De-escalating axillary surgery in node-positive breast cancer

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Introduction

• Multimodality treatment has improved breast cancer outcomes
  
  Additive benefit of individual treatment often small
  Treatment burden always cumulative

• Leveraging therapeutic advances to decrease the magnitude of surgery
  BCS after NACT
  Margins in DCIS
  Axillary management in primary BCS in cN0 patients

Axillary management in cN+ patients post NACT
De-escalating surgery in invasive breast cancer

• Surgical paradigms for managing the breast and axilla were largely developed in 1970 and 1980
• Improvements in systemic therapy and its more widespread use have resulted in dramatic decreases in LRR
• The magnitude of surgery does not alter bad biology
Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy for Advanced Breast Cancer: Results of Ganglion Sentinelle et Chimiothérapie Neoadjuvante, a French Prospective Multicentric Study

Jean-Marc Classe, Virginie Bordes, Loïc Campan, Hervé Mignotte, François Drauvet, Jean Leveque, Christine Sagan, Pierre François Dupre, Gilles Body, and Sylvia Glard

Original Articles

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy is Accurate and Reduces the Need for Axillary Dissection in Breast Cancer Patients

Kelly K. Hunt, MD, Min Yi, MS, Elizabeth A. Mittendorf, MD, Cynthia Guerrero, BA, Gildy V. Babiera, MD, Isabelle Bedrosian, MD, Rosa F. Hwang, MD, Henry M. Kuerer, MD, PhD, Merrick I. Ross, MD, and Funda Meric-Bernstam, MD
Management of the axilla in the patient receiving NACT

cN0
• NACT decreases the need for ALND
• An SLN can be identified in > 90% of patients
• Rates of LRR < 2%

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLND Without Neoadjuvant Chemotherapy</th>
<th>SLND With Neoadjuvant Chemotherapy</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td></td>
<td></td>
<td>0.1*</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (1.2)</td>
<td>12 (2.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3133 (98.8)</td>
<td>563 (97.9)</td>
<td></td>
</tr>
<tr>
<td>Regional recurrence</td>
<td></td>
<td></td>
<td>0.5*</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (0.9)</td>
<td>7 (1.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3143 (99.1)</td>
<td>568 (98.8)</td>
<td></td>
</tr>
<tr>
<td>Distant recurrence</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>87 (2.7)</td>
<td>43 (7.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3084 (97.3)</td>
<td>532 (92.5)</td>
<td></td>
</tr>
<tr>
<td>Clinical TNM stage</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>I</td>
<td>2560 (80.7)</td>
<td>72 (12.4)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>608 (19.2)</td>
<td>502 (87.4)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3 (0.09)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher exact test.

TNM indicates tumor, node, metastasis; SLND, sentinel lymph node dissection.
Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment

V. Galimberti a,*, S.K. Ribeiro Fontana a, P. Maisonneuve b, F. Steccanella a, A.R. Vento a, M. Intra a, P. Naninato a, P. Caldarella a, M. Iorfida c, M. Colleoni c, G. Viale d,e, C.M. Grana f, N. Rotmensz b, A. Luini a
Patients scheduled for neoadjuvant treatment

Initially cN0
- \( \text{cN0} \)
  - post-neoadjuvant
    - SN- (n=157)
    - SN+ (n=92)
  - Axillary recurrences
    - 1 (0.6%)
  - Ipsilateral breast recurrences
    - 10 (6.4%)
  - Distant metastases
    - 12 (7.6%)

Initially cN1/2
- \( \text{cN0} \)
  - post-neoadjuvant
    - SN- (n=70)
    - SN+ (n=77)
  - Axillary recurrences
    - 0
  - Ipsilateral breast recurrences
    - 5 (5.4%)
  - Distant metastases
    - 18 (19.5%)

Figure 1. Study flow chart.
<table>
<thead>
<tr>
<th>cN1/2 - ypT0/x (n=38)</th>
<th>cN1/2 - ypT1 (n=58)</th>
<th>cN1/2 - ypT2/3 (n=51)</th>
</tr>
</thead>
</table>

### Distant disease-free survival

- **SN- (no AD)**
- **SN+ (AD)**

- **Log-rank P=0.03**
- **Log-rank P=0.16**
- **Log-rank P=0.97**

*Figure 2. Distant disease-free survival, overall survival, and cumulative incidence of regional recurrence, according to clinical axillary status prior to neo-adjuvant treatment, and sentinel node status, in 396 women with cT1-4 N0-1/2 breast cancer. (AD = axillary dissection).*
Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study.


Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study.


Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial.

## Rationale for NACT in cN+ patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Nodal pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG Z1071 (2014)</td>
<td>694</td>
<td>41%</td>
</tr>
<tr>
<td>SN FNAC (2015)</td>
<td>145</td>
<td>35%</td>
</tr>
<tr>
<td>Mamtani (2016)</td>
<td>195</td>
<td>49%</td>
</tr>
</tbody>
</table>

*Boughey J, JAMA 2013
Boileau J, JCO, 2015
Mamtani, Ann Surg Onc 2016*
SLNB feasibility in cN+ after NACT

- 3 prospective single arm studies
- SLNB followed by back-up ALND in all cases
- Primary endpoint: calculate SLNB FNR – 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>cT</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>8.4%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>
## SLNB after NACT in cN+ patients

<table>
<thead>
<tr>
<th>No. of SLNs</th>
<th>FNR</th>
<th>ACOSOG Z1071</th>
<th>SENTINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*Boughey, JAMA 2013*

*Kuehn, Lancet Oncol 2013*
How often does NACT avoid ALND in cN+ patients: MKSCC prospective study

• Frequency with which NACT avoids ALND is uncertain
• Omission of ALND requires
  Identification of > 3 SLNs
  Sentinel nodal pCR

Aim: determine need for ALND by subtype after NACT in biopsy proven cN+ patients

*Mamtani, Ann Surg Onc 2016*
SLNB outcomes

- SLNB attempted: n = 128
- ≥ 3 SLN retrieved: n = 110
  - ypN+: n = 48
    - ALND: n = 48
  - ypNO: n = 62
    - No ALND: n = 62
SLNB outcomes

ALND was avoided in 62/128 (48%) of patients who underwent SLNB

Mamtani, Ann Surg Onc 2016
## Nodal pCR by receptor status

<table>
<thead>
<tr>
<th>Receptor Status</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>96 / 195</td>
<td>49%</td>
</tr>
<tr>
<td>ER+/HER2-</td>
<td>15 / 73</td>
<td>21%</td>
</tr>
<tr>
<td>ER-/HER2-</td>
<td>26 / 55</td>
<td>47%</td>
</tr>
<tr>
<td>ER+/HER2+</td>
<td>26 / 37</td>
<td>70%</td>
</tr>
<tr>
<td>ER-/HER2+</td>
<td>29 / 30</td>
<td>97%</td>
</tr>
</tbody>
</table>

*p < 0.0001*
Nodes vs. Breast differential pCR

- Breast pCR defined as no invasive carcinoma

<table>
<thead>
<tr>
<th>Receptor Status</th>
<th>Nodal pCR (%)</th>
<th>Breast pCR (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>49%</td>
<td>37%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ER+/HER2-</td>
<td>21%</td>
<td>10%</td>
<td>0.003</td>
</tr>
<tr>
<td>ER+/HER2+</td>
<td>70%</td>
<td>59%</td>
<td>0.3</td>
</tr>
<tr>
<td>ER-/HER2+</td>
<td>97%</td>
<td>70%</td>
<td>0.3</td>
</tr>
<tr>
<td>ER-/HER2-</td>
<td>47%</td>
<td>40%</td>
<td>&lt;0.0001</td>
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</table>
Can we select a subset of ER+/Her2- patients likely to benefit from NACT?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th># Patients</th>
<th>% Nodal pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR+ / High</td>
<td>117</td>
<td>14%</td>
</tr>
<tr>
<td>PR+ / Non-High</td>
<td>98</td>
<td>8%</td>
</tr>
<tr>
<td>PR- / High</td>
<td>48</td>
<td>35%</td>
</tr>
<tr>
<td>PR- / Non-High</td>
<td>29</td>
<td>0%</td>
</tr>
</tbody>
</table>

\[ p < .0001 \]

*Petruolo, SSO 2017*
# 21 gene assay and prediction of response to NACT

<table>
<thead>
<tr>
<th>Author</th>
<th>#Patients</th>
<th>Endpoint</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianni</td>
<td>89</td>
<td>pCR</td>
<td>.005</td>
</tr>
<tr>
<td>Yardley</td>
<td>161</td>
<td>pCR</td>
<td>.002</td>
</tr>
<tr>
<td>Soran</td>
<td>60</td>
<td>%tumor response</td>
<td>.21</td>
</tr>
</tbody>
</table>

Gianni, JCO 2005  
Yardley, Breast Cancer Res Treat 2015  
Soran, Breast Dis 2016
Concept of targeted axillary dissection

• TAD after NACT
• Pre-NACT marking of the biopsy-proven abnormal node
• SLNB combined with guided dissection of the marked node – provided nodal response (clinical and radiological CR)
• Aim – reduce FNR even further

• Technical caveats regarding localization
• Methods of assessment of nodal response
The MARI procedure


**Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure.**

Donker M¹, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, van Tinteren H, Sonke GS, Rutgers EJ, Vrancken Peeters MJ.
The MARI procedure

- Feasibility study
- 100 patients with cN+ baseline disease
- 95/100 patients underwent ALND+MARI dissection

30/95 pts had MARI pCR
of these pts – 5/30 residual nodal disease

**hence FNR 7%**

No Sentinel technique was employed as adjunct to the MARI procedure

Abigail S. Caudle, Wei T. Yang, Savitri Krishnamurthy, Elizabeth A. Mittendorf, Dalliah M. Black, Michael Z. Gilcrease, Isabelle Bedrosian, Brian P. Hobbs, Sarah M. DeSnyder, Rosa F. Hwang, Beatriz E. Adrada, Simona F. Shaitelman, Mariana Chavez-MacGregor, Benjamin D. Smith, Rosalind P. Candelaria, Gidy V. Babiera, Basak E. Dogan, Lumarie Santiago, Kelly K. Hunt, and Henry M. Kuerer
Clinically node-positive patients
N = 208

Neoadjuvant therapy

TAD not performed
n = 112

TAD performed
n = 96

ALND not performed
n = 11

Evaluable patients
n = 86

Pathologic node negative
n = 35 (41%)

SLN negative = 5 of 47
SLN not identified = 3

Pathologic node positive
n = 50 (59%)

Clipped node and SLNs negative
n = 1 of 50

False-negative rate
SLN alone = 10.8% (95% CI, 3.6 to 23.1)
SLN + evaluation of the clipped node = 2.0% (95% CI, 0.05 to 10.7)  
P = .13
Conclusions

• Select patients experience high nodal responses
• Axillary nodal recurrence is consistently low after ALND and/or negative SLND
• Axillary conservation is feasible after NACT

We need

• Long-term LRR and survival data after axillary conservation for cN+ baseline patients who convert to cN0
• Role of RNI
• Best imaging modality for assessing responses in the nodal basin