Role of Sentinel Lymph Node Biopsy and Axillary Dissection

Henry Kuerer, MD, PhD, FACS
Breast Surgical Oncology
• Revolutionized surgical practice
• Marked decreased need for axillary dissection
• Major decrease in lymphedema, shoulder dysfunction, pain/parasthesia rates
• Axillary lymph node dissection (ALND) in patients without SLN metastases is not indicated

• Patients with only 1 or 2 metastatic SLNs planning to undergo lumpectomy and whole-breast radiotherapy should not undergo ALND (for mastectomy, ALND is indicated)

Lyman et al J Clin Onc, 2014
SNB is appropriate for patients:

- receiving preoperative systemic therapy
- with previous breast/axillary surgery
- with ductal carcinoma in situ (DCIS) undergoing mastectomy
- with multicentric carcinoma

Lyman et al J Clin Onc, 2014
SNB should NOT be performed for patients:

- concurrent pregnancy
- pure ductal carcinoma in situ (DCIS) undergoing lumpectomy
- locally advanced and inflammatory breast cancer (T3/T4 tumors)
Lymphatic Mapping Technique

Radioactive colloid, blue dye
SLN Biopsy Using a Magnetic Tracer

- Superparamagnetic iron oxide (SPIO) contrast agent and uses a magnetic hand held probe

Nodal Ultrasound at Diagnosis

- All patients with invasive disease at MD Anderson receive whole breast and draining lymphatic basin ultrasound
  - Ipsilateral axilla, internal mammary, infra and supraclavicular
- Minute metastatic foci
Metastatic Nodal Disease
Ultrasound Guided FNA

Specificity: 100%
Positive Predictive Value: 100%

Krishnamurthy et al Cancer, 2002
SLN Trials
Recent Results from US Trials 1998-2004
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
### NSABP B-32

**Sentinel Node by Biopsy Type**

<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

Intraop cytology & postop HE

SN pos + AD

FU

SN Neg (SN only)

FU

2,011 patients

Stratification
Age
Clinical Tumor Size
Type of Surgery

B-32

1,975 patients

2,011 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
NSABP Protocol B-32

Disease-Free Survival for Sentinel Node Negative Patients

Data as of December 31, 2009

Krag et al. ASCO 2010

Krag et al. Lancet Oncol 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>
# Residual Morbidity at End of Follow-up

<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>

All differences p<0.001

Ashikaga et al JSO, 2010
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
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

ALND Arm N = 420

SLND only Arm N = 436

Intent-to-Treat Sample

ALND Arm N = 388
32 patients did not have ALND

SLND only Arm N = 425
11 patients had ALND

Treatment Received Sample
106 (27.4%) patients treated with ALND had additional positive nodes removed beyond SLN.
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>

\[ P = 0.11 \]

Median follow-up = 6.3 years

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

% Recurrence-Free and Alive

Time (Years)

ALND
No ALND

P-value = 0.14
Overall Survival

![Graph showing overall survival rates over time with ALND and no ALND groups. The graph indicates a P-value of 0.25.]

- **Overall Survival**
  - **X-axis:** Time (Years)
  - **Y-axis:** % Alive
  - **Legend:**
    - 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>Treatment</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>

\[ P = \text{N.S.} \]
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.
A randomised controlled trial of axillary treatment in women with early stage breast cancer who have metastases in one or two sentinel nodes

**POSitive Sentinel NOde**: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy

*N = 1,900*

NIHR Sponsored UK 82 and ANZ 35 Centres

Chief Investigator: Amit Goyal
Patients with operable invasive breast cancer <5 cm with normal clinical and ultrasound examination of the axilla undergoing lumpectomy or mastectomy and sentinel node biopsy

1 or 2 sentinel node macrometastases

CONSENT and baseline QOL questionnaires completed

RANDOMISE 1:1

Arm 1
Adjuvant therapy only

Breast/Chest wall radiotherapy, Systemic adjuvant therapy (chemotherapy and/or hormone treatment)

Arm 2
Adjuvant therapy plus axillary treatment (axillary radiotherapy or node clearance)

Follow Up 5 yrs
Follow-up (assessment of recurrence, arm morbidity): 6, 12, 24, 36, 48 & 60 months post-randomisation
Postal QOL, anxiety, EQ-5D questionnaires: 3, 6, 12, 24 & 36 months post-randomisation

Primary endpoint: Axillary recurrence
Secondary endpoints: arm morbidity, QOL, anxiety, costs to the NHS, breast or chest wall recurrence, distant metastasis, time to axillary recurrence, death, axillary recurrence free and disease free survival.
Can Axillary *Radiation* Be Substituted for Completion Axillary Lymph Node Dissection

When a Sentinel Lymph Node Contains Metastases?
AMAROS EORTC 10981

- Tumor $\leq$ 5 cm
- SLN-Positive (n=1425)
- Randomized Component of Trial
  - ALND vs. Axillary Radiotherapy (L 1-3, SC)

In ALND group, 244 (32.8%) patients had additional positive nodes.

Median follow-up = 6.1 years

<table>
<thead>
<tr>
<th></th>
<th>ALND N=744</th>
<th>AxRT N=681</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary recurrence</td>
<td>0.43%</td>
<td>1.19%</td>
</tr>
</tbody>
</table>

Axillary recurrence in SLN negative patients = 0.72%

Rutgers E, ASCO 2013
AMAROS

- No difference in DFS or OS

Rutgers E, ASCO 2013
AMAROS

- Decreased lymphedema with AxRT

*lymphedema observed or treated

Rutgers E, ASCO 2013
<table>
<thead>
<tr>
<th></th>
<th>Z0011</th>
<th>AMAROS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number SLN removed</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Macrometastases in SLN</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Additional positive nodes in ALND</td>
<td>27.3%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Axillary recurrence: ALND</td>
<td>0.5%</td>
<td>0.43%</td>
</tr>
<tr>
<td>Axillary recurrence: other tx</td>
<td>0.9%</td>
<td>1.19%</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>6.3 yrs</td>
<td>6.1 yrs</td>
</tr>
<tr>
<td>Breast conservation</td>
<td>100%</td>
<td>82%</td>
</tr>
</tbody>
</table>
Recommendations at MD Anderson for + SLN?

• 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

• NOW CHANGING 2014?

Axillary Management After Neoadjuvant Chemotherapy

- Node negative
  - SLND (after neoadjuvant chemotherapy)
  - ALND if SLN +

- Node positive
  - 2014 NCCN guidelines → ALND
  - Emerging role for SLND (Z1071)
Conversion of Axillary Metastases: FNA Positive to Pathologic Negative

**POSITIVE**
191 patients

**FAC X 4**

**23%**

**Pathologic NEGATIVE**
43 patients

**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

**74%**

**Median # LNs Removed = 19**

*Dominici et al. CANCER, 2010*
Sentinel Node Biopsy after Preoperative Chemotherapy for Node Positive Breast Cancer?
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


JAMA, 2013
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
Node positive disease 637 pts

Chemotherapy

Node negative 255 pts (40%)

Residual nodal disease 382 pts (60%)

SLN positive 326 pts

SLN negative / ALND positive 56 pts

SLN correctly identified nodal status in 91.2%
False negative rate among pts with cN1 disease and at least 2 SLNs examined

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

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

\[ FNR = 12.6\% \]

95% probability that the FNR lies in the range of 9.4 to 16.7%.
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 SLN</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>353</td>
<td>206</td>
<td>13.6%</td>
<td>9.2 - 19.0%</td>
</tr>
</tbody>
</table>
Can Identification and Removal of the Clipped Node with Biopsy Proven Mets Prior to Chemo Increase Accuracy of this Procedure after Chemo?
Nodal FNA and Placement of Clip Marker
Nodal FNA and Placement of Clip-Gel Marker

Wei Yang, MD
Eligibility:
- Abnormal axillary nodes on US metastases documented by cytology

Marker clip placed in node with metastases

Preoperative chemotherapy

Routine axillary node dissection
Prospective Registry of Breast Cancer Patients with Axillary Nodal Metastases Identified During Ultrasound Staging at MD Anderson Cancer Center: Protocol 11-1087

Routine ALND, identification of marked node, pathologic correlation (disease presence and size) with compared with other nodes
• 90 Patients completed chemotherapy and surgery

Clinicopathologic Features

<table>
<thead>
<tr>
<th></th>
<th>N=90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>49 (28-76)</td>
</tr>
<tr>
<td>Mean Tumor Size</td>
<td>4.7 cm (range 1.5-12)</td>
</tr>
<tr>
<td>ER Positive</td>
<td>63 (70%)</td>
</tr>
<tr>
<td>PR Positive</td>
<td>45 (50%)</td>
</tr>
<tr>
<td>HER2 Positive</td>
<td>28 (31%)</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>Number of Abnormal LN on US:</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41 (46%)</td>
</tr>
<tr>
<td>2</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>≥3</td>
<td>33 (37%)</td>
</tr>
</tbody>
</table>
Clipped Node Registry Trial
All Received Pre-op Chemo

N=90

No ALND Performed
N=5

ALND Performed
N=85

Converted to Node Negative
41% N=35

Residual Nodal Disease
59% N=50

False Negative Rate
6%
(95% CI 1.3-16.6)

False Negative Results
3/50

Caudle et al, MDACC PRELIMINARY DATA, June 2014
Clipped Node Registry Trial
Patients Undergoing SLND

- Clipped Node not a SLN (12/52) 23%

- SLND Performed
  - N=52

  - No ALND Performed
    - N=4

  - SLND and ALND Performed
    - N=48

    - Converted to Node Negative
      - N=17
    - Residual Nodal Disease
      - N=31

      - SLN negative
        - N=5
      - Clipped node and SLN negative
        - N=1

- False Negative Rate
  - SLND Alone = 16% (95% CI 5.4-34)
  - SLND + Evaluation of Clipped Node = 3% (95% CI 0.1-17)
Feasibility of Selective Image Guided Resection of Cytologically Documented Axillary Lymph Node Metastases Following Preoperative Chemotherapy: Protocol 12-0163

**T0 – T4**
FNA documented axillary metastases

+/- Preop Chemo

Repeat nodal ultrasound, FNA
Excision of marked nodes
Routine axillary node dissection

**OUTCOME**
Technical Success?
Correlation:
FNA results with Histology
Clip Node with Others
Targeted Axillary Dissection

*TAD*

Metallic clip placed when FNA of lymph node shows metastases

At surgery, remove:

- LN with *KNOWN* disease (with clip)

  and

- LNs most likely to harbor disease (SLN)

Methods of Localization

Wire-localization: Placed day of surgery (n=2)

\[ ^{125}I \] Seed: Placed 1-5 days before surgery
Addition of SLN to Clip Node Excision:

Technically successful with SLND (100%)
- $^{125}\text{I}$ seed does not interfere with Tc99M lymphoscintigraphy
Alternative Methods For Localization of Biopsy Proven Node

- Netherlands Cancer Institute-Amsterdam
  - Place $^{125}$I-seed and leave in for 4+ months during neoadjuvant chemo

- Stanford
  - Biopsy node then place India black ink into node for later localization

Donker et al *Ann Surg* 2014

Choy et al *SSO* 2014
Targeted Axillary Dissection (TAD): Removal of Known Axillary Disease

- Ultrasound with FNA highly sensitive and specific for identification of nodal metastases
- Marking of nodal metastases allows for targeted excision of disease
  - Assessment of response when preoperative therapy utilized
  - New procedure may be more accurate alone or in combination with SLN biopsy for known nodal disease after preop chemo
Patients for Preoperative Systemic Therapy

• Clinically negative axillary lymph nodes
  Axillary ultrasound; suspicious nodes should be sampled by FNA/core biopsy and clipped; positive clipped lymph nodes must be removed if biopsy was positive prior to pre-op therapy.

• Clinically positive axillary lymph nodes
  Sample by FNA/core biopsy, clipped, must be removed if biopsy was positive prior to pre-op therapy
Primary aim: Determine whether axillary and regional nodal radiation alone is not inferior to ALND + RNI

Clinical T1-T3, N1 Breast Cancer

Neoadjuvant Chemotherapy; Clinically Node- Negative on Physical Exam after Treatment

Surgery with SLND and Intraoperative Pathologic Evaluation

- No SLN identified
  - No Registration, Randomization

- Positive SLN
  - Intraoperative Registration, Randomization
    - Arm 1: ALND + Nodal RT
    - Arm 2: Axillary and Nodal RT

- Negative SLN
  - Await Final Pathology
    - Positive
      - Registration, Randomization
    - Negative
      - No Registration, Randomization

N=2,918
Ongoing Clinical Trials
NSABP B-51/RTOG1304

Primary aim: Evaluate whether the addition of PMRT and regional nodal irradiation will improve invasive DFS rates

N=1,636

Clinical T1-T3, N1 Breast Cancer

Neoadjuvant Chemotherapy

Pathologically negative lymph nodes (either by SLND or ALND)

Stratification Factors:
- Surgery type (lumpectomy, mastectomy)
- Hormone receptor status
- HER2 status
- Adjuvant chemotherapy (yes/no)
- pCR in breast (yes/no)

Randomization

Arm 1
No PMRT or regional nodal XRT

Arm 2
Regional nodal XRT
Indications for Axillary Node Dissection: Local Control

- Inflammatory
- Clinically node negative axilla with positive SLN:
  - in mastectomy patients
  - In BCT patients not meeting Z11 criteria
- Axillary recurrence
- PRACTICE EVOLVING Paradigm Shifting
  - Targeted surgery
  - Node positive disease before/after preoperative systemic therapy