Partial, Whole Breast Hypofractionated, and Intraoperative Radiotherapy

10th International Congress on the Future of Breast Cancer
August 4–7, 2011

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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
- Accelerated Whole Breast Irradiation
- Accelerated Partial Breast Irradiation
- Interstitial Brachytherapy
- Intracavitary Brachytherapy
- 3D conformal external beam
- Intraoperative Radiotherapy (IORT)
- Protons
- Permanent radioactive seed brachytherapy

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

What is it?

- Reduction of treatment time from 6 weeks to 3-4 weeks
- Maintains whole breast treatment target
- Increase dose per fraction (hypofractionation)
- $2.66 \times 16 = 42.56$ Gy (+/- boost)
- Use of standard external beam technique

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)
  - $50$ Gy in 25 fractions (2 Gy/fraction)

Local Recurrence
- short arm - 6.2%
- long arm - 6.7%

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

Skin: short arm - 8.9 %
- long arm - 3.2%

Subcutaneous tissue:
- short arm - 11.9%
- long arm - 10.4%

Mod/severe late radiation morbidity to:

- Skin: short arm - 8.9 %
- long arm - 3.2%

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Royal Marsden Randomized Trial Series:

START A TRIAL

- Pilot of Hyperfractionated 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
- $50$ Gy in 25 fractions (2 Gy/fraction) - LR rate - 3.6%
- $41.6$ Gy in 13 fractions (3.2 Gy/fraction) - LR Rate - 3.5%
- $39.6$ Gy in 13 fractions (3 Gy/fraction) - LR rate - 5.2%

START B Trial

- Parallel initiation with START A
- 2215 pts, pT1-3a pN0-1 M0, med f/u 6 years
- $50$ Gy in 25 fractions (2 Gy/fraction) - LR rate - 3.3%
- $40$ Gy in 15 fractions (2.67 Gy/fraction) - LR Rate - 2.2%
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
    - 210Gy 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 Radiotherapy

European Institute of Oncology (EIO)
Veronesi, et al.

- 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
- Thickness Measurement

ELIOT Technique Compliments Frank Vicini, MD
Intraoperative Radiotherapy with Electrons - ELIOT

- 1822 pts - 85% <2 cm, 71.4% NO, 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

- 2232 pts - 86% <2cm, 82% NO, 90% ER+
- Median F/U 2-3 yrs (?) ~ <20% of pts beyond 4 years
- Phase III randomized - multi-institutional
  - TARGIT (20 Gy to surface - 51-7 Gy to 1 cm)
  vs
  - External Beam Whole Breast
- 60 minutes in OR to deliver treatment
- In-breast Failure:
  - TARGIT 11.2%
  - EXBT 1.95%

Vaidya JS, Lancet 2010; 376: 91–102

- Hypofractionated Whole Breast Irradiation
- Intraoperative Radiotherapy (IORT)
- 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 = 17 Gy
  - Use of highly conformal dose delivery
    - Brachytherapy / CT-based 3D-CRT
Treatment Techniques
- 'Classic' three techniques
- New device based intracavitary

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

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, 2-5yr 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

Multi-Catheter Brachytherapy
placement - US, Stereotactic mammography, or CT guidance

3D conformal/IMRT
- Early pilot experiences
  - Vicini - supine
  - RTOG-0319
  - Formenti - prone
  - Taghion - supine
  - Accel. dose scheme

Phase III Clinical Studies

<table>
<thead>
<tr>
<th>Institution/Trial</th>
<th>Study Design</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B39/RTOG 0413</td>
<td>2-arm</td>
<td>WB +/1 + 1016 Gy Boost</td>
<td>2-arm WB +/1 + 1016 Gy Boost</td>
</tr>
<tr>
<td>National Institute of Oncology</td>
<td>Completed</td>
<td>50 Gy WB</td>
<td>10 Gy Boost</td>
</tr>
<tr>
<td>European Brachytherapy Breast Cancer BCC</td>
<td>Completed</td>
<td>50 Gy WB + 10 Gy Boost</td>
<td>50 Gy WB + 10 Gy Boost</td>
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<tr>
<td>European Institute of Oncology</td>
<td>Completed</td>
<td>50 Gy WB + 10 Gy Boost</td>
<td>50 Gy WB + 10 Gy Boost</td>
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<tr>
<td>University College of London</td>
<td>Completed</td>
<td>50 Gy WB + 10 Gy Boost</td>
<td>50 Gy WB + 10 Gy Boost</td>
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<tr>
<td>Canadian Trial RAPID</td>
<td>Mature</td>
<td>WB 42.5 Gy in 16 fractions or 50 Gy in 25 fractions +/1 10 Gy boost</td>
<td>38.5 Gy in 10 fractions</td>
</tr>
<tr>
<td>Medical Research Council - UK</td>
<td>Mature</td>
<td>WB 2.67 Gy in 15 fractions (1)</td>
<td>WP 2.4 Gy in 15 fractions (2)</td>
</tr>
</tbody>
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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:

- **ABS** - American Brachytherapy Society
- **ASBrS** - American Society of Breast Surgeons
- **GEC-ESTRO** - Groupe Europeen de Curietherapie-Europeen Society for Therapeutic Radiology and Oncology
- **ASTRO** - American Society of Radiation Oncology

- **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</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:

- Age 50-59
- T-stage T1 or T2
- Tumor Size 2.1-3.0 cm
- ER Status Negative
- Nodes NA
- Margins Close < 2 mm
- Histology any
- Pure DCIS ≤ 3 cm in size
- EIC ≤ 3 cm in size
- LVI Limited/focal
- Multicentricity Negative
- Neoadjuvant Chemo NA

Group 3

Unsuitable candidates:

Outside of a clinical trial, if any of these criteria are present:

- Age < 50
- T-stage T3 or T4
- Tumor Size > 3 cm
- ER Status NA
- Nodes pN1, pN2, pN3
- Margins Positive
- Histology NA
- Pure DCIS If > 3 cm in size
- EIC If > 3 cm in size
- LVI Extensive
- Multicentricity Present
- Neoadjuvant Chemo If used

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