Alternatives to standard whole breast radiation

Early Stage Breast Cancer

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Summary

- LC benefit of radiation
- Standard whole breast radiation
- Alternatives to standard course:
  - Hypofractionation
  - Accelerated partial breast irradiation (APBI)
  - Observation?!
Benefit of RT in BCS
<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up</th>
<th>Surgery</th>
<th>Systemic</th>
<th>RT Dose</th>
<th>LR RT(-)</th>
<th>LR RT(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06 (1976)</td>
<td>20 years</td>
<td>lumpectomy</td>
<td>N+: melphalan + 5-FU</td>
<td>50</td>
<td>39%</td>
<td>14%</td>
</tr>
<tr>
<td>Uppsala-Orebro (1981)</td>
<td>10 years</td>
<td>sector resection</td>
<td>none</td>
<td>54</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>St. George's (1981)</td>
<td>5 years</td>
<td>WLE</td>
<td>ER+: tamoxifen</td>
<td>?</td>
<td>35%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ER-: CMF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ontario (1984)</td>
<td>8 years</td>
<td>lumpectomy</td>
<td>none</td>
<td>40/16 + 12.5/5</td>
<td>35%</td>
<td>11%</td>
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<tr>
<td>Scotland (1985)</td>
<td>6 years</td>
<td>WLE</td>
<td>ER+: tamoxifen</td>
<td>50 + 10-30</td>
<td>24%</td>
<td>6%</td>
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<tr>
<td></td>
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<td></td>
<td>ER-: CMF</td>
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<tr>
<td>Tokyo (1985)</td>
<td>8 years</td>
<td>sector resection</td>
<td>yes</td>
<td>?</td>
<td>9%</td>
<td>7%</td>
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<tr>
<td>St. Petersburg (1985)</td>
<td>5 years</td>
<td>quadrantectomy</td>
<td>yes</td>
<td>?</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>Milan 3 (1987)</td>
<td>10 years</td>
<td>quadrantectomy</td>
<td>N+ high risk: chemo</td>
<td>50 + 10</td>
<td>23%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N+ low risk: tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-21 (1989)</td>
<td>8 years</td>
<td>lumpectomy</td>
<td>tamoxifen or none</td>
<td>50 +/- boost</td>
<td>16%</td>
<td>3%</td>
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<tr>
<td>Finland (1990)</td>
<td>12 years</td>
<td>lumpectomy</td>
<td>none</td>
<td>50</td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>SweBCG (1991)</td>
<td>5 years</td>
<td>sector resection</td>
<td>at discretion (in 9%)</td>
<td>48-54</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>German GBSG (1991)</td>
<td>10 years</td>
<td>BSC</td>
<td>2x2: +/- TAM</td>
<td>50 + 10-12</td>
<td>34%</td>
<td>10%</td>
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<tr>
<td>Canada (1992)</td>
<td>5 years</td>
<td>BCS</td>
<td>tamoxifen</td>
<td>40/16 + 12.5/5</td>
<td>8%</td>
<td>1%</td>
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<tr>
<td>CALGB 9343 (1994)</td>
<td>5 years</td>
<td>lumpectomy</td>
<td>tamoxifen</td>
<td>45 + 14</td>
<td>4%</td>
<td>1%</td>
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</tbody>
</table>
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials

Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10,801 women (67% with pathologically node-negative disease) in 17 trials.
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials
Technical aspects of RT
Standard Radiation

- Tangents: $50\text{Gy}/25\text{fx} = 5 \text{ weeks of daily}$
Standard radiation

- Tangents
Modern radiation

- Tangents
Comparison

(a) Transverse Plane
- Standard Plan
- Intensity Modulated Plan

(b) Coronal Plane
- Standard Plan
- Intensity Modulated Plan

Alternatives to conventional radiation
Hypofractionation: Concept

- **Standard in US:**
  - 50Gy/25fx (2Gy/day) ≥ 5+ weeks
  - Boost: 6 weeks
  - Based on NSABP trials

- **Standard in Canada:**
  - 40-45Gy/15-20fx (>2Gy/day) ≤ 4 weeks
  - Based on Ontario Clinical Oncology Group
Hypofractionation: Data

- Canada
  - 42.56Gy/16fx vs 50Gy/25fx
- UK START A
  - 41.6Gy/13fx (39Gy) vs 50Gy/25fx
- UK START B
  - 40Gy/15fx vs 50Gy/25fx
- Combined:
  - N ~ 5000 patients
  - 5 year follow up
    - no difference in LC
    - Less toxicity with shorter course

Hypofractionation

ASTRO Guidelines for whole breast radiation fractionation:

- ≥50 yo
- pT1-2No
  - Excluded DCIS
- No chemotherapy
  - ~80% of patients did not receive chemotherapy
  - No Herceptin
- Radiation dose homogeneity ± 7

Smith, B et al. IJROPB 2011
Hypofractionation: Update

- Canada
  - No difference in LR at 10 years
  - Subgroup analysis: LR for tumors with grade 3 15.6 vs 4.7% with experimental arm
  - No boost allowed

- UK START A/B
  - No difference in LR at 10 years
  - Potential trend for worse cosmetic results with hypofractionated regimen in women <50 yo
  - No difference with breast size, boost dose, chemotherapy use, or antiestrogen therapy use

Whelan et al. NEJM 2010; Haviland et al. Lancet 2013
Hypofractionation: Update

2013 Choosing Wisely List

1. Don’t initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early-stage invasive breast cancer without considering shorter treatment schedules.
   - Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5-6 weeks, often followed by 1-2 weeks of boost therapy.
   - Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (~4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.
Hypofractionation: Update

Updated Clinical Practice Guideline on Whole Breast Irradiation (in progress)

Authors: Reshma Jagsi, MD, PhD, Benjamin Smith, MD, Jennifer Bellon, MD, Rachel Blitzblau, MD, PhD, Bruce Haffty, MD, Carol Hahn, MD, Francine Halberg, MD, Karen Hoffman, MD, Kathleen Horst, MD, Jean Moran, PhD, Tim Whelan, BM, BCh, Jean Wright, MD

The proposed guideline will update the guideline originally published in 2011 in light of the considerable new evidence that has accumulated in the intervening years and also allow for a more comprehensive statement regarding techniques of whole breast irradiation, beyond the issue of fractionation alone.

This guideline is currently under development.
Hypofractionation

- <50 years old: discuss difference in toxicity
- BRCA or other genetic mutation
- Nodal radiation
APBI

- Accelerated partial breast radiation
- Most LR occur within 1 cm from lumpectomy cavity
- 34Gy/10fx delivered BID over 1 week
- Treatment can begin once pathology has been finalized
FIGURE 3. This photograph shows an example of a good cosmetic result with minor telangiectasia 5.0 years after brachytherapy.
## APBI: Data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year published</th>
<th>Number of patients</th>
<th>APBI technique</th>
<th>Followup (mo)</th>
<th>Findings</th>
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<tr>
<td>Neurontialized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guy’s Hospital (22)</td>
<td>1996</td>
<td>27</td>
<td>Interstitial (HDR)</td>
<td>72</td>
<td>37% IBTR at 8 y</td>
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<td></td>
<td></td>
<td></td>
<td>Interstitial (HDR)</td>
<td>75</td>
<td>No difference in outcomes and toxicities between APBI and EBRT cohort</td>
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<tr>
<td>Oslo Clinic (33)</td>
<td>2000</td>
<td>50</td>
<td>Interstitial (HDR)</td>
<td>47</td>
<td>9% IBTR at 4 y</td>
</tr>
<tr>
<td>University of Kansas (44)</td>
<td>2001</td>
<td>24</td>
<td>Interstitial (HDR)</td>
<td>42</td>
<td>0% LR at 4 y; 80% excellent/good cosmesis, and 99% with HDR</td>
</tr>
<tr>
<td>Virginia Commonwealth (25)</td>
<td>2003</td>
<td>44</td>
<td>Interstitial (HDR/LDR)</td>
<td>91</td>
<td>5-y IBTR 16.2% and 5% in-field</td>
</tr>
<tr>
<td>Ontario (26)</td>
<td>2003</td>
<td>39</td>
<td>Interstitial (HDR)</td>
<td>75</td>
<td>18% IBTR, 7% IBTR in-field, and 80% excellent/good</td>
</tr>
<tr>
<td>Guys’ Hospital (27)</td>
<td>2004</td>
<td>50</td>
<td>Interstitial (HDR-Cs)</td>
<td>144</td>
<td>Disease free and 50% poor cosmesis</td>
</tr>
<tr>
<td>Hungary (28)</td>
<td>2004</td>
<td>70</td>
<td>Interstitial (6°Co)</td>
<td>11</td>
<td>9% IBTR at 1 y</td>
</tr>
<tr>
<td>Czech Republic (29)</td>
<td>2005</td>
<td>25</td>
<td>Interstitial (HDR)</td>
<td>43</td>
<td>No LR</td>
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<td>Australia (30)</td>
<td>2006</td>
<td>7</td>
<td>Interstitial (HDR)</td>
<td>32</td>
<td>5-y IBTR 6.1% and beyond 5-y 90% excellent cosmesis</td>
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<tr>
<td>Tufts University (31)</td>
<td>2007</td>
<td>273</td>
<td>Interstitial (HDR)</td>
<td>70.5</td>
<td>5-y LR 2.2% low risk vs. 6.5% high risk (&lt;50 y. ER-, and LN+)</td>
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<tr>
<td>University of Wisconsin (32)</td>
<td>2008</td>
<td>273</td>
<td>Interstitial (HDR)</td>
<td>48.5</td>
<td>6-y LR 0% and 87.5% excellent/good cosmesis</td>
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<tr>
<td>Spain (33)</td>
<td>2008</td>
<td>26</td>
<td>Interstitial (HDR)</td>
<td>53</td>
<td>5-y IBTR 3% (HDR) and 6% (LDR)</td>
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<td>RTOG 9517 (34)</td>
<td>2008</td>
<td>99</td>
<td>Interstitial (HDR/LDR)</td>
<td>73</td>
<td>3%-9% Grade 3+ toxicity with HDR/LDR</td>
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<td>Sweden (35)</td>
<td>2009</td>
<td>50</td>
<td>Interstitial (PDR)</td>
<td>86</td>
<td>7-y LR 4% and 56% excellent/good cosmesis</td>
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<tr>
<td>Japan (68)</td>
<td>2009</td>
<td>45</td>
<td>Interstitial (HDR)</td>
<td>133</td>
<td>4% LR</td>
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<td>Hungary (37)</td>
<td>2010</td>
<td>45</td>
<td>Interstitial (HDR)</td>
<td>134</td>
<td>12-y IBTR 9.3% and 78% excellent/good cosmesis</td>
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<tr>
<td>MVH (38)</td>
<td>2011</td>
<td>50</td>
<td>Interstitial (LDR)</td>
<td>6.5</td>
<td>12-y LR 15%</td>
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<td>German-Austrian (39)</td>
<td>2011</td>
<td>274</td>
<td>Interstitial (HDR/PDR)</td>
<td>126</td>
<td>5-y IBT 2% and 90% excellent/good cosmesis</td>
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<tr>
<td>William Beaumont (40)</td>
<td>2011</td>
<td>109</td>
<td>Interstitial (HDR)</td>
<td>11</td>
<td>No difference in LR between APBI (18.0%) and WBI (3.8%) at 12 y</td>
</tr>
<tr>
<td>St. Vincent (41)</td>
<td>2004</td>
<td>32</td>
<td>Balloon</td>
<td>11</td>
<td>86% Excellent/good cosmesis and 25% acute erythema/desquamation</td>
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<tr>
<td>Rush (42)</td>
<td>2004</td>
<td>112</td>
<td>Balloon</td>
<td>&lt;1 y</td>
<td>Well tolerated and 4/112 punctured or ruptured balloon</td>
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<td>Kaiser Permanente (43)</td>
<td>2006</td>
<td>51</td>
<td>Balloon</td>
<td>16</td>
<td>6% LR and 51.6% excellent/good cosmesis</td>
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<tr>
<td>Multi-Institution (44)</td>
<td>2006</td>
<td>44</td>
<td>Balloon</td>
<td>14</td>
<td>82% Skin discoloration/inflammation and 18% telangiectasias</td>
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<tr>
<td>Germany (45)</td>
<td>2006</td>
<td>32</td>
<td>Balloon</td>
<td>20</td>
<td>26% Telangiectasia, 56% hyperpigmentation, and 91% erythema</td>
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<td>MammomSite Initial Trial (46)</td>
<td>2007</td>
<td>32</td>
<td>Balloon</td>
<td>22</td>
<td>5-y LR 0% and 83.3% excellent/good cosmesis</td>
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<td>William Beaumont (47)</td>
<td>2007</td>
<td>80</td>
<td>Balloon</td>
<td>24</td>
<td>3-y IBTR 2.9% 88.2% excellent/good cosmesis, and decreased cosmesis with</td>
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<td></td>
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<td>1.2% IBTR and 91% excellent/good cosmesis</td>
</tr>
<tr>
<td>Multi-Institution (48)</td>
<td>2008</td>
<td>483</td>
<td>Balloon</td>
<td>24</td>
<td>5-y IBTR 2.6%, 5.4%, and 5.3% by risk group and 90.4% excellent/good cosmesis</td>
</tr>
<tr>
<td>ASBS Registry (49, 50)</td>
<td>2011</td>
<td>144</td>
<td>Balloon</td>
<td>54</td>
<td>0% LR and 54% excellent/good cosmesis</td>
</tr>
<tr>
<td>Rocky Mountain (51)</td>
<td>2007</td>
<td>55</td>
<td>EBRT (IMRT)</td>
<td>10</td>
<td>10% Moderate/severe late toxicity, 25% Grades 2—4 fibrosis, and 81.7%</td>
</tr>
<tr>
<td>Tufts University (52)</td>
<td>2009</td>
<td>60</td>
<td>EBRT (IMRT)</td>
<td>15</td>
<td>excellent/good cosmesis</td>
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<tr>
<td>University of Michigan (53)</td>
<td>2010</td>
<td>34</td>
<td>EBRT (IMRT)</td>
<td>24</td>
<td>7/32 Unacceptable cosmesis</td>
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<tr>
<td>RTOG 0319 (54)</td>
<td>2010</td>
<td>52</td>
<td>EBRT</td>
<td>54</td>
<td>4-y IBTR 6% and 4% Grade 3 toxicity</td>
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</tbody>
</table>

ABS consensus statement. Brachytherapy 2013
# APBI: Recommendations

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<tr>
<td><strong>Age</strong></td>
<td>≥ 45</td>
<td>≥ 50</td>
<td>≥ 60</td>
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<tr>
<td><strong>Histology</strong></td>
<td>IDC or DCIS</td>
<td>IDC or DCIS</td>
<td>IDC</td>
</tr>
<tr>
<td>(updated 2013)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Size</strong></td>
<td>≤ 3cm</td>
<td>≤ 3cm</td>
<td>≤ 2cm</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>negative</td>
<td>negative</td>
<td>≥ 2mm</td>
</tr>
<tr>
<td><strong>Nodes</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>ER</strong></td>
<td>NA</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td><strong>LVSI</strong></td>
<td>NA</td>
<td>- (updated</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2013)</td>
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</table>
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

![Graph showing local recurrence and disease-free survival](Image)

**Figure 2:** Ipsilateral breast tumour recurrence
APBI—accelerated partial breast irradiation. WBI—whole-breast irradiation.

**Figure 3:** Disease-free survival

Strnad et al. Lancet 2016
Figure 1
NSABP B-39/RTOG 0413 Schema

Patients with Stage 0, I, or II Breast Cancer Resected by Lumpectomy
Tumor Size ≤ 3.0 cm
No More Than 3 Histologically Positive Nodes

STRATIFICATION
- Disease Stage (DCIS only, invasive and node negative, invasive with 1-3 positive nodes)
- Menopausal Status (premenopausal, postmenopausal)
- Hormone Receptor Status (ER-positive and/or PgR-positive, ER-negative and PgR-negative)
- Intention to Receive Chemotherapy (yes or no)

RANDOMIZATION

GROUP 1*
Whole Breast Irradiation (WBI)
50 Gy (2.0 Gy/fraction) or 50.4 Gy (1.8 Gy/fraction) to whole breast, followed by optional boost** to 60.0 Gy – 66.6 Gy

GROUP 2**
Partial Breast Irradiation (PBI)**
34 Gy in 3.4 Gy fractions using multi-catheter brachytherapy
   or
34 Gy in 3.4 Gy fractions using MammoSite® balloon catheter or other intracavitary device†
   or
38.5 Gy in 3.85 Gy fractions using 3D conformal external beam radiation
For all PBI techniques: RT given to tissue surrounding lumpectomy cavity only, BID (with a fraction separation of at least 6 hours), for a total of 10 treatments given in 5 days over a period of 5 to 10 days.
APBI: Devices
APBI: Devices

Original MammoSite®

MammoSite® ML

Contura™

SAVI™
Fig. 1. Strut-Adjusted Volume Implant (SAVI). This photo shows the 4 sizes available, from left: 10-1, 8-1, 6-1, and 6-1Mini.
Fig. 2. Strut-Adjusted Volume Implants (SAVI) with simultaneous close proximity to (a) skin and chest wall and (b) dosimetry.
APBI
Is there a group of patients who can avoid adjuvant radiation after BCS?
Observation?! IDC

**CALGB 9343**
- N = 636 pts
- >70 yo
- cT1No, ER+
- RT + tamoxifen vs tamoxifen
- Median follow up 12 years
- LR: 2 vs 10% at 10 years
- No difference in BCM or OS

**PRIME II**
- N = 658
- >65 yo
- cT1-2No (up to 3cm)
- Could not have both G3 and LVSI
- RT + endocrine therapy vs endocrine therapy
- Median follow up 5 years
- LR 1 vs 4%
- No difference in BCM or OS

Hughes et al. JCO 2013; Kunkler et al. Lancet Onc 2015
RTOG 9804
N = 636 (did not meet accrual goal of >1800)
Low- intermediate grade DCIS, <2.5cm, >3mm margins
RT vs obs (tamoxifen optional)
LR 1 vs 7% at 7 years
No difference in OS

McCormick et al. JCO 2015
There is no group identified that does not benefit from adjuvant radiation therapy in BCS in terms of local control.

In elderly women with favorable histology, there’s likely no survival benefit.
Figure 5: Local recurrence and breast cancer mortality for treatment comparisons that produce a less than 10% (upper panels) or more than 10% (lower panels) absolute reduction in 5-year local recurrence risk—15-year probabilities. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.