Highlights from San Antonio 2012: Perspectives in Loco-regional Control

Terry Mamounas, M.D., M.P.H, F.A.C.S.
Medical Director, Comprehensive Breast Program
MD Anderson Cancer Center, Orlando
Professor of Surgery
Northeastern Ohio University Medical College

Outline

• Sentinel Node Biopsy in the Setting of Neoadjuvant Chemotherapy
  – ACOSOG Z1071 Trial
  – SENTINA Trial
• Disparities in the Use of SLNB
  – MD Anderson Study
• Total Skin Sparing Mastectomy in BRCA Carriers
  – UCSF Study
• Hypofractionated RT and Intraoperative RT
  – START Trial
  – TARGIT Trial

Individualizing Loco-Regional Therapy with NC Achievements

• Conversion of patients with inoperable tumors to operable candidates
• Conversion of mastectomy candidates to candidates for BCS
• Improvement in cosmesis by reducing the size of lumpectomy in BCS candidates with large tumors
Individualizing Loco-Regional Therapy with NC
Promises

- Reduction in the extent of axillary surgery by down-staging involved axillary nodes (SNB)
- Reduction in the extent of L-R XRT by down-staging primary tumors and axillary nodes
- The above goals are predicated on the premise that SLNB after NC is accurate in patients who present with axillary nodal involvement before NC
- ACOSOG Z1071 Trial
- SENTINA Trial

The role of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0-T4, N1-2) who receive neoadjuvant chemotherapy – results from the ACOSOG Z1071 trial

Judy Boughey, Vera Suman, Elizabeth Mittendorf, Gretchen Ahrendt, Lee Wilke, Bret Taback, Marilyn Leitch, Teresa Flippo-Morton, David Byrd, David Oillio, Tom Julian, Sarah McLaughlin, Linda McCail, Fraser Symmans, Carisa Le-Petross, Bruce Haffty, Tom Buchholz, Kelly Hunt

ACOSOG Z1071: Background

- Standard therapy for node positive breast cancer treated with NAC is ALND
- 40% of node positive disease convert to node negative after NAC
- Improved systemic treatment and targeted therapy will likely increase conversion rates
- Axillary response is an important prognostic factor and may inform further treatment decisions

Is there a role for SLN surgery?
ACOSOG Z1071: Background

SLN after NAC in node + disease
Retrospective studies have reported false negative rates 5-30%

<table>
<thead>
<tr>
<th>Studies lacked:</th>
<th>Author</th>
<th>Year</th>
<th>N (SLN)</th>
<th>N (ALND)</th>
<th>FN SLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized SLN technique</td>
<td>Boughey et al</td>
<td>2006</td>
<td>142</td>
<td>96.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Standardized axillary imaging</td>
<td>Suen et al</td>
<td>2007</td>
<td>81</td>
<td>87.9</td>
<td>20</td>
</tr>
<tr>
<td>Robust sample size</td>
<td>Desouki et al</td>
<td>2008</td>
<td>45</td>
<td>91.5</td>
<td>15</td>
</tr>
<tr>
<td>Multicenter participation</td>
<td>Caranero et al</td>
<td>2009</td>
<td>27</td>
<td>94</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>Fornasier et al</td>
<td>2010</td>
<td>99</td>
<td>95.5</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>Caranero et al</td>
<td>2011</td>
<td>84</td>
<td>95.9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Altekrise et al</td>
<td>2012</td>
<td>121</td>
<td>93</td>
<td>26.8</td>
</tr>
</tbody>
</table>

ACOSOG Z1071

Hypothesis: SLN surgery is an accurate method of axillary staging after NAC in node positive patients

Primary Endpoint: False negative rate of SLN surgery in patients with node positive disease at presentation with at least 2 SLNs examined after NAC

Z1071: Schema

T0-4, N1-2, M0 invasive breast cancer (pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)

REGISTER

Neoadjuvant chemotherapy

REGISTER

SLN and ALND
Z1071: Methods

Recommended surgical standards
- Resection of minimum of 2 SLNs
- Use of dual tracer (radiocolloid and blue dye)

Pathologic assessment
- Standard processing with H&E staining
- Node positive defined as tumor >0.2mm on H&E

Z1071: Statistical Analysis

- Primary aim
  - To determine if the FNR is <10% among women with cN1 disease who had at least 2 SLNs excised
  - 10% FNR selected based on previous studies
    - FNR of SLN in early breast cancer without NAC
      - NSABP B-32: 9.8%
    - FNR of SLN after NAC
      - NSABP B-27: 10.7%
    - Meta-analysis of 21 studies: 12%

Z1071: Consort Diagram

- 756 women with T0-4, N1-2, M0 disease enrolled
- 761 women underwent axillary surgery (663 (87), 98 (13))
- 687 women attempted SLN and ALND completed (664 (98), 33 (42))
- 637 women SLN identified and ALND completed (621 (87), 14 (2))
- Exceptions
  - 34 post-lumpectomy prior to surgery
  - 24 pre-6 months old

Auxillary surgery
- 39 patients underwent completion based on ALND
  - 12 with SLN not detected
Z1071: Clinico-pathologic and Treatment Characteristics

All patients (N=798)

<table>
<thead>
<tr>
<th>Clinical T stage at diagnosis</th>
<th>N (n=798)</th>
<th>98 (14.8)</th>
<th>303 (40.4)</th>
<th>101 (28.6)</th>
<th>53 (6.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximated subtype:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 positive</td>
<td>211 (26.5)</td>
<td>69 (20.5)</td>
<td>132 (25.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>318 (50.7)</td>
<td>112 (35.3)</td>
<td>118 (22.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone receptor positive/HER2 negative</td>
<td>3 (1.4)</td>
<td>144 (43.2)</td>
<td>144 (43.2)</td>
<td>34 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>523 (53.7)</td>
<td>44 (13.5)</td>
<td>33 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline and taxanes</td>
<td>122 (17.4)</td>
<td>34 (13.1)</td>
<td>34 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline-based chemotherapy</td>
<td>122 (17.4)</td>
<td>34 (13.1)</td>
<td>34 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxane-based chemotherapy</td>
<td>523 (74.6)</td>
<td>44 (6.5)</td>
<td>33 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anthracycline or taxanes</td>
<td>122 (17.4)</td>
<td>34 (13.1)</td>
<td>34 (13.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Z1071: SLN Identification Rate

<table>
<thead>
<tr>
<th>Patients</th>
<th>N</th>
<th>SLN identified</th>
<th>SLN identification rate (%)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>689</td>
<td>639</td>
<td><strong>92.7</strong></td>
<td>90.5 - 94.6</td>
</tr>
<tr>
<td>cN1</td>
<td>651</td>
<td>605</td>
<td>92.9</td>
<td>90.7 - 94.8</td>
</tr>
<tr>
<td>cN2</td>
<td>38</td>
<td>34</td>
<td>89.5</td>
<td>75.2 - 97.1</td>
</tr>
</tbody>
</table>

False Negative Rate Among Pts with cN1 Disease and at least 2 SLNs Examined

\[
\text{FNR} = \frac{\text{# pts SLN - / ALND +}}{\text{# pts SLN + or ALND +}}
\]

310 patients had residual nodal disease
39 of these patients had negative SLNs

\[
\text{FNR} = 12.6\%
\]

95% probability that the FNR lies in the range of 9.4 to 16.7%.
### Z1071: FNRs in cN1 Patients with 2+ SLNs Examined

<table>
<thead>
<tr>
<th>Mapping Agent</th>
<th>310 patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue dye only</td>
<td>2/9 (22.2%)</td>
<td>p = 0.046</td>
</tr>
<tr>
<td>Radiolabeled colloid only</td>
<td>10/56 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Both blue dye and radiolabeled colloid</td>
<td>27/251 (10.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of SLN Examined</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19/96 (20.1%) p = 0.004</td>
</tr>
<tr>
<td>3</td>
<td>7/78 (9.0%)</td>
</tr>
<tr>
<td>4</td>
<td>4/60 (6.7%)</td>
</tr>
<tr>
<td>5+</td>
<td>9/82 (11.0%)</td>
</tr>
</tbody>
</table>


### Z1071: Only 1 SLN Identified

78 patients with cN1 had only 1 SLN examined

- 24 pts had no residual nodal disease
- 17 of the 54 pts with residual nodal disease had false negative SLN findings

**FNR = 31.5%**


### Histologic Changes in SLN among 525 Pts with cN1 Disease and 2+ SLNs Examined

<table>
<thead>
<tr>
<th>Histologic changes</th>
<th>N</th>
<th>FNR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not mentioned</td>
<td>339 (64.5%)</td>
<td>28/208 (13.5%)</td>
<td>9.1 – 18.9%</td>
</tr>
<tr>
<td>Present</td>
<td>186 (35.5%)</td>
<td>5/192 (2.6%)</td>
<td>0.9 – 18.9%</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>33 (6.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>15 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>17 (3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histiocyte infiltrate</td>
<td>88 (16.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effect NOS</td>
<td>33 (6.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clip Placement in Pts with cN1 Disease and 2+ SLNs Examined

172 of 525 (32.8%) patients had clip placed in LN at diagnosis.

<table>
<thead>
<tr>
<th>Clip</th>
<th>N</th>
<th>Nodal residual disease</th>
<th>FNR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clip placed and found in LN</td>
<td>96</td>
<td>54</td>
<td>7.4%</td>
<td>2.0 - 17.9%</td>
</tr>
<tr>
<td>Clip placed, not documented where located at surgery</td>
<td>76</td>
<td>50</td>
<td>14.0%</td>
<td>5.8 - 26.7%</td>
</tr>
<tr>
<td>Clip not placed</td>
<td>363</td>
<td>206</td>
<td>13.6%</td>
<td>9.2 - 19.0%</td>
</tr>
</tbody>
</table>

Z1071: Conclusions

- SLN surgery is a useful tool for detection of residual nodal disease in women with node positive disease receiving NAC
- Surgical technique important to minimize FNR
  - Use of dual tracer
  - Resection of minimum of 2 SLNs
- Potential further refinement with:
  - Clip placement in LNs at diagnosis
  - Pathologic review of SLNs for treatment effect
- Use of SLN surgery in these patients will enable reduction in extent of axillary surgery

Future Clinical Trials

ALLIANCE A10202 Schema
- Clinical Trials
- Neoadjuvant Chemotherapy
- BCT or mastectomy
- Sentinel lymph node surgery
- Sub Negative
- Sub Positive

NSABP B-01RTOG 1304 (NRG/332) Schema
- Clinical Trials
- Neoadjuvant Chemotherapy (FAC or capecitabine alone)
- Neoadjuvant Chemotherapy (FAC or capecitabine and trastuzumab for HER2 positive)
- Trastuzumab with or without adjuvant chemotherapy
- Neoadjuvant Chemotherapy
- Neoadjuvant Chemotherapy
- Neoadjuvant Chemotherapy
- Neoadjuvant Chemotherapy
- Neoadjuvant Chemotherapy

Sentinel Lymph Node Biopsy
Before or After Neoadjuvant Chemotherapy
Final Results from the Prospective, German Multiinstitutional SENTINA Trial


SENTINA Trial

- **Design:** 4-arm, prospective multicenter cohort study
- **Objective:** To evaluate a specific algorithm for the timing of a standardized SLNB procedure and provide reliable data for
  - SLN detection rates prior and after NCHT
  - FNR for patients, who convert from cN1 to cN0
  - Detect factors that might influence DR and FNR

SENTINA Trial Design and Patient Distribution

1737 Pts (103 Institutions)

- cN0: 1022
- cN1: 715
- pN0: 662
- pN1: 360
- ycN0: 592
- ycN1: 123

- **Arm A:** No axillary treatment
- **Arm B:** SLNB + ALND
- **Arm C:** SLNB + ALND + ALND
- **Arm D:** SLNB + ALND

NEOADJUVANT CHEMOTHERAPY (NACT)
Standardization of the SLNB Procedure
According to Interdisciplinary Consensus
(Cancer 2005)

- **Tracer**
  - Radiocolloid mandatory
  - Blue dye optional

- **Lymphoscintigraphy**
- **Injection Site**
  - Free (peritumoral, subcutaneous, periareolar)

- **Histologic Assessment**
  - Entire lymph node paraffin-embedded
  - Step sections at least 500 μm
  - No IHC

SLNs Detected and Removed

<table>
<thead>
<tr>
<th></th>
<th>SLNB Prior to Any Therapy</th>
<th>Re-SLNB after SLNB + NACT</th>
<th>SLNB after NACT for cN1 → ycn0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A + B</td>
<td>99.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>60.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td>80.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P < 0.001**

Target Count (per SLN)
According to Nodal Status

<table>
<thead>
<tr>
<th>Target count</th>
<th>P-value = 0.136</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>320 cts (Median)</td>
</tr>
<tr>
<td>pN1</td>
<td>307 cts (Median)</td>
</tr>
</tbody>
</table>

Target Count (Per SLN) According to Previous Treatment (Median)

<table>
<thead>
<tr>
<th>SLNB prior to any therapy</th>
<th>Re-SLNB after SLNB and NACT</th>
<th>SLNB after NACT for cN1 → ycN0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A+B</td>
<td>400 cts</td>
<td>305 cts</td>
</tr>
<tr>
<td>Arm B</td>
<td>129 cts</td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value < 0.001

False-Negative Rate

<table>
<thead>
<tr>
<th>ypN 0: 155 (70.8%)</th>
<th>ypN 1: 64 (29.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI 38.7% – 64.2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ypN 0: 248 (52.3%)</th>
<th>ypN 1: 226 (47.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI 9.9% – 19.4%</td>
<td></td>
</tr>
</tbody>
</table>

Arm B: Re-SLNB after SLNB and NACT
Arm C: SLNB after NACT for cN1 → ycN0

Multivariate Regression Analysis FNR
Arm C (SLNB after NACT for cN1 → ycN0)

| Lobular vs non-lobular tumor | OR=1.32 (0.07, 2.51), p=.178 |
| Unifocal vs multifocal       | OR=1.28 (0.40, 3.55), p=.741 |
| LD vs L1                     | OR=1.61 (0.32, 3.15), p=.365 |
| V0 vs V1                     | OR=2.31 (0.69, 7.52), p=.337 |
| Extracaps. extension no vs yes | OR=3.86 (1.03, 14.6), p=.137 |
| HER2-negative vs positive    | OR=4.55 (3.31, 5.37), p=.967 |
| HER2-negative vs positive    | OR=6.71 (4.06, 10.65), p=.466 |
| Large center vs small        | OR=1.47 (0.25, 7.37), p=.637 |
| Number of SLN (1 vs >1)      | OR=5.06 (0.36, 23.33), p=.008 |
| No pCR vs pCR                | OR=1.34 (0.24, 7.37), p=.737 |

**SENTINA Trial: Summary I (Feasibility / Detection)**

- The Detection Rate (DR) for the SLN is excellent for patients who receive SLNB prior to systemic treatment.
- Repeated SLNB is associated with unacceptable DR.
- Patients who convert under NACT from cN1 to ycN0 have a DR of only 80.1%.
- Previous local and systemic treatment significantly impairs the tracer uptake and the DR.
- Nodal involvement does not influence the tracer uptake in the SLN and the DR.

**SENTINA Trial: Summary II Reliability / FN Rate**

- The FNR for a repeated SLNB after NACT is unacceptable.
- The FNR for patients, who are downstaged through NACT from a positive to a negative axillary status appears less favourable compared to the FNR in pts who undergo primary surgery.
- SLNB as a diagnostic procedure is not a reliable tool in patients who convert under NACT from cN1 to cN0 compared to SLNB in primary surgery.

**Disparities in the Utilization of Axillary Sentinel Lymph Node Biopsy among Black and White Patients with Node-Negative Breast Cancer from 2002-2007**

Dalliah M Black MD, Jing Jiang MS, Henry M Kuerer MD, PhD, Thomas A Buchholz MD, and Benjamin D Smith MD
Among pathologic node-negative invasive breast cancer patients:

- Characterize racial disparities in the use of SLNB
- Evaluate racial disparities in clinical outcomes

Initial cohort of 51,063 women:
- SEER/Medicare database
- Invasive breast cancer diagnosed between 2002 and 2007
- Fee for service coverage
- No evidence of distant metastasis

Study cohort of 31,274 (61%) women:
- Pathologic negative axillary lymph nodes
- Documented axillary surgical procedure

Disparities in SLNB Utilization

Purpose

Methods: Study Cohort

Primary Outcome: Statistical Analysis

- Logistic regression analysis
  - Determine if race was an independent variable of receipt of SLNB
  - Adjusted for significant patient, tumor, and treatment variables
Methods: Secondary Outcome

- Cumulative incidence of lymphedema
  - determined from diagnosis to last follow-up date
  - with a second encounter

- Lymphedema determined using diagnosis codes
  - specified on claims
  - 457.0, 457.1, 457.2, 997.99

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>74 years</td>
</tr>
<tr>
<td>Black</td>
<td>4%</td>
</tr>
<tr>
<td>Tumor size: 0 – 2cm</td>
<td>75%</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>62%</td>
</tr>
<tr>
<td>SLNB</td>
<td>73%</td>
</tr>
<tr>
<td>SLNB median # nodes removed</td>
<td>2</td>
</tr>
<tr>
<td>ALND median # nodes removed</td>
<td>11</td>
</tr>
</tbody>
</table>

Use of SLNB by Race

<table>
<thead>
<tr>
<th>Race</th>
<th>%</th>
<th># SLNB</th>
<th># Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>62%*</td>
<td>1102</td>
<td>1767</td>
</tr>
<tr>
<td>White</td>
<td>74%</td>
<td>20541</td>
<td>27856</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>65%*</td>
<td>1073</td>
<td>1651</td>
</tr>
</tbody>
</table>

* P Value <0.001
Disparities in SLNB Utilization

SLNB Time Trends by Race

Disparities in SLNB Utilization

Independent Predictors of SLNB Use

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race</td>
<td>0.67</td>
<td>0.60-0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt; 80 years</td>
<td>0.80</td>
<td>0.74-0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Higher comorbidity</td>
<td>0.80</td>
<td>0.75-0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>0.20</td>
<td>0.18-0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Later year of diagnosis</td>
<td>4.4</td>
<td>4.0-4.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Disparity in SLNB Use is Independent of Lumpectomy vs Mastectomy

<table>
<thead>
<tr>
<th></th>
<th>% SLNB</th>
<th># SLNB</th>
<th># Total Patients</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Lumpectomy</td>
<td>81%</td>
<td>757</td>
<td>937</td>
<td>0.68</td>
<td>0.57-0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White Lumpectomy</td>
<td>86%</td>
<td>15109</td>
<td>17483</td>
<td>0.67</td>
<td>0.57-0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black Mastectomy</td>
<td>42%</td>
<td>345</td>
<td>830</td>
<td>0.67</td>
<td>0.57-0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White Mastectomy</td>
<td>52%</td>
<td>5432</td>
<td>10373</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Controlled for patient age, comorbidity, year of diagnosis and tumor size.
### Additional Factors Associated with Lymphedema

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary Dissection</td>
<td>1.82</td>
<td>1.66 – 1.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black race</td>
<td>1.42</td>
<td>1.21 – 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.76</td>
<td>1.43 – 2.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiation</td>
<td>1.40</td>
<td>1.22 – 1.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1.57</td>
<td>1.36 – 1.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


### Summary

- SLNB increased as it became the preferred staging method.
- Black patients were 12% less likely to have a SLNB.
- Doubling of lymphedema in black patients.

### Conclusions

- Focused education is needed in minority populations and their treatment teams.
- More contemporary data are needed.
**Study Limitations**

- Tumor registries ability to capture axillary surgery
- Data through 2007
- Retrospective claims study without reasons for treatment
- Limited number of patients of other races

---

**Total Skin-sparing Mastectomy in BRCA Mutation Carriers**

Warren Peled A, Hwang ES, Ewing CA, Alvarado M, Esserman LJ

- Total skin-sparing mastectomy (TSSM) with preservation of the nipple-areolar complex skin has become increasingly accepted as an oncologically safe procedure for both prophylactic and therapeutic indications
- The goal of this study was to evaluate the oncologic outcomes after TSSM in BRCA mutation carriers

---

**TSSM in BRCA Mutation Carriers**

**Methods**

- 53 BRCA-positive patients who underwent bilateral TSSM from 2001-2011:
  - Prophylactic indications (26 patients)
  - Therapeutic indications (27 patients)
- Cases were age-matched (for prophylactic cases) or age- and stage-matched (for therapeutic cases) with non-BRCA-positive patients who underwent bilateral TSSM during this time period
TSSM in BRCA Mutation Carriers

Outcomes

- Tumor involvement of the resected nipple tissue
- Development of new breast cancers in patients who underwent bilateral risk-reducing TSSM
- Development of any local-regional recurrence in patients who underwent therapeutic TSSM


TSSM in BRCA Mutation Carriers

Tumor Involvement of Resected Nipple Tissue Specimens

<table>
<thead>
<tr>
<th></th>
<th>PROPHYLACTIC</th>
<th>THERAPEUTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA+ (n = 53)</td>
<td>Non-BRCA+ (n = 52)</td>
</tr>
<tr>
<td>No tumor</td>
<td>51 (98.1%)</td>
<td>50 (96.2%)</td>
</tr>
<tr>
<td>In situ</td>
<td>1 (1.9%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Invasive</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


TSSM in BRCA Mutation Carriers

New Cancers and Local Recurrences

- With mean follow-up of 43 months, no new cancers developed in the prophylactic BRCA-positive or non-BRCA-positive cohorts

With a mean follow-up of 33 months, there were no LR in the BRCA-positive cohort and 1 LR in the non-BRCA-positive cohort

TSSM in BRCA Mutation Carriers

Conclusions

• TSSM is an oncologically safe procedure in BRCA-positive patients:
  - Low rates of tumor involvement of the nipple tissue and local-regional recurrence after therapeutic mastectomy
• In BRCA-positive patients undergoing TSSM as a risk-reducing strategy, five-year follow-up demonstrates no increased risk for the development of new breast cancers


The UK START (Standardisation of Breast Radiotherapy) Trials; 10-year follow-up results


START Trials: Design and Endpoints

Women with completely excised invasive breast cancer, T1-3 N0-1 M0

Primary endpoint:
- local-regional relapse

Secondary endpoints include:
- normal tissue effects (assessed by physicians, photographs & patients)
- disease-free & overall survival

Recruitment from 35 UK centres 1999-2002 with QA

Median follow-up:
9.3 years (Trial A)
9.9 years (Trial B)
Trial A: Any Moderate/Marked Adverse Effect in Conserved Breast (Physician Assessments)

% of patients with no moderate/marked effect in the breast

- 30 Gy
- 41.6 Gy
- 50 Gy

Hazard Ratio (95% CI)
- 41.6 Gy vs. 50 Gy: 0.54 (0.70-1.11)
- 30 Gy vs. 50 Gy: 0.80 (0.67-0.98)

Absolute difference at 10 years (95% CI)
- 4.1% (-12.9 to -1.4%)

Time from randomisation (years)


Trial A: Local-regional Tumor Relapse

% of patients with no LR relapse

Cumulative hazard rate

Hazard Ratio (95% CI)
- 41.6 Gy vs. 50 Gy: 0.91 (0.59 - 1.29)
- 30 Gy vs. 50 Gy: 1.10 (0.70 - 1.70)

Absolute difference at 10 years (95% CI)
- 1.3% (-4.5 to 5.2%)

Time from randomisation (years)


Trial B: Any Moderate/Marked Effect in the Conserved Breast (Physician Assessments)

% of patients with no moderate/marked effect in the breast

- 40 Gy
- 50 Gy

Hazard Ratio (95% CI)
- 40 Gy vs. 50 Gy: 0.77 (0.64-0.90)

Absolute difference at 10 years (95% CI)
- 0.7% (-12.4 to 3.7%)

Time from randomisation (years)


Trial B: Local-regional (LR) Tumor Relapse

<table>
<thead>
<tr>
<th>% of patients with no LR relapse</th>
<th>Cumulative hazard rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 0.4 0.6 0.8 1.0 1.2</td>
<td>0.02 0.04 0.06 0.08 0.1 0.12</td>
</tr>
<tr>
<td>0 Gy (5/2615: 4.2% rate; CI 1.3-1.9)</td>
<td>10 Gy (4/2110: 4.8% rate; CI 1.5-1.8)</td>
</tr>
<tr>
<td>0 Gy (5/2615: 4.2% rate; CI 1.3-1.9)</td>
<td>10 Gy (4/2110: 4.8% rate; CI 1.5-1.8)</td>
</tr>
</tbody>
</table>


Trials A & B: Other Late Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th></th>
<th>Trial B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic rib fracture</td>
<td>5 (0.7%)</td>
<td>7 (0.9%)</td>
<td>9 (1.2%)</td>
<td>17 (1.5%)</td>
</tr>
<tr>
<td>Symptomatic lung fibrosis</td>
<td>5 (0.7%)</td>
<td>9 (1.2%)</td>
<td>8 (1.1%)</td>
<td>18 (1.7%)</td>
</tr>
<tr>
<td>Ischaemic heart disease [left-sided tumours]</td>
<td>17 (2.5%)</td>
<td>10 (1.3%)</td>
<td>9 (1.2%)</td>
<td>25 (2.3%)</td>
</tr>
<tr>
<td>Cardiac-related deaths [left-sided tumours]</td>
<td>11 (1.5%)</td>
<td>16 (2.1%)</td>
<td>9 (1.2%)</td>
<td>13 (1.2%)</td>
</tr>
<tr>
<td>Tracheal plexopathy</td>
<td>0 (0.1%)</td>
<td>1 (0.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>


START Trials: Conclusions

- Breast cancer and the dose-limiting normal tissues respond similarly to fraction size; no advantage for 2Gy fractions
- Patients can be safely and effectively treated to a lower total dose with fewer fractions than the historical standard 50Gy/25F
- No detrimental effects of hypofractionation are identified in the subgroups studied
- Results support 40Gy in 15 fractions as UK standard for all patients with invasive breast cancer (NICE Guidance 2009)

The TARGIT-A trial
Update and First Analysis of Survival

Jayant S Vaidya, F Wenz, M Bulsara, D Joseph, JS Tobias, M Keshtgar, H Flyger; S Massarut, M Alvarado, C Saunders, W Eiermann, M Metaxas, Elena Sperk; M Sutterlin, D Brown, L Esserman, M Roncadin, A Thompson, J Dewar, H Holteveg, S Pigorsch, M Falzon, E Harris, A Matthews, C Brew-Graves, I Potyka, T Corica, NR Williams and Michael Baum

on behalf of the TARGIT trialists’ group

Scientific Rationale for TARGIT

Breast cancer is frequently multicentric…
But most recurrences occur near the primary tumour
So, it makes sense to target radiotherapy to the tumour bed

1st case performed at University College London on 2 July 1998

Mobile machine used in a standard operating room
Physical dose of 20Gy at the surface, delivered over 25 min
Breast Conserving Surgery, Age>=45 years
Unifocal invasive duct carcinoma - MRI not required
Size preferably < 3.5cm
Randomisation (Before or After Lumpectomy)

**TARGIT**
Risk-Adapted Radiotherapy
Single dose of TARGIT with Intrabeam
If high risk factors are found, add EBRT (in ~15%)

**EBRT**
One-size-fits-all Radiotherapy
Standard fractionated External Beam Radiotherapy (EBRT)

2000 –2012: 3451 pts randomised; Median F/U 2 yrs 5 mos

Pre-specified subgroups
Prepathology
Concurrent TARGIT
PgR +ve
n = 1625
PgR –ve
n = 366

Postpathology
Delayed TARGIT
n = 837
n = 188

IBTR (34 events)
Difference 2.01% (0.32-3.7)

Death (88 events)
Blue = TARGIT
Red = EBRT

San Antonio Breast Cancer Symposium – December 4-8, 2012

Loco-regional Recurrence

Blue = TARGIT  
Red = EBRT

All patients

Prepathology PgR+ve

HR 2.2 (1.2 - 4.2)  
Logrank p=0.02

HR 1.4 (0.48 - 4.6)  
Logrank p=0.52

This presentation is the intellectual property of Jayant S Vaidya. Contact jayant.vaidya@ucl.ac.uk for permission to reprint and/or distribute.


San Antonio Breast Cancer Symposium – December 4-8, 2012

Difference in ipsilateral breast recurrence mainly in the postpathology and PgR negative groups

Prepathology concurrent TARGIT  
Delayed TARGIT

PgR positive

n = 1625  
Difference in ipsilateral breast recurrence= 0.18%

n = 837  
1.96%

PgR negative

n = 366  
3.8%

n = 188  
11.3%

This presentation is the intellectual property of Jayant S Vaidya. Contact jayant.vaidya@ucl.ac.uk for permission to reprint and/or distribute.

San Antonio Breast Cancer Symposium – December 4-8, 2012

Prepathology PgR positive (n= 1625)

Ipsilateral Breast Recurrence

Death

HR 0.82 (0.22 – 3.06)  
Logrank p=0.77

HR 0.60 (0.34-1.08)  
Logrank p=0.08

Difference 0.18%  
(-1.62-1.98)

This presentation is the intellectual property of Jayant S Vaidya. Contact jayant.vaidya@ucl.ac.uk for permission to reprint and/or distribute.
Conclusion

- The absolute difference in ipsilateral breast recurrence between TARGIT and EBRT is 2% for unselected patients and 0.18% for Pre-pathology PgR +ve

- Compared with EBRT, TARGIT results in:
  - A trend for reduced mortality (difference -1.4% p=0.1)
  - Fewer non-breast-cancer deaths (difference -2.1% p=0.009)

Questions?