Managing Oligometastasis With Stereotactic Radiosurgery

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A Paradigm Shift

• Patients with metastatic disease have historically been treated with a palliative intent, with systemic and local therapies aimed at extending life in the short term or improving quality of life

• A new treatment paradigm is emerging for oligometastatic disease: prolongation of survival or cure is the goal

• Ablative therapy with SBRT is at the forefront of this movement
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

Purpose:

Compare SABR with current approaches of chemotherapy and conventional radiotherapy to assess the impact on overall survival and quality of life.

Primary Endpoint: Overall Survival

Secondary endpoints:
- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate at 2 and 4 years
- Number of cycles of further systemic therapy: Changed to binary variable “Receipt of systemic therapy” (Y/N)
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

- **Key Inclusion Criteria:**
  - Controlled primary tumor of any primary site
  - Up to 5 metastasis (definition of oligometastasis)
  - Maximum three lesions on any one site
  - All disease sites safely treatable

- **Exclusion Criteria:**
  - Serious medical comorbidities precluding radiotherapy
  - Bone metastasis in a femoral bone
  - Patients with 1-3 brain metastasis and no disease elsewhere Prior radiotherapy to a site requiring treatment
  - Complete response to first-line chemotherapy (i.e. no measurable target for SABR)
  - Malignant pleural effusion
  - Inability to treat all sites of active disease
  - Clinical or radiologic evidence of spinal cord compression OR tumor within 3 mm of spinal cord on Magnetic Resonance Imaging (MRI).
  - Dominant brain metastasis requiring surgical decompression
  - Pregnant or lactating women
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

**Dose and Fractionation**

<table>
<thead>
<tr>
<th>Metastatic Disease Site</th>
<th>Allowed Fractionation Schemes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>54 Gy / 3 fx</td>
</tr>
<tr>
<td></td>
<td>55 Gy / 5 fx</td>
</tr>
<tr>
<td></td>
<td>60 Gy / 8 fx</td>
</tr>
<tr>
<td>Bone</td>
<td>35 Gy / 5fx</td>
</tr>
<tr>
<td></td>
<td>30Gy / 3fx</td>
</tr>
<tr>
<td></td>
<td>16-20Gy / 1fx</td>
</tr>
<tr>
<td>Brain</td>
<td>SRS 18-24 Gy / 1fx</td>
</tr>
<tr>
<td></td>
<td>SABR 40 Gy / 5fx</td>
</tr>
<tr>
<td></td>
<td>WBRT optional</td>
</tr>
<tr>
<td>Liver</td>
<td>45-60 GY / 3-8 fx</td>
</tr>
<tr>
<td>Adrenal</td>
<td>60 Gy / 8 fx</td>
</tr>
</tbody>
</table>
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=99)</th>
<th>Control Arm (n=33)</th>
<th>SABR Arm (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Original Primary Tumor – n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>18 (18.2)</td>
<td>5 (15.2)</td>
<td>13 (19.7)</td>
<td>0.204</td>
</tr>
<tr>
<td>Colorectal</td>
<td>18 (18.2)</td>
<td>9 (27.3)</td>
<td>9 (13.6)</td>
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</tr>
<tr>
<td>Lung</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>16 (16.2)</td>
<td>2 (6.1)</td>
<td>14 (21.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>29 (29.3)</td>
<td>11 (33.3)</td>
<td>18 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Location of Metastases – n(%)</td>
<td></td>
<td></td>
<td></td>
<td>0.181</td>
</tr>
<tr>
<td>Adrenal</td>
<td>9 (4.7)</td>
<td>2 (3.1)</td>
<td>7 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>65 (34.0)</td>
<td>20 (31.3)</td>
<td>45 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>19 (10.0)</td>
<td>3 (4.7)</td>
<td>16 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>89 (46.6)</td>
<td>34 (53.1)</td>
<td>55 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.7)</td>
<td>5 (7.8)</td>
<td>4 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Number of Metastases – n(%)</td>
<td></td>
<td></td>
<td></td>
<td>0.591</td>
</tr>
<tr>
<td>1</td>
<td>42 (42.4)</td>
<td>12 (36.4)</td>
<td>30 (45.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32 (32.3)</td>
<td>13 (39.4)</td>
<td>19 (28.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (4.0)</td>
<td>2 (6.1)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
</tbody>
</table>
Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)

Surgery and/or RT vs. Standard Rx and/or Observation in Previously Treated Stage IV NSCLC (MDACC)

Randomized phase II trial to study

Background

Primary Endpoint = Progression-free survival (powered for 4 months MT/O vs. 7 months LCT, n=94)

Gomez et al., Lancet Oncol 2016.
**Surgery and/or RT vs. Standard Rx and/or Observation in Previously Treated Stage IV NSCLC (MDACC)**

*Experimental arm:* Patients undergo ablation of all residual local and metastatic sites of disease by surgery and/or EBRT.

After completion of LCT, patients undergo either surveillance or maintenance treatment at the discretion of the treating physician.

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**Key eligibility criteria:**

- Diagnosis of stage IV NSCLC
- ≤3 metastases after standard front-line systemic therapy
- Four cycles of platinum-doublet chemotherapy or 3 months of EGFR/ALK targeted therapy for appropriate molecular alterations
- ECOG performance status 0-2
- Eligible for “local consolidative therapy” (surgery/radiation therapy=LCT) to all sites of disease

*Gomez et al., Lancet Oncol 2016.*
Surgery and/or RT vs. Standard Rx and/or Observation in Previously Treated Stage IV NSCLC (MDACC)

**PFS**

**OS**

Gomez et al., Lancet Oncol 2016.
Purpose:

To study the effects of stereotactic body radiation treatment on patients with five or fewer prostate cancer bone metastases to determine if we can stall the use of hormonal therapy and/or prevent other bone metastases from developing elsewhere in the body.
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

**Trial Design**

- **Eligibility:**
  - Recurrent hormone-sensitive prostate cancer
  - 1-3 metastatic lesions ≤ 5 cm by CT, MRI, or bone scan
  - PSA doubling time < 15 months
  - ECOG performance status ≤ 2

- 54 men were randomized 2:1 to stereotactic ablative radiation (SABR) or observation for 6 months

- Follow-up every 3 months including H&P and PSA, with CT and bone scan performed at 6 months

- Correlative studies included prostate-specific membrane antigen (PSMA)-PET scans as well as analysis of T-cell repertoires and circulating tumor DNA.

*Phillips, R. Johns Hopkins, ASTRO 2019*
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

Total consolidation of PSMA-PET detected lesions at decreased risk of new metastasis formation

<table>
<thead>
<tr>
<th>Consolidation</th>
<th>New metastases at 6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 19)</td>
<td>16%</td>
<td>0.006</td>
</tr>
<tr>
<td>Subtotal (n = 16)</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

Phillips, R. Johns Hopkins, ASTRO 2019
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

Clonal T-cell expansion in SABR cases

Phillips, R. Johns Hopkins, ASTRO 2019
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

High-risk mutation associated with progression in SABR patients

Phillips, R. Johns Hopkins, ASTRO 2019
Phase II Randomized Trial of Observation vs. SABR for Oligometastatic Prostate Cancer (ORIOLE)

Conclusions

- SABR improves PFS in men with oligometastatic prostate cancer compared to observation alone.
- Total consolidation of PSMA radiotracer-avid lesions may decrease risk of new metastases and alter the natural history of this disease.
- SABR induced a systemic immune response in a prototypically “cold” tumor type.
- Continued biomarker development and validation may help us tailor individualized treatment approaches.

Phillips, R. Johns Hopkins, ASTRO 2019
## Published and Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Design</th>
<th>Primary Disease</th>
<th>Key Inclusion Criteria</th>
<th>Treatment Arms</th>
<th>Results</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT Southwestern</td>
<td>Phase IIR</td>
<td>NSCLC</td>
<td>Received 1st line chemo with partial response or stable disease; up to 6 sites extracranial disease</td>
<td>Maintenance chemo vs. SBRT + maintenance chemo</td>
<td>Increase in PFS in SBRT arm, 9.7 months vs. 3.5 months</td>
<td>JAMA Oncology, 2018.</td>
</tr>
<tr>
<td>NRG LU002</td>
<td>Phase IIR/III</td>
<td>NSCLC</td>
<td>Received 1st line chemo and/or immunotherapy with partial response or stable disease; up to 3 extracranial mets amenable to SBRT</td>
<td>Maintenance chemo vs. SBRT + maintenance chemo</td>
<td>N/A</td>
<td>Open</td>
</tr>
<tr>
<td>NRG BR002</td>
<td>Phase IIR/III</td>
<td>Breast</td>
<td>Up to 2 mets, at least 5cm apart; primary tumor control; all known disease amenable to resection or SBRT</td>
<td>Planned systemic treatment vs. Planned systemic treatment + 1-5 fraction SBRT and/or surgery</td>
<td>N/A</td>
<td>Open</td>
</tr>
</tbody>
</table>
Potential for Cure?

- The jury is still out…
  - Median follow up in SABER-COMET was 25 months
    - OS and PFS benefit
    - Various tumor types
  - Median follow up in MDACC Oligometastatic NSCLC trial was 38.8 months
    - OS and PFS benefit
    - Included pts who did not progress after first line therapy
- Areas needing attention:
  - Potential for cure remains with improved OS, though is not proven
  - Need data on patients alive without disease not just without progression
  - Timing of consolidative therapy
  - Total ablative therapy to all lesions or not
Some Key Takeaway Points

- Oligometastatic disease treatment paradigm changing from palliative to potentially curative
- SBRT as a key component of this therapeutic approach
- Growing body of randomized and cooperative data with ongoing clinical trials
- Better imaging may yield better results
- Body of knowledge should include immune and genetic parameters of primary tumor and oligometastasis
- Registry and “big data” key component to best scientific approach
THANK YOU!