OLIGOMETASTATIC DISEASE

A true clinical entity in Oncology?

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Yazid Belkacemi has reported no conflicts of interest
Nicolas Penel has reported no conflicts of interest
AGENDA

1. Definitions
2. Biology of oligometastatic disease
3. Best available evidence
4. Role of stereotactic ablative radiotherapy (SABR)
5. Future directions
6. Take-home messages
<table>
<thead>
<tr>
<th></th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Biology of oligometastatic disease</td>
</tr>
<tr>
<td>3</td>
<td>Best available evidence</td>
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<td>4</td>
<td>Role of stereotactic ablative radiotherapy (SABR)</td>
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<td>5</td>
<td>Future directions</td>
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<td>6</td>
<td>Take-home messages</td>
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</tbody>
</table>
There is no consensus on the definition of oligometastasis

A generic definition is available

However, we have to tailor the definition, at least, according to:

- the topic of “detectable” metastasis
- the time interval between diagnosis of primary and diagnosis of oligo-met
- the nature of the primary tumour

- Patients with a limited number of clinically detectable metastatic tumours
- Hypothetic transitional state between localised and widespread systemic disease
- Local control of oligometastasis could delay (or avoid) the systemic spreading?

Oligometastasis

- Metastatic state with limited burden
- 1 to 5 metastasis
Widely metastatic disease ≠ limited metastatic disease (≤5)

EDITORIAL

Oligometastases

Cancer treatment is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread.

Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread. Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread.

Hellman S & Weichselbaum RR, J Clin Oncol 1995
1. “True” oligometastatic disease as initially defined, with relative steady-state and slowly growing disease. In this case, local control of oligomet makes sense.

2. “False” oligometastatic disease. In this case the occult systemic spreading is ongoing, but a limited number of metastatic sites are detectable. In this case, systemic treatment is needed.

3. Does “True” Oligometastatic disease need confirmation at later time point?
DEFINITION LIMITS

“Detectable” metastasis depends on the detection method sensitivity
- Clinical exam only
  - Nobody agrees to define oligomet based on clinical exam only!
- Classical CT-Scan
- “Modern” (functional) imaging? …

Example of Prostate Cancer: what is the ideal method for defining oligometastasis?
- Whole body MRI
- (CT)-TEP: 18-FDG TEP, PMSA-TEP, FNA-TEP, Choline-TEP
- Combination of these methods?
### DEFINITION ACCORDING TO THE CONTROL OF PRIMARY

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligorecurrence</td>
<td>Limited metastases in the presence of a treated (controlled) primary lesion</td>
</tr>
<tr>
<td>Sync-oligometastases</td>
<td>≤5 metastatic or recurrent lesions in the presence of untreated (uncontrolled) primary tumour</td>
</tr>
<tr>
<td>Synchronous oligometastasis</td>
<td>Oligometastatic disease is detected at the time of diagnosis of the primary tumour, therefore there is an untreated (uncontrolled) primary tumour</td>
</tr>
<tr>
<td>Metachronous oligometastasis</td>
<td>Development of oligometastatic disease after treatment of the primary tumour; interval for classification of metachronous versus synchronous is not standardised; between controlled primary lesion except for concomitant primary and distant recurrence</td>
</tr>
</tbody>
</table>
TAILORED DEFINITION BY TUMOUR TYPE?

Items that could be included in a tailored definition

**Number of met** detected by the ideal method?
Taken into account the **natural history of the disease**?
Taken into account the **available method for treating oligometastasis**?
Taken into account **previously done treatment**?
Including the “aim” of local treatment of oligometastasis

- **Cure the patient?**
- **Avoid or delay the starting of systemic treatment?**
TAILORED DEFINITION BY TUMOUR TYPE?

Proposed definitions for oligometastatic prostate cancer

**Definition 1** - (Reeves F, BJU Int 2014)
Rising PSA following primary therapy, with oligometastasis on imaging, in which local treatment (surgical metastasectomy (usually lymph node – LN - dissection), or SBRT for bony mets or lymph node recurrence) is **required to defer initiation** of androgen deprivation therapy

**Definition 2** - (Reeves F, BJU Int 2014)
Castrate resistant prostate cancer with a rising PSA and oligometastasis on imaging, in which local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) **may allow deferral** of androgen deprivation therapy
1. Definitions

2. Biology of oligometastatic disease

3. Best available evidence

4. Role of stereotactic ablative radiotherapy (SABR)

5. Future directions

6. Take-home messages
BIOLOGY OF OLIGOMETASTASIS

2 protagonists

A – Tumour

- Example of colorectal cancer
- Example of clear cell renal cancer

B – Host (patient)
BIOLOGY OF OLIGOMETASTASIS

Basically, 2 protagonists

A – Tumour

- Example of colorectal cancer
- Example of clear cell renal cancer

B – Host (patient)

- Gene polymorphism
- Immune system ?
## BIOLOGY OF OLIGOMETASTASIS

Oligometastatic *versus* systemic disease: key-factors

<table>
<thead>
<tr>
<th></th>
<th>Oligometastatic disease</th>
<th>Systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour</td>
<td>Favourable microenvironment</td>
<td>Poor conditions creating undifferentiated aggressive clones</td>
</tr>
<tr>
<td>Sead (migrating cells)</td>
<td>Sloughed cancer cells</td>
<td>Actively migrating cells</td>
</tr>
<tr>
<td>Soils (target organs)</td>
<td>In hospitable target organs (trap)</td>
<td>Hospitable target organs</td>
</tr>
</tbody>
</table>
LIVER MET. FROM CRC

- 134 patients with resected liver oligometastasis from colorectal cancers
- 61% with only 1 met; 22% with 2 met. and 17% with 3 or more met

Methods
- Whole genome RNA sequencing of 95 samples
- Microsatellite instability analysis in 89 samples

Identification of 3 molecular sub-types with different outcomes
- Low-risk group: 10 year-OS = 94%
- Intermediate group: 10-year OS = 45%
- High-risk group: 10-year OS = 19%

LIVER MET. FROM CRC

(a) Stratified by integrated risk classification

- Overall survival (%)
- Years following surgery

<table>
<thead>
<tr>
<th>Years</th>
<th>Low risk</th>
<th>Int risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>21</td>
<td>34</td>
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<tr>
<td>2</td>
<td>12</td>
<td>17</td>
<td>19</td>
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<tr>
<td>3</td>
<td>11</td>
<td>10</td>
<td>8</td>
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<tr>
<td>4</td>
<td>9</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

P < 0.0001

(b) Recurrence or death

<table>
<thead>
<tr>
<th>Recurrence or death</th>
<th>High risk</th>
<th>Int risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-recur/Alive</td>
<td>14</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>Recur/Death</td>
<td>86</td>
<td>68</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of metastatic recurrences</th>
<th>High risk</th>
<th>Int risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mets</td>
<td>34</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>4+ mets</td>
<td>66</td>
<td>87</td>
<td>13</td>
</tr>
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</table>

Pitroda SP, et al. Nat Commun 2018;9:1793, DOI: 10.1038/s41467-018-04278-6, licensed under a Creative Commons Attribution 4.0 International license: http://creativecommons.org/licenses/by/4.0/.
## LIVER MET. FROM CRC

<table>
<thead>
<tr>
<th></th>
<th>Subtype 1 Canonical</th>
<th>Subtype 2 Immune</th>
<th>Subtype 3 Stromal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>33%</td>
<td>29%</td>
<td>39%</td>
</tr>
<tr>
<td>Molecular signature</td>
<td>↓Immune and stroma E2F/MYC signaling DNA damage and cell cycle</td>
<td>↑Immune Interferon signaling p53 pathway</td>
<td>↑Stroma KRAS signaling EMT and angiogenesis</td>
</tr>
<tr>
<td>Specific mutations</td>
<td>NOTCH1 and PIK3C2B</td>
<td>NRAS, CDK12, and EBF1</td>
<td>MAD3</td>
</tr>
<tr>
<td>Met. recurrences</td>
<td>Many</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Intermediate</td>
<td>Favorable</td>
<td>Unfavourable</td>
</tr>
</tbody>
</table>

CLEAR CELL RENAL CANCER

- 100 clear cell renal cancer – Evolutionary study of gene alterations in primary tumour and subsequent metastasis biopsy(ies)
- Validation on independent cohorts

- Loss of 9p21.3 is associated with poor outcome
- Diffuse metastatic pattern
- Death caused by CCRC (p = 0.0014)

- Distinct patterns of metastases are associated with some molecular signature rapid spreading versus oligometastasis

Distinct patterns of metastases are associated with some molecular signatures

- Rapid spreading versus oligometastasis
- Rapid spreading is associated with
  - Loss of 9p21.3
  - VHL wild type
  - BAP1 mutation
  - Low intra-tumoural heterogeneity and high chromosomal complexity

Metastatic spreading is associated with some polymorphisms

Case-control study of patient with carcinoma of unknown primary (by definition, systemic bulky metastatic disease) – genome-wide association study

- At least, 8 polymorphisms are associated with CUP diagnosis (p<10^-6)
- rs2660852 located closed to LTAH4H gene (leukotriene A4 hydrolase)
- rs477145 of TIAM1 gene (T-cell lymphoma invasion and metastases)
- s2835931 of KCNJ6 gene ...
- Genes involved in cellular motility, interaction cell control, cell adhesion ...

The putative role of the immune system has to be explored
AGENDA

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5. Future directions
6. Take-home messages
Methods for local (focal) therapies of oligometastasis are now largely available:

- Surgery
- Ablative radiotherapy
- Radiofrequency
- Cryotherapy …

Final demonstration of benefit of focal therapies of oligometastasis ideally requires unbiased randomised phase III trial

There are plenty of ongoing trials (phase III trials are rare)
The design of ideal randomised is straightforward

Oligo-met

Standard care

Standard care + Focal therapies

Primary endpoint

PFS or better OS

Standard care could be systemic treatment or observation
BEST AVAILABLE CLINICAL EVIDENCE

Design assessing the added value of systemic treatment to focal therapies

- Oligo-met
- Focal therapy alone
- Focal therapy + Systemic therapy
- Primary endpoint
  - PFS or better
  - OS

- Randomised phase III trial
- Patients with 1 to 3 brain met. (whatever the primary)
- 333 pts randomised between January, 1996 and June, 2001

**Standard arm**
- Whole brain radiotherapy (n=164)
- Median OS = 4.9 months

**Experimental arm**
- WBR + stereotactic radiosurgery (n=167)
- Median OS = 6.5 months (p=0.03)

**BEST AVAILABLE CLINICAL EVIDENCE**

**Level I evidence**
**BEST AVAILABLE CLINICAL EVIDENCE**


- Randomised phase II trial
- Patients with unresectable liver met (<10) without extra-hepatic met from CRC
- 119 patients randomised from April 2002 to June 2007

**Standard arm**

- Systemic treatment (n=59)
- 8-year OS: 9%

**Experimental arm**

- ST + radio-frequency ablation (n=60)
- 8-year OS: 36% (p=0.01)

- Randomised phase II trial
- Stage IV NSCLC, 3 or fewer metastatic lesions after 1st-line systemic therapy
- 49 patients randomised between Nov 2012 and Jan 2016. Early termination of the trial after 1st IDMC

**Standard arm**
- Maintenance systemic therapy alone (n=24)
- PFS = 3.9 months

**Experimental arm**
- Maintenance systemic therapy + local therapy [surgery or radiotherapy] (n=25)
- PFS = 11.9 months (p=0.0054)
BEST AVAILABLE CLINICAL EVIDENCE

Trial 4 – Iyengar P, et al. JAMA 2018

- Randomised Phase 1–2 trial
- Stage IV non-mutated NSCLC, 5 or fewer metastatic lesions after 1st-line therapy
- 29 patients randomised. Early termination of the trial after 1st IDMC

Standard arm
- Maintenance systemic therapy alone (n=15)
- PFS = 3.5 months

Experimental arm
- Maintenance systemic therapy + local ablative radiotherapy (n=14)
- PFS = 9.7 months (p=0.01)

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THE ROLE OF STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR OLIGOMETASTASES
STEREOTACTIC ABLATIVE RADIATION THERAPY

- High precision
- Small target volume
- Limited number of fractions (1-8)
- High dose per fraction
- Different radiobiologic considerations compared to standard fractionation
STEREOTACTIC ABLATIVE RADIATION THERAPY

Advantages of SABR

- Non invasive treatment
- High local control (70–100%)
- Few toxicities and low treatment mortality
- Cost-effective
- Can overcome (at least partially) radioresistance
# SABR: PROSPECTIVE STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>No of Patients</th>
<th>No metastases per patient</th>
<th>No metastases per patient</th>
<th>Dose(Gy)</th>
<th>Dose (Gy)</th>
<th>Follow-up (months)</th>
<th>Follow-up (months)</th>
<th>Metastasis control (%)</th>
<th>OS(%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Total</td>
<td># fractions</td>
<td>Median</td>
<td>Range</td>
<td></td>
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<td>Colorectal Cancer</td>
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<tr>
<td>Aarhus University (Aarhus, Denmark) [106]</td>
<td>64</td>
<td>2</td>
<td>1-6</td>
<td>45</td>
<td>3</td>
<td>52</td>
<td>20-76</td>
<td>2 years:86</td>
<td>4 years:13</td>
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<td>Vrije Universiteit Brussel (Brussels, Belgium) [191]</td>
<td>23</td>
<td>1</td>
<td>1-3</td>
<td>40</td>
<td>10</td>
<td>12</td>
<td>3-18</td>
<td>1-year: 54</td>
<td>1-year: 86</td>
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<td>Vrije Universiteit Brussel (Brussels, Belgium) [192]</td>
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<td>1</td>
<td>1-3</td>
<td>50</td>
<td>10</td>
<td>10</td>
<td>3-21</td>
<td>1-Year: 54</td>
<td>1-year: 78</td>
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<tr>
<td>Non-small cell lung cancer</td>
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<td></td>
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<tr>
<td>University Medical centre Maastricht (Maastricht, The Netherlands) [120]</td>
<td>39</td>
<td>1</td>
<td>1-3</td>
<td>60</td>
<td>30</td>
<td>27.7</td>
<td>16.7-46.1</td>
<td>95</td>
<td>3 years: 17.5</td>
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<td>Vrije Universiteit Brussel (Brussels, Belgium) [121]</td>
<td>26</td>
<td>1</td>
<td>1-5</td>
<td>50</td>
<td>10</td>
<td>16.4</td>
<td>3-40</td>
<td>85</td>
<td>1 year: 67</td>
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<td>UT Southwestern/University of Colorado [147]</td>
<td>24</td>
<td>2</td>
<td>1-5</td>
<td>19-40</td>
<td>1-5</td>
<td>11.6</td>
<td>3.4-60.3</td>
<td>9 months: 94</td>
<td>Median: 29.4</td>
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<td>Multi-institutional [187]</td>
<td>25</td>
<td>NR</td>
<td>1-3</td>
<td></td>
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<td></td>
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<tr>
<td>Breast cancer</td>
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<tr>
<td>University of Rochester (Rochester, NY) [171]</td>
<td>40</td>
<td>2</td>
<td>1-4</td>
<td>40-60</td>
<td>10</td>
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<td>4 years: 89</td>
<td>4 years: 59</td>
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<td>Prostate cancer</td>
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<tr>
<td>Ghent University Hospital (Ghent, Belgium) [151]</td>
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<td>NR</td>
<td>1-3</td>
<td>40-50</td>
<td>10</td>
<td>24</td>
<td>1-72</td>
<td>2-year: 100</td>
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<tr>
<td>Ludwig-Maximilian University (Munich, Germany) [129]</td>
<td>44</td>
<td>1</td>
<td>1-2</td>
<td>20</td>
<td>1</td>
<td>14</td>
<td>3-48</td>
<td>1 year: 96</td>
<td>17.5 months: 75</td>
</tr>
<tr>
<td>Azienda Ospedaliero Universitaria Pisana (Pisa, Italy) [152]</td>
<td>29</td>
<td>NR</td>
<td>1-3</td>
<td>24</td>
<td>1</td>
<td>11.5</td>
<td>2-40</td>
<td>NR</td>
<td>NR</td>
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| 27 | 3 | | | | | | | |
Trial 4 – Iyengar P, et al. JAMA 2018

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FUTURE DIRECTIONS

- Identifying biological factors associated with oligometastasis pattern
- Stratifying strategies according to these biological factors
- Better define oligometastatic disease for every clinical setting
- Conducting phase III trial with appropriate follow-up
- Combination of local treatment with systemic treatment
SABR AND IMMUNOTHERAPY

- Phase I: IL2 + SABR (1x20Gy, 2x20Gy or 3x20Gy)

  Before and after PET imaging in a patient with widely metastatic melanoma –
  Two liver lesions were treated with SBRT

From Sueng SK, et al. Sci Transl Med 2012: 4(137) Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—Tumor and Immunological Responses, Reprinted with permission from AAA
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Multiple definitions according to tumour type, method used for detecting metastasis…

Includes at least 2 entities: « true » indolent oligo-metastatic disease and ongoing systemic disease

Molecular signatures associated with oligometastasis in colorectal cancer and renal cell cancer

Role of host has to be better explored

At that time, limited evidence for the use of focal therapies in management of oligometastasis

On the contrary, technological development of focal therapies that are very appealing in the management of oligometastasis (SBRA, radio-ablation, cryotherapy, mini-invasive surgery…)

Large phase III trials are needed

Signatures of identifying oligometastasis are needed
THANK YOU!