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OLIGOMETASTATIC DISEASE

A true clinical entity in Oncology?

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DISCLOSURES

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

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1. **Definitions**
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DEFINITIONS

- 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**

GENERIC DEFINITION

1995 - Hellman S and Weichselbaum RR (JCO 1995)

- 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 sates 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 s 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

DEFINITION

TWO DIFFERENT ENTITIES

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

Concepts	Definition
Oligorecurrence	Limited metastases in the presence of a treated (controlled) primary lesion
Sync-oligometastases	≤5 metastatic or recurrent lesions in the presence of untreated (uncontrolled) primary tumour
Synchronous oligometastasis	Oligometastatic disease is detected at the time of diagnosis of the primary tumour, therefore there is an untreated (uncontrolled) primary tumour
Metachronous oligometastasis	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

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

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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

	Oligometastatic disease	Systemic disease
Primary tumour	Favourable microenvironment	Poor conditions creating undifferentiated aggressive clones
Sead (migrating cells)	Sloughed cancer cells	Actively migrating cells
Soils (target organs)	Inhospitable target organs (trap)	Hospitable target organs

LIVER MET. FROM CRC

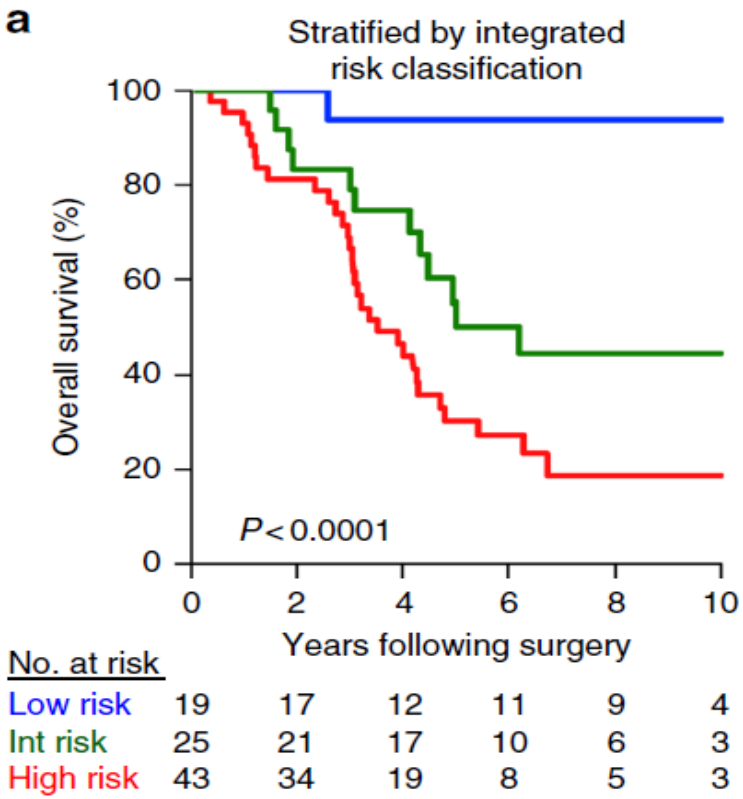
- 134 patients with resected liver oligometastasis from colorectal cancers
- 61% with only 1 met; 22% with 2 met. and 17% with 3 or more met
- Methods
  - Whole genome RNA sequencing of 95 samples
  - Microsatellite instability analysis in 89 samples

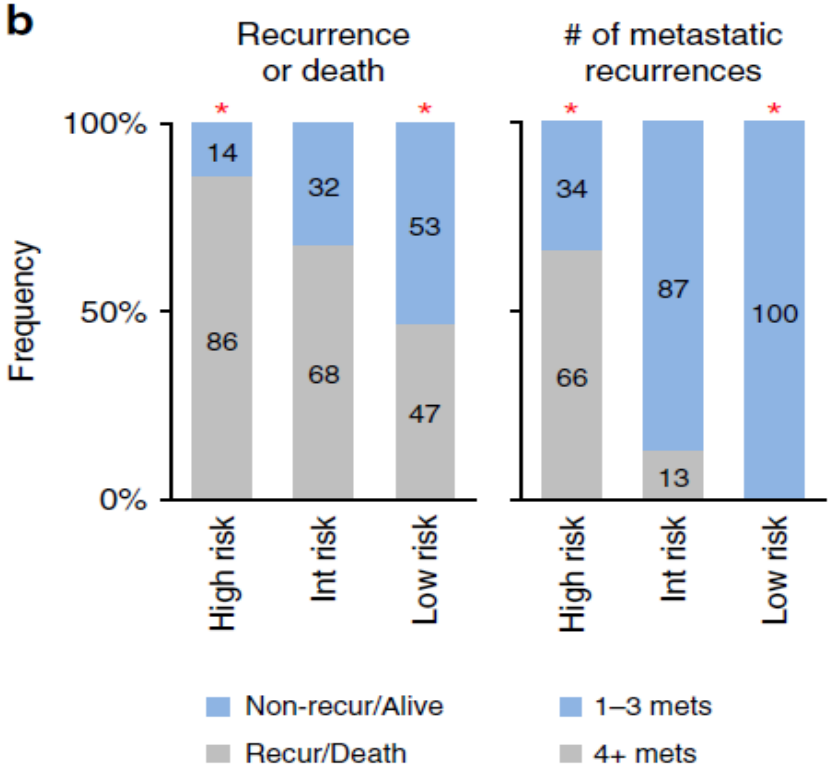
Identification of 3 molecular sub-types with different outcomes

- Low-risk group: 10 year-OS = 94%
- Intermediate group: 10-year OS = 45%
- High-risk group: 10-year OS = 19%

Pitroda SP, *et al.* Nature Comm 2018; 9(1): 1793 DOI: 10.1038/s41467-018-04278-6.

LIVER MET. FROM CRC





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

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

Pitroda SP, *et al.* Nature Comm 2018; 9(1): 1793 DOI: 10.1038/s41467-018-04278-6.

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

Turajlic S, *et al.* Cell 2018; 173:581-94.

CLEAR CELL RENAL CANCER

- 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

Turajlic S, *et al.* Cell 2018; 173:581-94.

BIOLOGY OF OLIGOMETASTASIS: WHAT ABOUT HOST ?

- 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 …

Hemminki K, *et al.* Oncotarget 2016; 7:22140-49

BIOLOGY OF OLIGOMETASTASIS: WHAT ABOUT HOST ?

The putative role of the immune system has to be explored

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BEST AVAILABLE CLINICAL EVIDENCE

- 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)

BEST AVAILABLE CLINICAL EVIDENCE

The design of ideal randomised is straightforward

Standard care could be systemic treatment or observation

BEST AVAILABLE CLINICAL EVIDENCE

Design assessing the added value of systemic treatment to focal therapies

BEST AVAILABLE CLINICAL EVIDENCE

Trial 1 - RTOG9508 - Andrews DW, *et al.* Lancet 2004

- 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

Trial 2 – CLOCC Trial /EORTC 40004 (Ruers T, *et al*. Ann Oncol 2012; Ruers T, *et al.* JNCI 2017)

- 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)**

BEST AVAILABLE CLINICAL EVIDENCE

Trial 3 – Gomez DR, *et al.* Lancet Oncol 2016

- 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)**

Iyengar P, *et al. Int* Nat J Radiation Oncol 2017;99(5):1314, LBA-3, presented at ASTRO 2017; Iyengar P, et al. JAMA Oncol 2018;4(1):e173501

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THE ROLE OF STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR OLIGOMETASTASES

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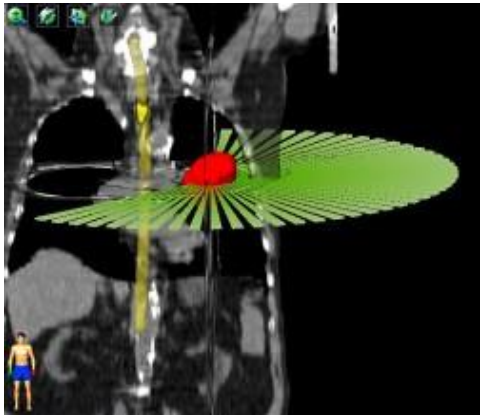
STEREOTACTIC ABLATIVE RADIATION THERAPY

- 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

Study	No of Patients	No metastases per patient	No metastases per patient	Dose(Gy)	Dose (Gy)	Follow- up (months)	Follow-up (months)	Metastasis control (%)	0S(%)
		Median	Range	Total	# fractions	Median	Range		
Colorectal Cancer									
Aarhus University (Aarhus, Denmark) [106]	64	2	1-6	45	3	52	20-76	2 years:86	4 years:13
Vrije Universiteit Brussel (Brussels, Belgium) [191]	23	1	1-3	40	10	12	3-18	1- year: 54	1- year: 86
Vrije Universiteit Brussel (Brussels, Belgium) [192]	24	1	1-3	50	10	10	3-21	1- Year: 54	1- year: 78
Non-small cell lung cancer									
University Medical centre Maastricht (Maastricht, The Netherlands) [120]	39	1	1-3	60	30	27.7	16.7-46.1	95	3 years: 17.5
Vrije Universiteit Brussel (Brussels, Belgium) [121]	26	1	1-5	50	10	16.4	3-40	85	1 years:67
UT Southwestern/University of Colorado [147]	24	2	1-5	19-40	1-5	11.6	3.4-60.3	9 months:94	Median: 20.4
Multi-institutional [187]	25	NR	1-3			18.7	NR	Locoregional:96	Maturing: 75
Breast cancer									
University of Rochester (Rochester, NY) [171]	40	2	1-4	40-60	10	NR		4 years:89	4 years:59
Prostate cancer									
Ghent University Hospital (Ghent, Belgium) [151]	24	NR	1-3	40-50	10	24	1-72	2-year: 100	NR
Ludwig-Maximilian University (Munich, Germany) [129]	44	1	1-2	20	1	14	3-48	1 year:96	17.5 months 75
Azienda Ospedaliero Universitaria Pisana (Pisa, Italy) [152]	29	NR	1-3	24	1	11.5	2-40	NR	NR
				27	3				

BEST AVAILABLE CLINICAL EVIDENCE

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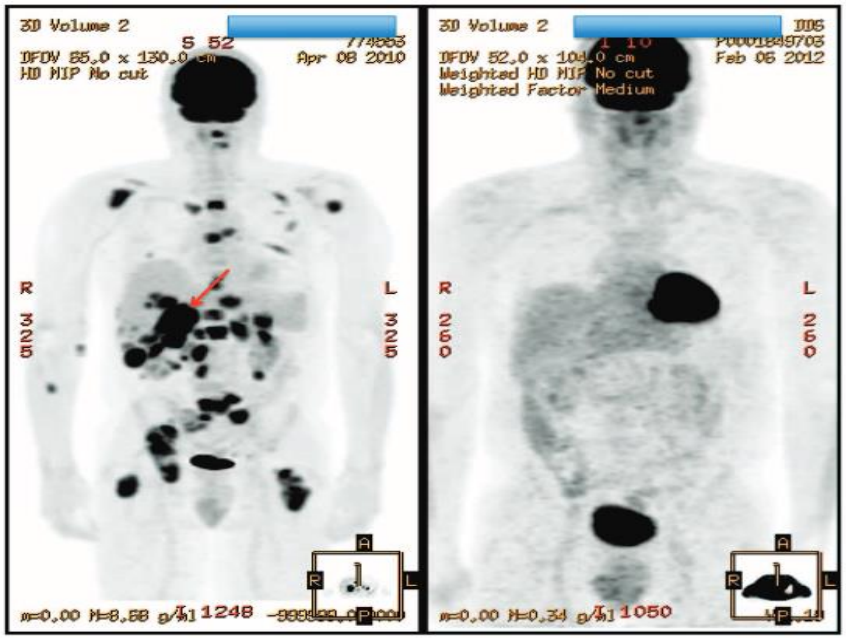
FUTURE DIRECTIONS

- 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 Tansl 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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TAKE-HOME MESSAGES

- 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!

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