How Much IS Too Much?
Who Needs Adjuvant Chemotherapy?

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What We Know: Survival Is Improved….But

- We treat many patients to benefit only a few

- 85% of patients with stage 1-2, node-negative, ER+ disease will never experience distant recurrence with tamoxifen alone (NSABP Study B-14, 1989)
  - Therefore only 15% of these women are at risk for metastatic disease, but we treat at least 50% of them with adjuvant chemotherapy!

- Adjuvant cytotoxic chemotherapy produces an absolute reduction in 10-year risk of distant recurrence of about 4% in this same population of early stage patients (NASBP Study B-20, 1997)
Oncologists prescribe adjuvant chemotherapy (CT) for many patients with a low risk of recurrence.

- **10 Year Recurrence Rate** (NSABP B-14: tamoxifen only arm):
  - 15% patients receiving CT for no medical benefit with high probability of toxicity.

- **Adjuvant CT Utilization Rate (% of Patients):**
  - 55%
Unmet Clinical Need for Better Markers of Recurrence

- Biopsy or Resection

  Patient Classifier

  - High risk
    - Optimize chemotherapy and/or targeted therapy
  - Low risk
    - Optimize local therapy and hormonal therapy
New Patient Classifiers have been developed in recent years

- **Clinically Validated Classifiers:**
  - Adjuvant! Online calculator tool
  - Oncotype DX™ Breast Cancer Assay

- **Investigational Classifiers:**
  - Bone Marrow Micrometastasis (BMM)
  - MammaPrint® (Amsterdam 70 Gene Assay)
Web-based computer model
  • Based on meta-analyses from clinical trials
  • Regularly updated: Version 8.0 (12/28/05)

Predicts 10-year DFS and OS based on classic pathologic criteria
  • Age & Menopausal status
  • Tumor size, nodal status, ER status, tumor grade
    • Can integrate HER-2 status
    • Includes genomic version to calculate mortality probability in conjunction with Recurrence Score

Assumes cancer completely resected
Adjuvant! Validation Study

- Projections validated by comparison with clinical and treatment data from British Columbia Cancer registry
  - n = 4083 women from 1989-1993
- Predicted overall survival within 1% of observations
  - Consistent with expectations for a tool based on meta-analysis compilation from large trials
  - Optimized for describing distributions of populations
- Can be overly optimistic in some cases
  - DFS in women < 35
  - DFS for women on chemotherapy
  - DFS for women on chemo and tam
Adjuvant! is an excellent tool

- Deemed useful for clinical practice >> with cautions
  - Outcomes are population based
  - Results no better than input values – if they are wrong, outputs will be wrong

- Should not supplant clinical judgment as it does not assess individual tumors directly

- Also includes extensive information on treatment side effects and various illustrations designed to be used in patient discussions – great discussion aids
Adjuvant! Example: Value of Adjuvant Chemotherapy

80% will be disease free in 10 years with hormonal therapy alone.

83% will be disease free in 10 years with the addition of adjuvant chemotherapy.

Therefore: In exchange for treating 100 women, only 3 women are likely to benefit from taking adjuvant chemotherapy in this example!

(Reference: www.adjuvantonline.com)
Gene Expression Profiling: Shifting focus to tumor biology by measuring activity inside cells
Complementary RNA Analysis Methods

RT-PCR Assay
- Fixed paraffin or unfixed tissue
- 100s of genes
- Wide dynamic range, high sensitivity, specificity, reproducibility

DNA Arrays (Chips)
- Unfixed or recently fixed tissue
- 1000s of genes
- Limited dynamic range and difficult to control

The Oncotype DX™ Story

A Multigene RT-PCR Assay for Predicting the Likelihood of Breast Cancer Recurrence and Response to Adjuvant Treatment
Candidate Gene Selection

From ~25,000 genes:

- Cancer Literature
- Microarray Data*
- Genomic Databases
- Molecular Biology

250 cancer-related candidate genes

OncoType DX™: Final Gene Set

**PROLIFERATION**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**HER2**
- GRB7
- HER2

**ESTROGEN**
- ER
- PGR
- Bcl2
- SCUBE2

**INVASION**
- Stromelysin 3
- Cathepsin L2

**REFERENCE**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

**CD68**

**BAG1**
Onco type DX™ Clinical Validation:
Recurrence Score as Continuous Predictor
First Primary Endpoint
*Recurrence Score Correlates with Clinical Outcome*

Primary Endpoint: Distant Recurrence-Free Survival

\[ P < 0.00001 \]

- **Low Risk** (Recurrence Score 0 to <18): 6.8\%
  - 95% CI: 4-9.6\%

- **Intermediate Risk** (Recurrence Score 18 to <31): 14.3\%
  - 95% CI: 8.3-20.3\%

- **High Risk** (Recurrence Score 31 to 100): 30.5\%
  - 95% CI: 23.6-37.4\%
OncoType DX™ NSABP B-14 Clinical Data

Recurrence Score vs NCCN Guidelines: Opportunity for Reclassification

All Patients  N = 668

NCCN: Low Risk

- 53
- 38
- 12
- 3

NCCN: High Risk

- 615
- 300
- 137
- 178

20%  40%  60%  80%  100%

% Distant Recurrence-Free at 10 Years

Paik et al. NEJM 2004;351:2817-26
Second Primary Endpoint

Recurrence Score is better than age and tumor size:

Primary Endpoint: Distant Recurrence-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Significance Excluding Recurrence Score</th>
<th>Significance Including Recurrence Score</th>
</tr>
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<tbody>
<tr>
<td>Age ≥ 50</td>
<td>p=0.004</td>
<td>p=0.084 (not significant)</td>
</tr>
<tr>
<td>Tumor Size &gt; 2.0 cm</td>
<td>p=0.058</td>
<td>p=0.231 (not significant)</td>
</tr>
<tr>
<td>Recurrence Score</td>
<td>N/A</td>
<td>p&lt;0.00001 (highly significant)</td>
</tr>
</tbody>
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58 year old postmenopausal
- 1.3 cm tumor, T1cNO
- IDC
  - ER: 100% IHC
  - PR: -
- HER2/neu: - (Fish)
- Grade 3
- 5% DCIS grade 2
- - margins

RS = 34
23% chance 10 yr DR

59 year old postmenopausal
- 1.4 cm tumor, T1cNO
- IDC
  - ER: 80% 3+ IHC
  - PR: 70% 3+ IHC
- HER2/neu: - (IHC 1+)
- Grade 2
- DCIS grade 2
- - margins

RS = 4
5% chance 10 yr DR
Oncotype DX™ in Clinical Practice

- Oncotype DX™ has been offered by Genomic Health, Inc., since January 2004
  - Genomic Health is a CLIA-approved reference lab
  - Send tumor block or 6 fixed, paraffin-embedded sections (10 µm each) using the Oncotype DX Specimen Kit
  - Turnaround time: 10-14 days
  - Cost: $3,460
  - Reimbursement: Genomic Health takes assignment of benefits and manages claims process
Oncotype DX™: Patient Report

- The patient report includes:
  - Recurrence Score (RS)
  - Average 10-year distant recurrence rate for that RS
  - Graph of 10-year recurrence risk as a function of RS in tamoxifen-treated patients

- The report is sent to:
  - Treating physician
  - Submitting pathologist

Recurrence Score (RS)

Average 10-year distant recurrence rate for that RS

Graph of 10-year recurrence risk as a function of RS in tamoxifen-treated patients
Almost the entire risk reduction benefit reported in the B-20 trial was seen in Patients with high Recurrence Scores.
Oncotype DX: Conclusions From Clinical Trials

For stage 1-2, node negative, ER+ patients with invasive breast cancer, who will receive hormonal therapy:

Oncotype DX™ is:

- Prognostic (quantifies disease aggressiveness)
- Predicts tamoxifen benefit
- Predicts chemotherapy benefit
  - Low RS associated with minimal chemotherapy benefit
  - High RS associated with large chemotherapy benefit
Commercial Utilization

- Genomic Health reports 2500+ physicians have ordered assay in US

- Over 7,000 women tested in 2005

- Clinical value driven by:
  - Reclassifying women from High >> Low
    - Reduced toxicity and cost
  - Reclassifying women from Low >> High
    - Reduced risk of recurrence if women take chemotherapy
  - Increased confidence when results confirm expectations based on traditional factors
Reimbursement Update: 2006

Medicare
- Medicare coverage effective: Feb. 27, 2006
- This policy will apply to patients in all 50 states

Private Health Plans
- In-network coverage policies established with:
  - Kaiser Permanente
  - Harvard/Pilgrim Health Plan
  - Federal Employee Health Benefits Program
  - Several large BC/BS carriers + other smaller payers
- Over 250 health plans have now paid for 1 or more tests
  - Extensive reimbursement support program from Benefits Investigation to Appeals
  - Uninsured Patient Program
  - Financial Assistance for those that are underinsured or have balances due
Investigational Tools
MammaPrint®
Amsterdam 70 Gene Expression Signature

- Microarray chip, requires fresh tumor tissue
- No longer marketed in the US, but still available in Europe from Agendia
- Controversial data interpretation with significantly less power in multi-center trial than originally seen in 2002 publication
- Prospective validation trial (MINDACT) to commence in 2006 with TRANSBIG consortium in Europe
  - To compare this genomic patient classifier against traditional methods

Cardoso, 2005; van de Vijver, 2005; breastinternationalgroup.org
Bone Marrow Micrometastasis

- Analysis of pooled data from 9 studies involving 4703 stage I, II, and III breast cancer patients provides evidence for negative prognostic value.
- Subgroup of 807 pT1N0 patients with no systemic adjuvant therapy and + BMM had significantly decreased OS (p=0.0001) and DFS (p=0.01).
- Potential marker for risk stratification and need for adjuvant therapy.
- Analysis can help plan clinical trials to assess BMM use in routine staging.
- It is invasive!

(Vogl, F.D., SABC 2005, abstract #5)
In Summary……

- We have 2 very good and very different tools!
- One applies to most patients but is population based and requires data to be entered
- One applies to a limited population but is more specific, looks at individual GEP (Genomic Expression Profile)
- Research is ongoing and getting more specific!
  - TAILORx Treatment Trial (PAACT-1)