Interpretation of Breast Pathology in the Era of Minimally Invasive Procedures

6th International Congress of Breast Disease Centers

February 4-6, 2016
Paris, France

Shahla Masood, M.D.
Professor and Chair
Department of Pathology and Laboratory Medicine
University of Florida College of Medicine – Jacksonville
Medical Director, UF Health Breast Center
Chief of Pathology and Laboratory Medicine
UF HealthJacksonville

The Plan

- To discuss the rationale behind the use of minimally invasive procedures
- To discuss the diagnostic challenges associated with interpretation of difficult to diagnose cases in samples obtained by needle biopsy
- To highlight similarities and differences between fine needle aspiration biopsy and core needle biopsy
- To summarize the appropriate clinical follow up including replacing the term low-grade ductal carcinoma insitu with borderline breast disease

Breast Cancer

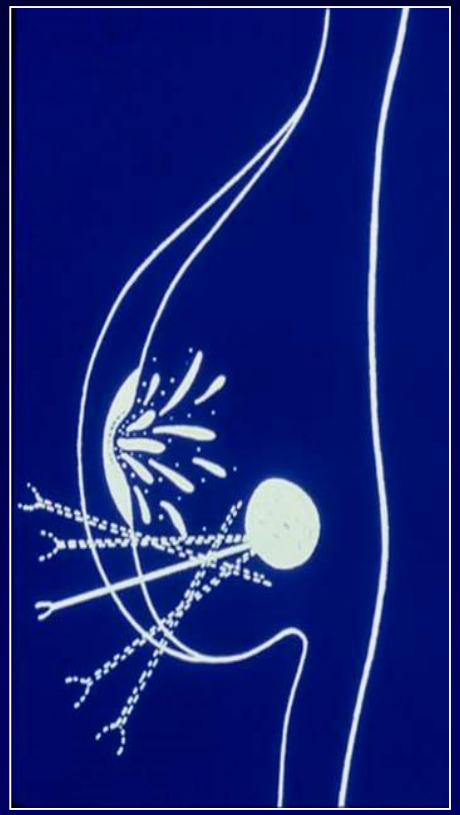
Advances

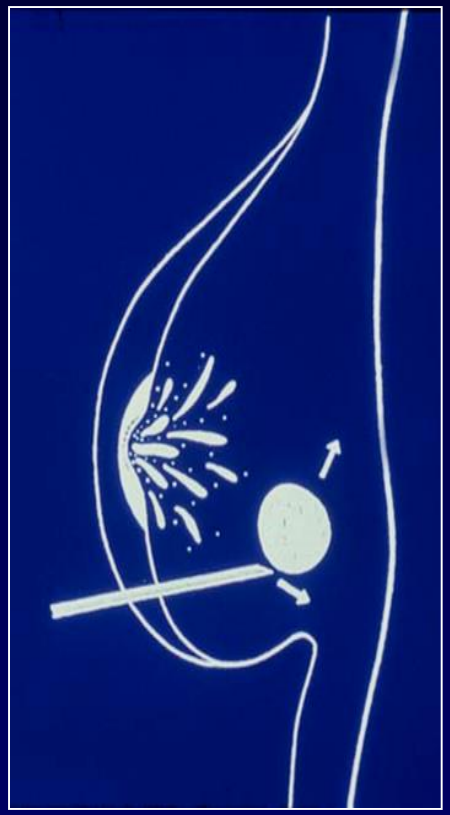
- Enhanced public awareness and screening
- Improvement in breast imaging
- Introduction of minimally invasive diagnostic and therapeutic procedures
- Interest in breast cancer risk reduction and prevention
- Discovery of breast cancer genes and molecular pathways
- Introduction of molecular targeted therapy

Minimally Invasive Procedures

Goals

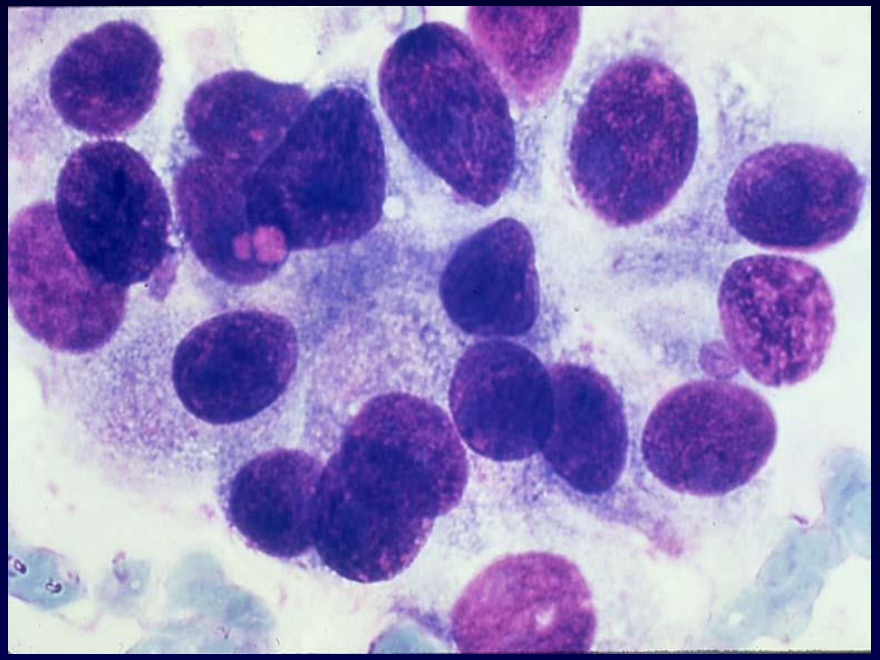
- To eliminate the need for open biopsy in benign disease
- To provide a non-surgical means to diagnose breast cancer



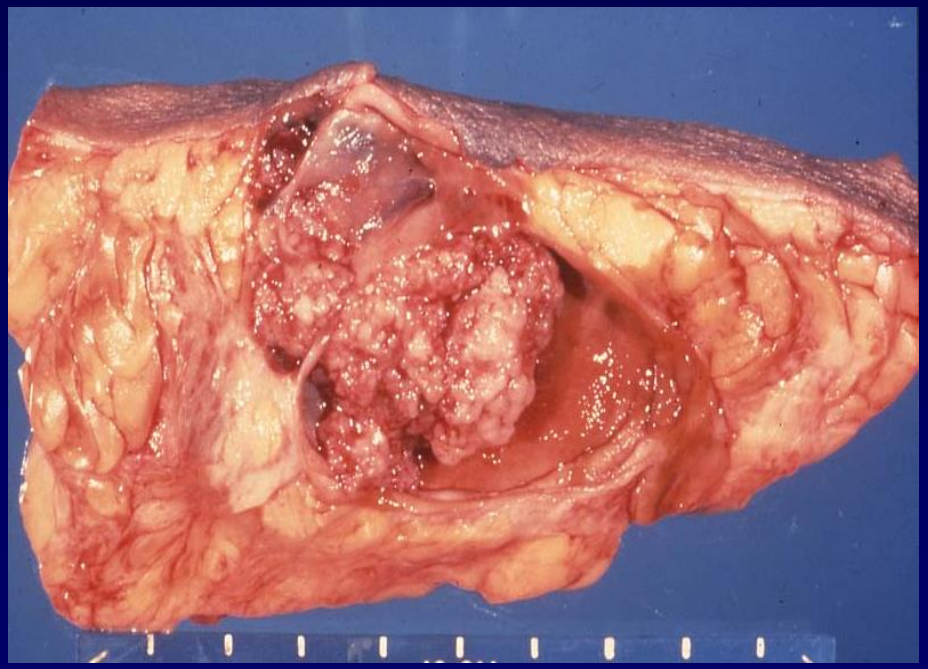


FNA BIOPSY VERSUS **CORE BIOPSY**

FNA Biopsy

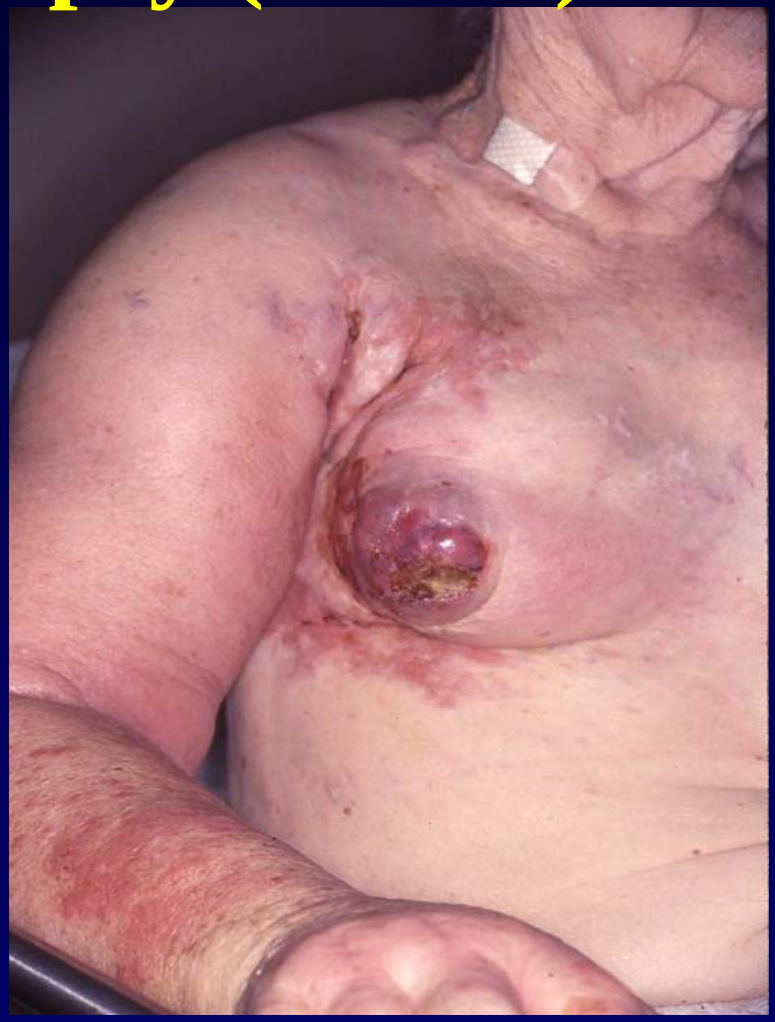


Surgical Specimen

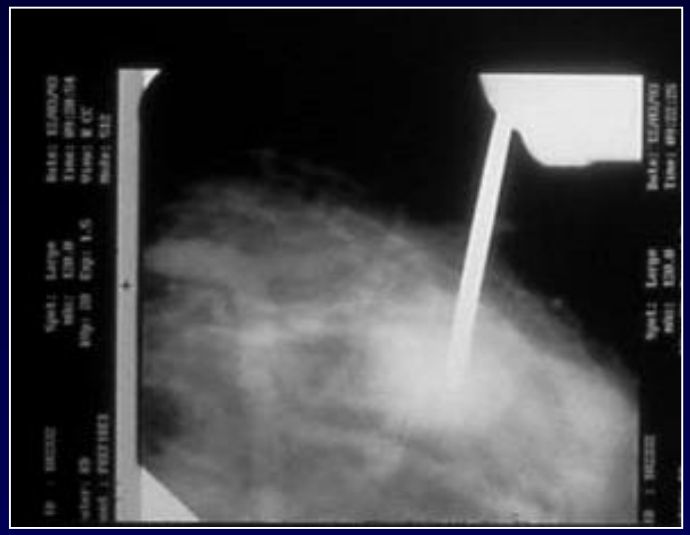


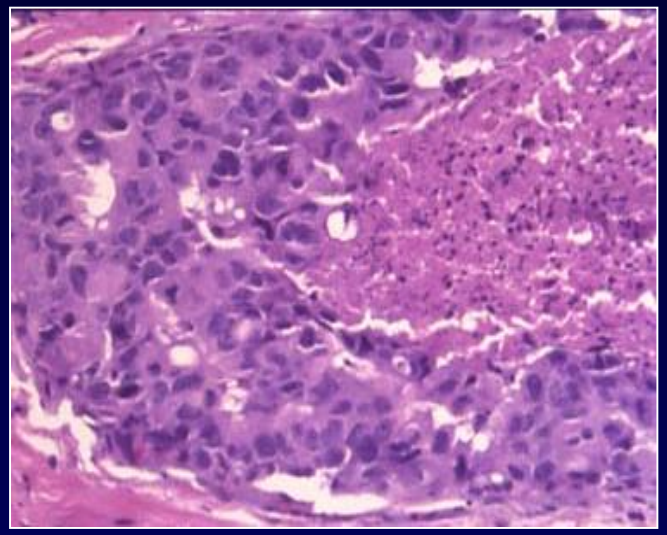
Breast Cancer Advantages of Fine Needle Aspiration Biopsy (FNAB)

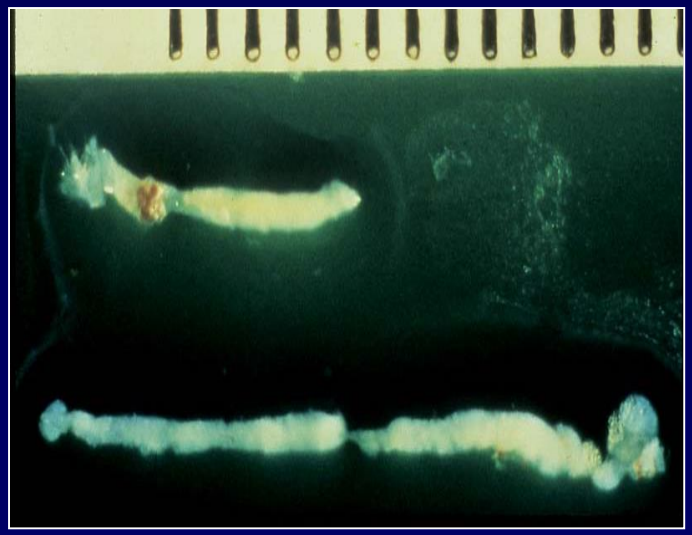
- Providing a diagnosis when surgical biopsy may not be available
- Therapeutic evacuation of benign cysts
- High acceptability
- Cost effectiveness

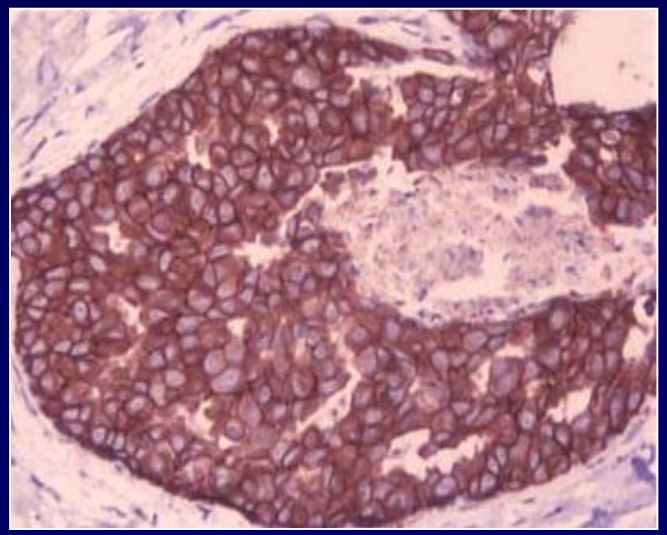


Breast Cancer Advantages of Core Needle Biopsy (CNB)









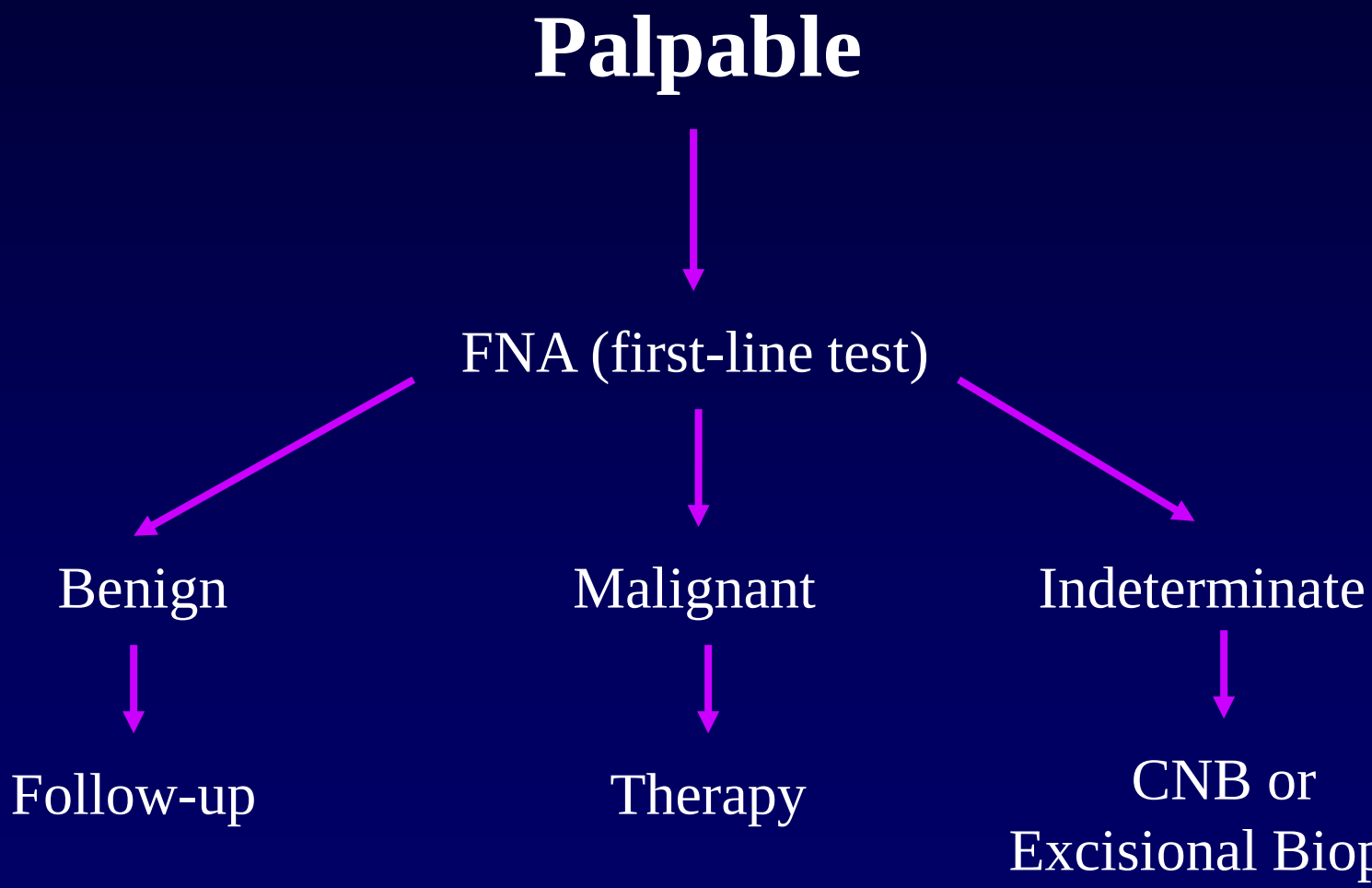
Common Issues in Minimally Invasive Sampling Procedures

- Small sample size
- Sampling errors
- Absolute need for an integrated approach among radiologists, pathologists and breast physicians

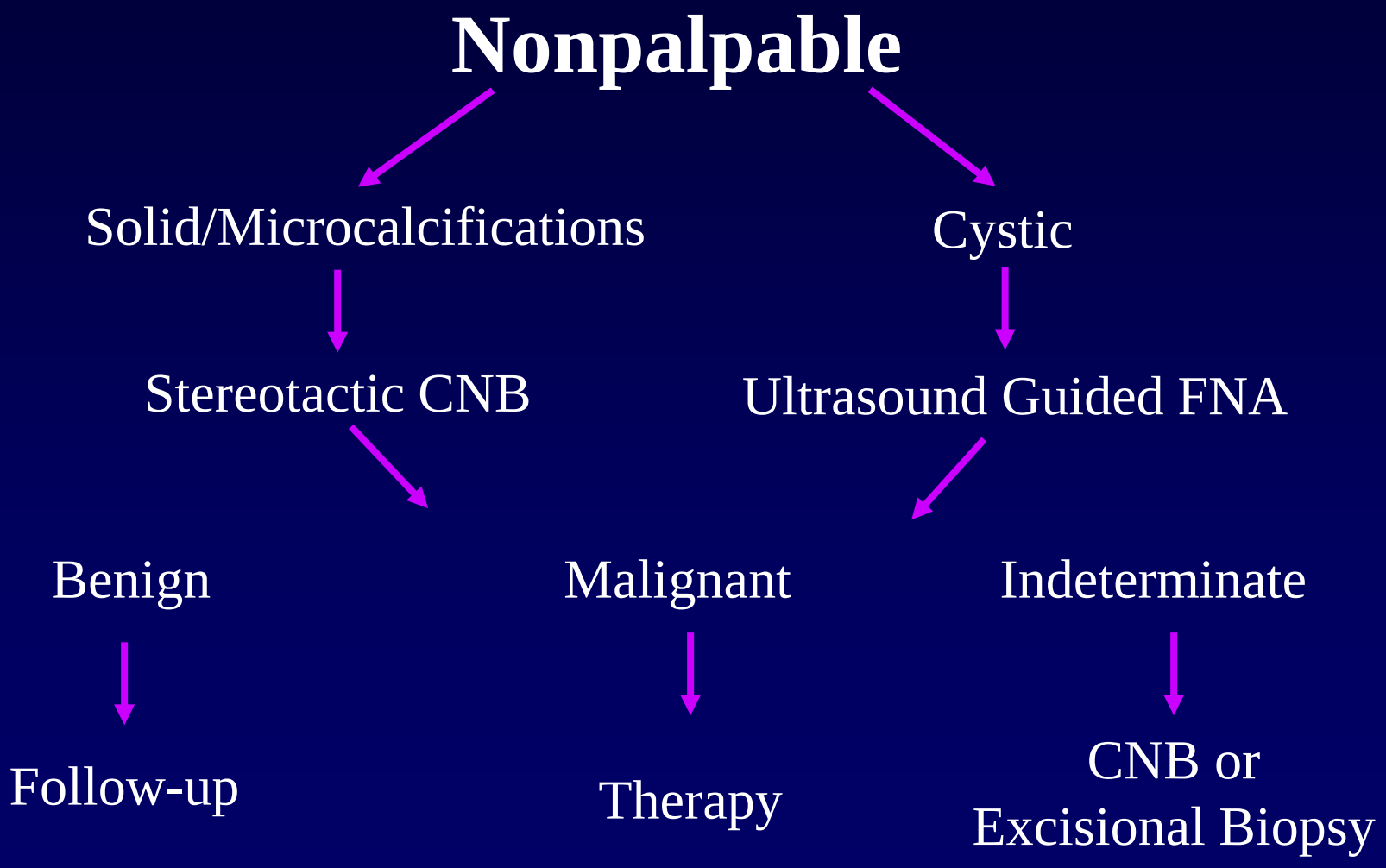
FNAB & CNB: A Comprehensive Approach

- **FNAB and CNB can and should be utilized together for the best management of patients with breast lesions. However, radiologic and clinical findings should guide the decision as to which procedure should be used**
- **Difficult to diagnose lesions are similar in FNAB and CNB. The Triple Test plays a critical role in the accurate interpretation of both**

Schematic Approach to the Evaluation of Breast Lesions



Schematic Approach to the Evaluation of Breast Lesions



Minimally Invasive Sampling Procedures

Diagnostic Issues

- Atypical ductal hyperplasia (ADH) versus low-grade ductal carcinoma in situ (DCIS)
- Papillary lesions (papilloma versus papillary carcinoma)
- Fibroepithelial lesions (fibroadenoma versus benign phyllodes tumor)
- Sclerosing lesions
- Mucinous lesions
- The status of invasion

Minimally Invasive Sampling Procedures

Pathology Features	Increased incidence of malignancy at excision
o Atypical ductal hyperplasia	13 – 66%
o Ductal carcinoma in situ	Up to 20%
o Atypical papilloma	33 – 83%
o Lobular neoplasia	Up to 25%

Why the Emphasis on Atypical Ductal Hyperplasia?

Atypical Ductal Hyperplasia

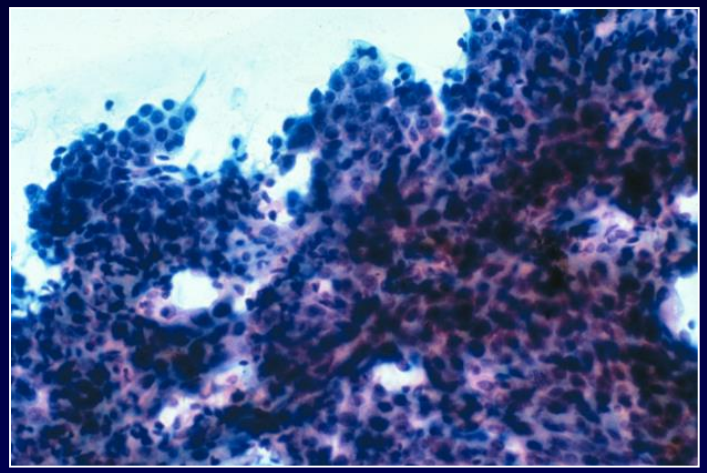
- Screening mammography and image detected biopsy have increased the diagnosis of atypical proliferative lesions and ductal carcinoma in situ
- Is considered as a morphologic risk factor
- Use of Tamoxifen as a chemopreventative agent has reduced the incidence of subsequent development of breast cancer in patients with ADH

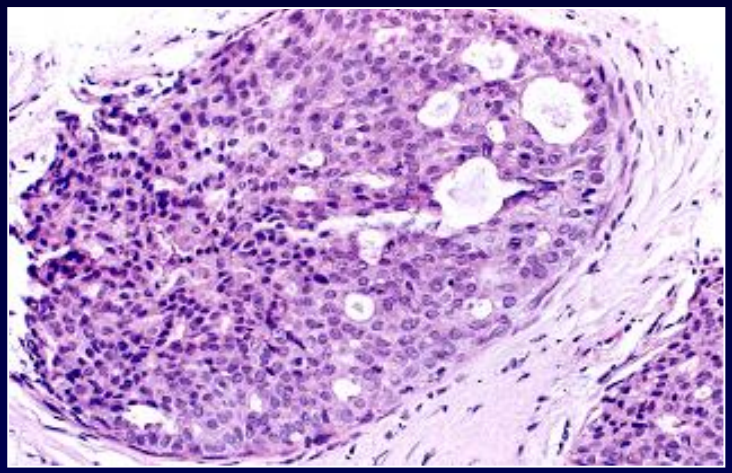
Continued

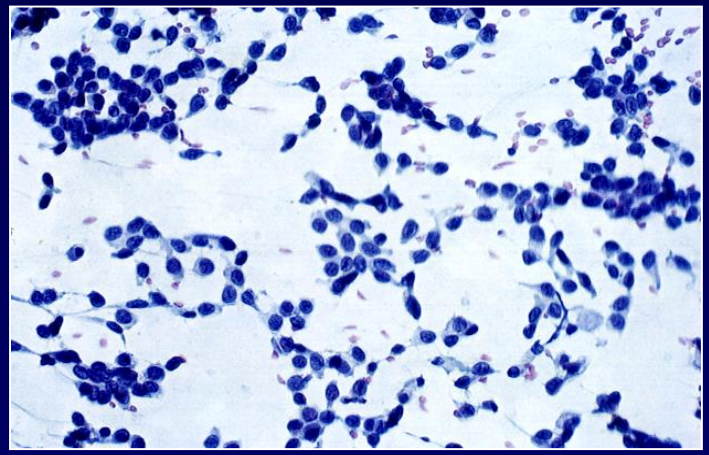
Atypical Ductal Hyperplasia

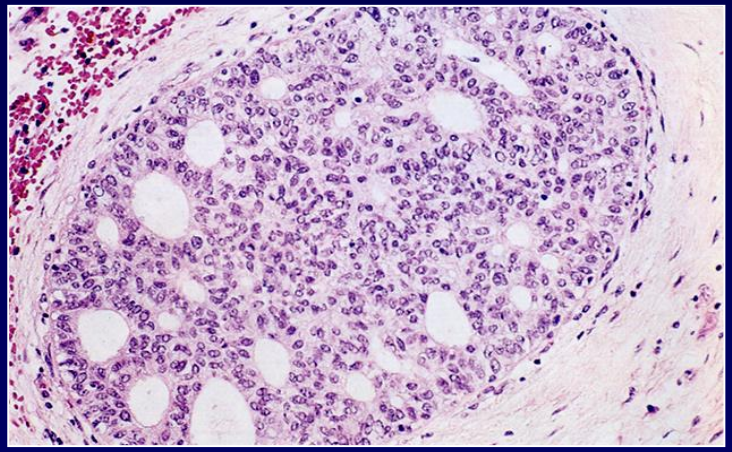
- The distinction between ADH from low-grade DCIS has remained a diagnostic challenge
- This problem commonly leads to over-diagnosis and overtreatment:
  - More expense
  - More patient anxiety
- There is evidence suggesting that low-grade DCIS may not need cancer therapy

ADH vs. DCIS





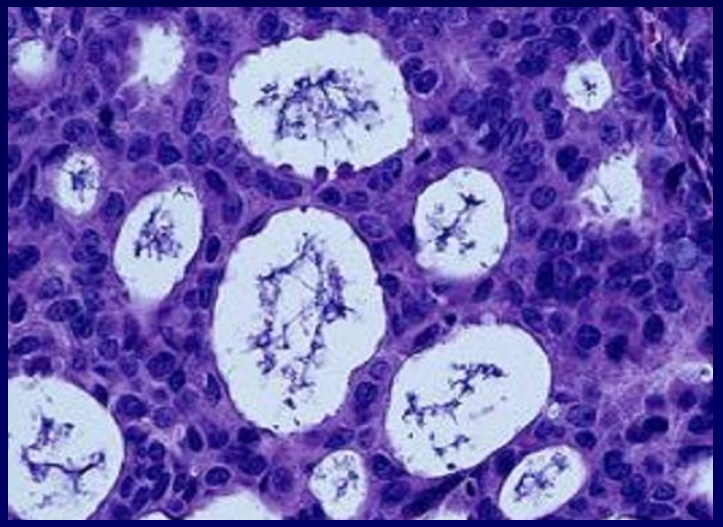




“An Entity Which Has Some but Not All The Features of Low Nuclear Grade Ductal Carcinoma In Situ”

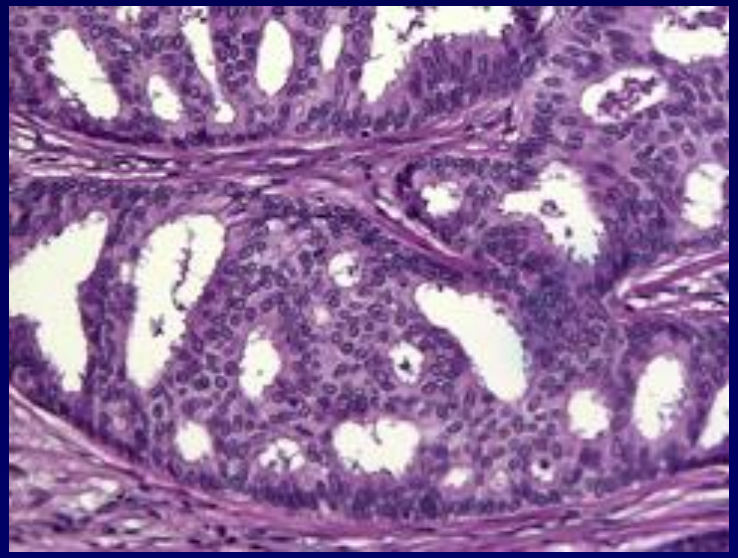
Morphologic Criteria for Low-Grade DCIS (Page and Anderson 1987)

- Two ductal spaces completely effaced in a single terminal ductal lobular unit
- Monomorphous population
- Non-polarized epithelium
- Cribriform bridges without attenuation
- Uniform lacunar spaces



Morphologic Criteria for Low-Grade DCIS (Tavassoli and Norris 1990)

- Minimum involvement of two duct spaces
- Sums of diameters of duct spaces must be ≥ 2mm



Interobserver Variability

Hyperplasia versus low-grade ductal carcinoma in situ

No Standardized Criteria:
10 Cases, 5 Pathologists

- **Number of Pathologists in exact agreement/ Percent of Cases:**
  - **5 of 5 agreed in 0% of cases**
  - **4 of 5 agreed in 20% of cases**
  - **3 of 5 agreed in 50% of cases**

Rosai J, Am J Surg Pathol 15:209-221, 1991.

Interobserver Variability

Hyperplasia versus low-grade ductal carcinoma in situ

Standardized Criteria:
24 Cases, 6 Pathologists

- **Number of Pathologists in exact agreement/ Percent of Cases**
  - **6 of 6 agreed in 58% of cases**
  - **5 of 6 agreed in 71 % of cases**
  - **4 of 6 agreed in 92% of cases**

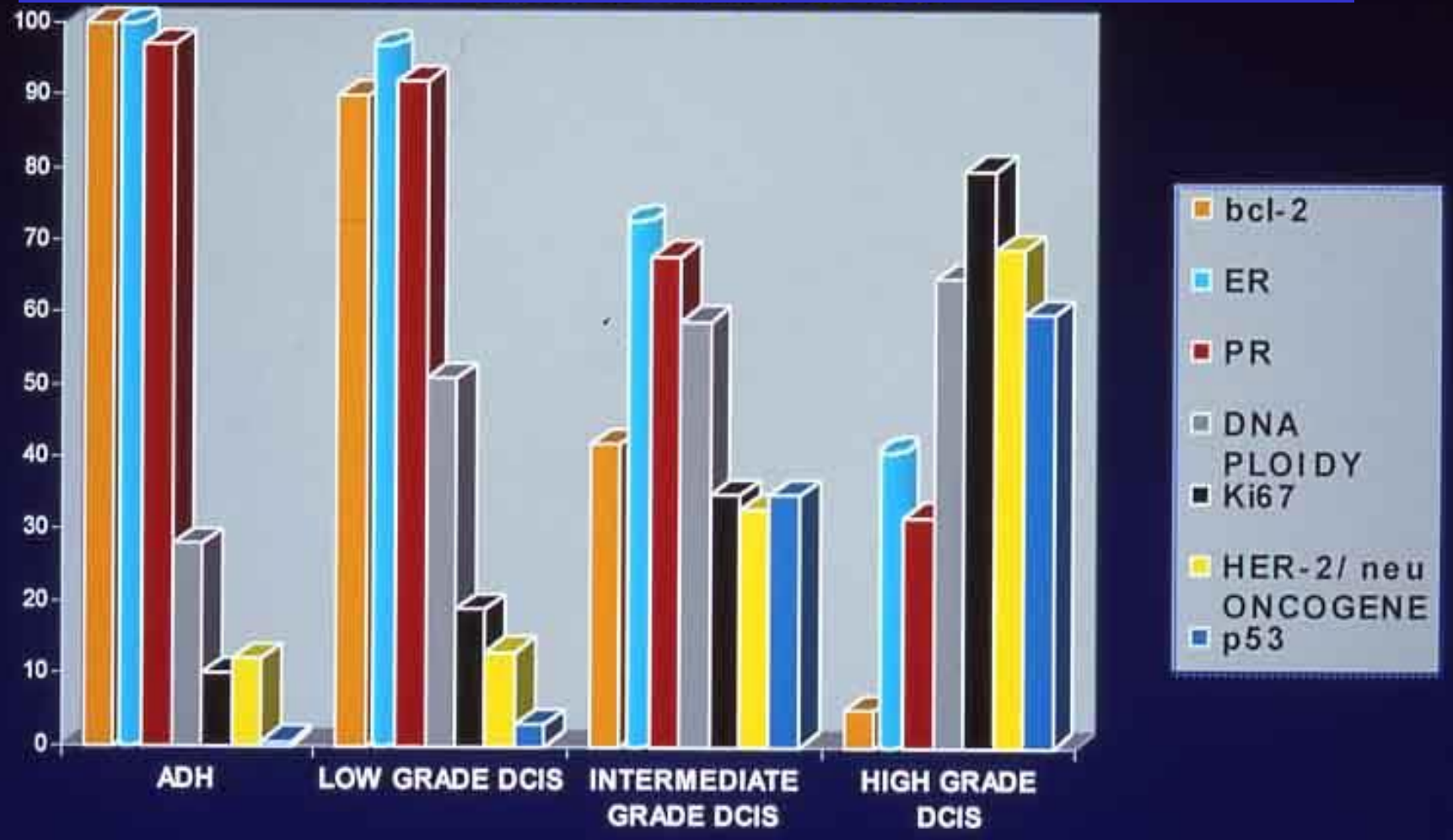
Schnitt SJ, et al. Am J Surg Pathol 16:1133-1143, 1992.

Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens

- Elmore conducted a study to assess the degree of agreement among expert breast pathologists and general pathologists
- Overall a set of 60 breast biopsies (240 total cases – 1 slide/case) were available
- Concordance rate of diagnostic interpretations of participating pathologists was 75.3% with highest level of concordance seen for invasive cancer
- Lower level of concordance was seen for DCIS and atypia

Elmore JG, Longton GM, Carney P, et al. Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens. JAMA Oncol. 2015;313(11):1122-1132.

PATTERN OF EXPRESSION OF VARIOUS BIOMARKERS IN ATYPICAL DUCTAL HYPERPLASIA (ADH) AND DUCTAL CARCINOMA IN SITU (DCIS)

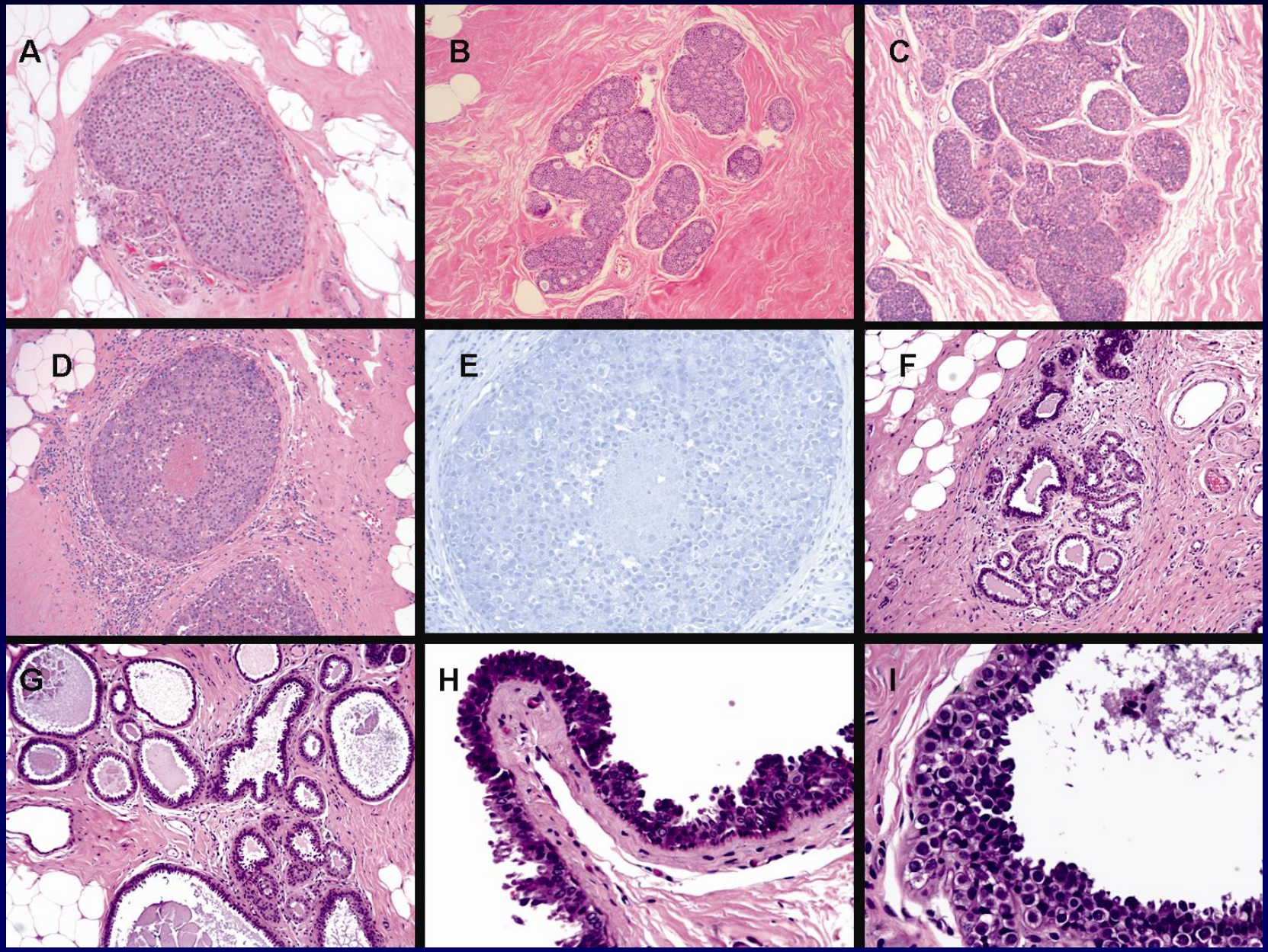


The Issue

“Is it possible that ADH and low-grade DCIS in reality represent the spectrum of the same entity?”

Suggested Terminology

- "Intraepithelial Mammary Neoplasia"
- "Ductal Intraepithelial Neoplasia"
- "Low Nuclear Grade Breast Neoplasia Family"
- "Borderline Breast Disease"



Masood S, Rosa M. Borderline breast lesions: diagnostic challenges and clinical implications. Adv Anat Patl 18(3):190-198, 2011.

ADH vs. DCIS

- **"There is no consensus presently on the criteria that should be adopted and how they should be applied for the distinction between atypical hyperplasia, and carcinoma *in situ*"**

Rosen P: Rosen Breast Pathology: Third Edition. 264-284, 2008.

ADH vs. DCIS

- **"Morphological criteria for the diagnosis of "atypia", implying increased breast cancer risk, and *in situ* carcinoma may be improved when it is possible to relate proliferative lesions to specific genetic or biochemical markers"**

Rosen P: Rosen Breast Pathology: Third Edition. 264-284, 2008.

Atypical Ductal Hyperplasia vs. Low-Grade Ductal Carcinoma In Situ

Diagnostic Challenge

- FNA biopsy
- Core needle biopsy
- Surgical biopsy

Atypical Ductal Hyperplasia

Morphologic Risk Factor

- Indicates increased risk to both breasts
- It is not a precursor for invasive breast cancer
- The patients diagnosed with ADH do not require cancer therapy

Ductal Carcinoma In Situ

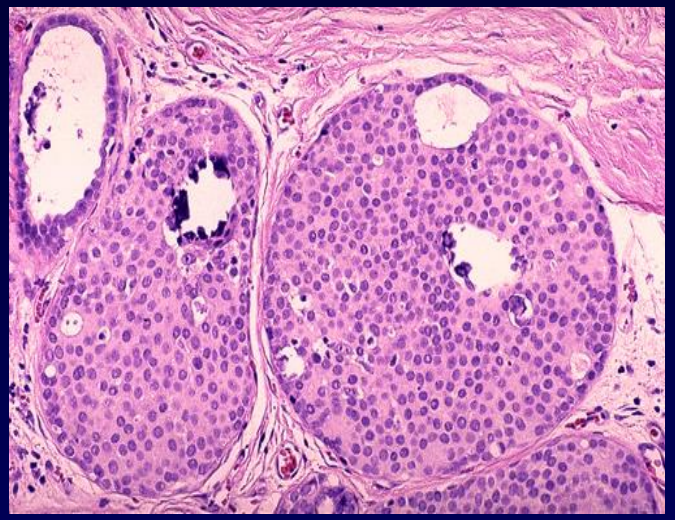
- May be a direct precursor to invasive cancer
- Rate of invasive transformation is dependent on grade
- Risk of invasion is limited to ipsilateral breast and generally same quadrant and site

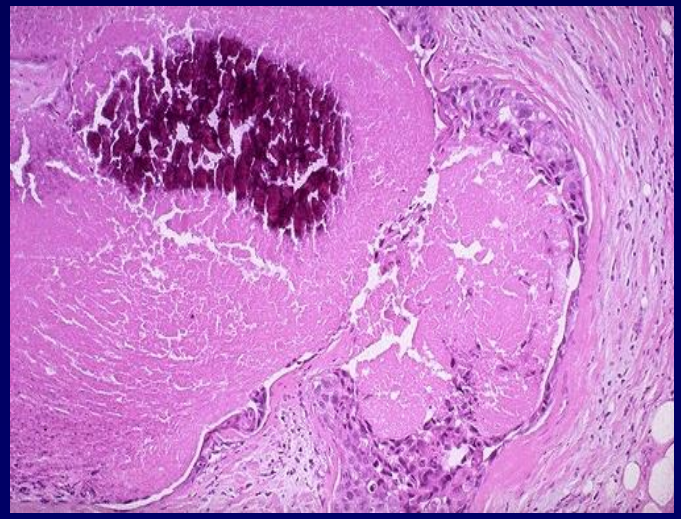
Molecular Biology of DCIS

- High grade lesions are often associated with unfavorable biological markers
- Genetic alterations and loss of heterozygosity at various chromosomal loci differ according to DCIS pattern and grade
- Low-grade lesions are associated with the "Low Nuclear Grade Breast Neoplasia Family"

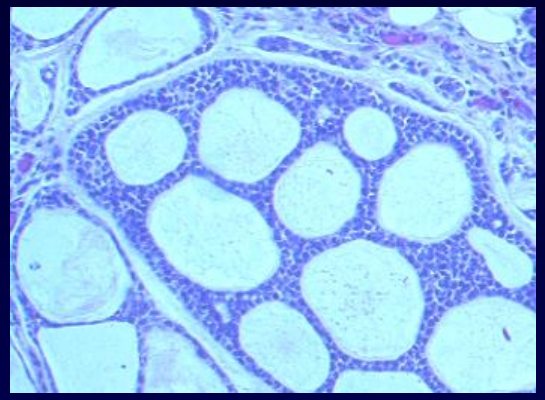
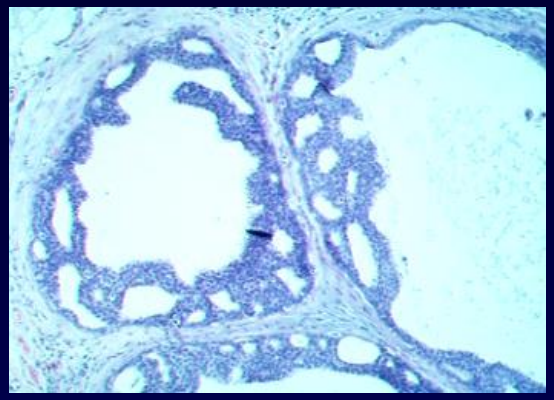
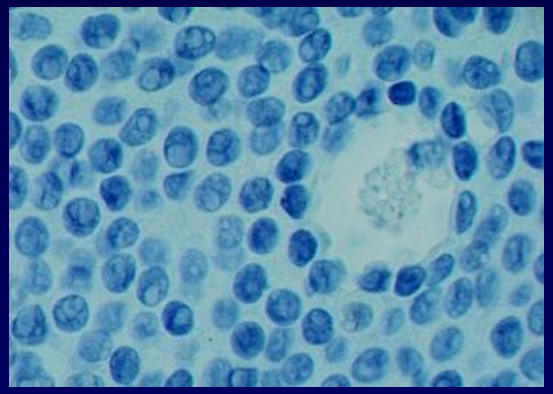
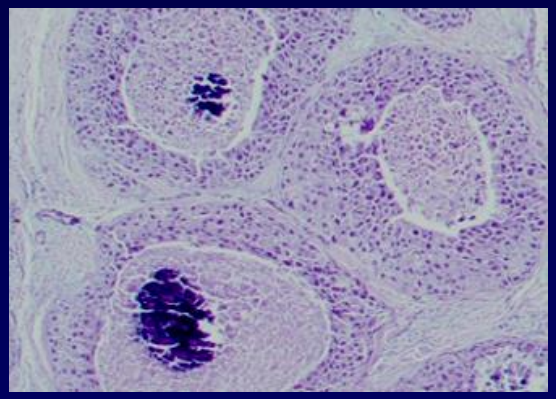
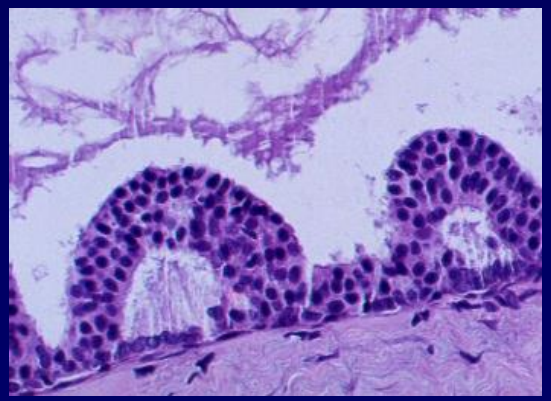
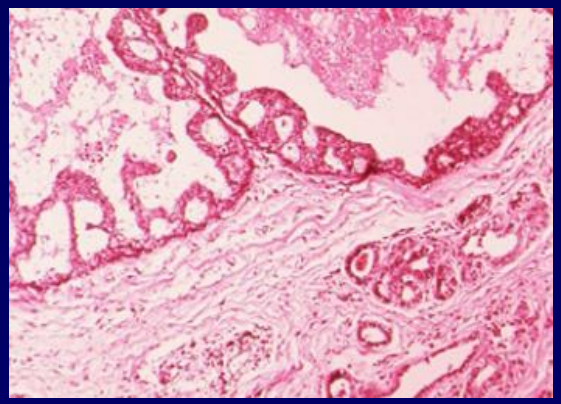
Ductal Carcinoma In Situ

DCIS is a heterogeneous disease characterized by neoplastic proliferation of ductal epithelial cells with no evidence of stromal invasion





Determinant of Biology of Ductal Carcinoma In Situ

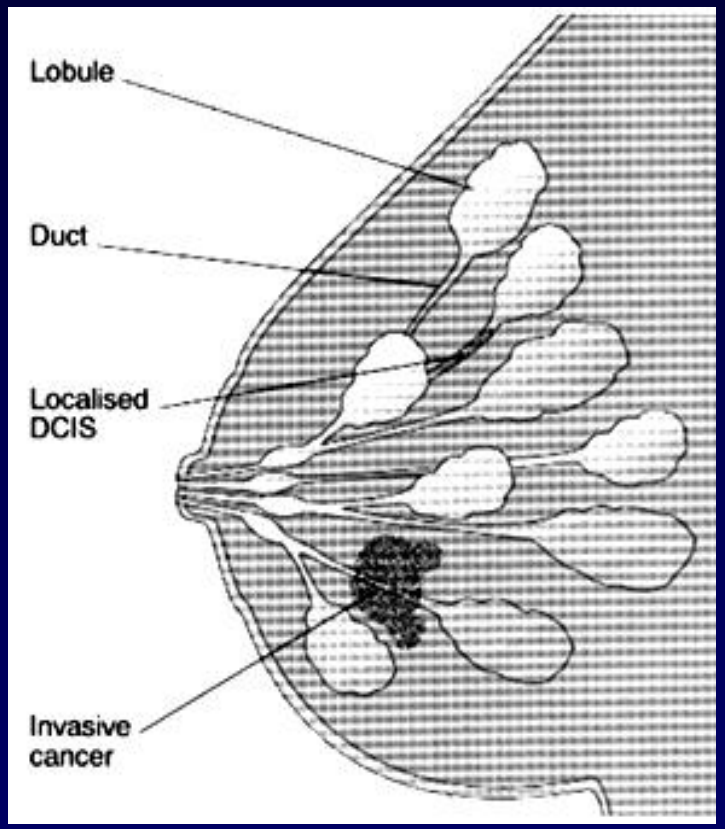







- Architectural pattern
- Nuclear grade
- Presence or absence of necrosis

Ductal Carcinoma In Situ

Treatment Options

- Local wide excision with and without radiation therapy
- Mastectomy



“ADH vs. Low-Grade DCIS”

ADH vs. Low-Grade DCIS

Breast Cancer Mortality After a Diagnosis of DCIS

- The study was designed to estimate 10-20 years mortality rate from breast cancer following the diagnosis of DCIS and standard cancer therapy
- This observational study used the information registered in the SEER database from over 100,000 women

Narod SA, Iqbal JI, Ginnakeas V. Breast Cancer Mortality After a Diagnosis of DCIS. JAMA Oncol. 2015;1(7):888-896.

ADH vs. Low-Grade DCIS

Breast Cancer Mortality After a Diagnosis of DCIS

- The risk of dying from breast cancer in these patients was 3.3%
- At 20 years, this risk was higher for the following patients
  - Young age (before age 40)
  - Black ethnicity
  - High grade DCIS
    - Large size >5cm
    - ER negative status
    - HER-2/neu oncogene positive status

ADH vs. Low-Grade DCIS

Breast Cancer Mortality After a Diagnosis of DCIS

- **The issue in question:**
  - **Do the patients with low-grade DCIS need to undergo therapy?**
  - **Do we need to abandon the use of the term "carcinoma" for lesions that are not biologically malignant?**

ADH vs. Low-Grade DCIS

- **Current data suggests that:**
  - **Low-Grade DCIS should be considered a "risk factor" for invasive breast cancer and an opportunity for targeted prevention**
  - **Radiation therapy should not be routinely offered after lumpectomy for DCIS lesions that are not high risk because it does not affect mortality**

Esserman L. Rethinking the Standard for Ductal Carcinoma *in Situ* Treatment. *JAMA Oncol*. 2015; 1(7):881-883.

ADH vs. Low-Grade DCIS

- **Current data suggests that:**
  - **We should continue to better understand the biological characteristics of the highest-risk DCIS (large, high-grade, hormone receptor negative, HER2 positive, especially in very young and African American women) and test targeted approaches to reduce death from breast cancer**

Esserman L. Rethinking the Standard for Ductal Carcinoma *in Situ* Treatment. *JAMA Oncol*. 2015; 1(7):881-883.

“The Current Challenges Associated with the Practice of Breast Pathology”

Current Issues in Breast Pathology

- Diversity in tissue handling, processing and reporting
- Insufficient evidence-based correlation between morphology and patient outcome
- Significant interobserver variability in diagnosis and test results
- Communication barriers among physicians involved in breast care

Current Issues in Breast Pathology

- There are no uniform guidelines to measure the rate of diagnostic errors
- Fear of disclosure and medicolegal issues limits the reporting of diagnostic errors
- There are many look-alikes in breast pathology that can mimic cancer

Current Issues in Breast Pathology

- Breast pathology is considered as a component of general surgical pathology
- Breast pathology fellowships are not accredited by ACGME
- Referral of pathology samples to commercial laboratories impairs communication

Suggestions

- To acknowledge the challenges associated with the current practice of breast pathology
- To design studies that can appropriately analyze the problems and quantitate their impact on therapy, patient outcome and health economy

Suggestions

- Establishment of quality assurance programs
  - Internal quality measures
    - Consensus slide conference
    - Mandatory second review of cancer cases
    - Mandatory adherence to established guidelines
- Second opinion
  - The review of outside pathology slides and reports by a local pathologist before the initiation of cancer therapy
- Involvement in external quality assurance programs

Suggestions

- Abandon the term of “Low-Grade Ductal Carcinoma In Situ”
- Use the term of “Borderline Breast Disease”
- Completely remove the entire lesion
- Offer risk assessment/risk reduction options

The Models to Follow

- Offer the options of “wait and watch” for borderline lesions/low-grade DCIS similar to low-grade prostate cancer

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. The Breast Journal 2013;19(2):127-129.

The Impact

- Reduced anxiety to the patient and her family
- Minimizing unnecessary expense
- Restoring patient trust

The Urgent Need

- Better define the morphologic and biologic characteristics of spectrum of high risk proliferative and precursors breast lesions
- Change the concept, terminology, and the pattern of practice

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. The Breast Journal 2013;19(2):127-129.