Molecular Testing in Breast Cancer: An Oncologist’s Perspective

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Disclosures

• I have no conflicts of interest to disclose.
• The views expressed here are mine alone and may not represent the views of the University of Utah, the State of Utah, or the Huntsman Cancer Institute
Objectives

• Understand how ER, PR, and HER2 testing are used in treatment decisions

• Recognize the options for genomic profiling of breast tumors

• Understand how genomic profiling is used in adjuvant treatment decisions

• Understand the potential roles for genomic profiling in metastatic treatment decisions
Decisions to be made

• Presentation
  • Surgery first or chemotherapy first?
  • Which neoadjuvant therapy to use?

• After surgery
  • What is the local recurrence risk?
  • What is the distant recurrence risk?
  • Is adjuvant chemotherapy needed, and if so which one?
  • Is adjuvant hormone therapy needed, and if so which one?
  • Is adjuvant biologic therapy needed?

• Metastatic disease
  • How long will she live?
  • What therapy to use when?
Options

• NCCN lists:
  • 21 adjuvant/neoadjuvant chemotherapies
  • 4 adjuvant endocrine therapies
  • 11 metastatic endocrine therapies
  • 34 metastatic chemotherapies

• How do we decide?
Decisions after surgery

• What is the local/distant recurrence risk?
  • Combination of biology and clinical factors
  • Clinical factors
    • Age
    • Size of primary tumor
    • Node positivity
    • Margins**
  • Biology
    • Estrogen receptor presence and activation
    • HER2 amplification
    • Proliferation
    • Grade
    • Lymphovascular invasion**
Local Recurrence after Mastectomy

- Margins ≥ 2mm
- Premenopausal
- Size > 2cm
- Lymphovascular invasion
Decisions after surgery

• What is the local/distant recurrence risk?
  • Combination of biology and clinical factors
  • Clinical factors
    • Age
    • Size of primary tumor
    • Node positivity
    • Margins**
  • Biology
    • Estrogen receptor presence and activation
    • HER2 amplification
    • Proliferation
    • Grade
    • Lymphovascular invasion**
How do we measure estrogen receptor presence and activation?

• Presence
  • Detected by immunohistochemistry
  • Number of positive cells and intensity are both important
  • Increasing ER by 1% decreases relapse by ~3%

• Activation
  • PR level
  • Gene expression analysis
Available gene expression tests

- Oncotype Dx recurrence score
- Mammaprint
- PAM50/Prosigna
- Breast Cancer Index
## Features of gene expression tests

<table>
<thead>
<tr>
<th>Feature</th>
<th>Oncotype</th>
<th>MammaPrint</th>
<th>Prosigna</th>
<th>Breast Cancer Index</th>
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</thead>
<tbody>
<tr>
<td>Number of Genes</td>
<td>21</td>
<td>70</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Able to be done on FFPE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Output</td>
<td>Score (0-100)</td>
<td>Binary (High/Low)</td>
<td>Score (0-100)</td>
<td>Score (0-10)</td>
</tr>
<tr>
<td>Population</td>
<td>ER-positive, HER2-negative</td>
<td>&lt;4 lymph nodes</td>
<td>ER-positive</td>
<td>ER-positive, node negative</td>
</tr>
<tr>
<td></td>
<td>Node negative (&gt;1 validation)</td>
<td></td>
<td>Node negative or node positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Node positive (1 validation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorporates clinical variables</td>
<td>Calculator on website</td>
<td>No</td>
<td>Score incorporates tumor size</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>integrates age, size, and grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictive of chemotherapy benefit</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Age, Size, and grade still matter
Gene expression tests give similar data
What about immunohistochemistry?

• **IHC4**
  - Combines quantitative assessments of ER, PR, Ki-67, and HER2
  - Compares favorably to gene expression tests
  - Not clear how to lab-to-lab variability affects score

• **Mammastrat**
  - Five gene score
  - Prognostic, but not clearly predictive
  - Has not been compared to gene expression based assays
  - Benefit in premenopausal women not established
What about node-positive ER-positive disease

- Historically and per NCCN, chemotherapy is indicated.

Dowsett M et al. JCO 2010;28:1829-1834
My approach in ER-positive, HER2-negative breast cancer

- > 4 nodes -> Chemotherapy followed by endocrine therapy
- Node-negative
  - Estimate range of possible recurrence risks based on clinical factors and recurrence scores
  - Determine chemotherapy based on recurrence risk and potential benefit from chemotherapy
- 1-3 nodes
  - Agonize
  - Consider enrolling on RxPonder
  - Recommend chemotherapy pending RxPonder results, but if gene expression test is low risk, strength of recommendation depends on clinical factors
Gene expression does not replace traditional HER2 testing

<table>
<thead>
<tr>
<th>IHC/FISH</th>
<th>RT-PCR in OncotypeDx</th>
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<tbody>
<tr>
<td></td>
<td>Equivocal</td>
</tr>
<tr>
<td>Equivocal</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>
Choice of regimen for HER2-positive cancers is based on clinical factors

• No test for withholding trastuzumab based on biologic factors
• Since trastuzumab must be given with chemotherapy, want to limit chemotherapy exposure in low risk women
• Node-positive -> chemotherapy plus trastuzumab plus pertuzumab
• > 3 cm, node negative -> chemotherapy plus trastuzumab plus pertuzumab
• 1-3 cm -> taxol and trastuzumab
• < 1cm -> controversial
Small HER2-positive cancers

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Recurrence-Free Survival (proportion)

0 0.2 0.4 0.6 0.8 1.0

Time Since Diagnosis (months)

JCO December 1, 2009 vol. 27 no. 34 5700-5706

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Hormone Receptor–Negative Group

Disease-Free Survival

0 0.2 0.4 0.6 0.8 1.0

No. at risk
HER2- HER2+ HER2-
71 70 63 54 43 30 20 9
HER2-
71 67 48 35 26 18 9

Log-rank P = .001
HR HER2+ v HER2-: 1.2 (95% CI, 0.3 to 4.7)

A

Hormone Receptor–Positive Group

Disease-Free Survival

0 0.2 0.4 0.6 0.8 1.0

No. at risk
HER2+ HER2+ HER2+
158 157 144 117 87 62 48 36
HER2+
79 77 71 54 45 32 21 18

Log-rank P = .013
HR HER2+ v HER2-: 5.2 (95% CI, 1.0 to 25.9)

JCO December 1, 2009 vol. 27 no. 34 5693-5699

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Recurrence-Free Interval (probability)

0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00

Time (years)

JCO July 10, 2014 vol. 32 no. 20 2151-2158
Current Clinical Dilemmas

• Adjuvant chemotherapy for clinically high risk but biologically chemotherapy-resistant tumors?
• Neoadjuvant endocrine therapy for very estrogen-sensitive tumors?
• Can we predict which endocrine therapy to use in the adjuvant setting?
• What size cutoff should be used for anti-HER2 therapy?
• Utility of adjuvant endocrine therapy in tumors with low ER-positivity?
Decisions at presentation

• Is therapy needed prior to surgery for localized disease?
  • Easy yes
    • Clinical T4 or Clinical N2
    • Why?
      • Surgeon needs easier surgery
      • Maximal therapy is needed
        • Anthracycline, taxane, trastuzumab, pertuzumab
  • Easy no
    • Anyone who may not need adjuvant therapy
    • Tumor < 1cm
    • Clinically node negative ER-positive
    • ER, PR, HER2 can’t be done on biopsy
Decisions at presentation

• Is therapy needed prior to surgery for localized disease?
  • Harder decisions
    • Adjuvant therapy will definitely be needed but no clear advantage to preoperative therapy
      • Triple-negative >1 cm
      • HER2-positive > 1 cm
      • Node-positive Triple-negative or HER2-positive
    • If I know what regimen is needed, based on clinical factors, comorbidities, or schedule, then may do preoperative therapy.
Metastatic breast cancer

• How long will she live?
• What therapy to use when?
Metastatic breast cancer

• Prognosis is affected by:
  • Clinical factors
    • Location of metastases
    • Performance status
    • Prior therapies
  • Biologic factors
    • Histology
    • Molecular subtype
    • Location of metastases
Circulating Tumor Cells (CTCs)

- Add prognostic information to clinical variables
- Change in AUC is ~0.02

Change in CTC count is prognostic
S0500: Does changing therapy base on CTC affect survival
S0500 results

• Changing therapy for women with unchanged CTCs did not improve PFS or OS

• Why?
  • Underpowered study
  • Therapy options are similar in mechanism
  • Women tend to see sequentially all classes of drugs
Can blood tests be used to identify targets for therapy?

- Mutations can be found in both CTCs and ctDNA
- Is knowledge of these mutations useful?
Can CTCs be used to identify targets for therapy?

• Targets in CTCs may not reflect the full biology
  • Phase 2 trial of lapatinib in women with HER2-positive CTCs but HER2-negative tumors
  • 7 of 96 women screened
  • No responses, 1 stable disease
Molecular Profiling to Determine Treatment

- SAFIR01/UNICANCER trial
- Feasibility study to see how often targeted treatments could be identified for women with metastatic breast cancer

SAFIR01: A mixed success

• Issues with targeting somatic genetic alterations
  • Context matters
  • Current drugs are suboptimal
  • 50% of women don’t have targetable alterations
Question 1

• Which of the following is a predictor for distant relapse of early ER-positive breast cancer independent of molecular features?

A. Grade  
B. Margin size  
C. Ki-67  
D. Germline BRCA status
Question 2

• RT-PCR testing for HER2 status in early breast cancer:
  A. Has equivalent accuracy to FISH or immunohistochemistry
  B. Is more likely to be called positive than FISH
  C. Should not be used to withhold anti-HER2 therapy
  D. Can be used when FISH is equivocal to decide whether to give anti-HER2 therapy
Question 3

• The presence of >5 circulating tumor cells/ml of blood in a woman with metastatic breast cancer:
  A. Predicts increased sensitivity to chemotherapy
  B. Decreases median overall survival by about 50%
  C. Can be used to determine HER2 status
  D. Determines the need for combination chemotherapy
Question 4

• Multigene mutation profiling of metastatic breast cancer:
  A. Can detect actionable mutations in the vast majority of women
  B. Can be performed on FFPE from most tumors
  C. Leads to a greater than 50% response rate from targeted therapies
  D. Works because targeted drugs will have the same effect regardless of histology
Question 5

Multigene gene expression tests are most helpful for:

A. A 50 year-old woman with a 3cm, ER-positive, PR-positive, HER2-negative invasive ductal cancer and negative nodes
B. An 85 year-old wheelchair bound woman with a 3cm, ER-positive invasive ductal cancer and negative nodes
C. A 40 year-old woman with a 3 cm, ER-negative, PR-negative, HER2-negative invasive ductal cancer and negative nodes
D. A 60 year-old woman with a 3 cm, ER-positive invasive ductal cancer and 5 positive lymph nodes
E. A 55 year-old woman with a 3 cm, ER-positive, PR-positive, HER2-positive invasive ductal cancer with negative lymph nodes
Thank you

• Questions?