BREAST CANCER

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Background

• Breast cancer is the most common cancer among women in the U.S.
• Second leading cause of cancer death among women in the U.S.
• Women have a 1 in 9 lifetime risk of developing breast cancer.

Estimated New Cancer Cases
10 Leading Sites by Gender

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>31%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>11%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>2%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>18%</td>
</tr>
</tbody>
</table>

SEER Breast Cancer Incidence and Mortality Data

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>180,000 / year</td>
<td>40,000 / year</td>
</tr>
</tbody>
</table>

Stages of Breast Cancer

• **Stage 0:** Cancer cells are present in either the lining of a breast lobule or a duct, but they have not spread to the surrounding fatty tissue or DCIS.
• **Stage I:** The tumor is <2 cm, the lymph nodes are not involved.
• **Stage II:** The tumor can range from 2-5 cm in diameter or <4 lymph nodes are involved.
• **Stage III:** Locally advanced cancer; tumor may be larger than 5 cm in diameter or >4 LN.
• **Stage IV:** Known as metastatic; cancer has spread to other parts of the body, such as bone, liver, lung, or brain.

- About 15% of breast cancer diagnoses are in situ disease
- 5-year survival for early stage breast cancer is very good

Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intake (&gt;2 drinks/day)</td>
<td>1.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.2</td>
</tr>
<tr>
<td>HRT use (&gt;5 years)</td>
<td>1.3</td>
</tr>
<tr>
<td>Early age of first menstrual period (&lt;12 years)</td>
<td>1.3</td>
</tr>
<tr>
<td>Late menopause (&gt;55 years)</td>
<td>1.2-1.5</td>
</tr>
<tr>
<td>Age at first birth (&gt;30 years or no children)</td>
<td>1.7-1.9</td>
</tr>
<tr>
<td>Current age (≥65 years)</td>
<td>5.8</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>5.2-20</td>
</tr>
<tr>
<td>Prior breast cancer</td>
<td>6.8</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>2nd degree relative with breast cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>1st degree relative, age ≥50</td>
<td>1.8</td>
</tr>
<tr>
<td>1st degree relative, age &lt;50</td>
<td>3.3</td>
</tr>
<tr>
<td>Prior Exposure to Radiation</td>
<td>5-80x</td>
</tr>
<tr>
<td>BRCA1/2 mutation carrier</td>
<td>15-200</td>
</tr>
</tbody>
</table>

Benign Breast Disease

Dupont et al. Cancer, 1993

<table>
<thead>
<tr>
<th>RR 1.0</th>
<th>1.5-2.0</th>
<th>4.0-5.0</th>
<th>10-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Proliferative</td>
<td>Pre-Cancerous Changes</td>
<td>In Situ</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Atypia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Benign Breast Disease

- Pre-Cancerous changes
- In situ

Breast Cancer Risk Assessment: Gail Model

Gail et al. JNCI, 1989

- Age
- Race
- Age of first menstrual period
- Age of first live birth
- Number of first degree relatives with breast cancer
- Number of breast biopsies
  - Presence of atypical hyperplasia

www.cancer.gov/bcrisktool

5-Year Risk = 2.6%
Lifetime Risk = 21.9%

How Much Breast and Ovarian Cancer Is Hereditary?

- Breast Cancer
- Ovarian Cancer

- Sporadic
- Family clusters
- Hereditary

www.cancer.gov/bcrisktool
Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

Comparing Relative Risk to other Risk Factors

<table>
<thead>
<tr>
<th>2-Fold</th>
<th>&gt;2-Fold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Menarche</td>
<td>Never Pregnant</td>
</tr>
<tr>
<td>Never Breastfed</td>
<td></td>
</tr>
<tr>
<td>Late Age at First Birth</td>
<td></td>
</tr>
<tr>
<td>Late Menopause</td>
<td></td>
</tr>
<tr>
<td>Lack of Exercise</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Hormone Use (HRT, OC)</td>
<td></td>
</tr>
</tbody>
</table>

Multi-modality Treatment of non-metastatic Breast Cancer

- Local therapy
  - Surgery
  - Radiation therapy
- Systemic therapy
  - Endocrine manipulations
  - Chemotherapy
  - Novel Therapies

Adjuvant Systemic Therapy for Breast Cancer: Decision making

Risks: Adverse Events
Benefits: Risk Reduction

Organ Function, Age, Co-morbidities
Prognostic & Predictive Factors

Adjuvant Systemic Therapy for Breast Cancer: Decision Making

- Prognostic Factors
  - Estimate outcome independent of systemic treatment
  - Reflect tumor biology: Who should be treated?
- Predictive Factors
  - Reflect a relative resistance or sensitivity to specific therapy
  - What specific treatment(s) should be offered to an individual?
Breast Cancer Prognostic Factors

<table>
<thead>
<tr>
<th>Strength</th>
<th>Cancer</th>
</tr>
</thead>
</table>

Gene arrays

Breast Cancer Predictive Factors

- Accepted
  - Age
  - ER
  - Grade
  - HER2

- Investigational
  - Gene arrays, proteomics
  - Novel imaging

Breast Cancer Subtypes

RS = +0.47 x HER2 Group Score
- 0.34 x ER Group Score
+1.04 x Proliferation Group Score
+0.10 x Invasion Group Score
+0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

OncotypeDX Recurrence Score (RS) Assay Predicts Distant Relapse Rates at 10 Years if Five Years of Tamoxifen

16 Cancer and 5 Reference Genes From 3 Studies

<table>
<thead>
<tr>
<th>PROLIFERATION</th>
<th>ESTROGEN</th>
<th>INVASION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67</td>
<td>ER</td>
<td>GSTM1</td>
<td>GAPDH</td>
</tr>
<tr>
<td>STK15</td>
<td>PR</td>
<td>BAG1</td>
<td>RPLPO</td>
</tr>
<tr>
<td>Survivin</td>
<td>Bcl2</td>
<td>CD68</td>
<td>GUS</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td>SCUBE2</td>
<td>HER2</td>
<td>TFRC</td>
</tr>
<tr>
<td>MYB2</td>
<td></td>
<td>HER2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GSTM1</td>
<td>GBST</td>
<td></td>
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</table>

Validation Study of Oncotype DX

Tamoxifen treated patients from NSABP B-14 (N=668)

Performance exceeded standard measures of patient age, tumor size
Inhibition of Estrogen-Dependent Growth

Tamoxifen: Oxford Overview Data

- Effective in all hormone receptor positive women:
  - ER+/PR+ > ER-/PR+ > ER+/PR-
- Regardless of age, stage, tumor grade
- Optimal duration: 5 years
  - 5 ys > 2 ys, but 10 ys not > 5 ys

5 years of Tamoxifen vs. Not: 15-year Probabilities of Recurrence and Breast Cancer Mortality (ER-positive/unknown, n = 10,386)

ATAC: Disease-Free Survival

1. Who should be treated?
2. Which regimen?
3. What duration?
4. How intense?
5. When to administer?
Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age 50-69)


Recurrence Breast Cancer Mortality

<table>
<thead>
<tr>
<th>Entry Age</th>
<th>Recurrence Rate</th>
<th>Breast Cancer Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69</td>
<td>15-year gain 3.0% (SE 1.3)</td>
<td>Logrank 2p&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>15-year gain 4.1% (SE 1.2)</td>
<td>Logrank 2p&lt;0.00001</td>
</tr>
</tbody>
</table>

Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age <50)


Recurrence Breast Cancer Mortality

<table>
<thead>
<tr>
<th>Entry Age</th>
<th>Recurrence Rate</th>
<th>Breast Cancer Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>15-year gain 12.3% (SE 1.6)</td>
<td>Logrank 2p&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>15-year gain 10.0% (SE 1.6)</td>
<td>Logrank 2p&lt;0.00001</td>
</tr>
</tbody>
</table>

2. Which Regimen? Results from the Oxford Overview

- Polychemotherapy is superior to single agent chemotherapy
- Anthracycline-based therapy is superior to CMF-based therapy
- All women gain benefit but younger women, and those with poorly differentiated, hormone receptor negative-tumors more likely to benefit


Common Breast Cancer Treatments

- Endocrine Therapies
  - Tamoxifen
  - Aromatase Inhibitors
  - Other
- Chemotherapy
- Novel Therapies
  - Trastuzumab (Herceptin)

Trastuzumab Targets the Human Epidermal Growth Factor Receptor 2 (HER2)

- The HER2 gene is localized to chromosome 17q
- HER2 is a tyrosine kinase transmembrane growth factor receptor


HER2 Overexpression Leads to Increased Signaling

- Increased cell proliferation
- Increased cell migration
- Resistance to apoptosis

**Trastuzumab Plus Chemotherapy**

**Increased Response Rates**


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin + Chemotherapy</td>
<td>67%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20%</td>
</tr>
<tr>
<td>Herceptin + Pfizer</td>
<td>16%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>11%</td>
</tr>
</tbody>
</table>

**B-31/N9831 Disease-Free Survival**

Years From Randomization

- AC=TH: 87%
- AC=T: 75%
- HR=0.48, 2P=3x10^-12

**B-31/N9831 Overall Survival**

Years From Randomization

- AC=TH: 95%
- AC=T: 95%
- HR=0.67, 2P=0.015

**Metastatic Breast Cancer: Goals of Therapy**

- Cure
- Improve overall survival
- Improve time to progression
- Improve symptoms related to the disease
- Improve quality of life

**Therapeutic options**

- Endocrine therapies
- Chemotherapy
- Novel therapies
- Supportive Therapy
  - Local therapy: surgery, radiation
  - Bisphosphonates
    - For women with skeletal metastases
    - Reduces pain/risk of fracture/RT requirements
    - Symptom management
- Monitoring Response
  - History and physical
  - Tumor markers
  - Imaging
    - Standard: CT, bone scan, MRI
    - Emerging: PET, functional imaging
  - Circulating cells
  - Other
Conclusions and Future Directions

- Many therapies available to women with metastatic breast cancer
  - Improve overall survival, time to progression, QOL
  - Well tolerated
- Individualized treatment
- Optimal dose, schedule, combination
- Numerous emerging novel therapies

Thank You