SBRT for Oligometastatic disease

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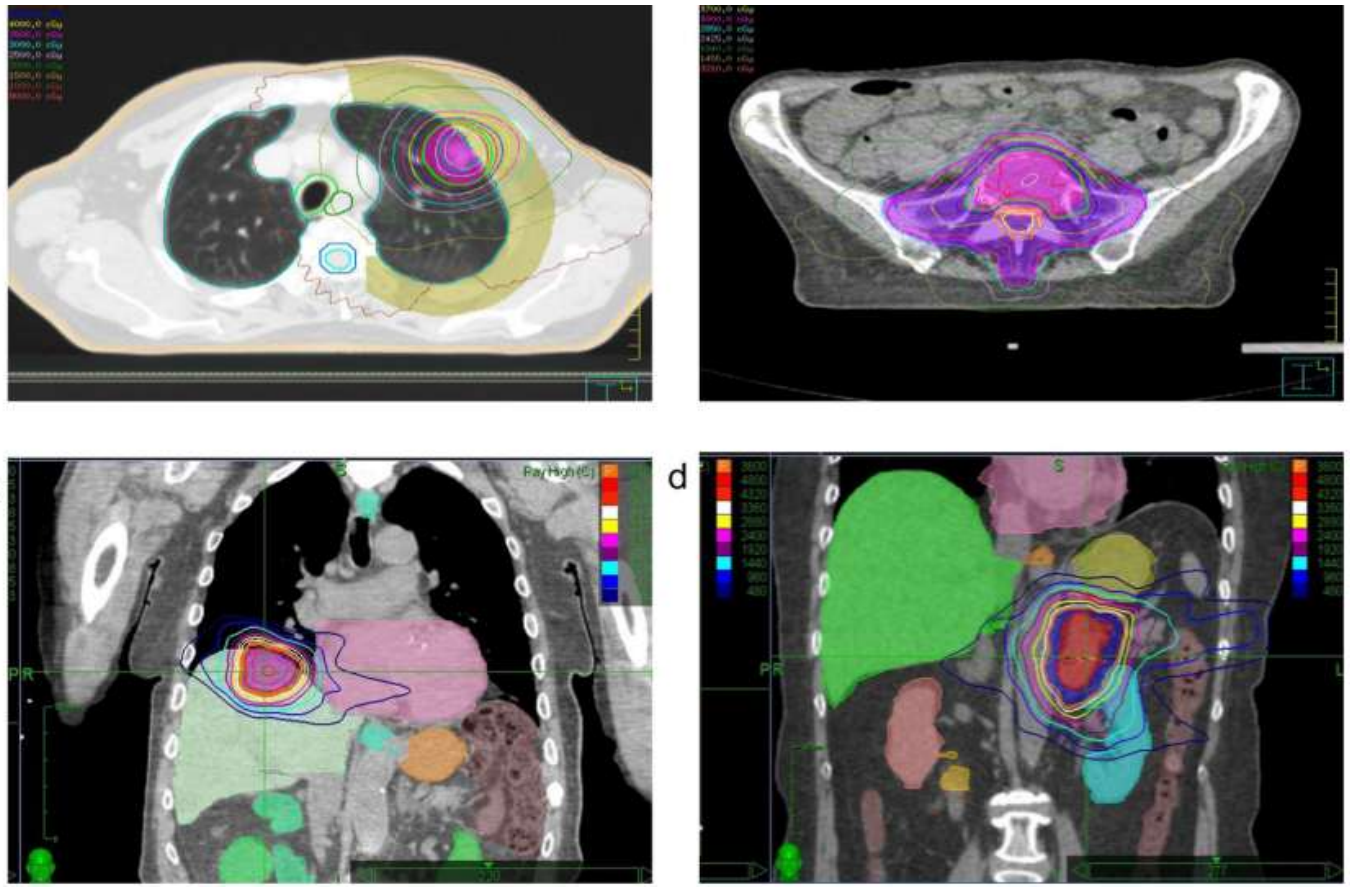


Overview

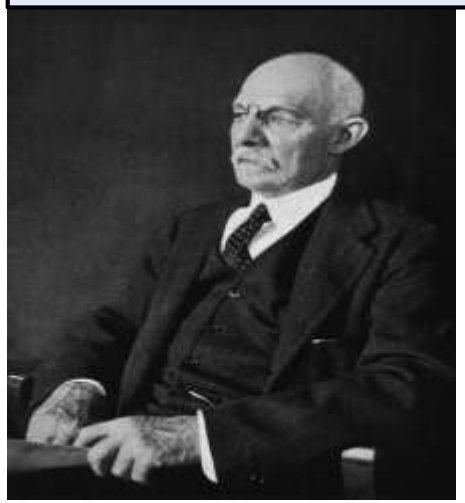
- Biology of metastatic disease (poly vs oligo)
- Definition
- Role of SBRT
- Best available evidence
- Future directions
- Take home messages

Theories of metastasis

Stephen Paget

Seed and soil theory

William Stewart Halsted

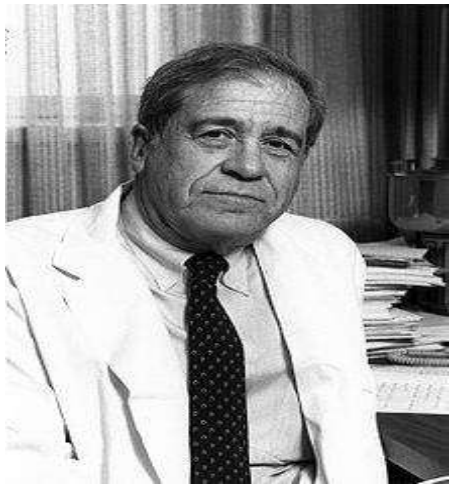


Contiguous manner

James Ewing

Particular site

Bernard Fisher



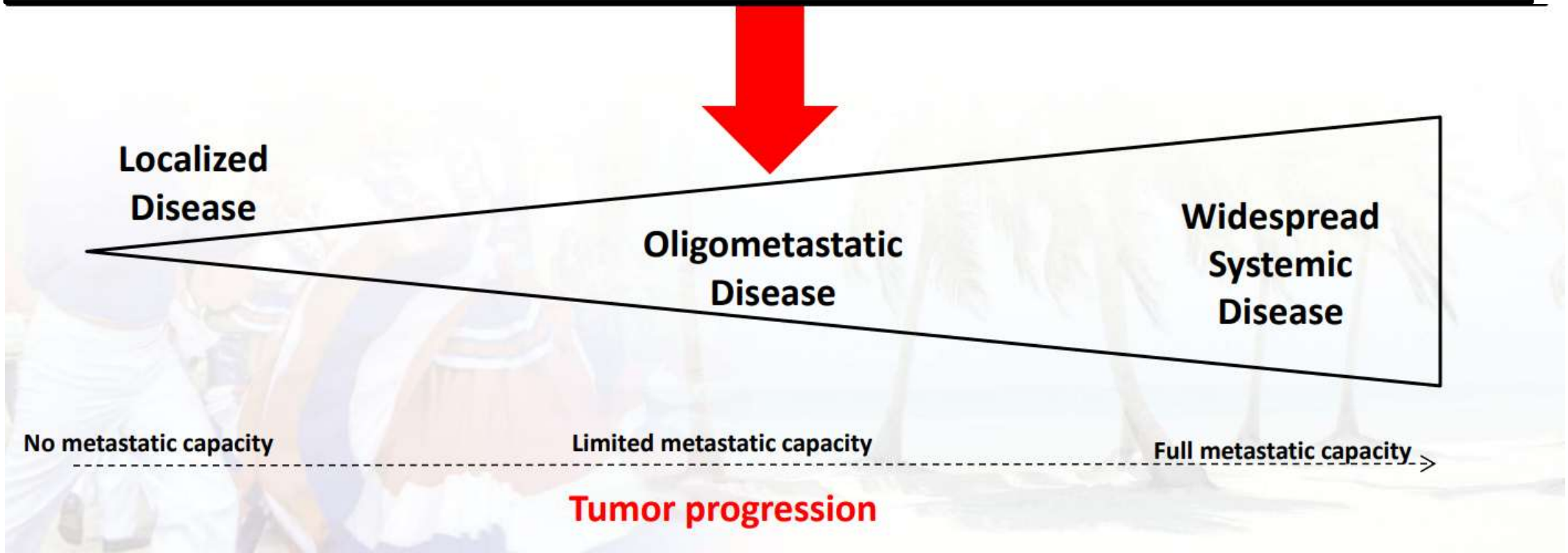
Systemic theory

Samuel Hellman

Spectrum theory

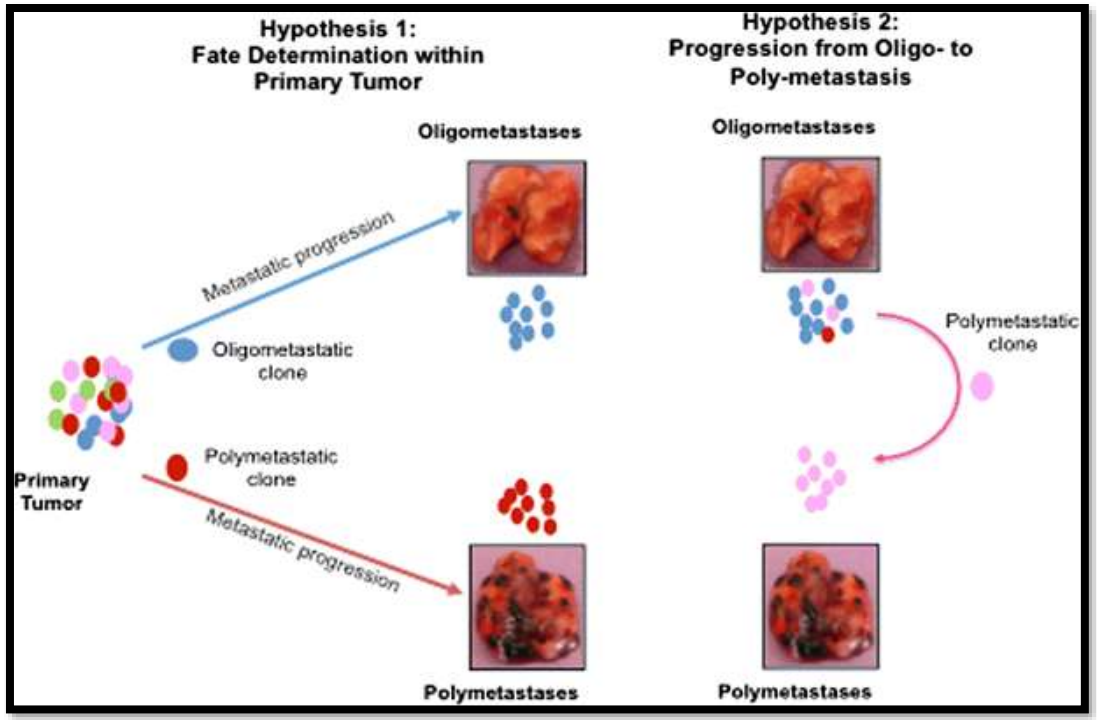
Oncotarget 2015;6(11):8491–524

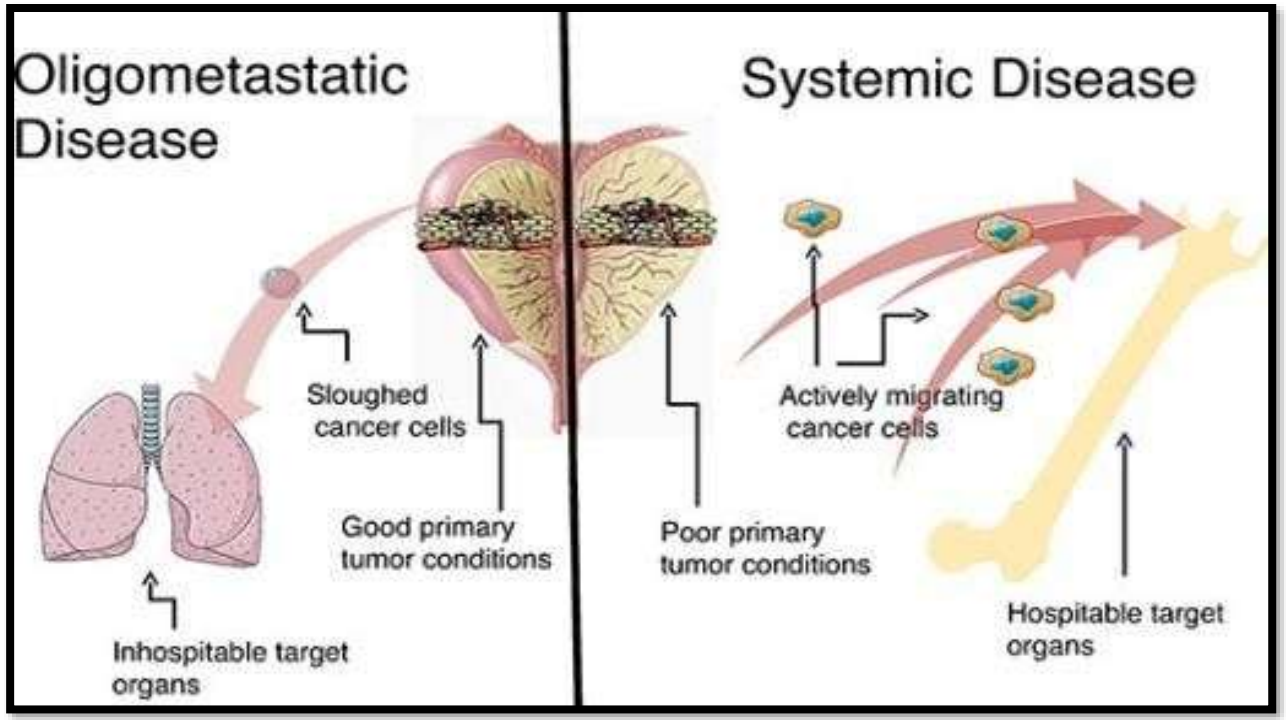
A disease state that exists in a transitional zone between localized and widespread systemic disease



An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy.

Oligometastatic disease vs systemic disease





- Type of mutations present in the cancer cells (quality of diaspora migrants)
- Quality of the original tumor site (factors in the homeland that cause the population to migrate)
- The quality of the new hostland (factors that allow immigrants to establish and flourish)

Oncotarget 2015;6(11):8491–524

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

Lancet Oncol 2020; 21: e18–28

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

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]

Radiother Oncol. 2020 Jul;148:157-166.

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- **OMD can be defined as 1–5 metastatic lesions.**
- **A controlled primary tumor being optional.**
- **Where all metastatic sites must be safely treatable.**

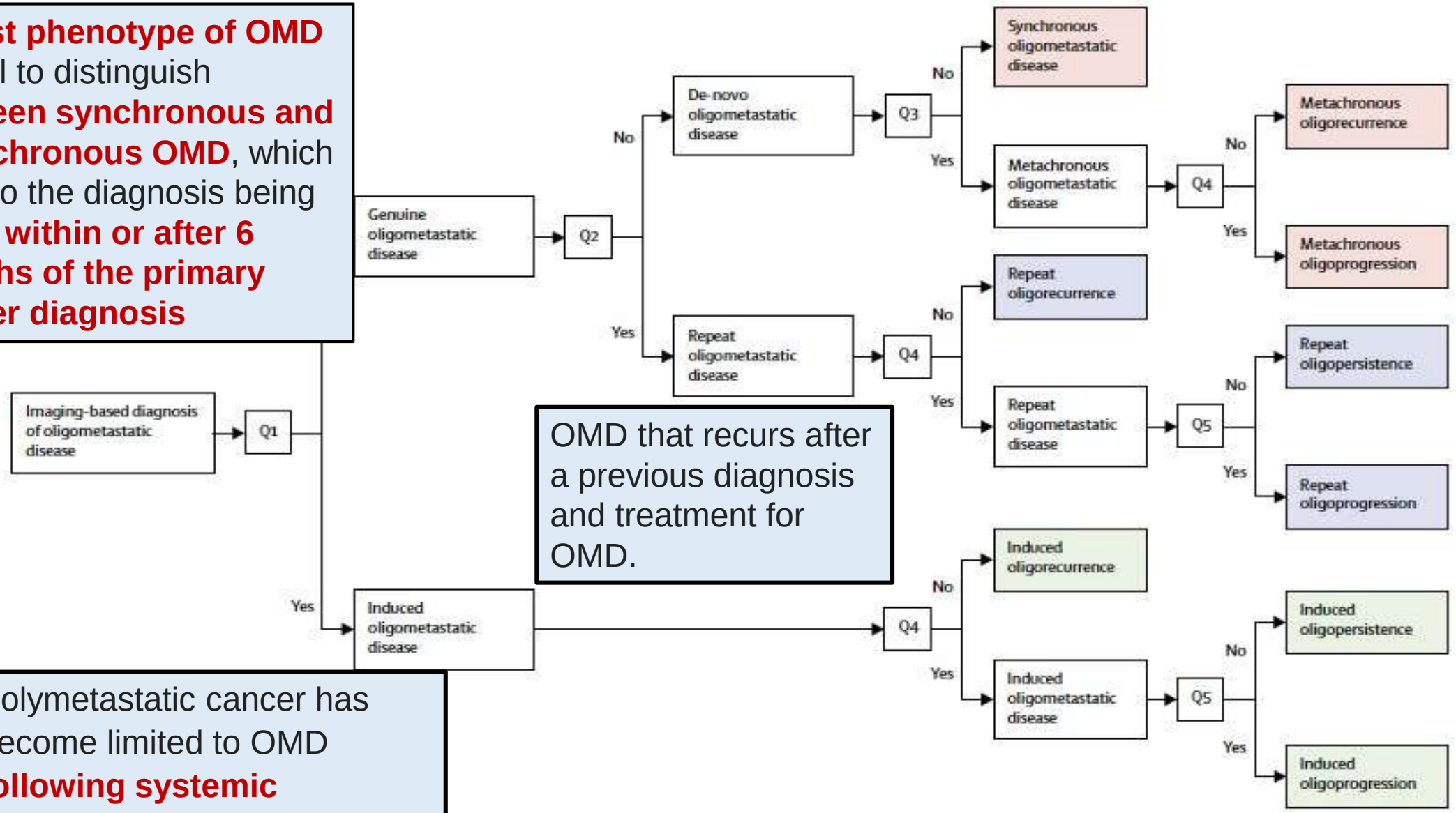
Consensus supported the ability to deliver safe and clinically meaningful radiotherapy with curative intent to all metastatic sites as a minimum requirement for defining OMD in the context of radiotherapy.

- Minimum common endpoints such as PFS and OS, local control, toxicity and quality-of-life should be reported; uncommon endpoints as deferral of systemic therapy and cost were endorsed.

Radiother Oncol. 2020 Jul;148:157-166.

Classification of oligometastatic disease

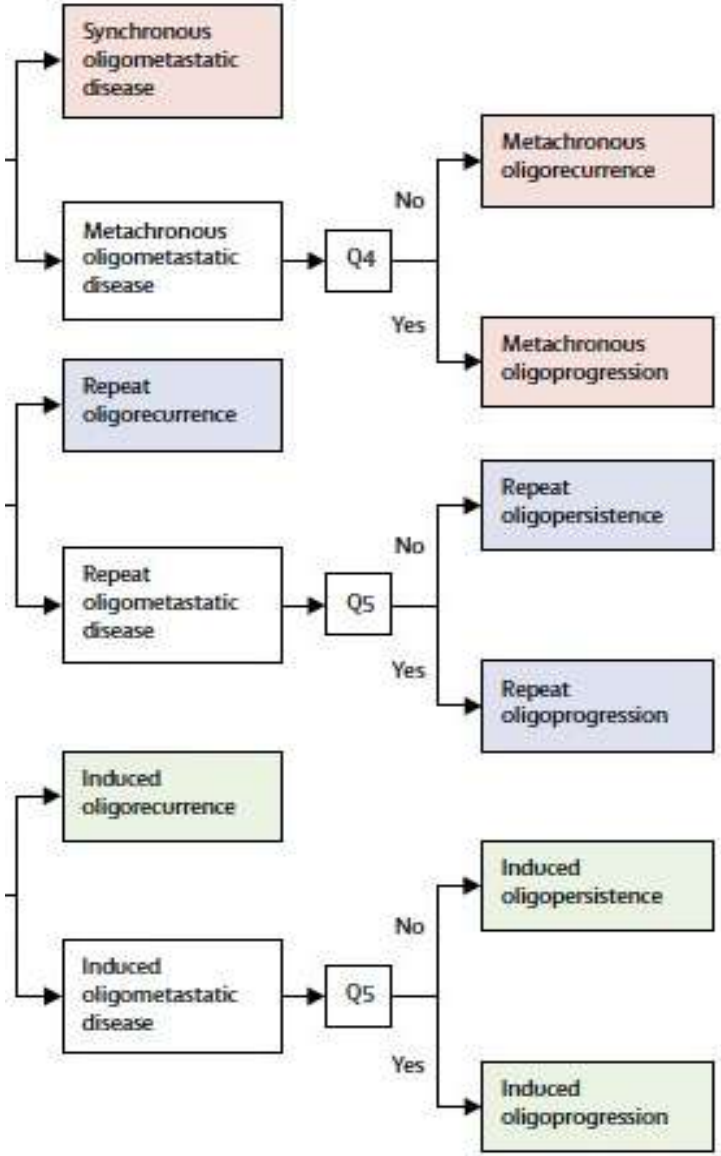
Purest phenotype of OMD
Useful to distinguish **between synchronous and metachronous OMD**, which refer to the diagnosis being made **within or after 6 months of the primary cancer diagnosis**

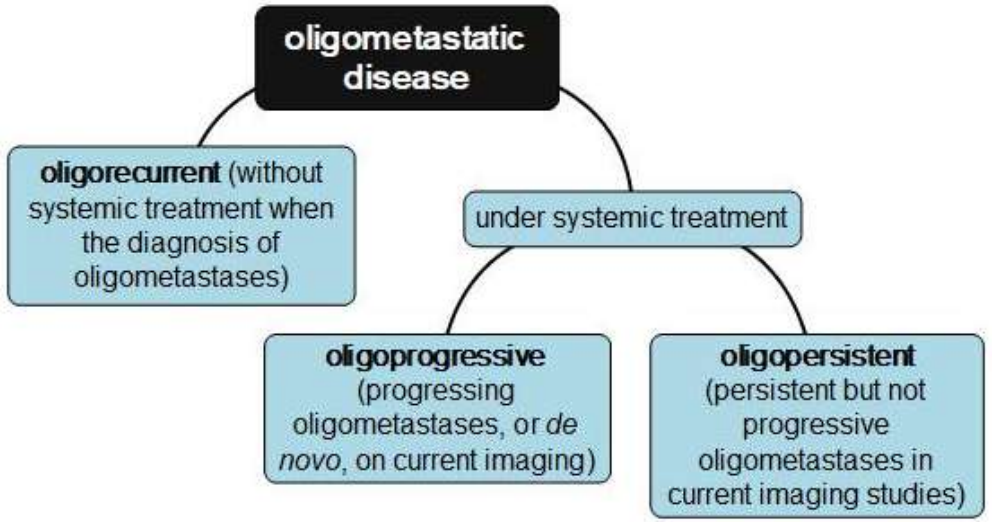


OMD that recurs after a previous diagnosis and treatment for OMD.

Polymetastatic cancer has become limited to OMD **following systemic treatment**

Guckenberger M et al., Lancet Oncol 2020





Oligorecurrence: OMD that recurs after initial treatment during a treatment-free period.

The conditions of oligorecurrence - primary site of cancer controlled, meaning that all gross recurrent or metastatic sites could be treated using local therapy

Oligoprogression: the OMD progresses during active systemic treatment.

Clinical scenario where a *few* metastases progress, whereas all other metastases are stable or responding to a systemic therapy strategy.

Characteristics of Indolent clinical metastasis

Clinical
Low number (1-5 lesions)
Metachronous presentation
No involvement of lymph nodes
Slow rate of progression (typically <0.6 new lesions per year)
Limited organ sites (typically 1-2 sites)
Favorable histology (including, but not limited to breast, prostate and kidney)
Biological
Activation of innate and adaptive immunity
Absence of mesenchymal features
Low degree of tumor aneuploidy
Low degree of intratumoral heterogeneity
Intact 14q chromosomal arm
Expression of microRNAs that suppress genes associated with metastasis
Nat Rev Clin Oncol 2019:16; 581–588

Imaging and its Impact on Defining the Oligometastatic State

- Imaging plays a key role
- The staging strategy should be tailored to the primary tumour and metastatic site(s).
- Imaging for assessment of OMD needs to be:
- **Sensitive —**

➢as it is crucial to avoid missing metastasis and ignoring PMD

- **Specific—**

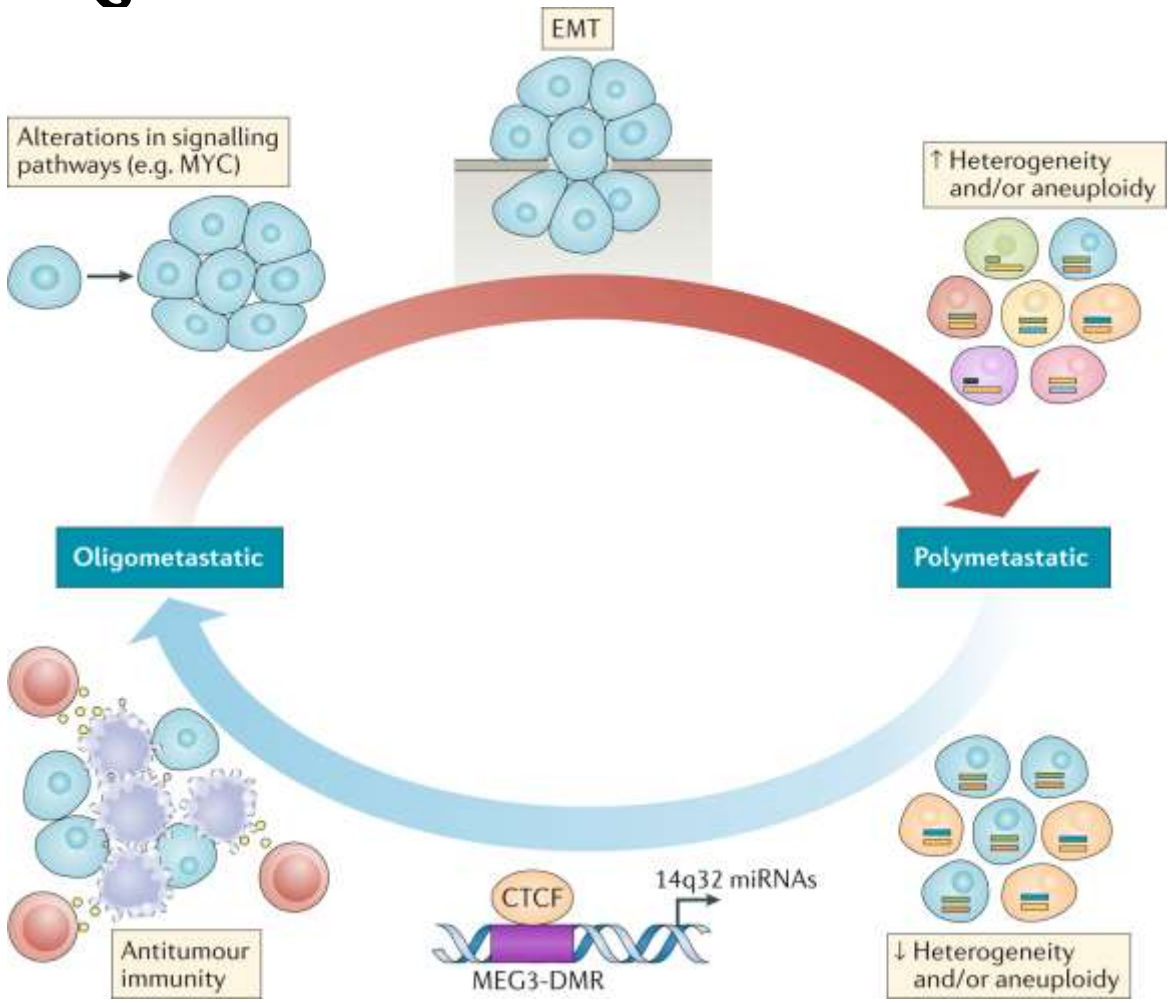
➢as a pathologic confirmation of all lesions is not realistic and acceptable.

- Clinical imaging recommendations for each tumor type are important for standardization and adequate patient management.

Biomarkers

- ctDNA
- Micro RNAs - central role of microRNAs (miRNAs) in the regulation of the metastatic phenotype.

14q32-encoded microRNAs mediate an oligometastatic phenotype.



Nat Rev Clin Oncol 2019:16; 581–588

Common primary tumor sites for subsequent development of OMD

- NSCLC
- Colorectal cancer
- Breast
- Prostate
- Soft-tissue sarcoma
- Renal cell carcinoma

Favorable histologies

- Breast
- NSCLCs with targetable mutations
- Prostate
- Kidney

J Clin Oncol 2020;38:2830-2838

Modalities of treatment for OMD

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

Biological Rationale of LAT for Oligometastasis

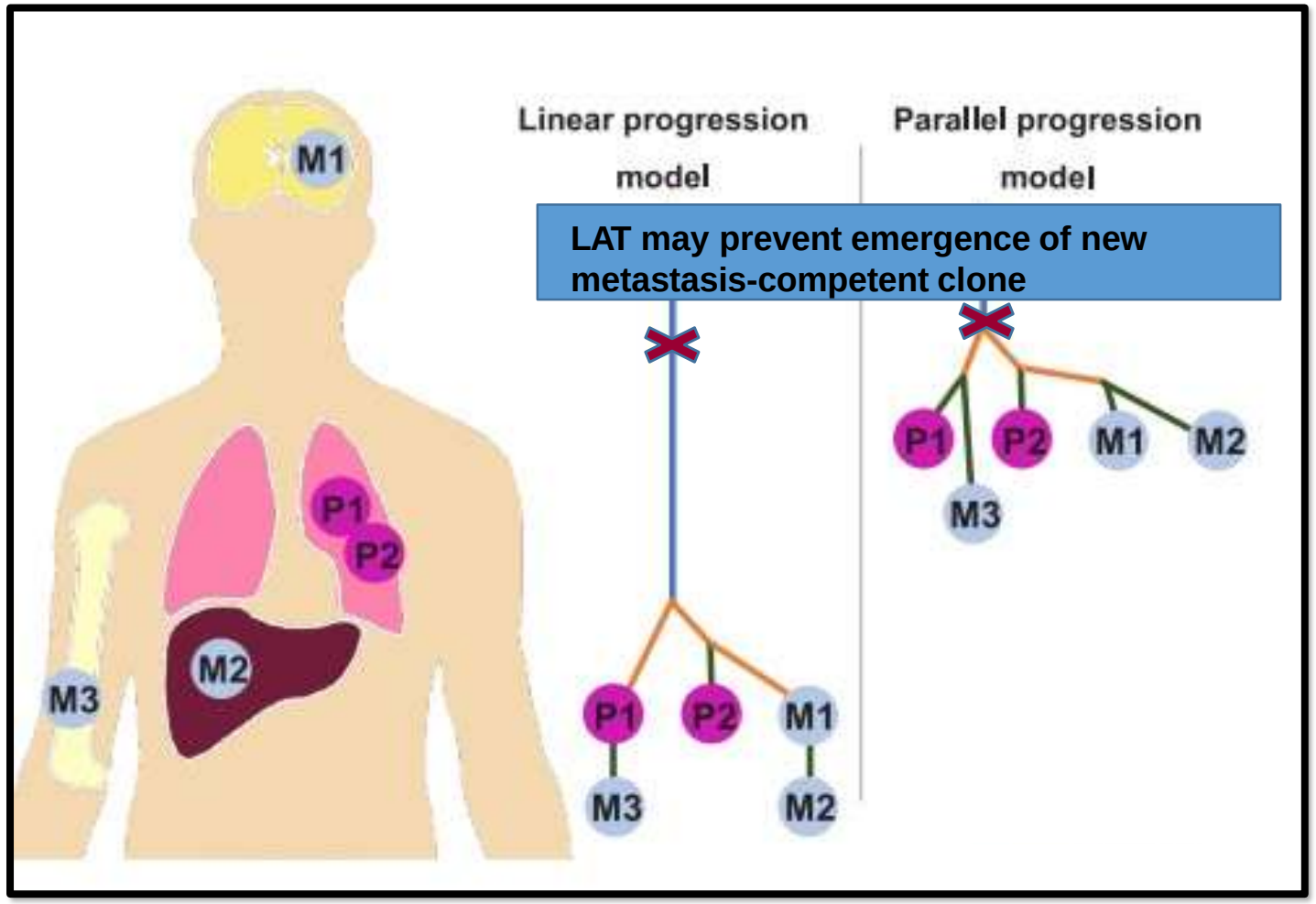
Metastatic cascade

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



Radiat Oncol J 2019;37(3):149-155

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
- Enhances antitumor immune-mediated effect by promoting cancer antigen presentation and lymphocytic tumor infiltration: **Abscopal effect**
- **Higher radiation doses overcomes hypoxic microenvironments found in metastases**

SBRT

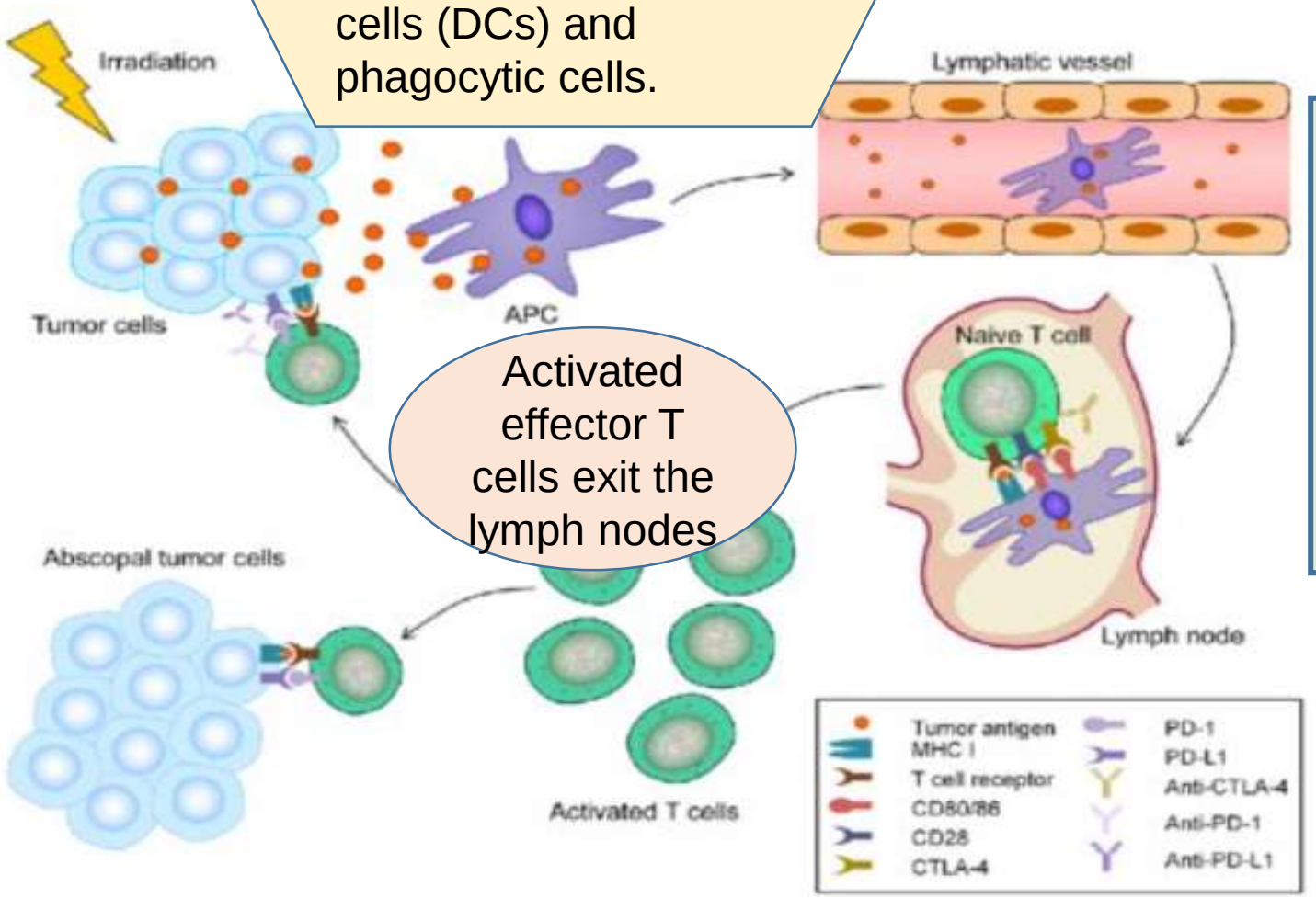
- High doses to small, well-defined targets in extreme hypofractionated scheme with a very high biological effectiveness.
- Not feasible to administer such BED in conventional fractionation.
- No delay in systemic therapy.
- SABR for metastatic lesions in various sites has shown good local control rates (70% to 100%)

Mechanism of the abscopal effect

Release of tumor antigens by irradiated tumor cells

Cytotoxic T cells circulate through the blood stream and are thus able to destroy remaining tumor cells in distant parts of the body which were not irradiated.

Neoantigens taken up by antigen-presenting cells such as dendritic cells (DCs) and phagocytic cells.

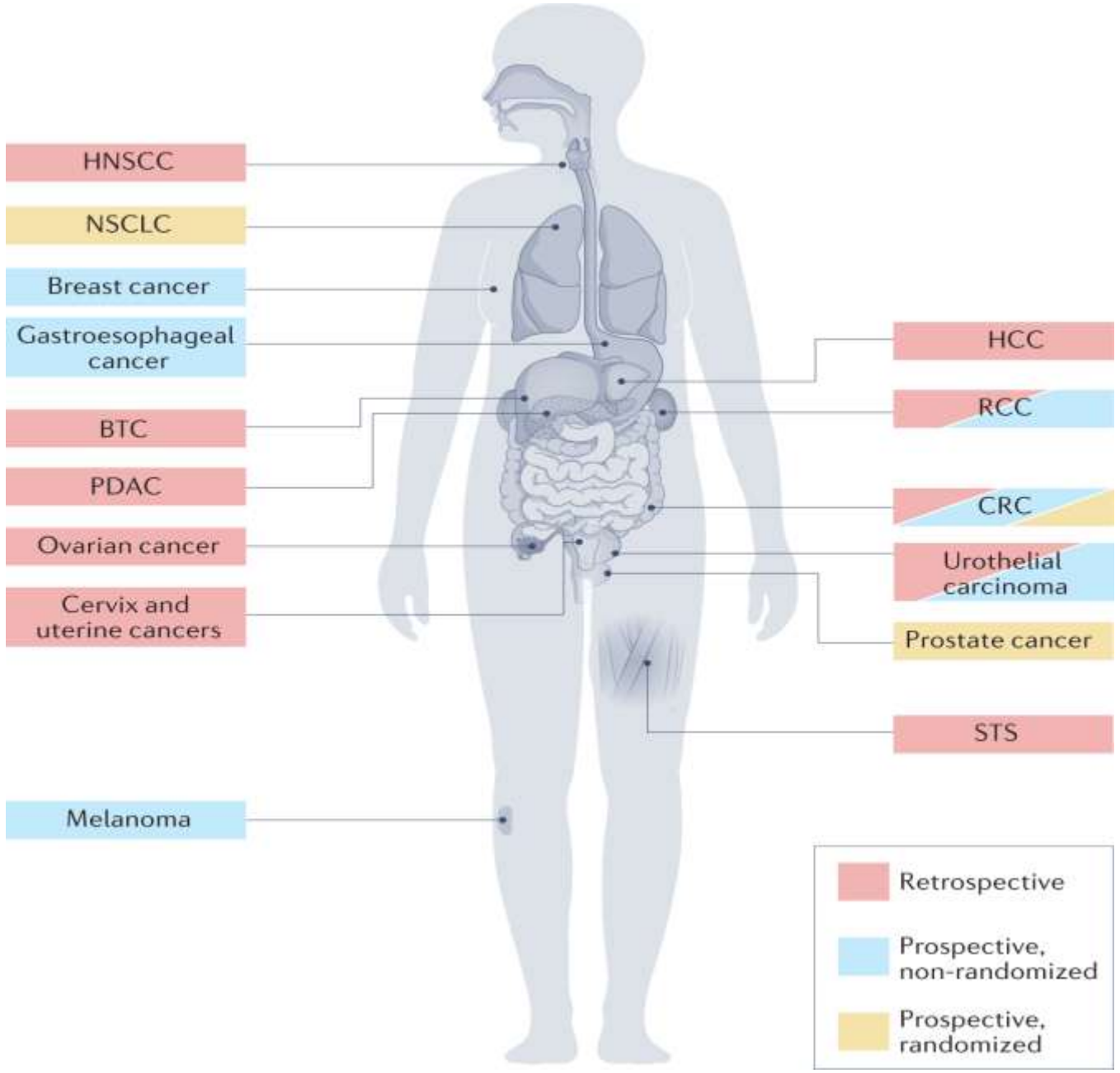


Migrate to the lymph nodes where they present antigens to T cells, a process that is mediated by the MHC pathway and other co-stimulatory signals, such as CD80 and CD28.

Oligometastatic patient selection for SABR

Prognostic factors	**Factors with favorable outcome**
Patient fitness	KPS≥70 Minimal comorbidities Perceived long expectancy
Slow growing cancers	Timing of metastasis (metachronous vs synchronous) Longer DFI between primary tumor and development of metastasis Favorable histology
Minimal disease burden	Limited number of metastatic sites (≤1 to 5 as per trial protocols) Primary tumor controlled or potentially treatable Size of largest metastasis Potential systemic therapy options
Ability to deliver an ablative dose	Location of metastasis Number of metastasis Proximity to organs at risk Previous radiotherapy at or near site

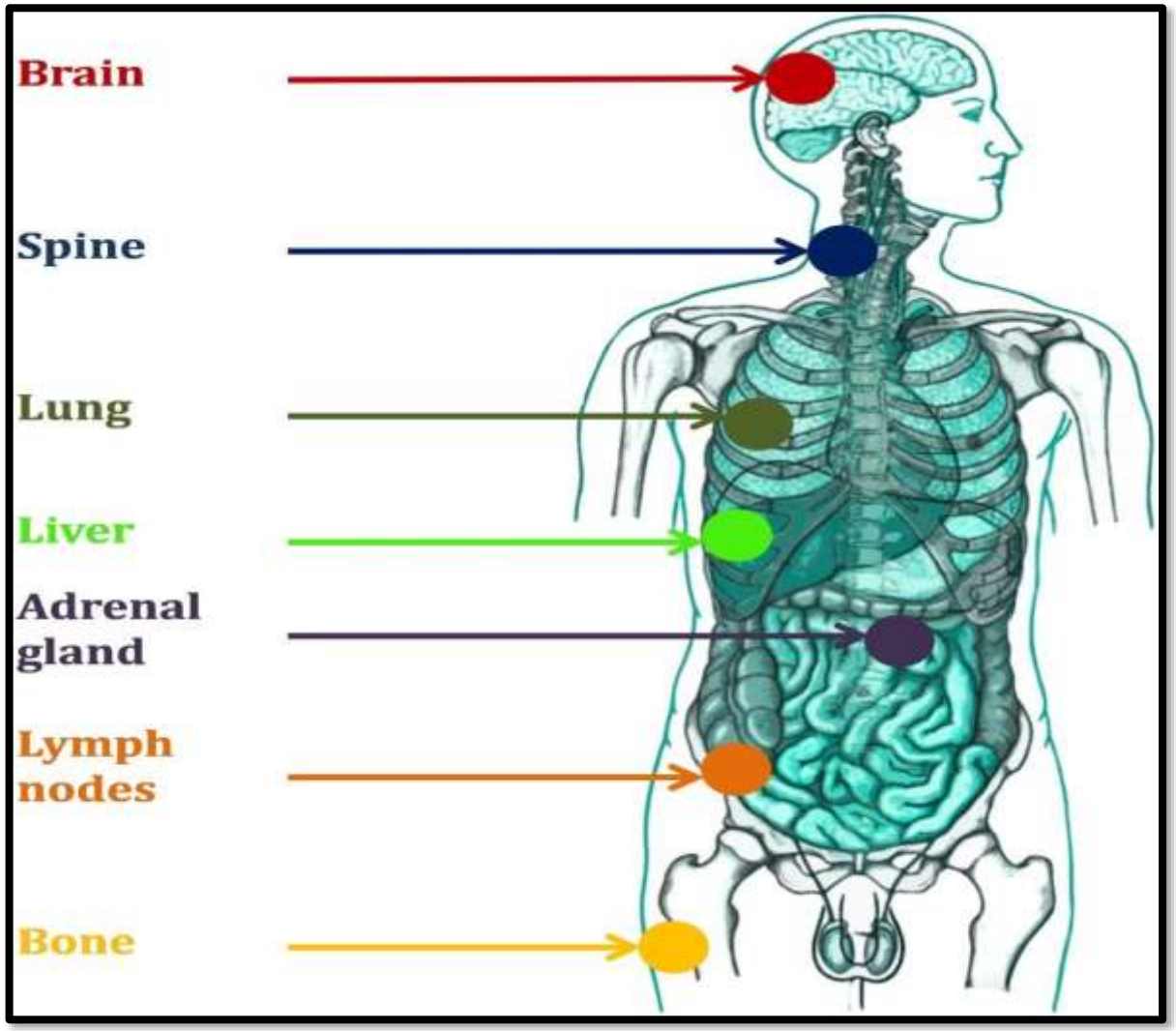
Jasper K. et al., J Clin Oncol 2022



Cancer	Incidence of OMD (%on metastatic presentation)
Lung (NSCLC)	5-10
Breast	5-20
Colorectal	10-15
Prostate	10-30
HCC	10-35
Cervical	5-15
Ovarian	5-15
Pancreatic	5

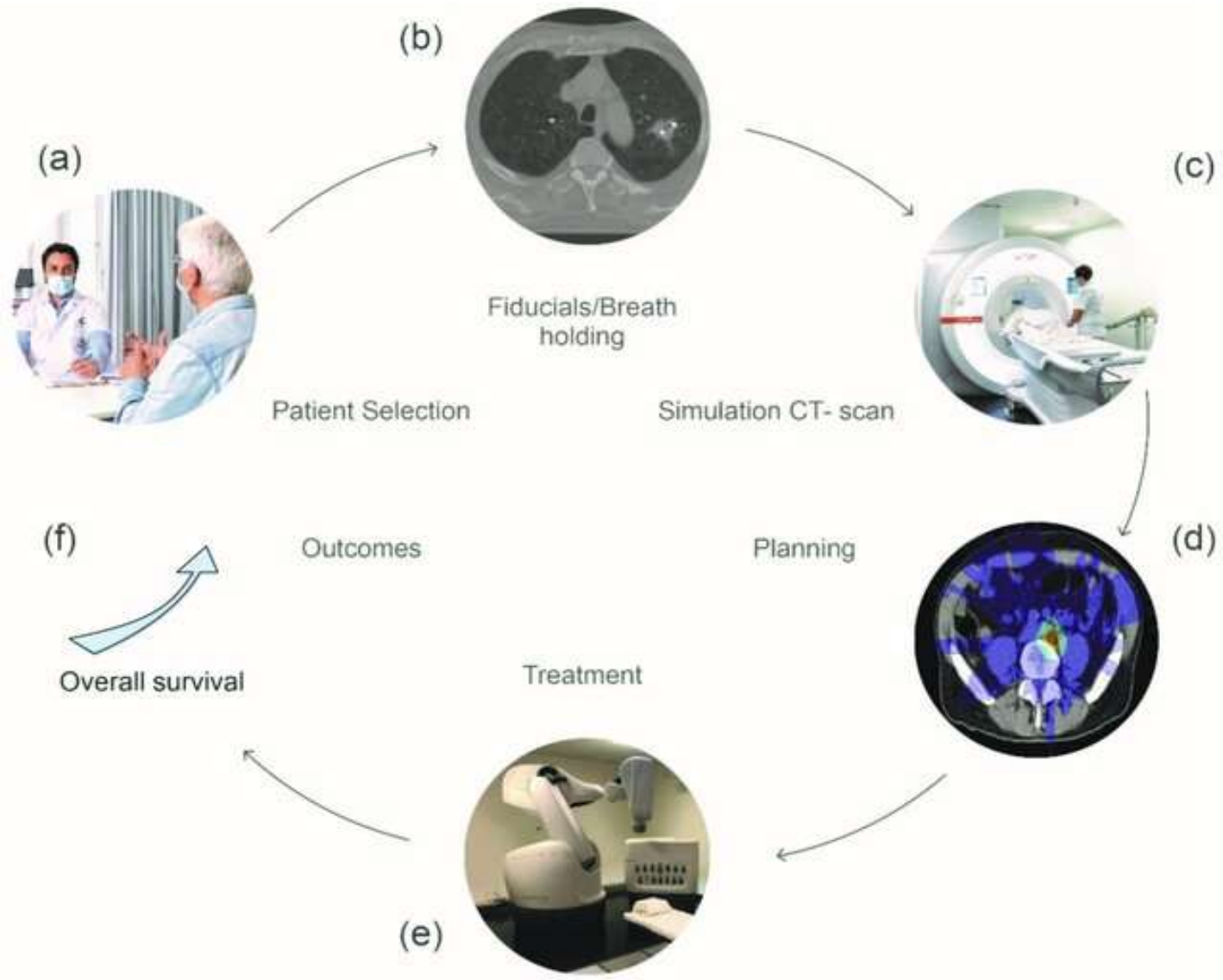
Nat Rev Clin Oncol. 2022 :585-599.

Metastatic sites treatable with SBRT



J Radiat Res, 2016, Pages i58–i68,

Steps for planning SBRT treatment



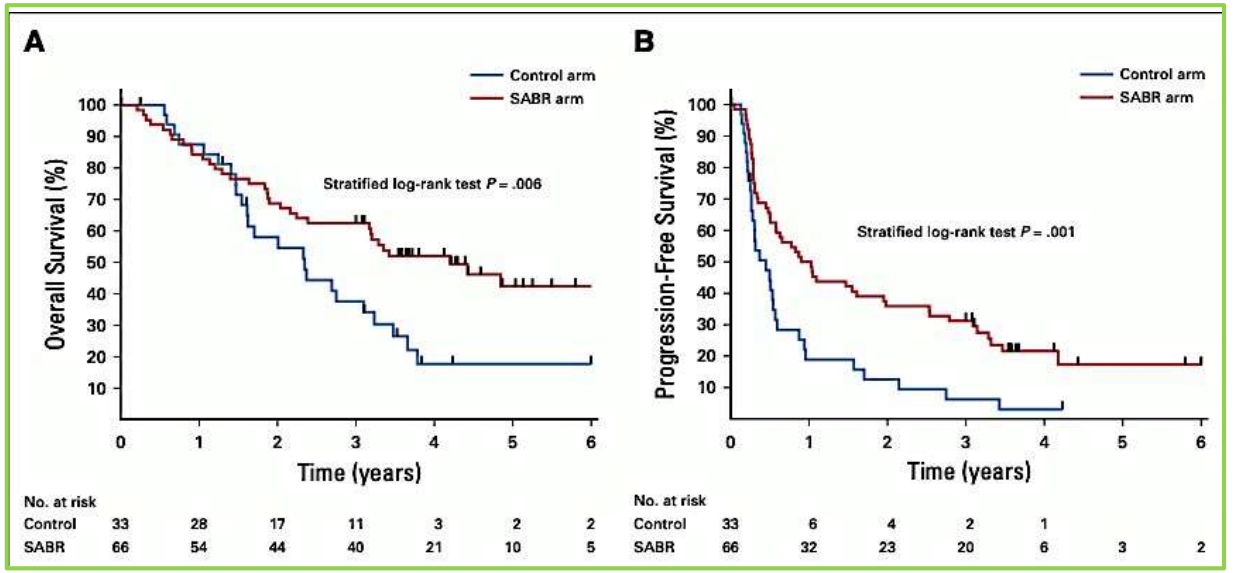
BEST AVAILABLE CLINICAL EVIDENCE

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

J Clin Oncol. 2020

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1];

- Open-label, multi-centric (10 centres in Canada, Australia, Scotland and Netherlands).
- 2012-2016
- 1st trial to directly test the oligometastatic paradigm, i.e. OS after Ablative vs Palliative t/t
- **Most common primary tumor types were breast, lung, colorectal, and prostate . Median follow-up was 51 months.**



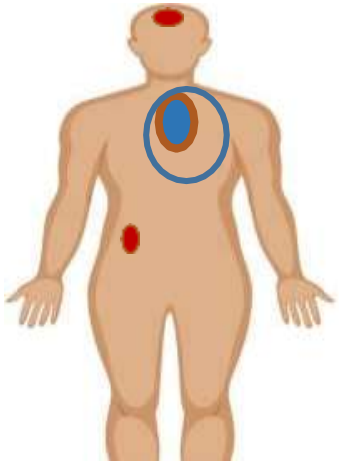
Conclusion:

Patients who received SABR demonstrated a **22- month improvement in median OS** compared with patients who received a standard-of-care approach alone, corresponding to an **absolute survival benefit of 25% at 5 years.**

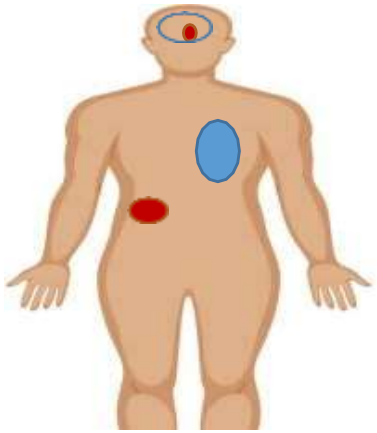
Role of SBRT in oligometastatic NSCLC and lung metastasis

Oligometastases : Target to be treated

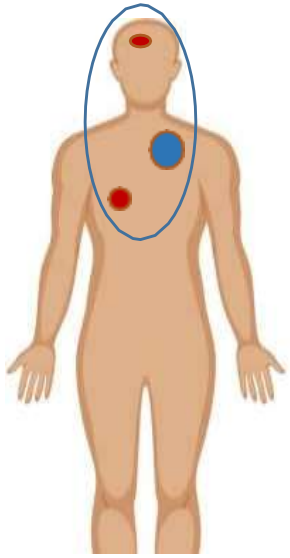
A. Primary



B. Metastases



C. **Both**



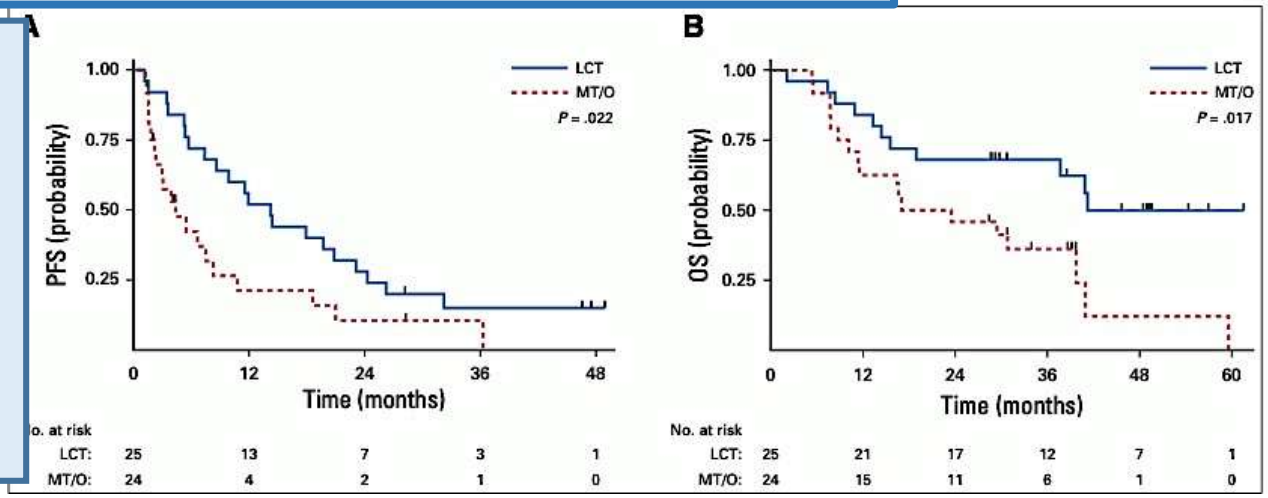
Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

ASCO Journal of Clinical Oncology®

J Clin Oncol. 2019 Jun 20;37(18):1558-1565.

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]; ...

Multicenter, randomized, phase II trial (49 patients) **≤3 metastases who did not progress on standard frontline systemic therapy** randomly assigned (1:1) to **maintenance therapy or observation (MT/O) or to LCT to all active disease sites.**



Conclusion:

In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.

Consolidative Radiotherapy for Limited Metastatic Non–Small-Cell Lung Cancer

A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD,[1] Zabi Wardak, MD,[1] David E. Gerber, MD,[2] Vasu Tumati, MD,[1] Chul Ahn, PhD,[3] Randall S. Hughes, MD,[2] Jonathan E. Dowell, MD,[2] Naga Cheedella, MD,[2] Lucien Nedzi, MD,[1] Kenneth D. Westover, MD, PhD,[1] Suprabha Pulipparacharuvil, PhD,[1] Hak Choy, MD,[1] and Robert D. Timmerman, MD[1]

- **29 patients**
- **EGFR & ALK negative patients**
- **1-5 synchronous oligometastasis**
- **Induction therapy given to all patients**
- **2 arms: Control arm & SABR arm**
- **PFS: 9.7 vs 3.7 months**

Doses:

- **21 -27 Gy in single fraction**
- **26.5 – 33 Gy in 3 fraction schedule**
- **30 – 37.5 Gy in 5 fraction schedule**

Conclusion:

- **Consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone**
- **No difference in toxicity.**

JAMA Oncol. 2018

Clinical characteristics of lung cancers associated with improved outcomes after consolidative localized therapy to metastatic sites

- Patients with ≤3 metastatic sites
- No lymph nodes involvement
- Patients with no bone metastatic disease
- Non-squamous histology
- Metachronous disease
- Smaller primary tumor

Transl Lung Cancer Res 2021

Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline

- CECT chest and upper abdomen (including liver, kidneys, and adrenal glands), but with a preference for a whole-body 18-FDG-PET-CT scan.
- In addition, MRI of the brain is recommended, especially in case of neurological symptoms.
- Radiation and surgery were the only recommended modalities for definitive local treatment of patients with OM NSCLC.
- Radiation may be preferable when treating multiple organ systems or when the clinical priority is to minimize breaks from systemic therapy.
- Upfront, definitive local treatment for symptomatic metastases.
- For asymptomatic patients with synchronous disease, investigators suggested at least 3 months of standard-of-care systemic therapy before starting definitive local therapy.

Pract Radiat Oncol. 2023;13(5):393-412.

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

Systematic Review

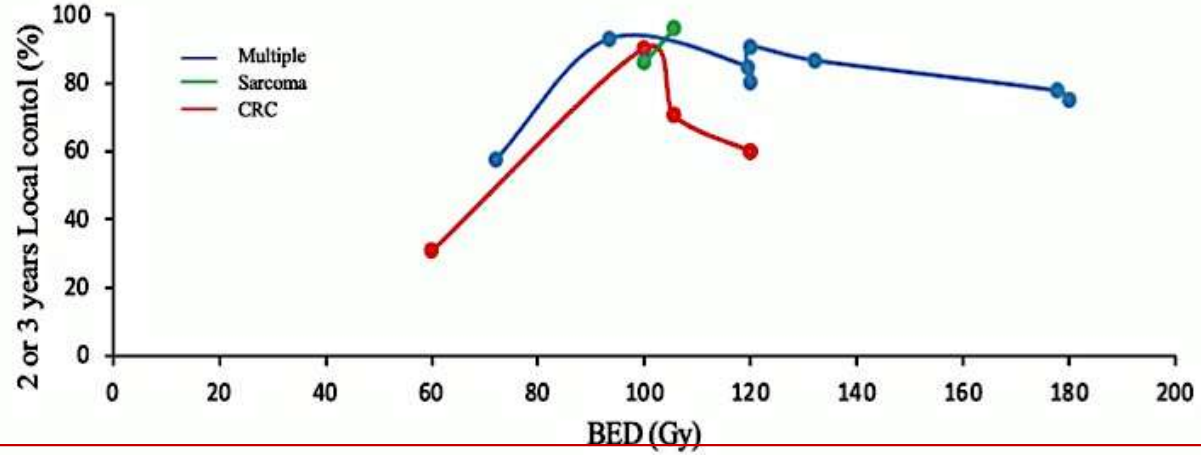
Stereotactic Body Radiotherapy for Patients with Lung Oligometastatic Disease: A Five-Year Systematic Review

Guillaume Virbel, Clara Le Fèvre, Georges Noël * and Delphine Antoni

cancers

Cancers 2021;13(14):3623.

- 5 years systematic review
- 2015 to 2020 published data analyzed
- 18 studies included (Retrospective studies)
- 1191 patients
- 1705 metastases were irradiated
- Diameter of tumor – 7mm to 124mm



Conclusions:

- SBRT is an efficient and well-tolerated treatment for lung metastases in oligometastasis
- Optimal treatment schedule is not definite.
- BED > 100 Gy, appear to be appropriate to obtain a LC comparable with that of surgery.

Dose schedules

		BED10 (Gy)	BED3 (Gy)
Peripheral	18Gyx3 (54Gy) 15Gyx3 (45Gy) 12Gyx4 (48Gy) 12Gyx5 (60Gy) 34 Gyx1 (34Gy)	151 112.5 105.5 132 150	378 270 240 300 419
In contact with the chest wall	11Gyx5 (55Gy) 10Gyx5 (50Gy)	115.5 100	257 270
Central	7.5Gyx8 (60Gy) 10Gyx5 (50Gy) 11.5Gyx5 (57.5Gy) 12Gyx5 (60Gy)	105 100 123.6 132	210 270 278 300
Ultracentral	7.5Gyx8 (60Gy) 8Gyx7 (56Gy) 60Gy/15#	105 101 84	210 205 140

Dose as per tumor site

- A dose and fractionation with BED of at least 100 Gy should be used
- Oligometastatic disease from colorectal cancer has been reported to fare better with higher BED10 of 132 Gy, compared to BED10 of <105.6Gy
- Adapting the SBRT dose based on metastasis histology is an area of clinical question with little data to create guidelines from.

Semin Radiat Oncol. 2023

Role of SBRT in liver metastasis

Liver metastasis

- Colorectal cancers commonly metastasize to the liver.
- Metastasectomy remains the gold standard for resectable liver metastases.
- SBRT is a recognized tool for ablation of liver metastases.
- SBRT is an option for unresectable disease and for medically inoperable patients.
- Tumor volume appears as an independent factor predictive of the local control of a tumor treated with SBRT

Factors associated with longer OS

- Certain histologies including breast, gynecological, lung adenocarcinoma metastases
- Smaller tumor volume
- Better performance status
- Absence of extrahepatic disease

Colorectal liver metastasis has been shown to be one of the most resistant primary histologies for liver SBRT.

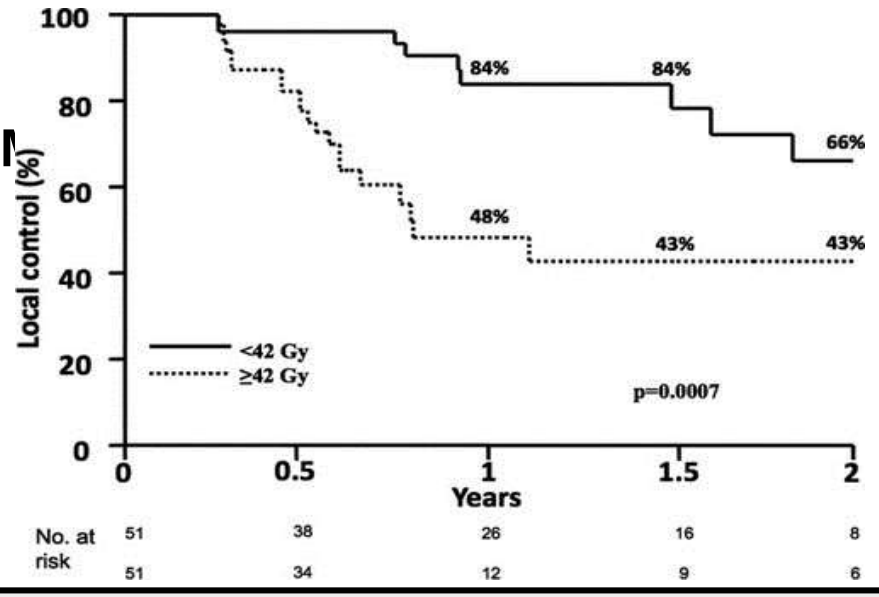
SABR for colorectal liver metastases requires higher biological effective doses to provide adequate local control.

Int J Radiat Oncol Biol Phys. 2016

Stereotactic Body Radiotherapy for Colorectal Liver Metastases

Daniel T. Chang, MD[1]; Anand Swaminath, MD[2]; Margaret Kozak, BA[1]; Julie Weintraub, MD[3]; Albert C. Koong, MD, PhD[1];

Pooled analysis
65 patients with 102 lesions treated from August 2003 to M
1 - 4 lesions
Received 1 - 6 fractions of SBRT
Radiological imaging 3 months post-treatment



Conclusion:

- **3-fraction regimen of SBRT of prescription dose of 48 Gy should be considered, if normal tissue constraints allow**
- **Patients without active extrahepatic disease have better OS than patients with active extrahepatic disease**

Cancer. 2011 Sep 1;117(17):4060-9.

Local Control Outcomes Using Stereotactic Body Radiation Therapy for Liver Metastases From Colorectal Cancer

Ji Hyeon Joo MD *, Jin-hong Park MD, PhD *, Jin Cheon Kim MD, PhD †, Chang Sik Yu MD, PhD †, Seok-Byung Lim

- 70 patients with 103 colorectal liver metastases
- 45 to 60 Gy in 3 to 4 fractions
- Median follow-up period was 34.2 months
- 2 years:OS (35%), PFS (75%)

2-year local control rates for biological equivalent dose

Group 1	</= 80 Gy	52
Group 2	100 - 112	83
Group 3	>/= 132	89

- **Longer local control can be expected if higher doses are used**
- **SBRT of liver metastases derived from colorectal cancer offers a locally effective treatment without significant complications**

Int J Radiat Oncol Biol Phys. 2017

Clinical Investigation

The Dutch—Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases

- Most common primary tumor origin was colorectal cancer (80.3%), followed by lung cancer (8.9%) and breast cancer (4%).
- The most-used fractionation scheme was 3x18-20 Gy (36.0%), followed by 8x7.5 Gy (31.8%), 5x11-12 Gy (25.5%), and 12x5 Gy (6.7%).
- Actuarial 1-year local control was 87%; 1-year overall survival was 84%.
- Toxicity of grade 3 or greater was found in 3.9% of the patients.

This multi-institutional study confirms the high rates of local control and limited toxicity in a large patient cohort.

Int J Radiat Oncol Biol Phys. 2021

Prospective studies

Author	Number of patients/metastases	% colorectal primary	Total dose/fractionation	Local control	Local control for CLMs	Overall survival
Folkert et al. 2021 [28••]	33/39	45.5%	30–40 Gy/1 fraction	96.4%, 4 yr	NRP	49.7%, 4 yr
Romero et al. 2020 [23]	515/668	80.3%	60 Gy/12 fractions 60 Gy/8 fractions 55–60 Gy/5 fractions 54–60 Gy/3 fractions	68%, 3 yr	68%, 3 yr	44%, 3 yr
Scorsetti et al. 2018 [27••]	61/76	47.5%	52.5–75 Gy/3 fractions	78%, 5 yr	75%, 5 yr	18%, 5 yr
McPartlin et al. 2017 [29]	51/93	100%	22.7–62.1 Gy/6 fractions	26%, 4 yr	26%, 4 yr	9%, 4 yr
Hong et al. 2017 [30••]	89/143	35.7%	30–50 Gy/5 fractions, protons	61.2%, 3 yr	44.7%, 3 yr	20.8%, 3 yr

Dose

Key considerations include tumor histology, number of lesions, and the size of lesions

Dose escalation above a BED10 of 100 Gy may result in improved LC in liver metastases (3-year local control 93% vs. 65%)
1-6 fractions with 3-5 fractions being the most commonly used regimens

Where a maximized local control probability is a priority, a BED of 100 Gy10 or greater to the PTV should be selected.
Second, the fractionation should be selected to respect dose constraints to the following OARs in decreasing priority: luminal gastro-intestinal (GI) tract (stomach, duodenum, small intestine, and large intestine), central biliary tree, chest wall and the liver (typically non-cirrhotic in oligometastatic patients).

Dose

- The dose required for a favorable result of the radiotherapy treatment

➢24–30 Gy in a single dose,

➢45–54 Gy in 3 fractions,

➢40–50 Gy in 5 fractions,

➢48–60 Gy in 6 fractions

- Dose of 45 to 54 Gy in three fractions for peripheral tumors limited in size and number and away from sensitive organs
- Higher range doses particularly used for metastases from colorectal carcinoma, renal cell carcinoma, or melanoma.
- For larger tumors more centrally located or near the bowel, esophagus, stomach, or heart, a dose of 40 to 50 Gy in five fractions is typically used

QUANTEC recommendations

The Quantitative Analysis for Normal Tissue Effect in the Clinic (QUANTEC) liver report has recommended :

- 13 Gy (3 fractions) and 18 Gy (6 fractions) as MLD limits for primary disease
- 15 Gy (3 fractions) and 20 Gy in (6 fractions) as MLD limits for metastatic lesions.

QUANTEC-recommended MLD limits would likely result in acceptable grade 3 liver enzyme toxicity risks (<20% probability).

Int J Radiat Oncol Biol Phys. 2021 May 1;110(1):196-205.

Table 4 Compilation of recommended dose constraints for liver SBRT[80,82,83]

Structure	Metric	One fraction	Three fractions	Five fractions	Fifteen fractions	End point
Uninvolved liver, noncirrhotic	Dmean		12-15 Gy	13-18 Gy	24 Gy	Grade 3+ liver function dysfunction Radiation-induced liver disease (classic or non-classic)
	D≥700cc	9.1-11.6 Gy	15-19 Gy	15-21.5 Gy	30 Gy	
Kidney cortex	Dmean		8.5 Gy	10 Gy		Grade 3+ renal dysfunction
	D≥200cc	8.4-9.5 Gy	14.7-16 Gy	17.5 Gy	24 Gy	
If solitary kidney	V10Gy	33%	33%	10-45%		
Renal hilum/vascular trunk	D15cc	14 Gy	19.5 Gy	23 Gy	37.5 Gy	Malignant hypertension
Esophagus†	Dmax	24 Gy	32.4 Gy	38 Gy	54 Gy	Grade 3+ stenosis/fistula
	D0.1cc	15.4-20 Gy	25.2-27.9 Gy	35 Gy		
	D5cc	15.4-20 Gy	25.2-27.9 Gy	32.5 Gy	45 Gy	
Stomach	Dmax	22 Gy	22-30 Gy	32-35 Gy	42-51 Gy	Grade 3+ ulceration/fistula
	D0.1cc	12.4-17.4 Gy	22-22.5 Gy	33-35 Gy		
	D5cc	12.4-17.4 Gy	22-22.5 Gy	26.5 Gy		
	D10cc	11.2 Gy	16.5 Gy	18-25 Gy		
	D50cc			12 Gy	39 Gy	
Duodenum†	Dmax	22 Gy	22-30 Gy	32-35 Gy	45-51 Gy	Grade 3+ ulceration
	D0.1cc	12.4-17.4 Gy	22-22.2 Gy	32-35 Gy		
	D5cc	12.4-17.4 Gy	16.5-22.5 Gy	18-26.5 Gy	39 Gy	
	D10cc	9 Gy	11.4 Gy	25 Gy		
Small bowel†	Dmax	20 Gy	25-28.5 Gy	32-34.5 Gy	45-46.5 Gy	Grade 3+ enteritis/obstruction
	D0.1cc	15.4-17.6 Gy	25.2 Gy	30-35 Gy		
	D5cc	11.9-17.6 Gy	17.7-20.7 Gy	19.5 Gy		
	D30cc	11.9-17.6 Gy	17.7-20.7 Gy	24 Gy		
	D120cc				39 Gy	
Large bowel†	Dmax	31 Gy	28-45 Gy	34-52.5 Gy	45-47 Gy	Grade 3+ colitis/fistula
	D0.1cc	18.4-20.5 Gy	24-28 Gy	34-38 Gy		
	D20cc	18.4-20.5 Gy	24-28 Gy	25-32.5 Gy	47 Gy	
Central bile ducts	Dmax	30 Gy	35.7-50 Gy	40.5-50 Gy		Stenosis
Heart	Dmax	22 Gy	30 Gy	38 Gy	48.9 Gy	Grade 3+ pericarditis
	D0.1cc	22 Gy	26-30 Gy	29-38 Gy		
	D15cc	16 Gy	24 Gy	29-32 Gy	42 Gy	
Great vessels	Dmax	37 Gy	45 Gy	53 Gy	65 Gy	Grade 3+ aneurysm
	D0.1cc	30-31 Gy	45 Gy	53 Gy		
	D10cc	30-31 Gy	39 Gy	47 Gy	57 Gy	
Skin	Dmax	27.5 Gy	33 Gy	38.5-39.5 Gy	57 Gy	Grade 3+ ulceration
	D0.1cc	26 Gy	33 Gy	38.5-39.5 Gy		
	D10cc	23-25.5 Gy	30-31 Gy	36.5 Gy	54 Gy	
Rib	Dmax	33 Gy	50 Gy	57 Gy		Pain or fracture
	D5cc	28 Gy	40 Gy	45 Gy		
Spinal Cord	D0.035cc	12.4-14 Gy	20.3-23.1 Gy	25.3-28 Gy	42 Gy	Radiation myelopathy
	D0.35cc	10 Gy	15.9 Gy	22 Gy	39 Gy	

Role of stereotactic body radiation therapy in liver metastasis: A pilot study from tertiary cancer institute in India

15 patients enrolled in this study from November 2014 to October 2015.
Patients having 1–3 liver metastasis
Dose prescribed was 36 Gy in 3#

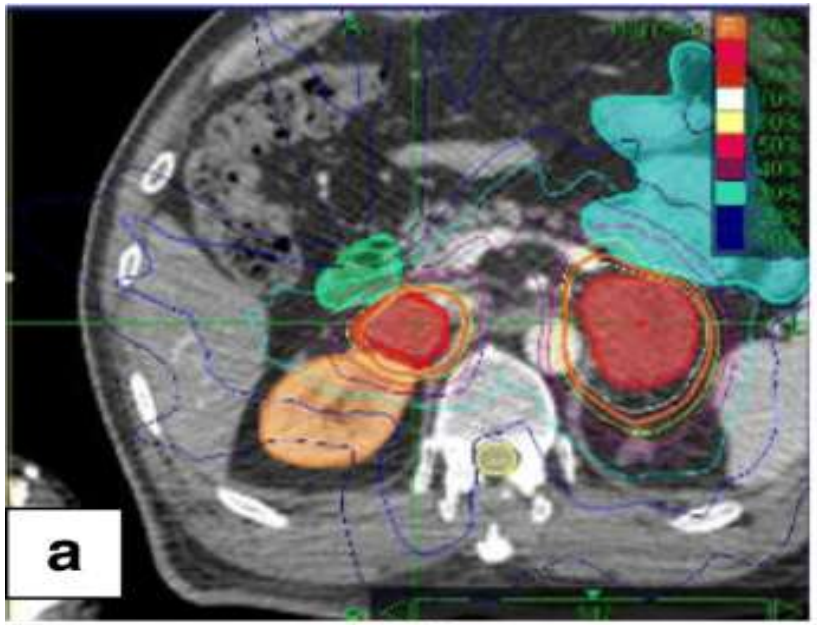
Out of 20 assessable lesions, 16 were controlled.
The actuarial LC was 77% at 6 months post SBRT.
The median PFS was 7 months.
Two patients experienced Grade 2 GI toxicity.

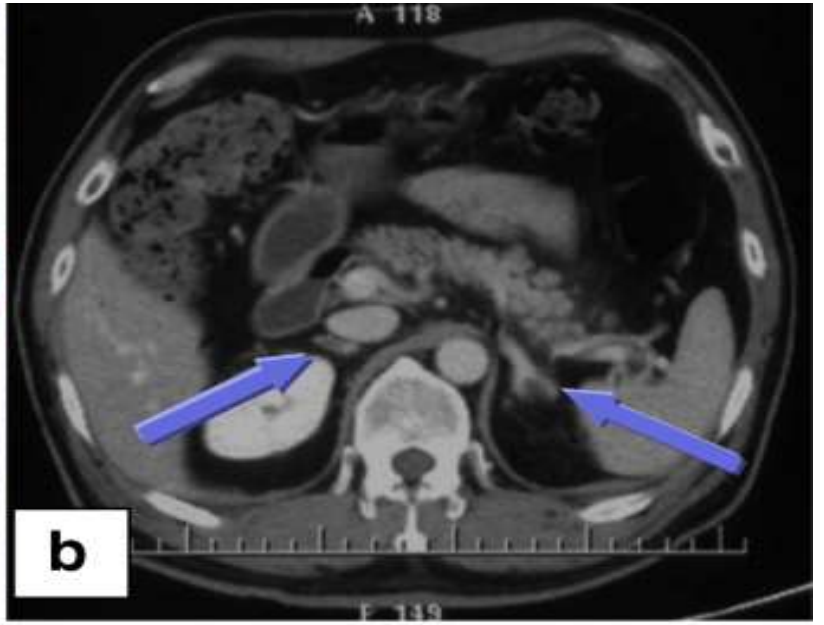
J Can Res Ther 2019;

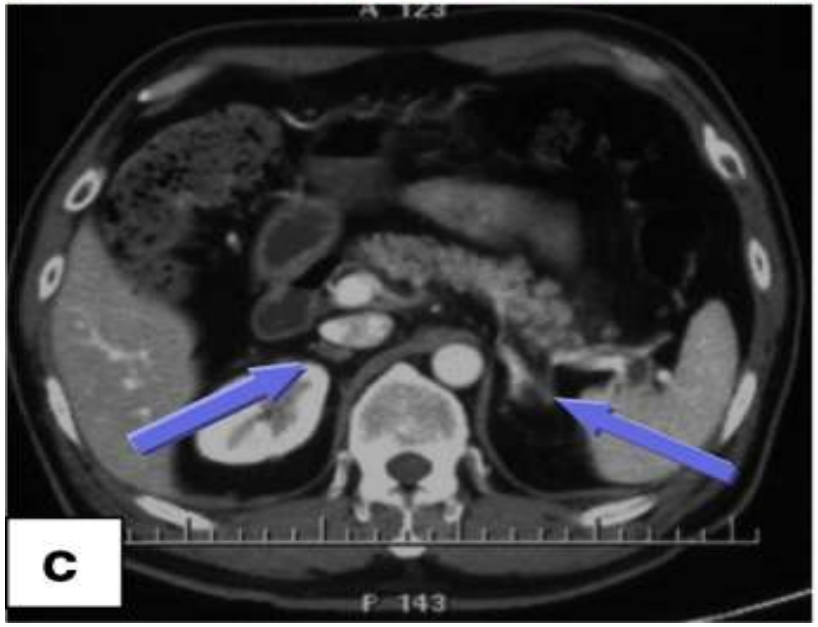
Role of SBRT in adrenal metastasis

Adrenal metastasis

- Adrenal glands - common site of metastases from lung cancer, breast cancer and melanoma.
- Surgical resection is considered the standard of care,
- SBRT represents a promising treatment for oligometastasis
- A BED10 > 72 Gy and the use of 4DCT for motion control should be considered for a high quality ablative treatment
- 3 prospective trials – Ahmed et al (45Gy/5#, BED10 – 85.5Gy), Franzese et al (45Gy/3# - BED10-112.5Gy) , Rudra et al (36Gy/3#- BED10 – 79.2Gy).







To contour the target volume, available diagnostic imaging including PET-CT, CT, and/or MRI should be fused with the CT acquired at the time of simulation

Clinical Investigation

Stereotactic Body Radiation Therapy of Adrenal Metastases: A Pooled Meta-Analysis and Systematic Review of 39 Studies with 1006 Patients

The pooled 1- and 2-year rates of LC were 82% and 63% respectively, and the pooled 1- and 2-year overall survival rates were 66% and 42%
The overall rate of CTCAE grade 3 or higher toxicity was 1.8%

	60 Gy	**80 Gy**	**100 Gy**
1 year LC	70.5%	84.8%	92.9%
2 year LC	47.8%	70.1%	85.6%

Int J Radiat Oncol Biol Phys. 2020

Dose schedules

Dose used for abdominopelvic tumors in NRG-LU002, which include adrenal metastases, was 45 Gy in 3 fractions (BED10 112.5 Gy).

SABR-COMET used a dose of 60 Gy in 8 fractions (BED10 108 Gy) for adrenal metastases

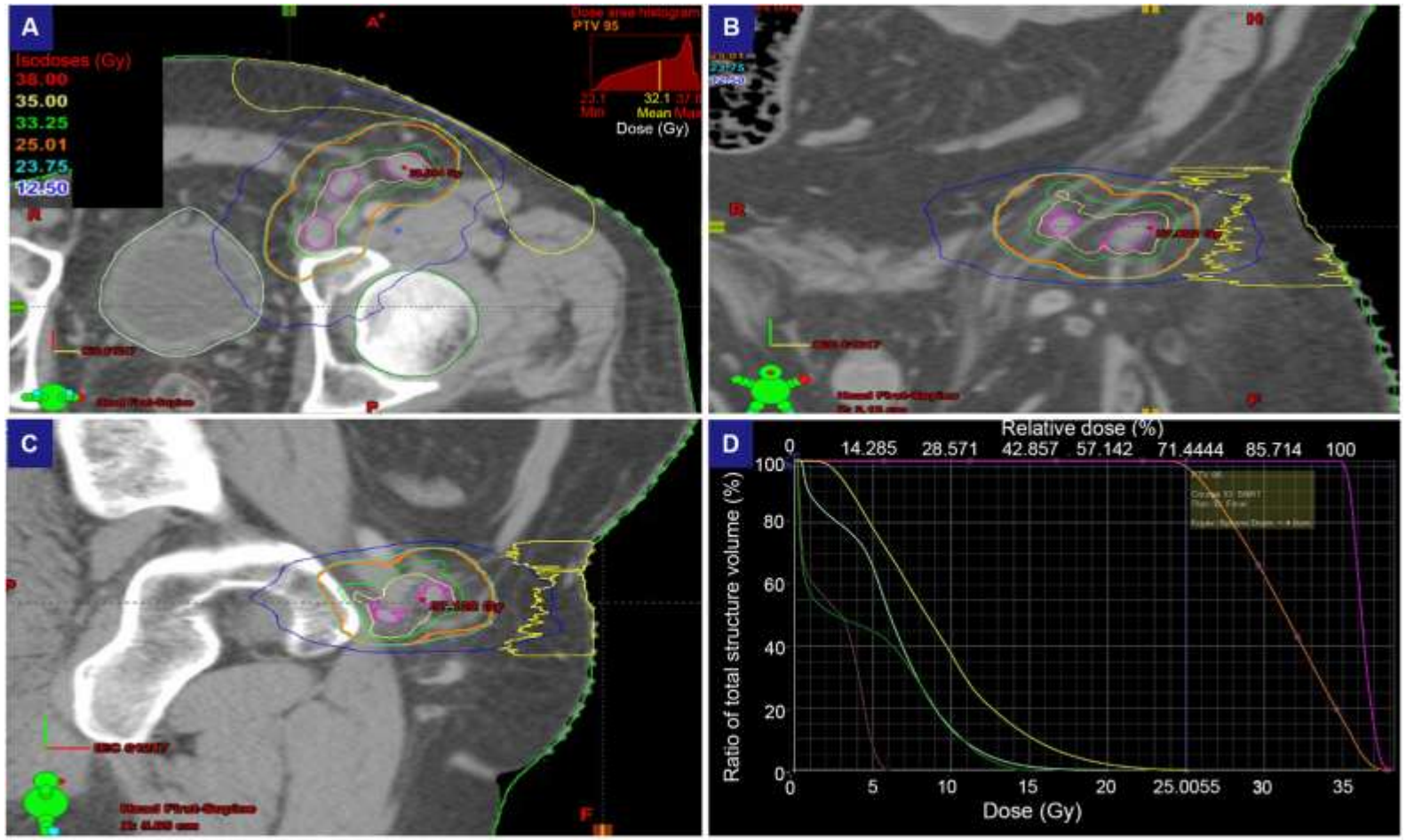
45 Gy delivered in three to five fractions with a decreased dose of 42 Gy

in three fractions if dose-limiting toxicities are expected

Role of SBRT in lymph node metastasis

Oligometastasis in Lymph nodes

- SBRT for oligometastases in lymph nodes is relatively safe and effective, particularly in cases in which the primary cancer was breast, gynecological, or prostatic cancer.
- Its incidence after curative treatment is very variable, from 7 % in prostrate tumors up to 15–20 % in colorectal and gynecological tumors.
- Because of their localization, the doses administered in SBRT of the affected lymph nodes are lower than in the SBRT of lung or liver lesions.
- Severe complications are rare, with the thorax being the most challenging site showing a grade ≥ 3 toxicity of 2.0%.



DVH line	Structure	Volume, cm^3	Min dose, Gy	Max dose, Gy	Mean dose, Gy
	GTV	3.6	34.66	38.28	36.26
	PTV	62.6	22.73	38.28	31.24
	Skin strip	80.5	0.90	25.28	8.98
	Left femur head	118.6	0.12	15.32	4.49
	Rectum	28.5	0.20	6.15	2.54

Asian J Urol. 2023 Jan;10(1):109-112.

Dose

- Four-dimensional CT (4DCT) and respiratory gating
- ITV margin must be determined using 4D-CT, especially for abdominal lymph nodes.
- Mobility of adenopathies at the paraaortic level has been estimated as an average of 3.8 mm craniocaudal displacement, and which was less on other axes.
- Total doses of 30–60 Gy in 5–8 fractions were proposed for mediastinal lymph node SBRT, with the spinal cord, esophagus, heart and proximal bronchial tree being the dose limiting OARs.
- Total doses ranged from 27 to 45 Gy in 3-5 fractions, for abdominal lymph nodes, with dose limiting OARs being the liver, kidneys, bowel and bladder.

Systematic review of stereotactic body radiotherapy for nodal metastases

Francesco Deodato[1] · Gabriella Macchia[1] · Milly Buwenge[2,3] · Mattia Bonetti[3] · Savino Cilla[4] · Alice Zamagni[2] · Alessia Re[1] · Donato Pezzulla[1] · Francesco Cellini[5] · Lidia Strigari[6] · Vincenzo Valentini[5,7] · Alessio G. Morganti[2,3]

Pooled 2-year LC reported in 11 studies was 79.3%
Pooled 2-year PFS reported in 8 studies was 35.9%

Clin Exp Metastasis. 2021

Stereotactic body radiotherapy of lymph node metastases under MR-guidance: First clinical results and patient-reported outcomes

Patients with lymph node metastases treated with MRguided SBRT

Median dose was 27 Gy in three fractions, prescribed to the 80% isodose.
At 1-year, estimated LC, PFS and OS were 92.6, 67.4 and 100.0%.

Strahlenther Onkol (2022)

Future directions

Future directions

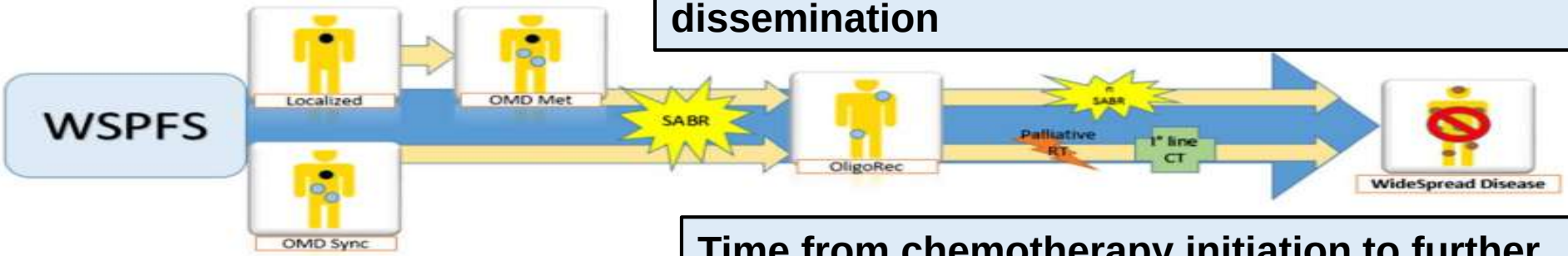
- Identifying biological factors associated with oligometastasis pattern
- Stratifying strategies according to these biological factors
- Better define oligometastatic disease for every clinical setting
- Conducting phase III trial with appropriate follow-up
- Combination of local treatment with systemic treatment

Biology based dosing

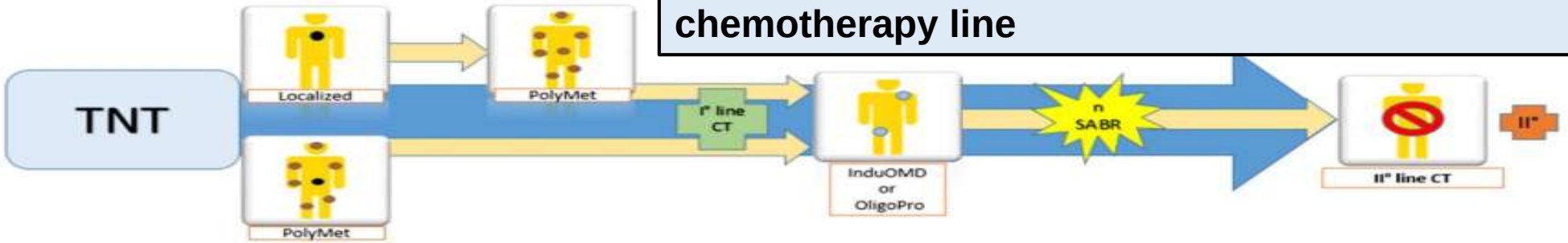
Novel end points

Time from first ALT to systemic treatment or best supportive care

Time from oligometastatic presentation to metastatic dissemination

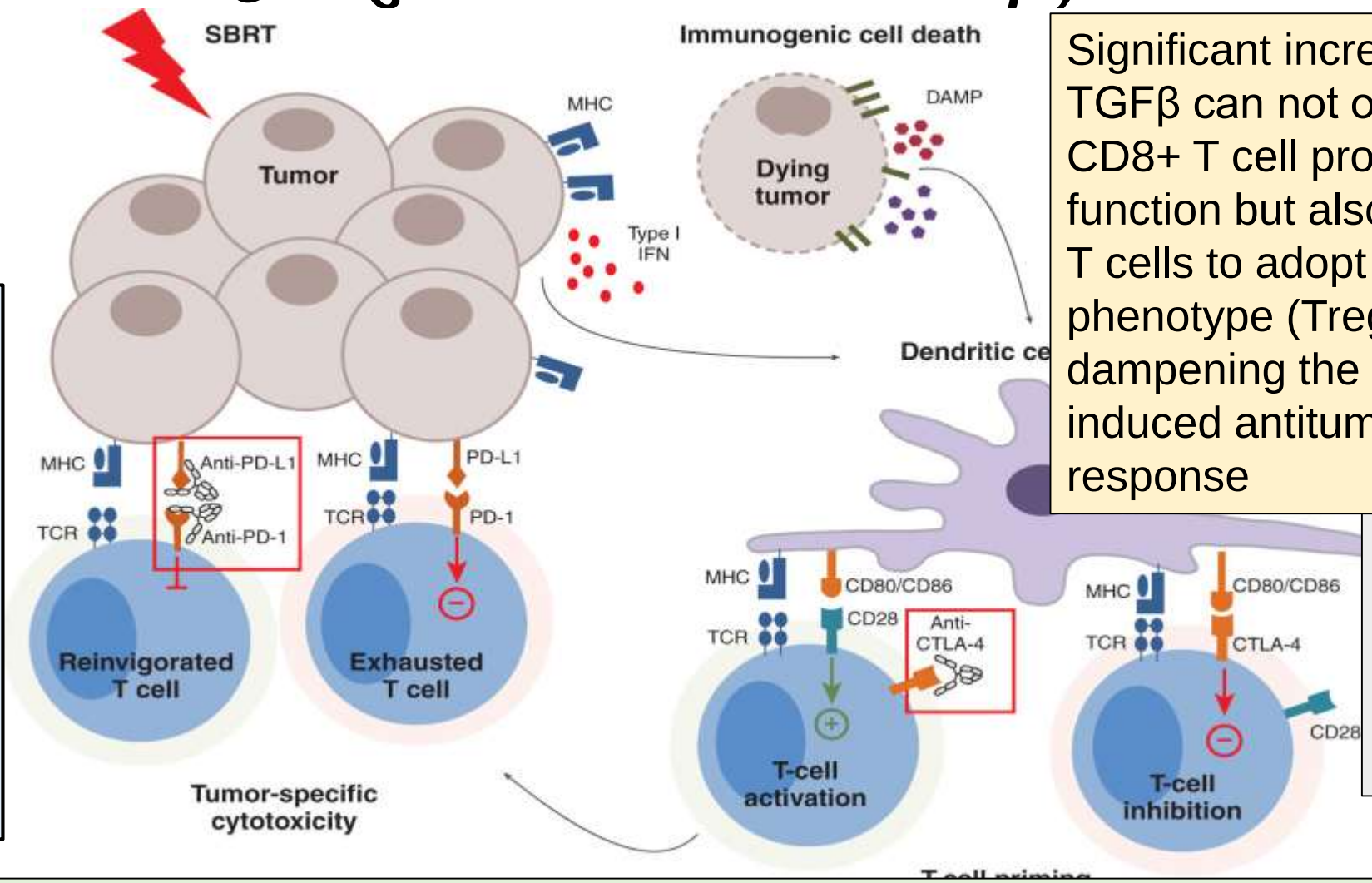


Time from chemotherapy initiation to further chemotherapy line



SBRT and Immunotherapy

The enhanced PD-L1 expression induced by SBRT could make patients more susceptible to subsequent PD-1/PD-L1 inhibitors



Significant increase in TGFβ. TGFβ can not only affect CD8+ T cell proliferation and function but also induce CD4+ T cells to adopt a regulatory phenotype (Treg), thus dampening the radiation-induced antitumor immune response

CTLA4 can compete with CD80/86 and inhibit T cell activation

SBRT can promote the release of TAAs, which further induces DC maturation, the cross-priming of CTLs, and lymphocyte recruitment to tumors, thus converting immunologically “cold” tumors to “hot” tumors

Take home messages

- OM represents a “spectrum of disease” containing different tumors, at different stages, with different biologic hallmarks and therefore with different prognosis.
- As a general practical guide to SBRT prescription, based on the available evidence treatments can be delivered reaching a BED10 of at least 100 Gy, provided that normal tissues tolerance is not exceeded.
- However lower BED should not preclude the opportunity to attempt a MDT approach to all sites of OMD.

Stereotactic body radiation therapy demonstrated high local control rate and increased survival outcomes in this setting with a low rate of toxicity

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- Dr Arun S Oinam
- Dr Ranjith Singh
- Residents
- Technologists
- All patients

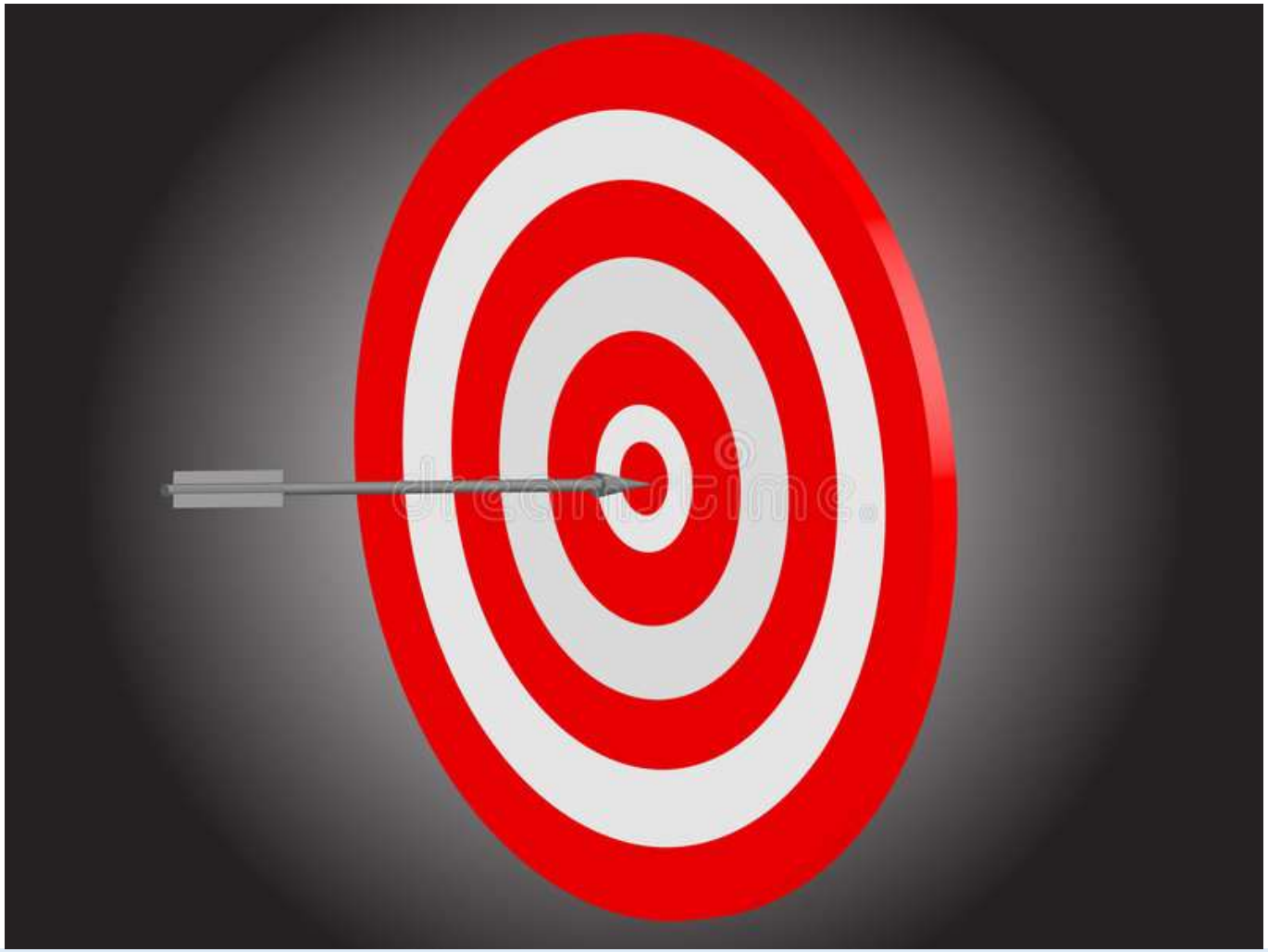
A phase 2 study of SBRT in extracranial oligometastatic disease and its impact on overall survival and quality of life (SBRT-ECOMD)

Department of Radiotherapy and Oncology, PGIMER (2022 onwards)

Ongoing

Number of patients to be recruited – 50
Patients treated – 25
Number of lesions treated – 32
Liver – 13
Lung – 8
Lymph nodes – 3
Bone - 8

Primary
Colorectal – 11
Lung – 5
Esophageal - 2
RCC – 2
Pancreas -2
Cholangiocarcinoma – 1
Thyroid – 1
Sarcoma - 1



Thank you