Adjuvant clodronate treatment does not reduce skeletal metastases in node positive breast cancer

- 299 patients – node positive breast cancer
- Clodronate 1600 mg daily or nil
- 3 years of treatment
- 5 years follow-up
- Endpoints – distant mets, survival

Saarto T et al. J Clin Oncol 2001; 19:10-17

Results
Saarto et al.

Bone mets	29 clodronate	24 nil
Non-bone mets	60 clodronate	36 nil
Survival	70%	83%

Saarto T et al. J Clin Oncol 2001; 19:10-17

- Powles
  - Clodronate improved 5 year survival for stage II and III disease 76.7% vs. 69.2%
  - At 10 years ↓ risk of death 23% overall and 26% in stage II and III disease
- Diel
  - Survival advantage at 103 months follow-up
- Saarto
  - Study criticized for imbalance of randomization ER status, PR status
  - ER(-) postmenopausal women treated with tamoxifen

Zoledronic acid in Premenopausal Women Treated with Adjuvant Ovarian Suppression + Tamoxifen or Ovarian Suppression + Aromatase Inhibitor, ± Zoledronic acid 4mg IV q 6 months

- 1801 premenopausal women endocrine responsive breast cancer
- End points
  - Primary DFS
  - Secondary RFS, OS
  - Exploratory bone mets free survival
- Median Follow-up 60 months
  - Results
    - **DFS improved with zoledronic acid (HR=0.64 [0.46-0.91]) p = 0.01**
    - Improved RFS p = 0.16
- Conclusion – zoledronic acid has anti-tumor activity

Zoledronic acid in post menopausal women with endocrine responsive primary breast cancer treated with adjuvant letrozole

- 1667 patients
- Zoledronic acid 4mg IV q 6 months (up front vs. delayed)
- End point 1° BMD LS at 12 months of study
  - 2° time to recurrence
  - Total hip BMD
  - Changes in bone turnover markers
  - safety
- Results
  - Improved BMD - LS and total hip
  - Fracture rates similar
- Recurrences
  - **7 in upfront group**
  - **17 in delayed group** P=0.043

NSABP B-34

- Primary breast cancer
- Clodronate vs. placebo
- 3323 subjects
- Closed to accrual March 31, 2004
- Analyses pending

Bone Metastases Prevention

- SWOG – RCT adjuvant bisphosphonate within 12 weeks of surgery (6000 participants)
  - Clodronate 1600mg po daily
  - Zoledronic acid 4mg IV q 4 weeks for 6 months, then q 3 months for 2.5 years
  - Ibandronate 50mg po daily

AZURE Trial

3360 participants

Adjuvant chemotherapy and/or endocrine therapy

Zoledronic acid 4 mg IV **q 3-4 weeks x 6 doses**
vs nil

q 3 months x 8 doses

q 6 months x 5 doses

Recommendation

No guideline additions pending large RCT data

Surgical Therapy: Sentinel Node Biopsy and Breast Conservation

Stephen B. Edge, MD
Professor of Surgery and Oncology
Roswell Park Cancer Institute
University at Buffalo

Dr. Roswell Park: Tradition in Cancer Research

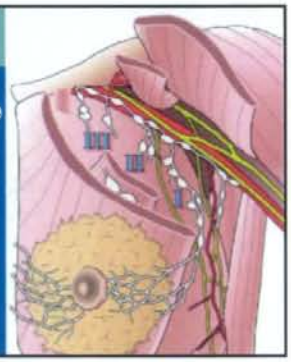
- 1898: Founded NY State Laboratory for the Study of Malignant Disease
  - Re-named Roswell Park Memorial Institute in 1942
    - RPMI 1640 culture media
- Chair, Dept of Surgery University at Buffalo
- Performing surgery in Niagara Falls when President McKinley shot at the 1901 Pan American Exposition in Buffalo

Overview

- Sentinel Node Biopsy
  - Indications for SNB
  - Need for completion axillary dissection
- Breast conservation
  - Techniques for resection of margins
  - Extent of resection with PCT
- Dr. Collins - Pathologic evaluation of margins
- Japanese Comment

Sentinel Node Biopsy

Indications

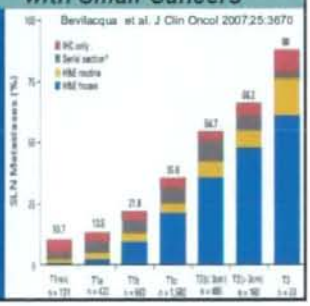


SNB with Clinically Negative Nodes

- Invasive breast cancer
  - Any situation requiring lymph node staging
  - Primary (neoadjuvant chemotherapy)
  - Local recurrence - repeat SNB?
- Ductal carcinoma *in situ*
  - Mastectomy
  - Other indications?

SNB Especially Important with Small Cancers

- Tumors < 1 cm
  - 15% positive nodes by H&E
  - Major impact on use of chemotherapy



SLNB Indication: Repeat SNB with Recurrence

- Uncertain role of systemic therapy
- Uncertain need for lymph node staging with local recurrence
- Repeat SNB technically possible in women with prior SNB
  - Breast conserving surgery
  - May be possible with prior mastectomy

Repeat Sentinel Node Biopsy

Series	Number	Successful mapping	Drainage outside axilla	Repeat SLN Positive
Moffitt	56	45	1	9 (20%)
John Wayne	6	5	2	0
MSKCC	54	40	3	5 (12.5%)
European Institute	65	63	7	7 (11%)
TOTAL	*181*	*152 (84%)*	*11 (6%)*	*20 (13%)*

Adapted from Cox et al. JACS 2008;207:57

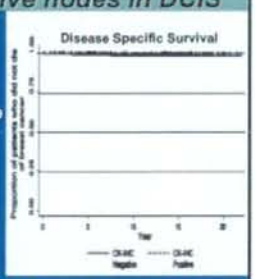
Lymph Node Surgery with DCIS

Most "Positive Nodes" with DCIS Only by IHC

Series	N Cases	Positive by H&E	Positive by IHC
Broekhuizen	66	1%	11%
Wilkie	559* All DCIS	1%	5%
Katz	110 High risk	4%	8%
Veronesi	508 All DCIS	2%	1%

No survival impact of IHC positive nodes in DCIS

- 301 pts with DCIS and negative nodes
- Median 10 yr follow-up
- Cytokeratin IHC on archived blocks
- 18 / 301 positive by IHC



El-Tamer et al. Ann Surg Onc Disease 2005;12:254

NCCN Guidelines: DCIS

- Lumpectomy:

  No lymph node surgery

- Mastectomy:

  Sentinel node biopsy

Lymph Node Surgery with Primary (Neoadjuvant) Chemotherapy

Pre-chemotherapy Sentinel Node Biopsy

	# pts	Negative SNB Before Chemo	Positive SNB Additional Positive Nodes After Chemo
Sabel – Michigan	25	12 (48%)	8 / 13 (60%)
Schrenk - Linz, Austria	21	12 (55%)	6 / 9 (66%)
Cox - Moffitt (LABC)	47	7 (15%)	27 / 40 (67%)
Van Rijk – Netherlands	25	14 (56%)	5 / 11 (45%)

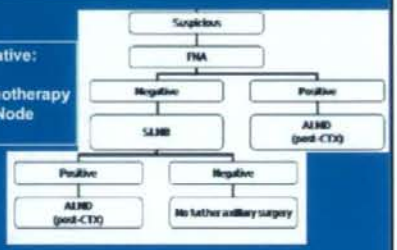
Axillary Management: Clinically / Ultrasound Negative

Pre-chemotherapy Sentinel Node Biopsy

Axillary Management: Clinically / Ultrasound Suspicious

FNA Negative:

Pre-chemotherapy Sentinel Node Biopsy



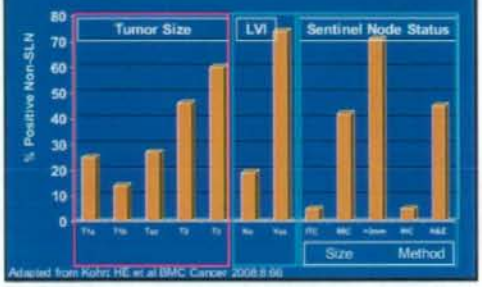
Kilbride KA Annals of Surgical Oncology 2008

Is Axillary Dissection Needed with Positive Sentinel Node?

Axillary Dissection with Positive Sentinel Node?

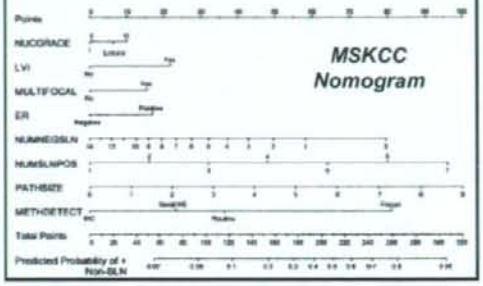
- What is the probability of additional positive nodes?
  - Is there a rate so low that dissection not warranted?
- Therapeutic impact of dissection
  - Do additional positive nodes alter choice of chemotherapy?
  - Control of cancer in axilla: Surgery vs. Radiation

Probability of Additional Positive Nodes



Adapted from Kohrt HE et al BMC Cancer 2008;8:66

Risk of Additional Involved Nodes with Positive SNB



Omit Axillary Dissection with Positive SNB?

- What risk of additional positive nodes is low enough?
- Most American oncologists perform axillary dissection for any positive nodes
- Major question is in cases of ITC and micrometstases detected by cytokeratin immunohistochemistry

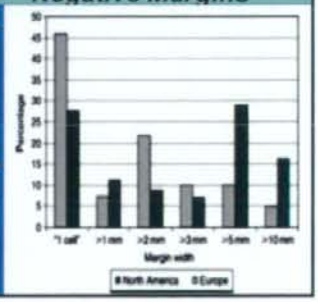
Surgical Margins

Surgical Margins

1. Techniques
2. Resection after Primary Chemotherapy
3. Pathology Evaluation Dr. Collins

Surgeons' Definition of Negative Margins

Survey of surgeons in North America and Europe on what is accepted as "negative margin".



Margin Management

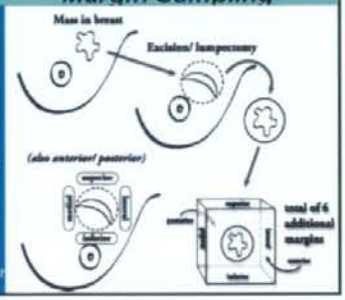
- Careful surgical planning
  - Pre-operative diagnosis of cancer
- Orient specimen
- Specimen mammography
  - Key for calcifications

Techniques for Margin Excision

- Primary excision
  - Single specimen versus
  - Shave margins after primary excision
- Re-excision
  - Whole cavity versus
  - Directed excision of specific margin
- Intraoperative evaluation
  - Specimen mammography
  - Gross
  - Microscopic - generally NOT performed

Separate Cavity Margin Sampling

- Excision of cancer
- Resection of additional tissue at each of 6 margins



Cao et al. Am J Surg Path 2005;29:1625

Cavity Margin Sampling

- Residual cancer in cavity margin sample in many cases
- Factors associated with residual cancer
  - Extensive intraductal component
  - High grade
  - Extent of margin involvement
- Reduced re-excision by 60%

Primary Lumpectomy Margin	Cavity Margin Sample Contained Residual Cancer
Positive (n=233)	30%
Negative (n=281)	10%

Cao et al. Am J Surg Path 2005;29:1625

Pre-Surgical Diagnosis Improves Margin Management

- Re-excision after lumpectomy common
- Negative margin more likely with pre-surgical diagnosis - FNA or core biopsy
- NCCN study of re-excision

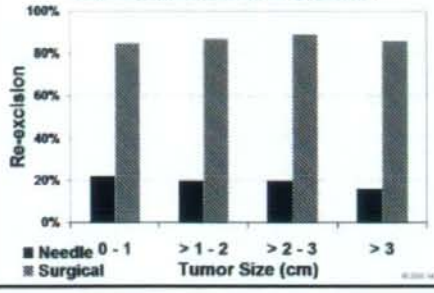
Frequency of re-excision among 6,131 women from 1997 - 2001 based on the type of initial biopsy

Re-excision by Type of Initial Biopsy

Type of Initial Biopsy	N	Percent Re-excision
Needle	3,481	23%
Surgical	2,650	92%*

*Using univariate logistic regression, association between the type of initial biopsy and re-excision is statistically significant (p-value <0.0001).

Re-excision by Tumor Size for Patients Receiving BCS



Factors Associated with Re-excision

	Odds Ratio
Use of surgical biopsy	3.35
Smaller breast	2.7
Lobular histology	1.93
Adjuvant vs. neoadjuvant	2.49

Waljee JF et al. Ann Surg Oncol 2008;15:1297

Re-Excision: Impact on Recurrence

Re-Excision Among 2,770 patients at Fox Chase
Overall Re-Excision Rate 60%

Number of Re-excisions	Number of patients	Local Recurrence	
		5 yr (%)	10 yr (%)
0	1119	2.5%	5.6%
1	1514	1.9%	5.7%
0 and 1	2633	2.1%	5.6%
2 or more	137	5.5%	10%

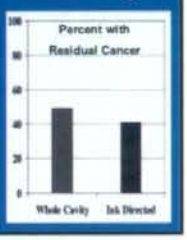
O'Sullivan MA et al. Ann Surg Oncol 2007;14:3133

Technique of Re-excision: Prefer Ink-Directed

Whole Cavity versus
Ink Directed Resection of Positive Margin

546 lumpectomy
- 245 (45%) - No re-excision
- 181 Whole Cavity
- 120 Directed Resection

- Less tissue removed
- Better cosmetic result
- No difference recurrence



Neoadjuvant Chemotherapy

Defining Extent of Resection

PCT - Extent of Resection

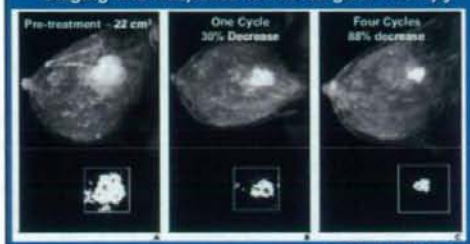
- Use imaging to define extent of cancer prior to and after chemotherapy
- Place marker to allow radiological localization
- Extend surgery around area of original cancer
- Experience and judgment

MRI Useful to Define Extent of Cancer

- Define size of cancer: supplements mammography
- May help define extent of DCIS
- Identify 2nd cancers

Magnetic Resonance Imaging:

Staging and Response to Pre-surgical Therapy



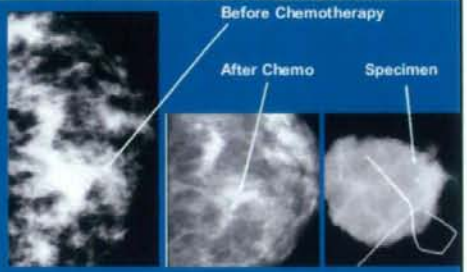
Partridge AJR 2005;184:1774

MRI underestimates residual disease

Pathologic Response	Response by MRI			
	CR	PR	NR	Prog
CR	12	0	0	0
PR	10	37	0	0
NR	1	1	7	1
Prog	0	0	0	0

Warren Br J Cancer 2004;90:1349

REMEMBER TO PLACE CLIP!!!



Rate of Positive Margin with Neoadjuvant Therapy

Positive Margins:

Neoadjuvant	21%
Not neoadjuvant	18%

Factors affecting positive margins:

Lobular cancer	43%
Ductal cancer	16%

Soucy G et al. J Am Coll Surg 2008;206:1116

Neoadjuvant Therapy: Impact on Extent of Surgery

- Neoadjuvant therapy reduces the extent of surgery
- Does not increase positive margins or re-excision

	Neoadjuvant	Primary Surgery
Volume	113 cm^3	213 cm^3
Re-excision	13%	16%

Boughey JC et al. Ann Surg 2006;244:464

Japanese Experience

- Sequential anthracycline / taxane
- 10% complete pathologic response
- 38% had lumpectomy
- 25% with positive margins

Fukutomi T. Breast Cancer 2006;13:147

ありがとうございました.

Ductal Carcinoma in Situ:
Differential Diagnosis with Benign Proliferative Lesions

Laura C. Collins, M.D.
Department of Pathology
Beth Israel Deaconess Medical Center and
Harvard Medical School
Boston, MA

Incidence of DCIS

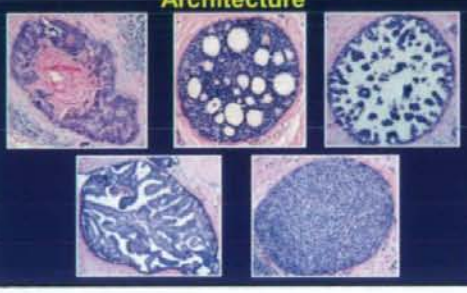
- ~60,000 cases per year (US population)
- DCIS accounts for 20% of mammographically-detected breast cancers

Accuracy of Core Needle Biopsy to Predict DCIS

- Atypical ductal hyperplasia
  - -14G carcinoma in 50-60% (2/3-3/4 DCIS; remainder invasive)
  - -11G DVA carcinoma in ~20%
- Ductal carcinoma in situ
  - -14 G invasive carcinoma in ~20%
  - -11G DVA invasive carcinoma in ~ 10%

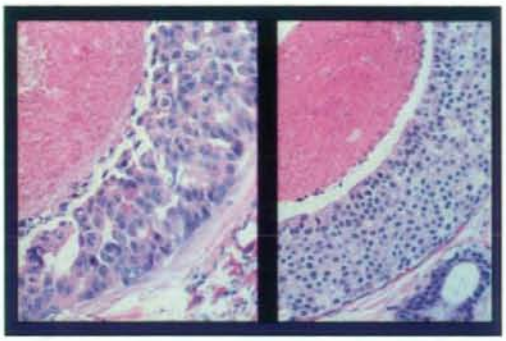
Classification Systems

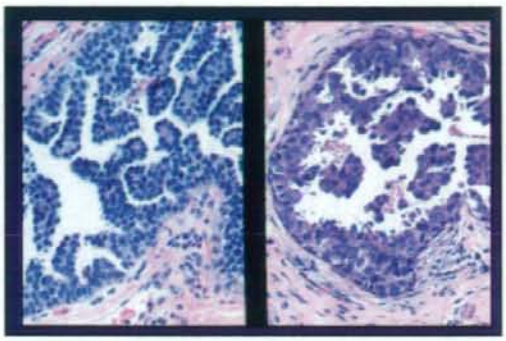
Pathologic Heterogeneity of DCIS: Architecture



Problems with Architectural Classification System

- Many lesions have a mixture of patterns
- Some lesions do not fit into any of the traditional categories
- Nuclear grade more consistent
- Need for classification system which is clinically relevant in era of breast conserving therapy





Problems with Architectural Classification System

- Many lesions have a mixture of patterns
- Some lesions do not fit into any of the traditional categories
- Nuclear grade more consistent
- Need for classification system which is clinically relevant in era of breast conserving therapy

Alternative Classifications for DCIS

- Based primarily on nuclear grade and/or necrosis
- Recognize three main categories of DCIS

Alternative Classification Systems for DCIS

Lagios	Van Nuys	European
Low grade	Non-high grade without necrosis	Well differentiated
Intermediate grade	Non-high grade with necrosis	Intermediately differentiated
High grade	High grade	Poorly differentiated

Classification of DCIS:2008

- Still no universally accepted classification system
- Presumed clinical importance of separating DCIS cases into low, intermediate, and high grade groups generally recognized

Current Issues

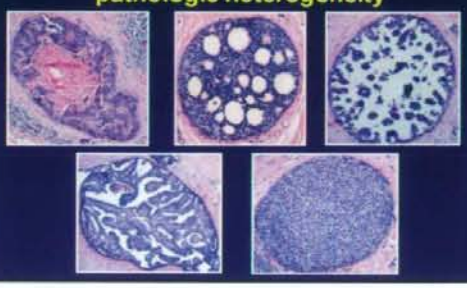
- Factors determining which DCIS will recur/progress to IBC
- Which patients can safely avoid additional therapy beyond local excision
- Are there different molecular phenotypes of DCIS as there are for IBC
- Accurate diagnosis of DCIS and distinction from other more benign or malignant lesions

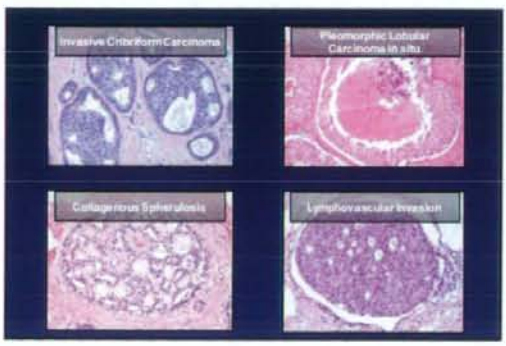
Current Issues

- Factors determining which DCIS will recur/progress to IBC
- Which patients can safely avoid additional therapy beyond local excision
- Are there different molecular phenotypes of DCIS as there are for IBC
- Accurate diagnosis of DCIS and distinction from other more benign or malignant lesions

In most cases the diagnosis of DCIS is straightforward

But, there is a great deal of pathologic heterogeneity





The diagnosis of DCIS is *not always* straightforward

How Often is the Diagnosis of DCIS a Problem?

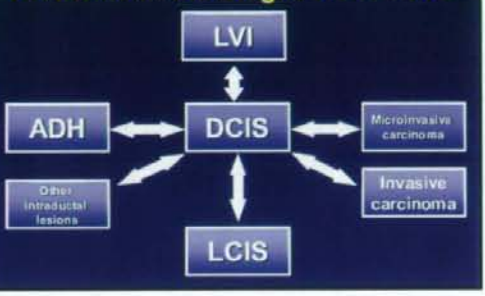
Pathologist Agreement: Local vs. Central Dx

Summary

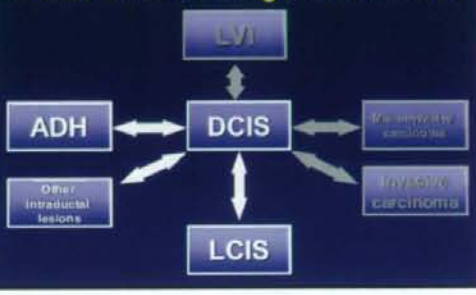
Study	#	% Not DCIS
NSABP B-17	818	6.2%
RDOG 5	123	7.0%
CRN DCIS	708	9.9%

Problems with both under-diagnosis and over-diagnosis

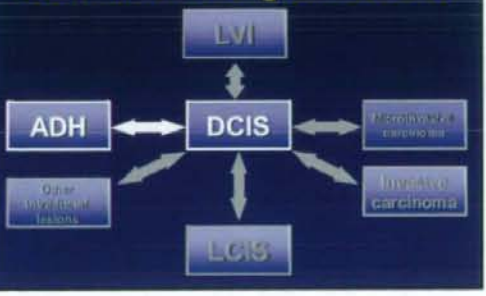
Problems in the Diagnosis of DCIS



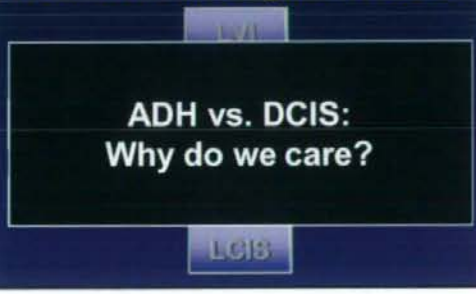
Problems in the Diagnosis of DCIS



Problems in the Diagnosis of DCIS



Problems in the Diagnosis of DCIS



Clinically Important Differences Between ADH and LG-DCIS

	ADH	LG-DCIS
Magnitude of risk	lower (3-5x)	higher (8-10x)
Laterality of risk	either	ipsilateral (same site)
Type of subsequent cancer	any histology; any grade	usually low grade
Management	observation ± tamoxifen	complete local eradication

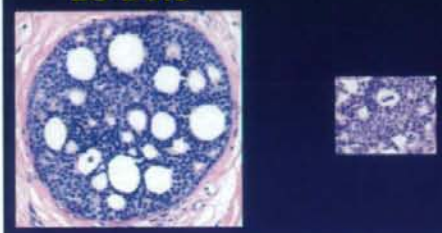
Distinction of ADH from DCIS

- Qualitative features (architecture, cytology)
- Quantitative features (size/extent)

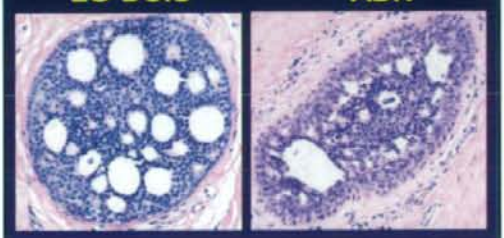
Qualitative Features of ADH

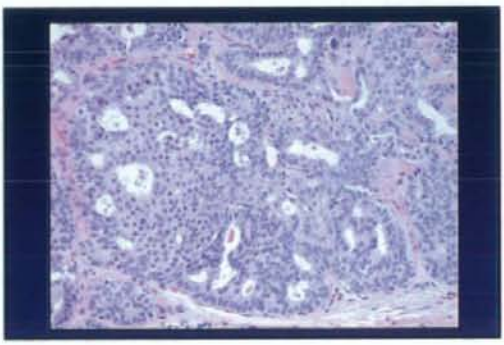
- *Architecture:*
  - –Some features of usual ductal hyperplasia and some features of DCIS (e.g., rigid, non-tapering bridges, club-shaped micropapillae, round fenestrations)
- *Cytology:*
  - –Cells similar to those seen in low grade DCIS present in a portion of the space (e.g., monomorphism, polarization around lumina or within micropapillae)

LG-DCIS



LG-DCIS ADH





- Observer agreement in equivocal cases is fostered by the standardization of diagnostic criteria

Diagnostic Reproducibility

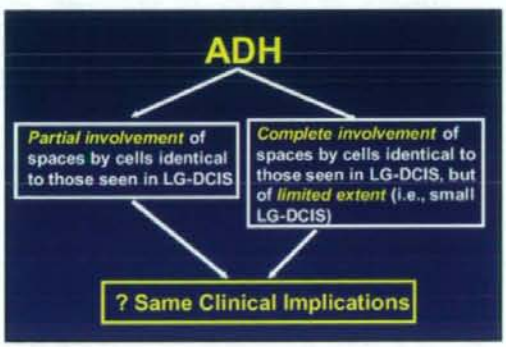
	Standardized criteria? No	Yes
Complete Agreement	0%	58%
All But 1 Agree	18%	71%

The Major Problem

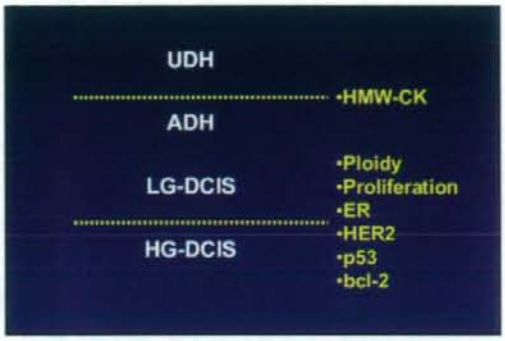
- There are no qualitative histologic features, singly or in combination, that permit the reliable distinction between ADH and LG-DCIS in all cases

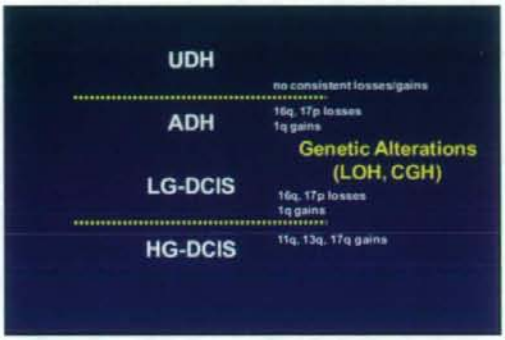
Quantitative Features

- Lesions that possess ALL of the qualitative features of LG-DCIS but are limited in extent are given the diagnosis of ADH:
  - –1985, Page et al: <2 spaces
  - –1990, Tavassoli and Norris: ≤2mm
  - –1998, Jensen and Page: <2-3mm



Are there more objective means to help distinguish ADH from LG-DCIS?





Biomarkers and Genetic Alterations

- No apparent differences between ADH and LG-DCIS
- But, many studies include as "ADH" small DCIS

Should We Continue to Attempt to Distinguish ADH from LG-DCIS?

- NO:
  - –Histologic criteria poorly defined; low level of interobserver agreement
  - –Morphologic similarities; any differences are only quantitative
  - –Immunophenotypic similarities
  - –Genetic similarities

Should We Continue to Attempt to Distinguish ADH from LG-DCIS?

- YES:
  - –Problematic cases account for only a minority of lesions
  - –Observer agreement improves with standardization of criteria
  - –Genetic/molecular studies incomplete; have used relatively crude techniques (LOH, CGH) and definitions of ADH that include small LG-DCIS

- –Immunophenotypic or even genetic similarity does not necessarily imply similar clinical behavior
- –Follow-up studies have documented clinically important differences between ADH and LG-DCIS that are considered in formulating patient management

ADH: Conceptual vs. Practical View

- Conceptually:
  - ADH appears to be a neoplastic, clonal proliferation of cells identical to those of LG-DCIS (at least using currently available techniques)
  - However, lesion less completely developed than LG-DCIS ("LG-DCIS in situ")
- Practically:
  - Given that there are documented, clinically important differences between ADH and fully developed LG-DCIS, these two processes should still be considered distinct with regard to patient management

Problems in the Diagnosis of DCIS

Other Intraductal Proliferative Lesions that May Mimic DCIS

- Usual ductal hyperplasia
  - Necrosis
  - UDH vs. intermediate nuclear grade DCIS
- Gynecomastoid hyperplasia
- Collagenous spherulosis
- Intraductal papilloma

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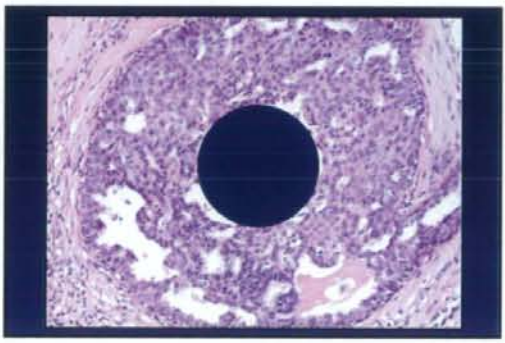

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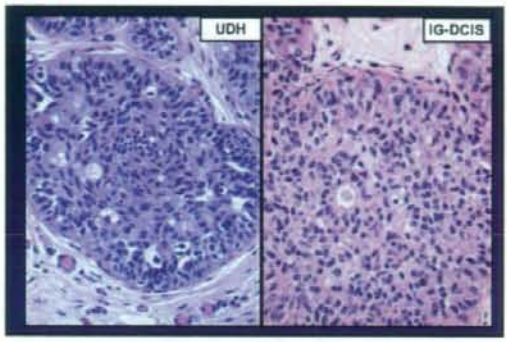
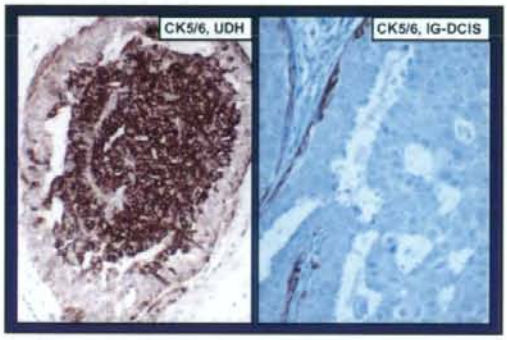
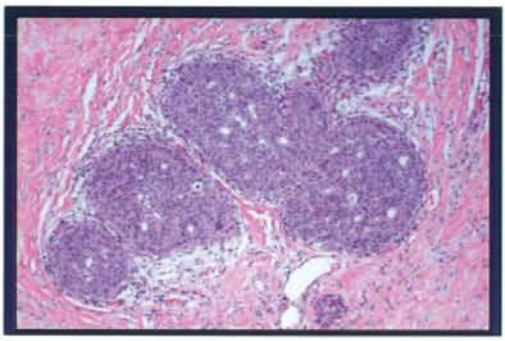
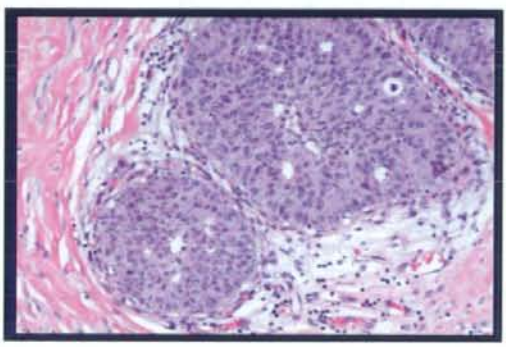
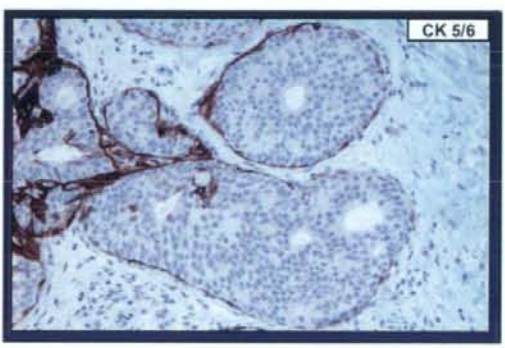


- HMW-CK immunostains may be particularly helpful in distinguishing UDH from intermediate nuclear grade DCIS in problematic cases









HMW-CK in Intraductal Proliferative Lesions
Caveats

- Not helpful in distinguishing ADH from LG-DICS or IG-DCIS (all generally negative for HMW-CK)
- Some HG-DCIS are HMW-CK-positive

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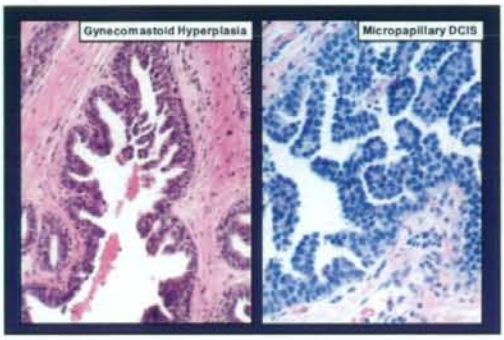

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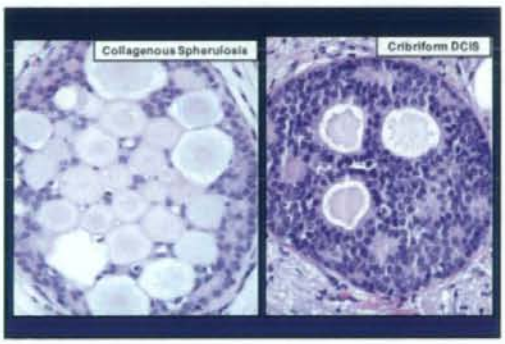

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