What is oligometastatic disease?

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Disclosure Slide

- In the last 2 years consultancy fees from:
  - AstraZeneca, Relay Therapeutics, Gritstone

- I was a full time employee for AstraZeneca from September 2017 to December 2019.
Outline

- Definition and conceptual framework

- The key role of the work-up methodology
  - Imaging
  - Liquid biopsies

- Molecular considerations
  - Oncogene-dependency, IO-sensitivity
  - Drivers of the oligometastatic process

- Therapeutic implications
Initial definition

25 years ago …

→ Intermediate biological status
  (ie restricted metastatic capacity)

→ Limited number of mets / organs involved

→ Transitional state to polymetastatic disease

Hellman S, Weichselbaum RR. J Clin Oncol 1995
Oligometastatic Disease

- Sloughed cancer cells
  - Good primary tumor conditions
  - In hospitable target organs

Systemic Disease

- Actively migrating cancer cells
  - Poor primary tumor conditions
  - Hospitable target organs

Reyes DK. Oncotarget 2015
Clinical definition

- ‘Accepted’ definition
  - 2 or 3 organs involved
  - and a maximum of 5 metastases

Referred to inclusion criteria from several trials recruiting oligometastatic diseases
Concept(s)

- Various entities
  - Oligometastases (ie synchronous, @ diagnosis)
  - Oligorecurrence (ie metachronous, primary cured)
  - Oligoprogression (ie metachronous, primary controlled)
A  De-novo oligometastatic disease

Synchronous oligometastatic disease

T0

- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

Metachronous oligorecurrence

- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) > 6 months after diagnosis of cancer

Metachronous oligoprogression

- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) > 6 months after diagnosis of cancer
A reality?

- Limited data
- **26-50%** of patients w synchronous or metachronous oligomestatic disease
- **10-15%** of lung cancer patients

Natural history of oligometastatic LC

- 423 pts
- 19% with oligom
- Median OS: 17 vs 14 months
- HR 0.73

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“Detectable” metastasis depends on the detection method sensitivity

- Classical CT-Scan
- MRI
- PET-CT scan

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?
Applications of Liquid Biopsy

Monitoring & Early Detection

Brain cancer DNA blocked by blood-brain barrier

Multiple Tumor Types
- Breast cancer
- Pancreatic cancer
- Colon cancer

Many tumors release DNA fragments that circulate in the bloodstream

ctDNA & Tumor Cell Analysis

Detection of Resistance Mutations

Targeted therapy

Response to therapy

Selective pressure

Resistance mutations

ctDNA of resistance mutations collected in blood sample

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Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT)

Anthony C. Wong MD, PhD, Sydeaka P. Watson PhD, Sean P. Pitroda MD ... See all authors

First published: 20 May 2016 | https://doi.org/10.1002/cncr.30058 | Cited by: 33

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, Ralph R. Weichselbaum

Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs

Abhineet Uppal, Mark K. Ferguson, Mitchell C. Posner, Samuel Hellman, Nikolai N. Khodarev, and Ralph R. Weichselbaum

Integrated molecular subtyping defines curable oligometastatic state in colorectal liver metastasis

Survival of patients with oncogenic driven NSCLC

Survival probability

Years

Log-rank p<0.001

Medan survival, years (95% CI)

• Oncogenic driver + no targeted therapy: 2.38 (1.81–2.93)
• Oncogenic driver + targeted therapy: 3.49 (3.02–4.33)
• No oncogenic driver: 2.08 (1.84–2.46)

Lung Cancer Mutational Consortium;
Overall survival with crizotinib and next-generation ALKi inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study

Michaël Duruisseaux1, Benjamin Besse1, Jacques Cadranel1, Maurice Pérol2, Bertrand Meneuclier3, Laurence Bigay-Game4, Renaud Descout5, Eric Dansin6, Clarisse Audigier-Valette7, Lionel Moreau8, José Huréau9, Remi Veillon10, Jossiane Otto10, Anne Madroszyk-Flandin10, Alexis Cortot10, Françoise Guichard10, Pascale Boudou-Rouquette10, Alexandra Langlais10, Pascale Missy10, Franck Morin10, Denis Moro-Sibilot10

Retrospective analysis, N=318
Crizotinib → next-gen ALKi (n=84)
Median OS = 89.6 months
Overall Survival

![Graph showing overall survival comparison between Pembrolizumab and Chemotherapy]

**Median (95% CI)**
- Pembrolizumab: 26.3 mo (18.3–40.4 mo)
- Chemotherapy: 13.4 mo (9.4–18.3 mo)

**Events, n (%)**
- Pembrolizumab: 103 (66.9%) HR = 0.62 (95% CI: 0.48–0.81)
- Chemotherapy: 123 (81.5%)

**No. at risk**
- Pembrolizumab: 154, 121, 106, 89, 78, 73, 66, 62, 54, 51, 20, 3, 0
- Chemotherapy: 151, 108, 80, 61, 48, 44, 35, 33, 28, 26, 13, 3, 0

ITT population. Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-(L)1 therapy; 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-(L)1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-(L)1 therapy). Data cutoff: June 1, 2020.
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Technological improvements

Surgery

Radiation

Interventional radiology
Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases

**Jan 2002 - July 2010** (prospective database: Institut Gustave Roussy & Institut Bergonié)

1037 metastases 4 to 70 mm (med=15)

566 patients including 188 CRC mets patients

<table>
<thead>
<tr>
<th>Local control</th>
<th>&lt;=3cm (n=840)</th>
<th>&gt;3cm (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>96.2 %</td>
<td>83.2 %</td>
</tr>
<tr>
<td>2 years</td>
<td>92.9 %</td>
<td>72.7 %</td>
</tr>
<tr>
<td>3 years</td>
<td>91.6 %</td>
<td>72.7 %</td>
</tr>
</tbody>
</table>

p<0.0001

Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month | Post 1 month |

1 months | 3 months | 6 months | 24 months
Lung metastases

Oncologic work-up / MDT

Palliation

Curative intent

General status/comorbidities
Respiratory function

Surgical candidate

Non Surgical candidate

PR or SD disease
No extra-heaptic disease

Oligometastatic (number ± up to 5)

≤ 3 cm
Multiples
several lobes

RFA
SBRT

≥ 3 cm
Single
Hilar

SBRT
Cryoablation
microwaves

≤ 3 cm
Multiples
several lobes

RFA – Surgery
SBRT

Multiples
Same lobe

Surgery

≥ 3 cm
Single
Hilar

Surgery

SBRT (fractionated)
Cryoablation
A new strategy to be widely implemented?

Key patient inclusion criteria
- Histologically confirmed NSCLC
- Stage IV disease
- ≤3 metastases
- No RECIST progression after FLST* (n=49)

Primary endpoint(s)
- PFS

Secondary endpoints
- OS, safety

LCT† +/- ST (n=25)

Stratification
- Nodal status, EGFR/EML4-ALK status, response to FLST, CNS metastases, number of metastases

ST alone (n=24)

Crossover to LCT allowed at progression

LCT local therapy (surgery or radiotherapy), ST: systemic TT  Gomez et al, Lancet Oncol 2016
Gomez et al, Lancet Oncol 2016

LCT
No LCT

mPFS, months
No-LCT arm: 3.9 (95%CI 2.2, 6.6)
LCT arm: 11.9 (95%CI 5.4, NA)
Conclusions

- A definition in evolution for multiple concepts
- The objective is trying to achieve ablation of all tumour masses, using ≠ techniques
- Balance organ-related risk with oncological benefit
- Oncogene-addiction and IO sensitivity may modify how aggressive you want to be
- Multiple hypotheses behind oligomet/oligoprogression but no clear biological framework
Acknowledgments

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