Radiotherapy: smaller volumes for shorter times. Why? How? When?

APBI: 3D CRT

B. Meduri, F. Bertoni

Brescia Meetings in Radiation Oncology
September 30th, 2011
Epidemiology

• Breast cancer has the highest incidence among all cancer types in females

• 60% of diagnosed breast cancer is early stage (screening programs)

There is a need for proper clinical management of early stage breast cancer

Early stage cancer

- Is radiotherapy the standard treatment after breast conservative surgery (BCS) in early stage cancer?

Yes!
Reduction in local recurrence produced by allocation to radiotherapy is substantial and highly significant (p=0.00001) in every separate trial.

The proportional risk reduction for breast cancer mortality is much less extreme than that for local recurrence but highly significant ($p=0.0002$)

Nowadays, whole breast irradiation is the procedure of choice
But…. 

• Women don’t receive BCT because of age, logistical issues, cost, type of hospital

• Another criticism of BCT relates to consumption of resources (breast irradiation may constitute more than 25% of a radiation department workload and not all countries have adequate resources)
Early stage cancer

- Dose/fraction increase
- Target volume decrease

Treatment time decrease
Early stage cancer

- Dose/fraction: increase
- Target volume: decrease
- Treatment time: decrease
APBI: Theoretical advantages

- Reducing treatment time, could improve compliance
- Decreasing dose to normal tissue, could reduce toxicity
- Less consumption of resources

Without compromising efficacy (??)
Waiting for ongoing phase III study
But...

• Can WBI rates of local control be achieved with radiation therapy delivered only to the tumor bed?

• Is accelerated partial breast irradiation (APBI) an acceptable option?
APBI: Rationale

Ongoing phase III trials are based on:

- 76–90% of local recurrence occurs close to the *tumor bed*
- Ipsilateral breast recurrences in areas other than the tumor bed ("elsewhere relapse") occurred in 3–4% of the cases
- Elsewhere relapse are similar to the recurrences of contra-lateral breast cancer (NSABP B-06 trial - Fisher ER, Cancer 2001; 91:1679–87.)

Sanders ME, J Clin Oncol 2007; 25:996–1002
APBI: Rationale

• Pathology studies: 47% of cases had disease that extended more than 1 cm beyond the grossly evident tumor, with 11% having residual foci outside of a 2-cm margin (Faverly D, Semin Diagn Pathol 11:193-198, 1994)

• Radiation-induced lung injury and increase in lung cancer incidence and mortality after WBI are well documented (Darby SC, Lancet Oncol 2005;6:557–65)

For selected patients WBI could be an over-treatment
APBI techniques: 3D-CRT
APBI: 3D -CRT

- Potential **advantages** over the other techniques:
  - **Non-invasive** (reduce the potential risk of surgical procedure complications)
  - The treatment can wait until completion of **pathological analysis** (resection margin, pathological prognostic factors)
  - Widespread availability
  - **Cheaper** than other techniques (especially if an extra surgical procedure are needed)
  - **Treatment results** with ERT may be more uniform between radiation oncologists (the outcome depends less on the experience of operators)
  - Better **dose homogeneity** (may result in a better cosmetic outcome)
APBI: 3D –CRT

Treatment planning studies comparing whole breast irradiation therapy against conformal, IMRT and tomotherapy for accelerated partial breast irradiation

- The four-field IMRT plan produced the best dosimetric results

If intra-fraction motion cannot be appropriately addressed

a four-field 3D conformal plan is superior.

Oliver M, Radiother Oncol 2007;82:317–23
3D –CRT Technique

• The most widely used 3D-CRT approach was initially described by investigators at the William Beaumont Hospital

• **GTV**: seroma cavity and surgical clips
• **CTV**: GTV with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall
• **PTV**: CTV with 1 cm uniform 3D expansion

3D –CRT Technique

• 3-5 non-coplanar beams

• Dose:
3.85 Gy twice daily to a total dose of 38.5 Gy delivered within 1 week
3D APBI: critical issues

• Patient setup:
  • Patient position
  • Setup errors and organ motion
• Target delineation
• Dose fractionation
• Patient selection
3D APBI: critical issues

- Patient setup:
  - Patient position
    - Setup errors and organ motion
  - Target delineation
  - Dose fractionation
  - Patient selection
Patient position

- **Standard** patient setup: supine, on a carbon fiber breast board, both arms above the head

- **Prone** position:
  - advantages for selected patients as large pendulous breasts: spare lung and heart, minimize target tissue movement
  - Requires a special immobilization device, uncomfortable for patients

3D APBI: critical issues

• **Patient setup:**
  • Patient position
  • **Setup errors and organ motion**

• Target delineation

• Dose fractionation

• Patient selection
Setup errors - organ motion

• The concept **CTV-PTV margin** uncommon for WBI

• APBI requires the use of this concept
  
  • Average positional difference between normal inhalation and normal exhalation: 6 mm
  • Adding a CTV-PTV “breathing only” margin of **5mm**, 98%-100% CTV is covered by 95% isodose
  • **5 mm** for additional components of setup error

A margin of **10 mm** seems to provide coverage for most patients

3D APBI: critical issues

- Patient setup:
  - Patient position
  - Setup errors and organ motion

- **Target delineation**

- Dose fractionation

- Patient selection
Target delineation

GTV: lumpectomy cavity or seroma volume

• GTV identification and contouring can be problematic (RT delayed after surgery)

• High variability in GTV contouring, even among experienced radiation oncologist (mean CI 0.6 range 0.27-0.84)
Target delineation

• The use of surgical clips may reduce inter-observer variability, superiority to locate the tumor bed compared with clinical methods.

• Training and contouring guidelines can improve consistency in seroma delineation.

• Multi-modality imaging: feasibility of using 3D ultrasound for delineation of tumor bed, improve interobserver consistency, especially in case with dense breast parenchyma.

Dzhugashvili M, Radiat Oncol 2009;4:70  
3D APBI: critical issues

- Patient setup:
  - Patient position
  - Setup errors and organ motion
- Target delineation
- **Dose fractionation**
- Patient selection
• There is still the question of the appropriate dose and fractional schedule for 3D-CRT–APBI

• Different doses and fractionation schedules

<table>
<thead>
<tr>
<th>Author</th>
<th>No of cases</th>
<th>Fractionation scheme</th>
<th>IBF</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vicini et al. [73]</td>
<td>52</td>
<td>3.85 Gy x 10 (bid)</td>
<td>6%</td>
<td>54</td>
</tr>
<tr>
<td>Vicini et al. [74]</td>
<td>91</td>
<td>3.85 Gy x 10 (bid)</td>
<td>0%</td>
<td>24</td>
</tr>
<tr>
<td>Chen et al. [75]</td>
<td>94</td>
<td>3.85 Gy x 10 (bid)</td>
<td>1.1%</td>
<td>51</td>
</tr>
<tr>
<td>Taghian et al. [76]</td>
<td>99</td>
<td>3.2 Gy x 4 (bid)§</td>
<td>2%</td>
<td>36</td>
</tr>
<tr>
<td>Formenti et al. [77]</td>
<td>10</td>
<td>5.0, 5.5, 6.0 Gy x 5 (10 days)</td>
<td>0%</td>
<td>36 (minimum)</td>
</tr>
<tr>
<td>Formenti et al. [78]</td>
<td>47</td>
<td>6.0 Gy x 5 (10 days)</td>
<td>0%</td>
<td>18</td>
</tr>
<tr>
<td>Magee et al. [79]</td>
<td>353</td>
<td>5.0–5.31 Gy x 8 (10 days)§</td>
<td>25%</td>
<td>96 (mean)</td>
</tr>
<tr>
<td>Leonard et al. [80]</td>
<td>55</td>
<td>3.85 Gy x 10 (bid)</td>
<td>0%</td>
<td>34 median</td>
</tr>
<tr>
<td>Hepel et al. [81]</td>
<td>60</td>
<td>3.85 Gy x 10 (bid)</td>
<td>n/a</td>
<td>15</td>
</tr>
<tr>
<td>Jagsi et al. [82]</td>
<td>34</td>
<td>3.85 Gy x 10</td>
<td>n/a</td>
<td>&gt;24</td>
</tr>
</tbody>
</table>

Cuttino et al. determined that the fraction size needed to deliver a hypofractionation treatment biologically equivalent to a standard post-operative RT schedule is 3.82 Gy/fr (TD 38.2 Gy in 10 fractions)

3D APBI: critical issues

• Patient setup:
  • Patient position
  • Setup errors and organ motion
• Target delineation
• Dose fractionation

• Patient selection
3D –CRT Trial

Data from recent phase II clinical studies evaluating the efficacy and safety are available

<table>
<thead>
<tr>
<th>Author</th>
<th>No of cases</th>
<th>Follow up (months)</th>
<th>Fractionation scheme</th>
<th>IBF</th>
<th>Good/Excellent cosmesis</th>
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</tr>
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<td>24</td>
<td>3.85 Gy × 10 (bid)</td>
<td>0%</td>
<td>90%</td>
</tr>
<tr>
<td>Chen et al. [75]</td>
<td>94</td>
<td>51</td>
<td>3.85 Gy × 10 (bid)</td>
<td>1.1%</td>
<td>89%</td>
</tr>
<tr>
<td>Taghian et al. [76]</td>
<td>99</td>
<td>36</td>
<td>3.2 Gy × 4 (bid)</td>
<td>2%</td>
<td>97%</td>
</tr>
<tr>
<td>Formenti et al. [77]</td>
<td>10</td>
<td>36 (minimum)</td>
<td>5.0, 5.5, 6.0 Gy × 5 (10 days)</td>
<td>0%</td>
<td>100%</td>
</tr>
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<td>60</td>
<td>15</td>
<td>3.85 Gy × 10 (bid)</td>
<td>n/a</td>
<td>81.7%</td>
</tr>
<tr>
<td>Jagsi et al. [82]</td>
<td>34</td>
<td>&gt;24</td>
<td>3.85 Gy × 10</td>
<td>n/a</td>
<td>79.5%</td>
</tr>
</tbody>
</table>
## Patient selection

### ASTRO

<table>
<thead>
<tr>
<th>Factors</th>
<th>“Suitable” group</th>
<th>“Cautionary” group</th>
<th>“Unsuitable” group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>≥60</td>
<td>50 to 59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Not present</td>
<td>NA</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>≤2 (^{[1]})</td>
<td>2.1–3.0 (^{[1]})</td>
<td>&gt;3 (^{[1]})</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3 or T4</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative by at least 2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>LVSI</td>
<td>No (^{[5]})</td>
<td>Limited/focal</td>
<td>Extensive</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative (^{[5]})</td>
<td>NA</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric only</td>
<td>NA</td>
<td>If present</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size ≤2 cm (^{[1]})</td>
<td>Clinically unifocal with total size 2.1 to 3.0 cm (^{[1]})</td>
<td>If microscopically multifocal &gt;3 cm in total size or if clinically multifocal</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypes **</td>
<td>Invasive lobular</td>
<td>NA</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤3 cm in size</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>≤3 cm in size</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Nodal factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>pN0 (i(^{-}), i(^{+}))</td>
<td>NA</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SN Bx or ALND (^{[1]})</td>
<td>NA</td>
<td>None performed</td>
</tr>
<tr>
<td><strong>Treatment factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
<td>NA</td>
<td>If used</td>
</tr>
</tbody>
</table>

Patient selection

<table>
<thead>
<tr>
<th>Factors</th>
<th>Suitable group by ASTRO [138]</th>
<th>Low Risk group by GEC-ESTRO [137]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 60 y</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>BRCA 1, 2 Mutation</td>
<td>Not present</td>
<td>na</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>&lt; 2 cm</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>T1-2</td>
</tr>
<tr>
<td>ER status</td>
<td>positive</td>
<td>any</td>
</tr>
</tbody>
</table>

Table 6 ASTRO and GEC-ESTRO suitable patient recommendation selections for APBI outside of clinical trials
The selection criteria for patient off-protocol could be:

- Age > 60
  - Tumor size <2.5 cm
  - Lymph node status: negative
  - Histology: non-lobular and negative margin (>2 mm)

<table>
<thead>
<tr>
<th>Organization</th>
<th>Patient age</th>
<th>Tumor size</th>
<th>Histology</th>
<th>Lymph node status</th>
<th>Margin status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>≥50</td>
<td>≤3</td>
<td>Infiltrating ductal carcinoma</td>
<td>Negative (by sentinel lymph node or axillary dissection)</td>
<td>Negative (at inked margin)</td>
</tr>
<tr>
<td>ASBS</td>
<td>≥45</td>
<td>≤2</td>
<td>Invasive ductal carcinoma or ductal carcinoma in situ</td>
<td>Negative (by sentinel lymph node or axillary)</td>
<td>Negative (&gt;2 mm)</td>
</tr>
<tr>
<td>ASTRO [181]</td>
<td>≥60</td>
<td>≤2</td>
<td>Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular and colloid)</td>
<td>Negative (by sentinel lymph node or axillary dissection)</td>
<td>Negative (&gt;2 mm)</td>
</tr>
<tr>
<td>GEC-ESTRO [180]</td>
<td>≥50</td>
<td>≤3</td>
<td>Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular and colloid)</td>
<td>Negative (by sentinel lymph node or axillary dissection)</td>
<td>Negative (&gt;2 mm)</td>
</tr>
<tr>
<td>NSABP B39/RTOG-0413</td>
<td>≥18</td>
<td>≤3</td>
<td>Invasive ductal carcinoma or ductal carcinoma in situ</td>
<td>Allows for 0–3 nodes involved (with negative sentinel lymph node or &gt;6 nodes sampled)</td>
<td>Negative (at inked)</td>
</tr>
</tbody>
</table>

Patient selection

Consensus “Partial Breast Irradiation”

Comitato di coordinamento: L. Cataliotti, R. Orecchia, L. Marotti

Chair: Roberto Orecchia (Milano)
### Ongoing 3D CRT Phase III trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Design</th>
<th>N</th>
<th>Inclusion</th>
<th>Control Arm</th>
<th>APBI technique (Experimental Arm)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP/</td>
<td>Equivalence</td>
<td>4300</td>
<td>≥ 18 years, stage 0, I, II (T &lt; 3 cm) DCIS or invasive adenocarcinoma, ≤ 3</td>
<td>WBI 50-50.4 Gy/25-28 fractions, optional 10-16 Gy boost</td>
<td>MIB Mammosite 34 Gy/10 fractions (5-10 days) 3D EBCRT 38.5 Gy/10 fractions (5-10 days)</td>
<td>Started in 2005 (accrual now closed to low risk patients)</td>
</tr>
<tr>
<td>RTOG 0413</td>
<td></td>
<td></td>
<td>nodes positive, Margin negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAPID</td>
<td>Equivalence</td>
<td>2128</td>
<td>≥ 40 years, DCIS or invasive carcinoma T &lt; 3 cm, margin negative, node</td>
<td>WBI 42.5 Gy/16 fractions/22 days (small breast) 50 Gy/25 fractions/35 days</td>
<td>3D CRT 38.5 Gy/10 fractions (5-8 days) Minimum daily fraction separation 6-8 hours</td>
<td>Started in January 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>negative, not BRCA 1/BRCA 2</td>
<td>(large breast plus optional boost 10 Gy/4-5 fractions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRMA</td>
<td>Non-inferiority</td>
<td>n/a</td>
<td>≥ 49 years, pT1-2 (&lt; 3 cm) invasive carcinoma pN0- N1 Margin ≥ 2 mm</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</td>
<td>Started in 2007</td>
</tr>
</tbody>
</table>
IRMA Trial

www.irmatrial.it
IRMA Trial

Documentation:

Trial synopsis

If you are interested to participate to the trial, please download: participation request notes and the: protocol participation form

fill in all fields of the form and send to the fax number reported on it

Operative Units of Radiotherapy involved into IRMA trial

ANKON
BELLINZONA
BOLOGNA AOSP
BOLOGNA AUSL
CASTELLANZA
COMO
COTIGNOLA
FERRARA
GENOVA
HAIFA
MELDOLA
MODENA
PARMA
PIACENZA
RAVENNA
REGGIO EMILIA
RIMINI
ROMA Unicampus
SAN GIOVANNI ROTUNDO
TREVIIGLIO
TORINO
VITERBO
## IRMA Trial

### Selection Criteria
- Stage I, II breast cancer >49 ys
- Invasive adenocarcinoma
- Tumor size ≤ 3 cm (unifocal)
- N-0, N-1 (≤ 3 positive nodes)
- Negative margins (≥ 2mm)
- Lumpectomy/whole breast ratio on CT ≤ 30%
- Lumpectomy cavity marked with at least 3 clips

### Technique
- GTV: seroma cavity and surgical clips
- CTV: GTV with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall
- PTV: CTV with 1 cm uniform 3D expansion
- 3-5 non-coplanar beams
- 3.85 Gy twice daily to a total dose of 38.5 Gy delivered within 1 week
IRMA Trial

Primary Endpoint:
• Ipsilateral breast tumor recurrence

Secondary endpoints:
• Recurrence free survival
• Distant disease-free survival
• Overall survival
• QoL: Cosmesis
IRMA Trial

Start: May 2007

Current accrual: 1128

WBI Arm => 563
  - Average age: 63.6 ys

PBI Arm => 565
  - Average age: 63 ys
Conclusions

- Partial breast irradiation has to be considered an experimental technique, although there are beginning evidence for a role in the management of a selected group of early breast cancer

- 3D CRT has significant potential for APBI, but further research is required to identify the optimal technique
Conclusions

• Patient selection is critical to the appropriate application of 3D CRT APBI
• The medical community has to wait for the phase III clinical trials demonstrating the efficacy and safety of APBI

We have to enroll in ongoing phase III clinical trials