BIOLOGIA E TRATTAMENTO RADIANTE CURATIVO DELLA **MALATTIA OLIGOMETASTATICA**

VIRTUAL
26 MARZO 2021

Attitudini biologiche e cliniche della malattia oligometastatica e oligoprogressiva: dagli studi traslazionali alle evidenze cliniche

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No conflict of interest to disclose

EDITORIAL

Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago
Chicago, IL

Oligometastases

- «One or a small number of metastases»

- What is a small number?

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

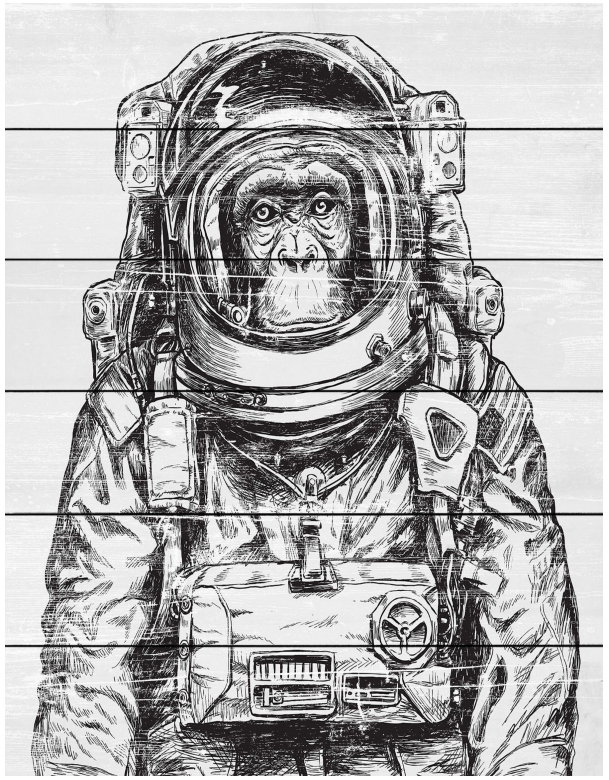
Consensus

Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

Check for updates

- All metastases that could be safely treated with ablative intent

……..with an upper bound of 5



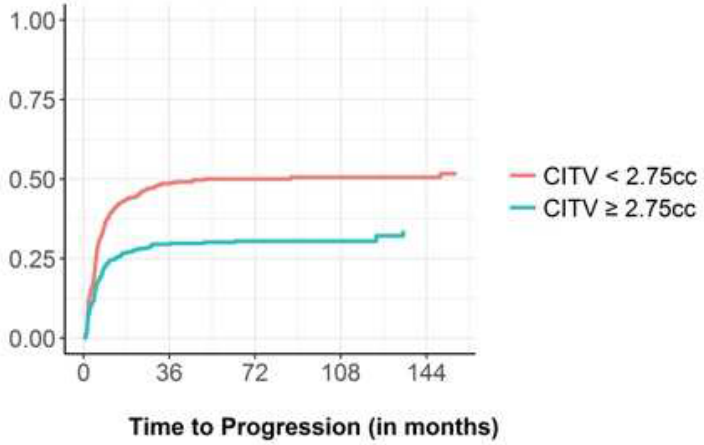
Lancet Oncol 2014; 15: 387–95

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

- No difference in OS between patients 2-4 BMs versus 5-10 BMs after SRS without WBI
- Possible negative influence on OS of cumulative tumor volume?

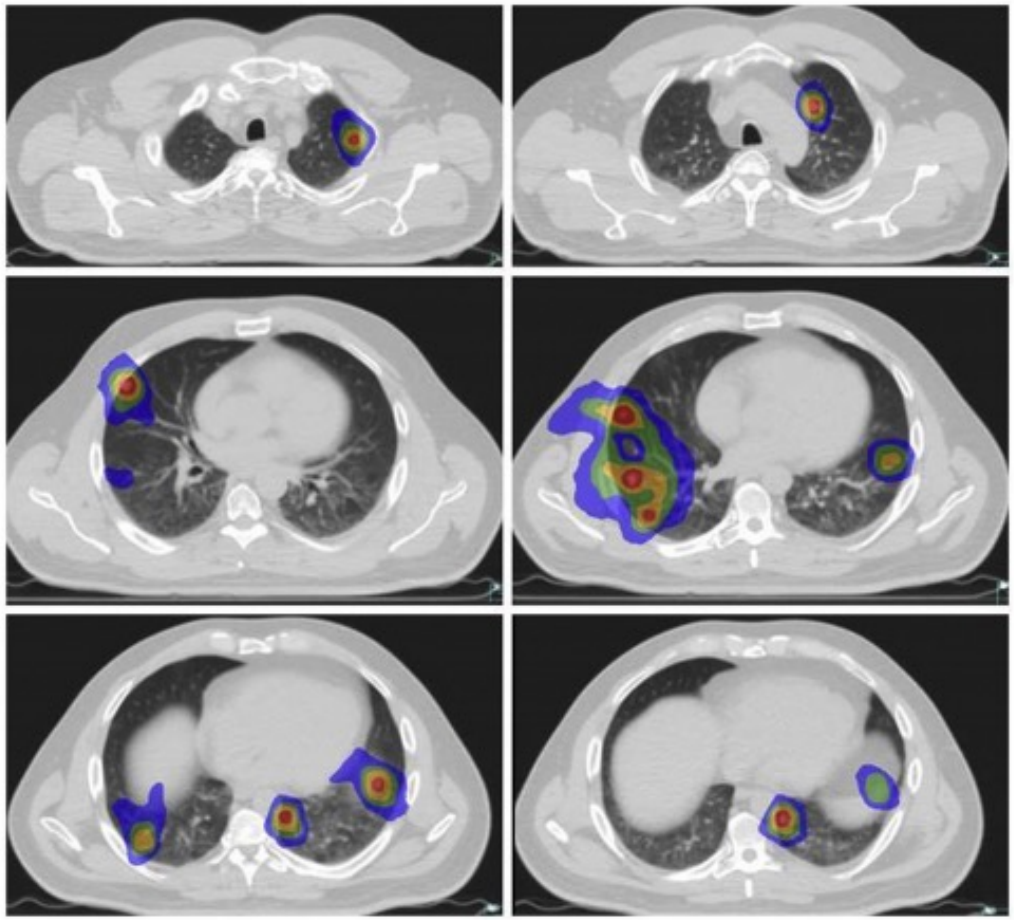
…possibly due to correlation with occurrence of new intracranial metastases?

Chen Radiat Oncol 2011
Sharma WNs 2017



STUDY PROTOCOL

Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial



Ablative Radiation Therapy to Restrain Everything Safely Treatable (ARREST)

ELSEVIER
Seminars in RADIATION ONCOLOGY

Modeling Growth Kinetics and Statistical Distribution of Oligometastases

H. Rodney Withers MD, DSc, and Steve P. Lee MD, PhD

Clinical history favoring development of an OM volume-frequency distribution

→ slowly growing, large primary tumor followed by a long metastasis-free interval after which a solitary metastasis emerges

→ For synchronous or early relapsing tumor (unlikely): high ratio of growth rate of metastases/primary, evidenced by a large difference between volumes of metastases

…may explain improved outcome in metachronous versus synchronous metastases

Fong Ann Surg 1999
Pastorino JTCVS 1997
Ashworth Clin Lung Can 2014

ORIGINAL ARTICLE

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

De Ruysscher JTO 2012

TABLE 9. Characteristics of Patients Showing no Disease Progression after 2 Years

64-yr-old man with a T2N2 NSCLC with a solitary brain metastasis treated with resection followed by whole-brain radiotherapy (30 Gy/10 fractions), 3 cycles of cisplatin-gemcitabine, and thereafter radiotherapy to the primary tumor and lymph nodes (54 Gy/ 30 BID fractions).

62-yr-old man with a T3N3 large cell carcinoma with a solitary pleural metastasis, for which 3 cycles neoadjuvant cisplatin gemcitabine, followed by radiotherapy to the primary tumor and lymph nodes (54 Gy/ 30 BID fractions).

60-yr-old man with a T2N2 squamous cell carcinoma with a solitary metastasis in the sternum, all treated with concurrent cisplatin vinorelbine and radiotherapy (69 Gy/42 fractions).

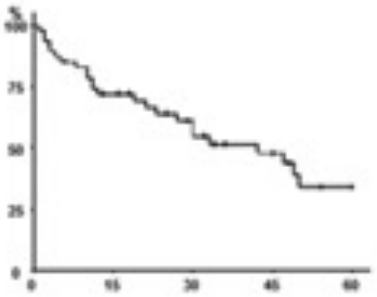
52-yr-old woman with a T2N0 adenocarcinoma with a solitary metastasis in the sacrum, treated with concurrent cisplatin-vinorelbine and radiotherapy (70.2 Gy/39 fractions on the primary tumor and 54 Gy/ 30 BID fractions on the sacrum).

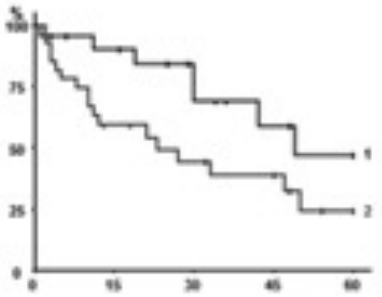
63-yr-old man with a T4N0 NSCLC with a solitary irresectable adrenal metastasis, treated with concurrent cisplatin-vinorelbine and radiotherapy (69 Gy/42 fractions on the primary tumor and 54 Gy/30 BID fractions on the adrenal metastasis).

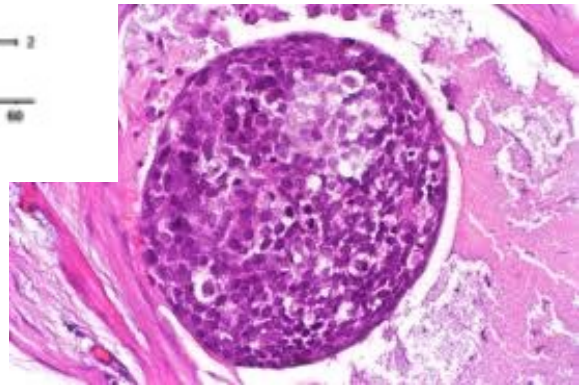
- Median OS 13 months
- 6/39 (15%) patients : no disease progression after 2 years → a subgroup of these patients may be cured or enjoy a long- lasting PFS.
- ”We believe that the future is to identify specific genetic characteristics that underlie the oligometastastic feature and the combination of specific agents with local treatment of metastases.”

Synchronous Oligometastatic Lung Cancer Deserves a Dedicated Management

Mauro Loi, MD,* Antonio Mazzella, MD,* Audrey Mansuet-Lupo, MD, PhD, Antonio Bobbio, MD, PhD, Emelyne Canny, MD, Pierre Magdeleinat, MD, Jean-François Régnard, MD, Diane Damotte, MD, PhD, Jean Trédaniel, MD, PhD, and Marco Alifano, MD, PhD

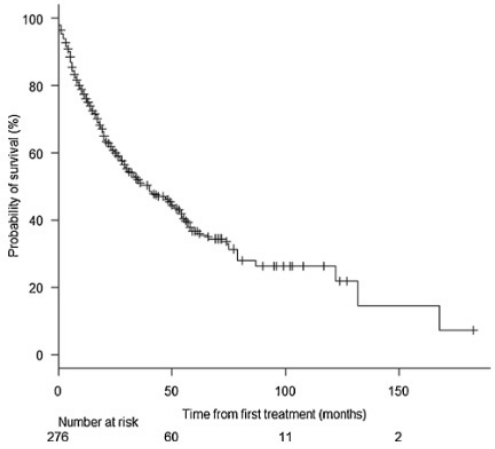






Contents lists available at ScienceDirect
Lung Cancer
journal homepage: www.elsevier.com/locate/lungcan

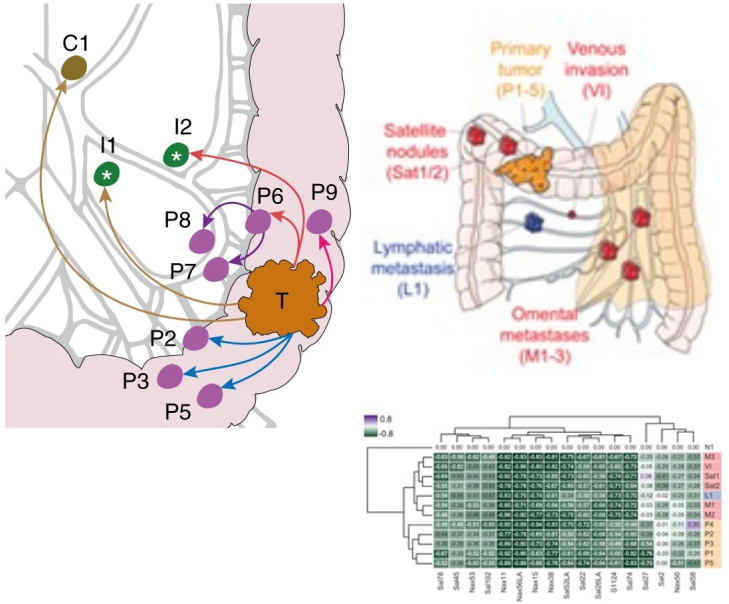
A risk stratification scheme for synchronous oligometastatic non-small cell lung cancer developed by a multicentre analysis



- Median OS 42 months
- No impact of pN stage
- Detrimental impact of vascular invasion (p=0.024)

Different clones may show a tendance toward local, locoregional or bloodstream dissemination

Colorectal Cancer

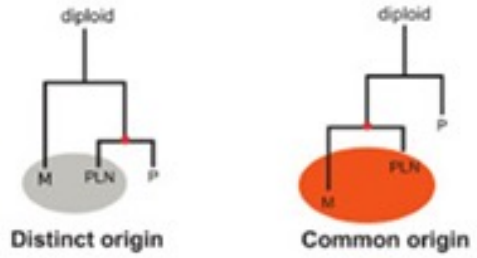


→ Subclonal origin of the local LN mets ≠ visceral distant mets

→ Genomic mapping of metastatic routes

Zhang Nat Comm 2020
Naxerova Science 2017

Breast Cancer

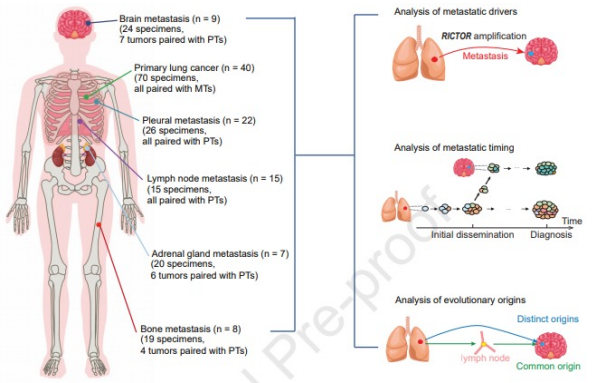


→ 75% of patients, primary tumor more closely related to the distant lesions than any positive lymph node, making a direct descent from the primary tumor more likely.

→ Biology may replace axillary dissection?

Venet Ebiomedicine 2020

Lung Cancer



→ Whole-exome sequencing

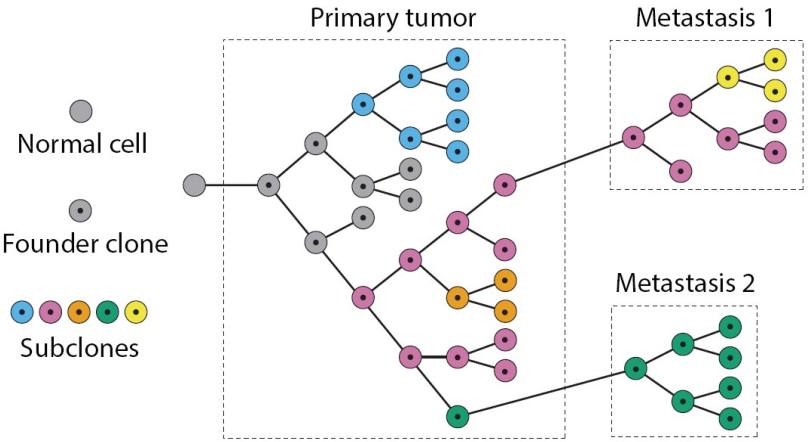
→ Model: 61% late dissemination (seeding 2.74 yrs before detection)

→ 87.5% non-LN mets seeded by primary tumor

Tang J Thorac Oncol 2021

- Intra-tumor heterogeneity usually refers to intra-primary-tumor heterogeneity, but it is also related to inter- and intra-metastatic heterogeneity

- Clonal selection is the main mechanism underpinning those differences



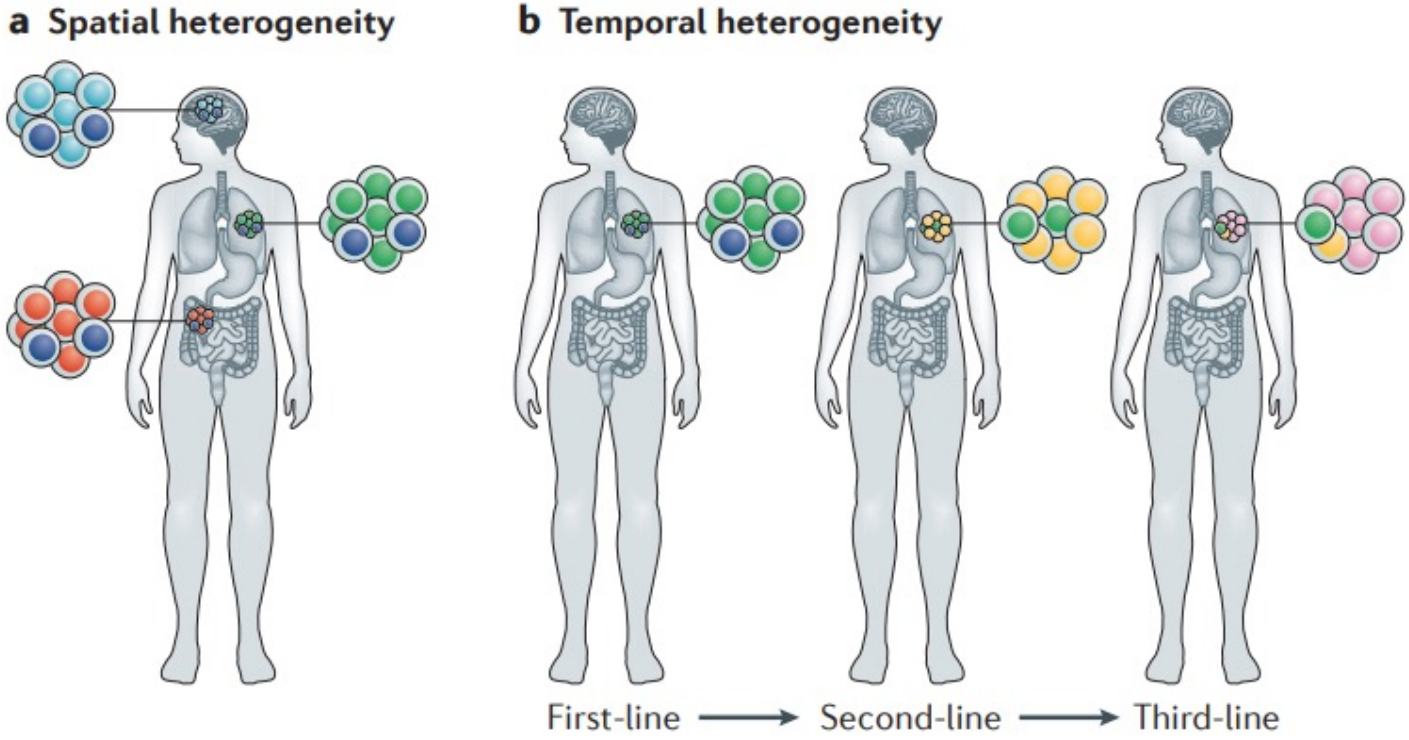
→ reduced intra-metastatic heterogeneity reported

Wei Ann Oncol 2017

→ more aggressive and lethal clones can arise from primary tumor even of relatively low grade

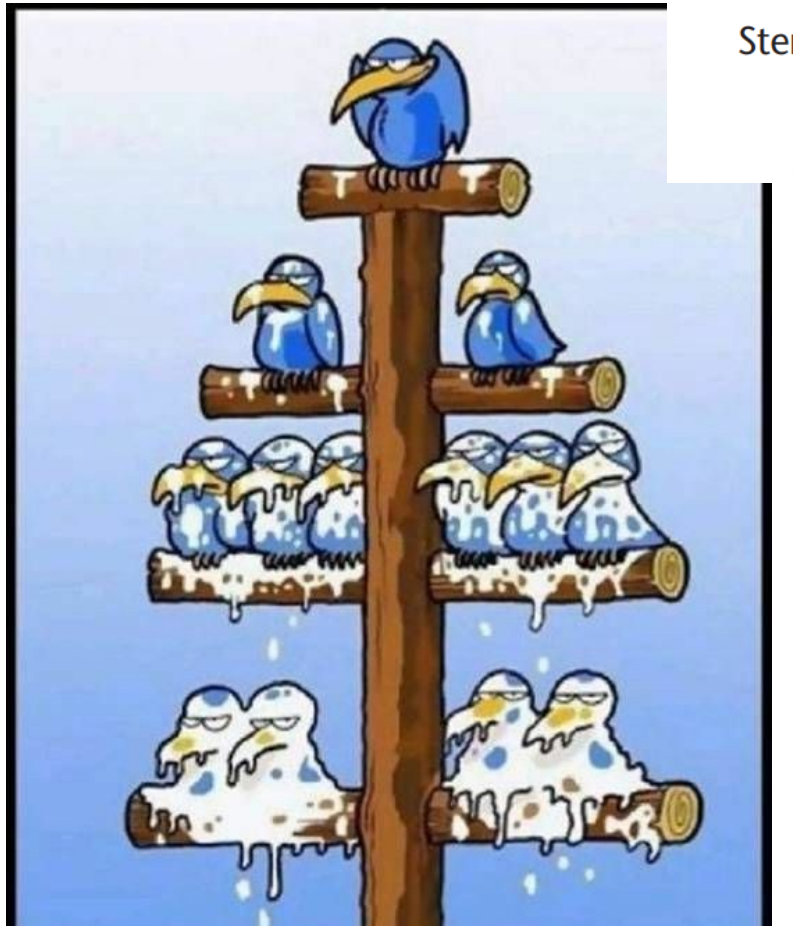
Talmadge Can Res 2010

- Genomic instability fosters genetic diversity in tumors
- Tumours with high levels of intratumoural heterogeneity might predispose patients to inferior clinical outcomes



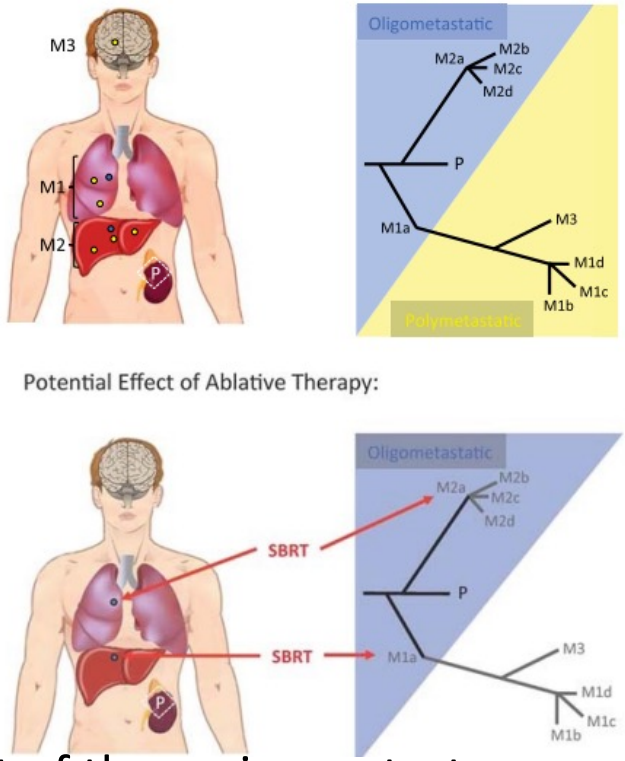
Dagogo Jack, Nat Rev Clin Oncol 2017

- This evolutionary view challenges the classical micrometastatic model (a metastatic “storm” sweeping across the body) → more a trajectory than a storm!!!



Stereotactic Body Radiotherapy for Oligometastasis
Opportunities for Biology to Guide Clinical Management

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



- This raise relevant considerations in favor of LOCAL treatment of the major metastases.

Acta Oncologica, 2009; 48: 578–583

informa
healthcare

ORIGINAL ARTICLE

Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis

KYLE E. RUSTHOVEN[1], SUSAN F. HAMMERMAN[2], BRIAN D. KAVANAGH[1], MICHAEL J. BIRTWHISTLE[2], MARK STARES[2], & D. ROSS CAMIDGE[2]

→ most disease progression occur at known sites rather than at occult, newly-emerging sites

original report

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

Daniel R. Gomez, MD[1]; Chad Tang, MD[1]; Jianjun Zhang, MD, PhD[1]; George R. Blumenschein Jr, MD[1]; Mike Hernandez, MS[1]; J. Jack Lee, PhD[1]; Rong Ye, MS[1]; David A. Palma, MD, PhD[2]; Alexander V. Louie, PhD, MSc[2]; D. Ross Camidge, MD, PhD[3]; Robert C. Doebele, MD, PhD[3]; Ferdinandos Skoulidis, MD, PhD[1]; Laurie E. Gaspar, MD[3]; James W. Welsh, MD[1]; Don L. Gibbons, MD[1]; Jose A. Karam, MD[1]; Brian D. Kavanagh, MD, MPH[3]; Anne S. Tsao, MD[1]; Boris Sepesi, MD[1]; Stephen G. Swisher, MD[1]; and John V. Heymach, MD, PhD[1]

…So ablation of all metastatic foci is possible… should I carry on systemic therapy if I truly believe metastatic disease is curable?

- Reduce overtreatment and toxicity
- Prolong treatment-free survival
- Save systemic therapy for effective palliation of symptoms

- Omission of an essential treatment that could delay death and deterioration in patients at risk of fast-pace metastatic dissemination

- WideSpread Progression (WSP): time to conversion from oligometastatic to polymetastatic state.

- Interestingly, first metastatic relapse after ALT was oligometastatic in 33%, thus possibly accessible to further local treatment.

- Conversely, WSP proved a late event (median 42.5 months), although a considerable proportion of patients (43%) experienced WSP within 1 year from SBRT

Poon, JAMA Oncol 2020

So what did we learn so far?

- Oligometastatic state is not a permanent condition

→rather a narrow time window to eradicate metastases before metastases can seed new metastases

- Patient selection is dictated by general rules.. For whom we have only “imperfect” surrogates

→ Tumor burden : *number of metastases*

→ Pace of dissemination : *timing of metastases vs primary*

→ Biological and TME features: *not implemented in clinical routine*

TUMOR BURDEN

→ Improved sensibility of imaging

- ORIOLE TRIAL: blinded use of PET-PSMA and detection of occult foci

6 months BRFS 62% vs 95% in patients with un-treated vs treated PSMA-avid metastases

Philips, JAMA Oncol 2020

→ Molecular burden of disease quantification

- Circulating tumor DNA (ctDNA) correlate with viable tumor cells and may allow for dynamic assessment of global and residual disease

Lebow IJROBP 2020

PACE OF DISSEMINATION

→ Biological characterization of metastatic spread

- Specimen from resected liver CRC metastases clustered in risk groups integrating biological features (canonical vs immune vs stromal): DFS 59 vs 35 vs 13 months; oligometastatic recurrence 100 vs 87 vs 34%

Pitroda Nat Comm 2018

- TRACERx initiative: rapid progression group (multiple sites of disease progression within 6 months of nephrectomy) and an attenuated progression group (single-site progression <6 months or multisite progression >6 months), correlated with intratumoral heterogeneity and somatic copy-number alterations (SCNA).

Turaijlic Cell 2018

- miRNA based classifier following lung metastasectomy: Low risk (<0.6 new metastases per year),intermediate-rate group (0.6 to 3.6 new metastases per year) and high-rate group (>3.6 new metastases per year)

Lussier PlosOne 2012

BIOLOGICAL FEATURES

→ Tumor-related surface protein expression

- SMAD4 predicts local versus metastatic progression in pancreatic cancer (78% vs 22%)

Iacobuzio-Donahue JCO 2009

→ Epigenetic markers

- 14q32 miRNA expression abrogated liver metastasis in vivo and correlates with OS in the clinical setting (hepatic metastases from colorectal cancer)

Oshima Cancer Res 2019

→Immune classifier

- The ImmunoScore (semiquantitative representation of CD3þ and CD8þ T-cell infiltration of tumor specimens) of the least immune-infiltrated colorectal cancer metastasis was associated with clinical outcome

Van den Einde Cancer Cell 2018

COULD WE REVERT POLYMETASTATIC DISEASE??

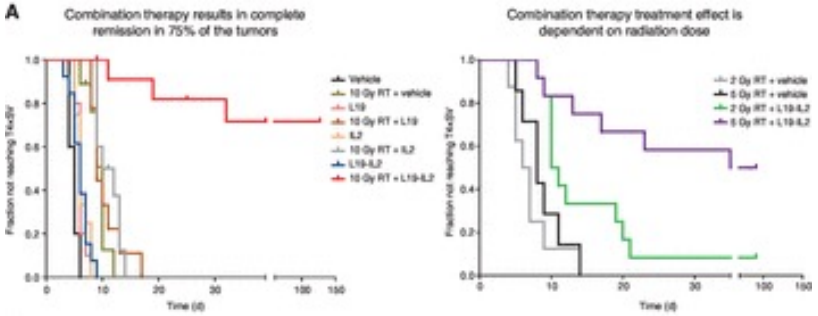
→ «Enflame» tumor microenvironment

Journal for ImmunoTherapy of Cancer

Releasing the brakes of tumor immunity with anti-PD-L1 and pushing its accelerator with L19–IL2 cures poorly immunogenic tumors when combined with radiotherapy

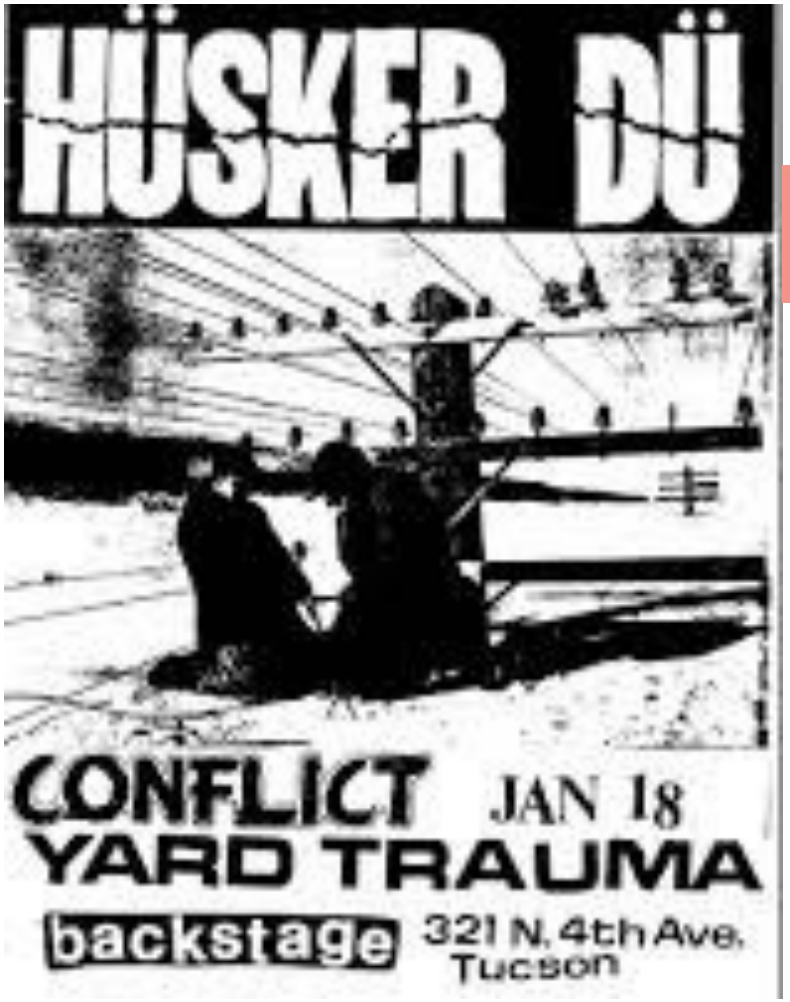
- Immunocytokine L19–IL2 combined with single-dose RT resulted in 75% tumor remission and a 20% curative abscopal effect in the T cell-inflamed C51 colon carcinoma model

Zegers CCR 2015



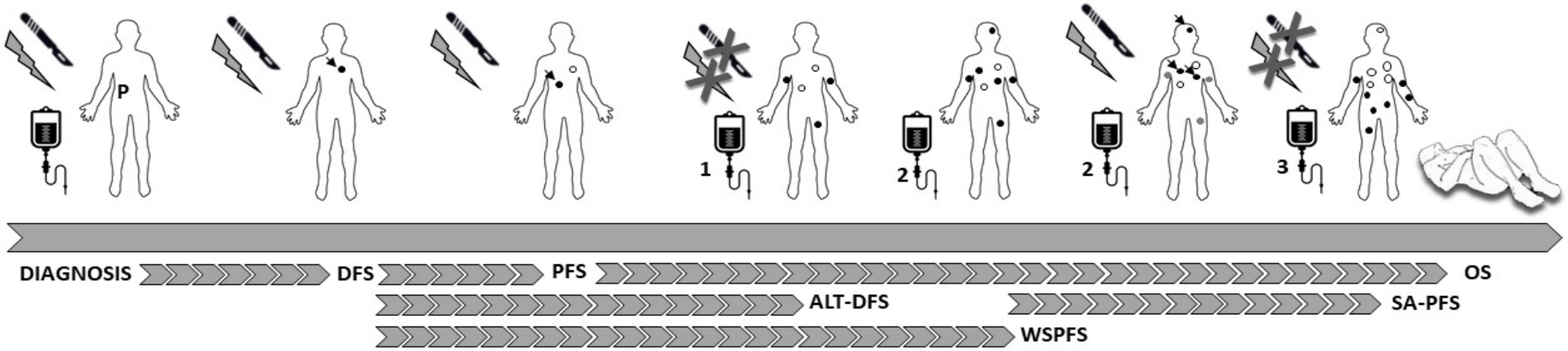
- Disappointing in real life

McBride JCO 2020
Voorwerk Nat Med 2019



THE REVOLUTION STARTS AT HOME

(preferably in the bathroom mirror)



The Oncologist®
Letters to the Editor

Judging a fish by its ability to climb a tree? A call for novel endpoints in the appraisal of Ablative Local Treatments (ALTs) of Oligometastatic Cancer

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- ALT-adjusted DFS(ALT-DFS)

→time from 1st ALT to systemic treatment or BSC

- WideSpread PFS (WSPFS)

→time from OM to polymetastatic dissemination

- Systemic Therapy+ALT-adjusted PFS (SA-PFS)

→time from chemotherapy initiation to further chemotherapy line

- Oligometastatic state is a transient condition of low tumor burden and slow dissemination rate → a time window in which curability could be achieved

- In most cases no metastatic storm, but stepwise dissemination sustained by biologic behaviour of tumor cell

- Focal ablation has a potential to halt metastatic trajectory

→ delay or prevent polymetastatic conversion

- Imperfect surrogates: number and timing of metastases

- Better characterization of OM state may justify ARREST or prevent omission of systemic therapy in patient with polymetastatic occult disease

- Biological correlates may identify candidates for both strategies

- Role of the host/tumor synergy to be further defined

→ key to revert polymetastatic into curable disease?

- Need for ALT-based endpoints to be implement in clinical practice to improve knowledge of determinants of OM

THANK YOU FOR YOUR ATTENTION