Using Oncotype DX for Radiotherapy Decisions in Breast Cancer

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Disclosure

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*Subject of this presentation
Outline

• Recurrence score (RS) and Locoregional Recurrence (LRR) in node negative breast cancer trials
• RS and LRR in node positive breast cancer trials
• Is LRR the whole story? MA-20/EORTC 22922
• Current Practice
• Future
Whelan Meta-analysis

> 6,300 pts – only trials that incorporated systemic chemotherapy

Overall Survival

![Image: Meta-analysis of locoregional radiation therapy randomized trials: mortality.]

**Study** | **N** | **OR** | **95% CI**
--- | --- | --- | ---
DeBoer    | 50   | 0.87 | 0.28, 2.65
Feroglia  | 78   | 0.38 | 0.14, 1.05
Kleftstrom| 79   | 0.17 | 0.04, 0.67
Trumperich| 89   | 1.25 | 0.53, 2.95
Bloomquist| 99   | 1.16 | 0.50, 2.70
Hayat     | 112  | 1.63 | 0.70, 3.77
Cervasio  | 112  | 1.11 | 0.61, 2.43
Muss     | 169  | 0.81 | 0.43, 1.50
Schmoor   | 193  | 0.72 | 0.32, 1.67
Gries    | 218  | 1.17 | 0.68, 1.99
McArdle  | 219  | 0.83 | 0.49, 1.43
Velez-Garcia | 239  | 0.70 | 0.42, 1.17
Martinez  | 241  | 1.12 | 0.67, 1.87
Olson    | 312  | 1.01 | 0.65, 1.58
Ragaz   | 315  | 0.66 | 0.42, 1.02
Tennwall-Nittby | 768  | 0.96 | 0.71, 1.30
Overgaard(TAM) | 1375 | 0.75 | 0.61, 0.93
Overgaard(CMF)  | 1700 | 0.73 | 0.61, 0.94

Random Effects OR = 0.83  95% CI = 0.74, 0.94

Radiation reduced odds of death by 17%
Background

21-gene Recurrence Score (RS) is a widely used gene expression profiling tool (OncotypeDX; Genomic Health Inc, Redwood City, CA).

Quantifies the risk of distant metastasis and predicts chemotherapy benefit at 10 years in node-negative and node-positive, ER positive, tamoxifen-treated breast cancer.
21-Gene RS and Distant Recurrence

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

**Estrogen**
- ER
- PR
- Bcl2
- SCUBE2

**Invasion**
- Stromelysin 3
- Cathepsin L2

**Her2**
- GRB7
- HER2

**GSTM1**

**CD68**

**BAG1**

**Reference Genes**
- Beta-actin, GAPDH, RPLPO
- GUS, TFRC

**NSABP B-14**
Validation Study:
Node(-)/ER (+)

![Graph showing disease-free survival (DFS) over years]

- Low Risk (RS <18)
- Intermediate Risk (RS 18 - 30)
- High Risk (RS ≥ 31)
RS AND LRR IN NODE NEGATIVE PATIENTS
RS has been correlated with LRR in retrospective studies of node negative NSABP B-14 and B-20 patients.
RS AND LRR IN NODE POSITIVE PATIENTS
NSABP B28

- Randomized phase III study, AC +/- Taxol
- All node positive
- All received chemotherapy
RS correlated with LRR in retrospective analysis of node positive NSABP B-28 patients

Mamounas E P et al. J Clin Oncol 30, 2012 (suppl 27; abstr 1)
Randomized phase III trial, N = 1477
ER and/or PR+, Node+, post-menopausal
Tamoxifen alone vs. Tamoxifen then CAF vs. Concurrent Tamoxifen + CAF
Optional tumor banking yielded specimens for RS determination by RT-PCR, N = 367
Methods

LRR and use of radiotherapy were extracted from charts of 367 patients with available RS.

Exclusions
- Mastectomy and radiation (37)
- BCS without radiotherapy (9)
- Unknown surgery type (5)

Cohort for this analysis, N = 316.
Methods (continued)

The effect of RS on LRR was assessed using cumulative incidence with censoring at last known contact if no LRR.

Intermediate (18-30) and high RS (>31) were grouped for the purpose of modeling.

Exploratory analysis confirmed optimal cutpoint at 18

Time to LRR was tested with log-rank tests and Cox regression for multivariate models.
### Similarity to Parent Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low RS (121)</th>
<th>Int/High RS (195)</th>
<th>Total (316)</th>
<th>Parent (927)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>61 yrs</td>
<td>60 yrs</td>
<td>60 yrs</td>
<td>61 yrs</td>
</tr>
<tr>
<td>+N 1-3</td>
<td>71.9%</td>
<td>63.1%</td>
<td>66.5%</td>
<td>58.4%</td>
</tr>
<tr>
<td>+N 4+</td>
<td>28%</td>
<td>36.9%</td>
<td>33.5%</td>
<td>41.6%</td>
</tr>
<tr>
<td>T vs CAF-T</td>
<td>36.4/63.6%</td>
<td>41/59%</td>
<td>39/61%</td>
<td>39/61%</td>
</tr>
<tr>
<td>Follow Up LRR</td>
<td>8.4 yrs</td>
<td>8.1 yrs</td>
<td>8.2 yrs</td>
<td>9.2 yrs</td>
</tr>
<tr>
<td>% LRR event</td>
<td>5.8%</td>
<td>13.9%</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>% DFS event</td>
<td>27.3%</td>
<td>43.1%</td>
<td>37%</td>
<td>42.6%</td>
</tr>
<tr>
<td>% Death</td>
<td>19%</td>
<td>30.8%</td>
<td>26.3%</td>
<td>34.4%</td>
</tr>
</tbody>
</table>
RS Associated with LRR on Multivariate Analysis

|                  | Hazard Ratio | Standard Error | Z    | P>|z| | 95% CI     |
|------------------|--------------|----------------|------|---------|-----------|
| Mod/High RS      | 2.36         | 1.01           | 2.02 | 0.04    | 1.02 – 5.45 |
| Mastectomy       | 1.10         | 0.51           | 0.22 | 0.82    | 0.45 – 2.71 |
| Nodes 4+         | 3.37         | 1.12           | 3.46 | 0.001   | 1.69 – 6.72 |
| Chemo            | 0.58         | 0.20           | 0.12 | 0.12    | 0.29 – 1.15 |
### Comparison of LRR over 10 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Log-rank p</th>
<th>10 year LRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS: 0-17 vs 18+</td>
<td>0.018</td>
<td>10% vs 17%</td>
</tr>
<tr>
<td>Nodes: 1-3 vs 4+</td>
<td>0.0002</td>
<td>9% vs 24%</td>
</tr>
<tr>
<td>Age groups</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>T vs CAF-T</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
LRR All Patients

Local/Regional Recurrence by Recurrence Score

- Recurrence Score 18+ (n=195)
- Recurrence Score 0-17 (n=121)

P = 0.018

- 16.8% Local/Regional Recurrence rate
- 9.7% Local/Regional Recurrence rate
LRR Mastectomy Without RT

Local/regional recurrence rate

Recurrence Score 18+ (n=160)
Recurrence Score 0-17 (n=92)
p = 0.025

Number at risk
- RS 18+: 160, 148, 133, 114, 88, 50
- RS 0-17: 92, 90, 84, 78, 59, 27

Years since Registration

Recurrence Score 18+ (n=160)
Recurrence Score 0-17 (n=92)
p = 0.025

7.7%
16.8%
LRR Mastectomy Without RT

Mastectomy 1-3 LN+

Mastectomy > 3 LN+

*BCT results are not presented due to insufficient events
MA-20/EORTC 22922

IS LRR THE WHOLE STORY?
Breast cancer stage I-III:
• Involved axillary nodes
• Central/medial tumour

ENDPOINTS
Main: Overall survival
Secondary: Disease -free survival
Metastases-free survival
Cause of death

IM-MS irradiation (50Gy)
No IM-MS Irradiation

EORTC 22922
Conclusions

• **Breast-cancer mortality** at 15 years was statistically significantly reduced from 19.8% to 16.0% (p=0.006).

• The probability of breast cancer recurrence within the first 15 years was reduced from 27.1% to 24.5% (p=0.024).

• Independent of LRR
Breast cancer stage I-III:
- Involved axillary nodes
- Central/medial tumour

Should all eligible patients get regional nodal irradiation?

EORTC 22922

3.8% Improved Breast Cancer Mortality
Molecular RT Benefit Predictors?

• Limited for radiotherapy to date
  – RS is prognostic, multiple secondary analyses of randomized trial data
  – Focus on LRR critical but may be too narrow
    • RT benefit independent of LRR

• Need to be tested in randomized radiation studies to assess predictive value
Endocrine Therapy Alone After BCS for Selected Biologically Low-Risk Tumors?

**NOT THE STANDARD OF CARE BUT AN AREA OF ONGOING INVESTIGATION**

<table>
<thead>
<tr>
<th>Lumina</th>
<th>Idea</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prospective multicenter cohort study in Canada</td>
<td>• Prospective multicenter cohort study in US (Michigan, MSKCC, Hopkins, Harvard/ Meghan, Harvard/BIDMC, Penn, Stanford, Yale, Loyola, MCW, ECU, UTSW, CINJ/ Rutgers, Northwell)</td>
<td>• Prospective multicenter cohort study in Boston (DFCI/BWH)</td>
</tr>
<tr>
<td>• Age 55+</td>
<td>• Age 50-69</td>
<td>• Age 50-75</td>
</tr>
<tr>
<td>• Unifocal Stage I (pN0), lumpectomy, negative margins (1 mm), no EIC, no LVI, no Grade 3</td>
<td>• Unifocal Stage I (pN0), lumpectomy, negative margins (2 mm)</td>
<td>• Unifocal Stage I (pN0), lumpectomy, no tumor on ink, no Gr 3</td>
</tr>
<tr>
<td>• ER+/PR+/Her2-</td>
<td>• ER+/PR+/Her2-</td>
<td>• ER+ (PR- allowed)</td>
</tr>
<tr>
<td>• Luminal A tumors (by IHC; centralized Ki67 not &gt;13%)</td>
<td>• Low Oncotype-DX RS (≤18)</td>
<td>• Prosigna PAM50&lt;40 and Luminal A</td>
</tr>
<tr>
<td>• Expect 500 pts, opened 2013</td>
<td>• Expect 200 pts, opened 2015</td>
<td>• Expect 345 pts, opened 2016</td>
</tr>
</tbody>
</table>
**Tailor RT**

*Patients with 1-3 positive axillary nodes* post-BCS or mastectomy that are ER +ve biomarker low risk**

Rx with endocrine therapy x 5 years

No Regional RT
- BCS – WBI
- Mastectomy – no RT

Regional RT
- BCS – WBI + regional nodes
- Mastectomy – chest wall + regional nodes

**Stratification**
1. Mastectomy or BCS
2. Axillary dissection – yes/no
3. Adjuvant chemo – yes/no
4. LVI – yes/no
5. Oncotype DX recurrence score (0-10, 11-17)

* Patients may be treated with axillary dissection with 1-3 positive nodes (macro mets) or SLNB alone: post-BCS with 1-2 positive sentinel nodes (macro mets) or post-mastectomy with only 1 positive SN (macro mets).

**Defined as Oncotype DX recurrence score < 18**
Today and beyond…

- RS is associated with risk of LRR in node negative and positive ER+ patients
- Significant association on multivariable analysis from secondary analyses of three randomized trial subsets spanning tamoxifen only and chemotherapy + tamoxifen treated patients
- RS may be useful in conjunction with clinical risk factors to make radiotherapy decisions
- Observation based solely on RS should be tested on trial
pN1 (macromets):
1. Age < 40, upfront surgery
2. 3+ LN's upfront surgery
3. ypN+
4. cT3 N1
5. ER-, upfront surgery
6. Age < 50 with RS >18, if known
7. SLNB only and >33% risk of additional nSLNS
8. >40, p1-2LN+, ER+ and at least two:
   • ~Luminal B (ki-67>20% or Her2+)
   • G3
   • LVSI
   • High genomic score
   • medial tumor location

pN0, pN0(i+) or micromets
1. At least three:
   • T3
   • N1(mic)
   • multiple mic nodes
   • medial tumor location
   • <45
   • G3
   • LVSI
   • ER-
   • Luminal B (High Ki-67 >20% or Her2+)
   • SLN only, >33% nomogram risk
   • high genomic score
A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study


- Genomically personalized radiation dose:
- Calculate radiation sensitivity Index (RSI)
- Substitute RSI into the linear quadratic model that relates radiation dose and repair to biologic effectiveness