Dr. Newman indicates no relevant financial relationships with any commercial interests.
I. BCS: Can we eliminate XRT?

PRIME Study

- Rationale: WBRT is costly; time-consuming; and adversely impacts cosmesis
- Factors associated with lower risk of locoregional failure
  - Older patient age
  - Hormone receptor positive/endocrine sensitive disease
  - Smaller size tumors, margin-negative resection
CALGB 9343
(CALGB + RTOG + ECOG)

Enrollment: 1994-1999
Age at least 70 yrs
T1, ER-positive breast CA
All clinically-neg axillae:
• ALND encouraged but not required
• 2/3 had no surgical staging of axilla

Median f/u: 12 years

Hughes K S et al.
JCO 2013;31:2382-2387

Enrollment (N = 647)
Excluded
(n = 11)
Did not meet
inclusion criteria
(n = 4)
Other reasons;
unknown
(n = 7)

Random assignment (n = 636)

Allocated to TamRT (n = 317)
Allocated to Tam (n = 319)

Analyzed (n = 317)  Analyzed (n = 319)

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CALGB 9343

Tam  TamXRT

IBTR only  20  6
IBTR + Distant  6  0
IBTR + Axillary Recurrence  1  0

©2013 by American Society of Clinical Oncology
S2-01
The PRIME 2 trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation

Dr. Kunkler: Nothing to disclose.
Dr. Williams: Nothing to disclose.
Dr. Jack: Nothing to disclose.
Dr. Canney: Nothing to disclose.
Dr. Prescott: Nothing to disclose.
Dr. Dixon: Nothing to disclose.

Eligibility and Follow-Up

- Age ≥ 65 years
- Histologically confirmed Unilateral Invasive breast cancer
- Pathology size ≤ 3cm
- Breast conserving surgery
- Excision margin of ≥1mm on histological assessment
- ER and/or PR-positive
- Treated with adjuvant endocrine therapy
  - 9% received neoadjuvant endocrine therapy
- No axillary node involvement on histological assessment
  - SLN biopsy or four-node sample
- Multicenter study: 98 sites; 6 countries
- Median Follow-up: 5 years
**Design**

- **WBI**, N=658
- **No WBI**, n=668

* 40 - 50Gy in 15 – 25 #

---

**Population**

<table>
<thead>
<tr>
<th></th>
<th>No Radiotherapy (n=668)</th>
<th>Radiotherapy (n=658)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Mean (sd)</strong></td>
<td>71.12 (4.96)</td>
<td>70.78 (4.74)</td>
</tr>
<tr>
<td><strong>Tumour size N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10mm</td>
<td>258 (38.6%)</td>
<td>265 (40.3%)</td>
</tr>
<tr>
<td>10.1-20mm</td>
<td>326 (48.8%)</td>
<td>319 (48.5%)</td>
</tr>
<tr>
<td>20.1-30mm</td>
<td>84 (12.6%)</td>
<td>74 (11.2%)</td>
</tr>
<tr>
<td><strong>Grade N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>271 (40.9%)</td>
<td>292 (44.4%)</td>
</tr>
<tr>
<td>2</td>
<td>368 (55.6%)</td>
<td>352 (54.6%)</td>
</tr>
<tr>
<td>3</td>
<td>23 (3.5%)</td>
<td>13 (2.0%)</td>
</tr>
<tr>
<td><strong>LVI N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>631 (95.2%)</td>
<td>628 (95.9%)</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (4.8%)</td>
<td>27 (4.1%)</td>
</tr>
<tr>
<td><strong>Pre-operative endocrine therapy N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>608 (90.9%)</td>
<td>598 (91.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>60 (9.1%)</td>
<td>54 (8.3%)</td>
</tr>
</tbody>
</table>
Local control

<table>
<thead>
<tr>
<th>Time to first local recurrence</th>
<th>Local recurrence</th>
<th>5 yr actuarial rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT (n=668)</td>
<td>26</td>
<td>4.1%</td>
</tr>
<tr>
<td>RT (n=658)</td>
<td>6</td>
<td>1.3%</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

ER status: Effect of RT (preliminary, unplanned analysis)

<table>
<thead>
<tr>
<th>ER*</th>
<th>Local recurrence/N (%)</th>
<th>No RT</th>
<th>RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (7-8)</td>
<td>19/594 (3.2%)</td>
<td>5/602 (0.8%)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Low (2-6)</td>
<td>7/63 (11.1%)</td>
<td>0/54 (0%)</td>
<td>0.015</td>
<td></td>
</tr>
</tbody>
</table>

* High ER is defined as ER+ve, ER≥7, fmol>20, staining>20%, and +++.
Anything else is low ER
### Multivariate Predictors of LR

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T size (ref 0-10mm)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10.1-20mm</td>
<td>0.53 (0.23, 1.22)</td>
<td>0.14</td>
</tr>
<tr>
<td>20.1-30mm</td>
<td>1.17 (0.43, 3.20)</td>
<td>0.76</td>
</tr>
<tr>
<td>LVI (ref No)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.28 (0.29, 5.59)</td>
<td>0.75</td>
</tr>
<tr>
<td>No</td>
<td>5.08 (1.95, 13.24)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ref 65-69)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>2.08 (0.95, 4.55)</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade (ref G1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>1.31 (0.59, 2.90)</td>
<td>0.51</td>
</tr>
<tr>
<td>G3</td>
<td>3.48 (0.89, 13.65)</td>
<td>0.07</td>
</tr>
<tr>
<td>LVI (ref No)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.28 (0.29, 5.59)</td>
<td>0.75</td>
</tr>
<tr>
<td>ER status (ref High)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2.84 (1.21, 6.65)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Overall survival (deaths)</th>
<th>5 yr actuarial rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT (n=668)</td>
<td>49</td>
<td>93.8%</td>
</tr>
<tr>
<td>RT (n=658)</td>
<td>38</td>
<td>94.2%</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

Survival

- *p*=0.24

Overall survival

- No RT
- RT
### Deaths

<table>
<thead>
<tr>
<th>Cause</th>
<th>No RT (n=668)</th>
<th>RT (n=658)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>BC present but not cause</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No Breast Cancer</td>
<td>36</td>
<td>29</td>
<td>65</td>
</tr>
<tr>
<td>Cause unknown</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50 (7.5%)</strong></td>
<td><strong>39 (5.9%)</strong></td>
<td><strong>89 (6.7%)</strong></td>
</tr>
</tbody>
</table>

- Breast cancer deaths 13.5% of all deaths
- Deaths without breast cancer: 73.0%
- Impact of compliance with endocrine therapy????
- Longer f/u needed

---

**II. Significance of axillary micrometastases: NSABP B-32**

- “Targeted” axillary surgery with lymphatic mapping and sentinel lymph node biopsy facilitates identification of microscopic foci of metastatic disease
  - Serial sectioning
  - Immunohistochemistry to detect cytokeratin
- Prognostic value of this information???
10-yr Follow-up Results of Occult Detected Sentinel Node Disease: NSABP B-32

A randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients

TB Julian, SJ Anderson, D Weaver, DN Krag, SP Harlow, T Ashikaga, JP Costantino, EP Mamounas, N Wolmark

NSABP B-32

Clinically Axillary Node-Negative Breast Cancer

Randomization

Group 1
SLN Bx followed by ALND
Pathologically SLN Positive
ALND
Pathologically SLN Negative
No ALND

Group 2
SLN Bx
Randomization
Clinically Axillary Node-Negative Breast Cancer

• 5,536 cases
• 0.7% dye rxns
• SLN id rate 97%
• 62% SLN mets only
• FN rate 9.7%

Evenly Balanced

- **Entry Characteristics**
  - Age: 75% > 49
  - Race: 90% Caucasian
  - Tumor size: 16% > 2cm
  - Hormone status: 80% positive
  - Surgical treatment plan: 87% BCS

- **Associated Treatments**
  - Systemic Therapy: 85% & 84%
  - Radiation Therapy: 82%

### NSABP B-32 Sentinel Node-Negative Patients Survival

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Deaths</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR+AD</td>
<td>1975</td>
<td>228</td>
<td>1.09</td>
<td>0.35</td>
</tr>
<tr>
<td>SNR</td>
<td>2011</td>
<td>252</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as of Dec 31, 2012

89/88%
### NSABP B-32: SLN Negative Cases

#### Local and Regional Recurrences as First Events

<table>
<thead>
<tr>
<th>Location</th>
<th>Group 1 (SN+AND) N=1975 No. (%)</th>
<th>Group 2 (SN) N=2011 No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>75 (3.8%)</td>
<td>66 (3.3%)</td>
</tr>
<tr>
<td>Axillary</td>
<td>4 (0.2%)</td>
<td>11 (0.5%)</td>
</tr>
<tr>
<td>Extra-axillary</td>
<td>5 (0.3%)</td>
<td>4 (0.2%)</td>
</tr>
</tbody>
</table>

Updated through Dec 31, 2012

---

### NSABP B-32

**Clinically Negative Axillary Nodes**

**Random Assignment**

**GROUP 1**

- SN + AD (2807)

**GROUP 2**

- SN (2804)

**Intraop cytology & post-op HE**

**Stratification**
- Age
- Clinical Tumor Size
- Type of Surgery

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. (pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1 SN + AD (SN+AD)</td>
<td>1,975</td>
</tr>
<tr>
<td>GROUP 2 SN (SN only)</td>
<td>2,011</td>
</tr>
<tr>
<td>SN Pos 829</td>
<td>793</td>
</tr>
<tr>
<td>SN Neg (SN+AD)</td>
<td></td>
</tr>
<tr>
<td>FU</td>
<td></td>
</tr>
</tbody>
</table>

NSABP B-32
Updated through December 31, 2012

- 3,989 – SN neg (71% of 5,611)
- 3,986 (99.9%) – follow-up information
- 131.1 months – median time on study
- 121.8 months – median follow-up time of patients who are still alive

IHC and detailed pathologic examination of the SNs performed centrally and results were not disclosed

NSABP B-32
Occult Metastases Detection Method

- 3,989 SNB negative patients
- 2 mm tissue blocks
- Additional sections obtained at 0.5 and 1 mm
- Routine H&E and IHC stains
- ITCs: ≤ 0.2 mm
- Micrometastases: > 0.2 mm & ≤ 2.0 mm
- Macrometastases: > 2.0 mm
### NSABP B-32

**Sentinel Node-Negative Patients with Follow-up: Occult Metastases Status**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th># of Patients</th>
<th># in SNR+AD arm</th>
<th># in SNR arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Metastases Status</td>
<td>Negative</td>
<td>3,268</td>
<td>1,608</td>
<td>1,660</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>616</td>
<td>316 (16.4%)</td>
<td>300 (15.3%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>102</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

616 Positive for Occult Metastases - 15.9%
430 had Isolated Tumor-Cell Clusters - 11.1%
172 had Micrometastases - 4.4%
14 had Macrometastases - 0.4%

### NSABP B-32

**Patients with SNB Occult Metastases Data (N=3,884)**

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>SNR + AD</th>
<th>SNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Entry†</td>
<td>&lt; 50</td>
<td>24.5</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>50 – 59</td>
<td>33.3</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>60 +</td>
<td>42.2</td>
<td>41.7</td>
</tr>
<tr>
<td>Clinical Tumor Size†</td>
<td>≤ 2 cm</td>
<td>83.5</td>
<td>84.2</td>
</tr>
<tr>
<td></td>
<td>2.1 – 4 cm</td>
<td>14.8</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>&gt; 4 cm</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Planned Surgery†</td>
<td>Lumpectomy</td>
<td>87.7</td>
<td>87.2</td>
</tr>
<tr>
<td></td>
<td>Total Mastectomy</td>
<td>12.3</td>
<td>12.8</td>
</tr>
</tbody>
</table>

† As reported at the time of random assignment
NSABP B-32 Sentinel Node-Negative Patients
Overall Survival
by Absence or Presence of Occult Metastases

Data as of Dec 31, 2012

8 years
p=0.03
HR= 1.37
AD= 1.2%

HR=1.26     Adjusted p=0.06

Occult Mets Absent  3268 pts., 378 deaths
Occult Mets Present 616 pts., 90 deaths

NSABP B-32 Sentinel Node Negative Patients
Disease-Free Survival
by Absence or Presence of Occult Metastases

Data as of Dec 31, 2012

8 years
p=0.02
HR= 1.27
AD= 2.8%

HR=1.25     Adjusted p=0.01

Occult Mets Absent  3268 pts., 738 events
Occult Mets Present 616 pts., 170 events
NSABP B-32 Sentinel Node Negative Patients
Cumulative Incidence of Local-Regional
Recurrences by Occult Metastasis Status

Data as of Dec 31, 2012

HR=1.32     Adjusted p=0.17

No Occult Mets  3268 pts.,  129 Local-Regional events
Occult Mets  616 pts.,  32 Local-Regional events

5.3%
3.9%

Group 1
(SN+AND)
N=1608
No. (%)  

Local  58 (3.8%)
Axillary  2 (0.1%)
Extra-axillary  5 (0.3%)

Group 2
(SN)
N=1660
No. (%)  

Local  56 (3.3%)
Axillary  6 (0.4%)
Extra-axillary  2 (0.1%)

Updated through Dec 31, 2012
NSABP B-32
Local and Regional Recurrences as First Events (Occult Mets)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (SN+AND)</th>
<th>Group 2 (SN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=316</td>
<td>N=300</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Local</td>
<td>16 (5.1%)</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>Axillary</td>
<td>2 (0.6%)</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Extra-axillary</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

Updated through Dec 31, 2012

NSABP B-32 Sentinel Node Negative Patients Overall Survival by Status within Occult Metastases

- No Occult Mets: 3268 pts., 378 deaths
- ITC: 431 pts., 61 deaths, HR=1.22
- Micromets: 171 pts., 28 deaths, HR=1.43

Data as of Dec 31, 2012
NSABP B-32 Sentinel Node-Negative Patients
Disease-Free Survival by Status within Occult Metastases

% Disease-Free

0 20 40 60 80 100
0 2 4 6 8 10

Years after Randomization

- No Occult Mets 3268 pts., 738 events
- ITC 431 pts., 122 events, HR=1.29
- Micromets 171 pts., 46 events, HR=1.23

Data as of Dec 31, 2012

NSABP B-32
Overall Survival with Occult Metastases

% Surviving

0 20 40 60 80 100
0 2 4 6 8 10

Years after Randomization

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Deaths</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR+AD</td>
<td>316</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNR</td>
<td>300</td>
<td>43</td>
<td>0.98</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Data as of Dec 31, 2012
**NSABP B-32**

**Disease-Free Survival with Occult Metastases**

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR+AD</td>
<td>316</td>
<td>94</td>
</tr>
<tr>
<td>SNR</td>
<td>300</td>
<td>76</td>
</tr>
</tbody>
</table>

HR=0.82     p=0.2

Data as of Dec 31, 2012

**NSABP B-32: Sentinel Node-Negative Patients With Occult Metastases**

**Cumulative Incidence Local-Regional Recurrences**

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR+AD</td>
<td>316 pts.</td>
<td>18</td>
</tr>
<tr>
<td>SNR</td>
<td>300 pts.</td>
<td>14</td>
</tr>
</tbody>
</table>

HR=0.8     p=0.52

Data as of Dec 31, 2012
NSABP B-32
Conclusions

- At ten years there continues to be no significant difference in OS, DFS, DDFS, or Regional Control for patients with clinically node-negative disease.

NSABP B-32
Occult Metastases Conclusions

- At ten years, for occult metastases there is not a significant difference in OS despite the absolute difference of 3.1%.
- A significant difference in DFS for occult metastases with an absolute difference of 4.7% is identified.
- This downward trend is seen for both ITC and micro-metastatic disease.
- However, the impact of occult metastatic nodal disease in this very large cohort of 5,611 patients with a OS HR of 1.09 and a DFS HR of 1.02 is clinically non significant.
- OS, DFS, and Local-regional recurrence is not affected by the 15.3% positive occult metastases in the SNR only group.
- Ax Node dissection for occult metastases is of no benefit.
- The routine use of IHC analysis for SNB is not recommended.

Outstanding question: Role of IHC in SLN for lobular histology???
**American College of Surgeons Oncology Group Z0010/11**

**Prognostic Study of SLN and Bone Marrow Micrometastases in Clinical T1/T2 N0 M0 Breast Cancer**

**Z0010 T1/T2: Breast Conservation Therapy**

**SLN Bx**

- **Bone Marrow Aspirate**

**SLN Negative by H&E**

- **Pt consents to Z0011**
- **Randomization**
- **ALND**

**SLN Positive by H&E**

- **Pt does not consent to Z0011**
- **Management as per patient & physician**
- **No ALND**

**ACOSOG Z0010: Study Population**

- **5,210 Eligible/Evaluable Patients**
  - SLN Identification Rate 95%
  - Median number of SLN=2

- **SLN mets detected by routine H&E in 24%**
  - IHC detected mets in additional 11%

- **3,413 BM cases**
  - IHC-positive in 104 (3%)
**Correlations**

- Increasing tumor size associated with increasing risk of SLN mets by H&E and by IHC
- No association between tumor size and BM results
- No concordance between IHC detection of mets in SLN and IHC detection of mets in BM compartments

**5-Year Survival Rates**

- Survival generally quite high in this sample of clinically early-stage breast cancer pts (90-96%)
- Survival by SLN Results
  - OS similar for H&E-negative and IHC-positive SLN pts (96%)
  - OS worse for H&E-positive SLN cases (93%; p=0.0009)
  - Same patterns with DFS
- Survival by BM Results
  - OS 90% for IHC-positive BM
  - OS 95% for IHC-negative BM (p=0.01)
III. Is breast surgery indicated for Stage IV disease at diagnosis?

Tata Memorial and Turkish Federation Studies

Background

• Conventional Approach: Breast surgery not indicated in Stage IV disease
  – Disruption of immunologically-mediated “balance” between primary tumor and total body metastatic burden

• Palliative breast surgery considered for control of ulcerated, fungating lesions
Survival from Recurrent Breast Cancer - Giordano et al

Improving Survival from Metastatic Breast Cancer

- Andre et al, JCO 2004
- Three cancer centers in France
- 724 pts with Stage IV breast cancer at presentation, 1987-2000

<table>
<thead>
<tr>
<th>Interval</th>
<th>N</th>
<th>3-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-1993</td>
<td>343</td>
<td>27%</td>
</tr>
<tr>
<td>1994-2000</td>
<td>381</td>
<td>44%</td>
</tr>
</tbody>
</table>
### Overview of Multivariate Analyses: Breast Surgery for Pts with Stage IV Disease

<table>
<thead>
<tr>
<th></th>
<th>NCDB (Khan, 2002)</th>
<th>Geneva (Rapiti, 2006)</th>
<th>MDACC (Babieri, 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Surgery</td>
<td>1.00/ref.</td>
<td>1.00/ref.</td>
<td>1.00/ref.</td>
</tr>
<tr>
<td>Margin-Positive</td>
<td>0.75 (0.71-0.79)</td>
<td>1.3 (0.8-2.1)</td>
<td>0.5 (0.21-1.19)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margin-Negative</td>
<td>0.61 (0.58-0.65)</td>
<td>0.6 (0.4-1.0)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Meta-Analysis of Breast Surgery in Stage IV Disease

Harris et al. Ann Surg Onc 2013
- 10 studies
- 28,693 cases
- 53% undergoing breast surgery
- Surgery cases more likely to have smaller tumors; fewer co-morbidities; and fewer mets
Surgical Removal Of Primary Tumor And Axillary Lymph Nodes In Women With Metastatic Breast Cancer At First Presentation: A Randomized Controlled Trial

PI: R A Badwe
Professor Surgical Oncology (Breast)
Tata Memorial Centre
Mumbai, India

Co-Investigators
V Parmar, R Hawaldar, N Nair, R Kaushik, S Siddique, A Nawle, A Budrukkar, I Mittra, S Gupta

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Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish Study (Protocol MF07-01)


On behalf of the Turkish Federation of Societies for Breast Diseases

ClinicalTrials.gov identifier number: NCT00557986.

This presentation is the intellectual property of the Turkish Federation of Societies for Breast Diseases. Contact asoran@upmc.edu
OVERALL SURVIVAL: Tata Memorial

HR = 1.04, 95% CI = 0.86 - 1.34, p = 0.79

OVERALL SURVIVAL: Turkish Federation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Death</th>
<th>Median (months)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>140</td>
<td>38</td>
<td>46</td>
<td>.76 (0.49-1.16)</td>
<td>.20</td>
</tr>
<tr>
<td>ST</td>
<td>138</td>
<td>48</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Can we generalize these results to U.S. practice patterns???

- Commonplace for American surgeons to monitor response to primary systemic therapy prior to considering surgery for Stage IV disease
  - Turkish study evaluated surgery as initial treatment
- American oncologists relatively aggressive in documenting metastatic disease (& markers) via Bx
  - Tata study did not provide anti-HER2/neu therapy
  - Turkish study demonstrated survival advantage in patients randomized to surgery first with solitary bone met, but some of these were not biopsy-proven

IV. BCS and Margins: Morrow and SSO ASTRO Consensus

What is the optimum negative margin thickness for lumpectomy cases????
### Improving BCS Outcome: Margin Control

<table>
<thead>
<tr>
<th>Study</th>
<th>Margin Status vs 5-yr LR Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR &gt; 7%</td>
</tr>
<tr>
<td>Schnitt</td>
<td>Multiple foci positive</td>
</tr>
<tr>
<td>Gage</td>
<td>Multiple foci positive EIC-pos; focally positive margin</td>
</tr>
<tr>
<td>DiBase</td>
<td>At least 2 foci positive</td>
</tr>
<tr>
<td>Touboul</td>
<td>Positive</td>
</tr>
<tr>
<td>Wazer</td>
<td>Multiple foci positive</td>
</tr>
<tr>
<td>Freedman</td>
<td>Close, less than 2 mm</td>
</tr>
</tbody>
</table>

### Rates of Re-excision

- Wide variation, 6-49%
- Morrow et al.
  - Population-based sample 2005-6
    - \( n = 800 \)
    - Stage I+II: **Re-excision rate 19%**
- McCahill et al.
  - Large convenience sample 2003-6
    - \( n = 2200 \)
    - **Re-excision rate 23%**

**48% of re-excisions done for negative margins**

Local Therapy in the Modern Era: Relevant or Relic?

Monica Morrow MD
Chief, Breast Surgery Service
Anne Burnett Windfohr Chair of Clinical Oncology
Memorial Sloan-Kettering Cancer Center

SSO-ASTRO Consensus Conference on Margins in Stage I and II Invasive Cancer

Primary question: What margin width minimizes the risk of IBTR?

Rationale: Wide variation in margin definitions and re-excision rates is leading to:
  - health care costs, cosmetic outcome?
  - contributing to mastectomy rate
## Joint SSO-ASTRO Consensus on Margins in Invasive Breast Cancer

**Co chairs:**
- Monica Morrow  
- Meena Moran  
- Suzanne Klimberg  
- Mariana Chavez MacGregor  
- Jay Harris, Gary Freedman, Janet Horton  
- Stuart Schnitt  
- Armando Giuliano, Seema Khan  
- Peggy Johnson  
- Nehmat Houssami

**Participants**
- ASBS: Suzanne Klimberg
- ASCO: Mariana Chavez MacGregor
- ASTRO: Jay Harris, Gary Freedman, Janet Horton
- CAP: Stuart Schnitt
- SSO: Armando Giuliano, Seema Khan
- Advocate: Peggy Johnson
- Methodologist: Nehmat Houssami

**Funded by a grant from Susan G. Komen**

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## SSO-ASTRO Consensus Evidence Base

Metaanalysis of 33 studies (870 abstracts screened)
- 28,162 patients
- 1,506 local recurrences

**Study eligibility:**
- > 90% Stage I+II
- Whole breast RT
- Minimum mean/median f/u 4 yrs
- LR in relation to margin status
- Patient age

**Houssami N, Ann Surg Oncol (In Press)**
A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a 2-fold increase in local recurrence.

This increase in LR is not nullified by:
- an RT boost
- systemic therapy
- favorable biology

### Metaanalysis Results

**Relationship Between LR and Threshold Margin Distance**

<table>
<thead>
<tr>
<th>Threshold Distance (mm)</th>
<th># studies</th>
<th># subjects/# LRs</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2376/235</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>8350/414</td>
<td>0.91</td>
<td>0.46-1.80</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>2355/103</td>
<td>0.77</td>
<td>0.32-1.88</td>
</tr>
</tbody>
</table>

P association 0.90
P trend 0.58

* Adjusted for f/u
### Impact of Margin Width on LR Selected Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th># studies</th>
<th>1mm</th>
<th>2mm</th>
<th>5mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18</td>
<td>1.0</td>
<td>0.91</td>
<td>0.77</td>
<td>0.53</td>
</tr>
<tr>
<td>Endocrine Rx</td>
<td>16</td>
<td>1.0</td>
<td>0.98</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>Radiation Boost</td>
<td>18</td>
<td>1.0</td>
<td>0.82</td>
<td>0.92</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Adjusted for follow-up*

---

### Consensus Statement

- Negative margins (no ink on tumor) optimize local control.

- Wider margin widths do not significantly improve local control.

- The *routine* practice of obtaining margins more widely clear than no tumor on ink is not indicated.
Local Recurrence by Study Year and Margin Width

Consensus Statement Subtype

- Margins wider than no ink on tumor are not indicated based on biologic subtype.

Bigger surgery does not overcome bad biology.
Conclusions

- It is possible that wider margins may have conveyed a small benefit in the past, but multimodality therapy obviates the need for wider margins.
- Evidence that margins more widely clear than no ink on tumor are beneficial is lacking.
- Avoidance of routine re-excision benefits patients and decreases health care costs.

Lumpectomy Margin Consensus

- Endorsed by SSO and ASTRO; ASCO endorsement pending
- Moving forward:
  - Programs should continue to monitor internal local recurrence rates, especially if adoption of consensus represents a change in practice
  - Post-lumpectomy mammography essential for cases associated with microcalcifications
V. Screening for breast cancer

• Screening for Breast Cancer
  – How much mammography is too much???
  – Is it ever too early to start screening for breast cancer???
  – As imaging technologies advance, is breast cancer screening worth any cost???

Disparities in the estimates of benefits and harms from mammography: Are the numbers really different?

Stephen W Duffy, Tony Hsiu-Hsi Chen
Robert A Smith, Amy Ming-Fang Yen
Laszlo Tabar

Presented by
Robert A. Smith, PhD
American Cancer Society
Atlanta, GA USA
### Number Needed to Screen (NNS) vs. Number Needed to Invite (NNI) to Prevent 1 Breast Cancer Death

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Swedish data (NNS)¹</th>
<th>USPSTF (NNI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>464</td>
<td>1,224</td>
</tr>
<tr>
<td>40-49</td>
<td>726</td>
<td>1,904</td>
</tr>
<tr>
<td>50-59</td>
<td>260</td>
<td>1,339</td>
</tr>
<tr>
<td>60-69</td>
<td>198</td>
<td>377</td>
</tr>
</tbody>
</table>

¹ Number Needed to Screen (NNS) Every 2 Years (40-49—18 mos.) for a Period of 10 Years, with 20 Years of Follow-up, to Save One Life. Source: Tabar, et al. Two County Trial, 2011

² Number Needed to Invite (NNI), estimated from RCT data with variable screening intervals, variable screening rounds, different rates of adherence and non-compliance, and variable periods of follow-up (14 yrs.) Source: USPSTF, 2009
Philosophy of Welch:

However: this theory ignores some important issues:
- Early detection can obviate the need for systemic therapy
- Systemic therapy effectiveness improves with diminished total body tumor burden

Long-Term Psychosocial Consequences of False-Positive Screening Mammography

ABSTRACT

PLANNED: Cancer screening programs have the potential to yield beneficial effects, but they also necessarily have unintended harms. In the case of mammography, the test involves harm to a relatively small population to measure a small percentage of women with breast cancer.

*NEW TRENDS:* In this cohort study with 3-year follow-up, we enrolled 414 women with breast cancer and 312 women with benign breast disease and randomly assigned women to screening mammography. Women in the screening group were monitored for the development of breast cancer. The incident rate of breast cancer was similar in the two groups. The median time to breast cancer was 3.6 years in the screening group and 3.7 years in the control group. The difference was not statistically significant.

RESULTS: We found that women with false-positive findings had lower overall quality of life compared with women with normal mammograms.

CONCLUSION: False-positive findings do not significantly impact overall quality of life. However, false-positive findings may lead to future false-negative findings, which may increase the risk of breast cancer.

3 year follow-up from initial mammogram

3 groups
- Breast Cancer (n = 174)
- False Positive (n = 272)
- Normal (n = 884)

Measure 12 psychosocial outcomes @ 5 points in time across 3 years
So what has actually happened to breast cancer incidence in the United States?

Effect of Three Decades of Screening Mammography on the Stage-specific Incidence of Breast Cancer in the United States

The view from space
Welch: “little compensatory decrease in the number of women presenting with late-stage disease”

Other Concerns Regarding Welch Philosophy

- Patient anxiety/fear related to mammography may be better addressed by education regarding realistic magnitude of breast cancer risk and significance of image-detected findings
- SEER data on incidence rates of local versus regional stage breast cancer are not necessarily appropriate surrogates for mammography screen-detected disease
  - Bulky tumors can be node-negative and biologically-aggressive but small/screen-detected tumors can be node positive
  - Lymphatic mapping and SLN biopsy has resulted in stage migration, and may have accounted for sluggish rates of declines in incidence of regional disease over past 20 years
Population-Based Incidence Rates of TNBC, by Race/Ethnicity and Age

Amirikia and Newman, CANCER, 2011

Early Stage TNBC: Detection and Outcomes

- Memorial Sloan Kettering Cancer Center
  – 194 cases of T1b N0 TNBC, 1999-2006
  – 69% detected by screening
  – Median follow-up 73 months
  – 58% received adjuvant CTX

<table>
<thead>
<tr>
<th></th>
<th>CTX</th>
<th>No CTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Yr Locoregional-Free Survival</td>
<td>96.2%</td>
<td>96%</td>
</tr>
<tr>
<td>5-Yr Distant Recurrence-Free Survival</td>
<td>95.9%</td>
<td>94.5%</td>
</tr>
</tbody>
</table>

Ho et al, Cancer 2012
Breast MRI

- Adjunct to mammography in screening “high-risk” women
  - >20-25% lifetime risk of breast cancer
- Evaluation for silicone leak
- Evaluation of women presenting with axillary metastases and occult breast primary
Purpose

MRI was systematically offered for screening to women at average risk of breast cancer

- **Primary aim**: To investigate the added cancer yield and accuracy of breast MRI in the average risk population

- **Secondary objective 1**: To investigate the biologic importance of MRI-only detected breast cancers in the average risk population

- **Secondary objective 2**: To investigate the age and mammographic breast density distribution of women with MRI-only detected breast cancers

Materials and Methods

**Study setup**

- Single academic tertiary care center, prospective, non-randomized trial

- Study period between January 2005 and December 2011

- 1705 annual screening MRI studies were performed

- Age of study participants:
  mean 54.6 years, median 56, range 40-71 years
Materials and Methods

Inclusion criteria: Women with

- No personal or family history of breast or ovarian cancer
- No breast tissue diagnosis of proliferative changes or atypias (e.g. ADH, LIN etc.)
- No previous chest irradiation (e.g. Hodgkin disease)
- Normal clinical breast examination
- Normal double read 2-view full-field digital screening mammogram
- Normal physician-performed high frequency breast ultrasound (>12 MHz) (in 1523 / 1705 (89%) women)
Cancer detection rate:
11/1000

Positive predictive value:
33% (18/54)
 if only BIRADS IV and BIRADS V accepted as true-positive
48% (26/54)
 if also “high risk” lesions accepted as positive results

The Mammographic Pyramid

1000
100
10
3

Screens
Call backs
Biopsy rec
Cancer
Summary

- In this cohort of women at average risk who had normal screening mammograms and normal screening ultrasound examinations, the additional cancer detection rate achieved through breast MRI was high (11/1000).
- Stage distribution of MRI detected additional cancers was favorable.
- The biologic profile of cancers was indicative of prognostically relevant disease.
- Age or mammographic breast density did not predict the likelihood with which cancers were identified through screening MRI.

Conclusion

- MRI screening of women at average risk of breast cancer appears to be useful. The additional cancer detection rate is high, even in heavily pre-screened women.
- In experienced hands, the PPV of MRI screening in this average risk cohort was comparable to those of mammographic screening programs or to that of MRI high risk screening cohorts.
- Further studies are needed to confirm our initial results.