Accelerated Partial Breast Irradiation with brachytherapy: Targets and Techniques

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Flow of presentation

• Definition
• Rationale
• Modalities of brachytherapy
• Clinical evidence
• Practical considerations
  – Discuss the technique
  – Target delineation
  – Plan evaluation
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 **hypo-fractionated** regimens practical for delivery
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:**
  - Intraoperative radiotherapy with electrons (ELIOT)
  - Targeted intraoperative radiotherapy (TARGIT)

- **External beam:**
  - Photons (3DCRT, IMRT, SBRT)
  - Electrons
  - Protons
Interstitial brachytherapy: most *mature and safe* technique

- **95%** for APBI
- **93%** for WBI

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

N=199 matches

Vicini et al, Radiotherapy Oncol 2011
Local recurrence (primary endpoint)
5.9% vs. 5.1% at median follow up of 10.2 years

<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
- Variable 4 to 5 cm balloon
- Radiation source port pathway

POST-OPERATIVE

- Inserted obturator to prevent bending or coiling of the catheter shaft
- Needleless injection site

CT scan image showing the placement of the catheter.
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

Log-rank $P < .001$

Risk of Mastectomy, %

Brachytherapy

Whole-breast irradiation

Year

No. of patients at risk
Brachytherapy 6952 6746 4287 2419 1176 442
Whole-breast irradiation 85783 81651 62268 43704 26991 11735

Sur 2013

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
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)
| Table: Accelerated partial-breast irradiation technique summary and guidelines |
|---|---|---|---|
| **Multicatheter interstitial brachytherapy** | Long-term followup | Technical complexity | Strong 
Off and on protocol |
| | Randomized data | | |
| | Cost-effective | | |
| **External beam: IMRT** | Randomized data—equivalent outcomes, lower toxicity | Increased cost vs. 3D-CRT APBI | Strong 
Off and on protocol |
| **Applicator brachytherapy** | Ease of use | Cost | Moderate 
Off and on protocol |
| | Prospective data | Lack of randomized data | |
| | Low rates of toxicity | | |
| **External beam: 3D-CRT** | Least costly APBI technique | Worse cosmesis | Moderate 
Off and on protocol |
| | Noninvasive | Increased subcutaneous toxicity/fibrosis | |
| | Updated results show low rates of toxicities | | |
| **Proton therapy** | Noninvasive | Small number of patients treated | Weak 
On protocol |
| | Updated results show low rates of toxicities | High rates of acute toxicity in initial studies | |
| **Intraoperative radiation therapy** | Single treatment | Higher rates of local recurrence | Weak 
On protocol |
| | Up to 20% require whole-breast irradiation | | |
| | Low-energy: question of volume coverage | | |
| **Electronic brachytherapy** | Single treatment | Small number of patients treated | Weak 
On protocol |
| | Lack of long-term clinical outcomes | Lack of mature toxicity outcomes | |

IMRT = intensity-modulated radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy; APBI = accelerated partial-breast irradiation.
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 DFS and OS, 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>

- 6% - 73%
Practical considerations: implant technique

- Implant quality is critical: dose optimization cannot compensate for poorly done implant
- Implant to cover the tumor bed with adequate margin (1-2 cm).
- The catheters need to be equally and evenly spaced (1-1.5 cm apart) within each implant plane
- Number and spacing between implant planes as well as the total number of catheters to be used depends on individual patient’s tumor bed location and anatomic geometry
- Preimplant CT scan will be helpful to decide the implant geometry
- Implant orientation:
  - Comfortable exit
  - Entry site where implant marks will be less visible (important for cosmetic outcome)
  - Ensure adequate coverage
Practical considerations: implant technique

**POST-OPERATIVE**

- Done after wound healing and final HPR
- Image guidance necessary for placing the adequate number of catheters in the right geometry relative to the cavity volume

**INTRA-OPERATIVE**

- Direct visualization (no geographical miss) and easy to implant
- Choose an orientation with least resistance to avoid tension after skin closure
- Cooperation between surgeon, pathologist, and radiation oncologist is crucial

Free-hand or template-based implantation can be done
CT Based Planning

1. Patient positioned supine and numbering of catheters
2. Acquisition of planning CT with dummy wires inside catheters
3. Target Delineation - contouring of tumour cavity, CTV & OARs
4. Catheter reconstruction
5. Optimising source dwell positions inside catheters
6. Confirm optimal dosimetry and adequate target coverage
7. Dose prescription: 34/10 or 32/8 or 30.1/7 or 36.4/7
What is the optimal CTV margin?

- 70-90% 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
- Intracavitary techniques employ 1 cm margin while interstitial brachy studies use 1-2 cm margin (NSABP trial used 1.5 cm)
- A uniform expansion ensures that at least 1.5 cm of the normal breast tissue is treated beyond the lumpectomy cavity
- In case of wide surgical margins, this is at the expense of treating unnecessary additional normal tissue without added benefit.
- To avoid the potential overtreatment, the GEC-ESTRO multicenter trial used differential CTV margin in accordance to the margin width in each direction

CTV delineated with a non-isotropic expansion taking into account the size of the free resection margin

- The total size of safety margin is always 20 mm, which is the sum of the surgical and added safety margins.
- If the surgical resection margin is larger than 20 mm, instead of zero margin a 5 mm margin is recommended to be used.
- CTV should be limited to chest wall/pectoral muscles and 5 mm below the skin surface.
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 surgery

- Acquisition of CT scan with wire on the scar
- Delineation of the clips: parenchymal and base
- Delineation of whole surgical scar (WS)
- Delineation imaging corelated targeted volume (ImTV)
- Delineation of estimated TB: clips+ WS + ImTV (formimg part of tumor bed)
- Delineation of CTV (20 mm – individual margin but minimum 10mm)
- Delineation of PTV
Impact of iso vs anisotropic margins on implant dosimetry

- N=100, 2015-2020
- Median TBV 37 cc and CTV (iso as well as gec) 116 cc
- Median margin width: 1.2 cm in A/M/L, 1.0 cm P/S and 0.9 in I directions
- Impact was more pronounced for smaller implants (<35 cc)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CTV_ISO</th>
<th>CTV_GEC</th>
<th>P VALUE</th>
<th>Clinically acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Coverage</td>
<td>0.94</td>
<td>0.93</td>
<td>0.667</td>
<td>Yes</td>
</tr>
<tr>
<td>CTV Coverage</td>
<td>0.86</td>
<td>0.84</td>
<td>0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>DHI</td>
<td>0.77</td>
<td>0.75</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>COIN</td>
<td>0.66</td>
<td>0.64</td>
<td>&lt;0.001</td>
<td>No</td>
</tr>
</tbody>
</table>

Wadasadawala et al, Brachy 2020
Planning target volume for evaluation (PTV_EVAL)
- equals - planning target volume (PTV)
- equals - clinical target volume (CTV)

5mm inside skin

1.5 cm

Excision Cavity

Excludes pectoralis muscles and chest wall
- **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.
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 that it represents subtracted
<table>
<thead>
<tr>
<th>DOSE CONSTRAINTS</th>
<th>ESTRO guidelines (Strnad, RO 2018)</th>
<th>ABS guidelines (Hepel et al, Brachy 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV coverage</td>
<td>V100 ≥90%</td>
<td></td>
</tr>
<tr>
<td>Maximal dose</td>
<td>V150 &lt; 65 cm³ (PTV) V200 &lt; 15 cm³ (PTV) COIN 0.65 (PTV) V_{PD} 300 cm³ (Implant) DNR 0.35 (Implant)</td>
<td>V150 &lt; 45 cm³ (PTV) V200 &lt; 14 cm³ (PTV) DHI &gt;0.75 (&gt;0.85 preferred)</td>
</tr>
<tr>
<td>Uninvolved breast</td>
<td>V90% &lt; 10% V50% &lt; 50%</td>
<td>V50% &lt; 60%</td>
</tr>
<tr>
<td>Ipsilateral lung</td>
<td>MLD &lt; 8% D0.1cm³ &lt; 60%</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>MHD &lt; 8% D0.1cm³ &lt; 50%</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>D1cm³ &lt; 90% D0.2cm³ &lt; 100% to 5 mm shell below the body</td>
<td>≤100% of prescription dose (≤60-70% preferred) at skin surface</td>
</tr>
<tr>
<td>Ribs</td>
<td>D0.1cm³ &lt; 90% D1cm³ &lt; 80%</td>
<td>≤125% of prescribed dose</td>
</tr>
</tbody>
</table>
Conclusion: APBI

- Randomized and prospective data from interstitial brachytherapy series prove safety and efficacy and hence can be considered an alternative in selected women.
- MIB is labour intensive and high quality assurance is mandatory.
- Guidelines also recommend MIB strongly over intra-luminal techniques.
- Adherence to contouring guidelines and dosimetric constraints achieve excellent outcome.
- Electronic brachytherapy and accuboost are currently considered investigational.