Advances in Breast Cancer

Learning Objectives

Upon completion, participants should be able to:

• Apply genomic medicine to treatment decisions for patients with HR+/HER2- early stage breast cancer
• Assess the range of radiotherapy doses and fractionation schemes that may be appropriate for patients with early stage breast cancer who undergo breast-conserving surgery
• Evaluate select clinical studies on the latest surgical techniques in breast cancer
Genomic Signatures: Changing the Face of HR+ Breast Cancer

Jeremy Force, DO

21-Gene RS Assay

16 Breast Cancer–Related Genes

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Proliferation</th>
<th>HER2</th>
<th>Invasion</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Ki-67</td>
<td>GRB7</td>
<td>Stromelysin 3</td>
<td>CD68</td>
</tr>
<tr>
<td>PR</td>
<td>STK15</td>
<td>HER2</td>
<td>Cathepsin L2</td>
<td>GSTM1</td>
</tr>
<tr>
<td>Bcl2</td>
<td>Survivin</td>
<td></td>
<td></td>
<td>BAG1</td>
</tr>
<tr>
<td>SCUBE2</td>
<td>Cyclin B1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MYBL2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 Reference Genes

<table>
<thead>
<tr>
<th>Beta-actin</th>
<th>GAPDH</th>
<th>RPLPO</th>
<th>GUS</th>
<th>TFRC</th>
</tr>
</thead>
</table>

The RS Result Reveals Individual Tumor Biology for ER+, LN-Negative Breast Cancer Treated With ET


Distant Recurrence at 10 Years

<table>
<thead>
<tr>
<th>RS Value</th>
<th>Low RS Disease</th>
<th>High RS Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td></td>
<td>Hormonal therapy–sensitive</td>
<td>Less sensitive to hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>Minimal, if any, chemotherapy benefit</td>
<td>Large chemotherapy benefit</td>
</tr>
</tbody>
</table>

The RS Result Identifies Patients With ER+ Tumors Who Would Derive the Greatest Benefit From Chemotherapy

*N = 651.

Patients with high RS:
- 28% absolute benefit from tamoxifen + chemotherapy
Background: Rationale for Adjusting RS Ranges in TAILORx: Large Chemotherapy Benefit in NSABP B-20 With RS > 25 Similar to RS ≥ 31

<table>
<thead>
<tr>
<th>RS</th>
<th>Patients</th>
<th>10-Year DRFS (%)</th>
<th>Recurrence by Addition of Chemotherapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Tam</td>
<td>Tam+Chemo</td>
<td>HR</td>
</tr>
<tr>
<td>0-10</td>
<td>177</td>
<td>27</td>
<td>98</td>
<td>95</td>
<td>1.788</td>
</tr>
<tr>
<td>11-25</td>
<td>279</td>
<td>43</td>
<td>95</td>
<td>94</td>
<td>0.755</td>
</tr>
<tr>
<td>26-100</td>
<td>195</td>
<td>30</td>
<td>63</td>
<td>88</td>
<td>0.285</td>
</tr>
</tbody>
</table>

TAILORx Methods: Treatment Assignment and Randomization Accrued Between April 2006 – October 2010
### TAILORx: RS < 11

**A** IDFS

- **B** Freedom From Recurrence of Breast Cancer at Distant Site

- **C** Freedom From Recurrence at Any Site

- **D** OS


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ER/PR+ HER2- LN negative Tumor 1.1-5.0 cm or, if grade 3, 0.6-1.0 cm

n = 1,626

99.3% 5-yr DFS

98.0% 5-yr OS

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### TAILORx: RS 11-25

- **A** DFS Probability

- **B** HR Arm B vs Arm C (95% CI)

- **C** Number at Risk

- **D** Months

836 IDFS events after median of 7.5 years

- 338 of 836 (40.3%) with recurrence as first event

- 199 of 836 (23.8%) were distant recurrence


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TAILORx-Defined Cutoff for Definitively Determining Chemotherapy Benefit With the 21-Gene RS Assay (LN-Negative, HR+, HER2-)

**Subgroup Age ≤ 50 Years**

<table>
<thead>
<tr>
<th>RS 0-10</th>
<th>RS 11-15</th>
<th>RS 16-20</th>
<th>RS 21-25</th>
<th>RS 26-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CT benefit</td>
<td>No CT benefit</td>
<td>~1.5% CT benefit</td>
<td>~7% CT benefit</td>
<td>Large CT benefit</td>
</tr>
</tbody>
</table>

~50% of patients ≤ 50 years have RS 0-15, 35% RS 16-25, and 15% RS 26-100

**Conclusion**

- The 21-gene RS assay is a well-validated tool for use in women with HR+/HER2-, LN-negative breast cancer
- Postmenopausal women with HR+/HER2-, LN-negative breast cancer and RS ≤ 25 can safely forgo chemotherapy
- Premenopausal women with HR+/HER2-, LN-negative breast cancer and RS 20-25 warrant a conversation about potential chemotherapy benefit
Goals

- Focus: external beam options
- Brachytherapy options also available and appropriate for select patients
Radiotherapy Fractionation

- Radiotherapy is most often a series of daily treatments over a number of weeks
- Each of these treatments is a “fraction” of radiotherapy
- Number of fractions and final dose varies by cancer type and patient factors
- Historically, after breast-conserving surgery, breast cancer patients received 5-8 weeks of daily treatments to the entire breast
- Growing evidence shows that shorter fractionation schedules and/or treatment of just a part of the breast is equally effective for select breast cancer patients


Hypofractionated Whole Breast Radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Local Recurrence, %</th>
<th>Survival, %</th>
<th>Cosmesis, %</th>
<th>Follow-Up, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Long</td>
<td>Short</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Whelan et al¹,²</td>
<td>1,234</td>
<td>6.7</td>
<td>6.2</td>
<td>84.4</td>
<td>84.6</td>
</tr>
<tr>
<td>START A³,⁴</td>
<td>2,236</td>
<td>7.4</td>
<td>6.3; 8.8</td>
<td>80.2</td>
<td>81.6; 79.7</td>
</tr>
<tr>
<td>START B³,⁴</td>
<td>2,215</td>
<td>5.5</td>
<td>4.3</td>
<td>80.8</td>
<td>84.1</td>
</tr>
</tbody>
</table>

2018 ASTRO Consensus Statement HF-WBI

- Wider application of HF-WBI, shared decision making
  - Age: any (prior: ≥ 50 years)
  - Stage: any when intent is to treat entire breast without regional nodal fields (prior: T1/2 N0)
  - Chemotherapy: any (prior: none)
  - Dose homogeneity: minimize 105% for all fractionation (prior: +/- 7%)
  - Also greater evidence now for use in DCIS patients

Partial Breast Irradiation

- **Preoperative**
  - Treat intact tumor before surgery
  - Clinical trials published
  - Ongoing clinical trials

- **Intraoperative**
  - Single dose in OR after lumpectomy performed
  - TARGIT and ELIOT trials

- **Postoperative 1 week**
  - “Classic” APBI
  - 10 treatments, twice daily, 5 days
  - External beam or brachytherapy
  - NSABP B-39 and many other trials

- **Postoperative 3 weeks**
  - Mini tangents
  - 15 fractions (START)²-⁴
  - IMPORT LOW trial

References:
## ASTRO Consensus Statement APBI

Patients “suitable” for APBI if all criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60 y; ≥ 50 y</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Not present</td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T1, Tis, or T1</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
</tr>
<tr>
<td>LVSI</td>
<td>No</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric only</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size ≤ 2.0 cm</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypes</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed; Low-risk DCIS</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed; RTOG 9504</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
</tr>
<tr>
<td>N stage</td>
<td>pN0 or pN+</td>
</tr>
<tr>
<td>Nodal factors</td>
<td>SLNB or ALNB</td>
</tr>
<tr>
<td>Treatment factors</td>
<td>Neoadjuvant therapy Not allowed</td>
</tr>
</tbody>
</table>

“Cautionary” group: Any of these criteria should invoke caution and concern when considering APBI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50-59 y; 40-49 y; &gt; 50 y if don’t meet suitable</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Tumor size 2.1-3.0 cm</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>T stage T0 or T2</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Margins &lt; 2 mm</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>LVSI Centrifugal</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>LVSI Extensive</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Multicentricity Present</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Multifocality Clinically unifocal with total size &gt; 3 cm</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>≤ 3 cm And not in suitable</td>
</tr>
<tr>
<td>EIC</td>
<td>≤ 3 cm</td>
</tr>
</tbody>
</table>

Patients “unsuitable” for APBI outside of a clinical trial if any of these criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50 y; &lt; 40 y; 40-49 y if don’t meet cautionary</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Present</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Tumor size &gt; 3 cm</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>T stage T3-4</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Margins Positive</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>LVSI Extensive</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Multicentricity Present</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td>Multifocality Clinically unifocal with total size &gt; 3 cm</td>
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<tr>
<td>Histology</td>
<td>invasive ductal or other favorable subtypes</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>&gt; 3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>&gt; 3 cm in size</td>
</tr>
<tr>
<td>N stage</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>None performed</td>
</tr>
<tr>
<td>Treatment factors</td>
<td>Neoadjuvant therapy Not used</td>
</tr>
</tbody>
</table>

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## UK IMPORT LOW Trial

- Multicenter, randomized, phase 3 noninferiority trial, 2007-2010
- N = 2,018; women age > 50 years, pT1-2 (< 3 cm), pN0-1, margins 2 mm
- Procedures (all 15 fractions):
  - 1: 40 Gy whole breast (control)
  - 2: 36 Gy whole breast and 40 Gy partial breast (reduced-dose group)
  - 3: 40 Gy partial breast (partial-breast group)
- Field-in-field, tangential beams (reduced tangents for partial breast)
- Primary: ipsilateral in breast relapse
- Relapse at 5 years: 1: 1.1%; 2: 0.2%; 3: 0.5%
- Conclusion: partial breast and reduced-dose whole breast radiotherapy are noninferior

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Conclusion

- Women with early stage, LN-negative breast cancer have many potentially appropriate radiotherapy treatment regimens
- Whereas historically the whole breast was treated for 5-7 weeks, there are now significant and growing data to support shorter treatment courses and partial breast regimens
- The vast majority of women with early stage breast cancer should now receive treatment courses of 1-4 weeks’ duration

Please also see position statements and practice guidelines for warnings, efficacy, risks, and safety associated with the treatment strategies discussed.
Lumpectomy Today

• Oncologically safe in the modern era
  – Meta-analysis of nearly 7,000 patients with stage I-III breast cancer in 9 clinical trials
  – Overall 5-year local recurrence rates after breast-conserving surgery: 4.2% (historical rates: 5%-10%)


NSM

• Oncologically safe in BRCA mutation carriers
  – 548 risk-reducing NSMs in 346 patients at 9 institutions
  – No breast cancers observed; median follow-up of 34 months (expected 22)
• Does not delay adjuvant therapy
  – NSM on 8,173 patients in NCDB: 8.7% N+, 10.6% triple negative, 15.3% HER2+
  – Readmission rate; positive margin rate and time to chemotherapy; PMRT or hormonal therapy similar for NSM and SSM patients

CPM

- Surgeons influence CPM choice
  - Population-based survey
    - 5,080 women, stages 0-II breast cancer treated 2013-2015 (70% response rate)
    - 377 surgeons (77% response rate)
  - Attending surgeon: explains 20% of variation in CPM rates
  - Attending attitudes: explains 25% of surgeon influence
  - CPM rate 34% vs 4% for surgeons who least favored vs most favored breast conservation


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TAD

- TAD = SLNB + removal of clipped/biopsied node
- Removing the clipped/biopsied node improves axillary evaluation after NACT
  - 208 patients, 191 ALND, residual disease in 120 (63%)
  - FNR for clipped node alone: 4.2% (95% CI, 1.4 to 9.5)
  - FNR for SLNB and ALND: 10.1% (95% CI, 4.2 to 19.8)
  - Clipped node was not retrieved as SLN in 23%
  - FNR TAD followed by ALND: 2.0% (1 of 50; 95% CI, 0.05 to 10.7)
- ACOSOG Z1071 (analysis of clipped nodes)
  - 203 with clipped node, clinical T0-T4,N1-N2,M0 breast cancer, SLNB and ALND
  - FNR for SLNB + clipped node: 6.8% (CI 1.9% to 16.5%; P = .20)


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Timing of Surgery

- Higher local recurrence rates after breast-conserving therapy for tumor downsized by NACT
  - 4,756 women in 10 randomized trials in early breast cancer, 1983-2002, median follow-up of 9 years
  - 15-year local recurrence rate: NACT 21.4% vs ACT 15.9% ($P = .0001$)
  - No significant differences in distant recurrence, breast cancer mortality, or death from any cause

Avoiding Surgery?

- No surgery for pCR patients
  - Feasibility study of 40 patients with HER2+ or triple-negative T1-3/N0-1
  - Breast pCR rate: 48%
  - Median initial tumor size was 3.3 cm; final tumor size was 1.1 cm
  - FNA + vacuum-assisted core biopsy: accuracy 98%, FNR 5%, NPV 95%

- Active surveillance for DCIS
  - Comparison of Operative to Monitoring and Endocrine Therapy (COMET) Trial For Low Risk DCIS: A Phase III Prospective Randomized Trial
  - Women ≥ 40 years; any grade I DCIS or any grade II DCIS without comedonecrosis; ER+ and/or PR+
  - Guideline-concordant care (surgery +/- radiation, ET) vs active surveillance (ET)
  - Primary outcome: proportion of new ipsilateral breast cancers at 2 years’ follow-up

2. ClinicalTrials.gov. NCT02926911.
Conclusion

- Contemporary local recurrence rates after breast-conserving therapy are lower today
- NSMs are oncologically safe in BRCA-mutation carriers and do not delay adjuvant therapies
- Targeted axillary dissections may become the standard of care for patients with excellent responses to NACT
- Some patients may have a higher risk of local recurrence after NACT and breast-conserving surgery
- Studies evaluating the possibility of omitting surgery for select breast cancer patients are ongoing; stay tuned!

Please also see position statements and practice guidelines for warnings, efficacy, risks, and safety associated with the treatment strategies discussed.

Contact Information

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Breast Cancer: Abbreviations and Acronyms

ACT = adjuvant chemotherapy
ALND = axillary lymphadenectomy
APBI = accelerated partial breast irradiation
BAG1 = Bcl-2 athanogene-1
Bcl2 = B-cell lymphoma 2
BRCA = breast cancer susceptibility gene
CPM = contralateral prophylactic mastectomy
CT = chemotherapy
DCIS = ductal carcinoma in situ
DFS = disease-free survival
DRFS = distant recurrence–free survival
EIC = extensive intraductal component
ER = estrogen receptor
ET = endocrine therapy
FNA = fine-needle aspiration
FNR = false-negative rate
GAPDH = glyceraldehyde 3-phosphate dehydrogenase
GB7 = growth factor receptor–bound protein 7
GSTM1 = glutathione-S-transferase M1
HER2 = human epidermal growth factor receptor 2
HF-WBI = hypofractionated whole-breast irradiation
HR = hormone receptor
IDFS = invasive disease-free survival
LCIS = lobular carcinoma in situ
LN = lymph node
LVSI = lymph-vascular space invasion
MYBL2 = MYB proto-oncogene like 2
NACT = neoadjuvant chemotherapy
NCDB = National Cancer Database
NPV = negative predictive value
NSABP = National Surgical Adjuvant Breast and Bowel Project
NSM = nipple-sparing mastectomy
OS = overall survival
pCR = pathologic complete response
PMRT = postmastectomy radiotherapy
PR = progesterone receptor
QOL = quality of life
RPLPO = ribosomal protein lateral stalk subunit P0
RS = recurrence score
SCUBE2 = signal peptide-CUB-epidermal growth factor-like domain-containing protein 2
SLNB = sentinel lymph node biopsy
SSM = skin-sparing mastectomy
TAD = targeted axillary dissection
TFRC = transferrin receptor