TO TREAT OR NOT TO TREAT
WHEN CAN RT BE OMITTED
AFTER BREAST CONSERVING
SURGERY?

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Professor of Radiation Oncology
Medical University of South Carolina
Overview: Omitting RT after BCS?

• DCIS
  – Adjuvant Radiation Therapy
  – WLE Alone
  – Recurrence Risk Assessment Tools
    • Oncotype DX DCIS Recurrence Score
    • MSKCC Nomogram
  – RTOG Trial of “Good Risk” DCIS: S +/- RT
Overview: *Omitting RT after BCS?*

- Invasive Cancer (Stage 1, ER+, Margin-)
  - ➔ 70 yo (CALGB 9343)
  - ➔ 65 yo (PRIME II)
  - ➔ 50 yo (Canadian Trial)

- Ongoing Trials
DCIS: Review

- DCIS: precursor lesion to invasive cancer
- Natural history of DCIS is poorly understood
- DCIS is a heterogeneous diagnosis
- Increasing incidence

*Horner et al SEER Cancer Stats Review 2009*
DCIS: Risk Factors for Recurrence

• Age
• Grade
• Margin Width (guidelines: 2mm for BCS+RT)
• Tumor Size
• Comedonecrosis
• ER status
• Era of diagnosis (improved radiographic detection and pathologic assessment)
## DCIS: Adjuvant Radiation Therapy

<table>
<thead>
<tr>
<th>Study name (reference)</th>
<th>Study dates</th>
<th>n</th>
<th>Median follow-up (years)</th>
<th>% Positive/unknown margins</th>
<th>Local recurrence</th>
<th>Local recurrence relative risk reduction due to RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17 (5)(^a)</td>
<td>1985–1990</td>
<td>813</td>
<td>17.25</td>
<td>0%</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>EORTC 10853 (4)(^a)</td>
<td>1986–1996</td>
<td>1,010</td>
<td>15.8</td>
<td>16%</td>
<td>31%</td>
<td>18%</td>
</tr>
<tr>
<td>SweDCIS (6)(^b)</td>
<td>1987–1999</td>
<td>1,046</td>
<td>17.5</td>
<td>20%</td>
<td>32%</td>
<td>20%</td>
</tr>
<tr>
<td>UK/ANZ DCIS (3)(^c)</td>
<td>1990–1998</td>
<td>475</td>
<td>12.7</td>
<td>0%</td>
<td>25%</td>
<td>9%</td>
</tr>
</tbody>
</table>
DCIS: WLE Alone, *Harvard Study*

- DCIS G1-2, $\leq 2.5\text{cm}$, $> 1\text{cm}$ margin width, No Tamoxifen
- N= 143, Median Age (51) Median follow up 11 years

<table>
<thead>
<tr>
<th>IBTR Rate</th>
<th>Inv Ca RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year</td>
<td>12%</td>
</tr>
<tr>
<td>10 year</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

“With ongoing follow up there is a substantial and ongoing risk of LR in patients with favorable DCIS treated with surgery alone.”

Changing What’s Possible.

*Wong et al Breast Cancer Res Treat 2014*
DCIS: WLE Alone, ECOG Study

• ECOG E5194 Low Risk Cohort
• DCIS G1-2, ≤ 2.5 cm, ≥ 3 mm margin width, Tamoxifen not randomly assigned (30%)
• N=561, Median Follow up 12.3yrs

<table>
<thead>
<tr>
<th>IBTR Rate</th>
<th>Inv Ca RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 year</td>
<td>14.4%</td>
</tr>
</tbody>
</table>

“individual patients and the physicians will need to decide if these 12 year risks are acceptable”

Solin et al JCO 2015
DCIS: Recurrence Risk Assessment Tools

- Oncotype DX DCIS Recurrence Score
- 12 gene assay used to predict risk of IBTR after excision alone
- Validated on the ECOG E5194 data set (N=327)

![Gene expression groups]

- **Proliferation group**
  - Ki67
  - STK15
  - Survivin
  - CCNB1 (cyclin B1)
  - MYBL2

- **Hormone receptor group**
  - PR

- **Reference group**
  - ACTB (β-actin)
  - GAPDH
  - RPLPO
  - GUS
  - TFRC

Solin et al J Nat Cancer Inst 2013
DCIS: Recurrence Risk Assessment

Tools

- Oncotype DX DCIS Recurrence Score

- MVA: Predictors of IBTR
  - Tumor size
  - Menopausal Status
  - DCIS Recurrence Score

Solin et al J Nat Cancer Inst 2013
DCIS: Recurrence Risk Assessment

Tools

• Oncotype DX DCIS Recurrence Score (Refined Estimates)
  • Combine analysis of 2 validation sets (ECOG and Ontario DCIS population study) and integrating Age and Tumor Size

• N=773

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>E5194 (n=327)</th>
<th>Ontario DCIS Cohort (n=446)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 cm</td>
<td>260 (79.5%)</td>
<td>181 (40.6%)</td>
</tr>
<tr>
<td>&gt; 1-2.5 cm</td>
<td>67 (20.5%)</td>
<td>238 (53.4%)</td>
</tr>
<tr>
<td>&gt; 2.5 cm</td>
<td>0</td>
<td>27 (6.1%)</td>
</tr>
</tbody>
</table>

83.5%

Rakovitch et al ASCO 2017 poster
Oncotype DX DCIS Recurrence Score (Refined Estimates)

- Combine analysis of 2 validation sets (ECOG and Ontario DCIS population study) and integrating Age and Tumor Size

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>Age (yr)</th>
<th>Low DCIS Score (0-38)</th>
<th>Intermediate DCIS Score (39-54)</th>
<th>High DCIS Score (55-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>≥ 50</td>
<td>7.2 (5.3-10.0)</td>
<td>11.3 (10.2-12.7)</td>
<td>14.6 (12.9-23.1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 50</td>
<td>10.2 (7.4-13.9)</td>
<td>15.8 (14.1-17.4)</td>
<td>19.6 (17.7-30.7)</td>
</tr>
<tr>
<td>1.1-2.5</td>
<td>≥ 50</td>
<td>10.1 (7.3-12.6)</td>
<td>13.9 (12.8-15.6)</td>
<td>19.5 (15.8-28.7)</td>
</tr>
<tr>
<td></td>
<td>&lt; 50</td>
<td>14.5 (10.1-17.2)</td>
<td>18.9 (17.4-21.1)</td>
<td>23.2 (21.4-37.2)</td>
</tr>
<tr>
<td>&gt; 2.5</td>
<td>≥ 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DCIS: Recurrence Risk Assessment Tools

- Memorial Sloan Kettering Nomogram (available “free” online)
- N=1681, treated 1991-2006
- Utilizes 10 clinical, pathologic, and treatment variables to estimate recurrence at 5 and 10 years after BCS
- Allows estimation of recurrence based on combinations of adjuvant treatments

Rudloff et al JCO 2010
MSKCC DCIS Nomogram Validation Community-based Cohort

Changing What’s Possible.

Collins et al Annals of Surg Onc 2015
Randomized Trial “Good Risk”
DCIS: S +/- RT

- DCIS, G1-2, mammographically detected, ≤ 2.5 cm (median 0.5 cm), > 3 mm margin width, N=636 (closed early due to low accrual)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Median = 58 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median = 58 yrs</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>78%</td>
</tr>
<tr>
<td>Grade</td>
<td>G1 44%, G2 56%</td>
</tr>
<tr>
<td>Size</td>
<td>Mean = 0.6 cm (61%, ≤0.5cm)</td>
</tr>
<tr>
<td>Margin Width</td>
<td>65% ≥ 1 cm</td>
</tr>
<tr>
<td>Tamoxifen received</td>
<td>WBRT 58%, OBS 65% (SS)</td>
</tr>
</tbody>
</table>
## RTOG 9804 Outcomes

<table>
<thead>
<tr>
<th>ARM</th>
<th>7yr IBTR</th>
<th>12yr IBTR</th>
<th>RT Relative Risk Reduction IBTR</th>
<th>RT Absolute Risk Reduction</th>
<th>Inv Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT</td>
<td>0.9%</td>
<td>2.8%</td>
<td>75%</td>
<td>8.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>OBS</td>
<td>6.7%</td>
<td>11.4%</td>
<td></td>
<td></td>
<td>5.8%</td>
</tr>
</tbody>
</table>
### RTOG 9804: Risk of Invasive Recurrence with OBS

<table>
<thead>
<tr>
<th>Failure event</th>
<th>NSABP B-17 LO (n = 403)</th>
<th>NSABP B-17 LRT (n = 410)</th>
<th>NSABP B-24 LRT + placebo (n = 900)</th>
<th>NSABP B-24 LRT + TAM (n = 899)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events</td>
<td>%†</td>
<td>Annual failure rate</td>
<td>No. of events</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>32</td>
<td>7.9</td>
<td>0.76</td>
<td>38</td>
</tr>
<tr>
<td>Invasive</td>
<td>25</td>
<td>6.2</td>
<td>0.59</td>
<td>23</td>
</tr>
<tr>
<td>DCIS</td>
<td>7</td>
<td>1.7</td>
<td>0.17</td>
<td>15</td>
</tr>
</tbody>
</table>
RTOG 9804: Conclusions

• Informs Physician – Patient decision making regarding the omission of RT for “Good Risk” DCIS

• Omission of Radiation Therapy is a reasonable treatment option in “Good Risk” DCIS for those patients who were well represented in the study population.

• **Caution** with omission of RT in patients with combinations of risk factors:
  - Young Age
  - Larger Tumor Sizes
  - + Family History
  - Decline Endocrine Therapy
Early Stage Invasive Cancer: *Omitting RT after BCS*

**CALGB 9343**

- 70y or older
- pT1
- ER+
- Clinically LN (-)
- Margin Negative
- No tumor on ink

Hughes at al, *NEJM* 2004
Early Stage Invasive Cancer: *Omitting RT after BCS*

**CALGB 9343 Trial Design**

Lumpectomy

Axillary LN dissection, $N=6$
- allowed but discouraged

XRT + TAM x 5 yrs

TAM x 5 yrs

*Hughes et al. NEJM 2004*
## Early Stage Invasive Cancer: Omitting RT after BCS CALGB 9343 10yr Results

<table>
<thead>
<tr>
<th>End Points</th>
<th>RT/Tam</th>
<th>Tam</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Mastectomy Free Survival</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>10 yr Breast Ca S S</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>61%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Hughes JCO 2013
Early Stage Invasive Cancer: *Omitting RT after BCS*  
*CALGB 9343*

- Conclusions:
  - Omitting radiation in those $\geq 70$ with T1 ER+, margin negative, node negative is an appropriate treatment option
  - Breast cancer mortality is not a major concern for this subset of older women
Early Stage Invasive Cancer: *Omitting RT after BCS*

**PRIME II**

- ≥65 yo (median age 70)
- T1-T2 (max 3 cm)
- Node negative (pN0)
- Margin negative (≥ 1mm)
- ER+, PR + or both
- G3 or LVI (not both)
- HER 2 status not assess

Kunkler et al, Lancet Oncology 2015

RT

BCS + HT

N=1326

OBS

Changing What’s Possible.
**Early Stage Invasive Cancer: Omitting RT after BCS: PRIME II**

<table>
<thead>
<tr>
<th>5yr End Points</th>
<th>RT/HT</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td>1.3%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>0.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>0.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>93.9%</td>
<td>93.9%</td>
</tr>
</tbody>
</table>

- SS
- NNT prevent 1 IBTR=31.8

Kunkler Lancet Oncology 2015
Early Stage Invasive Cancer: *Omitting RT after BCS PRIME II*

- Conclusions:
  - RT resulted in a modest benefit in IBTR rate
  - 5 years of follow-up too short
  - NCCN guidelines have not changed to reflect omitting RT in this population
  - Commission on Cancer quality metrics for RT have not adopted this paradigm
Early Stage Invasive Cancer: Omitting RT after BCS

Canadian Trial

- >50 yo
- pT1-T2
- Negative margins
  - (no tumor on ink)
- Node negative
  - (<65 required pN0, >65 could be cN0)
- Any ER status

BCS + Tam
N=769

Fyles et al NEJM 2004
Early Stage Invasive Cancer: *Omitting RT after BCS: Canadian Trial*

<table>
<thead>
<tr>
<th>5 yr End Points</th>
<th>RT/TAM</th>
<th>TAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td>0.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Regional Recurrence</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Disease Free</td>
<td>91</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8 yr End Points</th>
<th>IBTR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td>3.5</td>
<td>17.6</td>
</tr>
</tbody>
</table>

Fyles NEJM 2004
Early Stage Invasive Cancer: *Omitting RT after BCS: Canadian Trial*

- Conclusions:
  - Omitting RT in those early stage patients >50 resulted in unacceptably high rates of IBTR
Future Studies of Omitting RT after BCS

- Incorporate Tumor Biology: Breast Cancer Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>10-Year RRFS (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>587</td>
<td>24</td>
<td>97</td>
<td>96 to 99</td>
</tr>
<tr>
<td>Luminal B</td>
<td>295</td>
<td>20</td>
<td>92</td>
<td>88 to 95</td>
</tr>
<tr>
<td>Luminal-HER2</td>
<td>61</td>
<td>2</td>
<td>95</td>
<td>83 to 99</td>
</tr>
<tr>
<td>HER2 enriched</td>
<td>80</td>
<td>12</td>
<td>84</td>
<td>73 to 91</td>
</tr>
<tr>
<td>Basal-like</td>
<td>134</td>
<td>17</td>
<td>86</td>
<td>79 to 91</td>
</tr>
<tr>
<td>TNP-nonbasal</td>
<td>114</td>
<td>8</td>
<td>93</td>
<td>86 to 96</td>
</tr>
</tbody>
</table>
Future Studies of Omitting RT after BCS

• Incorporate Genomic Risks: Oncotype DX RS
Future Studies of Omitting RT after BCS

- LUMINA
  - Prospective Canadian multicenter trial
  - ≥ 60 yo
  - Unifocal, Stage I (pN0)
  - Negative margin (2mm)
  - ER+/PR+ Her 2 negative
  - No EIC, No lobular ca, No G3
  - Luminal A tumors
Future Studies of Omitting RT after BCS

• IDEA
  – Prospective multicenter US cohort
  – 50-69yo
  – Unifocal Stage I (pN0)
  – Negative margins (2mm)
  – ER+, PR+, Her2 negative
  – Low Oncotype-DX RS (≤18)
Future Studies of Omitting RT after BCS

• Precision
  – Prospective multicenter Boston cohort
  – 50-75 yo
  – Unifocal Stage I (pN0)
  – Margin negative (no tumor on ink)
  – No G3
  – ER+, PR+, Her 2 negative
  – Low risk PAM50 score