## EVOLVING TRENDS IN PATHOLOGIC EVALUATION OF AXILLARY LYMPH NODES IN BREAST CANCER

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## AXILLARY LYMPH NODE STATUS AND BREAST CANCER

- Identifies nodal metastasis
- Aids in regional control
- Guides treatment decisions
  - Systemic Therapy
  - Radiation Therapy
- Provides prognostic information

## PATHOLOGICAL EVALUATION OF AXILLARY LYMPH NODES

- Preoperative evaluation
- Intraoperative evaluation
- Final histopathological examination
EVALUATION OF LOCO-REGIONAL LYMPH NODE STATUS FOR INITIAL STAGING OF BREAST CANCER

ROLE OF US-GUIDED NEEDLE BIOPSY

- Increases the sensitivity and specificity of US examination
- Provides a more definite diagnosis than US alone

TWO CHOICES FOR NEEDLE BIOPSY

- US-GUIDED FNA
- US-GUIDED CNB

Preoperative Staging of Locoregional Lymph Nodes in Breast Cancer

META-ANALYSIS OF PREOPERATIVE US-GUIDED NEEDLE BIOPSY OF AXILLARY LYMPH NODES FOR INITIAL STAGING

FNA and CNB: SIMILAR IN PERFORMANCE

Houssami N et al; Ann Surg 254, 2011

PRE-OPERATIVE NEEDLE BIOPSY OF LOCO-REGIONAL LYMPH NODES FOR INITIAL STAGING OF BREAST CARCINOMA

Comparison of US-guided FNA vs CNB

<table>
<thead>
<tr>
<th></th>
<th>FNA</th>
<th>CNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72.5%</td>
<td>88.2%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PPV</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>NPV</td>
<td>81.7%</td>
<td>91.2%</td>
</tr>
</tbody>
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Rautianen S et al Radiology 10;2013
ROLE OF US-GUIDED FNA OF LOCO-REGIONAL LYMPH NODES IN PATIENTS SELECTED FOR NEOADJUVANT CHEMOTHERAPY

- Accurate staging of cancer before initiating neoadjuvant chemotherapy
- Provides baseline for evaluating response in LNs with metastasis
- Allows much faster marking of LNs positive for metastatic tumor than CNB and TP

IMMEDIATE ASSESSMENT IS VALUABLE

US-GUIDED FNA OF A MALIGNANT LYMPH NODE

US-GUIDED FNA OF AN INDETERMINATE LYMPH NODE
SENTINEL LYMPH NODES IN BREAST CANCER

MAJOR REVOLUTION IN THE SURGICAL TREATMENT OF EARLY BREAST CANCER

SENTINEL LYMPH NODE MAPPING

- PREFERRED METHOD OF LYMPH NODE STAGING FOR STAGE I TO STAGE II CLINICALLY NODE NEGATIVE INVASIVE BREAST TUMOR
- SAMPLING LYMPH NODES MOST LIKELY TO CONTAIN METASTATIC CARCINOMA
- SAFE, FEASIBLE, ACCURATE, REDUCED MORBIDITY

LYMPHATIC MAPPING AND SLN BIOPSY IN BREAST CANCER

- Lymphoscintigraphy using 99mTc sulfur colloid
- Identification of lymphatic channels using lymphazurin 1% (Isosulfan blue): blue dye technique
<table>
<thead>
<tr>
<th>SENTINEL LYMPH NODES IN BREAST CANCER</th>
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</thead>
<tbody>
<tr>
<td>• Strong predictor of the presence or absence of metastases in non-SLN.</td>
</tr>
<tr>
<td>• Sensitive and specific for predicting regional lymph node status resulting in accurate staging of axilla</td>
</tr>
<tr>
<td>• Avoids the morbidity of complete axillary dissection</td>
</tr>
<tr>
<td>Paresthesia, numbness, lymphedema, chronic pain</td>
</tr>
<tr>
<td>SENSITIVITY: 93% - 99%</td>
</tr>
<tr>
<td>FALSE NEGATIVE RATE: 5% - 11%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>LYMPHATIC MAPPING IN PATIENTS WITH BREAST CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with palpable and non-palpable breast T1 and T2 invasive tumors, clinically node negative</td>
</tr>
<tr>
<td>• Patients with prior excisional biopsy</td>
</tr>
<tr>
<td>• Patients with multicentric invasive carcinoma</td>
</tr>
<tr>
<td>• Male breast cancer</td>
</tr>
<tr>
<td>• Older/obese patients</td>
</tr>
<tr>
<td>• DCIS if mastectomy or immediate reconstruction planned or large sized with high nuclear grade</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LYMPHATIC MAPPING IN PATIENTS WITH BREAST CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT RECOMMENDED:</td>
</tr>
<tr>
<td>• Large or locally advanced T3 or T4 invasive breast tumor</td>
</tr>
<tr>
<td>• Inflammatory breast cancer</td>
</tr>
<tr>
<td>• DCIS when conservative surgery performed</td>
</tr>
<tr>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>
SENTINEL LYMPH NODE MAPPING IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY

- BEFORE OR AFTER CHEMOTHERAPY IN CLINICALLY NODE NEGATIVE PATIENTS
- CAN AVOID COMPLETION OF AXILLARY DISSECTION IF FOUND NEGATIVE

PERFORMED IN SELECTED PATIENTS WHO RECEIVE NEOADJUVANT CHEMOTHERAPY
FALSE NEGATIVE RATE: 15% - 30%
ACOSOG Z1071 TRIAL: 12.8%
SENTINA TRIAL: 14.2%

MEASUREMENT OF METASTATIC TUMOR IN LYMPH NODES

- MACROMETASTASIS: >2MM
- MICROMETASTASIS: >0.2MM AND ≤ 2MM
- ISOLATED TUMOR CELLS: ≤ 0.2MM

MEASUREMENT OF METASTASIS?
REGIONAL NODAL CLASSIFICATION
BREAST CANCER
AJCC CANCER STAGING MANUAL 7TH EDITION

- Measure the largest dimension of any group of cells that are touching one another confluent or contiguous tumor cells
- When there are multiple tumor deposits, the size of the largest contiguous deposit is used to classify
- If there is stromal reaction measure tumor + stromal reaction to determine size.
- When a single case contains multiple positive lymph nodes and the largest tumor deposit in each node is categorically distinct, the number of nodes in each category - recorded

REGIONAL NODAL CLASSIFICATION IN BREAST CANCER
AJCC CANCER STAGING MANUAL 7TH EDITION

ISOLATED TUMOR CELL CLUSTERS
Small clusters of cells not greater than 0.2mm in largest dimension
OR
Single cells with little if any stromal reaction
- Detected by routine histology or immunohistochemical methods
- Nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node section

ITCs IN SENTINEL LYMPH NODES
### Micrometastases
- Tumor deposits greater than 0.2mm but not greater than 2.0mm in largest dimension
- More than 200 individual tumor cells identified as single dispersed tumor cells or as a nearly confluent or spherical focus in a single histologic section
- Threshold of 200 cells in a single cross section is a guideline to help pathologists distinguish between ITC and micrometastases

### REGIONAL NODAL CLASSIFICATION IN BREAST CANCER

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastases identified histologically</td>
</tr>
<tr>
<td>pN0(i-)</td>
<td>No regional lymph node metastases histologically, negative IHC</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>Malignant cells in regional lymph node(s) no greater than 0.2mm (detected by H&amp;E or IHC including ITC, &lt;200 tumor cells)</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastases histologically negative molecular findings (RT-PCR)</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>Positive molecular findings (RT-PCR), but no regional lymph node metastases by histology or IHC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Metastases to movable ipsilateral level I, II axillary lymph nodes</td>
</tr>
<tr>
<td>pN1</td>
<td>Micrometastases; or metastases detected by SLN biopsy, not clinically detected</td>
</tr>
<tr>
<td>pN1mi</td>
<td>Micrometastases (greater than 0.2mm and/or more than 200 cells but none greater than 2.0mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastases in 1 to 3 axillary lymph nodes, at least one metastasis is greater than 2.0mm</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastases in internal mammary nodes with micrometastases or macrometastases detected in SLNs</td>
</tr>
<tr>
<td>pN1c</td>
<td>Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLN biopsy</td>
</tr>
</tbody>
</table>
GROSS PATHOLOGIC EVALUATION OF AXILLARY SLNs IN BREAST CANCER

<table>
<thead>
<tr>
<th>Gross Dimension</th>
<th>Color, Radioactive count in vivo/in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisect if &lt; 0.5 cm</td>
</tr>
<tr>
<td></td>
<td>If &gt; 0.5 cm serially slice at 2 mm intervals</td>
</tr>
</tbody>
</table>

INTRAOPERATIVE EVALUATION OF AXILLARY SENTINEL LYMPH NODES

- Gross Inspection
- Imprint Cytology
- Scrape Cytology
- Frozen Section
- Cytology and Frozen Section
- Molecular testing

CONSIDERED OPTIONAL
NOT MANDATORY

Touch Preparation
IMPRINT CYTOLOGY OF SENTINEL LYMPH NODES

**Advantages:**
- Simple, easy
- No loss of tissue
- No loss of micrometastasis
- Sample both surfaces of a LN section

**Disadvantages:**
- Samples fewer cells
- Cytology expertise
- Screening time
- Technique dependent
**FROZEN SECTION OF SENTINEL LYMPH NODES**

<table>
<thead>
<tr>
<th>Advantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conventional Method</td>
</tr>
<tr>
<td>• Preserved architecture</td>
</tr>
<tr>
<td>• Allows measurement of size of metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of tissue in cryostat</td>
</tr>
<tr>
<td>• Potential loss of micrometastasis</td>
</tr>
<tr>
<td>• Introduction of freezing artifacts</td>
</tr>
<tr>
<td>• Fatty LN, difficult to cut</td>
</tr>
</tbody>
</table>

Frozen Section
INTRAOPERATIVE EVALUATION OF SLNs IN BREAST CANCER

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Macrometastases</th>
<th>Micrometastases</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPRINT CYTOLOGY - 31 studies</td>
<td>63%</td>
<td>81%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>FROZEN SECTION - 47 studies</td>
<td>78%</td>
<td>94%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Specificity - 99 – 100%</td>
<td></td>
<td></td>
<td></td>
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Intraoperative Evaluation of Sentinel Lymph Nodes in Breast cancer

Support the surgeons in the decision making regarding completion of axillary dissection

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Touch Preparation</th>
<th>Frozen Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve Meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>63% (31)</td>
<td>78% (47)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>S/P Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>38-100 %</td>
<td>74-79%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98-100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

INTRAOPERATIVE EVALUATION OF AXILLARY SNLs IN BREAST CANCER

IC Approximately equivalent for detecting macrometastasis

Neither is reliable for detecting micrometastasis

FS better than TP for detecting micrometastasis

FS can provide size of metastasis
**POTENTIAL PITFALLS**

**False Positive**
- Fragments of lymphoid follicle with germinal center
- Histiocytes
- Endothelial Cells
- Floaters from staining bath
- Dendritic reticulum cells
- Nevus cells
- Benign epithelial inclusion
- Megakaryocytes from extramedullary hematopoiesis

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**Lymph Node Cutter**

**Step 1**
Place the cutter between the guides on the base at a 45 degree angle relative to the sample holder.

**Step 2**
Slice through the lymph node.

**Step 3**
Remove the node slices from between the blades.

Sysmex Japan

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**ONE STEP NUCLEIC ACID AMPLIFICATION (OSNA) ASSAY**

- **Walk-away Automation**
- **Results in ~30 minutes**
- **On-board Disposables**

**MEASUREMENT OF CK19 mRNA**
Sysmex real time analyzer
### OSNA RESULT INTERPRETATION

<table>
<thead>
<tr>
<th>Concentration (COPIES/ml)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 250</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>≥ 250</td>
<td>POSITIVE (+)</td>
</tr>
<tr>
<td>≥ 5,000</td>
<td>POSITIVE (++)</td>
</tr>
</tbody>
</table>

**MICROMETASTASIS** = +  
**MACROMETASTASIS** = ++

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### OSNA FOR EVALUATION OF AXILLARY SLNs IN BREAST CANCER

**OVERALL PERFORMANCE**

- **3631 SLNs analyzed**
- **Sensitivity** – 91.7%
- **Specificity** – 97.0%
- **Positive Predictive Value** – 85.8%
- **Negative Predictive Value** – 98.3%
- **False negative rate** – 8.3%
- **False reassurance rate** – 1.7%

*Cserni G, J Clin Pathol, 2012*

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### PATHOLOGIC EVALUATION OF AXILLARY LYMPH NODES IN BREAST CANCER

- **AVAILABILITY OF STANDARDISED MOLECULAR TESTING WHICH IS COMPARABLE TO HISTOLOGIC EVALUATION**
- **OBJECTIVITY IN CUTTING AND TESTING**
- **CAN OVERCOME CURRENT UNDERESTIMATION OF EVALUATION OF AXILLARY LYMPH NODES**
- **MOLECULAR TESTING MAY HAVE A ROLE FOR INTRAOPERATIVE AND COMPREHENSIVE EVALUATION OF AXILLARY LYMPH NODES**

**CURRENTLY INVESTIGATIONAL**
### REGIONAL NODE CLASSIFICATION
AJCC CANCER STAGING MANUAL
7TH EDITION

**DETECTION OF MACROMETASTASES**
METASTASES LARGER THAN 2MM
- First priority in pathologic evaluation of lymph nodes
- Entire lymph node to be submitted
- Larger nodes should be bisected or thinly sliced no thicker than 2mm
- A single histologic section of each slice has high probability of detecting all macrometastases

### CURRENT ASCO CLINICAL PRACTICE
GUIDELINES FOR SLN BIOPSY IN PATIENTS
WITH EARLY STAGE BREAST CANCER

- SLNs sectioned at no more than 2.0mm thickness
- A single H&E section should be prepared.
- CK IHC not regarded as a routine requirement

Lyman GH et al J CO, 32, 2014
WHY IS MEASUREMENT OF METASTASIS IN SLNs IMPORTANT

- Uniformity in reporting
- Accurate TNM staging
- Implications for management
- Ascertaining prognosis
EVOLUTION IN THE MANAGEMENT OF AXILLA: IS ALND NEEDED IN ALL PATIENTS WITH POSITIVE SLNs IN EARLY STAGE BREAST CANCER?

- ACOSOG Z0011
- EORTC 10981-22023 AMAROS (After mapping of the axilla, Radiotherapy or Surgery)
- IBCSG 23-01

ALND CAN BE AVOIDED IN PATIENTS WITH 1-2 POSITIVE SENTINEL LYMPH NODES WHO RECEIVE WHOLE BREAST RADIATION AND ADJUVANT SYSTEMIC THERAPY

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**AMERICAN COLLEGE OF SURGEONS ONCOLOGY GROUP**

**ACOSOG Z0011 TRIAL**

- Randomized Patients: N=891
- ALND Arm: N=445
- SLND only Arm: N=446
- Prior to surgery: 25 patients withdrew
- Intent-to-Treat Sample: 32 patients did not have ALND
- Treatment Received Sample: 11 patients had ALND
- NO DIFFERENCE IN LOCAL-REGIONAL RECURRENCES OR SURVIVAL


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**AMERICAN COLLEGE OF SURGEONS ONCOLOGY GROUP**

**ACOSOG Z0011 TRIAL**

- SENTINEL LYMPH NODE DISSECTION ALONE CAN OFFER EXCELLENT REGIONAL CONTROL EVEN WITH UP TO 2 POSITIVE LYMPH NODES
- SLN BIOPSY PROVIDES NECESSARY STAGING INFORMATION TO DIRECT ADJUVANT THERAPY AND MAY BE THERAPEUTIC
- REASONABLE MANAGEMENT FOR SELECTED PATIENTS WITH EARLY STAGE BREAST CANCER TREATED WITH BREAST CONSERVING THERAPY AND ADJUVANT SYSTEMIC THERAPY

**AMERICAN COLLEGE OF SURGEONS**  
**ONCOLOGY GROUP**  
**ACOSOG Z0011 TRIAL**

**NOT APPLICABLE**  
PALPABLE NODAL DISEASE  
SLN BIOPSY REVEALS EXTENSIVE METASTASES  
PATIENTS UNDERGOING MASTECTOMY  
PATIENTS RECEIVING PARTIAL BREAST IRRADIATION


**IMPLICATIONS OF ACOSOG Z-11 RESULTS**  
**AXILLARY DISSECTION**

**AVOIED:**  
T1/T2 Breast Cancer with 1-2 positive SLNs undergoing breast conserving surgery, selected for whole breast radiation and adjuvant systemic therapy  

**CONSIDER:**  
Premenopausal patients with ER negative diseases  
Metastatic Lobular Cancer

**CHANGE IN PRACTICE AT MDACC**

**BEFORE Z0011:**  
85% OF SLND + = ALND  

**AFTER Z0011:**  
24% OF SLND + = ALND  

**INTRAOPERATIVE EVALUATION:**

**BEFORE Z0011:** 69%  
**AFTER Z0011:** 26%  

MICROMETASTASES OR ISOLATED TUMOR CELLS IN SLNs AND THE OUTCOME OF BREAST CANCER

NETHERLAND STUDY

N=856 NODE NEGATIVE NO ADJUVANT THERAPY

N=856 ITC OR MICROMET NO ADJUVANT THERAPY

N=995 ITC OR MICROMET ADJUVANT THERAPY

FOLLOW UP-5.1 years

Maaike de Boer et al NEJM, 2009

IMPACT OF ISOLATED TUMOR CELLS AND MICROMETASTASES IN SLNs AND PROGNOSIS OF BREAST CANCER

Maaike de Boer et al NEJM, 2009

IMPACT OF ADJUVANT THERAPY ON MINIMAL VOLUME DISEASE IN AXILLARY SENTINEL LYMPH NODES

Maaike de Boer et al NEJM, 2009
MICROMETASTASES OR ISOLATED TUMOR CELLS AND THE OUTCOME OF BREAST CANCER

ITC or MICROMETASTASES

SLIGHTLY REDUCED 5 year Disease free Survival only in patients who did not receive adjuvant therapy

Maaike de Boer et al. NEJM, 2009

OCCULT METASTASES IN NODE-NEGATIVE BREAST CANCER

National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32

SLNs negative for metastasis

H&E At two levels
CK IHC
Occult metastases 15.9%
(3887 patients) (95% CI = 14.7-17.1)

Weaver DL et al., New Engl J Med 2011

OCCULT METASTASES IN NODE NEGATIVE BREAST CANCER

NSABP B-32 TRIAL

Occult Metastases Present Absent

Significant Differences
Overall Survival
Disease – free survival
Distant-disease-free survival
FIVE YEAR SURVIVAL
94.6% 95.8%

### OCCULT METASTASES IN NODE NEGATIVE BREAST CANCER

**NSABP B 32 TRIAL**

**Independent prognostic variable**

**Difference in outcome at 5 years**

- SMALL (1.2%)
- No clinical benefit of additional evaluation including IHC testing

Weaver DL et al, New Engl J of Med 2011

### CYTOKERATIN IHC OF SLNs

- Facilitates scanning of LN section
- Enhances detection of micrometastases and ITCs
- Detection of micrometastases or ITCs does not predict recurrence or improved survival
- Strategies to enhance their detection are not necessary or required
- IHC useful for confirmation or exclusion of suspicious findings for metastasis

Lyman et al, JCO, 32, 2014

Weaver D and Turner R

### EVOLUTION IN THE MANAGEMENT OF AXILLA: IS ALND NEEDED IN ALL PATIENTS WITH POSITIVE SLNs WHO RECEIVE NEOADJUVANT THERAPY?

- 40%-75% will have eradication of disease in lymph nodes
- Restage axilla after chemotherapy
- Can ALND be avoided in selected patients with good response?

MDACC CLINICAL TRIALS – TARGETED AXILLARY DISSECTION

NSABP-51/RTOG 1304 TRIALS

ALLIANCE A11202 TRIAL
TARGETED AXILLARY DISSECTION

- Patients selected for neoadjuvant chemotherapy with ALN positive by FNA/CNB before initiation of chemotherapy
- Positive lymph node marked with a marker clip
- Targeted removal of the clipped lymph node
- CAN THE CLIPPED LYMPH NODE AS A SURROGATE OF NON-CLIPPED LYMPH NODES?

PATHOLOGICAL EVALUATION

TARGETED AXILLARY DISSECTION

Feasibility of removing clipped lymph nodes separately
Needle localized or Radioactive seed localized

- Radiograph of the lymph node to document retrieval of Radioactive seed and visualization of marker clip
- Documentation of the status of the clipped lymph node
- Evaluation of the pathological status of the clipped lymph node with that of the remaining lymph nodes

CLIPPED AXILLARY LYMPH NODE
TARGETED AXILLARY DISSECTION

Evaluation of the pathological status of clipped axillary lymph node with other lymph nodes from axillary dissection

Radiograph of Axillary contents to identify the clipped lymph node

- Retrieval of the clipped lymph node and sampling separately
- Evaluation of the pathological status of the clipped lymph node with that of the remaining lymph nodes
**IMPLICATIONS OF THE EVOLVING CHANGES IN AXILLARY NODAL STAGING IN PATIENTS WITH BREAST CANCER**

- Majority of the needed pathological information to make treatment decisions obtained from standard of care pathology practice
- Radiograph of lymph node or axillary contents
- Documentation of the pathological status of the clipped lymph node separately to compare the status of the clipped lymph nodes with the remaining nodes

**INCORPORATION IN CLINICAL PRACTICE**

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**MIMICKERS OF METASTATIC BREAST CARCINOMA IN AXILLARY SLN/Non-SLN LYMPH NODES**

- Benign Epithelial Rests
- Ectopic breast lobule
- Squamous inclusion cysts
- Benign apocrine or ciliated gland - endosalpingiosis
- Nevus cell aggregates

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**? BENIGN MECHANICAL TRANSPORT**

- Lymphatic transport of epithelial cells: displaced by biopsy of the primary tumor : FNA or CORE BIOPSY
- Breast massage assisted SLN localization
- False positive findings in the SLNs

**CANNOT DISTINGUISH DISPLACED TUMOR CELLS FROM METASTASIS**
PATHOLOGIC EVALUATION OF NON-SENTINEL LYMPH NODES IN BREAST CANCER

- Axillary fat to be dissected for identifying lymph nodes ~ fresh
- Evaluation of at least 10 lymph nodes
- All identified lymph nodes to be submitted for histologic evaluation
- Lymph nodes > 0.5 cm to be bisected and if > 1.0 cm sectioned into multiple slices
- Accurate recording of lymph nodes submitted in cassettes
- In post neoadjuvant setting lymph node yield can be reduced

COMPLETE AXILLARY LYMPH NODE DISSECTION

Nomograms to help quantify the risk of non-SLN involvement and potential benefit of CALND

- Age
- Tumor size
- Lymphovascular invasion
- Hormone receptor status
- Size of SLN metastasis
- Number of positive SLN nodes
- Extranodal extension

EVALUATION OF SENTINEL AND NON-SENTINEL LYMPH NODES IN BREAST CANCER

- Make every attempt to detect macrometastases in SLNs
- Slicing SLNs thin at 2mm intervals
- Intraoperative evaluation only in selected patients:
  - Mastectomy
  - ER negative
  - Partial breast radiation
  - Neoadjuvant chemotherapy
- Grossly negative non-sentinel lymph nodes
  - Multiple slices entirely submitted
<table>
<thead>
<tr>
<th>EVALUATION OF SENTINEL AND NON-SENTINEL LYMPH NODES IN BREAST CANCER</th>
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<tbody>
<tr>
<td>• Cytokeratin immunostaining in selected patients</td>
</tr>
<tr>
<td>• No added incentive to detect ITCs and micrometastases particularly in SLNs in patients expected to receive adjuvant therapy</td>
</tr>
<tr>
<td>• Clinical trials for targeted axillary dissection particularly for patients receiving neoadjuvant chemotherapy</td>
</tr>
<tr>
<td>• UNDERSTANDING BIOLOGY OF METASTATIC TUMOR- PERSONALIZED TREATMENT</td>
</tr>
<tr>
<td>Prediction of aggressive behavior</td>
</tr>
<tr>
<td>Resistance/ Response to therapy</td>
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