that at least 75% of one lobule must be involved (Page DL et al. Diagnostic histopathology of the breast 1987. Rosen PP. Rosen's Breast Pathology 1997). Diagnostic criteria according to Page also requires that the abnormal cells must comprise all of the cells in the lobular unit, with no intercellular spaces between cells and at least 50% of the acini in the lobular unit must be distorted or expanded. ALH has less than 50% (Page 1987) or 75% (Rosen) of the affected lobule with the cytological appearance of LCIS.

LCIS can be characterized by two types of cells. Type A cells are small and uniform and have small uniform round to oval nuclei with a small amount of clear to lightly eosinophilic cytoplasm. Type B cells are larger and more pleomorphic. The pleomorphic subtype is defined by the presence of comedo necrosis, cell pleomorphism with cytologic and nuclear atypia and the presence of prominent large nucleoli.

Radiologic findings

Most cases of LCIS are discovered as an incidental finding with no associated clinical or radiologic findings. Microcalcification has been a described radiologic finding in some series (Lieberman L et al., Shin SJ et al., Georgian-Smith D et al.). One study showed that while calcification was associated with lobular neoplasia in about 15% of core biopsies, most of the calcification was associated with fibrocystic change (Menon et al.).

Risk Assessment

Both atypical lobular hyperplasia and lobular carcinoma in situ are considered risk factors for the development of carcinoma. The risk for the development of breast cancer is 4-5

times that of the general population for ALH and approximately 11 times after a diagnosis of LCIS (Page DL et al. Hum Pathol 1991, Page DL et al. Br Med J 1995, Page DL et al. Cancer 1985.). LCIS is often bilateral and multifocal and associated with an increased risk of invasive carcinoma of either breast. Recent genetic and molecular evidence have challenged the notion of LCIS as a risk factor but suggest that ALH and LCIS may be indolent precursors. Evidence to support a precursor concept includes: 1. the fact that most invasive carcinomas have developed in the same site as the LCIS lesion (Ottesen GL et al., Fisher ER et al.) and genomic clonality in paired samples from patients with LCIS and invasive carcinoma (Hwang ES et al.). The same mutation in the E-cadherin genes has been seen in invasive lobular carcinoma and in the adjacent LCIS (Vos CBJ et al.).

Percutaneous core biopsy

There have been limited studies on the finding of ALH and LCIS on percutaneous core biopsy. A diagnosis of ALH or LCIS on percutaneous core biopsy is uncommon and accounts for less than 2% of core biopsies in most series. While cases of ALH and LCIS identified at surgical excision are managed conservatively by clinical and radiologic follow-up, management guidelines for ALH and LCIS diagnosed at percutaneous core biopsy remain more controversial. While some studies find excision to be unnecessary (Renshaw AA et al. Am J Clin Pathol 2006.) the great majority of studies recommended surgical excision. Some recommended excision only for LCIS (not ALH), for LCIS with residual microcalcifications (Berg WA et al.) , LCIS with mass lesion (Middleton LP et al.), LCIS with associated high risk lesion, pleomorphic LCIS and cases of diagnostic confusion with DCIS (Bowman K et al.). Some studies required excision only when there was evidence of radiologic-pathologic discordance, when another high-risk lesion was present in the biopsy or when there were histologic findings that were indistinguishable from DCIS (Lieberman L et al., Nagi CS et al.). Most studies recommend excision as there is a significant risk, approximately 14% for ALH and 22% for LCIS of finding carcinoma at surgical excision after a diagnosis of either ALH or LCIS on core (Table 4). The problem with these studies is that the reported range of finding carcinoma at excision is very wide with many studies having no reported cases of carcinoma at excision. Kopans reported a significant bias with these studies in that the majority are retrospective and because there is rarely a radiologic correlate to LCIS most of these women who went to surgical excision after a core biopsy diagnosis of LCIS probably had a discordant imaging finding leading to the excision (Kopans DB). Prospective studies are needed to prove the true incidence of carcinoma after a core biopsy diagnosis of DCIS.

Pleomorphic LCIS should be managed like DCIS and thus excision is recommended. Lobular neoplasia with comedo necrosis but without pleomorphism has also been described (Fadare O et al.) The significance of this rarely described entity is uncertain thus excision should be recommended.

Table 4. Pure ALH and LCIS cases diagnosed on core biopsy and number with carcinoma (ductal carcinoma in-situ or invasive carcinoma) on surgical excision*

	CBdx	#CA at EB	CBdx	#CA at EB
	ALH		LCIS	
Arpino	17	1(6)	4	2(50)
Foster	14	2(14)	12	4(33)
Yeh	12	1(8)	3	0
Irfan	7	1(14)		
Dymtrasz	7	3(43)		
Lechner	84	18(21)	58	20(34)
Pacelli	7	0	7	0
O'Driscoll			7	3(43)
Berg	7	1(14)	8	0
Liberman	4	0	5	0
Renshaw2002	6	0	9	0
Shin	5	0	8	2(25)
Crisi	3	0	13	2(15)
Philpotts			4	1(25)
Middleton	6	4(67)	9	2(22)
Burak	6	1(17)		
Bauer			7	1(14)
Zhang	8	0	10	3(30)
Elskeikh 2001	20	5(25)	13	4(31)
Bonnett	24	2(8)		
Brown	3	0		
Mahoney	10	1(10)	10	4(40)
Zuiani	3	1(33)	3	1(33)
Margenthaler	19	3(16)	16	3(19)
Renshaw 2006	40	1(3)	52	2(4)
Karabakhtsian	63	5(8)	29	5(17)
Cangiarella	18	1(6)	20	2(10)
Brem	97	21(22)	67	17(25)
Hwang H	48	1(2)	39	9(23)
Lavoue			52	10(19)
Londero	8	1(13)	20	12(60)
Totals	546	74(14%)	485	109(22%)

CBdx: diagnosis at core biopsy

#CA at EB: number of carcinomas at excisional biopsy

*Only cases with surgical followup were included. Only cases with a diagnosis of ALH or LCIS without other high risk lesions (ADH, radial scar, papilloma etc were included in this analysis)

Factors associated with underestimation of carcinoma after a diagnosis of ALH or LCIS on percutaneous core biopsy

Removal of all microcalcifications by core biopsy still detected carcinoma in 1 of 6 patients in one series (Elsheikh TM et al. Am J Surg Path 2005). Significant underestimation of carcinoma in cases of LCIS on core biopsy occurred more often with biopsy of masses as compared to microcalcification, with higher BI-RADS category, with the use of a core device rather than a vacuum device and when less core biopsy samples were obtained (Brem RF et al.). The highest degree of underestimation occurred when less than 10 cores biopsies were obtained by core biopsy (40%) but there were no criteria that identified a subgroup that could avoid excision (Brem RF et al.).

One study did a detailed radiologic-pathologic review in 47 patients with a core biopsy diagnosis of LCIS (Menon S et al.). In this study, 25 patients underwent immediate surgical excision and nine were found to have carcinoma. Of the 9 patients, core biopsy missed a mass in 5 and calcifications in 2. In the cases of calcification, they appeared to be adequately sampled.

The pleomorphic type of LCIS can be indistinguishable radiographically from DCIS (Georgian-Smith D et al.). This can also be problematic histologically. Pleomorphic LCIS shows marked pleomorphism and the presence of necrosis and calcification makes distinction from DCIS difficult. The finding of pleomorphic LCIS on core is associated with a much higher percentage (33-60%) of associated invasive lesions at surgical excision (LavoueV et al.). At the molecular level there are noted partial chromosome deletions or acquisition of oncogenes such as c-myc (changes resembling those seen in DCIS) (Reis-Filho JS et al.). Distinguishing LCIS with pagetoid spread into ducts and DCIS with lobular cancerization can be difficult.

One study assessed radiologic and pathologic features in percutaneous core biopsies diagnosed as ALH or LCIS and found that 10 of 87 cases of ALH (1/48) or LCIS(9/39) were upgraded to carcinoma (Hwang H et al.). Of these 10 cases, 6 showed radiologic discordance and 3 showed nonclassic pathology (2 LCIS with necrosis, 1 pleomorphic LCIS). They concluded that cases of ALH and LCIS on core biopsy with concordant radiology and pathology could be managed with follow-up rather than surgery as only 1% of cases were upgraded after excluding radiologic discordant cases and cases with non classic histology (Hwang H et al.).

One study suggested that the extent of lobular neoplasia may be useful in predicting whether or not excision is necessary (Esserman LE et al.). Focal lobular neoplasia (less than or equal to one lobule per core) at percutaneous biopsy was not associated with carcinoma at excision and thus excision could be avoided in these cases.

Immunohistochemistry

Use of E-cadherin, a transmembrane glycoprotein involved in cell adhesion is useful to distinguish DCIS from LCIS as loss of expression is noted in LCIS and invasive lobular carcinomas.

Key Points

- The great majority of studies recommend excision after a diagnosis of ALH or LCIS on core biopsy as the underestimation rate of carcinoma at surgical excision is 14% and 22% respectively (mean) (Table 4).

- Pleomorphic LCIS can be confused with DCIS. Distinguishing LCIS with pagetoid spread into ducts and DCIS with lobular cancerization can be difficult. Immunohistochemical staining with E-cadherin can help distinguish DCIS (positive) from LCIS (negative).

Fibroadenomas versus Phyllodes neoplasm

Pathologic findings

Phyllodes neoplasms are rare comprising less than 1% of breast neoplasms. Discrimination of phyllodes neoplasms by clinical means, mammography or ultrasonography has been shown to be of little value. While phyllodes tumors are usually larger than fibroadenomas discriminating fibroadenomas from phyllodes tumors by size is not always reliable.

Phyllodes tumors have a leaf like architecture with marked stromal overgrowth, hypercellularity and infiltrating margins. While most phyllodes tumors can be distinguished from fibroadenomas by increased stromal hypercellularity and mitotic activity, benign phyllodes tumors are particularly difficult due to the lack of atypia and lack of mitotic activity. Juvenile fibroadenoma should also be considered as it may show increased cellularity with a uniform stromal proliferation. As compared to cellular fibroadenomas, the stroma in phyllodes tumors is often more prominent in the periductal areas. Core biopsy can miss a phyllodes tumor as the stromal cellularity is highly variable and heterogeneous and may not be sampled at core biopsy.

Radiologic findings

Mammography is rarely helpful but loss of definition on margins or lobulated masses were more likely associated with phyllodes tumors. Ultrasonographic features include lobulation, heterogeneous internal echo pattern, posterior acoustic enhancement or cystic areas (Yilmaz E et al., Chao TC et al.) On sonography, phyllodes tumors tend to be larger than fibroadenomas and more often are suspicious for malignancy.

Ultrasonography is unreliable in distinguishing fibroadenomas from phyllodes due to considerable overlap. In one study, 2 of 12 percutaneous core biopsies were diagnosed as fibroadenoma and at surgical excision were phyllodes tumors. Of these 12 phyllodes tumors, ultrasound diagnosed 5 as probably benign and 7 as equivocal. Conversely, 4 of 52 percutaneous core biopsies were diagnosed as phyllodes tumors but were fibroadenomas at excision (8%). Radiographically, 24 of these 52 fibroadenomas were classified as indeterminate or suspicious. (Bode MK et al.). Rapid growth or large size may be the only feature to suggest a phyllodes tumor (Foxcroft LM et al.)

Percutaneous core biopsy

A definitive diagnosis of phyllodes tumors is rarely made on core biopsy. In a series of 23 patients with a phyllodes neoplasm at surgical excision, the core biopsy diagnosis was fibroadenoma in 3 or benign in 6 (Dillon MF et al.) giving a false negative rate of 39%.

In a study by Dershaw et al. seven cases of fibroadenoma versus phyllodes were reported on core: 3 were phyllodes and 4 were fibroadenomas. Histologic distinction of phyllodes tumors from fibroadenomas is mainly made by evaluation of stromal cellularity and the presence of a leaf like pattern, features that may not be present on core biopsy. The presence of other histologic features that are used to diagnoses phyllodes tumors such as atypia, mitotic figures, pleomorphism, necrosis and the presence of infiltrating or pushing margins are not reliable on core biopsy. Another study that used core biopsy to distinguish fibroadenoma from phyllodes tumors studied 57 core needle biopsies of fibroepithelial lesions and found a negative predictive value of 93% if a fibroadenoma was diagnosed and a positive predictive value of 83% if a phyllodes tumor was diagnosed on core. (Komenaka IK et al.). In one study, 13 cases were missed by core biopsy, most of which were diagnosed as fibroadenoma (Yohe S et al.). The difficulty in diagnosing these cores as phyllodes tumors were due to tissue fragmentation of the cores with the suggestion of cystic spaces between fragments. As noted above, difficulties due to a heterogeneous biopsy with variability in stromal cellularity can lead to a misdiagnosis. Histologic features that have been noted to be more common in percutaneous core biopsy from phyllodes tumors as compared to fibroadenomas include increased stromal cellularity, stromal overgrowth (10X field with no epithelium), fragmentation of the cores and adipose tissue within stroma (Lee AH et al.)

Immunohistochemistry

There are no reliable immunohistochemical stains to distinguish phyllodes tumors from fibroadenomas. Ki-67 has been used to document proliferative activity and showed higher proliferation indices in phyllodes tumors as compared to fibroadenomas (Yohe S et al.).

Key Points

● **For benign phyllodes tumors a definitive diagnosis is rarely made on core biopsy due to the lack of atypia, lack of mitotic figures and variability of stromal hypercellularity.**

Radial scar

Pathologic findings

Radial scar is characterized histologically as a fibroelastotic core surrounded by radiating ducts and lobules with various amounts of ectasia, epithelial hyperplasia and adenosis. Radiographically and pathologically it is difficult to distinguish a radial scar from carcinoma.

Radiologic findings

The mammographic features characteristic of radial scars include the presence of thin radiating spiculations with parallel radiolucent lines, a central area of lucency or a heterogeneous center with lucency (Cawson JN et al.).

Risk assessment

Some data suggests that radial scars may be an independent risk factor for the development of breast carcinoma (Jacobs TW et al.). Most recommend surgical excision when the imaging findings are compatible with a radial scar.

Percutaneous core biopsy

There are only a limited number of studies pertaining to core biopsy in cases of radial scar as many are surgically excised without pre-operative biopsy (Table 5). Core biopsy for these lesions is challenging due to sampling error and the inability to distinguish them from carcinoma. One of the larger studies (Lopez-Medina A et al.) evaluated 43 lesions diagnosed as radial scar by core biopsy and found, at surgical excision, radial scar in 63%, radial scar with ADH in 18%, RS associated with carcinoma in 12% and only carcinoma in 7%. Histologic diagnosis of radial scars in limited specimens is difficult. The entrapped ductules in the entrapped fibroelastotic core may simulate invasive carcinoma, especially tubular carcinomas. Radial scars usually have a sclerotic stroma and elongated flattened tubules which contrasts with the desmoplastic stroma and angulated tubular glands noted in tubular carcinoma. Sclerosing adenosis should also be included in the differential. Sclerosing adenosis shows a disordered proliferation of acinar and ductal epithelial cells, myoepithelial cells and intralobular stroma that results in expansion and distortion of lobules. The lobulocentric nature of the process is helpful in making the correct diagnosis.

Table 5: Frequency of carcinoma at surgical excision in lesions diagnosed as radial scars at core biopsy

	Number of cases of carcinoma/ number of radial scars excised(%)	
Dalhstrom	0/3	
Dershaw	0/1	
Lee	1/4	DCIS
Meyer	0/4	
Jackman	2/5	DCIS, IDC
Philpotts	0/6	
Apsteguia	0/2	
Brenner	5/102	3DCIS, 2IDC
Cawson	0/27	
Brodie	2/16	2 DCIS
Lopez-Medina	6/38	3 tubular, 2 IDC, 1 DCIS
TOTALS	16/208(8%)	

*Radial scars with ADH on core are excluded

Immunohistochemistry

The presence of a myoepithelial cell layer by either H and E stain or by immunohistochemistry (p63, calponin or SMA) should help exclude a tubular carcinoma. Myoepithelial stains can also highlight the myoepithelial cell layer in sclerosing adenosis.

Key Points

- **Difficulty in diagnosis on core biopsy is due to sampling error and inability to distinguish from invasive carcinoma.**

- **8% of the radial scars diagnosed at core biopsy contained carcinoma (mainly DCIS) at core biopsy.**

Atypical ductal hyperplasia

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