Tailoring Breast Cancer Treatment: Has Personalized Medicine Arrived?

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Outline
- First, treatment of DCIS
- Sorting risk in invasive cancer—ER negative
- Sorting risk in invasive cancer—ER positive
- Lifestyle risk factors

Tailoring—What?
- Ductal carcinoma in situ
  - Diagnosis for about 20% of all new cases
  - Usually diagnosed by mammography
  - Not to be confused with invasive ductal carcinoma
  - May be diagnosed by core biopsy or excisional biopsy
  - Spans all ages and all risk factors
  - May be multifocal or diffuse, but is usually within a single quadrant

Variations--DCIS
DCIS: What is the Risk?

- Studies of DCIS risk have mostly looked at the risk of recurrence in the same breast
  - When DCIS recurs, about half of the cases are DCIS, and half are invasive breast cancer
  - When DCIS recurs, the vast majority recur in the same area of the breast where the first event took place
    - We think that we just didn't get it all out!
    - The risk of recurrence definitely is highest if the margins of the original biopsy have DCIS
- Careful pathologic review is VERY important
  - Rule out areas of invasive cancer
  - Check on resection margins

Age Affects DCIS Recurrence in the Same Breast

USC/VNPI DCIS Scoring Index

<table>
<thead>
<tr>
<th>Score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;15 mm 5/8 inch</td>
<td>16-40 mm 0.6-1.6 inch</td>
<td>&gt;41 mm 1.7 inch up</td>
</tr>
<tr>
<td>Margins</td>
<td>&gt;10 mm 3/8 inch</td>
<td>1-9 mm 0.4-3/8 inch</td>
<td>&lt;1 mm microscopic</td>
</tr>
<tr>
<td>Pathology</td>
<td>Not high grade No necrosis</td>
<td>Not high grade With necrosis</td>
<td>High grade</td>
</tr>
<tr>
<td>Age</td>
<td>≥61 years</td>
<td>40-60 years</td>
<td>≤39 years</td>
</tr>
</tbody>
</table>

Using the USC/VNPNI Risk Index

- Add up the points for each category
- Total is the risk rating
- Example:
  - A 55 year old woman with a 12 mm DCIS, removed with margins widely clear of DCIS (more than 10 mm all around). Pathology shows moderately differentiated DCIS with comedonecrosis.
  - Points: 1+1+2+2=6
Outcomes of DCIS Surgery Only by USC/VNPI Score

<table>
<thead>
<tr>
<th>USC/VNPI Score 4-6</th>
<th>USC/VNPI Score 7-9</th>
<th>USC/VNPI Score 10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recur at 10 yrs</td>
<td>4%</td>
<td>27%</td>
</tr>
<tr>
<td>% Invasive</td>
<td>0%</td>
<td>46%</td>
</tr>
<tr>
<td>Cancer Survival at 10 years</td>
<td>100%</td>
<td>97.7%</td>
</tr>
</tbody>
</table>

Evidence-Based DCIS Treatment

- Total mastectomy: reduces risk by >95%
- Partial mastectomy:
  - With good margins, risk as per USC/VPI
- Addition of breast radiation: reduces risk by 50%
- Addition of Tamoxifen: reduces risk by 25%
- All three—surgery, radiation, Tam: reduces risk by about 75%

DCIS Treatment Recommendations

- Mastectomy: Risk of subsequent recurrence certainly less than 5%, probably less than 2%
- Lumpectomy alone:
  - May be OK for low risk women, elderly
  - Requires careful long term surveillance
- Lumpectomy + radiation therapy:
  - Younger women, higher risk women
- Lumpectomy + radiation therapy + hormone therapy:
  - Highest risk women
  - Postmenopausal women probably should consider Arimidex or Femara
- Note: lymph nodes usually NOT sampled

Invasive Breast Cancer

- Tailoring primary surgical treatment:
  - Mastectomy an option for any patient
  - Partial mastectomy an option for those with
    - Tumors under 5 cm—before or after chemo
    - No inflammatory breast cancer
    - Acceptable cosmetic outcome
- Radiation therapy after surgery:
  - High risk of local failure on chest wall after Mx
  - Younger women with partial mastectomy
  - No radiation: lupus, scleroderma, refusal
Adjuvant Therapy Tailoring

- Risk of distant recurrence: “prognostic factors”
  - Size and node status
  - Progesterone receptor expression
  - Proliferation rate, differentiation
  - Her2 status
  - OncotypeDx
  - Mammaprint

- What treatment will work for this tumor: “predictive factors”
  - Estrogen and progesterone receptor status
  - Her2 status
  - Proliferation index; differentiation
  - Oncotype
  - ?Mammaprint

Adjuvant Therapy Tailoring

- Host factors:
  - Age of patient
  - Comorbid illnesses—factored with risk of recurrence, so ask which disease is patient likely to die from?
  - Comorbid illnesses—predicting risk of side effects from treatment and/or long term toxicity from treatment

Tailoring Decision Tree—Any Long Term Distant Recurrence Risk of 20% or More
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ER STATUS
- POSITIVE
  - HER2 STATUS
    - Positive
    - Negative
- NEGATIVE

Breast Chemotherapy and Comorbidities
- Serial clinical trials suggest:
  - Anthracycline containing chemo is superior to non-anthracycline therapy (maybe one exception)
  - Addition of taxane (Taxol, Taxotere) is also superior to non-taxane treatment
- But:
  - Taxanes cause neuropathy, sometimes irreversible
  - Anthracyclines can cause CHF

Triple Negative Breast Cancer
- Best available current adjuvant therapy is anthracycline based, usually also taxane based, chemotherapy
- Triple negative is more common in women under 50; therapy usually given to them
- Higher response to chemo vs ER +, but generally also worse relapse rate
- Older women less overall benefit, need to tailor for these women due to risks
**Tailoring to ER Negative, Her2 Negative Breast CA**

- High risk for CHF:
  - Combination of taxane and cyclophosphamide
  - Older: CMF (cyclophosphamide, methotrexate, fluorouracil)
- High risk for neuropathy:
  - Anthracycline, fluorouracil, cyclophosphamide
- Neither:
  - Anthracycline, cyclophosphamide, taxane

**ER Negative, Her2 Positive**

- Her2 is a cell surface growth factor receptor that is highly overexpressed in 20-25% of invasive breast cancer
  - Most tumors also ER negative
  - Rapidly growing; most chemo sensitive group
  - Probably most sensitive to anthracycline rx
- Herceptin—trastuzumab—is a monoclonal antibody to the external receptor that has a high level of antitumor activity in vitro
- Trastuzumab may be added to adjuvant chemotherapy—the standard is one year

**Trastuzumab Risks**

- Short term is well tolerated—only occasional infusion reactions
- INCREASES the risk of CHF when given after anthracyclines
  - Mechanism is unknown
  - Often reversible—longer term results not yet known
- Cuts the risk of relapse by 50%!
Tailoring Chemo/Trastuzumab

- Low Risk premenopausal women
  - Anthracycline + taxane + Herceptin
  - Overall relapse risk reduction about 80%
- Hypertension
  - Substitute non-anthracycline regimen
  - Taxane and Herceptin
- Older women
  - Non-anthracycline regimen + Herceptin
  - Very meticulous monitoring of LVEF

Tailoring Decision Tree—Any Long Term Distant Recurrence Risk of 20% or More

- ER STATUS
  - POSITIVE
  - NEGATIVE
    - HER2 STATUS
      - Positive
      - Negative
        - Comorbid?
          - Yes
          - No
        - Comorbid?
          - Yes
          - No

Tailoring Decision Tree—Any Long Term Distant Recurrence Risk of 20% or More

- ER STATUS
  - POSITIVE
  - NEGATIVE
    - High relapse risk?
      - No
      - Yes

Relapse Risk in ER + Breast Ca

- Positive lymph nodes
- Younger age
- High risk by Oncotype Dx
  - Risk applies to node neg and node positive
  - Low risk = no benefit from chemo
- ??High risk by Mammaprint
**Prognostic/Predictive Factors in Breast Cancer: Oncotype**

- 21-gene RT-PCR assay used for node-negative, ER positive (lower risk) tumors—predicts risk of metastases over 10 yrs
- Predicts responsiveness to chemotherapy for the high scoring tumors, no response for lowest scores

**Tailoring Decision Tree—Any Long Term Distant Recurrence Risk of 20% or More**

ER STATUS

- **POSITIVE**
  - High relapse risk?
    - No
    - Yes
      - Comorbid
        - No
          - Chemo + HT
        - Yes
          - HT ± mod chemo

- **NEGATIVE**
  - No
  - Yes

**Tailoring Hormone Therapy**

- **Postmenopausal women**
  - Aromatase inhibitors are treatment of choice
    - Superior in randomized trials
    - Arimidex, Femara, Aromasin
    - Effect greatest in oldest women
  - Tamoxifen second choice
    - Intolerance of aromatase inhibitors
    - Risks: thrombotic events, ca uterus
    - Some experts mix these two regimens
  - Both treatments are for five years

- **Premenopausal women**
  - Lose menses due to chemotherapy
    - Aromatase inhibitors for five years
    - Tamoxifen for five years
  - No loss of menses
    - Tamoxifen for five years
    - Lupron or other GNRH agonist for five years
      - Add either Tamoxifen or aromatase inhibitor
**Adjuvant Therapy Outcomes**

- Example: 64 yo woman with 3 cm ER+ tumor, but 10 nodes positive
  - Risk of relapse in 10 yrs is 82%!
  - Risk of relapse with chemo + hormones reduced by 45% to only 37%
- Example: 35 yo woman with 1.5 cm ER+ Her2 + cancer with 3 nodes
  - Risk of relapse in 10 yrs is 75%
  - Risk reduction with chemo, hormones, and Herceptin is about 65%, resulting in 10% risk

**What About BRCA Positive Women?**

- Risk of ca is quite high: up to 80% lifetime
- BRCA1: high rates triple negative cancer
- BRCA2: more varied types
- Most women are younger, so the treatment is more aggressive
- Bilateral mastectomy much more frequent when diagnosed with breast cancer
- Oophorectomy should be considered: may provide base for hormone therapy

**New Directions for BRCA patients: PARP inhibitors**

- Chemo induces DNA break
- PARP and BRCA are both DNA repair proteins
- Cancer cells in BRCA patients have no BRCA function at all; their normal cells have half the BRCA, but that works OK
- If you inhibit PARP in a BRCA cancer cell, then you can’t repair DNA damage; the normal cells survive
- Add a DNA damaging agent like cisplatin or carboplatin, and higher rates of cell death occur

**Risk Reducing Lifestyle Changes?**

- Diet
  -Everybody asks, nobody knows
  - Two large randomized trials of lowering sat fat and/or increasing vegetables had opposite outcomes in women after breast cancer
  - WHI results also negative for cohort with ca breast
- Alcohol: does increase risk of getting breast cancer
- Obesity: also increases risk
- Exercise: decreases risk of getting breast cancer
Improving Outcomes: Lifestyle Interventions after Breast Cancer

- **LACE Study: Kaiser Permanente**
  - 1897 women after diagnosis, self-reported alcohol use (90% wine!)
  - Compared to no alcohol, even amounts as low as ½ drink/day increased risk of
    - Recurrence—34%
    - Death due to breast cancer—51%
  - Stronger effect seen in postmenopausal women—51%
  - mortality due to breast cancer—51%
  - Even individually overweight/obese women—58%

- Yikes! Controversial, but we know that alcohol consumption increases risk of getting breast cancer
- Needs other large studies of women to look at this

Improving Outcomes: Effects of Overweight/Obesity

- **Danish Study**: based on national health records of 18,967 women with breast cancer
  - For BMI greater than 25
    - Recurrence risk increased 42-46%
    - Mortality due to breast cancer increased 26-38%
  - Worst risk groups: older postmenopausal women, BMI over 30—also associated with larger cancers, more + nodes
- Cannot sort out other variables, as this study from registries, but effect is important
- Analysis of E1199 study looking at African American outcomes showed that obesity was the ONLY risk factor that explained any outcome differences

Awaiting results: Exercise

- Retrospective studies comparing BrCa survivors to their friends consistently show reduced risk due to exercise, up to 50%
- Observational studies—Nurses, WHI, cardiac studies—also show consistent reduction in BC risk at all ages
- Many studies showing feasibility of exercise programs after BC
- NO large randomized trials

Summing Up

- Breast cancer is heterogeneous with respect to risk and sensitivity to therapy
- Patient choices particularly important for primary surgical/radiation therapy, especially for DCIS
- Comorbid conditions, particularly age and hypertension, alter treatment choices
- Predictive tests such as Oncotype also alter treatment choice for ER + tumors
- Lifestyle factors alter outcomes