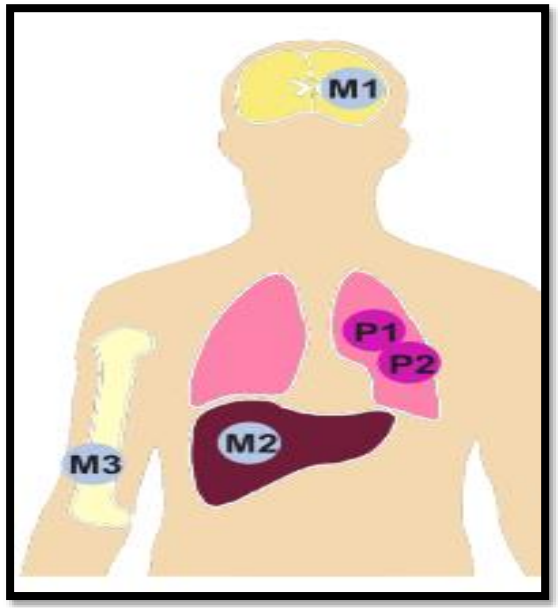
Role Of Radiotherapy In Oligo metastatic lung cancer (NSCLC)



Dr Sweety Gupta

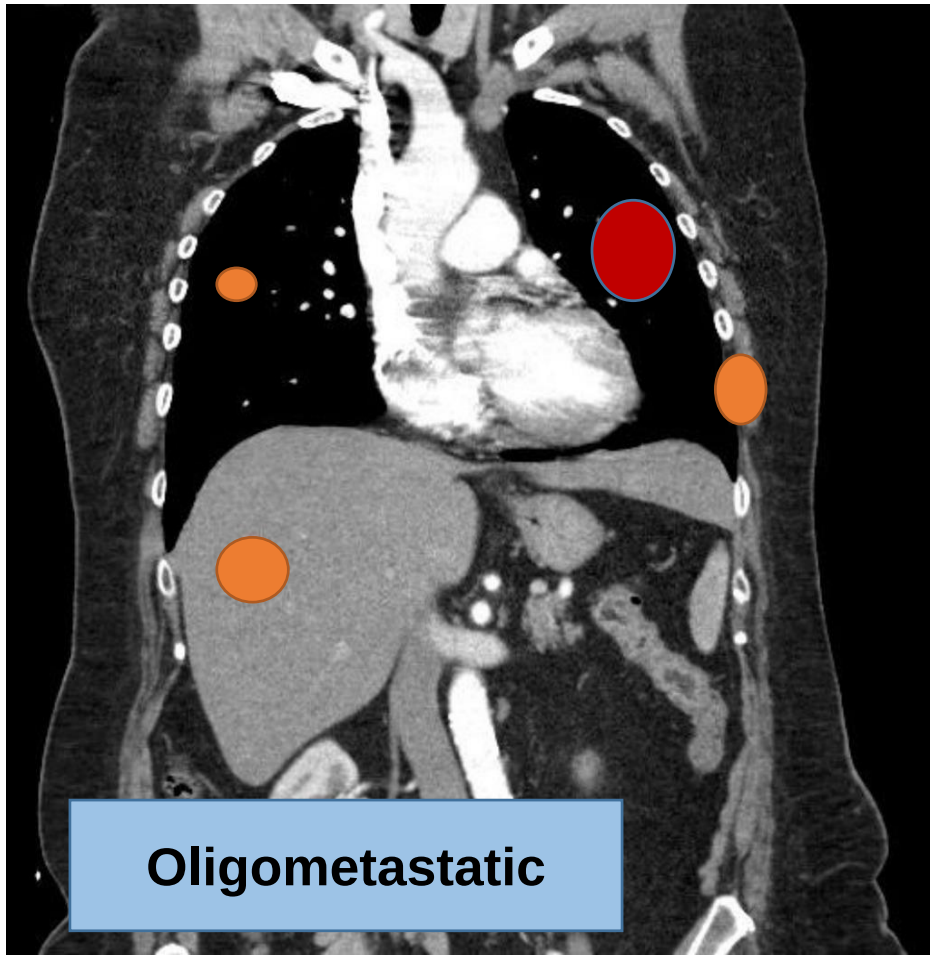
Associate Professor

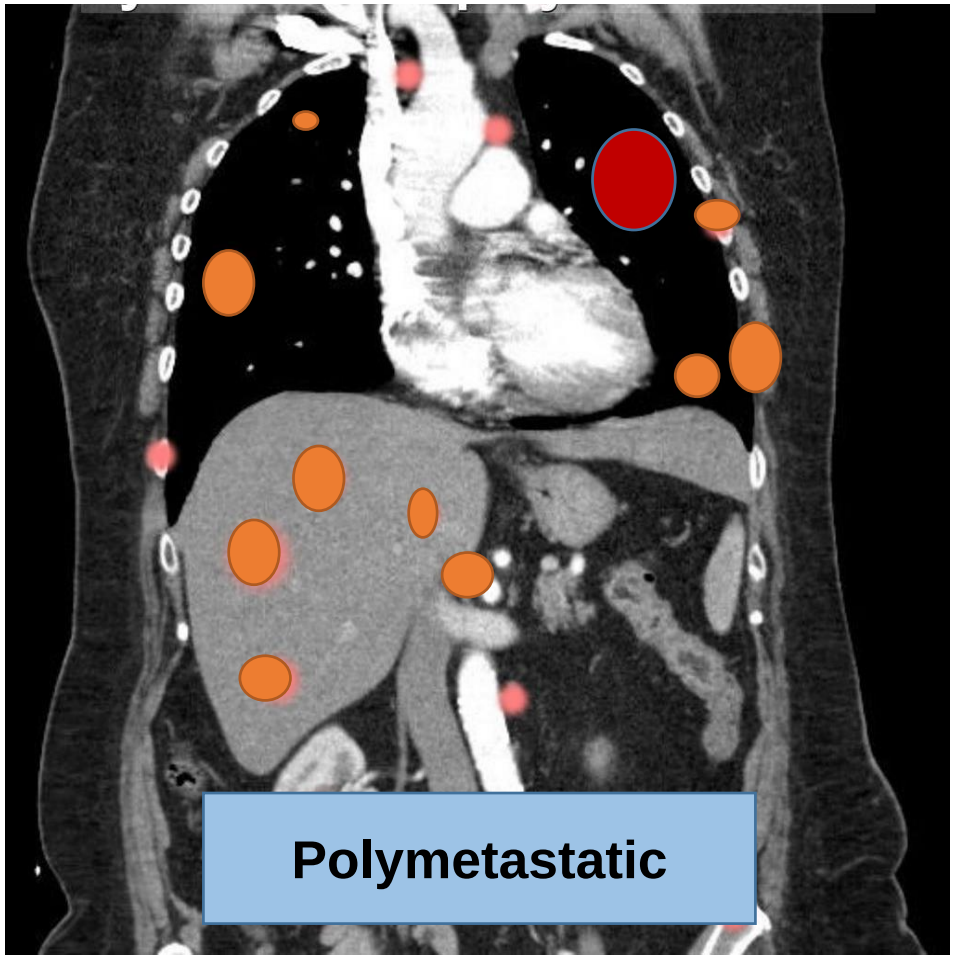
Dept of Radiation Oncology

AIIMS Rishikesh

54 years male diagnosed c/o of adenocarcinoma right lung with liver, lung and bone metastases

Stage	IV
Treatment	Palliative chemotherapy ± Radiotherapy to bone metastases
Prognosis	Poor


Oligometastatic


Polymetastatic

Introduction

Oligometastases(OMD):

- “**Oligos”:** Few ; **“Metastasis”:** removal from one place to another
- Postulated in 1995 by Hellman and Weichselbaum
- Special category of stage IV cancer
- Reduced tendency to widespread dissemination
- Hallmark- limited number of metastatic deposits (intermediate metastatic state)

Oligometastases: Definition

Current gold standard to diagnose oligometatstases relies on **number of metastases** and **metastatic sites** and determine whether they are amenable to local treatment, with the aim to prolong survival

ELSEVIER

Journal of Thoracic Oncology
Volume 14, Issue 12, December 2019, Pages 2109-2119

Original Article
Non–Small Cell Lung Cancer

Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report

Anne-Marie C. Dingemans MD, PhD [a, b, c], Lizza E.L. Hendriks MD, PhD [a, c], Thierry Berghmans MD, PhD [d, e], Antonin Levy MD, PhD [f, g], Baktiar Hasan PhD [h], Corinne Faivre-Finn MD, PhD [i, j], Matteo Giaj-Levra MD, PhD [k], Niccolò Giaj-Levra MD, PhD [l, m], Nicolas Girard MD, PhD [n], Laurent Greillier MD, PhD [o, p], Sylvie Lantuéjoul MD [q, r], John Edwards MD [s], Mary O'Brien MD [t], Martin Reck MD, PhD [u], Egbert F. Smit MD, PhD [v], Paul Van Schil MD, PhD [w], Pieter E. Postmus MD, PhD [x], Sara Ramella MD [y] ... Silvia Novello MD, PhD [ff]

Show more

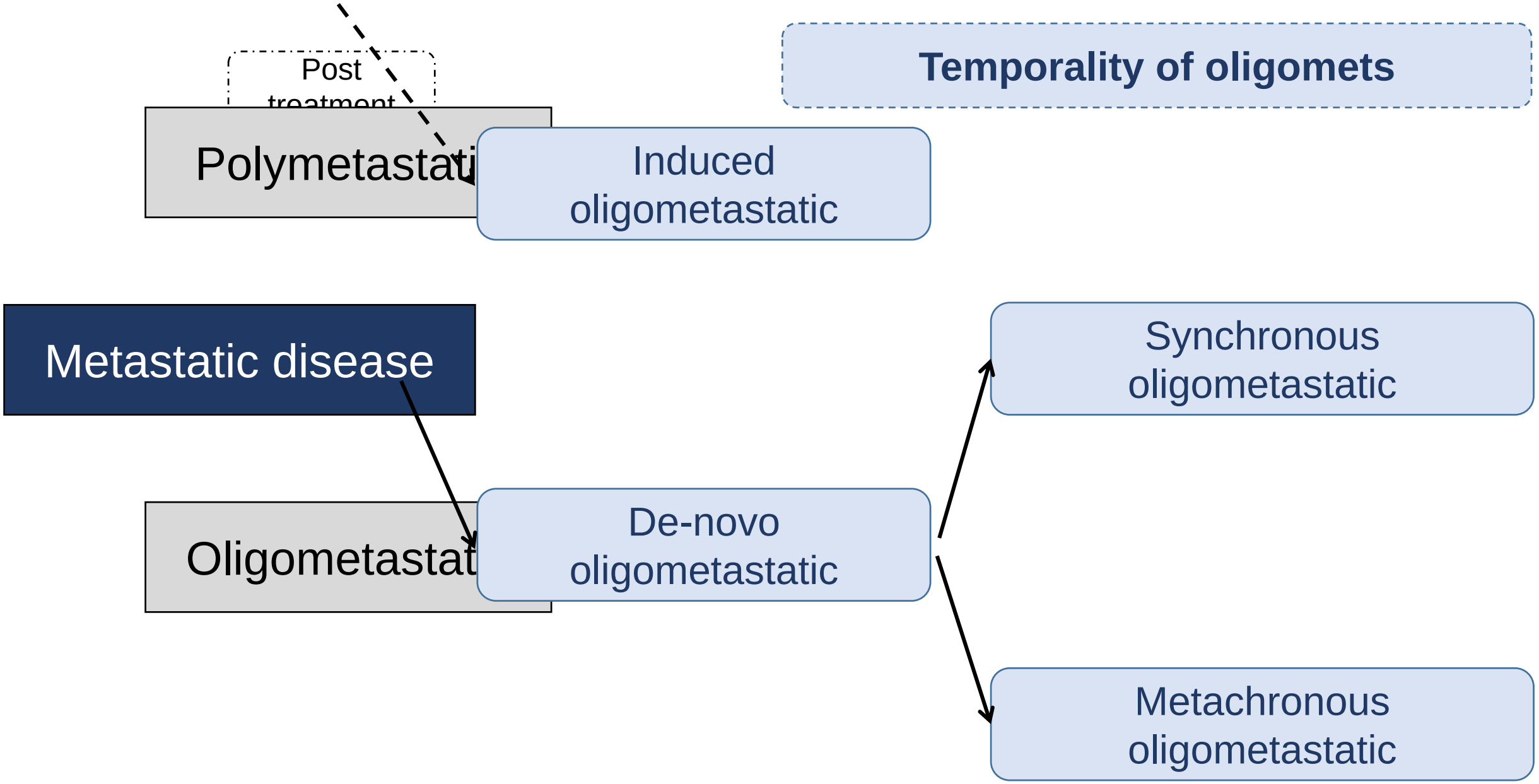
EORTC-LCG consensus statement(2019): “a **radical treatment** that may modify the disease course (leading to **long-term disease control**) is **technically feasible** for all tumor sites with acceptable toxicity”

It does not / cannot account for tumor markers, genomic signatures and micro environmental factors that have a strong influence on the clinical course of the disease

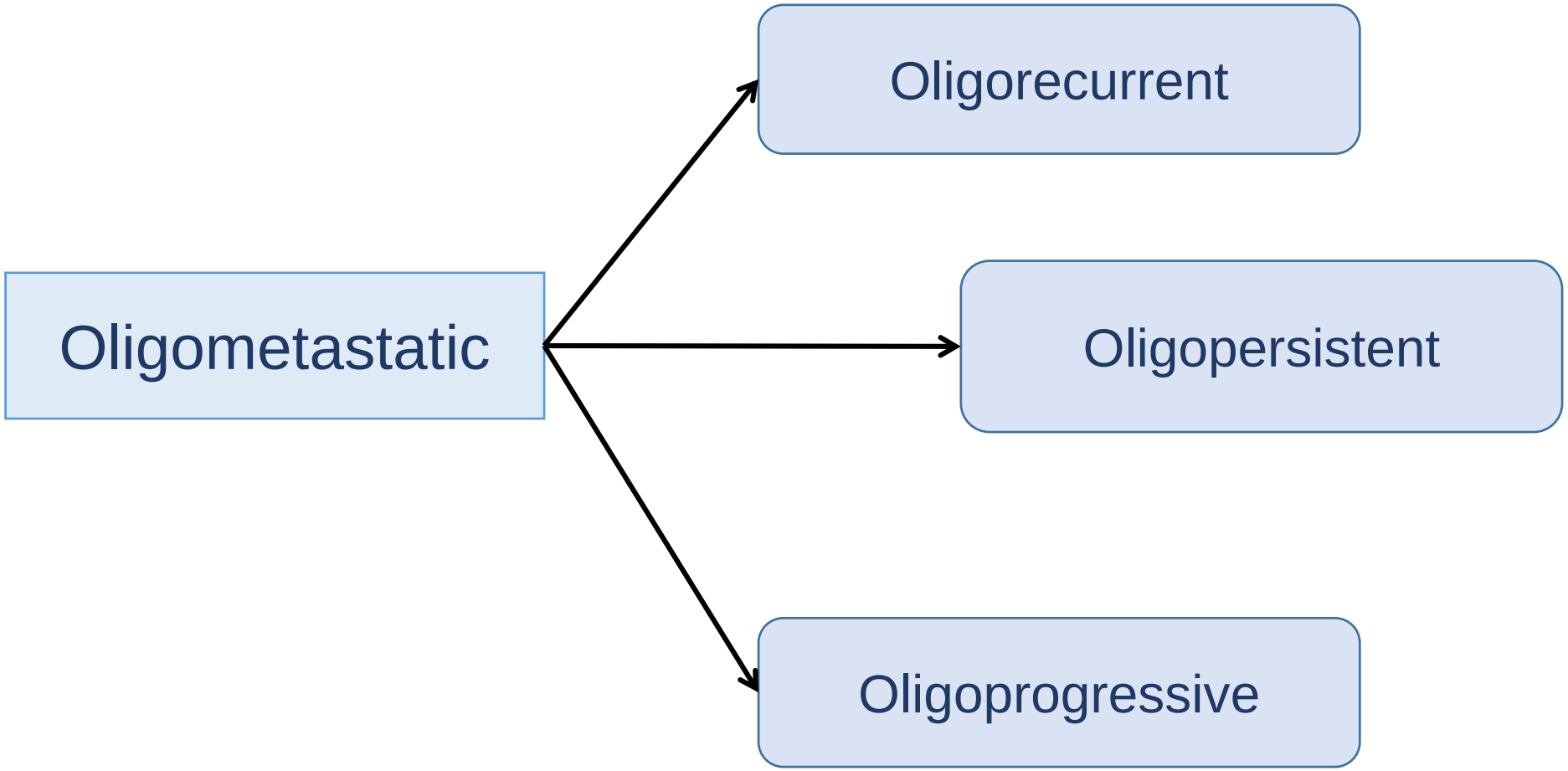
- ^{18}F-FDG PET–computed tomography and brain imaging are mandatory

- ***Diffuse serosal (meningeal, pleural, pericardial, and mesenteric) or bone marrow metastases are excluded***

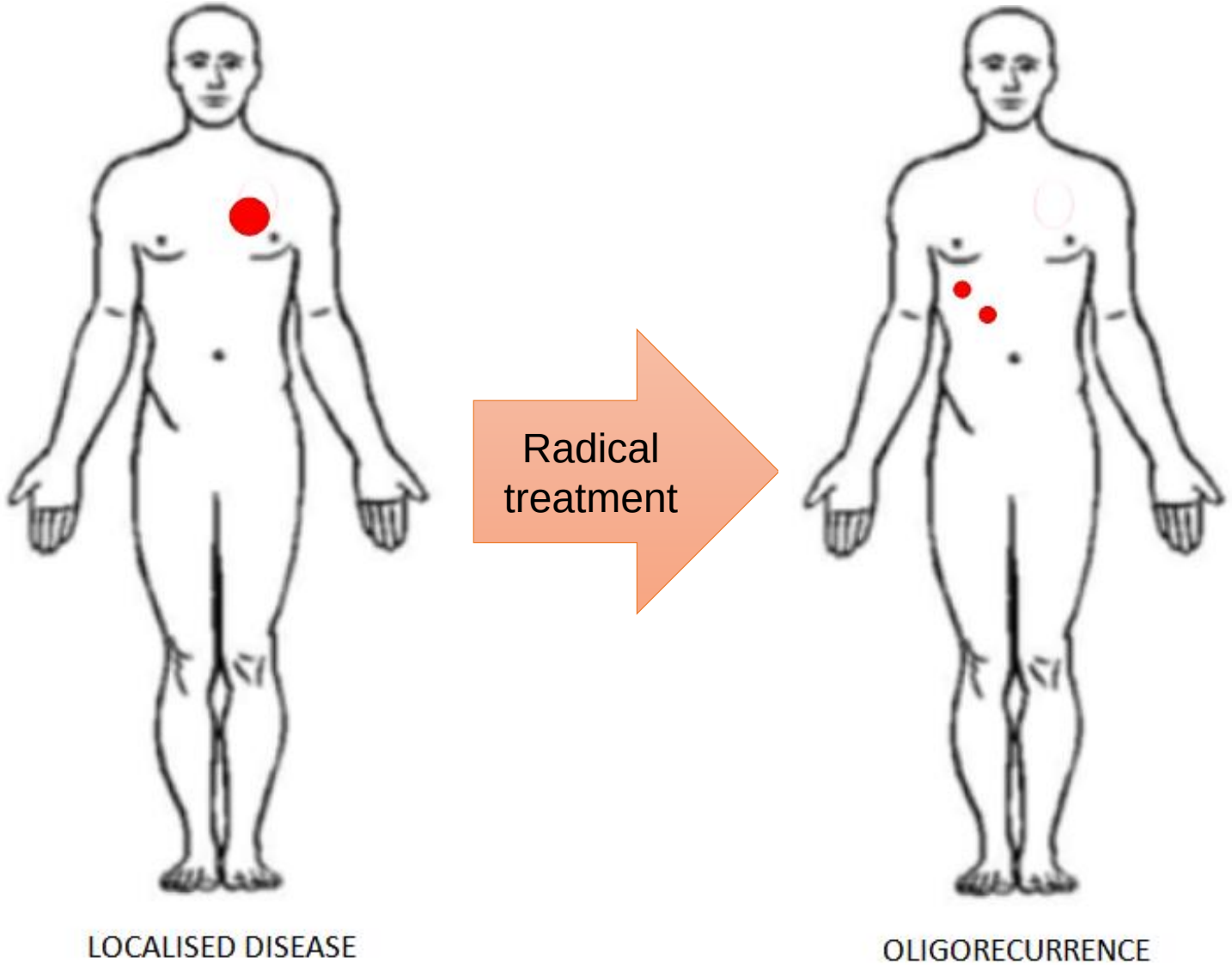
Oligometastases: Classification



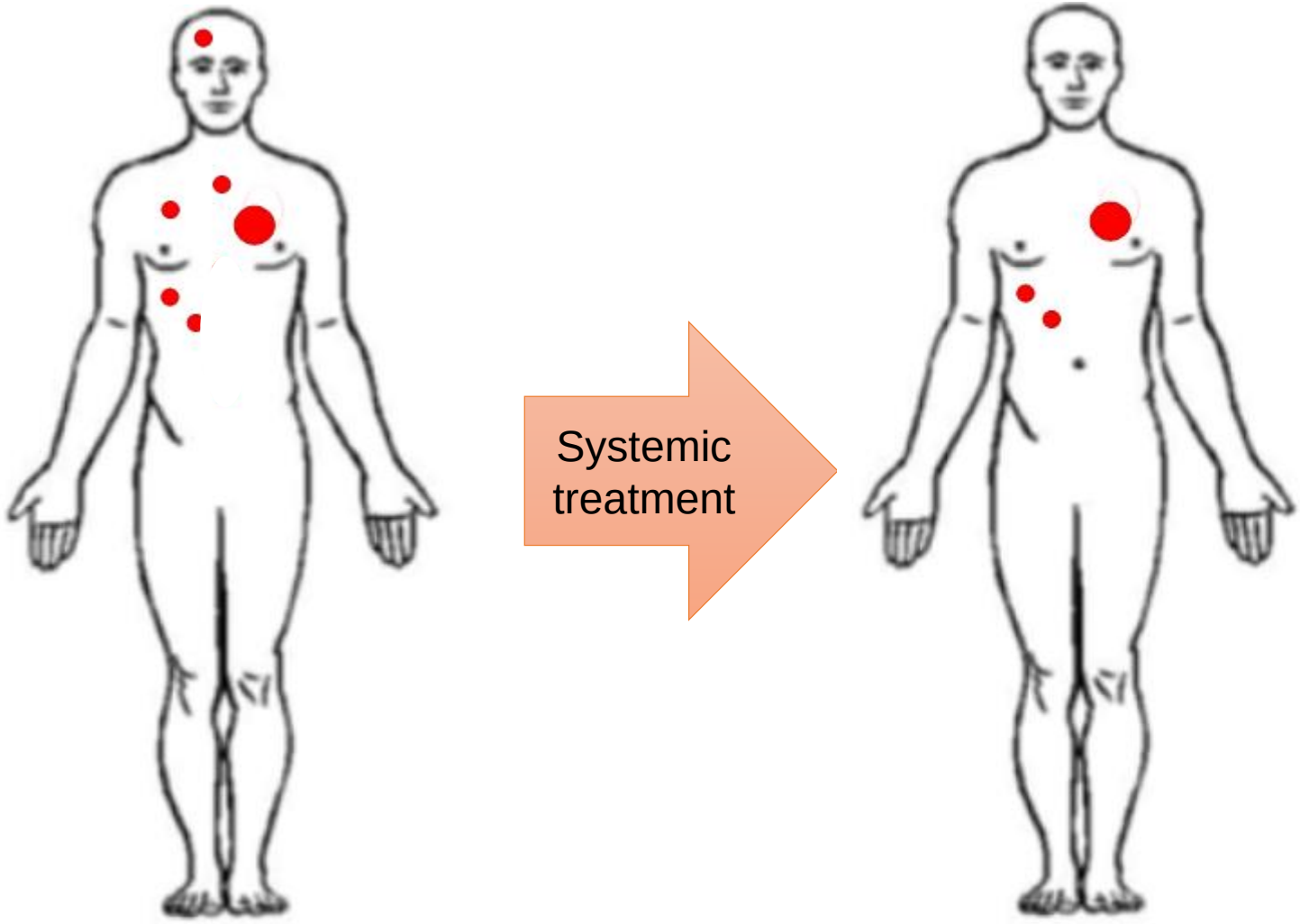
Response of oligomets to treatment



Oligorecurrent



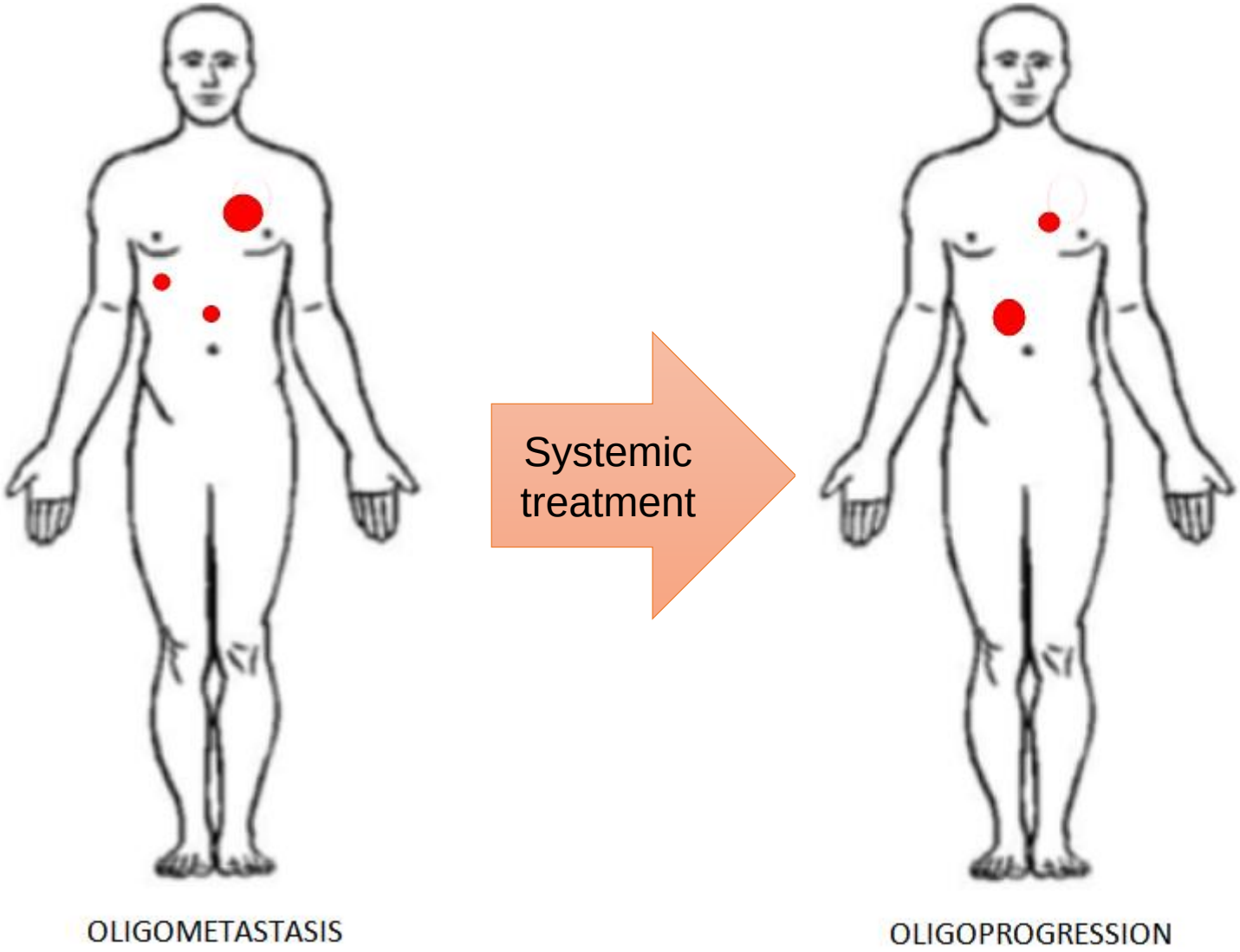
Oligopersistent



OLIGOMETASTASES

OLIGOPERSISTENT

Oligoprogression



Oligometastases: How frequent?

25-50% of NSCLC patients have Oligometastases at presentation

Organs involved:

- Bones (35.5%)
- Brain (25%)
- Adrenal gland (20%)
- Liver (12%)
- Skin, lymph nodes, or peritoneum (7.5%)

Oligometastases: Staging

- 18F-FDG PET-CT
- MRI brain
- Pathological confirmation of 1 metastasis is required unless risk outweighs benefit
- Solitary metastasis:
  - Solitary liver metastasis: MRI scan of liver
  - solitary pleural metastasis thoracoscopy and dedicated biopsies

Oligometastases NSCLC: Poor prognostic factors

- Synchronous lesions
- More nodal involvement
- Squamous cell histology
- Poor performance status
- Shorter interval from initial diagnosis to metastatic development
- Metastases to > one organ
- Extrapulmonary metastases

Oligometastases NSCLC : Management

- **Systemic therapy**
  - Chemotherapy/targeted therapy
  - Immunotherapy
- **Local therapy**
  - Surgery
  - Radiotherapy
    - EBRT
    - Brachytherapy
  - Radiofrequency ablation
  - Intra arterial embolization
  - Cryoablation

Oligometastases: Biological Rationale of Local Ablative therapy

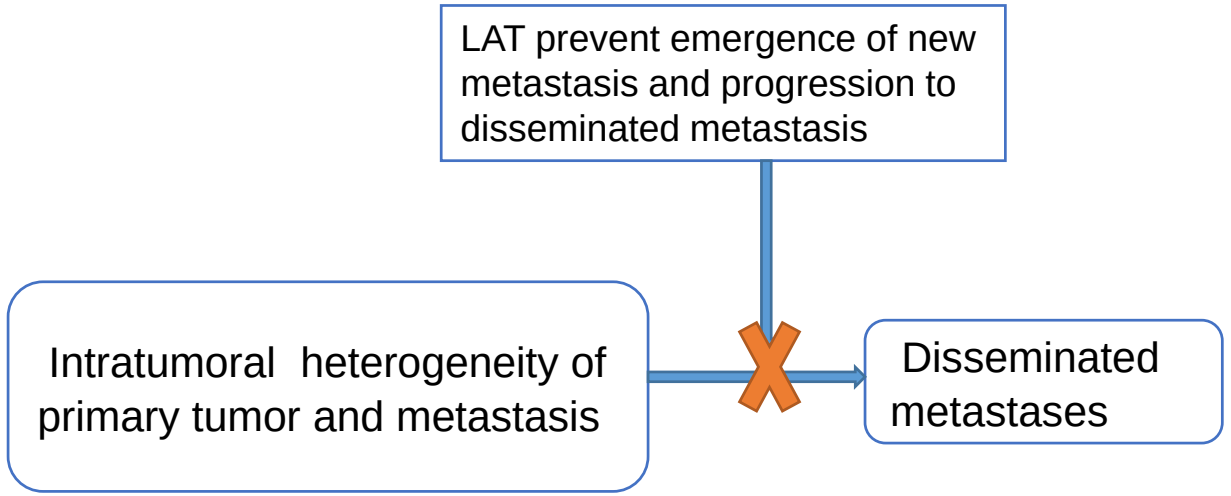
Metastatic cascade

Linear progression model

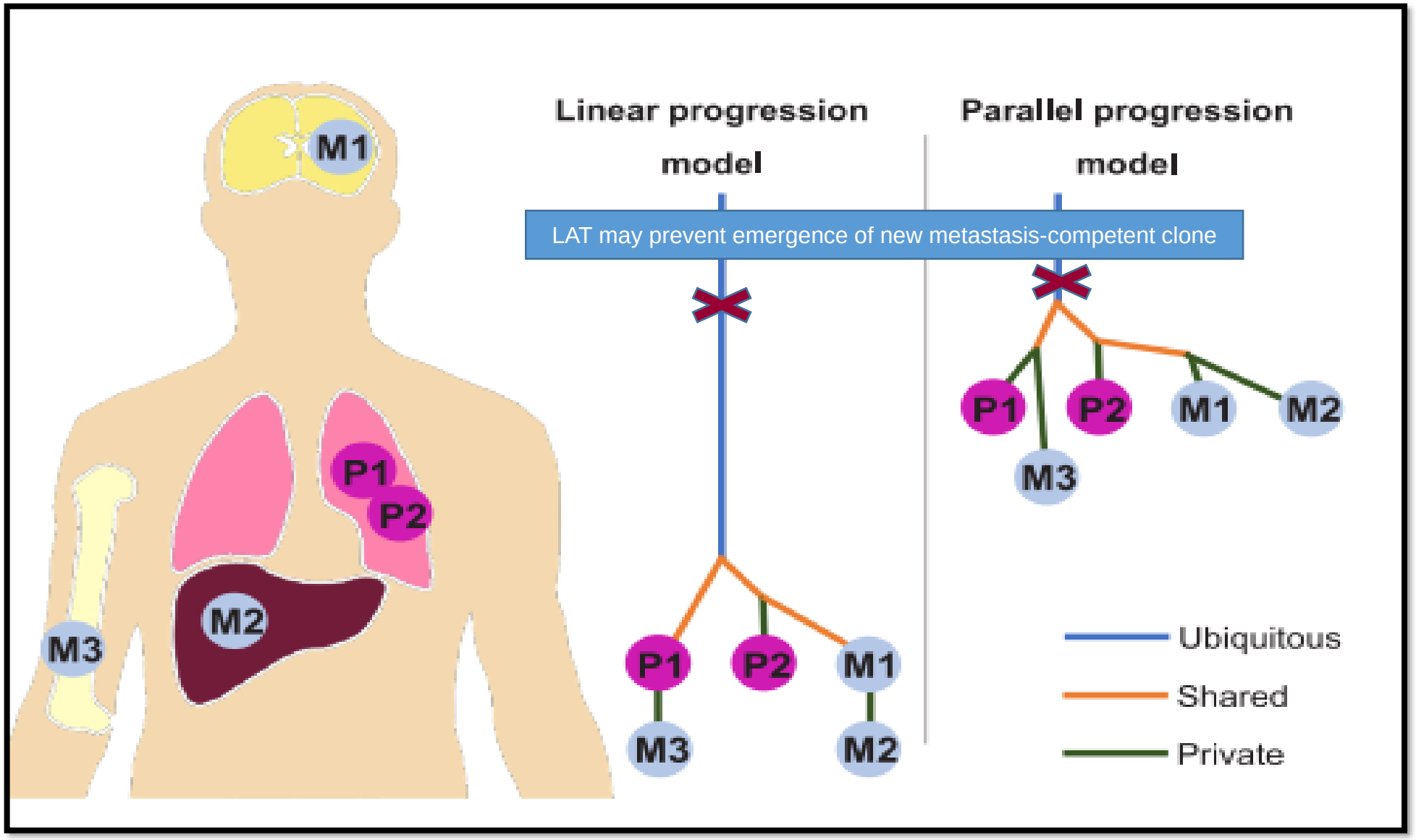
- late emergence of metastatic subclones
- low degree of genetic divergence

Parallel progression model

- Early emergence of metastatic subclones
- High degree of genetic divergence



Yang-Gun Suh et al E roj 2019


M1
P1
P2
M2
M3
Linear progression model
Parallel progression model
LAT may prevent emergence of new metastasis-competent clone
P1
P2
M1
M2
M3
P1
P2
M1
M3
M2
Ubiquitous
Shared
Private

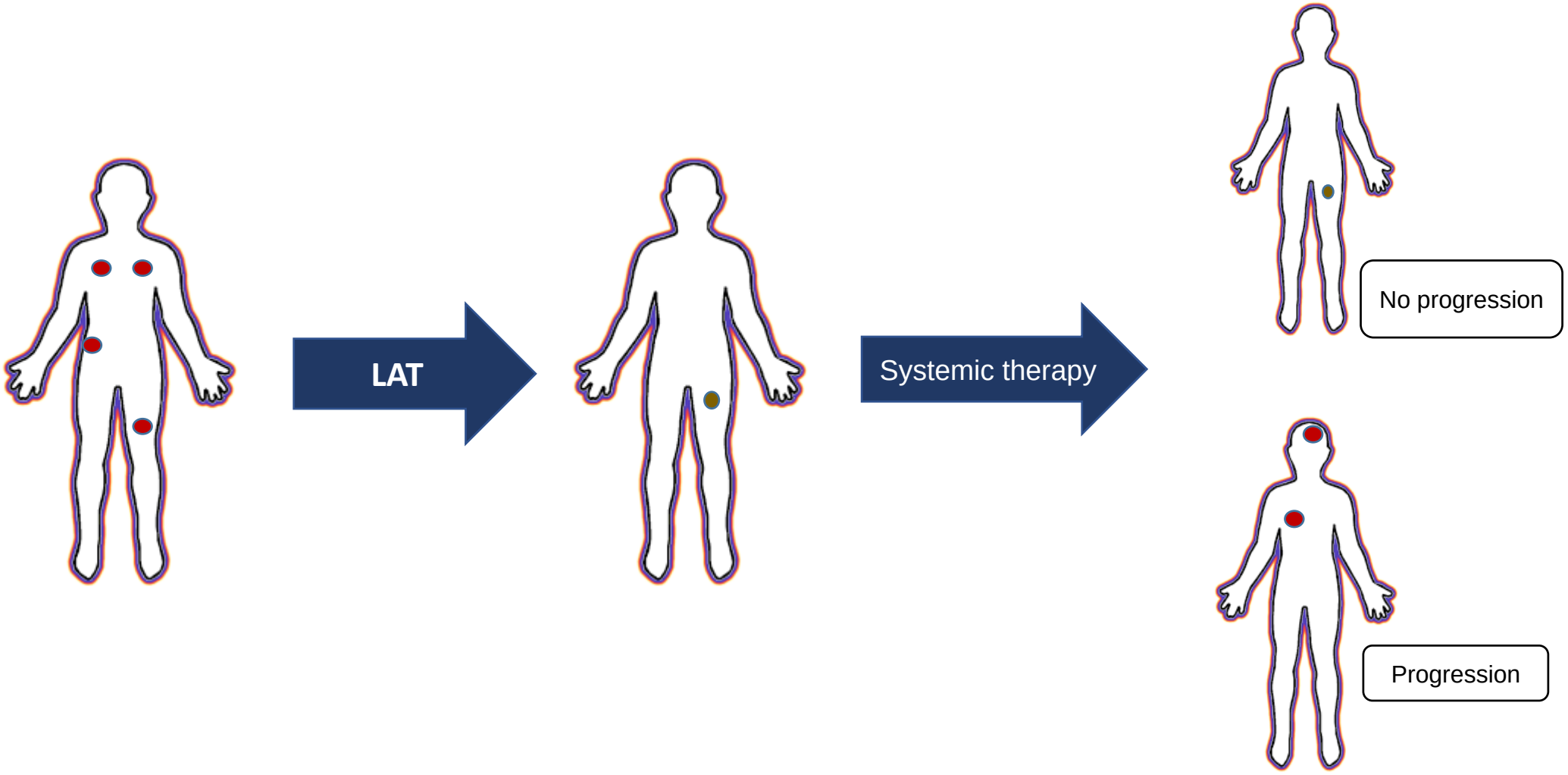
Oligometastases: Mechanism of local ablative therapies

- Reduced overall disease burden through direct cytoreduction
- Induces more systemic treatment-sensitive proliferative phase of surviving clonogens in the target lesion
- Curbs cancer growth and metastases, delaying progression due to emergence of treatment-resistant clonogens
- Enhances antitumor immune-mediated effect by promoting cancer antigen presentation and lymphocytic tumor infiltration: **Abscopal effect**

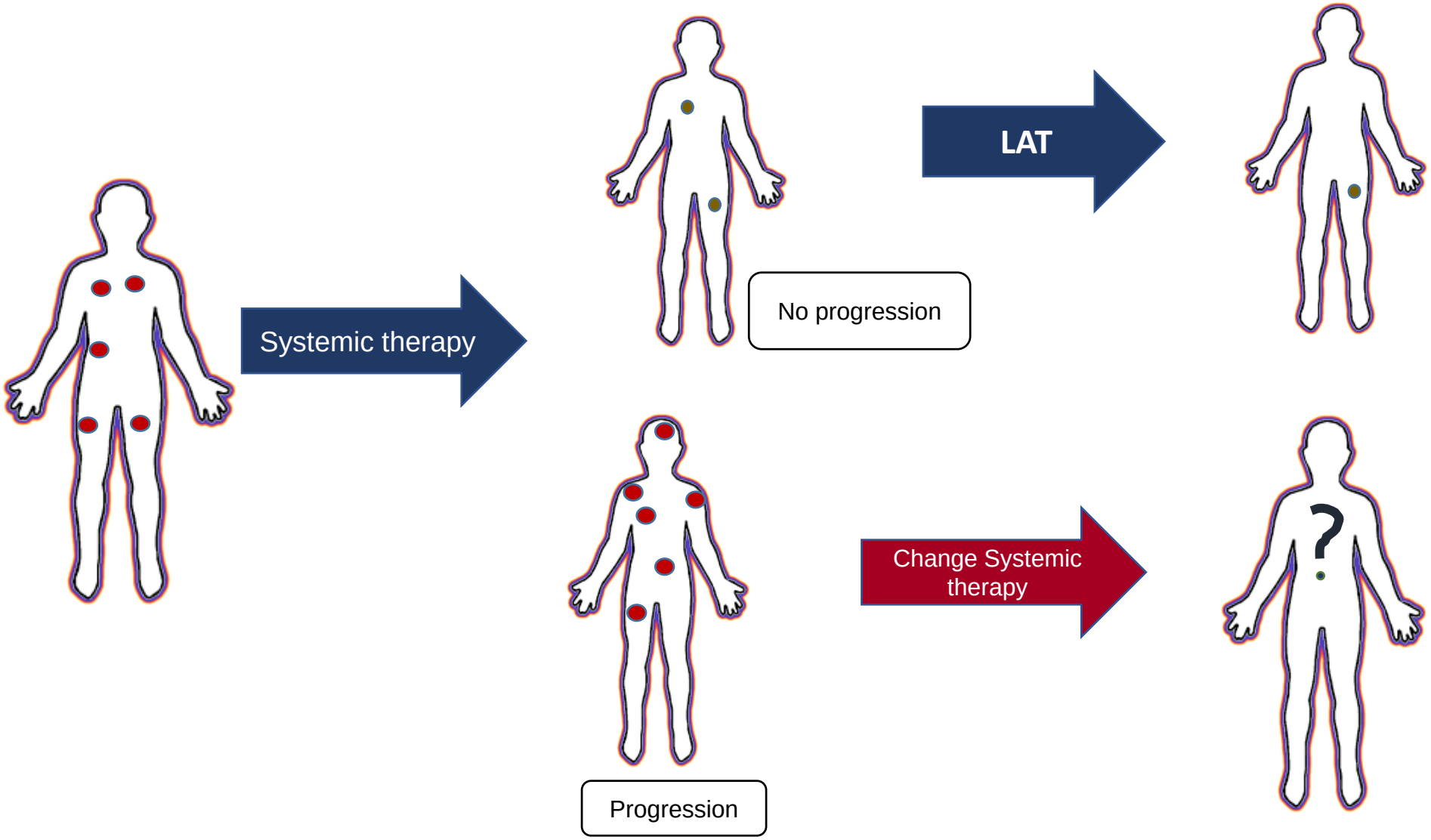
Oligometastatic NSCLC: Sequence of therapy

- Unclear and highly debated
- **Upfront LAT**: prevent more aggressive subclones from originating in anyone of the detectable disease sites
- **Upfront systemic therapy**: allows for response assessment before considering LAT

Oligometastatic NSCLC: Upfront LAT approach



Oligometastatic NSCLC: Upfront Systemic chemotherapy approach



Oligometastases: Surgery

- Surgical treatment has been the main modality historically
- Surgery has the attributes of being:
  - Diagnostic: pathologic confirmation of metastatic disease
  - Therapeutic: eliminating tumor and/or alleviating tumor-related symptoms
- Approximately 55% of all patients receive surgical treatment
  - Brain oligomets: 5-year OS rates 20%
  - Adrenal oligomets: 5-year OS rates 20-30%

Oligometastases: Radiotherapy

- Technical advancements in computing power, diagnostic imaging, and motion management → dramatic improvements in the planning and delivery of radiation treatments
- Non-invasive, well-tolerated and fewer interruptions to systemic therapy
- Intracranial and extracranial metastases
- Techniques
  - SRS/SBRT/ SABR and conventional techniques
  - Brachytherapy

Oligometastases: Why SBRT

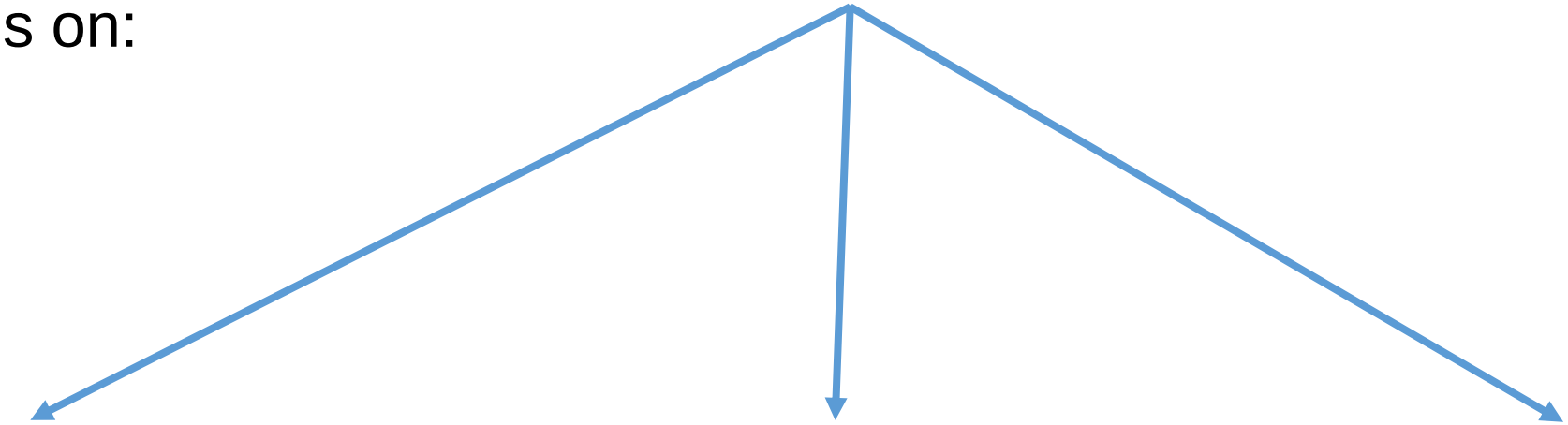
- Better technology
- Ablative dose with limited number of fractions
- No delay in systemic therapy
- Good number of studies
- SABR for metastatic lesions in various sites has shown good local control rates (70% to 100%)
- Acceptable treatment-related toxicities

Oligometastases: Should SABR replace surgery?

- No RCTs have compared SABR with surgical resection
- Limited data available comparing surgery with SABR support a position of equipoise between the two treatments
- Choice of SABR versus surgery should be personalized, determined by various factors including patient preferences and clinical scenario

Oligometastases: Patient selection for local treatment

Selection of most effective method for local treatment of oligometastases depends on:

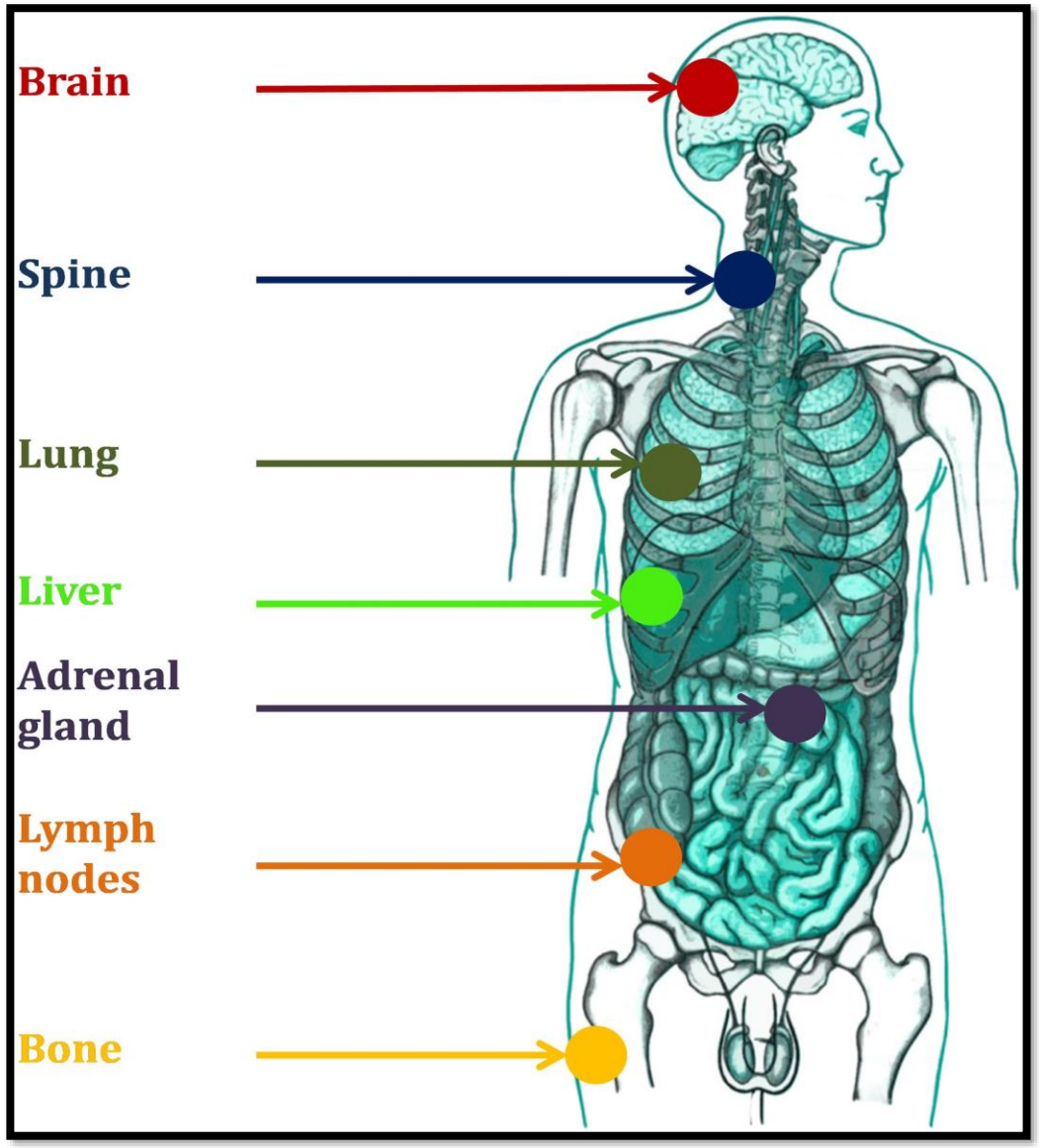


Patient-related factors
- Age
- Performance status
- Organ function
- Patient preferences

Tumour-related factors
- Location
- Size
- Proximity to vessels/critical organs

Treatment-related factors
- Availability of expertise
- Cost
- Waiting list

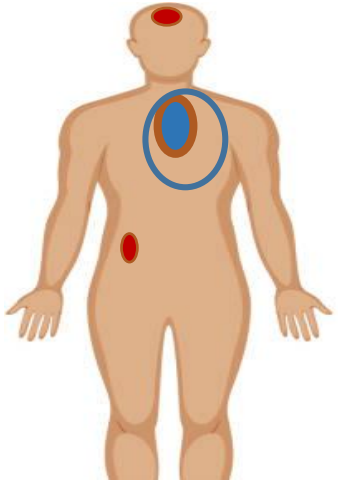
Metastatic sites treatable with stereotactic radiotherapy



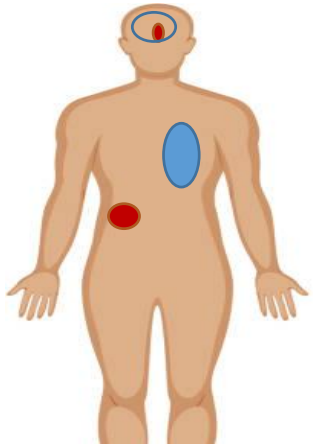
J Radiat Res, Volume 57, Issue S1, August 2016, Pages i58–i68, https://doi.org/10.1093/jrr/rrw006.

Oligometastases NSCLC: Target to be treated

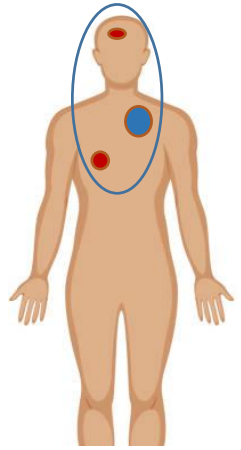
A. Primary



B. Metastases



C. **Both**



Oligometastases: Radiotherapy doses

Site	Dose
Brain	• 18-24 Gy (single fr) • 27-30Gy/3-5 fr
Lung	• Peripheral lesions <2 cm: 60 Gy in 3 fr • Peripheral lesions 2 -5 cm:48Gy in 4 fr • Central lesions: 60 Gy in 8 fr • 45 Gy in 15 fr
Adrenal	• 42 Gy in 6 fr • 20–40 Gy in 5 fr
Liver	• 30–60 Gy in 3 fr • 50 Gy in 5 fr
Bone	• 18 to 24Gy (single fr) • 24-27Gy in 2 or 3 fr • 30-35Gy in 5 fr

Oligometastases NSCLC: Summary of studies of radiation therapy

Trial (yr and design)	Patients (Mets per patient)	RT technique	Definitive thoracic therapy / Systemic therapy	Median progression free survival (months)	Overall survival (OS)	Toxicity
Gomez et al (2016) P	49 (≤3)	Various	Yes /All received induction chemo	11.9 (LCT) vs 3.9 (no LCT)	Median OS not reached	20vs 8.3% G3
Iyengar et al. (2014) P	24 (≤6)	SBRT	NA / All progressed through 1st line chemo, all received erlotinib	14.7	Median 20.4 months	2 G3 RT-related toxicities
Griffioen et al. (2013) R	61 (≤3)	Various	Yes / 84% chemo	6.6	2 years 38%	6.6% G3
Cheruvu et al. (2011) R	96 (≤8)	SBRT	NA /70% chemo	NA	2 years 25% (oligorecurrence) vs 43% (de novo oligometastases)	NA
Hasselle et al. (2012) R	25 (≤5)	SRS/ SBRT	NA / 76% prior to SBRT	7.6	1 year 81.1%	8% G3
SABR COMET trial: (2020) P	99 (≤5)	Standard-of-care:(arm 1),SOC plus SABR (arm 2)		5-year PFS rate was not reached in arm 1 and 17.3% in arm 2	5-year OS :17.7% -arm 1 versus 42.3% - arm 2	no Gr 2-5 adverse events, no differences in QOL between arms

Oligometastases NSCLC: Brachytherapy

- Limited data available

Study (pts)	NSCLC pts	Site	Technique	Dose	Toxicity	Median follow up (months)	OS
Walter F (106) 2021	5	Liver	Catheters	20 Gy	2 pts	9	76.3% 1 yr
Wang (53) 2020	25	Mixed	^{125} Iodine seeds	100-140 Gy	4 pts	13	12.8 m

Oligometastatic NSCLC: Ongoing trials

Trial	Arms	Primary outcome
OMEGA (Phase 3)	Standard treatment plus local ablative therapy (surgery and/ or radiotherapy) or to standard treatment alone	Overall survival
SARON (Phase 3)	Efficacy and safety of SABR in addition to chemotherapy compared to standard treatment alone	OS/PFS/QOL/Toxicity/ Local control
HALT (Phase 3)	SBRT plus TKI compared to TKI alone beyond oligo-progression in patients with oncogene-driven NSCLC	PFS/OS/toxicity/pattern of disease progression
OITROLC (Phase 3) optimal timing for radiation therapy	Upfront chemo plus concurrent radiotherapy to the primary and all metastatic sites versus a consolidative approach after two cycles of induction chemotherapy	Response rate / toxicity / QOL

Conclusions

- Oligometastatic NSCLC is a broad spectrum disease, with a variable prognosis
- Biology & behaviour of “intermediate state” of metastatic disease not fully understood
- Consensus definition has now been developed for NSCLC
- SBRT provides an attractive ablative option because it is well tolerated
- Additional studies are required for improved patient selection, optimal treatment schedule, and to define treatment related toxicities


Thank You