Lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) are relatively uncommon lesions. Breast lesions with some morphologic features similar to what we now recognize as ALH and LCIS were illustrated in publications by Ewing in 1919(1) and Broders in 1932(2). However, the features of classic LCIS were originally described in 1941 by Foote and Stewart who used the term “carcinoma in situ” to suggest similarities to ductal carcinoma in situ (DCIS) in part because the constituent cells resembled those found in invasive lobular carcinoma(3). More recently in situ carcinomas with ambiguous histologic features have been recognized. One of these variants, pleomorphic LCIS (PLCIS), exhibits the growth pattern of classic LCIS but is composed of larger and more pleomorphic cells. Because ALH and LCIS have identical cytologic features and are defined histologically by differing degrees of distension of involved spaces, some authorities have advocated using the term *lobular neoplasia* to encompass both entities. The term *lobular intraepithelial neoplasia* (LIN) has also been proposed to include the morphologic spectrum of classic ALH and LCIS through PLCIS, however this classification scheme has not found widespread epidemiological or clinical applicability.

This presentation will cover the following areas relating to LCIS:
1. Historical perspective
2. LCIS as a risk factor vs. non-obligate precursor
3. Morphologic issues and “variants”
4. Core needle biopsy issues

This text handout will specifically concentrate on morphologic “variants” and core needle biopsy issues.

**LCIS morphology and “variants**

In most cases, the categorization of carcinoma in situ (CIS) as either lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) does not usually present diagnostic difficulty. However as this case illustrates, there are areas of overlap between these two lesions. The distinction between LCIS and DCIS has important therapeutic implications. Patients with LCIS are most often managed by careful observation (with possible the addition of selective estrogen receptor modulators, e.g. tamoxifen), while the treatment of DCIS is aimed at eradication of the lesion (with wide local excision, excision and radiation therapy, or mastectomy). Furthermore, assessment of the microscopic margin status is clinically important in DCIS but not in LCIS (4). Lastly, how best to manage patients whose core needle biopsy shows LCIS (whether conventional type or variant) is currently an area of intense debate; in contrast,
the management of DCIS on core biopsy is more clear-cut, with all patients requiring further surgical intervention.

**LCIS versus DCIS**

LCIS may be confused with DCIS in the following situations:
1. DCIS may extend into recognizable lobules and be mistaken for LCIS (also known as “cancerization of lobules”) (5, 6) and LCIS may involve extralobular ducts, mimicking DCIS (7).
2. DCIS and LCIS may coexist in the same breast (8) and even in the same ductal-lobular unit (9).
3. In situ carcinomas may display ambiguous cytologic and/or architectural features which deviate from the usual patterns, making it difficult to determine if these proliferations are lobular or ductal in nature (i.e. *carcinomas in situ with indeterminate features*).

Although the first two situations rarely cause difficulties for pathologists, the third category of histologically ambiguous in-situ lesions provides both diagnostic and management challenges. There has been much discussion regarding the classification and treatment of such equivocal in situ carcinomas, with some authors proposing a combined or mixed ductal and lobular category (10), and others favoring categorization as one type or the other (11-15). Analysis of genetic and immunophenotypic characteristics of these histologically ambiguous in situ carcinomas, in comparison to unambiguous cases of LCIS and DCIS should provide useful information toward defining their biologic nature and assisting in their categorization.

**Potential Immunohistochemistry (IHC) Markers**

The role of immunohistochemical marker in categorization of ambiguous in situ carcinomas remains a subject of current debate, including the utility of E-cadherin, high molecular weight cytokeratin and catenins.

**E-cadherin** has shown recent promise in defining the nature of these indeterminate in situ carcinomas (16-21). E-cadherin protein expression is lost in most invasive lobular carcinomas (22-28) and in LCIS (23-26, 29), but not in invasive ductal carcinoma (23-28) or DCIS (23, 24, 26, 28, 29). We and others have reported the utility of IHC for E-cadherin in assisting to categorize carcinomas in situ with indeterminate histologic features (16-18). Recently, however, Da Silva et al (30) reported heterogeneous immunostaining of E-cadherin in invasive lobular carcinomas. Four of 25 invasive lobular carcinomas had some positive E-cadherin immunostaining; however all 4 cases had genomic features of invasive lobular carcinoma (16q loss, 1q gain, 11q loss). Therefore, positive immunostaining for E-cadherin does not exclude the diagnosis of an otherwise classic invasive lobular carcinoma by morphologic/H&E criteria. These findings have implications for categorization of in situ lesions based solely on E-cadherin immunohistochemistry.
**High molecular weight cytokeratin (HMW-CK):** Cytokeratin immunostaining in conjunction with E-cadherin has been proposed to differentiate lobular from ductal lesions (21, 28). In one recent study, IHC for HMW-CK using antibody 34ßE12 was reported to compliment E-cadherin immunostaining(21). All LCIS cases were positive for HMW-CK and negative for E-cadherin, in contrast to DCIS cases which were HMW-CK negative and E-cadherin positive. However, some cases showed similar staining with both antibodies (i.e. both positive or both negative for E-cadherin and HMW-CK), and the exact biologic nature of these cases with dual “hybrid” phenotype is unclear. It is also unclear which HMW-CK specificity of antibody 34ßE12 is relevant in these cases (i.e. CK 1, 5, 10 and/or 14). IHC with 34ßE12 is also prone to methodologic issues. Lastly, tonofilaments, the ultrastructural “epitope” for antibody 34ßE12, are known to be present in both ductal and lobular carcinomas by electron microscopy, calling into question the biologic validity of this approach.

**Catenins** are a group of proteins which associate with E-cadherin as a component of the intercellular adhesion complex. α-, β- and γ-catenins are complexed with the carboxy-terminal of the e-cadherin cytoplasmic tail, whereas p120-catenin attaches to the cytoplasmic portion of e-cadherin adjacent to the plasma membrane. Recent studies have shown that in ductal carcinomas, α-, β- and γ-catenins and p120 catenin show a membranous immunostaining pattern (similar to that of E-cadherin). In lobular carcinoma, expression of α-, β- and γ-catenins is lost, however p120-catenin dissociates from the cell membrane and exhibits a cytoplasmic immunostaining pattern(26, 31-33). An advantage is that the diagnostic IHC result for lobular lesions is positive (i.e. cytoplasmic staining), which is often more reassuring than a negative IHC finding (e.g. loss of membrane staining with E-cadherin).

**Carcinomas in situ with indeterminate histologic features - categorization**

Although these histologically ambiguous in situ carcinomas appear to be heterogeneous, for conceptual purposes, they can be assigned to three general groups, based primarily on their morphologic variation from classic LCIS:

1. Lesions with the dyshesive growth pattern characteristic of LCIS but with pleomorphic cells – also known as “pleomorphic LCIS” (PLCIS)
2. Lesions with uniform monomorphic cells characteristic of those in classic LCIS, but exhibiting cellular cohesion or an architectural pattern such as microacini.
3. Lesions with the characteristic cytologic features and growth pattern of LCIS but with significant necrosis (usually comedo-type)

1) CIS with Pleomorphic Dyshesive Cells or Pleomorphic LCIS (PLCIS):

These in situ carcinomas exhibits a growth pattern characteristic of LCIS but with individual cells showing marked nuclear pleomorphism, with increased nuclear size (approximately 4x the size of a lymphocyte), variation in nuclear size with irregularity, and easily seen nucleoli. Mitoses may also be found, and necrosis may be present. The cytologic features are usually similar to those found in the individual cells of high grade DCIS. Cases such as these have been referred to as pleomorphic LCIS (PLCIS)(12, 13, 34). All PLCIS cases have been shown to date to be negative for E-cadherin by
immunohistochemistry (16, 18, 35). In one study, Sneige and co-workers (35) compared a series of cases with “isolated” PLCIS (i.e. without invasive carcinoma) to cases of PLCIS with invasion. All their PLCIS cases had similar cytomorphologic features and biomarker expression profiles irrespective of the presence or absence of accompanying invasive carcinoma. In particular, all cases were negative for E-cadherin (akin to LCIS) but showed worrisome features not seen in LCIS and more often associated with DCIS (pleomorphic cytology, more frequently positive for p53 by IHC and higher Ki67 staining index) (35). In another interesting study, Reis-Filho, et al. (36) analyzed a case of PLCIS with invasive carcinoma by IHC, CISH and CGH. Although the PLCIS had some features similar to LCIS (e.g. negative for e-cadherin and beta-catenin by IHC, loss of 16q, gain of 1q), there were also “aggressive” characteristics (e.g. amplification of c-myc and HER2.) Recently, we studied the immunophenotypic and genetic characteristics of a cohort of PLCIS cases, some of which had distinctive apocrine features (37). All 31 cases were E-cadherin negative by IHC and the majority of cases showed 16q loss and 1q gain by CGH (features akin to LCIS). However, as compared to conventional LCIS, PLCIS cases showed significantly higher Ki67 index, lower estrogen receptor and progesterone receptor expression, and higher incidence of HER2 gene amplification. Furthermore, genomic instability was significantly more prevalent in cases of PLCIS with apocrine histology. The findings support a relationship between conventional LCIS and PLCIS; however, the high grade morphology, unfavorable biomarker profile and genomic instability suggest a that PLCIS is a more significant lesion than conventional LCIS. Nonetheless, the natural history of PLCIS is as yet not known. In particular it is not known if the level and laterality of breast cancer risk associated with these lesions is more similar to conventional LCIS or to DCIS. Although the follow-up was short (mean 17 months) in the study of Sneige et al. (35), it is interesting to note that the only case of isolated PLCIS to recur was one which was not adequately surgically excised initially. Meantime, in the absence larger clinical outcome studies with longer follow-up, it would be prudent to follow a conservative approach with regard to the management of these lesions.

2) CIS with small, uniform cells but with cohesion or some architectural pattern:

In situ carcinomas such as these have morphologic features found in both LCIS and DCIS rendering categorization very difficult if not impossible on routine histology. These problematic lesions are usually comprised of small, monomorphic neoplastic cells, with or without cytoplasmic vacuoles, akin to those found in classic LCIS. However, in some cases, these small uniform cells grow in a solid, cohesive, mosaic pattern suggestive of solid pattern DCIS. In other cases, the cells may grow in a primarily solid pattern and show microacinar-like structures, features suggestive of DCIS, albeit with evidence of cellular dishesion, a feature more characteristic of LCIS. In our series of carcinomas in situ with indeterminate features, we found this group to be quite heterogeneous with respect to E-cadherin immunostaining, with approximately equal numbers of cases E-cadherin positive (akin to DCIS), E-cadherin negative (akin to LCIS), or with both E-cadherin positive as well as E-cadherin negative tumor cells within the same ductal-lobular space (suggesting a mixed phenotype) (16). Some E-cadherin-positive cases probably represent true cases of DCIS with morphologic “artifacts” on routine hematoxylin and eosin staining (such as dishesion) mimicking
LCIS. Also, foci of residual benign epithelial and/or myoepithelial structures within the involved lobule may stain positive for E-cadherin but are not clearly discernable on routine hematoxylin and eosin staining (16). Therefore, this phenomenon may produce the illusion of DCIS-like architectural structures due to a scaffolding effect of residual benign structures (19). It is not uncommon to see Pagetoid involvement by lobular neoplasia of benign proliferations (15) and involvement of collagenous spherulosis by LCIS is one example where cribriform pattern DCIS may be mimicked (38). Loss of cohesion in cases of classic LCIS might also not readily be apparent in lobules distended by neoplastic cells which are packed together, giving the illusion of a solid proliferation and this may explain some E-cadherin negative cases. Histologically indeterminate in situ carcinomas which show both E-cadherin-positive tumor cells and E-cadherin-negative tumor cells probably represent cases with both DCIS and LCIS in the same lobule or duct. (16, 18, 19). As noted, the diagnoses of LCIS and DCIS are not mutually exclusive, with both lesions known to co-exist in the same breast (8) and even in the same ductal-lobular system (9); some authorities have suggested a combined ductal and lobular entity in morphologically ambiguous cases (10). Until further clinical outcome data are available, however, it would seem prudent therefore that cases which show both E-cadherin positive and negative cells in the same ductal-lobular space should be treated as for DCIS rather than LCIS. In an interesting retrospective study, Goldstein et al. (39) performed E-cadherin immunostaining on a series of cases previously classified as LCIS by H&E morphology. Interestingly, 11% of “LCIS” cases were focally positive for E-cadherin and these cases behaved closer to DCIS than those LCIS cases without any E-cadherin staining. However, it is unclear whether these “mixed cases” represent true LCIS with focal E-cadherin staining, true mixed CIS cases or merely DCIS.

3) LCIS-like lesions with necrosis:

This variant pattern consists of in situ carcinomas with the cytologic and architectural features typical of LCIS (i.e. distension of lobules by a proliferation of dyshesive small cells, with uniform, round-to-oval, usually eccentric nuclei) but exhibiting areas of comedo-type (central) necrosis. The exact classification and management of such lesions has been a topic of much debate, with a spectrum of opinions regarding the degree of necrosis that is permissible in LCIS. Page has suggested that the presence of more than focal necrosis precludes a lesion from categorization as LCIS (11). In contrast, Tavassoli (14) has stated that necrosis can occur in LCIS, and that its presence does not necessarily imply that the lesion should be considered DCIS; however, she cautions that this may be a reflection of “far-advanced lobular neoplasia”, and should possibly be managed similar to intermediate grade DCIS. Still, other authors have supported the notion that necrosis, even if abundant, does not necessarily exclude a diagnosis of LCIS (15). In all studies where in situ lesions have differed from LCIS only by the presence of comedo necrosis, E-cadherin expression by IHC was lost (analogous to the immunophenotype of conventional LCIS) (16-18, 20, 40). These observations indicate that carcinomas in situ with comedo necrosis in which the cells are characteristic of LCIS are probably variants of LCIS. However, it is not known if the natural history of such LCIS lesions with comedo necrosis is similar to that of conventional LCIS without comedo necrosis. In one recent study, 18 cases of LCIS with
comedo necrosis were studies (12 had associated invasive carcinoma(40). Apart from necrosis, all other phenotypic features were akin to LCIS (growth pattern, E-cadherin negative, ER/PR positive, HER2 negative). The association with invasive carcinoma in 2/3 of cases (albeit in a cross-sectional rather than longitudinal outcome study), suggests possibly a different biology as opposed to conventional LCIS.

In summary, it is important to reiterate that our current understanding of the biologic behavior of DCIS and LCIS is based on clinical follow-up studies of lesions classified according to histologic features alone (“classic” DCIS and LCIS). It is unclear whether these data can be generalized to carcinomas in situ with ambiguous histologic features classified as DCIS or LCIS by immunohistochemistry alone. We require prospective outcome studies utilizing morphology in conjunction with markers (such as E-cadherin) to evaluate risk assessment of these indeterminate lesions, determine clinical outcome such as local recurrence following surgery, and risk of progression to invasive carcinoma. In addition, newer molecular techniques (such as microdissection, comparative genomic hybridization, expression profiling) will broaden our understanding of these lesions(41). Meantime, the most prudent approach to in situ carcinomas with indeterminate histologic features would be to use immunostaining (e.g. for E-cadherin) as an adjunct, and in conjunction with histology, arrive at the most appropriate diagnosis.

**LCIS and core biopsy**

How best to manage patients whose CNB contains ALH or LCIS remains a matter of intense debate. It seems logical to conclude that since classic ALH or LCIS are multicentric and bilateral and at least in part considered a markers of a generalized increase in cancer risk which is approximately equal in both breasts (42-49), surgical excision is not necessary, just as further surgery is not recommended for patients when ALH or LCIS is diagnosed on an open surgical biopsy. Unfortunately, several of the studies regarding the findings in subsequent surgical excision specimens from patients who have had LCIS identified on CNB Have at least some limitations. In addition, data are extremely limited regarding the outcome of histologically ambiguous in situ carcinomas and LCIS variants found on CNB, particularly in relation to E-cadherin or other marker expression. One of the major reasons for the paucity of studies is that even histologically unambiguous LCIS is relatively uncommon, with the incidence ranging from 0.5% to 3.9% in surgical series(42, 43, 46, 50) and under 2% in most CNB series (51-61).

Many studies addressing the appropriate management of ALH and LCIS when identified on CNB have been limited by one or more of the following: (a) relatively small patient numbers; (b) retrospective design, raising the possibility of selection bias with regard to which patients underwent surgical excision. (In other words, studies have often only included core biopsy cases which had necessitated surgical excision due to an indication other than LCIS alone, such as radiologic-pathologic discordance (e.g. pleomorphic calcifications) or co-existence of a high risk lesion (e.g. atypical ductal hyperplasia), resulting in a relatively high frequency of malignancy on follow-up; (c) lack
of adequate radiologic-pathologic correlation; (d) inclusion of histologically ambiguous lesions such as PLCIS; and (e) lack of central pathology review (i.e. only review of pathology reports).

Liberman and coworkers (51) initially conducted a meticulously designed study of lobular neoplasia on CNB, in which they carefully correlated both the core biopsy histopathology as well as breast imaging findings with subsequent surgical follow-up. These authors identified LCIS in 16 of 1315 core biopsy specimens (1.2%), with subsequent surgical excision being performed in 14 cases. Overall, carcinoma was identified in 3 of these 14 cases. Among five cases in which the CNB specimens contained another “high risk” lesion in addition to LCIS (radial scar in 3, atypical ductal hyperplasia in 2), DCIS was found at excision in one case. Among four cases in which the LCIS on CNB had ambiguous features which overlapped those of DCIS, carcinoma was found at excision in two (DCIS in one case and infiltrating lobular carcinoma in one case). Importantly, of the 5 cases in which there was unambiguous LCIS alone on CNB, none had carcinoma on excision. Based on these data, the authors recommended that in patients with a diagnosis of LCIS on CNB, a surgical excision is warranted if another high risk lesion (such as a radial scar or atypical ductal hyperplasia) is present, if the LCIS has some histologic features which overlap with those of DCIS, or if there is discordance between the findings on the imaging studies and the histologic findings (e.g., a spiculated mass on the imaging studies and only LCIS on the CNB). In a similar study, Middleton et al (60) found invasive carcinoma at excision in 6 of 17 patients with LCIS on CNB. All 6 women with carcinoma had image detected mass lesions targeted, which were unaccounted for on their core biopsies. The remaining 11 patients without carcinoma on excision had excellent biopsy-radiology correlation. Of note, some of the LCIS in these 11 patients involved adenosis, ducts in a pagetoid fashion or was associated with calcifications, without adverse outcome. These results underscore the importance of good radiologic-pathologic concordance and confirm the validity of the algorithmic approach set forth by Liberman and co-workers (51).

Several recent studies have tended to advise surgical excision for patients with lobular neoplasia on CNB, however all have had one or more limitation (61-67). Foster et al. (62) found carcinoma at excision in 6 of 35 patients (35%), but the study was retrospective and data were extracted from pathology reports without pathologist review. In another retrospective study, Arpino et al (63) reported cancer on excision in 3 of 21 patients with lobular neoplasia on CNB. In a recent study (which included review of the literature), Elsheikh and Silverman (64) reported an 18% incidence of carcinoma on excision in patients who had a CNB with lobular neoplasia. Some limitations of this study were issues of radiologic-pathologic concordance (e.g. some carcinomas present excision were associated with mass lesions; type of calcifications targeted); the analysis was retrospective in 15 of 33 cases (45%); and cases of pleomorphic lobular carcinoma in situ (PLCIS) were included in the analysis. In another recent study, Karabakhtsian et al. (68) retrospectively analysed the excision outcome of 92 patients who had ALH and/or LCIS diagnosed on CNB. All cases with PLCIS or ADH on CNB were excluded. Overall, 10 cases (11%) had carcinoma at excision (5 invasive, 5 DCIS). Unfortunately, radiology-pathology correlation was not available in 21% cases. Nonetheless, of the 21 cases with “neoplastic calcifications” on CNB (assumed to be calcified ALH or LCIS, but not described or illustrated in the paper), 4 (19%) had
carcinoma at excision. Six (8%) of the remaining 71 cases had carcinoma at excision. Of these 71 cases, 15 were known to have mass lesions targeted by imaging (2 of which had carcinoma at excision). However, the exact radiology-pathology correlation of all the remaining 56 cases (4 of which had carcinoma) was not presented. One of the largest recent studies consisted of a retrospective review of CNBs from 14 institutions over a 12 year period (61). ALH/LCIS was found in 278 of 32,420 (0.9%) CNBs. Of the 164 patients with ALH/LCIS who underwent surgical excision, carcinoma was found in 38 (23%). These authors reported no significant difference between percentage of cases with carcinoma at excision and the type of lobular neoplasia (ALH or LCIS), biopsy guidance method (stereotactic or ultrasound), completeness of the biopsy or adequacy of the radiologic-pathologic concordance. Percentages of cases with carcinoma at excision did differ significantly amongst features such as the lesion targeted (calcifications vs mass), BI-RADS score, biopsy method (gun vs. vacuum), or number cores obtained, but the absolute numbers of cases with carcinoma remained substantial regardless of parameter. However, in addition to the retrospective nature of this study, other limitations included lack of pathologist review (only pathology reports were used) and lack of standardised radiologic-pathologic correlation amongst institutions. Nonetheless, the authors strongly recommended surgical excision for all patients with lobular neoplasia on CNB and reiterated that they “could identify no subgroup of lobular neoplasia lesions that does not require subsequent surgical excision.”

Interestingly, even if the biopsy site is excised following a CNB diagnosis of ALH/LCIS, it may still not be possible to completely avoid missing carcinoma. Renshaw et al. (69) found 7 carcinomas at excision follow-up of 92 CNBs with ALH or LCIS. Two of these carcinomas were separate from the core biopsy site and two occurred after a negative biopsy site excision.

Four recent studies have suggested that excision is not be necessary for “incidentally detected” ALH/LCIS (70-73). Nagi et al. (70) found carcinoma in 2 of 45 cases excised (one DCIS and one small invasive lobular). Hwang et al. (71) found cancer in 4 of 74 cases at excision (3 of which were discordant by imaging). Subhawong et al. (72) categorized core biopsies into those with ≤ 3 foci of ALH as “minimal” involvement; excluded ADH and other lesions requiring excision; and correlated all radiology. All 42 patients with “minimal” ALH on core biopsy had not carcinoma at excision, and these authors suggested that “incidental ALH” on core biopsy did not require excision. In the largest prospective study of excision follow-up of patients with classic ALH/LCIS on core, Luedtke et al evaluated 71 core biopsies (66% for calcifications, 10% for mass lesions and 24% for MRI abnormalities.) (73). All pathology was reviewed with excellent radiologic-pathologic correlation. At excision, only 2 cancers (3% of cases) were found and both were minute low grade tumors (2.3mm tubular carcinoma and 2mm DCIS.)

Data is particularly limited regarding the use of immunostains (e.g. E-cadherin) to assist in the management of ambiguous lesions on core biopsy. The only study to date to address E-cadherin expression in situ lesions on core biopsy with excision follow-up was retrospective review of 3401 consecutive CNB cases where 12 cases with ALH, 13 with LCIS and 5 with in situ carcinoma with both ductal and lobular features were found (56). No invasive carcinoma or DCIS was found among the 7 ALH
cases or among the 7 LCIS cases which were surgically excised. Of note, all five cases with in situ carcinoma with ductal and lobular features were negative for e-cadherin suggesting a lobular phenotype (16). However, on excision 3 of these cases (60%) were found to have invasive carcinoma(56). Therefore, this observation suggests that excision is warranted in cases of in situ carcinoma with ambiguous histologic features (e.g. PLCIS), even if the cells are E-cadherin negative by immunohistochemistry. Some investigators have utilized immunostaining for other markers such as high molecular weight cytokeratin (21) and catenins (in particular p120 catenin)(32, 33) in an attempt to categorize carcinomas in situ with ambiguous histologic features. However, to date there are no data regarding use of these markers in the management of ambiguous in situ lesions on CNB.

In an ideal world, an approach similar to that initially proposed by Liberman and co-workers might be feasible (51): i.e. when LCIS or ALH is identified on CNB, the patient should undergo a surgical excision: (a) if there is radiologic-pathologic discordance, suggesting that the targeted lesion was not represented in the CNB specimen (e.g., if the imaging studies show suspicious microcalcifications, a spiculated mass, or other soft tissue density); (b) if another lesion which by itself would be an indication for surgical excision is also present on the core biopsy (such as ADH); or (c) if the LCIS or ALH has ambiguous histologic features which create problems in distinguishing the lesion from DCIS (e.g. PLCIS, LCIS with comedo-type necrosis, etc., even if e-cadherin negative). In contrast, if histologically unambiguous LCIS or ALH in a CNB is a completely incidental finding, with good radiologic-pathologic correlation of the targeted lesion, surgical excision may not be necessary. Unfortunately, the management of patients with ALH or LCIS on CNB remains quite controversial, particularly in light of recent studies raising concern of an increased incidence of carcinoma at excision. In a recent multidisciplinary consensus conference(74), the expert panel stated the following: “The need to advise excision for patients with lobular neoplasia (ALH and lobular carcinoma in situ) incidentally diagnosed on percutaneous core needle biopsy generated substantial debate. Data from different studies on the risk of histologic upgrading are conflicting. The Panel did not reach consensus on this issue. Some believed that it is reasonable but not mandatory to perform excision after a core needle finding of lobular neoplasia. The majority believed that excision was required and that all centers should track and monitor their “upgrade” rate. But as stated earlier, some institutions use algorithms that may yield sufficiently low upgrade ratees to avoid excision of these lesions, particularly when incidental to radiologic findings. “
In the absence of sufficient data, the clinical decision is whether to over-treat or to under-treat patients. Issues are further compounded by medicolegal concerns. It therefore appears to be prudent at this time to advise excision of all patients who have a diagnosis of ALH or LCIS on CNB. Clearly, additional, prospective clinical outcome studies are required, with larger numbers of patients while also encompassing newer biologic markers (e.g. e-cadherin) to further define the management of in situ lobular lesions on core needle biopsy.
References

55. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. (Meeting Abstract). Mod Pathol. 2001;14:36A.
64. Elsheikh TM, Silverman JF. Follow-up Surgical Excision Is Indicated When Breast Core Needle Biopsies Show Atypical Lobular Hyperplasia or Lobular Carcinoma
Lobular Carcinoma in Situ: Past, Present and Future

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LCIS

- Historical perspective
- Cancer risk
- Morphology and “variants”
- Core biopsy
Historical Perspective

• Ewing 1919: “Neoplastic Diseases – A Textbook of Tumors”
• Broders 1932: “Carcinoma in Situ Contrasted with Benign Penetrating Epithelium”
• Foote and Stewart 1941: “Lobular Carcinoma in Situ – A Rare from of Mammary Cancer”
Foote and Stewart 1941
LCIS Classic Description

- No clinical or gross features
- Multicentric
- No necrosis
- Classic morphologic description
  - Uniform, loss of polarity
  - Mitoses very rare
  - May show “pagetoid” growth
- Similar in morphology to associated invasive lobular carcinoma
ALH/LCIS and Cancer
Risk Factor or Precursor?
## LCIS and Risk of Cancer

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ALH: RR = 4-5.5 (~ half of LCIS) (Nashville, NHS)

* Lobular Neoplasia
## LCIS and Laterality of Cancer

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Evidence for Generalized Risk Factor

- ~50% cancers contralateral
- More invasive ductal (up to 75%)
- LCIS often multifocal (50%), bilateral (30%)
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
- Observational
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
  - Inv lobular more prevalent: ~45% (5-14% expected)
  - Ipsilateral in ~ 2/3

Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study

Page, Schuyler, Dupont, Jensen, Plummer, Simpson
Lancet 2003;361:125-29

Subsequent Cancers

- Ipsilateral (n=34) 68%
- Contralateral (n=12) 24%
- Bilateral (n=2) 4%
- Unknown (n=2) 4%
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
- Observational
  - Proximity
  - Morphologic similarity
  - Immunohistochemistry
  - Genetic
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
- Observational
  - Proximity
    - CCC, FEA, ADH, LG DCIS
    - Invasive lobular CA
    - Tubular CA

Page 1996; Goldstein & O’Malley 1997; Fraser 1998; Rosen 1999; Moinfar 2000; Oyama 2000; Brogi 2001; Collins 2007; de Mascarel 2007; Abdel-Fatah 2007; Brandt 2008
Atypical Cystic Lobules in Patients with Lobular Neoplasia

Brogi, Oyama, Koerner
Int J Surg Pathol 2001;9:201-6

- 54 patients with lobular neoplasia:
- FEA ("ACL") in
  - 18/30 (60%) with LCIS
  - 11/24 (46%) with ALH
FEA with Adjacent ALH
TDLU with CCL and ALH
The “Rosen Triad”: Tubular Carcinoma, Lobular Carcinoma in Situ, and Columnar Cell Lesions
Brandt, Young, Hoda
Adv Anat Pathol 2008;15:140-146

- 86 cases of Tub CA
- 100% had CCL
- 53% had LCIS
- Rosen 1999 AJSP 23:1561
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
- Observational
  - Proximity
  - Morphologic similarity
  - Immunohistochemistry
  - Genetic
Evidence for Non-Obligate Precursor?

- Epidemiology/outcome
- Observational
  - Proximity
  - Morphologic similarity
  - Immunohistochemistry
  - Genetic
Clonality of Lobular Carcinoma in Situ and Synchronous Invasive Lobular Carcinoma
Hwang et al.
Cancer 2004;100:2562-72

- 24 synchronous LCIS and ILC
- Microdissection, array-based CGH
- Substantial genomic alteration in both LCIS and ILC
- 14 LCIS related more to paired ILC than any other ILC
Proposed Evolutionary Pathway of ILC through Columnar Cell Lesions Based on Histol and Genetics


- CCC $\rightarrow$ CCH $\rightarrow$ CCH with atypia $\rightarrow$ LN $\rightarrow$ ILC
- Morphology
- Genetic, -16q
- Low grade breast neoplasia family (Ellis 2010 Mod Pathol 23 Suppl 2: S1-7)
Predictors of Subsequent CA

• Clinical
  – e.g. FH (Columbia)

• Growth/Spaces
  – distension (NSABP)
  – > 10 involved (Ottesen)
  – LIN3 vs LIN 1,2 (AFIP)

• Cytology
  – Nuclear size (Ottesen)
  – Mixed A and B (NSABP)

• IHC
  – E-cad pos (Goldstein)

To date, no reliable, reproducible Features
ALH/LCIS

Risk Factor or Precursor?

- Yes!
- Both (or intermediate)
- Can’t tell which at present
Classic LCIS Recommendations

Until we can distinguish risk vs. precursor lesions:

- Clin follow-up ± tamoxifen
- Margins not important
- No radiation
Classic LCIS

Morphologic Considerations
ALH vs. LCIS

- Cells morphologically identical
- Degree of involvement of TDLU (e.g. >50% of space distended - Page and Anderson)
LCIS vs. ALH Distinction

• Unclear for “non-TDLU” situations

• Sclerosing adenosis, radial scar, fibroadenoma, etc.
Sclerosing Adenosis with: ALH or LCIS?
Sclerosing Adenosis with: ALH or LCIS?
Radial Scar with: ALH or LCIS?
Radial Scar with: ALH or LCIS?
LCIS

• Other terminology
  – Lobular Neoplasia
  – LIN 1, 2, 3 (Tavassoli/AFIP)

• Morphologic heterogeneity within classic LCIS
  – Type A, B
  – Signet rings, clear cell, etc.
Type “A” Cells
Type “B” Cells
Classic LCIS
What to do?

• If possible, distinguish between ALH and LCIS
• If not feasible (e.g. sclerosing adenosis, tiny biopsy) don’t perseverate over terminology
• Rather diagnose ALH/LCIS or Lobular Neoplasia but:
  • Don’t miss the lesion if subtle
  • Don’t confuse with mimickers…
LCIS/ALH
Differential Diagnosis

• Invasive carcinoma
• Myoepithelial cells
• Clear cell change
• Fixation artifact with “pseudodyshesion”
• DCIS
Myoepithelial Cells Mimicking ALH
Fixation Artifact – “Pseudodyshesion”
DCIS vs. LCIS

• Most mammary CIS are easily categorized as LCIS or DCIS
• However, occasionally there is overlap between these two lesions…
DCIS in a Lobule

LCIS in a Duct
LCIS & DCIS Co-existing
DCIS vs. LCIS
Therapeutic Implications

• DCIS treated by eradication
• LCIS treated by observation (+Tamoxifen)
• Margins important for DCIS, not LCIS
DCIS vs. LCIS
The Ideal World

Traditionally based on classic histologic features (H&E)
DCIS vs. LCIS
The Real World

Distinction in some cases may be impossible on morphology alone
In Situ Carcinomas with Indeterminate Histologic Features

- Cytologic and/or architectural features deviate from usual patterns of LCIS or DCIS
- How to categorize?
- Role of IHC (for E-cadherin, HMW-CK, catenins)?
- How best to manage?
Classic LCIS
Basic Requirements

1. Uniform small/medium sized cells
2. Cellular dyshesion
   No architectural pattern
3. Lack of significant necrosis
   (comedo-type)
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Uniform small/medium sized cells
2. Cellular dyshesion
   No architectural pattern
3. Lack of significant necrosis
   (comedo-type)
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Pleomorphic cells ("PLCIS")
2. Cellular dyshesion
   No architectural pattern
3. Lack of significant necrosis (comedo-type)
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Uniform small/medium sized cells
2. Cellular dyshesion
   No architectural pattern
3. Lack of significant necrosis
   (comedo-type)
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Uniform small/medium sized cells
2. Cellular cohesion ("mosaic")
   Architectural pattern (microacini)
3. Lack of significant necrosis
   (comedo-type)
With Variable Architecture
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Uniform small/medium sized cells
2. Cellular dyshesion
   No architectural pattern
3. Lack of significant necrosis
   (comedo-type)
In Situ Carcinomas with Indeterminate Histologic Features: Differences from Classic LCIS

1. Uniform small/medium sized cells
2. Cellular dyshesion
   No architectural pattern
3. Presence of significant necrosis
   (comedo-type)
With Comedo Necrosis
Indeterminate CIS
Is there a role for IHC?

• E-cadherin
• High MW CK
• Catenins
E-cadherin

- Cadherins: family of transmembrane adhesion receptor molecules
- E-cadherin expression lost in most invasive lobular carcinomas and LCIS but not in invasive ductal carcinoma or DCIS
  - LOH at 16q22
  - Gene mutations
  - Gene silencing (e.g. promoter methylation)
E-cadherin Immunostaining

Invasive Lobular Negative

Invasive Ductal Positive
E-cadherin Immunostaining
LCIS negative, DCIS positive
Pleomorphic (PLCIS)
E-cadherin Negative
With Comedo Necrosis
E-cadherin Negative
With Architecture
E-cadherin Negative
With Architecture
E-cadherin Negative
With Architecture
E-cadherin Positive
With Architecture
E-cadherin Mixed
Mixed Lesions
? Diagnosis
LCIS in Collagenous Spherulosis
E-cadherin Limitations

• Loss of E-cad is a characteristic of LCIS, but…

• E-cad staining does not preclude LCIS if histology appropriate:
  – Residual normal ducts
  – Myoepithelial cells
  – LCIS per se
Pictures

• Variable staining of LCIS
• Myoepithelial cells, normal (? Use Coll Sph)
• Etc.
4 of 25 invasive lobular carcinomas had some positive E-cad staining. All 4 had genomic features of ILC – 16q loss, 1q gain, 11q loss. E-cadherin positivity does not exclude a diagnosis of otherwise classic ILC! Implications for in situ lesions...
Clinical and Biological Significance of E-cadherin Protein Expression in Invasive Lobular Carcinoma of the Breast

- 38 of 239 (16%) histologically defined ILC were E-cad positive by IHC
- No association between E-cad positivity and clinical/prognostic variables in ILC
- E-cad~Catenin integrity impaired
- Breast cancers with classic ILC histology should not be interpreted as ductal based on E-cad expression
Indeterminate CIS
Is there a role for IHC?

- E-cadherin
- High MW CK
- Catenins
Combined E-Cadherin and High Molecular Weight Cytokeratin Immunoprofile Differentiates Lobular, Ductal, and Hybrid Mammary Intraepithelial Neoplasias

Bratthauer et al. Hum Pathol 2002;33:620

- Antibody 34βE12 (CK 1, 5, 10, 14)
- DCIS: HMW-CK neg, E-cad pos
- LCIS: HMW-CK pos, E-cad neg
34βE12 and Carcinoma In Situ
Bratthauer et al. *Hum Pathol* 2002;33:620

**Issues**

- How to interpret “hybrid” cases?
  - Both E-cadherin and HMW-CK pos or neg
- Which specificity of 34βE12 is relevant (CK 1, 5, 10 and/or 14)?
- IHC methodology issues
- What’s the biologic basis?
Indeterminate CIS
Is there a role for IHC?

• E-cadherin
• High MW CK
• Catenins
E-Cadherin-Catenin Adhesion Complex

- β-Catenin
- E-cadherin
- α-Catenin
- p120 Catenin
- F-actin, α-actinin etc, etc

Altered E-cadherin-Catenin Adhesion Complex in Lobular

• E-cadherin expression lost
• $\alpha$, $\beta$, $\gamma$-catenin expression lost
• p120-Catenin dissociates from complex $\rightarrow$ cytoplasmic

De Leeuw et al. *J Pathol* 1997;183:404
Sarrio et al. *Oncogene* 2004;23:3272
## E-cadherin-Catenin Complex

<table>
<thead>
<tr>
<th></th>
<th>DCIS</th>
<th>LCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E-cadherin</strong></td>
<td>Membrane Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>α-, β-, γ-</strong></td>
<td>Membrane Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>catenin</td>
<td>Membrane Positive</td>
<td></td>
</tr>
<tr>
<td><strong>p120</strong></td>
<td>Membrane Positive</td>
<td>Cytoplasm Positive</td>
</tr>
<tr>
<td>catenin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current understanding of biologic behavior of DCIS and LCIS is based on follow-up studies of lesions classified according to histologic features alone (“classic” DCIS and LCIS).

Unclear whether these data can be generalized to CIS with ambiguous histologic features classified as DCIS or LCIS by IHC alone.
Histologically Ambiguous Carcinoma in Situ

What data is available to guide management?
“LCIS with Comedo Necrosis”
Lobular Intraepithelial Neoplasia [Lobular Carcinoma In Situ] With Comedo-type Necrosis

- 18 cases
- 12 with invasive carcinoma
- Apart from necrosis, akin to LCIS:
  - Growth pattern
  - E-cadherin neg
  - ER/PR pos, HER2 neg
- Management, terminology issues?
  - CNB or at margins → excise
Excise if at margin
Excise if at margin

But what if only the “LCIS” without necrosis is at the margin?
PLCIS

• First description:
• Frost, Tsangaris, Silverberg. Pathology Case Reviews 1996
PLCIS: Morphologic Criteria

LCIS growth pattern and

- Moderate to marked nuclear pleomorphism
- At least some nuclei ≥ 4x lymphocyte
  - Sneige 2002 and Chen 2009

- At least 2x nuclear size variation
- Nuclear diameter > 2x lymphocyte
  - Ho, Lee & Ellis 2010
Sneige et al. Mod Pathol 2002;15:1044

<table>
<thead>
<tr>
<th></th>
<th>PLCIS</th>
<th>LCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Pleomorphic*</td>
<td>Monomorphomic</td>
</tr>
<tr>
<td>E-cadherin neg</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>p53 staining</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>Ki67 staining</td>
<td>10%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Nucleus ≥ 4x lymphocyte (vs. LCIS A = 1.5x, B = 2x)
Sneige et al. Mod Pathol 2002;15:1044

<table>
<thead>
<tr>
<th>PLCIS</th>
<th>Isolated</th>
<th>With Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Pleomorphic</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td>E-cadherin neg</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>p53 staining</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>Mod-high prolif</td>
<td>44%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Pleomorphic lobular carcinoma of the breast: role of comprehensive molecular pathology in characterization of an entity
Reis-Filho et al. J Pathol 2005;207:1

• Single case PLCIS + invasion
• Features akin to LCIS:
  – E-cadherin & β-catenin neg
  – Loss of 16q, gain of 1q
• Aggressive features:
  – Amplification of c-myc & HER2
Chen et al. AJSP 2009;33:1683

PLCIS Characteristics (n=31)

• Mammographic detection

• Features similar to LCIS:
  – 100% E-cadherin negative by IHC
  – Loss of 16q, gain of 1q by aCGH

• Features different from classic LCIS*:
  – †HER2 positive
  – †High proliferation by Ki67 IHC
  – †ER/PR negative by IHC
  – Genomic instability

  (*Apocrine PLCIS differed more)

• Suggestive of more “aggressive”
# PLCIS

## Summary of what we know

<table>
<thead>
<tr>
<th></th>
<th>Classic LCIS</th>
<th>Pleomorphic LCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Premenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Incidental</td>
<td>Mammographic</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Uniform</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td><strong>ER</strong></td>
<td>Pos</td>
<td>Pos/Neg</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>Neg</td>
<td>Pos/Neg</td>
</tr>
<tr>
<td><strong>Prolif/ Ki67</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Genomic</strong></td>
<td>Fewer</td>
<td>More</td>
</tr>
</tbody>
</table>
How to best manage “variant” in situ lesions e.g. PLCIS?

1. Use histologic features?
2. Use immunostaining to definitively categorize?
3. Should one over-treat or under-treat?
## PLCIS Management?

### LCIS features
- Lobular features (dyshesive etc)
- E-Cadherin neg
- 16q loss, 1q gain

### DCIS features
- Pleomorphic, mitoses, ± necrosis
- Bad markers
- Genomic alterations

### LCIS Management
- Risk Factor
- Observation ± Tam
- No margins

### DCIS Management
- Precursor Lesion
- Eradicate
- Margins
Manage as for DCIS

- Excision to negative margins?
- Radiation therapy?
- Mastectomy?
- Over- or undertreat?
What to do?

• Current understanding based on clinical outcome of classic LCIS and DCIS classified by histology

• In the absence of data → conservative approach is prudent

• Categorize as PLCIS, with a note, discuss at MDTB

• Until outcome data available, management remains unknown
LCIS on Core Biopsy

What should we do?
ALH/LCIS on CNB
To excise or not to excise?

Excision recommended if:
- Radiology-pathology discordant - targeted lesion not represented, mass, architectural distortion
- Another lesion for which excision indicated (e.g. ADH)
- Histologic features overlapping with DCIS (even if E-cadherin negative)

Excision not necessary?
- If LCIS/ALH is completely “incidental”
CNB for Microcalcifications
Calcs in Ducts

CNB for Microcalcifications
CNB for Microcalcifications

Calcs in Ducts

ALH, ? “Incidental”
“Incidental” ALH/LCIS on CNB

Issues

• Clinical and imaging context?
• Marker of risk and/or precursor lesion?
• Sampling issues…
• CNB is a sampling process

• Therefore, pathologic findings in the CNB may not accurately represent the radiologically detected target lesion

• Is ALH/LCIS a sampling issue per se?
## Marker of Risk vs. Sampling Issue

<table>
<thead>
<tr>
<th>Worse lesion (i.e. Cancer)</th>
<th>Risk Marker</th>
<th>Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anywhere</td>
<td>Target Site</td>
</tr>
<tr>
<td>Either breast</td>
<td>Either breast</td>
<td>Same breast</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time frame</th>
<th>Risk Marker</th>
<th>Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Future</td>
<td>Current</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADH</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALH/LCIS</td>
<td>Yes</td>
<td>?</td>
</tr>
</tbody>
</table>
Risk Terminology Issues

• Radiology: “high risk lesion” on CNB usually = requiring excision due to “risk” of worse lesion (i.e. cancer)
• = sampling issue
• (not a marker of cancer risk)
ALH/LCIS on CNB

Studies often limited by:

• Retrospective nature → selection bias; no controls
• Suboptimal radiologic-pathologic correlation
• Classic LCIS often lumped with PLCIS or other variants
ALH/LCIS on CNB
Recent reports – Excise all?

Yes
Foster 2004
Arpino 2004
Elsheikh 2005
Mahoney 2006
Karabakhtsian 2007
Cangierella 2008
Brem 2008

No
Renshaw 2006
Nagi 2008
Hwang 2008
Subhawong 2010
Luedtke 2011
## ALH/LCIS on CNB

### Recent reports – Excise all?

<table>
<thead>
<tr>
<th>Yes</th>
<th># excised</th>
<th>% CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster 2004</td>
<td>35</td>
<td>17%</td>
</tr>
<tr>
<td>Arpino 2004</td>
<td>21</td>
<td>14%</td>
</tr>
<tr>
<td>Elsheikh 2005</td>
<td>33</td>
<td>27%</td>
</tr>
<tr>
<td>Mahoney 2006</td>
<td>20</td>
<td>25%</td>
</tr>
<tr>
<td>Karabakhtsian 2007</td>
<td>92</td>
<td>11%</td>
</tr>
<tr>
<td>Cangierella 2008</td>
<td>38</td>
<td>8%</td>
</tr>
<tr>
<td>Brem 2008</td>
<td>164</td>
<td>23%</td>
</tr>
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</table>
### ALH/LCIS on CNB

#### Recent reports – Excise all?

<table>
<thead>
<tr>
<th>Yes</th>
<th>Retrosp</th>
<th>Path Rev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster 2004</td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>Arpino 2004</td>
<td>All</td>
<td>Yes</td>
</tr>
<tr>
<td>Elsheikh 2005</td>
<td>45%</td>
<td>Yes</td>
</tr>
<tr>
<td>Mahoney 2006</td>
<td>All</td>
<td>Yes</td>
</tr>
<tr>
<td>Karabakhtsian 2007</td>
<td>All</td>
<td>Yes</td>
</tr>
<tr>
<td>Cangierella 2008</td>
<td>All</td>
<td>Yes</td>
</tr>
<tr>
<td>Brem 2008</td>
<td>All</td>
<td>No</td>
</tr>
</tbody>
</table>
**ALH/LCIS on CNB**

**Recent reports – Excise all?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>Retrospec</th>
<th>Path Rev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arpino 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elsheikh 2005</td>
<td>4 mass lesions</td>
<td>Radiology in 70%</td>
</tr>
<tr>
<td></td>
<td>Included PLCIS, ADH</td>
<td>(mammo in 65%)</td>
</tr>
<tr>
<td>Mahoney 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karabakhtsian</td>
<td>14 institutions, 12 yrs</td>
<td>No path, rad-path varied</td>
</tr>
<tr>
<td>Cangierella 2000</td>
<td></td>
<td>CA at excision regardless:</td>
</tr>
<tr>
<td>Brem 2008</td>
<td></td>
<td>device, # cores, imaging, complete removal, rad-path concordance</td>
</tr>
</tbody>
</table>
## ALH/LCIS on CNB

**Recent Reports – Not Excise All?**

Path review; excluded PLCIS, ADH, etc.; radiology

<table>
<thead>
<tr>
<th>Study</th>
<th>Excised</th>
<th>CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renshaw (2006)</td>
<td>92 (43%)</td>
<td>7  (3 at bx site)</td>
</tr>
<tr>
<td>Naji (2008)</td>
<td>45 (46%)</td>
<td>2  (DCIS, tiny ILC)</td>
</tr>
<tr>
<td>Hwang (2008)</td>
<td>74 (41%)</td>
<td>4  (3 discordant)</td>
</tr>
<tr>
<td>Subhawong (2010)</td>
<td>56 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Luedtke (2011)</td>
<td>71 (100%)</td>
<td>2  (2 minute LG CA)</td>
</tr>
</tbody>
</table>
Incidental Minimal Atypical Lobular Hyperplasia on Core Needle Biopsy Correlation With Findings on Follow-up Excision


- “Minimal” ALH \leq 3 foci on CNB
- Excluded ADH, etc
- All radiology correlated
- All 42 with \leq 3 foci ALH \rightarrow no CA
- Incidental ALH \rightarrow not excise
Outcomes of Prospective Excision for Classic LCIS & ALH on Percutaneous Breast Core Biopsy

MSKCC (Luedtke et al.) USCAP 2011 (Abstr. 209)

- 71 CNB with ALH/LCIS only, all prospectively excised
- 66% calcs, 10% mass, 24% MRI
- All path reviewed, good rad-path correlation
- 2 cancers (3%) – minute low grade
  (2.3mm tubular CA, 2mm DCIS)
ALH/LCIS on CNB
Additional Considerations

• What is the indication/context
• What % upgrade is acceptable?
• LCIS really more heterogeneous (clinical, imaging, pathology/morphology, genetics)?
• Which lesions are markers of risk and which are precursors?
• We can’t reliably tell these apart
ALH/LCIS on CNB: What to do?

- Controversial; medico-legal issues
- Need prospective, multiinstitutional trials with all patients undergoing excision; but unlikely…
- In absence of sufficient data, does one over- or under-treat?

Excision probably prudent at this time