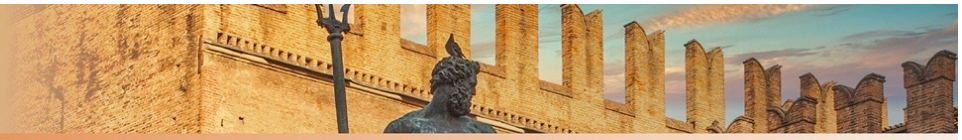
Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

La gestione dei pazienti candidati a radioterapia ablativa nella malattia oligometastatica

Prof Marta Scorsetti

Associazione Italiana Radioterapia e Oncologia clinica
Società Italiana di Radiobiologia

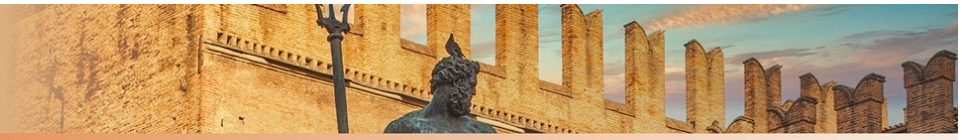


DICHIARAZIONE

Relatore: Marta Scorsetti

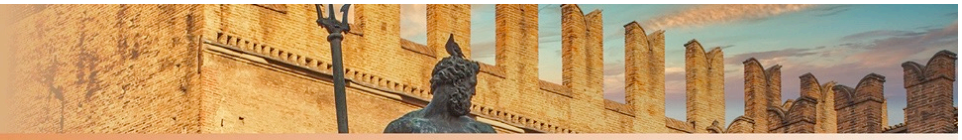
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Seagen)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(Brainlab, Varian, HEALTH4U,Sofar, Ipsen)**
- Partecipazione ad Advisory **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



OUTLINE

- Identification of oligometastatic patient
- SBRT rationale in oligometastatic patient
- Technical issues of RT
- Integration RT-drugs
- Follow up and patient management



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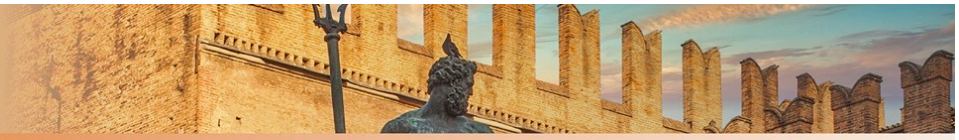

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theo
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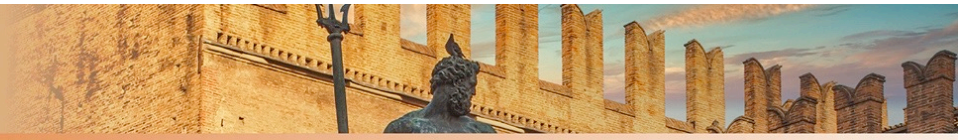
pothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there

mation, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding

An oligometastatic state is an "**intermediate state between purely localized lesions and those widely metastatic**". The state was expounded to be "**amenable to a curative therapeutic strategy**" and "**amenable to localized therapy**".

Hellman S, Weichselbaum RR. JCO 1995



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

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]

Guckenberger M et al. Lancet Oncol 2020
Lievens Y et al. RO 2020

2022

Consensus

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

Conclusion: While significant heterogeneity exists in the current OMD definitions in the literature, consensus was reached on multiple key questions. Based on available data, OMD can to date be defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable. Consistent definitions and reporting are warranted and encouraged in ongoing trials and reports generating further evidence to optimize patient benefits.

There are currently no validated biomarkers that differentiate between the oligometastatic and the polymetastatic state.

Lievens Y et al. RO 2020

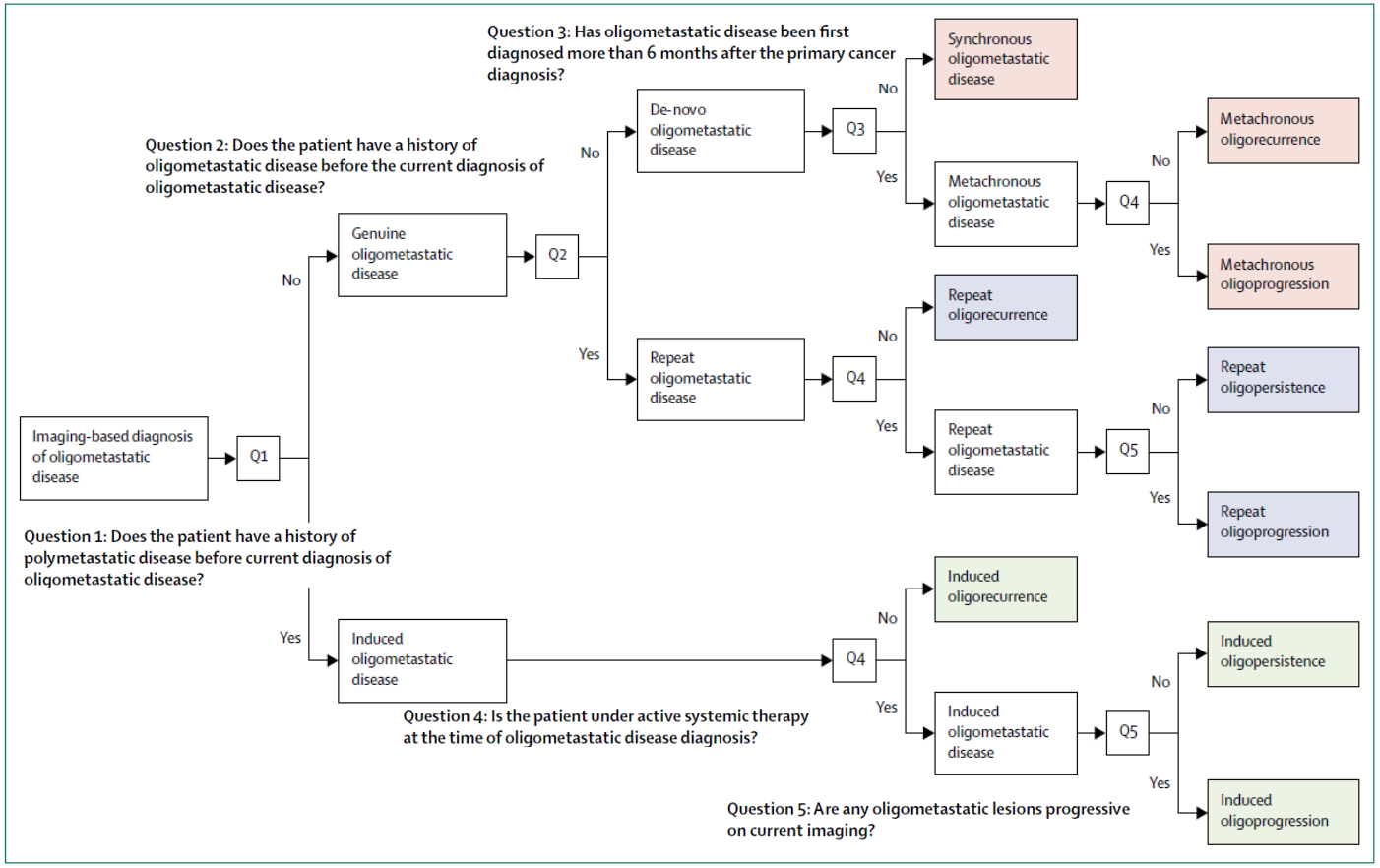
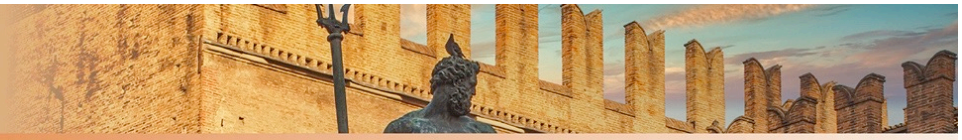
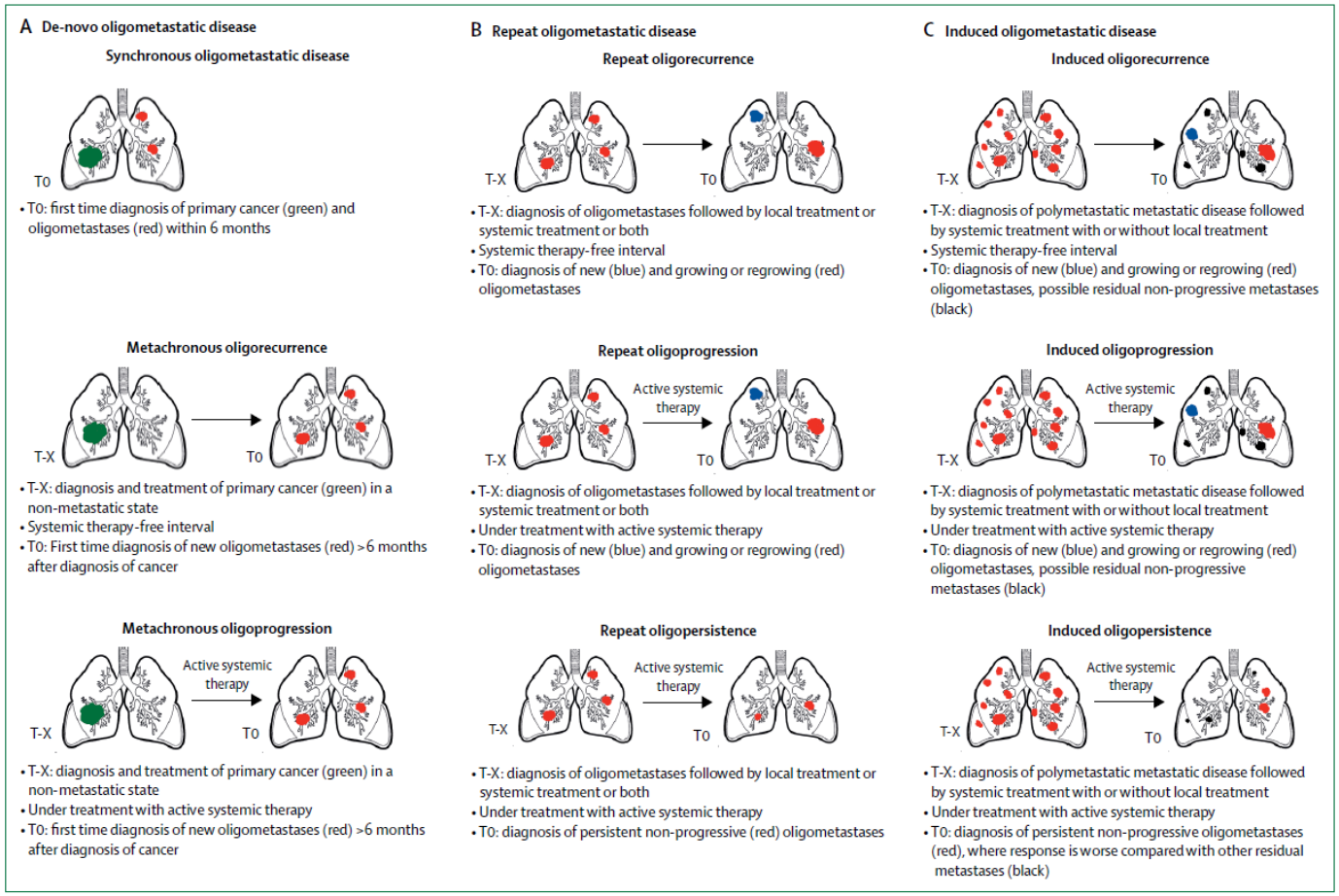


Figure 3: Decision tree for classification of oligometastatic disease

Guckenberger M et al. Lancet Oncol 2020





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

Oligometastases are a heterogeneous scenario

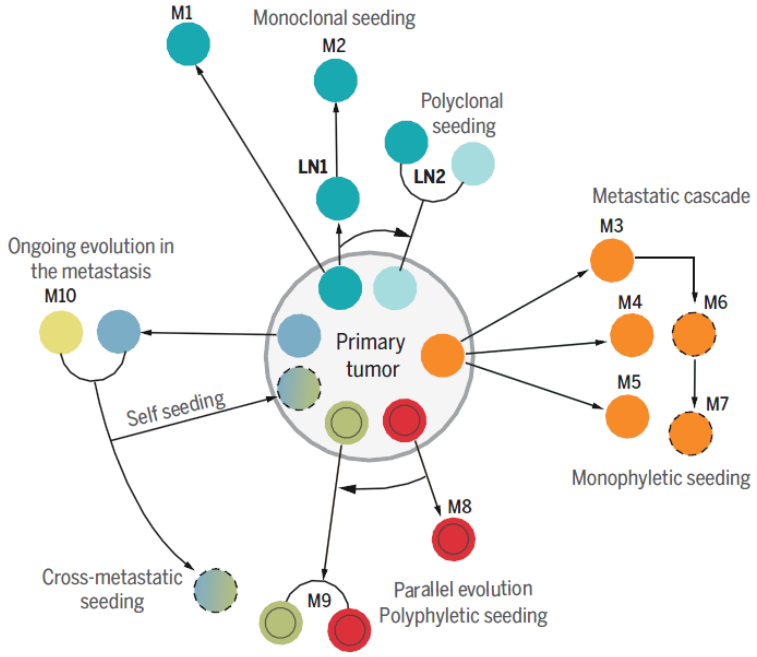
Guckenberger M et al. Lancet Oncol 2020

REVIEW

Metastasis as an evolutionary process

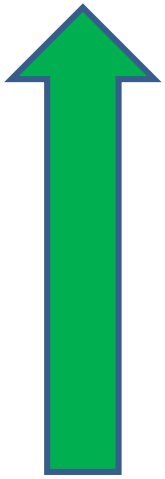
Samra Turajlic[1,2] and Charles Swanton[1,3]*

Very complex reality



Palma D, WCLC 2018

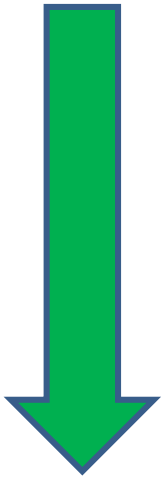
Easily accessible



Difficult availability

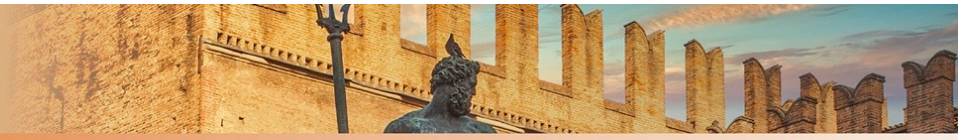
- Clinical
- Imaging
- Genetic/epigenetic

Less informative



Highly informative

The multidisciplinary evaluation is crucial in absence of reliable biomarkers



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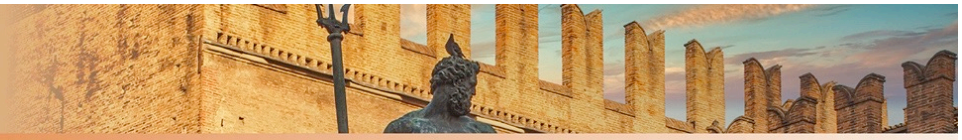
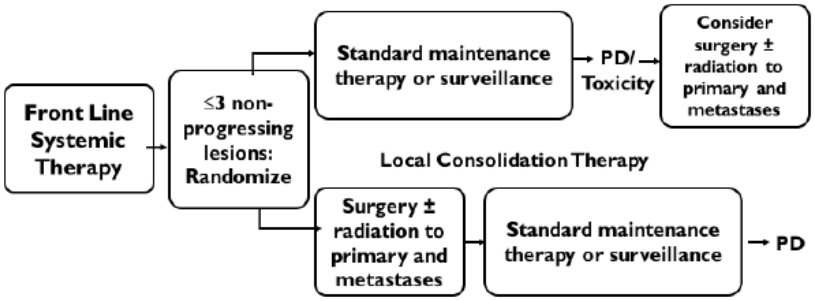
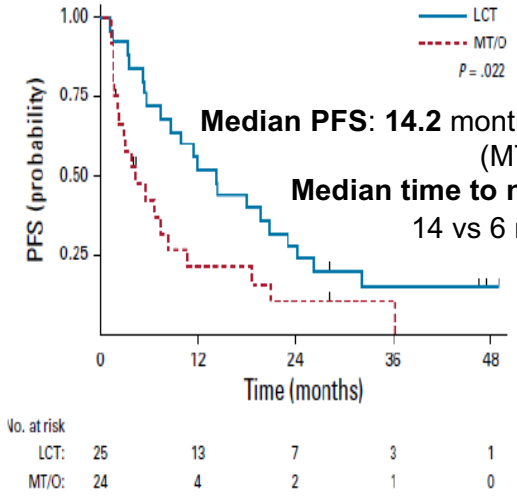


- **Increase local control** to prevent symptoms and maintain **quality of life**
- Ablate all visible metastases to **prolong PFS**
- Reduce tumor burden to **prolong OS**
- Ablate resistant clones to **prolong systemic therapy efficacy**
- Delay further disease progression to **delay the need to start systemic therapy**
- **Synergize with systemic therapies** to improve outcomes

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

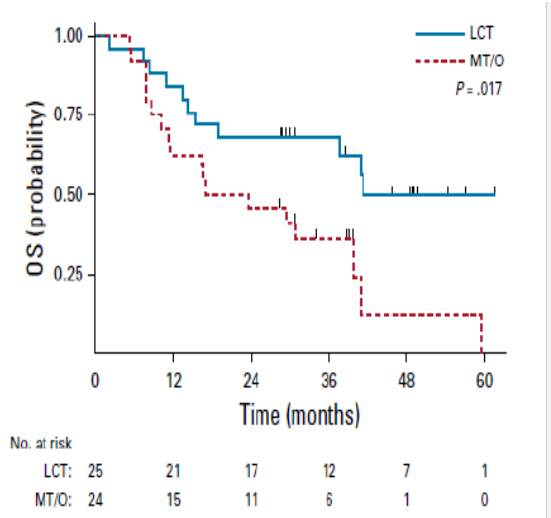




Median PFS: **14.2** months (LCT) vs 4.4 months (MT)

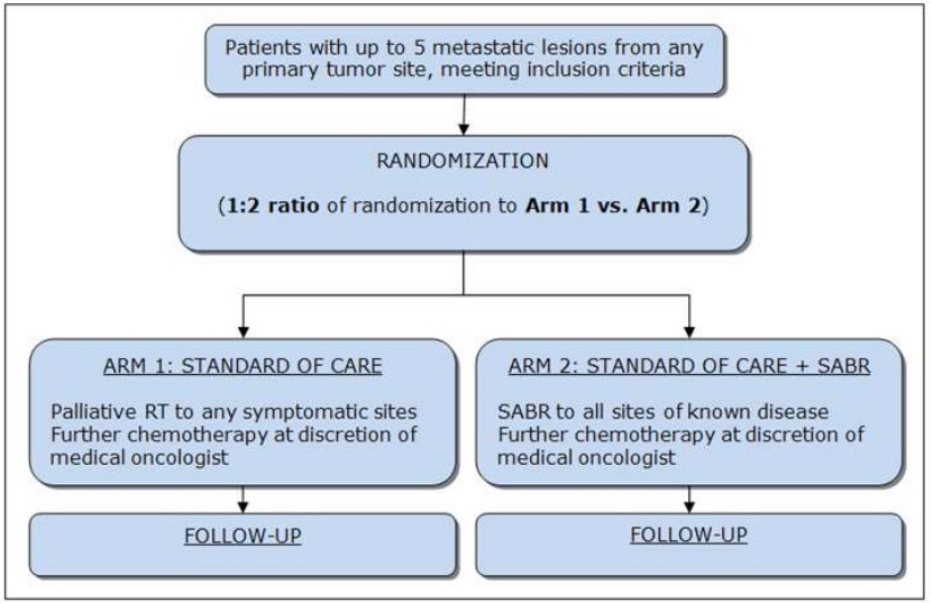
Median time to new metastases
14 vs 6 months

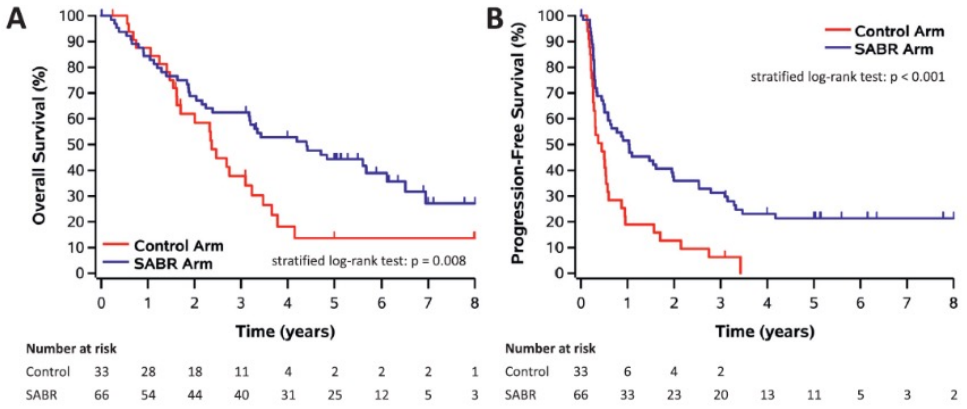
Median OS: **41.2** (LCT) vs 18.9 months (MT)
4 years OS: 50%



Gomez D et al. JCO 2019

Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes





8-year OS 27.2% vs 13.6%

8-year PFS 21.3% vs 0.0%

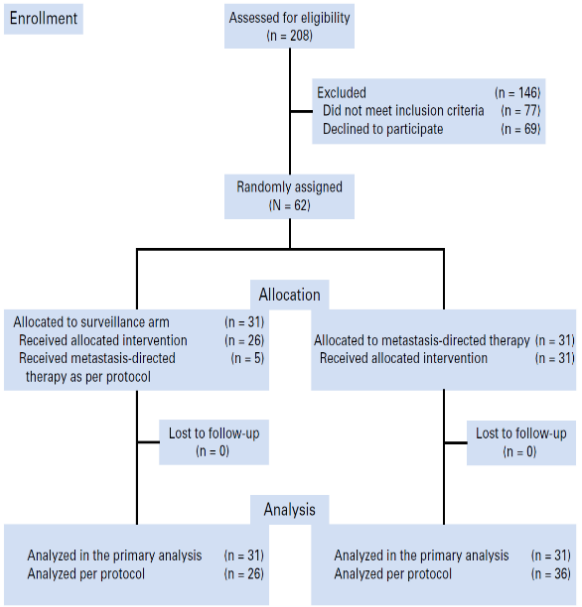
Palma D. ASTRO 2018
Harrow S et al., IJROPB 2022

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

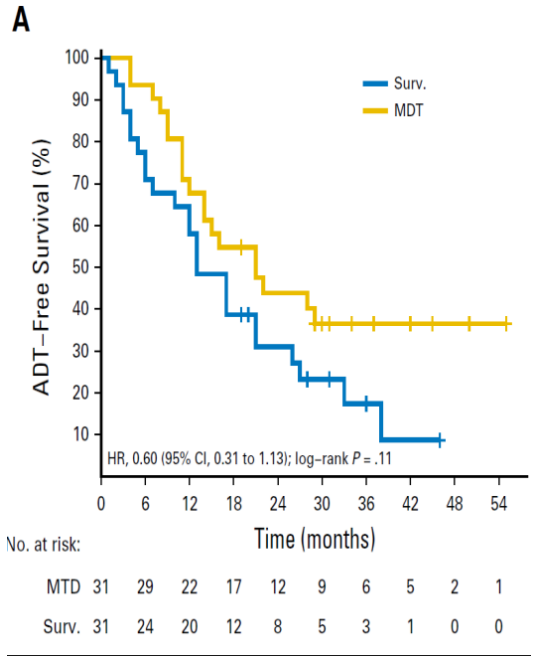
Phase II randomized trial

Patients with PCa with up to 3 metastases randomly assigned (1:1) to s**urveillance or local therapy** of all detected lesions (surgery or stereotactic body radiotherapy).

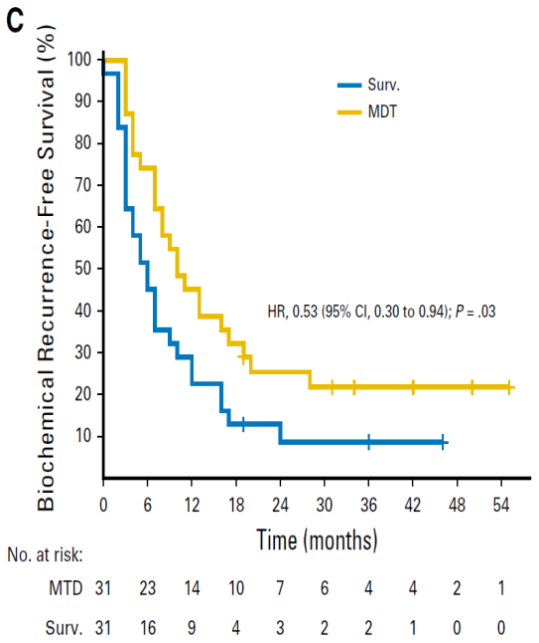
The primary end point was androgen deprivation therapy (ADT)–free survival.



Ost P et al JCO 2018

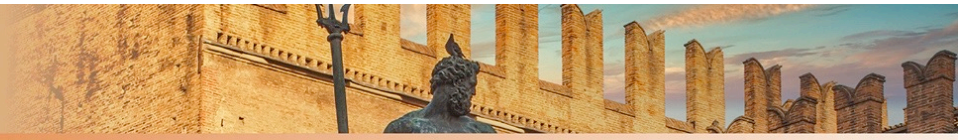


Median ADT-free survival was 21 vs 13 months



The median time until PSA progression was 10 vs 6 months

Ost P et al JCO 2018



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SBRT is safe, well studied and effective, but…

There are still many things to learn

Single-isocenter versus multiple-isocenters for multiple lung metastases: Evaluation of lung dose

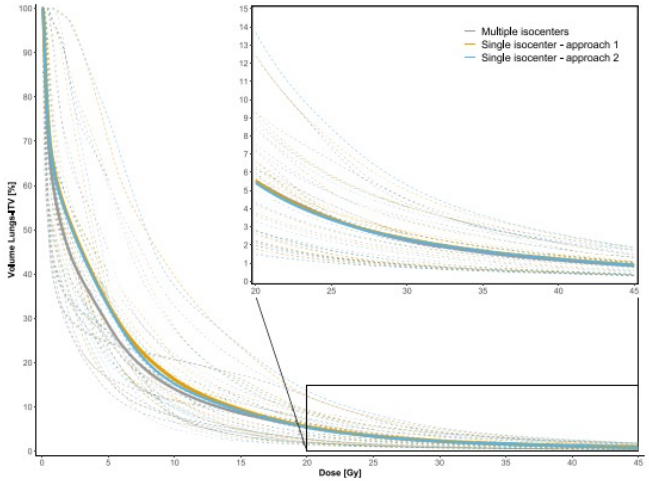
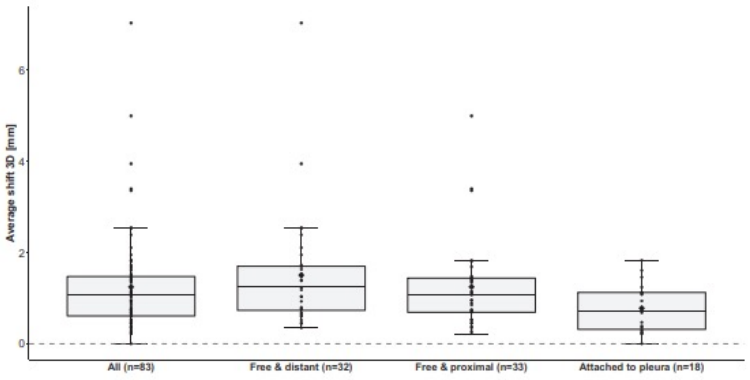


Fig. 2. Dose-volume histograms (DVHs) for all patients and all plans generated with full arcs, with the population-mean DVHs represented in bold.

A median (acceptable) increase in MLD and V20 with single-isocenter treatment plans compared to multiple isocenters. V20Gy

Margin calculation for multiple lung metastases treated with single-isocenter SBRT



Relative inter-lesion position variation is influenced by inter-target distance and location and can be compensated with additional safety margins of < 1 mm using single-isocenter SBRT

Technical research is ongoing for multiple SBRT in lungs

van Timmeren JE et al RO 2022
van Timmeren JE et al RO 2021

Long-term cancer survivors treated with multiple courses of repeat radiation therapy

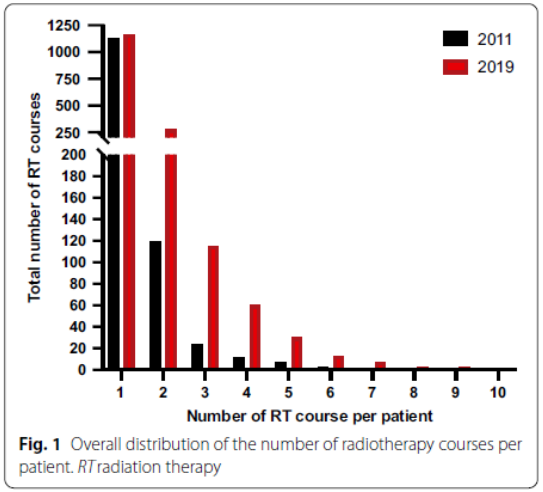
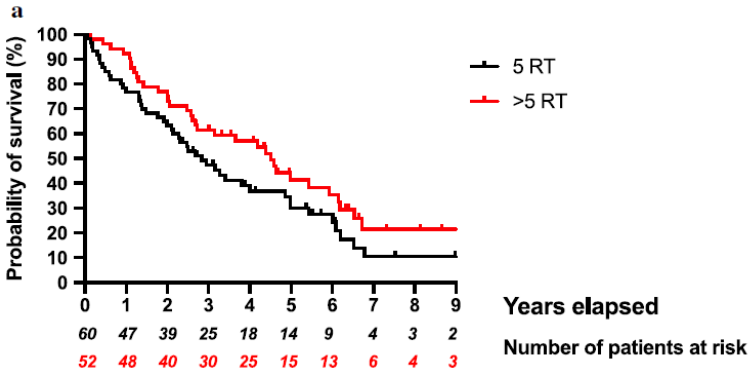


Fig. 1 Overall distribution of the number of radiotherapy courses per patient. *RT* radiation therapy



Oligometastases are not a single "once in a life" moment

Christ SM et al. Radiat Oncol 2021

Stereotactic body radiotherapy (SBRT) for multiple pulmonary oligometastases: Analysis of number and timing of repeat SBRT as impact factors on treatment safety and efficacy

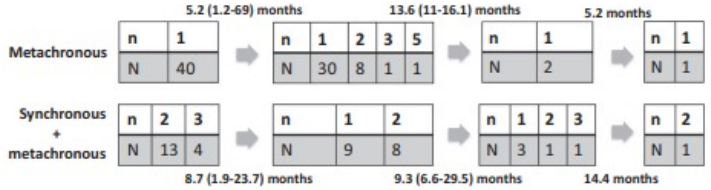
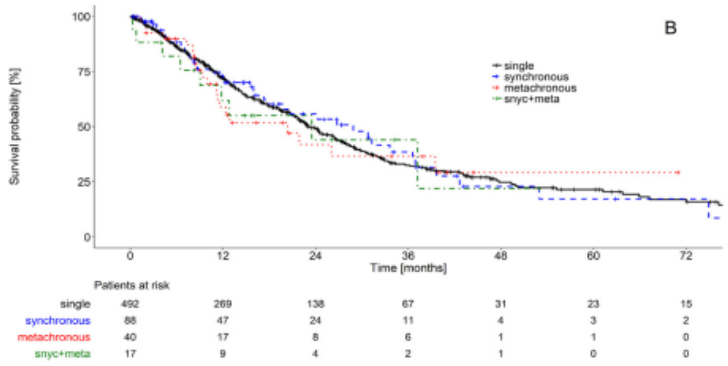


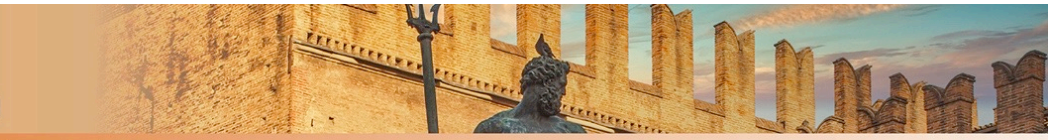
Fig. 1. Timing and treatments of repeat SBRT in the two patient groups receiving metachronous treatments. Each table represents one SBRT course and displays the number of patients (*N*) that were treated for a total of *n* metastases within that course.



OS was not significantly influenced by the overall number of SBRT treatments or the number and timing of repeat SBRT courses.

The risk of early death within 3 and 6 months was not increased in patients treated with multiple SBRT treatments, and no grade 4 or grade 5 toxicity was observed in these patients

Klement RJ et al RO 2018



Clinical Investigation

A Multi-Institutional Retrospective Study of Repeated Stereotactic Body Radiation Therapy for Intrahepatic Recurrent Hepatocellular Carcinoma

Repeated SBRT (n = 81 patients with 189 lesions)
- ≤2 HCC nodules, each up to 50 mm in diameter (T1–2 UICC7th)
- Child–Turcotte–Pugh (CTP) Class A or B
- Inoperable because of poor general condition or surgery refusal
- Unsuitable for radiofrequency ablation (RFA) or refusal

→ Oncologic outcomes CTCAE analysis

	No intrahepatic recurrence within 6 months	No intrahepatic recurrence within 1 year
1st SBRT course (n = 81 patients with 82 lesions)	67	56
2nd SBRT course (n = 81 patients with 85 lesions)	64	58
3rd SBRT course (n = 14 patients with 15 lesions)	12	11
4th SBRT course (n = 6 patients with 6 lesions)	6	4
5th SBRT course (n = 1 patient with 1 lesion)	1	1

No intrahepatic recurrence both in 1st and 2nd SBRT within 6 months 53 patients; within 1 year 39 patients

→ ALBI score analysis

Table 2 Grade 3 treatment-related toxicities after each course

Grade 3 toxicities*	First (n = 81)	Second (n = 81)	Third (n = 14)	Fourth (n = 6)	Fifth (n = 1)
Biochemical and hematologic toxicities (total)	9 (11%)	12 (15%)	1 (7.1%)	1 (17%)	0
Total bilirubin	0	1 (1.2%)	0	1 (17%)	0
AST/ALT	2 (2.5%)	5 (6.2%)	0	0	0
Albumin	0	0	0	0	0
Platelet	7 (8.6%) (2 patients before SBRT)	6 (7.4%) (3 patients before SBRT)	1 (7.1%) (1 patient before SBRT)	0	0
Nonbiochemical and hematologic toxicities (total)	0	0	0	0	0
Ascites	0	0	0	0	0
Pneumonitis	0	0	0	0	0
Portal thrombus	0	0	0	0	0
Bile duct stenosis	0	0	0	0	0
Gastrointestinal toxicities	0	0	0	0	0

Table 3 The ALBI score

	Baseline (mean)	SD	*P* value	After SBRT (mean)	SD	*P* value		Mean	SD	*P* value
Acute liver function (n = 53*)										
First SBRT	−2.81	0.39	.026	−2.54†	0.43	<.001	ΔFirst SBRT‡	0.262	0.28	.085
Second SBRT	−2.79	0.41		−2.35†	0.51		ΔSecond SBRT‡	0.343	0.27	
Late-phase liver function (n = 39§)										
First SBRT	−2.81	0.4	.009	−2.67‖	0.41	.006	ΔFirst SBRT‡	0.143	0.23	.484
Second SBRT	−2.77	0.42		−2.47‖	0.61		ΔSecond SBRT‡	0.195	0.38	

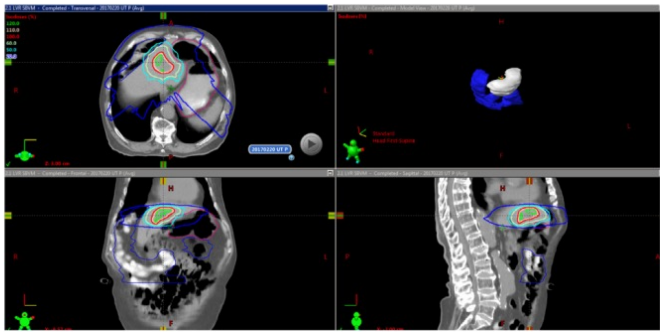
Abbreviations: ALBI = albumin-bilirubin; SBRT = stereotactic body radiation therapy; SD = standard deviation.

The frequency of grade 3 toxicity was not significantly different between the first and second SBRT. The deterioration in liver function after the first and second SBRT was not significantly different

Kimura T et al IJROPB 2020

Challenges in Reirradiation of Intrahepatic Tumors

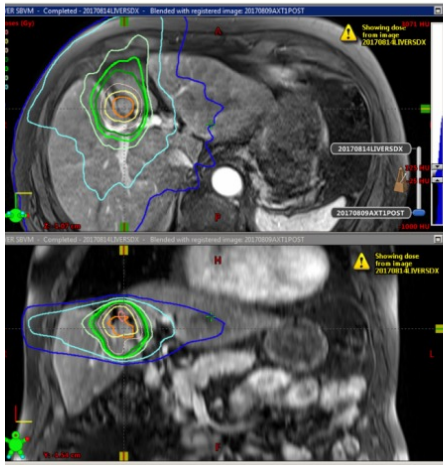
Case 1: Retreatment of Locally Recurrent Liver Metastasis



Questions

1. Would you have exceeded stomach tolerance to deliver more dose to the tumor, as this may have contributed to local/marginal recurrence in this case?
2. Would you offer definitive reirradiation as an option for this patient? If so, how would you account for safety to abutting stomach? Would you use deformable image registration (DIR) to help determine a safe dose? What dose and fractionation would you use?
3. What strategies can you use to mitigate gastric filling?
4. Would you prescribe a gastroprotectant (such as an H2 blocker or PPI (proton pump inhibitor)); if so, based on what information?
5. Would you feel obligated to refer this patient for treatment to a facility that could use protons or an MR-LINAC? Would any other modalities be considered for local liver-directed therapy?
6. If this patient had recurred 2 years later, and this was his only site of disease, would you have offered definitive reirradiation?

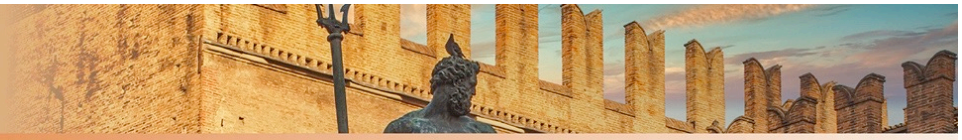
Case 2: Reirradiation of the Cirrhotic Liver



Questions

1. Would you offer this patient SBRT at this juncture? What dose and fractionation would you use?
2. What constraints would you use for the liver? How do you take into account prior treated liver volume?
3. Would you place any dose constraints on the biliary tree?
4. What if this patient had progression at 3 months in the SBRT field? Would you still offer SBRT?

Owen D et al Seminars in Rad Oncol 2020



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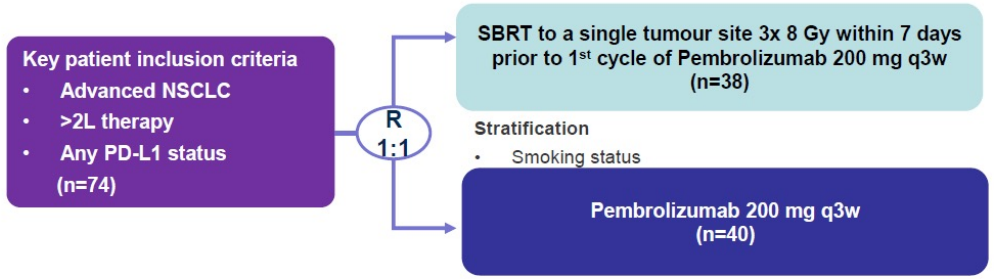
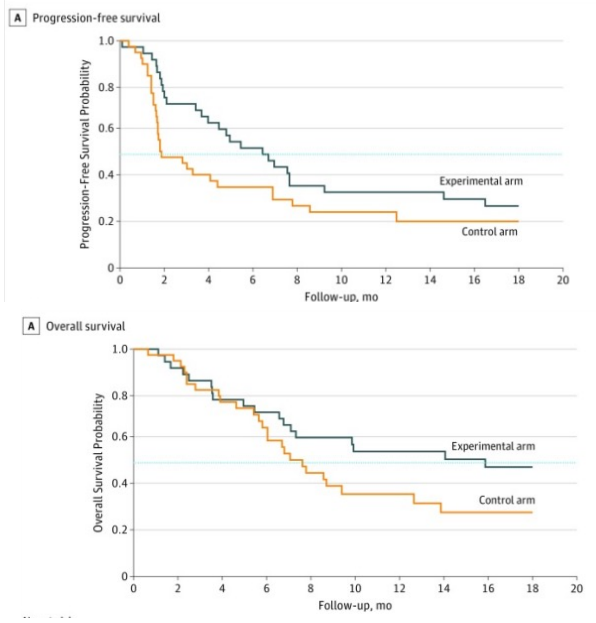
Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial





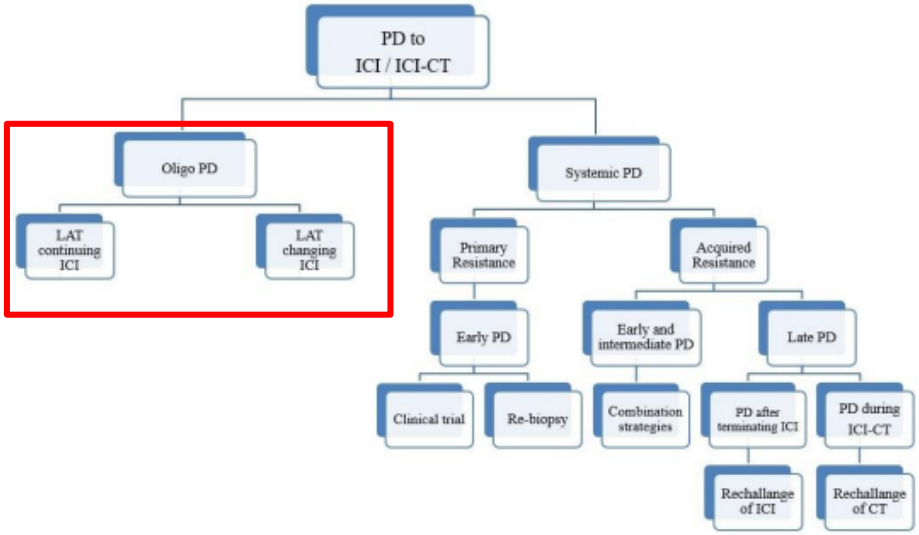
Median progression-free survival was 1.9 months vs 6.6 months

Median overall survival was 7.6 months vs 15.9 months

Theelen WSME A et al. Jama Oncol 2019

Review

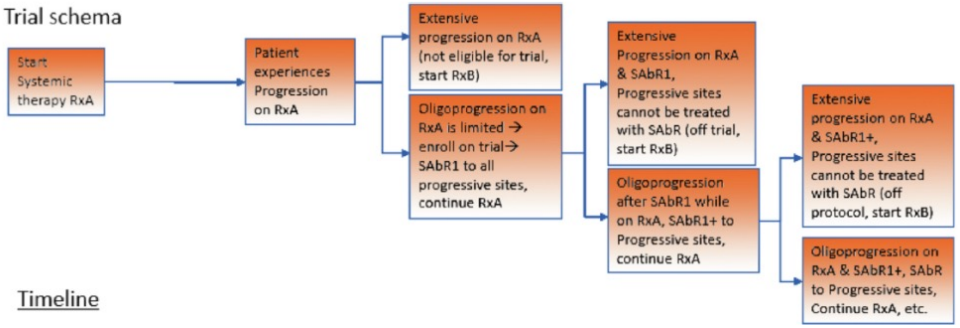
Beyond First-Line Immunotherapy: Potential Therapeutic Strategies Based on Different Pattern Progressions: Oligo and Systemic Progression



RT-IT synergism

Prelaj A et al. Cancers 2021

Phase II Trial of Stereotactic Ablative Radiation for Oligoprogressive Metastatic Kidney Cancer



The median duration of SAbR-aided systemic therapy was 24.4 months

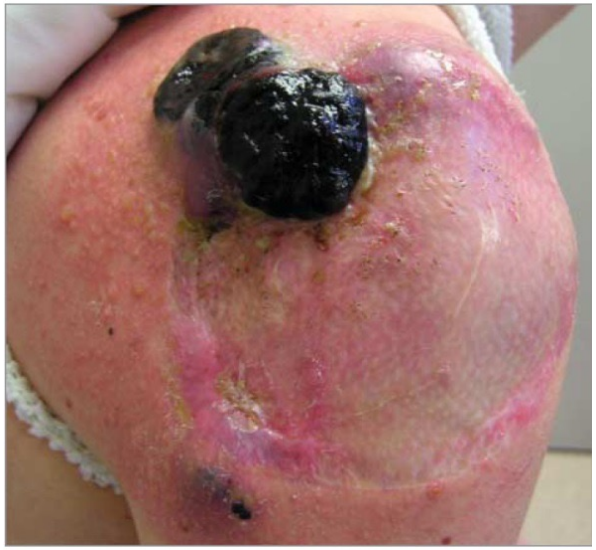
The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group

	Value (%)		
	All patients	Oligorecurrent patients	Oligoprogressive patients
Number of patients	207	91 (44.0)	116 (56.0)
Number of treatments	245	109 (44.5)	136 (55.5)
Number of lesions	385	165 (42.9)	220 (57.1)

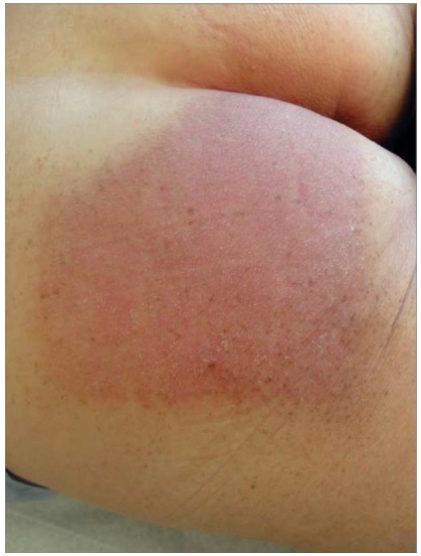
Median time to next systemic therapy was 15.8 months for OR patients, and 13.9 months for OP patients.

Hannan R et al. European Urology Oncology 2021
Franzese C et al. Clinical & Experimental Metastasis 2021

Vemurafenib and Radiosensitization

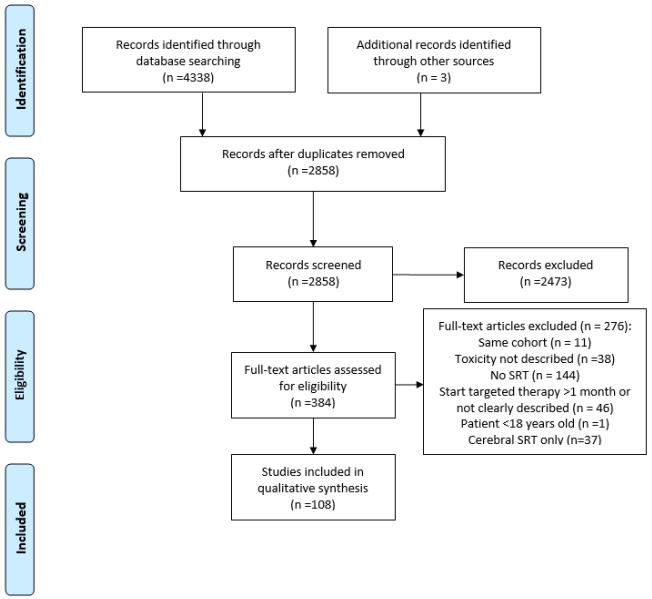


BRAF
inhibitors



Boussemart L et al JAMA Dermatology (2013)

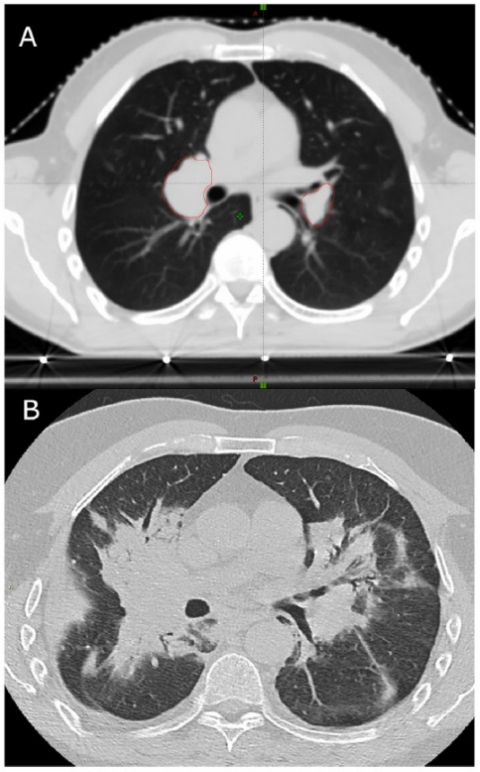
Stereotactic body radiotherapy in combination with targeted therapies or immunotherapy: consensus recommendations by the EORTC-ESTRO OligoCare Consortium.



Targeted agent group	Metastasis location treated with SBRT				
	Head and neck	Thorax	Abdomen	Bone	Body, NFS
Immune checkpoint inhibitors					
aCTLA4	-	12%	10%	8%	23%
aPD (L)1	0%	6%	5%	1%	3%
aPD (L)1+aCTLA4	-	26%	0%	8%	-
Monoclonal antibodies					
aVEGF	0%	-	12%	-	-
aEGFR	15%	-	-	-	-
aHER2	-	-	-	-	-
Small molecules					
mTKI	0%	0%	22%	1%	0%
mTORi	-	0%	0%	0%	0%
EGFRi	-	7%	0%	1%	0%
ALKi	-	0%	0%	0%	0%
ROS1i	-	-	-	-	-
NTRKi	-	-	-	-	-
RETi	-	-	-	-	-
METi	-	-	-	-	-
BRAFi/MEKi	-	-	-	0%	-
PARPi	-	-	-	-	-
HER2i	-	-	-	-	-
CDK4/6i	-	0%	-	0%	-

Severe toxicity events (≥grade 3) per SBRT treated lesion and per targeted agent group (n (%)).NFS=not further specified. Green represent low risk of toxicity (0-10%), orange represents intermediate risk of toxicity (11-20%) and increased risk (>20%) of toxicity.

Kroeze SGC et al. Submitted



Bilateral radiation recall pneumonitis during immunotherapy for an advanced renal cell carcinoma: A challenging case enhances the need for a multidisciplinary approach

January 2019: SRT on hylar nodes (45 Gy in 6 fractions)

September 2019: immunotherapy with nivolumab (240 mg, every 2 weeks)

November 2019: bilateral pneumonitis characterised by parenchymal consolidations with an air bronchogram and some areas of ground-glass opacity

MDT evaluation: **radiation recall pneumonitis**

De Giglio A et al. EJC (2021)

cancers
MDPI

Review

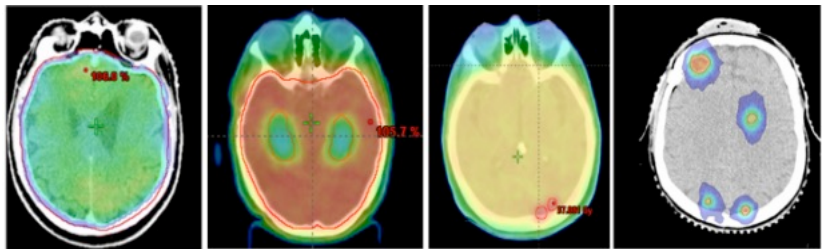
Radiotherapy for HER 2 Positive Brain Metastases: Urgent Need for a Paradigm Shift

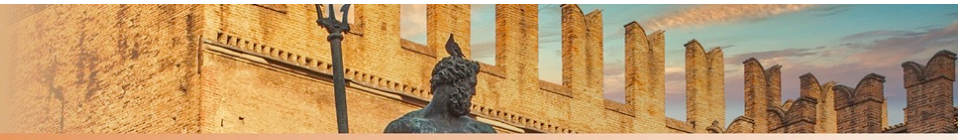
Edy Ippolito [1], Sonia Silipigni [1], Paolo Matteucci [1,*], Carlo Greco [1], Sofia Carrafiello [1], Vincenzo Palumbo [1], Claudia Tacconi [1], Claudia Talocco [1], Michele Fiore [1], Rolando Maria D'Angelillo [2] and Sara Ramella [1]

Recent advances both in radiation therapy and systemic treatment:

- SRT for multiple BM
- introduction of new drugs

This review summarizes the supporting literature and highlights the need for optimizing **combinations of the available treatments**





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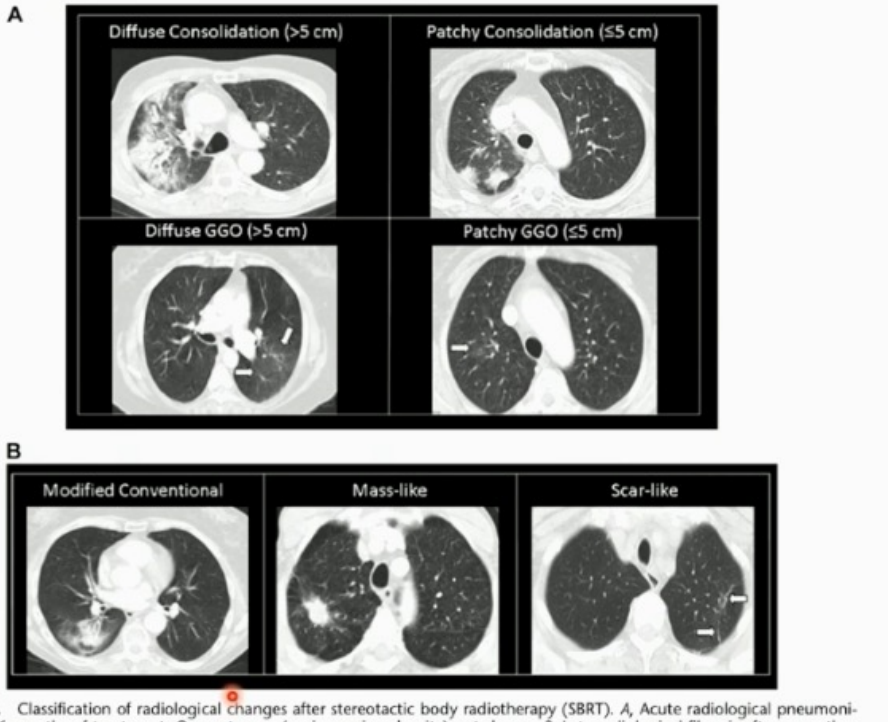
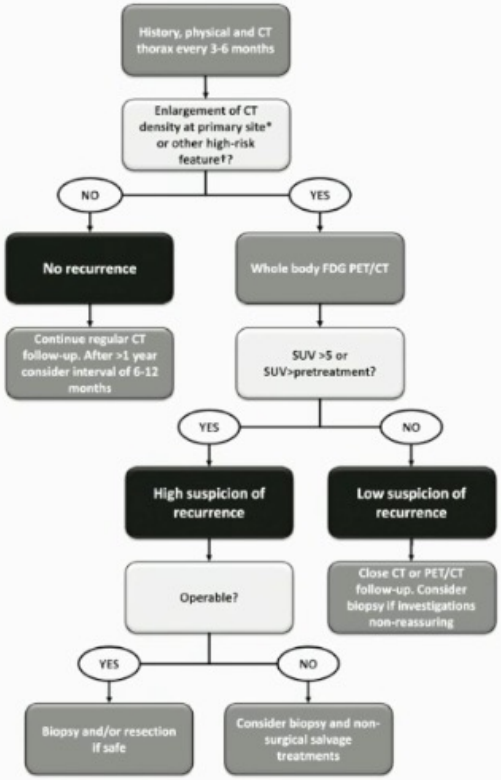


FIGURE 1. Classification of radiological changes after stereotactic body radiotherapy (SBRT). *A*, Acute radiological pneumonitis within 6 months of treatment. One category (no increasing density) not shown. *B*, Late radiological fibrosis after more than 6 months from the time of treatment. One category (no increasing density) not shown. GGO, ground glass opacity.



Challenging Follow up

Dahele M et al. ESTRO (2021)

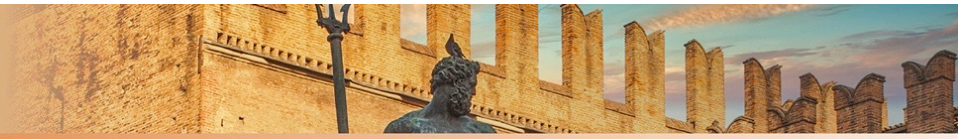


Table 1 – Main original publications concerning evaluation of response after SBRT for liver tumors. *Abbreviations:* SBRT, stereotactic body radiotherapy; RECIST, criteria of response in solid tumors; mRECIST, modified criteria of response in solid tumors; CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron-emission tomography; EASL, European Association of Study of the Liver; FDG, fluorodeoxyglucose; SUV, standard uptake value.

Study	Liver disease	Purpose	Imaging technology	Criteria	Material and methods	Findings
Jarraya et al.[35]	Liver metastases	Describe post-therapeutic transformations of liver metastases treated with cyberknife	CT	RECIST vs. new set of combined criteria (enhancement pattern and size)	28 patients 40 liver metastases	Use of RECIST criteria may be inadequate. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern.
Jarraya et al.[36]	Liver metastases	Validate relationship between lobulated enhancement occurrence and local relapse to predict local progression	CT	Occurrence of lobulated enhancement	46 patients 59 liver metastases	"Lobulated enhancement" pattern appears efficient to predict local progression In a specific, reproducible, and relatively sensitive way
Solanki et al.[37]	Liver metastases	Evaluate the utility of 18F-PET-CT as an indicator of treatment response in oligo-metastatic patients undergoing SBRT	18F-FDG PET/CT	RECIST vs. visual 18F-FDG uptake and SUV max	9 liver metastases	18F-PET-CT seems to realize a practicable evaluation of response to SBRT in oligo-metastatic disease. It shall allow in particular to recover complete response underestimated by RECIST criteria as stable disease
Stinauer et al.[38]	Liver metastases	Characterize SUV changes of hepatic metastases after SBRT. Evaluate normal tissue regeneration	18F-FDG PET CT	Lesion SUV max and total liver volume	27 patients 35 hepatic metastases	Maximum SUV of controlled lesions decreases to 3.1: similar to median SUVmax of normal liver. The cut-off to define local control failure consists in SUVmax ≥ 6. Liver volume after SBRT reached its NADIR (20% less) between 3 and 6 months.

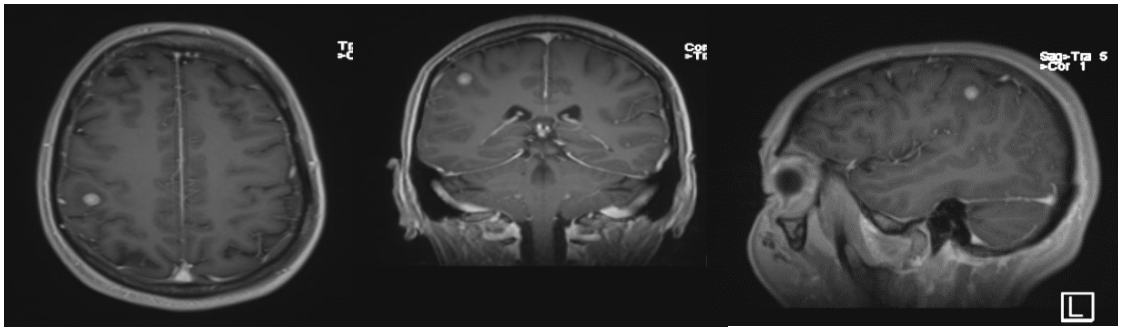
Evaluation of response after SBRT for liver tumors

Raphael Tétreau[a,], Carmen Llacer[b], Olivier Riou[b], Emmanuel Deshayes[a]*

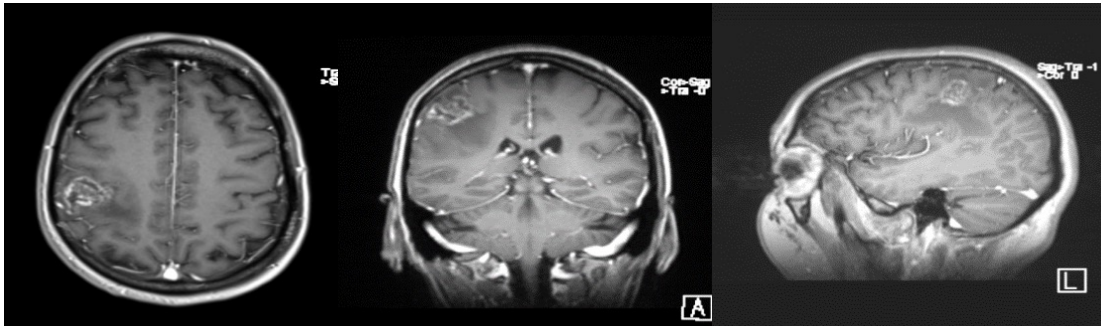
Use of RECIST criteria is also inadequate in the evaluation of response after SBRT for hepatic metastases. Response of liver metastases to SBRT is better assessed with a combination of size and enhancement pattern. The occurrence of a lobulated enhancement during follow up is efficient to predict local progression in a specific, reproducible, and sensitive way. Patients with FDG-avid hepatic metastases are also better evaluated with PET-CT and functional criteria than routine imaging and metric evaluation alone.

Reports of practical oncology and radiotherapy 22 (2017) 170–175

24.07.2017 SRS on right parietal lesion (24 Gy in 1 fraction) from kidney cancer

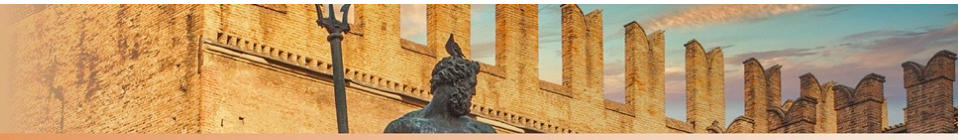


6.2020 MRI: dimensional increase of the parietal lesion with increase of the surrounding oedema



11.2020 Surgery: histopathological report 100% necrosis

Challenging Follow up



Original Investigation | Oncology

Evaluation of Definitive Stereotactic Body Radiotherapy and Outcomes in Adults With Extracranial Oligometastasis

After LAT for OM disease, 33.1% of progressing patients had a limited disease dissemination, still satisfying the criteria for OMD classification

Poon I et al. Jama Network 2020

Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence

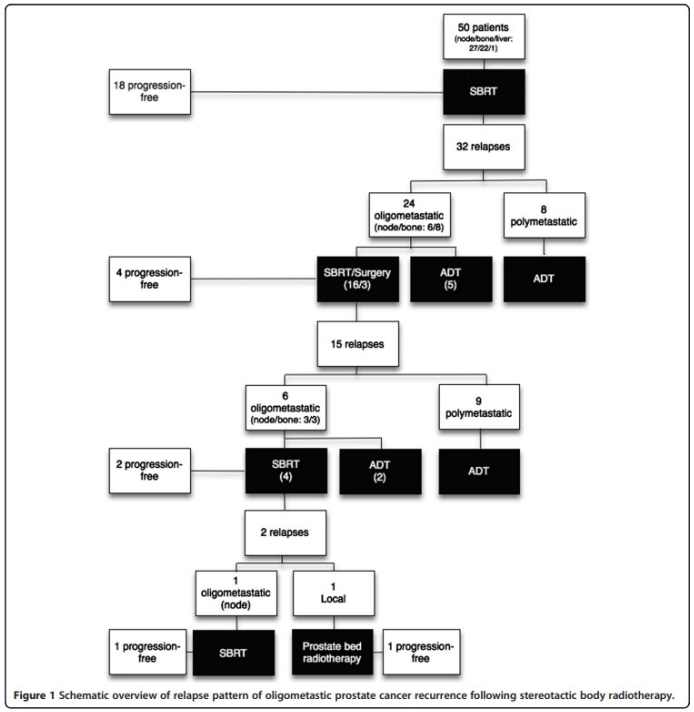
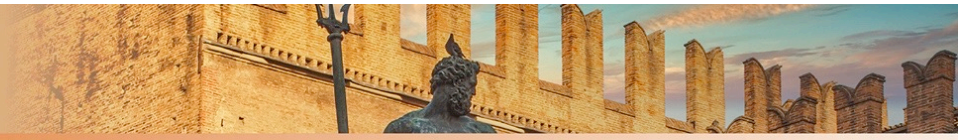


Figure 1 Schematic overview of relapse pattern of oligometastatic prostate cancer recurrence following stereotactic body radiotherapy.

Repeated SBRT for oligometastatic prostate cancer postpones palliative androgen deprivation therapy with 2 years without grade III toxicity.

Follow up to detect further oligorelapse

Decaestecker K et al. Rad Oncol 2014



Take Home Messages

- OM patient management requires a **multidisciplinary approach**

- OM patient management implies the right **identification and classification** of the patient itself in the various OM cathegories

- RT in OM patients requires **expertise and advanced technologies**, particularly in case of difficult presentations (i.e. challenging sites, previous treatments, etc.)

- OM patient management requires the **perfect knowledge of concomitant systemic treatments**, of their possible interactions with RT and also of the available therapeutic alternatives

- OM patient management implies also the **management of follow-up** to interpret response, to detect side effects and to identify early oligo-relapse amenable to further local approaches

Grazie per l'attenzione!

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