Patient Selection for APBI

C. Polgár
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Patient-, tumour- and treatment related factors affecting decision making in patient selection for APBI

- Patient age
- Histologic type
  - Invasive lobuläre carcinoma (ILC)
  - Ductal carcinoma in situ (DCIS)
- Histologic grade
- Tumour size (pT)
- Surgical margin status
- Multifocality, multicentricity
- Extensive intraductal components (EIC)
- Hormone receptor status
- Lympho-vascular invasion (LVI)
- Surgical nodal staging – pathologic axillary status (pN)
- Neoadjuvant chemotherapy
Why patient selection for APBI is so important?

Lessons learned from the results of early APBI studies

<table>
<thead>
<tr>
<th>Institute</th>
<th>Study period</th>
<th>APBI technique</th>
<th>Patient No.</th>
<th>Median FUP (y)</th>
<th>Crude LR%</th>
<th>Annual LR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie Hospital*</td>
<td>1982-87</td>
<td>ELE</td>
<td>353</td>
<td>8</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>Guy’s Hospital I.</td>
<td>1987-88</td>
<td>LDR BT – $^{192}$Ir</td>
<td>27</td>
<td>6</td>
<td>37</td>
<td>6.2</td>
</tr>
<tr>
<td>Cookridge Hospital*</td>
<td>1986-90</td>
<td>EBI</td>
<td>84</td>
<td>8</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>Guy’s Hospital II.</td>
<td>1990-92</td>
<td>MDR BT – $^{137}$Cs</td>
<td>49</td>
<td>6.3</td>
<td>18</td>
<td>2.9</td>
</tr>
<tr>
<td>Uzsoki Hospital</td>
<td>1987-92</td>
<td>MDR BT – $^{60}$Co</td>
<td>70</td>
<td>12</td>
<td>24</td>
<td>2.0</td>
</tr>
<tr>
<td>University Florence</td>
<td>1989-93</td>
<td>LDR BT – $^{192}$Ir</td>
<td>115</td>
<td>4.2</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td>London Reg. Cancer Center</td>
<td>1992-96</td>
<td>HDR BT</td>
<td>39</td>
<td>7.6</td>
<td>15</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>All pts.</strong></td>
<td><strong>1982-93</strong></td>
<td></td>
<td><strong>698</strong></td>
<td><strong>4.2-12</strong></td>
<td><strong>6-37</strong></td>
<td><strong>1.4-6.2</strong></td>
</tr>
</tbody>
</table>

* Phase III trial
### Patient “selection” and results of early APBI studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T-size</td>
<td>≤ 4 cm</td>
<td>≤ 5 cm</td>
<td>≤ 4.5 cm</td>
<td>≤ 4 cm</td>
<td>≤ 5 cm</td>
<td>≤ 5 cm</td>
<td>≤ 4.5 cm</td>
</tr>
<tr>
<td>Margins</td>
<td>10% pos. 90% UK</td>
<td>56% pos. 7% UK</td>
<td>100% UK</td>
<td>43% pos.</td>
<td>100% UK</td>
<td>8% pos. 7% UK</td>
<td>neg., 31% close</td>
</tr>
<tr>
<td>EIC</td>
<td>yes</td>
<td>41%</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>8%</td>
</tr>
<tr>
<td>Nodes</td>
<td>100% pNx</td>
<td>44% N+</td>
<td>41% N+</td>
<td>44% N+</td>
<td>4% N+ 80% pNx</td>
<td>38% N+</td>
<td>15% N+ 5% pNx</td>
</tr>
<tr>
<td>Age</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>&gt; 40 year</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>LR rate</td>
<td>20%</td>
<td>37%</td>
<td>12%</td>
<td>18%</td>
<td>24%</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Annual LR</td>
<td>2.5%</td>
<td>6.2%</td>
<td>1.5%</td>
<td>2.9%</td>
<td>2%</td>
<td>1.4%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

APBI with outdated techniques for unselected pts. → Annual LR: 1.4-6.2%
### Results of contemporary APBI studies (median FUP ≥ 4 ys) – Multicatheter brachytherapy series

<table>
<thead>
<tr>
<th>Institute</th>
<th>Study period</th>
<th>APBI technique</th>
<th>Patient No.</th>
<th>Median FUP (ys)</th>
<th>Crude LR%</th>
<th>Annual LR%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interstitial brachytherapy series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROMIS</td>
<td>1992-2013</td>
<td>LDR/HDR BT</td>
<td>1131</td>
<td>6.9</td>
<td>5.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Oschner Clinic</td>
<td>1992-93</td>
<td>LDR/HDR BT</td>
<td>51</td>
<td>6.25</td>
<td>2</td>
<td>0.32</td>
</tr>
<tr>
<td>W. Beaumont Hospital</td>
<td>1992-2001</td>
<td>LDR/HDR BT</td>
<td>199</td>
<td>10.7</td>
<td>5</td>
<td>0.47</td>
</tr>
<tr>
<td>Örebro Medical Center</td>
<td>1993-2003</td>
<td>PDR BT</td>
<td>51</td>
<td>7.2</td>
<td>5.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Budapest</td>
<td>1996-98</td>
<td>HDR BT</td>
<td>45</td>
<td>13.8</td>
<td>11.1</td>
<td>0.80</td>
</tr>
<tr>
<td>RTOG 95-17</td>
<td>1997-2000</td>
<td>LDR/HDR BT</td>
<td>99</td>
<td>7</td>
<td>6.1</td>
<td>0.87</td>
</tr>
<tr>
<td>Tufts University</td>
<td>1997-2001</td>
<td>HDR BT</td>
<td>33</td>
<td>5.9</td>
<td>9.1</td>
<td>1.54</td>
</tr>
<tr>
<td>Harvard, Boston</td>
<td>1997-2001</td>
<td>LDR BT</td>
<td>50</td>
<td>11.2</td>
<td>12</td>
<td>1.07</td>
</tr>
<tr>
<td>Budapest Phase III</td>
<td>1998-2004</td>
<td>HDR BT/ELE</td>
<td>128</td>
<td>10.2</td>
<td>5.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Ninewells Hospital</td>
<td>-1999</td>
<td>LDR BT</td>
<td>11</td>
<td>5.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>German-Austrian</td>
<td>2000-05</td>
<td>PDR/HDR BT</td>
<td>274</td>
<td>5.2</td>
<td>2.9</td>
<td>0.56</td>
</tr>
<tr>
<td>University Navarra</td>
<td>2000-07</td>
<td>HDR BT</td>
<td>26</td>
<td>4.4</td>
<td>3.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Washington University</td>
<td>2002-07</td>
<td>HDR BT</td>
<td>202</td>
<td>&gt;5</td>
<td>2.5</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>1992-2007</td>
<td></td>
<td>2300</td>
<td>4.4-13.8</td>
<td>0-11.1</td>
<td>0-1.54</td>
</tr>
</tbody>
</table>
# Patient selection and results in contemporary APBI studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Beaumont Hospital</th>
<th>Örebro</th>
<th>Budapest Phase III</th>
<th>German-Austrian Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-size</td>
<td>≤ 3 cm</td>
<td>≤ 4.2 cm</td>
<td>≤ 2 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td>Margins</td>
<td>≥ 2 mm</td>
<td>clear</td>
<td>clear (≥ 2 mm; 1999-)</td>
<td>≥ 2 mm</td>
</tr>
<tr>
<td>Unifocal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EIC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DCIS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nodes</td>
<td>&lt; 4 pos. (ECE neg.)</td>
<td>&lt; 4 pos.</td>
<td>N0-N1mi (micromet.)</td>
<td>N0-N1mi (micromet.)</td>
</tr>
<tr>
<td>Age</td>
<td>≥ 40 y</td>
<td>≥ 40 y</td>
<td>≥ 40 y (2001-)</td>
<td>≥ 35 y</td>
</tr>
<tr>
<td>Actuarial LR rate</td>
<td>5% (12-year)</td>
<td>4% (7-year)</td>
<td>5.9% (10-year)</td>
<td>5% (8-year)</td>
</tr>
<tr>
<td>Annual LR</td>
<td>0.42%</td>
<td>0.57%</td>
<td>0.59%</td>
<td>0.63%</td>
</tr>
</tbody>
</table>

APBI for selected pts.  ➔  Annual LR ~ 0.5%
• Majority of patients treated in early APBI studies were not acceptable candidates even for conventional breast-conserving treatment!

• High LR rates reflect inadequate patient selection, suboptimal QA and treatment technique!
ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM
THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Benjamin D. Smith, M.D.,*† Douglas W. Arthur, M.D.,† Thomas A. Buchholz, M.D.,†
Bruce G. Haffty, M.D.,§ Carol A. Hahn, M.D.,¶ Patricia H. Hardenbergh, M.D.,¶
Thomas B. Julian, M.D.,* Lawrence B. Marks, M.D.,**, Dorin A. Todor, Ph.D.,†
Frank A. Vicini, M.D.,†† Timothy J. Whelan, M.D.,†† Julia White, M.D.,§§ Jennifer Y. Wo, M.D.,||
and Jay R. Harris, M.D.,†††

Patient selection for accelerated partial-breast irradiation (APBI) after
breast-conserving surgery: Recommendations of the Groupe Européen de
Curiethérapie-European Society for Therapeutic Radiology and Oncology
(GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár *, Erik Van Limbergen , Richard Pötter , György Kovács, Alfredo Polo , Jaroslav Lyczek ,
Guido Hildebrandt , Peter Niehoff , Jose Luis Guinot , Ferran Guedea , Beng Johansson , Oliver J. Ott ,
Tibor Major , Vratislav Strnad , On behalf of the GEC-ESTRO breast cancer working group

The American Brachytherapy Society consensus statement
for accelerated partial breast irradiation

Chirag Shah, Frank Vicini, David E. Wazer, Douglas Arthur, Rakesh R. Patel

DEGRO practical guidelines: radiotherapy
of breast cancer I

Radiotherapy following breast conserving
therapy for invasive breast cancer
ASTRO consensus statement for APBI - 2009

CONSENSUS STATEMENT

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### Table 2. Patients “suitable” for APBI if all criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥60 y</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Not present</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤2 cm*</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative by at least 2 mm</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
</tr>
<tr>
<td>LVSI</td>
<td>No†</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric only</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size ≤2.0 cm‡</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Invasive ductal or other favorable subtypes§</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
</tr>
<tr>
<td><strong>Nodal factors</strong></td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>pN0 (i*, i⁺)</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SN Bx or ALND†</td>
</tr>
<tr>
<td><strong>Treatment factors</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

### Table 3. “Cautionary” group: Any of these criteria should invoke caution and concern when considering APBI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50–59 y</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>2.1–3.0 cm*</td>
</tr>
<tr>
<td>T stage</td>
<td>T0 or T2</td>
</tr>
<tr>
<td>Margins</td>
<td>Close (&lt;2 mm)</td>
</tr>
<tr>
<td>LVSI</td>
<td>Limited/focal</td>
</tr>
<tr>
<td>ER status</td>
<td>Negative†</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size 2.1–3.0 cm‡</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Invasive lobular</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>EIC</td>
<td>≤3 cm</td>
</tr>
</tbody>
</table>

### Table 4. Patients “unsuitable” for APBI outside of a clinical trial if any of these criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50 y</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Tumor size*</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>T stage</td>
<td>T3-4</td>
</tr>
<tr>
<td>Margins</td>
<td>Positive</td>
</tr>
<tr>
<td>LVSI</td>
<td>Extensive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Present</td>
</tr>
<tr>
<td>Multifocality</td>
<td>If microscopically multifocal &gt;3 cm in total size or if clinically multifocal</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td><strong>Nodal factors</strong></td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>None performed</td>
</tr>
<tr>
<td><strong>Treatment factors</strong></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>If used</td>
</tr>
</tbody>
</table>

Csaba Polgár a, Erik Van Limbergen b, Richard Pötter c, György Kovács d, Alfredo Polo e, Jaroslav Lyczek f, Guido Hildebrandt g, Peter Niehoff h, Jose Luis Guinot i, Ferran Guedea j, Bengt Johansson k, Oliver J. Ott l, Tibor Major a, Vratislav Strnad l, On behalf of the GEC-ESTRO breast cancer working group

- GEC-ESTRO recommendations for accelerated partial breast irradiation
- Cervical cancer brachytherapy
- Risk analysis in radiotherapy
Aim:

• To give recommendations on patient selection criteria for the use of APBI outside the context of prospective clinical trials based on available clinical evidence obtained from prospective APBI studies with a minimum median follow-up of 4 years.

Methods & Materials:

• Systematic literature search using the keywords ”partial-breast irradiation” and ”APBI” + handsearching of relevant conference abstracts and book chapters (published by the end of July 2009)
• 340 articles were identified
• 191 original articles (excl. reviews, letters, case reports, editorials)
• 75 articles remained (excl. dosimetric/technical articles)
• 3 randomized and 19 prospective non-randomized studies with a FUP ≥ 4 years were identified.
Results of APBI studies using suboptimal patient selection criteria with adequate (≥ 4 years) follow-up

<table>
<thead>
<tr>
<th>Institution</th>
<th>Technique</th>
<th>Median FUP (years)</th>
<th>LR% (n)</th>
<th>Annual LR% (n)</th>
<th>Comments on patient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uzoki hospital [37]</td>
<td>MDR</td>
<td>12</td>
<td>24 (17 of 70)</td>
<td>2</td>
<td>Max. tumour size: 5 cm; 100% unknown margins; 30% unknown pathological axillary status (pNx); 4% node positive; 10% lobular ca; multifocal tumours, LVI and EIC allowed; no patient age limitation</td>
</tr>
<tr>
<td>Christie hospital* [20]</td>
<td>EBI</td>
<td>8</td>
<td>20 (69 of 353)</td>
<td>2.5</td>
<td>Max. tumour size: 4 cm; 100% unknown margins; no surgical axillary staging; lobular ca, LVI and EIC allowed; no patient age limitation</td>
</tr>
<tr>
<td>Cookridge hospital* [11]</td>
<td>EBI</td>
<td>8</td>
<td>12 (10 of 84)</td>
<td>1.5</td>
<td>Max. tumour size: 4.5 cm; 41% node positive; lobular ca, LVI and EIC allowed; no patient age limitation</td>
</tr>
<tr>
<td>London Reg. Ca. C. [30]</td>
<td>HDR</td>
<td>7.6</td>
<td>15 (6 of 39)</td>
<td>2</td>
<td>Max. tumour size: 4.5 cm; 31% close margins; 15% node positive; 5% pN0; 8% EIC pos.; no patient age limitation</td>
</tr>
<tr>
<td>Tufts university [16]</td>
<td>HDR</td>
<td>7</td>
<td>9.1 (3 of 33)</td>
<td>1.30</td>
<td>45% Close margins; 9% node positive; 55% EIC pos.; no patient age limitation</td>
</tr>
<tr>
<td>Guy’s hospital I [12]</td>
<td>LDR</td>
<td>6</td>
<td>37 (10 of 27)</td>
<td>6.2</td>
<td>Max. tumour size &gt;4 cm; 56% positive margins; 44% node positive, 41% EIC positive; lobular ca and LVI allowed; patient age &gt;40 years</td>
</tr>
<tr>
<td>Guy’s hospital II [13]</td>
<td>MDR</td>
<td>6.3</td>
<td>18 (9 of 49)</td>
<td>2.9</td>
<td>Max. tumour size: 4 cm; 43% positive margins; 45% node positive; 14% lobular ca., LVI and EIC allowed; no patient age limitation</td>
</tr>
<tr>
<td>Osaka Med. center [26]</td>
<td>HDR</td>
<td>4.3</td>
<td>5.0 (1 of 20)</td>
<td>1.15</td>
<td>15% Positive margins; 35% EIC pos.; 5% lobular ca; 10% DCIS; no patient age limitation (25% with age &lt;45 years)</td>
</tr>
<tr>
<td>Florence hospital [10]</td>
<td>LDR</td>
<td>4.2</td>
<td>6 (7 of 115)</td>
<td>1.4</td>
<td>Max. tumour size: 5 cm; 8% positive and 7% unknown margins; 38% node positive; 20% lobular ca; LVI and BC allowed; no patient age limitation</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>4.2–12</td>
<td>17 (132 of 790)</td>
<td>1.15–6.2</td>
<td></td>
</tr>
</tbody>
</table>

APBI = accelerated partial-breast irradiation; FUP = follow-up period; LR = local recurrence; EIC = extensive intraductal carcinoma; LVI = lympho-vascular invasion; EBI = external beam irradiation; MDR = medium-dose rate; LDR = low-dose-rate; HDR = high-dose-rate.

* Randomized trial.
## Results of APBI studies using stringent patient selection criteria with ≥ 4 years FUP

<table>
<thead>
<tr>
<th>Institution/study</th>
<th>Technique</th>
<th>Median FUP (years)</th>
<th>LR% (n)</th>
<th>Annual LR%</th>
<th>Comments on patient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNIO, Budapest I [32,33,35,36]</td>
<td>HDR</td>
<td>11.1</td>
<td>8.9 (4 of 45)</td>
<td>0.80</td>
<td>Max. tumour size: 2 cm; clear margins; unifocal tumour; grade I–II; pN0 or pN1mi; no patient age limitation. Excluded: lobular ca., DCIS and EIC</td>
</tr>
<tr>
<td>WBH, Michigan [5,44]</td>
<td>LDR/HDR</td>
<td>9.7</td>
<td>5.0 (10 of 199)</td>
<td>0.52</td>
<td>Max. tumour size: 3 cm; margins ≥ 2 mm; pN0; patient age &gt;40 years. Excluded: lobular ca., DCIS, and EIC</td>
</tr>
<tr>
<td>Örebro Med. Centre [15]</td>
<td>PDR</td>
<td>7.2</td>
<td>5.9 (3 of 51)</td>
<td>0.83</td>
<td>Max. tumour size: 4.2 cm; clear margins; unifocal tumour; 12% node pos. (1–3 nodes); 8% lobular ca.; patient age ≥ 40 years. Excluded: DCIS and EIC</td>
</tr>
<tr>
<td>RTOG 95–17 [7]</td>
<td>LDR/HDR</td>
<td>7</td>
<td>6.1 (6 of 99)</td>
<td>0.91</td>
<td>Max. tumour size: 3 cm; clear margins; unicentric tumour; 20% node positive (1–3 pos. nodes without ECE); no patient age limitation. Excluded: lobular ca., DCIS, and EIC</td>
</tr>
<tr>
<td>HNIO, Budapest II* [33–36]</td>
<td>HDR/EBI</td>
<td>6.8</td>
<td>4.7 (6 of 128)</td>
<td>0.69</td>
<td>Max. tumour size: 2 cm; margins ≥ 2 mm; unifocal tumour; grade I–II; pN0 or pN1mi; patient age &gt;40 years. Excluded: lobular ca., DCIS, and EIC</td>
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<tr>
<td>Ochsner clinic [17]</td>
<td>LDR/HDR</td>
<td>6.25</td>
<td>2.1 (1 of 51)</td>
<td>0.32</td>
<td>Max. tumour size: 4 cm; clear margins; unicentric tumour; 18% node positive (1–3 nodes); 10% DCIS; 14% EIC; no patient age limitation</td>
</tr>
<tr>
<td>Ninewells hospital [38]</td>
<td>LDR</td>
<td>5.6</td>
<td>0 (0 of 11)</td>
<td>0</td>
<td>Max. tumour size: 3.5 cm; unifocal tumour, pN0 or pN1a (only 1 pt. node pos.); patient age &gt;40 years. Excluded: lobular ca., DCIS, and EIC</td>
</tr>
<tr>
<td>Germany-Austria [28,41]</td>
<td>PDR/HDR</td>
<td>5.25</td>
<td>2.9 (8 of 274)</td>
<td>0.55</td>
<td>Max. tumour size: 3 cm; margins ≥ 2 mm; unifocal tumour; grade I–II; pN0 or pN1mi; ER or PgR pos.; 16% lobular ca.; patient age &gt;35 years. Excluded: DCIS, EIC and LVI</td>
</tr>
<tr>
<td>FDA Trial, USA [9]</td>
<td>MammoSite</td>
<td>5.2</td>
<td>0 (0 of 43)</td>
<td>0</td>
<td>Max. tumour size: 2 cm; clear margins; unifocal tumour; pN0; patient age &gt;45 years. Excluded: lobular ca., DCIS, and EIC</td>
</tr>
<tr>
<td>Kiel-HNIO [25,36]</td>
<td>MammoSite</td>
<td>5</td>
<td>0 (0 of 11)</td>
<td>0</td>
<td>Max. tumour size: 2 cm; margins ≥ 5 mm; unifocal tumour; grade I–II; pN0; ER or PgR pos.; patient age ≥ 60 years. Excluded: lobular ca., DCIS, EIC and LVI</td>
</tr>
<tr>
<td>University Navarra [14]</td>
<td>HDR</td>
<td>4.4</td>
<td>3.8 (1 of 26)</td>
<td>0.86</td>
<td>Max. tumour size: 3 cm; margins ≥ 2 mm; unicentric tumour; pN0; no patient age limitation. Excluded: lobular ca. and EIC</td>
</tr>
<tr>
<td>Wisconsin university [29]</td>
<td>HDR/ MammoSite</td>
<td>4</td>
<td>2.9 (8 of 273)</td>
<td>0.72</td>
<td>Max. tumour size: 3 cm; margins ≥ 2 mm; unicentric tumour; 7% node positive (1–3 nodes without ECE); 13% DCIS; no patient age limitation. Excluded: lobular ca. and EIC</td>
</tr>
<tr>
<td>Kansas university [19]</td>
<td>LDR</td>
<td>4</td>
<td>0 (0 of 25)</td>
<td>0</td>
<td>Max. tumour size: 2 cm; clear margins; grade I–II, pN0; 12% (classical) lobular ca.; patient age &gt;60 years. Excluded: non-classical lobular ca., DCIS and EIC</td>
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All patients 4–11.1 [3.8 (47 of 1236)] 0–0.91
Results of APBI studies using stringent patient selection criteria with ≥ 4 years FUP

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<tr>
<th>Institution/study</th>
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<td><em>Ninewell</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(only 1 pt. node pos.); patient age ≥40 years. <em>Excluded:</em> lobular ca., DCIS, and EIC</td>
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**APBI for selected pts.**  
Annual LR: 0–0.91%
### GEC-ESTRO recommendations on patient selection for accelerated partial breast irradiation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-risk group - Good candidates for APBI</th>
<th>Intermediate-risk group - Possible candidates for APBI</th>
<th>High-risk group – Contraindication for APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>&gt;50 years</td>
<td>&gt;40-50 years</td>
<td>≤40 years</td>
</tr>
<tr>
<td>Histology</td>
<td>IDC, mucinous, tubular, medullary, and colloid cc.</td>
<td>IDC, ILC, mucinous, tubular, medullary, and colloid cc.</td>
<td>-</td>
</tr>
<tr>
<td>ILC</td>
<td>Not allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>DCIS</td>
<td>Not allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>HG</td>
<td>Any</td>
<td>Any</td>
<td>-</td>
</tr>
<tr>
<td>Tumour size</td>
<td>pT1-2 (≤30 mm)</td>
<td>pT1-2 (≤30 mm)</td>
<td>pT2 (&gt;30 mm), pT3, pT4</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative (≥2 mm)</td>
<td>Negative, but close (&lt;2 mm)</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric</td>
<td>Unicentric</td>
<td>Multicentric</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Unifocal</td>
<td>Multifocal (limited within 2 cm of the index lesion)</td>
<td>Multifocal (&gt;2 cm from the index lesion)</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Present</td>
</tr>
<tr>
<td>LVI</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Present</td>
</tr>
<tr>
<td>ER, PR status</td>
<td>Any</td>
<td>Any</td>
<td>-</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN0 (by SLNB or ALND*)</td>
<td>pN1mi, pN1a (by ALND*)</td>
<td>pNx; ≥pN2a</td>
</tr>
<tr>
<td>Neoadj. chemoth.</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>If used</td>
</tr>
</tbody>
</table>

*Radiother Oncol 2010;94:264-273*
The American Brachytherapy Society consensus statement for accelerated partial breast irradiation

Chirag Shah¹,², Frank Vicini³, David E. Wazer⁴,⁵, Douglas Arthur⁶, Rakesh R. Patel⁷,*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Acceptable criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥50 y old</td>
</tr>
<tr>
<td>Size</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>Histology</td>
<td>All invasive subtypes and DCIS</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Positive/negative</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative</td>
</tr>
<tr>
<td>Lymphovascular space invasion</td>
<td>Not present</td>
</tr>
<tr>
<td>Nodal status</td>
<td>Negative</td>
</tr>
</tbody>
</table>

DCIS = ductal carcinoma *in situ.*
Partial breast irradiation

<table>
<thead>
<tr>
<th>Statement RT 3 [74]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy restricted to parts of the affected breast (partial breast irradiation, PBI) as sole radiation treatment including sole intraoperative radiotherapy (IORT) represents no treatment standard (LoE 3b).</td>
</tr>
</tbody>
</table>

Comments and conclusions of the DEGRO panel

- Justification of APBI alone for selected patients beyond clinical trials was assessed controversially among the panel members. The majority of the panel finally agreed to concede APBI with established techniques like multicatheter brachytherapy or IORT as an option for elderly women fulfilling all of the following preconditions: age >70 years, tumor size <2 cm, invasive ductal carcinoma, negative axillary nodes, free surgical margins, absence of EIC and luminal A type (ER+ and PR+, G1–2, Her2/neu negative).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASTRO ”suitable” group</th>
<th>GEC-ESTRO ”good candidate” group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>≥ 60 years</td>
<td>&gt; 50 years</td>
</tr>
<tr>
<td>ER status</td>
<td>positive</td>
<td>any</td>
</tr>
<tr>
<td>Tumour size</td>
<td>≤ 2 cm</td>
<td>≤ 3 cm</td>
</tr>
</tbody>
</table>
### ABS Consensus Statement versus GEC-ESTRO Recommendations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ABS ”acceptable” group</th>
<th>GEC-ESTRO ”good candidate” group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>All invasive subtypes and DCIS</td>
<td>ILC not allowed DCIS not allowed</td>
</tr>
</tbody>
</table>
Controversies between ASTRO, ABS, and GEC-ESTRO recommendations

- Patient age cut-off (50 versus 60 years)
- ER status
- Tumour size cut-off (20 versus 30 mm)
- Histologic type
  - Invasive lobulare carcinoma (ILC)
  - Ductal carcinoma in situ (DCIS)
- Nodal status (pN0 versus pN1mic versus pN1a)
ACCELERATED PARTIAL BREAST IRRADIATION: 5-YEAR RESULTS OF THE GERMAN-AUSTRIAN MULTICENTER PHASE II TRIAL USING INTERSTITIAL MULTICATHETER BRACHYTHERAPY ALONE AFTER BREAST-CONSERVING SURGERY

Vratislav Strnad, M.D.,* Guido Hildebrandt, M.D., †† Richard Pötter, M.D., §
Josef Hammer, M.D., † Marion Hindemith, M.D., † Alexandra Resch, M.D., § Kurt Spiegl, M.D., †
Michael Lotter, Ph.D., * Wolfgang Uter, M.D., † Mayada Bani, ** Rolf-Dieter Kortmann, M.D., †
Matthias W. Beckmann, M.D., ** Rainer Fietkau, M.D.,* and Oliver J. Ott, M.D.*

- 274 patients
  - 50 Gy PDR or 8x4 Gy HDR BT
- 5-y actuarial LR rate: 2.3%
- 8-y actuarial LR rate: 5.0%

IJROBP 2011;80:17-24
### ACCELERATED PARTIAL BREAST IRRADIATION WITH INTERSTITIAL IMPLANTS: RISK FACTORS ASSOCIATED WITH INCREASED LOCAL RECURRANCE

**Characteristic** | 5-y LR % (n) | p-value |
--- | --- | --- |
Age | | 0.03 |
- ≥ 50 years | 1.1% (4/225) | |
- < 50 years | 7.5% (4/49) | |
Hormonal therapy | | 0.0087 |
- No | 15.1% (4/24) | |
- Yes | 1.0% (4/250) | |

ER & PgR status, tumour size, histologic type, pN status, HG, and HER-2 status had no significant impact on LR rate!

IJROBP 2011;80:1458-63
Budapest Phase III APBI study - 10-year actuarial results

Median FUP: 10.2 years

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>APBI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>5.1%</td>
<td>5.9%</td>
<td>0.77</td>
</tr>
<tr>
<td>CLBC</td>
<td>6.4%</td>
<td>8.3%</td>
<td>0.56</td>
</tr>
<tr>
<td>RR</td>
<td>1.7%</td>
<td>2.4%</td>
<td>0.65</td>
</tr>
<tr>
<td>DM</td>
<td>11.5%</td>
<td>7.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>DFS</td>
<td>84%</td>
<td>85%</td>
<td>0.97</td>
</tr>
<tr>
<td>OS</td>
<td>82%</td>
<td>80%</td>
<td>0.73</td>
</tr>
<tr>
<td>CSS</td>
<td>92%</td>
<td>94%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Radiother Oncol 2013;108:197-202

Annual LR rate:
APBI: 0.59%
WBI: 0.51%
Budapest phase III trial –
Univariate analysis of prognostic factors for LR

Menopausal status, ER & PgR status, tumour size, HG, NG and MAI had no significant impact on LR rate!

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>10-y LR % (n)</th>
<th>p-value</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>4.8% (11/249)</td>
<td>0.032</td>
<td>1</td>
</tr>
<tr>
<td>≤ 40 years</td>
<td>22.2% (2/9)</td>
<td></td>
<td>5.20</td>
</tr>
<tr>
<td>Systemic therapy*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10.1% (7/75)</td>
<td>0.053</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>3.6% (6/183)</td>
<td></td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Chemo and/or hormonal therapy
Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: Results of a matched-pair analysis

Chirag Shah, John Vito Antonucci, John Ben Wilkinson, Michelle Wallace, Mihai Ghilezan, Peter Chen, Kenneth Lewis, Christina Mitchell, Frank Vicini*

Department of Radiation Oncology, William Beaumont Hospital, MI, USA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>APBI</th>
<th>WBI</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.02*</td>
<td>0.66</td>
<td>0.003*</td>
</tr>
<tr>
<td>ER status</td>
<td>0.07</td>
<td>0.09</td>
<td>0.42</td>
</tr>
<tr>
<td>PR status</td>
<td>0.39</td>
<td>0.12</td>
<td>0.73</td>
</tr>
<tr>
<td>Her-2 status</td>
<td>-</td>
<td>0.31</td>
<td>-</td>
</tr>
<tr>
<td>Tumor size</td>
<td>0.74</td>
<td>0.53</td>
<td>0.92</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>0.42</td>
<td>0.03*</td>
<td>0.16</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.96</td>
<td>0.96</td>
<td>0.97</td>
</tr>
<tr>
<td>Margins</td>
<td>0.64</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Nodal status</td>
<td>0.73</td>
<td>0.85</td>
<td>0.74</td>
</tr>
<tr>
<td>ASTRO consensus group</td>
<td>-</td>
<td>0.88</td>
<td>-</td>
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Crude local recurrence rate as a function of patient age in prospective APBI studies

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<th>Germany/Austria LR% (n)</th>
<th>WBH LR% (n)</th>
<th>Wisconsin LR% (n)</th>
<th>RTOG 95-17 LR% (n)</th>
<th>Örebro LR% (n)</th>
<th>All studies LR% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40</td>
<td>33.3% (2 of 6)</td>
<td>0% (0 of 3)</td>
<td>0% (0 of 1)</td>
<td>0% (0 of 8)</td>
<td>0% (0 of 1)</td>
<td>10.5% (2 of 19)</td>
<td></td>
</tr>
<tr>
<td>&gt; 40-50</td>
<td>2.6% (1 of 39)</td>
<td>8.7% (4 of 46)</td>
<td>4.3% (1 of 23)</td>
<td>6.1% (4 of 66)</td>
<td>19% ‡ (4 of 21)</td>
<td>12.5% (2 of 16)</td>
<td>7.6% (16 of 211)</td>
</tr>
<tr>
<td>&gt; 50-60</td>
<td>6.9% (4 of 58)</td>
<td>1.2% (1 of 82)</td>
<td>8.7% (4 of 46)</td>
<td>2.2% (2 of 93)</td>
<td>4.2% (1 of 24)</td>
<td>0% (0 of 19)</td>
<td>3.7% (12 of 322)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>4.3% (3 of 70)</td>
<td>2.1% (3 of 143)</td>
<td>3.9% (5 of 129)</td>
<td>4.2% (5 of 120)</td>
<td>1.8% (1 of 54)</td>
<td>6.7% (1 of 15)</td>
<td>3.4% (18 of 531)</td>
</tr>
<tr>
<td>All age</td>
<td>5.8% (10 of 173)</td>
<td>2.9% (8 of 274)</td>
<td>5.0% (10 of 199)</td>
<td>3.8% (11 of 286)</td>
<td>6.1% (6 of 99)</td>
<td>5.9% (3 of 51)</td>
<td>4.4% (48 of 1083)</td>
</tr>
<tr>
<td>FUP</td>
<td>7.3 y</td>
<td>5.3 y</td>
<td>9.6 y</td>
<td>5 y</td>
<td>7 y</td>
<td>7.2 y</td>
<td>-</td>
</tr>
</tbody>
</table>

‡ Results for patients ≤40 years and >40-50 years were reported together
In most series tumour size did not affect local control significantly following BCS + RT.

Holland data*: microscopic spread beyond primary tumour is similar in T1 and T2 tumours.

However, at large volume (>160 cm³) implants the larger implant volume (V100) and high-dose regions (V150 and V200) were correlated with a higher incidence of fat necrosis.

Therefore, large tumours (>3 cm) might not be candidates for BT alone, because of high risk of late tissue toxicity caused by large volume implants.

### Invasive lobular carcinoma (ILC)

Incidence and site of local recurrence following breast-conserving therapy for lobular and non-lobular carcinomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>FUP (years)</th>
<th>ILC</th>
<th>IDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LR%</td>
<td>TR/MM%</td>
</tr>
<tr>
<td>Sastre-Garau [67]</td>
<td>10</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Peiro [66]</td>
<td>10</td>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>Warneke [70]</td>
<td>5</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Weiss [71]</td>
<td>5</td>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>Schnitt [68]</td>
<td>6.25</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Fodor [63]</td>
<td>15</td>
<td>13</td>
<td>93</td>
</tr>
<tr>
<td>Silverstein [69]</td>
<td>6.6</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>All studies</td>
<td>5–15</td>
<td>3–20</td>
<td>86–100</td>
</tr>
</tbody>
</table>

FUP = follow-up period; ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; LR = local recurrence; TR/MM = true recurrence/marginal miss; NR = not reported.

The incidence of EF is similar in case of ILC and IDC!
**German-Austrian Phase II trial – Univariate analysis of prognostic factors for LR***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5-y LR %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILC (n = 45)</td>
<td>2.4%</td>
<td>NS</td>
</tr>
<tr>
<td>All others (n = 229)</td>
<td>2.6%</td>
<td></td>
</tr>
</tbody>
</table>

However, to date only few women having ILC have been treated with APBI in prospective studies. Therefore, at this time there is only limited evidence for the treatment of ILC outside the context of clinical trials.

Outcomes of Breast Cancer Patients Treated with Accelerated Partial Breast Irradiation Via Multicatheter Interstitial Brachytherapy: The Pooled Registry of Multicatheter Interstitial Sites (PROMIS) Experience

N = 1131
Median FUP: 6.9 years

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Actuarial rate (%)</th>
<th>Actuarial rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years (95% CI)</td>
<td>10 years (95% CI)</td>
</tr>
<tr>
<td>Ipsilateral breast tumor recurrence</td>
<td>3.8 (2.7, 5.2)</td>
<td>7.6 (5.6, 10.1)</td>
</tr>
<tr>
<td>TR/MR failure</td>
<td>1.6 (1, 2.7)</td>
<td>2.3 (1.5, 3.7)</td>
</tr>
<tr>
<td>EF</td>
<td>1.5 (0.9, 2.6)</td>
<td>3.3 (2.1, 5.2)</td>
</tr>
<tr>
<td>Unknown location of failure</td>
<td>0.6 (0.3, 1.4)</td>
<td>1.9 (1, 3.8)</td>
</tr>
<tr>
<td>Regional failure</td>
<td>1.4 (0.8, 2.4)</td>
<td>2.3 (1.4, 3.7)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>2.4 (1.6, 3.6)</td>
<td>3.8 (2.5, 5.7)</td>
</tr>
<tr>
<td>Cause-specific survival</td>
<td>97.9 (96.6, 98.7)</td>
<td>96.3 (94.2, 97.6)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>95.4 (93.7, 96.6)</td>
<td>86.5 (83, 89.3)</td>
</tr>
</tbody>
</table>

Ann Surg Oncol
DOI 10.1245/s10434-015-4563-7
Published online: 28 April 2015
ER status, tumour size, histology, and nodal status had no significant impact on LR rate!
Inclusion criteria:
- **LIG group**: low-intermed. grade DCIS ≤2.5 cm; margins ≥3 mm
- **HG group**: high-grade DCIS ≤ 1 cm; margins ≥3 mm

---

Table 3. Comparison of IBTR Rates—Present Study Versus ECOG 5194

<table>
<thead>
<tr>
<th></th>
<th>LIG—E5194</th>
<th>LIG—present study</th>
<th>HG—E5194</th>
<th>HG—present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year IBTR</td>
<td>6.1%</td>
<td>0%</td>
<td>15.3%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

However, to date only few women having DCIS have been treated with APBI in prospective studies. Therefore, at this time there is only limited evidence for the treatment of DCIS outside the context of clinical trials.
However, to date only few node + women have been treated with APBI in prospective studies. Therefore, at this time there is only limited evidence for the treatment of node + pts. outside the context of clinical trials.
The significance of extensive intraductal component (EIC)


Pts. with EIC are more likely to have residual tumour beyond 2 cm distance from the reference tumour than without EIC (33% vs. 2%)
Local recurrence according to EIC after BCS

<table>
<thead>
<tr>
<th>Author</th>
<th>FUP (years)</th>
<th>LR%</th>
<th>Tumour bed dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazer [88]</td>
<td>7</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Fowble [89]</td>
<td>10</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Eberlein [77]</td>
<td>10</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Krishnan [90]</td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Fodor [62]</td>
<td>10</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Polgár [58]</td>
<td>5</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>All studies</td>
<td>5–10</td>
<td>9–27</td>
<td>3–10</td>
</tr>
</tbody>
</table>

FUP = follow-up period; LR = local recurrence; EIC = extensive intraductal component.
Local recurrence by Histological Grade

- Van Limbergen:
  - 5-y LR:
    - Grade I: 5%
    - Grade II: 10%
    - Grade III: 16% (p=0.12)

- Polgár:
  - HG did not have significant effect on LR rate, BUT
  - Time to LR:
    - Grade I-II: 38 months (range: 28-50)
    - Grade III: 20 months (range: 10-34)

Difficult to compare the results, because of the variety of grading systems and the difficulty in grading breast carcinomas.
## Local recurrence by surgical margin status

<table>
<thead>
<tr>
<th>Author</th>
<th>Margin + LR%</th>
<th>Margin – LR%</th>
<th>FUP (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansfield</td>
<td>16</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Smitt</td>
<td>18</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Spivack</td>
<td>18</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Anscher</td>
<td>10</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>DiBiase</td>
<td>14</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Polgár</td>
<td>18</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td><strong>10-18</strong></td>
<td><strong>2-8</strong></td>
<td></td>
</tr>
</tbody>
</table>

2014 ASTRO guidelines on margins: Negative margins = No tumour on ink!
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-risk group – Good candidates for APBI</th>
<th>Intermediate-risk group – Possible candidates for APBI</th>
<th>High-risk group – Contraindication for APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>&gt;50 years</td>
<td>&gt;40-50 years</td>
<td>≤40 years</td>
</tr>
<tr>
<td>Histology</td>
<td>IDC, mucinous, tubular, medullary, and colloid cc.</td>
<td>IDC, ILC, mucinous, tubular, medullary, and colloid cc.</td>
<td>-</td>
</tr>
<tr>
<td>ILC</td>
<td>Not allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>DCIS</td>
<td>Not allowed</td>
<td>Allowed</td>
<td>-</td>
</tr>
<tr>
<td>HG</td>
<td>Any</td>
<td>Any</td>
<td>-</td>
</tr>
<tr>
<td>Tumour size</td>
<td>pT1-2 (≤30 mm)</td>
<td>pT1-2 (≤30 mm)</td>
<td>pT2 (&gt;30 mm), pT3, pT4</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative (≥2 mm)</td>
<td>Negative, but close (&lt;2 mm)</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric</td>
<td>Unicentric</td>
<td>Multicentric</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Unifocal</td>
<td>Multifocal (limited within 2 cm of the index lesion)</td>
<td>Multifocal (&gt;2 cm from the index lesion)</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Present</td>
</tr>
<tr>
<td>LVI</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Present</td>
</tr>
<tr>
<td>ER, PR status</td>
<td>Any</td>
<td>Any</td>
<td>-</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN0 (by SLNB or ALND*)</td>
<td>pN1mi, pN1a (by ALND*)</td>
<td>pNx; ≥pN2a</td>
</tr>
<tr>
<td>Neoadj. chemoth.</td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>If used</td>
</tr>
</tbody>
</table>

Radiother Oncol 2010;94:264-273
## Budapest Phase III APBI trial – Patient characteristics according to the ASTRO and GEC-ESTRO prognostic groups

<table>
<thead>
<tr>
<th>GEC-ESTRO prognostic group</th>
<th>All pts. (n=258)</th>
<th>ASTRO prognostic group</th>
<th>All pts. (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good candidate:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>181 (70%)</td>
<td>98 (38%)</td>
<td></td>
</tr>
<tr>
<td><strong>Possible candidate:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age 41-50 y:</td>
<td>56 (22%)</td>
<td>96 (37%)</td>
<td></td>
</tr>
<tr>
<td>- pN1mi:</td>
<td>52 (20%)</td>
<td>91 (35%)</td>
<td></td>
</tr>
<tr>
<td>- Close margin:</td>
<td>9 (3.5%)</td>
<td>26 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.5%)</td>
<td>9 (3.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cautionary:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age 50-59 y:</td>
<td></td>
<td></td>
<td>96 (37%)</td>
</tr>
<tr>
<td>- ER neg:</td>
<td></td>
<td></td>
<td>91 (35%)</td>
</tr>
<tr>
<td>- LVI:</td>
<td></td>
<td></td>
<td>26 (10%)</td>
</tr>
<tr>
<td>- Close margin:</td>
<td></td>
<td></td>
<td>9 (3.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td><strong>Contraindication:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age ≤ 40 y:</td>
<td>21 (8%)</td>
<td>64 (25%)</td>
<td></td>
</tr>
<tr>
<td>- LVI:</td>
<td>9 (3.5%)</td>
<td>53 (20%)</td>
<td></td>
</tr>
<tr>
<td>- pN1mi:</td>
<td>9 (3.5%)</td>
<td>9 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>- pNx:</td>
<td>5 (2%)</td>
<td>5 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unsuitable:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age &lt; 50 y</td>
<td></td>
<td></td>
<td>64 (25%)</td>
</tr>
<tr>
<td>- pN1mi:</td>
<td></td>
<td></td>
<td>53 (20%)</td>
</tr>
<tr>
<td>- pNx:</td>
<td></td>
<td></td>
<td>9 (3.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>
Local control by GEC-ESTRO prognostic groups

**GEC-ESTRO-Good candidate - 10-year LR: 4.5% (9 of 181)**

**GEC-ESTRO-Possible candidate - 10-year LR: 1.8% (1/56)**

**GEC-ESTRO-Contraindicated - 10-year LR: 15.8% (3/21)**

\[ p_{\text{good vs. possible candidate}} = 0.2915 \]

\[ p_{\text{good candidate vs. contraindicated}} = 0.0759 \]

\[ p_{\text{possible candidate vs. contraindicated}} = 0.0265 \]

Local control by ASTRO prognostic groups

**ASTRO-Suitable - 10-year LR: 4.5% (4/98)**

**ASTRO-Cautionary - 10-year LR: 5.6% (5/96)**

**ASTRO-Unsuitable - 10-year LR: 6.7% (4/64)**

\[ p_{\text{suitable vs. cautionary}} = 0.7945 \]

\[ p_{\text{suitable vs. unsuitable}} = 0.5330 \]

\[ p_{\text{cautionary vs. unsuitable}} = 0.7164 \]
APBI – Direction of future clinical research

• Refinement of patient selection:
  – 40-50 years?
  – Lobular cc.?
  – DCIS?
  – Close, but negative margins?
  – 1-3 pos. lymph nodes?

• Selection of proper APBI technique:
  – Brachytherapy?
    • Multicatheter BT, MammoSite, Hybrid BT applicators
  – Teletherapy?
    • 3D-CRT, IMRT, IGRT
  – Proton therapy?

• Standardisation of PTV definition:
  – Selection of appropriate CTV to GTV (cavity) margin?
  – Selection of appropriate PTV to CTV margin?
  – How to avoid „interobserver variability”?
# Accelerated partial breast irradiation – 8 randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>APBI technique</th>
<th>Accrual goal</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budapest</td>
<td>NI0, Budapest</td>
<td>HDR BT</td>
<td>258</td>
<td>1998-2004</td>
</tr>
<tr>
<td>TARGIT</td>
<td>London/Australia multicentric</td>
<td>IORT - 50 kV photons</td>
<td>2232</td>
<td>2000-2009</td>
</tr>
<tr>
<td>ELIOT</td>
<td>Milan</td>
<td>IORT – electrons</td>
<td>1306</td>
<td>2000-2007</td>
</tr>
<tr>
<td>GEC-ESTRO</td>
<td>European multicentric</td>
<td>HDR/PDR BT</td>
<td>1192</td>
<td>2004-2009</td>
</tr>
<tr>
<td>RAPID</td>
<td>Canadian multicentric</td>
<td>3D-CRT</td>
<td>2128</td>
<td>2006-2011</td>
</tr>
<tr>
<td>NSABP-B39/RTOG-0413</td>
<td>USA multicentric</td>
<td>HDR BT/3D-CRT/MammoSite</td>
<td>4300</td>
<td>2005-2013</td>
</tr>
<tr>
<td>Italy</td>
<td>Univ. Florence</td>
<td>IMRT</td>
<td>520</td>
<td>2005-</td>
</tr>
<tr>
<td>IMPORT-LOW</td>
<td>MRC, UK multicentric</td>
<td>IMRT</td>
<td>1935</td>
<td>2006-</td>
</tr>
</tbody>
</table>

~ 14,000 pts.
### Patient selection – Phase III trials

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Budapest</th>
<th>GEC-ESTRO</th>
<th>NSABP-RTOG</th>
<th>ELIOT</th>
<th>IMPORT-LOW</th>
<th>RAPID</th>
<th>TARGIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&gt; 40 from 2001</td>
<td>&gt; 40</td>
<td>≥ 18</td>
<td>&gt; 48</td>
<td>≥ 50</td>
<td>≥ 40</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>T-size (cm)</td>
<td>≤ 2</td>
<td>≤ 3</td>
<td>≤ 3</td>
<td>≤ 2.5</td>
<td>≤ 2</td>
<td>&lt; 3</td>
<td>Any (excl. T4)</td>
</tr>
<tr>
<td>Unifocality</td>
<td>Yes</td>
<td>Yes</td>
<td>Same quadrant</td>
<td>Yes</td>
<td>Yes</td>
<td>Same quadrant</td>
<td>Yes</td>
</tr>
<tr>
<td>EIC</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lobular ca.</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DCIS</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>LVI</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grade</td>
<td>1-2</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>1-2</td>
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</tr>
<tr>
<td>Margin status</td>
<td>≥ 2 mm</td>
<td>≥ 2 mm</td>
<td>Clear</td>
<td>Clear</td>
<td>≥ 2 mm</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td>Nodal status</td>
<td>pN0-1mi</td>
<td>pN0-1mi</td>
<td>pN0-1a (no ECE)</td>
<td>pN0-1a</td>
<td>pN0</td>
<td>pN0</td>
<td>pN0-1</td>
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</table>
Conclusions

• APBI for a selected group of early-stage breast cancer patients produces long-term results similar to those achieved with conventional WBI.

• Until mature Phase III data: conservative patient selection criteria according to the GEC-ESTRO recommendations should be considered for selecting candidates for APBI.

• Long-term results of ongoing Phase III trials – guidelines for patient selection should be revised and might be extended.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Very low-risk</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
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<tr>
<td>RT</td>
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<td>APBI or AWBI or WBI</td>
<td>WBI or AWBI</td>
<td>WBI + boost</td>
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<td>Frequency</td>
<td>≥70 y, T1N0, ER+, margins ≥ 2mm, EIC-, LVI-</td>
<td>&gt; 50 y, T1-2 (≤ 3 cm) N0, margins ≥ 2 mm, EIC-, LVI-, unifocal tumour</td>
<td>T2 (&gt; 3 cm), margins ≥ 2mm, LVI+, N+, multifocal tumour</td>
<td>≤ 50 y, margins &lt; 2mm, EIC +</td>
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<tr>
<td></td>
<td>Max. 5%</td>
<td>25-30%</td>
<td>30-35%</td>
<td>30-35%</td>
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</tbody>
</table>
Thank you for your kind attention!
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