What is the optimal current axillary management after NAC?

Alessandra Cassano
Oncologia Medica
## Indications for NAC Are Changing

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inflammatory Cancer</td>
<td>• Large tumor/breast ratio in patient desiring BCT</td>
</tr>
<tr>
<td>• Other T4 tumors</td>
<td>• Reducing the need for ALND</td>
</tr>
<tr>
<td>• N2 or N3 disease</td>
<td></td>
</tr>
</tbody>
</table>
## SNB Feasibility In cN+ Patients After NAC

- 3 prospective single arm trials
- SNB → back-up ALND
- No LRR data

<table>
<thead>
<tr>
<th></th>
<th>ACOSOG Z1071</th>
<th>SN FNAC</th>
<th>SENTINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>689</td>
<td>153</td>
<td>592 (cN+)*</td>
</tr>
<tr>
<td>cTN</td>
<td>cT0-4 N1/2</td>
<td>cT0-3 N1/2</td>
<td>cN0/N1/N2</td>
</tr>
<tr>
<td>FNR (Overall)</td>
<td>12.6%</td>
<td>13.4%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

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Boileau J, J Clin Oncol 2015;33:258
Quehn T, Lancet Oncol 2013;14:609
Methods to minimize the False Negative Rate (FNR) of sentinel lymph node dissection after neoadjuvant chemotherapy for node positive breast cancer

Practical approach to the axilla after neoadjuvant chemotherapy: What the clinical trials don't address
Axillary Surgery – Why?

- Staging of the axilla
  - Guide adjuvant systemic therapy
  - Guide adjuvant radiation (indication and fields)
- Resection of disease
  - To render patient NED – no evidence of disease
- Long-term regional control
- Survival?

- pN0 vs pN+
- # of positive LNs
Evolution of Axillary Surgery

- **Routine ALND**
  - Removing all the LNs (10-25+)
  - Lymphedema risk 25%

- **SLN surgery**
  - 2-3 LNs
  - Lymphedema risk 6-8%

- **No axillary surgery**
  - Axillary Ultrasound
  - Patients at low risk of +LNs
  - Patients where axillary status does not impact management
Neoadjuvant Chemotherapy

- Decrease extent of disease in the breast
  - Increase rate of breast conservation
- Decrease likelihood of nodal positivity
  - Increase use of sentinel node surgery
- Assess response of tumor to chemotherapy
  - Prognostic information
  - Adjust adjuvant therapies
- Drug development
  - Advance development of therapy to improve breast cancer survival

Murphy et al. ASO 2018 Aug;25(8):2241-2248
Neoadjuvant Chemotherapy

Clinical Stage
- Physical examination
- Axillary Ultrasound
- MRI
- Percutaneous biopsy – cN1(f)
- AVOID axillary surgery

Chemotherapy

Surgery
- Repeat imaging to assess response
- Axillary surgery to assess for residual nodal disease
  - SLN/TAD?
  - ALND?
### AJCC – Definition of Regional Lymph Nodes

<table>
<thead>
<tr>
<th>CLINICAL N CATEGORY</th>
<th>PATHOLOGICAL N CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cN0</strong></td>
<td><strong>pN0</strong></td>
</tr>
<tr>
<td>No regional lymph node metastases (by imaging or clinical examination)</td>
<td>No regional LN metastases identified or ITCs only</td>
</tr>
<tr>
<td><strong>cN1</strong></td>
<td><strong>pN1</strong></td>
</tr>
<tr>
<td>Metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
<td>Micrometastases or metastases in 1-3 axillary LNs; and/or clinically negative internal mammary nodes with metastatic disease by SLN biopsy</td>
</tr>
<tr>
<td><strong>cN2</strong></td>
<td><strong>pN2</strong></td>
</tr>
<tr>
<td>Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases</td>
<td>Metastases in 4-9 axillary LNs; or positive internal mammary nodes by imaging in absence of axillary LN mets</td>
</tr>
<tr>
<td><strong>cN3</strong></td>
<td><strong>pN3</strong></td>
</tr>
<tr>
<td>InfrACLavicular (level III) or suprACLavicular LN involvement or in ipsilateral internal mammary nodes with axillary lymph node metastases</td>
<td>Metastases in 10+ axillary LNs</td>
</tr>
</tbody>
</table>
SLN after NAC in cN0 patients

1,456 patients from 16 studies

- SLN identification rate 96% [95% CI: 95%-97%]
- **SLN FNR 6%** (95% CI: 3%-8%)
  - Sensitivity 94% (95% CI: 92%-97%)
  - NPV 98% (95% CI: 98%-99%)
  - Accuracy 99% (95% CI: 99%-100%)

- SLN after NAC compared to surgery first
  - Similar SLN identification rates
  - Similar FNR
  - Lower nodal positivity rates
    - Fewer axillary dissections in T2 and T3
      - T2: 20.5% vs. 36.5%, p<0.0001
      - T3: 30.4% vs. 51.4%, p=0.04
  - Does not lead to higher local-regional failure rates

---

SLN feasible and accurate in cN0 disease

Geng et al PLoS One. 2016 Sep 8;11(9):e0162605
Response to neoadjuvant chemotherapy

Increasing pCR rates:
- Anthracyclines: 10-15%
- Anthracyclines + taxanes: 25-30%
- Targeted anti-Her2 therapy:
  - Trastuzumab + chemo: 40-50%
  - 2 anti-her2 agents + chemo: 50-60%

Nodal response rates (cN1 to ypN0):
- Anthracyclines: 30%
- Anthracyclines + taxanes: 40%
- Anti-Her2 therapy: up to 70-75%

Pathological Complete Response Rates in the Axilla

- Triple Negative: 49.4%
- HER2 Positive: 64.7%
- HR Positive, HER2 Negative: 21.1%

Outline

- SLN after NAC in cN1 disease – the trials
- Optimizing identification of the SLNs
- Decreasing the FNR
  - Technique
    - Number of SLNs removed
    - Dual tracer
  - Pathology
    - Treatment effect
    - IHC of SLNs
  - Removal of the clipped node
    - Ensuring identification of the clipped node
- Incorporating into clinical practice
### SLN identification rate

<table>
<thead>
<tr>
<th>Study</th>
<th>SLN identified</th>
<th>SLN ID rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z1071</td>
<td>639/689</td>
<td>92.7%</td>
</tr>
<tr>
<td>SENTINA</td>
<td>474/592</td>
<td>80.1%</td>
</tr>
<tr>
<td>SN FNAC</td>
<td>127/145</td>
<td>82.2%</td>
</tr>
<tr>
<td>Meta-analysis of these 3 trials</td>
<td>1240/1426</td>
<td>87.0%</td>
</tr>
<tr>
<td>Meta-analysis – pooled estimate across 17 studies</td>
<td></td>
<td>90.9%</td>
</tr>
</tbody>
</table>

SLN identification rates after NAC in Z1071

- SLN identification rate in pts undergoing surgery after NAC is higher with use of dual tracers for mapping
  - SLN ID rate with single tracer = 88.9% (95%CI: 82.6-93.5%)
  - SLN ID rate with dual tracers = 93.8% (95%CI: 91.4-95.6%)  
    \( p=0.048 \)

- No other clinical or pathologic factors significantly impacted SLN identification

Use of dual tracer is recommended when performing SLN in patients who have received NAC

Boughey et al. Ann Surg. 2015 Mar; 261(3); 547-52
FNR of SLN after NAC in cN1 patients

**SENTINA**
- FNR overall
  - 14.2%

**SN FNAC**
- FNR overall including IHC
  - 8.4%

**Z1071**
- FNR with ≥ 2 SLNs removed
  - 12.6%

Meta-analysis
- 3,398 patients
- FNR 13%
- pooled estimate across 19 studies

**Number of SLNs removed**

- **Z1071**
  
  ≥ 2 SLNs removed $\text{FNR} = 12.6\%$ (39/310)

- **SENTINA**
  
  ≥ 2 SLNs removed $\text{FNR} = 9.6\%$ (15/156)

- **SN FNAC**
  
  ≥ 2 SLNs removed $\text{FNR} = 4.9\%$ (3/61)

Meta-analysis of these 3 trials

≥ 2 SLNs removed $\text{FNR} = 57/527 = 10.8\%$

How frequently were ≥ 2 SLNs identified

<table>
<thead>
<tr>
<th></th>
<th>Z1071 310/388</th>
<th>SENTINA 156/226</th>
<th>SN FNAC 61/83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resect at least 2 SLNs</td>
<td>79.9%</td>
<td>69.0%</td>
<td>73.5%</td>
</tr>
</tbody>
</table>

## Use of dual tracer on SLN FNR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mapping agent</th>
<th>FN cases</th>
<th>FNR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z1071</td>
<td>Blue dye only</td>
<td>2/9</td>
<td>22.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiolabeled colloid only</td>
<td>10/50</td>
<td>20.0%</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Dual tracer</td>
<td>27/251</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>SENTINA</td>
<td>Radiocolloid only</td>
<td>23/144</td>
<td>16.0%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Dual tracer</td>
<td>6/70</td>
<td>8.6%</td>
<td></td>
</tr>
<tr>
<td>SN FNAC</td>
<td>Isotope only</td>
<td>4/25</td>
<td>16.0%</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Dual tracer</td>
<td>3/58</td>
<td>5.2%</td>
<td></td>
</tr>
</tbody>
</table>

Single tracer – 39/228 = 17.1%

Dual tracer – 36/379 = 9.5%

---

Use dual tracer

WAYS TO ENSURE SLN IS A NODE THAT WAS POSITIVE PRIOR TO CHEMO AND NOT A BYSTANDER NODE
## Treatment Effect / Histologic Changes

<table>
<thead>
<tr>
<th>Histologic changes</th>
<th>N</th>
<th>FNR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not mentioned</td>
<td>339 (64.5%)</td>
<td>28/208 = 13.5%</td>
<td>9.1 – 18.9%</td>
</tr>
<tr>
<td>Present</td>
<td>186 (35.5%)</td>
<td>11/102 = 10.8%</td>
<td>5.5 – 18.5%</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>33 (6.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>15 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>17 (3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histioyte infiltrate</td>
<td>88 (16.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effect NOS</td>
<td>33 (6.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consider pathologist to comment on presence of histologic changes in SLN
Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0–T4, N1–N2) Who Receive Neoadjuvant Chemotherapy

Results From ACOSOG Z1071 (Alliance)

Judy C. Boughey, MD,* Karla V. Ballman, PhD;† Huong T. Le-Petross, MD;‡ Linda M. McCall;§ Elizabeth A. Müntendorf, MD, PhD;¶ Gretchen M. Ahrendt, MD;‖ Lee G. Wilke, MD;¶ Bret Taback, MD,¶† Eric C. Felberri, MD,¶‡ and Kelly K. Hunt, MD¶

170 of 525 (32.4%) patients with cN1 disease and 2+ SLNs removed 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>107</td>
<td>59</td>
<td><strong>6.8%</strong></td>
<td>1.9 – 16.5%</td>
</tr>
<tr>
<td>Clip placed and found in ALND</td>
<td>34</td>
<td>21</td>
<td>19.0%</td>
<td>5.4 – 41.9%</td>
</tr>
</tbody>
</table>

Resect the clipped node

Clipped node not retrieved as a SLN

- ACOSOG Z1071: 24.1% (34/141)
- MDACC: 23.1% (31/134)
- UPMC: 26.7% (8/30)

Overall: 23.9% (73/305)

Caudle et al. JCO, 2016
Diego et al. ASO, 2016
Clipped node not retrieved as a SLN

- ACOSOG Z1071: 24.1% (34/141)
- MDACC: 23.1% (31/134)
- UPMC: 26.7% (8/30)

OVERALL: 23.9% (73/305)

Caudle et al. JCO, 2016
Diego et al. ASO, 2016
Marking Axillary Lymph Nodes With Radioactive Iodine Seeds for Axillary Staging After Neoadjuvant Systemic Treatment in Breast Cancer Patients

The MARI Procedure

- 100 cN1+ patients after NAC
- I-125 seed placed at initial LN biopsy (before NAC)
- Half-life of seed is 59.6 days
- Seed in place: 17 weeks (9-31 weeks)
- No SLN surgery, removal of + LN only using seed localization
- Identification rate: 97% (97/100)
- ALND in 95 patients

- FNR of clipped node: 7% (5/70)

Marking and removing the initial biopsy proven metastatic LN after NAC has a high identification rate and low FNR

Resection of Clipped Node & SLN – Targeted Axillary Dissection

- Localize clipped node prior to surgery
- Remove SLNs and clipped node
- MDACC experience

176 patients TAD and ALND

- FNR SLN alone 7.9%
- FNR clipped node alone 3.9%
- FNR SLN + clipped node 2.4%

Caudle et al. SSO 2017
Methods to identify biopsy proven node

Marking the positive node
- Clip
- Tattoo
  - India ink
  - Charcoal

Localizing the marked node
- Radioactive seed
- Other seeds
- Ultrasound
- Palpation
Impact of IHC in SN FNAC

- Primary endpoint included SLNs positive for ITCs – FNR 8.4%
- IF had limited to disease >0.2mm – then FNR would have been 13.3%

<table>
<thead>
<tr>
<th>Definition of positive node</th>
<th>FN cases</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any size, including N0(i+)</td>
<td>7/83</td>
<td>8.4%</td>
</tr>
<tr>
<td>&gt;0.2mm</td>
<td>11/83</td>
<td>13.3%</td>
</tr>
<tr>
<td>&gt;2mm</td>
<td>14/83</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

Boileau et al. JCO 2015 Jan 20;33(3):258-64
Impact of IHC and ITCs on SLN FNR in Z1071

- SLNs from 17 patients revealed disease ≤0.2mm in size on H&E or IHC

<table>
<thead>
<tr>
<th>Node positive definition</th>
<th>N</th>
<th>Residual disease identified in SLNs or ALND</th>
<th>FNR</th>
<th>95% CI</th>
<th>Pathologic nodal response</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN metastasis &gt;0.2mm by H&amp;E</td>
<td>470</td>
<td>301 (64.0%)</td>
<td>11.3%</td>
<td>8.0-15.4</td>
<td>36.0% (169/470)</td>
</tr>
<tr>
<td>SLN metastasis any size (including ≤0.2mm)</td>
<td>470</td>
<td>311 (66.2%)</td>
<td><strong>8.7%</strong></td>
<td>5.6-11.8</td>
<td>33.8% (159/470)</td>
</tr>
</tbody>
</table>

Boughey et al. SABCS 2014, updated data
Impact of IHC and ITCs on SLN FNR in Z1071

SLNs from 17 patients had disease ≤ 0.2mm identified on IHC or H&E

- 7 patients had positive nodes on ALND
  - changed from false negative to true positive
  - decreased the FNR of SLN surgery
  - did not impact the pathologic nodal response rate

- 10 patients were pN0 (negative SLNs and ALNs) pathologically
  - changed from pN0 to pN1
  - decreased the pathological nodal response rate
  - decreased the FNR of SLN surgery

In these 17 cases additional disease on ALND seen in 7 = 41%

Use IHC on SLNs
Axillary management

Without a clip in the LN at diagnosis
• If 0 or 1 SLN identified convert to ALND
• ≥2 SLNs – manage axilla based on pathology of SLNs

Clip in the LN at diagnosis
• If 0 SLNs or only 1 SLN without the clip convert to ALND
• If ≥2 SLNs or 1 SLN including the clip - manage axilla based on pathology of SLNs
Evolution of axillary surgery for cN1 patients after NAC at Mayo Clinic Rochester

431 patients with biopsy-proven cN1 patients treated with NAC between 1/2009 to 12/2017

Use of SLN surgery (+/- ALND) increased from 30% in 2009 to 86% in 2017 (p<0.001)

Performance of ALND decreased from 97% in 2009 to 38% in 2017 (p<0.001)

With short-term follow up (median 9 months, range 0-8 years), no nodal recurrences have occurred in patients without ALND

Nyugen....Boughey ASO 2018 Sep;25(9):2596-2602
Oncologic safety and locoregional recurrence

- 147 patients cN1/2 → cN0 after NAC at the European Institute of Oncology in Milan
- Median f/u 61 months
- Axillary recurrence (0.7%)
  - 1/77 SLN+ (ALND)
  - 0/70 SLN- (no ALND)
- Conclusion: SLN surgery is acceptable in cN1/2 patients who become cN0 after NAC

Galimberti et al, EJSO 2015
Preoperative Systemic Therapy Breast and Axillary Evaluation

Core biopsy with placement of image-detectable marker(s), if not previously performed, must be done to demarcate the tumor bed for post-chemotherapy surgical management.

Clinically negative axillary lymph node(s) should have axillary imaging; suspicious nodes should be sampled by FNA or core biopsy prior to neoadjuvant therapy.

If lymph node FNA or core biopsy negative, SLNB can be performed before or after neoadjuvant systemic therapy.

Clinically positive axillary lymph node(s) should be sampled by FNA or core biopsy prior to neoadjuvant therapy.

If lymph node FNA or core biopsy positive, axilla may be restaged after neoadjuvant systemic therapy; ALND should be performed if axilla is clinically positive; SLNB or ALND can be performed if axilla is clinically negative.

Surgical resection

See Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3, N1, M0 (BINV-3)

Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.
How to incorporate SLN after NAC in cN+ patients in your practice

• **Radiology / Surgery:** Consider placement of marker in LNs at time of percutaneous LN biopsy
  • Consider localization of biopsy positive node prior to surgery

• **Surgery:** Use dual tracer technique
  • Resect all SLNs (blue, radioactive, palpably abnormal)

• **Pathology:** Assessment of response to therapy effect in LNs
  • Incorporate IHC on the SLNs

• **Which patients to consider:**
  • Good clinical and radiological response in breast and LNs
# Surgical Standards for Management of the Axilla in Breast Cancer Clinical Trials with Pathological Complete Response Endpoint

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Clinical Node Negative</th>
<th>Clinical Node Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Chemo</td>
<td>Axillary ultrasound, if sonographic abnormal LNs</td>
<td>Axillary ultrasound, if sonographic abnormal LNs</td>
</tr>
<tr>
<td></td>
<td>FNA or CNB</td>
<td>FNA or CNB</td>
</tr>
<tr>
<td></td>
<td>No axillary surgery prior to chemotherapy</td>
<td>No axillary surgery prior to chemotherapy</td>
</tr>
<tr>
<td>Post-Chemo (Pre-Surgery)</td>
<td>Strongly consider localization of clipped node</td>
<td>Strongly recommend placement of clip in positive LN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axillary Surgery</th>
<th>SLN Surgery</th>
<th>SLN Surgery or ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN Surgery Approach</td>
<td>Recommended use of dual tracer</td>
<td>Require use of dual tracer</td>
</tr>
<tr>
<td></td>
<td>Resection of all radioactive nodes</td>
<td>Resection of all radioactive nodes</td>
</tr>
<tr>
<td></td>
<td>&gt;10% of hottest node</td>
<td>&gt;10% of hottest node</td>
</tr>
<tr>
<td></td>
<td>Resection of all blue nodes</td>
<td>Resection of all blue nodes</td>
</tr>
<tr>
<td></td>
<td>Resection of all palpably abnormal nodes</td>
<td>Resection of all palpably abnormal nodes</td>
</tr>
<tr>
<td></td>
<td>Resection of at least 2 SLNs recommended</td>
<td>If no clip placed, resection of at least 2 SLNs required</td>
</tr>
<tr>
<td></td>
<td>If Bx proven positive node clipped, ensure resection of the clipped node</td>
<td>If Bx proven positive node clipped, ensure resection of the clipped node</td>
</tr>
</tbody>
</table>

A011202 - A randomized phase III trial comparing axillary lymph node dissection to axillary radiation in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after receiving neoadjuvant chemotherapy

**Primary endpoint:** invasive breast cancer recurrence-free interval

- **Arm 1**
  - ALND – level I and II LNs
  - RT to the breast (BCS) or chest wall (mastectomy)
  - Regional nodal irradiation
    - level III LNs and supraclavicular fossa

- **Arm 2**
  - No ALND
  - RT to the breast (BCS) or chest wall (mastectomy)
  - Regional nodal irradiation
    - to level I, II, III LNs and supraclavicular fossa

As of Dec 1 2018
Registered 1364/1576 (86.5%)
Positive SLN after NAC

- Additional nodal disease found in 50-63% with +SLN
- MDACC scoring system (n=104, 38 cN+)
  - LVI, method of detection of SLN metastasis, multicentricity, initial lymph node status, and pathologic tumor size
- S. Korea (n=140 cN+)
  - pathologic T stage, lymphovascular invasion, SLN metastasis size, and number of positive SLN metastases

Jeruss et al, Cancer 2008, 112(12): 2646-54
Ryu et al, Clin Breast Cancer 2017; 17(7): 550-8
Barron et al, ASO 2018 Oct;25(10):2867-2874
Risk of additional nodal disease in setting of positive SLN after NAC

120 patients, 58 cN+
- cN+ vs cN0
- Her2 – vs Her2+
- Tumor grade
- # +SLNs
- Size SLN metastasis

Barron, Hoskin, Boughey. ASO 2018 Oct;25(10):2867-2874
## Likelihood of additional positive nodes at ALND based on size of SLN metastasis

<table>
<thead>
<tr>
<th></th>
<th>ITCs</th>
<th>Micromets</th>
<th>Macromets</th>
</tr>
</thead>
<tbody>
<tr>
<td>SN FNAC (all cN+)</td>
<td>4/7 (57%)</td>
<td>3/8 (37%)</td>
<td>34/61 (56%)</td>
</tr>
<tr>
<td>MSKCC (cN0 and cN+)</td>
<td>1/6 (17%)</td>
<td>28/44 (64%)</td>
<td>75/121 (62%)</td>
</tr>
<tr>
<td>Z1071</td>
<td>4/11 (36.4%)</td>
<td>164/273 (60.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td><strong>9/24 (37.5%)</strong></td>
<td><strong>31/52 (60%)</strong></td>
<td><strong>109/182 (60%)</strong></td>
</tr>
</tbody>
</table>

Boileau et al. JCO 2015 Jan 20;33(3):258-64
Moo et al. ASO 2018 Jun;25(6):1488-1494
### Role of IHC - Z1071 data

<table>
<thead>
<tr>
<th>Number of positive SLNs</th>
<th>Median (range)</th>
<th>SLN negative (n=186)</th>
<th>SLN positive ≤0.2mm (n=17)</th>
<th>SLN positive by H&amp;E (&gt;0.2mm) (n=267)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of positive nodes on ALND</td>
<td>0</td>
<td>159 (85.5%)</td>
<td>10 (58.8%)</td>
<td>106 (39.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of positive nodes on ALND</td>
<td>1</td>
<td>16 (8.6%)</td>
<td>3 (17.6%)</td>
<td>44 (16.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of positive nodes on ALND</td>
<td>2</td>
<td>11 (5.9%)</td>
<td>4 (23.5%)</td>
<td>116 (88.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Largest metastasis (SLN or ALN)</td>
<td>Median (range)</td>
<td>0.17 ± 0.49</td>
<td>0.41 ± 1.14</td>
<td>1.06 ± 0.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LRR-free</td>
<td>HR (95% CI)</td>
<td>1.00 (ref)</td>
<td>1.89 (0.23-15.7)</td>
<td>2.86 (1.17-6.99)</td>
<td>0.070</td>
</tr>
<tr>
<td>LRR-free</td>
<td>5 yr estimate (95% CI)</td>
<td>96.0 (91.3 – 98.2)</td>
<td>91.7 (53.9-98.9)</td>
<td>91.0 (86.4-94.1)</td>
<td></td>
</tr>
<tr>
<td>BCSS</td>
<td>HR (95% CI)</td>
<td>1.00 (ref)</td>
<td>3.66 (1.30-10.33)</td>
<td>3.45 (1.90-3.28)</td>
<td>0.0002</td>
</tr>
<tr>
<td>BCSS</td>
<td>5 yr estimate</td>
<td>94.1 (89.3–96.8)</td>
<td>88.2 (60.0 – 96.9)</td>
<td>81.6 (76.3-85.9)</td>
<td></td>
</tr>
</tbody>
</table>
Positive SLN after NAC

- Risk of additional positive nodes is higher than in patients with upfront surgery
- Varies by:
  - cN stage, tumor biology (subtype & grade), # positive SLNs, LVI, breast response
- Consider A11202
- ALND standard of care outside of clinical trial
Overview

- Status of SLNB after NAC in cNo patients

- Management of cN+ axilla after NAC
  - How often is ALND avoided in cN+ patients after NAC?
  - Can we select ER+ subsets that have a better response to NAC?
  - Is axillary imaging a useful tool post-NAC to determine eligibility for SLNB?
  - Controversial indications for ALND after NAC

- What is the optimal strategy to avoid ALND in cNo patients?
## SLNB Feasibility in cNo Patients after NAC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>IR (%)</th>
<th>FNR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xing¹ 2006</td>
<td>21</td>
<td>1273</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>Kelly² 2009</td>
<td>24</td>
<td>1799</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>van Deurzen³ 2009</td>
<td>27</td>
<td>2148</td>
<td>91</td>
<td>10.5</td>
</tr>
<tr>
<td>Tan⁴ 2011</td>
<td>10</td>
<td>449</td>
<td>94</td>
<td>7</td>
</tr>
<tr>
<td>Geng⁵ 2016</td>
<td>16</td>
<td>1456</td>
<td>96</td>
<td>6</td>
</tr>
</tbody>
</table>

**Identification rate similar with single-agent or dual-agent mapping**

**False-negative rate similar to upfront surgery setting**

¹Xing Y, Br J Surg, 2006;93:539
²Kelly A, Acad Radiol, 2009;16:551
³Van Deurzen C, Eur J Cancer, 2009;45:3124
⁴Tan V, J Surg Oncol 2011;104:97
⁵Geng C, PLoS One, 2016;11:e0162605
## Decreased Nodal Positivity After NAC in cNo Patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Nodal positivity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upfront surgery</td>
<td>NAC</td>
</tr>
<tr>
<td>NSABP B-18</td>
<td>1097</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>MDACC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>992</td>
<td>37%</td>
<td>21%</td>
</tr>
<tr>
<td>T3</td>
<td>106</td>
<td>51%</td>
<td>30%</td>
</tr>
</tbody>
</table>

SLNB after NAC can decrease the likelihood of ALND
### Outcomes of SLNB After NAC in cNo Patients

Although FNR similar to adjuvant setting, concerns for potential worse outcomes with SLNB alone after NAC due to possibility of leaving behind nodes with “chemo-resistant disease”

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median F/U</th>
<th>Nodal recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson (2009)</td>
<td>575</td>
<td>47 months</td>
<td>1.2%</td>
</tr>
<tr>
<td>GANEA 2 (2018)</td>
<td>419</td>
<td>36 months</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Management of the Clinically Node-Negative Axilla

- Sentinel lymph node biopsy should be performed after NAC
- Single agent or dual agent mapping
- High identification rate
- Acceptable false-negative rate
SLNB Feasibility in cN+ Patients after NAC

- 4 prospective, multi-institutional trials
- Primarily included cT1-3N1 patients
- SLNB → back-up ALND

<table>
<thead>
<tr>
<th></th>
<th>ACOSOG Z1071</th>
<th>SN FNAC</th>
<th>SENTINA</th>
<th>GANEA 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>689</td>
<td>153</td>
<td>592 (cN+)</td>
<td>307</td>
</tr>
<tr>
<td>cTN</td>
<td>cT0-4 N1/N2</td>
<td>cT0-3 N1/N2</td>
<td>cN0/N1/N2</td>
<td>pN1*</td>
</tr>
<tr>
<td>IR</td>
<td>92.7%</td>
<td>87.6%</td>
<td>80.1%</td>
<td>79.5%</td>
</tr>
<tr>
<td>FNR (Overall)</td>
<td>12.6%</td>
<td>13.3%</td>
<td>14.2%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

The use of dual tracer and removal of ≥ 3 SLNs resulted in FNR < 10%

References:
- Boughey J, JAMA 2013;310:1455
- Boileau J, J Clin Oncol 2015;33:258
- Kuehn T, Lancet Oncol 2013;14:609
- Classe J, Breast Cancer Res Treat 2018 (Epub)
How Often Are $\geq 3$ SLNs Identified?

Use of SLNB in cN+ patients as a strategy to avoid ALND is appropriate if removal of $\geq 3$ SLNs is feasible

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Removal of $\geq 3$ SLNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG Z1071</td>
<td>651</td>
<td>57%</td>
</tr>
<tr>
<td>SENTINA</td>
<td>592</td>
<td>34%</td>
</tr>
<tr>
<td>Mamtani (2016)</td>
<td>128</td>
<td>86%</td>
</tr>
</tbody>
</table>
Optimizing the SLNB Procedure in cN+ Patients after NAC

Meta-analysis 13 studies
1921 cN+ patients (biopsy-proven)
SLNB/ALND after NAC
Pooled IR 90%
Pooled FNR 14%
FNR 11% (6%-15%) dual mapping
FNR 4% (0%-9%) (≥3 SLNs removed)
Optimizing the SLNB Procedure in cN+ Patients after NAC

Meta-analysis 13 studies
1031 cN+ patients (biopsy proven)
None of the studies have reported benefit of nodal clipping with dual mapping and retrieval ≥ 3 SLNs

Pooled FNR 14%
FNR 11% (6%-15%) dual mapping
FNR 4% (0%-9%) (≥ 3 SLNs removed)

Tee S, Br J Surg 2018;105:1541
How Often Is ALND Avoided in cN+ Patients after NAC?

n = 128 cN+

≥ 3 SLNs retrieved
n = 110

ypN+

n = 48

ALND

n = 48

ypN0

n = 62

SLNB

n = 62

SLN Identification Rate 98%
How Often Is ALND Avoided in cN+ Patients after NAC?

n = 128 cN+  SLN Identification Rate 98%

≥ 3 SLNs retrieved  n = 110

ALND was avoided in 62 of 128 (48%) cN+ patients treated with NAC

ALND  n = 48

SLNB  n = 62
# Nodal pCR Varies by Receptor Subtype

<table>
<thead>
<tr>
<th>Receptor Status</th>
<th>Nodal pCR (%)</th>
<th>ACOSOG Z1071 n = 694</th>
<th>MSKCC n = 195</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>41%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>21%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>65%</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>49%</td>
<td></td>
<td>47%</td>
</tr>
</tbody>
</table>

**ACOSOG Z1071:** 89% HER2+ patients received trastuzumab  
**MSKCC:** 100% HER2+ received dual anti-HER2 therapy
### Nodal pCR Varies by Receptor Subtype

<table>
<thead>
<tr>
<th>Receptor Status</th>
<th>Nodal pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACOSOG Z1071</td>
</tr>
<tr>
<td>All</td>
<td>41%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>21%</td>
</tr>
<tr>
<td>HER2+</td>
<td>65%</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>100%</td>
</tr>
</tbody>
</table>

Do all ER+ patients have similar response to NAC?
Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

MSKCC
2007-2016
n = 402 ER+/HER2-
n = 301 (75%) cN+

Nodal pCR = 15%
16% (Ductal) vs 7% (Lobular), p = 0.09
Nodal pCR ↑ in PR-/high grade or poorly differentiated
Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

Multivariable analysis of effect of pathologic characteristics on nodal pCR

<table>
<thead>
<tr>
<th>Pathologic characteristics</th>
<th>Nodal pCR (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology (lobular vs. ductal)</td>
<td>0.49</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Differentiation (poor vs. well/moderate)</strong></td>
<td><strong>2.67</strong></td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td>PR status (negative vs. positive)</td>
<td>1.89</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Rates of nodal pCR by pathologic characteristics

<table>
<thead>
<tr>
<th>Receptor/grade/differentiation</th>
<th>Nodal pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>PR+/high or poor</td>
<td>16/117</td>
</tr>
<tr>
<td>PR+/non-high or non-poor</td>
<td>8/98</td>
</tr>
<tr>
<td><strong>PR-/high or poor</strong></td>
<td><strong>17/48</strong></td>
</tr>
<tr>
<td>PR-/non-high or non-poor</td>
<td>0/29</td>
</tr>
</tbody>
</table>

P < 0.0001
Can Oncotype be Used to Predict pCR in ER+ Patients Treated with NAC?

N = 89 patients with LABC
NAC = doxorubicin and paclitaxel
58% ER+

The probability of pCR increased with recurrence score (p = 0.005)
Is There a Subset of ER+/HER2- Patients Likely to Benefit from NAC?

PR- and/or poorly differentiated/high-grade features select patients with best response to NAC

pCR uncommon in node-positive lobular cancers or non-high-grade ductal cancers
What Are Nodal Recurrence Rates in cN+ Patients Treated with SLNB Alone after NAC?

Galimberti V et al
n = 147 cN1/N2
70 SLN negative after NAC, SLNB alone
Median f/u 61 months
No nodal failures

Nguyen TT et al
n = 430 cN1
n = 93 SLNB alone (88% SLN negative)
Median f/u 9 months
No nodal failures
MSK Approach to the Clinically Node-Positive Axilla after NAC

- cT1-3N1 breast cancer eligible for SLNB after NAC if convert to cNo
- SLNB performed with dual tracer mapping
- Do not require retrieval of clipped node
- Require retrieval of at least 3 SLNs to minimize false-negative rate
Selecting cN+ Patients for SLNB after NAC

1. Physical exam
2. Imaging
<table>
<thead>
<tr>
<th>SN FNAC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 153 cN+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 19 palpable adenopathy after NAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV 89% (17/19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MSKCC cohort</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 155 biopsy-proven cN1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 23 palpable adenopathy after NAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV 78% (18/23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is Palpable Adenopathy after NAC an Indication for ALND?

Palpable nodes not all the same

If nodes clinically suspicious and poor response to NAC in breast → ALND

Doubt → needle biopsy post-NAC

SLNB
Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

<table>
<thead>
<tr>
<th><strong>SN FNAC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 129 AUS + pathology</td>
</tr>
<tr>
<td>NPV = 48% (36/75)</td>
</tr>
<tr>
<td>PPV = 81% (44/54)</td>
</tr>
<tr>
<td>Accuracy = 62%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ACOSOG Z1071</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 611 AUS + available pathology</td>
</tr>
<tr>
<td>n = 430 normal AUS, 57% pN+</td>
</tr>
<tr>
<td>n = 181 abnormal AUS, 72% pN+</td>
</tr>
</tbody>
</table>

If patients with abnormal AUS triaged to ALND, 28% of patients would receive unnecessary ALND
Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

MSKCC
n = 129 breast cancer patients
Pre- and post-NAC MRI

<table>
<thead>
<tr>
<th>Axillary node status on MRI</th>
<th>pN- (n = 80)</th>
<th>pN+ (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pre- and post NAC (n = 32)</td>
<td>81%</td>
<td>19%</td>
</tr>
<tr>
<td>Abnormal pre-NAC, normal post-NAC (n = 50)</td>
<td>68%</td>
<td>32%</td>
</tr>
<tr>
<td>Abnormal pre- and post- NAC (n = 47)</td>
<td>43%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Should Axillary Imaging Be Performed after NAC to Determine Eligibility for SLNB?

Axillary imaging likely not a useful tool post-NAC as it cannot reliably predict the status of the axilla

Abnormal axillary imaging post-NAC should not be used to triage patients directly to ALND
Controversial Indications for ALND

1. Locally advanced breast cancer
2. Low-volume disease in the SLN
3. Absence of treatment effect in the SLN
Can SLNB Be Performed in cT4 or cN2/N3 Disease after NAC?

Stearns V et al
n = 8 inflammatory breast cancer
IR = 75%
FNR = 25%

Hidar S
n = 20 inflammatory breast cancer
IR = 80%
FNR = 18%

DeSnyder SM
n = 16 inflammatory breast cancer
IR = 25% (limited FNR assessment)

DeSnyder S, Clin Breast Cancer 2018;18:e73
Can SLNB Be Performed in cT4 or cN2/N3 Disease after NAC?

**ACOSOG Z1071**

- \( n = 33 \) cT4
- FNR not specified for cT4

- \( n = 38/701 \) cN2
- \( n = 26 \) at least 2 SLNs removed
- pCR = 46%
- FNR: 0% (95% CI: 0%-23.2%)

**SN FNAC**

- \( n = 10/153 \) cN2
- FNR: 0% (0/4)

**SENTINA**

FNR not assessed for cN1 and cN2 separately

---

*References:
- Boughey J, JAMA 2013;310:1455
- Boileau J, J Clin Oncol 2015;33:258
- Kuehn T, Lancet Oncol 2013;14:609*
Nodal pCR Similar in LABC Compared to Non-LABC

MSKCC prospective neoadjuvant database
195 cN+(biopsy proven)
  n = 40 cT4 or cN2/3
  n = 155 cN1

<table>
<thead>
<tr>
<th></th>
<th>cT4 or cN2/N3</th>
<th>cN1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodal pCR</strong></td>
<td>45%</td>
<td>50%</td>
</tr>
</tbody>
</table>

\( p = 0.5 \)
Tumor Biology Predicts Response to NAC in Locally Advanced Breast Cancer

n = 321 (2006-2016)  
cT4 and/or cN2/N3  
All HER2+ patients received HER2 targeted therapy

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>310</td>
<td>38</td>
</tr>
</tbody>
</table>

Nodal pCR: 43% (cN1) vs. 36% (cN2) vs. 32% (cN3) (p = 0.23)
Protocol 17-384: Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy in Patients Presenting with Locally Advanced Breast Cancer: A Prospective Study

- **Eligibility:**
  - Female breast cancer patients
  - cT4 and/or cN2/N3 treated with NAC
  - Clinically node negative after NAC

- **Design:**
  - Single-arm prospective trial
  - Eligible patients undergo SLNB with dual tracer mapping, followed by completion axillary dissection
  - Attempt to retrieve ≥ 3 SLNs

- **Primary Objective:**
  - Prospectively determine false-negative rate of SLNB after NAC in locally advanced breast cancer patients

PI: Andrea V. Barrio; Co-PI: Monica Morrow
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

Patients having upfront surgery → volume of disease in SLN predictor of additional disease in non-SLN

Micrometastases or isolated tumor cells in SLN
10-20% risk of additional non-SLN metastases

MSKCC
pNmic (n = 254): 20% non-SLN mets
pNoi+ (n = 250): 12% non-SLN mets

van Deurzen C, J Natl Cancer Inst 2008;100:1574
Kumar S, Ann Surg Oncol 2010;17:2509
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

July 2008-July 2017
n = 711 SLN procedures after NAC
Overall FNR of frozen section: 6.2%

76% of false negatives were micromets or ITCs
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

Patients having upfront surgery → volume of disease in SLN predictor of additional disease in non-SLN

Micrometastases or isolated tumor cells in SLN
10-20% risk of additional non-SLN metastases

**MSKCC**

- pN1mic (n = 254): 20% non-SLN mets
- pNoi+ (n = 250): 12% non-SLN mets
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

July 2008-July 2017

n = 711 SLN procedures after NAC
Overall FNR of frozen section: 6.2%

76% of false negatives were micromets or ITCs
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

July 2008-July 2017
n = 711 SLN procedures after NAC
Overall FNR of frozen section: 6.2%

Is return to OR for ALND necessary?

Moo T, Ann Surg Oncol 2018;25:1488
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

Frequency of additional positive non-SLN:

- ITC (n=6): 1/6
- Micromet (n=44): 2
- Macromet (n=121): 2

Approximately 1/3 of NSLN metastases were macromets.
Is ALND Needed for Low-Volume Disease in the SLN after NAC?

ALND is indicated for low-volume disease in the SLN, even when not initially seen on FS, due to high likelihood of additional non-SLN disease.
Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

- n = 528 biopsy-proven N+
- n = 204 ypNo after NAC
- Treatment effect in nodes identified in 192 (94%) patients

<table>
<thead>
<tr>
<th></th>
<th>ALND (n = 135)</th>
<th>SLNB (n = 69)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effect</td>
<td>131 (97%)</td>
<td>61 (88%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
### Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Treatment effect</th>
<th>No treatment effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>30</td>
<td>83%</td>
<td>17%</td>
<td>0.05</td>
</tr>
<tr>
<td>Triple neg</td>
<td>55</td>
<td>96%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>119</td>
<td>96%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Breast pCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pT0/is)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>141</td>
<td>97%</td>
<td>3%</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>63</td>
<td>89%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>
Is the Absence of Treatment Effect in the Nodes an Indication for ALND?

The absence of treatment effect in the SLN is not an absolute indication for ALND, and may occur due to biologic differences in tumor response.
What Is the Optimal Strategy to Avoid ALND in cNo Patients?

- cN+ → NAC
- cNo → Primary Surgery
  - NAC
Rates of ALND by Type of Surgery and Tumor Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Upfront BCS n = 669</th>
<th>NAC n = 271</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2-</td>
<td>15%</td>
<td>34%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HER2+</td>
<td>13%</td>
<td>8%</td>
<td>0.26</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>14%</td>
<td>7%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

1944 cT1-2N0
## Rates of ALND by Type of Surgery and Tumor Subtype

1944 cT1-2N0

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Upfront mastectomy n = 1004</th>
<th>NAC n = 271</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2-</td>
<td>37%</td>
<td>34%</td>
<td>0.62</td>
</tr>
<tr>
<td>HER2+</td>
<td>36%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>25%</td>
<td>7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
## Rates of ALND by Type of Surgery and Tumor Subtype

### Multivariable analysis assessing likelihood of ALND

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC vs. BCS (ER+/HER2-)</td>
<td>3.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NAC vs. mastectomy (HER2+)</td>
<td>0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NAC vs. mastectomy (ER-/HER2-)</td>
<td>0.25</td>
<td>0.007</td>
</tr>
</tbody>
</table>

1944 cT1-2N0
Summary

• SLNB is accurate in cNo patients and in cN+ patients if ≥3 SLNs retrieved, and reduces need for ALND

• Axillary imaging post-NAC unnecessary, as it cannot reliably predict status of the axilla

• Low-volume disease in the SLN is an indication for ALND

• The optimal strategy to avoid ALND in cNo patients is based largely on tumor subtype and type of breast surgery