PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Sentinel Node Biopsy After Neoadjuvant Chemotherapy: The Pros

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Aultman Cancer Center
Original Clinical Rationale for Neoadjuvant Chemotherapy

- Convert inoperable BC to operable BC
- Convert operable BC patients requiring mastectomy to candidates for BCS
Axillary Node Down-Staging with NC

% Conversion
From Node (+)
To Node (-)

30
19
37
43

AC NSABP B-18
FEC EORTC
AT→CMF ECTO
AC→TXT NSABP B-27*

*Assuming 30% nodal down-staging with neoadjuvant AC
Effect of NC on Axillary Nodal Metastases

• NC downstages axillary nodes in about 20-40% of the patients

• This was of no particular clinical significance when axillary dissection was the sole method for staging the axilla
Effect of NC on Axillary Nodal Metastases

• The advent of sentinel node biopsy introduced another potential benefit from neoadjuvant chemotherapy
• Potential for decreasing the extent of axillary surgery with SNB vs. AND if the axillary nodes are down-staged with NC
SNB After NC
Two Main Reasons Given by Those Who Oppose It

1. It does not work as well as it does before systemic therapy
2. By doing SNB after NC, we lose information that is important for further patient management
SNB After NC
Two Main Reasons for Opposing It

1. It does not work as well as it does before systemic therapy
2. By doing SNB after NC, we lose information that is important for further patient management
SNB After NC

• Is SNB after NC as feasible and accurate as before systemic therapy?
  • Does response to NC cause scarring that could affect the lymphatic drainage making SN identification more difficult and/or less accurate?
  • Is NC equally effective in down-staging SNs and non-SNs
SNB After NC
Feasibility and Accuracy

• Information from:
  • Single institution trials
  • Multicenter Trials
  • Meta-Analyses
SNB After NC
Single Institution Experience

- 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%)
<table>
<thead>
<tr>
<th>Author</th>
<th># Pts (Node +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
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<tbody>
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<td>Nason, 2000</td>
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<td>Stearns, 2002</td>
<td>34 (13)</td>
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<td>14</td>
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<td>Fernandez, 2001</td>
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<td>Haid, 2001</td>
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<td>Reitsamer, 2003</td>
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<td>Brady, 2002</td>
<td>14 (11)</td>
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<td>Schwartz, 2003</td>
<td>21 (11)</td>
<td>100</td>
<td>9</td>
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<td>Balch, 2003</td>
<td>32 (19)</td>
<td>97</td>
<td>5</td>
<td>Yes</td>
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<td>Aihara, 2004</td>
<td>20 (12)</td>
<td>85</td>
<td>8</td>
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<td>Piato, 2003</td>
<td>42 (18)</td>
<td>98</td>
<td>17</td>
<td>Yes</td>
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<tr>
<td>All</td>
<td>398 (182)</td>
<td>89.1</td>
<td>10.8</td>
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</table>
## SNB After NC: Single Institution Series

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts (Node +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, 2004</td>
<td>54 (27)</td>
<td>72</td>
<td>11</td>
<td>Yes</td>
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<tr>
<td>Jones, 2005</td>
<td>36 (18)</td>
<td>81</td>
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<td>Kinoshita, 2006</td>
<td>77 (27)</td>
<td>94</td>
<td>11</td>
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<td>Shimazu, 2004</td>
<td>47 (33)</td>
<td>94</td>
<td>12</td>
<td>Yes</td>
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<td>Julian, 2004</td>
<td>42 (19)</td>
<td>95</td>
<td>0</td>
<td>Yes</td>
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<td>Lang, 2004</td>
<td>53 (24)</td>
<td>94</td>
<td>4</td>
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<tr>
<td><strong>All</strong></td>
<td><strong>309 (160)</strong></td>
<td><strong>88.7</strong></td>
<td><strong>8.1</strong></td>
<td></td>
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SNB After NC
Multi-Center Studies: NSABP B-27 (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%

Mamounas EP: J Clin Oncol, 2005
SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

Conclusion:
SNB is a reliable tool for planning treatment after NC
## Comparison of False Negative Rates Between SN Multicenter Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>FNR</th>
<th>(SN-/N+)</th>
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<tbody>
<tr>
<td>Multicenter SB-2 Trial</td>
<td>11%</td>
<td>(13/114)</td>
</tr>
<tr>
<td>Italian Randomized Trial</td>
<td>9%</td>
<td>(8/91)</td>
</tr>
<tr>
<td>Ann Arundel</td>
<td>13%</td>
<td>(25/193)</td>
</tr>
<tr>
<td>University of Louisville</td>
<td>7%</td>
<td>(24/333)</td>
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<tr>
<td>NSABP B-32 Randomized Trial</td>
<td>10%</td>
<td>(75/766)</td>
</tr>
<tr>
<td>NSABP B-27 (After NC)</td>
<td>11%</td>
<td>(15/140)</td>
</tr>
<tr>
<td>Meta-Analysis (After NC)</td>
<td>12%</td>
<td>(65/540)</td>
</tr>
</tbody>
</table>

Krag DN: Surg Oncol 1993  
McMasters KM: J Clin Oncol 2000  
Mamounas EP: J Clin Oncol 2005  
Tafra L: Am J Surg 2001  
Xing Y: Br J Surg 2005  
Julian JB: SABCS 2004
SNB After NC: Optimal Candidates

• Optimal candidates should have low risk for a positive non-SN

• SNB inaccuracy rate is a function of:
  – False Negative Rate
    » Anatomic variability
    » Surgeon’s performance
  – Rate of axillary node positivity
NSABP B-27: Rate of Positive Nodes According to Tumor Response

P < 0.0001

Bear HD: J Clin Oncol 2003
NSABP B-27: SN Inaccuracy Rate According to Tumor Response

All Patients

\[ P = 0.36 \]

- cCR/pCR (1/56)
- cCR/pINV (4/99)
- c(PR+SD+PD) (8/158)

Mamounas EP: J Clin Oncol 2005
SNB After NC
Two Main Reasons for Opposing It

1. It does not work as well as it does before systemic therapy

2. By doing SNB after NC, we lose information that is important for further patient management
Clinical Assessment of Axillary Nodal Status Before NC

All this is fine

BUT

SNB Before NC is not!
SNB Before NC: Arguments in Favor

- Information on the status of SN can be obtained without the confounding effects of NC
- This may provide an advantage regarding:
  - Further surgical management of the axilla
  - Selection of optimal NC or adjuvant chemo after NC
  - Selection of optimal loco-regional XRT
SNB Before NC: Two Surgical Procedures

(-) SN $\rightarrow$ NC $\rightarrow$ BCT/MAST

(+): SN $\rightarrow$ AND $\rightarrow$ NC $\rightarrow$ BCT/MAST

NC $\rightarrow$ AND + BCT/MAST
Patients with large operable breast cancer have high likelihood of positive nodes (50-70%).

This approach does not take advantage of the downstaging effects of NC on nodes: 30-40% conversion from (+) to (-).
SNB **Before** NC Rather than **After** NC?

- This approach assumes surgeons are comfortable performing SNB alone before NC but not after NC.
- Outcome results from large randomized trials comparing SNB alone with axillary dissection are pending.
SNB at Diagnosis vs. After NC
Confidence Intervals Around FNR

Multicenter SB-2 Trial
Italian Randomized Trial
Ann Arundel
University of Louisville
NSABP B-32 Randomized Trial
NSABP B-27 (After NC)
Meta-Analysis (After NC)

Krag DN: Surg Oncol 1993
Mamounas EP: J Clin Oncol 2005
McMasters KM: J Clin Oncol 2000
Tafra L: Am J Surg 2001
Xing Y: Br J Surg 2005
Julian JB: SABCS 2004
SNB Before NC: Selection of Optimal NC?

- May be useful in patients who will not need chemotherapy if the SN is negative (uncommon situation among typical candidates for NC)

- Usually original tumor size, age and primary tumor markers are good guides for appropriate NC
**SNB Before NC:**
Selection of Adjuvant Chemo?

- Consideration for adjuvant chemo after NC depends on:
  - **What NC was used** (anthracyclines only or anthracyclines and taxanes)
  - **Clinical and path breast tumor response**
  - **Status of axillary nodes after NC**

- Uncertain significance of negative nodes after NC and prior SNB *(downstaging vs. prior removal of all (+) nodes)*
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.

Selection of Loco-Regional XRT?

Problem: Not much information exists on the subject!
NSABP B-18: Predictors of LRF after NC Multivariate Analysis

Cox Model
Neoadjuvant Chemotherapy

- Number of path-positive nodes ($p<0.0001$)
- Age ($p=0.005$)
- Breast tumor response ($p=0.054$)

10-year Cum. Incidence of LRF (%)

Updated LRF Analysis: NSABP B-18/B-27

- Univariante and multivariante analysis of predictors of LR failure
- Includes the preop AC arms from B-18 and B-27 and the preop AC→T arm from B-27
- Similar results were obtained by using only the two preop AC arms or by adding the third B-27 arm (AC→S→T)
- Analysis is based on 2192 pts and 229 events (LRF)
- Pathologic complete response (pCR) was defined as no invasive disease in the breast and negative axillary nodes
### MVA: Predictors of LRF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Clin. Tumor Size 2.1-5 vs. 0-2 cm</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Clin. Tumor Size &gt; 5 vs. 0-2 cm</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Clin. Node (+) vs. Clin. Node (-)</td>
<td>1.60</td>
<td>0.0007</td>
</tr>
<tr>
<td>Node(-)/No pCR vs. Node(-)/pCR</td>
<td>1.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Node(+) vs. Node(-)/pCR</td>
<td>2.58</td>
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</table>
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Clinical Tumor Size

- <= 2 cm: 10.8 (n=433)
- 2.1-5 cm: 9.6 (n=1333)
- > 5 cm: 13.3 (n=543)
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Clinical Nodal Status

<table>
<thead>
<tr>
<th>Clinical Nodal Status</th>
<th>n=1642</th>
<th>n=667</th>
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</thead>
<tbody>
<tr>
<td>Clin. Node (-)</td>
<td>9.3</td>
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</tr>
<tr>
<td>Clin Node (+)</td>
<td>14.2</td>
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</tbody>
</table>
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR

- Node (-) pCR: 6.6
- Node (-) No pCR: 8.4
- Node (+): 14.6

- Sample sizes: n=313, n=914, n=965
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR (Lumpectomy Pts)

- Node (-) pCR: IBTR 5.6, Regional 1.2
- Node (-) No pCR: IBTR 5.9, Regional 1.1
- Node (+): IBTR 6.4, Regional 3.4

Total n=518
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR (Mastectomy Pts)

- Node (-) pCR: 4.4 (1.5), 3 (5), 3.7 (11.2)
- Node (-) No pCR: 68 (270)
- Node (+): 11.2

Chest Wall and Regional Incidence
According to Path Nodal Status/pCR and Clinical Nodal Status

8-Year Cum. Incidence of LRF by Path Nodal Status/pCR and Clinical Nodal Status

Node (-)/pCR
Node(-)/No pCR
Node (+)

Clin. Node (-) | Clin Node (+)
--- | ---
6.1 | 7.7
n=196 | n=117
6.9 | 10.1
n=519 | n=395
12 | 17.3
n=510 | n=455
Conclusions

- SNB after NC is feasible and accurate with performance characteristics similar to those for SNB before systemic therapy.
- By performing SNB after NC, up to 40 percent of patients who present with involve axillary nodes may be spared from axillary dissection.
- 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.