EVALUATION OF AXILLARY LYMPH NODES AFTER NEOADJUVANT SYSTEMIC THERAPY

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Axillary lymph node metastasis is one of the most important prognostic factors in breast cancer.

- as an indicator of poor prognosis.
- with the 5-year survival decreasing by approximately 28% to 40% in patients with such a condition.

Preoperative identification of LNM in the axilla

- The surgical approach:
  - Axillary lymph node dissection
  - Neoadjuvant chemotherapy
NSABP B-04 TRIAL

- The aggressive axillary surgery for breast cancer patients with negative axillary lesions does not improve the overall survival of the patients
  - Routine ALND for patients with a clinically node-negative axilla is unnecessary
  - Removing healthy lymph nodes renders no benefit on OS

![Graphs showing cumulative incidence and relapse-free survival](image-url)
ALND provided **no survival benefit** over less invasive SLN dissection during a 6-year follow-up period in a selected cohort of patients with clinical T1–T2 invasive breast cancer, who had no palpable adenopathy and one or two biopsy-proven metastatic sentinel lymph nodes.
Identification of an SLN (lymph node that initially harbored cancer) by lymphatic mapping after NAC can be difficult because obstructions occur from live or necrotic tumor emboli from the tumor itself and/or fibrosis of lymphatic channels from chemotherapy.
The increasing use of neoadjuvant chemotherapy (NAC) for operable breast cancer has raised questions about optimal local therapy for the axilla.

- **The poor identification rate of SLN** due to possible alteration of lymphatics as a result of NAC.

- **The high false negative rate** because upfront chemotherapy may show different effects on sentinel and non-sentinel nodes;
  - The malignancy may be eradicated in sentinel nodes, while residual disease may persist in non-sentinel nodes.
SLNB AFTER NAC IN CLINICALLY NEGATIVE AXILLA

- SLNB in patients with cN0 axilla before NAC (n=980) and post-NAC (n=203).
  - SLN identification rate: 98% before NAC and 95% after NAC (p = 0.032)
- Patients who underwent SLNB after NAC had a higher chance of having negative SLN than those who underwent SLNB before NAC (67% vs. 54%, p=0.001) and had lesser chance of undergoing ALND (33% vs. 45%, p=0.006).
- SLNB after NAC in patients with cN0 axilla is a feasible treatment option, and additional axillary treatment is not necessary in those with negative SLN.
THE ACOSOG Z1071 TRIAL

- the utility of SLNB in the treatment of patients with bx-proven node(+) disease who underwent NAC(T0–T4,N1–N2,M0)
- phase 2 study of the clinical efficacy of substituting SLNB for ALND; false-negative rate (FNR) of SLNB, 10% of goal

- Boughey SABCS 2012: 31.5% FNR with one SLN
- Boughey JAMA 2013: 21.1% FNR with 2 SLN and single agent
Studies evaluating the IDENTIFICATION RATE & FALSE-NEGATIVE RATE among patients with **CLINICALLY NODE-POSITIVE DISEASE** undergoing SLNB following NAC

<table>
<thead>
<tr>
<th>Study</th>
<th>ACOSOG Z1071</th>
<th>SENTINA</th>
<th>SN FNAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Single arm</td>
<td>4 Arms</td>
<td>Single arm</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>756</td>
<td>Arm C (592)</td>
<td>153</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>T0-4, N1-2, M0</td>
<td>N1-2, M0</td>
<td>N1-2, M0</td>
</tr>
<tr>
<td>cN0 after NAC</td>
<td>100(^a)</td>
<td>83</td>
<td>Unknown(^a)</td>
</tr>
<tr>
<td><strong>SLN identification rate (%)</strong></td>
<td>92.9</td>
<td>80.1</td>
<td>87.6</td>
</tr>
<tr>
<td><strong>False negative rate (%)</strong></td>
<td>12.6</td>
<td>14.2</td>
<td>9.6</td>
</tr>
<tr>
<td>2 SLNs</td>
<td>21.1</td>
<td>18.5</td>
<td>4.9 (≥2 SLNs)</td>
</tr>
<tr>
<td>≥3 SLNs</td>
<td>9.1</td>
<td>7.3</td>
<td>-</td>
</tr>
<tr>
<td>Dual tracer technique</td>
<td>10.8</td>
<td>8.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Inclusion of ypN0(i+)</td>
<td>8.7</td>
<td>-</td>
<td>8.4</td>
</tr>
</tbody>
</table>

\(^a\) Ultrasound performed in all patients.
\(^b\) False-negative rate excluding immunohistochemically detected isolated tumor cells.
IN CURRENT CLINICAL PRACTICE, POSSIBLE ALGORITHM FOR AXILLARY STAGING IN PATIENTS WITH INVASIVE BREAST CANCER

T1 or T2 Breast Cancer

- Palpable Axillary nodes
  - FNA by Palpation or US Biopsy
    - +/- Ultrasound
      - Negative: SLNB
      - Positive: ALND

- No Palpable Nodes
  - Ultrasound
    - Suspicious: US biopsy
      - Negative: SLNB
      - Positive: ALND
    - Not suspicious: SLNB
### US FINDINGS OF AXILLARY LN - CORRELATED WITH FINAL SURGICAL RESULTS

<table>
<thead>
<tr>
<th>Cortical features</th>
<th>Surgical Results</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Thin</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Thick or lobular</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Hilar features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Eccentric</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Completely replaced</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

**Maximal cortical thickness ≥ 2.3mm**

Deurloo 2003 EJC
Koelliker et al  Radiology 2008
## Suspicious MR Findings of Axillary Nodal Metastases

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>SN (%)</th>
<th>SP (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irregular margin</strong></td>
<td>41.2</td>
<td>95.2</td>
<td>77.8</td>
</tr>
<tr>
<td><strong>Cortex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous</td>
<td>29.4</td>
<td>16.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Inhomogeneous</td>
<td>47.1</td>
<td>90.5</td>
<td>66.7</td>
</tr>
<tr>
<td>Nodular thickening</td>
<td>23.5</td>
<td>92.9</td>
<td>57.1</td>
</tr>
<tr>
<td><strong>Hilus sign</strong></td>
<td>52.9</td>
<td>4.3</td>
<td>20.0</td>
</tr>
<tr>
<td><strong>Perifocal edema</strong></td>
<td>29.4</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Rim sign</strong></td>
<td>23.5</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Asymmetry</strong></td>
<td>76.7</td>
<td>85.7</td>
<td>68.4</td>
</tr>
</tbody>
</table>
### Meta-analysis

<table>
<thead>
<tr>
<th>US criteria</th>
<th>Palpable</th>
<th>Non-palpable</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>size</td>
<td>+</td>
<td>+</td>
<td>69.2 (63.4–74.6)</td>
<td>75.2 (70.4–79.6)</td>
</tr>
<tr>
<td>morph</td>
<td>+</td>
<td>+</td>
<td>71.0 (65.2–76.3)</td>
<td>86.2 (82.6–89.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCE</td>
<td>Kvistad et al. 2000</td>
<td>Hieken et al. 2013</td>
<td>12.0% - 61.4%</td>
</tr>
<tr>
<td></td>
<td>Orguc et al. 2012</td>
<td>Abe et al. 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>He et al. 2012</td>
<td>An et al. 2014</td>
<td></td>
</tr>
</tbody>
</table>
IN CURRENT CLINICAL PRACTICE, POSSIBLE ALGORITHM FOR AXILLARY STAGING IN PATIENTS WITH INVASIVE BREAST CANCER

- **No Palpable Nodes**
  - Ultrasound/MR
    - **Suspicious**
      - US biopsy
        - Negative
          - SLNB
          - Negative
          - Chemotherapy
        - Positive
          - ALND
          - SLNB
          - Positive
    - Not suspicious
      - SLNB
      - Chemotherapy
      - Ultrasound/MR
- Imaging Evaluation of Axillary Lymph Nodes after Neoadjuvant Systemic Therapy
- How to improve the performance of Sentinel Node Biopsy after Neoadjuvant Chemotherapy: Targeted axillary dissection
IMAGING EVALUATION OF AXILLARY LYMPH NODES AFTER NEOADJUVANT SYSTEMIC THERAPY
Lymph node features on axillary ultrasound (US) images obtained after neoadjuvant chemotherapy associated with residual nodal disease:
- Increased cortical thickness (mean, 3.5 mm for node-pos vs 2.5 mm for node-neg)
- Longer short-axis diameter, longer long-axis diameter, absence of fatty hilum

Axillary US performed after neoadjuvant chemotherapy is useful for nodal response assessment, with longer short-axis diameter, longer long-axis diameter, increased cortical thickness, and absence of fatty hilum significantly associated with residual nodal disease after neoadjuvant chemotherapy.
AXILLARY ULTRASOUND IDENTIFIES RESIDUAL NODAL DISEASE AFTER CHEMOTHERAPY: RESULTS FROM THE ACSOG Z1071 TRIAL (ALLIANCE)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>PPV for residual</th>
<th>Odds Ratio for PCRn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node not seen</td>
<td></td>
<td>58%</td>
<td>Ref</td>
</tr>
<tr>
<td>Type I</td>
<td>no visible cortex</td>
<td>56%</td>
<td>1.07</td>
</tr>
<tr>
<td>Type II</td>
<td>a hypoechoic cortex $\leq$ 3 mm</td>
<td>56%</td>
<td>1.06</td>
</tr>
<tr>
<td>Type III</td>
<td>a hypoechoic cortex $&gt; 3$ mm</td>
<td>59%</td>
<td>0.94</td>
</tr>
<tr>
<td>Type IV</td>
<td>a generalized lobulated hypoechoic cortex</td>
<td>80%</td>
<td>0.35</td>
</tr>
<tr>
<td>Type V</td>
<td>focal hypoechoic cortical lobulation</td>
<td>68%</td>
<td>0.65</td>
</tr>
<tr>
<td>Type VI</td>
<td>a totally hypoechoic node with no hilum</td>
<td>80%</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Z1071 Pts with T0-4, N1-2, M0 BC underwent AUS after NAC

- The SLN FNR was not different based on AUS result
- The use of SLNB only when sonographic findings were negative, potentially reduce the FNR in Z1071 patients with 12.6% to 9.8%
- Preop/afterchemo AUS results are considered as part of SLN surgery.
SENTINEL NODE BIOPSY AFTER NEOADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE BREAST CANCER: DOES AXILLARY ULTRASOUND IMPROVE PERFORMANCE?

- Question whether AUS has anything to do with it.
  - Among negative AUS, the FNR of SLN biopsy was 15% (28 of 187)
  - Among positive AUS, the false-positive rate of AUS was 29% (39 of 138 patients)

- An abnormal AUS post-NAC is not sufficient for proceeding to ALND.
THE DIAGNOSTIC PERFORMANCE OF BREAST MRI FOR AXILLARY NODAL STAGING AFTER NAC

- A retrospective review using single institutional cancer registry.
- 135 Patients who started NAC from 2005 to 2010 with clinically node positive disease

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Total MRI, n = 135</th>
<th>Luminal, n = 73</th>
<th>HER2+, n = 34</th>
<th>TN, n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive, n (%)</td>
<td>42 (31)</td>
<td>18 (25)</td>
<td>9 (27)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>True negative, n (%)</td>
<td>23 (17)</td>
<td>8 (11)</td>
<td>11 (32)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>False positive, n (%)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>False negative, n (%)</td>
<td>67 (50)</td>
<td>47 (64)</td>
<td>13 (38)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>39</td>
<td>28</td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>88</td>
<td>100</td>
<td>92</td>
<td>67</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>93</td>
<td>100</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>26</td>
<td>15</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>48</td>
<td>36</td>
<td>59</td>
<td>68</td>
</tr>
</tbody>
</table>

PREOPERATIVE AXILLARY LYMPH NODE EVALUATION IN BREAST CANCER PATIENTS BY BREAST MAGNETIC RESONANCE IMAGING (MRI): *DIAGNOSTIC PERFORMANCE OF MRI ACCORDING TO NAC*

<table>
<thead>
<tr>
<th></th>
<th>Overall (%)</th>
<th>No-NAC (%)</th>
<th>NAC (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>51.3 (60/117)</td>
<td>51.7 (30/58)</td>
<td>50.8 (30/59)</td>
<td>0.911</td>
</tr>
<tr>
<td>Specificity</td>
<td>92.2 (284/308)</td>
<td>90.9 (229/252)</td>
<td>98.2 (55/56)</td>
<td>0.001</td>
</tr>
<tr>
<td>PPV</td>
<td>71.4 (60/84)</td>
<td>56.5 (30/53)</td>
<td>96.8 (30/31)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NPV</td>
<td>83.3 (284/341)</td>
<td>89.1 (229/257)</td>
<td>65.5 (55/84)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Advance (pN2/3)**

<table>
<thead>
<tr>
<th></th>
<th>Overall (%)</th>
<th>No-NAC (%)</th>
<th>NAC (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SN w/ cN1-3</td>
<td>80.0 (24/30)</td>
<td>91.7 (11/12)</td>
<td>83.3 (15/18)</td>
<td></td>
</tr>
<tr>
<td>SN w/ cN2-3</td>
<td>36.7 (11/30)</td>
<td>33.3 (4/12)</td>
<td>38.9 (7/18)</td>
<td></td>
</tr>
<tr>
<td>NPV w/cN0</td>
<td>98.2 (335/341)</td>
<td>99.6 (256/257)</td>
<td>94.0 (79/84)</td>
<td>0.039</td>
</tr>
<tr>
<td>NPV w/cN0/1</td>
<td>95.3 (388/407)</td>
<td>97.4 (294/302)</td>
<td>89.5 (94/105)</td>
<td>0.017²²</td>
</tr>
</tbody>
</table>
Patients with advanced ALN metastases were more likely to have a higher number (≥2) of positive LNs (OR, 8.06; P = 0.015) on restaging MR imaging.

No clinico-pathological factors were significantly associated with advanced ALN metastases.

A higher number of positive ALNs on restaging MR imaging was an independent predictor for advanced ALN metastases after NAC.

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of positive ALNs on initial staging MR imaging</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>5.91</td>
<td>6.04</td>
<td>0.080</td>
</tr>
<tr>
<td><strong>Number of positive ALNs on restaging MR imaging</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>12.04</td>
<td>8.06</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Short diameter of the largest ALN on restaging MR imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7.7mm</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;7.7mm</td>
<td>5.00</td>
<td>4.44</td>
<td>0.063</td>
</tr>
</tbody>
</table>
The AUC and sensitivity of restaging MR imaging plus PET/CT was higher than that of each restaging MR imaging and PET/CT; however, the differences were not statistically significant (AUC, $P = 0.318$ and $P = 0.119$, respectively; sensitivity, $P = 0.500$ and $0.063$, respectively).
HOW TO IMPROVE THE PERFORMANCE OF SENTINEL NODE BIOPSY AFTER NAC
Targeted axillary dissection (TAD)

- Placing a clip in the positive lymph node could sole the high FNR?
  - 31.5 % FNR with one SLN in Z1071 trial

- Data from Z1071: the FNR in cases with placing a clip in the positive lymph node was lower than that using dual tracer technique (7.4% vs 10.8%)

Targeted axillary dissection

- After completion of NAC, the clipped node is localized by using a wire or radioactive seed

- During the SLND procedure, taking both all SLNs and clipped node with localization
IDENTIFICATION AND RESECTION OF CLIPPED NODE DECREASES THE FNR OF SLNB IN NAC PTS PRESENTING WITH NODE (+) BC results from ACOSOG Z1071 (ALLIANCE)

False-negative Rate by Clip Location and Patient Group Analyzed

<table>
<thead>
<tr>
<th>N</th>
<th>Residual Disease identified in SLNs or ALND, n (%)</th>
<th>FNR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 2SLNs removed and cN1 disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clip in SLN</td>
<td>107</td>
<td>59 (55.1)</td>
<td>6.8</td>
</tr>
<tr>
<td>Clip in ALND</td>
<td>34</td>
<td>21 (61.8)</td>
<td>19.0</td>
</tr>
<tr>
<td>Clip location unknown</td>
<td>29</td>
<td>21 (72.4)</td>
<td>14.3</td>
</tr>
<tr>
<td>Clip not placed</td>
<td>355</td>
<td>209 (59.0)</td>
<td>13.4</td>
</tr>
</tbody>
</table>

- 525 patients with cN1 disease and ≥2 SLNs confirmed
- 170 clip in LN vs 355 no clip in LN
Selective Surgical Localization of Axillary Lymph Nodes Containing Metastases in Patients With Breast Cancer

- The feasibility of image-guided localization and resection of lymph nodes containing known metastases.

- 12 patients with ALN-meta confirmed by FNA, who had a clip placed in the lymph node targeted for biopsy.
  - US guided wire–needle localization (n=2) & radioactive iodine I_{125} (n=10)

- Image-guided localization & selective removal were successful in all 12 patients.
  - 80%: the clipped node = one of the SLNs
  - 20%: the clipped node ≠ one of the SLNs

- Without clip-localization, the biopsy-proven metastatic axillary node with the clip would not have been included in surgery in these 20% of patients.

Caudle JAMA 2015
Targeted axillary dissection (TAD)

Clinically node-positive patients with NAC N=208

No SLNB N=74
No ALND N=16

Evaluable patients (SLNB + ALND) N=118

Pathologic node Negative
N=44 (37%)

- SLN negative = 7 of 69
- SLN not identified = 5

False-negative rate
SLNB alone 10.1% (95% CI 4.2 to 19.8)
p=0.03

Pathologic node Positive
N=74 (63%)

- Clipped node & SLNs negative N=1 of 74
- Clipped node + SLNB 1.4% (95% CI 0.03 to 7.3)

Caudle JCO 2016
Free from tumor

Metastatic carcinoma with perinodal soft tissue extension (1.2cm)

Metastatic carcinoma without perinodal soft tissue extension (500μm)
Charcoal Tattooing of Metastatic ALN followed by SLNB after NAC in Breast Cancers in YUHS
CHARCOAL TATTOOING OF METASTATIC ALN FOLLOWED BY SLNB AFTER NAC IN BREAST CANCERS IN YUHS
SLN 1
1st Hot LN ≠ Blue colored LN ≠ Tattoo LN

SLN 2
2nd Hot LN = Blue colored LN ≠ Tattoo LN

ALN 1
Cold LN = Tattoo LN ≠ Blue LN

Metastasis, diameter 13mm
### Results of SLNB and axillary surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final ALN status after NCT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (n=10)</td>
<td>Negative (n=10)</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-sentinel ALN (+)</td>
<td>Non-sentinel ALN (-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLNB</td>
<td>Positive</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>2</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Modified SLNB</td>
<td>Positive</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

a) Modified SLNB is the final results of hot or blue-colored sentinel lymph nodes and initial cytology-proven, charcoal-tattooed lymph node excised during axillary sampling procedure.
NAC is increasingly used for patients with operable breast cancer to allow more limited surgery in the breast and axilla.

However, the diagnostic performance of imaging evaluation after NAC is limited. It could be helpful to exclude advanced nodal disease, but not sufficient to replace SLNB.

A multidisciplinary approach is needed to evaluate re-staging of axillary lymph node after NAC, using imaging findings, tumor biology, and localization of proven metastatic lymph nodes.