Loco-Regional Management After Neoadjuvant Chemotherapy

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Clinical Rationale for Neoadjuvant Chemotherapy

• Neoadjuvant chemotherapy is the standard of care for patients with LABC and 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
Unique LR Management Issues in Patients Treated with Neoadjuvant Chemotherapy

• Accurate assessment of the location and extent of the primary breast tumor before and after NC

• Accurate assessment of axillary nodal status before and after NC

• Appropriate surgical management of primary breast tumor and axillary lymph nodes

• Optimal use of radiotherapy following NC
Individualizing LR Therapy with Neoadjuvant Chemotherapy in the Primary Breast Tumor

- Conversion of patients with inoperable tumors to operable candidates
- Conversion of mastectomy candidates to candidates for breast conserving surgery
- Improvement in cosmesis by reducing the size of lumpectomy in breast conserving surgery candidates with large tumors
Challenges in Decreasing the Size of the Lumpectomy Specimen

- Sometimes difficult to define the extent of residual tumor and as a result the amount of breast tissue to be removed at lumpectomy

- Ideally one would want to remove less than originally required
How Do Tumors Shrink in Response to Neoadjuvant Chemotherapy?
What is Adequate Surgical Resection after Neoadjuvant Chemotherapy?
MRI Phenotypes

1: Single predominant mass with identifiable rim, displacing
2: Nodular pattern, irregular borders
3: Diffuse infiltrative pattern
4: Patchy enhancement
5: Septal spread

MRI Can Overestimate the Amount of Residual Disease

Before Neoadjuvant Chemo

After Neoadjuvant Chemo
Neoadjuvant Chemotherapy
Surgical Planning

• Identification of the exact tumor location in cases of clinical and radiologic complete response

• Preoperative titanium clip placement

Before NC

After NC
Ensuring Adequate Surgical Resection after Neoadjuvant Chemotherapy

- Identify pattern of shrinkage and extent of residual tumor preoperatively (mammogram, US, MRI)
- Accurately localize tumor bed area in cases of clinical/radiologic complete response
- Thoroughly evaluate margins (intraoperatively and postoperatively)
- Perform additional resection if necessary
Local Recurrence with Neoadjuvant vs. Adjuvant Chemotherapy
NSABP B-18

Cumulative Incidence of In-Breast Recurrence

P = 0.12

• Postop: 7.6 %
• Preop: 10.7 %

EBCTCG 2006 Overview Analysis: Neoadjuvant vs. Adjuvant Chemotherapy

Local Recurrence

- All patients had surgery in the adjuvant chemo group
- Not all patients had surgery after neoadjuvant chemotherapy
Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis

Loco-regional Recurrence

Avril/Mauriac
Danforth
Gazet
Makris
NSABP B-18
Scholl
Scholl/Broet
Semiglazov
Van der Hage
ALL

Risk Ratio (95% CI) for Neoadjuvant vs. Adjuvant Treatment

• Studies of XRT without Surgery:
  - RR 1.53
  - p=0.009
• Studies of Surgery + XRT:
  - RR 1.10
  - p=0.44

Tailoring Loco-Regional XRT with Neoadjuvant Chemotherapy
Rates and Predictors of LRR in the Adjuvant and Neoadjuvant Settings

- For pts with ESBC who receive surgery first there is abundant information on rates and predictors of LRR with or without adjuvant systemic therapy

- There is limited information on rates and predictors of LRR in patients who receive neoadjuvant chemotherapy
Limited Information on Rates and Predictors of LRR after NC

- Fewer patients with operable breast cancer are being treated with neo- vs. adjuvant chemo.

- By the time NC became established as an alternative to adjuvant chemo, the role of LRR XRT in node+ BC was well established.

- Thus, most available NC databases include patients who, at the discretion of the treating physician, were treated with postoperative XRT (either because of path + nodes at surgery or because of presumed node + status before NC).
NSABP B-18/B-27: Combined Analysis

B-18
Operable Breast Cancer

R

Surgery
AC x 4

Surgery
AC x 4

B-27
Operable Breast Cancer

R

Surgery
AC x 4

Surgery
AC x 4

Docetaxel x 4

Surgery

AC x 4

Surgery

Docetaxel x 4

3,088 Patients
356 LRR as First Events

# NSABP B-18/B-27: Combined Analysis

## Independent Predictors of LRF

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

Using Neoadjuvant Chemotherapy in Order to Tailor XRT

• These results indicate that node-positive patients at presentation (candidates for comprehensive XRT) who become pathologically node-negative after NC have low rates of LRR without any XRT (after mastectomy) or with breast XRT only (after lumpectomy) and may not need additional XRT.

• However, before such a strategy becomes the standard of care, randomized clinical trial data are needed to demonstrate that the use of XRT would not significantly improve breast cancer recurrence.
NSABP B-51/RTOG 1304 (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)

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
Conclusions

• In pts with operable BC, neoadjuvant chemotherapy has several potential clinical advantages

• Information on outcome based on tumor response 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 new neoadjuvant chemotherapy regimens (+ targeted biologics) become considerably more effective and as genomic and imaging technology allows for more accurate prediction and identification of pathologic complete responders