Accelerated Partial Breast Irradiation

OSCO/OU Stephenson Cancer Center
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Robert Kuske, MD, FAACE
Founder, Medical Director
Arizona Breast Cancer Specialists
Scottsdale, Arizona
Disclosures
Robert R Kuske, MD, FAACE

Unrestricted educational grant from Elekta for an interstitial brachytherapy collaborative clinical research study

Minor stock options for Cianna Medical
Radiation Oncology in Breast Cancer
Role of Radiation Oncology

1. DCIS
2. Survival advantage in invasive breast cancer
3. Breast Conservation Therapy
4. Altered fractionation schemes
5. Accelerated Partial Breast Irradiation
6. Post-mastectomy RT
7. Locally Advanced, Inflammatory, or Metastatic Breast Cancer
A major event of the Decade

• The Fisher Hypothesis dies

• Local therapies can have an impact on survival
Early Breast Cancer Trialists Group

• RT after lumpectomy ↓ 10 yr overall recurrence rate 35% to 19% (▲ 16%)  
  (p < 0.00001)

• RT ↓ 15 yr risk of a breast cancer death  
  25% to 21% (▲ 4%)  
  (p=0.00005)
Survival Advantage with Breast RT

1. Can not be realized if:
   - Systemic micrometastases are not eradicated
   - RT fails to control LR disease
   - There are no residual LR cancer cells after surgery

2. Subset most benefitting from RT:
   - LR subclinical ds after surgery but no hematogenous mets
   - Persistent LR ds and hematogenous mets after surgery, but effective chemo or endocrine therapy or the immune system has cleared the blood of all malignant cells
More major events of the Decade

- Breast Conservation rates rise to 75% by 2005
- Breast Conservation rates fall dramatically by 2014
- APBI rates rise to 12%, but are stable or falling now
- Canadian and British hypofractionation schemes for WBI
1991: First Modern Brachytherapy Alone PBI patient from Venezuela

After low-dose-rate Brachytherapy

10-year follow-up after APBI
Hypothesis 25 Years Ago

- The primary benefit to RT is eradication of microscopic malignant cells within 2 cm of the lumpectomy edge
Rationale for APBI

• Pathology studies
Rationale for APBI

• Pathology studies

• “Elsewhere” recurrence rates after BCT
Rationale for APBI

• Pathology studies
• “Elsewhere” recurrence rates after BCT
• Randomized studies of lumpectomy followed by WBI vs. No RT
Hypothesis 25 Years Ago

• Dose dense RT by brachytherapy would:
  1. Improve local control
Hypothesis 25 Years Ago

• **Dose dense RT by brachytherapy would:**
  1. Improve local control
  2. Reduce the time from 6 ½ weeks to 4 or 5 days
Hypothesis 25 Years Ago

• Dose dense RT by brachytherapy would:
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  2. Reduce the time from 6 ½ weeks to 4 or 5 days
  3. Minimize normal tissue exposure
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• Dose dense RT by brachytherapy would:
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  4. Reduce side effects of RT
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5. **Spare the heart for left breast cancers**
Hypothesis 25 Years Ago

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  5. Spare the heart for left breast cancers

6. **Result in excellent cosmetic outcomes**
Hypothesis 25 Years Ago

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  4. Reduce side effects of RT
  5. Spare the heart for left breast cancers
  6. Result in excellent cosmetic outcomes

7. Allow more women access to BCT
Hypothesis 25 Years Ago

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  2. Reduce the time from 6 ½ weeks to 4 or 5 days
  3. Minimize normal tissue exposure
  4. Reduce side effects of RT
  5. Spare the heart for left breast cancers
  6. Result in excellent cosmetic outcomes
  7. Allow more women access to BCT
  8. Lower Societal Cost of Breast Cancer Care
Methods of APBI: Interstitial Brachy

Technological Advances

• From free-hand with the wound open to CT-based image-guided placement of catheters precisely 1.5 - 2 cm beyond the lumpectomy cavity edge or clips

• Does not even require a cavity (Oncoplastic Surgery)

• Any size, any shape cavities, w or w/o pockets
Breast Cancer in Augmented Women: Avoiding capsular contracture
Brachytherapy with Catheters 2 cm beyond Lumpectomy Cavity
Turquoise = Tiny 200% hot spots
Methods

• A template with pre-drilled holes compresses the breast tissue up and away from the implant while pushing the implant away

• A CT of the breast with the template attached is obtained
Techniques of APBI

1. Interstitial Brachytherapy
2. Balloon catheters
3. Single-entry strut-based device
4. External beam PBI
5. Single dose intra-operative electron beam
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Partial Breast Irradiation
- 3D Conformal External Beam Radiotherapy -
Techniques of APBI

1. Interstitial Brachytherapy
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### Selection Criteria

<table>
<thead>
<tr>
<th><strong>Ochsner Trial</strong></th>
<th><strong>RTOG Phase II</strong></th>
<th><strong>NSABP/RTOG Phase III</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size &lt; 4cm</td>
<td>Tumor size &lt; 3cm</td>
<td>Tumor size &lt; 3cm</td>
</tr>
<tr>
<td>DCIS included</td>
<td>DCIS excluded</td>
<td>DCIS included</td>
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<tr>
<td>0 to 3 (+) Nodes</td>
<td>Same</td>
<td>Same</td>
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<td>Selection Criteria</td>
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<tr>
<td><strong>Ochsner Trial</strong></td>
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<tr>
<td>• Extra-capsular nodal extension: Prohibited</td>
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<tr>
<td>• EIC: Allowed</td>
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<tr>
<td><strong>RTOG Phase II</strong></td>
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<td></td>
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<td>• ECE: Prohibited</td>
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<td></td>
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<tr>
<td>• EIC: Prohibited</td>
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</tr>
<tr>
<td><strong>NSABP/RTOG Phase III</strong></td>
<td></td>
<td></td>
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<tr>
<td>• ECE: Prohibited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• EIC: Allowed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Selection Criteria

**Ochsner Trial**
- (-) Inked surgical margins
- LCIS or ILC: Allowed
- Col. Vasc. Ds: Allowed

**RTOG Phase II**
- Same
- Excluded

**NSABP/RTOG Phase III**
- Same
- Allowed
- Excluded
ASTRO Panel Consensus: Group 1 – Suitable if all of the following criteria are met:

- Age $\geq$ 60 years old
- Infiltrating ductal ca & favorable subtypes
- Size $\leq$ 2 cm
- Microscopically (-) margins $\geq$ 2 mm
- Axillary lymph nodes (-)
- ER (+)
- EIC (-)
- LVI (-)
I assume these are guidelines.
Is Accelerated Partial Breast Irradiation (APBI) ready for prime time?

- Multiple Phase II trials demonstrate excellent outcomes
- Three Phase III trials have shown equivalent tumor control and less toxicity
Long-term outcome from RTOG 9517: A phase I/II study of accelerated partial breast irradiation (APBI) with multicatheter brachytherapy (MCT) following lumpectomy for early-stage breast cancer.


Ohio State University, Radiation Therapy Oncology Group. - Alonna Breast Cancer Specialists. - Breast Clinic. - Indiana University. - University of Colorado. - Medical College of Wisconsin. - Mount Sinai Comprehensive Cancer Center. - Pittsburg Hospital. - Memorial Sloan Kettering.

BACKGROUND

Selection of APBI as standard whole breast irradiation (WBI) for breast conservation is ongoing in numerous randomized clinical trials. To some extent before the outcome from randomized trials evaluating the efficacy of APBI in comparison to WBI is known, APBI has increasingly gained acceptance in clinical practice, despite relatively limited long-term data.

INTERSTITIAL BRACHYTHERAPY is one of the earliest methods and can usually provide long-term cancer control in eligible patients. A phase I/II study with the goal of evaluating the safety and effectiveness of this therapy technique for APBI.

Efficacy

Table 1: Patient population

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Under 50</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
</tr>
</tbody>
</table>

Conclusions

This multi-institutional phase I/II trial studying MCT-APBI continues to report durable local control rates and long-term follow-up. The most common site of loco-regional recurrence is within the targeted ABPI volume with only 1 failure occurring elsewhere in the breast.
5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial

Vratislav Strnad, Oliver J Ott, Guido Hildebrandt, Daniela Kauer-Dorner, Hellen Knauerhase, Tibor Major, Jaroslaw Lyczek, Jose Luis Guinot, Jürgen Dunst, Cristina Gutierrez Miguelez, Pavel Slampa, Michael Allgäuer, Kristina Lössl, Bülent Polat, György Kovács, Arnt-René Fischedick, Thomas G Wendt, Rainer Fietkau, Marian Hindemith, Alexandra Resch, Anna Kulik, Leo Arribas, Peter Niehaff, Fernando Gudea, Annika Schlamann, Richard Pötter, Christine Gall, Martina Malzer, Wolfgang Uter, Csaba Polgár, on behalf of the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO)

Summary

Background In a phase 3, randomised, non-inferiority trial, accelerated partial breast irradiation (APBI) for patients with stage 0, 1, and IIA breast cancer who underwent breast-conserving treatment was compared with whole-breast irradiation. Here, we present 5-year follow-up results.

Published Online
October 20, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00421-7
Local control: APBI not statistically different from WBI

Figure 2: Ipsilateral breast tumour recurrence
APBI = accelerated partial breast irradiation. WBI = whole-breast irradiation.
Level 1 Evidence:
Similar tumor control
Less toxicity

Findings Between April 20, 2004, and July 30, 2009, 551 patients had whole-breast irradiation with tumour-bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. At 5-year follow-up, nine patients treated with APBI and five patients receiving whole-breast irradiation had a local recurrence; the cumulative incidence of local recurrence was 1.44% (95% CI 0.51–2.38) with APBI and 0.92% (0.12–1.73) with whole-breast irradiation (difference 0.52%, 95% CI –0.72 to 1.75; p=0.42). No grade 4 late side-effects were reported. The 5-year risk of grade 2–3 late side-effects to the skin was 3.2% with APBI versus 5.7% with whole-breast irradiation (p=0.08), and 5-year risk of grade 2–3 subcutaneous tissue late side-effects was 7.6% versus 6.3% (p=0.53). The risk of severe (grade 3) fibrosis at 5 years was 0.2% with whole-breast irradiation and 0% with APBI (p=0.46).

Interpretation The difference between treatments was below the relevance margin of 3 percentage points. Therefore, adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is not inferior to adjuvant whole-breast irradiation with respect to 5-year local control, disease-free survival, and overall survival.
Collaborative Group Registry Trials

- MammoSite
- Contura
- SAVI
- Interstitial multi-catheter brachytherapy

{Can treat any size or shape cavity with pre-determined margin}
Interstitial Brachytherapy Collaborative Group

PROMIS: 

*Pooled Registry of Multicatheter Interstitial Sites*
PROMIS Collaborative Group

- University of Wisconsin - 377 Women
- William Beaumont - 217 Women
- Arizona Breast Cancer Sp’s - 664 Women
- UCLA - 34 Women
- Gamma West - 80 Women
- Oklahoma City - 199 Women
- Total Number - 1571 Women
## Results – Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>LR (Crude)</th>
<th>5y (Actuarial)</th>
<th>10y (Actuarial)</th>
<th>Median time to (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR Total</td>
<td>5.2%</td>
<td>3.8%</td>
<td>7.6%</td>
<td>4.1 (0.8-18)</td>
</tr>
<tr>
<td>TR/MM</td>
<td>1.7%</td>
<td>1.6%</td>
<td>2.4%</td>
<td>3.7 (0.8-6.8)</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>2.4%</td>
<td>1.5%</td>
<td>3.4%</td>
<td>4.7 (1.1-13.8)</td>
</tr>
<tr>
<td>Ips Unk</td>
<td>1.2%</td>
<td>0.6%</td>
<td>1.9%</td>
<td>6.0 (1.6-18)</td>
</tr>
</tbody>
</table>
PROMIS

• DCIS: 5% actuarial IBTR at 7 years
• Tumor Biology “trumps” young age, node-positivity, stage, grade, and margins
• Triple-negative, Her-2 over-expressed correlate with higher recurrence rates
• ASTRO guidelines need to be re-written
Discrepancies in accelerated partial breast irradiation (APBI) treatment outcomes in younger women when using claims versus a database (PROMIS) with actual recurrence rates

“Big Data” Healthcare Claims Database

- Used 5-year subsequent mastectomy rates as a surrogate for IBTR
- Women under 50 years old with ER (-) tumors have higher mastectomy rates with APBI vs. WBI

Smith GL et al, IJROBP, 2015
Big Data Outcomes

- Median follow-up = 2.4 years

<table>
<thead>
<tr>
<th>Subseq.Mastect.</th>
<th>APBI %</th>
<th>WBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;50/ER-</td>
<td>24.4</td>
<td>9.0</td>
</tr>
<tr>
<td>Age≥50/ER-</td>
<td>8.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Age&lt;50/ER+</td>
<td>5.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Age≥50,ER+</td>
<td>4.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Question: What if we had real data and actual IBTR for an identical group of patients?

- PROMIS has over 1500 patients, of whom 528 met the same inclusion criteria as Smith, et al:
  1. Age ≤ 64 years
  2. Invasive ductal carcinoma with ≥ 1 year of FU
PROMIS patients

- 1997-2013
- 9.4% N1a
- Median age was 55 yrs (range 22-64)
- Median tumor size = 11.0 mm (range 0.15-35)
- Median FU time = 6.5 years, 1-20 yrs (>4 years more than Smith et al.)
PROMIS treatment

- All interstitial brachytherapy APBI
- Dose 3.4 Gy x 10 fractions HDR
- Minority received 4 Gy x 8 fractions or LDR
- 72% of women received anti-estrogen therapy and 30% received chemotherapy
Results

Women were classified into 4 categories:

<table>
<thead>
<tr>
<th>Groupings</th>
<th>Age &lt; 50/ER-</th>
<th>Age ≥ 50/ER-</th>
<th>Age &lt; 50/ER+</th>
<th>Age ≥ 50/ER +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26 (4.9%)</td>
<td>39 (7.3%)</td>
<td>127 (24%)</td>
<td>334 (63%)</td>
</tr>
<tr>
<td>5 year Actuarial Outcomes (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBTR</td>
<td>12.7</td>
<td>7</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Regional Failure</td>
<td>8.7</td>
<td>2.8</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Distant Metastasis</td>
<td>15.7</td>
<td>5.5</td>
<td>1.1</td>
<td>2</td>
</tr>
<tr>
<td>Ds Specific Survival</td>
<td>87</td>
<td>94.5</td>
<td>100</td>
<td>98.9</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>82.3</td>
<td>94.5</td>
<td>100</td>
<td>96.5</td>
</tr>
</tbody>
</table>
Conclusions:

• Women <50/ER—indeed have higher rates of IBTR
• Our “actual data” of failure rates, however, were much lower than the “mastectomy surrogate” rate (12.7% vs. 24.4%)
• Given that we have >4 years longer FU than Smith et al., our 12.7% actual IBTR is similar to the 9.0% mastectomy rate given for WBI for young ER (-) women
• For the 95% of patients without the aggressive combination of <50/ER-, rates of 2.6-7.0% IBTR at 6.5 years are very low with interstitial brachy APBI
Level 1 Evidence:
The NSABP B39/RTOG 0417
&
The GEC-ESTRO Randomized Phase III Clinical Trials

• The North American phase III trial is pending
• The European phase III trial has been published in Lancet Oncology
• The European Trial establishes non-inferiority between Interstitial Brachytherapy APBI and the Conventional 6 weeks of Whole Breast RT
APBI: Current Arizona Selection Criteria

- APBI appears to be an acceptable option for treatment of select tumors < 3 cm
- Excised with clear margins
- With 0-3 + nodes without extracapsular extension
Conclusions

1) Whole breast hypofractionated RT, with > 7,000 pts randomized to trials, may be offered to select women after BCS.
Conclusions

2) Over the last 25 years, PBI is a model for evidence-based medicine.

3) There are more pts enrolled onto the NSABP B39 trial (>4,200) than all the randomized clinical trials that took us from mastectomy to BCT, and there are a dozen other randomized trials!
Conclusions

4) Radiation Oncology is undergoing a revolution in many disease sites with tighter conformal fields delivered with dose-dense hypofractionation over as shorter time period with super-technology
Conclusions

5) Since breast RT improves survival, patient-selection is key

6) NSABP B39/RTOG 0411 has closed, with 4214 women enrolled, and the results will be of utmost importance
ATTENTION
PARADIGM SHIFT
• NOVAC 7: An IORT dedicated electron accelerator
• Conventional OR (no shielding needed)
• Mobile and easily docked
• Electron beams of 4 different energies: 3, 5, 7, 9 MeV
University College London
J Vaidya & M Baum

Intraoperative - Photoelectron
Level I Evidence: Randomized Trials of IORT vs. Whole Breast RT

- Progressive rise in local recurrence for IORT vs. WBI
  - ELIOT: 11X increase in recurrence with IORT
  - TARGIT-A: 2.5X increase in recurrence with IORT
Insights into IORT

- The concern is the divergent slopes of these curves.
- The Milan e (-) trial has some unfavorable selection criteria included.
- Despite the differences, the absolute difference in IBTR may be trivial.
- \(7\%\) ELIOT @ 9 yrs
- \(2.5\%\) TARGiT at 5 yrs