Sentinel Node Biopsy:
The Past, The Present, and The Future

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October 13, 2010

AD vs. no AD
Randomized Trials

All trials reported higher survival in the AD group


NSABP B-04

Operable Breast Cancer
Clinically Node-Negative

Radical Mast. Total Mast. Total Mast. + XRT

Overall Survival

Global p=0.68

Fisher B: NEJM, 2002
Sentinel Node Concept

• Metastasis to regional lymph nodes is not a random event but instead there is orderly progression of tumor cells within the lymphatic system.
• Primary draining or sentinel node is the first to contain metastases.
• Biopsy of this sentinel node can accurately predict axillary involvement

Sentinel Node Detection Techniques

SLNB: Rapid Clinical Adoption

• Over the past decade, SLNB alone has gained acceptance as the preferred method for staging the axilla in patients with negative SLN(s)
• Clinical guidelines (St. Gallen, NCCN) include SLNB alone as an acceptable method for staging the axilla in pts with operable BC
• Significant reduction in morbidity compared to ALND (particularly in arm numbness/paresthesia and lymphedema)
• Low rates of axillary recurrence after a (-) SLNB
• Outcome results from large RCTs not disclosed until now
NSABP B-32 Schema

Clinically Negative Axillary Nodes

Stratification
- Age
- Clinical Tumor Size
- Type of Surgery

Randomization

GROUP 1
Sentinel Node
Biopsy

GROUP 2
Sentinel Node
Biopsy*

*Auxiliary node dissection only if the SN is positive

Accrual: 5611
(5/99-2/04)

ASCO 2010 Abstract LBA 505

NSABP PROTOCOL B-32
A Randomized, Phase III Clinical Trial to Compare Sentinel Node Resection to Axillary Dissection in Clinically Node-Negative Breast Cancer Patients

Definitive Analysis of the Primary Outcomes

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

Lancet Oncology, 9/2010

B-32 Clinically Negative Axillary Nodes

Randomization

GROUP 1
SN + AD

GROUP 2
SN

Intraop cytology & postop HE

SN Neg (SN+AD)

FU
1,975 patients

SN Neg (SN only)

FU
3,011 patients
B-32: SN Detection Methods

- Technetium sulfur colloid
- Blue dye
- Palpation (~2% cases)

B-32: Standardized Path Protocol

- Intraop- Cytology
- Postop- HE

B-32: Core Trainers

Seth Harlow
Thomas Julian
David Krag
Fred Moffat
Roberto Kusminsky
Sheldon Feldman
Susanne Klimberg
Peter Bellach
R. Dirk Noyes
B-32 Analysis Plan

- 3,989 - SN neg (71% of 5611)
- 99.9% - follow-up information
- 95 months - average time on study
- Primary endpoints OS, DFS, Regional Control
- Study powered to detect 2% difference OS

NSABP Protocol B-32

Overall Survival for Sentinel Node Negative Patients

% Surviving

<table>
<thead>
<tr>
<th>Years After Entry</th>
<th>Trt</th>
<th>N</th>
<th>Deaths</th>
<th>SNR+AD</th>
<th>HR=1.20</th>
<th>p=0.117</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>SNR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1975</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2011</td>
<td>169</td>
<td></td>
</tr>
</tbody>
</table>

*300 deaths triggered the definitive analysis
*300 reported as of 12/31/2009

B-32 SN Negative Patients: Hazard Ratios of OS According to Stratification Variables

- Planned Mastectomy
- Planned Lumpectomy
- Tumor size >2 cm
- Tumor size ≤ 2 cm
- Patients 50+ at entry
- Patients < 50 at entry

*All patients with follow-up HR= 1.2

Hazard Ratio

SNR better SNR+AD better
NSABP Protocol B-32
Disease-Free Survival for Sentinel Node Negative Patients

- Free Free Free 60 80 100
- Free Free 2 4 6
- Free Free 0 2 4 6
- Free Free 1 2 3 4

B-32 SN Negative Patients: Hazard Ratios of DFS
According to Stratification Variables

- Planned Mastectomy
- Planned Lumpectomy
- Tumor size ≤2 cm
- Tumor size >2 cm
- Patients 50 + at entry
- Patients < 50 at entry

Hazard Ratio

All patients with follow-up
HR= 1.05

B-32 Hazard Ratios Between Groups
According to Site of Treatment Failure

- Dead, NED
- 2nd cancers
- Opposite Breast Cancers
- Distant Recurrences
- Local Regional Recurrences

All events
HR= 1.05

Hazard Ratio
Local and Regional Recurrences as First Events

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>54 (2.7%)</td>
<td>49 (2.4%)</td>
</tr>
<tr>
<td>Axillary</td>
<td>2 (0.1%)</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Extra-axillary</td>
<td>5 (0.25%)</td>
<td>6 (0.3%)</td>
</tr>
</tbody>
</table>

Residual Morbidity at End of Follow-up

- Lower in SN group
- Not nonexistent

<table>
<thead>
<tr>
<th></th>
<th>Group 1 SN + AD</th>
<th>Group 2 SN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder abduction deficit</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Arm volume difference &gt;5%</td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td>Arm numbness</td>
<td>31%</td>
<td>8%</td>
</tr>
<tr>
<td>Arm tingling</td>
<td>13%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Ashikaga et al JSO in press

All differences p<0.001

B-32: Conclusion

- No significant differences were observed OS, DFS, or Regional Control
- Morbidity decreased

* When the SN is negative, SN surgery alone with no further AD is appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.
SNB: Areas of Remaining Controversy and Future Directions

- Significance and management of IHC+ SNs and SNs positive for micrometastases
- Role of SNB in patients with DCIS
- Role of SNB in patients receiving neoadjuvant chemotherapy

Extensive Pathologic Evaluation of SNs and Minimal SN Involvement

- Multiple serial sectioning and IHC staining yield additional metastases in 10-30% of pts with negative SNs on routine H&E staining
- The clinical significance of identifying minimal SN involvement by the more sensitive techniques is a subject of controversy
- This question can only be definitively answered in large prospective trials of SNB +/- AND
- Retrospective outcome studies are subjected to selection bias regarding the use of AND/XRT or adjuvant systemic therapy

Rates of SLNB Alone in Pts With (+) SLN NCDB 1998-2005

- Proportion Resecting SN+ Ax+ (%) 15-20%
- Proportion Resecting SN+ Ax- (%) 40-45%
**2010 AJCC Breast Cancer Staging**

- **pN0**: No regional LN metastases identified histologically
- **pN0(i-)**: No regional LN metastases identified histologically, negative IHC
- **pN0(i+)**: Malignant cells in regional LN(s) no greater than 0.2 mm (detected by H&E or IHC including ITCs)
- **pN0(mol-)**: No regional LN metastases histologically, negative molecular findings (RT-PCR)
- **pN0(mol+)**: Positive molecular findings (RT-PCR) but no regional LN metastases detected by histology or IHC
- **pN1mi**: Micrometastases (greater than 0.2 mm and/or more than 200 cells but none greater than 2.0 mm.

**Stage 0**

- Tis N0 M0

**Stage IA**

- T1* N0 M0
- T0 N1mi M0
- T1* N1mi M0

**Stage IIA**

- T0 N1** M0
- T1* N1** M0
- T2 N0 M0
- T2 N1 M0
- T3 N0 M0

* T1 includes T1mi (microinvasion < 1 mm)
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IA and are classified as Stage IB

**Prognostic Significance of Occult Micrometastases in Axillary Nodes**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type/Period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowlatshahi</td>
<td>Review of all reported series 1948-1960</td>
<td>Definite survival disadvantage with occult metastases</td>
</tr>
<tr>
<td>Sakorafas</td>
<td>Review of all reported series 1966-2003</td>
<td>Micrometastases associated with worse prognosis</td>
</tr>
<tr>
<td>Kuijt</td>
<td>Einhoven Ca Reg (1975-1997)</td>
<td>Pts with micrometastases have worse survival</td>
</tr>
<tr>
<td>Melbouncedo</td>
<td>SEER Data (T1 tumors) 1988-2001 (n=43,921)</td>
<td>Slightly elevated risk of death with solitary (5.0%) or multiple (3.8%) micrometastases</td>
</tr>
<tr>
<td>Chen</td>
<td>SEER Data 1992-2003 (n=209,720)</td>
<td>Pts with micrometastases have intermediate prognosis between node (-) and node (+)</td>
</tr>
</tbody>
</table>
MSKCC Occult Axillary Metastases in BC 20-Year Follow-Up

- 368 pts diagnosed between 1976-78
- No systemic therapy
- Negative ALNs were examined per SLN protocol

Prognostic Implications of ITCs and MMs

Moffit Cancer Center Study

- Between 1997-2004, 2,381 patients underwent SLNB
  - 2108 were pN0(i-)
  - 122 were pN1mi (97 underwent AND)
  - 151 were pN0(i+) (107 underwent AND)
- DFS and OS was worse for pts with pN1mi compared to those with pN0(i-)
- DFS and OS were not different between pts with pN0(i+) and those with pN0(i-)


Prognostic Implications of ITCs and MMs

John Wayne Cancer Institute Study

- Between 1992-1999, 790 patients with stage I-II invasive BC were accrued in a prospective study:
  - 486 (62%) negative SLN
  - 84 (11%) ITCs (67 underwent AND)
  - 54 (7%) micrometastases (48 underwent AND)
  - 166 (21%) macrometastases
- Mean follow up: 72.9 months
- Patients with pN0(i+) or pN1mi did not have significantly worse 8-year DFS or OS compared with SN-negative patients

Prognostic Implications of ITCs and MMs
Anne Arundel SN Multicenter Study

- Between 1996-2005, 1,259 patients were accrued
  - 893 (71%) negative SLN
  - 25 (2%) ITCs (13 underwent AND)
  - 57 (5%) micrometastases (41 underwent AND)
  - 284 (23%) macrometastases
- Mean follow up: 4.9 years
- Distant recurrence rates: 6%, 8% 14% and 21%
- Presence of MMs was associated with worse DFS compared to pts with negative nodes (p<0.02)

Micrometastases and Isolated Tumor Cells as Prognostic Factors: the MIRROR Study

- Patients with favorable primary tumor characteristics
  - No indication for adjuvant systemic therapy
  - Sentinel node procedure
  - pN0, pN0(i+) or pN1mi
- Patients selected from the Netherlands Cancer Registry (1997-2005)
- Primary endpoint: 5-year disease-free survival (DFS)

<table>
<thead>
<tr>
<th>SLN Status</th>
<th>pN0 (n = 838)</th>
<th>pN0(i+)/pN1mi (n = 832)</th>
<th>pN0(i+) (n = 505)</th>
<th>pN1mi (n = 327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year DFS</td>
<td>86%</td>
<td>77%</td>
<td>77%</td>
<td>76%</td>
</tr>
<tr>
<td>P value*</td>
<td>NA</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .003</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.00</td>
<td>1.49</td>
<td>1.50</td>
<td>1.52</td>
</tr>
<tr>
<td>P value*</td>
<td>NA</td>
<td>.001</td>
<td>.003</td>
<td>.009</td>
</tr>
</tbody>
</table>

* Compared to pN0
MIRROR Study: Outcomes of Pts with Minimal SLN Involvement

<table>
<thead>
<tr>
<th>pN0(i+)/pN1mi</th>
<th>pN0(i+)</th>
<th>pN1mi</th>
</tr>
</thead>
<tbody>
<tr>
<td>– AST (n = 832)</td>
<td>+ AST (n = 958)</td>
<td>+ AST (n = 505)</td>
</tr>
<tr>
<td>5-year DFS</td>
<td>77%</td>
<td>83%</td>
</tr>
<tr>
<td>P value*</td>
<td>NA &lt; .0001</td>
<td>NA &lt; .05</td>
</tr>
<tr>
<td>Recurrence HR</td>
<td>1.00</td>
<td>0.57</td>
</tr>
<tr>
<td>P value*</td>
<td>NA &lt; .0001</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Compared to – AST

AST: Adjuvant Chemotherapy: 10%, Hormonal Therapy: 63%; Both: 23%


2010 ASCO: ACOSOG Z0010 Trial

Abstract CRA 505

- 5,539 pts were entered in a prospective, multicenter observational study to determine the clinical significance of SN and BM micromets
- Lumpectomy + SNB + bilateral iliac crest BM aspiration
- SN and BM were evaluated by central IHC and results were not reported to the investigator or treating clinician
- SNs were successfully identified in 5,184 pts (94.5%)
- Histologic SN mets were found in 23.9%
- IHC detected additional 350 pts (10.5%) with SN mets
- BM mets were identified by IHC 3% of the pts

Cote R et al: Proc ASCO 2010 CRA 504

2010 ASCO: ACOSOG Z0010 Trial

5-Year Overall Survival by SN and BM Status

<table>
<thead>
<tr>
<th>Group</th>
<th>% Alive in 5 Years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SN Histology Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>92.8 (91.3-94.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Negative</td>
<td>95.6 (95.0-96.3)</td>
<td></td>
</tr>
<tr>
<td>SN IHC Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>95.1 (92.7-97.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Negative</td>
<td>95.8 (95.0-96.5)</td>
<td></td>
</tr>
<tr>
<td>BM IHC Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>90.2 (84.6-96.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Negative</td>
<td>95.1 (94.3-95.8)</td>
<td></td>
</tr>
</tbody>
</table>

Cote R et al: Proc ASCO 2010 CRA 504
Meta-analysis of Non-SN Positivity Associated with Minimal SLN Involvement

- 25 studies reporting on non-SN involvement associated with low-volume SN involvement (789 pts H&E (+) SNs, 345 pts IHC (+) SNs)
- The weighted mean estimate for non-SN metastases after low-volume SN involvement is around 20%
- The incidence is around 9% if the SN involvement is detected by IHC alone


Rates of Non-SLN Involvement in Pts with Isolated Tumor Cells in the SLN

- Systematic Review
- 29 studies including 836 patients
- Overall pooled risk of NSN involvement: 12.3%
- 64% of pts with NSLN involvement had macromets
- Patients with ITCs in the SLN without other indications for adjuvant systemic therapy might be candidates for axillary dissection


Identification of Subsets at Low Risk for non-SLN Involvement

- Questions
  - Is there a threshold of comfort where AND can be omitted?
  - Can we reliably identify subgroups at or below that threshold?
  - Does omitting AND impact on overall survival or local recurrence?
  - Can we manage these patients with other modalities (adjuvant chemo, adjuvant XRT)?
Clinically Negative Axillary Nodes (N=5,611)

**NSABP B-32**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SE</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis Type (Micro, Macro)</td>
<td>0.190</td>
<td>&lt; .0001</td>
<td>3.42 (2.36-4.96)</td>
</tr>
<tr>
<td>Lymphatic Invasion (Negative, Positive)</td>
<td>0.175</td>
<td>.0004</td>
<td>1.85 (1.31-2.61)</td>
</tr>
<tr>
<td>Clinical Tumor Size</td>
<td>0.079</td>
<td>.044</td>
<td>1.37 (1.004-1.37)</td>
</tr>
</tbody>
</table>

* Continuous variable

**Predictive Factors for Non-SLN Metastases After Positive SLN Biopsy in NSABP B-32**

Multivariate Analysis

Lymphovascular Invasion Absent - Lymphovascular Invasion Present

- **Lymphatic Invasion**
  - Negative: 0.175, P = .0004, Odds Ratio: 1.85 (1.31-2.61)
  - Positive: 0.079, P = .044, Odds Ratio: 1.37 (1.004-1.37)

Lymphatic Invasion Absent

- Clinical Tumor Size
  - Probability of having one or more NSN positive
    - 0.0001: 0.2, 0.4, 0.6, 0.8, 1.0
Nomogram to Predict Likelihood of Positive Non-SN with Positive SN

Van Zee et al., Ann Surg Oncol., 2003

Omission of Axillary Therapy in Patients with pN1mi or pN0i+ by SLNB: MIRROR Study

- Patients with favorable primary tumor characteristics
- No indication for adjuvant systemic therapy
- Sentinel node procedure
- pN0, pN0(i+) or pN1mi

N = 2680 after central pathology review


- Patients selected from the Netherlands Cancer Registry (1998-2005) (N = 3205)
- Median follow-up 4.7 years

Sentinel node biopsy only (SN only) N = 1218
Completion axillary lymph node dissection (cALND) N = 1314
Axillary radiotherapy (axRT) N = 148

R = 2008 after central pathology review

Results: Multivariate Analysis

<table>
<thead>
<tr>
<th>Sentinel node status</th>
<th>Axillary therapy</th>
<th>N</th>
<th>5-yr axillary recurrence</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0 (i+)</td>
<td>cALND</td>
<td>135</td>
<td>1.5%</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>SN only</td>
<td>135</td>
<td>1.3%</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>cALND/axRT</td>
<td>460</td>
<td>0.9%</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>SN only</td>
<td>345</td>
<td>2.0%</td>
<td>2.39</td>
<td>0.67 - 8.48</td>
</tr>
<tr>
<td></td>
<td>cALND/axRT</td>
<td>345</td>
<td>2.0%</td>
<td>2.39</td>
<td>0.67 - 8.48</td>
</tr>
<tr>
<td></td>
<td>SN only</td>
<td>141</td>
<td>5.0%</td>
<td>4.30*</td>
<td>1.49 - 13.24</td>
</tr>
</tbody>
</table>

HR corrected for age, tumor size, grade, hormone receptor status, adjuvant systemic therapy and radiotherapy to the breast
* Statistically significant compared to cALND/axRT

• 97,314 patients with SLN metastases in the NCDB
• 21% underwent SLNB alone

In pts with macrometastases (n=20,075 during 1998 to 2000), there was a non significant trend toward better outcomes for SLNB+ALND vs. SLNB*
  - Axillary recurrence HR: 0.58 (95% CI, 0.32 - 1.06)
  - Overall survival HR: 0.89 (95% CI, 0.76 - 1.04)

In pts with micrometastases (n=2,203 during 1998 to 2000), there were no significant differences in axillary recurrence or survival between the 2 groups

*adjusted

SLN Biopsy Patterns and Outcomes NCDB 1998-2005

IBCSG TRIAL 23-01
T ≤ 5 cm cN0

Stratification –
Institution
Menopausal status
Preop SNB

Micrometastases
SNB

Observation
Axillary Dissection

Target sample size: 1,960
Opened: April, 2001

ACOSOG Z0011
Clinically Negative Patients 1-2 Positive SNs by H & E

Lumpectomy + Breast XRT
Randomization

Completion Axillary Node Dissection (n=445)
No Further Surgery (n=446)

Accrual: 991 pts

Adjuvant systemic therapy at the discretion of treating physician
### ACOSOG Z0011

#### Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SNB Alone</th>
<th>Completion AND</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Number of Nodes Removed</td>
<td>2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3 or More Positive Nodes</td>
<td>5%</td>
<td>17.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-Year In Breast Recurrence</td>
<td>2.1%</td>
<td>3.7%</td>
<td>0.16</td>
</tr>
<tr>
<td>5-Year Axillary Node Recurrence</td>
<td>1.3%</td>
<td>0.5%</td>
<td>0.44</td>
</tr>
<tr>
<td>5-Year Overall Survival</td>
<td>92.5%</td>
<td>91.9%</td>
<td>0.24</td>
</tr>
<tr>
<td>5-Year DFS</td>
<td>83.8%</td>
<td>82.2%</td>
<td>0.13</td>
</tr>
</tbody>
</table>


### NSABP B-32 Schema

**Clinically Negative Axillary Nodes**

- Randomization
- **GROUP 1**
  - Sentinel Node Biopsy
- **GROUP 2**
  - Sentinel Node Biopsy*
- Axillary Dissection

*Axillary node dissection only if the SN is positive

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

### Is Axillary Radiation an Alternative to Axillary Dissection in Patients with Minimal SN Involvement?

- Randomized trials comparing the two approaches are ongoing (AMAROS)
- Low axillary recurrence rates have been demonstrated in small studies of axillary XRT:
  - Short follow-up
  - Highly selected subgroups of patients
- Most available data on local control are with axillary dissection
DCIS and SNB
• By definition DCIS does not metastasize to nodes
• Routine AND was removed from clinical trials
• Historically node positive rate < 2%
• Recent data 10-15% positive SNB rate is associated with microinvasive or invasive cancer found with the DCIS
• High percentage of positive SNB by IHC
• Outcomes poorly understood or established

When to perform SNB in DCIS?
• Extensive DCIS requiring a mastectomy
  – Technically unable to perform SNB after Mx
• Following a lumpectomy for DCIS in which microinvasive or invasive disease is found after lumpectomy

Neoadjuvant Chemotherapy
• NC provides significant tumor down sizing
• NC provides significant axillary down staging
• Is SNB after NC as feasible and accurate as before systemic therapy?
• By doing SNB after NC, do we lose information that is important for further patient management?
SNB Experience After NC

- Limited experience
- Early - 12 single institutions – ID rate 89%, FNR 10.8%
- Late - 6 single institutions – ID rate 89%, FNR 8.1%

SNB After NC: Single Institution Series
Positive Axillary Nodes Before NC

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th># Pts (Node +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen, 2006</td>
<td>T1-T4, N1-N3</td>
<td>69(40)</td>
<td>93</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>Lee, 2006</td>
<td>T1-T4, N1 (Palpable and FNA (+) or &gt; 1cm thick with loss of fat hilum on US and SUV &gt; 2.5)</td>
<td>219 (124)</td>
<td>78</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>Newman, 2007</td>
<td>Resectable T1-3, N1 (FNA (+) under US)</td>
<td>40 (28)</td>
<td>96</td>
<td>11</td>
<td>Yes</td>
</tr>
</tbody>
</table>

All 328 (172) 54 11.6

SNB After NC
Multi-Center Studies: NSABP B-27 (n=428)

- Identification Rate: 85%
  - With blue dye: 78%
  - With isotope + blue dye: 88-89%
- False Negative Rate: 11%
  - With blue dye: 14%
  - With isotope + blue dye: 8.4%

Clinically Node (-): 12.4%  
Clinically Node (+): 7.0%  
\( P=0.51 \)
SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

- 21 studies
- 1273 patients
- Identification Rates: 72-100%
  -- Pooled estimate: 90%
- False Negative Rates: 0-33%
  -- Pooled estimate: 12%

SNB Before NC: Arguments in Favor

- Information on the status of SN can be obtained without the confounding effects of NC
- This may provide an advantage regarding:
  -- Further surgical management of the axilla
  -- Selection of optimal NC or adjuvant chemo after NC
  -- Selection of optimal loco-regional XRT

SNB Before NC: Pros and Cons

- This approach can be helpful if SN is negative
- Patients with large operable breast cancer have high likelihood of positive nodes (50-70%)
- This approach does not take advantage of the downstaging effects of NC on nodes: 30-40% conversion from (+) to (-) and avoidance of AND
May be useful in patients who will not need chemotherapy if the SN is negative (uncommon situation among typical candidates for NC)

Usually original tumor size, age and primary tumor markers are good guides for appropriate NC

Can We Use Tumor and Nodal Response to NC in Order to Individualize the Use of L-R XRT?

LRF Update: NSABP B-18/B-27
MVA: Predictors of LRF (2192 pts and 229 events)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clin. Tumor Size 2.1-5 vs. 0-2 cm</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Clin. Tumor Size &gt; 5 vs. 0-2 cm</td>
<td>1.36</td>
<td>0.0007</td>
</tr>
<tr>
<td>Node(-)/No pCR vs. Node(-)/pCR</td>
<td>1.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Node(+) vs. Node(-)/pCR</td>
<td>2.58</td>
<td></td>
</tr>
</tbody>
</table>
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR

SNB and NC
• For patients with operable BC, SNB after NC is feasible and accurate with similar performance characteristics to SNB before NC
• By performing SNB after NC, up to 40 percent of patients who present with involve axillary nodes may be spared from axillary dissection
• SNB before NC does not offer particular clinical advantages and reduces the number of patients who could benefit from the down-staging effect of NC in the axillary nodes

ACoSOG Z1071 and QUEBEC Schemas
T1-4 N1-2 invasive breast cancer
(pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)
↓
REGISTER*
↓
Patients receive neoadjuvant chemotherapy (stratify patients by age, stage and number of cycles and type of chemotherapy)
↓
REGISTER*
↓
SLN and ALND
*Patients can be registered pre or post chemotherapy.
Conclusions

• SNB accurately predicts axillary nodal status with decreased morbidity compared to axillary dissection
• SN micrometastases and IHC positivity are of clinical uncertainty and hence AND is controversial
• Long-term outcome data from large randomized trials have recently been presented
• The role of SNB for DCIS is very limited
• SNB following neoadjuvant therapy benefits the patient due to down staging of the axilla and avoiding needless AND. Trials pending.

Summary

CLINICAL TRIALS LEAD THE WAY