2016 Annual Meeting & Shelley Lecture

A collaboration between the North Carolina and South Carolina Societies of Pathologists and the Shelley Foundation

Focus on Breast Pathology

April 15-16, 2016
The Ballantyne Hotel, Charlotte, NC

SUNDAY, APRIL 16

This continuing medical education activity is jointly provided by the North Carolina Society of Pathologists and Southern Regional Area Health Education Center.
Lobular Carcinoma in Situ and Problematic in Situ Lesions of the Breast

Stuart J. Schnitt, M.D.
Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

Disclosures

• None

LOBULAR CARCINOMA IN SITU
A Rare Form of Mammary Cancer

Frank W. Foote, Jr., M.D., and Fred W. Stewart, M.D.
(From the Pathological Laboratories of the Memorial Hospital, New York, N.Y.)

Am J Pathol 1941;17:491

• Described essentially all key features of LCIS:
  – Not clinically evident
  – Histologic appearance (including loss of cohesion)
  – Multicentricity

Heterogeneity of LCIS

• Like DCIS, the term “LCIS” encompasses a heterogeneous group of lesions that differ in morphology, immunophenotype, genetic alterations and, possibly, clinical behavior
• Heterogeneity of LCIS has until recently been largely under-appreciated

LCIS: The Textbook View
(Classical LCIS)

• Detected in <5% of breast biopsies (usually incidental finding)
• More common in pre-menopausal women
• Multicentric (~50%), bilateral (~30%)
• No distinctive mammographic features
• Considered to be a marker of increased breast cancer risk (~1%/yr; RR ~10x)
• Also now recognized as a precursor
Classical LCIS

Classical LCIS, Type B Cells

Loss of E-cadherin Expression:
Defining Feature of LCIS (and ILC)

E-cadherin

- Calcium-dependent transmembrane protein
  - Intercellular adhesion
  - Maintenance of cell polarity
- Gene (*CDH1*) located on 16q22.1

E-cadherin

- Integral component of adherens-type intercellular junctions
  - Homodimerization of E-cad molecules on adjacent cells
  - Intracellular domain linked to actin cytoskeleton via α-, β-, γ-, and p120 catenins forming cadherin-catenin complex
Loss of E-cadherin Expression in LCIS (and ILC)

- LOH at 16q22
- Often accompanied by inactivating mutations or promoter methylation of CDH1
- Deletions, transcriptional repression (via mechanisms other than hypermethylation), miRNA modulation
- Bi-allelic silencing of gene and loss of protein expression

LCIS: Loss of E-cadherin Expression

Non-Classical Forms of LCIS

- Some LCIS exhibit subtle deviations from classical type with regard to growth pattern/cytology
- Others show substantial deviation from classical type
  - Considerable nuclear pleomorphism
  - Comedo necrosis
  - Mammographic microcalcifications
- No standard terminology

Non-Classical Forms of LCIS of Clinical Importance

- Pleomorphic LCIS
- LCIS with necrosis

Pleomorphic LCIS

- First described in 1996
- Post-menopausal women
- Growth pattern similar to classical LCIS
- Classical LCIS often co-exists
- Nuclear pleomorphism (2-3 fold variation in size)
- Mitoses may be present and numerous
- Comedo necrosis may be present
  - May present with mammographic microcalcifications mimicking high grade DCIS
- Non-apocrine and apocrine types
Biomarkers in Pleomorphic LCIS
Chen, AJSP 2009

- When compared with classical LCIS, pleomorphic LCIS:
  - Less often ER+
  - Higher proliferation rate (Ki67)
  - More often HER2+

Genomic Alterations in Pleomorphic LCIS by aCGH
Chen, AJSP 2009

- Consistently show 16q loss and 1q gain (“lobular signature”)
- When compared with classical LCIS:
  - More frequent chromosomal losses and gains (particularly apocrine type)

Differences Between Classical and Pleomorphic LCIS

<table>
<thead>
<tr>
<th></th>
<th>Classical LCIS</th>
<th>Pleomorphic LCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger (premenopausal)</td>
<td>Older (postmenopausal)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Incidental</td>
<td>Mammographic</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>+ or – (apocrine type)</td>
</tr>
<tr>
<td>HER2</td>
<td>-</td>
<td>- or + (apocrine type)</td>
</tr>
<tr>
<td>Ki67</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Genomic changes (aCGH)</td>
<td>Fewer</td>
<td>More numerous (apocrine type)</td>
</tr>
</tbody>
</table>

Non-Classical Forms of LCIS of Clinical Importance

- Pleomorphic LCIS
- LCIS with necrosis

LCIS with Necrosis

- Post-menopausal women
- Cytologic features of classical LCIS (type A, type B, mixed)
- Filling and often massive distension of involved spaces with foci of comedo necrosis
  - May present with mammographic microcalcifications mimicking high grade DCIS
- Included within “florid LCIS” category
Array-Based CGH of Florid LCIS
Shin, Hum Pathol, 2013

- Like classical LCIS:
  - 16q losses and 1q gains
- But:
  - Greater fraction genome loss
  - More chromosomal breakpoints
  - More frequent amplifications

How Does the Pathologist Distinguish These LCIS Variants from DCIS in Problematic Cases?

- Histologic features
- Adjunctive immunostains

Histologic Distinction Between LCIS Variants and DCIS

<table>
<thead>
<tr>
<th>Feature</th>
<th>LCIS Variants</th>
<th>DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of cohesion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intracytoplasmic vacuoles</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Pagetoid ductal involvement</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Associated classical LCIS</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Microacini</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Polarization of cells at periphery</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Adjunctive Immunostains
- E-cadherin
- p120 catenin
- β-catenin
**Adjunctive Immunostains**

- E-cadherin
- p120 catenin
- β-catenin

**DCIS**

E-cadherin Positive

- Low grade
- High grade

**LCIS**

E-cadherin Negative

**Limitations in Use of E-cadherin Immunostaining**

- Loss of E-cadherin expression by IHC characteristic of LCIS, but......
- Presence of E-cadherin expression does not preclude diagnosis of LCIS in the context of appropriate histologic features
  (i.e., E-cad positive ≠ DCIS)

**E-cadherin Expression in Lobular Lesions**

- Aberrant E-cadherin expression in neoplastic cells themselves
- E-cadherin staining of benign cells associated with LCIS cells
- Technical issues

**E-cadherin Expression in Lobular Lesions**

- Aberrant E-cadherin expression in neoplastic cells themselves
- E-cadherin staining of benign cells associated with LCIS cells
- Technical issues
ILC with Aberrant E-cadherin Expression

- ~15% of ILC show aberrant E-cadherin expression

Few studies with small numbers
- 0-9% of cases
- Higher in our practice
Patterns of Aberrant E-cadherin Expression in LCIS Cells

- Membranous
  - Fragmented/partial/beaded (but may even be complete)
  - Weak, moderate, strong
  - Focal, diffuse
- Cytoplasmic
  - Diffuse
  - Perinuclear dot-like (Golgi) pattern

LCIS with Aberrant E-Cadherin Expression

LCIS with Aberrant E-Cadherin Expression

LCIS with Aberrant E-Cadherin Expression
PLCIS with Aberrant E-Cadherin Expression

LCIS with Aberrant E-Cadherin Expression

LCIS with Aberrant E-Cadherin Expression
DCIS

vs

LCIS with aberrant E-cad Expression

Expected Expression of E-cadherin, p120 catenin and $\beta$-catenin

<table>
<thead>
<tr>
<th></th>
<th>Normal epithelium</th>
<th>LCIS and ILC</th>
<th>DCIS and IDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-cadherin</td>
<td>Membrane staining</td>
<td>Absence of membrane staining</td>
<td>Membrane staining</td>
</tr>
<tr>
<td>p120 catenin</td>
<td>Membrane staining</td>
<td>Cytoplasmic staining</td>
<td>Membrane staining</td>
</tr>
<tr>
<td>$\beta$-catenin</td>
<td>Membrane staining</td>
<td>Absence of membrane staining</td>
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<td>Membrane staining</td>
<td>Absence of membrane staining</td>
<td>Membrane staining</td>
</tr>
</tbody>
</table>
But sometimes you just can’t be sure……
In situ carcinoma with ductal and lobular features

E-cadherin Expression in Lobular Lesions
- Aberrant E-cadherin expression in LCIS cells
- E-cadherin staining of benign cells
- Technical issues

E-cadherin Staining of Benign Cells Can Be Mistaken for Tumor Cell Staining in LCIS
- Normal or proliferating benign epithelial cells
- Myoepithelial cells
E-cadherin Expression in Lobular Lesions

- Aberrant E-cadherin expression in LCIS cells
- E-cadherin staining of benign cells
- Technical issues

Technical Issues

- Careful attention to pre-analytic and analytic factors needed to avoid false negative and false positive E-cadherin staining results
- Lack of appropriate antibody optimization and validation may result in spurious E-cadherin staining

Management of Non-Classical Variants of LCIS

- No clinical follow-up studies akin to those available for classical LCIS and DCIS
- Natural history/biologic behavior unknown
- More often associated with contemporaneous invasive cancer than classical LCIS
- Risk factors for local recurrence/progression to invasive ca not established
- Appropriate management uncertain
What Does “Treat Like DCIS” Really Mean?

- Excision to negative margins?
- Radiation therapy?

What Does “Treat Like DCIS” Really Mean?

- Excision to negative margins?
- Radiation therapy?

In the absence of data, is it better to over-treat or under-treat?
Management of Patients with Pleomorphic LCIS
WHO 2012

• “Caution should be exercised in recommending more aggressive management strategies such as excision to negative margins or mastectomy as a routine practice after a diagnostic surgical biopsy reveals pleomorphic LCIS.”

LCIS with Necrosis

• Same issues as those discussed for PLCIS
  – Cells have a lobular phenotype but comedo necrosis is a worrisome feature
  – Natural history unknown
  – Treat like classical LCIS or like DCIS?

Non-Classical Variants of LCIS
Practice at BIDMC

• In core needle biopsy specimens:
  – Surgical excision

• In surgical excision specimens:
  – Management similar to DCIS
    » Report margin status (but only for variant component when lesion is mixed with classical LCIS)
    » Attempt to excise to negative margins
    » ?Radiation therapy
Update on HER2 testing and Molecular Tests in Breast Cancer
Chad A. Livasy, MD
Carolinas Pathology Group
Adjunct Professor, UNC-Chapel Hill

Breast HER2 positive disease
• Common features of HER2 positive disease
  • High-grade histology
  • Aggressive biology
  • Younger patients
  • Down-regulation of ER and PR expression

HER2 Testing With IHC and FISH: Complementary Approaches
• HER2 gene amplification or protein overexpression can be assessed via FISH or IHC, respectively
• FISH and IHC are complementary methodologies, examining different aspects of the biology of HER2-driven cancer
• HER2 gene amplification and protein overexpression have been shown to be correlated
• IHC and FISH are equally efficient in identifying patients who are likely to respond to HER2-targeted therapy


Disclosures
• None.

* IHC 3+ or FISH+.
Pre-analytical factors
- Cold ischemic time <1 hour
- Fixation in 10% NBF for 6-72 hours
- Decalcification (prefer agents that do not contain hydrochloric acid)
- Disclaimer statement added to negative reports

HER2 Positive Rate and Copy #
- Expect HER2 positive rate of 15-20%
- Each lab should monitor their HER2+ rate and compare with expected positive rate
- For HER2 IHC positive cases, there is no clear relationship between HER2 copy number and survival for patients treated with adjuvant trastuzumab
- Positive cases near the cutpoint do benefit from HER2-targeted therapy
- Reporting of results
  - Report both ratio and HER2 copy #
  - If HER2 is positive based on HER2 copy #, helpful to add explanation in interpretation
  - HER2 POSITIVE for amplification (based on HER2 copy number ≥6)

Case #1
- 45 yo woman with outside dx of breast cancer, node negative
- Outside pathology results:
  - IDC, Nottingham grade 3
  - Size=1.4 cm
  - Minor component of admixed DCIS
  - LVSI negative
  - Margin negative, all >2 mm
  - 0/2 SLNs
  - pT1c pN0(m)  
  - Receptors (performed on prior core biopsy)
    - ER positive (3+, >90%), PR positive (1+, 80%)
    - HER2 2+ by IHC
    - HER2 negative by FISH (ratio=1.4; HER2 copy=2.0)

Case #1
- Oncologist requested that tumor from excision specimen be sent for Oncotype DX assay to guide chemoTx decision
  - Recurrence Score=High risk (58)
  - Single gene section= HER2 reported as Positive
- Oncologist requested 2nd opinion on pathology
Case #1

- HER2 summary: HER2 positive with HER2 genetic heterogeneity (approximately 40% of tumor cells are HER2 amplified by FISH and show HER2 overexpression 3+ by IHC)
- Tumor sampled in the prior core biopsy was accurately classified as HER2 negative
- HER2 FISH results:
  - Amplified region (ratio=8.4)
  - Non-amplified region (ratio=1.3)
- Patient received 6 cycles adjuvant TCH chemotherapy
- No evidence of recurrence to date

Reporting Consideration with Heterogeneity

- This case should be reported as HER2 positive, and the percentage of the invasive tumor involved should be provided on the report.
  - Do not combine the ratios!
  - Could result in an equivocal or even negative result depending on which cells counted
- HER2 signals (and ratio) should be reported for both the minority amplified (≥10%) and the majority non-amplified portions of the tumor.

Pearls of Pathology: Heterogeneity

- Intratumoral heterogeneity for HER2 can be seen in breast cancer by IHC and FISH
  - Can lead to discordant results for HER2 analysis
  - Between IHC and FISH, cores vs excision, between blocks
  - Easier to detect with IHC (can be used to target FISH)
- Clinical significance of heterogeneity remains unclear however:
  - Patients with HER2 IHC 3+ (10-30%) and FISH ratio (2-2.2) appear to benefit from treatment with HER2-targeted therapy
- ASCO/CAP updated HER2 guideline definition for HER2+
  - HER2 IHC ≥10% of tumor cells with strong circumferential membrane staining (readily appreciated at low power)
  - HER2/CEP17 ratio of ≥2, observed in a homogenous contiguous population of at least 10% of tumor cells
Intratumoral HER2 genetic heterogeneity

- Not well studied, little data reported.
- Two patterns of heterogeneity
  - Geographic: Rare.
    - Likely clinically significant
  - Interspersed (scattered single cells with ratio >2.0): Not rare on ISH assays.
    - Likely clinically insignificant
- Histologic clues to possible HER2 heterogeneity
  - Variable histology identified on excision specimen with component of high-grade histology
  - Zonal downregulation of ER and/or PR expression within a tumor
HER2 Retesting (recent studies)

- USCAP 2016
  - Carter et al. Repeat HER2 Testing on Grade 3 Invasive Breast Carcinoma Resections (abstract 133)
  - 169 grade 3 IBCs (HER2- on core), retested on excision
  - 3 cases (1.8%) showed change to positive
- Ballard et al. HER2 FISH Equivocal Category: Does Retesting Resolve This Clinical Grey Zone? (abstract 114)
  - 79 cases initially classified as equivocal
  - Approximately 1 in 4 converted to positive with retesting on excision
  - Most cases remained in the equivocal category

Case #2

- 48 yo woman presented with self-detected breast mass, clinical T1 N0 mass
- Underwent US guided core biopsy
  - IDC, Nottingham grade 3
  - ER+ (1+, 95%), PR- (0%)
  - HER2 equivocal by IHC (score=2+)
  - HER2 equivocal by FISH (Ratio=1.7, HER2 copy=5.3)
- Underwent needle localized lumpectomy with SLN biopsy
  - IDC, Nottingham grade 3
  - Size: 1.8 cm
  - Margin negative (all >2 mm)
  - LVSI present
  - Micrometastasis (0.2 mm) involving 1 of 3 SLNs
  - pT1c N1mi(sn)
  - HER2 retesting on excision: Double equivocal by IHC and FISH
    - Ratio=1.6, HER2 copy=5.1
- Details of case were discussed with treating oncologist
- HER2 targeted therapy was added to this patient’s chemotherapy regimen based on high-risk features

Options for HER2 equivocal

- Test alternate specimen, block or site (e.g. positive lymph node)
- Repeat HER2 testing in same specimen using an alternate probe for centromeric region or for another gene in chromosome 17 not expected to co-amplify with HER2 (e.g. SMS, RARA, p53)
  - SMS and RARA are frequently amplified (data from TCGA)
  - TP53 amplifications less common
  - Different ratios often obtained with use of alternative chromosome 17 reference genes, but clinical significance is unknown
- Case discussion with treating oncologist to review clinicopathologic findings and individualized decision on HER2-targeted therapy
  - Oncologist may choose to give HER2 targeted therapy for equivocal results, particularly for high-risk tumors in which chemotherapy is planned
  - If there is uncertainty regarding chemotherapy, could send Oncotype Dx for information on chemotherapy benefit
  - Single gene IHC3-CitoscopeHER2 assay is typically resulted as negative

HER2 equivocal

- Oncologist treatment practices for HER2 equivocal cases is variable
- Important to regularly discuss these cases with treating oncologists
HER2 equivocal
- From our 2015 files
  - 1235 tumors tested for HER2
  - 6% were classified as equivocal
  - Actual % likely low due to retesting of equivocal cases
- HER2 FISH equivocal definition revised in 2013
  - Ratio <2.0, with HER2 copy number >24 and <6
  - Very little clinical data on response to HER2 targeted therapy for these patients
  - Based in part on understanding that there is instability in the genomic content of chromosome 17 centromeric region and these variations affect the HER2/CEP17 ratio

HER2 evaluation with RT-PCR
- No current defined utility in resolving equivocal/borderline cases
- Most double equivocal cases by IHC/FISH are negative by Oncotype RT-PCR single gene assay (personal experience)
    - N=841
    - Of 36 FISH positive cases: 10 positive, 12 equivocal and 14 (39%) negative by RT-PCR
    - "Unacceptable" false negative rate for Oncotype DX
    - Probably bias towards cases that are difficult to classify HER2 status
    - HER2+ tumors are rarely sent for Oncotype

Polysomy/monosomy 17
- CEP17 probe added to normalize for "polysomy 17" (thought to be due to increased copies of chromosome 17)
- CGH have subsequently demonstrated that whole chromosome polysomy is exceedingly rare
  - Much more complex than initially thought
  - Gains and losses seen throughout entire chromosome
  - Variations in CEP17 significantly affect HER2/CEP17 ratio.

Monosomy 17 with ratio >2.0
- These cases are rare (~1% of FISH cases in our experience)
- HER2 copy# <4
- These patients were included in first generation trastuzumab clinical trials
  - Little clinical data on benefit of HER2-targeted therapy
  - Often discordant with IHC

To determine whether the addition of trastuzumab to chemotherapy (TC or AC→WP) improves invasive disease free survival (DFS) in women with node positive or high-risk node negative breast cancer which is reported as HER2 low by all HER2 testing performed.
Other problematic ISH scenarios

- Loss of entire chromosome 17
  - Single signals for both HER2 and CEP17
  - Reported as non-amplified
- Total loss of CEP17 signals in tumor cells
  - Cannot calculate an accurate ratio; report HER2 copy #
  - Often resolved with IHC
  - Could try alternate reference probe
- Co-amplification of HER2 and CEP17
  - Problem resolved for most cases using current guidelines
  - Most cases are 3+ by IHC

HER2 Status May Change Between Primary Breast Cancer Diagnosis and Metastatic Disease

Studies show HER2 status changes* in 9% to 16% of breast cancer cases from early stage to late stage

<table>
<thead>
<tr>
<th>Study</th>
<th>HER2 Status Negative to Positive</th>
</tr>
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<tbody>
<tr>
<td>Simmons et al.</td>
<td>9% (2/22)</td>
</tr>
<tr>
<td>Guarneri et al.</td>
<td>16% (10/61)</td>
</tr>
<tr>
<td>Fabb et al.</td>
<td>11% (12/112)</td>
</tr>
</tbody>
</table>

Due to the aggressive nature of HER2 positive disease, it is advisable to rebiopsy and retest upon first recurrence of metastatic disease when original results were HER2-negative or unknown.

HER2 Testing in DCIS

- No current indication
- Awaiting results from NSABP B-43
  - HER2+ (confirmed centrally) treated with lumpectomy, final margins negative
  - Randomized to low-dose trastuzumab/WBI vs WBI alone
  - Primary end point
    - Ipsilateral IBC/DCIS recurrence
  - HER2+ rate observed for DCIS=33%

What Makes a Clinically Useful Assay?

- Consensus on analytic and clinical validity and clinical and economic utility
- Cost-neutral/saving, cost effective, better resource use
- Affects treatment decision making
- Outcome endpoints (i.e., prognostic, predictive)
- Reproducible and reliable
Molecular tests for early stage, ER+, invasive breast carcinoma

- Oncotype DX (RT-PCR gene expression, 21 genes)
  - Serial testing
  - FFPE tissue
  - Three-tier risk classification (low, intermediate, and high risk)-10 years
- MammaPrint (RNA gene microarray, 70 genes)
  - Central testing (MammaPrint, BluePrint, TargetPrint)
  - Fresh or FFPE tissue
  - Binary risk classification (low and high risk)-10 years
  - May send ER+ tumors
- Prosigna (Hybridization with gene specific labels-nCounter, 58 genes)
  - Serial testing
  - FFPE tissue
  - Three-tier risk classification (node-negative), two-tier (1-3 node positive)-10 years
  - Requires pathologist involvement for adequacy assessment and isolation of tumor for analysis

The Recurrence Score® Result Reveals Individual Tumor Biology for ER+ Breast Cancer

- Recurrence Score Value
  - Low Recurrence Score Disease
    - Hormone therapy—sensitive
    - Minimal, if any chemotherapy benefit
  - High Recurrence Score Disease
    - Aggressive
    - Large chemotherapy benefit

Patients with Recurrence Score® Results <11 Have Less than 1% Risk of Distant Recurrence at 5 Years

- 5 year DRFI Rate
  - 99.9% (95% CI 98.7%, 99.6%)
- n=1,626
- Median follow-up 69 months

SEER Breast Cancer Registry Study Design

- Characterize the Oncotype DX® assay testing and known chemotherapy (CT) use by nodal status in hormone receptor positive (HR+) invasive breast cancer
  - Determine prospective breast cancer-specific mortality (BCSM) outcomes by Recurrence Score® result and clinical and pathologic features
  - In a prospective clinical trial of N0, HR+, HER2- patients aged 40-84 years
  - In subgroups with N0 and node-positive (N+) macrometastatic and 1-3 positive nodes disease, including subgroups often underrepresented in clinical trials

Dr. et al. SABCS 2015

TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

- Eligible 10,215 patients prospectively enrolled (2006-2010)
  - Published in N Engl J Med 2015
  - Study Arms for Primary Analysis
    - Arm A: Hormonal Therapy Alone
    - Arm B: Hormonal Therapy Plus Herceptin®
  - Patients in Arm A were predominantly treated with AIs (59%) and tamoxifen (34%)
  - Patients in Arm B were predominantly treated with chemotherapy (34%) and AIs (59%)

Dr. et al. N Engl J Med 2015

Practicing Precision Medicine

16 Breast Cancer-Related Genes

<table>
<thead>
<tr>
<th>16 Breast Cancer-Related Genes</th>
<th>Oligo Cluster (Hybridization with gene specific labels—nCounter)</th>
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<tbody>
<tr>
<td>ER PR Her2</td>
<td>MammPrint Microarray 70 Genes (CMLA-21,212, SCUBE2)</td>
</tr>
<tr>
<td>Ki-67 HER2</td>
<td>Prosigna Gene Microarray 58 Genes (GUS, TLR12, CD68)</td>
</tr>
<tr>
<td>Stromelysin 3, Cathepsin L2</td>
<td>MammaPrint RNA microarray 70 genes (GAPDH, Actin)</td>
</tr>
</tbody>
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5 Reference Genes

- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

Dr. et al. SABCS 2015
5-year BCSM in Recurrence Score® Groups by Known Chemotherapy (CT) Use: ER+, N0, HER2(-) Patients

<table>
<thead>
<tr>
<th>Recurrence Score Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Known Chemotherapy</td>
<td>7%</td>
<td>34%</td>
<td>69%</td>
</tr>
<tr>
<td>No or Unknown Chemotherapy</td>
<td>93%</td>
<td>66%</td>
<td>31%</td>
</tr>
</tbody>
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Shak et al. SABCS 2015.

70-Gene cDNA Microarray Expression Profile (MammaPrint)

- Study included samples from heterogeneous patients with known recurrence status to evaluate whether known chemotherapy use impacts recurrence.
- 2 outcomes: distant recurrence vs. no distant recurrence.
- RNA extracted from fresh or frozen tissue, cDNA converted for gene expression analysis by gene specific probes.
- Full genome gene expression analysis.
- 70 prognosis genes.


RASTER study

  - 427 patients (cT1–T3 N0 M0, ages 18–61)
  - 219 patients classified as “low risk” by 70-gene assay
    - 85% of these patients did not receive chemotherapy
    - 97% were disease free after 5 years
  - 208 patients classified as “high risk” by 70-gene assay
    - 81% of these patients received chemotherapy
    - 91% were disease free after 5 years
- Conclusion: Assay identifies a group of woman who may omit adjuvant chemotherapy without compromising outcome.

PAM50 ROR Assay by NanoString nCounter®

- Extract RNA from FFPE tumor sample
- Run assay on NanoString nCounter Analysis System
- Capture patient expression profile
- Determine intrinsic subtype through Pearson’s Correlation to Centroids
- Calculate Risk of Recurrence (ROR) Score
- Determine Intrinsic Subtype Through Pearson’s Correlation to Centroids

Prosigna Pathologist Involvement

- Pathologist circles region of viable tumor, excluding surrounding non-tumor tissue
- Tumor cellularity estimated within circled area
  - >10% cellularity
  - >4 mm squared required
- Tumor tissue from unstained slides used for analysis

Table 1. Recommended state guidelines based on tumor surface area

<table>
<thead>
<tr>
<th>Tissue Surface Area</th>
<th>n-1000</th>
<th>n-10000</th>
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<tbody>
<tr>
<td>0-1.0</td>
<td>1</td>
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</tr>
<tr>
<td>1.0-5.0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5.0-10.0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>&gt;50.0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>&gt;100.0</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
Goals for Neoadjuvant Therapies for Locally Advanced Breast Cancer

- Locally advanced breast cancers represent approximately 4% of all breast cancers diagnosed in the United States.
- Management of locally advanced breast cancers has evolved over the last two decades and neoadjuvant systemic therapy is frequently used prior to surgery and/or radiation.
- The goals of neoadjuvant therapy are to improve surgical outcomes and options:
  - For operable breast cancer: Increase ability for breast conserving surgery in those who would otherwise require mastectomy.
  - For inoperable breast cancer: Downstaging of large tumors to improve surgical options and outcomes.
- Gene signatures can assist in selection of systemic neoadjuvant treatment by identifying patients more/less likely to respond to therapy.

Guiding Neoadjuvant Therapy Selection

Sample Case

**Patient:** 72 years old woman, desires BCT

**Medical history**
- ILC in the right breast

**Findings**
- Vague, poorly demarcated abnormality, MBD (5.6 cm)
- Tumor is ER+/PR+/HER2- (needle core biopsy)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>5.6 cm</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Negative</td>
</tr>
<tr>
<td>ER/PR status</td>
<td>ER+/PR+</td>
</tr>
<tr>
<td>HER2 status</td>
<td>Negative</td>
</tr>
<tr>
<td>Oncotype DX®</td>
<td>10</td>
</tr>
</tbody>
</table>

- Recurrence Score result of 10 indicates that she is more likely to respond to neoadjuvant endocrine therapy and less likely to respond to neoadjuvant chemotherapy than would a patient with a high score.

- Based on this, the doctor and patient decided to proceed with neoadjuvant endocrine therapy.

Guiding Duration of Adjuvant Endocrine Therapy

- **Breast Cancer Index Genetic Assay**
  - Marketed to help oncologist decision to extend or end endocrine therapy at year 5 and beyond for patients with early stage ER+, node-negative, IBC who are distant recurrence-free.
  - Also reports individualized risk of late recurrence of breast cancer (years 5-10).

- **Multi-gene quantitative RT-PCR assay**
  - Genes:
    - Extended endocrine therapy: HoxB13/IL17BR
    - Risk of late recurrence: BUB1B, CENPA, NEK2, RACGAP1, RRM2

DCIS Molecular Testing: Better Tools Are Needed

- Better tools to provide an individualized risk estimate that is based on the underlying tumor biology are needed.
- There is a need for tests that:
  - Provide an individualized estimate of LR risk
  - Provide confidence that you are making the right treatment recommendation
  - When clinical and pathologic features are incongruent
  - Confirming that a patient has a low risk of LR and could forego radiation
  - Identify patients thought to be low risk based on clinical and pathologic features but actually have higher-risk disease

How can genomics address this need?
**DCIS Score™ Result: Gene Selection**

<table>
<thead>
<tr>
<th>Proliferation</th>
<th>Hormone Receptor Group</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67</td>
<td>PR</td>
<td>Beta-actin</td>
</tr>
<tr>
<td>STK15</td>
<td></td>
<td>GAPDH</td>
</tr>
<tr>
<td>Survivin</td>
<td></td>
<td>RPLP0</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td>GSTM1</td>
<td>GUS</td>
</tr>
<tr>
<td>MYBL2</td>
<td></td>
<td>TFRC</td>
</tr>
</tbody>
</table>

The DCIS Score result:
- Is a continuous variable
- Is a quantitative risk assessment (number between 0-100)
- Reflects each individual patient’s tumor biology

**DCIS Score™ Result: 10-Year LR in E5194**

(10-year LR in patient with low/intermediate grade, ≤2.5 cm or high grade, ≤1 cm; ≥3 mm margin)

- Any Local Recurrence
- Invasive Local Recurrence

The ECOG E5194 study validated the DCIS Score result as a predictor of LR (increasing DCIS Score corresponds to increasing risk):
- Any DCIS or invasive LR
- An invasive LR

---

**NGS testing in metastatic breast cancer**

- Defining utility in breast cancer clinical decision making is a work in progress
- Objective is to identify actionable mutations to target
- Very little data to date to support tumor mutation profiling in breast cancer outside of research setting
- May serve as a screening tool for clinical trial enrollment
Local Treatment of Breast Cancer

- Breast conserving therapy now standard treatment for patients with invasive breast cancer
  - Breast conserving surgery and radiation therapy
  - Breast conserving surgery alone (for selected patients)
- Associated with high levels of local tumor control

Risk Factors for Recurrence in the Conservatively Treated Breast

- **Clinical factors**
  - Young age
- **Treatment factors**
  - Extent of excision
  - Details of radiation therapy
  - Use of systemic therapy
- **Tumor factors**
  - Gross multicentric disease
  - Extensive intraductal component
  - Molecular subtype
  - Margins

Basics of Margin Evaluation

- Margin evaluation is an exercise in probabilities (not absolutes)
- Patients with positive margins are more likely to have residual disease at or near the primary site than those with negative margins
- **But**
  - A positive margin does guarantee residual disease
  - A negative margin does not preclude extensive residual disease
The Goal of Margin Evaluation

• **IS NOT** to ensure that there is no residual tumor in the breast

The Goal of Margin Evaluation

• To identify those patients more likely to have a large residual tumor burden and who, therefore, require further surgery (re-excision or mastectomy)
• To identify those patients unlikely to have a large residual tumor burden and who, therefore, are suitable candidates for breast conserving therapy without further surgery

Limitations of Margin Assessment

• Technical and methodological
• Definition and interpretation
• Distribution of tumor in the breast
• Breast cancer biology
• Impact of systemic therapy

Technical and Methodologic Issues

• The “pancake phenomenon”

The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer


Occurs even in the absence of compression for specimen radiography
Technical and Methodologic Issues

- The “pancake phenomenon”
- Specimen orientation

Inking of Specimen Margins

Unoriented Specimen

Oriented Specimen

-- In addition to orienting specimen using S and L sutures, a 3rd stitch was randomly added to another margin
-- Surgeon-pathologist discordance about 3rd margin location in 31% of cases
Experimental model using oriented, partially filled water balloon
Three volunteers painted six surfaces
Area of each color on surface quantitated by image analysis
Area of some painted surfaces differed by as much as 100% between painters
Last surface painted on average 18% larger than the rest

Is this the orange margin or the blue margin?

Where is the margin?

<table>
<thead>
<tr>
<th>Color</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>100</td>
</tr>
<tr>
<td>Green</td>
<td>100</td>
</tr>
<tr>
<td>Blue</td>
<td>96</td>
</tr>
<tr>
<td>Red</td>
<td>100</td>
</tr>
</tbody>
</table>
Recognized and Discrimination of Tissue-Marking Dye Color by Surgical Pathologists

Recommendations to Avoid Errors in Margin Assessment

Andrew S. Williams, MD, and Kelly Dulan Hache, MD, PhD

Overall

<table>
<thead>
<tr>
<th>Color</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>100</td>
</tr>
<tr>
<td>Green</td>
<td>100</td>
</tr>
<tr>
<td>Blue</td>
<td>96</td>
</tr>
<tr>
<td>Red</td>
<td>100</td>
</tr>
<tr>
<td>Violet</td>
<td>75</td>
</tr>
<tr>
<td>Orange</td>
<td>56</td>
</tr>
<tr>
<td>Yellow</td>
<td>50</td>
</tr>
</tbody>
</table>

Technological and Methodologic Issues

- The “pancake phenomenon”
- Specimen orientation
- Problems with ink
- No uniform sampling method; sampling error

Sampling of Lumpectomy Specimens

- Ranges from limited sectioning to total sequential embedding
- Even with total, sequential embedding, only a small proportion of the specimen is examined microscopically

How “Total” is Total Sequential Embedding?

- 4.2 cm lumpectomy specimen
- Cut at 3 mm intervals resulting in 14 slices
- Each slice embedded in paraffin and cut at five microns
- Results in 14 five micron sections
- 70 microns of tissue examined from a 4.2 cm specimen = 0.2% of specimen

Complete Histologic Examination of this 4.2 cm Lumpectomy Specimen Would Require

8400 slides

Definitions and Interpretive Issues
At many institutions

- Proscribed minimum margin required for breast conserving treatment based on data from retrospective studies, local lore/urban legend, or how/where surgeons were trained.

- 25+ years after randomized trials, no general agreement among surgeons or radiation oncologists as to what constitutes an adequate negative margin.
  - No margin width about which >50% of surgeons or radiation oncologists agree is “adequate” or “negative.”
  - All available data from retrospective studies.
  - Issue never addressed in randomized trials.

What is an Adequate Margin?

Surgeons (Azu, 2010)

<table>
<thead>
<tr>
<th>Margin Preferences</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 mm</td>
<td>11.0</td>
</tr>
<tr>
<td>1-2 mm</td>
<td>42.0</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>27.9</td>
</tr>
<tr>
<td>&gt;3 mm</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Radiation Oncologists (Taghian, 2005)

![Graph showing margin preferences among radiation oncologists.]

Why does it matter?

- Extent of surgical resection most important determinant of cosmetic outcome.

48% of re-excisions performed on patients with negative margins.
Why does it matter?

- Re-excisions associated with
  - Patient anxiety
  - Poor cosmesis
  - Morbidity
  - Cost
  - Patients opting for mastectomy

How Well Does Any Given Margin Measurement Reflect Reality?

Distribution of Tumor in the Breast

Histologic Multifocality of Tis, T1-2 Breast Carcinomas
Implications for Clinical Trials of Breast-Conserving Surgery
ROLAND HOLLAND, MD; ROYKELE H. J. VELLOO, MD; D. MARCEL MAHLOON; AG; AND JON E. L. HEINRICKS, MS
Cancer, 1985
If this is the case, do millimeters really matter?

14,571 patients from 21 studies
No significant difference in LR rates associated with threshold margin widths of 1 mm, 2 mm or >5 mm when adjusted for use of radiation boost or endocrine therapy

Breast Cancer Biology

• More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width

Impact of Breast Cancer Biology on Local Recurrence

• More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width

• OncotypeDX recurrence score (developed to predict likelihood of distant recurrence) also predicts loco regional recurrence (Mamounas, 2010)
Impact of Breast Cancer Biology on Local Recurrence

- More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width
- OncotypeDX recurrence score (developed to predict likelihood of distant recurrence) also predicts loco-regional recurrence (Mamounas, 2010)
- Wider margins don’t overcome bad biology

Impact of Systemic Therapy

Effective Systemic Therapy Reduces Local Recurrence

<table>
<thead>
<tr>
<th></th>
<th>No Systemic Therapy</th>
<th>Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B14 ER+, N- (systemic Rx: none vs Tam)</td>
<td>14.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>NSABP B13 ER-, N- (systemic Rx: none vs MF)</td>
<td>13.4%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

All patients in both studies had NSABP-defined negative margins (i.e., no tumor touching ink)

Joint SSO-ASTRO Consensus on Margins in Invasive Breast Cancer

Joint SSO-ASTRO Consensus on Margins in Invasive Breast Cancer

Co-chairs: Monica Morrow SSO
Meena Moran ASTRO

Participants:
- ASBS: Suzanne Klimberg
- ASCO: Marina Chavez MacGregor
- ASTRO: Jay Harris, Gary Freedman, Janet Horton
- CAP: Stuart Schnitt
- SSO: Armando Giuliano, Seema Khan
- Advocate: Peggy Johnson
- Methodologist: Nehmat Houssami

Funded by a grant from Susan G. Komen
SSO-ASTRO Consensus

- Applies only to patients with invasive breast cancer treated with breast conserving surgery and whole breast irradiation
- Does not apply to:
  - Patients treated with partial breast irradiation
  - Patients treated with lumpectomy without radiation
  - Patients treated with neoadjuvant chemotherapy
  - Patients with DCIS

Margins Meta-analysis: Results

<table>
<thead>
<tr>
<th>Margin status</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.0</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Positive/Close</td>
<td>1.96</td>
<td>1.72-2.24</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2.44</td>
<td>1.97-3.03</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Notes:
1. Heterogeneity in definitions of positive and close margins
2. Panel felt that analysis of specific margin widths supersedes this

Margins Meta-analysis: Results

<table>
<thead>
<tr>
<th>Threshold Distance</th>
<th># studies</th>
<th># subjects/# LRs</th>
<th>OR*</th>
<th>95% CI</th>
<th>p (association) = 0.90</th>
<th>p (trend) = 0.58</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mm</td>
<td>6</td>
<td>2376/235</td>
<td>1.0</td>
<td>&lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mm</td>
<td>10</td>
<td>8350/414</td>
<td>0.91</td>
<td>0.46-1.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mm</td>
<td>3</td>
<td>2355/103</td>
<td>0.77</td>
<td>0.32-1.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for length of f/u
### Impact of Margin Width on LR

#### Treatment Covariates

<table>
<thead>
<tr>
<th>Margin Width: OR*</th>
<th>Treatment Covariate</th>
<th># studies</th>
<th>1 mm</th>
<th>2 mm</th>
<th>5 mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocrine Rx</td>
<td>16</td>
<td>1.0</td>
<td>0.98</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Radiation Boost</td>
<td>18</td>
<td>1.0</td>
<td>0.82</td>
<td>0.92</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Adjusted for length of f/u

### Meta-Analysis Results

#### Impact of Margin Width on Local Recurrence Adjusted for Treatment Covariates

<table>
<thead>
<tr>
<th>Margin Width: OR</th>
<th>Treatment Covariate</th>
<th># studies</th>
<th>1mm</th>
<th>2mm</th>
<th>5mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocrine Rx</td>
<td>16</td>
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<td>0.98</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Radiation Boost</td>
<td>18</td>
<td>1.0</td>
<td>0.82</td>
<td>0.92</td>
<td>0.86</td>
</tr>
</tbody>
</table>

### SSO-ASTRO Consensus

#### The Bottom Line

- A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a 2-fold increase in local recurrence
- Negative margins (no ink on tumor) optimize local control
- Wider margin widths do not significantly improve local control
- The routine practice of obtaining margins more widely clear than no ink on tumor is not indicated

### SSO-ASTRO Consensus

#### The Bottom Line

- The use of *no ink on tumor* as the standard for an adequate margin in invasive cancer in the era of multimodality therapy (which includes systemic therapy in most patients)
  - is associated with low rates of local recurrence
  - has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease healthcare costs

### Do These Statements Apply to Patient Subsets?

- Lobular carcinoma
- Age < 40
- Unfavorable biologic subtypes
- Extensive intraductal component (EIC)
**Consensus Statement**

**EIC**

- An EIC identifies cases that may have a large residual DCIS burden after lumpectomy.

- There is no evidence of an association between EIC and an increased risk of LR when margins are negative.

- Margins wider than no ink on tumor are *not routinely* indicated.

**Consensus Statement**

**EIC**

- Given the potential for considerable residual DCIS in EIC+ patients, consider:
  - Post excision mammography to document complete removal of calcifications
  - Other high-risk features, such as young age, multiple close margins

  to identify patients likely to benefit from re-excision.

**Practical Implications**

- Consensus guidelines are intended to help standardize practice; not a substitute for clinical judgment

- Provides the prospect for liberation from rules mandating re-excisions based merely on margin widths alone
  - Suggests reserving re-excisions for individuals likely to be at high risk for local recurrence when all relevant risk factors are considered together
SSO-ASTRO Consensus

Endorsed By

• Society for Surgical Oncology (SSO)
• American Society of Radiation Oncology (ASTRO)
• American Society of Breast Surgeons (ASBS)
• American Society of Clinical Oncology (ASCO)

St Gallen, 2015

NCCN Guidelines, 2016

February, 2014

What Does This Mean for Pathology Reporting of Margins?

• Consensus guidelines should influence how clinicians interpret our reports rather than how pathologists report margins
• Continue to report margins per CAP guidelines
  – Positive margin = ink on invasive cancer or DCIS
  – Report distance to negative margins in mm or fractions thereof for both invasive cancer and associated DCIS
Conclusions

• While wider margins may have conveyed a small benefit in the past, multimodality therapy obviates the need for wider margins in contemporary practice.

• The use of no ink on tumor as the standard for an adequate margin in invasive cancer in the era of multimodality therapy is associated with low rates of local recurrence and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease healthcare costs.

Breast Conservation Surgery and the Definition of Adequate Margins
More Is Not Better...It's Just More

JAMA Surgery, 2014

SSO-ASTRO-ASCO Consensus Guideline on Margins for DCIS

For pts with DCIS treated with excision and WBRT, the magic number is......

2 mm

The Future of Lumpectomy Margin Evaluation

• RF Spectroscopy/Electromagnetic response (MarginProbe)
• Spectral imaging
• Optical imaging
• High frequency ultrasound
• Molecular margins

NONE READY FOR PRIME TIME
Spindle Cell Lesions of the Breast

Siobhan M. O’Connor, MD
April 16, 2016

I have no conflicts of interest to declare.

Outline

• Case
• Consensus review of phyllodes tumors
• Excluding metaplastic carcinoma
• Benign spindle cell lesions
• Malignant spindle cell lesions

Case

• 59 year old female with left breast mass
• Mammography
  • Mixed density mass composed of fat, pleomorphic and dystrophic calcifications
  • Developing asymmetry along the anterior aspect measuring 5.4 cm x 4.2 cm x 3.9 cm
• Targeted ultrasound
  • Mixed echogenic mass containing cystic and solid components measuring 5.3 x 4.0 x 3.7 cm
  • Central echogenic foci consistent with microcalcification

Core biopsy

Spindle cell proliferation without epithelial component
Mild cytologic atypia
Case

- Core biopsy
  - Cytokeratin AE1/AE3 negative
  - HMWK negative
  - S-100 negative
  - Signed out as atypical spindle cell lesion

Case

- Extensive stromal overgrowth and periductal condensation
- Stromal atypia ranges from mild to severe
- Some areas of the tumor are well circumscribed while others show infiltration into surrounding breast tissue
- The mitotic count focally reaches 21 mitoses per 10 high power fields

Case

- Excisional biopsy
- Malignant phyllodes tumor with associated necrosis and calcifications
- 7.4 cm in greatest dimension

Consensus Review of Phyllodes Tumors

Consensus Review Phyllodes Tumors

- Grading
  - Fibroepithelial architecture with exaggerated intracanalicular pattern with leaf-like fronds protruding into cystic spaces
  - Stromal hypercellularity
  - Main feature distinguishing benign phyllodes tumor from FA with prominent intracanalicular growth pattern is increased stromal cellularity

Tan PH et al. Histopathology 2016;68:5

| WHO Criteria Distinguishing Benign, Borderline, Malignant PT |
|---------------------------------|----------------|----------------|
|                                  | Benign         | Borderline     | Malignant      |
| Tumor border                     | Well-defined   | Well-defined,  |
|                                 |                | may be focally |
|                                 |                | permeative     |
| Stromal cellularity              | Cellular,     | Cellular,      |
|                                 | usually       | usually        |
|                                 | mild,         | moderate,      |
|                                 | non-uniform   | non-uniform    |
|                                 | or diffuse    | or diffuse     |
| Stromal atypia                   | Mild or none   | Mild or moderate | Marked        |
| Mitotic activity                 | Usually few   | Usually frequent|
|                                 | <5/10 HPF      | 5-8/10 HPF     |
|                                 | Usually       | Usually         |
|                                 | abundant      | 10 HPFs        |
| Stromal overgrowth               | Absent        | Absent, or very|
|                                 |                | focal          |
| Malig heterologous elements      | Absent        | Absent, or very|
|                                 |                | focal          |
| Relative % PT                    | 60-75%         | 15-20%         |
|                                 |                | 10-20%         |

WHO Classification of Tumours of the Breast. 4th ed. 2012:45.
Consensus Review Phyllodes Tumors

• Grading
  • One study with 605 cases
  • Stromal atypia, mitoses, overgrowth, and surgical margins independently predict behavior
    • Surgical margins most important


Consensus Review Phyllodes Tumors

• Biological behavior
  • Recurrence rate overall in literature
    • Benign 10 to 17%
    • Borderline 14 to 25%
    • Malignant 23 to 30%


Consensus Review Phyllodes Tumors

• Biological behavior
  • Metastases and death always preceded by malignant diagnosis
  • Metastases invariably dismal prognosis with ensuing death
  • Suggests primary aim should be to recognize malignant phyllodes tumors, for effective therapy to be administered


Consensus Review Phyllodes Tumors

• Biological behavior
  • In a study of 335 PTs, metastases and death always preceded by malignant diagnosis
  • Rate of metastases ranges from 9.7 to 50% of malignant tumors
  • Metastases vanishingly rare in benign tumors
  • Suggests diagnoses should focus on accurately identifying malignant tumors


Consensus Review Phyllodes Tumors

• Relationship between FA and PT
  • Historically, PTs regarded as de novo lesions
  • Number of studies have found highly recurrent mediator complex subunit 12 (MED12) mutations in similar proportions of FAs and PTs
  • Evidence for direct evolution of PTs from FAs remains limited
    • But recent confirmation of linear progression in some cases


Consensus Review Phyllodes Tumors

• Cellular FA versus benign PT
  • Lawton et al, 21 cellular fibroepithelial lesions, evaluated by 10 specialist breast pathologists
    • Uniform agreement for only two cases
    • Were selected from consultation cases, difficult lesions over-represented
  • Cellular FAs and benign PTs combined and compared to borderline and malignant PTs
    • Complete concordance in 53%

Consensus Review Phyllodes Tumors

- Cellular FA versus benign PT
  - Important to keep in mind that FAs in pediatric age group tend to have increased stromal cellularity
    - And up to 7 mitoses per 10 HPFs have been reported
  - In pediatric lesions, diagnosis of PT should only be made in the presence of well-developed stromal fronds with increased stromal cellularity
  - In general, leafy architecture and increased stromal cellularity should be used to discriminate between cellular FA and benign PT


- Is it always necessary to distinguish benign PT from cellular FA, given similar recurrence rates?
  - WHO Working Group has suggested “benign fibroepithelial neoplasm” for equivocal cases
    - Recommend using term sparingly, as it does not represent a new category
  - Evidence that benign PTs may be treated less aggressively


- Reported recurrence rate for benign PT ranges from 0 to 10.9%
  - In two studies, no association with margin status
  - Benign PT may be handled conservatively after excision, even with positive margins
  - Recurrence rate for malignant PT is 29.6% with metastases and death in 22%
  - Complete surgical excision needed for malignant PT


- Axillary lymph node dissection not recommended
- Adjuvant therapy
  - Role of radiation therapy is controversial
    - May reduce local recurrence, but no evidence of increased overall survival
  - No randomized controlled trials evaluating use of adjuvant chemotherapy in malignant PTs


- Surgical margins
  - Traditionally, management consisted of surgical excision with wide margins, defined as at least 10 mm
  - Limited data supporting a precise width of tumor-free tissue which is significantly associated with reduced tumor recurrence
  - May be practical to consider tumor on ink, or <1 mm, as positive margin
    - Conservative approach to benign PT excised without margins
    - Recurrent and malignant PT should be excised with negative margins


Metaplastic Carcinoma
Metaplastic Carcinoma – Spindle Cell type

- Also known as sarcomatoid carcinoma and spindle cell carcinoma
- Must always be excluded when atypical spindle cell neoplasm encountered
- 0.25 to 1% invasive breast cancers
- Pure spindle cells or primarily spindle cells with minor glandular, squamous, or heterologous elements
- Range from cytologically bland to markedly pleomorphic


Metaplastic Carcinoma – Spindle Cell type

- Growth patterns
  - Fascicular
  - Fasciitis-like
  - Storiform
  - Haphazard
- Mitotic rate highly variable
- Usually infiltrative, but some show pushing border


Metaplastic Carcinoma – Spindle Cell type

- May need to perform panel of IHC
- IHC study of 20 pure sarcomatoid spindle cell metaplastic carcinomas
  - Pankeratin and basal cell keratins (K903, CK5/6, CK14, CK17)
    - 12 (60%) strong reactivity
    - 6 (30%) weak or focal
  - Myoepithelial markers (CD10, p63, SMA)
    - 16 (80%) reactive for at least 2
    - 3 (15%) reactive for one


Metaplastic Carcinoma – Spindle Cell type

- Low grade fibromatosis like carcinoma, or metaplastic spindle cell carcinoma – fibromatosis-like, deserves particular attention
- Proliferation of low grade, cytologically bland spindle cells
- Squamous or glandular epithelial elements may be admixed, but comprise <5% of tumor
- As name suggests, resembles fibromatosis


Metaplastic Carcinoma – Spindle Cell type

- Spindle Cell Carcinoma

Spindle Cell Carcinoma

Mitotic figure


Metaplastic Carcinoma – Spindle Cell type

- Infiltration into surrounding breast tissue
- Spindled to plumper round to oval nuclei

Benign Spindle Cell Lesions

Pseudoangiomatous Stromal Hyperplasia (PASH)
- Incidental finding in ~23% of breast biopsies
- Most common in premenopausal women
- Frequent component of gynecomastia
- Tumor forming PASH almost exclusively in women
- When symptomatic, presents as a firm, non-tender, unilateral mass

PASH – Imaging and Gross Features
- Mammography
  - Well circumscribed round to oval density without calcification
- Ultrasound
  - Solid hypoechoic mass
- Circumscribed, non-encapsulated mass
- 1 to 15 cm in greatest dimension
- Homogeneous or lobulated tan-pink to yellow cut surface
PASH – Microscopic Features

- May occur as isolated mass or coexist with any breast lesion
- Slit-like anastomosing spaces
- Lined by flat, elongated myofibroblasts
- Separated by bands of eosinophilic hyalinized tissue
- Myofibroblasts with scant cytoplasm and small, bland nuclei
- Usually involves interlobular stroma, but may also involve intralobular

Fascicular PASH
- More pronounced proliferation of myofibroblasts forming distinct bundles
- If mass-forming, DDx is myofibroblastoma

PASH – Immunohistochemistry

- Myofibroblasts show strong reactivity for vimentin
- CD34 positive in the majority of lesions
- Negative for cytokeratin and vascular markers
- Sometimes reactive for PR
  - ER usually negative, but sometimes weak reactivity

PASH – Treatment

- No treatment required unless mass-forming
- Ipsilateral recurrences have been reported, but uncommon
- Recurrent lesions behave in a benign fashion and can be managed with re-excision

Fibromatosis

- May occur at any age after adolescence
  - Most common between 20 and 40 years
- Rarely seen in men
- Gardner’s syndrome
- Rarely associated with familial adenomatous polyposis
- Role of trauma is controversial
**Fibromatosis – Presentation and Imaging**

- Presents as firm palpable mass
- May cause cutaneous or nipple retraction
- Mammography
  - Mass or area of architectural distortion
  - Usually devoid of calcifications

**Fibromatosis – Gross Features**

- Ill-defined or stellate mass
- Suggestive of invasive carcinoma
- White-gray cut surface and scar-like consistency
- 1 to 10 cm, with average 2.8 cm

**Fibromatosis – Microscopic Features**

- Long sweeping fascicles of myofibroblasts which infiltrate into breast parenchyma
- Cellularity ranges from low to focally moderate
- Collagen fibers intervene among myofibroblasts
- Spindle cells have scant cytoplasm, open chromatin, and inconspicuous nucleoli
- Lymphoid infiltrates common, especially at periphery
- Mitotic figures usually not present, but may be seen
  - May be numerous focally

**Fibromatosis -- Immunohistochemistry**

- Cells are strongly positive for vimentin
- Virtually never positive for CD34
- Reactive for smooth muscle actin
- May be reactivity for desmin and S-100, but usually in minority of cells
- ~75% positive for β-catenin, nuclear pattern
  - Not specific and may be seen in a minority of spindle cell carcinomas and in FAs, PTs
### Fibromatosis – Treatment

- Locally aggressive, wide local excision recommended
- Because ill-defined borders, difficult to judge adequacy of margins during surgery
- Local recurrence in 21% to 27%
- Risk higher with positive margins
- But reported in cases with negative margins
- Most within 3 years of diagnosis
- Cellularity, mitotic activity, pleomorphism not helpful in predicting recurrence

---

### Fibromatosis – Differential Diagnosis

- **MSCC-FL**
  - Greater nuclear atypia and higher mitotic rate (also in low grade sarcoma)
  - Desmoid-like foci and peripheral lymphoid aggregates suggest fibromatosis
  - Cytokeratins and myoepithelial markers negative in fibromatosis
  - Previous surgical site changes, trauma
  - Fat necrosis, multinucleated giant cells, hemosiderin deposition favor reactive/reparative process

---

### Nodular Fasciitis

- Uncommon in breast
- Subcutaneous tissue or parenchyma
- Rapidly growing mass that may be painful or tender
- Disappears spontaneously within a few months

---

### Nodular fasciitis

- Inflammatory cells dispersed more diffusely at periphery and within the lesion in nodular fasciitis
- Inflammation in fibromatosis usually isolated lymphoid aggregates at periphery of lesion
- Higher mitotic activity in nodular fasciitis
Nodular Fasciitis – Imaging and Gross Features

- Mammography
  - Usually mimics a fibroadenoma, but can simulate an invasive carcinoma
- Unencapsulated mass
- Pink-grey, mucoid cut surface

Nodular Fasciitis – Microscopic Features

- Generally well-circumscribed, but may simulate invasion into adjacent tissue focally
- Plump spindle cells arranged in short fascicles and whorls
- Stroma typically loose, myxoid, may show cystic change
- Likened to fibroblasts growing in tissue culture
- Extravasated RBC and mixed inflammatory infiltrates common

Nodular Fasciitis – Microscopic Features & IHC

- Mitotic figures readily identified and may be numerous, but nuclear atypia and necrosis usually absent
- Early lesions highly cellular; regressing less cellular with more stromal collagen
- Usually displaces adjacent breast ducts and lobules
- Myofibroblasts express smooth muscle actin, but may be focal
- Desmin expression occasionally seen, and generally focal

Nodular Fasciitis – Treatment

- Will usually spontaneously regress, but biopsy or excision almost always performed due to growing mass
- Local excision is adequate treatment

Nodular Fasciitis – Differential Diagnosis

- Fibromatosis – addressed previously
- Metaplastic carcinoma
  - Myoepithelial/epithelial markers positive in metaplastic carcinoma
  - Inflammatory cells in nodular fasciitis
  - Nodular fasciitis non-invasive
Myofibroblastoma

- Thought to occur more frequently in men
- Identified in greater numbers on screening mammography
- Now appear to occur with equal frequency in men and women
- More common after 50 years old

Myofibroblastoma – Imaging and Gross Features

- Mammography
  - Homogeneous, lobulated, well-circumscribed, lacks calcifications
- Ultrasound suggests fibroadenoma
- Ranges from 1 to 12 cm
- Circumscribed and rubbery
- Grey-white cut surface with areas of fat
- Lacks a true capsule
  - May have pseudocapsule consisting of compressed breast tissue

Myofibroblastoma – Microscopic Features

- Uniform and slender myofibroblasts
- Arranged in short, intersecting fascicles
- Intervening thick bands of brightly eosinophilic collagen
- Nuclear atypia absent or minimal
- Mitoses uncommon, rarely up to 1 to 2 mitoses/10 HPF
- Adipocytes intrinsic component
- Expansile growth and usually does not contain entrapped ducts
  - Infiltrative variant has been identified

Myofibroblastoma -- Immunohistochemistry

- Immunoreactive for CD34, bcl-2, CD99, vimentin
- Can be positive for desmin, smooth muscle actin, and, focally, h-caldesmon
- Expression of ER and PR in 70% to 90% of cells in nearly all cases
- Negative for cytokeratins, S-100, and myoepithelial markers
Desmin
ER
SMA

Myofibroblastoma -- Variants

- Collagenized or fibrous
- Epithelioid
- Cellular
- Infiltrative
- Myxoid


Myofibroblastoma, collagenized
- Tumor cells embedded in collagenous stroma
- May resemble fascicular PASH

Myofibroblastoma, epithelioid
- Arranged in alveolar groups
- Linear pattern reminiscent of lobular carcinoma

Myofibroblastoma, cellular
- Dense proliferation of spindle-shaped cells
- Collagenous bands may be absent in some areas

Myofibroblastoma, Infiltrative
- Characterized by invasive growth
- Fat, stroma, ducts, and lobules incorporated

Myofibroblastoma – Differential Diagnosis

- Sarcoma and metaplastic carcinoma usually more cellular with frequent mitoses
- Fasciitis and fibromatosis also contain myofibroblasts, but tend to be stellate and infiltrative
  - Plump myoid cells and inflammation of fasciitis not seen in myofibroblastoma
  - Fibromatosis shows abundant collagen and spindle cells arranged in broad bands rather than short fascicular clusters

Myofibroblastoma – Treatment

- No recurrences have been reported
- Almost all managed adequately by excisional biopsy
- Complete excision recommended when encountered in core

Malignant Spindle Cell Lesions

- Most commonly, represent spindle cell carcinoma or stromal component of malignant phyllodes
- Primary sarcomas of the breast are extremely rare
  - Comprise <0.1% of malignant breast tumors
- Angiosarcoma is the most common primary breast sarcoma
  - Differentiated from other sarcomas based on vascular morphology and vascular immunohistochemical markers

Malignant Spindle Cell Lesions

- In a series from Mayo Clinic with review of literature
  - 25 patients ranging in age from 24 to 81 years
    - 6 each fibrosarcoma, angiosarcoma, and pleomorphic sarcoma
    - 3 myxofibrosarcomas
    - 2 leiomyosarcomas
    - 1 each hemangiopericytoma and osteosarcoma
  - Tumor size ranged from 0.3 to 12 cm (mean 5.7 cm)
  - Local recurrence was seen in 11 patients and distant metastasis in 10 patients
  - Morphologically similar to extramammary sarcomas

In Summary

- Spindle cell lesions of the breast represent a wide spectrum of reactive and neoplastic processes
- Critical to exclude metaplastic carcinoma
- Excisional biopsy is often required for accurate diagnosis
- Immunohistochemical stains may be useful in morphologically challenging cases
- Primary sarcomas of the breast are extremely rare, and malignant spindle cell lesions are more likely to represent metaplastic carcinoma or stromal component of malignant phyllodes
End!

QUESTIONs?
Case Presentations

Stuart J. Schnitt, M.D.
Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

Disclosures

• None

Case 1

• May, 2005:
  – A 68 year old woman was found to have left breast mass in the 2:00 position on a screening mammogram.
  – An ultrasound-guided core needle biopsy was performed and a diagnosis of ductal carcinoma in situ was rendered at an outside hospital.

• June, 2005:
  – A surgical excision was subsequently performed at the outside hospital
  – Slides of the core needle biopsy and excision sent to BIDMC for consultation.
Excision Specimen  
Gross Examination

- 7 x 4.7 x 2 cm fibrofatty specimen containing a firm, relatively circumscribed mass measuring 0.9 cm
This is really weird!

**Approach to a breast tumor that looks really weird**

- Is it an unusual variant of a common breast lesion?
- Is it an uncommon breast lesion?
- Is it a skin lesion involving the breast?
- Is it a metastasis from an extra-mammary site?

**What can we say for sure?**

- Nested pattern of epithelial cells with fibrovascular stromal cores; some cores have foamy histiocytes
- Growth pattern worrisome for invasion
- Cells have columnar shape, eosinophilic cytoplasm and abnormal position of nuclei (toward apex rather than base of cells)

**Is it invasive?**
Is it invasive?
- Sure looks that way on both morphology and myoepithelial cell immunostains

What is the immunophenotype of the cells?
What is the immunophenotype of the cells?

- It’s as weird as the morphology!
  - Cells are cytologically low grade and express luminal cytokeratins
  - But, cells also express basal cytokeratins and are ER negative
  - Stain at least focally for GCDFP and mammaglobin consistent with breast origin

Other Markers

- PR negative
- HER2 negative
- CK20 negative
- TTF-1 negative
- Thyroglobulin negative
Outside Expert Opinions

1. Expert in analog lesions:
   Low-grade invasive adenocarcinoma with cutaneous adnexal features (based largely on strong CK5/6 expression)

2. Breast expert:
   Intraductal carcinoma with adnexal anlage features (acknowledged lack of myoepithelial cells but didn’t care about it)

Then, in 2007………

Case History

2007 Case

• 62 year old woman with new 9 mm mass on screening mammogram
• Core needle biopsy reported as showing DCIS
• Excisional biopsy performed
Still didn’t know what it was but I knew immediately that I had seen another case before!

Outside Expert Opinion

- Sent 2007 case and 2005 case (again) to same expert breast pathologist
- Dx for 2007 case: “Solid papillary intraductal carcinoma with adnexal features”
- This lesion and the 2005 lesion “are unique in my experience”.

What happened next?

- Since 2007, 11 more cases (total of 13)
- All females
- Median age 65 years (range 51-79 years)
- Mammographic mass or density
  - Median size 0.9 cm (range 0.6-1.5 cm)

Solid Papillary Carcinoma with Reverse Polarization (SPCRP)

- Solid, circumscribed nodules, many with fibrovascular cores (solid papillary pattern)
- Haphazard distribution of nodules between normal ductal-lobular structures and extending into fat
- Collagenous stroma with little or no desmoplasia
- Foamy histiocytes within fibrovascular cores
Solid Papillary Carcinoma with Reverse Polarization (SPCRP)
Key Histologic Features

• Columnar epithelial cells with eosinophilic cytoplasm
• Nuclei with low to intermediate grade atypia and occasional grooves and intracytoplasmic inclusions (prominent in only 1 case)
• Nuclei present in non-basal location (apparent reversal of normal polarity)

Less Frequent Histologic Features

• Jigsaw pattern of cell nests
  – Present to some degree in all cases
  – Prominent in one case
Solid Papillary Carcinoma with Reverse Polarization (SPCRP)

**Less Frequent Histologic Features**

- Jigsaw pattern of cell nests
  - Present to some degree in all cases
  - Prominent in one case
- Frankly papillary areas
  - Present in 5/12 cases (42%)

Solid Papillary Carcinoma with Reverse Polarization (SPCRP)

**Immunophenotype**

- No myoepithelial cells around tumor nodules in any case
- Positive for low AND high molecular weight cytokeratins
- GCDFP and mammaglobin each positive in ~60%
- All cases negative for TTF-1 and thyroglobulin

- 62% entirely ER negative; remainder low ER positive (1-10%)
- 15% PR positive
- All cases HER2 negative
- AR focally positive in 1 case
- Low proliferation rate by Ki67 (<5%)
- Rich vascular network around nests on CD31 and CD34 stains
Solid Papillary Carcinoma with Reverse Polarization (SPCRP)

Immunophenotype

- E-cadherin: Strong lateral membrane staining
- MUC1: Apical membrane staining seen on ends of cells closest to nucleus (reverse polarity)
**Solid Papillary Carcinoma with Reverse Polarization**

Genomic Alterations
(in collaboration with John Iafrate and Jorge Reis-Filho)

- **IDH2** mutations in 10/13 cases (77%)
  - Not previously reported in breast cancers
- 8 concurrently displayed mutations in PI3 kinase pathway (*PIK3CA* or *PIK3R1*)
- Functional studies
  - **IDH2** and **PIK3CA** mutations appear to be driver alterations resulting in reverse polarization phenotype

**Clinical Course**

- Mastectomy (3 pts); excision/lumpectomy +/- XRT (8 pts); unknown (1 pt)
- Sentinel lymph node biopsy (6 pts): All node negative
- Among 7 pts with f/u, all NED (median 31 months; range 12-77 months)

**Conclusions**

- Solid papillary carcinoma with reverse polarization (SPCRP) represents a histologically low grade breast carcinoma with distinctive morphologic, immunophenotypic and genotypic features

**Case 1**

**DIAGNOSIS**

Solid papillary carcinoma with reverse polarization (SPCRP)

**Conclusions**

- Appears to be the same lesion previously described as “breast tumor resembling the tall cell variant of papillary thyroid carcinoma”, but
  - No staining for thyroglobulin or TTF-1
  - No BRAF mutations
  - Distinct mutational profile (IDH2 mutations)
  - Unrelated to thyroid carcinomas
  - Solid papillary carcinoma with reverse polarization (SPCRP) preferred term
Case 2

- A 43 year old woman was found to have a mass on a screening mammogram
- A core needle biopsy was performed

Diagnosis
Invasive Lobular Carcinoma
Diagnosis
Invasive Lobular Carcinoma, ER+, PR+, HER2-

• Mastectomy recommended
• Patient came to BIDMC BreastCare Center for second opinion
• Slides brought along for review

Diagnosis
Myofibroblastoma, epithelioid variant
**Myofibroblastoma**

**Clinical Features**
- Males = females
- Increasingly detected on mammogram
- Peak 50-75 years
- Mobile, slowly growing
- Most < 4 cm; occasionally very large
- Also may occur outside breast
- **Benign; no recurrence**

**Myofibroblastoma**

**Pathologic Features**
- Rubbery firm, lobulated mass; cut surface homogenous gray to pink whorled or lobulated tissue
- **Classic type-histology:**
  - Circumscribed, no true capsule
  - Variable amounts of fat
  - Short fascicles of uniform spindle-shaped cells with round to oval nuclei
  - Broad bands of hyalinized collagen

---

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- Rubbery firm, lobulated mass; cut surface homogenous gray to pink whorled or lobulated tissue
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- Rubbery firm, lobulated mass; cut surface homogenous gray to pink whorled or lobulated tissue
- **Classic type-histology:**
  - Circumscribed, no true capsule
  - Variable amounts of fat
  - Short fascicles of uniform spindle-shaped cells with round to oval nuclei
  - Broad bands of hyalinized collagen
**Myofibroblastoma**

**Other Histologic Features**
- Usually no entrapped mammary ducts/lobules
- Perivascular lymphoplasmacytic infiltrates
- Mast cells
- Myxoid change
- Chondroid or smooth muscle metaplasia

**Immunophenotype**
- Cells positive for
  - Vimentin
  - CD34 (epithelioid variant may be negative)
  - ER
  - PR
  - AR
  - Actin
  - Desmin
  - bcl2
- Staining may be focal / variable

**Variants**
- Collagenized/fibrous
- Cellular
- Myxoid
- Lipomatous
- Infiltrative
- Atypical
- Deciduoid
- Epithelioid

*Images of histological sections labeled Collagenized/Fibrous and Cellular.*
Epithelioid Variant of Myofibroblastoma

- Polygonal or epithelioid cells arranged in cords or alveolar groups
- May constitute predominant growth pattern or be admixed with classic form
- Growth pattern may resemble invasive lobular carcinoma
**Myofibroblastoma**

**Additional Pearls**

- Cases with atypia/pleomorphism
  - ?clinical significance
- Similar lesions at extramammary locations, especially inguinal
- Relationship to spindle cell lipoma
  - Morphologic and immunophenotypic overlap
  - “13q/Rb family of tumors”: deletion or rearrangement of 13q14 with loss of Rb expression by IHC

**Myofibroblastoma**

**Differential Diagnosis**

- Reactive/benign spindle cell lesions
  - Nodular fascitis
  - Spindle cell lipoma
  - Solitary fibrous tumor
  - Nerve sheath tumors
  - Smooth muscle tumors
- PASH
- Spindle cell sarcomas
- Carcinomas
  - Metaplastic
  - Lobular

**Pseudoangiomatous Stromal Hyperplasia (PASH)**

- Primarily pre-menopausal women
- Most commonly seen as incidental microscopic finding (~25% of breast specimens)
- Tumor-forming PASH
  - Circumscribed mass with smooth external surface
  - Homogeneous tan, gray, or white cut surface

**Pseudoangiomatous Stromal Hyperplasia (PASH)**

- Slit-like, often anastomosing spaces in dense collagenous stroma
- Myofibroblasts present at edges of spaces may resemble endothelial cells
  - Positive for vimentin, CD34, actin, desmin
  - Often positive for PR, but usually ER negative
- Must be distinguished from vascular lesions, esp. angiosarcoma
Fascicular PASH

- Myofibroblasts in distinct fascicles in background of conventional PASH
- Most extreme examples have growth pattern similar to myofibroblastoma
Spectrum of Myofibroblastic Lesions

Myofibroblastoma, epithelioid variant
(confirmed on subsequent excision)
Today's Agenda

- Medicare Fee Schedule Changes
  - CMS' 2016 Physician Fee Schedule Final Rule
- Current Pay for Performance Programs
- MACRA –
  - Medicare Access and CHIP Reauthorization Act
- PAMA –
  - Protecting Access to Medicare Act

Payment for Pathology Services

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*Does not equal sum of RVU columns due to rounding.

- Reflect averages by specialty (based on Medicare utilization)
- For individual physicians and practices, the impact depends on mix of services and payers (Medicare and non-Medicare)
- Physicians receive pay from other Medicare payment systems
  - For instance, independent laboratories receive 83% of their Medicare revenue from CLFS

Prostate Biopsy Services

- In 2009, CMS created four G codes for the surgical pathology of prostate saturation biopsy services.
- In 2015, CMS required one code for all prostate biopsy specimens regardless of the number of specimens or technique used to obtain the biopsy.
  - G0416 – CMS stated this simplified the coding and mitigated overutilization incentives.
- 2015 final rule added service to misvalued code list

Prostate Biopsy Services

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- The AMA RUC evaluated TC and PC values
- TC reduced due to alignment of direct inputs to updated 88305 value
- Shifts in medical service volume and reporting specialties contributed to PC decline
- TC cuts are phased in over two years CMS
- Updated PC values anticipated in 2017
Payment for Pathology Add-on Services

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</tr>
<tr>
<td>88369</td>
<td>26 Mibhmrct alys ih qntsamq addl probe</td>
<td>$25.15</td>
<td>$31.89</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>88369</td>
<td>TC Mibhmrct alys ih qntsamq addl probe</td>
<td>$46.87</td>
<td>$76.67</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>88377</td>
<td>Mibhmrct alys ihqntsamqsemi multiplex</td>
<td>$214.88</td>
<td>$241.02</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>88377</td>
<td>26 Mibhmrct alys ihqntsamqsemi multiplex</td>
<td>$65.76</td>
<td>$66.28</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88377</td>
<td>TC Mibhmrct alys ihqntsamqsemi multiplex</td>
<td>$149.12</td>
<td>$345.74</td>
<td>132%</td>
<td></td>
</tr>
</tbody>
</table>

Payment for Pathology Services

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>MOD</th>
<th>DESCRIPTION</th>
<th>2015 Payment</th>
<th>2016 Payment</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>88184</td>
<td>Flowcytometry/1 marker</td>
<td>$94.51</td>
<td>$76.31</td>
<td>-20%</td>
<td></td>
</tr>
<tr>
<td>88185</td>
<td>Flowcytometry/tc add-on</td>
<td>$57.49</td>
<td>$46.22</td>
<td>-20%</td>
<td></td>
</tr>
<tr>
<td>88312</td>
<td>Special stains group 1</td>
<td>$59.70</td>
<td>$58.89</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88312</td>
<td>26 Special stains group 1</td>
<td>$26.93</td>
<td>$26.30</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88312</td>
<td>TC Special stains group 1</td>
<td>$70.07</td>
<td>$70.58</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88313</td>
<td>Special stains group 2</td>
<td>$68.27</td>
<td>$69.15</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88313</td>
<td>26 Special stains group 2</td>
<td>$12.58</td>
<td>$12.54</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>88313</td>
<td>TC Special stains group 2</td>
<td>$50.70</td>
<td>$56.61</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>88314</td>
<td>Histocchemical stains add-on</td>
<td>$75.10</td>
<td>$76.10</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>88314</td>
<td>26 Histocchemical stains add-on</td>
<td>$23.03</td>
<td>$23.39</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>88314</td>
<td>TC Histocchemical stains add-on</td>
<td>$52.10</td>
<td>$54.62</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Misvalued Code Initiative

- CMS will examine potentially misvalued services
  - This may include physician work surveys, data collection, research, and/or analyses
  - CMS also may use analytic contractors

<table>
<thead>
<tr>
<th>Code</th>
<th>Short Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10022</td>
<td>Fna w/image</td>
</tr>
<tr>
<td>36516*</td>
<td>Apheresis selective</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>88185</td>
<td>Flowcytometry/tc add-on</td>
</tr>
<tr>
<td>88189</td>
<td>Flowcytometry/1 marker</td>
</tr>
<tr>
<td>88321</td>
<td>Microslide consultation</td>
</tr>
<tr>
<td>88360</td>
<td>Tumor immunohistochem/manual</td>
</tr>
<tr>
<td>88361</td>
<td>Tumor immunohistochem/compud</td>
</tr>
</tbody>
</table>

PQRS and VBM: Background

Physician Quality Reporting System (PQRS)
A quality reporting program that provides payment adjustments to Medicare Part B reimbursement to eligible professionals based on whether or not they satisfactorily report data on quality measures for covered services.

Value-Based Payment Modifier (VBM)
A budget neutral payment adjustment applied to Medicare Part B reimbursement to a group based on the cost and quality of services provided to Medicare patients.
Pathology Measures

• Breast Cancer Resection Pathology Reporting
• Colorectal Cancer Resection Pathology Reporting
• Barrett's Esophagus
• Radical Prostatectomy Pathology Reporting
• Immunohistochemical (IHC) Evaluation of HER2 for Breast Cancer Patients
• Lung cancer reporting (biopsy/cytology specimens)*
• Lung cancer reporting (resection specimens)*
• Melanoma reporting*

Quality Reporting Initiatives

• VBM score is a calculation based on performance of the Group (defined by tax identification number (TIN))
  – Quality performance
  – Cost measures, which are based on the total cost of care attributed to the primary care physician
  – For pathology, we are considered to be average cost providers because we do not provide primary care services

Successful PQRS Participants in groups of 10 or more

<table>
<thead>
<tr>
<th>Quality/Cost</th>
<th>Low Cost</th>
<th>Average Cost</th>
<th>High Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Quality</td>
<td>+4.0%*</td>
<td>+2.0%*</td>
<td>+0.0%</td>
</tr>
<tr>
<td>Average Quality</td>
<td>+2.0%</td>
<td>+0.0%</td>
<td>-2.0%</td>
</tr>
<tr>
<td>Low Quality</td>
<td>+0.0%</td>
<td>-2.0%</td>
<td>-4.0%</td>
</tr>
</tbody>
</table>

• All Physicians are Subject to Quality Tiering

Quality Reporting Initiatives

• Ways to participate in 2016 PQRS
  – Individuals can report via claims or registry
  – Group practices can report via group practice reporting option (GPRO) registry or GPRO web interface
• A 2018 PQRS penalty of -2% will be applied to those unsuccessful in the 2016 PQRS program
  – Individuals who are unsuccessful also face an automatic 2 to 4% VBM penalty

Final Highlights

• CMS clarified pathologists billing from independent laboratories (POS 81) are not subject to PQRS/VBM payment adjustments.
• PQRS and VBM programs expire after 2018 and are replaced by the new Merit-Based Incentive Payment System (MIPS).
Medicare Access and CHIP Reauthorization Act (MACRA)

- Replaces the SGR with two payment pathways:
  - Merit-Based Incentive Payment System (MIPS)
  - Alternative Payment Models (APMs)
- Future payment updates under MIPS are tied to:
  - Quality performance metrics (formerly PQRS)
  - EHR Meaningful Use
  - Resource utilization (formerly VBM)
  - Clinical Practice Improvement Activities
- Effective 2019 based on 2017 performance

MACRA-MIPS

Potential Impact of MIPS on Pathology

<table>
<thead>
<tr>
<th>Year</th>
<th>Program</th>
<th>Possible Penalty</th>
<th>Total With Full Penalty (millions)</th>
<th>Projected Total (millions)</th>
<th>Total with Full Bonus (millions)</th>
<th>Possible Bonus</th>
<th>Difference in Full Penalty and Full Bonus (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>MIPS</td>
<td>-4%</td>
<td>$2,160</td>
<td>$2,214</td>
<td>$2,223</td>
<td>4%</td>
<td>$110</td>
</tr>
<tr>
<td>2020</td>
<td>MIPS</td>
<td>-5%</td>
<td>$2,180</td>
<td>$2,251</td>
<td>$2,262</td>
<td>5%</td>
<td>$141</td>
</tr>
<tr>
<td>2021</td>
<td>MIPS</td>
<td>-7%</td>
<td>$2,176</td>
<td>$2,277</td>
<td>$2,284</td>
<td>7%</td>
<td>$202</td>
</tr>
<tr>
<td>2022</td>
<td>MIPS</td>
<td>-9%</td>
<td>$2,171</td>
<td>$2,304</td>
<td>$2,313</td>
<td>9%</td>
<td>$268</td>
</tr>
<tr>
<td>2023</td>
<td>MIPS</td>
<td>-9%</td>
<td>$2,195</td>
<td>$2,331</td>
<td>$2,342</td>
<td>9%</td>
<td>$285</td>
</tr>
<tr>
<td>2024</td>
<td>MIPS</td>
<td>-9%</td>
<td>$2,218</td>
<td>$2,358</td>
<td>$2,369</td>
<td>9%</td>
<td>$278</td>
</tr>
<tr>
<td>2025</td>
<td>MIPS</td>
<td>-9%</td>
<td>$2,242</td>
<td>$2,384</td>
<td>$2,395</td>
<td>9%</td>
<td>$284</td>
</tr>
<tr>
<td>Total Impact on Pathology Specialty 2019-2025</td>
<td>$1.5 billion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Projections based on ten previous years of Medicare spending
**All dollar figures listed in $ millions

What is an eligible APM?

- A model under the Center for Medicare and Medicaid Innovation (CMMI)
- Medicare Shared Saving Program ACO
- A Health Care Quality Demonstration project
- APMs base payment on quality measures comparable to those under MIPS
- Require certified EHR technology
- Either bear more than nominal financial risk OR are a medical home under CMMI
### Qualifying for APM Bonuses

<table>
<thead>
<tr>
<th>Year</th>
<th>Medicare Only, % Payments in An Eligible APM</th>
<th>All Payer, % of Payment in An Eligible APM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019-2020</td>
<td>25%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>2021-2022</td>
<td>50%</td>
<td>25% Medicare 50% all payer</td>
</tr>
<tr>
<td>2023-2024</td>
<td>75%</td>
<td>25% Medicare 75% all payer</td>
</tr>
<tr>
<td>2025 and beyond</td>
<td>75%</td>
<td>25% Medicare 75% all payer</td>
</tr>
</tbody>
</table>

Qualifying physicians (QPs) in eligible APMs are excluded from MIPS and receive annual 5% bonuses for 2019 through 2024. In 2025, bonuses drop to 0.75% vs. 0.25% for non-QPs.

### MIPS: Pathologists Face Hurdles

- **PQRS**
  - Eight measures continued through 2016 but high performance may lead to discontinuation by CMS.
  - Value-Based Modifier (VBM) program is designed for primary care specialties and generally does not measure the value that pathologists provide to their patients.

- **Resource Use**
  - CAP has suggested activities that pathologists could successfully report.

- **Clinical Practice Improvement Activities**
  - CAP has secured relief from MU penalties through 2016, but it is not known how CMS will score pathologists on this category.

### CAP Economic Affairs Committee (EAC) has formed a Special MACRA Workgroup

- Ensure pathologists can comply with MIPS
- Engaging CMS on defining metrics that could get pathologists credit for clinical improvement activities
- Preparing members who opt for APM participation
- Proposed rule for MACRA expected in spring 2016
- Stay tuned to future updates on MACRA through STATLINE and upcoming webinar.

### Protecting Access to Medicare Act (PAMA)

- **Implementation of PAMA**
  - Establishes reporting requirements for labs, data used to set reduced CLFS reimbursements:
    - 10% 2017–2019
    - 15% 2020–2022
  - CMS issued a delayed proposed rule on September 25, 2015
  - Final rule, by statute, is overdue
  - CAP calling for data collection and data submission deadline extensions

### Implementation of PAMA

**CAP is advocating with CMS on PAMA:**

- Scope of entities required to submit data must be broadened
- Proposed limited scope of reporting entities reduces low expenditure threshold and revises majority of revenue definition based on Medicare lab revenues rather than Medicare revenue from the entire organization
- More specifics needed on reporting requirements

### Keep Informed...

- On the latest Advocacy efforts through STATLINE weekly issues and special alerts
- With webinars throughout 2016 on:
  - Final PAMA regulation
  - FDA guidance on LDT oversight
  - 2017 Medicare Physician Fee Schedule
  - Other emerging issues
- By attending the CAP Policy Meeting
2016 CAP Policy Meeting

- May 2-4 in Washington, DC
  - Register at CAP.org
- Receive insights from CMS and FDA officials and health policy leaders
  - e.g. Panel on MACRA, MIPS, APMs
  - Keynote speakers: David Gregory and Harold Miller
- Engage with members of Congress during the CAP's Annual Hill Day