Oligometastatic NSCLC: The changing role of radiotherapy

Professor Suresh Senan
VU University Medical Center
• 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
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>
</tr>
<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>
<td></td>
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<tr>
<td>Lower risk of radiation necrosis when combined with whole-brain radiation therapy</td>
<td></td>
</tr>
</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>Bloemgren 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>
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<td>51</td>
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<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>86</td>
<td>38, 13h</td>
<td>Lung, liver, and adrenal</td>
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<tr>
<td>Hof et al</td>
<td>2007</td>
<td>61</td>
<td>71</td>
<td>63</td>
<td>47.8</td>
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<tr>
<td>Rusthoven et al</td>
<td>2009</td>
<td>47</td>
<td>63</td>
<td>92</td>
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<td>Rusthoven et al</td>
<td>2009</td>
<td>38</td>
<td>63</td>
<td>90</td>
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<td>Kang et al (colorectal cancer)</td>
<td>2010</td>
<td>59</td>
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<td>66</td>
<td>48</td>
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<tr>
<td>Okunieff et al</td>
<td>2006</td>
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<tr>
<td>Katz et al</td>
<td>2007</td>
<td>69</td>
<td>174</td>
<td>57</td>
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<tr>
<td>Lee et al</td>
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<td>70</td>
<td>143</td>
<td>71</td>
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<tr>
<td>Milano et al</td>
<td>2011</td>
<td>121</td>
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<tr>
<td>Breast cancer</td>
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<td>39</td>
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<td>87</td>
<td>74, 47</td>
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</tr>
<tr>
<td>All others</td>
<td></td>
<td>82</td>
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<td>65</td>
<td>39</td>
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<td>Salama et al</td>
<td>2011</td>
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<td>Multiple</td>
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<td>Bae et al (colorectal cancer)</td>
<td>2012</td>
<td>41</td>
<td>50</td>
<td>64, 57</td>
<td>64, 38</td>
<td>Lung, liver, and lymph node</td>
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<td>Norihisa et al</td>
<td>2008</td>
<td>34</td>
<td></td>
<td>90</td>
<td>84.3</td>
<td>Lung</td>
</tr>
</tbody>
</table>

Corbin KS, JCO 2013
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]
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
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<tbody>
<tr>
<td>1</td>
<td>Completed</td>
<td>Concurrent and Non-concurrent Chemo-radiotherapy or Radiotherapy Alone for Patients With Oligo-metastatic Stage IV Non-small Cell Lung Cancer (NSCLC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Stage IV (Oligo-metastases); Non-small Cell Lung Cancer</td>
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<tr>
<td></td>
<td></td>
<td>Intervention: Radiation; Radiotherapy</td>
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<tr>
<td>2</td>
<td>Unknown †</td>
<td>Chemotherapy With or Without Radiosurgery for Asymptomatic Oligo Brain Metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Nonsmall Cell Lung Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Radiation; Radiosurgery; Radiation: Observation</td>
</tr>
<tr>
<td>3</td>
<td>Not yet recruiting</td>
<td>Assessment of Toxicity of the Immunocytokine L19-IL2 Administered Directly After the Course of Stereotactic Ablative Body Radiotherapy in Patients Suffering From Oligometastatic Non-small Cell Lung Cancer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Non-small Cell Lung Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Drug; L19-IL2</td>
</tr>
<tr>
<td>4</td>
<td>Recruiting</td>
<td>ATOM_local Ablative Therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: NSCLC; Activating EGFR Mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Radiation; preemptive local ablative therapy</td>
</tr>
</tbody>
</table>
MicroRNA Expression Characterizes Oligometastasis(es)

Yves A. Lussier, H. Rosie Xing, Joseph K. Salama, Nikolai N. Khodarev, Yong Huang, Qingbei Zhang, Sajid A. Khan, Xinan Yang, Michael D. Hasselle, Thomas E. Darga, Renuka Malik, Hanli Fan, Samantha Perakis, Matthew Filippo, Kimberly Corbin, Younghee Lee, Mitchell C. Posner, Steven J. Chmura, Samuel Hellman, Ralph R. Weichselbaum

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

Dahele M, JTO 2011
Lung fibrosis vs. recurrence after SABR

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

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
The changing role of radiotherapy

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- 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
Toxicity concerns: SABR and systemic Rx

Issues: treatment beyond progression, tumor flares, oligoprogression.

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Proposed schema of therapy

ALK+ NSCLC Rx crizotinib or 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

Non-Small Cell Lung Cancer

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE

FIRST-LINE THERAPY

- EGFR mutation discovered prior to first-line chemotherapy
  - Erlotinib (category 1)
  - Afatinib (category 1)

- EGFR mutation discovered during first-line chemotherapy
  - Interrupt or complete planned chemotherapy, start erlotinib or afatinib
  - May add erlotinib, afatinib to current chemotherapy (category 2B)

SECOND-LINE THERAPY

- Isolated lesion
  - Consider local therapy and continue erlotinib or afatinib
- Multiple lesions
  - Consider WBRT and continue erlotinib or afatinib

- Brain
  - Multiple lesions
    - Consider local therapy and continue erlotinib or afatinib
  - Symptomatic
    - Systemic
      - Isolated lesion
        - Consider platinum doublet + bevacizumab + erlotinib
      - Multiple lesions
        - Continue erlotinib or afatinib
- Asymptomatic

Progression: See third-line therapy (NSCLC 2014)
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