Surgical Approach to the Axilla in 2018

Cancer De Mama
Sao Paulo, Brazil 2018

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Breast Surgical Oncology
Objectives

- Discuss changes in staging of breast cancer.
- Discuss management of the axilla in patients undergoing surgery first.
- Discuss the role of nodal staging after chemotherapy.
Timeline for Breast Cancer Treatment

1890 - Radical mastectomy

1960 - Trials in Breast Conserving Therapy

1980 - Tamoxifen

1990-2000 - Trials in Sentinel Node Surgery

1990 - Trastuzumab

2000 - Description of breast cancer subtypes
Prognostic Factors

- Tumor size
- Lymph node status
- Histologic type
- Angiolymphatic invasion
- Age and comorbidities
- Race
- Grade
- Estrogen receptor
- Progesterone receptor
- HER2 status
- 21 gene recurrence score
- Mammaprint
Prognosis and Staging

• AJCC TNM stage:
  – T: primary tumor
  – N: regional (ipsilateral) lymph nodes
  – M: distant Metastasis

• Pathologic stage (PS): Definitive stage is determined after surgery by pathologic evaluation of the primary tumor and regional lymph nodes.
Hierarchical Clustering Reveals Clinically Relevant Gene Expression Profiles in Breast Cancer

<table>
<thead>
<tr>
<th>Each column is data from one patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each row is color coded values of one gene</td>
</tr>
</tbody>
</table>

Sorlie et al., PNAS, 2001
Case Considerations

- 49 yo female undergoes BCT and SLN dissection, pT1cN0M0 invasive ductal carcinoma, intermediate grade, ER 90%, PR 30%, HER-2/neu negative

- 54 yo female undergoes BCT and SLN dissection, pT1cN0M0 invasive ductal carcinoma, high grade, ER negative, PR negative and HER-2/ neu negative

- Same TNM, anatomic stage
- Different prognosis
Novel Staging Systems

- Six different staging systems were assessed: (1) PS; (2) PS and grade; (3) PS, grade, and LVI; (4) PS, grade, and ER; (5) PS, grade, and combination of ER and PR; and (6) PS, grade, and combination of ER, PR, and HER2.

- Model performance was quantified using Harrell’s concordance index (C-index).

- Similar to area under the receiver operating characteristic (ROC) curve, C-index can range from perfect concordance (1.0) to random predictions (0.5).
External Validation

- SEER database - Patients were included if they had stage I–IIIA breast cancer.
- Patients with unknown stage, grade, ER status, or PR status and those lost to follow-up within 2 years were excluded.
- There were 26,711 in the external validation cohort.

Incorporation of Biologic Factors into Novel Staging System


Pathologic Stage

PS + GE

C-index: 0.68
AIC: 2,038.4

C-index: 0.80
AIC: 1,931.9

PS

PS + GE

Follow-Up Time (years)

Follow-Up Time (years)

Hypothesis: Patients treated with neoadjuvant therapy could be better stratified incorporating the following:
  – Clinical stage
  – Pathologic stage
  – Biologic factors

Staging Following Neoadjuvant Chemotherapy

Clinical Stage

Pathologic Stage

CPS+EG
Management of the Regional Nodes
Assessment of Nodal Basins

- False negative rate of physical exam: 45%
- Ultrasound with FNA of abnormal nodes\(^1\):
  - Sensitivity: 86.4%
  - Specificity: 100%
  - Diagnostic Accuracy: 79%
  - False Negative Rate: 11.6%
- Ultrasound identified metastases in:
  - 93% nodes if metastases >0.5 cm
  - 44% nodes if metastases <0.5 cm

\(^1\)Krishnamurthy S, et al. *Cancer* 2002
MD Anderson Approach

• All patients with invasive breast cancer undergo US evaluation of regional nodal basins:
  – Axilla
  – Infraclavicular
  – Internal mammary chain

• If abnormal axillary nodes seen, supraclavicular is added
Sentinel Lymph Node Dissection

Meric and Hunt, Breast Cancer, 2007
Primary Objective: To assess whether OS after SLND alone was not inferior to that for patients who underwent completion ALND for a positive SLN.
Z0011 Results – 10 Year Follow-up

27% of SLND+ALND had additional +nodes

14% had 4 or more positive nodes

<table>
<thead>
<tr>
<th>Cumulative Locoregional recurrence at 10 years</th>
<th>Local Recurrence</th>
<th>Regional Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB only</td>
<td>12 (3.8%)</td>
<td>5 (1.5%)</td>
</tr>
<tr>
<td>ALND</td>
<td>19 (5.6%)</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>

P = 0.13

P = 0.36

## Radiation to Regional Nodes?

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>Local</th>
<th></th>
<th>Regional</th>
<th></th>
<th></th>
<th>Total LRR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events (10-y CI)</td>
<td>P</td>
<td>No. of Events (10-y CI)</td>
<td>P</td>
<td>No. of Events (10-y CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>WBI done (from CRF)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>540</td>
<td>16 (3.3%)</td>
<td>0.002</td>
<td>5 (1.0%)</td>
<td>—</td>
<td>21 (4.3%)</td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>6 (12.2%)</td>
<td>0.004</td>
<td>0 (0.0%)</td>
<td>—</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td><strong>RT done (355 pts with extra info)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>228</td>
<td>4 (1.9%)</td>
<td>0.004</td>
<td>4 (1.9%)</td>
<td>0.80</td>
<td>8 (3.8%)</td>
</tr>
<tr>
<td>No</td>
<td>107</td>
<td>8 (9.1%)</td>
<td>0.64</td>
<td>1 (1.1%)</td>
<td>0.82</td>
<td>9 (10.2%)</td>
</tr>
<tr>
<td><strong>High Tangents (228 pts with extra info)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>73</td>
<td>3 (4.3%)</td>
<td>0.64</td>
<td>1 (1.4%)</td>
<td>0.82</td>
<td>4 (5.8%)</td>
</tr>
<tr>
<td>No</td>
<td>69</td>
<td>1 (1.5%)</td>
<td>1 (1.6%)</td>
<td>0.82</td>
<td>2 (3.0%)</td>
<td>—</td>
</tr>
<tr>
<td><strong>N/A or Unknown</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>0 (0.0%)</td>
<td>2 (2.8%)</td>
<td>0.82</td>
<td>2 (2.8%)</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>4 (2.3%)</td>
<td>0 (0.0%)</td>
<td>—</td>
<td>0 (0.0%)</td>
<td>—</td>
</tr>
<tr>
<td>Supraclavicular (228 pts with extra info)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185</td>
<td>0 (0.0%)</td>
<td>—</td>
<td>0 (0.0%)</td>
<td>—</td>
<td>8 (4.6%)</td>
</tr>
<tr>
<td>No</td>
<td>185</td>
<td>4 (2.3%)</td>
<td>—</td>
<td>4 (2.3%)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

As previously reported by Jagsi et al, there were radiation protocol deviations among 335 patients in both treatment arms. Of the 335 patients, 228 had port films available for review and 107 had no radiation treatment. There were no significant differences between treatment arms in the use of protocol-prohibited nodal fields. High tangents were used in 51% of patients. Fifteen percent of patients received third-field treating supraclavicular nodes. There were no differences between the 2 treatment arms related to patient or tumor characteristics and prevalence of supraclavicular irradiation. Further analysis of the recurrence data from these 335 patients revealed that only “no radiation” was associated with an increased risk of local recurrence ($P = 0.004$) but not regional recurrence ($P = 0.80$) (Table 5).
**AMAROS**

- Hypothesis: AxRT provides comparable local control and survival as ALND with fewer side effects
- cT1b-2 N0
- BCT or mastectomy
- Pts with ≥ 1+ SLN randomized to ALND or AxRT
AMAROS

- No difference in DFS or OS

HR: 1.18; 95CI: 0.93-1.15

HR: 1.17; 95CI: 0.85-1.62

Rutgers E, ASCO 2013
• Decreased lymphedema with AxRT

*lymphedema observed or treated

Rutgers E, ASCO 2013
Indications for Axillary Node Dissection?

- Clinically node negative axilla with positive SLN
  - Some patients undergoing mastectomy (AMAROS and IBCSG 23-01)
  - BCT patients not meeting Z0011 criteria
- Axillary recurrence
- Inflammatory breast cancer
- Locally advanced breast cancer

🔹 PRACTICE EVOLVING Paradigm Shifting
  - Targeted axillary surgery
  - Node positive before/after preoperative systemic therapy
Axillary Management after Chemotherapy

Nodal Ultrasound

- Negative
  - Sentinel Node Dissection

- Positive
  - FNA
  - Axillary Node Dissection??

Neoadjuvant Chemotherapy

Alternatives to ALND...
Pathologic Complete Response Rates in the Axilla

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

*p<0.0001*

SLND After Chemotherapy in Clinically Node Positive Patients

- 3 recently published trials:
  - ACOSOG Z1071\(^1\) – USA
  - SENTINA\(^2\) - Europe
  - SN FNAC\(^3\) - Canada

\(^1\)Boughey et al. *JAMA*, 2013
\(^2\)Kuehn et al. *Lancet Oncology*, 2013
\(^3\)Boileau et al. *JCO*, 2015
Trial Design

cT1-4 N1-2 invasive breast cancer ↓
Neoadjuvant Chemotherapy ↓
SLN and ALND

*Endpoint*: Compare SLN pathology to the remaining axillary nodes (FNR)
Clinically Node Positive Patients

- Neoadjuvant chemotherapy (NAC) is often used
- 40-70% of clinically node-positive patients convert to node-negative with NAC\(^1\)\(^-\)\(^3\)
- Use of SLND in patients who convert to node-negative is limited by high false negative rate (FNR)

\[
FNR = \frac{\text{SLN-negative but lymph node+}}{\text{Total lymph node+}}
\]

\(^2\)Hennessy et al. *J Clin Oncol*, 2005
## SLND for Clinically Node Positive Patients

<table>
<thead>
<tr>
<th>Nodal Eligibility Criteria</th>
<th>ACOSOG Z1071(^1)</th>
<th>SENTINA (Arm C)(^2)</th>
<th>SN FNAC(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN1-2*Endpoints reported for cN1</td>
<td>cN1-2</td>
<td>cN1-2</td>
<td>cN1-2</td>
</tr>
<tr>
<td>Biopsy required to confirm metastases?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>cN1=603 cN2=34</td>
<td>592</td>
<td>153</td>
</tr>
<tr>
<td>SN Identification Rate</td>
<td>92.7%</td>
<td>87.8%</td>
<td>87.6%</td>
</tr>
<tr>
<td>Overall FNR (No IHC)</td>
<td>12.6%</td>
<td>14.2%</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

\(^1\) Boughey et al. *JAMA*, 2013  
\(^2\) Kuehn et al. *Lancet Oncology*, 2013  
\(^3\) Boileau et al. *JCO*, 2015
ACOSOG Z1071
Clip placement in cN1 patients and 2+ SLNs examined

170 patients had clip placed in the node at the time of biopsy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Residual Nodal Disease</th>
<th>FNR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clip found in SLN</td>
<td>107</td>
<td>59</td>
<td>6.8%</td>
<td>1.9-16.5</td>
</tr>
<tr>
<td>Clip in ALND specimen</td>
<td>34</td>
<td>21</td>
<td>19%</td>
<td>5.4-41.9</td>
</tr>
<tr>
<td>Clip location unknown</td>
<td>29</td>
<td>21</td>
<td>14.3%</td>
<td>3-36.3</td>
</tr>
</tbody>
</table>

Staging US shows abnormal lymph nodes

Needle Biopsy confirms metastases

Patient receives neoadjuvant chemotherapy

Surgery
Axillary LNs removed

Clip placed in sampled node

Xray to identify the clipped node
Clipped node pathology reported separately

1NCCN Guidelines, Version 2.2014
Pathologic Evaluation of Clipped Node

Clinically Node Positive Patients
N=191

Neoadjuvant therapy

Path Node Negative
N=71 (37%)

Path Node Positive
N=120 (63%)

False Negative Results*
5/120

False Negative Rate
4.2% (95% CI 1.4 – 9.5)

*Climped node showed no disease but other nodes in axillary specimen contained metastases

Does evaluation of the clipped node improve axillary staging over SLND?
Patients Undergoing SLND

Clinically Node Positive Patients
SLND and ALND Performed
N=118

Path Node Negative
N=44 (37%)

Path Node Positive
N=74 (63%)

SLN negative = 7/69
SLN not identified = 5

Clipped node and SLN negative
N=1/74

Neoadjuvant therapy

False Negative Rate

SLND Alone = 10.1% (95% CI 4.2 – 19.8)
SLND + Evaluation of Clipped Node = 1.4% (95% CI 0.03-7.3)
P=0.03

Why Localize the Clipped Node?

Clipped node not retrieved as a SLN:

- MDACC\textsuperscript{1}: 23% (31/134)
- Pittsburgh\textsuperscript{2}: 27% (8/30)
- ACOSOG Z1071\textsuperscript{3}:
  - Clipped node was a SLN: 63% (107/170)
  - Clipped node in ALND: 20% (34/170)
  - Unknown: 17% (29/170)

\textsuperscript{1}Caudle et al. *J Clin Oncol*, 2016
\textsuperscript{2}Diego et al. *Ann Surg Oncol*, 2016
\textsuperscript{3}Boughey et al. *Ann Surg*, 2015
Can we selectively remove clipped nodes at surgery?
Targeted Axillary Dissection

1-5 Days Before Surgery

Breast Imaging
$I^{125}$ seed placed in marked node

Nuclear Medicine
Radioisotope injection for SLND

Day of Surgery

Node containing $I^{125}$ seed selectively removed

SLNs removed

Remaining axillary nodes removed

Patients Undergoing TAD

TAD Performed After NCT
N=85

Neoadjuvant therapy

Path Node Negative
N=35 (41%)

Path Node Positive
N=50 (59%)

Clipped node and SLN negative
N=1/50

Caudle et al. JCO, 2016

False Negative Rate
TAD (SLNs + Clipped Node) = 2.0% (95% CI 0.05-10.7)
Conclusions

- False Negative Rates:
  - SLND Alone = 10.1%
  - Evaluation of clipped node alone = 4.2%
  - Targeted Axillary Dissection = 2.0%

- Evaluation of the clipped node is valuable in nodal staging after neoadjuvant chemotherapy

- Targeted axillary dissection (TAD) improves axillary staging over SLND alone
Is TAD better in some patients than others?
# Accuracy of TAD

## Burden of Nodal Disease at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>&lt; 4 Abnormal Nodes on US</th>
<th>≥4 Abnormal Nodes on US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>227</td>
<td>86</td>
</tr>
<tr>
<td>Nodal pCR</td>
<td>33.5%</td>
<td>31.4%</td>
</tr>
<tr>
<td>FNR of clipped node</td>
<td>2.0%</td>
<td>11.9%</td>
</tr>
<tr>
<td></td>
<td>3/151 (95% CI 0.4-5.7)</td>
<td>7/59 (95% CI 4.9-22.9)</td>
</tr>
<tr>
<td>FNR of TAD</td>
<td>1.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>1/92 (95% CI 0.03 – 5.9)</td>
<td>2/35 (95% CI 0.7-19.2)</td>
</tr>
</tbody>
</table>
## Accuracy of TAD

<table>
<thead>
<tr>
<th></th>
<th>T1-2 with &lt; 4 nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>167</td>
</tr>
<tr>
<td><strong>Nodal pCR</strong></td>
<td>24.1%</td>
</tr>
<tr>
<td><strong>FNR of clipped node</strong></td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
<td>2/112 (95% CI 0.2-6.3)</td>
</tr>
<tr>
<td><strong>FNR of TAD</strong></td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>0/69 (95% CI 0 – 5.2)</td>
</tr>
</tbody>
</table>
TAD in Clinical Practice

• Offer TAD with possible omission of ALND if < 4 abnormal nodes on initial US
• Recommend ALND for those with ≥4 nodes
• Multidisciplinary discussion is important
  – Radiation Oncology
  – Plastic Surgery
• No outcome data available
Important Ongoing Cooperative Group Trials

**ALLIANCE A11202 Schema**

- Clinical T1-3 N1 M0 BC
- Neoadjuvant Chemotherapy
- BCT or Mastectomy
  - Sentinel Lymph Node Surgery
    - SLN Negative
    - SLN Positive
      - Randomization
        - ALND \(\oplus\)
          - Breast/chest wall and nodal XRT
        - No further axillary surgery.
          - Breast/chest wall and nodal XRT

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

- Clinical T1-3 N1 M0 BC
- Axillary nodal involvement
  - (FNA or core needle biopsy)
  - Pre-op chemo
  - Surgery with negative axillary nodes (either by axillary dissection or by SLNB \(\pm\) 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
Surgery followed by adjuvant therapy

Outcome assessed as events occur over time

Neoadjuvant approach

Pathologic assessment of response
Thank you!