Radiation Oncology Updates In Breast Cancer: Molecularly based signatures for radiation decision making

Where are we now and where are we going?

Corey Speers MD, PhD
University of Michigan
Midwest Regional SABCS Review
Corey Speers MD, PhD- Co-founder and unpaid consultant for PFS Genomics
Educational Objectives

• Review the recent updates of radiation-related studies from SABCS 2019

• Review the development of prognostic and predictive gene signatures to guide systemic chemotherapy decisions

• Review the development of prognostic and predictive gene signatures to guide radiotherapy decisions

• Summarize all ongoing genomically stratified clinical trials, including those for radiation omission
Question

Which of the following molecular signatures has been validated as a prognostic biomarker for women with breast cancer?

(A) Oncotype Dx
(B) MammaPrint
(C) ProSigna
(D) All of the above
(E) None of the above
Question

Which of the following molecular signatures has been validated as a predictive biomarker of radiation response for women with breast cancer?

(A) DBCG-RT  
(B) Radiation Sensitivity Index (RSI)  
(C) Radiation and Immune-based Signature  
(D) Radiotype Dx  
(E) All of the above  
(F) None of the above
Question

There are currently numerous ongoing genomically stratified clinical trials for radiation omission

(A) True
(B) False
Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer

10-year follow up results of the APBI IMRT Florence randomized phase 3 trial

Icro Meattini¹,², Calogero Saieva³, Sara Lucidi¹, Monica Io Russo¹, Vieri Scotti², Isacco Desideri¹,², Livia Marrazzo², Gabriele Simontacchi², Monica Mangoni¹,², Carlotta Becherini¹, Lisa Paoletti³, Erika Moretti³, Luca Triggiani³, Marco Bernini³, Lorenzo Orzalesi¹,², Luis Sanchez², Jacopo Nori², Stefania Pallotta¹,², Simoettta Bianchi¹,², and Lorenzo Liviti,²

¹University of Florence, Florence; ²Azienda Ospedaliero-Universitaria Careggi, Florence; ³Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence; ⁴Ospedale Santa Maria Annunziata - Azienda Usl Toscana centro, Florence; ⁵Ospedale S. Stefano - Azienda Usl Toscana centro, Prato; ⁶University of Brescia, Brescia; Italy
**Background**

**ESTRO and ASTRO recommendation identified suitable patients for PBI outside clinical trials**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Risk Factor</th>
<th>2009</th>
<th>2016 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASTRO Suitable</strong></td>
<td>Age</td>
<td>≥60</td>
<td>≥50</td>
</tr>
<tr>
<td></td>
<td>Margins</td>
<td>≥ 2 mm</td>
<td>≥ 2 mm</td>
</tr>
<tr>
<td></td>
<td>Nodal status</td>
<td>pN0</td>
<td>pN0</td>
</tr>
<tr>
<td></td>
<td>T stage</td>
<td>T1</td>
<td>Tis or T1</td>
</tr>
<tr>
<td></td>
<td>ER/PgR</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>Not allowed</td>
<td>G1-2; ≤2.5 cm</td>
</tr>
<tr>
<td></td>
<td>Lobular invasive</td>
<td>Not allowed</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Risk Factor</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESTRO Low Risk</strong></td>
<td>Age</td>
<td>≥ 50</td>
</tr>
<tr>
<td></td>
<td>Margins</td>
<td>≥ 2 mm</td>
</tr>
<tr>
<td></td>
<td>Nodal status</td>
<td>pN0</td>
</tr>
<tr>
<td></td>
<td>T stage</td>
<td>T1-2</td>
</tr>
<tr>
<td></td>
<td>ER/PgR</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td></td>
<td>Lobular Invasive</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

Polgar C, et al. R&O 2010
Smith BD, et al. IROBP 2009
Correa C, et al. PRO 2016
Trial design- APBI IMRT Florence

Phase III trial (n=520 patients)
- Breast conserving surgery
- pT <25 mm
- Final surgical margins ≥5 mm
- Age >40 years

APBI using IMRT
30 Gy in 5# non-consecutive

1:1 randomization

CF-WBI
50 Gy in 25# + 10 Gy in 5# boost

Follow Up

Primary endpoint
- IBTR

Secondary endpoints
- Overall (OS) and breast cancer specific-survival (BCSS)
- Contralateral breast cancer (CBC)
- Early and late toxicity
- Physician-rated cosmesis

Livi L, et al. EJC 2015

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APBI USING S&S IMRT TECHNIQUE
Target Delineation and OARs dose thresholds

Surgical Clips
(4 mandatory)
CTV identification

CTV
Surgical Clips + 1 cm

PTV
CTV + 1 cm
limiting to 3 mm from skin and to 4 mm intrusion in homolateral lung

OAR | Constraint
--- | ---
Contralateral Lung | V5 <10%
Homolateral Lung | V10 <20%
Heart | V3 <10%
Homolateral breast (uninvolved tissue) | V15 <50%
Contralateral Breast | Max 1 Gy in each point

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## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>APBI N (%)</th>
<th>WBI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>41 (15.8)</td>
<td>45 (17.3)</td>
</tr>
<tr>
<td>51-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>84.2</td>
<td>82.7</td>
</tr>
<tr>
<td>≥70</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-2</td>
<td>90.0</td>
<td>87.3</td>
</tr>
<tr>
<td>G3</td>
<td>28 (10)</td>
<td>33 (12.7)</td>
</tr>
<tr>
<td><strong>pT stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pTis</td>
<td>23 (8.8)</td>
<td>32 (12.3)</td>
</tr>
<tr>
<td>pT1</td>
<td>85.8</td>
<td>81.9</td>
</tr>
<tr>
<td>pT2</td>
<td>14 (5.4)</td>
<td>15 (5.8)</td>
</tr>
<tr>
<td><strong>No. N+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>89.2</td>
<td>81.9</td>
</tr>
<tr>
<td>1-3</td>
<td>19 (7.3)</td>
<td>33 (12.7)</td>
</tr>
<tr>
<td>No ALDN</td>
<td>9 (3.5)</td>
<td>14 (5.4)</td>
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<td><strong>ER status</strong></td>
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<td></td>
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<tr>
<td>Positive</td>
<td>95.4</td>
<td>95.8</td>
</tr>
<tr>
<td>Negative</td>
<td>12 (4.6)</td>
<td>11 (4.2)</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>APBI N (%)</th>
<th>WBI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ki67 index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>193 (72.2)</td>
<td>174 (72.2)</td>
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<tr>
<td>≥20%</td>
<td>50 (20.6)</td>
<td>67 (27.8)</td>
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<tr>
<td><strong>Molecular Subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal A-like</td>
<td>94.9</td>
<td>92.8</td>
</tr>
<tr>
<td>Luminal B-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+ (non luminal)</td>
<td>6 (2.8)</td>
<td>13 (6.2)</td>
</tr>
<tr>
<td>Triple negative</td>
<td>5 (2.3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Systemic treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>35.8</td>
<td>28.8</td>
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<tr>
<td>Endocrine therapy (ET) only</td>
<td>155 (59.5)</td>
<td>162 (62.3)</td>
</tr>
<tr>
<td>Chemotherapy (CT) only</td>
<td>5 (1.9)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>CT and ET</td>
<td>7 (2.7)</td>
<td>20 (7.7)</td>
</tr>
<tr>
<td><strong>Risk Class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRO Suitable</td>
<td>133 (51.2)</td>
<td>113 (43.5)</td>
</tr>
<tr>
<td>ASTRO Intermediate-unsuitable</td>
<td>127 (48.8)</td>
<td>147 (56.5)</td>
</tr>
<tr>
<td>ESTRO Low Risk</td>
<td>190 (73.1)</td>
<td>166 (63.8)</td>
</tr>
<tr>
<td>ESTRO Medium-High Risk</td>
<td>70 (26.9)</td>
<td>94 (36.2)</td>
</tr>
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</table>
No differences in locoregional recurrence, distant metastasis, disease specific survival, or contralateral breast cancers
Acute reactions - skin toxicity

Results - Acute Adverse Events
RTOG & EORTC acute toxicity scale

<table>
<thead>
<tr>
<th>Any skin toxicity</th>
<th>APBI (n=246) N</th>
<th>%</th>
<th>WBI (n=274) N</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>194</td>
<td>78.9</td>
<td>87</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>Yes, any Grade</td>
<td>52</td>
<td>21.1</td>
<td>173</td>
<td>66.5</td>
<td>0.0001</td>
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<tr>
<td>None</td>
<td>194</td>
<td>78.9</td>
<td>87</td>
<td>33.5</td>
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<td>Grade 1</td>
<td>47</td>
<td>19.1</td>
<td>75</td>
<td>28.8</td>
<td>0.0001</td>
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<td>Grade 2</td>
<td>5</td>
<td>2.0</td>
<td>81</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>6.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Grade 0-1</td>
<td>241</td>
<td>98.0</td>
<td>162</td>
<td>62.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>5</td>
<td>2.0</td>
<td>98</td>
<td>37.7</td>
<td></td>
</tr>
</tbody>
</table>

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Late reactions - skin toxicity

### Results - Late Adverse Events

**RTOG & EORTC late toxicity scale**

<table>
<thead>
<tr>
<th>Any skin toxicity</th>
<th>APBI (n=246)</th>
<th>WBI (n=274)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>235 / 95.5%</td>
<td>182 / 70.0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Yes, any Grade</td>
<td>11 / 4.5%</td>
<td>78 / 30.0%</td>
<td></td>
</tr>
<tr>
<td>Grade 0-1</td>
<td>246 / 100%</td>
<td>253 / 97.3%</td>
<td></td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>0 / 0%</td>
<td>7 / 2.7%</td>
<td>0.015</td>
</tr>
</tbody>
</table>

**Skin Toxicity Distribution**

- None
- Grade 1
- Grade 2
- Grade 3
- Grade 4

*p = 0.0001*

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### Results – Cosmesis

#### Harvard Breast Cosmesis Scale

<table>
<thead>
<tr>
<th></th>
<th>APBI (n=246)</th>
<th>WBI (n=274)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Physician</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>235</td>
<td>95.5</td>
<td>199</td>
</tr>
<tr>
<td>Good</td>
<td>11</td>
<td>4.5</td>
<td>70</td>
</tr>
<tr>
<td>Fair</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Poor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>44</td>
<td>17.9</td>
<td>14</td>
</tr>
<tr>
<td>Good</td>
<td>200</td>
<td>81.3</td>
<td>220</td>
</tr>
<tr>
<td>Fair</td>
<td>2</td>
<td>0.8</td>
<td>40</td>
</tr>
<tr>
<td>Poor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Other trials of APBI reported at SABCS 2018

These results add to the previously presented and published data on APBI

• The Canadian/NZ/Australian RAPID trial (2,135 pts) using 3D conventional treatment (APBI using 38.5 Gy in 10 fractions BID vs. standard fractionation/hypofractionated RT)
  – Similar rates of IBTR with worse late cosmesis

• RTOG 0413/NSABP B-39 trial (4,216 pts) of 38.5 Gy in 10 fractions BID vs. standard fractionation (3D or brachytherapy).
  – Numerically higher rates of IBTR and non-equivalence for treatment effect between the treatment arms
  – Slightly higher rates of late Grade 3 and Grade 4-5 toxicity in PBI patients

• Numerous other brachytherapy trials
Molecular signatures in Breast Cancer

• Prognostic and predictive signatures and the relationship to chemotherapy response

• Radiation response signatures for invasive breast cancer

• Ongoing radiation trials for invasive disease using molecularly stratified inclusion criteria
Two ends of the treatment spectrum

• For certain patients, more effective surgical and systemic therapies have made adjuvant radiation therapy unnecessary

• For other patients, current multi-modality therapy is ineffective in prevent disease recurrence and/or progression
  • Ineffective therapies
  • Inadequate risk stratification
>6000 women treated with breast conserving surgery

Who needs adjuvant radiotherapy?

Which individual (rather than which group) will benefit from adjuvant therapy?

Up to 40% of patients with a poor prognosis as defined by conventional clinicopathological parameters will remain disease free without adjuvant radiation therapy.

The benefit from adjuvant radiotherapy for patients with lymph node–negative (LN-) disease is not uniform; some patients relapse despite therapy (10%) and others are already cured by local treatment (60-70%).
Prognostic and Predictive Signatures

The likelihood of developing distant recurrence in this patient population is only 15% at 10 years, which means 85% of patients are overtreated if they all receive chemotherapy.

Who benefits from chemotherapy?
Who can we safely spare?

Oncotype DX® was developed to quantify the likelihood of disease recurrence in women with ER+, LN- breast cancer and was found to be useful in predicting response to chemotherapy.
Sixteen cancer-related genes and five reference genes were selected from the candidate genes. The 16 cancer-related genes were then used to develop an algorithm based on the expression levels of these genes, thus allowing a Recurrence Score™ (RS) to be computed for each specimen. This RS correlated with the rate of distant recurrence at 10 years.

Sixteen Cancer and Five Reference Genes

<table>
<thead>
<tr>
<th>PROLIFERATION</th>
<th>INVASION</th>
<th>HER2</th>
<th>ESTROGEN</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67, STK15, Survivin, Cyclin B1, MYBL2</td>
<td>Stromelysin 3, Cathepsin L2</td>
<td>GRB7, HER2</td>
<td>ER, PGR, Bcl2, SCUBE2</td>
<td>Beta-actin, GAPDH, RPLPO, GUS, TFRC</td>
</tr>
<tr>
<td></td>
<td>Best RT-PCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>performance and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>most robust</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>predictors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Oncotype Dx® Breast Recurrence Score**
Oncotype Dx® Validation

NSABP Study B-20
The Oncotype Dx® Recurrence Score assay not only quantifies the likelihood of breast cancer recurrence in women with N-, ER+ breast cancer, but also predicts the magnitude of chemotherapy benefit.

Additional NSABP studies showing predictive in LN-positive patients (and SWOG 8814) and lack of chemotherapy benefit in patients with an intermediate risk score (RS= 11-25) (TAILORx)
MammaPrint® - Agenda

LOW RISK

No distant metastasis within 5 years

“Untreated” tumor samples with up to 20 year follow-up

Full human genome 25K

70 most significant genes predictive of recurrence risk were identified

HIGH RISK

Distant metastasis within 5 years

Full human genome 25K
MammaPrint® Validation

MINDACT validation in patients with discordant clinical and genomic risks

TRANSBIG Validation Results

Probability of metastasis free survival

Time to Distant Metastases (years)

111 MammaPrint Low Risk Signature
191 MammaPrint High Risk Signature

n=302
p=0.001
Prosigna® Breast Cancer Prognostic Gene Signature Assay - Nanostring

Development of Prosigna™ is Based on PAM50 Gene Signature

- **2000**: Researchers first describe breast cancer intrinsic subtypes based on microarray experiments.
- **2009**: Researchers first describe “PAM50” gene expression signature.
- **2010**: NanoString exclusively licenses PAM50 gene expression signature.
- **2012/13**: Prosigna launches after receiving CE Mark for Europe & Israel; FDA 510k clearance in US.

PAM50 developed by a consortium of four academic breast cancer experts:
- Charles Perou, PhD, University of North Carolina
- Dr. Matt Ellis, Washington University School of Medicine
- Torsten Nielsen, MD, PhD, Pathologist, BC Cancer Agency
- Philip Bernard, MD, University of Utah / Huntsman Cancer Institute

Source: Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes, JCO, 2009
Question

Which of the following molecular signatures has been validated as a prognostic biomarker for women with breast cancer?

(A) Oncotype Dx
(B) MammaPrint
(C) ProSigna
(D) All of the above
(E) None of the above
What about signatures to predict radiation response?

Several under development, but what about the previously derived signatures for chemotherapy benefit?
Prognostic and Predictive Signatures for Personalized Radiation Decisions

Previously derived
• Oncotype Dx®
• Oncotype Dx® for DCIS
• IHC surrogates for subtype

Radiation specific signatures
Invasive disease
• Danish Breast Cancer Group (DBCG-RT)
• Radiation Sensitivity Index (RSI)
• Radiosensitivity and Immune Gene Signature
• Radiation Sensitivity Signature (RSS or Radiotype Dx®) and Adjuvant RadioTherapy Intensification Classifier (ARTIC)
Previously derived signatures applied to radiation questions

**Previously derived**
- Oncotype Dx®
- Oncotype Dx® for DCIS
- IHC surrogates for subtype
Previously derived signatures applied to radiation questions

**Previously derived**

- Oncotype Dx®
- Oncotype Dx® for DCIS
- IHC surrogates for subtype
Locoregional recurrence using Oncotype Dx® in node-negative patients

**NSABP B-14**: ER+, node-negative patients s/p TM or lumpectomy, ALND, and RT randomized to +/- tamoxifen

**NSABP B-20**: ER+, node-negative patients s/p TM or lumpectomy, ALND, and RT randomized to chemo + tamoxifen vs tamoxifen alone

Locoregional Recurrence using Oncotype Dx® in Node-negative patients

**A**

- **Tamoxifen**
  - RS < 18
  - RS 18-30
  - RS ≥ 31
  - Log-rank P < .0001
  - 0.4 Proportion of Locoregional Recurrence
  - Time (years) 0 2 4 6 8 10
  - B14 and B20 pts tam pts

**B**

- **Placebo**
  - RS < 18
  - RS 18-30
  - RS ≥ 31
  - Log-rank P = .022
  - 0.4 Proportion of Locoregional Recurrence
  - Time (years) 0 2 4 6 8 10
  - B14 placebo pts

**C**

- **Chemotherapy + Tamoxifen**
  - RS < 18
  - RS 18-30
  - RS ≥ 31
  - Log-rank P = .028
  - 0.4 Proportion of Locoregional Recurrence
  - Time (years) 0 2 4 6 8 10
  - B20 chemo+tam pts

Factors associated with locoregional recurrence in NSABP B-14 and B-20

Importantly, there is no data regarding recurrence rates by recurrence score in women treated with lumpectomy WITHOUT RT, nor are there differences in LRR rates by RS score in RT treated pts.

Locoregional Recurrence using Oncotype Dx® in Node-positive patients

NSABP B-28: AC x 4 cycles vs. AC x 4 + T x 4 in N+ patients.
- tamoxifen in young ER+ and older than 50 yr old patients
- RT for lumpectomy patients, not given to mastectomy patients

All NSABP B-28 patients (n = 3060)

- No tissue blocks, ER-negative (n = 1945)
  - Clinically ineligible (n = 8)
  - No tamoxifen (n = 17)
  - Mastectomy and RT (n = 7)

- With tissue blocks, estrogen-receptor positive (n = 1115)
  - Insufficient RNA qPCR sample quality (n = 11)
  - Processed by GHI (n = 1083)
    - Had successful 21-gene assay (n = 1065)
      - AC (n = 519)
      - AC→P (n = 546)

Locoregional Recurrence using Oncotype Dx® in Node-positive patients

Mix of mastectomy (no radiation-604 pts) and lumpectomy (received RT-461 pts)

Locoregional Recurrence using Oncotype Dx® in Node-positive patients

**A** 1-3 positive nodes

- RS high: 205 events, 17 LRR events
- RS intermediate: 249 events, 12 LRR events
- RS low: 268 events, 11 LRR events

\[ P = .12 \]

**B** ≥ 4 positive nodes

- RS high: 110 events, 22 LRR events
- RS intermediate: 115 events, 13 LRR events
- RS low: 118 events, 5 LRR events

\[ P = .001 \]

**All patients**

Locoregional Recurrence using Oncotype Dx® in Node-positive patients - association with RT

Not significant in patients treated with mastectomy and 1-3 nodes positive (only 4 or more)

Not significant in BCT+RT patients with 1-3 nodes positive (only 4 or more)

Intriguing in that subset of post-mastectomy patients with 4+ nodes but low RS, radiation may not be necessary. AVOID OVERTREATMENT

Important and useful data, but mixed treatment means it does not directly address the radiation question

Locoregional Recurrence using Oncotype Dx® in Node-positive patients- association with RT

SWOG 8814 assessment of LRR by Recurrence Score
(led by Wendy Woodward at MD Anderson CC)

SWOG 8814: Tamoxifen With or Without Combination Chemotherapy in Postmenopausal Women Who Have Undergone Surgery for Breast Cancer

- Randomized phase III trial, N = 1477
- ER and/or PR+, Node+, post-menopausal randomized to tamoxifen alone vs. Tamoxifen then CAF vs. Concurrent Tamoxifen + CAF
- RS determined using RT-PCR
Locoregional Recurrence using Oncotype Dx® in Node-positive patients - association with RT

SWOG 8814: Post mastectomy patients without RT

1-3 nodes positive

>3 nodes positive
Prognostic and Predictive Signatures for Personalized Radiation Decisions

Previously derived

• Oncotype Dx®
• Oncotype Dx® for DCIS
• IHC surrogates for subtype

Radiation specific signatures

Invasive disease

• Danish Breast Cancer Group (DBCG-RT)
• Radiation Sensitivity Index (RSI)
• Radiosensitivity and Immune Gene Signature
• Radiation Sensitivity Signature (RSS or Radiotype Dx®) and Adjuvant RadioTherapy Intensification Classifier (ARTIC)
Radiation specific signatures for treatment decisions

- Danish Breast Cancer Group (DBCG-RT)- radiation necessity signature based on benefit of post-mastectomy radiation on Danish 82b/c trials\(^1\) — IDENTIFIES RADIATION BENEFIT GROUP
- Radiation Sensitivity Index (RSI)- pan cancer radiation signature to predict benefit of radiation based on radiation sensitivity of NCI-60 cell lines\(^2\) — IDENTIFIES RADIATION RESISTANT GROUP
- Radiation Sensitivity and Immune Signature- public datasets used to predict benefit of radiation\(^3\) — IDENTIFIES RADIATION BENEFIT AND RESISTANT GROUP
- Radiation Sensitivity Signature (RSS or Radiotype Dx\(^®\))- breast cancer cell line-specific signature to predict utility and efficacy of radiation in women treated with RT after lumpectomy\(^4\) — IDENTIFIES RADIATION BENEFIT AND RESISTANT GROUP
- Adjuvant RadioTherapy Intensification Classifier (ARTIC)\(^5\) — IDENTIFIES RADIATION BENEFIT AND RESISTANT GROUP

2. Torres-Roca JF et al., Cancer Res 2005: 65(16):7169-76
3. Cui Y, et al., Clin Cancer Res. 24(19) October 1, 2018
5. Sjöström et al, JCO Oct. 16, 2019; JCO.19.00761
A DBCG-RT gene profile was identified and validated within the same patient cohort. Discovery using fresh frozen tissue, validated in FFPE

7 genes (HLA-DQA, RGS1, DNALI1, hCG2023290, IGKC, OR8G2, and ADH1B) were identified, and the derived DBCG-RT profile divided the 191 patients into “high LRR risk” (75% of the cohort) and “low LRR risk” groups (25% of the cohort). Mix of +/- PMRT in the training cohort to evaluate for RT interaction. Then transferred to FFPE, lost 3 genes and ended with 4 gene signature (IGKC, RGS1, ADH1B, and DNALI1)

PMRT significantly reduced risk of LRR in “high LRR risk” patients
PMRT did NOT reduce LRR risk in the “low LRR risk” patients

RT benefit
No RT benefit
Predictive impact of the identified DBCG-RT profile is presented in the training set of 191 patients (A and B), in the subset of 146 patients from the training set, where FFPE was available (C and D), and in 112 patients with high-risk breast cancer patients in the validation dataset.

Radiation Sensitivity Index (RSI)

Radiosensitivity molecular signature (RSI) which was developed as a biomarker of cellular radiosensitivity (NCI-60 cell lines, mostly non-breast)

Signature is based on gene expression for 10 specific genes (AR, cJun, STAT1, PKC, RelA, cABL, SUMO1, CDK1, HDAC1, IRF1)

Initially evaluated in rectal, esophageal, and H&N SCC; extended into breast cancer evaluation in Swedish and Dutch cohorts

Radiation Sensitivity Index (RSI)

Karolinska dataset: Post BCS; mostly predicted radiation resistant (RR)

Signature identifies radiation benefit, not prognostic or predictive in non-irradiated patients

Radiation Sensitivity Index (RSI)

Erasmus dataset: Postmastectomy; mostly predicted radiation resistant (RR)

Signature identifies radiation benefit, not prognostic or predictive in non-irradiated patients

Radiation Sensitivity Index (RSI)

Predictive value seen in ER+ patients but not ER- in this cohort

Unlike previous study, predictive value seen in ER- patients but not ER+ in this cohort (4 Dutch and 1 French non-randomized cohorts)

Went on to look at value of determining a genomic adjusted radiation dose (GARD) for breast and other types of cancers

While RSI did not uniformly predict for local recurrence across the entire cohort, it may identify a sub-population of TNBC (RSI-determined radioresistant patients) with the highest risk of local recurrence.

Radiation and Immune Gene Signature

Cui et al., Clin Cancer Res; 24(19) October 1, 2018
Combined radiation/immune signature shows improved DSS for the “predictive sensitive” group in RT treated patients, but worse DSS with RT in the “predicted resistant” groups.

Neither RSI nor Oncotype DX showed a significant interaction with radiotherapy as continuous variables in multivariate Cox regression analyses.

Cui et al., Clin Cancer Res; 24(19) October 1, 2018
Radiotype Dx development

67 genes increased in radioresistant cell lines

80 Genes decreased in radioresistant cell lines

147 Genes Correlated with Radiation Sensitivity

Speers et al., Clin Cancer Res. 2015 Aug 15;21(16):3667-77.
Radiotype Dx validation

Sensitivity for recurrence: 85%
Negative Predictive Value: 97%
Log-rank P-value <0.001
Hazard Ratio: 6.1 (95% CI 4.48-12.65)

Speers et al., Clin Cancer Res. 2015 Aug 15;21(16):3667-77.
Efforts to improve Radiotype Dx

SweBCG (1991): 1185 pts
Development of **Adjuvant RadioTherapy Intensification Classifier (ARTIC)**

### Training of Model

**16 matched samples from Lund FF and SweBCG 91-RT**
- For each gene, correlate expression of Lund FF to SweBCG 91-RT
- Calculate variance for expression for each gene in Lund FF and SweBCG 91-RT, separately

**Training cohort: Servant, N=343**
- Vary
  - Threshold for gene expression correlation between fresh frozen and FFPE samples
  - Threshold for gene expression variance
  - Threshold for the univariable Cox p-value as calculated only within training cohort to the local recurrence endpoint
- Train ridge-penalized Cox models

**Testing cohorts**
- vandeVijver, N=228
- Sjöström et al, N=102

**Final locked model**
- Model selected by choosing model that minimized the product of the p-values in a Cox proportional hazards model in the testing cohorts
- As patient age was the strongest clinical factor for the endpoint in the training dataset, the linear model was retrained to include patient age as a variable in addition to the genes

**Final Model (ARTIC)**
- 27 genes and patient age

**Validation cohort**
- SweBCG 91-RT, N=748

- **Performed by L. Chang**
- **Performed by M. Sjöström**

---

**External validation of locked model in phase III randomized trial of +/- RT**
Performance of ARTIC for prognostication of locoregional recurrence and treatment prediction for adjuvant radiotherapy in the SweBCG91-RT validation cohort.

Cumulative incidence of locoregional recurrence for high and low classifier scores (as split by the 75th percentile score) and interaction with RT.

*Sjöström et al, JCO Oct. 16, 2019; JCO.19.00761*
Performance of ARTIC- Prognostic

Prognostic performance of ARTIC in the SweBCG91-RT validation cohort.
Cumulative incidence of locoregional recurrence for patients split by the 75th percentile score in the radiation therapy treated arm (A) and in the no radiation therapy arm (B).

Sjöström et al, JCO Oct. 16, 2019; JCO.19.00761
Performance of ARTIC- Interaction Test

Interation of radiation therapy and ARTIC

Continuous classifier scores are presented with the risk for locoregional recurrence with or without radiation therapy. The 10-year LRR free interval risk was calculated by fitting a cause-specific Cox regression model to time-to-LRR using the interaction of calculated ARTIC scores and RT status. Predicted survival curves and variances were generated using Efron's approach and the confidence intervals were constructed using the log approach.

No interaction with RT (i.e not predictive)= parallel lines

Significant interaction with RT (i.e IS predictive)= lines converge

Sjöström et al, JCO Oct. 16, 2019; JCO.19.00761
ARTIC does not just recapitulate intrinsic BC subtypes

Subtype proportions by ARTIC quartiles

**Entire cohort**

<table>
<thead>
<tr>
<th>IHC Subtype</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple Negative (65, 8.8%)</td>
<td>61</td>
<td>53</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>HER2+ (54, 7.3%)</td>
<td>102</td>
<td>56</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Luminal B (HER2-) (210, 26.4%)</td>
<td>112</td>
<td>56</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>Luminal A (411, 55.5%)</td>
<td>187</td>
<td>182</td>
<td>186</td>
<td>185</td>
</tr>
</tbody>
</table>

Sjöström et al, JCO Oct. 16, 2019; JCO.19.00761
Comparative performance of other signatures

<table>
<thead>
<tr>
<th>Signature</th>
<th>Full Cohort</th>
<th>RT Arm</th>
<th>No RT Arm</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIC</td>
<td>2.3 [1.8-4.4], p=0.001*</td>
<td>3.4 [2.5-9.0], p&lt;0.0001*</td>
<td>1.6 [1.1-2.3], p=0.03*</td>
<td>0.005* *Statistically significant</td>
</tr>
<tr>
<td>21-gene like (OncotypeDx)</td>
<td>1.2 [0.8-1.6], p=0.41</td>
<td>1 [0.5-2.0], p=0.94</td>
<td>1.2 [0.8-1.8], p=0.35</td>
<td>0.97</td>
</tr>
<tr>
<td>70-gene like (Mammaprint)</td>
<td>1.3 [0.9-1.8], p=0.13</td>
<td>1.9 [1.1-3.4], p=0.024*</td>
<td>1.1 [0.7-1.7], p=0.62</td>
<td>0.51</td>
</tr>
<tr>
<td>Cui 2018</td>
<td>1.3 [0.9-1.8], p=0.14</td>
<td>1.6 [0.9-2.8], p=0.13</td>
<td>1.2 [0.8-1.7], p=0.47</td>
<td>0.54</td>
</tr>
<tr>
<td>Eschrich 2009 (RSI)</td>
<td>1.2 [0.8-1.6], p=0.36</td>
<td>1.1 [0.6-2.0], p=0.8</td>
<td>1.2 [0.8-1.8], p=0.35</td>
<td>0.46</td>
</tr>
<tr>
<td>Sjostrom 2018 Intensification</td>
<td>1.6 [1.1-2.3], p=0.0058*</td>
<td>2.1 [1.2-3.9], p=0.012*</td>
<td>1.5 [0.97-2.2], p=0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>Sjostrom 2018 Omission</td>
<td>1.4 [1.2], p=0.034</td>
<td>1.6 [0.9-2.9], p=0.14</td>
<td>1.4 [0.9-2.1], p=0.58</td>
<td>0.6</td>
</tr>
<tr>
<td>Zhang 2016</td>
<td>1.1 [1.2], p=0.034</td>
<td>1.6 [0.9-2.9], p=0.14</td>
<td>1.3 [0.9-2.0], p=0.14</td>
<td>0.59</td>
</tr>
</tbody>
</table>

ARTIC validates as prognostic for LRR and predictive for RT benefit. Conversely, while 2 of the 7 previously published signatures were prognostic for the LRR endpoint (p<0.05), none were predictive for benefit from RT in SweBCG 91-RT.
Radiation specific signatures for treatment decisions

Others generated previously but not under clinical development

– Preclinically derived signatures:
  - Radiation induction signature\(^1\), Interferon-based signature\(^2\) (that worked for chemo and radiation), Wound-response signature\(^3\)

– Clinically derived signatures:
  - Swedish signature in breast cancer\(^4\), Dutch signature in breast cancer\(^5\)

Challenge has been lack of validation, or inability to validate in external datasets

5. B. Kreike et al., Clin Can Res vol. 15, no. 12, pp. 4181–4190, 2009
Which of the following molecular signatures has been validated as a predictive biomarker of radiation response for women with breast cancer?

(A) DBCG-RT
(B) Radiation Sensitivity Index (RSI)
(C) Radiation and Immune-based Signature
(D) Radiotype Dx
(E) All of the above
(F) None of the above
What about signatures for radiation benefit in DCIS?
Previously derived signatures applied to radiation questions

Previously derived

- Oncotype Dx®
- Oncotype Dx® for DCIS
- IHC surrogates for subtype
**What about radiation omission for non-invasive disease (DCIS)**

**Oncotype Dx® for DCIS**: Developed in 5 cohorts that included studies of 1) either DCIS only or both DCIS and invasive breast carcinoma, but without clinical outcome data; or 2) invasive breast carcinoma with clinical outcome data.

Validated in ECOG E5194 which was a trial of DCIS who were selected for low-risk clinical and pathologic characteristics. Patients were enrolled onto one of two study cohorts (not randomly assigned): cohort 1: low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (n = 561); or cohort 2: high-grade DCIS, tumor size 1 cm or smaller (n = 104). Negative margins at least 3 mm. Tamoxifen (not randomly assigned) was given to 30% of the patients.

**No RT**

<table>
<thead>
<tr>
<th>Proliferation group</th>
<th>Hormone receptor group</th>
<th>Reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>PR</td>
<td>ACTB (β-actin)</td>
</tr>
<tr>
<td>STK15</td>
<td></td>
<td>GAPDH</td>
</tr>
<tr>
<td>Survivin</td>
<td></td>
<td>RPLPO</td>
</tr>
<tr>
<td>CCNB1 (cyclin B1)</td>
<td></td>
<td>GUS</td>
</tr>
<tr>
<td>MYBL2</td>
<td></td>
<td>TFRC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GSTM1</td>
</tr>
</tbody>
</table>

16 cancer related genes in Oncotype Dx®
7 cancer related genes for Oncotype Dx for DCIS®

Mix of 5 cohorts for training (invasive and DCIS cohorts)

- ECOG E5194 for validation

LJ Solin et al., JNCI: Volume 105, Issue 10, 15 May 2013, Pages 701–710,
Population-based Canadian cohort of individuals diagnosed with DCIS treated with BCS alone from 1994 to 2003 (571 patients with negative margins.)

Validation of Oncotype Dx® for DCIS

Want 10 year risk of recurrence <10%
Radiation specific signatures for DCIS treatment decisions

- DCISionRT® from PreludeDx™

Cancer Pathway Comparison

<table>
<thead>
<tr>
<th>Hormone Receptor</th>
<th>HER2</th>
<th>Proliferation / Cell Cycle</th>
<th>Stress Response</th>
<th>Invasion</th>
<th>Clin / Path &amp; Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR [FOXA1]</td>
<td>HER2</td>
<td>Ki-67</td>
<td>COX2 SIAH2</td>
<td>FOXA1 p16/INK4A [Ki-67]</td>
<td>Age Size Margin Palpability</td>
</tr>
</tbody>
</table>

DCIS

OncotypeDX

PR

Ki-67 STK15 Survivin Cyclin B1 MYBL2

GSTM1

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Low risk group is clinically low risk
- Similar to contralateral risk
Elevated risk group is clinically high risk
- Similar to risk for women with BRCA mutations

Non-randomized cohort from Uppsala and UMass

DCISionRT reclassification in US cohort

Low Risk
Clin/Path Patients
Reclassified by DCISionRT Kaiser Permanente Network Study

59%
Reclassified
High Risk

DCISionRT upstaged 59% of patients in the Clin/Path low risk as elevated risk

High Risk
Clin/Path Patients
Reclassified by DCISionRT Kaiser Permanente Network Study

29%
Reclassified
Low Risk

DCISionRT downgraded 29% of patients in the Clin/Path high risk as low risk

MSKCC Factors in Analysis:
• Age
• Family Hx
• Presentation
• Grade
• Margin
• No. of Excisions

Median follow-up 10.4 years, n = 455
Validation of DCISionRT in the SweBCG trial

Low Risk Group (DS<3†)

SweDCIS: 10-Year Invasive Breast Cancer Risk

Complete Assay Data with Clear Margins, (1986-1999), n=506

- Absolute RT Difference
  - HR 0.84, p=NS

Elevated Risk Group (DS>3†)

- Absolute RT Benefit
  - HR 0.24, p=0.012

†DS = DCISionRT Score (Scale from 0 to 10)

Numerous studies showing Oncotype Dx Recurrence Score or breast cancer intrinsic subtype (ProSigna) associated with local recurrence risk


In those subsets with a very low risk of recurrence, can this information be used to omit radiation?

AVOID OVERTREATMENT
Same general design, lumpectomy and endocrine therapy alone: For whom is radiation omission appropriate?

1. **Individualized Decisions for Endocrine Therapy Alone (IDEA)-OncotypeDx (PI: Dr. Reshma Jagsi, Univ. of Michigan)** Non-randomized, 202 pts
   - 50-69 yo women with RS ≤18, 1º endpoint rates of locoregional recurrence at 5 yrs

2. **Profiling Early Breast Cancer for Radiotherapy Omission (PRECISION)- ProSigna (PI: Dr. Jennifer Bellon, Dana Farber)** Non-randomized phase II, 690 pts
   - 50-75 yo women with low risk, 1º endpoint rates of ipsilateral locoregional recurrence at 5 yrs.

3. **EXamining PErsontalised Radiation Therapy for Low-risk Early Breast Cancer (EXPERT)-(Study Chair: Dr. Boon Chua, Prince of Wales Hospital; International Breast Cancer Study Group (IBCSG)** Randomized phase III, 1167 pts
   - ≥50 yo Luminal A pts by Prosigna (PAM50) with ROR score ≤60, 1º endpoint 10 yr LR

4. **LUMINA- IHC (Pis: Dr. Tim Whelan-OCOG and Dr. Sally Smith-BCCA)** Non-randomized observational, 500 pts
   - Luminal A patients by ER/PR/Her2/Ki67, 1º endpoint 5 yr IBTR

5. **PRIMETIME- IHC4 (PI: Dr. Charlotte Coles, Univ. of Cambridge)** Non-randomized observational, 2,400 pts
   - Luminal A patients by ER/PR/Her2/Ki67, , 1º endpoint 5 yr IBTR

*IHC 4, ProSigna (subtype), and Oncotype RS NOT the same*
Same general design, but for N+ patients: For whom is radiation omission appropriate?

1. **MA.39 (TAILOR RT)** - OncotypeDx (*PI: Dr. Timothy Whelan on behalf of Canadian Cancer Trials Group*) Randomized phase III, 2140 pts
   - ≥40 yo women with Oncotype Dx RS ≤18
   - 1-3 positive axillary nodes (macrometastases, > 2 mm) with ALND, 1-2 positive LN with SLNB
   - Includes BCS and mastectomy treated pts, randomized to +/- RT
     - For BCS pts: Whole breast irradiation (WBI) +/- regional nodal RT (supraclavicular, non-dissected axillary, and internal mammary)
     - For mastectomy pts: +/- chest wall and regional nodal RT
   - 1° endpoint: BCRFS between patients that received regional RT or not

Additional genomically stratified ongoing clinical trials for radiation omission in N+ patients:

One additional trial similar to previous in patients with node-negative disease progressing through the US cooperative groups, led by NRG
Question

There are currently numerous ongoing genomically stratified clinical trials for radiation omission

(A) True
(B) False
Summary

• APBI a reasonable option for women at low risk of recurrence
• Genomic-based signatures now commonplace in guiding systemic therapy decisions
• Genomic-based signatures not yet validated for clinical use to guide radiation decisions—though we are getting close
• Validation awaited for:

  Invasive disease
  • Oncotype Dx®
  • ProSigna
  • IHC based subtyping
  • Radiation-specific signatures (DBCG-RT, RSI, Radiotype Dx, ARTIC, etc.)

DCIS
  • Oncotype Dx® for DCIS
  • DCISionRT-
Questions?