Removal of the Breast Primary in Metastatic Breast Cancer Patients

Mylin A. Torres
Assistant Professor
Department of Radiation Oncology
Emory University
Background

Flanigan et al. NEJM 2001

![Graph showing survival rates for Interferon alone and Nephrectomy plus Interferon over months, with numbers at risk for each group also provided.](image-url)
Potential Mechanisms

• Remove a source of tumor promoting growth factors or immunosuppressive cytokines

• Decrease tumor burden and the number of “seeds” to plant in the “soil”
  – Increase the interval of time before a lethal tumor burden accumulates
Surgery to remove the Breast Primary in Breast Cancer Patients with Metastatic Disease

### Institutional Series

**Showing Survival Benefit**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Surgery N(%)</th>
<th>Multivariate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fields et al (2007)</td>
<td>409</td>
<td>187 (46)</td>
<td>Sx: 0.53 (0.42 – 0.67)</td>
<td></td>
</tr>
<tr>
<td>Blanchard et al (2008)</td>
<td>395</td>
<td>242 (61)</td>
<td>Sx: 0.71 (0.56 - 0.91)</td>
<td></td>
</tr>
<tr>
<td>Bafford et al. (2009)</td>
<td>147</td>
<td>64 (41)</td>
<td>Sx: 0.47 (p=0.003)</td>
<td></td>
</tr>
<tr>
<td>Le Scodan et al (2009)</td>
<td>581</td>
<td>71 (12)</td>
<td>RTh: 0.70 (0.58 -0.85)</td>
<td></td>
</tr>
<tr>
<td>Shien et al (2009)</td>
<td>344</td>
<td>160 (47)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Nguyen et al (2011)</td>
<td>733</td>
<td>378 (52)</td>
<td>Sx and/RTh: 0.78 (0.64 – 0.94)</td>
<td></td>
</tr>
<tr>
<td>Pathy et al (2011)</td>
<td>375</td>
<td>139 (37)</td>
<td>Sx: 0.72 (0.56 – 0.94)</td>
<td></td>
</tr>
<tr>
<td>Perez-Fidalgo (2011)</td>
<td>208</td>
<td>123 (59)</td>
<td>p = 0.001</td>
<td></td>
</tr>
</tbody>
</table>
# Population Based Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sx N (%)</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiterkamp et al (2009)</td>
<td>728</td>
<td>288 (40)</td>
<td>Sx: 0.62 (0.51 – 0.76)</td>
</tr>
<tr>
<td>Gnerclich et al (2007)</td>
<td>9734</td>
<td>4578 (47)</td>
<td>Sx: 0.62 (0.59 – 0.66)</td>
</tr>
<tr>
<td>Rapiti et al (2006)</td>
<td>300</td>
<td>127 (42)</td>
<td>0.6 (0.4 -1.0)</td>
</tr>
<tr>
<td>Khan et al. (2002)</td>
<td>16023</td>
<td>9162 (57)</td>
<td>Sx: 0.61 (0.58 – 0.65)</td>
</tr>
</tbody>
</table>
Surgical Removal Of Primary Tumor And Axillary Lymph Nodes In Women With Metastatic Breast Cancer At First Presentation: A Randomized Controlled Trial

PI: R A Badwe
Professor Surgical Oncology(Breast)
Tata Memorial Centre
Mumbai, India

Co-Investigators
V Parmar, R Hawaldar, N Nair, R Kaushik, S Siddique, A Nawle, A Budrukkar, I Mittra, S Gupta
To assess the effect of removal of primary tumor on overall survival in women presented with metastatic breast cancer
• N=350
• Detect an expected improvement in overall survival of 6 months in patients treated with breast surgery compared to baseline median survival of 18 months in patients not treated with surgery. alpha = 0.05, power of 80%
TRIAL SCHEMA

Randomization (N=350)

Loco-regional Treatment (#173)

LR Surgery* +/- Ovarian Ablation (40)

Radiotherapy + Hormone Therapy in hormone sensitive tumors** (84)

No Loco-regional Treatment (#177)

Hormone Therapy (96) whenever indicated including Ovarian Ablation (34)

---

* Loco-regional Therapy: BCT / MRM with supraclavicular lymph node clearness whenever indicated
** Tamoxifen in pre menopausal women and AI in Post menopausal women/ post Oophorectomy in pre menopausal women
Local Progression Free Survival

HR = 0.16, 95%CI = 0.10 - 0.26  p = 0.00

At Risk
No LRT 177  75  28  13  9  4  1
LRT 173  91  45  20  5  3  1

Cum Survival

Time in Months

LRT (N=173) 89%
No LRT (N=177) 47.5%
Distant Progression Free Survival

HR = 1.42, 95% CI = 1.08 - 1.85, p = 0.01

No LRT (N=177) 47.5%
LRT (N=173) 28.3%
Conclusions

• Loco-regional treatment of the primary tumor in women with metastatic breast cancer did not confer any survival advantage and hence should not be offered as a routine practice.

• The lack of survival benefit is due to a tradeoff between local control and distant disease progression.

• Removal of the primary tumor appeared to confer a growth advantage on distant metastases.
Limitations

- Her2+ patients did not receive trastuzumab
- Statistical assumption regarding baseline median survival in patients with metastatic breast cancer is low
- Study was not powered to detect a difference of <6 months or <4% change in overall survival
- Survival was low in both arms compared with more modern series
- Supraclavicular lymph node surgical clearance in N3 patients
Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish Study (Protocol MF07-01)


On behalf of the Turkish Federation of Societies for Breast Diseases
Design MF07-01

**Presentation**
- Stage IV Breast Cancer

**Randomization**
- Systemic Therapy
- Initial Local Therapy of Breast ± Axilla Plus Systemic Therapy

**Follow-up**
- Local therapy for local progression
- Time to local Progression
- Overall Survival
- Time to local Progression
- Overall Survival
Objectives

• Primary: To assess if early surgical treatment of the primary breast cancer in women presenting with Stage IV disease effects overall survival

• Secondary:
  – Progression Free Survival (local)
  – Quality of Life
  – Morbidity
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Death</th>
<th>Median (months)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>140</td>
<td>38</td>
<td>46</td>
<td>.76 (0.49-1.16)</td>
<td>.20</td>
</tr>
<tr>
<td>ST</td>
<td>138</td>
<td>48</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overall Survival and Number of Bone Metastasis

Solitary Bone Met.

Multiple bone Met.

<table>
<thead>
<tr>
<th>Solitary Bone</th>
<th>n</th>
<th>Death</th>
<th>Median</th>
<th>Mean</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>33</td>
<td>3</td>
<td>NR</td>
<td>47.5</td>
<td>.23 (0.86-0.89)</td>
<td>.02</td>
</tr>
<tr>
<td>ST</td>
<td>20</td>
<td>8</td>
<td>42</td>
<td>33.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple Bone</th>
<th>n</th>
<th>Death</th>
<th>Median</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>40</td>
<td>11</td>
<td>46</td>
<td>1.02 (0.43-2.43)</td>
<td>.94</td>
</tr>
<tr>
<td>ST</td>
<td>35</td>
<td>10</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• No statistical difference in overall survival at early follow-up

• Potentially important subgroup differences
  – Patients with solitary bone metastases had prolonged survival
  – Patients with aggressive phenotypes appear to derive less benefit from early surgical intervention
  – Multiple liver and/or pulmonary metastases had a significant worse prognosis with initial surgery
Limitations

- Biopsy was not required of metastatic disease even if solitary lesion was found
- Heterogeneous local and systemic treatments
- Patients did not have to achieve a CR or PR to systemic therapy before randomization
- Multiple unplanned subset analyses with small patient numbers without Bonferroni correction
- Short Follow-up
Take Home Message

• Neither study of metastatic disease supports the use of surgery to remove the primary breast tumor in women with metastatic breast cancer
Could Breast Surgery still benefit MBC patients?

- Oligometas
- Good performance status
- Her2+ patients treated with trastuzumab/pertuzumab
- Hormone receptor positive patients
- Patients with indolent disease
ECOG 2108: opened Feb 2011

880 368 Women with intact primary tumors
Metastatic disease at any site
(exclude sites with very poor prognosis)

Optimal systemic therapy
(eg NCC Planned drop-out rate 30%, actual 17%

Randomize 660 258 women with response or stable disease
Stratified by type of initial therapy
(endocrine/cytotoxic/combination)

330 129 Early local therapy once response/stable
Planned cross-over rate 15%, actual 12.5%
documented (surgery plus RT)

330 129 Delayed local therapy,