Assessment of Risk Recurrence: Adjuvant Online, OncotypeDx & Mammaprint

William J. Gradishar, MD
Professor of Medicine
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Can we identify those for whom endocrine therapy is all that is needed to confer an excellent outcome?
Traditional Pathology
There is room for improvement!

LOW Risk
INTERMEDIATE Risk
HIGH Risk

In reality!
In reality!
### “Classical” Prognostic/Predictive Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prognostic?</th>
<th>Predictive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM Stage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>N of ALNs</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Size of primary</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ER/PgR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>HER2</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient Age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Genomic Profiling in Breast Cancer Treatment

- Do genomic profiles assist in assigning baseline prognosis independent of classic prognostic factors?
- Do genomic profiles provide predictive information independent of classic predictive factors?
Estimates:
- Risk of cancer-related mortality or relapse without therapy
- Risk reduction with therapy
- Risk of side effects from therapy

Limitations
- Prognostic factors not all inclusive
  - HER2 status not included
  - Small tumors not well characterized
ER ++, PgR ++, HER2 – Ki67 < 5%
Grade I

- Endocrine responsiveness: “HIGH”
- Need to “optimize” endocrine therapy: TEXT trial discussed
- Added benefit from chemotherapy: “MODEST”

46-year-old, premenopausal
T = 1.4cm (ductal)
One micrometastasis

CONSULT ADJUVANT ON LINE!
Shared Decision Making

Name: ___________________________ (Breast Cancer)
Age: 46   General Health: Good

Estrogen Receptor Status: Positive   Histologic Grade: 1
Tumor Size: 1.1 - 2.0 cm   Nodes Involved: 0
Chemotherapy Regimen: Anthracycline (Overview 2000)

Decision: No Additional Therapy

- 80 out of 100 women are alive and without cancer in 10 years.
- 18 out of 100 women relapse.
- 2 out of 100 women die of other causes.

Decision: Hormonal Therapy

- 7 out of 100 women are alive and without cancer because of therapy.

Decision: Chemotherapy

- 8 out of 100 women are alive and without cancer because of therapy.

Decision: Combined Therapy

- 12 out of 100 women are alive and without cancer because of therapy.
Oncotype Dx

- RT-PCR Multiplex Assay using formalin-fixed paraffin embedded tissue sections
- Commercially available Centralized Testing
- 21 Gene Recurrence Score for Node Negative ER+ (IHC) Patients
- Initial study using NSABP tissues showed strong positive and negative predictive value for disease recurrence in patients treated with tamoxifen alone and with CMF chemotherapy
- Recent ASCO 2005 presentation showed strong stand alone prognostic value in untreated patients
- Of the 21 genes, the ER and Ki-67 have the most predictive power (Bcl2 augments ER)
- Recent evidence is emerging that ER mRNA measurement may outperform IHC in correctly predicting response to tamoxifen and AI’s.
21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

**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

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0 – 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>RS &lt; 18</td>
</tr>
<tr>
<td>Int risk</td>
<td>RS ≥ 18 and &lt; 31</td>
</tr>
<tr>
<td>High risk</td>
<td>RS ≥ 31</td>
</tr>
</tbody>
</table>
Objective

- Validate Recurrence Score as predictor of distant recurrence in N-, ER+, tamoxifen-treated patients

Pre-specified 21 gene assay, algorithm, endpoints, analysis plan

Blinded laboratory analysis of three 10 µ sections

Paik et al, NEJM 2004
## B-14 Results
### DRFS—Low, Intermediate and High RS Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>% of Patients</th>
<th>10-yr Rate</th>
<th>95% CI Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (RS&lt;18)</td>
<td>51%</td>
<td>6.8% 4.0%, 9.6%</td>
<td></td>
</tr>
<tr>
<td>Intermediate (RS 18-30)</td>
<td>22%</td>
<td>14.3% 8.3%, 20.3%</td>
<td></td>
</tr>
<tr>
<td>High (RS≥31)</td>
<td>27%</td>
<td>30.5% 23.6%, 37.4%</td>
<td></td>
</tr>
</tbody>
</table>

Test for the 10-year DRFS comparison between the Low and High risk groups: $p<0.00001$

Paik et al, NEJM 2004
B-14 Results
DRFS—Low, Intermediate and High RS Groups

Paik et al, NEJM 2004
Tamoxifen Benefit and 21 Gene Recurrence Score (RS) Assay

NSABP B-14 Tam Benefit Study in N-, ER+ Pts

**Design**
- Randomized
  - Placebo—Eligible
  - Tam—Eligible

**Objective**
Determine whether the 21 gene RS assay captures:
1) prognosis
2) response to tamoxifen
3) both
B-14 Benefit of Tam By Recurrence Score Risk Category

Low Risk (RS < 18)
- N = 171 (Placebo: 142, Tamoxifen: 142)

Intermediate Risk (RS 18-30)
- N = 85 (Placebo: 69, Tamoxifen: 69)

High Risk (RS ≥ 31)
- N = 99 (Placebo: 79, Tamoxifen: 79)

Interaction p = 0.06

Paik et al SABCS 2005
**Design**

Randomized

- Tam + MF
- Tam + CMF
- Tam

**Objective**

Determine the magnitude of the chemotherapy benefit as a function of 21 gene Recurrence Score assay
Benefit of Chemotherapy Based on RS

Low Risk (RS<18)

Int Risk (RS 18-30)

High Risk (RS≥31)

Paik et al SABCS 2005
Important Caveat

- Likely that many patients in B-14 & B-20 had microscopic nodal involvement as more intense scrutiny of nodes was not routinely done!!
“The Oncotype DX tumor marker test is recommended for patients with node-negative breast cancer that is ER-positive and/or PR-positive, which is the case for 50 percent of breast cancer patients. The test measures multiple genes at once to estimate the risk of breast cancer recurrence. Patients with a low recurrence score may be able to receive only hormone therapy and avoid chemotherapy. Sparing patients from unnecessary treatment may not only improve their quality of life, but it also will reduce overall health care costs”.

JCO 11.20.07
Original E2197: Study Design and Results

Figure 1: E2197 Study Design and Results

Operable Breast Cancer
0-3 Positive Nodes
T>1 cm if Node Negative
N = 2885 Eligible Patients

AC
Doxorubicin 60 mg/m²
Cyclophosphamide 600 mg/m²
Every 3 Weeks x 4 Cycles

Tamoxifen x 5 Years
If HR-Positive
(Amended to Allow AIs)
Plus RT if Indicated

AT
Doxorubicin 60 mg/m²
Docetaxel 60 mg/m²
Every 3 Weeks x 4 Cycles

Tamoxifen x 5 Years
If HR-Positive
(Amended to Allow AIs)
Plus RT if Indicated

RESULTS:
- No difference between arms
- Median follow-up 76 months
- 96.8% reported follow-up until death or for at least 5 years
Objectives in E-2197 Genomic Analysis

General:
- Improve ability to identify individuals who benefit from chemotherapy, or specific chemotherapy regimens that vary in duration or drugs used

Specific:
1. To evaluate the prognostic utility of 21 Gene Assay RS in pts with HR-Pos disease treated with adjuvant chemotherapy
2. To perform an exploratory analysis for individual genes associated with prognosis in patients with HR-Pos and HR-Neg disease treated with adjuvant chemotherapy (analysis ongoing)
3. To perform an exploratory analysis to identify individual genes associated with differential sensitivity to AC versus AT (analysis ongoing)

ASCO - Goldstein, Abstract #526
### Results: Distribution of RS by HR Status

<table>
<thead>
<tr>
<th>Group</th>
<th>RS</th>
<th>HR-Pos*</th>
<th>HR-Neg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 18</td>
<td>198 (46%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>18 - 30</td>
<td>142 (30%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>High</td>
<td>≥ 31</td>
<td>125 (24%)</td>
<td>308 (99%)</td>
</tr>
</tbody>
</table>

- RS Distribution for HR-Pos Disease Similar to Prior Studies Including Only Node-Negative Disease
Outcomes by Nodal Status

All of these patients received chemotherapy (either AC or AT)

![Graph showing outcomes by nodal status](image)
All of these patients received chemotherapy (either AC or AT)
Recurrence Rates Are Very Low (≤ 5%) if the RS < 18 Irrespective of Axillary Lymph Node Status

<table>
<thead>
<tr>
<th>RS</th>
<th>Nodes</th>
<th>RFI (%)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt;18</td>
<td>Neg</td>
<td>96</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>95</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>Int 18-30</td>
<td>Neg</td>
<td>86</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>87</td>
<td>77</td>
<td>86</td>
</tr>
<tr>
<td>High ≥31</td>
<td>Neg</td>
<td>87</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>75</td>
<td>61</td>
<td>72</td>
</tr>
</tbody>
</table>
Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in Postmenopausal, Node-Positive (N+), ER-Positive (ER+) Breast Cancer
SWOG 8814, TBCI 0100

K. Albain, for The Breast Cancer Intergroup of North America
Phase III SWOG 8814 (TBCI 0100)  
Postmenopausal, N+, ER+

RANDOMIZE

\[ \text{tamoxifen x 5 yrs} \quad \text{(n = 361)} \quad \text{CAF x 6, with concurrent tam} \quad \text{(n = 550)} \quad \text{CAF x 6, then tamoxifen} \quad \text{(n = 566)} \]

Superior Disease-Free Survival (DFS) and Overall Survival (OS) over 10 Years

SWOG 8814/TBCI 0100
Sample Size for This Analysis

Patients with samples - 666
(45% of parent trial)

RT-PCR obtained - 601 (90%)

Tamoxifen alone 148
CAFT (concurrent) 234
CAF-T (sequential) 219

Final sample for primary analysis
148 + 219 = 367 (40% of parent trial)
Outcomes in RS Subset Mirror Those Reported in Main Trial: Superiority of CAF-T

Disease-Free Survival

Stratified log-rank p-value = 0.054 at 10 years (adjusted for nodal status)

- Tamoxifen (n=148, 63 events)
- CAF-T (n=219, 74 events)
### Comparative Distribution of RS
#### SWOG 8814: Less Low RS, More High RS

<table>
<thead>
<tr>
<th>Study</th>
<th>Low Risk (RS &lt; 18)</th>
<th>Int. Risk (RS 18-30)</th>
<th>High Risk (RS ≥ 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B14*</td>
<td>51%</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>NSABP B20*</td>
<td>54%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Kaiser controls*</td>
<td>56%</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>ECOG 2197**</td>
<td>49%</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>SWOG 8814***</td>
<td>40%</td>
<td>28%</td>
<td>32%</td>
</tr>
</tbody>
</table>


**node- or 1-3+: Goldstein, et al. Proc ASCO 2007

***node+, postmenopausal: this analysis - no difference by age
SWOG 8814/TBCI 0100
21-Gene Recurrence Score is Prognostic for DFS and OS in Tamoxifen Arm

Disease-Free Survival by Risk Group
(tamoxifen alone)

Overall Survival by Risk Group
(tamoxifen alone)

Stratified log-rank p = 0.017 at 10 years

Stratified log-rank p = 0.003 at 10 years

10-yr:  60%, 49%, 43%

10-yr:  77%, 68%, 51%
No benefit to CAF over time if low RS

Strong benefit if high RS

Disease-Free Survival by Treatment

Low risk (RS < 18)

Stratified log-rank p = 0.97 at 10 years

Disease-Free Survival by Treatment

High risk (RS ≥31)

Stratified log-rank p = 0.033 at 10 years

Disease-Free Survival by Treatment

Intermediate risk (RS 18-30)

Stratified log-rank p = 0.48 at 10 years
<table>
<thead>
<tr>
<th>Recurrence Score Risk Category</th>
<th>Tamoxifen Alone</th>
<th>CAF followed by tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ($&lt; 18$)*</td>
<td>60% (40%, 76%)</td>
<td>64% (50%, 75%)</td>
</tr>
<tr>
<td>Intermediate (18-30)</td>
<td>49% (32%, 63%)</td>
<td>63% (48%, 74%)</td>
</tr>
<tr>
<td>High ($\geq 31$)</td>
<td>43% (28%, 57%)</td>
<td>55% (40%, 67%)</td>
</tr>
</tbody>
</table>

*40% event rate over 10 years and resistance to CAF
Comparison of CAF-T to Tamoxifen Alone

DFS hazard ratios adjusted for nodal status

Trial Subset

- Overall trial
- Entire RS sample
- Low RS
- Intermediate RS
- High RS

Hazard Ratio

0 0.5 1 1.5 2

Chemotherapy benefit No chemotherapy benefit
CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS

Five-Year Probability of Death or Disease Recurrence
Linear model for Recurrence Score and interactions with treatment

Chemo benefit 4+ nodes
Chemo benefit 1-3 nodes
The RS is Also Predictive for Overall Survival in SWOG 8814/TBCI 0100

- No benefit to CAF in low RS in first 5 years (HR 1.05) or over entire time period (HR 1.18)

- Strong impact of CAF in high RS first 5 years
  HR 0.43 (0.21, 0.90)
  and over entire period
  HR 0.56 (0.31, 1.01)

10-year estimates:
Tam 51% (35%, 65%)
CAF-T 68% (51%, 79%)

Overall Survival by Treatment

Stratified log-rank test p = 0.027 at 10 years
70 Gene Assay

- 70 gene assay predicts for distant recurrence in patients with node-negative breast cancer
- Requires frozen tissue
- Has not been validated as a predictor for outcome from hormonal therapy or chemotherapy
- MINDACT Trial (Microarray In Node negative Disease may Avoid ChemoTherapy) trial is ongoing
ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

**CONCLUSIONS**

**Insufficient evidence of clinical utility**

**Evidence of clinical utility**

- **CA 15-3**
- **CA 27-29**
- **CEA**

  for monitoring response in MBC

- **ER**
- **PgR**
- **HER2**

  for tailoring therapy

- **UPA**
- **PA-1**

  for avoiding adjuvant chemo if low and ER high

- **21 Gene Assay**

  for avoiding adjuvant chemo if RS low

- **DNA PLOIDY (Flow cytometry)**
  - Ki67
  - p53
  - Cathepsin P
  - Cyclin E
  - Topoisomerase II

- **Proteomics**
  - **70 Gene Assay**

  Bone marrow micrometastases

  Circulating tumor cells
TAILORx (n=10,500 women) and MINDACT (n=6,000 women) Bringing Molecular Prognostic Signatures to Daily Clinical Practice

Node-negative B.C. population

- High risk 21-gene R.S. OR
- High risk 70-gene signature +
- High risk adjuvant on line

- Medium risk 21-gene R.S. OR
- Discordant risk group (mostly low risk 70-gene signature but high risk adjuvant on line)

- Low risk 21-gene R.S. OR
- Low risk 70-gene signature +
- Low risk adjuvant on line

Chemotherapy
- RANDOMIZE CHEMO YES or NO (TailorX)
- RANDOMIZE FOR the decision-making tool (Mindact)

Endocrine Therapy