Radiation Update 2014: Intra Operative Radiotherapy for Early Stage Breast Cancer

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I have no disclosures
Session 61

Learning Objectives

• IORT – definition
• Advantages and barriers
• Methods
• Application for IORT in breast cancer practice-
  – Boost
  – Partial Breast Irradiation
• Review the current and emerging clinical evidence
Definitions

Intraoperative Radiotherapy (IORT):
– the delivery of a single high dose (~18-21 Gy) of irradiation directly to the post excision tumor bed during surgery

Breast Cancer and IORT Applications

• Boost –
  – after whole breast irradiation (WBI)
  – additional dose of radiation
  – targeted to the highest risk portion of the breast around the lumpectomy cavity

• Partial Breast Irradiation (PBI) –
  – Radiation targeted ONLY to the highest risk portion of the breast around the lumpectomy cavity

IORT

Relevance in breast cancer practice related to 3 developments:

1. Patterns of failure post breast conservation
   • Tumor bearing quadrant – highest risk
   • Emergence of Accelerated Partial Breast irradiation (APBI) (adjuvant, 5-10 radiation fractions over 5-8 days)

2. Radiobiology of Breast Cancer
   • Response of breast cancer versus normal tissue re-evaluated
   • Mathematical models adjusted to better predict biologically effective doses
   • Efficacy of hypofractionated WBI in RCT’s

3. Technology Development
   • More mobile linear accelerators
   • Intrabeam
IORT

ADVANTAGES
• Very localized dose
• Direct visualization of area to treat
• Reduce patient burden of care
  – Reduce travel for external beam \textit{WBI}
  – Spare second procedure for brachytherapy \textit{APBI}

DISADVANTAGES
• Too localized dose
• Final pathology unknown
• Patient may receive unnecessary treatment
• Evidence still evolving
• Additional O.R time

IORT Methods

• Electrons – 6-9 MeV
  – Shielded operating room
• Brachytherapy – HDR Ir 192
  – Shielded operating room
• Intrabeam – low energy x-rays – 50 kV
  – No extra shielding
  – Developed for breast cancer IORT

Electron IORT

MOBETRON

The James Comprehensive Cancer Center
Electron IORT Breast Cancer

- Mobile linear accelerators in O.R.
- 6-8 MeV electrons (4-15 MeV)
- 5-8 cm diameter cones for treatment
- ~1 – 3 cm depth of breast tissue
- ELIOT
  - Developed European Institute of Oncology, Milan, Italy
  - Added lead shield under mobilized breast to protect chestwall
The TARGIT Technique

A miniature electron generator and accelerator accurately delivers radiotherapy from within the breast in about 25 minutes.

Radiotherapy Target Volumes Differ for Targit and ELIOT IORT

21 Gy at Surface
~ 5-7 Gy at depth of 10 mm

Targit: 5 mm
ELIOT: 20 mm
Whole breast irradiation plus "Boost"

- Boost: 10-16 Gy 5-8 Fractions
- Total Cavity dose: 60-66 Gy 30-33 Fractions
- Whole breast dose: 50 Gy 25 Fractions

IORT BOOST
International Society of Intraoperative Radiotherapy (ISIORT)

- Pooled analysis of 6 European institutions
- 1131 patients treated between 1998-2005
- Lumpectomy and Axillary surgery
- IORT: Median dose 9.7 Gy (5-17 Gy)
- Whole breast irradiation: 50 – 54 Gy (1.7 -2 Gy daily fractions)
  - Median 6.6 week interval (3 weeks w/o Chemo and 18 weeks w/ Chemo)
ISIORT: Boost Pooled Analysis

<table>
<thead>
<tr>
<th>Population (%)</th>
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<tbody>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>&gt; T-2</td>
</tr>
<tr>
<td>Nodes</td>
</tr>
<tr>
<td>N-0</td>
</tr>
<tr>
<td>&gt; N-1</td>
</tr>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>1-2</td>
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<tr>
<td>3</td>
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</table>

Results:
- Median F/U: 52.3 months
- 5 in-breast recurrences
- 99.4% Local control
- 44 Mastectomy for “massive” positive margins

Sedlmayer, Strahlen Onkol, 183: 2007

Intrabeam TARGIT: Boost

- Single arm prospective pilot
- 302 cases treated 1998-2005
- IORT:
  - 18-20 Gy applicator surface,
  - 5-7 Gy at 1 cm
- Whole breast irradiation: 45-50 Gy, 25 fractions, 5 weeks

Vaidya, IJROBP, 66:2006

TARGIT: Boost

<table>
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<tr>
<td>Nodes</td>
</tr>
<tr>
<td>N-0</td>
</tr>
<tr>
<td>&gt; N-1</td>
</tr>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>1-2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&gt; 51</td>
</tr>
<tr>
<td>&lt; 51</td>
</tr>
</tbody>
</table>

- Median F/U: 24 months
- 4 in-breast recurrences
- 5 year actuarial LR rate: 2.6%

Vaidya, IJROBP, 66:2006
Electrons Intraoperative Therapy (ELIOT): Boost

- 211 premenopausal women accrued 2004-2007
- Prospective single arm trial
- IORT: 12 Gy - 4 cm diameter cone
  - 5-7 MeV (~ 1.5 cm thickness)
- Hypofractionated WBI (HEBRT) - 37.05 Gy/13 fractions
- Acceptable toxicity:
  - Grade 3 acute: 28%
  - Grade 3 late: < 0.5%
- Median follow-up 11 months – No recurrences so far.

Ivaldi, IJROBP, 2008

HIOB - Hypofractionated Whole-Breast Irradiation after IOERT Boost

- Single arm prospective clinical trial, ISIORT
- Open January 2011
- IOERT: 11 Gy
  - minimum target volume dose of 90% encompassing the PTV
- WBI: 40 Gy, 15 fractions, 2.7 Gy
  - To start 6-8 weeks postop or post chemo
- Eligibility:
  - Histological proven invasive breast carcinoma
  - Age: ≥ 35 years
  - Tumor stage T1-2
  - Nodal status: NO-1

PI: Sedlmayer, NCT01343459

Summary: IORT Boost

- Boost - is an established component of WBI known to reduce in-breast recurrence
- IORT Boost –
  - Excellent local control
  - Acceptable toxicity
- Advantages of IORT boost:
  - Targeting accuracy
  - Shortens treatment course
  - Good use of IORT
IOERT: PBI Verona

- Phase II prospective trial
- Treatment – IORT 21 Gy after lumpectomy
  - 80% dose to cover target
  - Target: cavity + 2 cm
- Eligibility “low risk”: (select)
  - Invasive ductal cancer,
  - age > 50,
  - T-size < 3 cm
- Endpoints:
  - Primary: True local recurrence (same quadrant)
  - Secondary: Toxicity and Cosmesis
- 226 women accrued 2006-2009

Population (%)

<table>
<thead>
<tr>
<th>Feature</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes</td>
<td>N-0</td>
<td>N-1</td>
</tr>
<tr>
<td>Grade</td>
<td>1-2</td>
<td>3</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60</td>
<td>≤ 60</td>
</tr>
</tbody>
</table>

- Mean F/U: 46 mo.
- 1 local recurrence (0.4%)
TARGIT – A: Phase III randomized trial of Targit vs WBI

- ARMS: - Intrabeam (20 Gy surface, 5-7 Gy 1 cm) * ~ 15% WBI
- WBI

- Population
  - Median age: 63 years
  - 82% ≥ age 55 (post menopausal)
  - 81.4% - T1
  - 17% - N1
  - ER +: 90% (anti endocrine therapy 67%)
  - Grade 1-2: 85%

Vaiyda, Lancet 376: 2010, SABC 2010

Results:

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>n</th>
<th>% LR 4 Year</th>
<th>% RTOG G3 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrabeam device</td>
<td>1113</td>
<td>1.25</td>
<td>0.54</td>
</tr>
<tr>
<td>WBI</td>
<td>1119</td>
<td>0.95</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Vaiyda, Lancet 376: 2010, SABC 2010

5-year Results for Local Control and Overall Survival From the TARGIT-A Randomised Trial

- ARMS: - Intrabeam (20 Gy surface, 5-7 Gy 1 cm) * ~ 15% WBI
- WBI

- Median follow up: 29 months
- Population
  - Median age: 63 years
  - 82% ≥ age 55 (post menopausal)
  - 81.4% - T1
  - 17% - N1
  - ER +: 90% (anti endocrine therapy 67%)
  - Grade 1-2: 85%

Vaiyda, Lancet 383, 2014
Results:

- Median F/U: 36.1 mo.
- Ipsilateral Local recurrence: 2.3%
- New primary: 1.3%

<table>
<thead>
<tr>
<th>Tumor</th>
<th>T1</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2</td>
<td>35</td>
</tr>
</tbody>
</table>

Veronesi, Breast Can Res Treat 124:2010

ELIOT PBI

- 1822 breast cancer patients
- 2000-2008 study period
- 21 Gy IORT post quadrantectomy
- Population: (%)

- Tumor T1 85
  T2 15
- Nodes N0 71
  N1 29
- Grade 1-2 55
  3 25
- Age > 50 78
  < 50 32
- ER + 89

Veronesi, Breast Can Res Treat 124:2010

ASTRO Consensus Statement for Treatment with APBI Outside a Clinical Trial

<table>
<thead>
<tr>
<th>Suitable</th>
<th>Cautionary</th>
<th>Unsuitable</th>
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<tbody>
<tr>
<td>Patient Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60 years</td>
<td>50-59</td>
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<tr>
<td>BRCA 1-2</td>
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<td>no</td>
</tr>
<tr>
<td>Path Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-size</td>
<td>≤ 2 cm</td>
<td>2-3 cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>T2-T3</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative (≤ 2 mm)</td>
<td>Close (≤ 2 mm)</td>
</tr>
<tr>
<td>LN</td>
<td>No</td>
<td>Limited, focal</td>
</tr>
<tr>
<td>ER</td>
<td>Pos.</td>
<td>Neg.</td>
</tr>
<tr>
<td>Multicentric</td>
<td>unicentric</td>
<td>unicentric</td>
</tr>
<tr>
<td>Multifocal</td>
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<tr>
<td>Histology</td>
<td>IBC</td>
<td>ILC</td>
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<tr>
<td>DCIS, EIC</td>
<td>No, No</td>
<td>Yes, Yes (≤ 3 cm)</td>
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<tr>
<td>N stage</td>
<td>pN0 (0-3)</td>
<td>pN1, N2-3</td>
</tr>
<tr>
<td>Nodal Surgery</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Smith, IJROBP,4:2009
ELIOT PBI: by ASTRO Consensus Guidelines for APBI

<table>
<thead>
<tr>
<th></th>
<th>Suitable</th>
<th>Cautorous</th>
<th>Unsuitable</th>
<th>p</th>
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<tbody>
<tr>
<td>n</td>
<td>294</td>
<td>668</td>
<td>812</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral in-breast recurrence</td>
<td>1.5 %</td>
<td>4.4 %</td>
<td>8.8 %</td>
<td>0.003</td>
</tr>
<tr>
<td>Regional nodal failure</td>
<td>1.5 %</td>
<td>1.9 %</td>
<td>1.1 %</td>
<td>0.55</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1.5 %</td>
<td>1.7 %</td>
<td>3.9 %</td>
<td>0.047</td>
</tr>
<tr>
<td>Cause specific survival</td>
<td>99.1 %</td>
<td>98.7 %</td>
<td>96.5 %</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Leonardi, IJROBP, 2011

ELIOT Phase III Randomized Trial

- 2000 -2007
- 1305 women ≥ 48 years
- T size < 2.5 cm

Quadrantectomy

ELIOT 21Gy

50 Gy WBI + Boost

Veronesi et al, Lancet Oncol 14:2013

ELIOT Phase III Randomized Trial

5-year event rates

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>ELIOT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral in-breast recurrence</td>
<td>0.7 %</td>
<td>3.3 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In quadrant</td>
<td>0.7 %</td>
<td>1.2 %</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Outside quadrant</td>
<td>0</td>
<td>2.1 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional nodal</td>
<td>0.4 %</td>
<td>1.1</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Median follow-up 5.8 years

Veronesi et al, Lancet Oncol 14:2013
Patient Preferences Regarding Radiotherapy: IORT versus WBI

- 81 women had (74%) or planning (20%) WBI
- Intro educational section about WBI and IORT
  - Time: WBI 5-6 weeks and IORT “adding about 30 min”
  - Cost: WBI 5-6 times greater than IORT
  - Toxicity: WBI damage to ribs, nerves, heart or lungs and radiation induced cancers and “unknown” for IORT
  - Local recurrence: relationship to cancer mortality - (removed after first 68 cases)
- Median (mean) additional accepted risk for IORT: 2.3% (3.2%)

Summary IORT PBI

- Randomized clinical trials results demonstrate acceptable recurrence rate for IORT – but significantly improved by WBI.
- Selection criteria important!
- Stick to ASTRO consensus guidelines “suitable”!!
- Better characterization of cosmetic results and late toxicity, particularly patient reported outcomes needed