Klinik für RadioOnkologie | UniversitätsSpital Zürich | Universität Zürich

32nd Residential Course, MRO, Modern Radiation Oncology:
Multidisciplinarity in the era of omics and AI guided Oncology

Omics and AI driven radiation oncology in Oligometastatic patients

Matthias Guckenberger

@matguc

USZ Universitäts Spital Zürich

Universität Zürich[UZH]

Conflicts of interest

None

What`s in the title

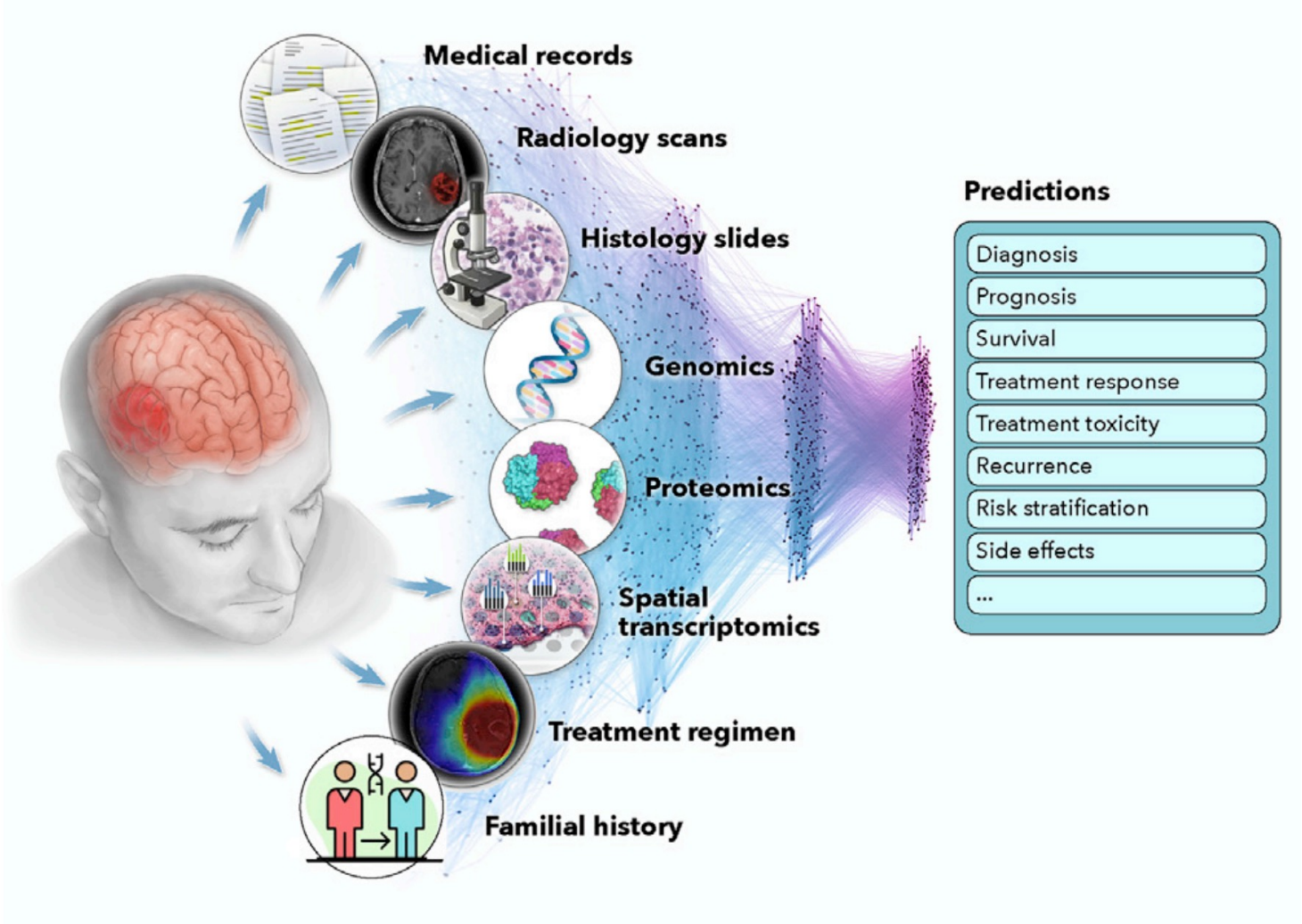
Oligometastatic

Omics

Artificial intelligence

Radiation Oncology

AI for multimodal data integration in oncology



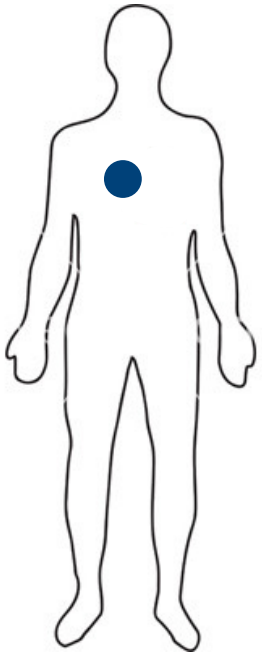
REFERENCES: *Lipcova Cancer Cell 2022*

AI for multimodal data integration in oncology

➢ What is the goal / are the goals of integrating local RT into a multimodality Tx strategy for oligometastatic patients ?

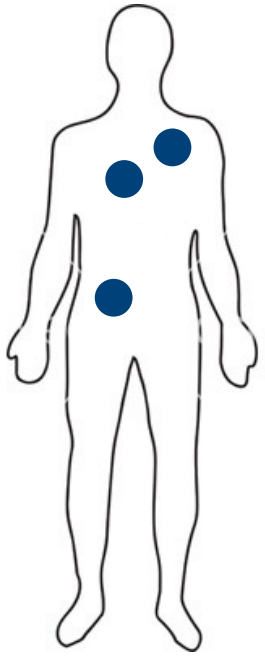
Oligometastatic Disease (OMD)

Localized



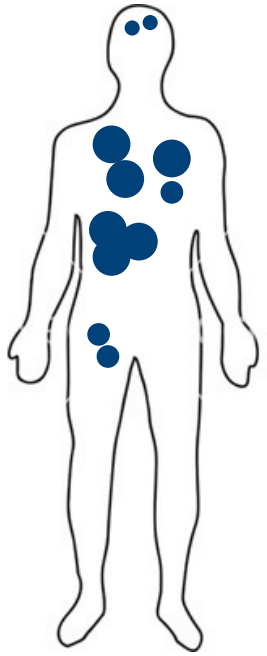
Cure with local treatment

Oligometastatic



Possibility of cure with local & systemic treatment

Systemic



Local Tx for symptom control

REFERENCES: *Hellman & Weichselbaum JCO 1995*

Oligometastatic Disease (OMD)

The specific challenge in OMD

- To safely deliver definitive radiotherapy to **multiple** sites of disease

while

- the risk of microscopic disease is addressed by patient selection OR effective systemic therapy.

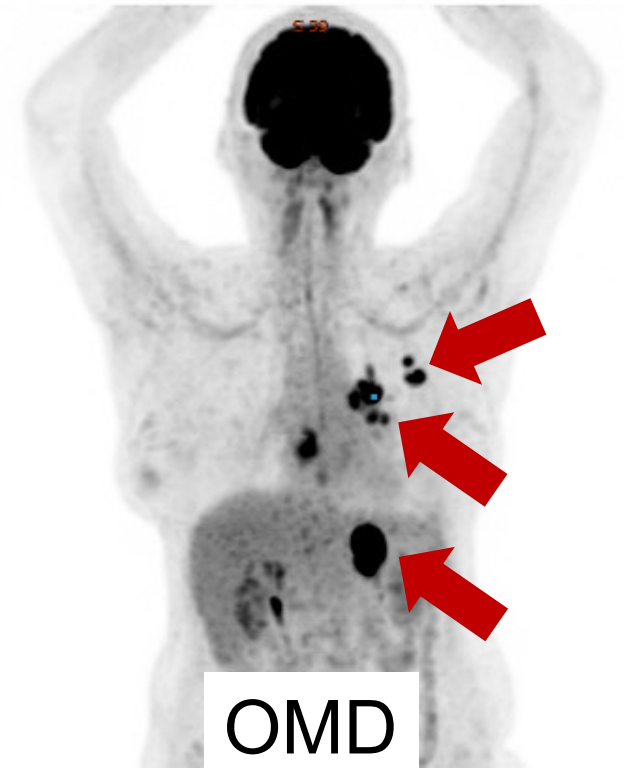
Oligometastatic Disease (OMD)

Clinical goal	Study	Tumor site	Endpoint	Result
Cure	*Ruers JNCI 2017*	Colorectal Ca	OS	HR=0.58
	Palma Lancet 2019	Agnostic	OS	HR=0.5
	Gomez JCO 2019	NSCLC	OS	HR=0.41
	Wang JNCI 2021	NSCLC	OS	HR=0.44

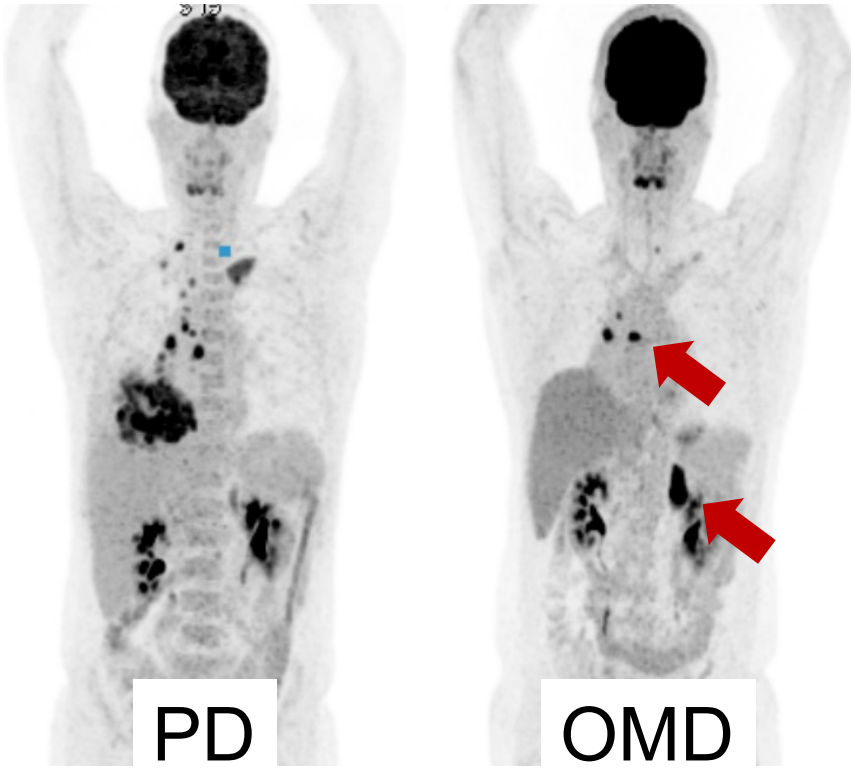
➢ Different clinical goals and new clinical endpoints

Heterogeneity of OMD

OMD Patient A

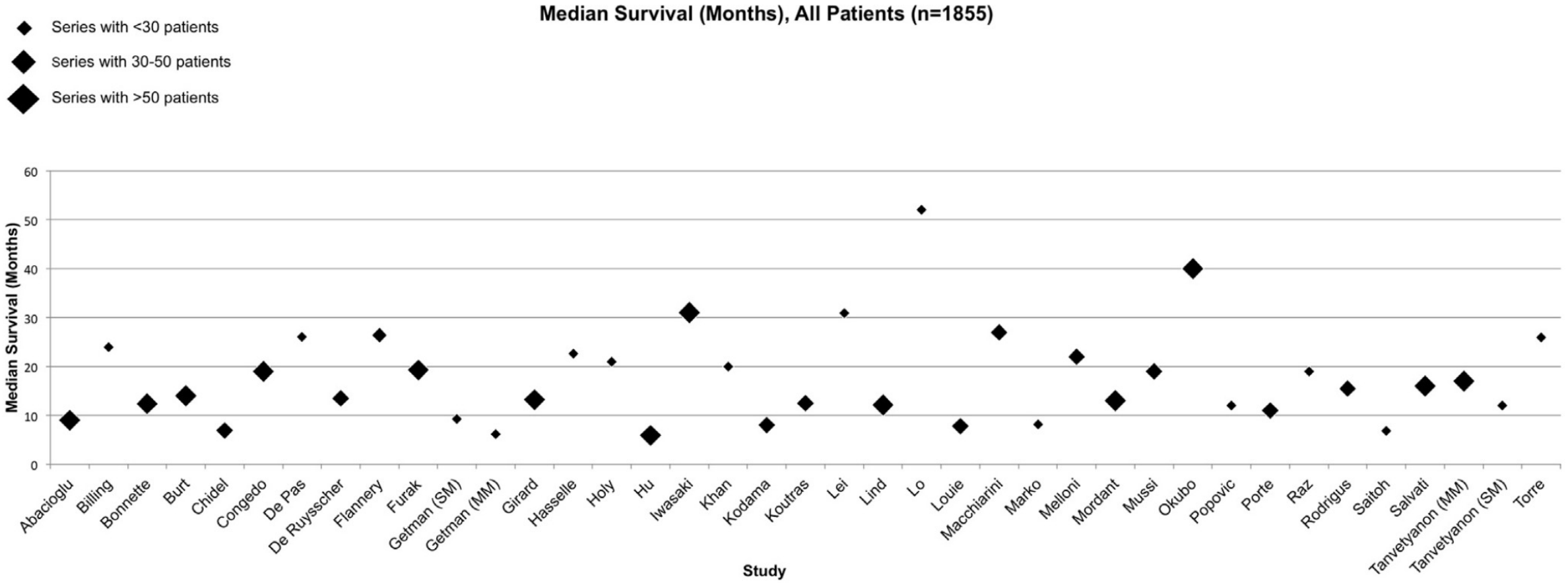


OMD Patient B



➢ Need for more comprehensive OMD characterization

Heterogeneity of OMD



- 5a overall survival in oligometastatic NSCLC: 8.3 - 86%
- Heterogeneity comparable to variation between stage I – IV

REFERENCES: *Ashworth Lung cancer 2013*

OMD characterization and classification

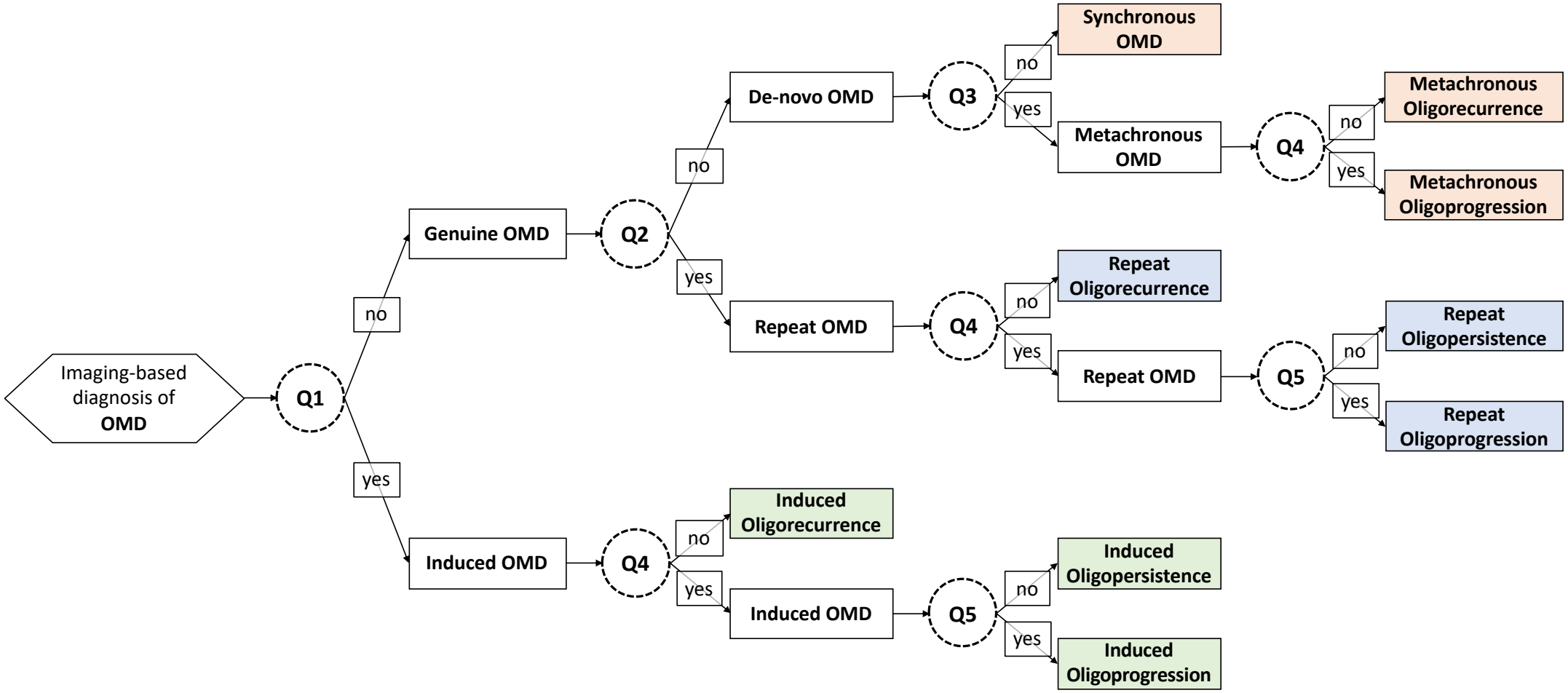
Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans, Beatrice Fournier, Coen Hurkmans, Frédéric E Lecouvet, Icro Meattini, Alejandra Méndez Romero, Umberto Ricardi, Nicola S Russell, Daniel H Schanne, Marta Scorsetti, Bertrand Tombal, Dirk Verellen, Christine Verfaillie, Piet Ost

- To develop a consensus nomenclature and comprehensive system for OMD characterization and classification

REFERENCES: *Guckenberger Lancet Oncology 2020*

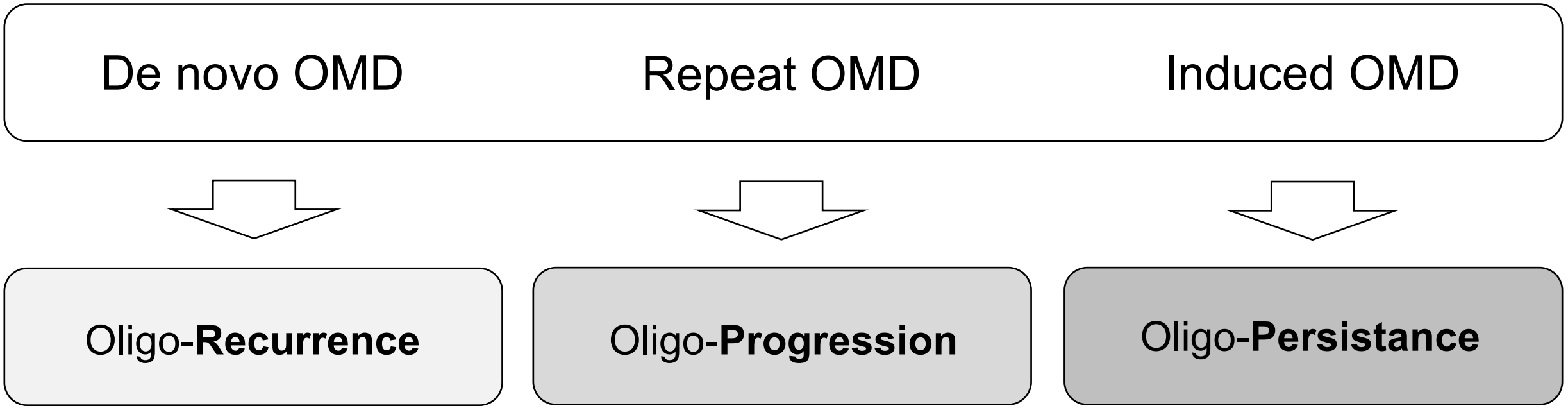
OMD characterization and classification



Decision tree resulting in 9 different states of OMD

REFERENCES: *Guckenberger Lancet Oncology 2020*

OMD characterization and classification

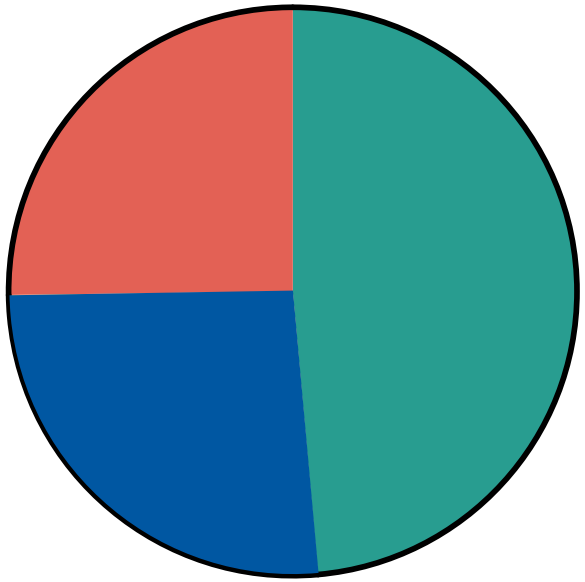


- Consensus proposal of different OMD states, exclusively depending on clinical factors

REFERENCES: *Guckenberger Lancet Oncology 2020*

OMD characterization and classification

– N=389 OMD patients treated for max 5 mets @ USZ

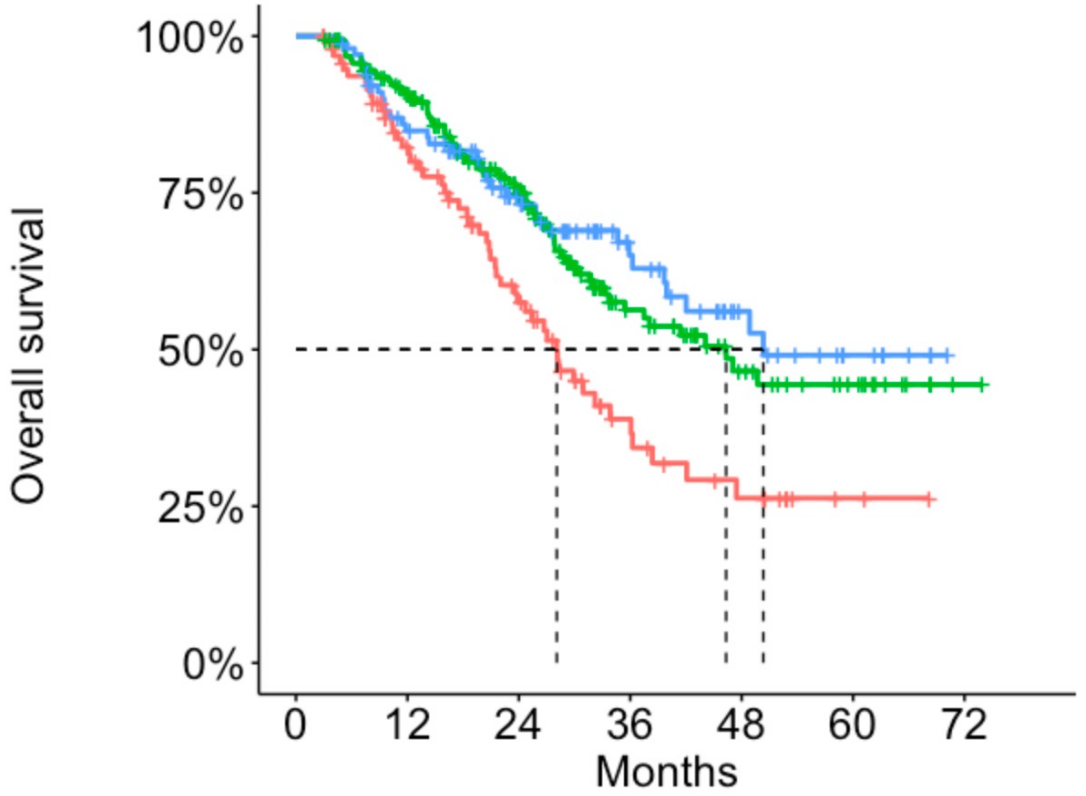


Total=389

De-novo OMD

Repeat OMD

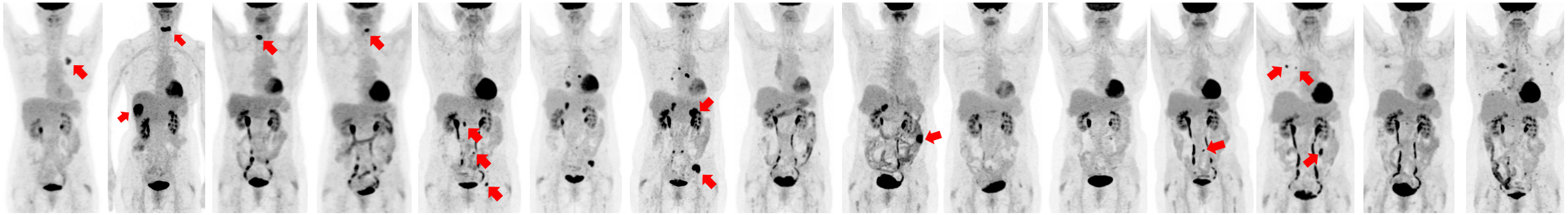
Induced OMD



➢ Independent prognostic factor

REFERENCES: *Willmann Radiother Oncol 2022*

OMD characterization and classification

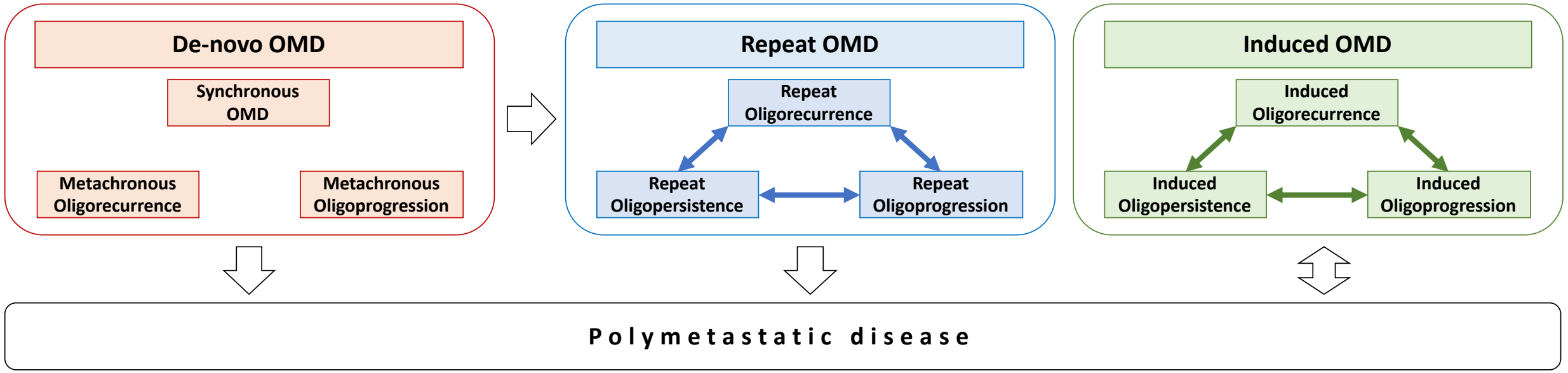


04/2014	05/2015	04/2016	09/2016	12/2016	06/2017	09/2017	06/2018	05/2019	08/2019	03/2020	07/2020	03/2021	09/2021	02/2022
Localized	Oligo	Oligo	Oligo	Oligo	Poly	Poly	PR	Oligo	CR	CR	Oligo	Oligo	CR	Poly
Surgery	2x SBRT	1x SBRT	1x SBRT	3x SBRT	-	2x Pall RT	-	1x SBRT	-	-	1x SBRT	3x SBRT		

- 8 year history of NSCLC
- n=1 surgery in curative intent
- n=2 lines of systemic therapy (chemotherapy & Nivolumab)
- n=12 SBRT for n=7 phases of OMD

REFERENCES: *Guckenberger Lancet Oncology 2020*

OMD characterization and classification

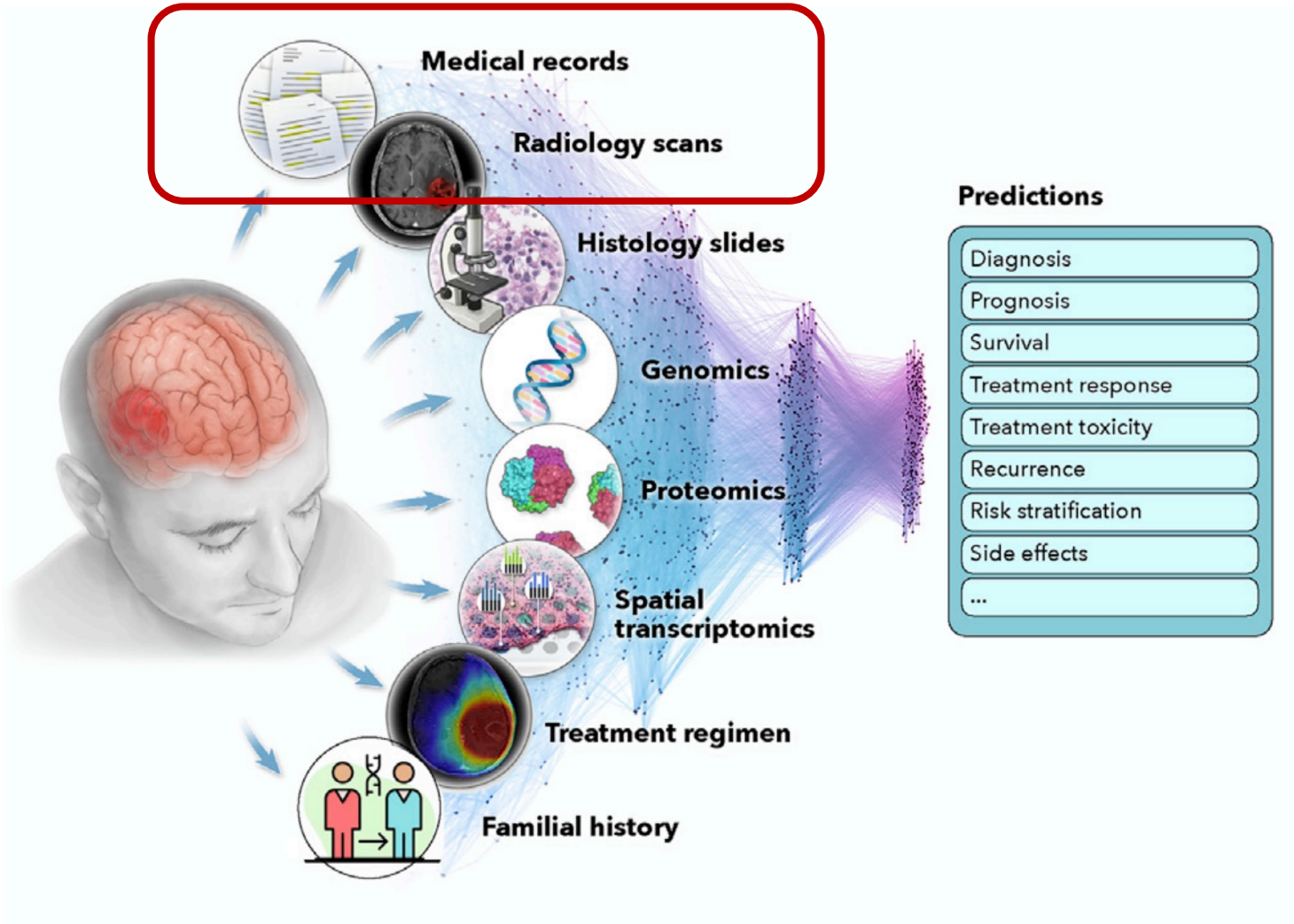


Dynamic oligometastatic states model

- Depending on response and failure pattern to multiple lines of systemic and / or local therapy

REFERENCES: *Guckenberger Lancet Oncology 2020*

AI for multimodal data integration in oncology



REFERENCES: *Lipcova Cancer Cell 2022*

Tumor burden for definition of OMD

1 **2** **3** **4** **5**

Guideline and clinical trial perspective:

- ➢ No need for Omics and AI covering if you can count to 5

Tumor burden for definition of OMD

Study	# patients	Tumor site	# of metastses	Primary
Iyengar Jama Oncol 2018	N=29	NSCLC	**5**	**active**
Gomez JCO 2019	N=49	NSCLC	**3**	**active**
Wang JNCI 2021	N=133	EGFR pos NSCLC	**5 in max. 2 organs**	**active**
Ost JCO 2018	N=62	Prostate	**3 (N1 included)**	**controlled**
Phillips JAMA Oncol 2020	N=54	Prostate	**3 (N1 included)**	**controlled**
Ruers JNCI 2017	N=119	Colorectal liver mets	**9**	**controlled**
Palma JCO 2019	N=99	Agnostic	**5**	**controlled**

- Mostly maximum n=5 or n=3 metastases
- 7 randomised phase II trials, 6 different OMD definitions

Tumor burden for definition of OMD

Analysis of n=7.000 PET images acquired in 2020 @ USZ

PET/CT or PET/MRI images
N=7.000

Solid malignancy
N=5.358

Individual pts with M+
N=1.155

Individual OMD pts
N=601

Pancreas, liver, and gallbladder	37/63	**59%**
Skin Ca	116/204	**57%**
Prostate Ca	80/141	**57%**
Head & neck Ca	53/93	**57%**
Colorectal Ca	39/69	**57%**
Lung and pleura Ca	160/292	**55%**
Upper GI Ca	13/26	**50%**
Breast Ca	47/119	**39%**
Genitourinary Ca	27/69	**39%**
CUP	8/31	**26%**
Other	21/44	**48%**

➢ Between 40% and 55% of metastatic cancer patients are oligometastatic based on PET and c-MRI imaging

REFERENCE: *Christ IJROBP 2022*

Tumor burden for definition of OMD

Of n=637 pts with ≦5 metastases in whole body PET/CT imaging

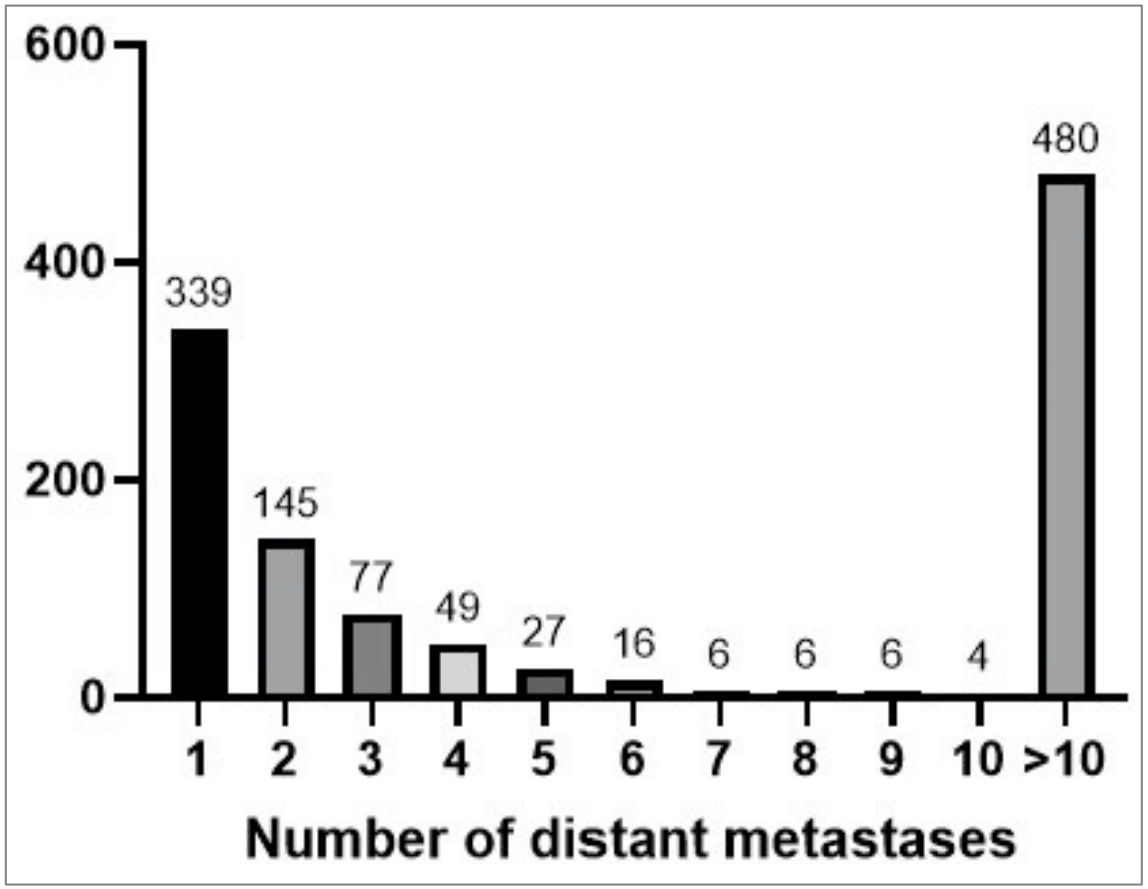
- Cranial MRI performed in 130 / 637 pts (20%) within 4 weeks of PET imaging
- 36/130 (**28%**) pts with brain mets such that total # of metastases exceeded OMD definition

- Not surprisingly, imaging matters !
- Relevance of brain metastases
  - Exclusion criteria in some trials
  - Efficacy of systemic Tx variable

REFERENCE: *Christ IJROBP 2022*

Tumor burden for definition of OMD

n=1,754 FDG-PET or PSMA-PET studies from 1,155 unique cancer patients showed presence of metastatic disease



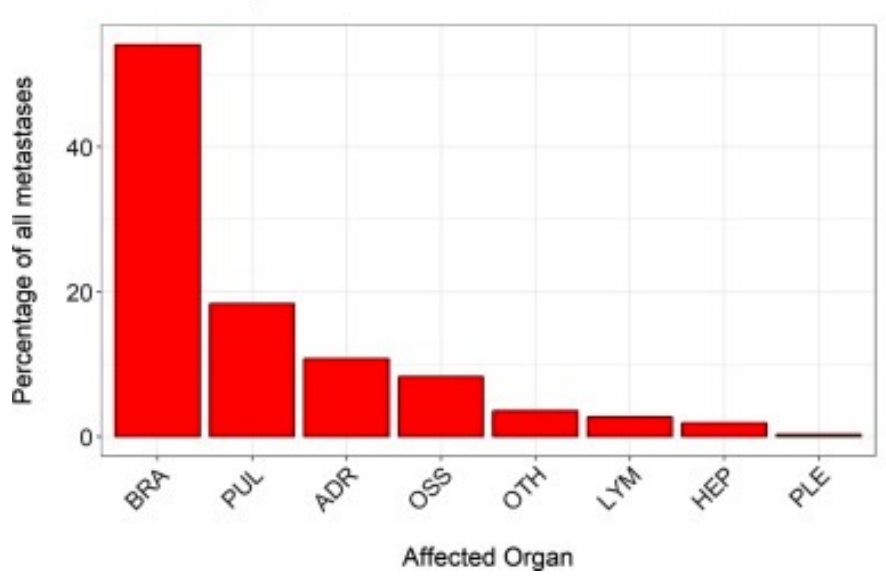
- Biphasic distribution with either very few or multiple metastases
- No cut-off in between
- Implications for clinical trial design
- Distribution mimicking patient characteristics from clinical trials

REFERENCE: *Christ in preparation*

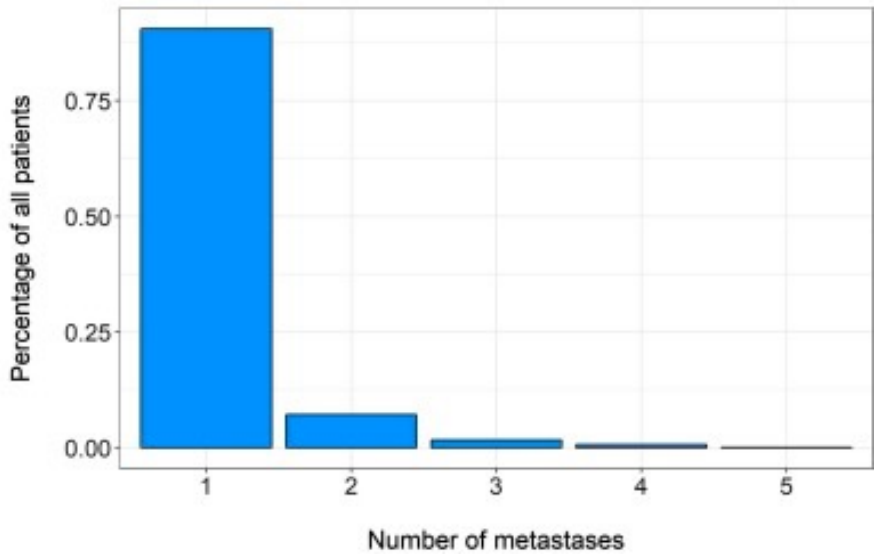
Tumor burden for definition of OMD

Systematic review of oligometastastic NSCLC

Site of oligometastases



of oligometastases



➢ Evidence in OMD - strongly based on solitary metastases

REFERENCES: *Schanne Cancer Treatment Reviews 2019*

Tumor burden for definition of OMD

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

Yolande Lievens [a,*], Matthias Guckenberger [b], Daniel Gomez [c], Morten Hoyer [d], Puneeth Iyengar [e], Isabelle Kindts [f], Alejandra Méndez Romero [g], Daan Nevens [h], David Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]

Maximum disease burden

KQ 5: Is OMD defined by a maximum number of lesions and/or sites?	
No, the possibility to safely deliver curative intent metastasis-directed radiotherapy determines the maximum number	82% (9/11)

➢ Cancer including OMD - a spectrum of diseases

REFERENCE: *Pitroda Nature Reviews 2019, Lievens Radiother Oncol 2020*

Tumor burden for definition of OMD

Proportion of NSCLC pts developing distant metastases

Stage I	Stage III	OMD	Stage IV
SBRT	PACIFIC	Multimodality	Chemo IO
Chan Lancet Oncol 2021	*Spigel JCO 2022* *Bradly JCO 2020*	*Gomez JCO 2019*	*Gandhi NEJM 2018*
10%	**24% - 52%**	**72%**	**100% ?**

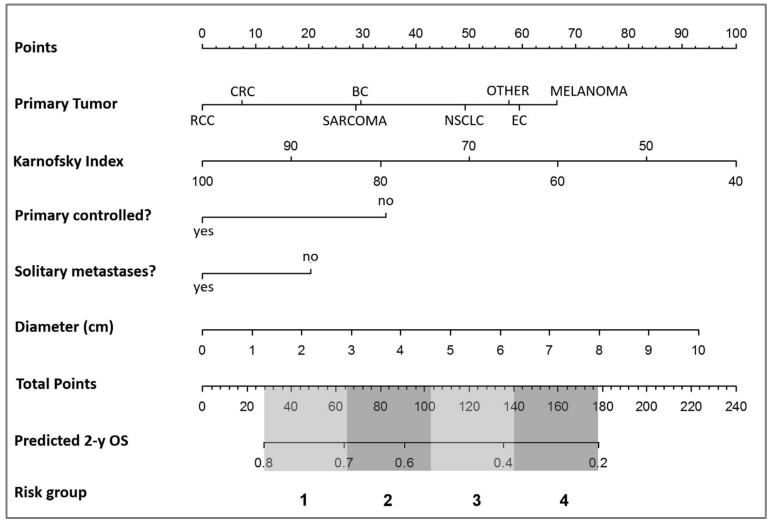
➢ Macroscopic tumor burden surrogate for risk / burden of microscopic disease

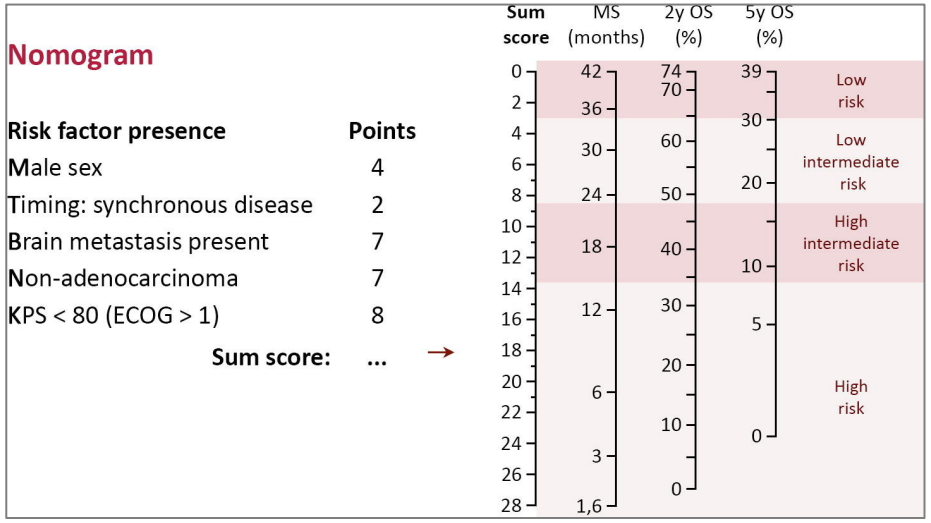
Clinical criteria for definition of OMD

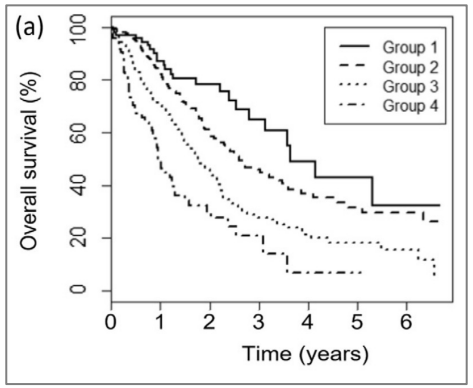
Elekta OMD consortium	DEGRO OMD Project	Zurich OMD Cohort
Poon JAMA Network Open 2020	*Tandini-Lang Radiother Oncol 2017*	*Willmann IJROBP 2022*
N=1033	N=907	N=385
Primary tumor	Primary tumor	Primary tumor
Synchonous vs metachronous		
Organ involvement		
	Performance status	
	Primary controlled	
	Solitary metastasis	
	Size of largest metastasis	
		OMD state

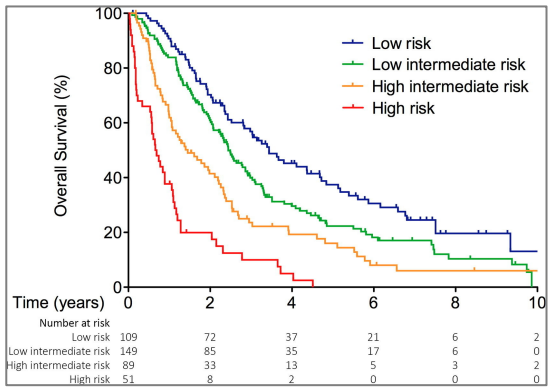
➢ Heterogeneous

Clinical criteria for definition of OMD







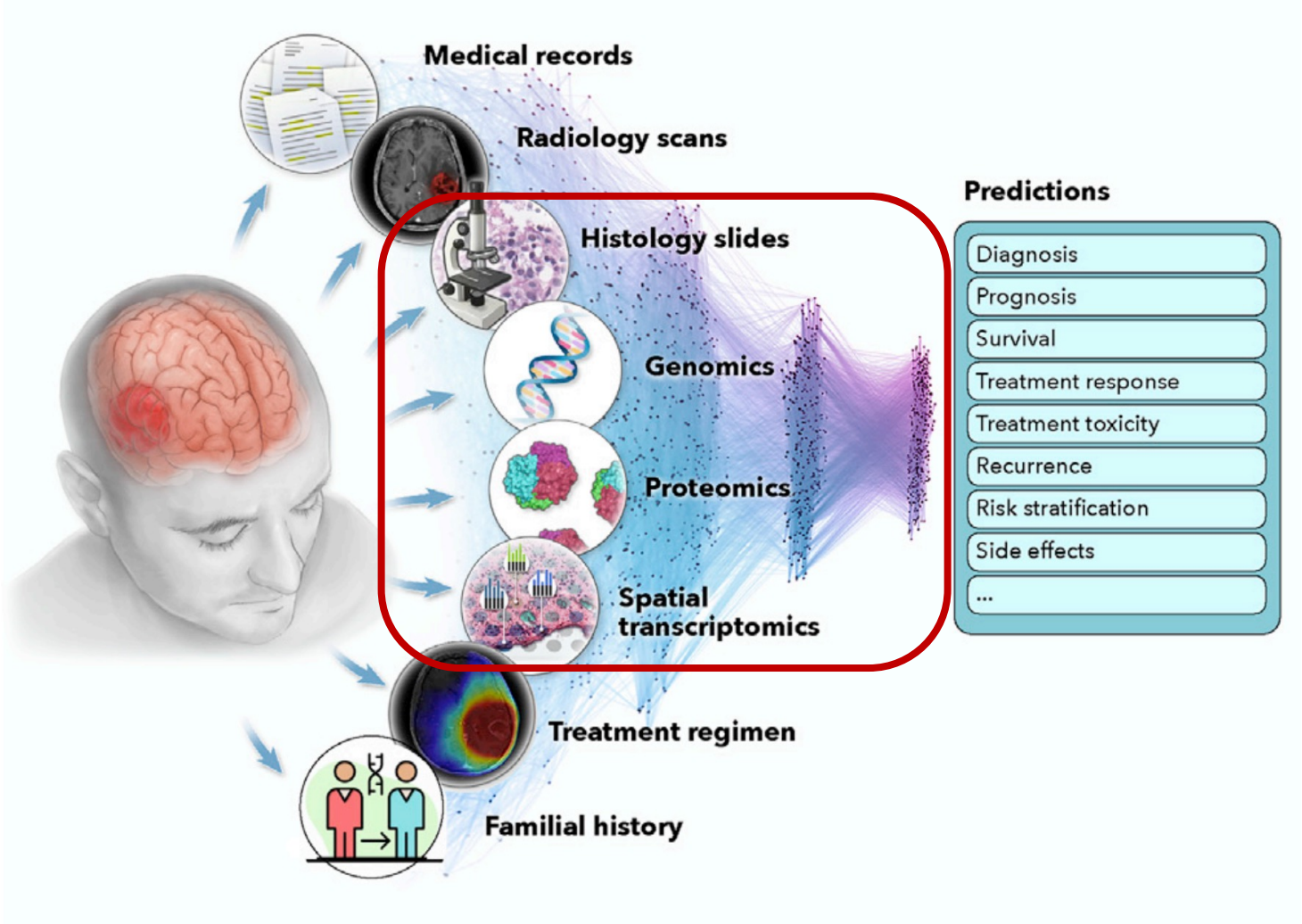


➢ Prognostic but not predictive !

USZ Universitäts Spital Zürich | Universität Zürich[UZH]

REFERENCE: Tandini-Lang Radiother Oncol 2017; van den Begin Radiother Oncol 2019

AI for multimodal data integration in oncology

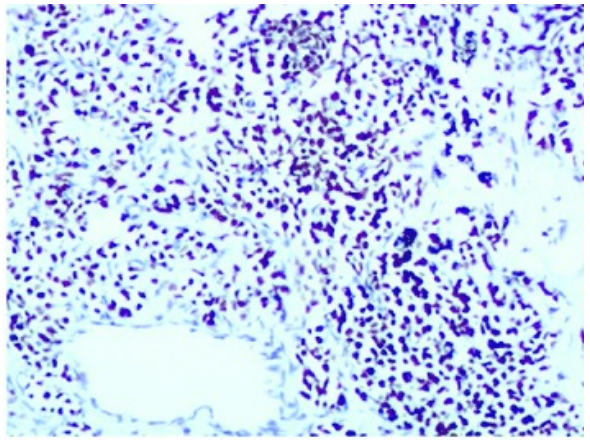


REFERENCES: *Lipcova Cancer Cell 2022*

Tissue biomarkers

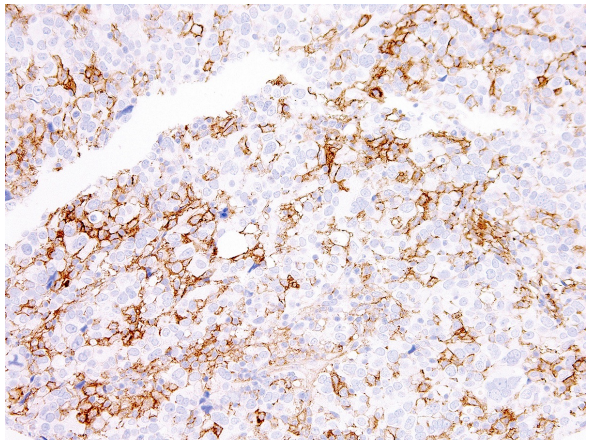
OMD: biologically a disease state with **limited metastatic capacity**

EGFR



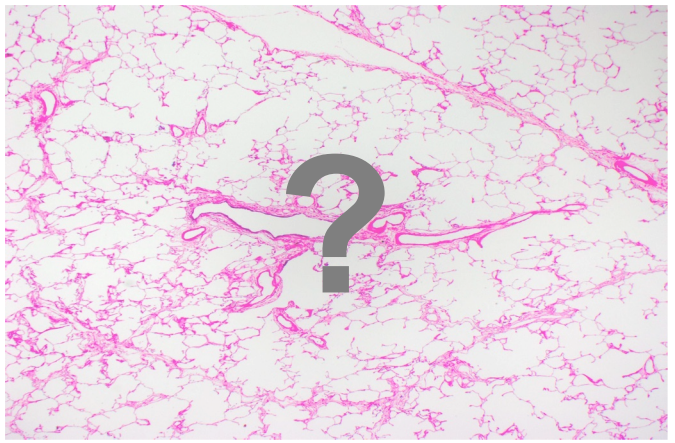
Osimertinib

PD-L1



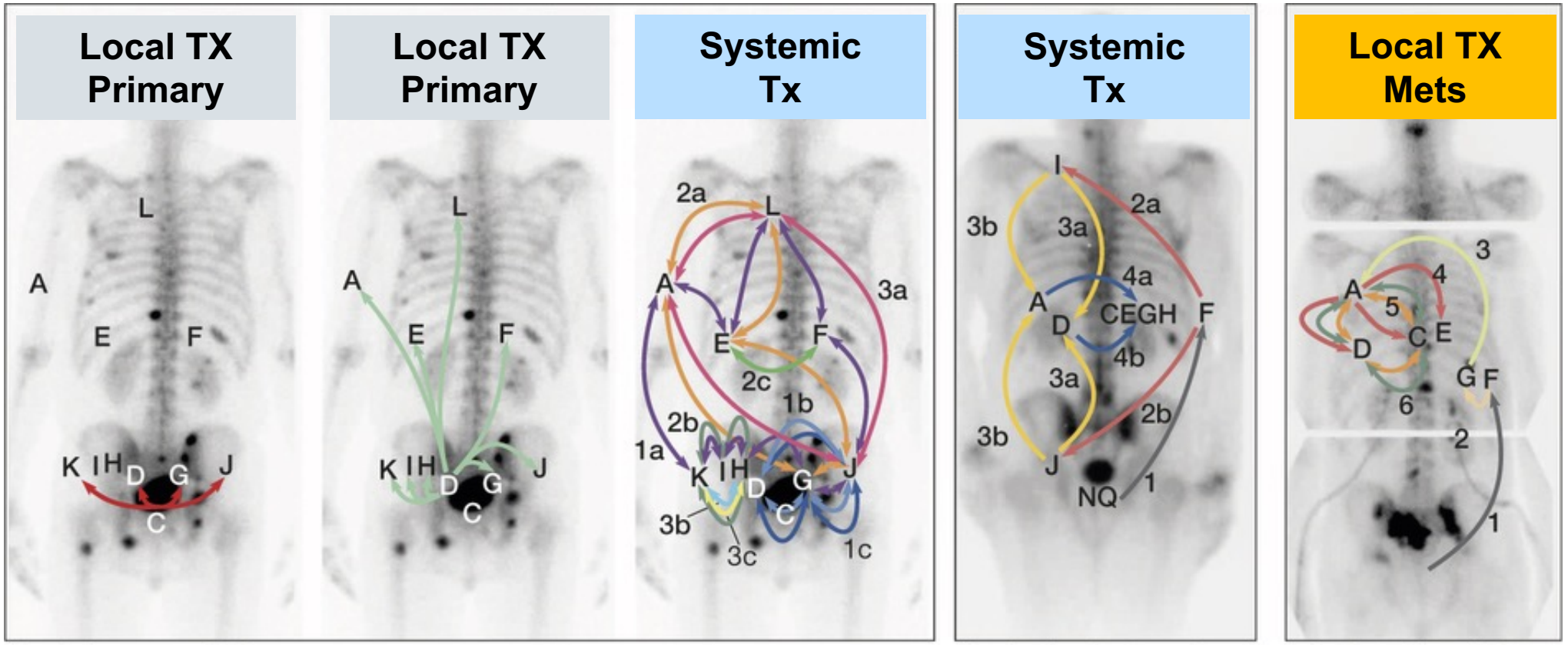
Pembrolizumab

OMD



SBRT

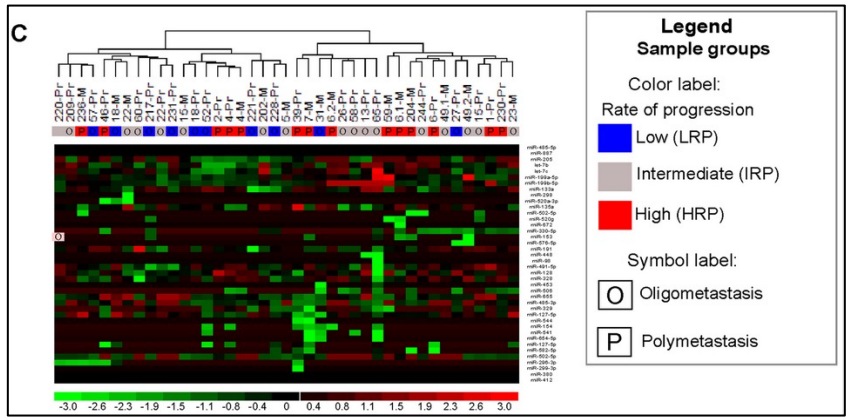
Tissue biomarkers

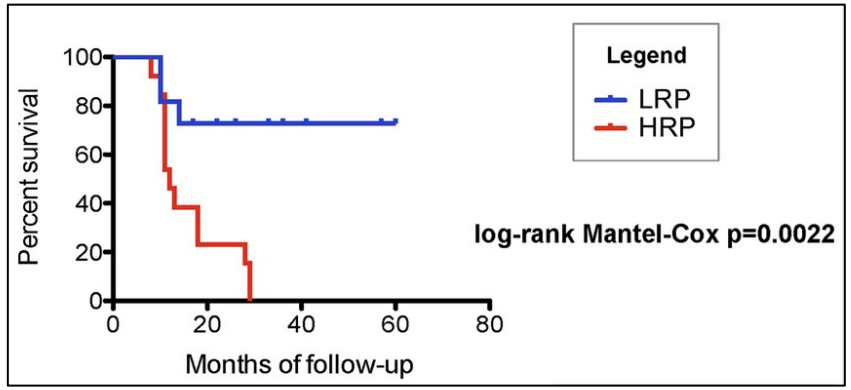


➢ Autopsy strategy too late …

REFERENCES: *Gundem Nature 2015*

Tissue biomarkers





Oligometastatic lung disease

- Surgical resection of oligometastatic lung disease in 42 pts
- Micro-RNA expression profile

➢ Correlation with systemic progression and survival

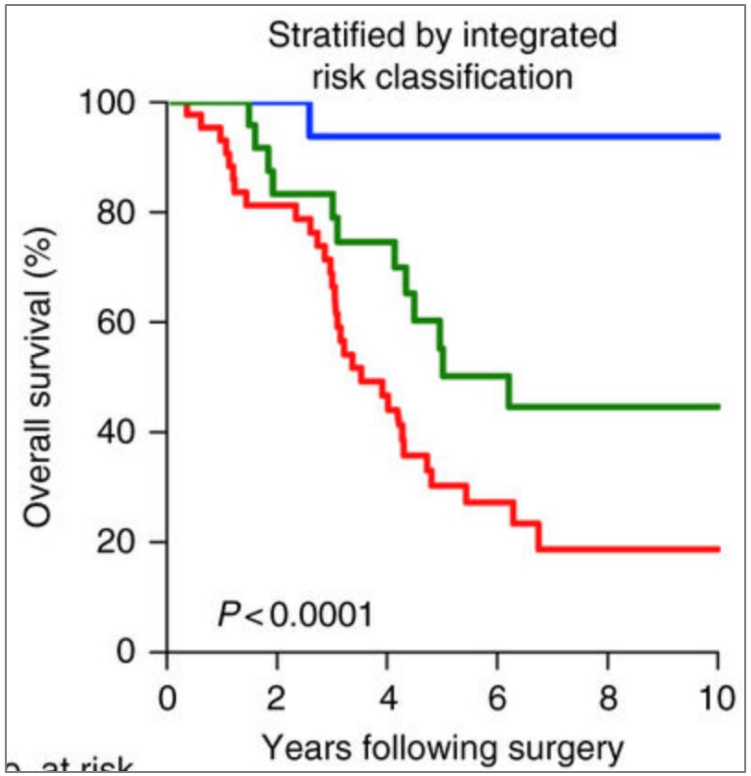
➢ Lack of validation despite 8 years old

REFERENCES: *Lussier PLOS 2012*

Tissue biomarkers

Retrospective study of 134 patients treated surgically for colorectal liver metastases

	Subtype 1 canonical	Subtype 2 immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	↓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*	*SMAD3*
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

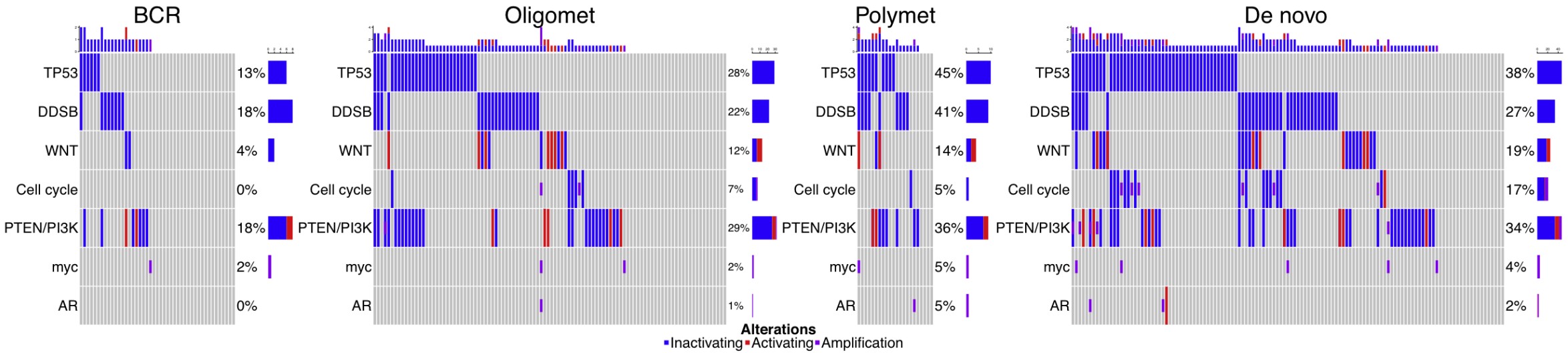


➢ Hypothesis generating w/o validation so far

REFERENCES: *Pitroda Nature Communication 2018*

Tissue biomarkers

Somatic mutations across metastatic castration-sensitive prostate cancer



- Mutations in TP53 and DNA double-strand break repair associated with a higher number of metastases
- Mutations in TP53 associated with rPFS and the development of CRPC

➢ Spectrum of diseases

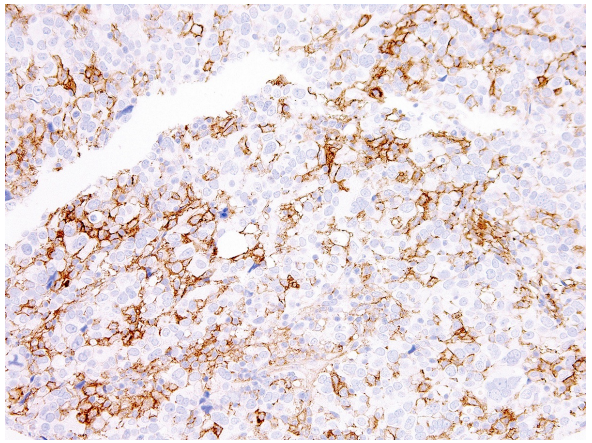
USZ Universitäts Spital Zürich | Universität Zürich[UZH]

REFERENCES: *Deek European Urology 2020*

Tissue biomarkers

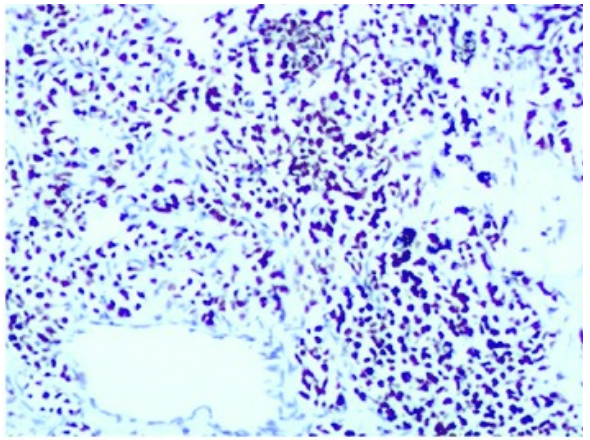
OMD: biologically a disease state with **limited metastatic capacity**

PD-L1



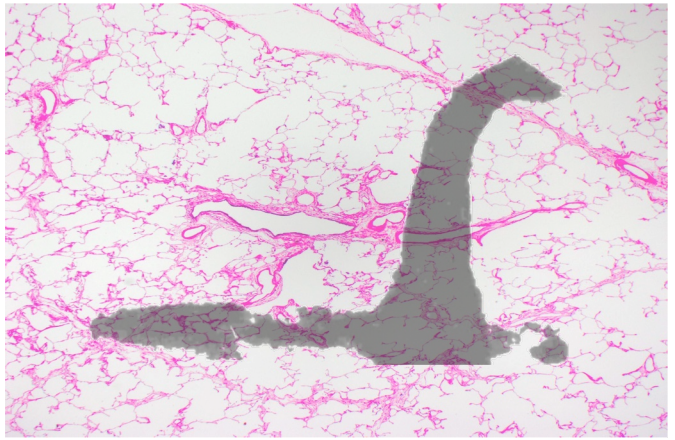
Pembrolizumab

EGFR



Osimertinib

OMD

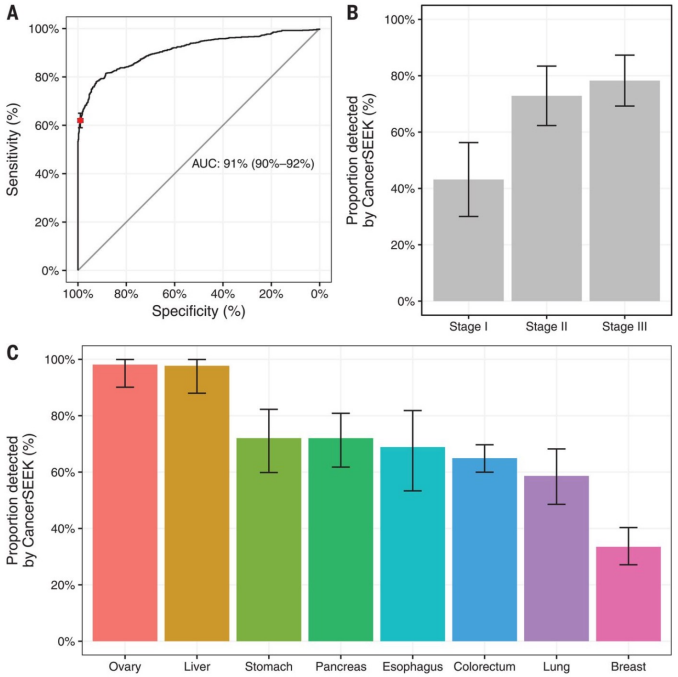


SBRT

- Component for risk stratification, no „OMD biomarker“

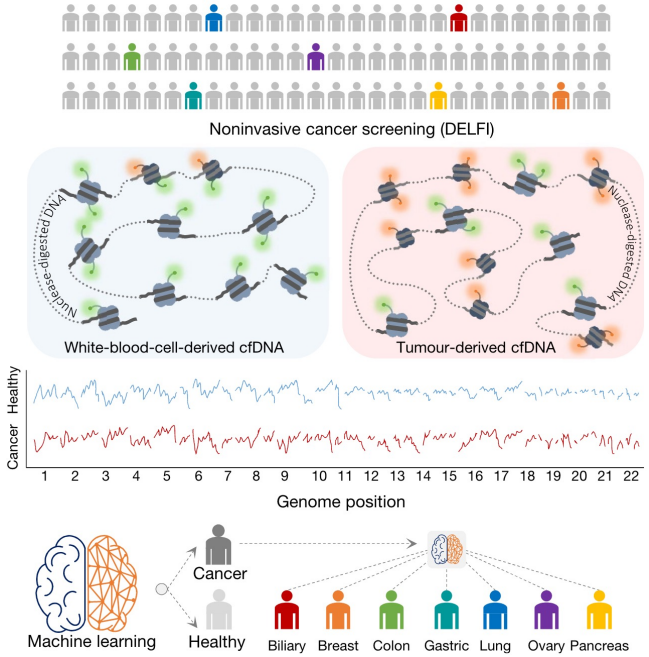
Liquid biomarkers

CancerSEEK



Eight circulating protein biomarkers and tumor-specific mutations in circulating DNA

Cell-free DNA fragmentation



Machine learning model incorporating genome-wide cell-free DNA fragmentation

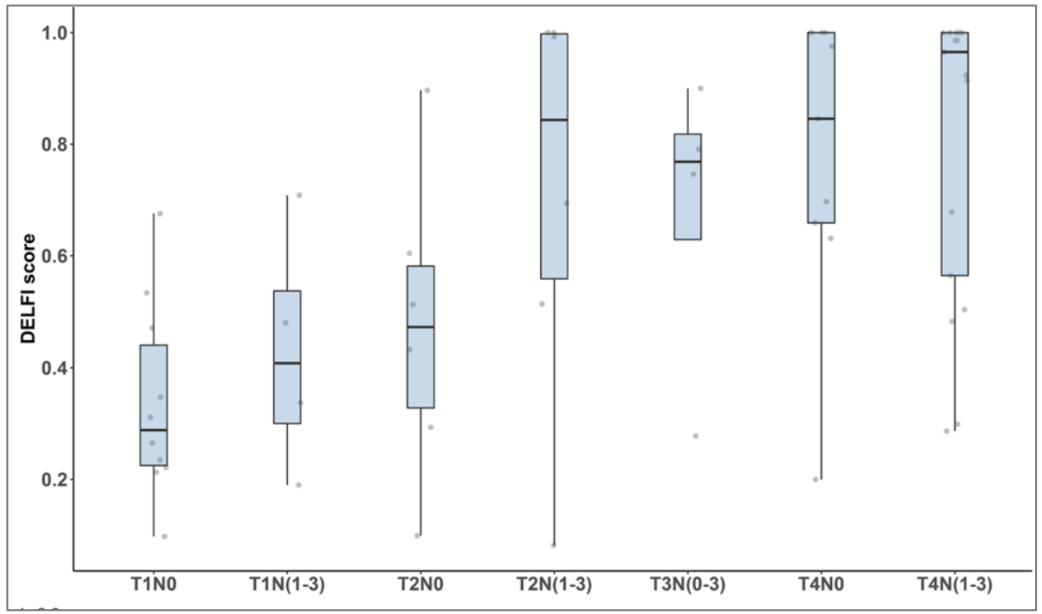
➢ Liquid biopsy for cancer screening

REFERENCES: *Cohen Science 2018, Christiano Nature 2019*

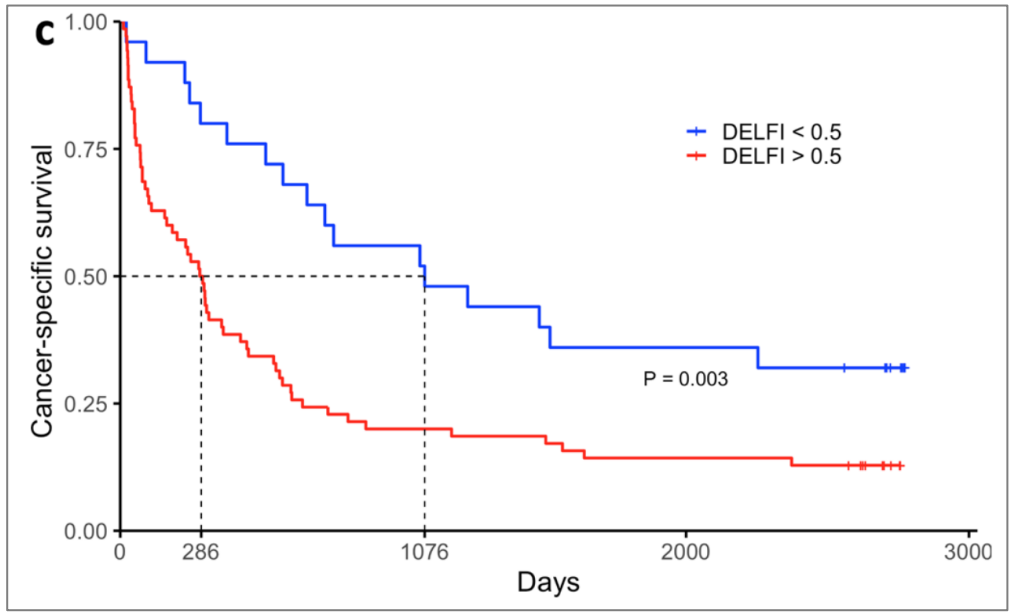
Liquid biomarkers

Characterization of lung cancer using cell-free DNA fragmentomes

DELFI score vs Tumor stage



Prognostic value of DELFI score

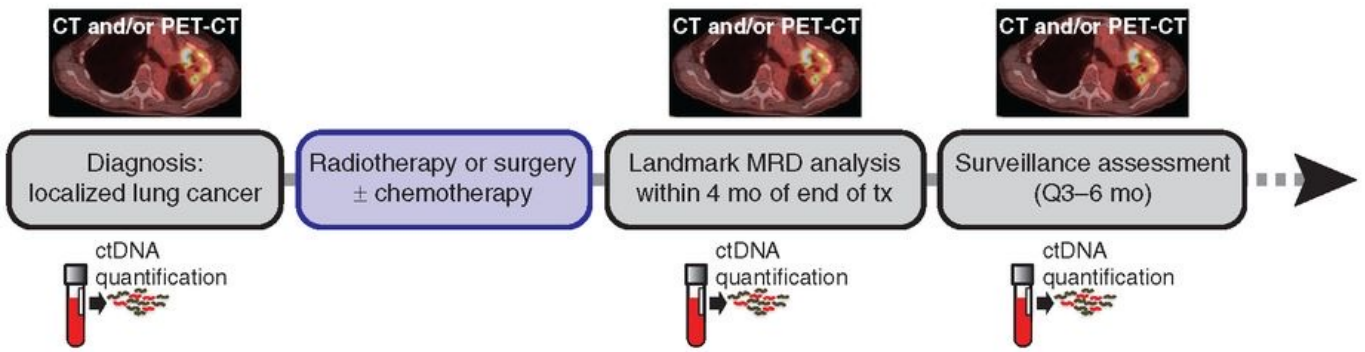


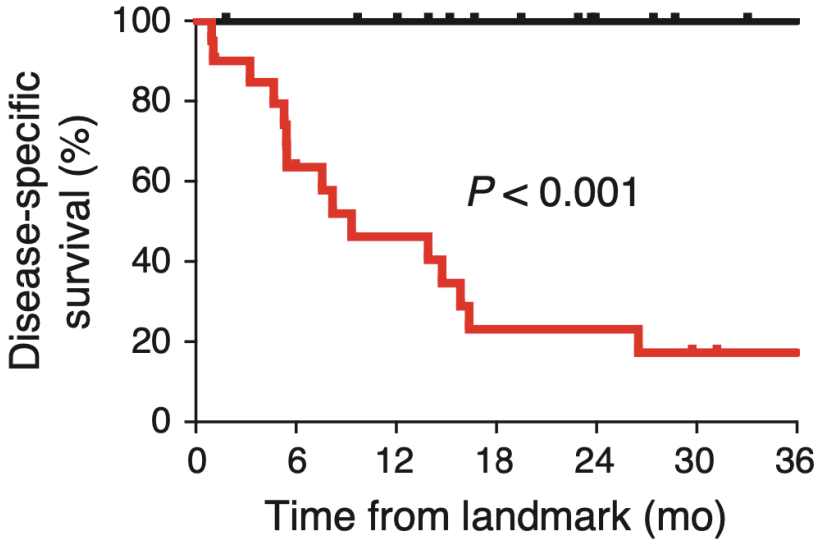
- Association with macroscopic tumor burden
- Independent **prognostic** factor in lung cancer patients

REFERENCES: *Mathios Nature Communications 2021*

Liquid biomarkers

Early Detection of **Molecular Residual Disease** in Localized Lung Cancer by Circulating Tumor DNA Profiling





Molecular Residual Disease (MRD) for

- response monitoring
- early recurrence detection

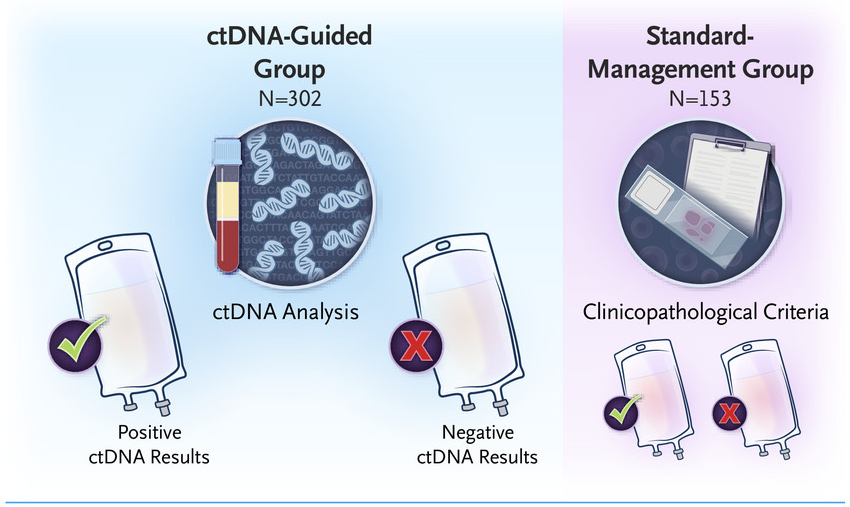
REFERENCES: *Chaudhuri Cancer Discovery 2017*

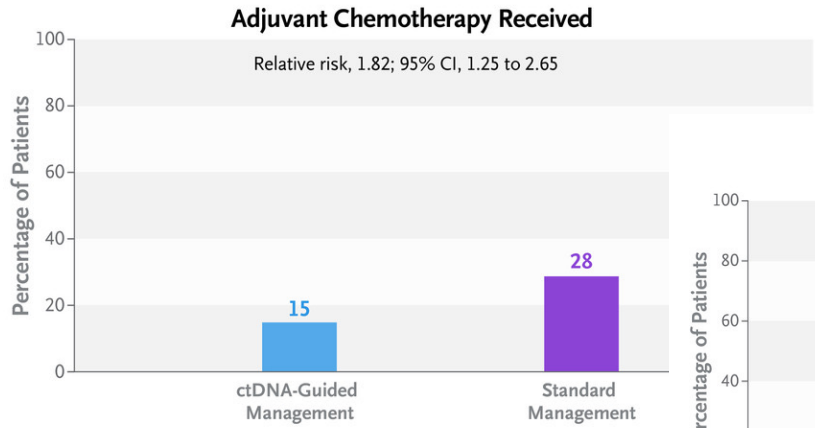
Liquid biomarkers

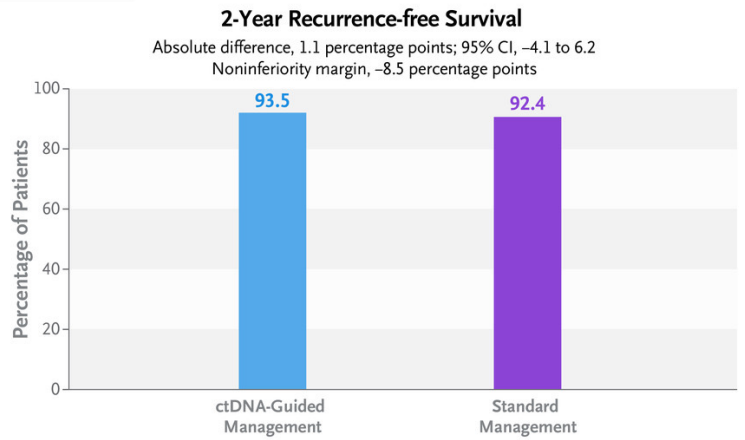
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer







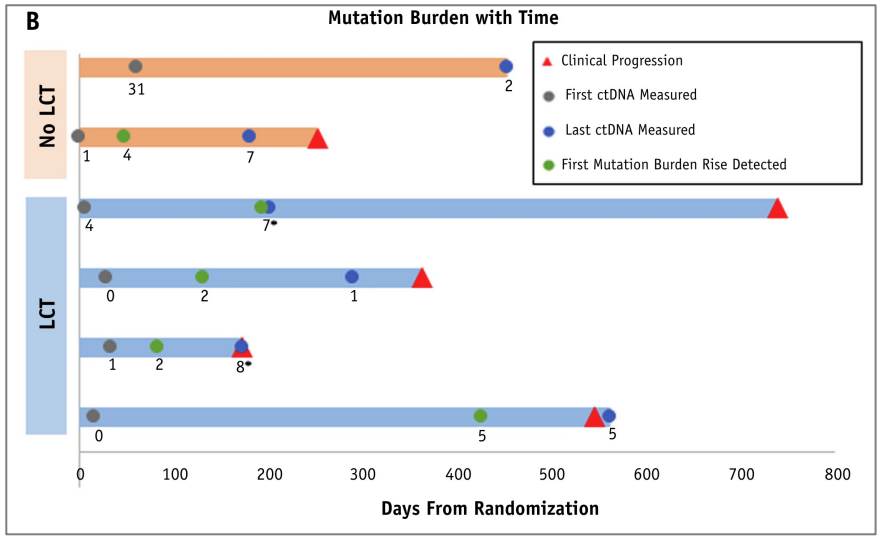
- First RCT demonstrating the **predictive** value of circulating tumor DNA in decicion making for or against adjuvant CHT

REFERENCES: *Tie NEJM 2022*

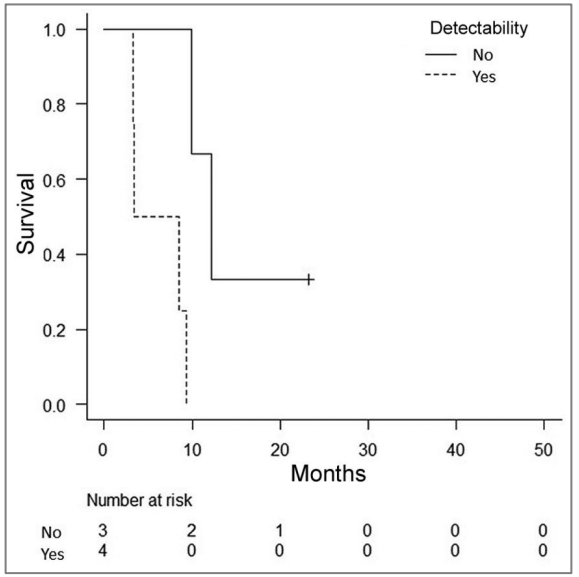
Liquid biomarkers

Cell-free DNA follow-up after Tx of oligometastatic pts

NSCLC OMD after LCT



Colorectal OMD after SBRT

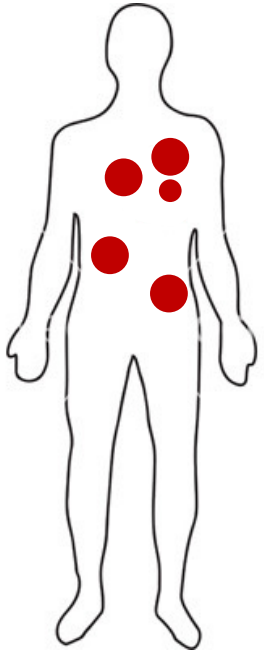


➢ Much to study in OMD !

REFERENCES: *Tang IJROBP 2020; Nakamura Anticancer Research 2021*

Imaging biomarkers

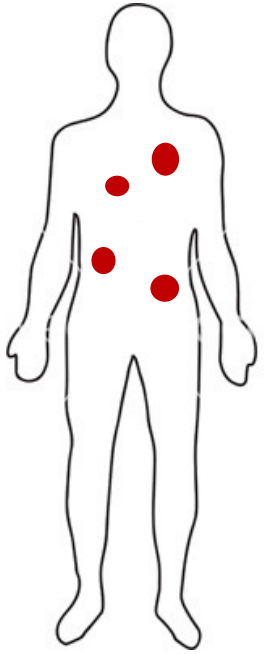
Primary diagnosis



Induction phase

MRD positive

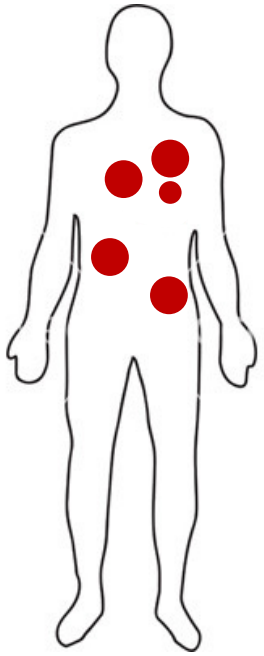
Re-Staging after induction



- Metastasis-individual analysis for identification of local target volume

Imaging biomarkers

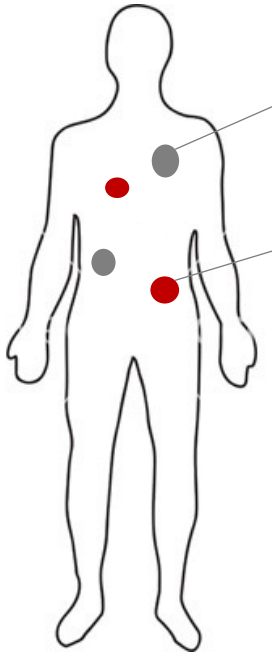
Primary diagnosis



Induction phase

MRD positive

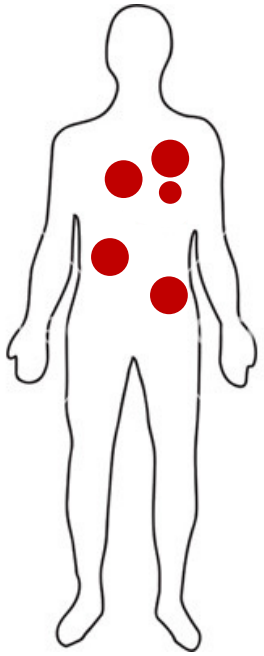
Re-Staging after induction



- Metastasis-individual analysis for identification of local target volume
  - ➢ Differentiation between active vs non-active disease
  - ➢ Identification of resistance metastases

Imaging biomarkers

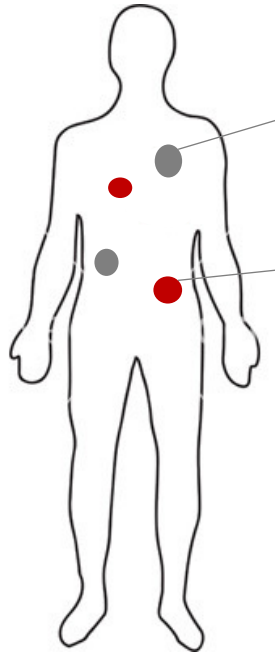
Primary diagnosis



Induction phase

MRD positive

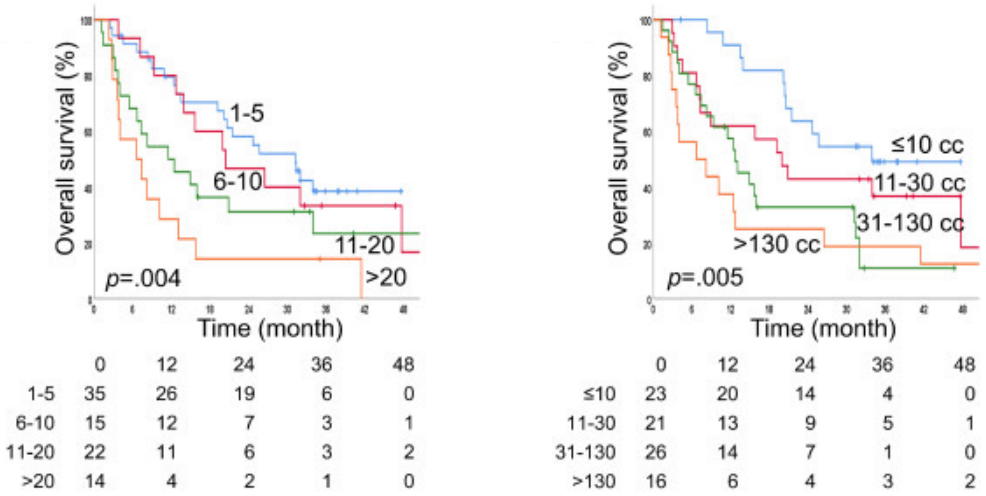
Re-Staging after induction



- Metastasis-individual analysis for identification of local target volume
  - ➢ More in depth analysis of each individual metastases using Radiomics

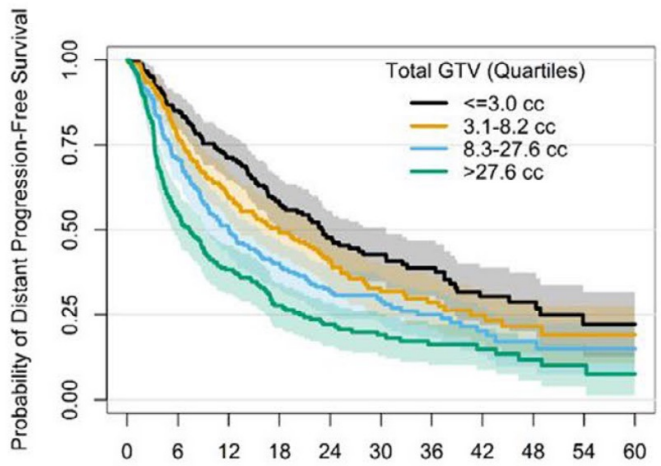
Imaging biomarkers

Metastatic melanoma pts treated with IO



Cumulative tumor volume indendent prognostic factor, not # of mets

OMD pts treated with SBRT

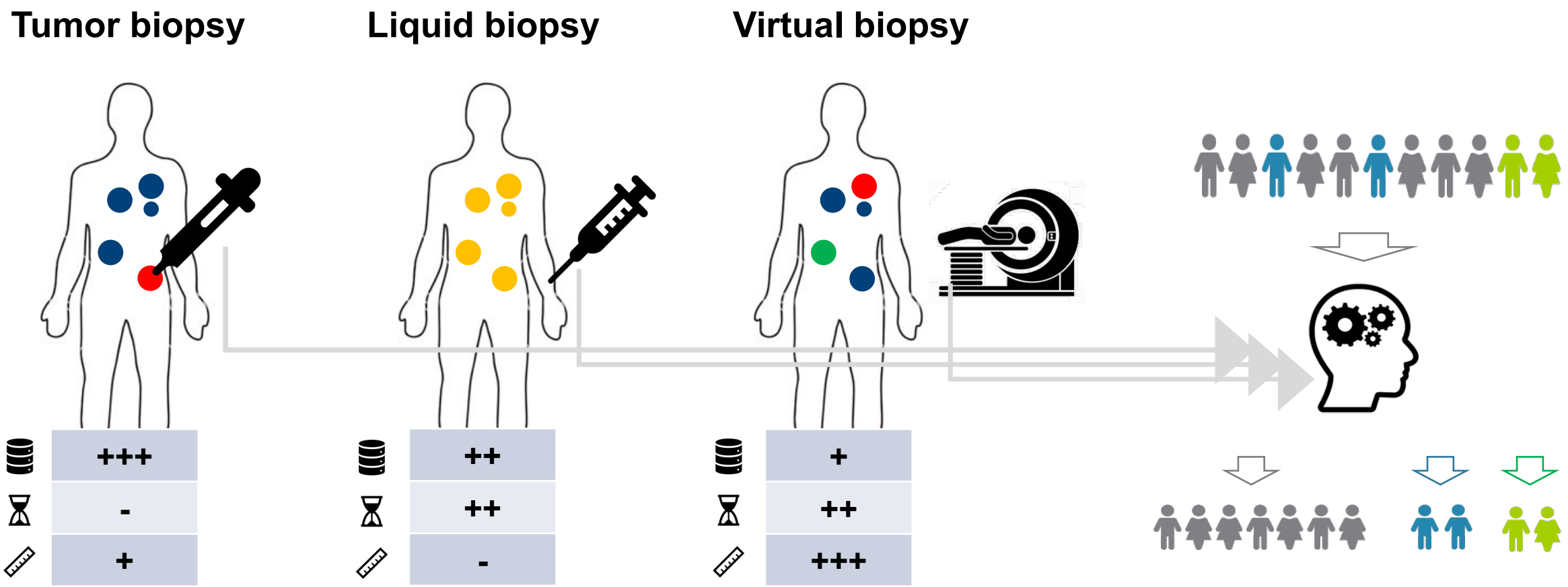


Cumulative tumor volume indendent prognostic factor in OMD pts

➢ Macroscopic tumor burden surrogate for risk / burden of microscopic disease -> automation needed

REFERENCE: *Kim IJROBP 2022; Cao Cancer Med 2021*

Multi-Omics approch in OMD



- To integrate results of tissue, liquid and imaging biomarkers in OMD patients

Radiotherapy for OMD

Phase I ARREST trial

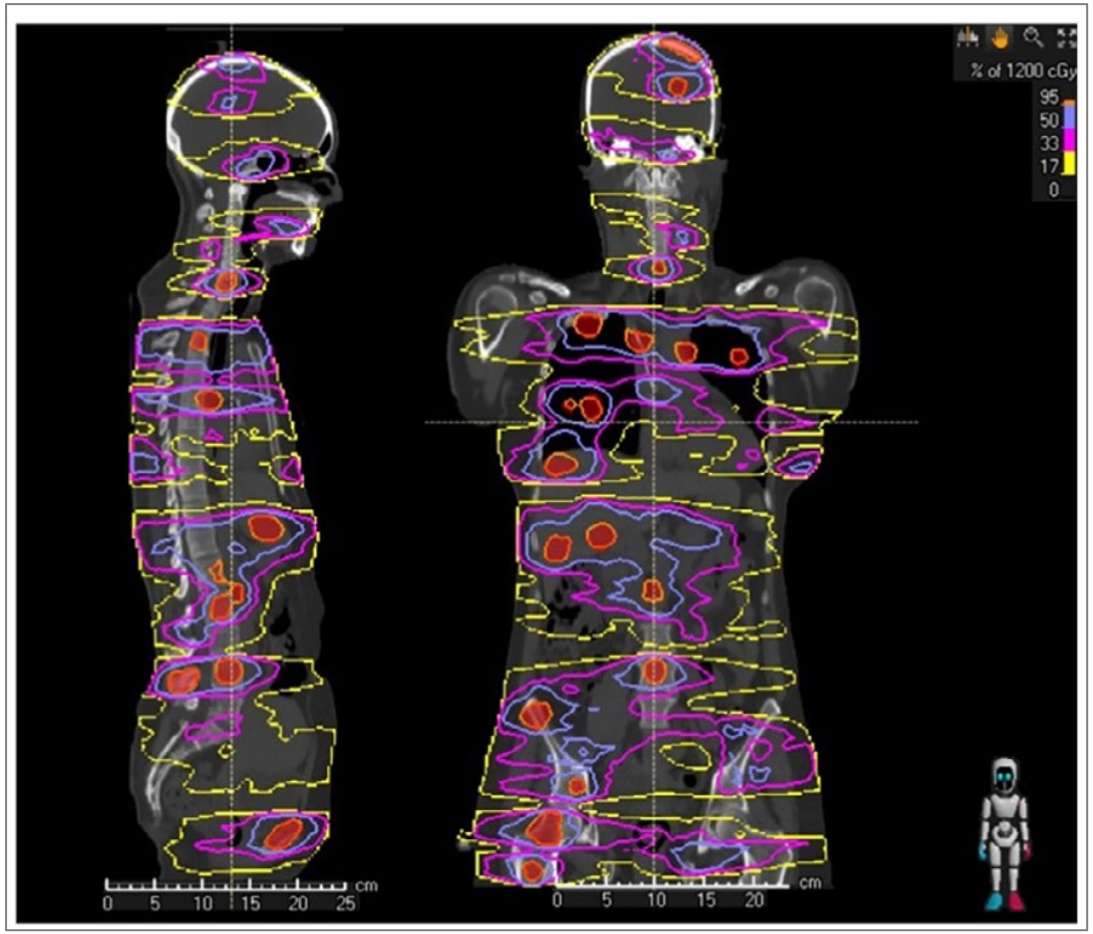
- Patients with > 10 metastases
- No available systemic treatment option

De-escalation dose level

- Dose level 0: 6Gy × 1 fraction to all sites in 1 week.

Escalation dose levels

- Dose level 1: 6Gy × 2 fractions to all sites in 2 weeks.
- Dose level 2: 6Gy × 3 fractions to all sites in 3 weeks.
- Dose level 3: 6Gy × 4 fractions to all sites in 4 weeks.
- Dose level 4: 6Gy × 5 fractions to all sites in 5 weeks.

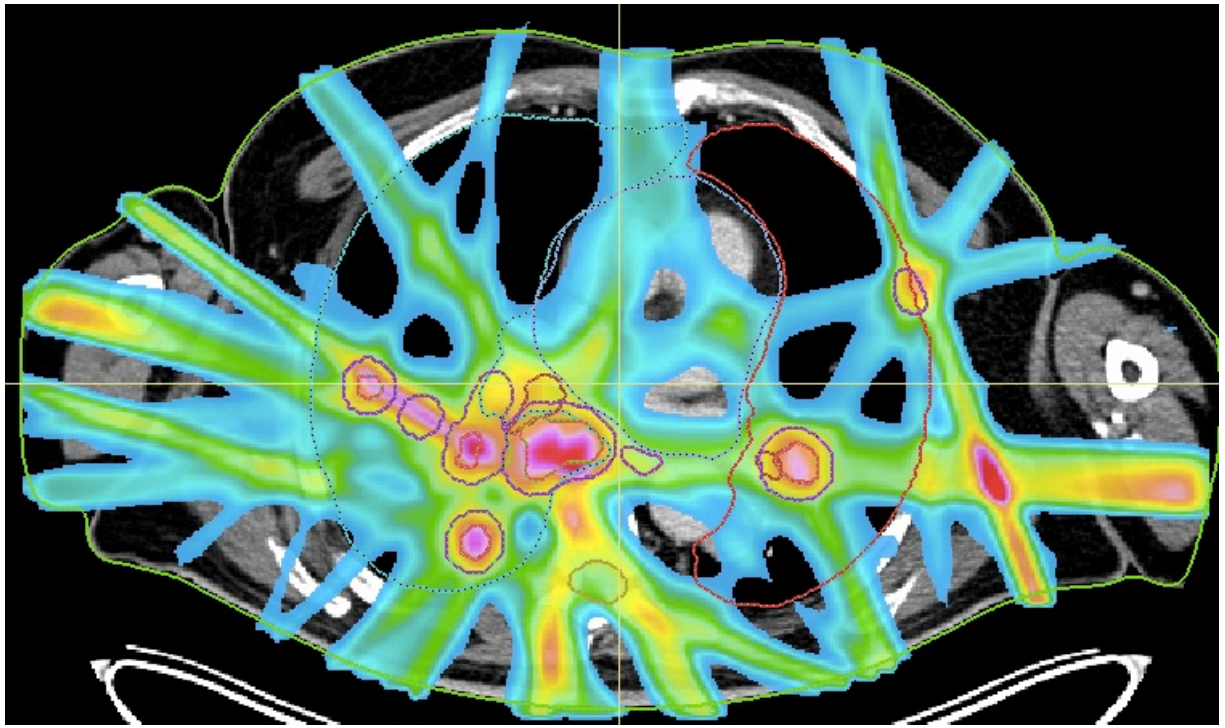


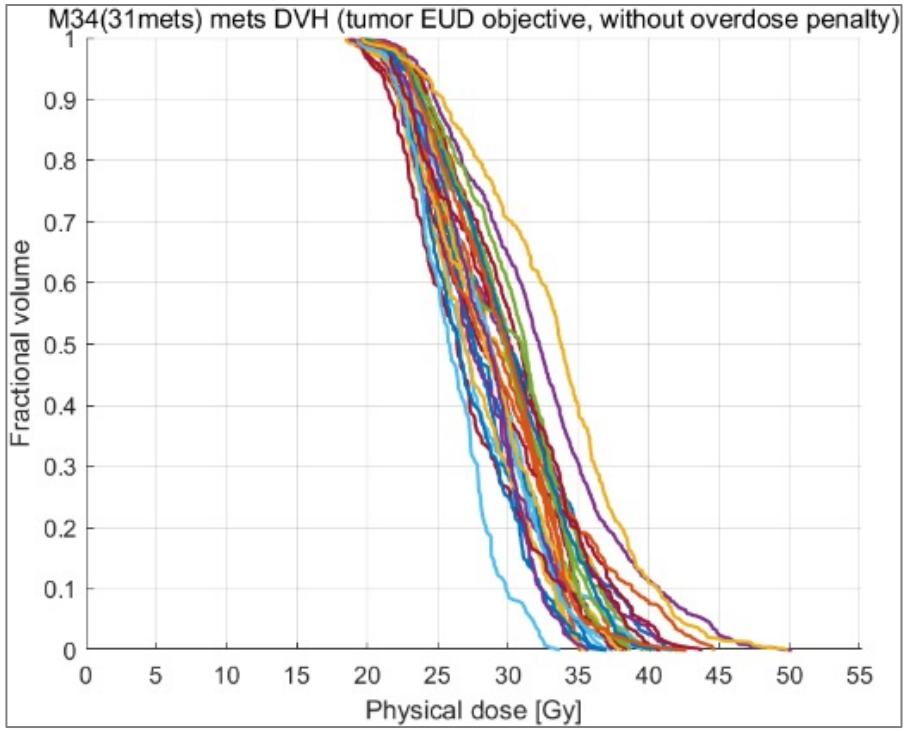
➢ **Planning study:** feasibility of delivering 30Gy/5 (n=2) and 12Gy/2 (n=1) in 3 pts with 24 – 50 metastases

REFERENCES: *Corkum Advances in Radiation Oncology 2021; Baumann BMC Cancer 2021*

Radiotherapy for OMD

EUD based cell killing modell for planning of n=34 pulmonary metastases





➢ Treating multiple metastases will required more intelligent approches of RT than one size fits all

REFERENCES: *Unkelbach & Guckenberger, unpublished data*

Summary & Conclusion

- Concept of OMD offers hope for many cancer patients
- Initial trial results based one phase II data are promising
- Lack of consistent prognostic markers, total lack of predictive markers
- Strong need for increased efforts in clinical and translational research

OligoCare cohort of ESTRO & EORTC E2Radiate

Prospective registry trial to identify patient, tumor, staging and treatment characteristics impacting overall survival. Thus, overall survival is the primary endpoint of this research project.

First cohort within the EORTC ESTRO E2R study

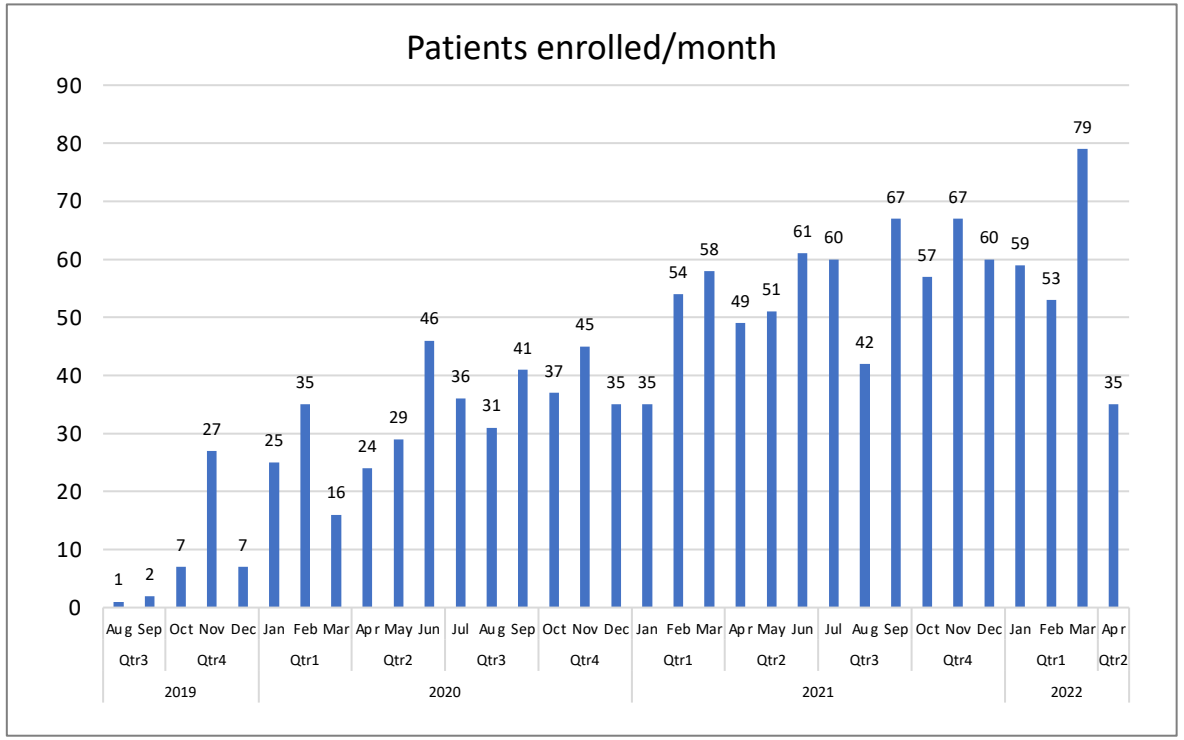
Matthias Guckenberger, Piet Ost

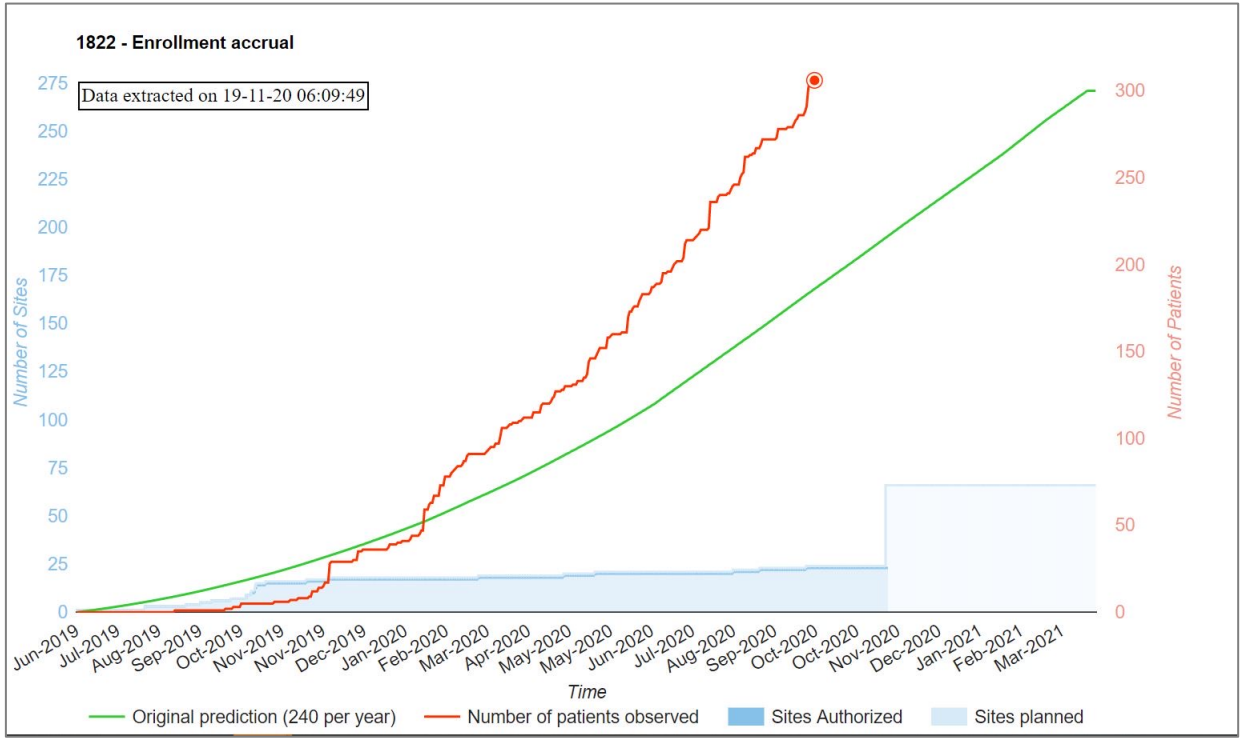
EORTC

The future of cancer therapy

ESTRO

ESTRO & EORTC OligoCare





- >1.600 included pts included, 80 pts per month
- Italian centers are THE TOP RECRUITERS – THX !

USZ Universitäts Spital Zürich
Universität Zürich[UZH]