Hypofractionation in Breast Cancers: When and How
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Radiotherapy after breast-conserving surgery, generally with axillary clearance (BCS±RT) in all women (node-negative or node-positive) (7311 women, 17% with node-positive disease)

Hypothesis – START Trial
"Breast cancer is as sensitive to fraction size as late-reacting AE"
If so, small fractions spare breast cancer as much as the late-reacting AE
This suggests NO disadvantages
(& shorter treatment times may help tumour control)

Prof John Yarnold, ICR

EBCTCG Lancet 2011; 378: 1707-16
Some Cancers are more sensitive to fraction size

- Ellis Isoeffect Formula: 45 Gy in 15 fractions is equivalent to 50 Gy in 25 fractions
- Worse Cosmesis, RAGE review
- Hypofractionation (in breast cancers) was written off

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### Trials in Breast Cancer Hypofractionation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ontario</th>
<th>START A</th>
<th>START B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Dose Comparator to 50 Gy/25 fr weeks</td>
<td>42 Gy/15 fr 3 weeks</td>
<td>40 Gy/15 fr 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Boost</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cosmesis (Late changes in breast appearance)</td>
<td>Similar</td>
<td>Significantly better for 39 Gy Hypofractionation (HR 0.85, p=0.06)</td>
<td></td>
</tr>
</tbody>
</table>

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### What is the likely alpha/beta ratio for breast cancers?

The estimated radiobiological parameters from different clinical data (95% CI).

<table>
<thead>
<tr>
<th>Author</th>
<th>Estimate</th>
<th>Alpha</th>
<th>Beta</th>
<th>T2 (day)</th>
<th>Alpha (Gy)</th>
<th>Beta (Gy)</th>
<th>T2 (day)</th>
<th>Alpha (Gy)</th>
<th>Beta (Gy)</th>
<th>T2 (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whelan</td>
<td>3.21</td>
<td>3.86</td>
<td>0.16</td>
<td>0.10</td>
<td>10.4</td>
<td>17.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Owens</td>
<td>4.39</td>
<td>7.45</td>
<td>0.05</td>
<td>0.04</td>
<td>12.2</td>
<td>26.2</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shelby</td>
<td>2.21</td>
<td>1.59</td>
<td>0.13</td>
<td>0.06</td>
<td>21.3</td>
<td>71.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>START A</td>
<td>3.93</td>
<td>3.47</td>
<td>0.02</td>
<td>0.06</td>
<td>17.1</td>
<td>58.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>START B</td>
<td>2.49</td>
<td>1.63</td>
<td>0.09</td>
<td>0.02</td>
<td>13.9</td>
<td>9.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark</td>
<td>1.44</td>
<td>1.27</td>
<td>0.03</td>
<td>0.10</td>
<td>10.8</td>
<td>48.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arraigada</td>
<td>3.80</td>
<td>6.25</td>
<td>0.04</td>
<td>0.04</td>
<td>11.0</td>
<td>12.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
International Guidance

- NICE Recommended 40Gy in 15 fractions for all curative adjuvant radiotherapy
- ASTRO (Guarded recommendation 2011)
  - >50yrs
  - T1-2, N0
  - No Chemotherapy
  - Dose to be kept between 93-107%

Concern 1: Age <50yrs

- EBCTCG overview- 20-35% risk of LR at 10yrs
- Boost Studies suggested age trend with LR
- Canadian study- stratified recruitment -No difference in LR
- START 10year data (1389 patients) – No difference in LR

Concern 2: Safe to treat Grade 3 tumours?

- Ontario study subgroup analysis >LR in Gr 3
  - Unplanned subgroup
  - START data does not show any difference with respect to grade
  - British Columbia 1335patients data analysis showed no difference in LR for Gr 3 patients following hypofractionation
Concern 3: Cardiac Toxicity

- **Contributing factors**
  - Hypofractionation in 4.3Gy per fraction
  - Parasternal Photon use
  - (More use of PF in 4.3Gy group)
  - (No difference in Left/right sided RT)

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Heart Dose: How Low is Good?

- Hypofractionation reduces cardiac dose and does not increase Cardiac Death
- Chan et al. Radiotherapy and Oncology 2012
- Appelt et al. Clin Oncol (RCC) 2013
Other Toxicities

- No increase in Brachial plexopathy in the 4 RCTs
- No increase in Pulmonary fibrosis reported in the START A/B studies

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Is it fair to generalise the data?

<table>
<thead>
<tr>
<th>Grade</th>
<th>T2 and above</th>
<th>Node Positive</th>
<th>Age &lt;50yrs</th>
<th>SCF treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients in START A/B/START Pilot studies</td>
<td>up to 28.1%</td>
<td>up to 48.6%</td>
<td>&gt;20%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Chatterjee S et al Clin Onc (RCR) 2012
What dose volume planning requirements are mandatory for hypofractionated breast RT?

- Large Breasts could lead to more heterogeneity leading to more toxicity (double trouble)
- Ontario Study allowed patients with separation of 25cm or less
- START A/B studies had breasts with separation more than 25cm (17.2% START B)
- 2d Planning was required
- 95-105% dose in central axis
- Wedges and compensators used

Dose Heterogeneity and Cosmesis in hypofractionation

- Conformal Planning or IMRT Can improve cosmesis by restricting dose of 107% or less in <2cc breast volume
- Within 95-107% dose heterogeneity did not affect cosmesis on photographic changes even for more extreme hypofractionation

Current Practice: National

- Increasing uptake of START B type regime
- Likely to increase throughput
- Optimise resources
- At least 2d treatment plans must be generated
- Dose homogeneity must be optimised in the breast by simple techniques
What about the Indian population?

Data from Tata Medical Center, Kolkata

Audit of Demographics data Eastern (Patient Characteristics)
Audit of Changed Practice: India

- Published Early Toxicity

**Table 2. Skin Toxicity (in numbers)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>END RT</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>III</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mastectomy Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>49</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Heart Dose: Comparable to published data

Audit of Outcome Data/ Demographics

Local Control at 2yrs – projected to be 94%

Heart Dose: Comparable to published data

Can Hypo-fractionation work post Mastectomy?

- Published full text
  - 133 patients from New Zealand database
  - 40Gy 16 fr
  - No Gr 3 toxicity, 10% Gr 2
  - 5yr LC 97.6%

- Abstract ESTRO 2015
  - Mastectomy 41% (206) patients with median follow up of 21 months
  - LC rate same a BCS group
  - Acute toxicity similar (Gr1 91%)
Does Hypofractionation work in DCIS?

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>T1-3</th>
<th>N0-1</th>
<th>Disease</th>
<th>Hypofractionation</th>
<th>Trial</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Johns, 2011</td>
<td>2011</td>
<td>35%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>Ellis, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>Lim, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>Sultan, 2013</td>
<td>2013</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>van Herwijlen, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>de Bock, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>Wollschlager, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>Siegfried, 2014</td>
<td>2014</td>
<td>50%</td>
<td>50%</td>
<td>-</td>
<td>42.5 Gy</td>
<td>-</td>
<td>98</td>
</tr>
</tbody>
</table>

Summary: Hypofractionation

Invasive Cancer
- Robust RCT evidence exists for T1-3, N0-1 disease
- Level 2 data exists for all subgroup of patients
- India specific published data is now available
- It is as safe and as effective as conventional doses

Caution
- One must try do at least 2d planning and ensure dose homogeneity in the central axis between 95-107%
- In DCIS although evidence and use of hypofractionation is emerging Level 1 data is awaited
- It is recommended that data is added after changes in practice

Further Hypofractionation
- FAST Trial – FASTer radiotherapy for breast cancer patients
- Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy
- in terms of late normal tissue responses and tumour control
- Control arm: 50.0 Gy in 25 fractions of 2.0 Gy over 35 days
- Test arm 1: 30.0 Gy in 5 fractions of 6.0 Gy over 35 day (α/β value = 4 Gy)
- Test arm 2: 28.5 Gy in 5 fractions of 5.7 Gy over 35 days (α/β value = 3 Gy)
Randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer

Ct: Professor Murray Brunt

Simultaneous Integrated Boost: Further Hypofractionation

- Beware OAR doses

**IMPORT HIGH: Simultaneous integrated boost (SIB)**

- 2.4Gy
- 2.7Gy
- 3.2Gy

15 fractions

Slide Courtesy: Dr Charlotte Gates
First Multi-Centre Collaborative Hypofractionation Breast Cancer Study from India with external Peer QA

Centres Collaborating
- TMC Kolkata
- CMC Vellore
- SGPGI Lucknow

- Recruited 100 cases in 3 months
- 2 centres will go live within next 2 weeks (Site QA being performed and IRB Clearance received in each centre)

Thank You