Oligometastatic disease: State of the art

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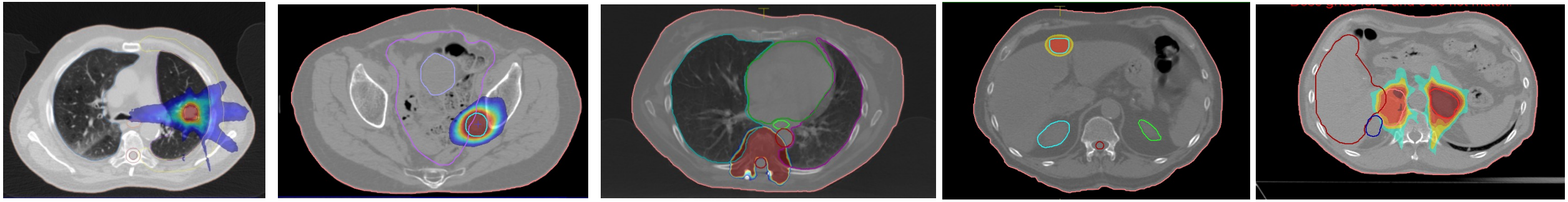
Stereotactic Body Radiation Therapy (SBRT)
Stereotactic ABlative Radiotherapy (SABR)

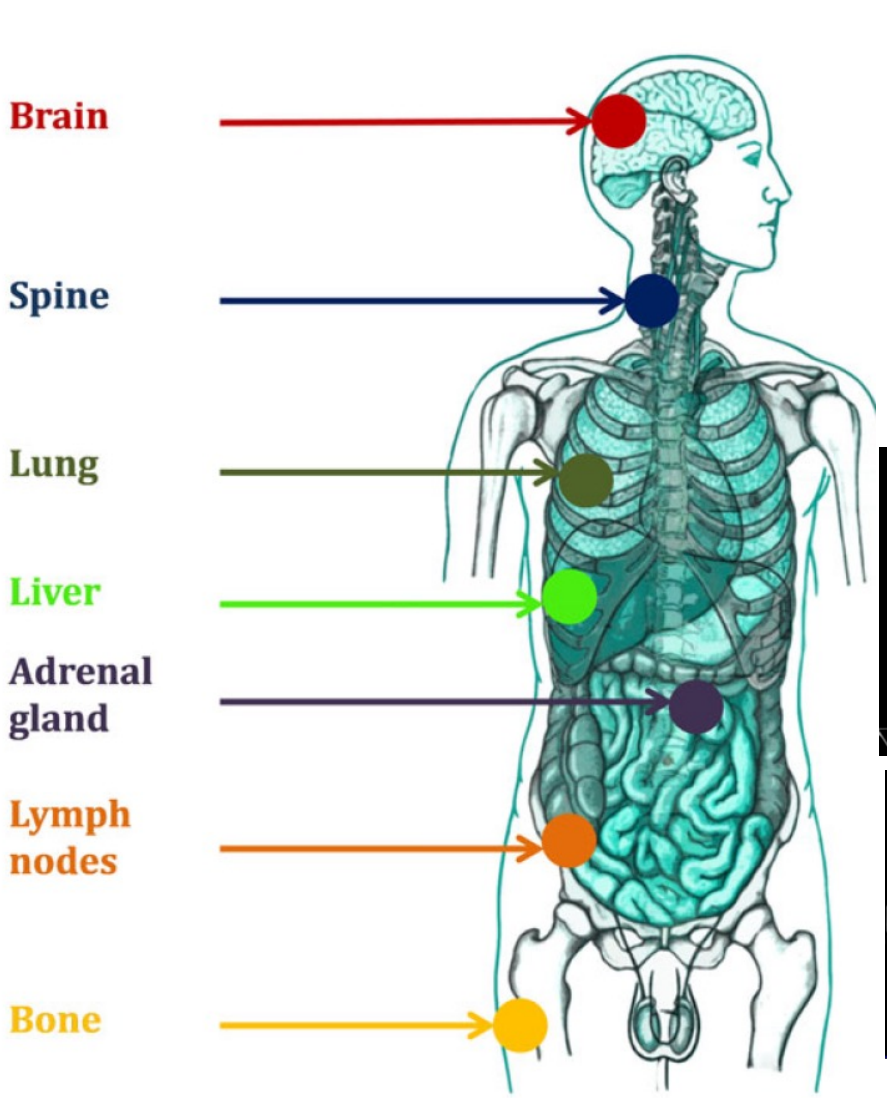


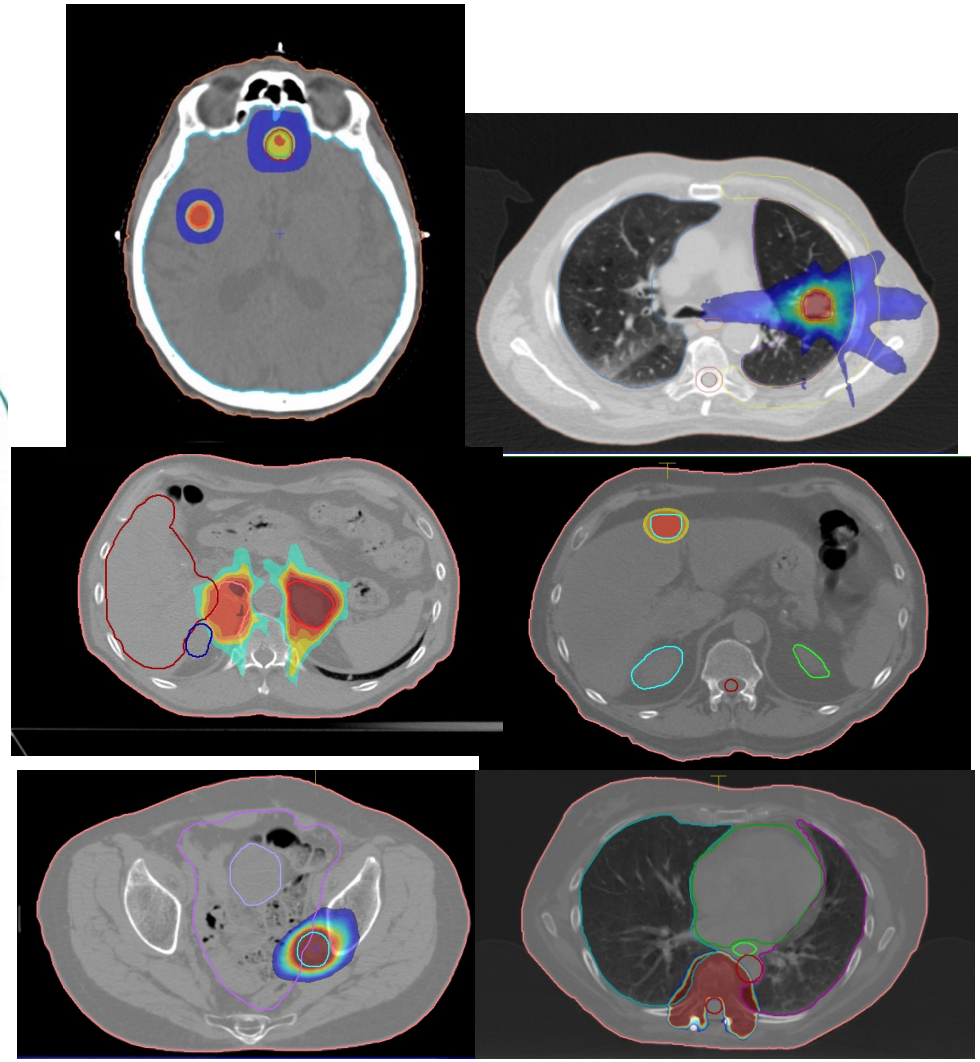
A technique for delivering external beam radiotherapy

- with a high degree of accuracy to an extra-cranial target,
- using high doses of irradiation,
- in 1-8 treatment fractions

S. Senan, U. Ricardi, M. Guckemberger, K.E. Rosenzweig, and N. Ohri:
Stage I NSCLC and oligometastatic disease
The IASLC Multidisciplinary approach to Thoracic Oncology, 2017 (Pass, Scagliotti, Ball)

Metastatic sites amenable with SBRT



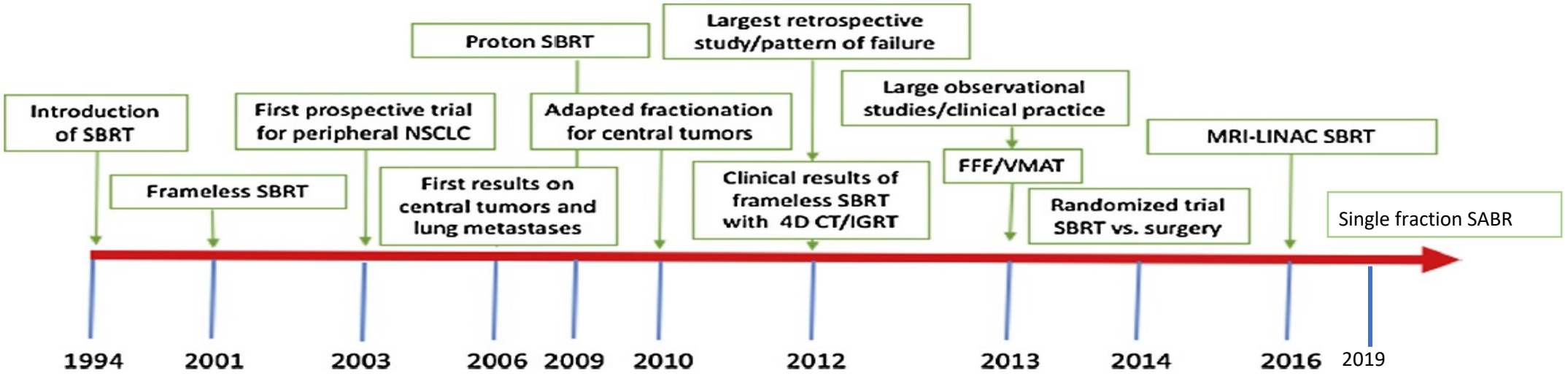


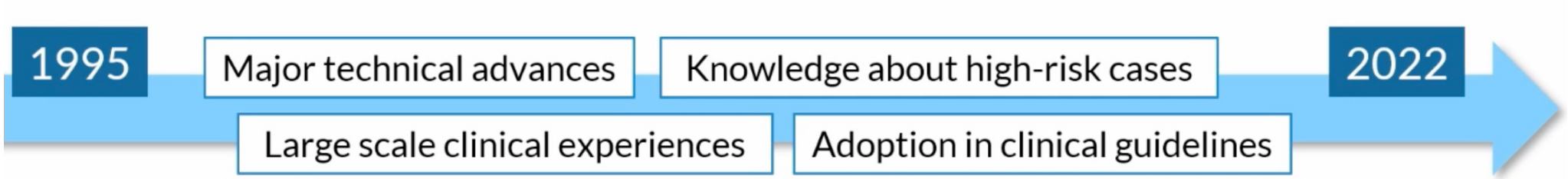
Acta Oncologica Vol. 34, No. 6, pp. 861–870, 1995

STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM





[adapted form Ricardi et al, Phys Med 2017]

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Selected studies on SABR in lung metastases

Study (year)	Patients (n)	Dose and fractionation	Median follow-up (months)	Local control	Overall survival	Toxicity
Wulf *et al.* (2001)	27	30 Gy/3 fractions; 36 Gy/3 fractions	15	2 years: 71%	1 year: 48%; 2 years: 21%	G5: 2.2%
Onimaru *et al.* (2003)	45	48 Gy/8 fractions; 60 Gy/8 fractions	18	3 years: 69.6 and 100% for 2 dose levels	2 years: 47.1%	G5: 3.7%; G3: 3.7%
Yoon *et al.* (2006)	53	30 Gy/3 fractions; 40 Gy/4 fractions; 48 Gy/4 fractions	14	70, 77 and 100% for 3 dose levels	1 year: 89%; 2 years: 51%	No >G2
Okunieff *et al.* (2006)	50	50 Gy/10 fractions; 48 Gy/6 fractions; 57 Gy/3 fractions	18.7	3 years: 91%	2 years: 50%	G2: 6.1%; G3: 2%
Norihisa *et al.* (2008)	34	48 Gy/4 fraction; 60 Gy/4 fractions	27	2 years: 90%	2 years: 84%	G2: 12%; G3: 3%
Brown *et al.* (2008)	35	5 Gy/1 fractions; 60 Gy/4 fractions	18	Crude: 77%	2 years: 72.5%	G3/G4: 2.8%
Rusthoven *et al.* (2009)	38	60 Gy/3 fractions	15.4	2 years: 96%	2 years: 39%	G3: 8%
Ricardi *et al.* (2012)	61	45 Gy/3 fractions; 26 Gy/1 fraction	20.4	2 years: 89%	2 years: 66.5%	G3: 1.6%

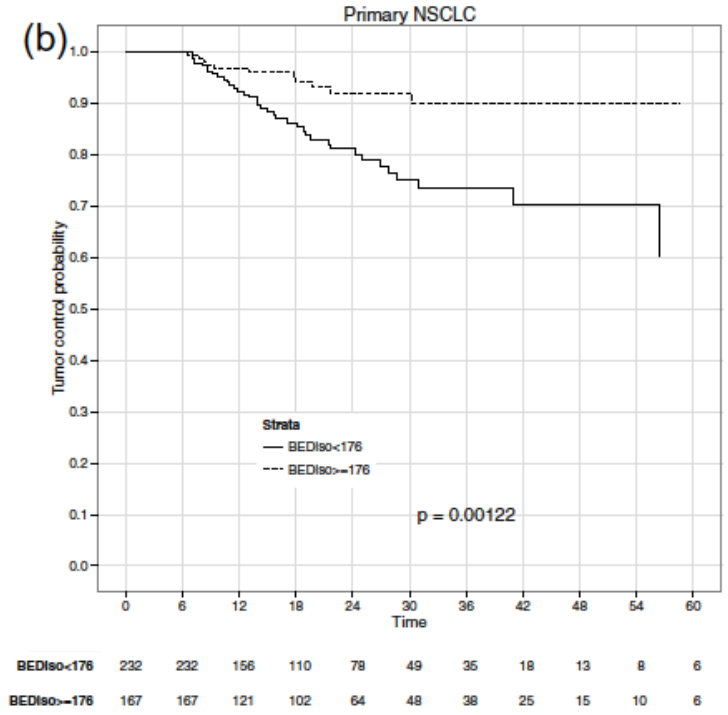
Ricardi, Exp Rev Anticancer Ther 2013

Original article

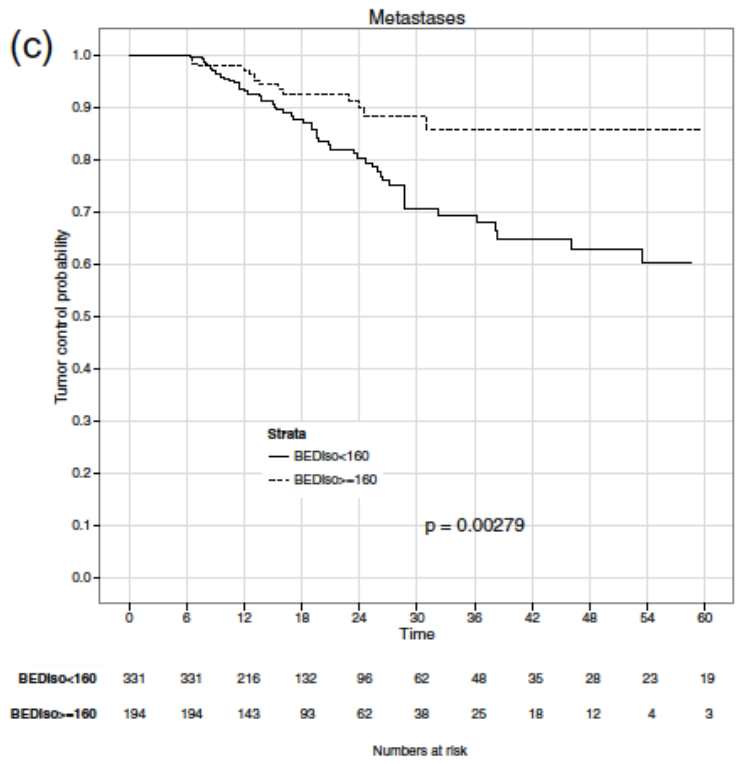
Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy

M. Guckenberger, Radiother Oncol 2015

Primary NSCLC (N = 399)



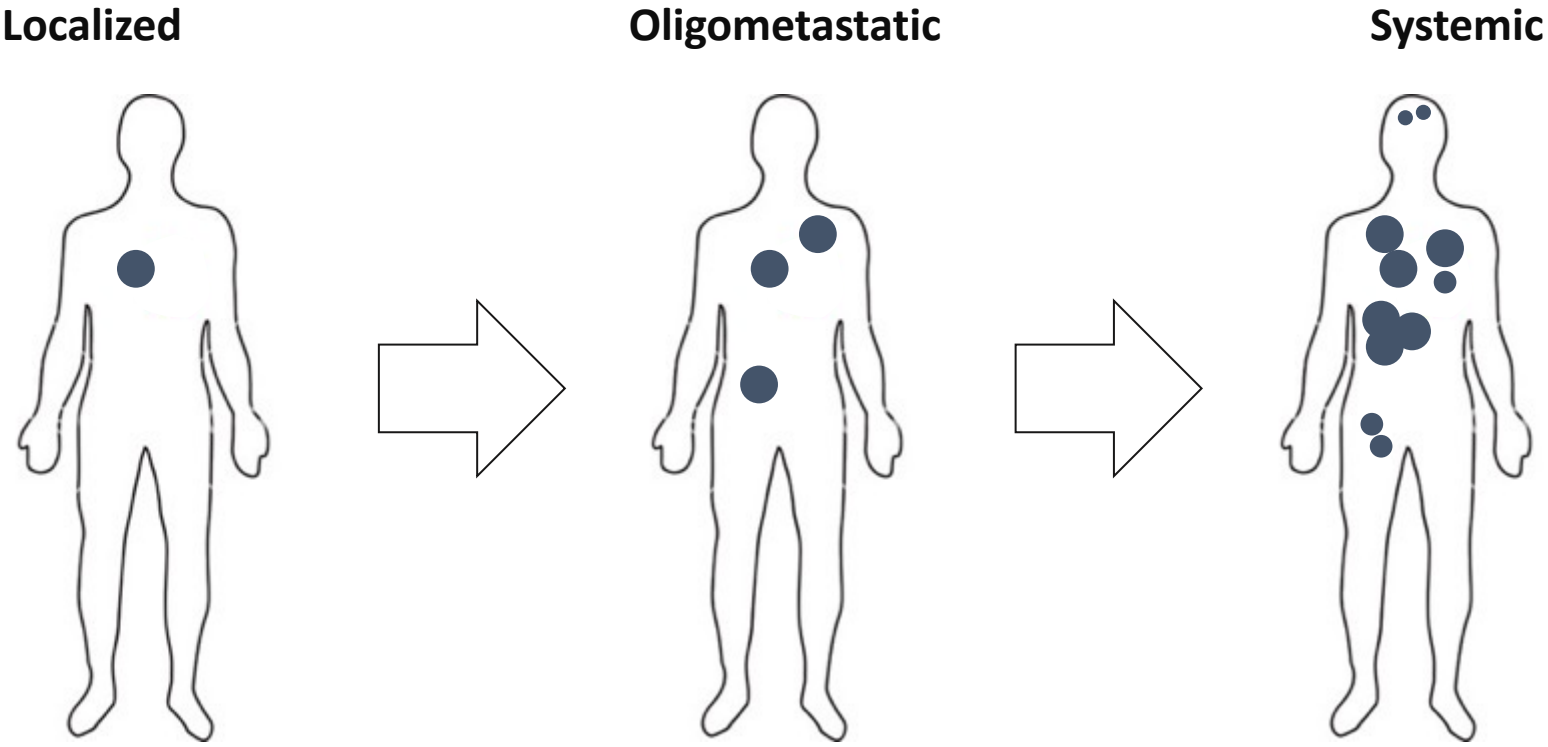
Pul. metastases (N = 397, 525 lesions)



- Radiosensitivity not significantly different between primary NSCLC and lung metastases

The concept of OLIGOMETASTASES

Hellman & Weichselbaum JCO 1995



Cure with local treatment

Cure with local treatment possible

Local Tx for symptom control

➢The beauty: a simple concept

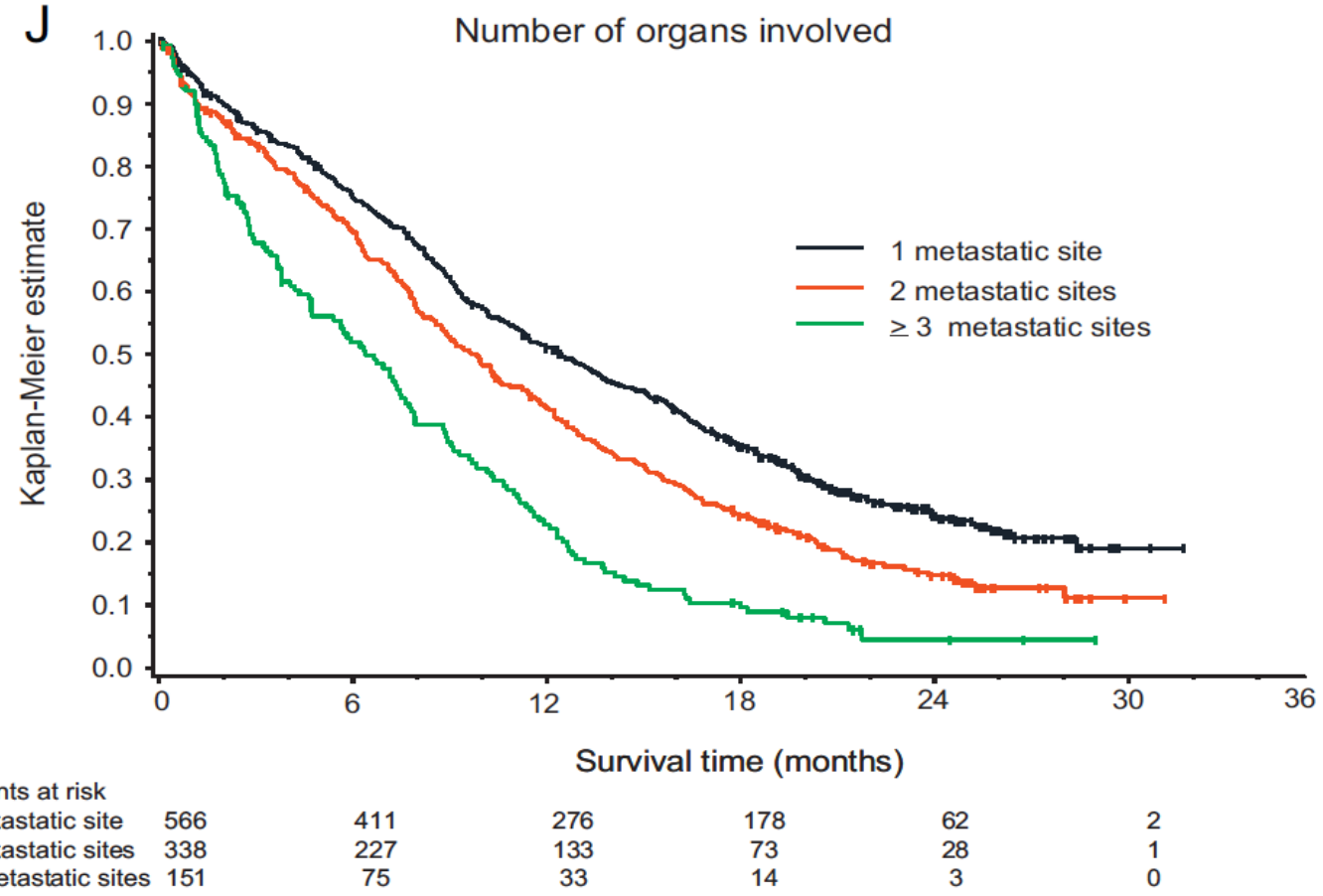
Courtesy: Matthias Guckenberger

The Oligometastatic State

Do patients with limited metastatic disease behave differently than those with more widespread metastases?

Phase III FLEX study in stage IV NSCLC

Metastases to **1**, **2** and **3** sites had an overall survival of **12.4** months vs **9.8** months vs **6.4** months, respectively



Patients at risk						
1 metastatic site	566	411	276	178	62	2
2 metastatic sites	338	227	133	73	28	1
≥3 metastatic sites	151	75	33	14	3	0

Pirker R, Lung Cancer 2012

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

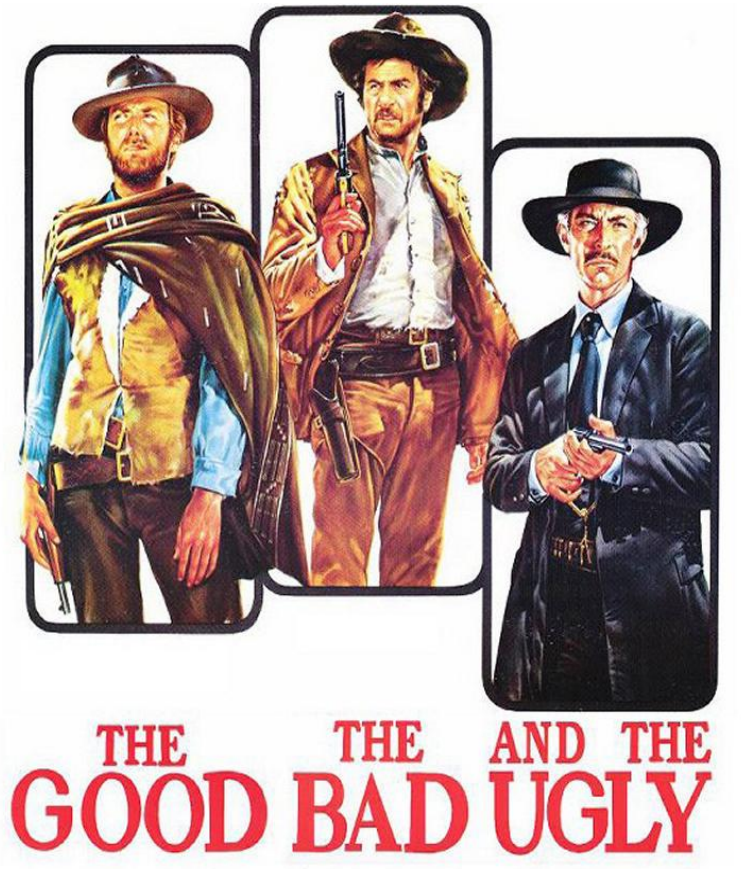
Yolande Lievens [a,*], Matthias Guckenberger [b], Daniel Gomez [c], Morten Hoyer [d], Puneeth Iyengar [e], Isabelle Kindts [f], Alejandra Méndez Romero [g], Daan Nevens [h], David Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]

OMD definitions used across publications.

Oligometastatic disease (OMD)
Many refer to the original definition of Hellman and Weichselbaum [6]: An intermediate state between local and systemic disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential
+ *Outcome* An intermediate state in which local or treated metastasis control may yield improved systemic control
+ *Disease burden* Limited number of metastases: oligometastatic is defined as a small number of low volume metastases, 5 or less, 3 or less Limited number of sites/regions Single or limited number of organs Limited number of metastases and sites Limited number of distant metastatic regions (typically ≤5) that contain the primary tumor

The authors agreed that 5 lesions should be considered an upper bound off protocol, until further data emerges

Oligomets from biology point of view



- Oligo and polymetastatic cancers are more than two distinct entities
- Subclasses (biomolecular subtypes, not just number of metastases)
- Waiting from the lab…

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

[Guckenberger M, Lancet Oncol 2020]

Dynamic oligometastatic state model

Guckenberger et al, Lancet Oncol 2020

The OMD classification system defines the oligometastatic state at one timepoint in the patient's history

Descriptive tumour characteristics

- Primary tumour characteristics: primary tumour site, histology, stage according to TNM Classification of Malignant Tumours, mutational status, tumour marker
- History of cancer progression: time interval since first diagnosis, disease-free interval, treatment-free interval
- History of treatment of primary tumour: method of local treatment, radical or palliative intent, controlled primary tumour
- History of systemic therapy before diagnosis of oligometastatic disease: types of systemic therapy, number of lines of systemic therapy
- Oligometastatic disease staging: imaging method, anatomical areas covered, invasive staging
- Involved organs of oligometastatic disease

Quantitative characteristics

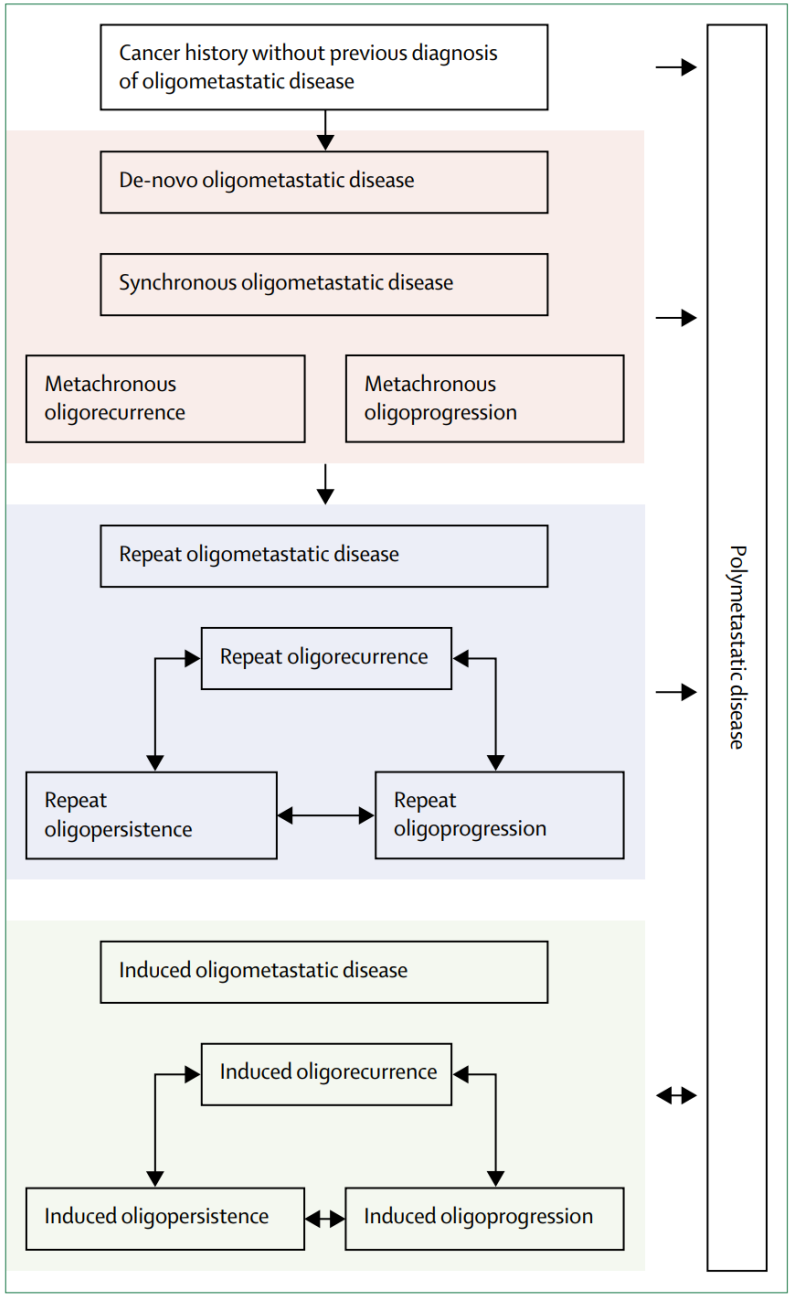
- Number of metastatic lesions
- Number of involved organs
- Number of lesions per organ
- Maximum size or volume of individual metastasis

Developmental characteristics

- Does the patient have a history of polymetastatic disease before oligometastatic disease diagnosis?
- Does the patient have a history of oligometastatic disease before current diagnosis?
- Is oligometastatic disease diagnosed within 6 months after diagnosis of the primary tumour?
- Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis?
- Are any oligometastatic lesions progressive on current imaging?

Metastases-specific characteristics

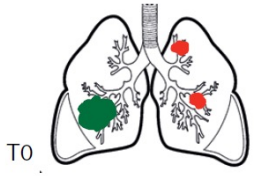
- Is the oligometastatic lesion a newly developed metastatic lesion?
- Is treatment of the oligometastatic lesion possible with radical intent?



However, one patient might develop several and different states of oligometastatic disease throughout the course of disease, resulting in multiple courses of radical local and systemic treatment

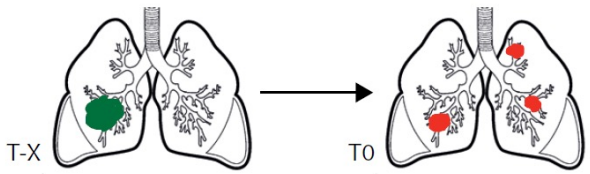
A De-novo oligometastatic disease

Synchronous oligometastatic disease



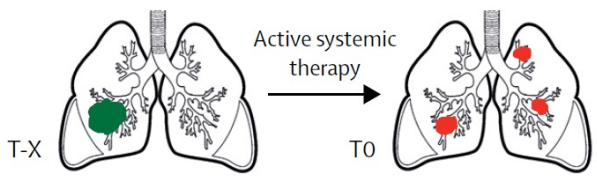
- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

Metachronous oligorecurrence



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

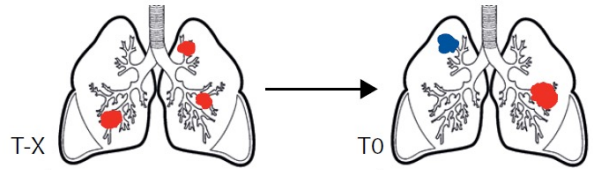
Metachronous oligoprogression



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

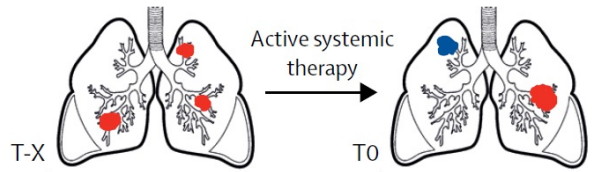
B Repeat oligometastatic disease

Repeat oligorecurrence



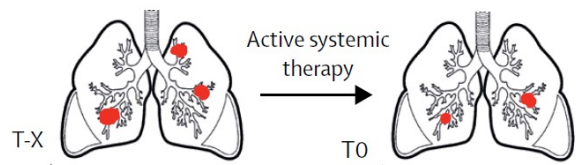
- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligoprogression



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligopersistence



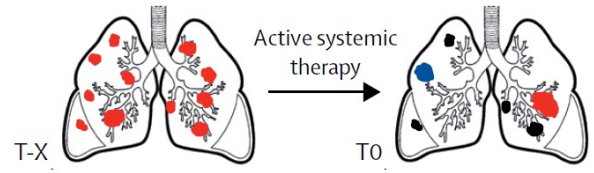
- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive (red) oligometastases

C Induced oligometastatic disease

Induced oligorecurrence

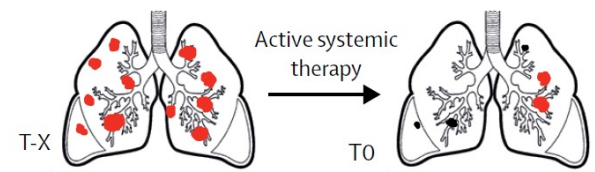
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligoprogression



- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligopersistence

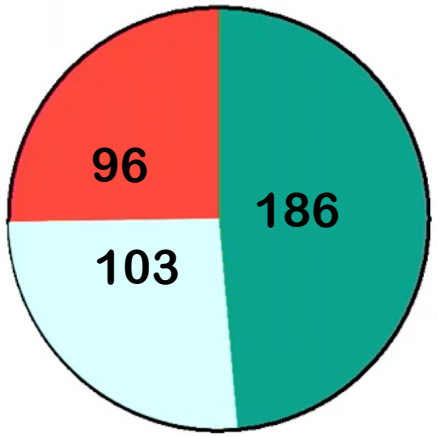


- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive oligometastases (red), where response is worse compared with other residual metastases (black)

Evaluation of the prognostic value of the ESTRO EORTC classification of oligometastatic disease in patients treated with stereotactic body radiotherapy: A retrospective single center study

[Willmann et al R&O 2022]

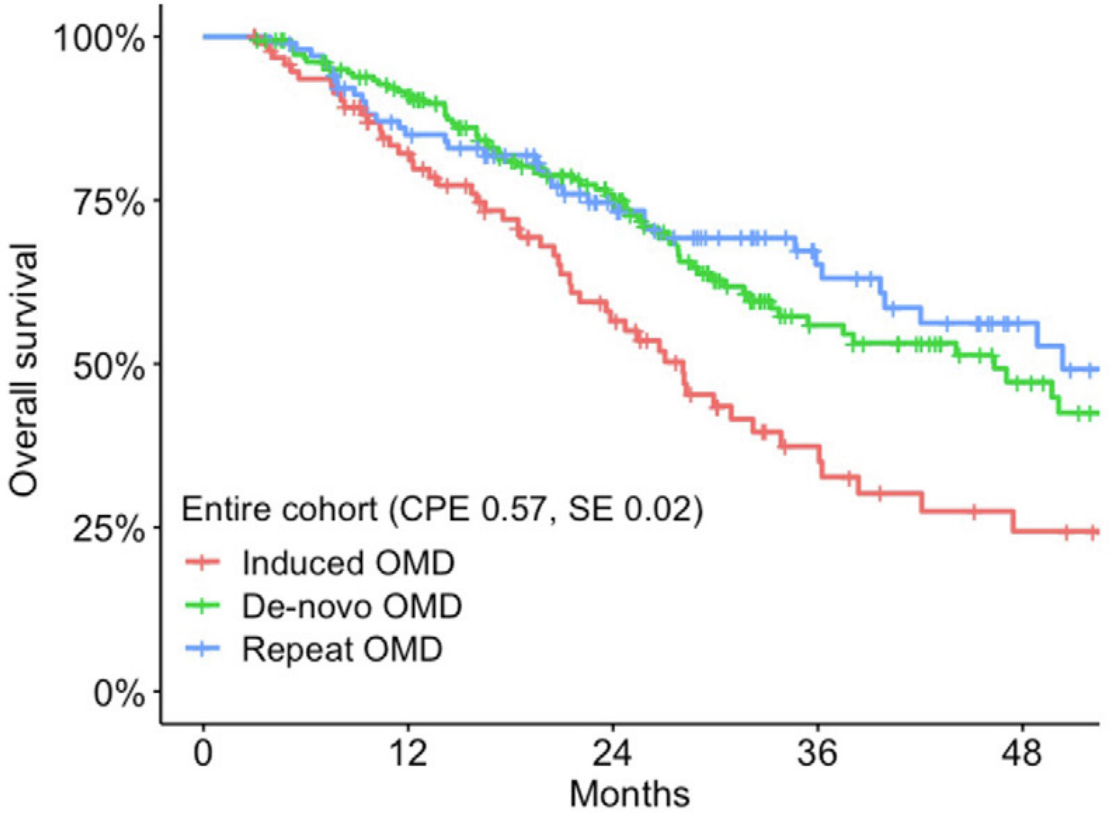
N= 385 OMD patients treated for max 5 mets @ USZ



De-novo OMD

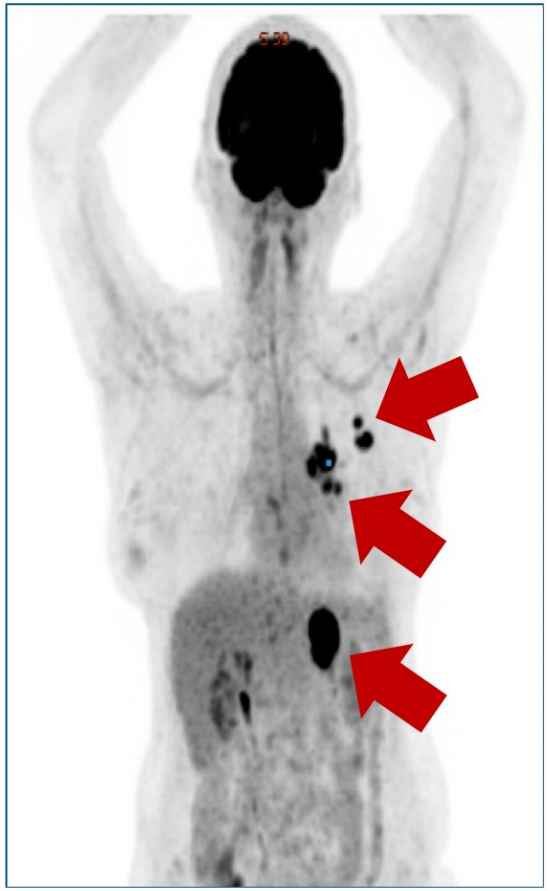
Repeat OMD

Induced OMD



→ Independent prognostic factor

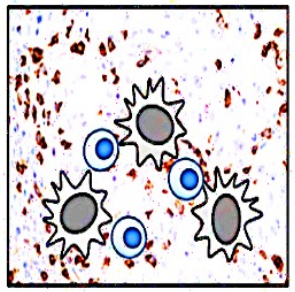
Ideal local treatment modality in OMD



- Evidence-based ↑
- High local efficacy ↑
- Simultaneous Tx of multiple lesions & sites ↑
- Synergistic combination with systemic Tx ↑
- Non-invasive ↑
- Low toxicity profile ↑
- Histopathological evaluation ↓

Courtesy: Matthias Guckenberger

Immunogenic cell death= Priming



Local and abscopal anti-tumor Immune responses

Radiation stimulates tumor antigen release and anti-tumor immunity, activating the adaptive and innate immune response

Original Investigation | Oncology

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

Ian Poon, MD; Darby Erler, MRT(T), MHSc; Roi Dagan, MD; Kristin J. Redmond, MD; Matthew Foote, MD; Serena Badellino, MD; Tithi Biswas, MD; Alexander V. Louie, MD, PhD; Young Lee, PhD; Eshetu G. Atenafu, MSc; Umberto Ricardi, MD; Arjun Sahgal, MD

Table 1. Patient Demographic Characteristics

Variable	Patients, No. (%) (N = 1033)
Age, median (range), y	68.0 (18.0-94.3)
Sex	
Male	601 (58.2)
Female	432 (41.8)
Primary tumor type	
Breast	84 (8.1)
Colorectal	235 (22.7)
Kidney	63 (6.1)
Lung	260 (25.2)
Prostate	132 (12.8)
Melanoma	37 (3.6)
Sarcoma	36 (3.5)
Head and neck	47 (4.5)
Thyroid	11 (1.1)
Pancreas	28 (2.7)
Hepatic or biliary	18 (1.7)
Gynecologic	19 (1.8)
Other gastrointestinal	18 (1.7)
Other genitourinary	17 (1.6)
Unknown	5 (0.5)
Other	23 (2.2)

1033 patients treated between 2008 and 2016

Median age: 68 years (18-94 yo)

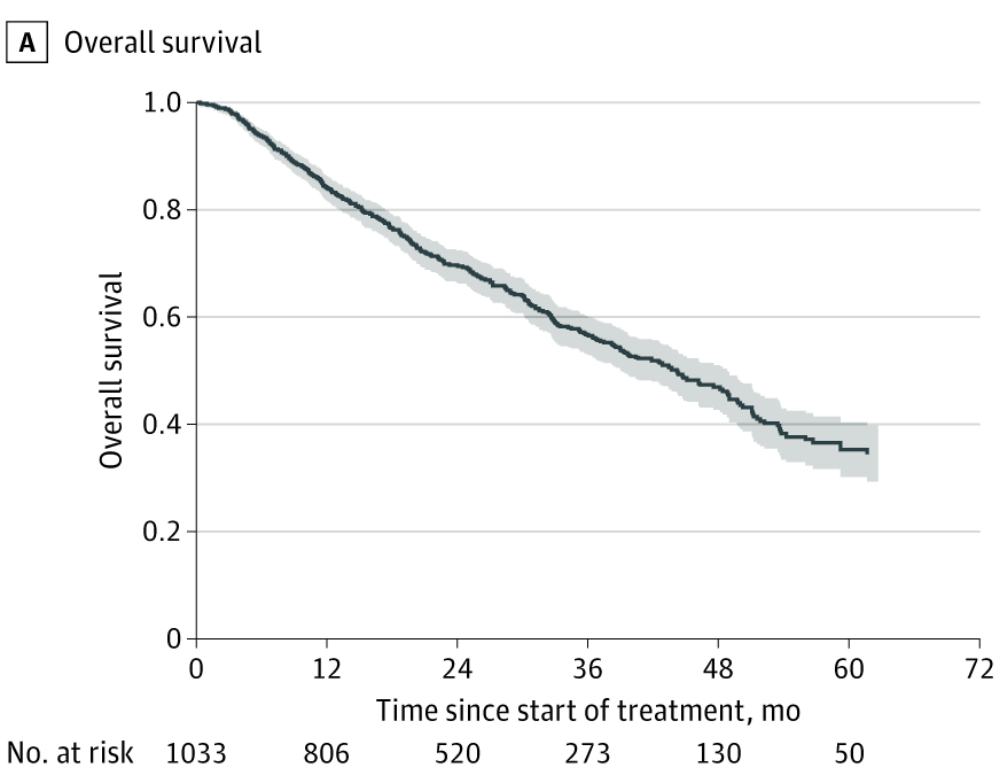
Median follow-up: **24 months** (0-105 months)

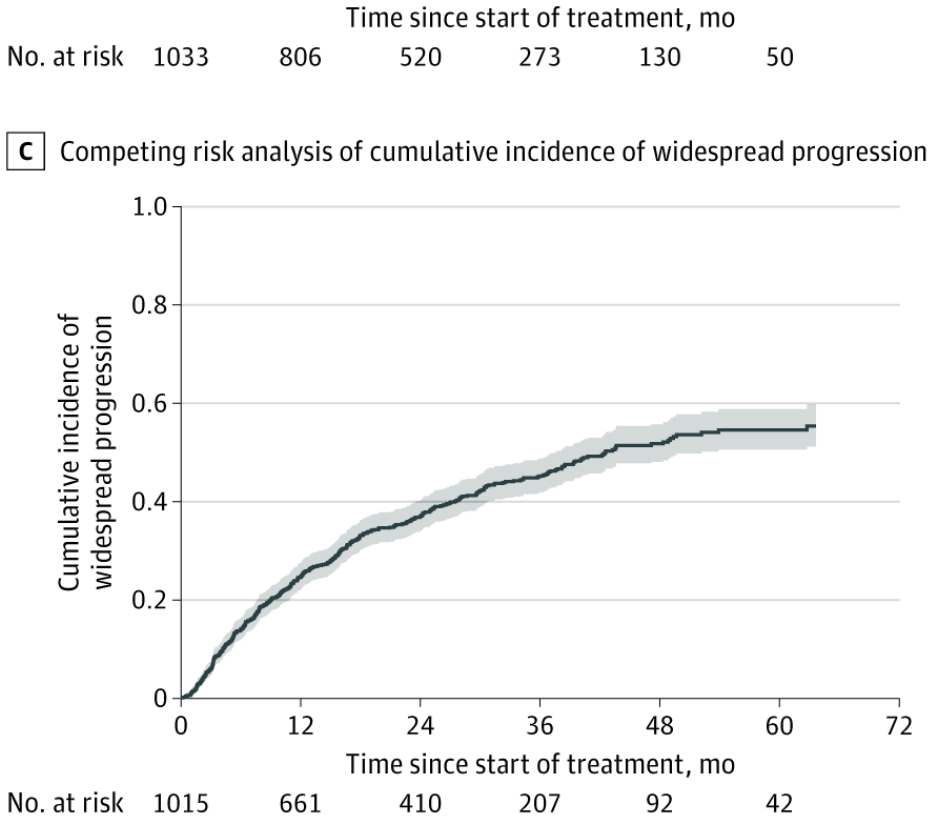
[Poon et al, JAMA Network Open November 2020]

Histology	
Adenocarcinoma	589 (57.0)
Squamous cell	129 (12.5)
Ductal carcinoma	67 (6.5)
Renal cell	63 (6.1)
Sarcoma	36 (3.5)
Melanoma	37 (3.6)
Other	86 (8.3)
Unknown	26 (2.5)
Metastatic presentation	
Synchronous	279 (27.0)
Metachronous	754 (73.0)
Metastatic interval (range), mo	17.3 (0-293.0)
No. of metastases	
1	596 (57.7)
2	245 (23.7)
3	105 (10.2)
4	55 (5.3)
5	32 (3.1)
No. of organs involved	
1	875 (84.7)
2	140 (13.6)
3-4	18 (1.7)

Prior definitive metastasis-directed therapy	
No	805 (77.9)
Yes	228 (22.1)
Prior systemic therapy for metastatic disease	
No	665 (64.4)
Yes	368 (35.6)
Type of prior systemic therapy for metastatic disease	
Chemotherapy	218 (21.1)
Hormone therapy	134 (13.0)
Target therapy	65 (6.3)
Immunotherapy	14 (1.4)
All known sites of disease treated	
No	49 (4.7)
Yes	981 (95.0)
Unknown	3 (0.3)
Prior systemic therapy for primary disease	
No	477 (46.2)
Yes	555 (53.7)
Unknown	1 (0.1)
Type of prior systemic therapy for primary disease	
Chemotherapy	431 (41.7)
Hormone therapy	134 (13.0)
Target therapy	65 (6.3)
Immunotherapy	14 (1.4)
Not specified	5 (0.5)

Outcome analysis: OS and WSP





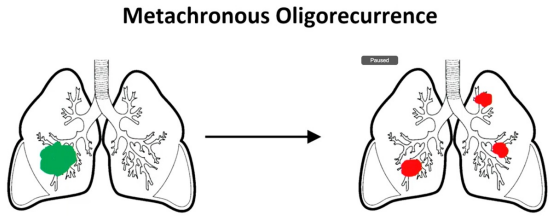
- Median OS **44.2 months** (3-year OS: 56.7%, 5-year OS: 35.2%)
- For the entire cohort, an overall median time to WSP of **42.5 months** was observed → this finding suggests that WSP is <u>not</u> an early pattern of progression.

Emerging evidence

Benefit of local ablative therapies (LAT) in the oligometastatic setting

Histology	Trial name / Author	Type of Ablative Therapy	Results
NSCLC	Gomez et al.	RT / Surgery	↑ OS and PFS
	Iyengar et al.	SABR	↑ PFS
	SINDAS / Wang et al.	SABR	↑ OS and PFS
Prostate cancer	STOMP / Ost et al.	RT / Surgery	↑ ADT-free survival
	ORIOLE / Phillips et al.	SABR	↑ PFS
Colorectal cancer	EORTC 40004 / Ruers et al.	RFA (liver)	↑ OS and PFS
	PulMICC / Treasure et al.	Surgery (lung)	No improvement of outcomes
Multiple	SABR-COMET / Palma et al.	SABR	↑ OS and PFS

Extended long-term results of SABR-COMET



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

Stephen Harrow, MBChB, PhD,* David A. Palma, MD, PhD,† Robert Olson, MD, MSc,‡ Stewart Gaede, PhD,† Alexander V. Louie, MD, PhD,†,§ Cornelis Haasbeek, MD, PhD,‖ Liam Mulroy, MD,¶ Michael Lock, MD,† George B. Rodrigues, MD, PhD,† Brian P. Yaremko, MD, MSc, PEng,† Devin Schellenberg, MD,# Belal Ahmad, MD,† Sashendra Senthi, MD, PhD,** Anand Swaminath, MD,†† Neil Kopek, MD,‡‡ Mitchell Liu, MD,§§ Roel Schlijper, MD,‡ Glenn S. Bauman, MD,† Joanna Laba, MD,† X. Melody Qu, MD, MPH,† Andrew Warner, MSc,† and Suresh Senan, MBBS, PhD‖

INTERNATIONAL JOURNAL OF
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Follow-up of > **5 years** from enrollment for each patient

2022

99 patients
2:1 randomization
NSCLC: 6:12 patients

Primary endpoint:

- Overall Survival (**OS**)

Secondary endpoints:

- Progression-Free Survival (**PFS**)
- Toxicity (CTCAE 4.0)
- QoL (FACT-G)
- Lesional control rate
- Need for further systemic therapy

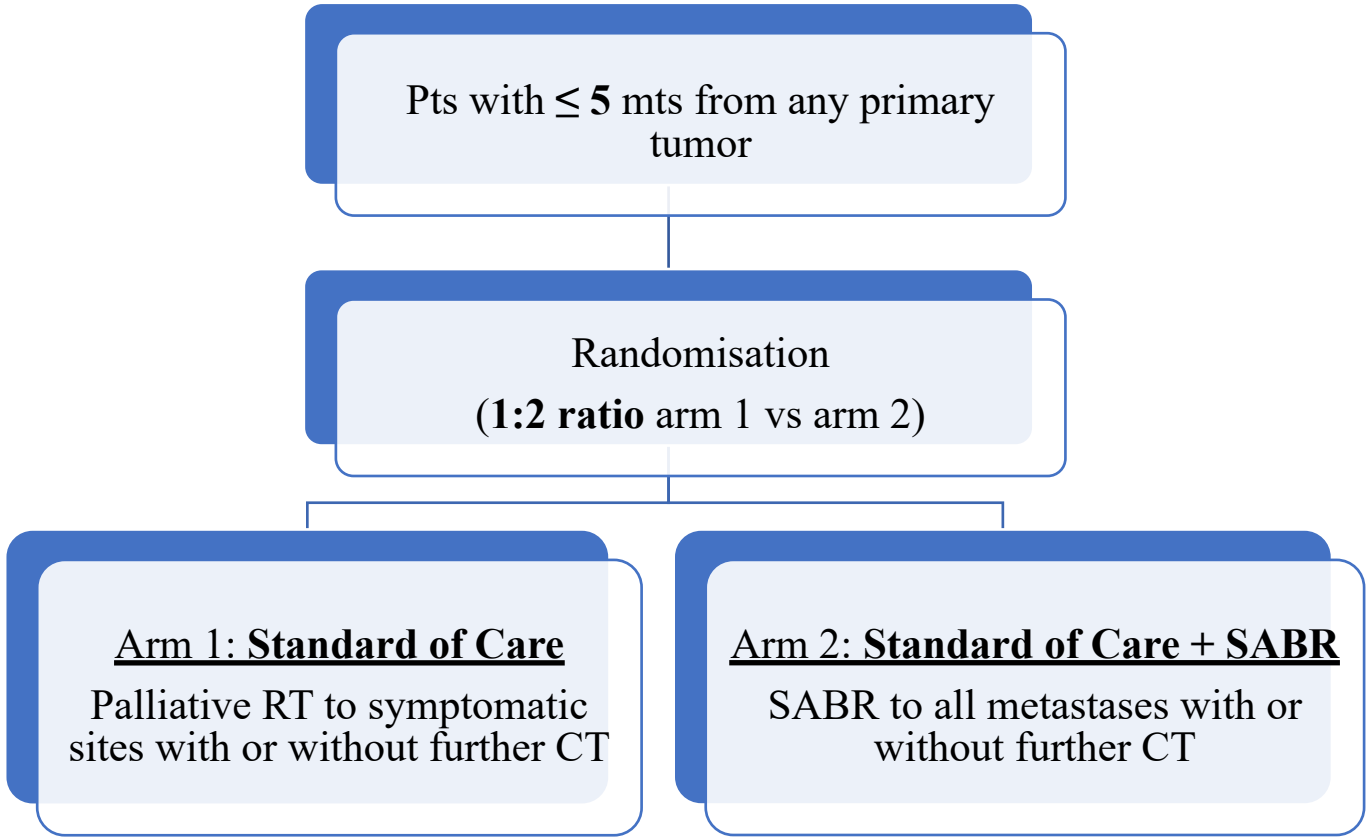
Extended long-term results of SABR-COMET

Inclusion criteria

- Age ≥ 18 years
- ECOG PS 0-1
- Life expentancy ≥ 6 months
- **Controlled primary tumour**
- **N° metastases ≤ 5** (all SABR-eligible)

Exclusion criteria

- RT contraindication (comorbidity)
- Prior RT to the site requiring treatment
- Malignant pleural effusion
- Spinal cord proximity (≤ 3 mm)
- Brain mts requiring surgical decompression

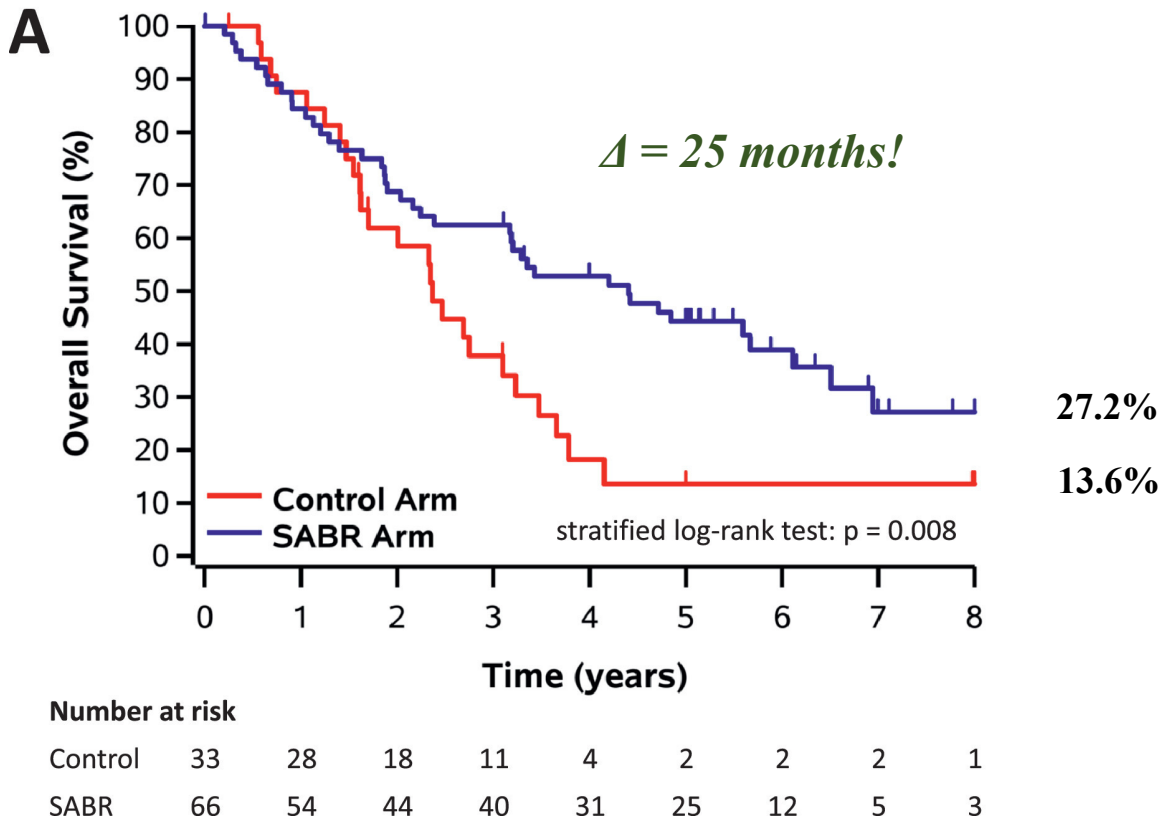


99 patients randomised between Feb 2012 and Aug 2016

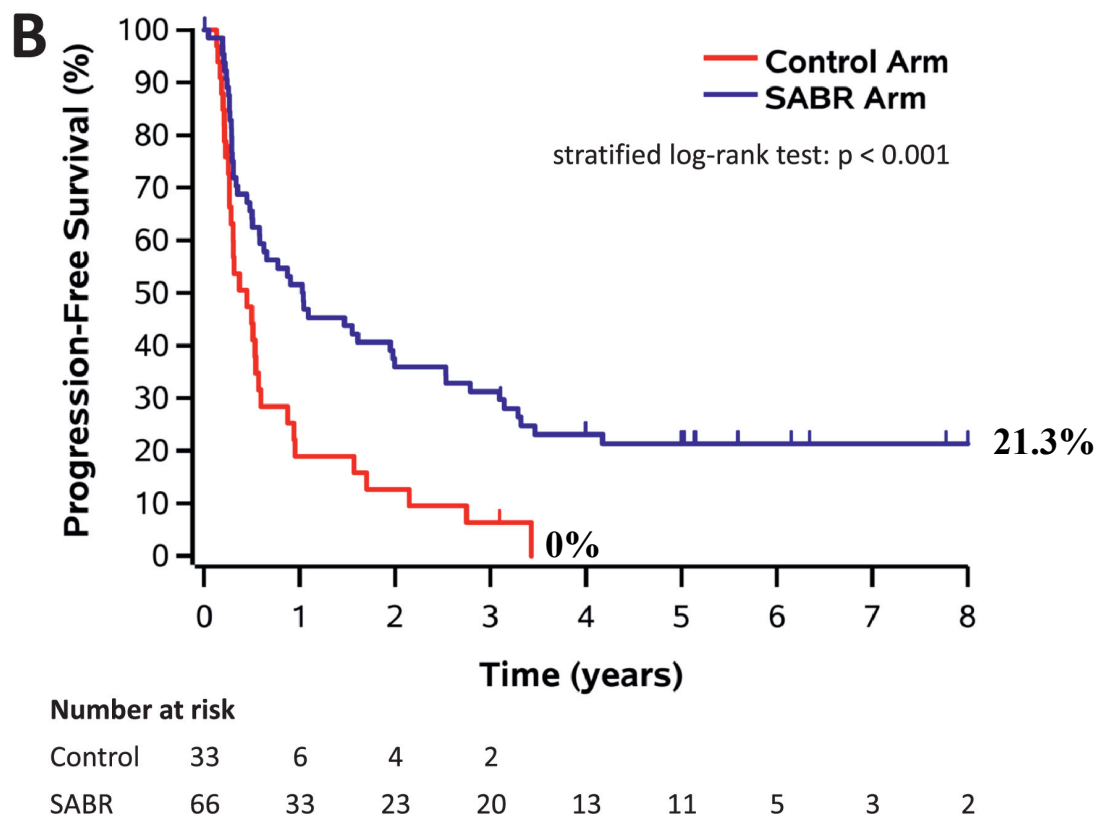
Results

Median follow-up of 68 months (5.7 years)

Overall Survival



Progression Free Survival



Median OS:

- Control arm: 28 months (95% CI 19-39 months)
- SABR arm: **53** months (95% CI 29-73 months)

Median PFS:

- Control arm: 5.4 months (95% CI 3-7 months)
- SABR arm: 12 months (95% CI 6-24 months)

Ongoing Projects

Phase III trial

Study protocol | Open Access | Published: 05 May 2020

Stereotactic ablative radiotherapy for the comprehensive treatment of 1–3 Oligometastatic tumors (SABR-COMET-3): study protocol for a randomized phase III trial

Robert Olson, Lindsay Mathews, Mitchell Liu, Devin Schellenberg, Benjamin Mou, Tanya Berrang, Stephen Harrow, Rohann J. M. Correa, Vasudeva Bhat, Howard Pai, Islam Mohamed, Stacy Miller, Famke Schneiders, Joanna Laba, Derek Wilke, Sashendra Senthi, Alexander V. Louie, Anand Swaminath, Anthony Chalmers, Stewart Gaede, Andrew Warner, Tanja D. de Gruijl, Alison Allan & David A. Palma

BMC Cancer **20**, Article number: 380 (2020) | Cite this article

Study protocol | Open Access | Published: 19 August 2019

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

SHORT COMMUNICATION | ARTICLES IN PRESS

Planning Trade-offs for Stereotactic Ablative Radiotherapy in Patients with 4-10 Metastases: A Sub-study of the SABR-COMET-10 randomized trial

Samaher Ashram, MD • Houda Bahig, MD, PhD • Aisling Barry, MD • ... Andrew Warner, MSc • Stewart Gaede, PhD • David A. Palma, MD, PhD • Show all authors

Published: June 03, 2022 • DOI: https://doi.org/10.1016/j.ijrobp.2022.05.035

SABR planning on 4-10 metastases was achievable in most cases (challenging in spinal/nodal sites)

Two possible ways to define “oligometastatic”

1. Cancers are oligometastatic when there is a chance of cure

    - We don’t have a clear definition of cure for many cancers
    - Likely a decreasing probability of cure with increasing number of mets

2. Cancers are oligometastatic when patients benefit from ablative treatment

    - Might be no upper limit- patients might benefit with 15 lesions, and that is clearly not oligo

RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

Volumetric burden of metastatic lesions drives outcomes in patients with extracranial oligometastatic disease

Yilin Cao[1] | Hanbo Chen[2] | Arjun Sahgal[2] | Darby Erler[2] | Serena Badellino[3] | Tithi Biswas[4] | Roi Dagan[5] | Matthew C. Foote[6] | Alexander V. Louie[2] | Ian Poon[2] | Umberto Ricardi[3] | Kristin J. Redmond[1]

- Volumetric metastatic burden, quantified as the summed volume of all SBRT-targeted PTVs, was **independently prognostic** for distant PFS, WSP, and OS in a time-dependent fashion.

- This remained true even after adjusting for **key confounders** (i.e.: histology, n° of OM)

[Cao et al, Cancer medicine 2021]

TROG 13.01 SAFRON II

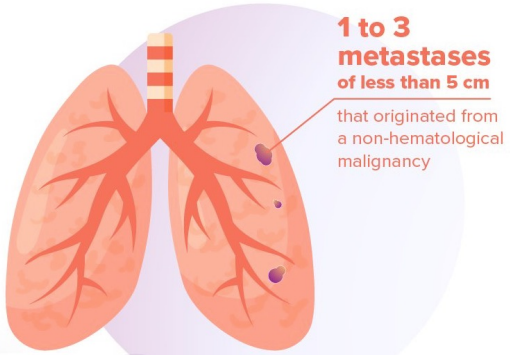
TROG CANCER RESEARCH

What is the optimal radiation approach for oligometastatic disease?

There is currently no evidence to guide an optimal approach for Stereotactic Ablative Body Radiotherapy (SABR) in patients with pulmonary oligometastases.

90 **patients** recruited between 2015 and 2018

13 **sites** across Australia and New Zealand



1 to 3 metastases of less than 5 cm that originated from a non-hematological malignancy

Randomization

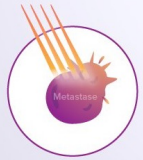
balanced by number of metastases and tumour histology

133 **metastases** treated

Median follow-up: 3 years

Multiple Fraction (MF) SABR

4 x 12Gy
over 2 weeks
Total of 48 Gy

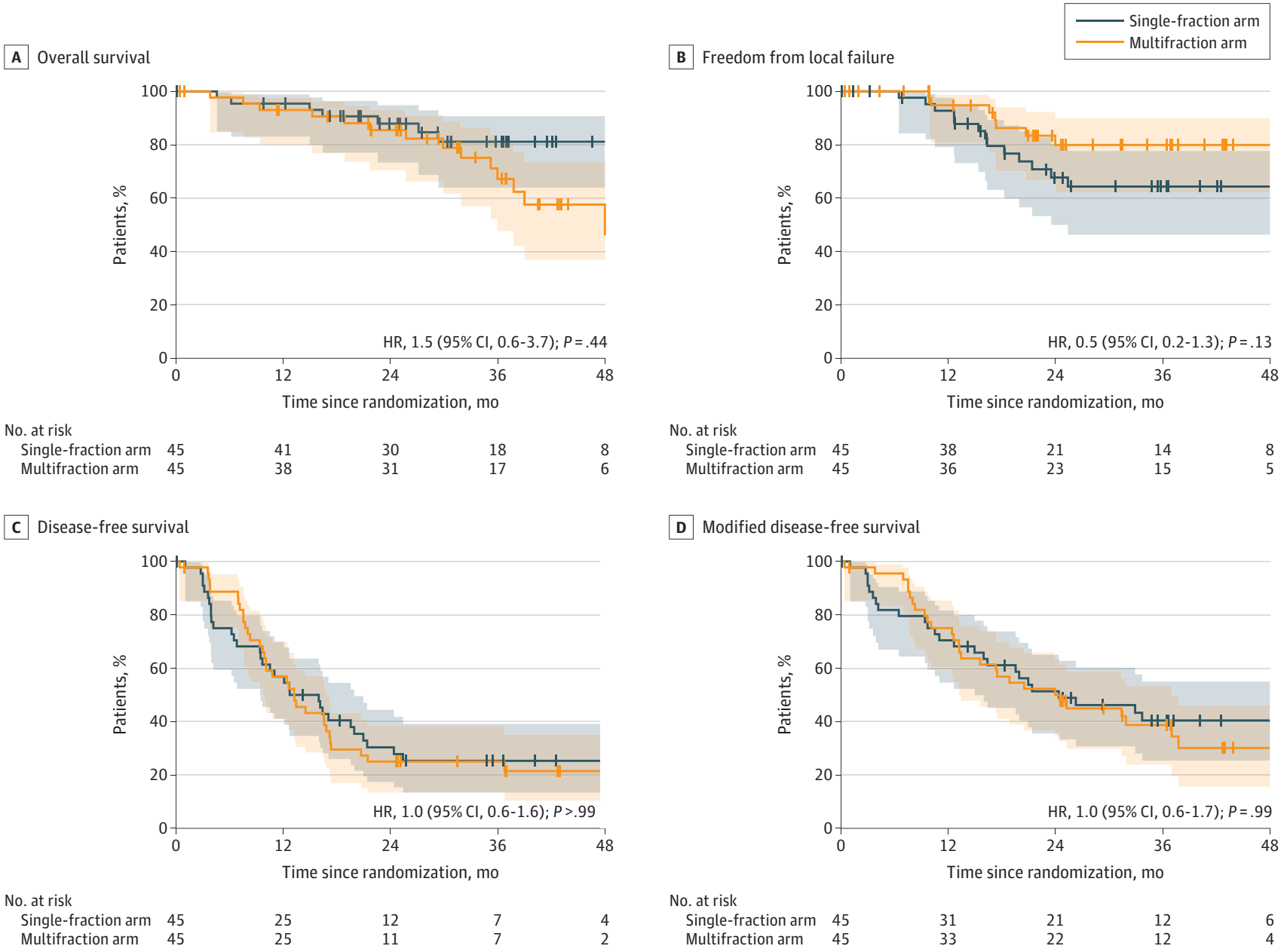


Single Fraction (SF) SABR

1 x 28Gy

[Siva et al Jama Oncol 2021]

Figure 2. Efficacy Outcomes After Stereotactic Ablative Body Radiotherapy Comparing Each Arm

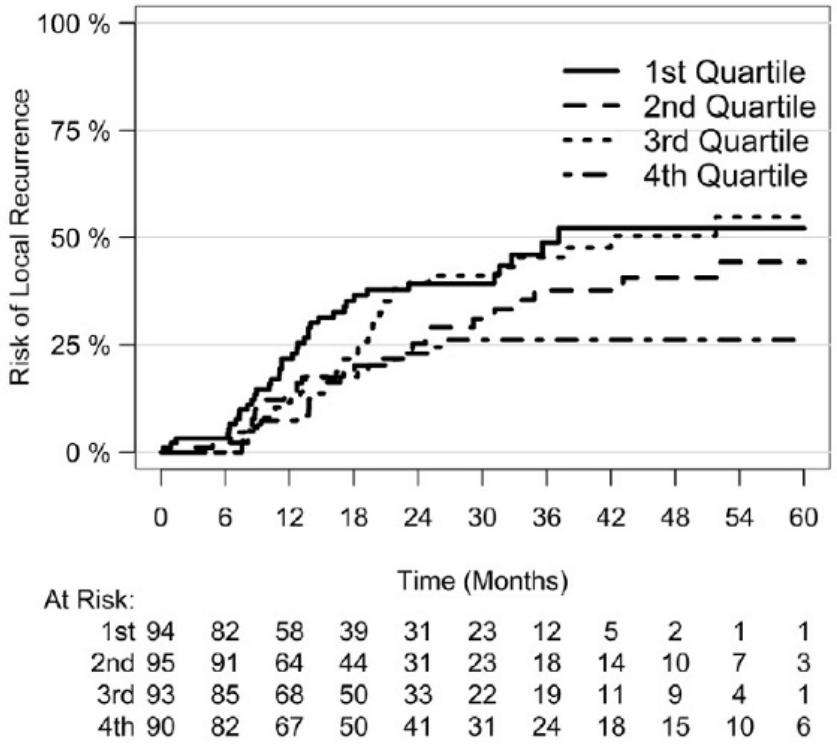


[Siva et al Jama Oncol 2021]

An analysis of a large multi-institutional database reveals important associations between treatment parameters and clinical outcomes for stereotactic body radiotherapy (SBRT) of oligometastatic colorectal cancer

Saad Sheikh [a], Hanbo Chen [b], Arjun Sahgal [b], Ian Poon [b], Darby Erler [b], Serena Badellino [c], Roi Dagan [d], Matthew C. Foote [e], Alexander V. Louie [b], Kristin J. Redmond [f], Umberto Ricardi [c], Tithi Biswas [a,*]

Radiotherapy and Oncology 167 (2022) 187–194



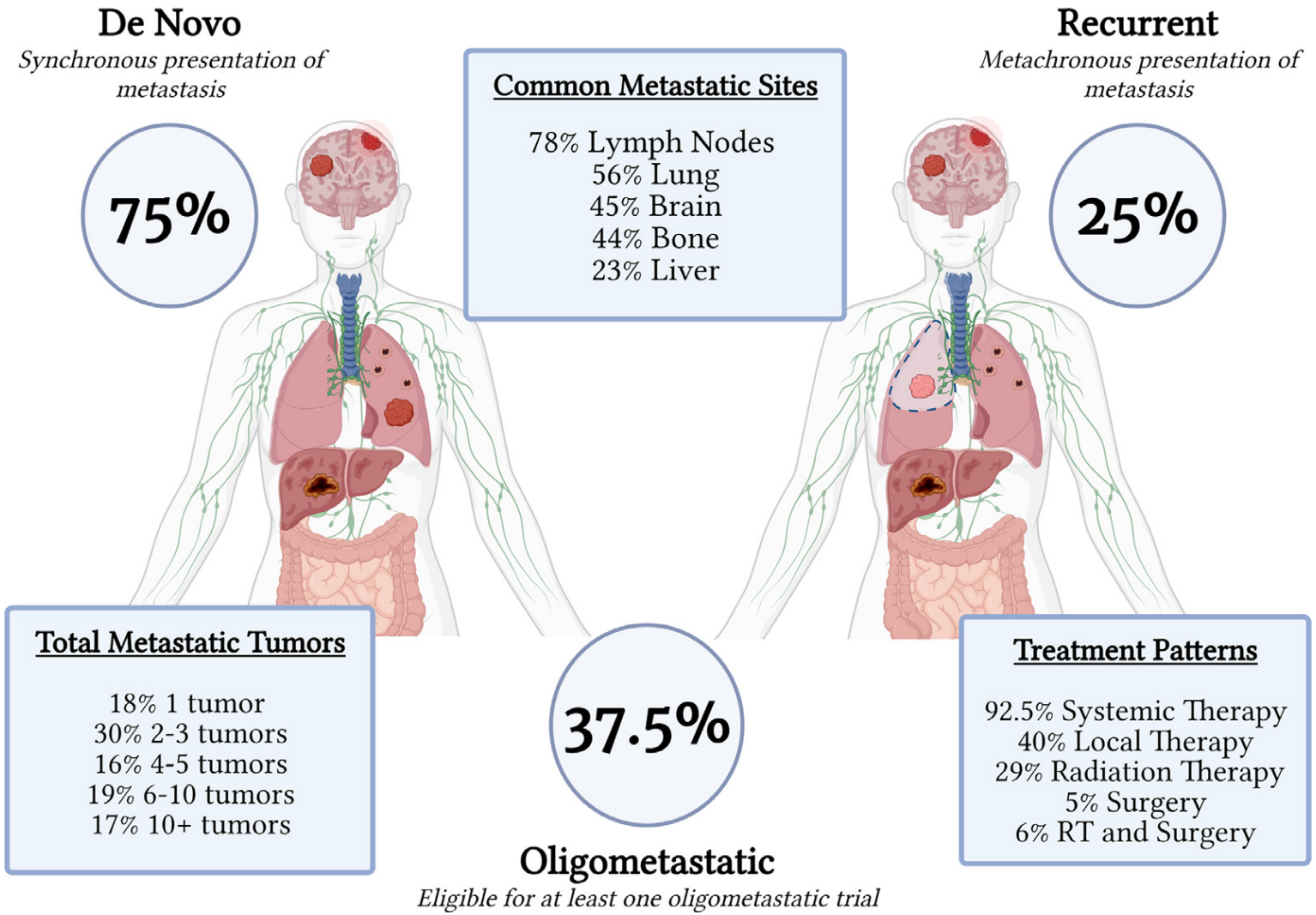
Local recurrence as a function of biological equivalent dose (BED10)

1° Quartile: 28.8 to 93.6 Gy
2° Quartile: 93.6 to 100 Gy
3° Quartile: 100 to 119.6 Gy
4° Quartile: 119.6 to 180.0 Gy

SBRT using a BED of greater than 120 Gy (4° quartile) reduces local recurrence when compared to 1° quartile (p = 0.014)

Conclusion: This large multi-institutional analysis found that the use of SBRT for oligometastatic colorectal cancer resulted in favorable overall survival. However, local recurrence is higher than expected for ablative radiation treatment. An increase in BED_{10} should be considered if feasible and safe.

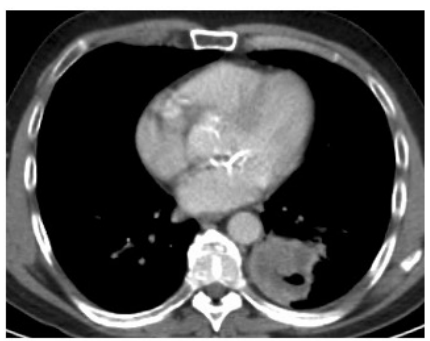
Characterization of Metastatic Non-Small Cell Lung Cancer and Oligometastatic Incidence in an Era of Changing Treatment Paradigms



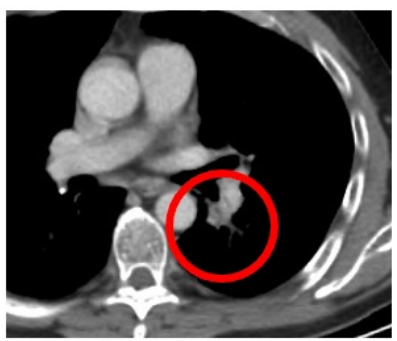
[Hyunsoo J, IJROBP 2022]

Male 54 yrs, PS 0, ex-smoker

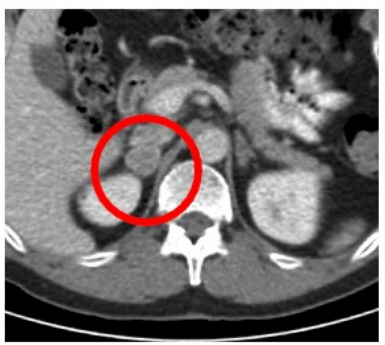
- TBLB + US-guided biopsy adrenal R - ischiorectal node :
  all proven EGFR-Wt ALK-negative lung adenocarcinoma
- Staging LLL cT2bN1M1b(adrenal R + pelvic node)



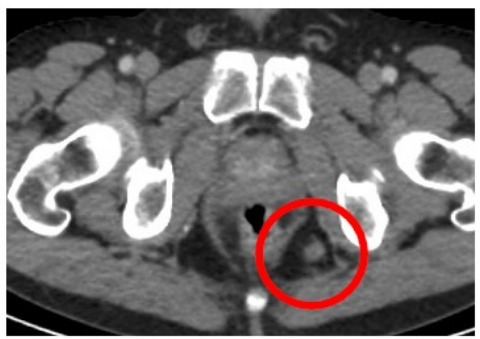
LLL 56mm



N1 station 11L



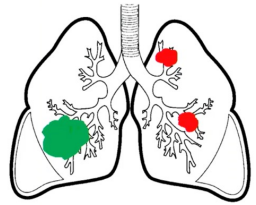
adrenal 24mm

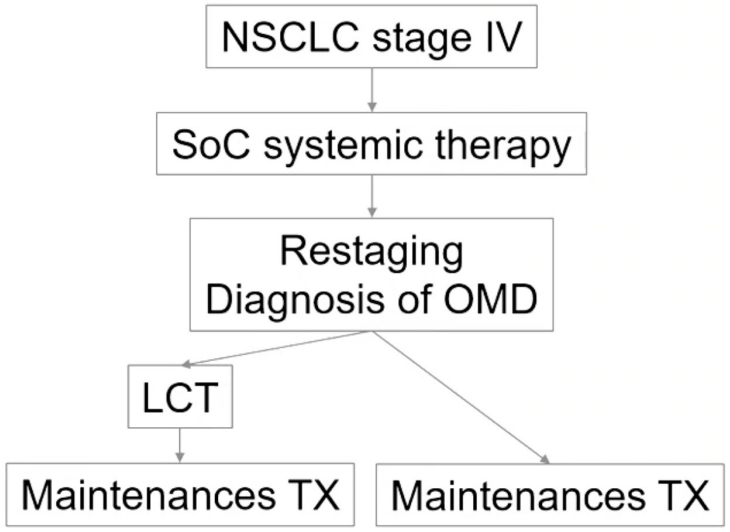


pelvic node 14mm

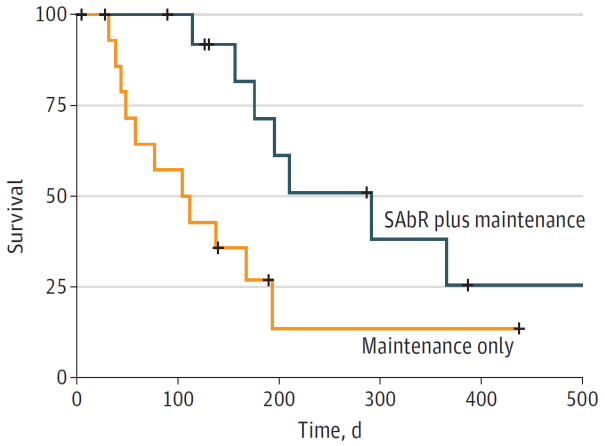
Local consolidation→ Two small but positive studies showing consistent results

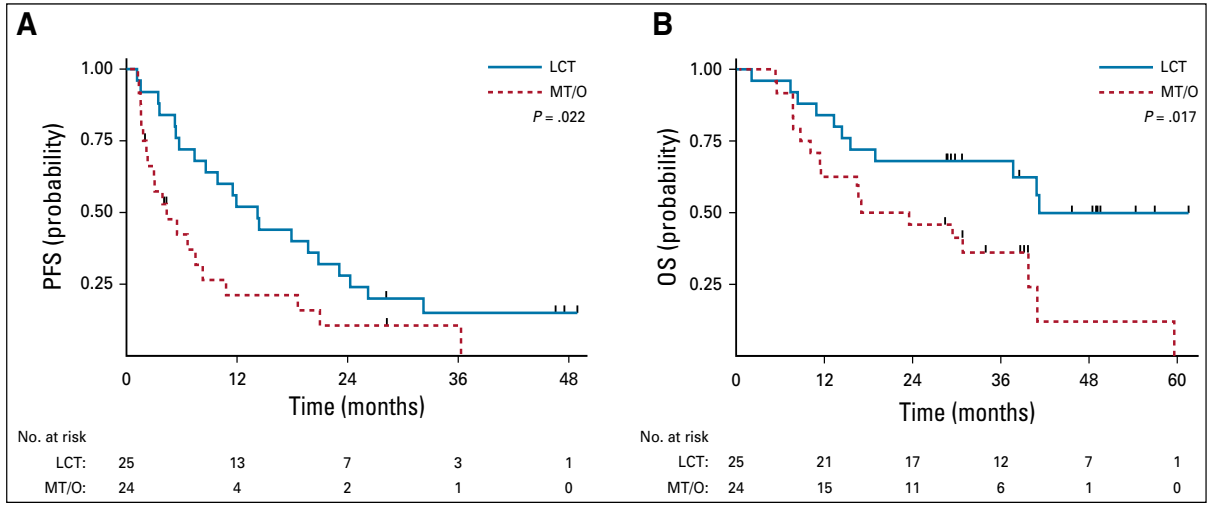
Synchronous OMD





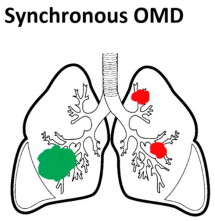
	PFS	OS	Toxicity
Iyengar et al.	9.7 vs 3.5 months (p= 0.01)	-	SABR: 29% G3, no G4-G5 Control: 20% G3-G4, no G5
Gomez et al.	14.2 vs 4.4 months (p= 0.022)	41.2 vs 17 months (p= 0.017)	SABR: 20% G3, no G4-G5 Control: 8% G3, no G4-G5





[Iyengar P et al, JAMA Oncol 2017]
[Gomez et al, JCO 2019]

Role of consolidative radiation for OM NSCLC with sensitive mutations



Multicenter, open-label, randomized phase III trial in China (January 2016 - June 2019)
200 pts EGFR mutated synchronous Oligometastatic NSCLC (adenocarcinoma) without BMs

SINDAS Interim Analysis: 68% accrual: 133 patients

[Wang et al, J Natl Cancer Inst 2022]

Adult patients with *EGFR*-mutated NSCLC;
≤5 metastases;
≤2 lesions in any organ;
ECOG PS 0-2
(**N = 133**)

→ **EGFR TKI*** + **SBRT** 25-40 Gy in 5 fractions (n = 68)

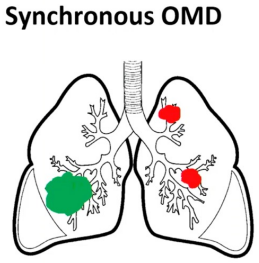
→ **EGFR TKI*** (n = 65)

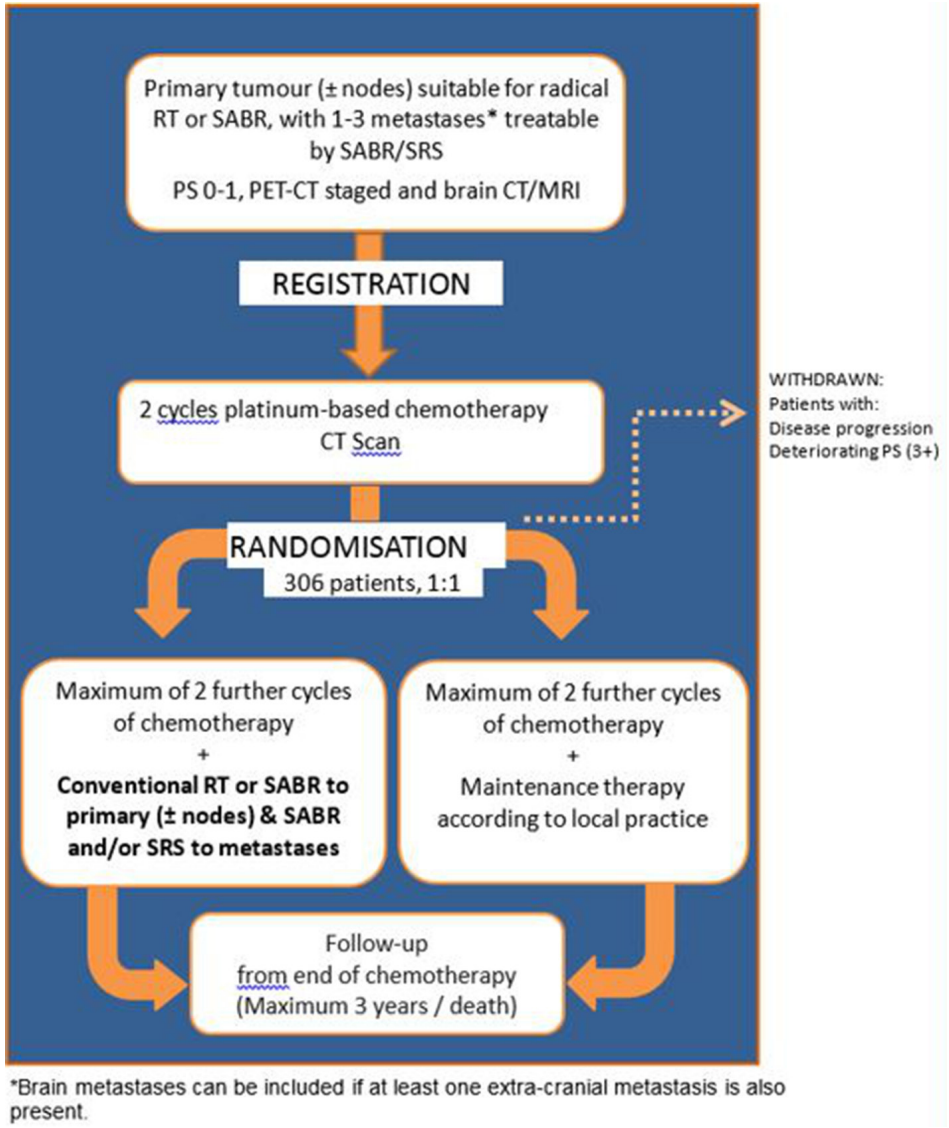
→ ***Follow-up***

*Gefitinib 250 mg QD, erlotinib 150 mg QD, or icotinib 125 mg TID.

Median Outcome, Mos	EGFR TKI + SBRT (n = 68)	EGFR TKI Only (n = 65)	HR
PFS (primary endpoint)	20.2	12.5	0.618 (95% CI: 0.394-0.969; log-rank *P* < .001)
OS (secondary endpoint)	25.5	17.4	0.682 (95% CI: 0.456-1.001; log-rank *P* < .001)

Ongoing studies Local Consolidation→ SARON trial (UK)

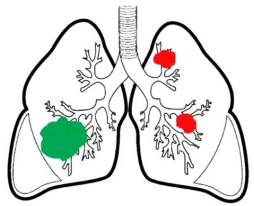




*Brain metastases can be included if at least one extra-cranial metastasis is also present.

- Opened in 2015
- Actively enrolling across 21 study locations
- Expected accrual: 340 patients at august 2022

Ongoing studies Local Consolidation→ LONESTAR trial



N = 270
Eligibility:
- Stage IV NSCLC
- Immunotherapy naïve
- EGFR and ALK wild type
- Must have tissue available

Stratification:
- Histology: SCC vs. non-SCC
- Number of metastasis: oligo vs. poly
- Prior therapy: naïve vs. chemo

Ipilimumab 1 mg/Kg, q 6 w **+ Nivolumab** 3 mg/Kg, q 2 w **12 weeks**

Restaging scans **at least** 10 days after the last day of nivolumab.

Non-Progressive Disease RANDOMIZATION

Ipilimumab 1 mg/Kg, q 6 w **+ Nivolumab** 3 mg/Kg, q 2 w **(up to 2 yrs)**

Progression, Off Treatment, Continue to f/u for OS

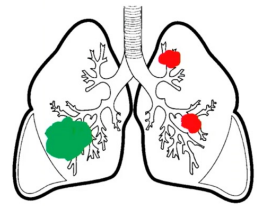
LCT (no sooner than 14 days after the last dose of nivolumab):
A) If ≤ 3 lesions, LCT to all lesions
B) If > 3 lesions, LCT to number of lesions at physician discretion

Ipilimumab 1 mg/Kg, q 6 w **+ Nivolumab** 3 mg/Kg, q 2 w **(up to 2 yrs)**

Progression, Off Treatment, Continue to f/u for OS

Co-Primary Endpoints:
1 - OS in the overall population
2 - OS in the oligometastatic subgroup (if no significant difference in full study population)

Ongoing studies: Local Consolidation→ NORTHSTAR trial



Eligibility
- TKI naïve *EGFR* mut
Or
- Acquired T790M *EGFR*
no prior 3rd gen TKI

Enrollment Window
0-12 weeks

Osimertinib
6-12 weeks

Osimertinib
80 mg daily PO

n = 60

Non-PD
Randomization

n = 60

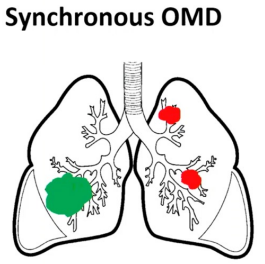
Primary Outcome: PFS
Secondary Outcomes: OS, time to progression of target lesions, time to appearance of new metastases, PFS in oligomet subgroup, safety

If ≤ 3 lesions LCT to all lesions
If > 3 lesions LCT to number of Lesions at physician discretion

Osimertinib
80 mg daily PO

Primary Endpoint:
PFS
Stratification Factors:
1) Line of therapy
2) ≤ 3 vs. > 3 mets
3) PR vs. SD
4) CNS Mets (yes vs. no)

Ongoing studies: Local Consolidation→ BRIGHTSTAR trial



Eligibility
TKI-naive
ALK+ advanced
NSCLC

Enrollment Window

Brigatinib × 8 weeks

CT / PET
Brain MRI

non-PD

Local
Consolidative
Therapy ≤ 3 wks

Brigatinib
until PD

If ≤ 3 active sites of disease then LCT to at sites

If > 3 active sites of disease then LCT to sites at physican discretion

1° endpoint
- Safety and feasibility

2° endpoint
- PFS, OS
- Time to progression of non-LCT lesions

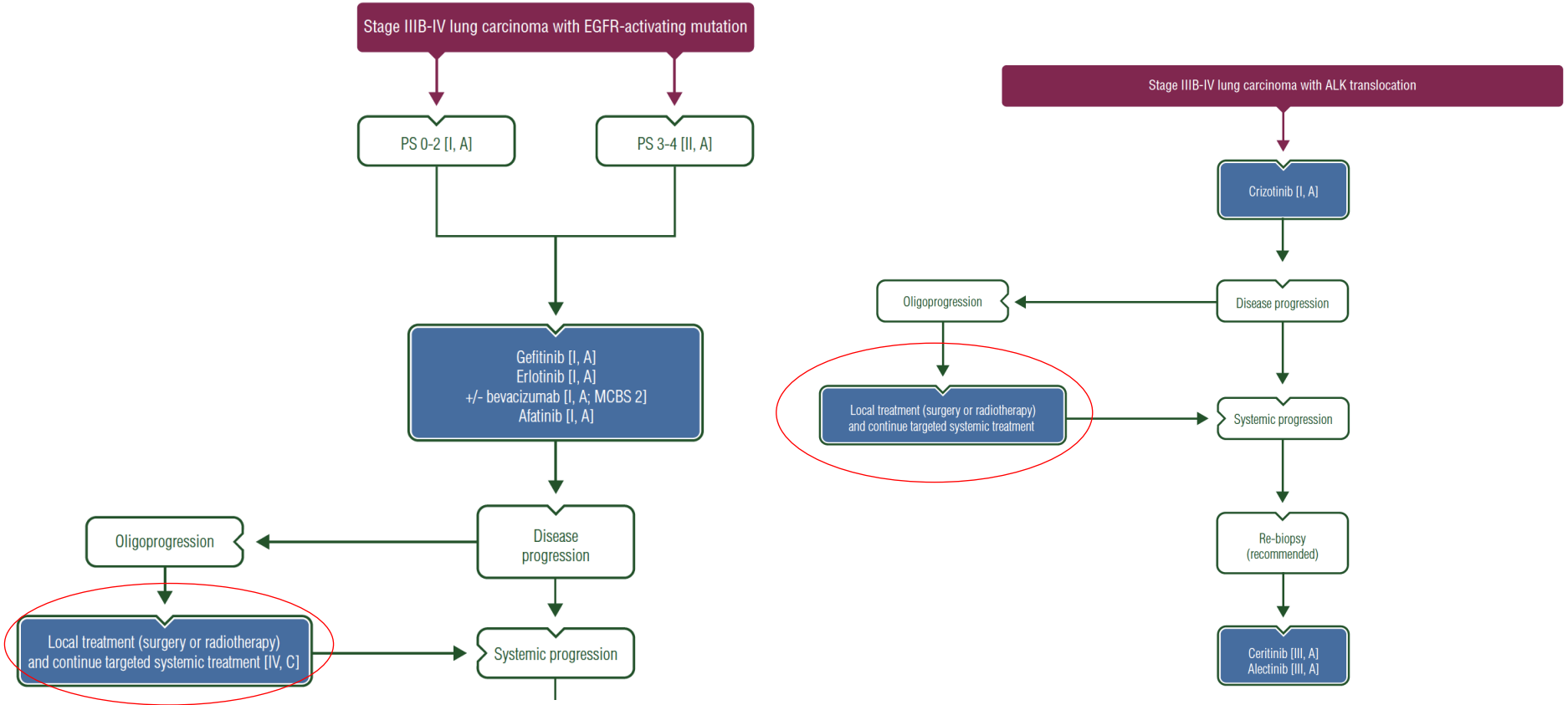
LAT in oligoprogressive disease

Author	Histology	Systemic Therapy	N	Local Therapy	Median PFS (months)	Median OS (months)
Shukuya 2011	NSCLC EGFR+	Gefitinib/ Erlotinib	17 intracranial	SRS, WBRT	2.7 with lepto 4.8 w/o lepto	13.4
Weickhardt 2011	NSCLC EGFR+ ALK+	Erlotinib/ crizotinib	25 Intracranial or extracranial	SRS, WBRT, RT, Surgery	6.2	N/A
Yu 2013	NSCLC EGFR+	TKI	18 Extracranial	RFA, SBRT, Surgery, RT	10	41
Gan 2014	NSCLC ALK+	Crizotinib	14 Extracranial	Hypofx RT, SBRT, Surgery	5.5	N/A

Annals of Oncology 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello[1], F. Barlesi[2], R. Califano[3,4], T. Cufer[5], S. Ekman[6], M. Giaj Levra[7], K. Kerr[8], S. Popat[9], M. Reck[10], S. Senan[11], G. V. Simo[12], J. Vansteenkiste[13] & S. Peters[14] on behalf of the ESMO Guidelines Committee*

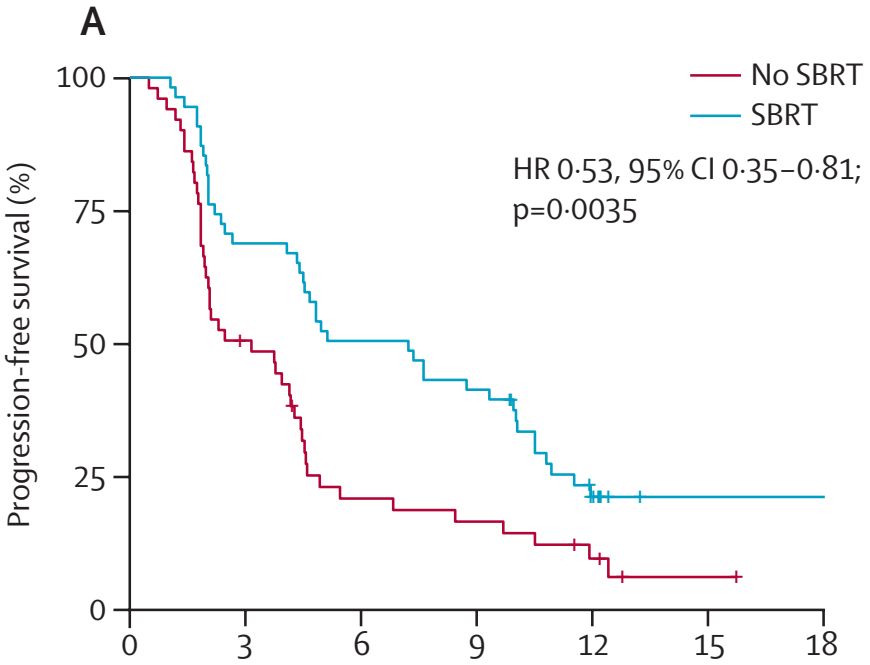


LAT in oligoprogressive disease

CURB trial (breast & NSCLC) (NCT03808662)

a Phase II, randomized, controlled, single-institution study from MSKCC
SABR to all sites of oligoprogression (up to 5) versus SOC palliative therapy alone

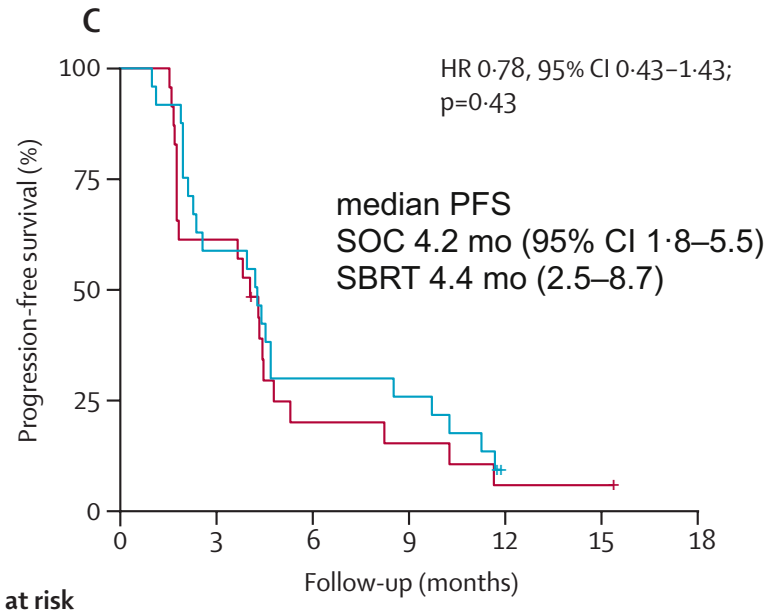
Breast 47 pts + Lung 59 pts (median follow up: 52 weeks)



Median PFS: 3.2 months (95% CI 2.0–4.5) SOC
7.2 months (4.5–10.0) SBRT group

CURB Trial: Progression- free Survival (median follow up: 52 weeks)

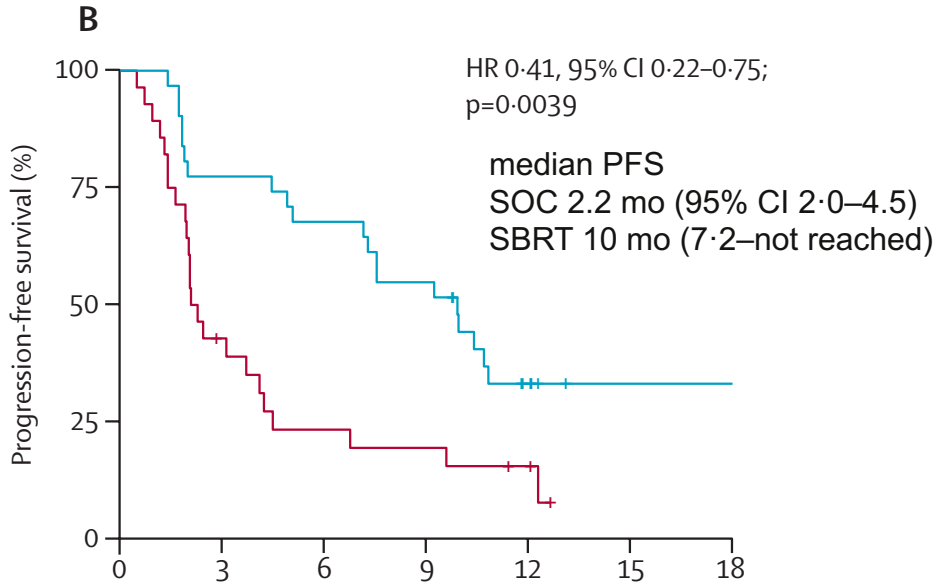
BREAST



Number at risk (number censored)							
No SBRT	23 (0)	14 (0)	4 (1)	3 (1)	1 (1)	1 (1)	0 (2)
SBRT	24 (0)	14 (0)	7 (0)	6 (0)	2 (0)	0 (2)	0 (2)

Treatment arm	Time 6	Time 9
No SBRT	19% (8%, 46%)	14% (5.1%, 41%)
SBRT	29% (16%, 54%)	25% (13%, 50%)

NSCLC

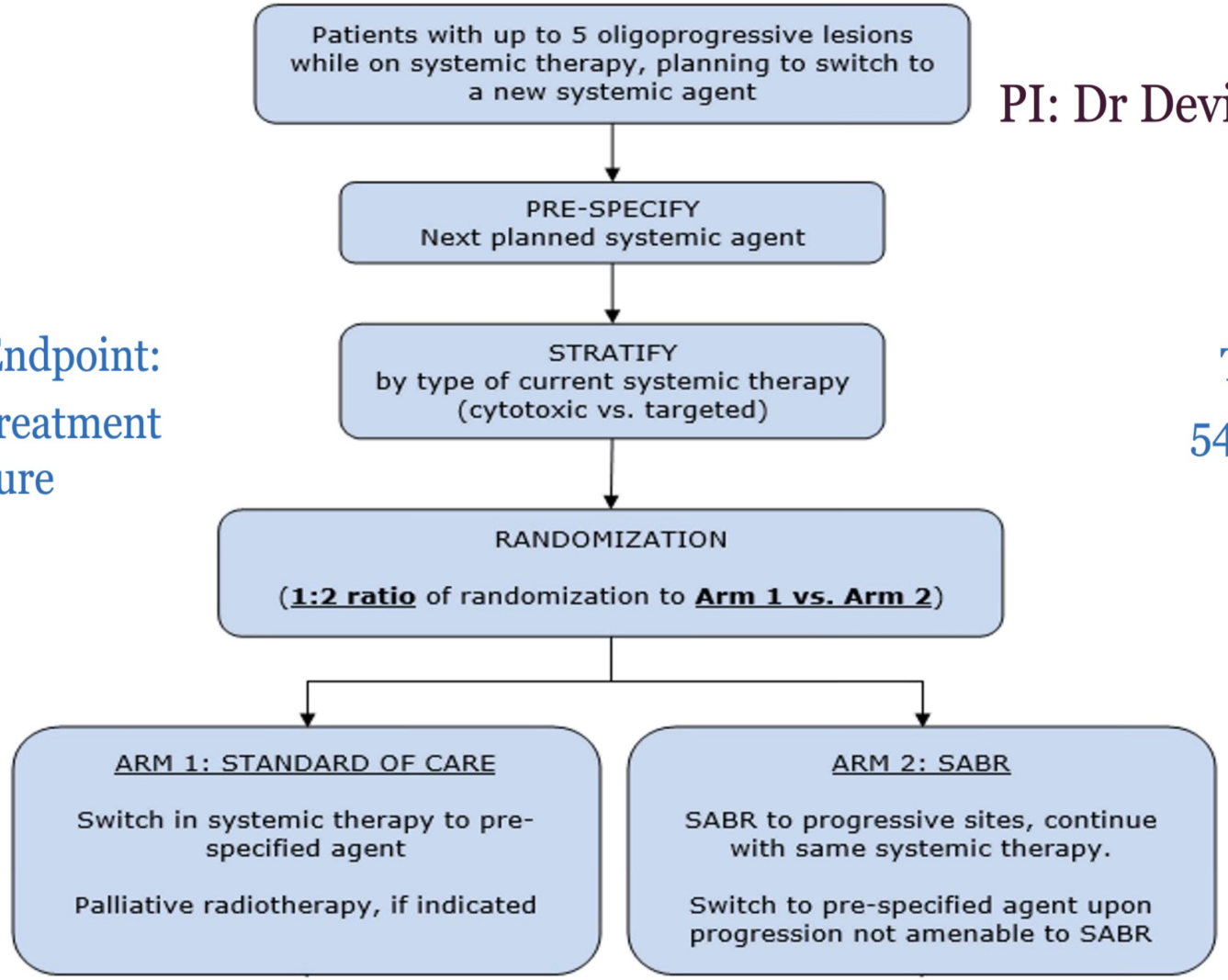


Number at risk (number censored)							
No SBRT	28 (0)	11 (1)	6 (1)	5 (1)	3 (2)	0 (4)	0 (4)
SBRT	31 (0)	24 (0)	21 (0)	17 (0)	5 (6)	1 (10)	1 (10)

Treatment arm	Time 6	Time 9
No SBRT	23% (12%, 47%)	19% (9%, 42%)
SBRT	68% (53%, 86%)	55% (40%, 75%)

Ongoing studies→ LAT in oligoprogressive disease

STOP trial: **S**BR**T** for **O**ligo-**P**rogression in NSCLC (NCT02756793)



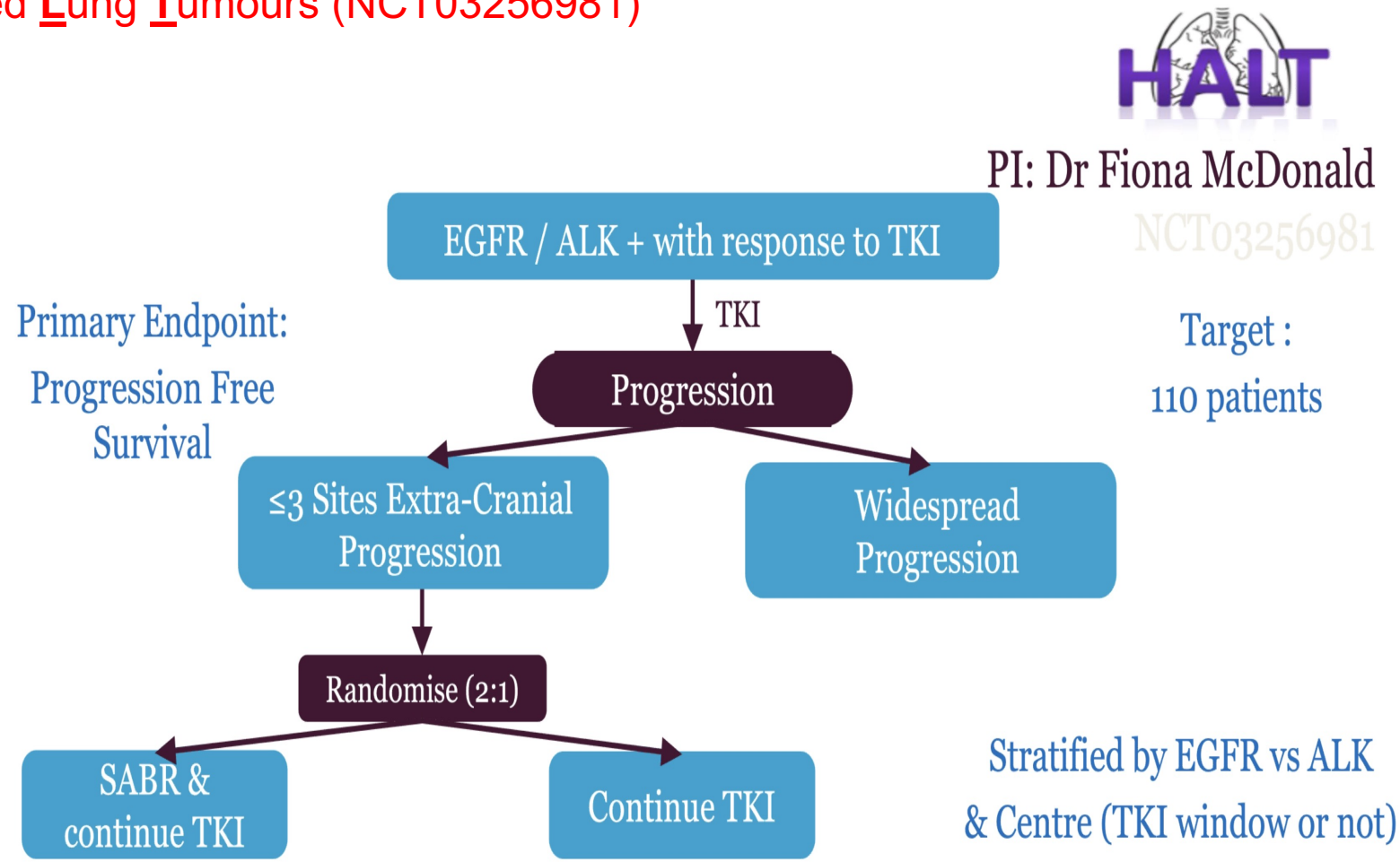
PI: Dr Devin Schellenberg
NCT02756793

Primary Endpoint:
Time to Treatment Failure

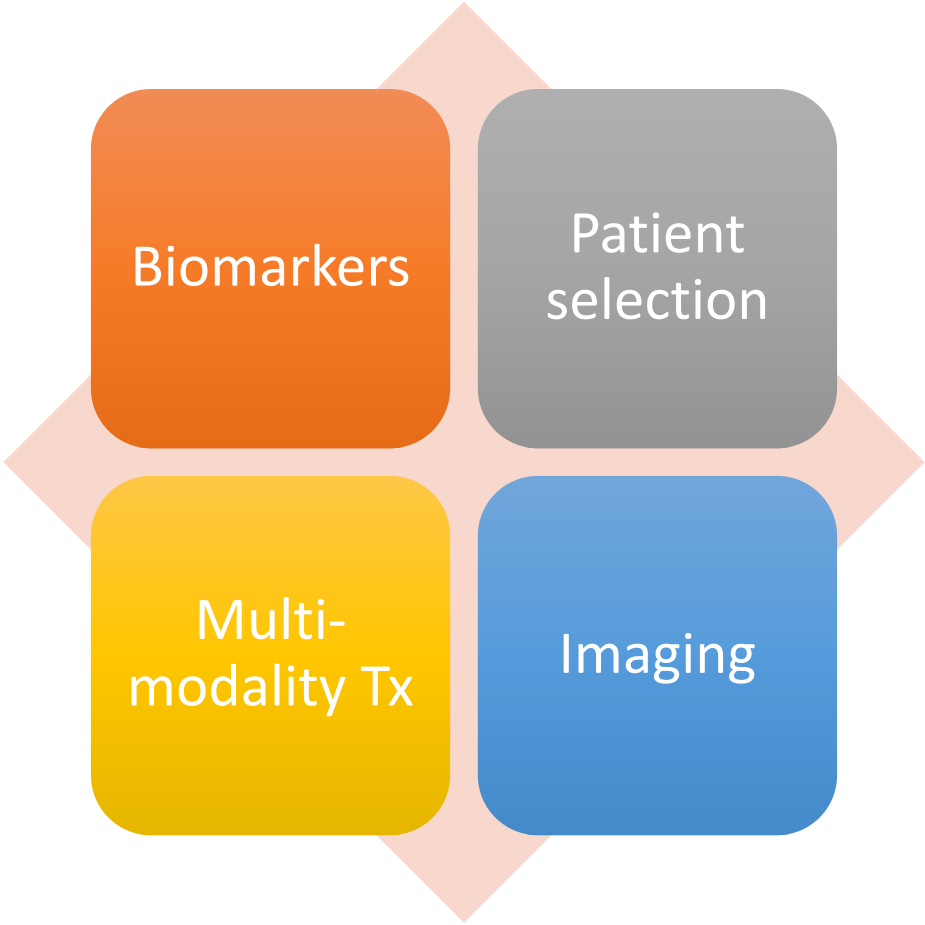
Target:
54 patients

Ongoing studies→ LAT in oligoprogressive disease

HALT trial: Targeted therapy with or without dose intensified radiot**H**erapy for oligo-progressive disease in oncogene-**A**ddicted **L**ung **T**umours (NCT03256981)



Room for improvement



AND: better evidence……..

How to select patients ?

	Patient selection	Toxicity risk	Timing
Best candidates	Good performance status Low burden of disease (one oligometastasis) Multiple systemic therapy options	Small lesions Treatment unlikely to cause toxicity (eg, small resection or tumor far from critical structures)	Metachronous oligometastases Responding to systemic therapy
Less favorable	Borderline performance status (eg, ECOG 2) Moderate burden of disease (two to five oligometastases)	Larger lesions Moderate risk of toxicity or impact on organ function	Synchronous oligometastases Overlapping toxicities (eg, immunotherapy and thoracic radiotherapy)
Unfavorable	Poor performance status High burden of disease (> 5 metastases)	Very large lesions High risk of toxicity Comorbidities precluding radiotherapy or surgery	No response to systemic therapy Rapid disease progression

[Jasper et al JCO 2022]

Development of a Prognostic Model for Overall Survival in Patients With Extracranial Oligometastatic Disease Treated With Stereotactic Body Radiation Therapy

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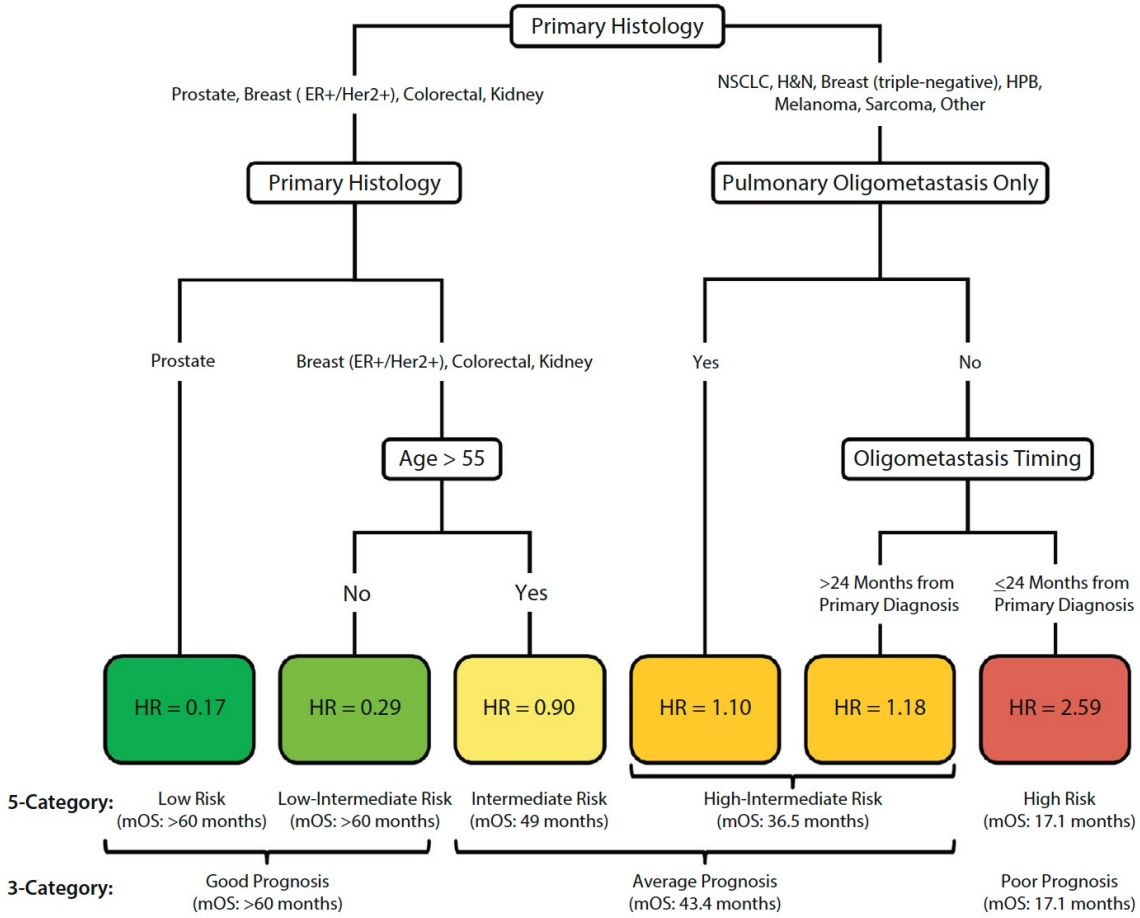
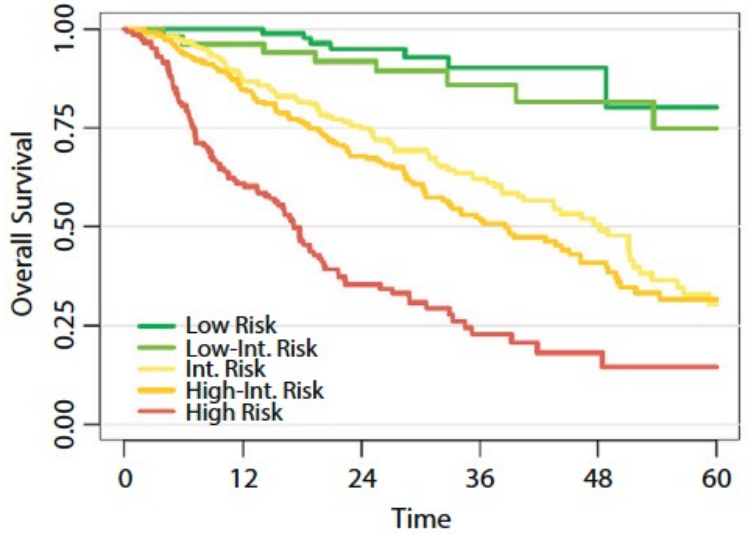
INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org
2022





Number at risk:

Low	104	93	59	26	9	1
Low-Int.	52	47	38	22	12	9
Int.	237	188	132	75	36	13
High-Int.	239	192	123	67	35	16
High	143	82	35	14	5	1

Future evidence generation

primary tumour

- type & stage
- treatment & response

oligometastases

- definition & diagnosis
- timing
- numbers & size
- nodal *vs.* distant
- organs & location

treatment

- dose & fractionation
- technique & technology
- other treatment modalities

trial & endpoints

- survival *vs.* intermediary endpoints
- QOL & PROMs
- costs

ESTRO & EORTC initiative:

OligoCare

A Pragmatic Observational Basket Study to Evaluate Radical Radiotherapy for Oligo-Metastatic Cancer Patients

ESTRO

EORTC

The future of cancer therapy