Oligometastatic NSCLC:

The changing role of radiotherapy

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VU University Medical Center
Disclosures

• The Department of Radiation Oncology at VUMC has a research agreement with Varian Medical Systems.

• S Senan has received speakers honoraria from Varian Medical Systems.
The changing role of radiotherapy

- Use of ablative radiotherapy (SRS, SABR/SBRT)
- Which patients are most likely to benefit?
- SABR/SRS versus other ablative treatments

**Issues to address:**

Clinical trials
Tumor biology
Immunology
Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy
Oligomets: Who are the eligible patients?

An Individual Patient Data Meta-Analysis of Outcomes and Prognostic Factors after Treatment of Oligometastatic Non-Small Cell Lung Cancer

Allison B. Ashworth¹, Suresh Senan², David A. Palma¹, Marc Riquet³, Yong Chan Ahn⁴, Umberto Ricardi⁵, Maria T. Congedo⁶, Daniel R. Gomez⁷, Gavin M. Wright⁸, Giulio Melloni⁹, Michael T. Milano¹⁰, Claudio V. Sole¹¹, Tommaso M. De Pas¹², Dennis L. Carter¹³, Andrew J. Warner¹ and George B. Rodrigues¹.

Systematic review of the literature to identify reports.

- 757 NSCLC patients with 1-5 synchronous or metachronous metastases
- Median patient age at diagnosis was 61 years
- 98% of patients had a good performance status
- 2/3 had otherwise early-stage intra-thoracic disease staged IA-IIB (after excluding metastatic disease)

Manuscript under review
Median OS of 26 months, 1-year OS 70.2%, and 5-year OS 29.4%.

Surgery was the most commonly used treatment modality for the primary (n=635, 83.9%) and for metastases (n=339 62.3%).

Predictors of OS: synchronous vs. metachronous metastases (p<0.001), N-stage (p=0.002) and adenocarcinoma histology (p=0.036)

Recursive Partitioning Analysis for risk groups:

**Low-risk**: metachronous metastases (5-year OS 47.8%);

**Intermediate risk**: synchronous metastases and N0 disease (5-year OS 36.2%);

**High risk**: synchronous metastases and N1/N2 disease (5-year OS 13.8%).
Stereotactic radiosurgery (SRS) for brain mets

Table 2. Advantages of Surgery and Stereotactic Radiosurgery for Brain Metastases.

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Suh J, NEJM 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of larger lesions (&gt;4 cm in diameter)</td>
<td></td>
</tr>
<tr>
<td>Rapid resolution of mass effect and edema</td>
<td></td>
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<tr>
<td>Removal of cancer</td>
<td></td>
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<tr>
<td>Histologic confirmation of cancer</td>
<td></td>
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<tr>
<td>Rapid tapering of the dose of corticosteroids used to treat symptomatic lesions</td>
<td></td>
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<tr>
<td>Less intensive follow-up</td>
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<tr>
<td>Lower risk of radiation necrosis when combined with whole-brain radiation therapy</td>
<td></td>
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</tbody>
</table>

**Stereotactic Radiosurgery**

- Treatment of small, deep lesions or eloquent areas
- Minimally invasive or noninvasive approach
- General anesthesia not required
- Outpatient procedure
- Treatment of multiple lesions during same session
- Short recovery time (<1 wk)
- Potential avoidance of whole-brain radiation therapy
- Rapid initiation of systemic therapies
Stereotactic ablative radiotherapy (SABR / SBRT)

A technique for delivering external beam radiotherapy to an extra-cranial target
(i) with a high degree of accuracy,
(ii) using high doses of irradiation,
(iii) delivered in 1-8 treatment fractions.

Senan, Guckenberger, Ricardi, IASLC textbook 2014
# Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

<table>
<thead>
<tr>
<th>Radiation Series</th>
<th>Year</th>
<th>Patients</th>
<th>Lesions</th>
<th>Local Control (%)</th>
<th>Survival (%)</th>
<th>Site</th>
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<tbody>
<tr>
<td>Blomgren et al</td>
<td>1995</td>
<td>31</td>
<td>42</td>
<td>80</td>
<td>Not reported</td>
<td>Liver, lung, and retroperitoneum</td>
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<tr>
<td>Wulf et al</td>
<td>2004</td>
<td>41</td>
<td>51</td>
<td>80</td>
<td>33</td>
<td>Lung</td>
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<tr>
<td>Hoye et al (colorectal cancer)</td>
<td>2006</td>
<td>64</td>
<td>141</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;, 13&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Lung, liver, and adrenal</td>
</tr>
<tr>
<td>Hof et al</td>
<td>2007</td>
<td>61</td>
<td>71</td>
<td>63&lt;sup&gt;i&lt;/sup&gt;</td>
<td>47.8&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Lung</td>
</tr>
<tr>
<td>Rusthoven et al</td>
<td>2009</td>
<td>47</td>
<td>63</td>
<td>92&lt;sup&gt;g&lt;/sup&gt;</td>
<td>30&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Liver</td>
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<td>Rusthoven et al</td>
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<td>38</td>
<td>63</td>
<td>96&lt;sup&gt;g&lt;/sup&gt;</td>
<td>39&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Lung</td>
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<tr>
<td>Kang et al (colorectal cancer)</td>
<td>2010</td>
<td>59</td>
<td>78</td>
<td>66&lt;sup&gt;i&lt;/sup&gt;</td>
<td>48&lt;sup&gt;i&lt;/sup&gt;</td>
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<td>Okunieff et al</td>
<td>2006</td>
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<td>125</td>
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<td>25&lt;sup&gt;i&lt;/sup&gt;</td>
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<td>Katz et al</td>
<td>2007</td>
<td>69</td>
<td>174</td>
<td>57&lt;sup&gt;k&lt;/sup&gt;</td>
<td>24&lt;sup&gt;m&lt;/sup&gt;</td>
<td>Liver</td>
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<tr>
<td>Lee et al</td>
<td>2009</td>
<td>70</td>
<td>143</td>
<td>71&lt;sup&gt;m&lt;/sup&gt;</td>
<td>47&lt;sup&gt;m&lt;/sup&gt;</td>
<td>Liver</td>
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<td>Milano et al</td>
<td>2011</td>
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<td></td>
<td></td>
<td>Multiple&lt;sup&gt;P&lt;/sup&gt;</td>
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<tr>
<td>Breast cancer</td>
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<td>39</td>
<td></td>
<td>87&lt;sup&gt;o&lt;/sup&gt;</td>
<td>74&lt;sup&gt;o&lt;/sup&gt;, 47&lt;sup&gt;o&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>All others</td>
<td></td>
<td>82</td>
<td></td>
<td>65&lt;sup&gt;o&lt;/sup&gt;</td>
<td>39&lt;sup&gt;o&lt;/sup&gt;, 3&lt;sup&gt;o&lt;/sup&gt;</td>
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<tr>
<td>Salama et al</td>
<td>2011</td>
<td>61</td>
<td>111</td>
<td>66.7&lt;sup&gt;o&lt;/sup&gt;</td>
<td>56.7&lt;sup&gt;o&lt;/sup&gt;</td>
<td>Multiple</td>
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<td>50</td>
<td>64, 57&lt;sup&gt;h&lt;/sup&gt;</td>
<td>64&lt;sup&gt;h&lt;/sup&gt;, 38&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Lung, liver, and lymph node</td>
</tr>
<tr>
<td>Norihisa et al</td>
<td>2008</td>
<td>34</td>
<td></td>
<td>90&lt;sup&gt;r&lt;/sup&gt;</td>
<td>84.3&lt;sup&gt;r&lt;/sup&gt;</td>
<td>Lung</td>
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The changing role of radiotherapy

• Use of ablative radiotherapy (SRS, SABR/SBRT)
• Which patients are most likely to benefit?
• SABR/SRS versus other ablative treatments

Issues to address:
- Immunology
- Clinical trials
- Tumor biology
- Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy
• Consecutive patients referred to a multidisciplinary team in a university-hospital from 2007-2010.
• Surgery was considered the first choice, and SABR otherwise
• 110 patients (surgery, n=68; SABR, n=42)

• Estimated OS rates at 1, 3 and 5 years:
• 87%, 62%, and 41% for surgery, and
• 98%, 60%, and 49% for SABR, respectively (logrank-test, p=0.43).

• Local control at two years was 94% (SABR) and 90% (surgery)
• Progression-free survival was 17% at three years

Widder J, Radioth Oncol 2013
Pulmonary oligometastases: metastasectomy or SABR?

Overall survival, PME (pulmonary metastasectomy) versus SABR (stereotactic ablative radiotherapy).

Widder J, Radioth Oncol 2013
Radiation Therapy to Convert the Tumor into an In Situ Vaccine [Formenti SC, IJROBP 2012]
MicroRNA Expression Characterizes Oligometastasis(es)

Yves A. Lussier1,2,3,4, H. Rosie Xing1,2,5,6,7, Joseph K. Salama8,9, Nikolai N. Khodarev1,5,9, Yong Huang1,3,9, Qingbei Zhang3,6,9, Sajid A. Khan7,9, Xinan Yang3,9, Michael D. Hasselle5,9, Thomas E. Darga5, Renuka Malik5, Hanli Fan6, Samantha Perakis5, Matthew Filippo5, Kimberly Corbin5, Younghee Lee3, Mitchell C. Posner7, Steven J. Chmura5, Samuel Hellman2,5, Ralph R. Weichselbaum1,2,5,9

Lussier YA et al. PlosOne 2011
Post-SABR radiological changes

Dahele M, JTO 2011
Systematic review of literature on recurrences

**High-risk features (HRF):**

- enlargement of mass
- sequential enlargement on CT
- growing mass after 12 months
- bulging margin
- linear margin disappears
- air bronchograms disappear

Huang K, Radioth Oncol 2012
Fibrosis or recurrence after SABR?

Blinded scoring of 12 path. proven recurrences matched with 24 non-recurrences

A. No Recurrence

Pre-SABR  3 months  6 months  12 months  24 months  36 months

HRF: Enlarging Opacity

B. Recurrence

Pre-SABR  6 months  12 months  21 months  21.5 months

HRFs: Enlarging Opacity  Craniocaudal Growth  Sequential Enlargement  Enlargement after 12 months  Linear Margin Disappearance  Bulging Margin  Loss of Air Bronchogram

Huang K, Radioth Oncol 2013
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Issues to address:

Immunology
Clinical trials
Tumor biology

Toxicity issues

SRS- stereotactic radiosurgery; SABR/SBRT – stereotactic body radiotherapy
Toxicity concerns: SABR and systemic Rx

Issues: treatment beyond progression, tumor flares, oligoprogression.

*Weickhardt et al.* Journal of Thoracic Oncology • Volume 7, Number 12, December 2012

**Proposed schema of therapy**

- **ALK+ NSCLC**
  - Rx crizotinib

- **EGFR-MT NSCLC**
  - Rx EGFR-TKI

**Oligoprogressive disease** → **Radiation or surgery to sites of progression** → **Continue Crizotinib or EGFR-TKI**

**Widespread progression** → **Chemotherapy or Clinical trial**

**FIGURE 2.** Proposed schema for incorporating local ablative therapy into therapy at time of first progression with *ALK*+ or *EGFR-MT* NSCLC patients treated with TKI therapy. *ALK*+, anaplastic lymphoma kinase gene rearrangement; *EGFR-MT* NSCLC, epidermal growth factor receptor-mutant non–small-cell lung cancer; TKI, tyrosine kinase inhibitors.
How should oligometastatic progression during TKI be managed?

Local therapies including radiation, radiofrequency ablation, and metastasectomy are established treatment strategies in certain cancers including renal cell carcinoma, sarcoma, and colorectal cancer. Several experiences also support the use of local therapies (surgery, stereotactic radiation) with continued EGFR or ALK inhibition in cases of oligometastatic progression, resulting in minimal toxicity and in months to years of disease control [65]. Prior to proceeding with local therapy, patients should have a full evaluation of the extent of disease, including CNS imaging.

Recommendation 27: In case of oligometastatic progression during TKI treatment, use a local treatment (such as surgery or radiotherapy) and continue/resume TKI.
Strength of recommendation: C
Level of evidence: V
Changing approach to metastases
Clinical Investigation: Gastrointestinal Cancer

Increased Bowel Toxicity in Patients Treated With a Vascular Endothelial Growth Factor Inhibitor (VEGFI) After Stereotactic Body Radiation Therapy (SBRT)

Brandon M. Barney, MD,* Svetomir N. Markovic, MD, PhD,† Nadia N. Laack, MD,* Robert C. Miller, MD,* Jann N. Sarkaria, MD,* O. Kenneth Macdonald, MD,‡ Heather J. Bauer, RN,* and Kenneth R. Olivier, MD*

*Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; †Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota; and ‡Therapeutic Radiologists Incorporated, Kansas City, Kansas

Received Mar 29, 2013, and in revised form May 3, 2013. Accepted for publication May 5, 2013
Acquired Resistance to Targeted Therapies

Gandara D, Clin Lung Cancer 2014
The changing role of radiotherapy

• Timing of SABR (consider planned post-ablative systemic therapy; phased SABR)

• Registries; expert radiological assessment post-SABR

• Trial enrollment according to RPA groups (Ashworth A)
  • Low-risk: metachronous metastases (5-year OS 47.8%);
  • Intermediate risk: synchronous metastases and N0 disease (5-year OS 36.2%);
  • High risk: synchronous metastases and N1/N2 disease (5-year OS 13.8%).
Thank you for listening