Ablative Radiotherapy for Oligo Metastatic Breast Cancer

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I have no disclosures relative to the presented material
Agenda

- General consideration
- Local Therapy
- NRG Clinical Trial
- Summary
Trends for Overall Survival for Metastatic Breast Cancer

- SEER 1998-2003
- 15,438 with MBC
- Median cancer specific survival 23 months.
- Improved with year diagnosed
- AA poorer survival

Dawood et al, JCO 26:2008
Improved Survival in MBC

• Development and widespread availability of modern systemic therapies

• Modern diagnostic tools allow the detection of early metastatic disease,

• “Lead time bias” - earlier diagnosis of metastatic disease falsely increasing the survival times of these patients

Is there a “potentially curable” subset?
• 263 (16.6%) achieved complete responses (CR) and
• 49 (3.1%) remained in CR for more than 5 years.

Greenberg JCO 1996
Do Oligometastases Exist?

Data Suggest:

- Metastases are not always widely disseminated
- Metastases do not always progress in multiple sites
- Patients with limited sites of metastases may not progress or progress only in sites of initial disease
- Therefore there may be a role for local therapy in selected patients
Lung Metastectomy
467 Breast Cancer Patients
International Registry of Lung Metastases

- 1960-1994
- 66% Solitary
- 84% complete (R0)
- Mean age 53 years
- Mean DFI 43 mo.
- Survival:
  - 5-year 35%
  - 10-year 20%
  - 15-year 18%
- Median survival - 35 months.
- Prognostic: R0, DFI > 36 months

Liver Resection: Breast Cancer Metastases

- Retrospective, highly selected, < 1 % of MBC
- Median survival range 14.5 – 63 mo.'s
- % 5-year survival – 14-61%

Pagani et al, JNCI 102: 2010

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of patients</th>
<th>Median OS (mo)</th>
<th>5-y OS (%)</th>
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<td>Adam, 2006</td>
<td>85</td>
<td>46</td>
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<td>Pocard, 2001</td>
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<td>ND</td>
<td>46 (4-y)</td>
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<td>Elias, 2003</td>
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<td>34</td>
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<tr>
<td>Pocard, 2000</td>
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<td>42</td>
<td>65 (3-y)</td>
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<td>Raab, 1998</td>
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<td>Sakamoto, 2005</td>
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<td>Vlastos, 2004</td>
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<td>Yoshimoto, 2000</td>
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<td>Elias, 1995</td>
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<td>Ercolani, 2005</td>
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<td>Singletary, 2003</td>
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<td>40 (DFS)</td>
<td>55 (3-y DFS)</td>
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<td>Pocard, 1997</td>
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<td>ND</td>
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</table>
Stereotactic Body Radiotherapy (SBRT)

- Immobilization
- Stereotaxis
  - Precise localization in 3 dimensions
- CT guides IGRT) each treatment
- Radiosurgery
  - Delivery of high doses of radiation in 1-5 treatments
  - 6-20 Gy/ fraction
  - Conformal
Advantages SBRT for Oligometastases

- Non invasive
- No surgical side effects/ Post op recovery
- Anatomical sites more amenable
# Stereotactic Body Radiotherapy for Oligometastases

<table>
<thead>
<tr>
<th>Radiation series</th>
<th>Year</th>
<th>Patients</th>
<th>Survival, %</th>
<th>Site</th>
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</thead>
<tbody>
<tr>
<td>Hoyer et al. (CRC)</td>
<td>2006</td>
<td>64</td>
<td>38-13</td>
<td>Lung, liver, adrenal</td>
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<tr>
<td>Hof et al</td>
<td>2007</td>
<td>61</td>
<td>47.8</td>
<td>Lung</td>
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<td>Kutz et al.</td>
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<td>69</td>
<td>24</td>
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<td>Rusthoven et al.</td>
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<td>Lee et al.</td>
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<td>70</td>
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<td>Kang et al. (CRC)</td>
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<td>Milano et al.</td>
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<td>Multiple</td>
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<td><strong>Breast cancer</strong></td>
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<td>74-47</td>
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<td><strong>All others</strong></td>
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<td>39-9</td>
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<td>Salama et al.</td>
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<td>56.7</td>
<td>Multiple</td>
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<td>Bae et al. (CRC)</td>
<td>2012</td>
<td>41</td>
<td>64-57</td>
<td>Lung, liver, lymph nodes</td>
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</tbody>
</table>

Retrospective, mostly solitary sites treated
Oligometastatic breast cancer treated with curative-intent SBRT

- 40 patients treated with curative intent
- OS: 2-year 76% and 4-year 59%,
- PFS: 2-year 44% and 4-year 38%,
European School of Oncology–Metastatic Breast Cancer Task Force (ESO–MBC)

• “A small but very important subset of MBC patients, for example those with a solitary metastatic lesion, can achieve complete remission and a long survival. A more aggressive and multidisciplinary approach should be considered for these selected patients. A clinical trial addressing this specific situation is needed”

NRG BR002/ Alliance Phase II/III Trial of Ablative Therapy For Oligometastatic Breast Cancer

(Formerly RTOG 1312)
NRG BR002/ ALLIANCE

Phase II

Breast Cancer Oligometastases (≤ 2) < 6 months first line systemic therapy

Randomization

ARM 1
- Standard Systemic Therapy
- Symptom Directed Palliative Therapy

Arm 2
- Total ablation of all metastases
- Standard systemic therapy

Targeted accrual = 143

STRATIFICATION:
- 1 v >1 metastasis
- Hormone receptor status
- Her 2 neu status
- Chemotherapy for MBC
Eligibility

• Pathologic confirmation of MBC
• ≤ 6 months first line systemic therapy
• ≤ 2 metastasis (≤ 4 pending NRG BR001)
• Local regional disease controlled (*No Overlap with E2108*)
• All metastasis amenable to SBRT or Resection (<5cm),
• Individual metastasis maximum diameter (in any dimension ≤ 5 cm)
• Zubrod performance status ≤ 2
Ineligibility

- Brain metastases
- Prior radiation treatment for metastatic disease
- Uncontrolled primary disease
- Exudative, bloody or cytological proven malignant effusions
Target Dose and Normal Tissue Constraints

<table>
<thead>
<tr>
<th>Metastatic Locations</th>
<th>Initial Starting Dose</th>
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<tbody>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
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<tr>
<td>Lung—Central</td>
<td>50 Gy (5 fractions)</td>
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<tr>
<td>Mediastinal/Cervical Lymph Node</td>
<td>50 Gy (5 fractions)</td>
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<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
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<tr>
<td>Spinal/Paraspinal</td>
<td>30 Gy (3 fractions)</td>
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<tr>
<td>Osseous</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Abdominal-pelvic metastases (lymph node/adrenal gland)</td>
<td>45 Gy (3 fractions)</td>
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</table>
ARM 2: Ablative Therapy

- SBRT for all metastases should be completed within 3 weeks of the first dose of SBRT.
- It is recommended that metastases are treated on an every other day schedule.
- Not all metastases need to receive radiation therapy on the same day.
Minimal Disruption To Systemic Therapy

- All SOC endocrine, Her 2, and bone drugs continue
- Experimental Tx need 30 day wash out
- Chemo hold prior to SBRT is very liberal
  - (ie: 14-21 days for 14-28 day cycles, 7 days for weekly regimens)
  - TDM-1 and everolimus follow chemo holds
- Can resume held drugs 14 day post SBRT
Statistics (Phase IIR)

Primary Endpoint:
Demonstrate improved PFS with the addition of Ablative Therapy to SOC v. SOC

130 evaluable patients will provide 95% power to detect improvement in PFS from

10.5 months to 19 months (HR=0.55)

One-sided type I error of 0.15.

- PFS will be measured from the date of randomization to the date of first PFS failure or last follow-up.
- Imaging q3 months for 2 years or until progression.
- After 2 years, imaging will be lengthened to q6 months or progression.
- After 5 years without progression, imaging per best clinical practice is recommended.)
Statistics (Phase III)

Primary Endpoint:
Demonstrate improved OS with the addition of Ablative Therapy to SOC v. SOC

246 additional evaluable patients for will provide 85% power to detect improvement in OS from:
28% to 42.5% (HR=0.67)
One-sided type I error of 0.025.
Total Phase IIIR/III accrual: 402 patients.

Integrated phase II/III design: 81% power for OS analysis at p= 0.025 (1-sided)
Oligometastases and CTC

- Hypothesis
  - ablative therapy -> prolonged PSF in patients with few or no CTCs at registration
  - ablative therapy that eradicates all CTCs -> prolonged PFS.
    - (zero CTCs at follow-up in patients with at least two at registration)

- Hypothesis-generating: compare PFS in both arms (low CTCs at registration and eradicated CTCs).
- May correlate ctDNA to CTC
Translational Endpoints: CTC Collection

**RAND.**

CTC
Before treatment

CTC
4-6 weeks
(if SBRT/Surgery)

CTC Draw

Time of Progression
NRG-BR001: Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

- Metastatic breast, prostate or NSCLC lung cancer ≤ 4 metastases; all metastases not resected must be amenable to SBRT

1. **REGISTER**

2. **SBRT** (in 3 or 5 fractions) to all existing metastases in 1-3 weeks
## Feasibility

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Phase</th>
<th>n</th>
<th>ER/PR + (%)</th>
<th>HER2+</th>
<th>(&lt; 2) met sites (%)</th>
<th>(&lt; 4) Met Sites (%)</th>
<th>Arms</th>
<th>PFS (Mo.)</th>
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<tr>
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<td>II</td>
<td>599</td>
<td>32</td>
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<td>1 Sunitinib+ Docetaxel 2. Docetaxel</td>
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<td>Sledge 2003</td>
<td>III E1193</td>
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<td>1. Doxorubicin 2. Paclitaxel 3. Doxorubicin + Paclitaxel</td>
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<td>8.2*</td>
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</tbody>
</table>
International Survey of SBRT use for Oligometastases:

- 1000 respondents
  - 43 countries
  - >8000 distributed
- 83% began SBRT use after 2005
- 61% use SBRT to treat ≤ 3 metastases
  - Most common reasons for use:
    - Demonstration of durable local control
    - For research purposes
  - Most common reasons NOT used:
    - Lack of convincing data

Lewis et al, In Submission, 2004
International Survey: SBRT use for Oligometastases Increasing

- 63% currently using plan to *INCREASE* volume
- 59% not using SBRT for OM plan to start
  - 88% of these in next 3 years
- No RND data is the most common reason for not using SBRT

Lewis et al, In Submission, 2004
Anticipated Outcomes Clinical Trial

• If *Ablative Therapy of all Metastases* improves OS when added to standard systemic therapy, then the paradigm shifts to multidisciplinary treatment.

• If *Ablative Therapy of all Metastases* does not improve OS when added to standard systemic therapy, then off-protocol use of SBRT stops
  – Cost reduction and toxicity avoidance

• Determine *optimal dose* for multiple site SBRT.
Thank you