Partial, Whole Breast Hypofractionated, and Intraoperative Radiotherapy

10th International Congress on the Future of Breast Cancer
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Professor
Whole Breast Irradiation post BCT

Historical Perspective

- Early Pathologic studies suggested diffuse pattern of residual microscopic disease following Breast Conserving Surgery

- Whole Breast Irradiation used to eradicate assumptions:
  - Who needed XRT? - everyone
  - Target? - whole breast
  - Dose? - conventional fractionation with boost
Traditional Whole Breast Irradiation - perspective

- Anticipated results from traditional WBI with boost:
  - 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!
Proposed Alternatives to Traditional WBI

Pandora's Box?

• Lumpectomy only

• Permanent radioactive seed brachytherapy

• Protons

• Intraoperative Radiotherapy (IORT)

• Accelerated Partial Breast Irradiation

• Accelerated Whole Breast Irradiation

• Interstitial Brachytherapy

• Intracavitary Brachytherapy

• 3D conformal external beam

• Intraoperative Radiotherapy (IORT)
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 Therapy “MENU”

• Studies needed to clarify extent of treatment
As we explore/evaluate new approaches to radiation therapy -

• **Goal** - Disease control with 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
  - Where speculation - proceed cautiously and conservatively!!
Approaches with Supporting Data

• Accelerated Whole Breast Irradiation
• Intraoperative Radiotherapy (IORT)
• Accelerated Partial Breast Irradiation
• 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)
    - $2.66\text{Gy} \times 16 \text{ days} = 42.56 \text{ Gy (+/- boost)}$
  - 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

42.5 Gy in 16 fractions (2.66 Gy/fraction) vs 50 Gy in 25 fractions (2 Gy/fraction) (no boost either arm)

Local Recurrence
- short arm - 6.2%
- long arm - 6.7%
** (?) less effective in G3 (15.6% v 4.7%)

Good/Excellent cosmesis
- short arm - 69.8%
- long arm - 71.3%

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%

## START A TRIAL
- Pilot of Hypofractionated WBI
- Seeking equivalent 13 day regimen
- 2236 pts, 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>Treatment</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>vs 41.6 Gy in 13 fractions (3.2 Gy/fraction)</td>
<td>3.5%</td>
</tr>
<tr>
<td>vs 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

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<td>50 Gy in 25 fractions (2 Gy/fraction)</td>
<td>3.3%</td>
</tr>
<tr>
<td>vs 40 Gy in 15 fractions (2.67 Gy/fraction)</td>
<td>2.2%</td>
</tr>
</tbody>
</table>
Perspective

- Large numbers of Patients
- f/u 5-12 years
- Excellent in-breast control
- Acceptable cosmetic outcome

- Most patients
  - >50yo
  - Invasive disease
  - Small to moderate size breast
  - T1 lesions
  - Node negative
  - Treatment - breast only (no regional nodes)
  - Boost dose application varied
  - no Chemotx
  - Received Hormonal therapy
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
  - 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
  - RTOG 1005
    • high risk patients and simultaneous integrated boost
Outline

- 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) - Kv 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

Skin Sparing

Treatment delivery

Compliments Frank Vicini, MD
Intraoperative Radiotherapy with Electrons - ELIOT

- 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?
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
• 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 X 5 days = 34 Gy
  - Use of highly conformal dose delivery
    - Brachytherapy / CT-based 3D-CRT
Treatment Techniques

- ‘Classic’ three techniques
- New device based intracavitary
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, 2-5 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, <5yr f/u, <5% IBTR
  - 2 reports of unacceptable toxicity
  - NSABP B39/RTOG 0413 - toxicity acceptably low and equal to other techniques
  - Presently inconclusive
# Phase III Clinical Studies

<table>
<thead>
<tr>
<th>Institution/Trial</th>
<th># Cases</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B 39/RTOG 0413</td>
<td>4300</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>258 Completed</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>1233 Completed</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>1200 Completed</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>2232</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>2128</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>1935</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>

**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?**
# APBI - Indications

Multiple Societies have weighed in:

<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
## ASTRO APBI evidence based guidelines

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Suitable candidates if all of the following criteria present:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$\geq 60$</td>
</tr>
<tr>
<td>T-stage</td>
<td>T1</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>$\leq 2 \text{ cm}$</td>
</tr>
<tr>
<td>ER Status</td>
<td>Positive</td>
</tr>
<tr>
<td>Nodes</td>
<td>pNO</td>
</tr>
<tr>
<td>Margins</td>
<td>$&gt; 2 \text{ mm}$</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>
## ASTRO APBI evidence based guidelines

### Group 2
**Cautionary candidates:**
Any of these criteria should invoke caution and concern when considering APBI:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</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: outside of a clinical trial if any of these criteria are present

**ASTRO APBI evidence based guidelines**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Criteria Details</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>ER Status</td>
<td>NA</td>
</tr>
<tr>
<td>Nodes</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Margins</td>
<td>Positive</td>
</tr>
<tr>
<td>Histology</td>
<td>NA</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>If &gt; 3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>If &gt; 3 cm in size</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
Conclusions

• Proceed conservatively
• Treatment tailored to individual
  - Several tx options for most patients
• Monitor data
• Enroll on phase III trial NSABP 39/RTOG 0413
• All Tx Guidelines should be updated and refined as additional data becomes available