Definition of oligometastatic NSCLC in the context of innovative treatments

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Disclosures

Nothing to disclose
The term «oligometastases» was first introduced in 1995 by Hellman and Weichselbaum to describe a particular subgroup of patients that suffered from a single metastasis.

An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or radiation ablation of one or a small number of pulmonary, hepatic, or even brain metastases is evidence of a limited form of the oligometastatic state. The complete resection...
Oligometastatic Breast Cancer: biological & clinical definition

new biological and clinical concept

- Intermediate biological state of restricted metastatic capacity
- Limited number of organ sites of metastases

Rationale for “curative intent” of OligoMetastatic Cancer:
- To prevent further clonal evolution that could lead to the acquisition of full potential of widespread metastases

Weichselbaum and Hellmann, JCO 1995 and NRCO 2011
miR-127-5p, miR-544a, and miR-655-3p encoded in the 14q32 microRNA cluster. These miR co-regulate pathways related to adhesion, invasion, motility and intracellular signaling.
Oligometastatic disease: an open issue

- **Lack of univocal definition**
  - *ESMO*: «...mostly defined as at maximum 5 metastatic lesions in the body»
  - *NCCN*: «...isolated or limited metastatic disease»

- **Heterogeneous group of NSCLCs**
  - Synchronous vs metachronous oligometastases
  - Different sites: brain, adrenal, contralateral lung
  - Different treatment options: surgery, stereotactic body radiotherapy (SBRT)

- **Lack of clinical trials:**
  few data mainly from retrospective analyses of small series

- **Clinical practice:**
  oligometastatic NSCLC is often defined as a limited disease in the chest with secondary lesions amenable to radical intent treatment (i.e. 1 to 3 metastases in no more than 2 sites) → single center expertise
Oligometastatic disease...an increasingly frequent issue

- Improved imaging (role of PET-CT/FDG)
- Increased availability of locoregional treatments (radiofrequency, stereotactic radiotherapy, vertebroplasty, minimally invasive surgery)
- Availability of more efficacious systemic treatments (targeted therapies for oncogene addicted NSCLC, immunotherapy)
- Multidisciplinary approach
Metastasectomy rate for lung cancer over time

Metastasectomy for cancer types: colorectal 87,407; lung 58,245; breast 26,271; melanoma 20,298

Bartelett EK et al, Cancer 2015
Prevalence of oligometastatic NSCLC

- Few data
- Limited retrospective series
- Different definition
- Dynamic concept
Prevalence of oligometastatic NSCLC

- ~7% of stage IV NSCLCs have single site metastasis (either synchronous or metachronous)

- ~50% of patients who develop metastasis after radical lung cancer treatment (1-3 metastatic sites)

Ettinghausen SE et al, JCO 1991
Pfannschmidt J et al, Lung Cancer 2010
Torok et al, Clin Lung Cancer 2017
The oligometastatic concept in Lung cancer

1 - Timing

2 - Number

3 - Sites

4 - Molecular dysregulation

5 – Available evidence
The oligometastatic concept in Lung cancer

Local and systemic treatment: a complex relationship

**SYSTEMIC TREATMENT**
- Reduced tumor burden and local invasivity
- Potential complications limiting feasibility of local treatment

**LOCAL TREATMENTS**
- Reduction of tumor burden
- Alteration of immune response
- Potential complications affecting systemic treatment
The oligometastatic concept in Lung cancer

1 - Timing

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Diffuse vs Oligo-metastasis: a different disease

Torok et al, Clin Lung Cancer 2017
The oligometastatic concept in Lung cancer

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### Prognosis classification: number & sites count!!

<table>
<thead>
<tr>
<th>Favourable</th>
<th>Relatively favourable</th>
<th>Relatively unfavourable</th>
<th>Unfavourable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oligo-recurrence</strong> 1-2 lesions &amp; 1 site</td>
<td>Oligo-recurrence</td>
<td></td>
<td>&gt; 5 sites (polymetastases)</td>
</tr>
<tr>
<td>(brain or adrenal gland)</td>
<td>3-5 lesions &amp; 1 site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(brain or adrenal gland)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Synchronous oligometastasis</strong></td>
<td>Synchronous oligometastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 lesions &amp; 1 site (brain or adrenal gland)</td>
<td>3-5 lesions &amp; 1 site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(brain or adrenal gland)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Niibe et al, Pulm Med 2013
Diffuse vs Oligo-metastasis: a different disease?

Retrospective data collection (n=368)

<table>
<thead>
<tr>
<th>Site</th>
<th>Unknown (n = 9)</th>
<th>Diffuse (n = 175)</th>
<th>Oligometastatic (n = 184)</th>
<th>Total (n = 368)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>6 (66.7)</td>
<td>46 (26.3)</td>
<td>56 (30.4)</td>
<td>108 (29.3)</td>
<td>.4136</td>
</tr>
<tr>
<td>Lung</td>
<td>2 (22.2)</td>
<td>73 (41.7)</td>
<td>41 (22.3)</td>
<td>116 (31.5)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Pleural</td>
<td>0 (0.0)</td>
<td>28 (16.0)</td>
<td>0 (0.0)</td>
<td>28 (7.6)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0 (0.0)</td>
<td>27 (15.4)</td>
<td>26 (14.1)</td>
<td>53 (14.4)</td>
<td>.7673</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (22.2)</td>
<td>48 (27.4)</td>
<td>17 (9.2)</td>
<td>67 (18.2)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Lymph</td>
<td>0 (0.0)</td>
<td>26 (14.9)</td>
<td>19 (10.3)</td>
<td>45 (12.2)</td>
<td>.2060</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (11.1)</td>
<td>79 (45.1)</td>
<td>39 (21.2)</td>
<td>119 (32.3)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Other</td>
<td>1 (11.1)</td>
<td>18 (10.3)</td>
<td>18 (9.8)</td>
<td>37 (10.1)</td>
<td>.9999</td>
</tr>
</tbody>
</table>

1-3 sites

Torok et al, Clin Lung Cancer 2017
Brain

- Most frequent oligometastatic site
- Local brain treatment is an accepted first therapeutic approach
- No differences between synchronous and metachronous metastases
- Median OS ranges from 7-24 mos. (significantly better in case of NO disease)
- Multiple available approaches:
  ✓ Surgery plus WBRT
  ✓ WBRT plus SRS
  ✓ SRS alone (≤ 4 lesions, ≤ 3 cm in diameter)

Adrenal

- 1.6 - 4% of metastatic NSCLC: single adrenal metastasis

- Up to 50% benign adenoma at histologic examination

- Ipsilateral vs contralateral:
  5-year survival rate 83% vs 0% in small series

Ettinghausen SE et al, JCO 1991
Kim HK et al, Lung Cancer 2007
Raz DJ et al, Ann Thorac Surg 2011
Lung

- Synchronous vs metachronous

- Ipsilateral vs contralateral

- Differential diagnosis of multiple primary tumors
  (in this case a curative-intent treatment is recommended)

Loukeri A, Clin Lung Cancer 2015
Synchronous lung metastasis or multiple lung tumors?

✓ **Imaging**: timing of evolution

✓ **Pathology**: subtypes distribution

✓ **Molecular profiling**: driver mutations
Synchronous lung metastasis or multiple lung tumors? IMAGING

Bonanno L et al, Lung Cancer 2016
Synchronous lung metastasis or independent multiple tumors? PATHOLOGY

Bonanno L et al, Lung Cancer 2016
Synchronous lung metastasis or independent multiple tumors? MOLECULAR PROFILING

Table 1
Pattern of EGFR mutations in multiple adenocarcinoma lesions from the same patient by pyrosequencing.

<table>
<thead>
<tr>
<th>Site</th>
<th>Prevalent morphology</th>
<th>EGFR-Pyrosequencing</th>
<th>Tumor cells percentage</th>
<th>Mutated allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle lobe</td>
<td>Lepidic</td>
<td>Exon 19 Deletion</td>
<td>70%</td>
<td>NA</td>
</tr>
<tr>
<td>Left upper lobe #1</td>
<td>Acinar</td>
<td>Exon 21 L858R</td>
<td>70%</td>
<td>8%</td>
</tr>
<tr>
<td>Left upper lobe #2</td>
<td>Papillary</td>
<td>Wild-type</td>
<td>70%</td>
<td>NA</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>Acinar</td>
<td>Exon 21 L858R</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>Liver progression</td>
<td>Acinar</td>
<td>Exon 21 L858R</td>
<td>45%</td>
<td>15%</td>
</tr>
</tbody>
</table>

NA: not available. The percentage of mutated allele may not be evaluated for exon 19 deletions with pyrosequencing.

Table 2
Results of NGS analysis.

<table>
<thead>
<tr>
<th>Right Middle Lobe Nodule</th>
<th>Left Upper Lobe Nodule #1</th>
<th>Left Upper Lobe Nodule #2</th>
<th>Liver Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant</td>
<td>Mutant allele Fraction</td>
<td>Variant</td>
<td>Mutant allele Fraction</td>
</tr>
<tr>
<td>EPHA3 (p.P422S)</td>
<td>0.11</td>
<td>PIK3CA (p.E542K) 0.10</td>
<td></td>
</tr>
<tr>
<td>EGFR (p. delE745-A750)</td>
<td>0.84</td>
<td>EGFR (p.L858R) 0.33</td>
<td></td>
</tr>
<tr>
<td>MET (p.G198D)</td>
<td>0.14</td>
<td>TP53 (p.R280T) 0.17</td>
<td></td>
</tr>
</tbody>
</table>

NGS libraries were run on MiSeq (Illumina). Only variants found in > 10% of the reads (mutant allele fraction) and coverage > 600 reads are reported. The colors highlight identical mutations found in different tumor samples.

Bonanno L et al, Lung Cancer 2016
Bone

• 27% of patients with single site metastasis

• Median survival: 12.1 m

• 57 patients undergoing surgery on primary lesions and
  - Bone surgery/fixation plus radiotherapy (median OS 13.9 mos.)
  vs
  - Radiotherapy alone (median OS 11.6 mos.)

“SINGLE-SITE BONE INVOLVEMENT IS LIKELY TO BE EXCLUDED FROM OLIGOMETASTATIC CONCEPT”

Xu Q et al, Clin Transl Oncol 2013
Nodal involvement

Prospective observational study-1

- cT1-2 cN0-1
- 1-3 synchronous or metachronous resectable metastatic lesions (single organ)
- 34 patients (17 pts synchronous brain, 12 pts syn/meta lung, 5 pts sync/meta others)
- 20 patients with complete resection of primary & metastatic site
- 5 y OS: 44.7% (similar to stage IIA/IIB disease)

Selected patients without nodal involvement undergoing radical-intent local treatment on primary tumor and 1-3 metastasis could have similar outcome to locally advanced disease

Nodal involvement

Prospective observational study-2

- cT1-3 c N0-2
- 23 patients
- Solitary synchronous and resectable metastasis
- Platinum-based induction CT → resection of all remaining sites of disease
- Median OS: 11 mos.

Selected patients with nodal involvement undergoing radical-intent local treatment on primary tumor and single metastasis had similar outcome to metastatic patients

Downey RJ et al, Lung Cancer 2002
Nodal involvement

- n = 99
- N0 46.5%
- N+ 48.5%
- Nx 5%

Retrospective study

\[ p = 0.011 \]

Tonnies M et al, Ann Thor Surgery 2014
The oligometastatic concept in Lung cancer

1 - Timing

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5 – Available evidence
Prognosis

• Indolent biological phenotype
  - molecular dysregulations
  - targeted agents
  - immunotherapy

• Efficacy of local treatments
  - surgical & radiotherapy expertise
  - technologies

• Number and sites of metastasis
  - single vs multiple
  - N2 involvement
  - brain & adrenal vs others
  - lung
The oligometastatic concept in Lung cancer

1 - Timing

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5 - Available evidence
Limited evidence of efficacy (does not mean lack of efficacy...)

- Data from retrospective case series & prospective observational studies
- Heterogeneity of treatments
- One meta-analysis
- Few data from a small prospective trial
## Retrospective studies (> 20 pts, from 2000)

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>Oligometastatic site</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Getman et al, 2004</td>
<td>65</td>
<td>Brain</td>
<td>19</td>
</tr>
<tr>
<td>Billing et al, 2001</td>
<td>28</td>
<td>Brain</td>
<td>21</td>
</tr>
<tr>
<td>Bonnette et al, 2001</td>
<td>103</td>
<td>Brain</td>
<td>11</td>
</tr>
<tr>
<td>Furak et al, 2005</td>
<td>65</td>
<td>Brain</td>
<td>19</td>
</tr>
<tr>
<td>Strong et al, 2007</td>
<td>94</td>
<td>Adrenal</td>
<td>29</td>
</tr>
<tr>
<td>Mercier et al, 2005</td>
<td>23</td>
<td>Adrenal</td>
<td>23</td>
</tr>
<tr>
<td>Porte et al, 2001</td>
<td>43</td>
<td>Adrenal</td>
<td>12</td>
</tr>
<tr>
<td>Pham et al, 2001</td>
<td>78</td>
<td>Adrenal</td>
<td>40</td>
</tr>
<tr>
<td>Raz et al, 2011</td>
<td>20</td>
<td>Adrenal</td>
<td>34</td>
</tr>
<tr>
<td>Tanvetyanon et al, 2008</td>
<td>114</td>
<td>Adrenal</td>
<td>25</td>
</tr>
<tr>
<td>Yano et al, 2010</td>
<td>138</td>
<td>Brain, adrenal, lung</td>
<td>38.7</td>
</tr>
<tr>
<td>Congedo et al, 2012</td>
<td>53</td>
<td>Various sites</td>
<td>23.5</td>
</tr>
<tr>
<td>Tonnies et al, 2014</td>
<td>99</td>
<td>Various sites</td>
<td>38</td>
</tr>
</tbody>
</table>
### Prospective studies (> 20 pts, from 2000)

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>Oligometastatic site</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al, 2013</td>
<td>213</td>
<td>Various sites</td>
<td>4.5</td>
</tr>
<tr>
<td>Endo et al, 2014</td>
<td>34</td>
<td>Brain, adrenal, lung</td>
<td>44.7</td>
</tr>
<tr>
<td>Downey et al, 2002</td>
<td>23</td>
<td>Various sites</td>
<td>20</td>
</tr>
<tr>
<td>De Ruysscher et al, 2012</td>
<td>39</td>
<td>Various sites</td>
<td>3-y 17.5</td>
</tr>
</tbody>
</table>
Metanalysis

- 49 articles, 84% retrospective series, 2176 NSCLC patients
- 60.3% brain mets only, 24% mixed mets, 10.6% adrenal mets only, 5% lung mets only
- 53.6% solitary mets, 31.2% 1-3 mets, 15.2% 1-5 mets
- 39.1% synchronous only, 13% metachronous only, 47.8% synchronous or metachronous
- Surgical metastasectomy (55%), SRS, SABR (45%), Conventional RT (1 study)

<table>
<thead>
<tr>
<th>Location of oligometastases</th>
<th>No. patients (n)</th>
<th>MS range (months)</th>
<th>Overall MS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1436</td>
<td>5.9–52</td>
<td>13.6</td>
</tr>
<tr>
<td>Controlled</td>
<td>1082</td>
<td>6.8–52</td>
<td>19.7</td>
</tr>
<tr>
<td>Solitary Metastasis</td>
<td>294</td>
<td>5.9–52</td>
<td>9.3</td>
</tr>
<tr>
<td>Controlled</td>
<td>215</td>
<td>6.2–52</td>
<td>19.7</td>
</tr>
<tr>
<td>Mixed</td>
<td>431</td>
<td>13–30.9</td>
<td>20</td>
</tr>
<tr>
<td>Controlled (all)</td>
<td>190</td>
<td>11–21</td>
<td>17</td>
</tr>
<tr>
<td>Lung (one study only)</td>
<td>76</td>
<td>40</td>
<td>n/a</td>
</tr>
</tbody>
</table>

- great heterogeneity of outcome: median OS 15 mos (range 6-52 mos)
- main prognostic factors: control of primary site, N0 and DFS> 6-12 mos.

Ashworth et al, Lung Cancer 2013
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

Lancet Oncol 2016; 17: 1672–82

CONSOLIDATIVE LOCAL TREATMENTS

Primary lung lesion: RT, SABR, Surgery
Metastatic sites: RT, SABR, ChemoRx+RT
Randomized phase II trial of consolidation therapy in NSCLC

Median PFS: 11.9 (6-21) vs 3.9 (2-7) m; HR: 0.35

☑ Progression was mainly systemic
☑ Only type of treatment and EGFR/ALK status affected PFS with statistical significance

Gomez DR et al, Lancet Oncol 2016
Evidence to guide our decisions

• Mainly limited retrospective data
• Heterogeneity of treatments
• One meta-analysis
• Very little prospective trial
Thoracic Oncology Padova proposal

Prospective observational trial of oligometastatic NSCLC with molecular characterization before and after systemic treatment

- maximum of 3 metastasis in two sites
- N0-1 or single station (non-bulky) N2

SYSTEMIC TREATMENT
(Upfront Surgery or RadioSurgery in case of Brain Mets)

RADICAL-INTENT LOCO-REGIONAL THERAPY (Lung & Metastases)

Conte PF, Rea F