The Clinical Implications of the NCIC-CTGMA20 Trial

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Does Regional Therapy Reduce Systemic Failure and Improve Breast Cancer-Specific Survival?
Clinical Implications of the MA20 Trial

Twenty-five year follow-up of BO4: RM vs. TM vs. TM + RT

Despite 18% axillary failure rate in clinical No treated with TM, no difference in DDFS, DFS, OS.

Fisher et al. NEJM 2002
Clinical Implications of the MA20 Trial

MA20 Study Schema: A Phase III Study of Regional Radiation Therapy in Early-Stage Breast Cancer

Stratify

- Number of positive nodes (0, 1-3, >3)
- Number of nodes removed (<10, ≥10)
- Type of chemotherapy (i.e., anthracycline, other, none)
- Hormonal therapy (yes, no)
- Treatment center

Randomize

Breast Alone Radiation Therapy
Breast and Nodal Radiation Therapy

NCIC-CTG MA20 Eligibility Criteria

Inclusion Criteria

- Invasive, female breast cancer
- Breast conserving surgery plus Level I, II axillary dissection (or SLN only if node negative)
- Systemic therapy with chemotherapy, hormones, or both
- Moderate to high risk of regional recurrence on the basis of:
  - Involved axillary nodes
  - Or if node-negative, patients must have tumors ≥2.0 cm in diameter, have <10 nodes dissected, and have either grade 3 histology, estrogen receptor-negative disease, or the disease present in lymphovascular spaces in the breast

Clinical Implications of the MA 20 Trial

- Planned accrual 1822 patients (actual 1832)
- Powered to detect 5% improvement in survival at 5 years
- DSMC approved plan for protocol specified interim analysis of patterns of recurrence, survival and toxicity at 5 year
- Based upon results at interim analysis, DSMC advised results be released

Whelan et al. ASCO 2011 LBA1003
# Clinical Implications of the MA 20 Trial

## MA20

**5-Year Results**

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>WBI + RNI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated LR DFS*</td>
<td>94.5%</td>
<td>96.8%</td>
<td>.02</td>
</tr>
<tr>
<td>Distant DFS</td>
<td>87.0%</td>
<td>92.4%</td>
<td>.002</td>
</tr>
<tr>
<td>DFS</td>
<td>84.0%</td>
<td>89.7%</td>
<td>.003</td>
</tr>
<tr>
<td>OS</td>
<td>90.7%</td>
<td>92.3%</td>
<td>.07</td>
</tr>
</tbody>
</table>

*identical no. IBTR’s in each group

*Whelan et al. ASCO 2011 LBA1003*
Clinical Implications of the MA 20 Trial

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>WBI</th>
<th>WBI + RNI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis ≥ grade 2</td>
<td>0.2%</td>
<td>1.3%</td>
<td>.01</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.1%</td>
<td>7.3%</td>
<td>.004</td>
</tr>
</tbody>
</table>

Whelan et al. ASCO 2011 LBA1003
A second trial from the EORTC is asking a similar question…
EORTC Phase III Trial 22922/10925

Irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer: Trial with 4004 patients.

Philip Poortmans, Alain Fourquet, Laurence Collette, Henk Struikmans, Harry Bartelink, Carine Kirkove, Volker Budach, Philippe Maingon, Maria Carla Valli, Walter Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups
EORTC Trial Design

Resectable breast cancer, stage I-III

A pN+

B pN-; central or medial

→ ARM 1: no irradiation of IM-MS nodes.

R

→ ARM 2: IM-MS node irradiation (50 Gy).
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>No IM-MS</th>
<th>IM-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>54.0 years</td>
<td>54.0 years</td>
</tr>
<tr>
<td><strong>Post-menop.</strong></td>
<td>58.8 %</td>
<td>58.9 %</td>
</tr>
<tr>
<td><strong>BCT</strong></td>
<td>77.0 %</td>
<td>76.4 %</td>
</tr>
<tr>
<td><strong>pT1/T2/T3</strong></td>
<td>61/35/3 %</td>
<td>60/36/4 %</td>
</tr>
<tr>
<td><strong>pN0/N+</strong></td>
<td>45/55%</td>
<td>45/55%</td>
</tr>
<tr>
<td><strong>Adjuvant ther.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15.1 %</td>
<td>16.4 %</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24.7 %</td>
<td>24.5 %</td>
</tr>
<tr>
<td>Horm. therapy</td>
<td>30.5 %</td>
<td>28.9 %</td>
</tr>
<tr>
<td>Both</td>
<td>29.7 %</td>
<td>30.2 %</td>
</tr>
</tbody>
</table>

Clinical Implications of the MA 20 Trial

Provocative Results!

2% improvement in LRC translates into 5% improvement in DDFS and DFS at 5 years

Unclear if magnitude of LR benefit is only 2% since no radiographic assessment of nodal involvement
Should MA 20 results change management?

Could say “No, wait for EORTC results”

But these results do not stand alone….

- PMRT data overall
- PMRT results with 1-3 positive nodes

(Loco-) Regional control improves breast cancer-specific survival
Post-Mastectomy Radiotherapy

EBCTCG Overview

Effect of RT on breast cancer mortality and on all-cause mortality after mastectomy with axillary clearance

*EBCTCG, Lancet, 2005*
Patterns of Failure in Danish Trials 82b and 82c

Frequency and Localization of Locoregional Recurrence (first site of failure) as a Function of Radiation Therapy

<table>
<thead>
<tr>
<th>Localization of Recurrence</th>
<th>No Local Recurrence</th>
<th>Chest Wall</th>
<th>Axilla</th>
<th>Sup./Inf. Clavicular</th>
<th>All Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>92%</td>
<td>5% (2%)</td>
<td>2% (1%)</td>
<td>2% (1%)</td>
<td>8% (3%)</td>
</tr>
<tr>
<td>No radiotherapy</td>
<td>67%</td>
<td>16% (3%)</td>
<td>13% (2%)</td>
<td>5% (2%)</td>
<td>33% (6%)</td>
</tr>
</tbody>
</table>

Data from 3,083 patients included in DBCG 82 b & c trials
Numbers in parentheses indicate patients with concomitant distant metastasis

*Overgaard et al. Sem Rad Onc 1999*
Post-Mastectomy Radiotherapy: Indications for Treatment

The Danish Breast Cancer Cooperative Group

- Paraffin blocks from 1,000 patients with 8 or more nodes removed randomized on DBCG 82B and 82C stained for ER, PR, HER-2
- Median F/U 17 years for 1,000 patients
- Established three prognostic subgroups

Kyndi et al, Radio Oncol, 2009
Post-Mastectomy Radiotherapy: Indications for Treatment

High local recurrence is not associated with large survival reduction after PMRT

3 prognostic groups established:

**Good:** four out of five favorable criteria (< 3 positive nodes, tumor size < 2 cm, grade 1; ER + or PR+, HER2 neg)

**Poor:** at least two out of three unfavorable criteria (>3 positive nodes, tumor size > 5 cm, grade 3)

**Intermediate:** other than good or poor

*Kyndi et al, Radio Oncol, 2009*
5-year local recurrence probability and 15-year breast cancer mortality within the good, the intermediate and the poor prognostic subgroups in high-risk breast cancer patients randomly assigned to receive or not receive PMRT

*Kyndi et al, Radio Oncol, 2009*
How should we interpret these findings given the results from Z-11?
**Z-11**

- Patients randomized: n=891
- cl T<sub>1,2</sub> N<sub>0</sub>
  - BCT
  - SLND only: n=446
  - ALND: n=445

No difference in regional control, DFS, OS

**MA-20**

- Patients randomized: n=1832
- cl T<sub>1-3</sub>, N<sub>0-1</sub> *
  - BCT
  - ALND: n=916
  - ALND+RNI: n=916

Significant benefit in regional control, DDFS, DFS

* 85% patients with 1-3 positive nodes
Statistical Issues

- MA-20 completed accrual; Z-11 did not

- Both underestimated survival, especially Z-11
  
  Z-11 based power of trial on 5x more deaths than number observed. Due to overestimation of number of deaths, planned interim analyses abandoned. However, Type I error that SLND not inferior to ALND preserved. And while power was decreased, less of concern since positive trend in favor of SLND.

MA-20: Amendment to conduct POF and toxicity analysis at first interim in analysis for survival
Comparing the Two Studies: My Thoughts

• Trials asking different but related questions regarding regional control and impact on BCSS

• Tumor burden appears to be greater in patients enrolled on MA-20 but populations appear to be overlapping to some degree

• QA of RT fields on MA-20. No QA in Z-11. Do we really know how patients were treated?

We do not want to deny patients a potential DFS advantage but also do not want to over-treat (although complication risks modest in MA-20).
My Thoughts….

We need more information to better understand disparate results.

- MA-20: Outcome data by number positive nodes/involvement of micromets

- Z-11: Information regarding RT fields; outcomes by extent of nodal disease (beyond micromets); further follow-up since 83% had ER disease and late recurrences likely

In the meantime, we each will need to decide where to “set the bar”
I am comfortable not offering SCV, ICV, IMN RT in presence of micromets only after SLND.

Very good prognosis (now Stage IB) although B32 did show small but significant worsening of DDFS, DFS and OS with occult metastases; cannot say results would have differed by type of surgery.

But I use high tangents to cover axillary bed.

For patients with 1 or 2 macromets/p SLND and no ALND, I discuss RNI (consistent with our PMRT policy).
Use of high tangential fields to cover axillary nodal levels I and II

Alco et al. Br J Radiol 2010
This is where I have set the bar:

- SLND and micromets: Breast and lower axillary RT
- SLND and 1-2 macromets: Discuss risks vs. benefits; strongly consider axillary, SCV, IMN RT with breast RT
- ALND and 1-2 macromets: Discuss risks vs. benefits; strongly consider SCV, IMN RT with breast RT
Where will you set the bar?
1. Different breast cancer population than Z-11

2. The relationship of local failure and survival is novel compared to historical trials
<table>
<thead>
<tr>
<th></th>
<th><strong>Z-11</strong></th>
<th><strong>MA. 20</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong> median / mean(yrs)</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td><strong>TUMOR SIZE (%)</strong> T-2</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td><strong>ER (%)</strong> Negative</td>
<td>16.5</td>
<td>25</td>
</tr>
<tr>
<td><strong>GRADE (%)</strong></td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td><strong>Sentinel node biopsy (%)</strong></td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td><strong>Median nodes removed</strong></td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

*Whelan et al., ASCO, 2011*
*Giuliano et. al., JAMA, 305:2011*
*Giuliano et. al., Ann. of Surg., 252: 2010*
# NCIC MA.20 Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>WBI</th>
<th>WBI + RNI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 916</td>
<td>n = 436</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>90.7%</td>
<td>92.5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Disease Free Survival</td>
<td>84 %</td>
<td>89.7 %</td>
<td>0.003</td>
</tr>
<tr>
<td>Distant Disease FS</td>
<td>87%</td>
<td>92.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>Local Regional Recurrence</td>
<td>5.2%</td>
<td>3.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>2.7%</td>
<td>2.7 %</td>
<td>-</td>
</tr>
<tr>
<td>Axillary Recurrence</td>
<td>2.3%</td>
<td>0.4%</td>
<td>-</td>
</tr>
</tbody>
</table>
EBCCTG: Outcome by Initial Risk of Local Recurrence

12 comparisons with >10% local recurrence risk: 25 276 women, 51% with node-positive disease

- 5-year gain 18.7% (SE 0.5)
- 15-year gain 5.0% (SE 0.8)

Logrank 2p < 0.00001

> 10% local recurrence risk
5-year local recurrence probability and 15-year breast cancer mortality within the good, the intermediate and the poor prognostic subgroups in high-risk breast cancer patients randomly assigned to receive or not receive PMRT

Kyndi et al, Radio Oncol , 2009
Stockholm Trial: Competing Risk Analysis

- 1971-76, n = 960 MRM
- 316 Preop RT, 323 Postop RT, 321 No RT
- preop excluded from this analysis
- No systemic therapy
- F/U 16.3 years

PMR in Node + cases may decrease the incidence of DM by preventing LR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% LR (p-value)</th>
<th>% DM (p-value)</th>
<th>% OS (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node -</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>25 (p&lt; 0.004)</td>
<td>27 (p = ns)</td>
<td>64</td>
</tr>
<tr>
<td>S + RT</td>
<td>5 (p&lt; 0.004)</td>
<td>27 (p = ns)</td>
<td>67</td>
</tr>
<tr>
<td>Node +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>56</td>
<td>72</td>
<td>61</td>
</tr>
<tr>
<td>S + RT</td>
<td>19 (p&lt; 0.004)</td>
<td>40 (p = 0.01)</td>
<td>70</td>
</tr>
</tbody>
</table>

Arriagada, JCO 13:1995
## My Bar: RNI after BCS and ALND

<table>
<thead>
<tr>
<th>Stage</th>
<th>WBI</th>
<th>WBI + RNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-1, N-1 (1-2+)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>T-1, N-1, (3+)</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>II B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-2 (&lt; 3 cm), N -1 (1+)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>T-2 (&gt; 3 cm), N-1, (&gt; 1+)</td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>