Post-Mastectomy RT after Neoadjuvant Chemotherapy (NAC)

Jay R. Harris, M.D.
Dana-Farber Cancer Institute
Brigham and Women’s Hospital
Harvard Medical School
Conclusions

• When considering PMRT, use both initial clinical and final path stages
• If LABC, give PMRT even if pCR
• If ypN+, give PMRT
• If early stage with pCR, no PMRT
• After mastectomy, survival gain isn’t linked to LRR risk → need RCT’s
Neoadjuvant Chemotherapy (NAC)

It is ironic that NAC, which was developed in the hope of improving the results of chemotherapy, has had its major practical impact on improved (i.e., less) local therapy.
Major Issues regarding RT after NAC

• The guidelines for the use of RT after NAC are not well established

• Which patients are appropriate for BCT?

• Which patients are appropriate for PMRT?
Timing of SNB

• Many radiation oncologists in the U.S. favor doing SNB prior to NAC

• However, the advantages of delayed SNB clearly outweigh the disadvantages

• These include 1 not 2 operations, ability to assess response, and fewer ALND’s
Axillary Staging Prior to NAC

• We also favor axillary US and FNA if suspicious

• With FNA+, there is increasing evidence that delayed SNB is a viable option

• This is particularly true with use of dual tracer and resection of at least 2 SLNs
Which patients are appropriate for PMRT?

- This is a harder question and we are still getting data on this issue

- So far, we have learned that the need for PMRT is determined both by the initial clinical stage and the final path stage
LR after NAC followed by Mastectomy and no RT (MD Anderson)

- Retrospective analysis of 150 patients treated with either pre-op Doxorubicin regimen or Paclitaxel without post-op RT

- Stage: I - 1%; II - 43%; IIIA - 23%; IIIB - 25%; and IV - 7%

(Ref: Buchholz TA et al. IJROBP0: 53; 880, 2002)
NAC and MRM, No RT

• Crude 5-Yr LR related to pN:
  0+: 10%    1-3+: 17%    4-9+: 47%

• These LR rates after NAC by nodal stage are greater than rates after initial surgery

• NB: Among 18 patients with pT&N CR, the 5-Yr rate of LR = 19%
5-Year LR by # + Nodes: Post-op vs. Pre-op

- 0 +LN: ADJ 7%, NEO 12%, p=0.143
- 1-3 +LN: ADJ 10%, NEO 18%, p=0.087
- >3 +LN: ADJ 23%, NEO 53%, p=0.001
Matching Patients by Clinical Stage

• Clinical stage was more advanced for pre-op patients than for post-op patients and later matched by clinical stage

• Much, but not all, of the difference in LR is corrected by use of clinical stage
5-Year LR by # + Nodes: Post-op vs. Pre-op (matched by cTN)
Clinical Implication

• Path stage after PST does not have the same prognostic value for LR as the same path stage with initial surgery

• Key Observation: Both the initial clinical and the final pathologic stage must be used to determine the LR risk
Implications: Pre-op Ctx + MRM

- LABC patients should receive PMRT regardless of final path findings
- Use of PMRT in Stage I/II patients with 1-3+ nodes after NAC less well defined
- Experience from NSABP is most informative
NSABP Experience

• Includes the preop AC arm from B-18 and the preop AC +/- T arms from B-27

• Analysis is based on 1,071 mastectomy patients with 131 LR’s

• SNB performed after NAC; pCR was defined as no residual invasive disease

Ref: Mamounas E et al JCO 2012 30: 3960
MVA: Predictors of LRR after Mastectomy

• Clinical tumor size at presentation
• Clinical node status at presentation
• Path node status after PST
• Path response in the breast

Both the initial clinical and the final path stage must be used to determine LR risk
<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT:  &gt; 5 v \leq 5 cm</td>
<td>1.58</td>
<td>1.12 – 2.23</td>
<td>.0095</td>
</tr>
<tr>
<td>cN+ v cN-</td>
<td>1.53</td>
<td>1.08 - 2.18</td>
<td>.017</td>
</tr>
<tr>
<td>ypN-/no breast pCR v ypN-/breast pCR</td>
<td>2.21</td>
<td>0.77 – 6.30</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ypN+ v ypN-/breast pCR</td>
<td>4.48</td>
<td>1.64 – 12.21</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
Notes:

Any ypN+ $\rightarrow$ LRR > 10%

pCR $\rightarrow$ LRR is low

(A) Mastex T ≤ 5-cm

(B) Mastex T > 5-cm
Which patients should get PMRT?

- The need for PMRT is determined by the initial cStage and the final pStage
- LABC patients should get PMRT even pCR
- Any ypN+ patient should get PMRT
- Operable patients with pCR should not
- Patients with ypN-/no breast pCR: ? PMRT
PMRT with ypN-/no breast pCR

- Consider degree of response (MP, RCB)
- Consider especially in -/-/- patients
- Consider in younger patients with less competing risks
Who get a Survival Gain from PMRT?

• It was initially thought that reduction in LRR was linked to survival gain (2005)

• So called 4 to 1 ratio between reduction in LRR at 5 years and survival gain at 15 yrs

• Newer data from EBCTCG and others no longer shows this linkage
Newer Data on LRR and Survival Gain

• Updated data from EBCTCG now shows greater survival gain for PMRT with 1-3+ nodes than with > 3+ nodes even though greater reduction in LRR with > 3+ nodes

• This is supported by results from MA.20

Refs: EBCTCG Preliminary Data shown 2012
Whelan T et al, ASCO 2011 abstract
Trials of Mast+AD±RT (EBCTCG)

• Reduction in recurrence (LR or DM) is similar for patients with 1-3+ vs ≥ 4+ nodes, but improvement in survival is somewhat greater in 1-3+ patients

• This is due to the greater competing risk of DM in the ≥ 4+ patients
Trials of Mast+AD±RT: pN1-3, full AD

**Recurrence**
- 1314 women
- 10-year gain 11.4% (SE 2.9)
- Mast+AD 45.8%
- Mast+AD+RT 34.4%

**Breast Cancer Mortality**
- 1314 women
- 15-year gain 9.4% (SE 2.9)
- Logrank 2p = 0.005

65% had chemotherapy, mostly CMF

Trials of Mast+AD ±RT: pN1-3, full AD
Trials of Mast+AD±RT: pN4+ full AD

**Recurrence**
- 1652 women
- Mast+AD 75.0%
- Mast+AD+R 65.9%
- 10-year gain 9.1% (SE 2.7)

**Breast Cancer Mortality**
- 1652 women
- Mast+AD 68.7%
- Mast+AD+RT 66.4%
- 15-year gain 2.3% (SE 2.9)
- logrank 2p > 0.1; NS
Updated EBCTCG Results

• The survival benefit of PMRT is not linked to reduction in LR → Need RCT’s

• PMRT is at least as beneficial in patients with 1-3+ as in ≥ 4 + nodes

• Impact of chemotherapy unclear; impact seen with ≥ 4 + nodes, but not 1-3+
Regional Node Irradiation (RNI):
- All patients had ALND
- SC and Axillary Apex
- IMN’s
MA.20 Patients

- BCS with clear margins
- All patients had a level I/II ALND
- 85% had 1-3 positive nodes
- 91% received adjuvant chemotherapy
- HR+ patients received hormonal rx
## 5-Year Results

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>LR DFS</th>
<th>Distant DFS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBI</strong></td>
<td>84.0%</td>
<td>94.8%</td>
<td>87.3%</td>
<td>89.5%</td>
</tr>
<tr>
<td><strong>WBI + RNI</strong></td>
<td>89.7%</td>
<td>96.8%</td>
<td>91.6%</td>
<td>91.9%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>
## Hazard Rate (HR) Results

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>LR DFS</th>
<th>Distant DFS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.67</td>
<td>0.58</td>
<td>0.64</td>
<td>0.76</td>
</tr>
<tr>
<td>P-value</td>
<td>0.003</td>
<td>0.02</td>
<td>0.002</td>
<td>0.07</td>
</tr>
</tbody>
</table>
MA.20

Need to see manuscript (currently at NEJM)

Results are striking, but a bit surprising: 1 – Δ DM = Δ LRR

The recent results of the similar EORTC trial support MA.20 (European Cancer Congress)
EORTC 22922/10925 Study Design

- **N+ or Medial N- post-BCS or Mastectomy**

  - **No RNI**
  - **RNI**

**Regional Node Irradiation (RNI):**
- SC and Axillary Apex
- IMN’s
EORTC Patients

- 56% were N+ and 14.2% were stage III
- 76% had BCT
- 73% of mastectomy patients had CW RT
- Adjuvant systemic therapy in 99% of N+ patients and 66% of N- patients
- Median FU = 10.9 years
# Hazard Rate (HR) Results

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>Distant DFS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.89</td>
<td>0.86</td>
<td>0.87</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04</td>
<td>0.02</td>
<td>0.056</td>
</tr>
</tbody>
</table>
Recent Trials of PMRT/RNI

• With routine adjuvant systemic therapy, these preliminary data suggest benefit to PMRT/RNI (in intermediate risk patients)

• Survival benefit not longer linked to reduction in LR

• Need RCT’s to assess survival benefit
New Trials of Local Rx after NAC in U.S.

- NRG 9353
- Alliance A11101
NRG 9353

cT1-3N1M0  Axillary Node (+ by fna or core)
NAC + antiHer2 if HER2+
pN- (SNB or ALND)
Randomized to

No Regional Nodal RT
Breast RT alone if BCT
No CW RT if mastex

or

Regional Nodal RT
With breast if BCT
CW RT if mastex
Alliance A11101

cT1-3N1M0  Axillary Node (+ by fna or core)  
NAC + antiHer2 if HER2+

pN+ (SNB or ALND)

Randomized to

Breast/CW + Regional Nodal RT

or

ALND and Breast/CW + Regional Nodal RT
Conclusions

• When considering PMRT, use both initial clinical and final path stages

• If LABC, give PMRT even if pCR

• If ypN+, give PMRT

• If early stage with pCR, no PMRT

• After mastectomy, survival gain isn’t linked to LRR risk → need RCT’s