FAST Forward:
A way ahead in Breast Irradiation

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Disclosures

- None
Flow of the Presentation

• Introduction
• Evidence in support of moderate hypofractionation
• FAST Forward Study
• Possible future of FAST-Forward
• Applicability to Indian patients
• TMC Experience
• Cost-Effectiveness
• Summary
Hypofractionation & Breast Cancer

• Various Forms of Hypofractionation practiced

What about Hypofractionation for the whole breast with EBRT?
Hypofractionation & Breast Cancer

- Cohen et. al. 1952 Inop Breast cancer → Initial reports of $\alpha/\beta = 3.8$
- Manchester Fractionation
- 4 main Prospective RCTs (n=7095; 1986 - 2001)

<table>
<thead>
<tr>
<th></th>
<th>START-P$^8$</th>
<th>START-A$^{10}$</th>
<th>START-B$^{11}$</th>
<th>Ontario$^7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>1410</td>
<td>2236</td>
<td>2215</td>
<td>1234</td>
</tr>
<tr>
<td>Standard arm (Gy/ft/weeks)</td>
<td>50/25/5</td>
<td>50/25/5</td>
<td>50/25/5</td>
<td>50/25/5</td>
</tr>
<tr>
<td>Test arm A (Gy/ft/weeks)</td>
<td>42.9/13/5</td>
<td>41.6/13/5</td>
<td>40.0/15/5</td>
<td>42.5/16/3.1</td>
</tr>
<tr>
<td>Test arm B (Gy/ft/weeks)</td>
<td>39/13/5</td>
<td>39/13/5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>54.5</td>
<td>57.2</td>
<td>57.4</td>
<td>Not reported</td>
</tr>
<tr>
<td>Node+ (%)</td>
<td>32.7</td>
<td>28.8</td>
<td>22.8</td>
<td>0</td>
</tr>
<tr>
<td>Mastectomy (%)</td>
<td>0</td>
<td>15</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Tumour size $\geq T_2$ (%)</td>
<td>42.5$^a$</td>
<td>48.6$^b$</td>
<td>35.9$^b$</td>
<td>20.0$^b$</td>
</tr>
<tr>
<td>Boost (%)</td>
<td>74.5</td>
<td>60.6</td>
<td>42.6</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>13.9</td>
<td>35.5</td>
<td>22.2</td>
<td>11</td>
</tr>
<tr>
<td>Regional radiotherapy (%)</td>
<td>20.6</td>
<td>14.2</td>
<td>7.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Yarnold J. BJR 2019
Efficacy of Hypofractionation

- Excellent Local Control; Numerically superior to conventional Fractionation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomisation (Gy/fraction)</th>
<th>% 5 year local relapse (95% CI)</th>
<th>% 10 year local relapse (95% CI)</th>
<th>&gt;2.0 Gy fractions better</th>
<th>2.0 Gy fractions better</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>START-P(^9,13)</td>
<td>50.0/25</td>
<td>7.9 (5.4–10.4)</td>
<td>12.1 (8.8–15.5)</td>
<td>Age &lt;50yrs</td>
<td>0.84 (0.62, 1.15)</td>
<td>0.67 (0.63, 1.38)</td>
</tr>
<tr>
<td></td>
<td>42.9/13</td>
<td>7.1 (5.4–10.4)</td>
<td>9.6 (6.7–12.6)</td>
<td>Age ≥50yrs</td>
<td>1.07 (0.83, 1.38)</td>
<td>0.67 (0.63, 1.38)</td>
</tr>
<tr>
<td></td>
<td>39.0/13</td>
<td>9.1 (6.4–11.7)</td>
<td>14.8 (11.2–18.3)</td>
<td>Breast conserving</td>
<td>0.97 (0.79, 1.20)</td>
<td>0.51 (0.46, 1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mastectomy</td>
<td>1.00 (0.82, 1.20)</td>
<td>0.51 (0.46, 1.19)</td>
</tr>
<tr>
<td>START-A(^10,13)</td>
<td>50.0/25</td>
<td>3.4 (2.3–5.1)</td>
<td>6.7 (4.9–9.2)</td>
<td>pN−</td>
<td>1.10 (0.66, 1.40)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
<tr>
<td></td>
<td>41.6/13</td>
<td>3.1 (2.0–4.7)</td>
<td>5.6 (4.1–7.8)</td>
<td>pN+</td>
<td>1.10 (0.43, 2.90)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
<tr>
<td></td>
<td>39.0/13</td>
<td>4.4 (3.1–6.2)</td>
<td>8.1 (6.1–10.7)</td>
<td>Grade 1</td>
<td>0.66 (0.51, 1.82)</td>
<td>0.86 (0.59, 1.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 2</td>
<td>1.07 (0.72, 1.59)</td>
<td>0.86 (0.59, 1.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3</td>
<td>0.95 (0.66, 1.38)</td>
<td>0.81 (0.57, 1.14)</td>
</tr>
<tr>
<td>START-B(^11,13)</td>
<td>50.0/25</td>
<td>3.3 (2.4–4.6)</td>
<td>5.2 (2.7–5.2)</td>
<td>No cytotoxic</td>
<td>1.09 (0.86, 1.38)</td>
<td>0.86 (0.57, 1.14)</td>
</tr>
<tr>
<td></td>
<td>40.0/15</td>
<td>1.9 (1.2–3.0)</td>
<td>3.8 (2.7–5.2)</td>
<td>Cytotoxic</td>
<td>1.09 (0.86, 1.38)</td>
<td>0.86 (0.57, 1.14)</td>
</tr>
<tr>
<td>Ontario(^12)</td>
<td>50.0/25</td>
<td>3.2(^a)</td>
<td>6.7(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42.5/16</td>
<td>2.8(^a)</td>
<td>6.2(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UK-START Studies

- **Diverse patient populations**
  - Younger
  - Post Mastectomy
  - Grade III
  - Receipt of CT
  - Regional Nodal RT (mostly SCF & upper Axilla n=470)

- **Diverse End-points**
  - Radiation sensitivity
  - LRC
  - Toxicity
  - DFS/ OS

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Table 5. START pilot, A & B (n = 5861): patient and treatment characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 years</td>
<td>1389</td>
</tr>
<tr>
<td>Age = 50 years</td>
<td>4472</td>
</tr>
<tr>
<td>Breast conserving</td>
<td>5348</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>513</td>
</tr>
<tr>
<td>pN-</td>
<td>4318</td>
</tr>
<tr>
<td>pN+</td>
<td>1421</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1213</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2398</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1271</td>
</tr>
<tr>
<td>No cytotoxics</td>
<td>4346</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>1480</td>
</tr>
</tbody>
</table>
UK-START B: Efficacy & Toxicity

- Excellent Local Control, DFS, OS & Toxicity profile
- MRM/ DCIS/ Recon not well represented

Haviland et. al 2013 Lancet Oncol
Mastectomy & Hypofractionation

<table>
<thead>
<tr>
<th>Hypofractionation (n)</th>
<th>Dose</th>
<th>Median FU</th>
<th>Gr III toxicity</th>
<th>5 yr LRFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ko et. al.</td>
<td>133</td>
<td>5.03 yrs</td>
<td>None</td>
<td>97.5%</td>
</tr>
<tr>
<td>Wang et. al.</td>
<td>406</td>
<td>~5 yrs</td>
<td>Acute Skin: 8 Vs 3% (SS)</td>
<td>5yr LRFS =91.7% NS</td>
</tr>
<tr>
<td>Chitapanarux et. al</td>
<td>980</td>
<td>~6 yrs</td>
<td>Gr ≥II Skin &amp; Subcut Significantly better</td>
<td>5yr LRFS=96% NS</td>
</tr>
<tr>
<td>Khan et. al.</td>
<td>744</td>
<td>~3 yrs</td>
<td>Implant loss 24%</td>
<td>3 yr LRFS=89.2%</td>
</tr>
</tbody>
</table>

- Clearly established the safety and the efficacy of hypofractionation in PMRT as expected
- Consistently better rates of toxicity
Mastectomy & Hypofractionation

- Meta-analysis; 25 controlled studies (n=3871)

NS different with respect to efficacy/ toxicity postmastectomy

Liu et al. 2020 Radiation Oncology
TROG 07.01 A randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast. → 2yr QoL no difference between Conv vs mod Hypofrac (42.5/16fr)
Reconstructed breast & Hypofractionation

• Ph-II prospective of Stage II/III
• N=69, 2010-2014
• 36.63Gy/11 fr @ 3.33Gy/fr +
• 13.32Gy/4fr e- scar boost (~60Gy BED)
• ~60% recon breast (88% TE, 7% Immediate, 5% augmentation)
• 28% Gr-II skin tox
• No Gr-III or more acute/late tox
• 6 patients implant failure (<10% vs 18-30% in literature)
• Alliance A221505 (RT CHARM) → RCT 42.5Gy/16fr

Table 4  Treatment-related toxicities

<table>
<thead>
<tr>
<th>Grade 1 toxicities</th>
<th>Grade 2 toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute, n</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (55)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (22)</td>
</tr>
<tr>
<td>Pain</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>0</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
</tr>
<tr>
<td>Other*</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

* Bronchospasm (wheezing), shoulder stiffness.

Poppe et al. IJROBP 2020
Moderate Hypofractionation

• Similar efficacy & toxicity across patients populations

- BCS
- MRM
- DCIS
- RNI
- Young & Elderly
- Reconstruction
Intercomparison of different fractionation regimen

- **50Gy/25fr/5wks**
  - UK START-B RCT: LRC Same; 40GY/15fr Less Acute / Late Toxicity

- **40Gy/15fr/3wk** (daily)
  - UK FAST RCT: 10-yr Toxicity & LRC same

- **28.5Gy/5fr/4wk** (once weekly)
  - UK FAST Forward RCT: 5-yr LRC & Tox same

- **26Gy/5fr/1wk** (daily)
  - 5-yr LRC & Tox same

R Sarin, TMC
Randomized Groups

**FAST** (2004-2007; n=915)

- Standard: (n=302)
  - 50Gy/25 fr; 5 weeks
- Experimental Arm 1: (n=308)
  - 30Gy/5 fr; once a week, 5 weeks
  - $\alpha/\beta = 4$ for late toxicity
- Experimental Arm 2: (n=305)
  - 28.5Gy/5 fr; once a week, 5 weeks
  - $\alpha/\beta = 3$ for late toxicity

**FAST FORWARD** (2011-2014; n=4110)

- Pilot testing: (n=30)
  - 30Gy/5 fr; 3 weeks
- Standard: (n=1368)
  - 40Gy/15 fr; 3 weeks
- Experimental Arm 1: (n=1370)
  - 27Gy/5 fr; 1 week, $\alpha/\beta = 3$
  - Assuming No TT compensation
- Experimental Arm 2: (n=1372)
  - 26Gy/5 fr; 1 week, $\alpha/\beta = 3$
  - Assuming TT compensation
- Stratified by risk groups
- 10 or 16 Gy TBB with $e$-
Study Inclusions

FAST

• ≥ 50 years
• Invasive carcinoma,
• BCS only
• margin –ve, pT<3.0 cm,
• pN0
• ER +ve allowed HT

Exclusion
• MRM
• Need for RNI/ TBB
• Neoadjuvant or adjuvant cytotoxic therapy

FAST FORWARD

• ≥ 18 years
• Invasive carcinoma,
• Any Sx, Negative margins
• pT1-3 pN0-1 (1-2)* M0
• ER +ve allowed HT
• Her2-Neu +ve → Trastuzumab

Exclusion
• ≥65yrs, pT1 G1/2, ER+ve/Her2 -ve Microinvasive disease
• Concurrent CT
• Previous Malignancy/ RT to chest
• ≥10 nodes +ve/ SCF nodes/ IMN Nodes
Outcome Measures

**FAST**

- **Primary:**
  - Change in photographic breast appearance (baseline, 2 & 5 years)

- **Secondary:**
  - Local tumor control
  - Radiation-induced changes in the breast and other later responding tissues

**FAST FORWARD**

- **Acute Toxicity pilot**
- **Primary:**
  - 5-yr Local Relapse rates

- **Secondary:**
  - Prevalence of late breast toxicities at 5 years
  - PROM
  - Health Economics study
RT planning

**FAST**

• Supine on a BB
• Reproducibility → orthogonal laser
• CTV: whole breast up to deep fascia, not include underlying muscle and ribcage (ESTRO)
• PTV: 1cm 3D expansion limits: midline & mid-axillary line
• Max Lung: 2cm on CT/ conv simulator.
• Cardiac shielding
• Prescription: ICRU point
• Central plane Max- min dose ≤ 10%
• No Cobalt RT

**FAST FORWARD**

• Supine on BB or Vacuum Bag
• Only 3D CT based planning
• Planning was similar in most ways
• TBB delineation was mandatory and was strongly advised to use clips/ gold markers
• Field based PTV may be used for dosimetric reporting
• Mandatory contouring of I/I Lung, Heart
• Lymphatic arm → Brachial Plexus
• Bitangential RT/ FiF-IMRT
• Tissue heterogeneity correction applied
Set-up Verification & QA requirements

- Daily imaging using EPID (KV/ MV)
- All displacements are corrected at each fraction
- After correction $\rightarrow$ > 5mm difference $\rightarrow$ repeat set-up/ re-sim
- Similar verification for all the fractions of conformal photon boost
- For e- boost $\rightarrow$ Visual verification with skin marking
- QA and credentialing of the contouring, treatment technique assessment, homogeneity, prescription points, IMRT technique
- Assessment of Daily QC protocols, measurement of phantom* readings
- QC Image verification protocol
- Complete verification of the 1st 3 patients treated incl CT dataset quality
- In-vivo dosimetry on the 1st day of test arm and within 1 week of control arm
Study Results

Estimated cumulative incidence of IBTR 5 years was 2.1% (95% CI 1.4 to 3.1) for 40 Gy (expected incidence 2%), 1.7% (1.2 to 2.6) for 27 Gy & 1.4% (0.9 to 2.2) for 26 Gy

Estimated absolute differences in IBTR versus 40 Gy
−0.3% (−1.0 to 0.9) for 27 Gy &
−0.7% (−1.3 to 0.3) for 26 Gy

Brunt et. al. Lancet Oncol 2020
Physician reported NTEs

Brunt et. al. Lancet Oncol 2020

- Similar between Standard and 26Gy arm
- Significantly higher for all the NTEs for the 27Gy arm except Breast/ CW discomfort
- 26Gy arm appears to equally safe as the 40Gy/15 fr

**Table:**

<table>
<thead>
<tr>
<th>Any adverse event in the breast or chest wall*</th>
<th>Number of moderate or marked events/total number of assessments over follow-up</th>
<th>Odds ratio for schedule (95% CI)</th>
<th>p value for comparison with 40 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Gy</td>
<td>651/6121 (10.6%)</td>
<td>1 (ref)</td>
<td>0.0001</td>
</tr>
<tr>
<td>27 Gy</td>
<td>1004/6393 (15.9%)</td>
<td>1.55 (1.32–1.83)</td>
<td>0.0001</td>
</tr>
<tr>
<td>26 Gy</td>
<td>774/6327 (12.2%)</td>
<td>1.12 (0.94–1.34)</td>
<td>0.20</td>
</tr>
<tr>
<td>Breast distortion†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy</td>
<td>224/5724 (4.0%)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>27 Gy</td>
<td>363/5953 (6.1%)</td>
<td>1.51 (1.15–1.97)</td>
<td>0.0028</td>
</tr>
<tr>
<td>26 Gy</td>
<td>299/5945 (5.0%)</td>
<td>1.20 (0.91–1.60)</td>
<td>0.19</td>
</tr>
<tr>
<td>Breast shrinkage†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy</td>
<td>330/5728 (5.8%)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>27 Gy</td>
<td>503/5944 (8.5%)</td>
<td>1.50 (1.20–1.88)</td>
<td>0.0004</td>
</tr>
<tr>
<td>26 Gy</td>
<td>369/5943 (6.2%)</td>
<td>1.05 (0.82–1.33)</td>
<td>0.71</td>
</tr>
<tr>
<td>Breast induration (tumour bed†)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy</td>
<td>185/5713 (3.2%)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>27 Gy</td>
<td>304/5948 (5.1%)</td>
<td>1.56 (1.19–2.05)</td>
<td>0.0013</td>
</tr>
<tr>
<td>26 Gy</td>
<td>236/5937 (4.0%)</td>
<td>1.19 (0.90–1.60)</td>
<td>0.23</td>
</tr>
<tr>
<td>Breast induration (outside tumour bed†)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy</td>
<td>45/5712 (0-8%)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>27 Gy</td>
<td>137/5943 (2-3%)</td>
<td>2.79 (1.74–4.50)</td>
<td>0.0001</td>
</tr>
<tr>
<td>26 Gy</td>
<td>97/5930 (1-6%)</td>
<td>1.90 (1.15–3.14)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

- **Interpretation:** 26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control, and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.
Comparison of START-B with FAST-Forward

Haviland et. al 2013 Lancet Oncol
Lower Event rates & Continued separation

Brunt et. al. Lancet Oncol 2020
Late Toxicity & Hypofractionation

• Cardiac toxicity is dose dependent
• Assuming an $\alpha/\beta$ as low as 1.5
• The regimen is itself safer

<table>
<thead>
<tr>
<th>$\alpha/\beta$</th>
<th>$50\text{Gy}/25\text{fr}$</th>
<th>$40\text{Gy}/15\text{fr}$</th>
<th>$26\text{Gy}/5\text{fr}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>50</td>
<td>45.5</td>
<td>42.64</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>46.7</td>
<td>46.8</td>
</tr>
<tr>
<td>1.5</td>
<td>50</td>
<td>48</td>
<td>49.7</td>
</tr>
</tbody>
</table>

• Cardiac safety $\rightarrow$ Treatment planning & adopting DIBH/ Prone breast RT
• Long term data from UK-START $\rightarrow$ no excess mortality
• Breast Shrinkage START-B: 10 yrs 31.2% Vs 26.2%
• Long-term results will mostly be similar to 5 year results but in the absence of retrospective evidence $\rightarrow$ Not standard
<table>
<thead>
<tr>
<th></th>
<th>START B (n=1110)</th>
<th>FAST (n=613)</th>
<th>FAST-Forward (n=2735)</th>
<th>TMH (n=1721)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (yrs)</strong></td>
<td>61</td>
<td>62</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>709 (63.8%)</td>
<td>496 (80.9%)</td>
<td>1859 (67.9%)</td>
<td>279 (16.2%)</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>&gt;2cm: 288 (25.9%)</td>
<td>117 (19%)</td>
<td>813 (29.7%)</td>
<td>1013 (58.8%)</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>NK</td>
<td>0</td>
<td>55 (2%)</td>
<td>429 (24.9%)</td>
</tr>
<tr>
<td><strong>Gr-I/ II</strong></td>
<td>843 (75.9%)</td>
<td>542 (88.4%)</td>
<td>1968 (71.9%)</td>
<td>283 (16.4%)</td>
</tr>
<tr>
<td><strong>Gr-III</strong></td>
<td>267 (24%)</td>
<td>69 (11.2%)</td>
<td>767 (28%)</td>
<td>1438 (83.5%)</td>
</tr>
<tr>
<td><strong>HR+/Her2-ve</strong></td>
<td>976* (87.9%)</td>
<td>613 (100%)</td>
<td>2227 (81.4%)</td>
<td>782 (45.5%)</td>
</tr>
<tr>
<td><strong>HR+-/Her2+ve</strong></td>
<td>^5-7%</td>
<td>0</td>
<td>196 (7%)</td>
<td>281 (16.3%)</td>
</tr>
<tr>
<td><strong>TNBC</strong></td>
<td>~7% (No HT)</td>
<td>0</td>
<td>224 (8.2%)</td>
<td>301 (17.5%)</td>
</tr>
<tr>
<td>**BCS *</td>
<td>1018 (91.7%)</td>
<td>613 (100%)</td>
<td>2637 (96.4%)</td>
<td>927 (53.8%)</td>
</tr>
<tr>
<td><strong>MRM</strong></td>
<td>92 (8.2%)</td>
<td>0</td>
<td>209 (7.6%)</td>
<td>794 (46.1%)</td>
</tr>
<tr>
<td><strong>pN0</strong></td>
<td>804 (72.4%)</td>
<td>613 (100%)</td>
<td>2234 (81.6%)</td>
<td>866 (50.3%)</td>
</tr>
<tr>
<td><strong>pN+</strong></td>
<td>266 (24%)</td>
<td>0</td>
<td>499 (18.2%)</td>
<td>855 (49.6%)</td>
</tr>
<tr>
<td><strong>Boost</strong></td>
<td>446 (43.8%)</td>
<td>0</td>
<td>669 (24.4%)</td>
<td>883 (95%)</td>
</tr>
<tr>
<td><strong>No Boost</strong></td>
<td>565 (55.5%)</td>
<td>613 (100%)</td>
<td>2058 (75.2%)</td>
<td>44 (5%)</td>
</tr>
<tr>
<td><strong>NACT</strong></td>
<td>0 (491 adj 44.2%)</td>
<td>0</td>
<td>99 (3.6%) adj 694: 25.3%</td>
<td>763 (44.4%)</td>
</tr>
<tr>
<td><strong>No NACT</strong></td>
<td>1110 (100%)</td>
<td>613 (100%)</td>
<td>2634 (96.3%)</td>
<td>958 (55.6%)</td>
</tr>
</tbody>
</table>
Hypofractionation: TMH Experience

- Adopted as a policy since 2014 for all patients receiving RT to breast/chestwall +/- SCF
- Unpublished data Courtesy Dr. Ashwini Budrukkar & Dr. Niranjan Dash
- Conventional Vs Hypofractionated RT → no significant differences in LFS, LRFS and OS
  Fewer Hospitalizations from RT induced Gr-III toxicity increased throughput/quality Rx

3 year LFS for BCT (n=268) 97 & 97.6%; OS: 97 & 98.1%

5 year LFS for MRM (n=478) 85.8 & 86.2%; OS: 78.2 & 71.9%
Pandemic Blues: Opportunity in adversity

- 50Gy/25fr/5wks
  - UK START - B RCT
    - LRC Same;
    - 40GY/15fr Less Acute / Late Toxicity

- 40Gy/15fr/3wk (daily)
  - UK FAST RCT
    - 10-yr Toxicity & LRC same
  - UK START-B RCT
    - LRC Same;
    - 40GY/15fr Less Acute / Late Toxicity

- 26Gy/5fr/1wk (daily)
  - UK FAST Forward RCT
    - 5-yr LRC & Tox same

- 28.5Gy/5fr/4wk (once weekly)

- 33Gy/5fr Tumour Bed
- 48Gy/15fr tumour bed
- 32Gy/5fr tumour bed

*Radio-biologically equivalent SIB dose used in TMH for cases requiring boost*
TMH Experience

- >1100 women (median age 49yrs; ~40% postmenopausal)
  - ER/PR +ve/ Her2 -ve ~50%
  - Triple +ve ~15%
  - Her2 enriched ~10%
  - TNBC ~20%
- ~50% recd NACT; 68% recd Adj CT; >95% recd CT
- Nearly all Her2 +ve patients recd. at least conc Trastuzumab
- ~50% MRM; Oncoplasty in 8% cases,
- 70% FF/ 30% F
- RNI → ~75%; TBB among pts with BCS: ~85%
- 60-70% → with Fif-IMRT, DIBH <5%, Inv IMRT ~25%
- TBB → SIB ; PMRT → Bolus all fr, no scar boost

Unpublished work from the TMC Mumbai Unconventional Fractionation Registry
Acute Toxicity

• Skin
  • Gr 0  15%
  • Gr 1  80%
  • Gr 2  4%
  • Gr 3  0.1%

• Odynophagia
  • Gr 0  60%
  • Gr 1  33%
  • Gr 2  5%
  • Gr 3  0.1%

• No Brachial Plexopathy
• No excess acute toxicity
• Toxicity for FF peaks by 2\textsuperscript{nd} -3\textsuperscript{rd} week

Unpublished work from the TMC Mumbai Unconventional Fractionation Registry
Pyramid of Priority

- Survival Benefit
- Freedom from Progression
- Reduction in Toxicity
- Improved QoL
- Logistics & Compliance
Challenges in LMICs (India)

- Large population and country with Cultural/Regional Diversity
- Heterogenous practices across oncologists (Medical/ Surgical& Radiation)
- Poor access to specialized healthcare and oncological training (Medical/ Paramedical)
- Poor penetration of breast conservation → Lack of RT services/ Additional expenses/ Lack of awareness
- Healthcare → Low priority reflected in budget allocation → Essentially Self paid
- Govt aided centres → Lack of state-of-the-art facilities
Breast Conservation Gap

- Eligible patients
- Refuse conservation
  - Non-availability if RT centre
  - Avoid RT
  - RT Unaffordable
  - Fear of recurrence

Hassan Ali et al. 2019 IJC

<table>
<thead>
<tr>
<th>Region</th>
<th>Population of each region (%)</th>
<th>Area of each region (%)</th>
<th>Number of machines available in each region (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simulator</td>
</tr>
<tr>
<td>Central</td>
<td>8.10</td>
<td>13.6</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>East</td>
<td>22.33</td>
<td>12.8</td>
<td>4 (10)</td>
</tr>
<tr>
<td>North</td>
<td>24.82</td>
<td>20.5</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>North-East</td>
<td>3.57</td>
<td>7.8</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>South</td>
<td>21.09</td>
<td>19.4</td>
<td>12 (30)</td>
</tr>
<tr>
<td>West</td>
<td>20.09</td>
<td>26.0</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>


Munshi et al. 2019 IJC
Mitigation Strategies

- Increase the RO to Patient Ratio
- Improve the patient to machine ratio
- Reduce the direct + indirect cost of RT
- Improve Awareness of breast conservation safety
Cost of RT

• Cost of healthcare → rising due to rapid technological advancement
• Misconception → Costs of RT driven by cost of equipment
• Labour-intensive planning & delivery → **Wages drive costs**
• Misconception for complex plans → **RT planning** will become more significant **driver of cost than delivery**
• Planning 1 time process << Time for delivery remains high and adds cost of QA
• Cost of RT essentially driven by **total treatment time**
• 25% case load breast ca → Major impact
Impact of Hypofractionation on Cost

• Physician
  • US/Europe Remuneration structure → Fixed fee / Fee-for-service
  • ROs in 77% countries → 10 to ~40% reduction in revenue due to adoption of hypofractionation

• Loss of revenue from Medicare reimbursement
  • OZ → ~$2000/ pt, USA → $4300

• Indirect cost:
  • Transportation (average number of miles/day, the average reimbursement rate per mile)
  • Parking costs,
  • Loss of hourly wages by hours spent during treatment & displacement

Marta et al. Clinical Oncology 2020
Cost Effectiveness of 5 fr for LMIC?

- Boscoe et al. → >75 km for treatment are ~1.4 times more likely to choose mastectomy
- Geographic & logistic barriers → precluded from BCS
- Markov Chain modelling using data from SKMCH Pakistan (APBI eligible)
- Simulate the real-life implications of a major change in treatment strategy

- External validity of the model → 15-yr OS results from EBCTCG/Oxford meta-analyses

\[\begin{align*}
30000 \text{ fr} & \quad N=2098 \\
1469 & \quad \text{BCS} \\
629 & \quad \text{MRM} \\
+769 & \quad \text{BCS} \\
+329 & \quad \text{MRM}
\end{align*}\]
Impact on OS (Society)

- Absolute gain in OS ~4% and DFS ~7% at 15 years
- OS after BCS improved from 54% to 62%
- Improvement in OS at population level → Limited access
- Future studies should evaluate this for common malignancies

Khan et al. IJROBP 2017
Benefits of Ultra-hypofractionated RT

**Patient**
- Reduced hospital visits → Reduce infection risk
- Reduced expenditure on stay and travel to the hospital
- Lower toxicity → Lower expenses
- Improved access to RT without compromising outcomes → Increased acceptance to BCS
- Reduced treatment interruptions
- Improved QOL → Priceless

**Hospital**
- Reduced hospital visits → Reduce infection risk & PPE use
- Improved access to care: number of patients that can be treated in limited hours & resources
- Reduced working hours of the machine & its running cost (Electricity/ Water/ HR)
- Improvement in quality of the treatment → lower rates of toxicities & higher patient satisfaction
- Early Breakeven
Summary

- Pre-requisite for Hypofractionated RT → Strict QA → Uniform treatment policies & standard planning & treatment techniques
- FAST- Forward RT arm 26Gy/5 fr → safe and effective as 40Gy/15 fr
- Planned with techniques routinely used in most centres (Fif-IMRT/3DCRT)
- Like START studies → Like FAST Forward studies
- TMC Mumbai experience of UHF-RT → Unique aspect SIB further reducing the TT
- Early results suggest: ISO-EFFECTIVE, ISO-TOXIC, & COST-EFFECTIVE
- Beyond pandemic currently: Highly select population
- FAST → Favorable patient population (Low risk)
- FAST FORWARD → EBC, Node negative, No NACT, Favorable biology
- In future → 5 or fewer fractions may be the way forward!
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• Breast DMG Members → Team effort

• Residents of Breast Unit

• Ms. Ashwini Khandavalli (Research Associate)

• Patients