Should Response to Neoadjuvant Chemotherapy Tailor Radiation And Surgical Care?

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Clinical Rationale for Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy is the standard of care for patients with locally advanced breast cancer
- 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 Chemo for Operable BC
Loco-Regional Endpoints

- High clinical response rates (80-90%)
- 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
- Increase in the rate of lumpectomy in RCTs
- Decrease in the rate of axillary positivity in RCTs
  - 30% with anthracyclines
  - Up to 40% with anthracyclines/taxanes
  - Probably > 50% with chemo + anti-HER-2 therapies
How Can We Maximize the Impact of Neoadjuvant Chemotherapy

- Develop more effective regimens that will improve outcome by decreasing
  - Distant recurrence and death
  - Loco-regional recurrence

- Use primary tumor/nodal response as a surrogate endpoint for long-term outcome

- Identify better predictors of pCR:
  - Baseline biomarkers
  - Early changes in biomarkers with treatment

- Use primary tumor response as a guide for tailoring L-R and systemic therapy

GeparTRIO Trial: pCR Rates by Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A (N=572)</td>
<td>20</td>
</tr>
<tr>
<td>Luminal B (HER2-) (N=217)</td>
<td>25</td>
</tr>
<tr>
<td>Luminal B (HER2+) (N=281)</td>
<td>30</td>
</tr>
<tr>
<td>HER2+ (non-luminal) (N=178)</td>
<td>35</td>
</tr>
<tr>
<td>Triple-negative (N=362)</td>
<td>40</td>
</tr>
</tbody>
</table>

NeoALTTO Efficacy - pCR and tpCR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pathological Complete Response</th>
<th>Loco-regional (total) pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>29.7% (p=0.0001)</td>
<td>20.0% (p=0.13)</td>
</tr>
<tr>
<td>T</td>
<td>39.5% (p=0.001)</td>
<td>40.0%</td>
</tr>
<tr>
<td>L+T</td>
<td>51.3%</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

Von Minckwitz G et al, SABCS 2011
**NeoSphere Primary Outcome Measure: pCR**

- Pathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery.
- T = docetaxel, H = trastuzumab, P = pertuzumab.

**NeoSphere Primary Outcome Measure: pCR**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>pCR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC+HP x3</td>
<td>61.6%</td>
</tr>
<tr>
<td>FEC x3</td>
<td>66.2%</td>
</tr>
<tr>
<td>TCH+P x6</td>
<td>57.3%</td>
</tr>
</tbody>
</table>

**Pathologic Complete Response by HR-Status**

- ER- and PR-negative
- ER-and/or PR-positive

**Pathologic Complete Response by HR-Status**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Pathologic Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC+HP x3</td>
<td>64.4%</td>
</tr>
<tr>
<td>FEC x3</td>
<td>62.5%</td>
</tr>
<tr>
<td>TCH+P x6</td>
<td>83.8%</td>
</tr>
</tbody>
</table>

**Pathologic Complete Response by HR-Status**

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<th>Treatment Group</th>
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<td>FEC+HP x3</td>
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<td>FEC x3</td>
<td>50.0%</td>
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<tr>
<td>TCH+P x6</td>
<td>83.0%</td>
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</tbody>
</table>
NSABP B-41: pCR Breast and Negative Nodes

Using Clinical and Pathologic Response to NC to Tailor Further Loco-Regional Rx

Individualizing Loco-Regional Therapy with Neoadjuvant Chemotherapy

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

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 some loco-regional therapy altogether (surgery or XRT) with the use of more active regimens and/or with appropriate patient selection with biomarkers

SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

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

SNB After NC: Single Institution Series
Positive Axillary Nodes Before NC

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th># Pts (Nods +)</th>
<th>Success Rate (%)</th>
<th>FN Rate (%)</th>
<th>Accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen, 2006</td>
<td>T1-T4, N1-N3</td>
<td>69(40)</td>
<td>93</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>Lee, 2006</td>
<td>T1-T4, N1 (Palpable and FNA (+) or &gt;1cm thick with loss of fat hilum on US and SUV &gt; 2.5)</td>
<td>219 (124)</td>
<td>78</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Neumman, 2007</td>
<td>Resectable T1-3, N1 (FNA (+) under US)</td>
<td>40 (28)</td>
<td>98</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>328 (172)</td>
<td>84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Z1071: SLNB + AND After NC

T1-4 N1-2 invasive breast cancer
(pretreatment axillary ultrasound with FNA or core biopsy
documenting axillary metastases)

REGISTER

↓

Patients receive neoadjuvant chemotherapy
(stratify patients by age, stage and
number of cycles and type of chemotherapy)

↓

REGISTER

↓

SLN and ALND

Target
Accrual: 550 pts

SNB Before NC: Pros and Cons

- Helpful if the SN is negative
- Patients with large operable breast cancer have high likelihood of positive nodes (50-70%)
- Does not take advantage of the downstaging effects of NC on nodes: 30-40% conversion from (+) to (-)
- Requires two surgical procedures

SNB Before NC: Selection of Loco-Regional XRT?

Problem:
Not much information exists on the subject!
NSABP B-18/B-27 Combined Analysis

Operable Breast Cancer

3,088 Patients
356 LRR as First Events

10-Year Cum. Incidence of LRR According to Treatment Arm

According to Type of Surgery

## Combined Analysis of B-18/B-27 Independent Predictors of LRF

<table>
<thead>
<tr>
<th>Lumpectomy + XRT (1890 Pts, 190 Events)</th>
<th>Mastectomy (1070 Pts, 128 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;50 years vs. &lt;50 years)</td>
<td>Clinical Tumor Size (&gt;5 cm vs. ≤5 cm)</td>
</tr>
<tr>
<td>Clinical Nodal Status (+) vs. (-)</td>
<td>Clinical Nodal Status (+) vs. (-)</td>
</tr>
<tr>
<td>Node(+) vs. Node(-)/pCR</td>
<td>Node(+) vs. Node(-)/pCR</td>
</tr>
</tbody>
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### 10-Year Cum. Incidence of LRF

#### Lumpectomy Patients, ≥50 years

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>n=90</td>
<td>3.3</td>
<td>3.1</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=348</td>
<td>3.4</td>
<td>4.4</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=123</td>
<td>2.5</td>
<td>2.7</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=31</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=58</td>
<td>1.7</td>
<td>1.7</td>
<td>7.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Lumpectomy Patients, <50 years

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n=135</td>
<td>2.9</td>
<td>4.9</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=376</td>
<td>5.3</td>
<td>5.3</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=223</td>
<td>7.3</td>
<td>7.3</td>
<td>11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=346</td>
<td>2.9</td>
<td>3.9</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=135</td>
<td>4.9</td>
<td>5.9</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10-Year Cum. Incidence of LRF
Mastectomy Patients, ≤ 5 cm


10-Year Cum. Incidence of LRF
Mastectomy Patients, > 5 cm


10-Year Cum. Incidence of LRF
According to Number of Positive Nodes

10-Year Cum. Incidence of LRF According to Number of Positive Nodes

<table>
<thead>
<tr>
<th>Number of Positive Nodes</th>
<th>Mastectomy ≤ 5 cm</th>
<th>Mastectomy &gt; 6 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clin. Node Negative</td>
<td>11.3</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Nomogram for Prediction of 10-Year Rate of LRR After NC: Lumpectomy + XRT

| Clin N (+) | Clin N (-) |

Nomogram for Prediction of 10-Year Rate of LRR After NC: Mastectomy

| Clin N (-) | Clin N (+) |
Summary of NSABP B-18/B-27

- The results of B-18/B-27 clearly demonstrate that in addition to age and clinical factors available before NC (such as clinical tumor size and clinical nodal status), pCR in the breast and pathologic axillary nodal status have major impact on the rates of LRR.

- The results further suggest that pCR in the breast with negative axillary nodes minimizes the effect of age, clinical tumor size, and clinical nodal status on the rates of LRR.

Using NC in Order to Tailor XRT

- These results indicate that node-positive pts at presentation (candidates for comprehensive XRT) who become pathologically node-negative after neoadjuvant chemotherapy have low rates of LRR without XRT after mastectomy or breast XRT after lumpectomy and may not need more XRT.

- However, before such a strategy becomes the standard of care, RCT data are needed to demonstrate that the use of XRT would not significantly improve breast cancer recurrence.

- If so, this will produce a major paradigm shift in the LR management of early-stage BC.

NRG 9353: Schema

Clinical T1-3N1M0 BC

Axillary Node (+) (FNA or Core Needle Biopsy)

Neoadjuvant Chemo (+ Anti-HER-2 Therapy for HER-2 neu + Pts)

Path Negative Axillary Nodes at Surgery (Axillary Dissection or SNB + Axillary Dissection)

Stratification
- Type of Surgery
- ER Status, HER-2 Status
- pCR in Breast

Randomization
- No Regional Nodal XRT with Breast XRT if BCS and No Chest Wall XRT if Mastectomy
- Regional Nodal XRT with Breast XRT if BCS and Chest Wall XRT if Mastectomy
NRG 9535: Objectives

- **Primary:** To evaluate whether the addition of comprehensive XRT will significantly reduce BC recurrence.
- **Secondary objectives:**
  - To evaluate whether the addition of comprehensive XRT will significantly prolong overall survival, reduce LRR, reduce distant recurrence.
  - To compare patterns of postmastectomy reconstruction and the effect of XRT on cosmetic outcomes.
  - To compare the effect of adding XRT on QOL in patients who receive postmastectomy reconstruction.

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**Trial in Development:**
No Surgery in Patients with pCR

Operable Breast Cancer

- Complete clinical response
- Negative Ultrasound, Mammogram, MRI
- Negative Clip-guided biopsy (6 cores)

**RANDOMIZATION**

- No Surgery
- Lumpectomy

Breast Radiotherapy

**Endpoint:** Local Recurrence and Disease-Free Survival

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**Summary**

- In pts with operable BC, NC results in equivalent outcomes to those achieved with adjuvant chemotherapy but has several potential advantages.
- Information on outcome based on response to NC can be obtained on an individualized basis.
- Loco-regional therapy can be tailored based on tumor response in the breast and axillary nodes.
- This approach holds great promise as NC regimens (+ targeted biologics) become considerably more effective and as genomic and imaging technology allows for more accurate prediction and identification of pathologic complete responders.