Accelerated Radiation Treatment for Early Stage Breast Cancer

update and perspective

School of Breast Oncology
Atlanta, 11/2012

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Professor
Traditional Whole Breast Irradiation
WBI - 25-28 daily tx followed by 5-8 boost tx

- Anticipated results:
  - In-breast failures rates of ≤1% per year
  - 85-90% good to excellent cosmetic results

- In-Breast Failure
  - Psychologically damaging
  - Leads to mastectomy
  - Has the potential to negatively impact survival

- Toxicity
  - Negatively impacts cosmesis
  - Negatively impacts quality of life
  - May lead to mastectomy

• New techniques should have sufficient data to prove they have met these high standards!
Why mess with success?

Observations and Questions:

- Many patients have difficulties with 6-7 weeks of tx
- WBI not needed in all patients
- Unable to reliably identify patients in which surgery has removed all microscopic disease and radiotherapy can be safely omitted

Throughout this time progress made!

- Mammography/MRI detecting earlier – smaller, less extensive dz
- Surgery and Pathologic assessment – increased disease clearance
- Has the group benefitting from XRT decreased in size?
Proposed Alternatives to Traditional WBI - an assorted Tool Box?

- Lumpectomy only
- Accelerated Whole Breast Irradiation
- Accelerated Partial Breast Irradiation
  - Interstitial Brachytherapy
  - Intracavitary Brachytherapy
  - 3D conformal external beam
- Intraoperative Radiotherapy (IORT)
- Protons
- Permanent radioactive seed brachytx
Direction of Continued Investigation

• The role and extent of surgery has been successfully reduced

• Can we reduce the extent of Radiotherapy?
  - What is gained, What is compromised?

• Breast Conservation Tx “MENU”/“Box of tools”
As we explore/evaluate new approaches to radiation therapy -

- **Goal** - Disease control with acceptable cosmesis/limited toxicity

With Radiation Treatment this is dependent on balance between:
- What is the target, is it covered?
- Total dose
- Fraction size
- Sensitivity of tumor and of normal tissue
- Volume of tissue

- **Some aspects known** - Some speculated
  - Minor differences may have major impact
Menu Concept

• Not all patients appropriate for BCT
  - Tumor size/extent, breast size
  - Cosmetic expectations
  - Anxiety levels
  - Etc.

• Not all patients appropriate for all adjuvant XRT techniques
  - Tumor characteristics
  - Cavity size, location, dimensions
  - Breast size
  - Etc.

- Example....
Treatment Techniques

Same goals – achieving in different ways
- Lessons learned from on not always transferable

Necessary components for success:

- Opportunity for Patient selection
- Documentation of Target coverage
- Quality Assurance
- Ease of reproducibility
Technique Menu/Tool Box

Lumpectomy + WBI

- Lumpectomy + Hypofx WBI
- Lumpectomy + APBI
- Lumpectomy + IORT
- Lumpectomy Only

In general -> age, <tumor size, low grade, larger margins
• Breast Conserving Surgery only
• Accelerated Whole Breast Irradiation
• Intraoperative Radiotherapy (IORT)
• Accelerated Partial Breast Irradiation
Breast Conservation Surgery only

With Selection - see In-breast failures

- 4 prospective randomized trials
  - NSABP B-21
  - Princess Margaret Hospital - Fyles AW, NEJM 2004
  - CALGB trial - Hughes KS, NEJM 2004, ASCO 2010

- Era of modern mammography, surgery, pathology
- Tamoxifen/Anastrozole vs WBI -
- Attempted selection of patients with low risk of residual microscopic disease
Local Control vs Overall Survival?

- What risk of failure is acceptable?
- How can we individualize?

- Life insurance longevity tables
  - Life expectancy if reach 70 yo - 15 years
  - Life expectancy if reach 80 yo - 9 years

- Oxford Overview - Lancet, 2010
  - Impact of Radiotherapy after BCS
  - 10yr recurrence and 15 yr breast cancer death

<table>
<thead>
<tr>
<th>Node negative</th>
<th>no XRT</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10yr recurrence risk reduction</td>
<td>31%</td>
<td>15.6%</td>
</tr>
<tr>
<td>15yr breast Ca death reduction</td>
<td>20.5%</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

(Dependent on age, grade, ER status, tam use, extent of sx)
How should we incorporate?

- Identified (?) a subpopulation where XRT can be omitted
  - < 8-10% risk of in-breast failure, no impact on overall survival
- Need to consider pts overall status and co-morbidities
- What is the compliance, off-protocol, with antiestrogen therapy
- Do trials select for compliant patients?
  - Do studies reporting no survival benefit reflect on a group of patients motivated to follow up?
  - Can we translate this to all patients?
  - Should we contract with off-study patients for follow-up like we do with on-study patients to assure similar outcomes?
• Breast Conserving Surgery only
• **Accelerated Whole Breast Irradiation**
• Intraoperative Radiotherapy (IORT)
• **Accelerated Partial Breast Irradiation**
Accelerated Whole Breast Irradiation

What is it?

- Reduction of treatment time from 6 weeks to 3-4 weeks
  - Maintains whole breast treatment target
  - Increase dose per fraction (hypofractionation)
    - 2.66Gy X 16 days = 42.56 Gy (+/- boost)
  - Use of standard external beam technique
Accelerated Whole Breast Irradiation

- Canadian CCO
- Royal Marsden Hospital, UK
Canadian Randomized Trial:

- 1234 patients (T1 - T2)
- Median f/u 144 months
- Accelerated Whole Breast Irradiation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose (Gy)</th>
<th>Fraction Count</th>
<th>Fraction Size (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Arm</td>
<td>42.5</td>
<td>16</td>
<td>2.66</td>
</tr>
<tr>
<td>Long Arm</td>
<td>50</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

** Good/Excellent cosmesis **
- Short arm - 69.8%
- Long arm - 71.3%

** Local Recurrence **
- Short arm - 6.2%
- Long arm - 6.7%

** Mod/severe late radiation morbidity to: **
- Skin
  - Short arm - 8.9%
  - Long arm - 3.2%
- Subcutaneous tissue
  - Short arm - 11.9%
  - Long arm - 10.4%

**(?) less effective in G3 (15.6% v 4.7%)**

Royal Marsden Randomized Trial Series:

**START A TRIAL**
- Pilot of Hypofractionated WBI
- Seeking equivalent 13 day regimen
- 2236 pts, \( \text{pT1-3a pN0-1 M0, med f/u 5.1 years} \)
- All given over 5 weeks - to equate overall time delivered

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>LR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy in 25 fractions (2 Gy/fraction)</td>
<td>3.6%</td>
</tr>
<tr>
<td>41.6 Gy in 13 fractions (3.2 Gy/fraction)</td>
<td>3.5%</td>
</tr>
<tr>
<td>39 Gy in 13 fractions (3 Gy/fraction)</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

**START B Trial**
- Parallel initiation with START A
- 2215 pts, (pT1-3a pN0-1 M0), Med f/u 6 years

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>LR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy in 25 fractions (2 Gy/fraction)</td>
<td>3.3%</td>
</tr>
<tr>
<td>40 Gy in 15 fractions (2.67 Gy/fraction)</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

The START Trialists’ Group Lancet Oncol 2008; 9: 331–41
The START Trialists’ Group Lancet 2008; 371: 1098–107
How should we incorporate?

Patient selection

• ASTRO evidence based guidelines

  Smith, et al IJROBP, 2010

  - Patient is ≥50 yo at diagnosis
  - Stage T1-T2, N0 (DCIS not included)
  - Appropriate for breast-conserving therapy
  - Treated with breast-conserving surgery
  - Not treated with systemic chemotherapy
  - Treatment planning confirms homogeneity with +/- 7% of prescribed dose along central axis

• Continue to Study

  - Open for accrual RTOG 1005 trial
    • high risk patients and simultaneous integrated boost
How should we incorporate?

- Must consider
  - Patient Age
  - Disease Stage
  - Grade
  - Resection Margin (boost?)
  - Amount of lung and heart in field
  - If chemotx is to be delivered
Outline

• Breast Conserving Surgery only
• Accelerated Whole Breast Irradiation
• Intraoperative Radiotherapy (IORT)
• Accelerated Partial Breast Irradiation
Intraoperative Radiotherapy (IORT)

What is it?

- Reduction of treatment time from 6 weeks to 1 intraoperative tx
  - Decrease volume of tissue
    - Lumpectomy cavity plus ? - <1-2cm margin
  - Increase dose per fraction
    - 21Gy to target - electrons
    - 5-8 Gy to target (21 Gy at cavity edge) - Kx energy
  - Surgeon and Rad Onc working together to cover target with dose
Intraoperative electrons

- IORT mobile accelerator
- NOVAC 7: An IORT dedicated electron accelerator
- Conventional O.R. (no shielding needed)
- Mobile and easily docked
- Electron beams of 4 different energies: 3, 5, 7, 9 MeV
ELIOT Technique

Quadrantectomy
Thoracic Wall Protection

Thickness Measurement

Skin Sparing

Treatment delivery

Compliments Frank Vicini, MD
Intraoperative Radiotherapy with Electrons - ELIOT (off-study patient group)

- 1822 pts – 85% <2 cm, 71.4% N0, 89.2% ER+
- Median f/u – 36.1 months
- 21 Gy in one fraction
- 30-40 minutes in OR to deliver treatment

- True recurrences - 2.3%
- Elsewhere failures - 1.3%

- Increased failure rates in:
  - <50 yo, size >2cm, grade 3, ER-, Her2+
  ? result of technique vs consistent with all techniques?

Intraoperative Radiotherapy with Electrons - ELIOT (study patient group)

<table>
<thead>
<tr>
<th>5 Yr Endpoint</th>
<th>ELIOT</th>
<th>WBRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>LR+IBR</td>
<td>37</td>
<td>5</td>
<td>0.7%</td>
</tr>
<tr>
<td>LR (&quot;true&quot;)</td>
<td>23</td>
<td>5</td>
<td>0.7%</td>
</tr>
<tr>
<td>IBR (&quot;else&quot;)</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Regional</td>
<td>9</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>OS</td>
<td>97%</td>
<td>97%</td>
<td>NS</td>
</tr>
</tbody>
</table>

As presented by R. Orecchia at (ABS/GEC-ESTRO) Annual Meeting, Barcelona, Spain, May 10, 2012
University College London
Vaidya
Intraoperative - Photoelectron
University College London
Vaidya
Intraoperative - Photoelectron
Targeted Intraoperative Radiotherapy - TARGIT-A

• 2232 pts - 86% <2cm, 82% N0, 90% ER+
• Median F/U 2-3 yrs (?) - <20% of pts beyond 4 years
• Phase III randomized - multi-institutional
  - TARGIT (20 Gy to surface - 5-7 Gy to 1 cm)**** vs External Beam Whole Breast
• 60 minutes in OR to deliver treatment

• In-breast Failure:
  TARGIT - 1.2%   EXBT - .95%

Vaidya JS, Lancet 2010; 376: 91-102
• Breast Conserving Surgery only
• Hypofractionated Whole Breast Irradiation
• Intraoperative Radiotherapy (IORT)
• **Accelerated Partial Breast Irradiation**
Accelerated Partial Breast Irradiation

What is it?

- Reduction of treatment time from 6 weeks to 5 days
  - Decrease volume of tissue
    - Lumpectomy cavity plus 1-2cm margin
  - Increase dose per fraction
    - 3.4Gy bid × 5 days = 34 Gy
  - Use of highly conformal dose delivery
    - Brachytherapy / CT-based 3D-CRT
Treatment Techniques

- ‘Classic’ three techniques
- Single-entry Multi-Catheter intracavitary devices
Multi-Catheter Brachytherapy placement – US, Stereotactic mammography, or CT guidance
IntraCavitary Applicators

- Answer to the over simplification of single lumen
- Simplicity of single entry
- Tools for dose shaping for Radiation Oncologist
- Single lumen < multi-lumen intracavitary
3D conformal/IMRT

- Early pilot experiences
  - Vicini - supine
    - RTOG 0319
  - Formenti - prone
  - Taghian - supine
- Accel. dose scheme
APBI - Data Review Blitz

- **Interstitial APBI data** - low risk patients
  - >700 pts reported, 5->10yr f/u, majority <5% IBTR

- **MammoSite data** - preliminary
  - >2000 pts reported, 2-6 yr f/u, <5% IBTR
  - Some 5-year data available - cont. excellent results
  - Monitor for new toxicities/efficacy

- **3D Conformal PBI** - limited pts and f/u
  - <500 pts reported (>1000 on toxicity), <5yr f/u, <5% IBTR
  - 2 reports of unacceptable toxicity
  - NSABP B39/RTOG 0413 - toxicity acceptably low and equal to other techniques
  - Presently inconclusive
references

APBI - Data Review Blitz

- First completed/published contemporary phase III PBI trial using interstitial APBI shows equivalent results to WBI at 7-yrs

*Mature phase III data (7 trials)* will not be available for several years (2015-2020)

*What should we do until additional phase III data are available?*
- *both Who and How*
2 observational studies say


- **They:**
  - Higher rates of complications/failures
  - Abandon or protocol only

- Insufficient time to completely discuss
- Use of surrogate endpoints - not superior to Phase III trial
- Represents earliest use of single-lumen balloon
- Represents 2-D planning and learning curve
- Does not translate to all techniques
- Conflicts with Phase II and early Phase III data

- **Me:**
  - Suggests need to appropriately select patients and
treat and manage conservatively
# APBI - Indications

Multiple Societies have weighed in on WHO:

<table>
<thead>
<tr>
<th>Society</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>American Brachytherapy Society</td>
</tr>
<tr>
<td>ASBrS</td>
<td>American Society of Breast Surgeons</td>
</tr>
<tr>
<td>GEC-ESTRO</td>
<td>Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology</td>
</tr>
<tr>
<td>ASTRO</td>
<td>American Society of Radiation Oncology</td>
</tr>
</tbody>
</table>

- **Inclusion criteria**: conservative + data supported
- **Exclusion criteria**: common sense, bias - no data

All similar - ASTRO most conservative
references

- http://www.americanbrachytherapy.org/resources.abs_breast_brachydtherapy_taskgroup.pdf
- http://www.breastsurgeons.org/apbi.shtml
### ASTRO APBI evidence based guidelines

**Group 1**  
Suitable candidates  
if all of the following criteria present:  
Acceptable for off-protocol treatment

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60</td>
</tr>
<tr>
<td>T-stage</td>
<td>T1</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>ER Status</td>
<td>Positive</td>
</tr>
<tr>
<td>Nodes</td>
<td>pNO</td>
</tr>
<tr>
<td>Margins</td>
<td>&gt; 2 mm</td>
</tr>
<tr>
<td>Histology</td>
<td>IDC or favorable</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>LVI</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unifocal</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>
Group 2
Cautionary candidates:
any of these criteria should invoke caution and concern when considering APBI:

Off-protocol treatment reasonable if preceded by thorough patient discussion regarding strength of supporting data.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50-59</td>
</tr>
<tr>
<td>T-stage</td>
<td>T1 or T2</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>2.1-3.0 cm</td>
</tr>
<tr>
<td>ER Status</td>
<td>Negative</td>
</tr>
<tr>
<td>Nodes</td>
<td>NA</td>
</tr>
<tr>
<td>Margins</td>
<td>Close &lt; 2 mm</td>
</tr>
<tr>
<td>Histology</td>
<td>any</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>≤ 3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>≤ 3 cm in size</td>
</tr>
<tr>
<td>LVI</td>
<td>Limited/focal</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Negative</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
<td>NA</td>
</tr>
</tbody>
</table>
**Group 3**

Unsuitable candidates:

Acceptable if on-protocol

Not Acceptable if for off-protocol treatment if any of these features present

<table>
<thead>
<tr>
<th>Feature</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>T-stage</td>
<td>T3 or T4</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>Nodes</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Margins</td>
<td>Positive</td>
</tr>
<tr>
<td>LVI</td>
<td>Extensive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Present</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
<td>If used</td>
</tr>
</tbody>
</table>

**THINK NSABP B39/RTOG 0413**
***APBI outcome data has not yet validated exclusion criteria

- Large APBI series, >5 year f/u
  - Pts do equally well across Categories
  - Yet to identify a group with poor outcome

- Future: As additional data is published, Guidelines may/will need revision
Continued Investigation & New Directions
## Phase III Clinical Studies

<table>
<thead>
<tr>
<th>Institution/Trial</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSABP B 39/RTOG 0413</strong></td>
<td>50-50.4 Gy WB +/- 10-16 Gy Boost</td>
<td>(1) Interstitial Brachytx, or (2) MammoSite™, or (3) 3D Conformal EBRT</td>
</tr>
<tr>
<td>National Institute of Oncology Budapest, Hungary</td>
<td>50 Gy WB</td>
<td>(1) Interstitial Brachytx (5.2 Gy X 7) or (2) Electrons (50 Gy)</td>
</tr>
<tr>
<td>European Brachytherapy Breast Cancer GEC-ESTRO Working Group</td>
<td>50-50.4 Gy WB + 10 Gy Boost</td>
<td>Brachytherapy Only 32.0 Gy 8 fractions HDR 30.3 Gy 7 fractions HDR 50 Gy PDR</td>
</tr>
<tr>
<td>European Institute of Oncology ELIOT</td>
<td>50 Gy WB + 10 Gy Boost</td>
<td>Intra-operative Single fraction EBRT 21 Gy x 1</td>
</tr>
<tr>
<td>University College of London TARGIT</td>
<td>WB RT (per center) + Boost</td>
<td>Intra-operative Single fraction EBRT 5 Gy x 1</td>
</tr>
<tr>
<td>Canadian Trial RAPID</td>
<td>WB 42.5 Gy in 16 or 50 Gy in 25 +/- 10 Gy boost</td>
<td>3D CRT only 38.5 Gy in 10</td>
</tr>
<tr>
<td>Medical Research Council – UK IMPORT LOW</td>
<td>WB 2.67 Gy X 15</td>
<td>(1) WB 2.4 Gy X 15 PB 2.67 Gy X 15 (2) PB only 2.67 Gy X 15</td>
</tr>
</tbody>
</table>
Current and future

• NSABP B39/ RTOG 0413
  - Phase III partial breast trial
  - 4167 of 4300 accrued (10/2012)
  - DSMB – no concerning outcomes to date

• RTOG 1014
  - Phase I/II - Repeat Breast Preserving Surgery and 3D-CRT PBI for Local Recurrence of Breast Carcinoma
  - Now open

• RTOG 1005
  - Phase III - Accelerated Whole Breast Irradiation with simultaneous boost - higher risk patients
Current and future

• **FAST trial - Royal Marsden**
  - Randomized trial - now complete
    
    | 50 Gy (2.0 Gy X 25) vs 27.5 Gy (5.7 Gy X 5) - 1 fx/wk vs 30 Gy (6.0 Gy X 5) - 1fx/wk |

• **Accelerated (Hypofractionated) Partial breast/± WBI**
  - IMPORT Low trial (low risk)
  - IMPORT High trial (high risk)

• **Overnight Trial - APBI brachytherapy**
  - Small Multi-institutional trial, fractionation escalation
  - Bridge time gap between 5 day APBI and IORT
  - Bid X 2 days → qd X 2 days
Conclusions

- Proceed conservatively
- Treatment tailored to individual
  - Several tx options for most patients
- Monitor data
- Recognized that results from one technique may not apply to another