Strategies for Neoadjuvant Chemotherapy

Lymph Node Clipping for post-chemo identification

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Breast Surgical Oncology
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
Approach to Axillary Staging MD Anderson: Preoperative Systemic Therapy

- Nodal ultrasound +/- FNA for staging at presentation (do not perform SLN before preop chemo)
- Surgery in the axilla following pre-op therapy
  - Initial node negative: SLN and ALND ONLY if positive
  - Initial node positive (US/FNA+): Historically has been ALND
Conversion of Axillary Metastases: FNA Positive to Pathologic Negative

- **POSITIVE**
  - 191 patients

- **FAC X 4**

- **Pathologic NEGATIVE**
  - 43 patients

- **23%**

- **Median # LNs Removed = 16**

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*
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

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%.
Clip placement in patients 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 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?
Clip Placement in Axillary Nodes

- 179 patients axillary ultrasound
- US saw a node and a micro clip was placed (n=145); 121 had core biopsy
Nodal FNA and Placement of Clip Marker
Nodal FNA and Placement of Clip-Gel Marker

Wei Yang, MD
What is the fate of individual nodes with documented metastases?
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
• 101 consented to study, 2-28-14
  • 42 completed preop chemo and surgery
• pCR in lymph nodes: 43%
• Residual nodal disease: 57%
  • Clipped LN neg but ALND (+) = 1 patient
• False Negative Rate = 4.2%
  • (95% CI 0-12%)

Caudle et al, MDACC PRELIMINARY DATA, Feb 2014
• SLND performed with ALND: 19
  • **Clipped node was one of SLN: 74%**
  • Residual disease: 65%
    • FNR of SLND alone: 8%
    • FNR of SLND + removal of clipped node: 0%

Caudle et al, **MDACC PRELIMINARY DATA**, Feb 2014
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
Wire Localization of LN
I$^{125}$ Localization of LN
Feasibility of Selective Image Guided Resection of Cytologically Documented Axillary Lymph Node Metastases Following Preoperative Chemotherapy: Protocol 12-0163

- **Patient 001**
- 58 T2N1 ER+, Her2-, Ki67 50%
- FNA Clip Node
- T-FAC
- US resolution-fatty replacement
- Repeat FNA and US Localization

Path: 4 mm IDC

Path: No mets; 0/14
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
Preop Chemo Upcoming U.S. Coop Group Studies

**ALLIANCE A11202 Schema**

- Clinical T1-3 N1 M0 BC
- Neoadjuvant Chemotherapy
- BCT or Mastectomy
  - Sentinel Lymph Node Surgery
    - SLN Negative
    - SLN Positive
      - Randomization
        - ALND + Breast/chest wall and nodal XRT
        - No further axillary surgery. Breast/chest wall and nodal XRT

**NSABP B-51/RTOG 1304 (NRG 9353) Schema**

- Clinical T1-3 N1 M0 BC
- Axillary nodal involvement (FNA or core needle biopsy)
- Pre-op chemo
- Surgery with negative axillary nodes (either by axillary dissection or by SLNB ± axillary dissection)
  - Stratification
    - Type of surgery (mastectomy vs lumpectomy)
    - ER status (+ vs -), HER-2 status (+ vs -)
    - pCR in breast (yes vs no)
  - Randomization
    - No Regional Nodal XRT with breast XRT if BCS & No chest wall XRT if mastectomy
    - Regional Nodal XRT with breast XRT if BCS and chest wall XRT if mastectomy

N=2,918  N=1,636
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
The SENTINA Trial involved 1737 patients across 103 institutions. The trial was designed to evaluate the efficacy of sentinel lymph node biopsy (SLNB) in the management of early-stage breast cancer.

For patients with cN0 metastasis:
- pN0: No axillary surgery.
- pN1: Re-SLNB + ALND.

For patients with cN1 metastasis:
- ycN0: Neoadjuvant Chemotherapy followed by SLNB + ALND.
- ycN1: Neoadjuvant Chemotherapy followed by ALND.

The trial concluded with N = 592 patients in the neoadjuvant chemotherapy arm. The study was published in Lancet Oncol, 2013, by Kuehn et al.
## SENTINA Trial

<table>
<thead>
<tr>
<th>Arm</th>
<th>Identification Rate</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-NAC SLNB</td>
<td>99.1%</td>
<td></td>
</tr>
<tr>
<td>Re-SLN post-NAC</td>
<td>60.8%</td>
<td>51.6%</td>
</tr>
<tr>
<td>SLNB post-NAC</td>
<td>80.1%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

- **FNR** 24% 1 SLN, 19% 2 SLN, < 10% > 3 SLN
<table>
<thead>
<tr>
<th></th>
<th>Identified by SLN N= 518</th>
<th>Identified by U/S N=149</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of + LN</td>
<td>2.2</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number of + LN:</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>290 (56%)</td>
<td>44 (30%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>127 (25%)</td>
<td>38 (25%)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>101 (19%)</td>
<td>67 (45%)</td>
<td></td>
</tr>
<tr>
<td>Largest LN Metastasis (Mean)</td>
<td>5.29 mm</td>
<td>13.42 mm</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extra-nodal Extension Present</td>
<td>124 (24%)</td>
<td>75 (50%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Caudle et al, ASCO Breast, 2013
Standard Axillary Management: Clinical and Ultrasound Normal

- Proceed to IOLM and SLN biopsy
- Negative: about 70% no further surgery
- Positive (pN1): about 30%
  - No further surgery if BCT and only 1 or 2 positive nodes, systemic therapy, whole-breast XRT (ACOSOG Z11 criteria)
  - If mastectomy and no XRT- axillary node dissection
Integration of Preoperative Systemic Therapy with Nodal Staging and Management

General Indications/Considerations:
- Stage III breast cancer
- Large primary desiring BCT
- Documented node positive disease
SLNB After Preoperative Chemotherapy for cN0 Patients

- MD Anderson 1997-2007
- 3,746 clinically node negative patients with invasive breast cancer
  - 3,171 (85%) underwent surgery as first intervention
  - 575 (15%) underwent SLND after chemotherapy

SLN Identification Rates

- Overall 98.5%
- Surgery first 98.7%
- Chemotherapy first 97.4%

No impact of age, T size, histology, tumor location, biopsy type, surgery type

False Negative and Nodal Recurrence Rates

- **Surgery first**
  - 542 planned SLNB + ALND
  - 22 FN events = 4.1%
  - Nodal recurrence = 0.9%

- **Chemotherapy first**
  - 84 planned SLNB + ALND
  - 5 FN events = 5.9%
  - Nodal recurrence = 1.2%

P=NS