Illinois Medical Oncology Society

ER+/PR– Breast Cancer
Pathology and Outcome Correlations from a single center cohort study

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University of Illinois at Chicago
Background

- Estrogen, Progesterone and their receptors, play key roles in breast cancer (BCa) development and progression

- ER signaling is necessary to induce PR expression and >50% of ER+ BCa express PR

- HER2 – cell membrane receptor involved in cell growth and differentiation, overexpressed in 30% of BCa
Background

- Current Guidelines
  - stratify patients into prognostic subsets
  - suggest preferred treatment protocols on the basis of reported estimates of efficacy

- Treatment for early BCa is defined by:
  - ER
  - PR
  - HER2

- Other markers have been assessed, such as Ki67, but not included in current paradigm

Yerushalmi et al, Lancet Oncology 2010; 11: 174-83
Current clinical view of Bca (based on ER, PR and HER2 status)

- ER+: best variant, effective strategies to block, downgrade or deprive ER of its efficacy
- HER2+: amenable to management by HER2-blocking therapies
- TNBC: worst category, no easy targets to block; though poly-ADP ribose polymerase inhibitors seem promising
- ER+/PR- ???
Background

- ER and PR are both weak prognostic factors

- 70% of BCa are ER+, sensitive to endocrine therapy, while ER- tumors are hormone independent

- Based on this, currently the treatment for ER+/PR+ and ER+/PR- tumors is similar

Background

- Clinical studies suggest PR- is associated with:
  - Lower levels of ER expression
  - More positive nodes
  - Aneuploidy
  - Larger tumor size
  - Higher rates of proliferation
  - Higher expression of EGFR and HER2
  - Tamoxifen-resistance

Background

Molecular studies suggest PR- is due to:

- Low serum Estrogen
- Estrogen pathway Switch from Nuclear to Membrane initiated steroid signaling due to High growth factor signaling (HER, PI3k/Akt/mTOR)
- Hypermethylation of PR promoter
- Loss of heterozygosity at Progesterone gene locus

Therefore, both clinical and molecular studies suggest that ER+/PR- tumors may be a distinct subset of Bca

Genetic profiling

- There are specific gene expression signature patterns of ER+/PR+ and ER-/PR- Bca

- ER+/PR- tumors share gene expression patterns with both ER+/PR+ and ER-/PR- with 3 possible types:
  - ER+/PR+ signature (? False IHC)
  - ER-/PR- signature (? False IHC)
  - Neither ER+/PR+ or ER-/PR- signatures

Genetic profiling predictive power

- Patients with tumors designated as ER+/PR- by profiling rather than by clinical assay alone (neither ER+/PR+ or ER-/PR- signatures):
  - Have poorer prognosis (at least as bad as ER-/PR- tumors)
  - Show increased DNA copy number alteration
  - Gene signature of oncogenic pathway PI3K/AKT/mTOR is manifest

Objective

We sought to

- Describe the characteristics of patients treated for ER+/PR- BCa at a large, academic center
- Compare ER+/PR- to ER+/PR+ patients
- Evaluate outcomes achieved with current treatments
- Establish predictors of worse outcomes
Methods

- All pts with dx of Bca biopsied at UIC between 2005-2010 were included in a database
- Extensive electronic medical records review
- Data collected: demographic, medical, obstetric, pathologic, treatment and outcome
- IRB approval
- Standard statistics (p<0.05 significant)
Methods - Pathology

- Standard IHC methods used per current guidelines

- Reference ranges (nuclear staining in tumor cells):
  - ER: 0% Negative; 1-9% Low Positive; > 10% Positive
  - PR: 0% Negative; 1-39% Low positive; > 40% Positive
  - P53: 0-19% Negative; >20% Positive
  - Ki-67: 0-19% Low proliferative rate; >20% High proliferative rate
## Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>ER+/PR- (N=101)</th>
<th>ER+/PR+ (N=150)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (mean, std dev)</td>
<td>57 10</td>
<td>59 13</td>
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<tr>
<td>Menarche</td>
<td>12 2</td>
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<td>Number of pregnancies</td>
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<td>BMI (kg/m2)</td>
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<td>Fam hx BCa</td>
<td>33/101 (33%)</td>
<td>20/150 (13%)</td>
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## Results

<table>
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<tr>
<th>Variable</th>
<th>ER+/PR- (N=101)</th>
<th>ER+/PR+ (N=150)</th>
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<tbody>
<tr>
<td>ER %</td>
<td>77 29</td>
<td>88 17</td>
<td>0.0003</td>
</tr>
<tr>
<td>PR %</td>
<td>12 12</td>
<td>82 19</td>
<td>0.0001</td>
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<tr>
<td>HER2+ (%)</td>
<td>20%</td>
<td>6%</td>
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<tr>
<td>Ki67 %</td>
<td>29 25</td>
<td>18 18</td>
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<td>P53+ (%)</td>
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<td>Grade 3 (%)</td>
<td>35/101 (35%)</td>
<td>23/150 (15%)</td>
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## Results

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<thead>
<tr>
<th>Variable</th>
<th>ER+/PR- (N=101)</th>
<th>ER+/PR+ (N=150)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>85/101 (85%)</td>
<td>128/150 (85%)</td>
<td>0.8582</td>
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<tr>
<td>Neoadjuvant Chemotherapy</td>
<td>3/101 (3%)</td>
<td>6/150 (4%)</td>
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<td>Adjuvant Chemotherapy</td>
<td>48/101 (48%)</td>
<td>37/150 (25%)</td>
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<td>Radiation Therapy</td>
<td>53/101 (53%)</td>
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<td>Aromatase Inhibitors</td>
<td>50/101 (50%)</td>
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<tr>
<td>Tamoxifen</td>
<td>14/101 (14%)</td>
<td>49/150 (33%)</td>
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</table>
# Results

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<thead>
<tr>
<th>Variable</th>
<th>ER+/PR- (N=101)</th>
<th>ER+/PR+ (N=150)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Days of followup</td>
<td>984 586</td>
<td>1028 483</td>
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<tr>
<td>Recurrence</td>
<td>15/101 (15%)</td>
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<td>Mortality</td>
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<td>2/150 (0.66%)</td>
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<td>Recurrence and Mortality</td>
<td>15/101 (15%)</td>
<td>6/150 (4%)</td>
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## Results

<table>
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<tr>
<th>Variable</th>
<th>ER+/PR- Recurrence (N=15)</th>
<th>ER+/PR- No recurrence (N=86)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (mean, std dev)</td>
<td>57 10</td>
<td>60 13</td>
<td>0.4121</td>
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<tr>
<td>Menarche</td>
<td>12 2</td>
<td>12 2</td>
<td>0.96</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>2 2</td>
<td>3 3</td>
<td>0.26</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>12/15 (80%)</td>
<td>71/86 (83%)</td>
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<td>BMI (kg/m2)</td>
<td>30 7</td>
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<td>0.6721</td>
</tr>
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<td>Fam hx BCa</td>
<td>5/15 (33%)</td>
<td>28/86 (33%)</td>
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## Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>ER+/PR- Recurrence (N=15)</th>
<th>ER+/PR- No recurrence (N=86)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER %</td>
<td>63 35</td>
<td>80 27</td>
<td>0.0333</td>
</tr>
<tr>
<td>PR %</td>
<td>10 10</td>
<td>12 12</td>
<td>0.5625</td>
</tr>
<tr>
<td>HER2+ (%)</td>
<td>6/15 (40%)</td>
<td>14/86 (16%)</td>
<td>0.0714</td>
</tr>
<tr>
<td>Ki67 %</td>
<td>45 13</td>
<td>25 25</td>
<td>0.0039</td>
</tr>
<tr>
<td>P53+ (%)</td>
<td>8/15 (53%)</td>
<td>29/86 (34%)</td>
<td>0.1589</td>
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<td>Grade 3 (%)</td>
<td>7/15 (47%)</td>
<td>28/86 (33%)</td>
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# Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>ER+/PR- Recurrence (N=15)</th>
<th>ER+/PR- No recurrence (N=86)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>10/15 (67%)</td>
<td>75/86 (87%)</td>
<td>0.0591</td>
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<tr>
<td>Neoadjuvant Chemotherapy</td>
<td>1/15 (7%)</td>
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<tr>
<td>Adjuvant Chemotherapy</td>
<td>12/15 (80%)</td>
<td>36/86 (42%)</td>
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<td>Radiation Therapy</td>
<td>9/15 (60%)</td>
<td>44/86 (51%)</td>
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<td>Aromatase Inhibitors</td>
<td>10/15 (67%)</td>
<td>40/86 (47%)</td>
<td>0.3977</td>
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<tr>
<td>Tamoxifen</td>
<td>2/15 (12%)</td>
<td>12/86 (14%)</td>
<td>0.8798</td>
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Discussion

- As compared to ER+/PR+ group, ER+/PR- had
  - Lower ER and PR expression
  - Higher HER2, Ki67 and p53 expression
  - Higher rate of recurrence or death at 3-year followup
Discussion

- Within the ER+/PR- group
  - Ki67 was predictive of recurrence
  - Lower ER expression was associated with recurrence
  - There was a trend towards higher HER2 expression in the recurrence group
Ki67

- Identified in 1980 in Hodgkin's lymphoma cell
- Named for Kiel University and plate number
- Nucleolar protein involved in cell division (polymerase I dependant rRNA synthesis)
- Measured by IHC method and reported as % of cells stained ($30/test)
- Healthy breast tissue level <3% (only in ER- cells)

Yerushalmi et al, Lancet Oncology 2010; 11: 174-83
Ki67 - Prognostic Role

- Expressed in 40% of DCIS, where it can predict recurrence.

- Ki67, ER, PR and HER2 performed similarly to a 50-gene expression profile in segregating the luminal Bca into A (low level) and B (high level).

- Ki67 >14% associated with worse prognosis (recurrence and death).

- Recent meta-analysis of 15970 Bca pts:
  - shorter OS with Ki67+: HR 1.73 (95% CI 1.37-2.17)

Yerushalmi et al, Lancet Oncology 2010; 11: 174-83
Stuart-Harris R et al. Breast 2008;17:323-34
Ki67 - Predicting Treatment?

- **Adjuvant studies:**
  - no support for a predictive role for the benefit of chemotherapy over endocrine treatment alone
  - High Ki67 might predict a benefit for:
    - adjuvant taxane regimen vs non-taxane
    - letrozole vs tamoxifen

- **Neoadjuvant studies:**
  - High Ki67 might predict response to chemotherapy
  - Low Ki67 may benefit more from endocrine Rx

- **Metastatic studies:** no good data

Yerushalmi et al, Lancet Oncology 2010; 11: 174-83
Ki67 - Recent Trends

- St Gallen International Expert Consensus recommends use of proliferation markers (Ki67 and mitosis) and multigene assays when choosing systemic treatment.

- Oncogene Dx gene test ($4000) – multigene assay in which 5 genes (including Ki67) reflect proliferative status and are heavily weighted in the formula used to predict recurrence.

- TailorX study = large RCT assessing this approach in node-negative, hormone-positive tumors to determine benefit of chemotherapy.

Yerushalmi et al, Lancet Oncology 2010; 11: 174-83
ER+/PR- type of breast cancer is a Luminal B-type with high expression of Ki67, the level of which can predict recurrence (and survival).

ER+/PR- type is genetically and clinically different than ER+/PR+ type of breast cancer.
Addition of Ki67 testing by IHC adds significant prognostic information with little cost

Treatment for ER+/PR- should be different than for ER+/PR+ and individualized chemotherapy should strongly be considered in early stages, mainly based on proliferation markers (Ki67)
Acknowledgements

- Divyesh Mehta, MD
- Jigisha Thakkar, MD
- John Quigley, MD
- Howard Ozer, MD