Role and Techniques of Accelerated Partial Breast Irradiation

Tabassum Wadasadawala
Associate Professor of Radiation Oncology
Tata Memorial Centre
Mumbai, INDIA
twadasadawala@actrec.gov.in
Changing paradigms of Radiotherapy in EBC

- **Radical mastectomy** (Halsteadian paradigm)

- **Breast Conserving Therapy** (Whole Breast RT compensated for less extensive surgery)

- **Accelerated Partial Breast Irradiation** (Irradiation of the tumour bed with 1-2 cm margins using a regime of accelerated RT)

- **Omission of radiotherapy** (No adjuvant RT after BCS for elderly women with low risk of local recurrence)
Flow of presentation

• Definition
• Rationale
• Case selection
• Methods
• Clinical outcome
• Future directions
Definition

• Acceleration: 1 day to 1 week (single # and up to 10 fractions)

• Partial breast: Target volume is the tumor bed alone with margins
Why APBI?

15-30% drop out rate after BCT

- Lack of commitment to usual 3-4 weeks course of adjuvant RT
- Logistics (ambulatory status, social support, temporary loss of employment)
- Availability of expertise & facility
- **Prolonged waiting time**
- Cost saving
- **Patient age** (Ballard et al: *JNCI* 88:716-725, 1996)

Women opt for mastectomy though eligible for BCS or never receive RT after BCS even in the west

Lazovich DA, *JAMA*, 1991

Advances in radiotherapy
- **Reduced toxicities** markedly secondary to treatment
- Made **hypofractionated** regimens practical for delivery
Strong clinico-pathological rationale

- 69-90% recurrences occur at the immediate vicinity of the primary tumor
- Incidence of elsewhere failures 0.9-3.5%
- Several studies on mastectomy specimens suggest residual disease may extend **1 to 2.5 cm** margin around excision cavity

Skowronek J, JCB 2012, Faverly DR Cancer 2001
### Table 4: Clinical outcome of PBI with suboptimal patient selection or techniques

<table>
<thead>
<tr>
<th>Institution</th>
<th>APBI technique</th>
<th>Number of patients [median follow up (years)]</th>
<th>Criticism of selection or technique</th>
<th>Breast recurrence</th>
<th>Cosmesis and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie Hospital RCT&lt;sup&gt;31&lt;/sup&gt;</td>
<td>External electrons 40Gy/8#/10 days</td>
<td>353 [8]</td>
<td>Lobular cancer -15% Margins unknown or +ve in 19%. Inadequate target coverage and fractionation</td>
<td>25% (8 year actuarial). Excess recurrences in lobular cancer</td>
<td>Marked telangiectasia in 33% and marked fibrosis in 14%. Cosmesis NA</td>
</tr>
<tr>
<td>Guys Hospital&lt;sup&gt;45&lt;/sup&gt;</td>
<td>LDR 55 Gy over 5 days</td>
<td>27 [6]</td>
<td>Positive margins in 55% and EIC in 40% cases</td>
<td>37% (crude)</td>
<td>Cosmesis good to excellent in 83%. Telangiectasia in 4%</td>
</tr>
<tr>
<td>Uzaoki Hospital, Budapest&lt;sup&gt;40&lt;/sup&gt;</td>
<td>LDR 50 Gy in 10–22 hours</td>
<td>70 [12]</td>
<td>Cut margins not known; lobular component in 10%. Single plane implant with unacceptable dose rate</td>
<td>24% (crude) (7% outside tumour bed)</td>
<td>Poor cosmesis in 50%. Grade 3 or 4 radiation sequelae in 59%</td>
</tr>
<tr>
<td>London Regional Cancer Centre, Ontario&lt;sup&gt;39&lt;/sup&gt;</td>
<td></td>
<td>39 [7.5]</td>
<td>Average implant volume only 30 cc. Single plane in 11. Cut margins &lt;2 mm in 12 and EIC in 3 patients</td>
<td>16% (10% outside tumor bed)</td>
<td>Cosmesis—median score 90. Fat necrosis in 13%</td>
</tr>
<tr>
<td>Tufts New England&lt;sup&gt;43&lt;/sup&gt;</td>
<td></td>
<td>33 [5]</td>
<td>HDR technique optimal but 55% had EIC</td>
<td>6%</td>
<td>Cosmesis good to excellent in 87%. Fat necrosis in 24%</td>
</tr>
<tr>
<td>University of Kansas&lt;sup&gt;47&lt;/sup&gt;</td>
<td>LDR 20–25Gy</td>
<td>25 [4]</td>
<td>Inadequate LDR dose</td>
<td>0</td>
<td>Cosmesis good to excellent in 100%; no late complication</td>
</tr>
</tbody>
</table>

<sup>4</sup>Not conforming to the ABS guideline.<sup>4</sup> #, Number of fractions.
Partial-breast treatment for early breast cancer: emergence of a new paradigm

Rajiv Sarin

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of patients</th>
<th>Median follow up (years)</th>
<th>5-year actuarial ipsilateral breast recurrence rates</th>
<th>Contralateral breast cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ochsner Clinic</td>
<td>160</td>
<td>7</td>
<td>2.5% (crude) 1.2% (crude)</td>
<td>NA</td>
</tr>
<tr>
<td>NIO, Budapest, phase I/II</td>
<td>45</td>
<td>6.7</td>
<td>4.4% 4.4%</td>
<td>0</td>
</tr>
<tr>
<td>William Beaumont</td>
<td>199</td>
<td>5.4</td>
<td>1.2% 0.6%</td>
<td>1%</td>
</tr>
<tr>
<td>Virginia Commonwealth University</td>
<td>59</td>
<td>4.2</td>
<td>5.1% 2.6%</td>
<td>0</td>
</tr>
<tr>
<td>Orebro</td>
<td>49</td>
<td>4.6</td>
<td>4% (crude) 2% (crude)</td>
<td>NA</td>
</tr>
<tr>
<td>RTOG 9517 phase II</td>
<td>99</td>
<td>3.7</td>
<td>3% (4 year) NA</td>
<td>3%</td>
</tr>
<tr>
<td>All mature series</td>
<td>611</td>
<td>4–7</td>
<td>1–5% 0.6–4.4%</td>
<td>0–3%</td>
</tr>
</tbody>
</table>

*Patient selection and treatment quality assurance generally conforming to the American Brachytherapy Society (ABS) guidelines.*

None of these series have reported an unacceptable incidence of adverse cosmetic outcome or symptomatic late sequelae.

*Present or earlier reports from the Ochsner clinic, William Beaumont and the Budapest phase I/II studies show APBI results comparable to matched controls treated with whole-breast irradiation.*
## Older recommendations

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>ABS</th>
<th>ASBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>&gt;= 45 years</td>
<td>&gt;= 50 years</td>
</tr>
<tr>
<td>TUMOR SIZE</td>
<td>Up to 3 cm</td>
<td>Up to 2 cm</td>
</tr>
<tr>
<td>NODE</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HISTOLOGY</td>
<td>IDC</td>
<td>IDC OR DCIS</td>
</tr>
<tr>
<td>MARGINS</td>
<td>Microscopically negative</td>
<td>2 mm</td>
</tr>
</tbody>
</table>
### ASTRO GUIDELINES 2009

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60 years</td>
<td>50-59 years</td>
<td>&lt; 50 years</td>
</tr>
<tr>
<td>BRCA mutation</td>
<td>Not present</td>
<td>-</td>
<td>Present</td>
</tr>
<tr>
<td>Tsize</td>
<td>≤ 2 cm</td>
<td>2.1-3.0 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>Tstage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentricity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or favorable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤ 3 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>EIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nstage</td>
<td>pN₀</td>
<td>-</td>
<td>pN₁-pN₃</td>
</tr>
<tr>
<td>Nsurgery</td>
<td>SLN Bx or ALND</td>
<td>-</td>
<td>None performed</td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
<td>-</td>
<td>If used</td>
</tr>
</tbody>
</table>

### UPDATED ASTRO GUIDELINES (2016)

- Suitable age group ≥ 50 yrs
- Patients who are aged 40-49 yrs and who meet all other elements of suitability are considered cautionary
- Patients with low-risk DCIS, as per RTOG 9804 criteria, were categorized in the “suitable” group
- Patients with age less than 40 years or those who are 40 – 49 years without meeting other elements of suitable to be retained in the “unsuitable” group

*Smith et al J. Radiation oncology 2009*
## GEC-ESTRO GUIDELINES 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A/low risk- Good candidates</th>
<th>B/ intermediate risk- possible candidates</th>
<th>C/high risk- contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt;50 years</td>
<td>&gt;40–50 years</td>
<td>≤40 years</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>IDC, mucinous, tubular, medullary, and colloid cc.</td>
<td>ILC, IDC, mucinous, tubular, medullary, and colloid cc.</td>
<td></td>
</tr>
<tr>
<td><strong>ILC</strong></td>
<td>Not allowed</td>
<td>Allowed</td>
<td></td>
</tr>
<tr>
<td><strong>Associated LCIS</strong></td>
<td>Allowed</td>
<td>Allowed</td>
<td></td>
</tr>
<tr>
<td><strong>DCIS</strong></td>
<td>Not allowed</td>
<td>Allowed</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>Any</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>pT1–2 (≤30 mm)</td>
<td>pT1–2 (≤30 mm)</td>
<td>pT2 (&gt;30 mm), pT3, pT4</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>Negative (≥2 mm)</td>
<td>Negative, but close (&lt;2)</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Multi-centricity</strong></td>
<td>Uni-centric</td>
<td>Uni-centric</td>
<td>Multi-centric</td>
</tr>
<tr>
<td><strong>Multi-focality</strong></td>
<td>Uni-focal</td>
<td>Multi (&lt;2 cm from index)</td>
<td>Multi (&lt;2 cm from index)</td>
</tr>
<tr>
<td><strong>EIC</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>LVI</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>ER/PR status</strong></td>
<td>Any</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td><strong>Nodes</strong></td>
<td>pN0</td>
<td>pN1mi or pN1a</td>
<td>4 or more</td>
</tr>
<tr>
<td><strong>NACT</strong></td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>If used</td>
</tr>
</tbody>
</table>

*Polgar et al Radiation Oncology 2010*
Variable recommendations

- Hormone receptor status (ASTRO)
- Histology (?all lobulars)
- Node positivity (NSABP, unsuitable, higher risk)
- Lymphatic invasion (ASTRO, ESTRO, ?extent)
- Width of negative margins (minimum 2 mm)
- Tumor size
- Age (NSABP >18 years)

- Disregards:
  - Her2neu status
  - Grade
Ten year outcome of patients treated with Accelerated Partial Breast Irradiation (APBI) using interstitial brachytherapy at Tata Memorial Hospital: Limited role of ASTRO consensus statement guidelines in clinical application

- $N=102$
- 1998-2005
- Median age 57 years
- Median pTsize 2cm
- Dose 34 Gy in 10 fractions
- Intraop 66 and postop 36
- 2 dimensional planning
- **Median FU 125 months**

Wadasadawala et al, Proceedings of Breast Oncology Conference, Kochi, 2014
<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>N</th>
<th>Technique</th>
<th>Median FU (months)</th>
<th>Tsize (Median)</th>
<th>Histology</th>
<th>ASTRO CS group (Percent/LR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferraro DJ, 2012</td>
<td>202</td>
<td>IBT</td>
<td>64</td>
<td>1.0 cm</td>
<td>IDC/DCIS/ILC</td>
<td>Suitable:28.7% Cautionary:51.5% Unsuitable:19.8%</td>
<td>NS at 5 years, ASTRO CS failed to predict LR, LRR or DFS</td>
</tr>
<tr>
<td>Wilkinson JB*, 2012</td>
<td>1813</td>
<td>All except IORT</td>
<td>60.6</td>
<td>1.0 cm</td>
<td>IDC/DCIS</td>
<td>Suitable:36.5% Cautionary:46.9% Unsuitable:16.7%</td>
<td>NS at 5 years</td>
</tr>
<tr>
<td>Vicini FA 2011</td>
<td>199</td>
<td>IBT</td>
<td>133</td>
<td>NR</td>
<td>IDC</td>
<td>Suitable:47.7% Cautionary:31.7% Unsuitable:20.6%</td>
<td>NS at 10 years, ASTRO CS did not predict LR</td>
</tr>
<tr>
<td>MacHaffie DR, 2011</td>
<td>136</td>
<td>MammoSite</td>
<td>60</td>
<td>1.0 cm</td>
<td>IDC/DCIS</td>
<td>Suitable:24.6% Cautionary:42.2% Unsuitable:33.2%</td>
<td>NS at 5 years</td>
</tr>
<tr>
<td>TMH, 2014</td>
<td>112</td>
<td>IBT</td>
<td>91</td>
<td>2.0 cm</td>
<td>IDC</td>
<td>Suitable:27.1% Cautionary:62.5% Unsuitable:29.5%</td>
<td>10 year LR not as per ASTRO CS group</td>
</tr>
</tbody>
</table>

ASTRO-CS: Does not predict risk of LR
Recent cohort: impact of molecular sub-type

- N=157
- Median FU 35 months
- 2012-2016
- Median age 60 years
- Median tumor size 2.1 cm
- Molecular subtype:
  - Luminal A 34.4%
  - Luminal B 36.3%
  - TNBC 18.5%
  - Her2 10.8% (only one third patients received 12 weeks of trastuzumab)

Wadasadawala et al, Journal Of Contemporary Brachytherapy, 2018
A range of External beam & Brachytherapy techniques for APBI

Interstitial Implant

MammoSite

TARGET

Intra op electrons [ELIOT]

3DCRT / IMRT
Classification of techniques

• **Brachytherapy:**
  – Multi-catheter Interstitial (MIB)
  – Intraluminal (Mammosite, SAVI, Contura, Clearpath)
  – Permanent breast seed implant (PBSI)
  – Electronic breast brachytherapy (EBB)
  – Non-invasive image guided breast brachytherapy (NIBB)

• **Intra-operative:**
  – ELIOT
  – TARGIT

• **External beam:**
  – Photons
  – Electrons
  – Protons
Interstitial brachytherapy: most *mature and safe* technique

Median follow up: **14.5** years in WBI arm and **10.7** years in APBI arm

N=199 matches

Vicini et al  Radioth Oncol 2011
Local recurrence (primary endpoint)
5.9% vs. 5.1% at median follow up of 10.2 years
5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial

<table>
<thead>
<tr>
<th>5 year outcome</th>
<th>APBI</th>
<th>WBI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>1.44%</td>
<td>0.92%</td>
<td>0.42</td>
</tr>
<tr>
<td>DFS</td>
<td>95.0%</td>
<td>94.5%</td>
<td>0.79</td>
</tr>
<tr>
<td>OS</td>
<td>95.5%</td>
<td>97.3%</td>
<td>0.11</td>
</tr>
<tr>
<td>Late grade 2-3 skin</td>
<td>3.2%</td>
<td>5.7%</td>
<td>0.08</td>
</tr>
<tr>
<td>Late grade 2-3 subcutaneous</td>
<td>7.6%</td>
<td>6.3%</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Figure 2: Ipsilateral breast tumour recurrence
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

Strnad Lancet 2015 & 2017
Intracavitary techniques: Tremendous popularity with Mammosite

• Approval of MammoSite® (Hologic, Inc., Beford, MA) by the US FDA in May 2002

• The new device was adopted aggressively in non trial setting: better tolerated, reproducible and easy to implant

• Balloon is inflated with saline solution mixed with a small amount of contrast material (35 – 70 ml)

• Balloon is inflated to a size that would completely fill the lumpectomy cavity and ensures conformance of the tissue to the balloon.

• An Ir-192 radioactive source, connected to HDR remote after-loader, is inserted through the catheter into the balloon to deliver the prescription radiation dose

• Dose prescription at 1 cm from the balloon surface in the plane transverse to the balloon’s axis
MammoSite Brachytherapy

**INTRA-OPERATIVE**

- Multilumen, silicone catheter
- Radiation source port pathway
- Variable 4 to 5 cm balloon

**POST-OPERATIVE**

- Inserted obturator to prevent bending or coiling of the catheter shaft
- Needleless injection site
Implant quality:
1. Balloon conformance to the lumpectomy cavity
2. Distance from the surface of the balloon to the skin surface
3. Symmetry of the balloon in relationship to the central catheter.

Treatment planning:
1. Diameter of the inflated balloon
2. PTV
3. Dose distribution

Adequate conformance is considered to have been achieved when less than 10% of the PTV is composed of fluid or air.
Pros and Cons: technical

• Advantages:
  – Relatively easier application
  – Less expertise required
  – Good to excellent cosmesis (In ASBS registry trial, RO, 2009)
  – Near symmetric geometric distribution

• Disadvantages:
  – Poor balloon conformance
  – Balloon rupture
  – Inadequate skin spacing—may not be suitable in patients with small breast or for tumours located in the upper-inner quadrant because of the requirement for skin-to-cavity distances.
  – Interposition of air or liquids
  – Limited sizes of balloons
  – Not suitable for irregular cavities
Clinical outcome: a word of caution

- IBB has a single large hotspot at the surface of the balloon applicator unlike MIB.
- Increased risk of infection (9% vs. 4.9%).
- Increased late complications (mass 26.7% vs. 7.3% or telangectasia 24% vs. 4%).
- Adverse impact on cosmesis.
- Increased recurrence and mastectomy rates.

Smith et al, JAMA 2012

3.95% vs. 2.18%
Multi-lumen balloon devices

- Next generation balloon applicators to improve upon fixed geometry and inflexible dosimetry of single lumen ones
- 2 such devices:
  - A. Contura: has one central lumen with 4 peripheral arched lumens
  - B. MammoSite Multi-Lumen: has one central lumen with 3 peripheral lumens
Multi-lumen Cage like device

STRUT ADJUSTED VOLUME IMPLANT (SAVI) : Central strut and 6, 8 or 10 peripherally positioned struts/lumen
Air inside cavity

Fluid inside cavity

Planning target volume for evaluation (PTV_EVAL)
- equals - planning target volume (PTV)
- equals - clinical target volume (CTV)

5mm inside skin

Contoured ‘device surface’ – defined by contour connecting struts

1 cm

Excludes pectoralis muscles and chest wall

Air/fluid outside ‘device surface’ – PTV will be beyond isodose coverage – must be contoured and the percent of PTV
Seed Brachytherapy: Palladium 103

- Patient undergoes a pre-planning CT scan followed by surface marking of the representative points for insertion of seeds
- Size of PTV restricted to 125 cc (median 61 cc)
- Average 75 seeds needed
- Seed activity: 2.5 U/seed (range 2.3-2.7 U)
- Prescribed minimum peripheral dose is 90 Gy.
- Homogeneity criteria: V150 of 60-65% and V200 <25%.
- Planned skin dose is limited to <90% of prescription over 1 cm².
- Seed insertion is done under ultrasound guidance and general anesthesia using a template
- Discharged next day and advised not to sleep on the same side as well as use Xenoprene shield under the bra for 3 weeks
- Repeat CT at 4 weeks, 6 months and annually
- Main late toxicity is induration (23-40%) and telangiectasia (22-24%)

Crook et al, Brachytherapy 2019
Pignol et al, IJROBP 2015
Electronic Brachytherapy

- Utilises electronic generation of kV X-rays instead of a radioactive source
- Example: Axxent X-Ray Source (Xoft) approved by FDA in 2009
- An electronic microminiature X-ray tube: 50 kV X rays are used in breast BT, translating to average energy of 28 keV with radial dose function
- It is a disposable source intended to be used for maximum 10 fractions
- Dosimetric analysis by Dickler et al 2010: Lung and heart doses lower due to rapid dose fall-off. V200 and V300 are higher, approaching constraints for fat necrosis
- ABS guidelines do not recommend this as a modality for APBI (Tom et al, Brachytherapy 2018)
NIBB: Accuboom

- Completely non invasive technique
- Limited clinical experience
- Three-step process:
  - Breast immobilization (compression between two MMG paddles)
  - Imaged-guided target delineation (30kVp X rays)
  - Treatment with collimated photon emission using 192Ir HDR brachytherapy (from two orthogonal angles)
### Comparison of APBI brachytherapy techniques

<table>
<thead>
<tr>
<th>APBI technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **IMB**                             | • Mature clinical experience  
• Flexible to conform to complex tumor bed geometry                           | • Invasive—catheters in place for 1 wk  
• Multiple percutaneous catheters not acceptable to some patients  
• Placement of catheters is technically demanding and requires specialized expertise |
| **Single-lumen IBB**                | • Simple insertion technique  
• Simple spherical dosimetric geometry  
• Large clinical experience, just beginning to mature | • Invasive—catheter in place for 1 wk  
• Fixed dosimetric geometry, not flexibility to shape dose especially when skin or chest wall close to balloon |
| **Multilumen IBB**                  | • Simple insertion technique  
• Simple spherical dosimetric geometry  
• Improved flexibility to shape dose but limited | • Invasive—catheter in place for 1 wk  
• Limited clinical experience |
| **Multilumen cage-like intracavitary** | • Simple insertion technique  
• Flexibility to shape dose                                                                 | • Invasive—catheter in place for 1 wk  
• Multiple hotspots at catheter-tissue interface (unclear clinical significance)  
• Limited clinical experience |
| **EBB**                             | • Simple insertion technique  
• Simple spherical dosimetric geometry  
• No vault shielding required  
• Reduced heart, lung and nontarget breast dose | • Invasive—catheter in place for 1 wk  
• Fixed dosimetric geometry  
• Increased surface dose (unclear clinical significance)  
• Higher RBE (unclear clinical significance)  
• Limited clinical experience |
| **PBSI**                            | • Single 1-day procedure  
• Increased convenience  
• Increased access in remote areas  
• Flexible to conform to complex tumor bed geometry  
• LDR may improve therapeutic ratio | • Invasive—single procedure without indwelling catheters  
• Permanent seeds may not be acceptable to some patients  
• Not appropriate for large CTV volumes  
• Not appropriate for large seroma cavities  
• Limited clinical experience |
| **NIBB**                            | • Noninvasive  
• Breast immobilization and image guidance  
• Sparing of nontarget breast tissue compared with external beam techniques | • Skin dose may be increased if there is significant skin overlap between orthogonal axes (exclusion criteria)  
• Limited clinical experience |

**APBI** = accelerated partial breast irradiation; **IMB** = interstitial multicatheter brachytherapy; **IBB** = intracavitary balloon brachytherapy; **EBB** = electronic balloon brachytherapy; **PBSI** = permanent breast seed implant; **NIBB** = noninvasive image-guided breast brachytherapy; **LDR** = low-dose rate; **RBE** = radiobiologic effect; **CTV** = clinical tumor volume.
Intra-operative radiotherapy

- Intra-operative radiation therapy (IORT) refers to the delivery of a single fractional dose of irradiation directly to the tumor bed during surgery.
- Post surgery tissue has rich vascularization, with aerobic metabolism, more sensitive to the action of the radiation (oxygen effect).
- Accurate dose delivery: by permitting delivery of the radiation dose directly to the surgical margins, NO RISK OF GEOGRAPHICAL MISS
- Decreasing healthcare cost because it is one fraction as opposed to 25 fractions.
- Disadvantages: Final pathology not available, extra shielding required, resource intense, expensive technology, inadequate coverage
- Available in two forms: Electron based (ELIOT- Mobetron, NOVAC & LIAC) and X-ray based (TARGIT-Intarbeam)
Dosimetric concerns

- Treatment time ranges from 20-40 mins
- The pyramid shaped lumpectomy is made spherical by wrapping the breast tissue around the applicator
- Movement of the X-ray source by a mm in TARGIT or bevel angle in ELIOT can change the dosimetry significantly

Vaidya et al, EJSO 2002
Veronesi et al, EJC 2001
Randomised, 2000-2012, 3451 patients

Figure 1: Kaplan-Meier analysis of breast cancer deaths and non-breast-cancer deaths
2000-2007, 1305 pts aged 48–75 years
Medium FU 5.8 years
Max diameter 2 · 5 cm
1 dose 21Gy during surgery vs WBI
35 pts in IORT and 4 in ERT had IBTR (p<0.0001)
5-year event rate 4.4% vs 0.4% (HR 9.3)
5-year OS 96.8% vs 96.9%
Fewer skin SE with IORT (p=0.0002)
Pulmonary fibrosis- 4 in IORT and 38 in ERT (p<0.0001).
• 4 studies 5415 patients (2 RCTs and 2 non-RCTs)
• IBTR significantly higher IORT vs WBI (RR 2.83)
• Overall mortality did not differ significantly
• Prudent selection of suitable patients with low risk of LR necessary
Median FU 36 months, 2135 patients
Grade 1/2 toxicities increased with APBI (p 0.001) 35% v 17%
Grade 3 toxicity 4.5% vs. 1% (p <0.001)
Telangiectasia, breast induration, breast pain increased
Fat necrosis significantly more likely after APBI (3% v 0.9%; P .01).
Inferior cosemsis

**Conclusion** - Cautioned against the use of 3D-CRT APBI due to increased toxicity
Increase in dose conformity with more normal tissue sparing.

>40 yrs, ≤25 mm

30 Gy to tumour bed in five non consecutive #

520 patients 2004-2013, LR and survival as endpoint

Median follow-up of 5.0 years

IBTR rate was 1.5% in both

5-year OS 96.6% for WBI vs 99.4% for APBI

Better results considering acute (66.5% vs 19.9%, p = 0.0001), late (11.2% vs 4.5%, p = 0.004), and cosmetic outcome (89.6% vs 95.1%, p = 0.045) with APBI
Primary: Ipsilateral Breast Tumor Recurrence (IBTR), both invasive and DCIS, as a first recurrence

Equivalence design with 50% increase in hazard ratio chosen as acceptable margin
Definitive analysis was planned to occur after 175 IBTRs or at 10 years of median FU

No difference in grade 3 and above toxicity 10.5% vs 7.4% or second cancers
IBTR by PBI Method

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th># of Pts</th>
<th># of Events</th>
<th>Hazard Ratio (HR)</th>
<th>HR 95% Confidential Interval</th>
<th>10-yr Cum Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBI</td>
<td>2,011</td>
<td>67</td>
<td>REF</td>
<td></td>
<td>3.8%</td>
</tr>
<tr>
<td>PBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-catheter brachytherapy</td>
<td>130</td>
<td>9</td>
<td>2.21</td>
<td>1.10 – 4.46</td>
<td>7.7%</td>
</tr>
<tr>
<td>Single-entry brachytherapy device</td>
<td>358</td>
<td>24</td>
<td>2.15</td>
<td>1.34 – 3.44</td>
<td>7.8%</td>
</tr>
<tr>
<td>3DCRT (external beam)</td>
<td>1,535</td>
<td>55</td>
<td>1.04</td>
<td>0.73 – 1.49</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

This analysis used a per-protocol population, which excluded those who did not receive their randomly assigned treatment.
Take home message

• PBI did not meet the criteria for equivalence to WBI in controlling IBTR on the upper limit of the HR CI (1.58 instead of 1.5)
• The trial results favour the use of PBI for early stage breast cancer as the difference in the absolute rates of local recurrence and any first recurrence are clinically acceptable
• It may be worthwhile not offer PBI to younger women and those with node positive disease till further results on sub-group analysis are available
• The decision on the appropriate PBI technique cannot be made in view of imbalance of numbers across the three techniques
• We already have the safety data for interstitial brachytherapy from another recently published trial of GEC-ESTRO (Lancet 2015)
GEC ESTRO breast cancer recommendations

Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery

Radiotherapy and Oncology xxx (2015) xxx–xxx

Original article

Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery

Vratislav Strnad a,⇑, Jean-Michel Hannoun-Levi b, Jose-Luis Guinot c, Kristina Lössl d, Daniela Kauer-Dorner e, Alexandra Resch e, György Kovács f, Tibor Major g, Erik Van Limbergen h, On behalf of Working Group Breast Cancer of GEC-ESTRO
<table>
<thead>
<tr>
<th></th>
<th>MIB (32 Gy in 8 fractions BID) (Strnad, RO 2018)</th>
<th>IMRT (30 Gy in 6 fractions over 2 wks) (Livi, EJC 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV coverage</td>
<td>V100 $\geq$90%</td>
<td>V100% $\geq$95%</td>
</tr>
<tr>
<td>Maximal dose</td>
<td>V150 $&lt; 65$ cm$^3$ (PTV)</td>
<td>$&lt; 105%$</td>
</tr>
<tr>
<td></td>
<td>V200 $&lt; 15$ cm$^3$ (PTV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COIN $0.65$ (PTV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$V_{PD} 300$ cm$^3$ (Implant)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNR $0.35$ (Implant)</td>
<td></td>
</tr>
<tr>
<td>Minimal dose</td>
<td>NA</td>
<td>$&gt; 93%$ (28 Gy)</td>
</tr>
<tr>
<td>Uninvolved breast</td>
<td>V90% $&lt; 10%$</td>
<td>V15Gy(V50%) $&lt; 50%$</td>
</tr>
<tr>
<td></td>
<td>V50% $&lt; 50%$</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral lung</td>
<td>MLD $&lt; 8%$</td>
<td>V10Gy $&lt; 20%$</td>
</tr>
<tr>
<td></td>
<td>D0.1cm$^3$ $&lt; 60%$</td>
<td></td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>NA</td>
<td>V5Gy $&lt; 10%$</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>NA</td>
<td>Dmax $&lt; 1$ Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>MHD $&lt; 8%$</td>
<td>V3Gy $&lt; 10%$</td>
</tr>
<tr>
<td></td>
<td>D0.1cm$^3$ $&lt; 50%$</td>
<td></td>
</tr>
<tr>
<td>Skin (5 mm shell below the body)</td>
<td>D1cm$^3$ $&lt; 90%$</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>D0.2cm$^3$ $&lt; 100%$</td>
<td></td>
</tr>
<tr>
<td>Ribs</td>
<td>D0.1cm$^3$ $&lt; 90%$</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>D1cm$^3$ $&lt; 80%$</td>
<td></td>
</tr>
</tbody>
</table>
Future Directions

• Newer modalities:
  Stereotactic radiotherapy
  (Cyberknife, Gamma pod)

• Protons

• Further acceleration: 1-3 fractions (Hannoun Levi et al, Brachy 2017, Khan et al, IJROBP 2019)

• Pre-operative approach
## Ongoing trials of APBI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Inclusion</th>
<th>Control</th>
<th>Experimental</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRMA</td>
<td>Non inferiority</td>
<td>983</td>
<td>≥ 49 years pT1-2 (&lt; 3 cm) invasive carcinoma, pN0- N1</td>
<td>WBI 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50.4 Gy/ 28 Fractions</td>
<td>3D CRT 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 Hours over 5 days</td>
<td>Ongoing</td>
</tr>
<tr>
<td>SHARE</td>
<td>Equivalence</td>
<td>2796</td>
<td>≥ 50 years, invasive adenocarcinoma, T ≤ 2 cm, margin ≥ 2 mm, pNO-pNmi</td>
<td>Standard WBI: 50Gy/25 fractions + 16 Gy boost</td>
<td>3D CRT: 40 Gy total in 10 fractions (4 Gy per fraction), twice a day with an interval of at least 6 Hours over 5-7 days</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**Figure 1.** Design of the SHARE trial. APBI=accelerated partial breast irradiation; fr=fractions; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; rt=radiotherapy.
Conclusion: APBI

• Randomized and prospective data from interstitial brachytherapy series: reassuring and can be considered standard in selected women in centers having expertise for the same
• A word of caution for intra-operative techniques
• IMRT better than 3DCRT for APBI
• Adherence to contouring guidelines and dosimetric constraints can be in excellent outcome
• ASTRO-CS not useful for patient selection
• There is still a scope for further acceleration