The Role of Sentinel Lymph Node Biopsy and Axillary Dissection

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University of Texas
MD Anderson Cancer Center
SLN Biopsy

- Revolutionized surgical practice
- Marked decreased need for axillary dissection
- Major decrease in lymphedema, shoulder dysfunction, pain/parasthesia rates
Lymphatic Mapping Technique

Radioactive colloid, blue dye
2010 AJCC Staging Changes: Definitions

- pN0(i+): Cluster < 0.2 mm
- Classification of ITC < 200 cells on histologic section
- Micrometastases: 0.2 to 2 mm
- Stage I now TWO GROUPS
  - IA: T1 NO MO
  - IB: T0 N1mi M0

Edge et al, 2009
SLN Trials
Recent Results from US Trials 1998-2004
Practice Patterns: US National Cancer Database 1998 - 2005

NSABP Protocol B-32 N=5,611

Clinically Negative Axilla

RANDOMIZATION

SLN Biopsy* and Axillary Dissection

SLN Biopsy

Pathologically Positive SLN

Axillary Dissection

Pathologically Negative* SLN

No Axillary Dissection

* IHC performed on Neg SLNs
NSABP B-32 False Negative Rate

9.7%

(7.6 - 11.9)*

*95% CI
Julian et al, SABC, 2004
<table>
<thead>
<tr>
<th>Type</th>
<th>Technical Success %</th>
<th>False Negative Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>97.1</td>
<td>9.7</td>
</tr>
<tr>
<td>FNA/Core</td>
<td>97.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Incisional</td>
<td>97.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Excisional</td>
<td>97.3</td>
<td>15.2</td>
</tr>
</tbody>
</table>

P=0.83  P=0.02
Clinically Negative Axillary Nodes

**Randomization**

**GROUP 1**
SN + AD

- SN Pos
- SN Neg (SN+AD)
  - FU
  - 1,975 patients

**GROUP 2**
SN

- SN pos + AD
- Intraop cytology & postop HE
- SN Neg (SN only)
  - FU
  - 2,011 patients

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

**B-32**

1975 patients

2011 patients
B-32 Analysis Plan

- 3,989 - SN neg (71% of 5611)
- 99.9% - follow-up information
- 7.92 years - average time on study

- Primary endpoints OS, DFS, Regional Control
- Study powered to detect 2% difference OS

Krag et al ASCO 2010
NSABP Protocol B-32

Disease-Free Survival for Sentinel Node Negative Patients

Trt N Deaths
SNR+AD 1975 315
SNR 2011 336 HR=1.05 p=0.542

Data as of December 31, 2009

Krag et al Lancet Oncol 2010
Krag et al ASCO 2010
## 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>

Krag et al Lancet Oncol 2010

Krag et al ASCO 2010
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>

Krag et al Lancet Oncol 2010
Ashikaga et al JSO, 2010

All differences p<0.001
Effect of Occult Metastases on Survival in “Node-Negative” Patients: NSABP B-32

- Occult metastases: 15.9%
- Independent predictor of prognosis
- Overall survival difference: 1.2%
  - 94.6% v. 95.8%
- Concluded no clinical benefit of serial sectioning and or IHC

Weaver et al, *NEJM*, 2011
NSABP B-32
Overall Conclusions

- No significant differences were observed OS, DFS, or Regional Control SLN vs AD
- 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.
American College of Surgeons Oncology Group SLN Trial

T1 and T2 Tumors Clinically Negative Axilla BREAST CONSERVATION

- Bone Marrow IHC
  - Axillary Observation

+ Randomization
  - Axillary Observation
  - Axillary Dissection
ACOSOG Z0010 - Methods

• SLNs processed - standard pathology and H&E staining
• SLNs neg by H&E subjected to IHC for cytokeratin (investigators blinded to results)
<table>
<thead>
<tr>
<th>Z0010 Treatment Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total SLNs Removed</strong></td>
</tr>
<tr>
<td>Median (Min, Max)</td>
</tr>
<tr>
<td>2 (0,32)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>689</td>
</tr>
<tr>
<td><strong>ALND Performed, N(%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>925(18.0)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>4203(82.0)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>82</td>
</tr>
<tr>
<td><strong>Chemotherapy, N(%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>2297(53)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>2035(47)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>878</td>
</tr>
<tr>
<td><strong>Hormonal Rx, N(%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>2943(67.9)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>1389(32.1)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>878</td>
</tr>
<tr>
<td><strong>Radiation Rx, N(%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>3884(90.8)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>394(9.2)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>932</td>
</tr>
<tr>
<td><strong>Any Adj Rx, N(%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>4210(98.4)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>68(1.6)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>932</td>
</tr>
</tbody>
</table>
Overall Rate IHC Positive SLNs Z10

5210 Eligible and Evaluable Patients

SLN H&E Positive
N=1215 (24%)

SLN H&E Negative
N=3995 (76%)

IHC Negative
N=2977 (90%)

IHC Positive
N=349 (10%)
ACOSOG Z0010: Occult Micrometastases

- 5-year overall survival was significantly higher with a negative vs. positive result for:
  - SLN H&E (≈ 96% vs. 93%; \( P = .0009 \))
  - BM IHC (95% vs. 90%; \( P = .01 \))
- SLN IHC was NOT significantly associated with overall survival.

### Overall Survival

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Multivariable Analysis (Positive vs. Negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
</tr>
<tr>
<td>SLN H&amp;E</td>
<td>1.44 (1.11-1.88)</td>
</tr>
<tr>
<td>BM IHC</td>
<td>1.88 (1.12-3.17)</td>
</tr>
<tr>
<td><strong>SLN H&amp;E</strong>- Patients</td>
<td></td>
</tr>
<tr>
<td>SLN IHC</td>
<td>0.98 (0.62-1.54)</td>
</tr>
<tr>
<td>BM IHC</td>
<td>2.22 (1.21-4.10)</td>
</tr>
</tbody>
</table>

Giuliano et al *JAMA* 2011
ACOSOG Z10 Conclusions

- IHC detected SLN metastases do not appear to impact overall survival
- Routine examination of SLN by IHC is not supported in this patient population by this study
ACOSOG Z0011: A Randomized Trial of Axillary Node Dissection in Women with Clinical T1-2 N0 M0 Breast Cancer who have a Positive Sentinel Node

Giuliano AE, McCall L, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt K, Morrow M, Ballman KV

Giuliano et al JAMA 2011

SN-Positive Randomized Patients  
N = 891

- ALND Arm  
  N = 445
  25 patients withdrew prior to surgery

- SLND only Arm  
  N = 446
  10 patients withdrew

Intent-to-Treat Sample

- ALND Arm  
  N = 420
- SLND only Arm  
  N = 436

Treatment Received Sample

- ALND Arm  
  N = 388

- SLND only Arm  
  N = 425

11 patients had ALND
106 (27.4%) patients treated with ALND had additional positive nodes removed beyond SLN
72.6% patients treated with SLND had all positive nodes removed with the technique.
Patient Characteristics Z11

- Median age: 55 years
- 70% T1 tumors
- 82% ER-positive disease
- All patients had node positive breast cancer (overall low burden)
  - 58% had only one node positive
  - Only 21% had ≥ 3 positive nodes
### Locoregional Recurrences

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>ALND (420 pts)</th>
<th>SLND (436 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local (Breast)</td>
<td>15 (3.6%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>Regional (Axilla, Supraclavicular)</td>
<td>2 (0.5%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>Total Locoregional</td>
<td>17 (4.1%)</td>
<td>12 (2.8%)</td>
</tr>
</tbody>
</table>

*Median follow-up = 6.3 years*

Regional recurrence seen in only 0.7% of the entire population
Disease-Free Survival

Time (Years)

% Recurrence-Free and Alive

ALND

No ALND

P-value = 0.14
Overall Survival

Time (Years)

% Alive

ALND
No ALND

P-value = 0.25
IMPORTANT Caveats

- WHOLE BREAST RADIATION
- Breast conserving therapy
- Adjuvant Systemic Therapy
## Adjuvant Systemic Therapy

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>SLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>57.9%</td>
<td>58.0%</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>46.4%</td>
<td>46.6%</td>
</tr>
<tr>
<td>Either/Both</td>
<td>96.0%</td>
<td>97.0%</td>
</tr>
</tbody>
</table>

\[ P = \text{N.S.} \]
Recommendations at MD Anderson for + SLN?

• *Must be individualized*

• **No dissection:**
  – T1/T2
  – One or two positive SLNs
  – If Whole-breast radiotherapy
  – Receiving systemic therapy

Recommendations for Axillary Node Dissection at MD Anderson

- Positive SLN
  - Mastectomy
  - Partial breast radiotherapy
  - Neoadjuvant chemotherapy

Sentinel Node
Evolving
Controversies
Complicated

Does the axilla need to be treated when positive SLN?

Many radiation oncologists will treat the axilla when a positive SLN is obtained and no dissection is performed.
Extended Field Radiotherapy?

- Which patients?
- Recent presented MA.20 results
- Concern for over treatment/risk
Toxicity?

- Overall Survival for early Stage II breast cancer very high (>90%)
- What will be the long term effects on healthy:
  - Lymphatics?
Can Axillary *Radiation* Be Substituted for Completion Axillary Lymph Node Dissection

When a Sentinel Lymph Node Contains Metastases?
AMAROS EORTC 10981

- Tumor ≤ 5 cm
- 4827 Total Patients
- SLN-Positive
- Randomized Component of Trial
  - ALND vs. Axillary Radiotherapy

Sentinel Node Biopsy Before or After Neoadjuvant Chemotherapy?
SLN Biopsy Before Neoadjuvant Therapy

- Commits patients to an extra axillary operation
- SLN Negative: Two operations
- SLN Positive: Commits patients to axillary lymph node dissection with a positive SLN before therapy
Conversion of Axillary Metastases: FNA Positive to Pathologic Negative

- **POSITIVE**
  - 191 patients

- **FAC X 4**

- **Pathologic NEGATIVE**
  - 43 patients

**23%**

Median # LNs Removed = 16

Kuerer et al, Ann Surg, 1999
Conversion of Axillary Metastases: FNA Positive to Pathologic Negative

**POSITIVE**

109 patients

HER2+

**Pathologic NEGATIVE**

81 patients

Trastuzumab + A or T

74%

Median # LNs Removed = 19

Dominici et al. CANCER, 2010
Impact of Nodal Disease Eradication on DFS
Independent Prognostic Factor

Annals of Surgery, 1999

$P = 0.00003$
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%

Mamounas EP: J Clin Oncol, 2005
SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

• Xing et al M D Anderson
• 21 studies
• 1273 patients
• Identification Rates: 72-100%
  – Pooled estimate: 90%
• False Negative Rates: 0-33%
  – Pooled estimate: 12%

Conclusion: SNB is a reliable tool for planning treatment after NC
## 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>98</td>
<td>11</td>
<td>Yes</td>
</tr>
</tbody>
</table>
ACOSOG Z1071

SLN surgery after neoadjuvant chemotherapy for node positive breast cancer

PI - Judy C. Boughey MD
Z1071 schema

T1-4 N1-2 invasive breast cancer
(Pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)

REGISTER*

↓

Patients receive chemotherapy
(stratify patients by age, stage and number of cycles and type of chemotherapy)

REGISTER*

↓

SLN and ALND
Alternatives to SLN Biopsy BEFORE Neoadjuvant Chemotherapy?
Initial Nodal Ultrasound and FNA Biopsy
Avoiding Surgical SLN Biopsy

Krishnamurthy et al, Cancer 2002
Pros and Cons in Timing of SLN Biopsy with Neoadjuvant Therapy

• Presence of axillary metastases can be identified with either SLN biopsy or FNA before neoadjuvant therapy

• Chemotherapy can eradicate lymph node metastases in 30 to 40% – Axillary dissection may be avoided if SLN biopsy performed after pre-op therapy
Should Patients with DCIS be Offered SLN Biopsy?
Sentinel Lymph Node Biopsy
Patients With ‘Pure’ DCIS

- European Institute of Oncology
- 223 unselected patients with DCIS
- Metastases in 3.1%, most micromets
- Completion dissection no additional mets
- Select patients – palpable mass? Diffuse disease?

Intra et al, Arch Surg 2003
SLN Biopsy for ‘High Risk’ DCIS

- DCIS with microinvasion (N=31)
  - 10% Positive SLN
- ‘High-Risk’ DCIS (N=76)
  - Palpable or mass on MMG
  - Extensive high-grade lesions
    - 12% Positive SLN
- Mastectomy = Lose chance for later SLN

Selective Use of SLN Biopsy in DCIS

- 399 patients with INITIAL diagnosis of DCIS
- 20% of patients will have invasive carcinoma on final pathology
  - Predictors: CORE Biopsy diagnosis, age < 55, HG tumors, > 4 cm on MMG
- 10% positive SLN (H and E in 93%, n = 141)
  - Highly selected group of patients

Yen et al, *Journal American College of Surgeons*, 2005
Is Any Axillary Surgery in Elderly Women With ER+ Breast Cancer Needed?
Axillary Surgery in the Elderly

• Info gained may not influence adjuvant therapy selection or outcome

• Three prospective trials:
  – Evidence suggests that selected patients > 70 years, clinical normal axilla, ER+, < 2 cm, receiving endocrine therapy can safely avoid

IBCSG *J Clin Onc*, 2006
New Trials and Next Steps

- Sentinel node vs. Observation after axillary Ultrasound (SOUND)
- N=1,560
- European Institute of Oncology, Milan
- Eligibility: <2 cm, any age, negative preop axillary US, breast conservation

Gentilini & Veronesi, Breast 2012
Current Indications and Standards for Sentinel Node Biopsy

Clinically *NEGATIVE* axilla

- T1, T2, T3 tumors

- If a SLN is found to be positive:
  - Mastectomy: Completion dissection
  - Breast Conserving w WBT: Individualize

- DCIS: High-risk for Invasive and receiving mastectomy
Current Indications and Standards for Sentinel Node Biopsy

• Neoadjuvant therapy
  – Before or after chemo; prefer nodal ultrasound with FNA biopsy
  – Risks and benefits should be discussed in detail with patient