San Antonio Breast Cancer Symposium 2010 Highlights – Radiotherapy

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The Optimal SEquencing of Adjuvant Chemotherapy and Radiotherapy in Early Breast Cancer
Results of a UK Multicentre Prospective Randomised Trial (SECRAB)

Questions:
- Can local control be improved with synchronous chemotherapy and radiotherapy?
- Can the two treatments be given together safely?

Fernando IN, et al. S4-4. SABCS 2010
Early breast cancer requiring CT & RT after BCS or Mast

Recruitment
Apr 98-July 04

Synchronous Schedule
CT + RT
1150 patients

CMF
Anthracycline → CMF
Other

Sequential Schedule
CT → RT
1146 patients

40 Gy in 15 fx/3 weeks
50 Gy in 25 fx/5 weeks

Synchronous Schedule

Fernando IN, et al. S4-4 SABCS 2010
### Sequential Schedule

![Sequential Schedule Diagram](image)

### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Synchronous (n=1150)</th>
<th>Sequential (n=1146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>52 (24-77)</td>
<td>51 (24-79)</td>
</tr>
<tr>
<td>Type of surgery, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>634 (55)</td>
<td>647 (56)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>516 (45)</td>
<td>497 (43)</td>
</tr>
<tr>
<td>Nodes involved, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>428 (37)</td>
<td>444 (39)</td>
</tr>
<tr>
<td>1-3</td>
<td>444 (39)</td>
<td>440 (38)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>277 (24)</td>
<td>261 (23)</td>
</tr>
<tr>
<td>Tumor Grade, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>77 (7)</td>
<td>68 (6)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>414 (36)</td>
<td>411 (36)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>654 (57)</td>
<td>658 (57)</td>
</tr>
<tr>
<td>Tumor Size, median (range)</td>
<td>22 (1-100)</td>
<td>22 (2-210)</td>
</tr>
</tbody>
</table>

Fernando IN, et al. S4-4 SABCS 2010
Median follow up = 8.8 years

<table>
<thead>
<tr>
<th></th>
<th>Synchronous</th>
<th>Sequential</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year LRR</td>
<td>5.4%</td>
<td>7.4%</td>
<td>0.19</td>
</tr>
<tr>
<td>5 year in-field LRR</td>
<td>2.8%</td>
<td>4.9%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Loco-regional Recurrence (LRR)

No difference regardless of:
- Chemotherapy or RT regimen
- Use of boost
- Number of LN involved
- Margin status
- Tumor size or grade

* All favored Synchronous arm
### Disease Free Survival and Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Synchronous</th>
<th>Sequential</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year DFS</td>
<td>79%</td>
<td>78%</td>
<td>0.8</td>
</tr>
<tr>
<td>5 year OS</td>
<td>83%</td>
<td>82%</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Fernando IN, et al. S4-4 SABCS 2010

### Contralateral and Other Malignancies

<table>
<thead>
<tr>
<th></th>
<th>Synchronous (n=1150)</th>
<th>Sequential (n=1146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral breast cancer, n (%)</td>
<td>31 (3)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>Distant, n (%)</td>
<td>260 (23)</td>
<td>255 (22)</td>
</tr>
<tr>
<td>Other primary cancer, n (%)</td>
<td>30 (3)</td>
<td>34 (3)</td>
</tr>
</tbody>
</table>

Fernando IN, et al. S4-4 SABCS 2010
Acute and late toxicity results from the SECRAB trial: the optimal SEquencing of adjuvant Chemotherapy and RAdiotherapy in early Breast cancer

Toxicity Conclusions:

- Increase in acute skin reactions in synchronous arm, predominantly in patients treated with >15 fractions

- Increase in late skin telangiectasia in synchronous arm, but only significant in patients treated with >15 fractions

- No difference in other late toxicities
Conclusions

With CMF type regimen:

- Feasible to give sandwich RT without a significant increase in toxicity in selected patients (15 fx)

- Shortens treatment time with no disadvantage in terms of LC or OS

- Even with close margins, no evidence that RT has to be given earlier

What’s Next?

- QOL
- Cosmesis
- Meta-analysis with other sequencing trials
- Synchronous chemo-radiotherapy feasible in other regimens (FEC → T)?
**Synchronous vs Sequential**

Comments:
- Can safely give concurrent tx with older regimens
  - Unclear with current regimens (AC → T)
- Shortens treatment time
  - Hypofractionated whole breast
  - APBI
- Synergy with combined tx? (fewer in-field LR)
  - Other radiosensitizers

**Posters:**
**Randomized Trials**
25-year Results in the Treatment of Early Breast Carcinoma with Mastectomy Versus Breast Conservation Therapy: The National Cancer Institute Randomized Trial

Simone NL, et al. SABCS 2010. P4-10-01

237 patients with Stage I or II breast cancer (1979-1987)
Randomized to MRM or lumpectomy + RT

Median follow up = 25.4 years

<table>
<thead>
<tr>
<th></th>
<th>MRM</th>
<th>BCT</th>
<th>p</th>
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<tbody>
<tr>
<td>DFS</td>
<td>82%</td>
<td>57%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>46%</td>
<td>38%</td>
<td>0.43</td>
</tr>
</tbody>
</table>

22% IBTR in patients with BCT → Salvaged by mastectomy
No differences in distant metastasis

Long-Term Follow-Up of SweBCG 91RT, a Randomized Trial of Breast Conservation Surgery with and without Radiotherapy from the Swedish Breast Cancer Group

Malmstrom P et al. SABCS 2010. P4-10-03

1197 patients with T1-2 N0 breast cancer treated with BCS
Randomized to XRT vs no further treatment
Median tumor size = 12 mm

Median follow up = 15 years

<table>
<thead>
<tr>
<th></th>
<th>BCS + XRT</th>
<th>BCS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI of LR</td>
<td>12%</td>
<td>24%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RFS</td>
<td>63%</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>71%</td>
<td>68%</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Accelerated Partial Breast Irradiation

Accelerated Partial Breast Irradiation for DCIS: Analysis of the Susan G Komen Clinical Trial

5 Institutions (2003-2009)
MammoSite after BCS for DCIS
34 Gy in 10 fractions over 5 days

45 patients (treatment completed in 40)
Mean age = 57.6 yrs
Median follow up = 47.8 months

Only 2 grade 3 toxicities
At 12 mos, 89% of patients rated good/excellent outcome

IBTR in 4 patients (10%)
All DCIS outside of treatment field

APBI for DCIS

Comments:

- 10% recurrence at median f/u of 48 mos
  - ASBS Registry trial: 5-yr actuarial LRR = 3.39%
- No information regarding size/grade of DCIS
- Other data support use of APBI for DCIS but suggest higher recurrence rate with high grade DCIS
- Awaiting results of randomized data
- Per ASTRO guidelines → “unsuitable off clinical trial”

Late Toxicity and Patient Self-Assessment of Breast Appearance/Satisfaction on RTOG 0319: A Phase II Trial of 3D-CRT PBI Following Lumpectomy for Stage I and II

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0319

A PHASE III TRIAL TO EVALUATE THREE DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) CONFINED TO THE REGION OF THE LUMPECTOMY CAVITY FOR STAGE I AND IIA BREAST CARCINOMA

SCHEMA

R
E 39.5 Gy Total/10 fractions (3.95 Gy per fraction)
G 2 fractions/day (separated by 6 hours)
I Given in 5 consecutive working days
S Radiotherapy should begin within eight weeks of surgery
T (if chemotherapy is given first, RT begins 2 weeks after the last cycle of chemotherapy)
E
R

Late Toxicity and Patient Self-Assessment of Breast Appearance/Satisfaction on RTOG 0319: A Phase II Trial of 3D-CRT PBI Following Lumpectomy for Stage I and II


MammoSite® Balloon
Late Toxicity and Patient Self-Assessment of Breast Appearance/Satisfaction on RTOG 0319: A Phase II Trial of 3D-CRT PBI Following Lumpectomy for Stage I and II

Question:
- Will large fraction sizes and volume increase the rate of unacceptable cosmesis and AEs → Late toxicity

Accrual: Aug 2003 – April 2004
58 patients (52 evaluable; 2 deaths at 3 yrs)
Median follow up = 5.3 years

Self-Reported Cosmesis at 3 years
86% (31/36) patients were satisfied with their overall treatment
100% (36/36) would choose 3D-CRT PBI again

<table>
<thead>
<tr>
<th>Overall score</th>
<th>excellent</th>
<th>good</th>
<th>fair</th>
<th>poor</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>25/3</td>
<td>5/31</td>
<td></td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td>1 year</td>
<td>37/45</td>
<td></td>
<td>6/45</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>2 years</td>
<td>33/41</td>
<td></td>
<td>8/40</td>
<td></td>
<td>77%</td>
</tr>
<tr>
<td>3 years</td>
<td>25/36</td>
<td></td>
<td>13/36</td>
<td></td>
<td>64%</td>
</tr>
</tbody>
</table>

Adverse Events (AEs)
Worst AE reported as probably, possibly, or definitely related to treatment:
- Grade 1: 19/52 = 36.5%
- Grade 2: 26/52 = 50.0%
- Grade 3: 3/52 = 5.8%

Only 3 patients had grade 3 AEs, which were:
- Patient #1 - skin fibrosis and telangiectasia
- Patient #2 - radiation dermatitis and myositis
- Patient #3 - skin fibrosis
Late Toxicity and Patient Self-Assessment of Breast Appearance/Satisfaction on RTOG 0319: A Phase II Trial of 3D-CRT PBI Following Lumpectomy for Stage I and II

Conclusions:
- All patients would choose 3D-CRT again
- Very few grade 3 AEs
- No increase in clinically significant fibrosis
- No significant cosmetic concerns
- Awaiting results of ongoing phase III trials

Comments:
- 81% good/excellent cosmesis at 3 mos → 64% at 3 yrs
- Data from single institutions suggest poor cosmetic outcome with this regimen
- Volume may be important with accelerated treatments
- Await follow up of Phase III trials

CNS Metastasis in Her2+ Breast Cancer

Population-Based Outcomes after Whole Brain Radiotherapy in Patients with Metastatic Breast Cancer in the Pre and Trastuzumab Eras

441 women with metastatic breast cancer and brain radiotherapy (2000-2007) = T era

128 women with metastatic breast cancer and brain radiotherapy (1986-1992) = pre-T era

Population-Based Outcomes after Whole Brain Radiotherapy in Patients with Metastatic Breast Cancer in the Pre and Trastuzumab Eras

Table 3: Trastuzumab era

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UVA</th>
<th>MVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>BRA status</td>
<td>Yes</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>256</td>
</tr>
<tr>
<td>SRS boost</td>
<td>Yes</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>361</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>Yes</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>192</td>
</tr>
<tr>
<td>Her2 status</td>
<td>Positive</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>210</td>
</tr>
<tr>
<td>Hormones at brain mets</td>
<td>Yes</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>205</td>
</tr>
<tr>
<td>Herceptin at brain mets</td>
<td>Yes</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>235</td>
</tr>
</tbody>
</table>

Population-Based Outcomes after Whole Brain Radiotherapy in Patients with Metastatic Breast Cancer in the Pre and Trastuzumab Eras

Conclusions:

- No difference in survival after brain radiotherapy between the pre-Trastuzumab and Trastuzumab eras for patients with Her2 negative disease

- Survival after XRT for brain metastases in women with Her2 positive disease has increased significantly in the Trastuzumab era compared to pre-Trastuzumab era
Randomized trial of Prophylactic Cranial Irradiation in patients treated with trastuzumab

Closed early due to poor accrual

PCI in patients treated with trastuzumab in metastatic/locally advanced breast cancer

There have been 10 events (development of symptomatic brain metastases), 3 in the PCI arm and 7 in the no PCI arm. P = 0.18 for the comparison of the cumulative incidence between the arms. The estimated hazard ratio (PCI/no PCI) is 0.39 (95% CI 0.10 to 1.56).

PCI in patients treated with trastuzumab in metastatic/locally advanced breast cancer


Overall survival by study arm. P= 0.867.

PCI in patients treated with trastuzumab in metastatic/locally advanced breast cancer

PCI in patients treated with trastuzumab in metastatic/locally advanced breast cancer

Conclusions:

- No excess toxicity in the PCI arm compared to no PCI in terms of QOL, cognitive function

- PCI resulted in halving of symptomatic brain metastases, but only 10 events

Comments:

- PCI may reduce the incidence of brain metastases, however likely not acceptable to patients

- Improvement in systemic therapies important in combination with brain radiotherapy (whole brain + radiosurgery)