Local-regional Recurrence
Invasive Breast Cancer

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Helen Diller Family
Comprehensive Cancer Center
UCSF

Issues to Address

- Magnitude of problem
  - Breast conserving surgery +/- RT
  - Mastectomy +/- RT

- Impact systemic therapy
- Options for subsequent local treatment
  - Ipsilateral breast tumor recurrence

Patterns of Failure Breast Cancer

<table>
<thead>
<tr>
<th>Initial Rx</th>
<th>NED</th>
<th>DM</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS + RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy + RT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sites of Local-regional Failure
Breast Cancer

<table>
<thead>
<tr>
<th>Local</th>
<th>Regional</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR</td>
<td>Axilla</td>
</tr>
<tr>
<td>BCS</td>
<td>SNB</td>
</tr>
<tr>
<td>BCS + RT</td>
<td>AD +/- SNB +/- RT</td>
</tr>
<tr>
<td>Chest wall</td>
<td>Supraclavicular node</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>RT vs. none</td>
</tr>
<tr>
<td>Mastectomy + RT</td>
<td>IMN</td>
</tr>
<tr>
<td></td>
<td>RT vs. none</td>
</tr>
</tbody>
</table>
**EBCTG Meta-analysis Randomized Trials**

**Magnitude of the Problem**

**EBCTG Meta-analysis Randomized Trials**

**Mastectomy + AD +/- RT**

<table>
<thead>
<tr>
<th>LRF%</th>
<th>Mast</th>
<th>Mast + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 10 15 yr</td>
<td>5 10 15 yr</td>
</tr>
<tr>
<td>Node Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1296 pts</td>
<td>7 9 ---</td>
<td>2 3 ---</td>
</tr>
<tr>
<td>1-3 positive nodes</td>
<td>3222 pts</td>
<td>20 25 26</td>
</tr>
<tr>
<td>≥ 4 positive nodes</td>
<td>2794 pts.</td>
<td>33 40 41</td>
</tr>
</tbody>
</table>

Darby S San Antonio 12/2009

**Impact of Systemic Therapy on Local-regional Recurrence**

**EBCTG Meta-analysis Randomized Trials**

**BCS +/- RT**

<table>
<thead>
<tr>
<th>IBTR%</th>
<th>BCS</th>
<th>BCS + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7334 pts.</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>5 yr.</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>10 yr.</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>15 yr.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1111 pts.</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>5 yr.</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>10 yr.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Darby S San Antonio 12/2009
## IBTR BCS+RT
### NSABP Adjuvant Therapy Trials
#### Axillary Node Negative

<table>
<thead>
<tr>
<th>Systemic therapy</th>
<th>No. Pts.</th>
<th>10 Yr. CI IBTR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3799</td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>653</td>
<td>11</td>
</tr>
<tr>
<td>Tam</td>
<td>505</td>
<td>4</td>
</tr>
<tr>
<td>Tam +/- chemo</td>
<td>530</td>
<td>6</td>
</tr>
<tr>
<td>Chemo</td>
<td>2111</td>
<td>5</td>
</tr>
</tbody>
</table>

*Percentages may not add up to 100% due to rounding.*

**Notes:**
- **ER+**
- **ER-**

**Source:**
Anderson SJ. *JCO* 27:2466, 2009

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## EBCTCG Effect of Chemotherapy on Post-mastectomy Local Recurrence Rates

### Absolute Reduction
#### 5 Yr. Local Recurrence with RT

<table>
<thead>
<tr>
<th>1-3+ Nodes</th>
<th>≥ 4+ Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo*</td>
<td>9% (1006)</td>
</tr>
<tr>
<td>No chemo</td>
<td>19% (670)</td>
</tr>
</tbody>
</table>

**Notes:**
- *Primarily CMF* ( ) No. pts.

**Source:**
Darby S San Antonio 12/10

---

## EBCTCG Absolute Reduction
### 5 Yr. Post-mastectomy Local Recurrence with Radiation

<table>
<thead>
<tr>
<th>No. pos. Nodes</th>
<th>% Absolute Decrease LRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts.</td>
<td>No chemo</td>
</tr>
<tr>
<td>1</td>
<td>398</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:**
Darby S San Antonio 2009

---

## Effect of Taxanes on Local-regional Recurrence
### CALGB 9344 Node Positive

<table>
<thead>
<tr>
<th>No.</th>
<th>5 Yr. LRF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>AC</td>
</tr>
<tr>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>BCS+RT</td>
<td>269</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>565</td>
</tr>
<tr>
<td>1-3+</td>
<td>254</td>
</tr>
<tr>
<td>≥ 4+</td>
<td>244</td>
</tr>
<tr>
<td>Mastectomy + RT</td>
<td>185</td>
</tr>
</tbody>
</table>

**Source:**
Sartor CI et al. *JCO* 23:30-40, 2005
### Effect of Taxanes on Local-regional Recurrence MDA

<table>
<thead>
<tr>
<th></th>
<th>FAC x 8</th>
<th>Tx4 → FAC x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>12 yr. LRF</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>12 Yr. OS</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>BCS+RT</td>
<td>64%</td>
<td>74%</td>
</tr>
<tr>
<td>(67 pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>70%</td>
<td>52%</td>
</tr>
<tr>
<td>(60 pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy +RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(36 pts.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oh JL et al. IJROBP 75:S79, 2009

### Effect of Trastuzumab Local-regional Recurrence

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts.</td>
<td>Median FU Yrs.</td>
<td>Local-regional Rec. %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemo</td>
<td>Chemo+Herceptin</td>
</tr>
<tr>
<td>Herceptin</td>
<td>3387</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>3401</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>NSABP B31</td>
<td>1736</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>1615</td>
<td>1.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Kuerer H SSO St. Louis 3/2010

### Changes in Practice and Effect on IBTR BCS+RT Stage I-II

|                |          |          |          |          |          |
|----------------|----------|----------|----------|----------|
| Years studied  |          |          |          |          |
| Change observed|          | ↑ mean age|↓ tumor size|↑ re-excision and |
|                |          |↑ neg. margins|↑ systemic |
|                |          |↑ systemic therapy|     |
| No. pts.       | 607      | 1355     |          |          |
| 5 Yr.          | 8%       | 1%       | 6%       | 1%       |
| 12 Yr.         | 21%      | 9%       |          |          |

Kuerer H SSO St. Louis 3/2010

### Post-mastectomy Local-regional Recurrence in Patients Receiving Doxorubicin Based Regimens MDA

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pos.</td>
<td>1-3*</td>
<td>1</td>
</tr>
<tr>
<td>No. RT</td>
<td>13(437)</td>
<td>3(173)</td>
</tr>
<tr>
<td>RT</td>
<td>3(119)</td>
<td>8(71)</td>
</tr>
</tbody>
</table>

*Median no. nodes examined = 17
Molecular Subtypes Breast Cancer

**Definition Molecular Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. Pts.</th>
<th>Definition</th>
<th>% of Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>1304</td>
<td>ER or PR+ [Her2-, Ki-67&lt;14%]</td>
<td>44</td>
</tr>
<tr>
<td>Luminal B</td>
<td>713</td>
<td>ER or PR+ [Her2-, Ki-67≥14%]</td>
<td>24</td>
</tr>
<tr>
<td>Luminal Her2</td>
<td>185</td>
<td>ER or PR+, [Her2+]</td>
<td>6</td>
</tr>
<tr>
<td>Her2+</td>
<td>227</td>
<td>ER-, PR-, [Her2+]</td>
<td>8</td>
</tr>
<tr>
<td>Basal-like</td>
<td>295</td>
<td>ER-, PR-, [EGFR+ or CK5/6+]</td>
<td>10</td>
</tr>
<tr>
<td>TPN-non basal</td>
<td>261</td>
<td>ER-, PR-, [EGFR-, CK5/6-]</td>
<td>9</td>
</tr>
</tbody>
</table>

Voduc KD et al JCO 28:1684-9,2010

**Tumor Characteristics Related to Molecular Subtype BC**

<table>
<thead>
<tr>
<th></th>
<th>Luminal</th>
<th>Her 2</th>
<th>Basal</th>
<th>TN*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>1304</td>
<td>227</td>
<td>295</td>
<td>261</td>
</tr>
<tr>
<td>Age &lt;55 yrs.</td>
<td>33%</td>
<td>42%</td>
<td>92%</td>
<td>45%</td>
</tr>
<tr>
<td>T1-2</td>
<td>97%</td>
<td>93%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>Node pos.</td>
<td>41%</td>
<td>55%</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>35%</td>
<td>77%</td>
<td>90%</td>
<td>67%</td>
</tr>
<tr>
<td>LVI+</td>
<td>39%</td>
<td>54%</td>
<td>40%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Voduc KD et al JCO 28: 1684-9,2010

**Tumor Characteristics Related to Molecular Subtype MSK**

<table>
<thead>
<tr>
<th></th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Her 2</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>4336 (71%)</td>
<td>476 (8%)</td>
<td>368(6%)</td>
<td>892(15%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>58 yrs.</td>
<td>52 yrs.</td>
<td>53 yrs.</td>
<td>54 yrs.</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>43%</td>
<td>52%</td>
<td>57%</td>
<td>44%</td>
</tr>
<tr>
<td>N&gt; 4+</td>
<td>11%</td>
<td>20%</td>
<td>28%</td>
<td>14%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>29%</td>
<td>62%</td>
<td>88%</td>
<td>85%</td>
</tr>
<tr>
<td>LVI+</td>
<td>28%</td>
<td>43%</td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td>EIC+</td>
<td>15%</td>
<td>25%</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>Multifocal/ multcentric</td>
<td>27%</td>
<td>30%</td>
<td>37%</td>
<td>22%</td>
</tr>
</tbody>
</table>

## Local Recurrence Triple Negative Breast Cancer

<table>
<thead>
<tr>
<th>Local-reg. Failure %</th>
<th>Yale</th>
<th>Harvard</th>
<th>FCCC</th>
<th>Penn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple negative</td>
<td>17(117)</td>
<td>7(89)</td>
<td>5(98)</td>
<td>6(90)</td>
</tr>
<tr>
<td>Non-triple negative</td>
<td>17(365)</td>
<td>1.8(429)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+, PR+</td>
<td>3(600)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her 2-</td>
<td>0.8(595)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her 2+</td>
<td>2(77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her 2+, ER-</td>
<td>8(32)</td>
<td>5(55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up yrs.</td>
<td>7.9</td>
<td>5.8</td>
<td>5 act.</td>
<td>3.9</td>
</tr>
</tbody>
</table>

( ) no. pts. No pts treated with Herceptin

---

## IBTR Related to Molecular Subtype

<table>
<thead>
<tr>
<th>No. Pts.</th>
<th>10 Year</th>
<th>10 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>587</td>
<td>92</td>
</tr>
<tr>
<td>Luminal B</td>
<td>295</td>
<td>90</td>
</tr>
<tr>
<td>Luminal Her2</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td>Her2+</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Basal like</td>
<td>134</td>
<td>86</td>
</tr>
<tr>
<td>TN-non basal</td>
<td>114</td>
<td>92</td>
</tr>
</tbody>
</table>

No pts trastuzumab Chemo 24% Hormones 31%

Voduc KD et al JCO 28:1684-91, 2010

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## Post-mastectomy Local-regional Recurrence

<table>
<thead>
<tr>
<th>No. Pts.</th>
<th>%PMRT</th>
<th>10 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>717</td>
<td>21</td>
</tr>
<tr>
<td>Luminal B</td>
<td>418</td>
<td>29</td>
</tr>
<tr>
<td>Luminal Her2</td>
<td>124</td>
<td>31</td>
</tr>
<tr>
<td>Her2+</td>
<td>147</td>
<td>41</td>
</tr>
<tr>
<td>Basal like</td>
<td>161</td>
<td>42</td>
</tr>
<tr>
<td>TN-non basal</td>
<td>147</td>
<td>24</td>
</tr>
</tbody>
</table>

No pts trastuzumab Chemo 26% Hormones 44%

Voduc KD et al JCO 28:1684-91, 2010
### Chest Wall Recurrence Related to Molecular Subtype T1-2N0-1 Grade 3 Post-mastectomy No RT

<table>
<thead>
<tr>
<th>Subtype</th>
<th>10 Yr. CW Rec. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>8%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>22%</td>
</tr>
<tr>
<td>Luminal B-Her 2+</td>
<td>12%</td>
</tr>
<tr>
<td>HER 2+</td>
<td>19%</td>
</tr>
<tr>
<td>Basal</td>
<td>14%</td>
</tr>
<tr>
<td>TN non-basal</td>
<td>9%</td>
</tr>
</tbody>
</table>

No pts. trastuzumab  
Median follow-up 12 yrs.  
Voduc KD et al JCO 28:1684-91,2010

### Regional Node Recurrence Related to Molecular Subtype T2N0-1 Grade 3 BCS+RT or Mastectomy No RT RN

<table>
<thead>
<tr>
<th>Subtype</th>
<th>10 Yr. RN Rec. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>9%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>11%</td>
</tr>
<tr>
<td>Luminal B-Her 2+</td>
<td>11%</td>
</tr>
<tr>
<td>HER 2+</td>
<td>8%</td>
</tr>
<tr>
<td>Basal</td>
<td>24%</td>
</tr>
<tr>
<td>TN non-basal</td>
<td>15%</td>
</tr>
</tbody>
</table>

No pts. trastuzumab  
Median follow-up 12 yrs.  
Voduc KD et al JCO 28:1684-91,2010

### DBCG 82 b and c Outcome Related to Receptor Status

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. Pts.</th>
<th>ER+</th>
<th>ER-PR-Her2+</th>
<th>ER+ Her2+</th>
<th>ER+ Her 2+</th>
<th>Triple Neg</th>
<th>ER-PR-Her2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts.</td>
<td>628</td>
<td>96</td>
<td>152</td>
<td>120</td>
<td>57</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>% ≥ 4+ nodes</td>
<td>46</td>
<td>57</td>
<td>48</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Yr. LRF %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>3*</td>
<td>3*</td>
<td>15*</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>32</td>
<td>48</td>
<td>32</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Yr. OS %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>44*</td>
<td>38</td>
<td>39</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>33</td>
<td>15</td>
<td>32</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER+ = ER+ and/or PR+  
* Significant p value  
No pts received trastuzumab  

### Local-regional Failure Triple Negative Breast Cancer MDA

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. Pts.</th>
<th>5 Yr. LRF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>93</td>
<td>11</td>
</tr>
<tr>
<td>Node neg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast.+RT</td>
<td>143</td>
<td>22</td>
</tr>
<tr>
<td>1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

All pts received chemotherapy  
Doxorubicin based 96%, taxane 78% or both 75%  
Settle SH et al IJROBP 75:S9-10, 2009
Oncotype DX

NSABP B14 and B20
10 Yr. LRF Related to Recurrence Score

Age < 50 Yrs.

<table>
<thead>
<tr>
<th>Score</th>
<th>10 Yr. LRF%</th>
<th>CS+RT</th>
<th>Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18</td>
<td>12.5 (72)</td>
<td>1.5 (73)</td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>27.7 (23)</td>
<td>7.6 (31)</td>
<td></td>
</tr>
<tr>
<td>&gt; 31</td>
<td>26.5 (45)</td>
<td>23.8 (49)</td>
<td></td>
</tr>
</tbody>
</table>

( ) No. pts    Node negative with Tamoxifen


NSABP B14 and B20
10 Yr. LRF Related to Recurrence Score

Age > 50 Yrs.

<table>
<thead>
<tr>
<th>Score</th>
<th>10 Yr. LRF%</th>
<th>CS+RT</th>
<th>Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18</td>
<td>3.6 (139)</td>
<td>2.6 (189)</td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>3.7 (58)</td>
<td>3.8 (82)</td>
<td></td>
</tr>
<tr>
<td>&gt; 31</td>
<td>4.8 (53)</td>
<td>12.8 (49)</td>
<td></td>
</tr>
</tbody>
</table>

( ) No. pts    Node negative with Tamoxifen


Magnitude of the Problem
Local-regional Failure Breast Cancer

<table>
<thead>
<tr>
<th>Node negative</th>
<th>10 Yr. L+/-RF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS + Tam*</td>
<td>10</td>
</tr>
<tr>
<td>BCS + RT + Tam</td>
<td>4-6</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>9</td>
</tr>
</tbody>
</table>

Node positive

<table>
<thead>
<tr>
<th>Mastectomy + chemo</th>
<th>No RT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3+</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>≥ 4</td>
<td>41</td>
<td>13</td>
</tr>
</tbody>
</table>

* Older women
Ipsilateral Breast Tumor Recurrence

Following BCS+RT

<table>
<thead>
<tr>
<th>%BC</th>
<th>IBTR*</th>
<th>No. IBTR per 100 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>44</td>
<td>4%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>30</td>
<td>9%</td>
</tr>
<tr>
<td>Her 2+</td>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>Triple negative</td>
<td>19</td>
<td>10%</td>
</tr>
<tr>
<td>Total IBTR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Voduc KD et al JCO 28:1684-91, 2010
*Millar EKA et al JCO 27:4701-4708, 2009

General Consensus
Local-regional Failure Breast Cancer

Local and/or regional recurrence adversely affects outcome
- Increased distant metastases
- Decreased survival

Prognostic factors outcome following IBTR
- Interval to recurrence
- Method of detection recurrence
- Histology recurrence- DCIS vs. invasive
- Initial nodal status and nodal status recurrence
- Size and extent of recurrence
- Location recurrence
- Estrogen receptor status

Survival Following IBTR BCS+RT
NSABP Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th>Node Neg.</th>
<th>Node Pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. pts.</td>
<td>3799</td>
</tr>
<tr>
<td>No. IBTR</td>
<td>342</td>
</tr>
<tr>
<td>Interval IBTR ≤5 yrs.</td>
<td>37%</td>
</tr>
</tbody>
</table>

5 Yr. OS After IBTR
- All pts | 77% | 60% |
- ER+ | 83% | ----- |
- ER- | 67% | ----- |

### IBTR and Survival NSABP

#### Node Negative NSABP Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th>Interval</th>
<th>Shorter</th>
<th>Longer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yrs.</td>
<td>39</td>
<td>85</td>
</tr>
<tr>
<td>3 yrs.</td>
<td>51</td>
<td>88</td>
</tr>
<tr>
<td>4 yrs.</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td>5 yrs.</td>
<td>61</td>
<td>88</td>
</tr>
</tbody>
</table>

*Anderson SJ et al. JCO 27:2466-73, 2009*

#### Node Positive Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th>Interval</th>
<th>Shorter</th>
<th>Longer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yrs.</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>3 yrs.</td>
<td>57</td>
<td>88</td>
</tr>
<tr>
<td>4 yrs.</td>
<td>62</td>
<td>89</td>
</tr>
</tbody>
</table>

*Wapnir I JCO 24:2028, 2006*

### Ipsilateral Breast Tumor Recurrence

#### Salvage Treatment

- Frequency relatively low
- Majority of studies focus on outcome of IBTR following BCS+RT
- Limited information salvage IBTR following BCS without RT
- Details of salvage therapy frequently missing

### Options for Salvage

#### Local Treatment IBTR

- Initial BCS without RT
  - Breast conserving surgery + RT
  - Mastectomy +/- reconstruction +/- RT
- Initial BCS + RT
  - Breast conserving surgery
  - Breast conserving surgery + re-irradiation
  - Mastectomy +/- reconstruction
Perception of Cause of IBTR and Options for Local Therapy

Failure of initial treatment
- Surgery
- Radiation

Development of new cancer in conserved breast
- Different location
- Different histology
- Long interval to failure

New Primary vs. Recurrence

Is the concept relevant in the era of molecular subtypes and gene expression profiles? Is it the biology of the disease that determines outcome?

Local Recurrence Related to Molecular Subtypes

<table>
<thead>
<tr>
<th>BCS+RT</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Basal</th>
<th>Her 2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pts.</td>
<td>394</td>
<td>23</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Median age yrs.</td>
<td>62</td>
<td>57</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>Median follow-up yrs.</td>
<td>6.9</td>
<td>5.9</td>
<td>7.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>17%</td>
<td>70%</td>
<td>90%</td>
<td>69%</td>
</tr>
<tr>
<td>LVI+</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>EIC+</td>
<td>7%</td>
<td>22%</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>IBTR</td>
<td>4%</td>
<td>9%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Median interval IBTR</td>
<td>6.7 yrs.</td>
<td>6.5 yrs.</td>
<td>1.7 yrs.</td>
<td>1.9 yrs.</td>
</tr>
</tbody>
</table>

No pts treated with Herceptin

Millar EKA et al JCO 27:4701-4708, 2009

NCCN Guidelines

Salvage Treatment IBTR

NCCN Breast Cancer Panel

- Surgeons 4
- Plastic surgeons 1
- Pathologists 2
- Medical oncologists 17
- Radiation oncologists 2
2010 NCCN Guidelines
Salvage Treatment IBTR

Initial treatment BCS+RT
- Mastectomy and AD if not previously done
- SNB accuracy not proven

Category recommendation 2A
- Lower level evidence but uniform consensus that recommendation is appropriate

Outcome IBTR After Initial BCS without RT

<table>
<thead>
<tr>
<th>No pts.</th>
<th>Treatment recurrence</th>
<th>Location rec.</th>
<th>Nodal status rec.</th>
<th>Subsequent CW rec.</th>
<th>5 Yr. OS</th>
<th>5 Yr. DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Mastectomy + AD</td>
<td>60% T/M</td>
<td>28% 0-3+, 72% ≥ 4+</td>
<td>32% (? RT)</td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Chemo +/- Hormones 40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormones 8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7 years (.75-5.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median interval IBTR

<table>
<thead>
<tr>
<th>No. IBTR</th>
<th>Systemic Rx</th>
<th>5 Yr. (10) OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn</td>
<td>112</td>
<td>39%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>266</td>
<td>4%</td>
</tr>
<tr>
<td>SEER</td>
<td>568</td>
<td>NS</td>
</tr>
<tr>
<td>Yale</td>
<td>116</td>
<td>29%</td>
</tr>
<tr>
<td>Milan</td>
<td>134</td>
<td>NS</td>
</tr>
<tr>
<td>Marseille</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>MSK</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Harvard</td>
<td>106</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cajucom CC et al Cancer 71:1774-9, 1993

Results of Salvage Mastectomy
Invasive IBTR Following BCS+RT

<table>
<thead>
<tr>
<th>No. pts.</th>
<th>Subsequent CW Rec.%</th>
<th>Med. Follow-up after rec. yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Harvard</td>
<td>82</td>
<td>7</td>
</tr>
<tr>
<td>Marseille</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Netherlands</td>
<td>208</td>
<td>25</td>
</tr>
<tr>
<td>Penn</td>
<td>93</td>
<td>3</td>
</tr>
<tr>
<td>Sweden</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Milan</td>
<td>114</td>
<td>4</td>
</tr>
<tr>
<td>Yale</td>
<td>116</td>
<td>7</td>
</tr>
</tbody>
</table>
Results of Salvage Mastectomy
IBTR Triple Negative Recurrence Yale

<table>
<thead>
<tr>
<th></th>
<th>Triple Neg.</th>
<th>Non-triple neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Interval to IBTR ≤ 3 yrs.</td>
<td>50%</td>
<td>24%</td>
</tr>
<tr>
<td>Location IBTR</td>
<td>T/M</td>
<td>T/M</td>
</tr>
<tr>
<td>Size of IBTR ≤ 3 cm</td>
<td>64%</td>
<td>83%</td>
</tr>
<tr>
<td>5 Yr. DMFS</td>
<td>49%</td>
<td>91%</td>
</tr>
<tr>
<td>5 Yr. OS</td>
<td>73%</td>
<td>97%</td>
</tr>
</tbody>
</table>


Results of BCS as Salvage
Invasive IBTR Following BCS+RT

<table>
<thead>
<tr>
<th></th>
<th>Yale</th>
<th>Sweden</th>
<th>Netherlands</th>
<th>Milan</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>16</td>
<td>30</td>
<td>16</td>
<td>161</td>
</tr>
<tr>
<td>Subsequent IBTR %</td>
<td>31</td>
<td>26</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Med. Follow-up after rec. yrs.</td>
<td>3.3</td>
<td>3.6</td>
<td>4.3</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Harvard
Osaka
Marseille
Netherlands
Sweden
Milan
Yale

Results of Salvage Treatment
Invasive IBTR Following BCS+RT

<table>
<thead>
<tr>
<th></th>
<th>Yale</th>
<th>Sweden</th>
<th>Milan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent local rec. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>7 (116)</td>
<td>15 (60)</td>
<td>4 (134)</td>
</tr>
<tr>
<td>BCS</td>
<td>7 (30)</td>
<td>36 (14)</td>
<td>19 (57)</td>
</tr>
<tr>
<td>Survival following IBTR %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>66</td>
<td>-----</td>
<td>70</td>
</tr>
<tr>
<td>BCS</td>
<td>58</td>
<td>-----</td>
<td>85</td>
</tr>
<tr>
<td>Interval reported</td>
<td>10 yr.</td>
<td>5 yr.</td>
<td>5 yr.</td>
</tr>
</tbody>
</table>

( ) no. pts.
Outcome IBTR After BCS+RT
SEER Registry Data 1998-2004

<table>
<thead>
<tr>
<th></th>
<th>BCS</th>
<th>Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>179</td>
<td>568</td>
</tr>
<tr>
<td>Mean age</td>
<td>64 yrs.</td>
<td>60 yrs.</td>
</tr>
<tr>
<td>ER+</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>ER-</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>34%</td>
<td>47%</td>
</tr>
<tr>
<td>Initial stage I</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>RT for recurrence</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td>Survival</td>
<td>5 Yr.</td>
<td>10 Yr.</td>
</tr>
<tr>
<td>All pts.</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>T1N0 or NX</td>
<td>82</td>
<td>68</td>
</tr>
</tbody>
</table>


Survival Impact of Mastectomy vs. BCS
IBTR BCS+RT

Survival Impact of Mastectomy vs. BCS
IBTR BCS+RT T1N0 or NX

Favorable recurrence
Initial stage I, ER positive
Recurrence < 2 cm, path node negative
Low grade, no LVI, no EIC
Long interval to recurrence (>3-5 yrs.)
Low probability multicentric disease

### Incidence Multicentricity Salvage Mastectomy IBTR BCS+RT

<table>
<thead>
<tr>
<th></th>
<th>No. Pts.</th>
<th>Multicentricity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B06</td>
<td>110</td>
<td>14%</td>
</tr>
<tr>
<td>Yale</td>
<td>116</td>
<td>24%</td>
</tr>
<tr>
<td>Penn</td>
<td>52</td>
<td>31%</td>
</tr>
<tr>
<td>Harvard</td>
<td>25</td>
<td>22%</td>
</tr>
</tbody>
</table>

### Factors Associated Multicentric Disease IBTR BCS+RT Yale

<table>
<thead>
<tr>
<th>Factor Recurrence</th>
<th>Multicentricity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts.</td>
<td>24 (116)</td>
</tr>
<tr>
<td>Size recurrence cm</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>5 (43)</td>
</tr>
<tr>
<td>1-2</td>
<td>15 (33)</td>
</tr>
<tr>
<td>2-3</td>
<td>33 (15)</td>
</tr>
<tr>
<td>4-5</td>
<td>66 (3)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>78 (9)</td>
</tr>
<tr>
<td>Histology recurrence</td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>18 (22)</td>
</tr>
<tr>
<td>IDC</td>
<td>22 (37)</td>
</tr>
<tr>
<td>IDC+DCIS</td>
<td>32 (47)</td>
</tr>
</tbody>
</table>

Alpert TE et al IJROBP 63:845-51, 2005

### Factors Associated Multicentric Disease IBTR BCS+RT Yale

<table>
<thead>
<tr>
<th>Factor primary tumor</th>
<th>Multicentricity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts.</td>
<td>24 (116)</td>
</tr>
<tr>
<td>ER</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>21 (54)</td>
</tr>
<tr>
<td>Negative</td>
<td>41 (27)</td>
</tr>
<tr>
<td>Path N status</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Positive</td>
<td>33 (15)</td>
</tr>
<tr>
<td>BRCA 1/2 status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Negative</td>
<td>17 (52)</td>
</tr>
</tbody>
</table>

Alpert TE et al IJROBP 63:845-51, 2005
Factors Associated with Second IBTR
Salvage BCS

<table>
<thead>
<tr>
<th></th>
<th>No. pts</th>
<th>Second IBTR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age yrs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Family hx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>Negative</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Interval to IBTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 yrs.</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>&gt; 2 yrs.</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>43</td>
</tr>
</tbody>
</table>

Komoike Y et al Oncology 64:1-6, 2003

Second IBTR Following BCS for IBTR After Initial BCS+RT

<table>
<thead>
<tr>
<th></th>
<th>No. pts</th>
<th>5 Yr. CI Second IBTR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>161</td>
<td>31</td>
</tr>
<tr>
<td>Age yrs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>Time to IBTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 yrs.</td>
<td>87</td>
<td>42</td>
</tr>
<tr>
<td>&gt; 4 yrs.</td>
<td>74</td>
<td>18</td>
</tr>
</tbody>
</table>


Second IBTR Following BCS for IBTR After BCS+RT

<table>
<thead>
<tr>
<th></th>
<th>No. pts</th>
<th>5 Yr. CI Second IBTR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>161</td>
<td>31</td>
</tr>
<tr>
<td>Size of rec. cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>135</td>
<td>22</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>Multifocal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>No</td>
<td>136</td>
<td>31</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>125</td>
<td>26</td>
</tr>
<tr>
<td>Negative</td>
<td>35</td>
<td>49</td>
</tr>
</tbody>
</table>

Second IBTR Following BCS for IBTR After BCS+RT

<table>
<thead>
<tr>
<th>No. Pt.</th>
<th>5 Yr. CI</th>
<th>Second IBTR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>161</td>
<td>31</td>
</tr>
<tr>
<td>Tumor size ≤ 2 cm</td>
<td>135</td>
<td>22</td>
</tr>
<tr>
<td>Interval ≤ 4 yrs.</td>
<td>71</td>
<td>30</td>
</tr>
<tr>
<td>Interval &gt; 4 yrs.</td>
<td>64</td>
<td>13</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>16</td>
<td>71</td>
</tr>
</tbody>
</table>


Factors Associated with Second IBTR with Salvage BCS

Low risk
- Low risk
- Multicentricity
  - Detection mammo only
  - Interval > 3 yrs.
  - DCIS
  - Recurrence ≤ 2 cm
- BRCA negative

Low risk
- Second IBTR
  - Older age
  - Interval > 4 yrs
  - Ki67 < 20%
  - Recurrence ≤ 2 cm

Role of Re-irradiation IBTR After BCS+RT

Local control
Cosmesis
Complications
- Fibrosis
- Pain
- Necrosis
- Cardiac and pulmonary
Second malignancy
- Sarcoma

Series of Re-irradiation IBTR BCS+RT

<table>
<thead>
<tr>
<th>No.</th>
<th>Median Age yrs.</th>
<th>Median Interval IBTR</th>
<th>T1</th>
<th>Systemic Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marseille</td>
<td>69</td>
<td>58</td>
<td>7.5 yrs.</td>
<td>62%</td>
</tr>
<tr>
<td>Pittsburg</td>
<td>39</td>
<td>?</td>
<td>5.2 yrs.</td>
<td>21%</td>
</tr>
<tr>
<td>Vienna</td>
<td>17</td>
<td>49.5</td>
<td>4.2 yrs.</td>
<td>82%</td>
</tr>
<tr>
<td>Beth Israel</td>
<td>15</td>
<td>54</td>
<td>7.8 yrs.</td>
<td>80%</td>
</tr>
<tr>
<td>Barcelona</td>
<td>36</td>
<td>51</td>
<td>3.2 yrs. &lt; 3 cm</td>
<td>20%</td>
</tr>
<tr>
<td>Univ Paris</td>
<td>38</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
### Results of Re-irradiation IBTR BCS+RT

<table>
<thead>
<tr>
<th>No. RT</th>
<th>Dose</th>
<th>IBTR</th>
<th>Follow-up Med. Yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marseille</td>
<td>LDR Brachy</td>
<td>30.45-50 Gy</td>
<td>16%</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>EBT PB</td>
<td>50 Gy</td>
<td>21%</td>
</tr>
<tr>
<td>Univ. Paris</td>
<td>LDR Brachy</td>
<td>30 Gy</td>
<td>27%</td>
</tr>
<tr>
<td>Vienna</td>
<td>PDR Brachy</td>
<td>40.2-50 Gy</td>
<td>0%</td>
</tr>
<tr>
<td>Vienna</td>
<td>WB + Brachy</td>
<td>30 Gy</td>
<td>50%</td>
</tr>
<tr>
<td>Beth Israel</td>
<td>LDR Brachy</td>
<td>30-45 Gy</td>
<td>11%</td>
</tr>
<tr>
<td>Barcelona</td>
<td>HDR Brachy</td>
<td>30/10 fx</td>
<td>11%</td>
</tr>
<tr>
<td>Allegheny</td>
<td>Mammosite</td>
<td>34/12 fx</td>
<td>0%</td>
</tr>
</tbody>
</table>

* DCIS

### Results of BCS as Salvage Invasive IBTR Following BCS+RT

<table>
<thead>
<tr>
<th>No. Subsequent pts</th>
<th>IBTR.%</th>
<th>Med. Follow-up after rec. yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Osaka</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Marseille</td>
<td>55</td>
<td>27</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>Sweden</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Milan</td>
<td>161</td>
<td>31</td>
</tr>
<tr>
<td>Yale</td>
<td>30</td>
<td>7</td>
</tr>
</tbody>
</table>

### Second IBTR Following BCS for IBTR Initial BCS+RT

<table>
<thead>
<tr>
<th>No.</th>
<th>5 Yr. CI</th>
<th>Second IBTR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>161</td>
<td>31</td>
</tr>
<tr>
<td>Tumor size &lt; 2 cm</td>
<td>135</td>
<td>22</td>
</tr>
<tr>
<td>Interval &lt; 4 yrs.</td>
<td>71</td>
<td>30</td>
</tr>
<tr>
<td>Interval &gt; 4 yrs.</td>
<td>64</td>
<td>13</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>16</td>
<td>71</td>
</tr>
</tbody>
</table>


### Results of Re-irradiation IBTR BCS+RT

<table>
<thead>
<tr>
<th>No. Pts.</th>
<th>Cosmesis Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univ. Paris</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>39</td>
</tr>
<tr>
<td>Vienna</td>
<td>17</td>
</tr>
<tr>
<td>Barcelona</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Radiation Induced Angiosarcoma Breast

Scow JS et al J Surg Oncol 101:401-07, 2010

Radiation (BCS+RT) Induced Angiosarcoma Hypofractionated Radiation

| No. pts | 14 |
| Extent of disease |  |
| Microscopic | 5 |
| Gross | 9 (7/9 post RT resection) |
| Radiation Treatment area | Primary site + wide margin |
| Dose | 50-75 Gy (1 Gy tid) |
| Outcome |  |
| Local-regional control | 86% |
| 5 Yr. OS | 79% |
| 5 Yr. PFS | 64% |

Palta M et al Cancer 116:1872-8, 2010

Nipple Sparing Mastectomy

Mastectomy and Immediate Reconstruction IBTR Helsinki

| No. pts. | 60 |
| Eligibility |  |
| IBTR < 3 cm, node neg. Interval > 3 yrs. |
| Type of mastectomy |  |
| Skin sparing | 100% |
| Type of reconstruction |  |
| Free TRAM | 67% |
| Latissimus +/- implant | 30% |
| Implant | 3% |
| Systemic therapy | 38% |
| Local recurrence | 10% |

Lindford AJ et al Ann Surg Oncol 2010 epub
Potential or Current Studies
Evaluating Re-irradiation IBTR
BCS+RT

Milan
NSABP B37
IBCSG 27-02
BIG 1-02

- Intra-operative electrons
- APBI 3-D conformal
- BED 40 Gy
- Optional for neg. margins
- Required for pos. margins

Looking Forward
Regional Node Failure
Role of Axillary Surgery
Salvage Treatment IBTR

<table>
<thead>
<tr>
<th></th>
<th>No. Pts.</th>
<th>No. AD</th>
<th>Positive Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale</td>
<td>146</td>
<td>60</td>
<td>30%</td>
</tr>
<tr>
<td>Penn</td>
<td>93</td>
<td>19</td>
<td>39%</td>
</tr>
</tbody>
</table>

Alpert TE et al IJROBP 63:845-51, 2005
Doyle T et al IJROBP 51:74-80, 2001
Application of molecular profiling to locoregional risk assessment and management lags far behind and is relatively underdeveloped.

Haffty BG and Buchholz TA
JCO 28 epub 2010

Sentinel Node Biopsy with Salvage Surgery IBTR

<table>
<thead>
<tr>
<th>No. pts</th>
<th>SNB Successful</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>117</td>
</tr>
<tr>
<td>Initial BCS</td>
<td>25</td>
</tr>
<tr>
<td>Initial BCS+RT</td>
<td>92</td>
</tr>
<tr>
<td>Initial SNB</td>
<td>54</td>
</tr>
<tr>
<td>Initial AD</td>
<td>63</td>
</tr>
<tr>
<td>Initial No. Nodes</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>25</td>
</tr>
<tr>
<td>3-5</td>
<td>20</td>
</tr>
<tr>
<td>6-8</td>
<td>15</td>
</tr>
<tr>
<td>≥ 9</td>
<td>52</td>
</tr>
</tbody>
</table>


Sentinel Node Biopsy with Salvage Surgery IBTR MSK

Lymphoscintogram 112 pts
  Drainage 55%
  Ipsilateral axilla 70%
  Non-ipsilateral axilla 30%
Sentinel node positive 16%
False negative* 17%

* False negative = false neg./ true pos. + false neg.


Regional Node Failure BCS+RT
NSABP Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th>Node Neg.</th>
<th>Node pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. pts.</td>
<td>3799</td>
</tr>
<tr>
<td>No. RNF</td>
<td>77</td>
</tr>
<tr>
<td>10 Yr CI RNF %</td>
<td></td>
</tr>
<tr>
<td>All pts.</td>
<td>2</td>
</tr>
<tr>
<td>Systemic Rx</td>
<td></td>
</tr>
<tr>
<td>None, ER-</td>
<td>0.8</td>
</tr>
<tr>
<td>Chemo ER-</td>
<td>2</td>
</tr>
<tr>
<td>None, ER+</td>
<td>3</td>
</tr>
<tr>
<td>Tam ER+</td>
<td>1</td>
</tr>
<tr>
<td>Tam +/- chemo ER+</td>
<td>2</td>
</tr>
</tbody>
</table>

Interval to RNF and Survival
NSABP Adjuvant Therapy Trials
BCS+RT

<table>
<thead>
<tr>
<th>Interval</th>
<th>Node Neg.</th>
<th>Node Pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 yrs.</td>
<td>73%</td>
<td>81%</td>
</tr>
</tbody>
</table>

5 Yr. OS after RNF

<table>
<thead>
<tr>
<th>Interval</th>
<th>3 Yr. OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>35% 24%</td>
</tr>
<tr>
<td>ER+</td>
<td>48% 24%</td>
</tr>
<tr>
<td>ER-</td>
<td>21% 21%</td>
</tr>
</tbody>
</table>


RNF and Survival NSABP
Node Positive Adjuvant Therapy Trials
BCS+RT

<table>
<thead>
<tr>
<th>Interval</th>
<th>Shorter</th>
<th>Longer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yrs.</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>3 yrs.</td>
<td>24</td>
<td>57</td>
</tr>
<tr>
<td>4 yrs.</td>
<td>27</td>
<td>66</td>
</tr>
</tbody>
</table>


DDFS Related to Site of Regional Node Failure NSABP Node Positive Adjuvant Therapy Trials BCS+RT

<table>
<thead>
<tr>
<th>Site RNF</th>
<th>5 Yr. DDFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla</td>
<td>32</td>
</tr>
<tr>
<td>SCV</td>
<td>12</td>
</tr>
</tbody>
</table>

Wapnir I et al JCO 24:2028, 2006

Isolated Axillary Failure
BCS+RT

Is mastectomy indicated?
Axillary Recurrence after Sentinel Node Biopsy MSK

<table>
<thead>
<tr>
<th></th>
<th>No. pts</th>
<th>Axillary Recurrence%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNB -, AD</td>
<td>326</td>
<td>0</td>
</tr>
<tr>
<td>SNB -, no AD</td>
<td>2340</td>
<td>0.12</td>
</tr>
<tr>
<td>SNB +, AD</td>
<td>1132</td>
<td>0.35</td>
</tr>
<tr>
<td>SNB +, no AD</td>
<td>210</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Axillary Recurrence Negative SNB and No Axillary Dissection

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>Axillary Recurrence</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK</td>
<td>2340</td>
<td>0.12%</td>
<td>2.5 med</td>
</tr>
<tr>
<td>Moffitt</td>
<td>1530</td>
<td>0.26%</td>
<td>4.9 mean</td>
</tr>
</tbody>
</table>

Meta-analysis Axillary Recurrence Negative SN and No AD

<table>
<thead>
<tr>
<th></th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. studies</td>
<td></td>
</tr>
<tr>
<td>No. pts.</td>
<td>14,959</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>2.8 yrs.</td>
</tr>
<tr>
<td>Axillary recurrence</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Patterns of Regional Node Failure Post-Mastectomy in Patients Receiving Doxorubicin Based Systemic Therapy

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>Regional Failure %</th>
<th>Interval Yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA</td>
<td>1031</td>
<td>Axilla 3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supraclav 8</td>
<td></td>
</tr>
<tr>
<td>NSABP</td>
<td>5758</td>
<td>1-3 N+ 2.4-3.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-9 N+ 5.4-8.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 10 6.7-10.9</td>
<td></td>
</tr>
</tbody>
</table>

Kiluk JV et al Ann Surg Oncol 2009


IBTR BCS+RT
NSABP Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th></th>
<th>Node Neg.</th>
<th>Node pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. pts.</td>
<td>3799</td>
<td>2669</td>
</tr>
<tr>
<td>No. IBTR</td>
<td>342</td>
<td>259</td>
</tr>
</tbody>
</table>

10 Yr CI IBTR %

<table>
<thead>
<tr>
<th></th>
<th>All pts.</th>
<th>Systemic Rx</th>
<th>None, ER-</th>
<th>Chemo ER-</th>
<th>None, ER+</th>
<th>Tam ER+</th>
<th>Tam +/- chemo ER+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. IBTR</td>
<td>6</td>
<td>6</td>
<td>15</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Interval IBTR ≤5 yrs.

IBTR

6 9

Outcome IBTR Related to Estrogen Receptor Status NSABP Node Negative Adjuvant Therapy Trials

Gene Expression Profiling Molecular Subtypes

Anderson SJ JCO 27:2466, 2009
Wapnir I JCO 24:2028, 2006

Anderson SJ et al JCO 27:2466-73, 2009
Local-regional Failure BCS+RT
NSABP Adjuvant Therapy Trials

<table>
<thead>
<tr>
<th></th>
<th>Node Neg.</th>
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</tr>
<tr>
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<td>73%</td>
<td>81%</td>
</tr>
</tbody>
</table>

IBTR          6         9
RNF           2         6

10 Yr CI %


Gene Expression Profiling

<table>
<thead>
<tr>
<th>Intrinsic subtype predictor</th>
<th>No. genes</th>
<th>Tissue type</th>
<th>Commercially Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A and B</td>
<td>496</td>
<td>Frozen</td>
<td>No</td>
</tr>
<tr>
<td>Basal-like, HER 2 positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotterdam 76 gene set</td>
<td>76</td>
<td>Frozen</td>
<td>No</td>
</tr>
<tr>
<td>Wound response indicator</td>
<td>512</td>
<td>Frozen</td>
<td>No</td>
</tr>
<tr>
<td>Invasive gene signature</td>
<td>186</td>
<td>Frozen</td>
<td>No</td>
</tr>
<tr>
<td>HOXB13:IL17BR ratio</td>
<td>2</td>
<td>Fixed</td>
<td>Yes</td>
</tr>
<tr>
<td>MammaPrint 70-gene profile</td>
<td>70</td>
<td>Frozen</td>
<td>Yes</td>
</tr>
<tr>
<td>Wound response indicator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>21</td>
<td>Fixed</td>
<td>Yes</td>
</tr>
<tr>
<td>Mammostrat*</td>
<td>5</td>
<td>Fixed</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Antibodies

10 Yr. LRF NSABP B14 and B20 Related to Recurrence Score

BSC+RT

<table>
<thead>
<tr>
<th>Score</th>
<th>10 Yr. LRF %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 50</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>12.5 (72)</td>
</tr>
<tr>
<td>18-30</td>
<td>27.7 (23)</td>
</tr>
<tr>
<td>≥ 31</td>
<td>26.5 (45)</td>
</tr>
</tbody>
</table>

( ) No. pts  Node negative with Tamoxifen

Mamounas EP et al JCO 28: 2010 epub

NSABP B14 and B20
10 Yr. LRF Related to Recurrence Score

Mastectomy

<table>
<thead>
<tr>
<th>Score</th>
<th>10 Yr. LRF %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 50</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>1.5 (73)</td>
</tr>
<tr>
<td>18-30</td>
<td>7.6 (31)</td>
</tr>
<tr>
<td>≥ 31</td>
<td>23.8 (49)</td>
</tr>
</tbody>
</table>

( ) No. pts  Node negative with Tamoxifen

Mamounas EP et al JCO 28: 2010 epub
Gene Expression Profiling
Netherlands Cancer Institute

70 gene prognosis profile (proliferation, invasion, metastasis, stromal integrity, angiogenesis)
Hypoxia profile (36 hypoxia response signature and 125 non-hypoxia)
Wound response signature (65 activated wound response, 96 quiescent wound response)

161 women age <53 years, CS+RT invasive cancer
Median follow-up = 7.7 yrs
10 yr. IBTR = 15%


IBTR Related to Gene Expression Profiling

<table>
<thead>
<tr>
<th>10 Yr. IBTR%</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 gene</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Wound</td>
<td>5</td>
<td>29</td>
</tr>
</tbody>
</table>

Nuyten DSA et al Breast Cancer Res Treat 8:R62 2006

Risk Factors for IBTR CS+RT

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hazard ratio for local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 yrs.</td>
<td>2.542</td>
</tr>
<tr>
<td>Tumor size T1/T2</td>
<td>1.683</td>
</tr>
<tr>
<td>Boost no/yes</td>
<td>1.343</td>
</tr>
<tr>
<td>Wound signature</td>
<td></td>
</tr>
<tr>
<td>High vs. low risk</td>
<td>16</td>
</tr>
</tbody>
</table>

Nuyten DSA et al Breast Cancer Res Treat 8:R62 2006

Gene Expression Profiling IBTR

<table>
<thead>
<tr>
<th></th>
<th>NKI-1</th>
<th>NKI-2*</th>
<th>Oncotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment dates</td>
<td>1984-95</td>
<td>1984-2000</td>
<td>B14+B20</td>
</tr>
<tr>
<td>No. pts.</td>
<td>161</td>
<td>Cases Controls</td>
<td>390</td>
</tr>
<tr>
<td>No. IBTR</td>
<td>17</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Age yrs.</td>
<td>&lt;53</td>
<td>≤ 51</td>
<td>36%&lt;50</td>
</tr>
<tr>
<td>Node +</td>
<td>44%</td>
<td>44%</td>
<td>45%</td>
</tr>
<tr>
<td>Systemic Rx</td>
<td>47%</td>
<td>36%</td>
<td>43%</td>
</tr>
<tr>
<td>ER+</td>
<td>75%</td>
<td>59%</td>
<td>71%</td>
</tr>
<tr>
<td>Positive margins</td>
<td>17%</td>
<td>27%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Kreike B et al Clin Cancer Res 15:4181, 2009*
### Gene Expression Profiling IBTR

<table>
<thead>
<tr>
<th>Follow-up yrs.</th>
<th>NKI-1</th>
<th>NKI-2</th>
<th>Oncotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7 med.</td>
<td></td>
<td>13.9 med.</td>
<td>10 act</td>
</tr>
<tr>
<td>No. pts.</td>
<td>161</td>
<td>Cases Controls</td>
<td>390</td>
</tr>
<tr>
<td>No. IBTR</td>
<td>17</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Gene assays</td>
<td>70 gene Hypoxia</td>
<td>70 gene, 76 gene, Wound resistance, hypoxia</td>
<td>81 gene, 21 gene</td>
</tr>
<tr>
<td>Significant Predictor IBTR</td>
<td>Wound response</td>
<td>45 gene proliferation*</td>
<td>21 gene</td>
</tr>
<tr>
<td>* Young age strongest predictor IBTR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Randomized Trials Comparing Mastectomy and CS+RT

<table>
<thead>
<tr>
<th>LRF%</th>
<th>Overall Survival%</th>
<th>FU Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>CS+RT</td>
<td>M</td>
</tr>
<tr>
<td>NSABP</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>B06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan*</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>DBCCG</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>NCI</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>IGR*</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>EORTC</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>EORTC+</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>DBCCG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* Stage 1

### Prospective Randomized Trials Post-mastectomy Systemic Treatment +/- Radiation

<table>
<thead>
<tr>
<th>No. pts.</th>
<th>Chemo</th>
<th>Rx yrs.</th>
<th>Median no. nodes</th>
<th>Node positive</th>
<th>Systemic Rx</th>
<th>Follow-up median</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia Premenopausal</td>
<td>DBCG 82b Premenopausal</td>
<td>DBCG 82c Postmenopausal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>1997</td>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1979-86</td>
<td>1982-89</td>
<td>1982-90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>318</td>
<td>1708</td>
<td>1375</td>
<td></td>
<td>100%</td>
<td>CMF</td>
<td>12.5 yrs.</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>7</td>
<td></td>
<td>92%</td>
<td>CMF</td>
<td>9.5 yrs.</td>
</tr>
</tbody>
</table>

### Retrospective Analyses of Systemic Therapy Randomized Trials

<table>
<thead>
<tr>
<th>No. pts.</th>
<th>Chemo</th>
<th>Rx yrs.</th>
<th>Median no. nodes</th>
<th>Median FU yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP</td>
<td>5758</td>
<td>CMF</td>
<td>1984-94</td>
<td>16</td>
</tr>
<tr>
<td>IBCSG</td>
<td>5352</td>
<td>None</td>
<td>1978-93</td>
<td>15</td>
</tr>
<tr>
<td>ECOG</td>
<td>2016</td>
<td>CMF, Tam</td>
<td>1978-87</td>
<td>15</td>
</tr>
<tr>
<td>MDA</td>
<td>1031</td>
<td>Doxorubicin</td>
<td>1975-94</td>
<td>17</td>
</tr>
<tr>
<td>CALGB</td>
<td>498</td>
<td>AC +/- Taxol</td>
<td>1994-97</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Post-mastectomy Local-regional Recurrence Rates in Patients Receiving Chemotherapy and No Radiation

<table>
<thead>
<tr>
<th>Chemo</th>
<th>Local-regional recurrence %</th>
<th>Interval Yrs.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-3</td>
<td>≥ 4</td>
<td>≥ 10</td>
</tr>
<tr>
<td>DBCCG 82b CMF</td>
<td>30</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>British Columbia CMF</td>
<td>21</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>IBCSG CMF</td>
<td>20</td>
<td>30*</td>
<td>25</td>
</tr>
<tr>
<td>ECOG CMF</td>
<td>13</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>MDA FAC</td>
<td>10</td>
<td>21*</td>
<td>22</td>
</tr>
<tr>
<td>NSABP 90% doxorubicin</td>
<td>13</td>
<td>24*</td>
<td>32</td>
</tr>
<tr>
<td>CALGB AC</td>
<td>9</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>AC+T</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

* Includes more than one site

### Sites of Local-regional Failure Mastectomy

<table>
<thead>
<tr>
<th></th>
<th>ECOG</th>
<th>IBCSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>2016</td>
<td>5352</td>
</tr>
<tr>
<td>Node pos.</td>
<td>100%</td>
<td>76%</td>
</tr>
<tr>
<td>Median FU</td>
<td>12.1 yrs.</td>
<td>12-15.5 yrs.</td>
</tr>
<tr>
<td>LRF%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CW</td>
<td>6.5 (3.3)</td>
<td>15</td>
</tr>
<tr>
<td>SCV</td>
<td>3.2 (2.4)</td>
<td>7</td>
</tr>
<tr>
<td>Axilla</td>
<td>1.5 (0.7)</td>
<td>3.6</td>
</tr>
<tr>
<td>IMN</td>
<td>0.05 (0.05)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Includes more than one site

### Distribution of Local-regional Failures Post Mastectomy

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>SCV</th>
<th>Axilla</th>
<th>IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP No RT</td>
<td>57%</td>
<td>23%</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>MDA* No RT</td>
<td>68%</td>
<td>40%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>39%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Includes more than one site

### EBCTCG Trials Post-mastectomy Radiation

<table>
<thead>
<tr>
<th>No. positive Nodes</th>
<th>Isolated LRF without RT %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Yr.</td>
</tr>
<tr>
<td>1-3</td>
<td>15.5(19.1)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>26.3(32.3)</td>
</tr>
</tbody>
</table>

* ( ) 2005-2006 data

EBCTCG Lancet 366:2087-2106, 2005
Post-mastectomy Local-regional Recurrence Rates DBCG 82 b+c
Node Positive ≥ 8 Nodes Examined

<table>
<thead>
<tr>
<th>No. nodes examined</th>
<th>&lt;8</th>
<th>≥ 8</th>
<th>Fu Yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish 82 b+c</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>&lt;5</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td>10 act</td>
</tr>
<tr>
<td>&lt;5</td>
<td>7</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>NSABP</td>
<td></td>
<td></td>
<td>10 act</td>
</tr>
<tr>
<td>&lt;5</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td></td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Total no. pts. = 1152

Overgaard M et al Radiother Oncol 2007

Post-Mastectomy Axillary Recurrence Related to the Number of Nodes Examined

Axillary Failure%

<table>
<thead>
<tr>
<th>No. nodes examined</th>
<th>&lt;8</th>
<th>≥ 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish 82 b+c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>≥8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up 18 years. Axillary recurrences 45% of local-regional recurrences.


Patterns of Failure Breast Cancer CALGB 9344 Adjuvant AC vs. AC→T Axillary Node Positive

<table>
<thead>
<tr>
<th></th>
<th>BCS+RT</th>
<th>Mast.</th>
<th>Mast.+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-3</td>
<td>≥4</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>13%</td>
<td>14%</td>
<td>26%</td>
</tr>
<tr>
<td>DM + LRF</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Local → DM</td>
<td>5%</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Local</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Median follow-up 5.6 yrs.

Sartor C et al JCO 23:30-40, 2005
Effect of Taxanes on Local-regional Recurrence CALGB 9344 Node Positive

<table>
<thead>
<tr>
<th>No. pts.</th>
<th>% 5 YR. Isolated (Total) Local-regional Rec.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AC</td>
</tr>
<tr>
<td>Mast. + RT</td>
<td>185</td>
</tr>
<tr>
<td>Mast.</td>
<td>565</td>
</tr>
</tbody>
</table>

EBCTCG 1-3 Positive Nodes Post Mastectomy Radiation 2005-6

<table>
<thead>
<tr>
<th>Local recurrence%</th>
<th>5 yr</th>
<th>10 yr</th>
<th>15 yr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>No RT</td>
<td>RT</td>
<td>No RT</td>
</tr>
<tr>
<td>No Chemo</td>
<td>21</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Chemo</td>
<td>14</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Breast Cancer Mortality %

<table>
<thead>
<tr>
<th>No chemo</th>
<th>25</th>
<th>21</th>
<th>40</th>
<th>34</th>
<th>49</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>20</td>
<td>19</td>
<td>34</td>
<td>32</td>
<td>44</td>
<td>40</td>
</tr>
</tbody>
</table>

Effect of Taxanes on Local-regional Recurrence CALGB 9344 Node Positive

<table>
<thead>
<tr>
<th>No.</th>
<th>5 Yr. Isolated (Total) LRF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>AC</td>
</tr>
<tr>
<td>BCS+RT</td>
<td>269</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>565</td>
</tr>
<tr>
<td>Mastectomy + RT</td>
<td>185</td>
</tr>
</tbody>
</table>

Breast Cancer Mortality %

<table>
<thead>
<tr>
<th>No chemo</th>
<th>25</th>
<th>21</th>
<th>40</th>
<th>34</th>
<th>49</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>20</td>
<td>19</td>
<td>34</td>
<td>32</td>
<td>44</td>
<td>40</td>
</tr>
</tbody>
</table>

Darby S San Antonio 2009

Sartor CI et al JCO 23:30-40, 2005
### Post-mastectomy Local-regional Recurrence Related to Molecular Subtype

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>No. Pts.</th>
<th>Definition</th>
<th>% PM RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>717</td>
<td>ER or PR+ Her2-, Ki-67&lt;14%</td>
<td>21</td>
</tr>
<tr>
<td>Luminal B</td>
<td>418</td>
<td>ER or PR+ Her2-, Ki-67&lt;14%</td>
<td>29</td>
</tr>
<tr>
<td>Luminal Her2+</td>
<td>124</td>
<td>ER or PR+, Her2+</td>
<td>31</td>
</tr>
<tr>
<td>Her2+</td>
<td>147</td>
<td>ER-, PR-, Her2+</td>
<td>41</td>
</tr>
<tr>
<td>Basal-like</td>
<td>161</td>
<td>ER-, PR-, Her2- EGFR+ or CK5/6+</td>
<td>42</td>
</tr>
<tr>
<td>TPN-non basal</td>
<td>147</td>
<td>ER-, PR-, Her2- EGFR-, CK5/6-</td>
<td>24</td>
</tr>
</tbody>
</table>

Voduc KD et al JCO 28:2010 epub

### Post-mastectomy Local-regional Recurrence Related to Molecular Subtype Vancouver, BC

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>No. pts.</th>
<th>Mastectomy</th>
<th>Mastectomy+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>717</td>
<td>21</td>
<td>92</td>
</tr>
<tr>
<td>Luminal B</td>
<td>418</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>Luminal HER2+</td>
<td>124</td>
<td>31</td>
<td>80</td>
</tr>
<tr>
<td>HER2+</td>
<td>147</td>
<td>41</td>
<td>83</td>
</tr>
<tr>
<td>Basal-like</td>
<td>161</td>
<td>42</td>
<td>81</td>
</tr>
<tr>
<td>TPN-non basal</td>
<td>147</td>
<td>24</td>
<td>87</td>
</tr>
</tbody>
</table>

Median follow-up 12 yrs.

Voduc KD et al JCO 28:2010 epub

### Local-regional Recurrence Related to Molecular Subtype Post-mastectomy +/- RT

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>No. pts.</th>
<th>%PM RT</th>
<th>10 Yr. LRFS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>717</td>
<td>21</td>
<td>92</td>
</tr>
<tr>
<td>Luminal B</td>
<td>418</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>Luminal HER2+</td>
<td>124</td>
<td>31</td>
<td>80</td>
</tr>
<tr>
<td>HER2+</td>
<td>147</td>
<td>41</td>
<td>83</td>
</tr>
<tr>
<td>Basal-like</td>
<td>161</td>
<td>42</td>
<td>81</td>
</tr>
<tr>
<td>TN Non-basal</td>
<td>147</td>
<td>24</td>
<td>87</td>
</tr>
</tbody>
</table>

No pts. received trastuzumab

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### Local-regional Failure Triple Negative Breast Cancer MDA

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>No. Pts.</th>
<th>5 Yr. LRF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS+RT</td>
<td>252</td>
<td>10</td>
</tr>
<tr>
<td>Mastectomy Node neg</td>
<td>93</td>
<td>11</td>
</tr>
<tr>
<td>Mast.+RT 1-3</td>
<td>143</td>
<td>22</td>
</tr>
<tr>
<td>Mast.+RT ≥4</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

All pts received chemotherapy
Doxorubicin based 96%, taxane 78% or both 75%

Settle SH et al IJROBP 75:S9-10, 2009
NSABP B14 and B20
10 Yr. LRF Related to Recurrence Score

Mastectomy + Tam

<table>
<thead>
<tr>
<th>Score</th>
<th>Age Yrs.</th>
<th>&lt; 50</th>
<th>&gt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18</td>
<td>1.5 (73)</td>
<td>2.6 (189)</td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>7.6 (31)</td>
<td>3.8 (82)</td>
<td></td>
</tr>
<tr>
<td>≥ 31</td>
<td>23.8 (49)</td>
<td>12.8 (81)</td>
<td></td>
</tr>
</tbody>
</table>

p value .001 .005

( ) No. pts Total no. pts. 505, node negative

Mamounas T et al JCO 2010 epub

Effect of Taxanes on Local-regional Recurrence MDA

<table>
<thead>
<tr>
<th>No. pts.</th>
<th>FAC x 8</th>
<th>Tx4 → FAC x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 yr. LRF</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>isolated</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>12 Yr. OS</td>
<td>BCS+RT (67 pts)</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Mastectomy (60 pts)</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>Mastectomy +RT (36 pts.)</td>
<td>70%</td>
</tr>
</tbody>
</table>

Oh JL et al IJROBP 75:S79, 2009

Local-regional Failure Triple Negative Breast Cancer MDA

<table>
<thead>
<tr>
<th>No. Pts.</th>
<th>5 Yr. LRF%</th>
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<tbody>
<tr>
<td>BCS+RT</td>
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<td>143</td>
</tr>
<tr>
<td>Mast.+RT</td>
<td>1-3</td>
</tr>
<tr>
<td>≥4</td>
<td></td>
</tr>
</tbody>
</table>

All pts received chemotherapy
Doxorubicin based 96%, taxane 78% or both 75%

Settle SH et al IJROBP 75:S9-10, 2009

Salvage Local Therapy IBTR

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial BCS</td>
</tr>
<tr>
<td>BCS +/- RT</td>
</tr>
<tr>
<td>Mastectomy</td>
</tr>
<tr>
<td>Initial BCS+RT</td>
</tr>
<tr>
<td>BCS +/- RT</td>
</tr>
<tr>
<td>Mastectomy</td>
</tr>
</tbody>
</table>
## Effect of Chemotherapy

Post-mastectomy LRF 1-3+ Nodes

EBCTCG 2005-6

<table>
<thead>
<tr>
<th>No.</th>
<th>LRF%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No RT</td>
</tr>
<tr>
<td>Pts.</td>
<td></td>
</tr>
<tr>
<td>No chemo</td>
<td>670</td>
</tr>
<tr>
<td>Chemo</td>
<td>1026</td>
</tr>
</tbody>
</table>

*Darby S San Antonio 12/2009*