Invasive Breast Cancer
Special Types

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Section Chief of Breast Pathology
Breast Cancer

- Complex and multifaceted disease
- Include great variety of entities
- Show considerable variation
  - Clinical
  - Morphologic
  - Molecular
Breast Cancer Morphology

Heterogeneous
Breast Cancer Prognosis

Grade 1 vs 3

Stage size and LN status

[Graphs showing cumulative survival over time for different grades and stage sizes.]
Problems Remain

• Same type differing behavior
• Same grade/stage differing behavior
• Same treatment differing response
Classification of BC

• In situ vs Invasive
• Histologic subtype
  – Mostly Ductal, NOS
  – Special subtypes
• Grade
Histologic Types of BC

- Ductal
- Lobular
- Tubular
- Cribriform
- Medullary
- Mucinous
- Apocrine
- Papillary
- Micropapillary
- Metaplastic
- Secretory
- Lipid rich
- Oncocytic
- Adenoid cystic
- Acinar
- Clear Cell
- Sebaceous
- Neuroendocrine
Histologic Types of BC

- Invasive ductal carcinoma (pure) = 55%
- Invasive ductal carcinoma (mixed) = 25%
- Invasive lobular carcinoma = 10%
- Medullary carcinoma = 2%
- Tubular carcinoma = 4%
- Mucinous carcinoma = 2%
- Others = 2%
# Histologic Types of BC

## Categorization of Special Types of Invasive BC Based on Prognosis

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Intermediate</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
<td>Medullary</td>
<td>HG Metaplastic</td>
</tr>
<tr>
<td>Cribriform</td>
<td>Secretory</td>
<td>Micropapillary</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Invasive Lobular (classic type)</td>
<td>Signet Ring Cell</td>
</tr>
<tr>
<td>Adenoid Cystic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Protein Expression Subtypes

- What proteins does the cancer express in abnormal levels?
- Hormone receptors
- HER2 over-expression
- Proliferation markers

[Image showing histological sections with labels: ER/PR, Her-2, Ki-67]
BC Subtypes by Gene Expression Profiling

Intrinsic Subtypes
Perou et al., Nature, 2000
Sorlie et al., PNAS, 2003
Usary et al., Oncogene, 2004
Parker et al., JCO, 2009
Prat et al., BCR, 2010
Prat et al., JCO, 2012
Dowsett et al., JCO, 2013
Sestak et al., JNCI, 2013
Luminal Type Carcinomas

<table>
<thead>
<tr>
<th>Luminal-A</th>
<th>Luminal-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Good prognosis with endocrine therapy</td>
<td>• Poor outcome with endocrine therapy alone</td>
</tr>
<tr>
<td>• Low sensitivity to chemotherapy (pCR=5%)</td>
<td>• Moderately sensitive to chemotherapy (pCR=20%)</td>
</tr>
<tr>
<td>• &gt;50% are low grade</td>
<td>• &gt;50% are high grade</td>
</tr>
<tr>
<td>• Low proliferation rate</td>
<td>• High proliferation rate</td>
</tr>
<tr>
<td>• Low p53 mutation rate</td>
<td>• p53 mutation is common</td>
</tr>
<tr>
<td>• MammaPrint low risk</td>
<td>• MammaPrint high risk</td>
</tr>
<tr>
<td>• Oncotype DX low risk</td>
<td>• Oncotype DX high risk</td>
</tr>
<tr>
<td></td>
<td>Luminal A</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Proliferation:</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>PR and FOXA1:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ER:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mutation rate:</strong></td>
<td>Similar (14%)</td>
</tr>
<tr>
<td><strong>Copy # changes:</strong></td>
<td>Low (12%)</td>
</tr>
<tr>
<td><strong>P53 mutations:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>GATA3 mutations:</strong></td>
<td>Similar (14%)</td>
</tr>
<tr>
<td><strong>PIK3CA mutations:</strong></td>
<td>More (45%)</td>
</tr>
</tbody>
</table>
## Intrinsic Subtype Characteristics

<table>
<thead>
<tr>
<th>Molecular Subtypes:</th>
<th>Basal</th>
<th>HER2-E</th>
<th>Luminal B</th>
<th>Luminal A</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of breast cancers:</td>
<td>15-20%</td>
<td>10-15%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Receptor expression:</td>
<td>HER2+</td>
<td>ER+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic grade:</td>
<td>High grade</td>
<td>Low grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis:</td>
<td>Poor</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to therapy:</td>
<td>Chemotherapy</td>
<td>HER2 Rx</td>
<td>Hormone Rx</td>
<td></td>
</tr>
</tbody>
</table>
Basal-like Subtype

- Most unique and robust subtype
- More similar to ovarian serous carcinoma than other BC subtypes
- Most frequent subtype in BRCA1+ pts
- Different ethnic distribution = more common in African Americans
- Different age range = younger
- Risk factors: Increased parity, less time breast feeding

Sorlie et al., Proc Natl Acad Sci U S A 2003 July 8; 100(14): 8418–8423
## Luminal and Basal-like Cancer

<table>
<thead>
<tr>
<th>Luminal</th>
<th>Basal-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 40% of first relapses occur in the bone</td>
<td>• 8% of first relapses occur in the bone</td>
</tr>
<tr>
<td>• Hazard of recurrence is prolonged over 10-15 years</td>
<td>• Hazard drops steeply after first 3 years</td>
</tr>
<tr>
<td>• Variable grade</td>
<td>• 85% are high grade</td>
</tr>
<tr>
<td>• Responds to endocrine thx</td>
<td>• No response to endocrine thx</td>
</tr>
<tr>
<td>• Extreme chemotherapy sensitivity is rare (pCR = 8%-10%)</td>
<td>• Extreme chemotherapy sensitivity is relatively common (pCR = 25%-35%)</td>
</tr>
<tr>
<td>• Variable proliferative rate</td>
<td>• High proliferative rate</td>
</tr>
</tbody>
</table>
Basal-like Breast Cancer

- Heterogeneous group of tumors
- 12-20% of all BCs
- Some special histologic types of BC consistently display basal like phenotype
Basal-like Breast Cancer

BL1: Basal-like 1
BL2: Basal-like 2
IM: Immunomodulatory
M: Mesenchymal-like
MSL: Mesenchymal Stem Like
LAR: Luminal; Androgen Receptor

Basal-like Breast Cancer

• Clinical features
  – Younger patients (47-55 yrs)
  – African American women
  – ? Hispanic women
  – Interval cancers
  – BRCA-1 mutations
  – Prevalence of brain and lung metastases
  – Early metastases (2-3 yrs)
Basal-like Breast Cancer

- More aggressive
  - Higher rate of relapse
  - Decreased OS in metastatic disease
- Subsets of pts respond well to standard chemotherapy
- Pts achieve pCR after NAC have survival rates similar to those with non-TNBC
BRCA1 and Sporadic BLBC

- Most BC in BRCA1 mutation carriers are basal-like
- Most basal-like BC are not in BRCA1 mutation carriers
- Defects in Homologous Recombination
  - 30-40% of TNBC without BRCA mutation
Basal-like Breast Cancer

BL-1: cell cycle, DNA repair and proliferation genes

BL-2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

- 40-60% of BLBCs
- EGFR pathway activation
- IGFR1R pathway activation
- ?BRCA1 carriers?
- p53 mutant
- Highly proliferative

Immunomodulatory Basal-Like BC

- 10-15% of BLBC
- enriched in immune cell processes
- medullary BC
- ?BRCA1 carriers
- p53 mutant

IM: immune cell Processes

Mesenchymal-like Subtypes

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

- 20-30% of BLBCs
- cell motility
- EMT
- angiogenesis
- BRCA1 carriers?
- p53 mutant
- PIK3CA mutations
- MSL- low expression of proliferation genes
Breast Cancer Classification

How do conventional histologic classes relate to molecular subtypes?
Breast Carcinoma

Mucinous Ca

Tubular Ca
TNBC and Basal-like Breast Ca

- 15-30% are ER+, PR+, or HER2+
- 75% TNBC and Basal-like

Triple negative but not basal 10-30%

Basal but not triple negative 15-30% are ER+, PR+, or HER2+
Histopathologic Types of BC

- Ductal
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- Adenoid cystic
- Acinic cell
- Clear Cell
- Sebaceous
- Neuroendocrine
T N B C: Histopathologic Features

- **Pushing borders**
- **High grade**
- **High proliferation**
- **Lymphocytic stroma**
- **Myofibroblastic stroma**
- **Geographic necrosis**
T N B C: Histopathologic Features

- Expansile/pushing margins
- Poorly differentiated
- Solid architecture
- Absence of tubules and glands
- Lymphocytic infiltrate
- High mitotic index
- Geographic necrosis
- Central fibrotic, acellular zones
Immunoprofile of T N B C

- ER-, PR-, HER2-
- Expression of basal keratin
  - CK14, CK17, CK5/6
- EGFR and c-kit expression
- Vimentin +

These are also features of the normal myoepithelial cells and tumors with myoepithelial differentiation
“Triple Negative Immunophenotype”:
ER –
PR –
Her2 –

Ki67 index HIGH
T N B C: IHC Features

CK5/6

CK14

EGFR

CK8/18

C-KIT
TNBC Are Heterogeneous

- IDC NOS, high grade
- ILC high grade, pleomorphic
- High grade metaplastic
- High grade myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Medullary
- Adenoid-cystic/Acinic cell
- Secretory
- Metaplastic, low grade
  - Low-grade adenosquamous
  - Fibromatosis-like
Medullary Carcinoma

Morphological Criteria
- Good limitation
- Solid growth > 75%
- Lack of tubular structures
- Atypical nuclei
- High mitotic rate
- Moderate to marked inflammatory infiltrate
Medullary Carcinoma
Medullary Carcinoma

- Women with BRCA1 mutation: 30% MBC
- 15% of MBC occur BRCA1+
- Prognosis better than high grade IDC
- 10-year survival from 50 to 90%
- 90% MBC are N0
- Very good chemo and radiosensitivity
Overall survival depending on the type and histological grade

Overall survival in grade III tumors depending on the type and stromal inflammation

1579 patients operated on between 1974 and 1988 - No adjuvant treatment

Rakha et al Eur J Cancer 2009, 45, 1780-1785
Immunomodulatory Basal-Like BC

- 10-15% of BLBC
- enriched in immune cell processes
- medullary BC
- ?BRCA1 carriers
- p53 mutant

IM: immune cell Processes

Prognostic Value of TILs

All Patients

TNBC

PD-L1 in TNBC

Metaplastic Carcinoma

Heterogeneous group of tumors

pure epithelial form
- squamous/adenosquamous ca
- ca with spindle cell metaplasia
- mucoepidermoid ca

mixed forms (epithelial/mesenchymal)
- ca with chondroid or osseous differentiation
- matrix producing ca
- carcinosarcoma
- high grade sarcomatoid ca
Metaplastic Carcinoma

- 1% of breast cancer
- Large tumors, often rapid growth
- EGFR activation, wnt pathway activation, BRCA methylation
- Low rate of lymph node involvement
- Poor overall survival
  - 70% at 3 years
  - 55% at 5 years
Metaplastic Carcinoma
Metaplastic Carcinoma
PI3K Aberrations

- High incidence of PIK3 pathway activating aberrations
- VEGF/HIF1-a production
Better Response in Metaplastic TNBC

P=0.02

P=0.44

Basho et al AACR 2016
Response Higher in Metaplastic Cancers with PI3K Aberrations

Basho et al. JAMA Oncology, 2016
Secretory Carcinoma

- <1% of breast ca
- 1/3 children and teens
- 2/3 between 20 and 50yrs
- Good prognosis
- Specific molecular alteration
  \[ t(12;15) \text{ (ETV6; NTRK3)} \]
Secretory Carcinoma

- Rare variant of invasive ductal carcinoma
- First described in children as “juvenile carcinoma”
- A wide range of ages (3-87 years), most of pts are adults (mean age, 25)
Secretory Carcinoma

- Well circumscribed slow-growing mobile mass with lobulated margins and white-to-tan cut surface
- size ranges from 1-12 cm (median, 3 cm)
Secretory Carcinoma

- Abundant intracellular and extracellular secretions
- Growth patterns:
  - Nested cysts
  - Cribriform
  - Papillary
  - Solid
  - Trabecular
  - Glandular/tubular
Reciprocal Translocation (12;15)

ETV6 - NTRK3 is the molecular signature

12p13 der(12)t(12;15)(p13;q25) der(15)t(12;15)(p13;q25) 15q25

ETV6-NTRK3
Secretory Carcinoma
Potential Targeted Therapy

- NTKR 3 (Neurotrophic Tyrosine Kinase, Receptor, Type 3) inhibitors
Prognosis

- Usually excellent
- Regional nodal metastasis may occur at the time of diagnosis
- Distant recurrence may occur and fatal
Adenoid Cystic Carcinoma

• Definition
  – Identical to salivary gland counterpart
  – May be associated with microglandular adenosis

• Epidemiology
  – Rare, 0.1% of breast carcinomas
  – Mean age 50-63 years, range 25-80 years
  – 50% are sub-periareolar
2 types of lumens
  – True lumen lined by acinar/glandular cells with secretions
  – Pseudolumen lined by basal cells contains basement membrane material
Adenoid Cystic Carcinoma

CK5/6

CK14

CK17

C-kit
Adenoid Cystic Carcinoma

• Treatment and prognosis
  – Good to excellent prognosis
  – Recurrence or metastasis are less than usual ductal carcinoma
  – Axillary nodal metastases are rare
  – Treatment is excision with clear margins, possibly radiation, axillary dissection may not be necessary
Adenoid Cystic Carcinoma

Grading scheme:
grade I: complete glandular/cystic
grade II: solid component <30%
grade III: solid component >30%

Ro JY et al. Hum Pathol 1987;18(12):1276
Recurrent t(6;9) in ACC

Modified from Clin Cancer Res 2010 Oct 1;16(19):4722-31
Different Morphology - Different Biology - Different Prognosis

80% 5-10% 5-10% 3% 2%

IDC
Grade III

Medullary

Metaplastic

Adenoid cystic

Low grade adeno-squamous

Different Therapy Options
Targeting Subtypes

• Distinctly different subtypes
• Challenges grouping diverse biology into a limited number of categories
• Stroma likely matters
Cancer stem cell markers are enriched in normal tissue adjacent to triple negative breast cancer and inversely correlated with DNA repair deficiency

Rachel L Atkinson¹, Wei T Yang², Daniel G Rosen⁶, Melissa D Landis⁷, Helen Wong⁷, Michael T Lewis⁵, Chad J Creighton⁵, Krystal R Sexton⁵, Sue G Hilsenbeck⁵, Aysegul A Sahin⁴, Abenaa M Brewster¹, Wendy A Woodward³+ and Jenny C Chang⁷+⁺
Cellular Stroma of T N B C
Summary

- Triple-negative BC is not a single disease entity
  - Differences in chemosensitivity
  - Differing potential therapeutic options for resistant disease
- Much of the biology of TNBC is now being defined
- No single target for TNBC
- Several promising “targeted” options are being tested
ER
Dextran coated charcoal beads to quantify ER

Immunohistochemistry for ER on tissue sections

New molecular subtypes
- Claudin-low
- Molecular apocrine
- Interferon-related

Massively Parallel Sequencing
TCGA (>500 tumours)
ICGC (>100 tumours)
Data analysis across multiple platforms (DNA copy number arrays, DNA methylation, exome sequencing, RNA arrays and sequencing, protein arrays)

Integrated gene expression and DNA copy number analysis
METABRIC
(2,000 breast cancers)
→ 10 integrative clusters

Loss of Heterozygosity (LOH) and Comparative Genomic Hybridization (CGH)
(losses, gains and amplifications of genomic DNA sequences)

cDNA microarray based gene expression profiling
Intrinsic molecular subtypes associated with distinct clinical outcomes:
- Luminal A & B
- Basal-like
- HER2-enriched
- Normal breast-like

Gene expression based prognostic signatures
- Oncotype DX®
- MammaPrint®
- PAM50

Targeted gene sequencing cancer gene panels

Breast Cancer Classification


Targeted Therapies
Immunotherapy

1970
1990
2000
2010
2014
2020

Intrinsic molecular subtypes associated with distinct clinical outcomes:
- Luminal A & B
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Targeted gene sequencing cancer gene panels

Immunotherapy
Targeted Therapies
Breast Cancer

Ideal Classification Method

• Distinguish different prognostic categories among patients with similar clinical features and tumor characteristics

• Predict response to various therapy types in an individual patient
Pathologists as “Diagnostic Oncologists”

Translation and integration of biologic information

Treatment Team

Patient Factors

Individualized Treatment Decisions