Towards a radical treatment of oligometastases

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Hospital General Universitario Gregorio Marañon
Madrid, Spain

2017
The paradigm, the challenge, the opportunity... The evidence!

- Oligo-metastasis
- Oligo-recurrence
- Oligo-progression

- Technology
- Innovation
- Clinical tailoring
Definitions & Paradigm Transit... Clinical value

- **Oligo-metastasis 1995:**
  “...limited number of secondary lesions...”

- **Oligo-recurrences 2006:**
  “…the rate of metastasis development...< 5... primary recurrent...”

- **Sync-oligomet 2012:**
  “primary + < 5”

- **Oligo-progression 2016**
  “primary controlled...< 5 mets... > 2 years

- **Oligocancer 2017:**
  *any of the above conditions + biology*
Definitions & Paradigm Transit... Clinical value

- **Oligometastasis 1995:**
  "...limited number of secondary lesions..."

- **Oligorecurrences 2006:**
  "...the rate of metastasis development...< 5...recurrence with primary controlled..."

- **Sync-olimets 2012:**
  "primary + < 5"

- **Oligocancer 2017:**
  any of the above conditions + biology

**Limited # of lesions**

Ablative treatment availability

Spatially confined sites involvement
OPINION

Oligometastases revisited

Ralph R. Weichselbaum and Samuel Hellman

Abstract | We previously proposed a clinical state of metastasis termed ‘oligometastases’ that refers to restricted tumor metastatic capacity. The implication of this concept is that local cancer treatments are curative in a proportion of patients with metastases. Here we review clinical and laboratory data that support the hypothesis that oligometastasis is a distinct clinical entity. Investigations of the prevalence, mechanism of occurrence, and position in the metastatic cascade, as well as the determination of molecular markers to distinguish oligometastatic from polymetastatic disease, are ongoing.


<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>5-year survival rate (%)</th>
<th>10-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes et al. (1996)</td>
<td>607</td>
<td>33</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Nordlinger et al. (1996)</td>
<td>1,568</td>
<td>28</td>
<td>No 10-year follow up</td>
</tr>
<tr>
<td>Fong et al. (1999)</td>
<td>1,001</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Pawlik et al. (2005)</td>
<td>557</td>
<td>58</td>
<td>No 10-year follow up</td>
</tr>
</tbody>
</table>
Figure 1 | Survival of patients undergoing pulmonary resection of metastatic tumors. Each curve represents the survival of patients with an increasing number of risk factors for recurrence as determined by a retrospective review of the data. These categories are: group I, a single resectable metastasis with a disease-free interval from primary tumor to metastasis of ≥36 months; group II, multiple metastases or a disease-free interval <36 months; group III, multiple metastases and a disease-free interval <36 months. The size, number and tumor type are risk factors for recurrence. Permission obtained from Elsevier © Pastorino, U. et al. J. Thorac. Cardiovasc. Surg. 113, 37–49 (1997).
Stereotactic Body Radiotherapy for Oligometastasis
Opportunities for Biology to Guide Clinical Management

Roham J.M. Correa, MD, PhD,* Joseph K. Salama, MD,†
Michael T. Milano, MD, PhD,‡ and David A. Palma, MD, MSc, PhD, FRCPC*

Linear progression model

Parallel progression model

(Cancer J 2016;22: 247–256)
Clinical Investigation: Metastases

Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study

Michael T. Milano, M.D., Ph.D.,* Alan W. Katz, M.D., M.P.H.,* Hong Zhang, Ph.D., M.D., * and Paul Okunieff, M.D. *,†

*Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY; and †Department of Radiation Oncology, University of Florida, Gainesville, FL

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SBRT body (no brain SRS)
121 pts
< 5 mets
Breast cancer 16 / 39 alive
Other sites 7 / 82 alive
Metastatectomy vs SBRT: systematic review *(Radiat Oncol 2014)*

<table>
<thead>
<tr>
<th>Lung</th>
<th>SURGERY</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(References) years pub</td>
<td>(10) 1998-2011</td>
<td>(6) 2006-2013</td>
</tr>
<tr>
<td>Patients</td>
<td>3.443</td>
<td>321</td>
</tr>
<tr>
<td>Primaries</td>
<td>Melanoma/colorectal/renal/STS/Germ/GYN</td>
<td>Mixed/colorectal/NSCLC</td>
</tr>
<tr>
<td>Outcome</td>
<td>21-69% OS @ 5y</td>
<td>48-97% LC @ 1y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic</th>
<th>SURGERY</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(References) years pub</td>
<td>(5) 2005-2010</td>
<td>(6) 2001-2011</td>
</tr>
<tr>
<td>Patients</td>
<td>2.040</td>
<td>240</td>
</tr>
<tr>
<td>Primaries</td>
<td>Non-colorectal/breast/STS</td>
<td>Mixed/colorectal</td>
</tr>
<tr>
<td>Outcome</td>
<td>26-49% OS @ 5y</td>
<td>56-92% LC @ 1y</td>
</tr>
</tbody>
</table>

15 references 20% >2011 5.483 > 20% OS @ 5y 561 > 48% local control @ 1y
## The biology and treatment of oligometastatic cancer

**Diane K. Reyes, Kenneth J. Pienta**

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2. Departments of Pharmacology and Molecular Sciences, and Chemical and Biomolecular Engineering, The Johns Hopkins Medical Institutions, Baltimore, MD, 21287, USA

**Correspondence to:**
Kenneth J. Pienta, e-mail: kpienta@jhmi.edu

**Keywords:** metastasis, therapy, tumor, spectrum theory, oligometastatic cancer

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### CANCER (R) YEARS STUDY/DEF PATIENTS TREATMENT OUTCOME

<table>
<thead>
<tr>
<th>Cancer</th>
<th>(R) Years</th>
<th>Study/Def</th>
<th>Patients</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>(6) 2002-2014</td>
<td>4 R; &lt;5 1-2 org</td>
<td>408</td>
<td>3CT; 2S; 4RT</td>
<td>OS @ &gt;3y 39-59%</td>
</tr>
<tr>
<td>Lung</td>
<td>(20) 2006-2014</td>
<td>17R; &lt;5 brain</td>
<td><strong>3.917</strong></td>
<td>CT; S; CRT; SBRT; RS</td>
<td>OS @ 5y 15-38%</td>
</tr>
<tr>
<td>Colo-rectal</td>
<td>(9) 2010-2014</td>
<td>6 R; 1 to &lt;5</td>
<td><strong>1.377</strong></td>
<td>3S; 6 SBRT</td>
<td>OS @ 5y 29-52%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>(2) 2008-2014</td>
<td>2 R; 1 to &gt;7</td>
<td>297</td>
<td>1S; 1RT; 2CT</td>
<td>MST 43.5 mo</td>
</tr>
<tr>
<td>Renal</td>
<td>(5) 2001-2014</td>
<td>3 R; &lt;5</td>
<td>384</td>
<td>3S; 2 SBRT</td>
<td>OS @ 5y 27%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>(2) 2004-2012</td>
<td>2 R; 1 or &lt;3 N+</td>
<td>954</td>
<td>1S; 1RT; 1IT</td>
<td>OS @ 5y 17%</td>
</tr>
<tr>
<td>Prostate</td>
<td>(13) 2004-2014</td>
<td>12 R; &lt;5 or LN+(3)</td>
<td><strong>2.714</strong></td>
<td>HT; S; RT; 6 SBRT</td>
<td>OS @ 5y 73-96%</td>
</tr>
</tbody>
</table>

7 primaries  54 references; 65% >2010  84% retrospective  10.051  CMT + 65% RT  OS @ 5y 15-96%
Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Wachtelbaum, University of Chicago Medical Center, Chicago, IL

Stereotactic body radiotherapy for oligometastases

Alison C Tree, Vincent S Kho, Rowland A Edles, Marina Ahmed, David P Dranolely, Mania A Hawkins, Robert A Huddart, Christopher M Netting, Peter J Ostrile, Nicholas Juan As

Figure 2: Disease-free survival in patients with oligometastatic disease at 17-48 months’ follow-up
Dotted line represents mean proportion of patients who were disease free at the reported timepoint, weighted for number of patients in each cohort. Error bars represent 95% confidence intervals.
Panel: Evidence-based practice for extracranial oligometastases

- Stereotactic body radiotherapy results in a high control rate of treated metastases (~80%)
- About 20% of patients are progression free at 2–3 years after stereotactic body radiotherapy
- Toxicity is low
- Stereotactic body radiotherapy should be considered in patients with isolated metastases, especially if the disease-free interval is longer than 6 months
- Randomised trials are needed to establish whether stereotactic body radiotherapy improves progression free and/or overall survival

- Patients most likely to benefit from stereotactic body radiotherapy have:
  - Long disease-free interval
  - Breast histology
  - One to three metastases
  - Small metastases
  - Higher radiation dose delivered (biologic effective dose >100 Gy)
“Local treatment of metastatic disease with SBRT would effectively be a new indication for radiotherapy, resulting in potentially dramatic growth in the average raditherapy practice. Interestingly, the rational becomes even stronger with the discovery of more effective systemic therapies”.
## Studies Oligometastatic Disease: Cancer-Type Oriented
Clinical Trials. Gov CTG @ 2 / 1 / 2015

<table>
<thead>
<tr>
<th>CANCER</th>
<th># REFERENCES</th>
<th>EU / USA / Others</th>
<th>Tx ALGORITHM</th>
<th>OUTCOME End-p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung NSCLC</td>
<td>9</td>
<td>1 5 3</td>
<td>RT + Erlotinib TKI EGFR Pembrolizumab</td>
<td>PFS OS Toxicity Response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SBRT</strong></td>
<td></td>
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<tr>
<td>Prostate</td>
<td>8</td>
<td>4 3 1</td>
<td>IMRT + HT</td>
<td>BC; ADT-FS; Toxicity; Inmune effect</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>2 3 1</td>
<td>HD-CT + RT; RT + CT <strong>SBRT</strong> + MK-3475**SBRT +/- Trastuzumab</td>
<td>CTCs TTP PFS</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>- 3 -</td>
<td><strong>SBRT</strong> + Ipilimumab</td>
<td>PFS</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2</td>
<td>- 2 -</td>
<td><strong>SBRT</strong></td>
<td>Local C; OS</td>
</tr>
<tr>
<td>Colo-rectal</td>
<td>1</td>
<td>1 - -</td>
<td>RT + Beva + Cape</td>
<td>PFS</td>
</tr>
<tr>
<td><strong>6 cancer types</strong></td>
<td><strong>29 references</strong></td>
<td><strong>55% USA</strong></td>
<td><strong>SBRT/90% systemic</strong></td>
<td><strong>65% PFS</strong></td>
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</table>
Studies Oligometastatic Disease: Target-Organ Oriented Clinical Trials. Gov CTG @ 2 / 1 / 2015

<table>
<thead>
<tr>
<th>CANCER</th>
<th># trials</th>
<th>EU / USA / Others</th>
<th>TX ALGORITHM</th>
<th>OUTCOME End-p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mets</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SBRT</strong></td>
<td>Toxicity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Interleukin II</td>
<td>PFS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nelfinavir</td>
<td>OS</td>
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<tr>
<td>Liver mets</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SBRT</strong></td>
<td>Local control</td>
</tr>
<tr>
<td>Lung mets</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SBRT</strong></td>
<td>Toxicity</td>
</tr>
<tr>
<td>Brain recurrent</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SRS</strong></td>
<td>Toxicity</td>
</tr>
<tr>
<td>23% of all trials</td>
<td>9</td>
<td>5</td>
<td>100% technology</td>
<td>Early end-points</td>
</tr>
</tbody>
</table>

Target-organ + Technology- driven = Evidence-weaknesss
First clinical evidences prospective + radomized...

SBRT consolidative NSCLC!

...2016
Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Findings Between Nov 28, 2012, and Jan 19, 2016, 74 patients were enrolled either during or at the completion of first-line systemic therapy. The study was terminated early after randomisation of 49 patients (25 in the local consolidative therapy group and 24 in the maintenance treatment group) as part of the annual analyses done by the Data Safety Monitoring Committee of all randomised trials at MD Anderson Cancer Center, and before a planned interim analysis of 44 events. At a median follow-up time for all randomised patients of 12.3–39 months (IQR 5.52–20.30) the median progression-free survival in the local consolidative therapy group was 11.9 months (90% CI 5.7–28.9) versus 3.9 months (2.3–4.6) in the maintenance treatment group (hazard ratio 0.35 [90% CI 0.18–0.66], log-rank p=0.005). Adverse events were similar between groups, with no grade 4 adverse events or deaths due to treatment. Grade 3 adverse events in the maintenance therapy group were fatigue (n=1) and anaemia (n=1) and in the local consolidative therapy group were oesophagitis (n=2), anaemia (n=1), pneumothorax (n=1), and abdominal pain (n=1, unlikely related).

2012 – 2016 NSCLC
74 pts estables o respondedores 1ra línea QT < 3 mets (75% SBRT)
PFS 3.9 vs 11.9 meses (p= 0.005)

Interpretation Local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone. These findings suggest that aggressive local therapy should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.
Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake

Checkpoint blockade immunotherapy has received mainstream attention as a result of striking and durable clinical responses in some patients with metastatic disease and a reasonable response rate in many tumour types. The activity

“seed and soil”
“...and soil”
1995

Oligometastases

Cancer treatment is based on an often unstated paradigm of disease pathogenesis. Since 1994, when H. C. Blikstein initially described a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiological approaches to more cancers have been based on this theory. The Blikstein theory proposed that cancer spread to the regional lymph nodes or primary tumor through the lymphatic system and then to distant sites. Radical or ablative surgery, such as radical neck dissection in combination with removal of the primary tumor, radiation hypertherapy and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. Recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer. This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node micrometastases, which are often present in patients with early breast cancer, are not an indicator of a systemic disease, rather a number of distant disease. Systemic metastases are multiple and widespread, and when untreated are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

Both the systemic and clinical theories of cancer pathogenesis are too restricting and do not consider what is now known about tumor progression during clinical evolution. A third paradigm, one that synthesizes the systemic and clinical theories, has been suggested by one of us to explain the natural history of breast cancer. This theory argues that cancer comprises tissue origin in situ tumor cells that give rise to metastatic cells. It suggests that cancer is a systemic process, that is systemic when first diagnosed with many intermediate stages. Metastatic cells function as both tissue origin and tumor progression.

While much research is occurring during the past years, we suggest that there is a progression of malignancy during the clinical evolution of a cancer. There is some evidence to support this progression of cancer because pathologists grade small tumors with tumor size, with smaller tumors being of lower grade than large ones. This may play a role in the more rapid growth of high-grade tumors. It also correlates with tumor progression during the clinical evolution of cancer. The high-grade tumors have a larger number of cells with increasing metastatic capacity during the clinical apparent period is receiving increasing support as we learn more about the underlying nature of the development of malignancy.

15 years later...

2011

Oligometastases revisited

Ralph R. Weichselbaum and Samuel Heilman

Abstract: We previously proposed a clinical state of metastasis termed "oligometastases" that offers a new model of tumor biology and behavior. The implication of this concept is that local treatment of small numbers of tumor cells may be curative, a notion that has been supported by a number of patients. This model is consistent with the hypothesis that the primary tumor cell and metastatic cell have a spectrum of capacity. The implication of this concept is that local treatment of small numbers of tumor cells may be curative, a notion that has been supported by a number of patients.

Weichselbaum and Heilman

Weichselbaum and Heilman