Sentinel Node Biopsy: Before or After Neoadjuvant Chemotherapy?

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Clinical Rationale for Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy is the standard of care for patients with LABC and a reasonable alternative to adjuvant chemotherapy for those with large operable disease.

- Several RCTs have shown no differences in outcome between neoadjuvant and adjuvant chemotherapy.

- Achievement of pathologic complete response (pCR) correlates with excellent long-term outcome.
Neoadjuvant Chemotherapy for Operable BC
Loco-Regional Endpoints

- **High clinical response rates (>90%)**
- **Increase in the rates of lumpectomy**
- **Increasing pathologic complete response rates:**
  - 10-15% with anthracyclines
  - 25-30% with anthracyclines/taxanes
  - 40-50% with chemo + trastuzumab in HER-2 (+)
  - 50-60% with chemo + two anti-HER agents
- **Decrease in the rates of axillary positivity**
  - 30% with anthracyclines
  - Up to 40% with anthracyclines/taxanes
  - Probably > 50% with chemo + anti-HER-2 therapies
Individualizing Loco-Regional Therapy with Neoadjuvant Chemotherapy

Past Achievements

• Conversion of patients with inoperable tumors to operable candidates

• Conversion of mastectomy candidates to candidates for BCS

• Improvement in cosmesis by reducing the size of lumpectomy in BCS candidates with large tumors
Individualizing Loco-Regional Therapy with Neoadjuvant Chemotherapy

Future Promises

• Reduction in the extent of axillary surgery by down-staging involved axillary nodes (SNB)

• Reduction in the extent of L-R XRT by down-staging primary tumors and axillary nodes

• Potential for eliminating loco-regional therapy altogether with the use of more active regimens and/or with appropriate patient selection with biomarkers
Decreasing the Extent of Axillary Surgery With NC

- This concept is currently applicable to patients with operable breast cancer ($cT_{1-3} N_0-cN_1$)
- Most available data on the performance of SNB before or after NC have been obtained in patients with operable BC
- Feasibility and accuracy of SNB after NC is questionable in patients with LABC ($T_4$, $cN_2$, IBC)
Ultrasound of the axilla with FNA of indeterminate/suspicious nodes:
  - Simple, minimally invasive
  - Can provide useful clinical information (avoid SNB, demonstrate direct chemosensitivity)

Sentinel node biopsy before NC is controversial
SNB After NC
Feasibility and Accuracy

- Information from:
  - Single institution trials
  - Multicenter trials
  - Meta-analysis
Limited early experience with SNB after NC

Initial small studies have shown variability in:

- Rates of SN identification (72-100%)
- Rates of false negative SN (0%-33%)

SNB After NC
Single Institution Experience

Pooled Data:

SN Identification: 89%
False Negative Rate: 10%
NSABP B-27: SNB After NC (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%

Clinically Node (-): 12.4%
Clinically Node (+): 7.0%
P=0.51
# Identification Rate

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>No. of Patients</th>
<th>Total Patients</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90.1</td>
<td>176</td>
<td>195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>94.6</td>
<td>123</td>
<td>130</td>
<td></td>
<td>0.008</td>
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<tr>
<td>N1</td>
<td>81.5</td>
<td>53</td>
<td>65</td>
<td></td>
<td></td>
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</tbody>
</table>

# False Negative Rate

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>No. of Patients</th>
<th>Total Patients</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11.5</td>
<td>6</td>
<td>52</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>N0</td>
<td>9.4</td>
<td>3</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>15.0</td>
<td>3</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

• 24 studies
• 1779 patients

Identification Rates: 63-100%
– Pooled estimate: 89.6%

False Negative Rates: 0-33%
– Pooled estimate: 8.4%

Conclusion:
SNB is a reliable tool for planning treatment after NC

Kelly A et al: Acad Radiol 2009
**SNB After NC: MD Anderson Experience**

<table>
<thead>
<tr>
<th></th>
<th>SNB After NC (n=575)</th>
<th>SNB Upfront (n=3171)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification Rates</td>
<td>97.4%</td>
<td>98.7%</td>
<td>0.017</td>
</tr>
<tr>
<td>False Negative Rates</td>
<td>5.9%</td>
<td>4.1%</td>
<td>0.39</td>
</tr>
<tr>
<td>Nodal Positivity Rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>12.7%</td>
<td>19.0%</td>
<td>0.2</td>
</tr>
<tr>
<td>T2</td>
<td>20.5%</td>
<td>36.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T3</td>
<td>30.4%</td>
<td>51.4%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Conclusion:** SLN surgery after NC is as accurate as SLN surgery prior to chemotherapy, results in fewer positive SLNs and decreases unnecessary axillary dissections.

SNB After Neoadjuvant Chemotherapy in Patients with Documented Involvement of Axillary Nodes

• **Retrospective studies:** Variability in SN Identification rates (78%-98%) and SN false negative rates (5%-30%)

• Two prospective trials were recently published (ACOSOC Z1071 and SENTINA)
  - **Identification rates are lower** with SNB after neoadjuvant chemotherapy (80-93%) compared to upfront SNB (>95%)
  - **False negative rates** range between 12% -14% and are mainly affected by the number of SNs removed
ACOSOG Z1071:
FNR According to Type of Mapping and Number of SNs Removed

<table>
<thead>
<tr>
<th>Mapping Agent</th>
<th>310 patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue dye only</td>
<td>2/9 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Radiolabeled colloid only</td>
<td>10/50 (20.0%)</td>
<td>p = 0.046</td>
</tr>
<tr>
<td>Both blue dye and radiolabeled colloid</td>
<td>27/251 (10.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of SLN Examined</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19/90 (21.1%)</td>
<td>p = 0.004</td>
</tr>
<tr>
<td>3</td>
<td>7/78 (9.0%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4/60 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>5+</td>
<td>9/82 (11.0%)</td>
<td></td>
</tr>
</tbody>
</table>

SENTINA Trial: FNR According to Number of SNs Removed

- FNR 14.2% (32/226)

<table>
<thead>
<tr>
<th># SLNs removed</th>
<th>FN cases</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17/70</td>
<td>24.3%</td>
</tr>
<tr>
<td>2</td>
<td>10/54</td>
<td>18.5%</td>
</tr>
<tr>
<td>3</td>
<td>3/41</td>
<td>7.3%</td>
</tr>
<tr>
<td>4</td>
<td>0/28</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>2/33</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

- FNR consistently <10% when 3+ SLN
- If limit to cases with 2+ SLN removed, FNR = 9.6%

Kuehn et al. Lancet Oncology 2013; 14 (7); 609-18
### SENTINA Trial: FNR According to Type of Mapping

<table>
<thead>
<tr>
<th>Mapping agent used</th>
<th>FN cases</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiocolloid alone</td>
<td>23/144</td>
<td>16.0%</td>
</tr>
<tr>
<td>Radiocolloid and blue dye</td>
<td>6/70</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Kuehn et al. Lancet Oncology 2013; 14 (7); 609-18
SNB Following NeoAdjuvant Chemotherapy in Biopsy Proven Node-positive BC: The SN FNAC study

- 153 patients enrolled between 3/09-12/12
- SLNs with metastases of any size [ypN0(i+), ypN1mi and ypN1] were classified positive
- SLN Identification: 87.6%
- FNR: 9.6% (includes N0i+)
  - Central path review: FNR only 8.4%
  - FNR in 2+ SLNs removed = 4.9%

Boileau et al. ASCO 2013
## FNR According to Number of Removed Nodes

<table>
<thead>
<tr>
<th></th>
<th>ACOSOG Z1071</th>
<th>FN SNAC</th>
<th>SENTINA</th>
<th>Across studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of patients</strong></td>
<td>756</td>
<td>153</td>
<td>592</td>
<td>1501</td>
</tr>
<tr>
<td><strong>FNR with single SLN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.5%</td>
<td>18.2%</td>
<td>24.3%</td>
<td>26.0%</td>
</tr>
<tr>
<td></td>
<td>17/54</td>
<td>4/22</td>
<td>17/70</td>
<td>38/146</td>
</tr>
<tr>
<td><strong>FNR if 2 or more SLNs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.6%</td>
<td>4.9%</td>
<td>9.6%</td>
<td>10.8%</td>
</tr>
<tr>
<td></td>
<td>39/310</td>
<td>3/61</td>
<td>15/156</td>
<td>57/527</td>
</tr>
<tr>
<td><strong>FNR with dual tracer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.8%</td>
<td>-</td>
<td>8.6%</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>27/251</td>
<td>-</td>
<td>6/70</td>
<td>33/321</td>
</tr>
<tr>
<td><strong>FNR if &gt;2 SLNs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.1%</td>
<td>-</td>
<td>4.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td></td>
<td>20/220</td>
<td>-</td>
<td>5/102</td>
<td>25/322</td>
</tr>
</tbody>
</table>
NSABP B-32: False-Negative Rate According to Number of Removed SNs

SNB Before Neoadjuvant Chemotherapy: Pros and Cons

- Helpful if the SN is negative
- Patients with large operable breast cancer have high likelihood of positive nodes (>$50\%$)
- Does not take advantage of the down-staging effects of neoadjuvant chemotherapy on nodes: $30\text{-}40\%$ conversion from $(+)$ to $(-)$
- May remove the only positive node(s)
  - Interferes with direct assessment of chemosensitivity
- Requires two surgical procedures
Breast XRT: Should be always given after lumpectomy

Chest Wall and Regional XRT: Consider factors predicting local-regional failure after NC

These factors may predict LR failure more accurately than the original pathologic nodal status before NC

Can We Use Tumor and Nodal Response to NC in Order to Individualize the Use of L-R XRT?

Can We Use Tumor and Nodal Response to NC in Order to Individualize the Use of L-R XRT?
Recently Activated US Clinical Trials

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

- Clinical T1-3 N1 M0 BC
- Axillary nodal involvement (FNA or core needle biopsy)
- Neoadjuvant chemo (+ Anti-HER-2 therapy for HER-2 neu ⊕ pts)
- Definitive surgery with histologic documentation of 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

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
Summary I

• For patients with operable BC who are candidates for NC, ultrasound of the axilla and FNA of suspicious lymph nodes should be considered as part of the staging workup.

• SNB before NC does not offer particular clinical advantages and reduces the number of patients who could benefit from the down-staging effect of NC in the axillary nodes.
• SNB after NC is feasible and accurate with similar performance characteristics to SNB before NC, even in patients who present with involved axillary nodes.

• By performing SNB after NC, up to 40 percent of patients with initially involved axillary nodes may be spared from axillary dissection.

• For patients who present with clinically (or pathologically) involved nodes before NC and undergo SNB, removal of 2 or more nodes and dual mapping reduce FNR to less than 10%.