Current Concepts in Radiation Oncology

Accelerated Partial Breast Radiation

Bruce G. Haffty, MD
Professor and Chairman
Dept. of Radiation Oncology
Cancer Institute of New Jersey
Rutgers University-RWJMS-NJMS
I have no conflicts of interest to disclose
Background

• Limitations of CF-WBI
  – Long overall treatment time
    • Patient inconvenience
    • Cost
      – Limited access in rural areas
      – Perhaps unnecessary toxicity due to irradiation of uninvolved portions of breast and normal tissue
Rationale for Partial Breast Radiation

- The majority of all local recurrences occur within the region of initial lumpectomy
  - With or without whole-breast radiation therapy
- Why do we need to radiate the whole-breast
- Early Phase I/II data on partial breast irradiation appears promising for selected patients
Potential Advantages of APBI

• All local therapy completed prior to chemotherapy
• Treatment of tissue at most increased risk of sub-clinical disease – rather than healthy breast tissue/skin may actually improve cosmesis
Potential Disadvantages

• Local relapses may be higher
• Fibrosis with larger fractions may be significant with longer follow-up
• Prospective randomized data proving its effectiveness is lacking
APBI-Treatment Approaches

- Multi-catheter Interstitial
- Single Catheter Balloon Based
- External Beam
- Intraoperative
Multi-Catheter Brachytherapy placement – US, Stereotactic mammography, or CT guidance
Partial breast irradiation

• Interest in PBI surged after May, 2002 sparked by the FDA approval of the Mammosite device
• FDA approved the device, not the concept of PBI
• FDA approval was based on concept of the MammoSite as a boost after whole breast RT
• “The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.”
  – FDA-www.accessdata.fda.gov
MammoSite Device

Variable 4 to 5 cm balloon
50 – 70 cc

Radiation source port pathway

Injection Port
Ideal Case for MammoSite

Placed by Surgeon or Rad Onc - at the time of lumpectomy or post lumpectomy

Target conforms to balloon surface
IntraCavitary Applicators

- MammoSite (Cytyc)
- SAVI (Cianna)
- ClearPath (North American Scientific)
- Xoft
- Contura MLB (SenoRx)
Key Study
William Beaumont
N=199
82% stage I
100% negative margins
10-yr in-breast recurrence: 3.8%
Excellent/good cosmetic outcome: 99%

Limitations

• Invasive
• Risk of infection
• Operator-dependent
• Limited diffusion
• Heterogeneous clinical outcomes
Key Study

ASBS Mammosite Registry

N=1,449

>90% stage I

ER Negative associated with higher IBTR

5-yr in-breast recurrence: 3.8%

Excellent/good cosmetic outcome: 90.6%

APBI: Balloon-based

Limitations

• Invasive
• Risk of infection and seroma
• Short follow up
• Not appropriate for superficial tumors
Key Study
RTOG 0319
N=53
92% stage I
100% negative margins
3-yr in-breast recurrence: 6% (95% 0-12%)

Limitations

- Very short follow up
- Few patients treated
- Uncertainty in target delineation
- Uncertainty day to day setup
- Increased integral dose to breast
APBI: External Beam

Limitations

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• Few patients treated
• Uncertainty in target delineation
• Uncertainty day to day setup
• Increased integral dose to breast
## 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><strong>NSABP B 39/RTOG 0413</strong></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><strong>National Institute of Oncology Budapest, Hungary</strong></td>
<td>258/258</td>
<td>50 Gy WB</td>
<td>(1) Interstitial Brachytx (5.2 Gy X 7) or (2) Electrons (50 Gy)</td>
</tr>
<tr>
<td><strong>European Brachytherapy Breast Cancer GEC-ESTRO Working Group</strong></td>
<td>1170/657</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><strong>European Institute of Oncology ELIOT</strong></td>
<td>1200/1200</td>
<td>50 Gy WB + 10 Gy Boost</td>
<td>Intra-operative Single fraction EBRT 21 Gy x 1</td>
</tr>
<tr>
<td><strong>University College of London TARGIT</strong></td>
<td>1600/850</td>
<td>WB RT (per center) + Boost</td>
<td>Intra-operative Single fraction EBRT 5 Gy x 1</td>
</tr>
<tr>
<td><strong>Canadian Trial RAPID</strong></td>
<td>2128/400</td>
<td>WB 42.5Gy in 16 or 50Gy in 25 +/- 10 Gy boost</td>
<td>3D CRT only 38.5 Gy in 10</td>
</tr>
<tr>
<td><strong>Medical Research Council – UK IMPORT LOW</strong></td>
<td>1935</td>
<td>WB 2.67Gy X 15</td>
<td>(1) WB 2.4Gy X 15 PB 2.67Gy X 15 (2) PB only 2.67Gy X 15</td>
</tr>
</tbody>
</table>
B-39/0413 Protocol Design

Eligible patient treated with lumpectomy
Post-Lumpectomy CT evaluation

Stratification
Disease stage – DCIS, invasive N0, invasive N1 (1-3)
Age - ≤49, ≥50
Hormone receptor status (ER-, ER+)

Randomization

WBI
50–50.4 Gy in 1.8-2.0 Gy fractions to whole breast, followed by electron boost to surgical bed with margin for total dose of 60-66.6 Gy

VS

APBI
34 Gy in 3.4 Gy bid x 5-7 days
Interstitial Brachytherapy
or
34 Gy in 3.4 Gy bid x 5-7 days
Mammosite Balloon Catheter
or
38.5 Gy in 3.85 Gy bid x 5-6 days
3D Conformal External Beam
## APBI: Randomized Phase III Data

<table>
<thead>
<tr>
<th>Trial</th>
<th># patients</th>
<th>Median F/U</th>
<th>Results</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI, Hungary</td>
<td>258</td>
<td>5.5 years</td>
<td>3.4% vs. 4.7% (IBTR)</td>
<td>NS</td>
</tr>
<tr>
<td>Christie Hospital</td>
<td>708</td>
<td>5.4 years</td>
<td>11% vs. 19.6% (IBTR)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yorkshire BCG</td>
<td>174</td>
<td>8 years</td>
<td>9% vs. 24% (LRF)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
APBI: Clinical Outcomes

- Median follow up 5.5 years
- Risk of in-breast recurrence
  - WBI: 3.4%
  - APBI: 4.7%
  - P = .50

**Implication**: APBI may produce comparable results to WBI in highly selected patients

External Beam Toxicity (Using 385 twice daily over 5 treatment days to 3850)

- 34 Patients treated with 385 BID to 3850
- Used IMRT and Breath Holding as opposed to 3-D Conformal and Free Breathing which may “Feather” the dose slightly
- “Unacceptable” Cosmesis in 7 Patients

Jagsi et al. Int J. Rad Onc Biol Phys, 2010
APBI External Beam Toxicity

- 60 Patients treated with NSABP/RTOG program of 385 BID to 3850
- At 15 months moderate to severe toxicity (fibrosis mainly) in 10% of patients

Hepel et al. Int J Rad Oncol Biol Phys, 2009
External Beam APBI Toxicity: 385 BID to 3850

- Tufts Data Recently Updated by Leonard et al.
  - 80 pts tx with 385 BID to 3850; 32 mos follow-up
  - Fat necrosis 11%; Fair/Poor Cosmesis in 19%
- However, ASTRO abstract by Julien et al. claimed no significant adverse effects in reported data to date from external beam APBI in NSABP/RTOG trial using this fractionation scheme
- Canadian Rapid Trial and NSABP trials using this fractionation scheme
Stratification

- Age: < 50, > 50
- Histology: DCIS, invasive disease
- Tumour size: < 1.5 cm, > 1.5 cm
- ER status: +ve, -ve
Summary of RAPID Late Breaking Abstract

- 2135 women randomized to WBRT vs APBI
- Whole breast (50 Gy/25 Fractions) or Canadian (42.5 Gy/16 fractions) +/- Boost
- APBI 3.85 BID to 38.5 Gy all External Beam Conformal
- Cosmesis assessed by Study Nurse and Patient:
  - At Baseline and At Follow-up (3 Years)
- Cosmesis also assessed by panel of trained radiation oncologists unaware of tx arm using digital photos
- Planned interim analysis based on nurse assessment at 2.5 years
- DSMC recommended release of results based on highly significant findings
Highlights of Results of RAPID LBA

- Critical strength of this trial is measures of cosmesis at baseline and over time
  - Adverse at baseline in 17.2% WB and 18.9% APBI prior to therapy
- Adverse cosmesis deteriorated by Nurse Assess with APBI (from 18.9% 31.5%) but remained stable in the whole breast arm (17.2% 18.6%) over 3 Years
- Adverse cosmesis was also worse with APBI when assessed by both patients and radiation oncologist panel
- Grade I/II late toxicities increased in APBI arm
- Grade III/IV late toxicities rare in both arms
### Adverse Cosmetic Assessment
#### 3 Independent Measures

<table>
<thead>
<tr>
<th></th>
<th>Whole Breast</th>
<th>APBI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse Assessment</td>
<td>18.6%</td>
<td>31.5%</td>
<td>.0001</td>
</tr>
<tr>
<td>Patient Assessment</td>
<td>18.4</td>
<td>26.2</td>
<td>.004</td>
</tr>
<tr>
<td>RO Panel Assessment</td>
<td>16.6</td>
<td>35.1</td>
<td>.0001</td>
</tr>
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</table>
RAPID Toxicity Data
Clearly the most robust objective data on this issue to date

• 18-20% of patients started out with “Adverse” Cosmetic Outcomes

• The strength of their observation is that cosmesis remained stable in the WBRT group but deteriorated in the APBI group

• This robust comparison between whole breast and APBI can only be accomplished through this type prospective analysis from a randomized trial

• This was confirmed to be statistically significant across three cosmetic assessment methodologies—nurses, patients, and radiation oncologist panel
Where to go from here?

- Await detailed results full details of RAPID toxicity and cosmetic outcome manuscript-JCO in Press with Editorial by Jagsi and Haffty
- Await results of RTOG/NSABP Cosmesis
- Await the results of efficacy (long term local control and toxicity of RAPID, NSABP, and others) of randomized APBI trials
Intraoperative Electrons-ELIOT

21 Gy Delivered in Approximately 20 Minutes to Tumor Bed
Intra-operative Electrons

- Randomized trial comparing intra-operative electrons to standard course of EBRT pending
- Recent report of 1822 cases of treated with BCS and intraoperative electrons (21 Gy delivered in a single session to the tumor bed intraoperatively
- With mean followup of 36 months there have been 42 local relapses (2.3%) and 24 “New Primary Tumors in the breast (1.3%)
- Toxicity and complications acceptable

TARGIT-Single Dose Intraoperative Radiation with Kilovoltage Applicator
TARGIT-Intraoperative APBI

- Large trial-1113 to intraop; 1119 to standard 5-6 week course of external beam radiation with or without a boost
- Surface of TARGIT receives 20 Gy which attenuates to 5-7 Gy at 1 cm from the surface
- At 4 years 6 local relapses in Targit (1.2%) vs 5 in Standard External Beam (0.95%)
- Complications and Toxicities Acceptable

Vaidya JS et al. Lancet, 2010
Issues with TARGIT trial

• Short follow-up
• Exceedingly low local relapse rates in both arms of approximately 1% at 4 years
• Doses of radiation are homeopathic—at 1 cm from the surface of the applicator the total dose is 500 cGy. Compared to 340-385 to the tumor bed twice daily to 3400-3480 with Balloon Based or External Beam APBI or 2100 cGy delivered in single dose with ELIOT.
• Some patients will have positive margin and convert to external beam with the TARGIT used as a boost.
## ASTRO - Suitable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Age</td>
<td>≥ 60</td>
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<tr>
<td>T-stage</td>
<td>T1</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>≤ 2 cm</td>
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<tr>
<td>Margins</td>
<td>&gt; 2 mm</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
</tr>
<tr>
<td>LVI</td>
<td>No</td>
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<tr>
<td>ER Status</td>
<td>Positive</td>
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<tr>
<td>Multicentricity</td>
<td>Unifocal ≤ 2 cm</td>
</tr>
<tr>
<td>Histology</td>
<td>IDC or favorable</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Nodes</td>
<td>pNO</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
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### ASTRO - Cautionary

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<tr>
<td>Age</td>
<td>50-59</td>
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<tr>
<td>T-stage</td>
<td>T0 or T2</td>
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<tr>
<td>Tumor Size</td>
<td>2.1-3.0 cm</td>
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<td>Margins</td>
<td>Close &lt; 2 mm</td>
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<td>Grade</td>
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<td>LVI</td>
<td>Limited/focal</td>
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<td>ER Status</td>
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<td>Multicentricity</td>
<td>NA</td>
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<tr>
<td>Histology</td>
<td>Invasive lobular</td>
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<tr>
<td>EIC</td>
<td>≤ 3 cm in size</td>
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<tr>
<td>Pure DCIS</td>
<td>≤ 3 cm in size</td>
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<tr>
<td>Nodes</td>
<td>NA</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
<td>NA</td>
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</tbody>
</table>
## ASTRO - Unsuitable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50</td>
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<tr>
<td>T-stage</td>
<td>T3 or T4</td>
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<tr>
<td>Tumor Size</td>
<td>&gt; 3 cm</td>
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<tr>
<td>Margins</td>
<td>Positive</td>
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<tr>
<td>Grade</td>
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<tr>
<td>LVI</td>
<td>Extensive</td>
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<td>ER Status</td>
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<tr>
<td>Multicentricity</td>
<td>Present</td>
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<td>Histology</td>
<td>NA</td>
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<tr>
<td>EIC</td>
<td>If &gt; 3 cm in size</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>If &gt; 3 cm in size</td>
</tr>
<tr>
<td>Nodes</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Neoadjuvant Chemo</td>
<td>If used</td>
</tr>
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</table>
Patients should be counseled regarding alternative treatments with level I evidence:

- CF-WBI
- HF-WBI
- Omission of RT if age $\geq 70$ years
CONCLUDING REMARKS

- Until further data are available, use of APBI in ASTRO’s “cautionary and unsuitable groups” should ideally be restricted to protocols.

- Many unanswered questions regarding optimal approaches, fractionation schedules, techniques and toxicities remain for h APBI: Studies and protocols to address these issues, and encouraging patients to participate in these studies is encouraged.
Thank you for your attention!

BRUCE G HAFFTY, MD
Rutgers-RWJMS
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