Rare Breast Cancers and Male Breast Cancer

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Breast Cancer

• Primary Cancers (97% of breast malignancies)
  – Epithelial
  – Non-epithelial
    • Phyllodes
    • Sarcoma
    • Lymphoma

• Secondary Cancers (3% of breast malignancies)
  – Metastases from contralateral breast cancer (87%)
  – Non-breast metastases (in order of frequency)
    MSKCC, Mod Path 2013;26:343-349
    • Sarcoma
    • Melanoma
    • Ovarian serous
    • Lung
Rare Breast Cancers

- Phyllodes Tumor
- Encapsulated Papillary Carcinoma
- Metaplastic Carcinoma
- Small Cell Carcinoma
- Male Breast Cancer
A Large Breast Mass in 13 Year Old Girl
Phyllodes Tumor

**Fibroadenoma:** Developmental abnormality of a lobule

**Phyllodes Tumor:** Neoplasm of mammary stromal cells

Some evidence that phyllodes can arise from fibroadenoma (uncommon)
The Diagnosis was Benign Phyllodes Tumor
Classification and Biology of Phyllodes Tumors

Classifications
- Low grade
- Intermediate
- Malignant

Features
- Cellular atypia
- Mitoses
- Margin characteristics
- Stromal cellularity

Recognized as inadequate for reliably predicting behavior

Biology

Enormous inter-tumoral and intra-tumoral heterogeneity
Epithelium/Stroma may be monoclonal or polyclonal
Epithelium and stroma may be clonally linked
Extensive chromosomal abnormalities
  - Loss of p53 and p16 function
  - Activating mutations in NRAS

miR-21 reduces Smad-7 and PTEN activating myofibroblasts

Phyllodes

• *Benign and intermediate types* difficult to distinguish from fibroadenoma without excision.

• *Phyllodes* can metastasize – LUNG

• **Local Recurrence Risk**
  – ~20% at 20 years (same for benign and malignant)
  – 26% of benign phyllodes recur as malignant

*Strongest Predictors*
– Fibroproliferation in surrounding breast tissue
– Necrosis

Margin status influences time course of recurrence but not absolute recurrence rate

Chaney AW, Cancer 2000;89:1502-11

Ann Surg Oncol 2007;14:2961-2970
Ann Surg Oncol 2014;21:3304-3309
Phyllodes: Rare Cancer Network

Median Follow-up: 106 months
Local Recurrence: 19%
Distant metastases: 3.4%

Predictors of Local Control
- Benign histology
- R0 resection
- Radiation therapy

N = 443

Benign  Borderline  Malignant

LR = 0% for 46 borderline or malignant phyllodes treated with excision + RT and followed for a median of 56 mo.

Staging and Treatment of Phyllodes

• ? Chest X-ray or Chest CT (Malignant)
• Local excision with a 1 cm margin
  – Mastectomy if cosmetic local excision cannot be achieved
• Axillary dissection for path node positive only (rare)
• Radiation is still controversial but could be considered for:
  – Intermediate and malignant tumors treated by breast conservation.
  – Large tumors (e.g. >10 cm) regardless of surgery type
Encapsulated Papillary Carcinoma

- Arise in dilated ducts, not simple cysts
- Separated from surrounding stroma by a dense fibrous capsule

Rodriquez MCH, el al. RadioGraphics 2010;30:2021-2027
Encapsulated Papillary Carcinoma

*Is it in situ or invasive?*

Often lacks a myoepithelial layer (smooth muscle myosin)

Usually expresses Collagen IV (like DCIS)

**Two Viewpoints (both are likely correct)**

EPC constitutes a spectrum of intraductal and invasive carcinoma

EPC is a low risk invasive cancer with an expansile growth pattern


Encapsulated Papillary Carcinoma

Main Sub-types

Intracystic Papillary Carcinoma

- Associated DCIS: 70%
- Associated Invasive Cancer: 13–32%
- LN positive: 3%

Solid Papillary Carcinoma

- Associated DCIS: 67%
- Associated Invasive Cancer: 45–80%
- LN positive: 12%

Intracystic Papillary Carcinoma

California Cancer Registry 1988 - 2005
N = 917
Mean age: 69.5 years
47% in situ
53% invasive
7.8% of invasive regional (direct extension or nodes)
0.4% metastatic

Encapsulated Papillary Carcinoma

1-2% of breast cancers
Mean age ~70.
Can be diagnosed in men

Treatment
Wide local excision and SLN biopsy

Presentation
• palpable mass
• imaging abnormality
• bloody nipple discharge

Adjuvant therapy guided by associated pathology
• Lymph node status
• Associated DCIS
• Associated invasive cancer

Tumor Features
• Rarely high grade
• Usually ER(+)PR(+)HER2(-)

Value of radiation unclear for pure IPC
Metaplastic Breast Cancer

A breast epithelial malignancy with mesenchymal/myoepithelial differentiation.

Some classify as a basal phenotype breast cancer.

May have worse DFS and OS than TNBC

*J Clin Pathol* 2012;65:441-446

*Breast Cancer Res Treat* 2012;131:41-48

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Squamous Cell Carcinoma

Spindle Cell Carcinoma

Matrix Producing Carcinoma

Carcinoma with Central Acellular zones (CAC)

Rapidly metastasizing to the lung and brain


## Metaplastic vs. Usual Ductal Carcinoma

### National Cancer Database

<table>
<thead>
<tr>
<th></th>
<th>Metaplastic</th>
<th>Usual Ductal</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>892</td>
<td>255,164</td>
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<tr>
<td>Mean age</td>
<td>61.1</td>
<td>59.7</td>
<td>0.001</td>
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<tr>
<td>Black</td>
<td>14.1%</td>
<td>10.2%</td>
<td>0.001</td>
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<tr>
<td>Hispanic</td>
<td>5.5%</td>
<td>3.9%</td>
<td>0.001</td>
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<tr>
<td>T1</td>
<td>29.5%</td>
<td>65.2%</td>
<td>0.001</td>
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<tr>
<td>N0</td>
<td>78.1%</td>
<td>65.7%</td>
<td>0.001</td>
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<tr>
<td>Poorly Differentiated</td>
<td>67.8%</td>
<td>38.8%</td>
<td>0.001</td>
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<tr>
<td>ER(+)</td>
<td>11.3%</td>
<td>74.1%</td>
<td>0.001</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>38.5%</td>
<td>55.8%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Molecular Biological Features of Metaplastic Breast Cancer

Correlation with the CD44+/CD24-/low gene expression profile

Poster Child for Epithelial-to-Mesenchymal Transition

- Dysregulation of the wnt pathway
  Clin Cancer Res 2008;14:4038-4044

- Expression of Laminin-5

- PI3K mutations or loss of PTEN (~50%)
  Cancer Res 2009;69:4116-4124

- VEGF production
Phase 1 Trial of DAT in Chemo-refractory Metaplastic Breast Cancer

- **Phase I Clinical Trial**
- Liposomal doxorubicin 20-30mg/m² IV every 3 weeks
- Bevacizumab 15mg/kg IV every 3 weeks
- Temsirolimus 25mg IV monthly

- **N = 14 patients (10 evaluable)**
- Median of 2 prior regimens
- Response rate 30%
  - CR (1)
  - PR (2)
  - SD (3)

- Responses more common in sarcomatoid/spindle cell variety

Moulder S, J Clin Oncol 2011;29:e572-e575
Metaplastic Carcinoma - Summary

• A breast epithelial cell malignancy
• Basal phenotype, CD$^{44+}$CD$^{22-}$/low-like, EMT
• BRCA1-deficient-like. Platins? PARP inhibition?
• Pulmonary metastases most common
• Generally resistant to standard chemotherapy
  – 1 cCR with DAT - J Clin Oncol 2011;29:e572-e575
  – Neoadjuvant pCR rate 10% (same as TNBC in this series) J Clin Pathol 2012;65:441-446
  – Known pCR with paclitaxel, bevacizumab, and carboplatin.
• Staging and treatment currently the same as other ductal cancers.
Primary Small Cell Carcinoma

Median Age: 55 years (41 – 71)
Median Size: 3.5 cm (1.3 – 14.5)
LN positive: 68%
Associated DCIS: 71%
ER Positive: 35%
Neuroendocrine markers: 60%

• Alternate differentiation pathway for breast epithelial cells
• Exclude Metastatic Carcinoma from Non-breast Primary (e.g. Lung)
  – No clinical evidence for non-breast primary
  – Associated DCIS
  – Areas of ductal, lobular or papillary differentiation

Tumori 2011;97(4):473-8
Primary Small Cell Carcinoma

Treatment

- Multimodal as for any advanced primary breast cancer
  - FAC, FEC, CMF, cisplatin, VP-16
- Neoadjuvant chemotherapy where appropriate
  - One pCR reported with VP-16 and cisplatin
- Mastectomy or breast conservation as appropriate
- Radiation as per usual indications

Prognosis, stage for stage, should be similar to other breast cancers
Male Breast Cancer

• <1% of cancers in males
• 0.7% of all breast cancers
• Incidence is increasing slightly
• Major risk factors related to imbalance in testosterone versus estrogen.
  – Risk factors for gynecomastia are risk factors for MBC
Male Breast Cancer Incidence and Outcome Trends

The incidence of male breast cancer is 114-times lower than female breast cancer.

The incidence of MBC is increasing slightly.

Outcome for male and female breast cancer is improving.

Anderson, Breast Cancer Research Treat 2004;83:77-86
Risk Factors for Male Breast Cancer

• Genetic
  – BRCA1/2 (5 – 13% of MBC) J Natl Cancer Inst 2007;99:1811-4
    • BRCA1 1.2% lifetime risk
    • BRCA2 6.8% lifetime risk
    • PALB2, PTEN, CHK2, CYP15 polymorphisms
  – Klinefelter’s Syndrome (XXY) – RR 19 – 58 Acta Paediatrica. 2011; 100:814-8
  – Family history of breast cancer

• Reduced Testosterone/Estrogen
  – Obesity
  – Estrogen or anti-androgens (prostate cancer treatment)
  – Liver disease
  – Testicular dysfunction

• Environmental/Occupational
  – High ambient temperatures
  – Exhaust emissions
  – Alcohol

• Chestwall Radiation
Male Breast Cancer Pooling Project

11 case-control and 10 cohort studies
2405 cases
52,013 controls

History of fracture for >66 y/o OR 1.41 (95% CI 1.07-1.86)

Characteristics of Male Breast Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Postmenopausal Female</th>
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<tbody>
<tr>
<td>Median Age</td>
<td>67</td>
<td>62</td>
</tr>
<tr>
<td>High Grade</td>
<td>40%</td>
<td>37%</td>
</tr>
<tr>
<td>DCIS</td>
<td>4 - 10%</td>
<td>25 – 30%</td>
</tr>
<tr>
<td>Lobular Histology</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>Papillary Histology</td>
<td>2 – 5%</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Lymph Node Positive</td>
<td>40%</td>
<td>29%</td>
</tr>
<tr>
<td>Estrogen receptor (+)</td>
<td>88%</td>
<td>80%</td>
</tr>
<tr>
<td>Progesterone receptor (+)</td>
<td>86%</td>
<td>68%</td>
</tr>
<tr>
<td>Androgen receptor (+)</td>
<td>39 – 95%</td>
<td>48 – 78%</td>
</tr>
<tr>
<td>Her-2/neu (+)</td>
<td>2 - 5%</td>
<td>20 – 25%</td>
</tr>
</tbody>
</table>

Usually ER-positive (90%)
Usually Luminal A (75%)

Intrinsic Subtypes by IHC

- Luminal A
- Luminal B
- Basal
- TNBC_other

Mod Pathol 2012;25:398-404
Mean Expression of 21-gene RS Genes in Males (347) and Females (82,434)

Shak et al., ASCO 2009, #549

Distribution of RS is the same for female and male breast cancer

Oncology 2014;87:1-6
Aromatase Inhibition is Controversial in Male Breast Cancer

Animal Data
Reduced estradiol may trigger an increase in FSH which may increase testicular testosterone production.

Human Data
AI’s increase testosterone AR signaling may be very important in male breast cancer *Breast Cancer Res Treat* 2011;127:601-10

Conclude
• Tamoxifen is first line hormonal therapy in men
• Letrozole + Leuprolide acetate may be effective second line

*Breast Cancer Res Treat* 2014;147:227-235
Aromatase Inhibitors in Male Beast Cancer

Experience in Metastatic Breast Cancer
- Objective responses have been reported
- Response after progression on AI has been reported for
  - Changing to a different AI
  - Adding a GnRH agonist

Adjuvant AI vs. Tamoxifen
A German cancer registry study
N = 257

Breast Cancer Res Treat 2013;137:465-470

Clinical Trials
Phase II adjuvant, neoadjuvant and metastatic trial is accruing (German)
Phase III exemestane +/- entinostat in advanced/metastatic includes MBC
# Sentinel Node Biopsy in Male Breast Cancer

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<tr>
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<th>MDACC</th>
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<th>MSKCC</th>
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<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Number</td>
<td>30</td>
<td>2,784</td>
<td>78</td>
</tr>
<tr>
<td>SLN Identification</td>
<td>100%</td>
<td>98.3%</td>
<td>97%</td>
</tr>
<tr>
<td>Mean # SLN</td>
<td>3.0</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>SLN (+) Rate</td>
<td>37.0%</td>
<td>22.3%</td>
<td>49%</td>
</tr>
<tr>
<td>Non-SLN(+) rate</td>
<td>62.5%</td>
<td>20.7%</td>
<td></td>
</tr>
<tr>
<td>Median largest met</td>
<td>10 mm</td>
<td>3 mm</td>
<td></td>
</tr>
</tbody>
</table>

Sentinel node biopsy is a valid approach for axillary staging in men

Flynn LW, J Am Coll Surg 2008;206:616-621
Male Breast Cancer - Outcome

Stage for stage the outcome of male breast cancer is the same as female breast cancer

Matched case-case studies
- BMC Cancer 2011;11:335

Population-based Study
- (better relative survival)
- J Clin Oncol 2011; 29:4381-6

Stage for stage the outcome of male breast cancer is worse than female breast cancer

Matched case-case study.
- Use of adjuvant therapies the same between groups
- Acta Oncologica 2011;50:1083-1088
# Second Primary Cancers

<table>
<thead>
<tr>
<th>Standardized Incidence Ratios</th>
<th>Sweden</th>
<th>SEER</th>
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<tbody>
<tr>
<td>Number MBC</td>
<td>3,409</td>
<td>1,788</td>
</tr>
<tr>
<td>Contralateral Breast Cancer</td>
<td>93.1</td>
<td>29.6</td>
</tr>
<tr>
<td>Any Non-breast Cancer</td>
<td>1.34</td>
<td>0.99</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.29</td>
<td>2.41</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.61</td>
<td>1.09</td>
</tr>
<tr>
<td>Liver, gallbladder, bile ducts</td>
<td>1.07</td>
<td>1.51</td>
</tr>
<tr>
<td>Small intestine</td>
<td>4.95</td>
<td>NR</td>
</tr>
<tr>
<td>Myeloid leukemia</td>
<td>3.42</td>
<td>NR</td>
</tr>
<tr>
<td>Lymphoid leukemia</td>
<td>1.86</td>
<td>NR</td>
</tr>
</tbody>
</table>

Swedish: 12.5% risk of non-breast malignancy

Hemminki (Sweden), Br J Cancer 2005;92:1288-1292
Auvinen (SEER), J Natl Cancer Institute 2002;94:1330-1332
Male Breast Cancer Treatment Guidelines

Surgery
- Modified radical mastectomy
- Total Mastectomy and sentinel node biopsy
- Nipple preservation has been reported
  Breast 2007;16:653-6

Radiation
- T3 or T4
- $\geq 4$ (+) LN

Chemotherapy
- $> 1$ cm
- LN (+)
- Other adverse prognostic markers (21-gene Recurrence Score?)

Hormonal Therapy
- Tamoxifen for ER (+)
A Few Take Home Points

• **Phyllodes:** Renewed interest in RT for borderline and malignant tumors.

• **Encapsulated Papillary Carcinoma:** A very good prognosis breast cancer. Don’t over treat.

• **Metaplastic:** a basal type breast cancer that may be more responsive to “BRCA1-like” treatments.

• **Primary Small Cell Carcinoma:** An aggressive extrapulmonary small cell carcinoma frequently with neuroendocrine differentiation. Treat like small cell carcinoma.

• **Male Breast Cancer:** Aromatase inhibitors are still controversial, tamoxifen is standard.