Local and Regional Therapy
Highlights of the 2014 San Antonio Breast Cancer Symposium

David Euhus, MD, FACS
Professor of Surgery
Chief, Breast Surgery Section
Johns Hopkins Hospital

Quality Breast Surgery

Local/regional Control

Functioning
physical
psychosocial
sexual

Contour and symmetry

Sense of well being
Local and Regional Treatment of Breast Cancer

Outline

1. Trends in Bilateral Mastectomy
   a) Who, Why, and How

2. Breast Conservation
   a) Margins
   b) Radiation
      i. Hypofractionation
      ii. Partial breast
      iii. Intra-operative

3. Regional Radiation

4. Pushing the Envelope: Controversial Trials

---

Trends in Bilateral Mastectomy

- Breast conservation rates have risen to about 65% while mastectomy rates have declined
- The trend is beginning to reverse
- Unilateral mastectomy is declining while bilateral mastectomy is increasing.

Surgical treatment of breast cancer is polarized
Who is Opting For Bilateral Mastectomy?

California Cancer Registry

Kurian AW, et al. JAMA 2014;312:902-914

Young Women’s Breast Cancer Study

≤ 40 years old

Ann Partridge SABCS 2014
Why Women Chose Bilateral Mastectomy

Mostly patient-driven (Partridge, Young Women’s Breast Cancer Study)
- Reduce contralateral breast cancer risk
- Achieve peace of mind
- Improve outcome (i.e. survival)

Bilateral Mastectomy and Outcome
• 8 observational studies suggest breast cancer-specific mortality is reduced
• California Cancer Registry study found no difference
  
  Kurian, JAMA 2014;312:902-914
• Recent SEER study: significant decrease in non-breast cancer mortality
  

SELECTION BIAS: Healthier women chose bilateral mastectomy
Reconstruction

Trends in Reconstruction

Any Reconstruction

Implants

Autologous Tissue

Satisfaction Over Time


Satisfaction with Mastectomy

Strongest predictors of satisfaction

Avoiding complications

Pre and post-operative interactions

- The Surgeon
- Quality of information

Minor predictors

- Choosing bilateral over unilateral
- Autologous versus implant reconstruction

- Bilateral implant reconstruction better symmetry over time
- Satisfaction at 6 years: flap reconstruction > BCS > implant reconstruction

- Bilateral nipple-sparing with implants symmetrical over time (unilateral not)
- Nipple-sparing mastectomy: better psychosocial and sexual well-being
<table>
<thead>
<tr>
<th>UNILATERAL MASTECTOMY</th>
<th>BILATERAL MASTECTOMY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLAP</strong></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Flap UNILATERAL" /></td>
<td><img src="image" alt="Flap BILATERAL" /></td>
</tr>
<tr>
<td><strong>IMPLANT</strong></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Implant UNILATERAL" /></td>
<td><img src="image" alt="Implant BILATERAL" /></td>
</tr>
</tbody>
</table>

Andrea Pusic SABCS 2014

Breast Conserving Surgery
Ipsilateral Breast Tumor Recurrence

**Non-modifiable Factors**
- Age
- Genetics
  - BRCA1/2
  - Others
- Tumor Biology
  - Intrinsic subtype
  - OncotypeDx score

**Modifiable Factors**
- Margin-negative Resection
- Radiation Therapy
- Systemic Adjuvant Therapy
  - Specimen mammography
  - Intraoperative sonography
  - Localization
    - Wire
    - Radioactive seed
    - HydroMark
  - Cavity shave margins
  - Frozen section
  - Others

Maximizing Margin-negative Resection


Intraop sono, shave margins and frozen section.
- 5 of 208 (2.4%) required second surgery for close or positive margins.
- There was no residual tumor in any.

P1-16-10: Cox, Pilot study of a passive non-radioactive electromagnetic wave technology to localize non-palpable breast lesions, Tampa, FL

SAVI SCOUT, Cianna Medical. A radio wave reflector
Successful excisions in 24 of 24.
Maximizing Margin-negative Resection

**Intra-operative Margin Assessment**


*ClearEdge* by LsBioPath: 334 margins in 58 patients (not available in the US)

- Sensitivity 84%
- Specificity 82%
- False Positive: 18%

P1-16-06: Blohmer, Margin Probe device is able to reduce re-excision rate of breast conserving surgery in invasive and pre-invasive breast cancer independent from any patient or tumor related factors, Berlin.

MarginProbe by Dune Medical Devices (radiofrequency spectroscopy)

<table>
<thead>
<tr>
<th></th>
<th>MarginProbe</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>150</td>
<td>156</td>
</tr>
<tr>
<td>Re-excision Rate</td>
<td>15%</td>
<td>30%</td>
</tr>
</tbody>
</table>

ASTRO-SSO Meta-analysis

**Overall IBTR rate 0.8%/year**

<table>
<thead>
<tr>
<th>Relationship between IBTR and margin status</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Adjusted OR of IBTR</th>
<th>95% CI</th>
<th>P (association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin category (model one)</td>
<td>35</td>
<td>26,162</td>
<td>1.96</td>
<td>1.72-2.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Choos/positive</td>
<td>33</td>
<td>6,178</td>
<td>1.96</td>
<td>1.72-2.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>33</td>
<td>21,984</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Margin category (model two)</td>
<td>19</td>
<td>13,081</td>
<td>2.44</td>
<td>1.97-3.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>1,641</td>
<td>2.44</td>
<td>1.97-3.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Close</td>
<td>19</td>
<td>2,407</td>
<td>1.74</td>
<td>1.42-2.15</td>
<td>—</td>
</tr>
<tr>
<td>Negative</td>
<td>19</td>
<td>9,033</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Threshold distance (model two)</td>
<td>6</td>
<td>2,376</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1 mm</td>
<td>10</td>
<td>8,359</td>
<td>0.91</td>
<td>0.46-1.80</td>
<td>—</td>
</tr>
<tr>
<td>2 mm</td>
<td>3</td>
<td>2,355</td>
<td>0.77</td>
<td>0.32-1.82</td>
<td>—</td>
</tr>
</tbody>
</table>

Impact of margin width on IBTR adjusted for individual covariates and follow-up

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No. of studies</th>
<th>Threshold distance negative margin: adjusted OR (mm)</th>
<th>P (association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18</td>
<td>1.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>16</td>
<td>1.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Radiation boost</td>
<td>18</td>
<td>1.0</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Ann Surg Oncol 2014;21:704-716
ASTRO-SSO Statement

• NO INK ON THE TUMOR IS THE ACCEPTABLE MARGIN

• A radiation boost does not “fix” positive margins (IBTR ~1.7%/year)
• Effective adjuvant systemic therapy does not “fix” positive margins
• There are no tumor subtype that do not benefit from negative margins
• Lobular cancers do not require wider margins than any other cancer
• Young patients do not require wider margins than older patients.
• Advised individualizing for extensive intraductal component.

Ann Surg Oncol 2014;21:704-716

Margin Width

P1-16-03: Campo, Residual disease after breast conservation surgery: To excise or not to excise? New York.
1998- 2013, 828 BCS patients who had a re-excision
• 230 (28%) had residual disease in a re-excision.
• 103 (12.4%) required a 3rd excision.
Predictors of Residual Disease (multivariate model)
• Number of margins < 2mm
• Any margin < 2mm for DCIS

P1-16-01: Sagara, Effect of margin width on local recurrence in invasive lobular carcinoma treated with multimodality therapy, Dana-Farber
399 patients with pure ILC or mixed IDC/ILC
Median F/U 72 mo.
• 12 (3.1%) IBTR.
• Positive margin was associated with LRR (HR 5.1) and DFS (HR 8.9).
• Re-excision improved LRR rate for those with positive margins but did not affect those with close margins.
• Conclude that “no ink on tumor” is appropriate standard for mixed and pure ILC treated with multimodal therapy.
Radiation after Breast Conserving Surgery

Hypofractionated Whole Breast Radiation

Standard fractionation: 2Gy x 25 = 50Gy
Hypofractionated: e.g. 2.7Gy x 15 = 41Gy

Randomized Hypofractionated Breast Radiation Trials
(All show non-inferiority)
• 2002 Ontario (5 year)
• 2006 Royal Marsden (10 year)
• 2006 UK START (5 year)
• 2010 Ontario (10 year)
• 2013 UK START 2013 (10 year)
Adoption of Hypofractionated Radiation Therapy

P1-15-02: Utilization of hypofractionated radiation therapy for early stage breast cancer in women over 50 years of age
P1-15-04: The adoption of hypofractionated whole breast irradiation for early-stage breast cancer: A national cancer data base analysis
P1-15-10: Low utilization of hypofractionated radiotherapy for the treatment of early-stage breast cancer in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>Utilization %</th>
<th>Community Cancer Center</th>
<th>Comprehensive Community Cancer Center</th>
<th>Academic Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2005</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2006</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2007</td>
<td>15</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2008</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2009</td>
<td>25</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2010</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2011</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**From P1-15-10**

**HFRT is used most commonly for:**
- Low grade tumors
- Smaller tumors
- Hormone sensitive tumors
- Older patients
- White women
- Greater distance from treatment center

---

**Hypofractionated Radiation Therapy**

**P1-15-07:** Leonardi, Simultaneous integrated boost incorporated into a hypofractionated regimen using tomoDirect: Acute toxicity assessment, Milan

Hypofractionated scheme including a simultaneous integrated boost, with intensity modulated radiotherapy.
Phase II Trial  N = 194

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>End of Treatment</th>
<th>1 month F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 Erythema</td>
<td>58%</td>
<td>23%</td>
</tr>
<tr>
<td>Grade 2 Erythema</td>
<td>37%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3 Erythema</td>
<td>0.5%</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1 Edema</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Grade 2 Edema</td>
<td>4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Dry desquamation</td>
<td>&lt;10%</td>
<td>17%</td>
</tr>
<tr>
<td>Patchy moist desquamation</td>
<td>4%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**P1-15-24:** Paul, Skin toxicities of obese African American breast cancer patients treated with hypofractionated radiation therapy, Detroit.

N= 15. Median BMI 42.2 (prone), 29.7 (supine)

*Conclude: Obese African-American pts can safely be treated with HFRT in the prone position.*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Dermatitis</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>60%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>34%</td>
</tr>
<tr>
<td>Desquamation</td>
<td>20%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td></td>
</tr>
<tr>
<td>Faint</td>
<td>40%</td>
</tr>
<tr>
<td>Moderate</td>
<td>47%</td>
</tr>
<tr>
<td>Severe</td>
<td>6.5%</td>
</tr>
</tbody>
</table>
Why Partial Breast Irradiation?

**Whole Breast Radiation Therapy**

Risk of major coronary events

Risk of second malignancies
Grantza T, et al. Radiother Oncol 2014, Nov 7
- Lung (RR 1.39 → 1.66)
- Esophagus (RR 1.53 → 2.17)
- Sarcoma (RR 2.53)

Skin and chest wall toxicity
Burdensome treatment schedule

---

**Accelerated Partial Breast Irradiation**

**APBI Techniques**
3D conformal external beam
Single lumen catheter
Multilumen catheter
Multi-catheter
Stereotactic Body Radiation Therapy (SBRT)

Available data suggest local recurrence risk acceptable
- Hungarian trial only randomized trial
NSABP B-39 is only U.S. large, randomized trial -- no outcomes reported yet

Educational Symposium: *What have we learned from the randomized trials of partial breast irradiation.*  Ivo A. Olivotto

- Local toxicity can adversely impact long term cosmetic outcomes
- We may not have the dosing optimized
Accelerated Partial Breast Irradiation


- Multi-catheter brachytherapy
- Cardiac dose is similar to WBI for inner and central tumors

P1-15-17: Bergom, Sustained acceptable cosmetic outcomes and local control following accelerated partial breast irradiation using CT-guided IMRT in the prone position: Results from a phase I/II feasibility study, Milwaukee

- Prone, CT-guided APBI in 20 patients
- Median F/U 60 months
- Good – excellent cosmesis: 80%

Intraoperative Radiation Therapy (IORT)

ELIOT: single 21Gy electrons, Milan, 1305 patients


- 20 minutes to set up 3-5 minutes to deliver
- 5.8 yr median f/u, 5-Yr IBTR 4.4% vs 0.4%
- 2/3 LR were in the primary site
- High risk tumors (large, ER(-), high grade, LN(+) \(\rightarrow\) >10% LR)

TARGIT: Single 5-7Gy, IntraBeam kV photons, 3451 patients


- 10 minutes set up, 20-45 min treatment delivery
- ? Median f/u. Most 2.5 yrs. IBTR 2.1% vs. 1.1%
- 22% also had WBR

IntraBeam IORT may be associated with an acceptably low rate of local recurrence in a selected low risk population.

Would that population do just as well with no radiation?
Intraoperative Radiation Therapy (IORT)

P1-15-13: Shai, Short term toxicity of intra-operative radiotherapy for patients with breast cancer treated at a single center, Israel

- IntraBeam 20Gy in single fraction
- 393 treated between 2006 – 2012
  - 11.0% Infection
  - 10.2% Seroma (significant)
  - 8.2% Wound dehiscence
  - 0.5% Grade 4 skin toxicity

P1-15-05: Leonardi, Long-term outcome of electron intraoperative boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women, Milan

- Electron IORT boost (12 Gy) followed by hypofractionated RT.
- 357 stage 0 – IIIC premenopausal women
- Median F/U 83.1 mo
  - 2.3% local recurrence

Intraoperative Radiation Therapy (IORT)

Ongoing Clinical Trial

OT1-4-01: Reitsamer, HIOB trial - Hypofractionated whole-breast irradiation preceded by intraoperative radiotherapy with electrons as anticipated boost, Salzberg.

- 10Gy IORT followed by 2.7Gy x 15
- 1500 women ≥35 y/o, T1-2/N1-2, any grade
- Endpoints are LR and toxicity
- Single arm

<table>
<thead>
<tr>
<th>Age</th>
<th>LR Rate per year</th>
<th>Trial Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 – 50</td>
<td>0.72-1.2%</td>
<td>CONSORT EORTC 22881</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.4 – 0.7%</td>
<td>START B EORTC 22881</td>
</tr>
</tbody>
</table>
Regional Nodal Irradiation

P1-15-08: Belkacemi, Tangential fields (TgF) breast radiotherapy (RT): Prospective evaluation of the dose distribution in the sentinel lymph node area (SLNa) as determined intra operatively by clip placement, France

Standard tangential fields provided total coverage of the SLN region (defined as 1.5 cm around the clips) in < 50%

P1-15-09: Belkacemi, Patterns of practice of regional node irradiation in the sentinel node biopsy era: Results of the nodal radiotherapy (NORA) survey. On behalf of the EORTC Breast Working Party of the Radiation Oncology Group (ROG), France

Regional nodal irradiation practice patterns are very heterogeneous.
Regional Nodal Irradiation
Ongoing Clinical Trial

OT1-3-02: Mamounas, Will chest wall and regional nodal radiotherapy post mastectomy or the addition of regional nodal radiotherapy to breast radiotherapy post lumpectomy reduce the rate of invasive cancer events in patients with positive axillary nodes who convert to ypN0 after neoadjuvant chemotherapy? NSABP B-51/RTOG 1304 a phase III trial, NSABP

Controversial Trials

OT1-3-01: Imoto, Phase II study on radiofrequency ablation in stage 0 and I breast cancer without extensive intraductal components, Japan
  - Cool-Tip radiofrequency ablation device
  - Previously showed 96% 5-year IBTR-free in 420 T1 breast cancers after mean F/U 50 months. (ASCO 2012 #1119)
  - Now want to determine if there is pathologic complete ablation of the tumor
  - Tis(<2 cm) and T1/N0-N1mic
  - Ablation followed by core needle biopsy 1 month later

OT3-5-01: Tucker, A prospective, randomized trial of sentinel lymph node biopsy versus no additional staging in patients with T1-T2 invasive breast cancer and negative axillary ultrasound, Wash U.
  - 460 cT1-2N0 (by axillary sono)
  - Randomized to SLN biopsy or no axillary surgery
  - Primary endpoint is axillary recurrence rate

OT3-6-01: Elshof, The LORD trial: A randomized, non-inferiority trial, between active surveillance versus standard treatment in patients with low risk ductal carcinoma in situ, Netherlands
  - 1,842 Age ≥ 49, grade 1 DCIS diagnosed as microcalcifications on screening mammogram
  - Randomized to active surveillance (annual mammography) or local standard treatment
  - Primary endpoint is time to development of invasive cancer or higher grade DCIS
  - Includes tissue repository
Key Points

• Use of unilateral mastectomy is declining
• Use of bilateral mastectomy is increasing
  o Contralateral breast cancer rates are decreasing
  o Patient driven
    -Younger women
    -Peace of mind
    -Availability of reconstruction
• Savi-Scout has the potential to replace wire- or seed-localization
• Intraoperative margin assessment devices may have promise
• The U.S. has been slow to adopt hypofractionated radiation
• Partial breast irradiation: variable approaches, variable adoption, variable cosmesis
  -Awaiting clinical trial data (NSABP B-39)
• IORT
  o May be adequate in selected patients
  o Use as a boost with WBRT?