ASTRO Spring Refresher Course 2014: Management of Breast Cancer

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Disclosures

• **My Wife is a Medical Oncologist**

• RTOG
  – Breast Working Group
  – Advanced Technology and Integration Committee

• NRG Oncology
  – Breast Steering Committee
  – Radiation Committee

• UpToDate

*I do not speak on behalf of the ABR. No content is privileged nor designed to be an oral boards answer*
Management Outline

• Early stage breast cancer
• Node positive breast cancer
• Locally advanced and inflammatory breast cancer
• Metastatic breast cancer – Oligometastasis
Early Stage Breast Cancer
Key Topics

• Screening and the Role of MRI
• Management of DCIS
• Management of early stage invasive disease
  – The benefit of tumor bed boost
  – Altered fractionation
  – Planning target goals in the 3D era
  – Partial Breast Radiotherapy
  – Select patient populations for lumpectomy alone
Screening
Screening Mammography

• **USPSTF Screening recommendations:**
  – For average risk patients: Screen patients between 50-74 q 2 yrs.
  – For women <50 yo, beginning regular screening should be based on a patient’s specific context

• **Meta-analyses estimate 20-35% relative reduction in breast cancer mortality in women age 50-69.**

• In women **40-49**, RR reduction is **15%**
  – 40-49: NNT=1904 to prevent one death
  – 50-59: NNT=1339 to prevent one death
  – 60-69: NNT=377 to prevent one death
## MRI Imaging

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCE</td>
<td>50%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>MMG</td>
<td>68%</td>
<td>75%</td>
<td>86%</td>
</tr>
<tr>
<td>U/S</td>
<td>83%</td>
<td>34%</td>
<td>73.5%</td>
</tr>
<tr>
<td>MRI</td>
<td>94.4%</td>
<td>26%</td>
<td>73.6%</td>
</tr>
</tbody>
</table>

*Berg et al, Radiology 2004*

### High risk women

<table>
<thead>
<tr>
<th></th>
<th>CBE</th>
<th>MMG</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>17.9%</td>
<td>33.3%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.1%</td>
<td>95%</td>
<td>89.8%</td>
</tr>
</tbody>
</table>

*Krieg et al, NEJM, 2004*
Randomized Trial: COMICE

- 2001-2007 MRI vs. no MRI

- Primary endpoint: Need for further
  - Surgery
  - Mastectomy
  - Avoid mastectomy

- 2nd
  - Change management and QOL

1625/5498 Randomized

Excluded for Eligibility

- 817 pts CBE+MAM+MRI
- 807 pts CBE+MAN

Turnbull et al, Lancet, 2010
COMICE Trial

- Re-excision rate equal
- MRI predicted
  - WLE 84%
  - mastectomy 62%
- Sens/Spec for Mastectomy = 50%/89.3%
- No diff in QOL

<table>
<thead>
<tr>
<th>Initial operation</th>
<th>MRI (n=816)</th>
<th>No MRI (n=807)</th>
<th>Total (n=1623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide local excision</td>
<td>750 (92%)</td>
<td>787 (98%)</td>
<td>1537 (95%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>58 (7%)</td>
<td>10 (1%)</td>
<td>68 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (&lt;1%)</td>
<td>0</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Did not undergo initial surgery</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
</tr>
<tr>
<td>Lost to follow-up or missing data</td>
<td>3 (&lt;1%)</td>
<td>8 (1%)</td>
<td>11 (&lt;1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Repeat operations within 6 months</th>
<th>MRI (n=816)</th>
<th>No MRI (n=807)</th>
<th>Total (n=1623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further wide local excision</td>
<td>85 (10%)</td>
<td>90 (11%)</td>
<td>175 (11%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>48 (6%)</td>
<td>61 (8%)</td>
<td>109 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Pathologically avoidable initial mastectomy or patient choice</td>
<td>19 (2%)</td>
<td>4 (&lt;1%)</td>
<td>23 (1%)</td>
</tr>
<tr>
<td>Did not undergo further surgery</td>
<td>659 (81%)</td>
<td>645 (80%)</td>
<td>1304 (80%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td>10 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Table 3: Initial and repeat operations*
MRI Conclusion

• Sensitive *NOT* specific

• Randomized data and large single institution data fail to demonstrate screening benefit

• May have role in
  – High risk women
  – Screening for PBI (Dorn et al)
DCIS
## Classic DCIS trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>#</th>
<th>FU</th>
<th>BC</th>
<th>BC+RT</th>
<th>~50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP</td>
<td>516</td>
<td>8-yr</td>
<td>29%</td>
<td>13%</td>
<td>~50%</td>
</tr>
<tr>
<td>EORTC</td>
<td>1010</td>
<td>51 mo</td>
<td>16%</td>
<td>10%</td>
<td>~50%</td>
</tr>
<tr>
<td>UK/ANZ</td>
<td>1030</td>
<td>53 mo</td>
<td>14%</td>
<td>6%</td>
<td>~50%</td>
</tr>
</tbody>
</table>

*About a **50%** relative benefit across the randomized trials*

EBCTCG DCIS Meta-analysis

Use of tamoxifen (in both treatment arms)

Tamoxifen not given

3189 women

5-yr gain 10.8% (SE 1.3)
10-yr gain 15.6% (SE 1.7)
logrank 2P < 0.00001

Tamoxifen given

540 women

5-yr gain 8.3% (SE 2.7)
10-yr gain 9.0% (SE 4.6)
logrank 2P = 0.002

Any ipsilateral breast event

% 60
50
40
30
20
10
0

Years since randomization

~50%

BCS 28.8%

BCS + RT 13.2%

~50%

BCS 18.3%

BCS + RT 9.3%
## Margin status and LRR

<table>
<thead>
<tr>
<th>Series</th>
<th>FU</th>
<th>#</th>
<th>Margin Width</th>
<th>LRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B17</td>
<td>8y</td>
<td>267</td>
<td>&gt;1mm</td>
<td>13%</td>
</tr>
<tr>
<td>Intl Collab</td>
<td>10y</td>
<td>98</td>
<td>&gt;1 cell</td>
<td>10%</td>
</tr>
<tr>
<td>JCRT</td>
<td>5y</td>
<td>11</td>
<td>&lt;1mm</td>
<td>9% vs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>&gt;1mm</td>
<td>2%</td>
</tr>
<tr>
<td>Fox Chase</td>
<td>64mo</td>
<td>12</td>
<td>&lt;2mm</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68</td>
<td>&gt;2mm</td>
<td>1%</td>
</tr>
<tr>
<td>Beaumont</td>
<td>7mo</td>
<td>15</td>
<td>&lt;2mm</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>82</td>
<td>&gt;2mm</td>
<td>6%</td>
</tr>
</tbody>
</table>

### Predicted probabilities of IBTR stratified by margin threshold and treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Positive margin (95% CI)</th>
<th>0 mm (95% CI)</th>
<th>2 mm (95% CI)</th>
<th>5 mm (95% CI)</th>
<th>10 mm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS plus RT</td>
<td>20% (16 to 24), N = 698</td>
<td>10% (8 to 13), N = 2057</td>
<td>9% (6 to 11), N = 742</td>
<td>11% (1 to 20), N = 23</td>
<td>4% (3 to 6), N = 86</td>
</tr>
<tr>
<td>BCS alone</td>
<td>35% (29 to 41), N = 423</td>
<td>20% (16 to 23), N = 1262</td>
<td>17% (12 to 22), N = 163</td>
<td>20% (3 to 36), N = 10</td>
<td>9% (5 to 12), N = 421</td>
</tr>
</tbody>
</table>

*Negative surgical margins should be obtained for DCIS patients after BCS regardless of radiotherapy*
Can we select a population that can avoid radiotherapy?
What is “Good Risk” DCIS

• No symptoms: either mammographic finding or incidental finding in otherwise benign bx

• **ONLY** low or intermediate grade

• Size (mammogram) ≤ 2.5 cm

• Margin width ≥ 3 mm
## Schema

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>1. &lt; 50</td>
<td></td>
</tr>
<tr>
<td>2. ≥ 50</td>
<td></td>
</tr>
<tr>
<td><strong>Final Path Margins</strong></td>
<td></td>
</tr>
<tr>
<td>1. Negative (re-excision)</td>
<td></td>
</tr>
<tr>
<td>2. 3-9 mm</td>
<td></td>
</tr>
<tr>
<td>3. ≥ 10 mm</td>
<td></td>
</tr>
<tr>
<td><strong>Mammographic/Pathologic Size of Primary</strong></td>
<td></td>
</tr>
<tr>
<td>1. ≤ 1 cm</td>
<td></td>
</tr>
<tr>
<td>2. &gt; 1 cm to ≤ 2.5 cm</td>
<td></td>
</tr>
<tr>
<td><strong>Nuclei Grade</strong></td>
<td></td>
</tr>
<tr>
<td>1. Low</td>
<td></td>
</tr>
<tr>
<td>2. Intermediate</td>
<td></td>
</tr>
<tr>
<td><strong>Tamoxifen Use</strong></td>
<td></td>
</tr>
<tr>
<td>1. No</td>
<td></td>
</tr>
<tr>
<td>2. Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Arm 1**
Observation ± tamoxifen 20 mg per day for 5 years

**Arm 2**
Radiation therapy to the whole breast, ± tamoxifen 20 mg per day for 5 years
Local/Contra-Lateral Failure

- Ipsilateral failure - Observation
- Ipsilateral failure - RT
- Contra-lateral breast failure - Observation
- Contra-lateral Breast failure - RT

Years after Randomization:
- 5-Year: 3.4% 2.2% 4.8%
- 7-Year: 3.9% 3.5% 6.4%

Additional notes:
- 2x increase 2y
- 5-Year: 3.5% 6.4%
- 7-Year: 2.2% 4.8%
- 0.4% 0.9%

Total 5.5%
OncotypeDX and risk of recurrence in DCIS

~300 Patients!
Continuous DCIS Score of 10-Year risk (ECOG E5194)

- Low (<39)
- Intermediate (39–54)
- High (≥55).

Management of DCIS

• Addition of radiotherapy improves local control with or without tamoxifen historically by 50%

• Margin status increases risk of IBR +/- XRT

• Modern randomized data: Low risk clinical population benefit of XRT <6% at 7 Years

• Recent data suggest multigene expression assays may further delineate high vs. low risk DCIS – **support NRG Oncology!!!!**

• More data to inform our patients and our choices
Management of early stage invasive disease
Defining Breast Cancer Subtypes to drive treatment choices
Possible Outcomes of Adjuvant Chemotherapy in Early Stage Breast Cancer

All patients with the same diagnosis

- No Benefit No Toxicity
- + Benefit + Toxicity
- + Benefit No Toxicity

Walgren et al. JCO 2005;23:7342-7349
Intrinsic Breast Cancer Subtypes described by Perou et al.

**Luminal A**
- Express ↑ amounts of luminal cyto-keratins
- Express ↑ levels of EGFR, c-kit, and growth factors like hepatocyte growth factor and IGF

**Luminal B**
- Genetic markers of luminal epithelial cells of normal tissue

**HER2+**

**Basal-like**

**HER2-negative**
- ER-negative

**HER2-positive**
- ER-positive or ER-negative

**Pathological Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal-like (%)</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER2-like (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive (IHC)</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>ER-positive (IHC)</td>
<td>12</td>
<td>96</td>
<td>97</td>
<td>46</td>
</tr>
<tr>
<td>Grade III</td>
<td>84</td>
<td>19</td>
<td>53</td>
<td>74</td>
</tr>
<tr>
<td>Tumor size &gt;2 cm</td>
<td>75</td>
<td>53</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>Node-positive</td>
<td>40</td>
<td>52</td>
<td>65</td>
<td>66</td>
</tr>
</tbody>
</table>

Impact on Metastases and OS

Impact on IBTR post WBRT

- Luminal A
- Luminal B/Her2
- TN-nonbasal
- Basal-like/ Her2 Enriched
Breast Conservation
## Contraindications to BCT

### Contraindications
- Diffuse-appearing microcalcifications
- \( \sim \)T4 disease
- Repeated attempts at negative margins
- Current Pregnancy

### Possible Contraindications
- Multicentric disease
  - **Alliance Z11102**
    - 2-3 Foci \( \geq 3 \text{cm} \) separation
    - \( \leq 2 \) quadrants
- Previous RT
  - **RTOG 1014**
    - \( \geq 12 \) months from first tx
    - \( \leq 3 \text{cm} \)
    - 45Gy PBI (BID 1.5Gy)
    - Re-irradiation of chest wall select series
- Large tumor/breast ratio leading to likely poor cosmetic outcome
- Connective tissue disease (scleroderma)
## MRM vs. BCT (with RT)

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>PTS</th>
<th>F/U</th>
<th>Time pt (y)</th>
<th>Distant Failure</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>French</td>
<td>179</td>
<td>15</td>
<td>__</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>MILAN I</td>
<td>701</td>
<td>20</td>
<td>20</td>
<td>24%</td>
<td>41%</td>
</tr>
<tr>
<td>NSABP-06</td>
<td>1444</td>
<td>21</td>
<td>20</td>
<td>51%</td>
<td>47%</td>
</tr>
<tr>
<td>US-NCI</td>
<td>279</td>
<td>18</td>
<td>20</td>
<td>33%</td>
<td>58%</td>
</tr>
<tr>
<td>EORTC 10801</td>
<td>903</td>
<td>13</td>
<td>10</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>Denmark 82TM</td>
<td>859</td>
<td>3</td>
<td>6</td>
<td>34%</td>
<td>79%</td>
</tr>
</tbody>
</table>

6 RCT have shown no OS advantage after mastectomy or BCT
# Whole Breast Radiotherapy Reduces Local failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Pts</th>
<th>Time point (y)</th>
<th>Local failure</th>
<th>Death, All Causes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B06</td>
<td>1137</td>
<td>20</td>
<td>CS</td>
<td>CS+RT</td>
</tr>
<tr>
<td>Uppsala-Orbero</td>
<td>381</td>
<td>10</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Ontario</td>
<td>799</td>
<td>Crude, 91 mo</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>Milan III</td>
<td>567</td>
<td>10</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Scotland</td>
<td>585</td>
<td>Crude, 68 mo</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>
EBCTCG: Local Failure and Mortality

Women with pN0 disease (n=7287)

- 10-year gain 15.4% (SE 1.1)
  - RR 0.49 (95% CI 0.45-0.55)
  - Log-rank 2p<0.00001

- 15-year gain 3.3% (SE 1.3)
  - RR 0.83 (95% CI 0.73-0.95)
  - Log-rank 2p=0.005

Any first recurrence (%)

- 5 years: 5.6%
- 10 years: 10.6%
- 15 years: 15.6%

- BCS
- BCS+RT

Breast cancer death (%)

- 5 years: 12.7%
- 10 years: 17.2%
- 15 years: 20.5%

- BCS
- BCS+RT
The benefit of tumor bed boost
EORTC 22881-10882: RND Boost Trial

Purpose:
- Most large randomized trials providing long term IBTR did not use tumor bed boost
  - Example NSABP trials
- Rationale for Boost: Most recurrences near original lumpectomy cavity
- Single institution trials suggested a benefit of a tumor bed boost

Endpoint:
- OS and IBTR

 Endpoint data:
- 5318 Pts <70yo
  - T1-2,N0-1

Trial design:
- 2nd RND for +Margins
- 50Gy/25fx WBRT
- WBRT +16Gy Boost

Reference:
### EORTC Boost vs. No Boost Trial

#### Cumulative Incidence (%)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>No boost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Gy boost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HR = 0.59**

**99% CI, 0.46 to 0.76**

**P < .0001**

#### OS vs. LR (all)

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>LR (all)</th>
<th>&lt;40</th>
<th>41-50</th>
<th>51-60</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Boost</td>
<td>81.7%</td>
<td>10.2%</td>
<td>23.9%</td>
<td>12.5%</td>
<td>7.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Boost</td>
<td>81.7%</td>
<td>6.2%</td>
<td>13.5%</td>
<td>8.7%</td>
<td>4.9%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

**p < .0001**

**p = 0.014**

**Fibrosis**

<table>
<thead>
<tr>
<th></th>
<th>1.6%</th>
<th>4.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Boost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p < .0001**

**~40% Reduction IBTR**

*Bartelink, JCO, 2007*
EORTC Boost trial: subgroup analysis

**Goal:** Determine prognostic factors Central path review
- SM, LVI, grade, extend of DCIS, Mitotic Index
- + SM (14%), close (0-2mm) (27%, neg (> 2 mm)
- Median f/u 10 yrs

**Results:**
MVA for LR:
- Boost dose, high grade tumor, age < 50 y/o
- 10 yr Cumulative Incidence of IBTR:
  - 7.3% (low)
  - 8.4% (int)
  - 13.7% (high)

**Conclusions:**
-Patients at high risk for recurrence are those < 50 y/o and high grade tumor.

*Boost helps decrease the absolute risk most in these groups.*

---

The Boost

• Improved local control for all groups

• Most benefit in younger patients (<50yo) and high grade

• There is a cost, in terms of fibrosis (3%)

• Consider WBRT only in >50yo, ER+, no risk factors
Surgical Margins
Margin Status and BCT

• Most randomized trials treated whole breast radiotherapy without a boost (ex. NSABP)

• Controversy exists in modern era of boost as to surgical margin

• Consensus statement 2014
SSO & ASTRO Consensus Guidelines 2014

Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

International Journal of Radiation Oncology*Biology*Physics
Volume 88, Issue 3, 1 March 2014, Pages 553–564
Key Findings

Positive margins

• A positive margin, defined as ink on invasive cancer or DCIS -> 2-fold increase in IBTR.

• This increased risk in *IBTR is not nullified by*:
  – Delivery of a boost dose of radiation
  – Delivery of systemic therapy (endocrine therapy, chemotherapy, or biologic therapy), or
  – Favorable biology
Key Findings

Margin Width

• Negative margins (no ink on tumor) minimize the risk of IBTR.

• Wider margin widths do not significantly lower this risk.

• Systemic chemotherapy *does NOT* lower risk

• The routine practice to obtain negative margin widths wider than no ink on tumor is not indicated.
Hypofractionation
Hypofractionation Rationale

• Shorten treatment course
  • Improve experience for patients
  • Improve access to breast conservation

• Biology
  • Increase dose per fraction without compromising BED
  • Predict > local control

• Decrease cost to deliver care (USA)

• Concerns
  • Toxicity
  • Long term local control since BED is a flawed model
UK START B (2001)

2215 pts
pT1-3/N0-1

88% Lumpectomy
85% N0
RLNI: 7.5%

50Gy/25
43% 10Gy Boost Each arm
40/15

2D Planning
+/- 5% central axis
<table>
<thead>
<tr>
<th>Tx Arm</th>
<th>5 Yr LRR</th>
<th>5Yr Distant Relapse</th>
<th>5 Yr Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy/25 fx</td>
<td>3.3%</td>
<td>10.2%</td>
<td>89%</td>
</tr>
<tr>
<td>40 Gy/15 fix</td>
<td>2.2%</td>
<td>7.6%</td>
<td>92%</td>
</tr>
</tbody>
</table>

P-value: 0.21 0.01 0.03

START Trialists’ Group, Lancet 371: 2008
### Cosmesis

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>50 Gy</th>
<th>41.6 Gy</th>
<th>461</th>
<th>462</th>
<th>457</th>
<th>458</th>
<th>241</th>
<th>271</th>
</tr>
</thead>
</table>

**Kaplan-Meier 5 year event rate**

<table>
<thead>
<tr>
<th></th>
<th>50 Gy</th>
<th>40 Gy</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast shrinkage since radiotherapy*</td>
<td>24.4 (20.3–28.4)</td>
<td>23.2 (19.3–27.2)</td>
<td>0.89 (0.70–1.12)</td>
</tr>
<tr>
<td>Breast hardness since radiotherapy*</td>
<td>42.3 (37.6–46.9)</td>
<td>38.2 (33.6–42.7)</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Change in skin appearance since radiotherapy</td>
<td>27.8 (23.8–31.8)</td>
<td>22.9 (19.3–26.6)</td>
<td>0.77 (0.61–0.98)</td>
</tr>
<tr>
<td>Swelling in area of affected breast</td>
<td>12.4 (9.5–15.2)</td>
<td>10.5 (7.9–13.2)</td>
<td>0.93 (0.65–1.33)</td>
</tr>
<tr>
<td>Change in breast appearance since radiotherapy*</td>
<td>39.4 (34.8–44.0)</td>
<td>34.4 (30.0–38.9)</td>
<td>0.86 (0.70–1.05)</td>
</tr>
<tr>
<td>Change in breast appearance (photographic)*</td>
<td>42.2 (37.3–47.4)</td>
<td>36.5 (31.8–41.6)</td>
<td>0.83 (0.66–1.04)</td>
</tr>
</tbody>
</table>

*Breast conserving patients only

**Hazard ratio (95% CI)**

Favours 40 Gy  | Favours 50 Gy
The “Canadian” Trial: Ontario

1234 Pts ~55yo
T1-2,N0

<25cm separation
11/41% chemo/tam

50Gy/25fx
WBRT

42.6/16fx
No boost

### The Canadian Trial

**Figure 2.** Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 50 \text{ yr} )</td>
<td>1.02 (0.62–1.70)</td>
<td>0.67</td>
</tr>
<tr>
<td>(&lt; 50 \text{ yr} )</td>
<td>0.77 (0.35–1.70)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 2 \text{ cm} )</td>
<td>0.99 (0.49–1.98)</td>
<td>0.90</td>
</tr>
<tr>
<td>(&lt; 2 \text{ cm} )</td>
<td>0.95 (0.55–1.64)</td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen-receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.71 (0.41–1.23)</td>
<td>0.36</td>
</tr>
<tr>
<td>Negative</td>
<td>1.32 (0.62–2.82)</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>1.30 (0.22–7.81)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.70 (0.31–1.58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.57 (0.29–1.12)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.08 (1.22–7.76)</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.86 (0.48–1.55)</td>
<td>0.65</td>
</tr>
<tr>
<td>Yes</td>
<td>1.06 (0.58–1.97)</td>
<td></td>
</tr>
</tbody>
</table>

Hypofractionated Regimen Better

Standard Regimen Better

---

The “Canadian” Trial: 2010

<table>
<thead>
<tr>
<th></th>
<th>LRF (%)</th>
<th>OS (%)</th>
<th>Cosmesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.56Gy</td>
<td>6.2</td>
<td>84.6</td>
<td>69.8</td>
</tr>
<tr>
<td>50Gy/2</td>
<td>6.7</td>
<td>84.4</td>
<td>71.2</td>
</tr>
</tbody>
</table>

Median f/u 12 yrs

Cosmetic outcome worsened over time, but no difference in the two groups

- **Significant: High grade: LRF=4.7% (Std) vs. 15.6% (Hypo)**
- Need for higher risk RND trial
  - High grade tumors, neoadjuvant chemo, boost, cardiac issues.
Why we do RND trials
A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation plus Concurrent Boost versus Standard Whole breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer
RTOG 1005- Goals

• Primary
  – Local control

• Secondary
  – Cardiac toxicity
  – Feasibility of IMRT/3 D conformal methods
    • Establish DVH
  – Cosmetic results
  – Treatment costs
  – Gene expression/biologic host factors
Stage I or II and
- Age < 50
- Positive nodes
- Lymphovascular invasion
- Focally positive margin
- One close margin and EIC
- More than 2 close (≤ 2 mm) margins
- ER/PR –
- G3
- Oncotype score > 25

Stage O and
- Grade 3
- Age < 50

ypStage O, I, II after neoadjuvant chemotherapy
“Don’t initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules.”

- Age 50 or older at diagnosis
- pT1-T2 N0
- No chemotherapy
- Dose homogeneity
  - along the central axis of ± 7%

- Remember:
  - Hypofractionation may be WORSE in grade 3 or ER-
  - No boost in Canadian trial, no subgroup analysis in START
IMRT/3DCRT vs 2D
RND Trial: IMRT/3DCRT vs 2D

358 Pts ~57yo
T1-2,N0

Endpoint: Acute tox

Inverse planning (1)
FIF (1)
Vs.
Wedge

2D:
50Gy/25fx WBRT+/-16Gy Boost

“IMRT”
50Gy/25fx WBRT+/-16Gy Boost

Pignol, Toronto, JCO, 2008
3DCRT/IMRT allows for improved acute toxicity

### Primary endpoint: acute skin toxicity

#### Results:
- $<V105, 107, 110$
- $<$ Max dose 105% vs 110%
- Moist desquamation: 31.2% vs 47.8%
- Correlated to pain and reduced QOL

---

**Table 2. $\chi^2$ Analysis Between the True Arms**

<table>
<thead>
<tr>
<th>End Point</th>
<th>BIMRT (%)</th>
<th>Standard (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin toxicity grade 3-4 (NCI CTC 2.0)</td>
<td>27.1</td>
<td>36.7</td>
<td>.06</td>
</tr>
<tr>
<td>Moist desquamation, all breast</td>
<td>31.2</td>
<td>47.8</td>
<td>.002</td>
</tr>
<tr>
<td>Moist desquamation, inframammary crease</td>
<td>26.5</td>
<td>43.5</td>
<td>.001</td>
</tr>
<tr>
<td>Pain grade 2-4 (NCI CTC 2.0)</td>
<td>23.5</td>
<td>25.5</td>
<td>.68</td>
</tr>
</tbody>
</table>

Abbreviations: BIMRT, two-field, breast intensity-modulated RT; NCI CTC 2.0, National Cancer Institute Common Toxicity Criteria version 2.0. *RT using wedge compensation.
RND Trial: IMRT vs 2D Cosmesis

Primary endpoint: change in photographic appearance

306Pts ~57yo
T1-3,N0-1

Inverse planning (1)
FIF (1)
Vs.
Wedge

2D:
50Gy/25fx WBRT+ 10Gy Boost

“IMRT” (≤4 seg)
50Gy/25fx WBRT+/- 10Gy Boost

Donovan et al 2007, Radio and Onc
RND Trial: IMRT vs 2D Cosmesis
Long term results (7y)

Results:
• Dosimetry SS improved IMRT arm (195% >20% vs >1% of patients)

• Change in breast:
  – Photographs:
    • 58% (2D) vs.
    • 40% (IMRT) based on 5 yr photographs
  – 105% predicted change in
    • 62% had no changes in breast appearance (<105%) vs.
    • 42.4% (>105%) SS
  – IMRT decreased 7y rates of
    • Fewer patients had palpable induration assessed in breast, pectoral fold, inframammary fold and boost

• No differences in breast discomfort or quality of life.

Conclusions: IMRT can decrease dose inhomogeneity and long-term changes in the breast
Planning goals in a 3D/IMRT era
Breast Planning Target Volume for evaluation (PTV-eval)
- excludes bony thorax from anterior rib surface
- extends within 5 mm of skin
### Institutional/RTOG goals

<table>
<thead>
<tr>
<th>CTV</th>
<th>PTVeval Coverage</th>
<th>Max Dose PTVeval</th>
<th>Max Point dose</th>
<th>OAR Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>95/95, 90/90</td>
<td>&lt;30%/&gt;100%</td>
<td>&lt;115%</td>
<td></td>
</tr>
<tr>
<td>Contra Breast</td>
<td></td>
<td>&lt;5% 186cGy</td>
<td>310cGy</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td></td>
<td>&lt;15% &gt;20Gy</td>
<td>&lt;5% &gt;20Gy (L)</td>
<td>Mean 4Gy</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TIP:** In 2014 avoid talking about inches of lung.
RT Planning Summary

• Hypofraction in select patients per ASTRO guidelines appears equal to WBRT

• High risk populations -> RTOG 1005

• A good plan (3DCRT or IMRT) is superior in acute and late toxicity to 2D

• 2014: The 3D era is here and get on board
Accelerated Partial Breast Irradiation
Rationale

– Biology:
  • Most recurrences occur within 2cm of lumpectomy from prospective and RND trials (>2/3 1st failure)

– Decreased Treatment time and QOL?

– Potential reduction in treatment toxicity

– Multiple different techniques with short follow up
Established methods

- External beam (3.85gy BID x 5 days)
  - Most common in USA
- Interstitial Brachytherapy: LDR, HDR
  - Multi-catheter
- Intracavitary:
  - Intraoperative Electrons: ELIOT
  - Intraoperative Orthovoltage Photons: TARGIT-A
  - Mammosite
Retrospective and registry studies demonstrate excellent local control.

Excellent cosmesis is reported.

Meta-Analysis (2010) and Seer data (2014) show decreased control.

Large US randomized trials and IBTR of Canadian (RAPID) await.

APBI: Current state
Mammosite

• Single lumen catheter

• Typical dose (and on NSABP B31)
  • RT: 34 Gy in 3.4 Gy fractions, prescribed 1 cm from balloon
  • About 20% of RND trial
  • *Needed balloon-to-skin dist >5 mm, cavity size < 6 cm*

• **Results** at 3 years from registry:
  – IBTR = 2.15% (4 yr=2.65%)
  – 3 yr axillary recurrence = 0.36% (4 yr=0.6%)
  – DM=1.1%
  – OS=95.6%

• **Toxicity:**
  – infection: 9.5%,
  – Seroma: 27% (13% symptomatic)
  – 2% fat necrosis

• Cosmesis: Good or excellent at 4 yrs: 91%

**Conclusions: Data consistent with other APBI techniques**

Interstitial APBI

- Matched Pair: Intersitial PBI vs. WBI
- Methods:
  - 199 pts with early-stage breast CA (Stage I/II)
  - RT: LDR 50 Gy at 0.52 Gy/hr (60%) or HDR 32 Gy in 4 Gy or 34 Gy in 3.4 Gy

<table>
<thead>
<tr>
<th></th>
<th>IBTR%</th>
<th>Regional%</th>
<th>DM%</th>
<th>OS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT</td>
<td>9</td>
<td>0.5</td>
<td>9</td>
<td>82</td>
</tr>
<tr>
<td>APBI (int)</td>
<td>5</td>
<td>1.6</td>
<td>5</td>
<td>72</td>
</tr>
</tbody>
</table>

_Cosmesis: Good to excellent in 98.3% of pts_
Primary Endpoint: IBTR

Secondary: DM, Contralateral CA, OS

Awaiting initial results

- WBRT 50Gy/2 + Boost
- 38.5Gy 3D CDRT 3.85 BID(75%) Mammocyte and multilumen

>4300pts accrued
Tis-T2,N1-3 <3cm

Stratified
ER status
DCIS/invasive/n1
Menopausal
Chemotherapy

NSABP B39 / RTOG 0413
Initial cosmetic results from RAPID

• RAPID (Olivotto et al) WBRT vs. APBI
  – No IBTR results yet
  – Worse patient reported cosmesis in APBI from physician, nurse, and patient 36mo median FU

2135 women
>40yo
DCIS or Invasive
≤3cm
Node Neg

RAPID

WBRT
50gy/25 or
42.5/16
+/−Boost

3D APBI
42Gy/16 qD

Intraoperative APBI
Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase III trial
Methods:

- 70% median FU 2.5 years

- The primary outcome was ipsilateral local failure

- Device summary
  - Low energy x-rays (50 kV maximum) placed at the tip of the tumor bed
  - Dose to the surface of the tumor bed was 20Gy falling sharply to 5Gy at 1cm depth from resection margin

- WBRT delivered from 46-66Gy depending on institution and policies for “boost”
Targit A: 2013

A Local recurrence
- TARGIT 23 events
- EBRT 11 events

Log-rank p=0.042

A Breast cancer deaths
- TARGIT 20 events
- EBRT 16 events

Log-rank p=0.56

C Postpathology, local recurrence
- TARGIT 13 events
- EBRT 5 events

Log-rank p=0.069

At risk
- TARGIT: 572, 461, 360, 237, 175, 100
- EBRT: 569, 457, 355, 230, 164, 96
Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial (2013)
Key differences from TARGIT

• Done in Italy only
• IORT 21Gy with Electrons vs 50Gy+10Gy boost
• “Equivalence” defined as 7.5% of IBTR

• Results
  – 5y IBTR WBRT: 0.4%
  – 5y IBTR Intraop: 4.4%
  – OS same
Intra-op Conclusions

• Randomized data demonstrate safety and efficacy
• Allows post-surgery RT for high risk groups without toxicity
• Statistically Significant increase LRR vs WBRT
• Long term data still lacking
• Continue to follow patients....
APBI - ASTRO 2009 Consensus Statement:

**Suitable group:** APBI outside of a clinical trial is acceptable
- Age >= 60
- node negative pN0(i-/i+)
- invasive ductal (or favorable histology),
- tumor <=2 cm, T1, unicentric, clinically unifocal + total size <= 2cm (may be microscopic multifocality as long as unifocal by ultrasound + mammogram),
- assoc LCIS
- any grade, ER+
- Brca1/2 neg
- margins negative (>= 2mm)

**Cautionary group:** caution and concern should be used when considering APBI outside of a clinical trial
- Age 50-59,
- tumor 2.1-3.0 cm, T2 or T0
- close margins (<2 mm)
- limited or focal LVSI,
- ER-
- invasive lobular
- pure DCIS <= 3cm, EIC <= 3 cm
- microscopic multifocality allowed (if total size 2.1-3.0 cm)

**Unsuitable group:** APBI outside of a clinical trial is not generally warranted
- Age <50
- BRCA1/2 mutation
- tumor >3 cm, T3 or T4
- positive margins
- extensive LVSI
- multicentric tumor, multifocal tumor >3cm in total size or clinically multifocal
- DCIS > 3cm
- EIC > 3cm
- pN1-N3 or pNx (no nodal surgery performed), neoadjuvant therapy

Selecting APBI for Patients

• Multiple consensus statements from ASTRO, ASBS, and ESTRO can guide conversation
• Encourage enrollment in clinical trials for patients
• Outcomes from RTOG 0413/NSABP B39 and the RAPID trial await
• Have stringent quality assurance and follow-up procedures in place
What is next for APBI

• ? Is 3.85 BID (RAPID) best fractionation?

• Can we do an external beam method quicker and more convenient

• Value in Pre-Operative RT(Proposed NRG Oncology trial)
Select patient populations for lumpectomy alone
Avoiding RT in highly selected patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Nodes</th>
<th>Max size</th>
<th>Features</th>
<th>Margin</th>
<th>Tam?</th>
<th>Follow up (mo)</th>
<th>No of pts</th>
<th>LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan III</td>
<td>≥66</td>
<td>pN0/1</td>
<td>2.5</td>
<td>-</td>
<td>Neg</td>
<td>Option</td>
<td>109</td>
<td>23</td>
<td>4%</td>
</tr>
<tr>
<td>Women’s College</td>
<td>≥65</td>
<td>pN0</td>
<td>NA</td>
<td>Er+, No LVI</td>
<td>Neg</td>
<td>None</td>
<td>109</td>
<td>34</td>
<td>9%</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-21</td>
<td>Any</td>
<td>pN0</td>
<td>1</td>
<td>ER+</td>
<td>Neg</td>
<td>All</td>
<td>89</td>
<td>197</td>
<td>10%</td>
</tr>
<tr>
<td>Ontario-BC Trial</td>
<td>≥51</td>
<td>c/pN0</td>
<td>1</td>
<td>ER or PR+</td>
<td>Neg</td>
<td>All</td>
<td>67</td>
<td>139</td>
<td>3%</td>
</tr>
<tr>
<td>Uppsala-Orbrebro</td>
<td>≥56</td>
<td>pN0</td>
<td>2</td>
<td>No comedo</td>
<td>Neg</td>
<td>None</td>
<td>103</td>
<td>84</td>
<td>11%</td>
</tr>
<tr>
<td>CALBG 9343</td>
<td>≥70</td>
<td>p/cN0</td>
<td>2</td>
<td>ER+</td>
<td>Neg</td>
<td>All</td>
<td>60</td>
<td>319</td>
<td>4%</td>
</tr>
</tbody>
</table>

- 5 Yr End points shown
- Highly selected patients may have reduced risk of local recurrence, especially if tamoxifen is used
Can RT be spared in older Patients?

- **RND:** Tam vs Tam+RT
- **Surgery:**
  - Lumpectomy with negative SM
  - 33% axilla addressed
- **RT:** 45Gy/1.8 Gy+ 14Gy boost, Cobalt or 6MV
- **Tamoxifen:** 20mg daily x 5 yrs; begun during or after RT

Endpoints: IBTR, freedom from mastectomy, OS

Hughes, CALGB, Intergroup, NEJM, 2004

>636 Patients
>70yo
ER+
T1 tumors, cN0

33% had axilla addressed

negative margins

WBRT 45Gy/1.8 + Boost TAM

TAM Alone
12.6y median follow-up
10y outcome data

<table>
<thead>
<tr>
<th></th>
<th>Tam + RT</th>
<th>Tam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
<td>Axilla</td>
</tr>
<tr>
<td>IBTR</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>10 YR FF mastectomy</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>10 YR FFDM</td>
<td>95%</td>
<td>93%</td>
</tr>
<tr>
<td>10 YR BCSS</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>OS</td>
<td>66%</td>
<td>67%</td>
</tr>
</tbody>
</table>

- 67% of patients alive at last follow-up demonstrating significant co-morbidities

- *At 5 years the IBTR was 1% vs 4% - Long term follow up needed to assess true IBTR*

Lumpectomy alone...

- Randomized data: **Local Control** benefit from WBRT in *All patients*

- Examine carefully studies with short median follow-up as the failures will increase over time

- EBCTGC demonstrates that local control with invasive disease does impact survival

- Consider in low risk (T1N0, Luminal A) patients with comorbidities limiting life expectancy
The End of Early
Node Positive Breast Cancer
Key Topics

• Node + and Breast Conservation

• Post Mastectomy Radiotherapy (PMRT)

• Implications of Neoadjuvant Chemotherapy
  – Breast Conservation
  – PMRT
EBCTCG: N+ in BCT

Women with pN+ disease (n=1050)

Any first recurrence (%)

- BCS: 63.7%
- BCS+RT: 53.7%
- 10-year gain: 21.2% (SE 3.4)
- RR 0.53 (95% CI 0.44-0.64)
- Log-rank 2p<0.00001

Breast cancer death (%)

- BCS: 51.3%
- BCS+RT: 42.8%
- 15-year gain: 8.5% (SE 3.4)
- RR 0.79 (95% CI 0.65-0.95)
- Log-rank 2p=0.01

NSABP B06: BCS + RT

Breast ONLY radiotherapy – no RLNI

ACSOG Z0011: Sentinel Node Positive

891 Patients
T1/T2
H&E SNL+ 1-2/No ECE

Axillary dissection
+/-Chemo
+2F Tangents

+/-Chemo
2F Tangents

 Giuliano et al JAMA 2011;305:569-75.

Survival %

Alive

Log-rank P = .25

No. at risk
ALND 420 408 398 391 378 313 223 141 74
SLND alone 436 421 411 403 387 326 226 142 74
What volumes were covered?

- Z11 not designed for extensive QA

- Many dosimetric series demonstrate at least 80% level 1 coverage and 50% level 2 with high tangents

- Jagsi et al (San Antonio 2013)
  - 18.9% RNI
  - ~50% high tangents
  - Equal both arms

RT field QA records available for ~25% of patients
ASCO 2011: MA.20 – 2F vs RLNI

1832pts

N+ or

“High risk node-”

- 1-3+ Nodes  85%
- HR N0       10%
- >4 Nodes    5%

- 91% AC chemotherapy/71% Endocrine

Whelan et al ASCO 2011
ASCO 2011: MA.20 – 2F vs RLNI

- OS 92.3% vs 90.7% (HR .76, p = .07)

- LR DFS 96.8% vs 94.5% (HR .59, p .02)

- **Distant DFS 89.7% vs 84 % (HR .68, p = .003)**

- WBRT+RNI:
  - >2 pneumonitis (1.3% and 0.2% respectively, p=.01),
  - and lymphedema (7.3% and 4.1% respectively, p=.004)
87% vs. 92.4%
116 events vs. 77 events

Decrease in mets as 1st event and subsequent to LRR

HR=0.64 (95% CI 0.47 to 0.85)
P=0.002 (Stratified)
NSABP Pooled Analysis: Post IBTR

Median FU: 13.3y

<table>
<thead>
<tr>
<th>Protocol</th>
<th>B-15</th>
<th>B-16</th>
<th>B-18</th>
<th>B-22</th>
<th>B-25</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at risk</td>
<td>624</td>
<td>340</td>
<td>210</td>
<td>596</td>
<td>899</td>
<td>2,669</td>
</tr>
<tr>
<td>Median time on study, years</td>
<td>16.5</td>
<td>16.7</td>
<td>12.6</td>
<td>13.0</td>
<td>10.2</td>
<td>13.0</td>
</tr>
<tr>
<td>IBTR, %</td>
<td>12.2</td>
<td>6.5</td>
<td>11.0</td>
<td>10.7</td>
<td>8.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Patients with IBTR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Year cumulative IBTR incidence</td>
<td>6.1</td>
<td>1.2</td>
<td>4.8</td>
<td>4.2</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>5-Year cumulative IBTR incidence</td>
<td>7.7</td>
<td>2.4</td>
<td>6.7</td>
<td>6.4</td>
<td>5.9</td>
<td>6.1</td>
</tr>
<tr>
<td>10-Year cumulative IBTR incidence</td>
<td>10.0</td>
<td>4.8</td>
<td>9.1</td>
<td>10.1</td>
<td>8.3</td>
<td>8.7</td>
</tr>
<tr>
<td>oLRR, %</td>
<td>8.0</td>
<td>6.5</td>
<td>8.6</td>
<td>6.0</td>
<td>4.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Patients with oLRR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Year cumulative oLRR incidence</td>
<td>5.0</td>
<td>2.7</td>
<td>3.8</td>
<td>3.0</td>
<td>2.3</td>
<td>3.3</td>
</tr>
<tr>
<td>5-Year cumulative oLRR incidence</td>
<td>6.8</td>
<td>4.4</td>
<td>7.7</td>
<td>5.0</td>
<td>3.4</td>
<td>5.0</td>
</tr>
<tr>
<td>10-Year LRR incidence</td>
<td>7.6</td>
<td>5.4</td>
<td>8.7</td>
<td>6.1</td>
<td>4.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

- 5y post IBTR
  - 51.4% DFS.
  - Annual Death and Metastatic rate:
    - 10.2% and 14.9%

- 5y post oLRR worse
  - 18.8% (95% CI, 13.0% to 27.4%) DMFS.
  - Annual death
    - 28.8% and 45.7%

Rates of IBTR and other LRR After Lumpectomy

Early Node+ Summary

• Data demonstrates that SLNBx and WBRT provides excellent LRC in low risk patients

• Z11 was not a 3DCRT trial – volume data limited

• MA.20 awaiting final results – suggests RLNI benefits higher risk (from z11)

• Must weigh increased toxicity from RLNI to presumed benefit
Post Mastectomy Radiotherapy
The Poles and Spectrum

- Halsted vs. Fisher:
- Spectrum Hypothesis – “Hellman Groupies”

Systemic therapy eradicates micro-metastatic disease today

- Hormones
- Chemotherapy
- Biologics
Long term DFS

- MBC treated at the M.D. Anderson Cancer Center with doxorubicin-containing chemotherapy
  - 1.7% of 1,581 patients remained alive in complete remission after long-term follow-up (>10 years)
  - Retrospective data from Lung, Colon, Sarcoma and Breast suggest
    - Aggressive surgical/RT intervention in patients associated with long term DFS
Rationale

• A population of patients exists where persistent local microscopic disease will lead to distant metastasis.

• Provides a window to irradiate local disease to improve Overall Survival.

• Roth D, Bayat H; The role of residual tumor in the chest wall in the late dissemination of mammary cancer.
  
  – 90% of patients dying with metastatic disease have microscopic residual disease.
  
PMRT in 2014

Randomized studies from Overgaard and British Columbia demonstrate (T3N0, txN1-3, facia or skin)

Improved local control
  – Improved DFS
  – Improved FFDM
  – Improved OS ~10% c/w meta-analysis

• Controversies remain:
  – Can we avoid RT in some patients (N1 or pN0)
  – Can we reduce the volume to the chest wall
Early Breast Cancer Trialists’ Collaborative Group

- High Risk for LRR
- Node Positive Breast Cancer

15y Gain in LRR, BC Death, and OS:
Prevent 4 local failures -> OS
Age and impact on LRR (NSABP)

<table>
<thead>
<tr>
<th>Age</th>
<th>#</th>
<th>Isol LRR</th>
<th>LRR+/-DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>1130</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>40-49</td>
<td>2050</td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td>50-59</td>
<td>1600</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>60+</td>
<td>978</td>
<td>10%</td>
<td>14%</td>
</tr>
</tbody>
</table>

p=0.13  
p<0.0001

Mastectomy N 1-3+ Breast Cancer

- 1-3 positive nodes
- No XRT
- 273 patients
- Most systemic tx

So we randomise
Conclusion
Local therapy changes long term patterns of failure from local to distant
One to three LN (+) – Absolute survival benefit with RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>1-3 LN (+)</th>
<th>≥ 4 LN (+)</th>
<th>Absolute difference</th>
<th>1-3 LN (+)</th>
<th>≥ 4 LN (+)</th>
<th>Absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overgaard</td>
<td>1997</td>
<td>54</td>
<td>62</td>
<td>8</td>
<td>20</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Overgaard</td>
<td>1999</td>
<td>44</td>
<td>55</td>
<td>11</td>
<td>17</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Overgaard (&gt; 8 LN)</td>
<td>2007</td>
<td>48</td>
<td>57</td>
<td>9</td>
<td>12</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Ragaz</td>
<td>2005</td>
<td>50</td>
<td>57</td>
<td>7</td>
<td>17</td>
<td>31</td>
<td>14</td>
</tr>
</tbody>
</table>

## Danish 82b-c 18 Year Update

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>LRR (+/- DM)</th>
<th>Any DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMRT+RLNI</td>
<td>41%</td>
<td>14%</td>
<td>53%</td>
</tr>
<tr>
<td>OBS</td>
<td>27%</td>
<td>49%</td>
<td>64%</td>
</tr>
</tbody>
</table>

- 3,083 pts combined
- Median FU 18 yrs
- <50yo -> CMF
- TAM when appropriate

*Remember: T3N0, N+, or Skin or Facia involvement*
Danish 1-3 LN – Overgaard 2007

- 1152 pts with > 8 LN removed analyzed
- Benefit not limited to > 4 LN
- Similar LRR

Table 2
The Bottom line estimate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1–3 pos. nodes</th>
<th>4+ pos. nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint: loco-regional recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid an LRR</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Endpoint: death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Number of patients needed to treat to avoid a death</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Relative and absolute risk reduction and number of patients needed to treat to achieve benefit of postmastectomy radiotherapy as a function of number of positive lymph nodes. Estimates are calculated for the benefit of avoiding an isolated first loco-regional recurrence or death.
British Columbia Trial: Young Patients

- **Median # of nodes 11**
  - CMF 6 months -> 2nd RND in ER+ to oophrectomy
  - Radiotherapy: CW+RLNI 37.5/16

- **20 YR Data**:
  - OS: 47% (CMF+RT) vs. 37% (CMF), RR 0.73
  - 20Y LRBCFS: 87% (CMF+RT) vs. 61% (CMF), RR 0.32 (SS)
  - 20Y BCFS: 48% (CMF+RT) vs. 30% (CMF), RR 0.63 (SS)
  - No increase in cardiac death

- Improved LRC \(\rightarrow\) Improve OS

Cardiac Toxicity over time: EBCTCB 2005

Table 1
Cardiac mortality in radiation trials before 1973 and after 1993

<table>
<thead>
<tr>
<th></th>
<th>Cardiac deaths$^a$</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed before 1973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up &lt;5 years</td>
<td>230/180</td>
<td>1.19 (0.98 to 1.45)</td>
</tr>
<tr>
<td>Follow up &gt;5 years</td>
<td>189/145</td>
<td>1.21 (0.97 to 1.50)</td>
</tr>
<tr>
<td>Diagnosed after 1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up &lt;5 years</td>
<td>230/180</td>
<td>0.95 (0.79 to 1.14)</td>
</tr>
<tr>
<td>Follow up &gt;5 years</td>
<td>189/145</td>
<td>0.99 (0.73 to 1.50)</td>
</tr>
</tbody>
</table>

$^a$Left-sided radiation versus right-sided radiation.

- Trials before 1970 -> cardiac mortality rates increased by 19 to 21% (hazard ratio (HR) = 1.19 to 1.21)

- **After 1970 -> no increased risk (HR = 0.95 to 0.99)**
Using Biology to Enrich Patients to benefit from PMRT
Triple Negative Breast Cancer

Chinese RND stage I-II TNBC:
Median f/u = 86 mos

681 pts
T1/2, N0
TNBC

Stratify
<50 (69%)
>50
Tumor size

AC (most) or CMF
AC/CMF +50Gy/2Gy
RLNI optional

Wang, J. et al., Radiother Oncol, 100: 200-4, 2011
## Triple Negative Breast Cancer

### 5 Year Chemo vs. Chemo+RT

<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>Chemo+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse free survival</td>
<td>75%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.02</td>
</tr>
<tr>
<td>Overall survival</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Wang, J. et al., Radiother Oncol, 100: 200-4, 2011
Oncotype and LRR In Node +/ER +

- B-28 RND AC vs AC→T
- n=3096 (n=1096 N+, ER+)
- ER or PR positive received Tam
- Lumpectomy: RT to breast
- Mastectomy: No RT

Mamounas et al: SSO 2013
LRR in Patients with Mastectomy (n=604)

1-3 Positive Nodes (N=386)

>4 Positive Nodes (N=218)

- RS Low
- RS Intermediate
- RS High

P-value = 0.64

Cumulative Incidence Rate

Mamounas et al: SSO 2013
# Institutional/RTOG goals

<table>
<thead>
<tr>
<th>CTV</th>
<th>PTVeval Coverage</th>
<th>Max Dose PTVeval</th>
<th>Max Point dose</th>
<th>OAR Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Wall</td>
<td>95/95 90/90</td>
<td>&lt;50%/&gt;90%</td>
<td>&lt;115%</td>
<td></td>
</tr>
<tr>
<td>Contra Breast</td>
<td>&lt;5% 186cGy</td>
<td>310cGy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td></td>
<td></td>
<td></td>
<td>&lt;30% &gt;20Gy &lt;50% &gt;10Gy</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td>&lt;5% &gt;25Gy (Left) Mean 4Gy</td>
</tr>
</tbody>
</table>

**TIP:** In 2014 avoid talking about liters of heart
Post Mastectomy Radiation

• PMRT can be safely delivered and most modern evidence suggests no cardiac toxicity increase in the pre IMRT and DIBH era

• PMRT improves LRR and OS in all population

• Magnitude increased slightly in N2

• Comprehensive nodal RT is SOC in PMRT

• Can biology and a Recurrence Score help us select with clinical factors the real patients to treat?

• 3D era is here to stay
Indications for radiation after neoadjuvant chemotherapy and BCT
Rationale for Neoadjuvant Chemotherapy

• High response rates in locally advanced breast cancer.

  • Use of primary response as an *in vivo* measure of tumor (presumed distant) chemo sensitivity
    – 2012 FDA Approved endpoint

• Reduce size of primary tumor to increase rates of breast-conserving surgery or to improve cosmetic outcome.
NSABP B-18 and NSABP B-27

• B18:
  – 1523 patients
  – ACx4 Neo vs. adjuvant (1:1 RND)
  – T1-3, n0-1,M0
  – >50yo received TAM
  – No PMRT or regional nodal RT

• B27
  – 2x2 design with Taxotere added
  – *All women* received TAM (about 75% ER+)
  – No PMRT or regional nodal RT
Importance of pCR

- NSABP B-18 and B-27
- pCR is prognostic for survival.
- Increased rate of pCR by
  - Grade 3
  - Nonlobular
  - ER negative
  - High Ki-67
  - HER-2 positive

**NSABP B-18 Breast Conservation**

- Modest increase in breast conservation

**IBTR (%) as site of 1st treatment failure**

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
<th></th>
<th>Preop</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># Chemo</td>
<td>448</td>
<td>7.6</td>
<td>503</td>
<td>10.7</td>
</tr>
<tr>
<td>p</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Downstaged lump initially proposed

<table>
<thead>
<tr>
<th></th>
<th>Downstaged</th>
<th></th>
<th>Lump initially proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td># to lump</td>
<td>69</td>
<td>15.9</td>
<td>434</td>
</tr>
<tr>
<td># proposed</td>
<td></td>
<td></td>
<td>9.9</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

• Breast Conservation: Note for N+ In breast relapse higher
B18/27 LRR post NeoAdj

Lumpectomy + XRT

cN(+), ypN(+)
cN(+), ypN(-) / No breast pCR
cN(+), ypN(-) / Breast pCR
cN(-), ypN(+)
cN(-), ypN(-) / No breast pCR
cN(-), ypN(-) / Breast pCR

10-Year Probability (%) LRR

Age (years)

Good population to study

Neoadjuvant Chemotherapy

- NSABP B-18 and B-27 and others demonstrate equal overall survival (neo vs adj)

- Pathologic CR rates highest in TNBC/Her2 and are FDA approved as endpoints due to prediction of DFS/OS

- BCT post neoadjuvant downsizing shows equal OS but increase LRR

- Current trials ask: can we alter treatment volumes based on pCR for Stage II
Indications for radiation after neoadjuvant chemotherapy and mastectomy
Patterns on LRR combined B18/27

- cN0  cN+

Mastectomy: (Left) <5cm (right) >5cm

Low LRR with pCR with negative nodes irrespective of tumor size and clinical nodal status (1 local recurrence in 94 patients)

Clinical T3N0

Nodal ypN0

Nodal ypN+

0/13 complete breast and nodal pCR LRR – need more data

NSABP-51/RTOG 1304: Phase III Chemotherapy Response Adapted RT

- 1636 Patients
- Endpoint OS and LRR

**cT1-3 +FNA LN**

**NeoAdjuvant Chemotherapy**
- SLBx/Ax
  - Continue if pN0

**Branches**
- (a) WBRT
  - (b) No PMRT
- (a) WBRT + RLNI
  - (b) PMRT
Locally advanced and inflammatory breast cancer
LABC Management
Tri Modality Therapy

LABC

- T4a-T4c
- ≥N2 Axillary Disease
- Supraclavicular Nodes (N3)
- Internal Mammary Nodes (N3)

Neoadjuvant Chemotherapy

MRM

PMRT (CW+RNI)

85-95% LRC/5 OS 50%
Prognosis

• 5 yr survival for LABC about 50%
• Prognostic factors
  – Age
  – Tumor stage and histologic grade
  – Clinical response
  – LN status
  – HR status
  – HER2 status
10Y Patterns of failure w/o PMRT

- All 5 trials Anthracycline based

<table>
<thead>
<tr>
<th>SIZE</th>
<th>1-3 LN+</th>
<th>4-9 LN+</th>
<th>≥10 LN+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤2</td>
<td>2.1-5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1,045</td>
<td>1,489</td>
<td>229</td>
</tr>
<tr>
<td>Isolated LF, %</td>
<td>4.3</td>
<td>7.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Isolated RF, %</td>
<td>2.4</td>
<td>3.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Isolated LRF, %</td>
<td>6.0</td>
<td>9.7</td>
<td>7.5</td>
</tr>
<tr>
<td>LRF with or without DF, %</td>
<td>10.6</td>
<td>15.3</td>
<td>11.4</td>
</tr>
<tr>
<td>DF, %</td>
<td>24.6</td>
<td>35.7</td>
<td>40.5</td>
</tr>
</tbody>
</table>
Fig 1. Rate of local-regional recurrence (LRR) for patients treated with radiation (RT; 542 patients, 50 events) and without RT (134 patients, 28 events).

Table 3. Ten-Year Actuarial Rates of LRR According to Clinical and Pathological Disease Status

<table>
<thead>
<tr>
<th>Factor</th>
<th>No Radiation (%)</th>
<th>Radiation (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical T-stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
<td>8</td>
<td>.535</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>7</td>
<td>.408</td>
</tr>
<tr>
<td>T3</td>
<td>22</td>
<td>8</td>
<td>.002</td>
</tr>
<tr>
<td>T4</td>
<td>46</td>
<td>15</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Clinical N-stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>23</td>
<td>10</td>
<td>.014</td>
</tr>
<tr>
<td>N1</td>
<td>14</td>
<td>9</td>
<td>.062</td>
</tr>
<tr>
<td>N2-3</td>
<td>40</td>
<td>12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pathological tumor size, cm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0-2</td>
<td>13</td>
<td>8</td>
<td>.051</td>
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<tr>
<td>2.1-5.0</td>
<td>31</td>
<td>14</td>
<td>.002</td>
</tr>
<tr>
<td>≥ 5.1</td>
<td>52</td>
<td>13</td>
<td>.001</td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11</td>
<td>4</td>
<td>.010</td>
</tr>
<tr>
<td>1-3</td>
<td>13</td>
<td>11</td>
<td>.638</td>
</tr>
<tr>
<td>≥ 4</td>
<td>59</td>
<td>16</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviation: LRR, local regional recurrence.

IMN Radiotherapy

- Most PMRT randomized trials included IMN fields (EBCTCG – Lancet 2005, 24/25 trials)
- MA.20 included IMN
- RTOG 1305/NSABP B51 includes IMN (RNI arm)
- Concern over cardiac toxicity in the modern chemotherapy era remain despite meta-analysis (EBCTG)
Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy (2013)

- Powered to detect 10% OS benefit at 10 years
- 25% were node negative
Management of LABC

• Tri Modality therapy remains standard of care

• PMRT has significant
  – local control benefit and
  – OS benefit

• Most PMRT data includes IMN radiotherapy

• EORTC 22922 IMN trial (mastectomy or BCT)
Management of Inflammatory Breast Cancer
Clinical Findings

- <6mo onset
- >33% breast

Confirm IBC

T4D
Historical Treatment Recommendations

- Surgery alone: 5 yr OS <5%
- Surgery + RT: 5 yr OS 5-10%
- RT alone: 5 yr OS 10% (MDACC) but 50% LC
Tri Modality Therapy

- NeoADJ CTX
- Response cCR?
- Surgery (operable) >cCR
  - XRT
- Pre-op RT/CRT <cCR
  - Surgery

Improves 5OS >40%
Clinical response is most important Prognostic Indicator

DFS

OS

Ueno et al; Cancer Chemother Pharmacol 1997
Can dose escalation help in $<_{pCR}$?

- MDACC
- Dose escalation for $<$ partial chemotherapy response, close/positive margins, and age $< 45$ years

Who Benefits From Dose Escalation?

<table>
<thead>
<tr>
<th></th>
<th>60 Gy</th>
<th>66 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; PR to induction chemo</td>
<td>32%</td>
<td>70%</td>
</tr>
<tr>
<td>Age &lt; 45 yrs</td>
<td>65%</td>
<td>86%</td>
</tr>
<tr>
<td>Close/positive margins</td>
<td>60%</td>
<td>83%</td>
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</table>

MDACC (Bristol et al, IROBP 2008)
Show of Hands

• 55 yo Inflammatory BC
• Triple negative
• Neoadjuvant ddACT
• MRI demonstrates CR

Who would consider BCT
Management of Inflammatory

- Tri modality therapy has improved OS
- Response to chemotherapy best prognostic factor
- No role for BCT
- Role for Dose escalation in high risk patients to improve LRC?
Metastatic Breast Cancer
Oligometastasis
Does Ablative therapy of all known metastases (Oligometastasis) Change the natural history of Metastatic Breast Cancer?
Do Oligometastases Exist?

• Data Suggest:
  • Metastases are not always widely disseminated
  • Metastases do not always progress in multiple sites
  • Patients with limited sites of metastases may not progress or progress only in sites of initial disease
  • Therefore there may be a role for local therapy in selected patients

Widely Metastatic Disease

Limited Metastatic Disease
Show of Hands

- 39 yo T2N1
- Luminal B
- Disease free 2 years
- CT shows single lung lesion

Who would consider SBRT or surgery
1. Off trial
2. On RND trial
Frequency in Breast Cancer

• A retrospective multi-institutional review of Stage I-III (91% I-II) breast cancer patients (n=3,249; 1978-2012)

• **5-year OS 59.6%(OM) 11.6% (PM)**
  • Of 21 long-term survivors, 20 received local therapy with surgery and/or radiation.
Clinical Questions

• Clinical and molecular characterization of subsets of metastasis may provide a therapeutic window for cure by combined modality therapy

• Safety, efficacy, and toxicity of such an approach
<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Phase</th>
<th>n</th>
<th>ER/PR+ (%)</th>
<th>HER2+</th>
<th>&lt; 2 met sites (%)</th>
<th>&lt; 4 Met Sites (%)</th>
<th>Arms</th>
<th>PFS (Mo.)</th>
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</thead>
<tbody>
<tr>
<td>Bergh 2012</td>
<td>III</td>
<td>593</td>
<td>72</td>
<td>Pos.</td>
<td>52</td>
<td>-</td>
<td>1 Sunitinib+ Docetaxel 2. Docetaxel</td>
<td>8.6 8.3</td>
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<tr>
<td>Tawfik 2013</td>
<td>II</td>
<td>30</td>
<td>77</td>
<td>Neg.</td>
<td>50</td>
<td>-</td>
<td>1. Vinorelbine, capecitabine</td>
<td>8.6*</td>
</tr>
<tr>
<td>Hurvitz 2013</td>
<td>IIR</td>
<td>137</td>
<td>54</td>
<td>Pos</td>
<td>49.3</td>
<td>-</td>
<td>1. Trastuz + Docetaxel 2. T-DM1</td>
<td>9.2 14.2</td>
</tr>
</tbody>
</table>
Stereotactic Body Radiosurgery
SBRT

• Delivery of high dose radiation therapy using 1-5 fractions

• Biologic dose >100Gy appears to lead to equal control in primary early lung

• *For metastatic breast cancer, Local Control 65-90% (Milano et al, Pooled CO and IN)*

• *RTOG has demonstrated doses for single lesions, outcomes, and dosimetry*
Why should this be tested?
Are patients with limited metastasis being treated with SBRT?

http://tinyurl.com/oligomet
International Survey of SBRT use for Oligometastases:

• >1000 respondents
  – 43 countries
  – >8000 distributed

• 61% use SBRT to treat ≤ 3 metastases
  – Most common reasons for use:
    • Demonstration of durable local control
    • For research purposes
  – Most common reasons NOT used:
    • Lack of convincing data
SBRT use for oligometastases is increasing

- 63% currently using plan to *INCREASE* volume
- 59% not using SBRT for OM plan to start
  - 88% of these in next 3 years
- No RND data is the most common reason for not using SBRT
Hypothesis

- **Phase IIr:**
  - *Hypothesis:* ablative local therapy all *VISIBLE* lesions with systemic therapy -> *signal* for meaningful improvement in the *PFS* to warrant continuation to Phase III trial
    - “*Rolls over*” into Phase III with a sufficient efficacy signal for PFS (i.e., Go / no Go)

- **Phase III:**
  - *Hypothesis:* Multi-Modality treatment of Oligometastases -> *superior 5y OS*
Phase IIr – Eligibility

- Pathologic confirmation of MBC
- ≤ 2 metastasis (≤ 4 pending NRG BR002)
- Local regional disease controlled (*No Overlap with E2108*)
- All metastasis amenable to SBRT or Resection (<5cm), No brain metastasis
- Zubrod performance status ≤ 2
OLIGOMETASTATIC BREAST CANCER
Controlled Locoregional Disease and ≤ 2 Metastases
≤ 6 months systemic therapy without progression

STRATIFICATION
1 v >1 metastasis
Hormone receptor status
Her 2 neu status
Chemotherapy for MBC (yes or no)

RANDOMIZATION

ARM 1
Standard *systemic* therapy
Symptom directed palliative therapy as needed

ARM 2
*Total ablation of all metastases*
Standard systemic therapy
Primary Endpoint:
Demonstrate improved PFS with the addition of Ablative Therapy to SOC v. SOC

130 evaluable patients will provide 95% power to detect improvement in PFS from

10.5 months to 19 months (HR=0.55)
One-sided type I error of 0.15.

- PFS will be measured from the date of randomization to the date of first PFS failure or last follow-up.
- Imaging q3 months for 2 years or until progression.
- After 2 years, imaging will be lengthened to q6 months or progression.
- After 5 years without progression, imaging per best clinical practice is recommended.)
Primary Endpoint:
Demonstrate improved OS with the addition of Ablative Therapy to SOC v. SOC

246 additional evaluable patients will provide 85% power to detect improvement in OS from:

28% to 42.5% (HR=0.67)

One-sided type I error of 0.025.
Total Phase IIIR/III accrual: 402 patients.

Integrated phase II/III design: 81% power for OS analysis at p= 0.025 (1-sided)
Minimal disruption to systemic therapy

- All SOC HT, Her 2, and bone drugs continue

- Experimental Tx need 30 day wash out

- Chemo hold prior to SBRT is very liberal
  - (ie: 14-21 days for 14-28 day cycles, 7 days for weekly regimens)
  - TDM-1 and everolimus follow chemo holds

- Can resume held drugs 14 day post SBRT
NRG-BR001

A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases
Phase I: SBRT Multiple Site Design

3-4 metastases:
Each ≤ 5cm diameter

2 metastases:
Within ≤ 5cm of each other
Each ≤ 5cm diameter

Surgical resection of 1 metastasis
No surgical resection

SBRT to all remaining known metastases (1-4)
1) Multiple Treatment Sites
2) Varying dose/fraction

<table>
<thead>
<tr>
<th>Metastatic Locations</th>
<th>Initial Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Lung—Central</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Mediastinal/Cervical Lymph Node</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Spinal/Paraspinal</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Osseous</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Abdominal-pelvic metastases (lymph node/adrenal gland)</td>
<td>45 Gy (3 fractions)</td>
</tr>
</tbody>
</table>
Translational Endpoints
Oligometastases and CTC

- Hypothesis
  - ablative therapy -> prolonged PSF in patients with
    - few or no CTCs at registration
  - ablative therapy that eradicates all CTCs -> prolonged PFS.
    - (zero CTCs at follow-up in patients with at least two at registration)

- Hypothesis-generating: compare PFS in both arms (low CTCs at registration and eradicated CTCs).

- May correlate ctDNA to CTC
CTC Collection

RND → Time of Progression

CTC Draw

CTC
Before treatment

CTC
4-6 weeks (if SBRT/Surgery)

Epithelial cell adhesion molecule enrichment
Anticipated Outcomes

• If **Ablative Therapy of all Metastases** improves OS when added to standard systemic therapy, then the paradigm shifts to multidisciplinary treatment

• If **Ablative Therapy of all Metastases** does not improve OS when added to standard systemic therapy, then **off-protocol use of SBRT stops**
  • Cost reduction and toxicity avoidance

• Determine **optimal dose** for multiple site SBRT
Conclusions

• Rates of failure for both DCIS and early IDCA are significantly less than classic data

• Randomizing two low risk populations will lead to low risk of recurrence

• Suggests we can use clinical and biologic factors to select patients

• Advanced breast cancer needs triple modality therapy

• Some metastatic disease may be cured

• If a question is being randomized, and the patient is being treated off trial, treat via the standard of care arm
March 10, 2014

End Transmission