SBRT nella malattia oligometastatica: differire o integrare la terapia sistemica?

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DI PAVIA

DISCLOSURE

- No conflicts of interest to disclose

Bibliometric Analysis of the Top-Cited Publications and Research Trends for Stereotactic Body Radiotherapy

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TABLE 3 | Research domains of the 100 most cited papers in SBRT until 2021.

Research domains[a]	Number of papers	Total citations	Average citations per year (per paper)	Publication year
Primary carcinoma	54	15475	31.94	2002-2019
Lung cancer	33	10683	36.77	2002-2019
Prostate carcinoma	7	1445	21.90	2009-2013
Liver carcinoma	9	2383	27.74	2006-2016
Pancreatic carcinoma	5	964	21.71	2008-2015
Metastatic carcinoma	38	8562	30.80	2002-2020
Spinal metastasis	8	1415	17.27	2009-2013
Oligometastases[b]	30	7147	34.40	2002-2020
Radiobiology	2	600	25.66	2012-2014
Radiophysics	3	527	11.11	2000-2009
Clinical practice of SBRT	8	2395	27.43	2004-2016
SBRT + immunotherapy	4	786	63.32	2016-2019

[a]*Some papers belonged to two domains.*
[b]*The studies about oligometastases included metastases in multiple sites.*

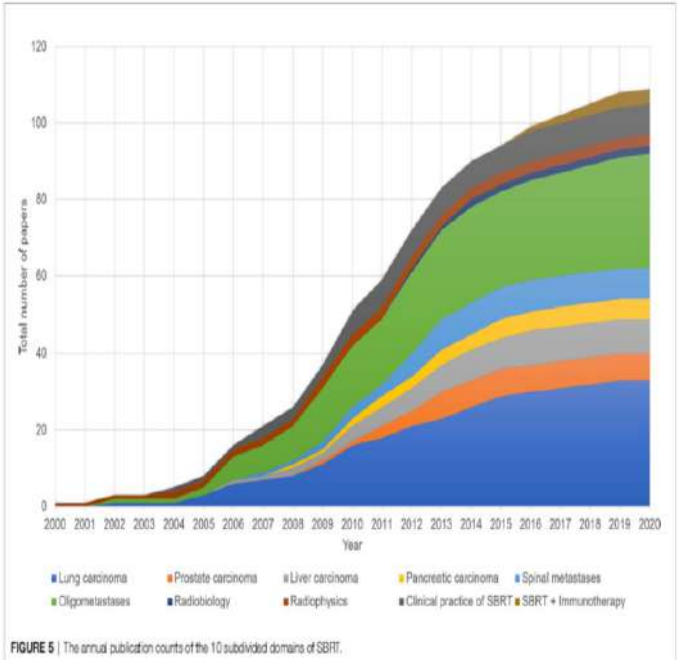


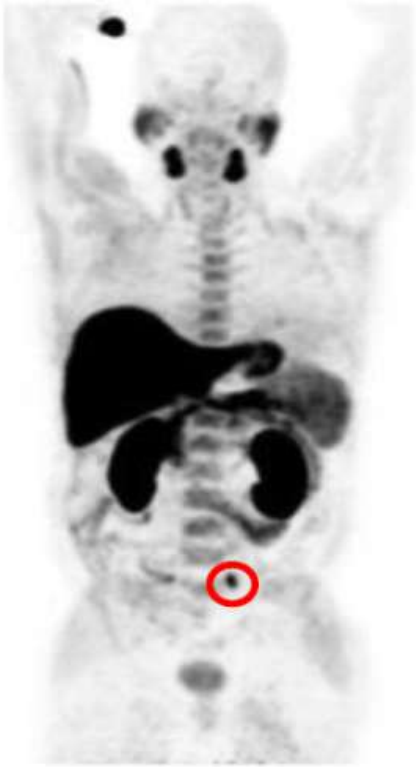
FIGURE 5 | The annual publication counts of the 10 subdivided domains of SBRT.

TABLE 1 | The 10 most cited papers in SBRT until 2021.

Rank	Title	Corresponding Author	Journal	Year	Total citations	Average citations per year (rank)
1	Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer	Timmerman	JAMA	2010	1688	146.78 (2)
2	Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer	Timmerman	J. Clin. Oncol.	2006	1009	67.64 (7)
3	Stereotactic body radiation therapy: The report of AAPM Task Group 101	Benedict	Med. Phys.	2010	949	85.62 (6)
4	Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials	Chang	Lancet Oncol.	2015	818	130.88 (4)
5	Outcome in a Prospective Phase II Trial of Medically Inoperable Stage I Non-Small-Cell Lung Cancer Patients Treated with Stereotactic Body Radiotherapy	Baumann	J. Clin. Oncol.	2009	620	[illegible]
6	Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial	Palma	Lancet	2019	588	252 (1)
7	Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study	Fakiris	Int. J. Radiat. Oncol. Biol. Phys.	2009	577	[illegible]
8	Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases	Scheffer[a]	J. Clin. Oncol.	2009	572	46.07 (14)
9	Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame	Nagata	Int. J. Radiat. Oncol. Biol. Phys.	2005	481	30.54 (30)
10	Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma	Bujold	J. Clin. Oncol.	2013	441	52.92 (10)

Oligometastases: do you believe?

- An intermediate status with favorable survival compared to widespread metastatic disease
- No consensus definition, but somewhere around ≤ 5 lesions
- Increasingly diagnosed due to:
  - Closer patient monitoring
  - Molecular imaging



Courtesy of T. Zilli

Hellman S, Weichselbaum R.
Oligometastases.
Journal of Clin Oncol, Vol 13, No 1 (January), 1995: pp 8-10

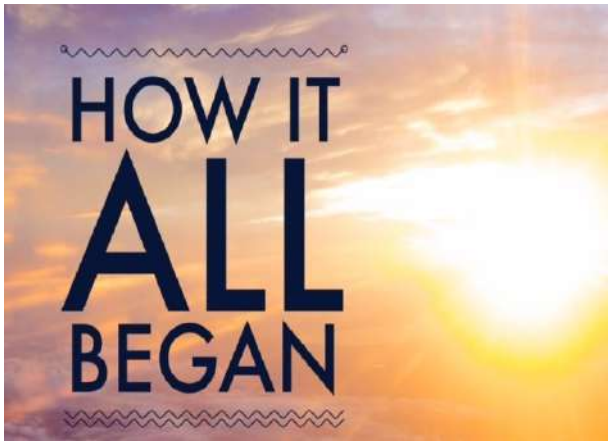
EDITORIAL

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 theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis 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 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 are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, 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

- There is a progression of malignancy during clinical evolution of cancer
- The likelihood, number and sites of metastases may reflect the state of tumor development
- There are tumor states intermediate between purely localised and widespread metastatic
- Some oligometastatic patients are amenable to a curative therapy

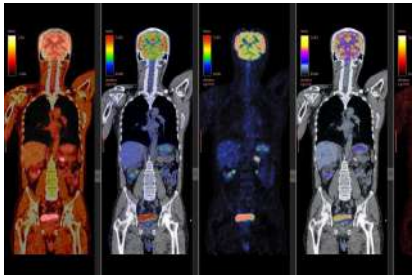


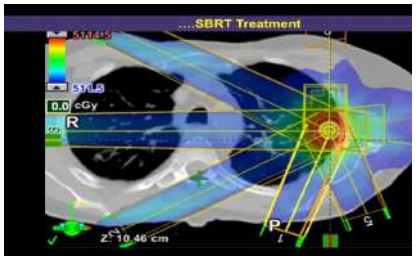
a) **Improved diagnostic for early and accurate detection of low disease burden**

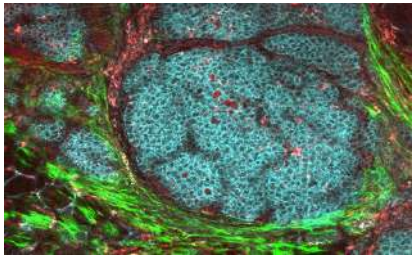
b) **Clinical implementation of high-precision locally-ablative treatments**

c) **Effective systemic treatments** → **prolonged OS**

d) **Better biological and clinical understing of tumor behaviour**







Schanne DH et al, Cancer Treat Rev, 2019

Characterization of Oligometastatic disease

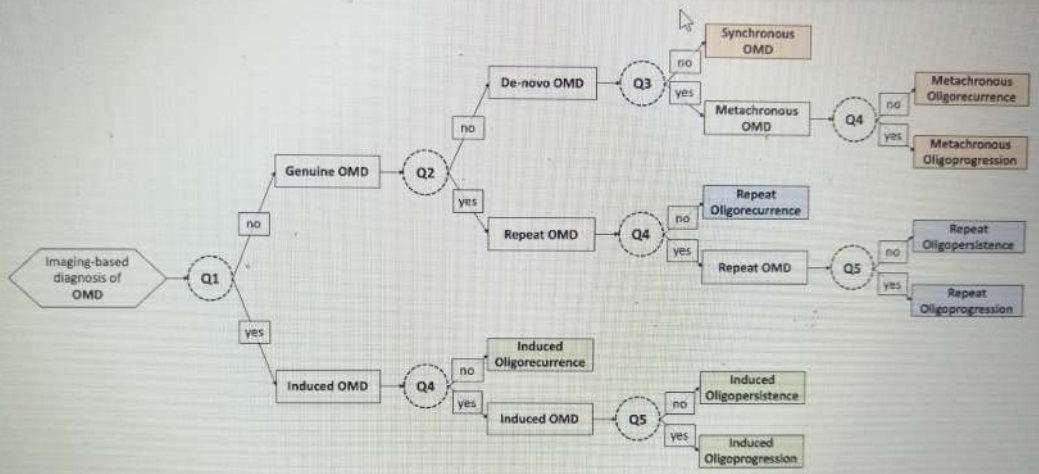
Oligo-metastases ?

Oligo-progression ?

Oligo-persistence?

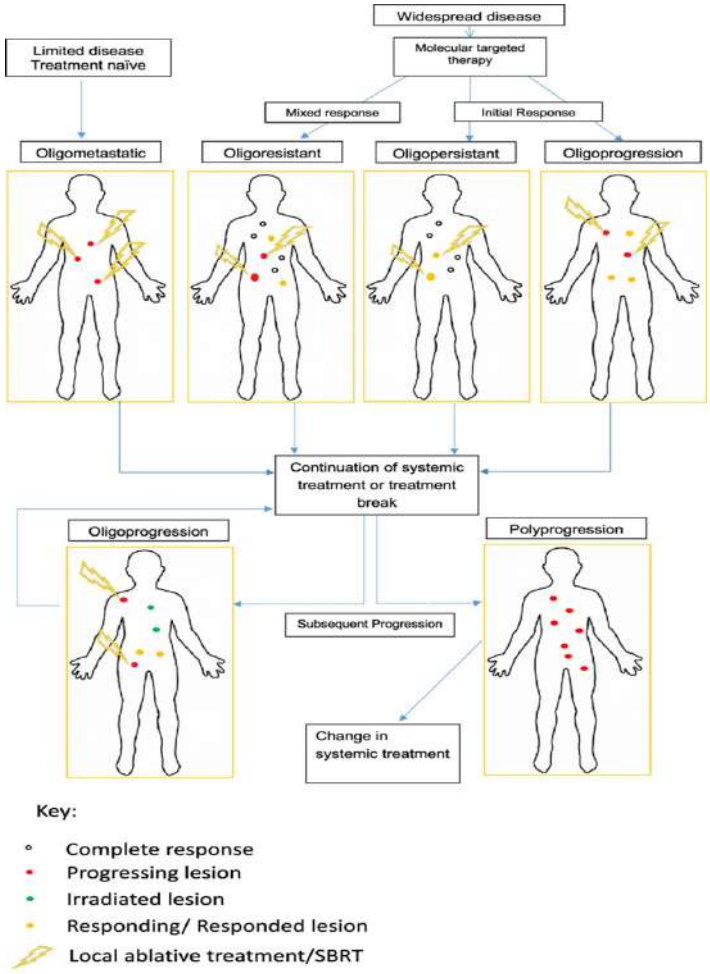
Poly-confusion !?

ESTRO / EORTC OMD classification

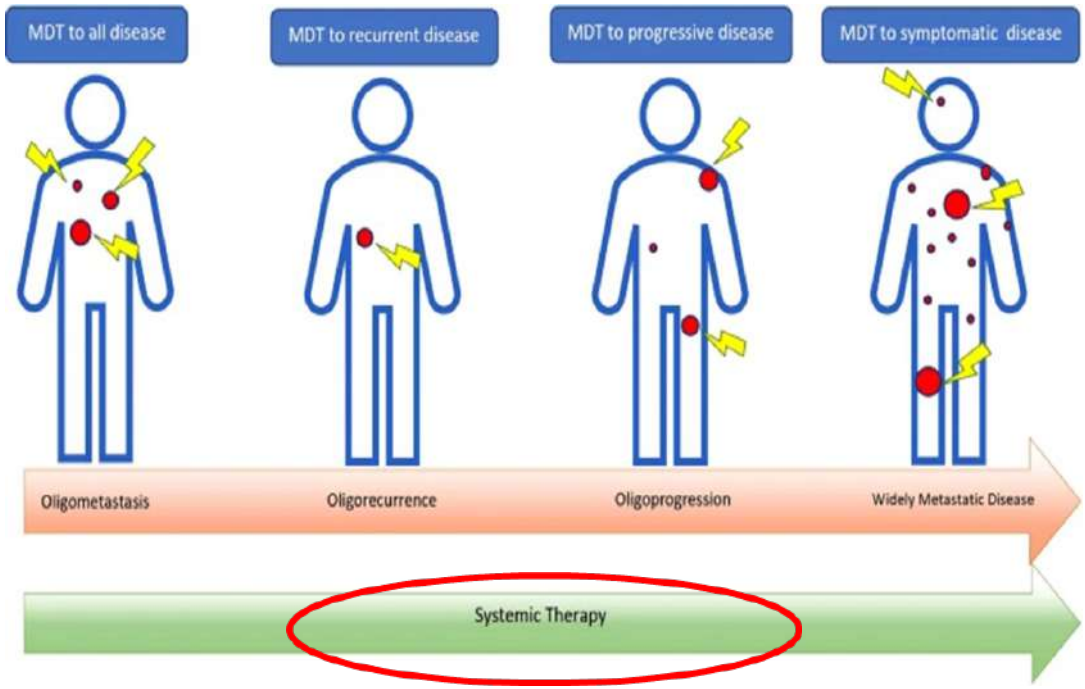


Decision tree resulting in 9 different states of OMD

- Too complex ?



Courtesy of M. Guckenberger



Oligometastatic Disease Management: Finding the Sweet Spot

Petr Szturz[1], Daan Nevens[2,3] and Jan B. Vermorken[3,4]*

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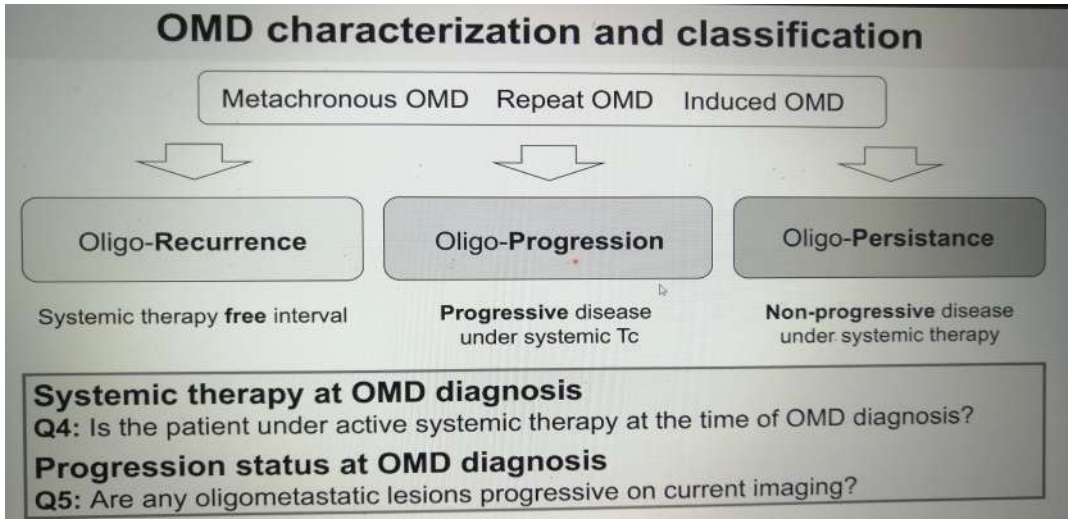
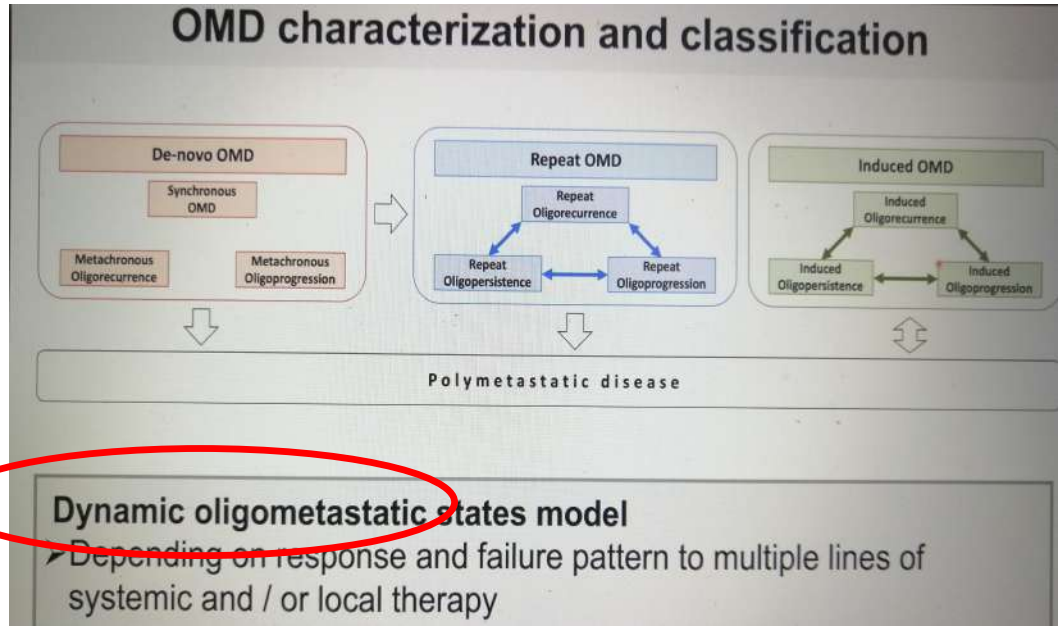




SABR-COMET (2019)

STOMP (2018)

ORIOLE (2019)

«Gomez Trial» (2019)

Iyengar et al (2018)

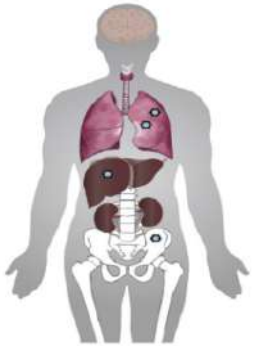
rapid communication

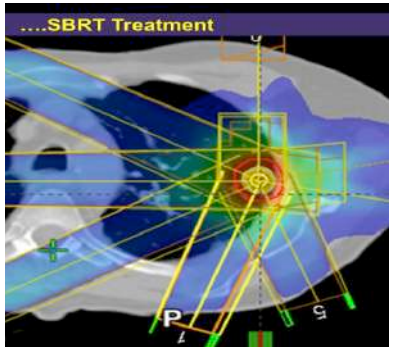
Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

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]; Brian P. Yaremko, MD, PEng[1]; Devin Schellenberg, MD[7]; Belal Ahmad, MD[1]; Sashendra Senthi, MD, PhD[8]; Anand Swaminath, MD[9]; Neil Kopek, MD[10]; Mitchell Liu, MD[11]; Karen Moore, MSc[3]; Suzanne Currie, MSc[3]; Roel Schlijper, MD[2]; Glenn S. Bauman, MD[1]; Joanna Laba, MD[1]; X. Melody Qu, MD, MPH[1]; Andrew Warner, MSc[1]; and Suresh Senan, MBBS, PhD[5]

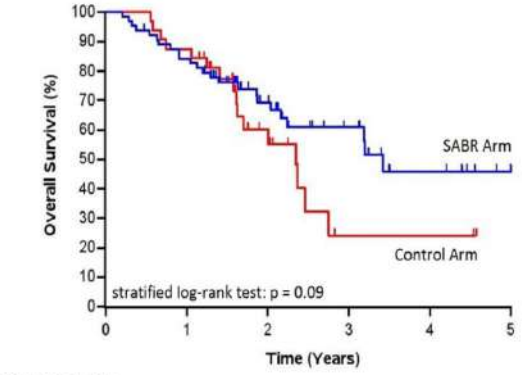
Background

- Patients with metastatic cancer are generally considered incurable, but oligometastatic theory proposes that a few, small spots can be eliminated with radiation/surgery
- Stereotactic radiation (e.g., SABR, SBRT) delivers substantially higher doses of radiation very precisely to the tumor site in 1-5 treatment sessions
- This is the first RCT to directly test the oligometastatic paradigm
  - Directly compares OS after ablative vs. palliative approaches for patients with up to 5 metastatic lesions





Results: Overall Survival



Number at risk:

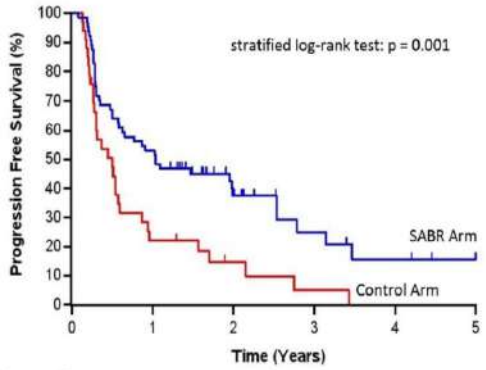
Control	33	28	12	2	2	
SABR	66	53	29	15	7	1

Median Overall Survival

Control Arm: 28 months
(95% CI: 19-33 months)

SABR Arm: 41 months
(95% CI: 26 months to 'not reached')

Results: Progression-free Survival



Number at risk:

Control	33	7	3	1		
SABR	66	34	15	6	3	1

Median PFS

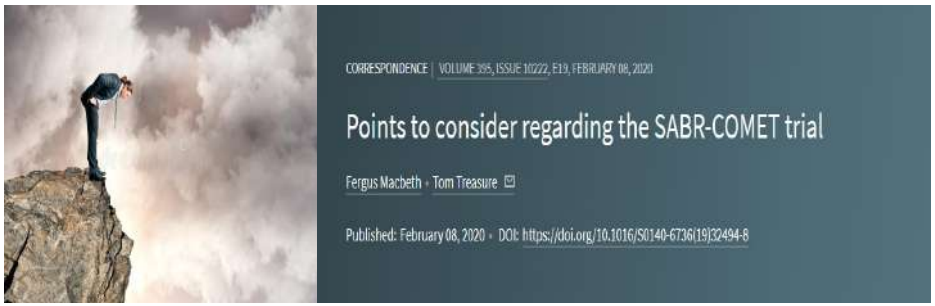
Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)

….UPDATE ASTRO 2020

- Median OS benefit of 22 months (vs 13), which corresponds to an absolute benefit of 25% at 5 yrs
- 5-yrs PFS rate not reached in SOC arm vs. 17% in SOC + SABR arm
- No detrimental effect on QOL
- SABR well tolerated in the majority of patients (toxicity $\geq$ G2 in only 29% of pts)

…the Non-Believers



- **<u>Imbalance in cancer types</u>** (+ BC and PC pts and - CRC pts in the intervention group)
- **Pts stratified** between 1-3 vs 4-5 mts – **NOT ADEQUATE**
- 10% **excess of pts. with solitary metastasis in the intervention** group
- a sta**tistically significant 20% increase in G2 or worse AEs (p=0·026) in the intervention group** and **three (4·5%) intervention-related deaths**

PE: Toxicity (Safety defined if G3 AEs <25%, G4 < 10%, G5 < 5%)

380 pts included, **Median FUP 28 mo**

14.2% G2 AEs (n = 54), **4.2% G3** (n = 16), **0% G4** and **0.3% G5** (n = 1, biliary stenosis with recurrent infections)

Caution in liver and adrenal mets (disproportionate G3 events)

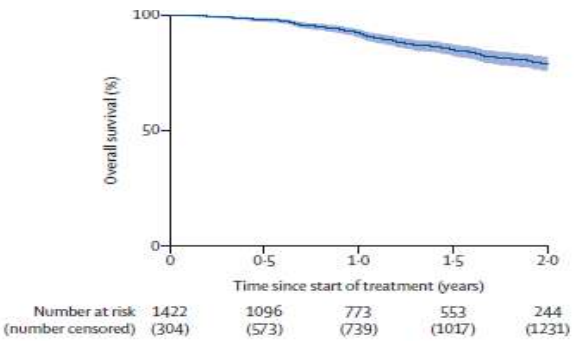

2021


RAISE
THE
BAR

Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study

Anastasia Chalkidou, Thomas Macmillan, Mariusz T Grzeda, Janet Peacock, Jennifer Summers, Saskia Eddy, Bola Coker, Hannah Patrick, Helen Powell, Lee Berry, Gareth Webster, Peter Ostler, Peter D Dickinson, Matthew Q Hatton, Ann Henry, Stephen Keevil, Maria A Hawkins, Nick Slevin, Nicholas van As

- **Up to 3 methacronous mets, not previously irradiated**
- **SBRT doses: 24-60 Gy in 3 to 8 fr.**
- **Systemic therapy discontinued (except OT)**



	Patients (n=1422)
Primary tumour diagnosis	
Prostate cancer	406 (28·6%)
Colorectal cancer	397 (27·9%)
Renal cancer	143 (10·1%)
Breast cancer	78 (5·5%)
Lung cancer	64 (4·5%)
Melanoma	58 (4·1%)
Other†	276 (19·4%)

✓ 1 and 2yr OS: 92 and 79%

✓ 1 and 2yr LC: 86 and 72%

✓ 1 and 2yr MFS: 84 and 52%

✓ No G5 events

Extremely rare G4 events (increased liver enzymes)

Low rate of G3

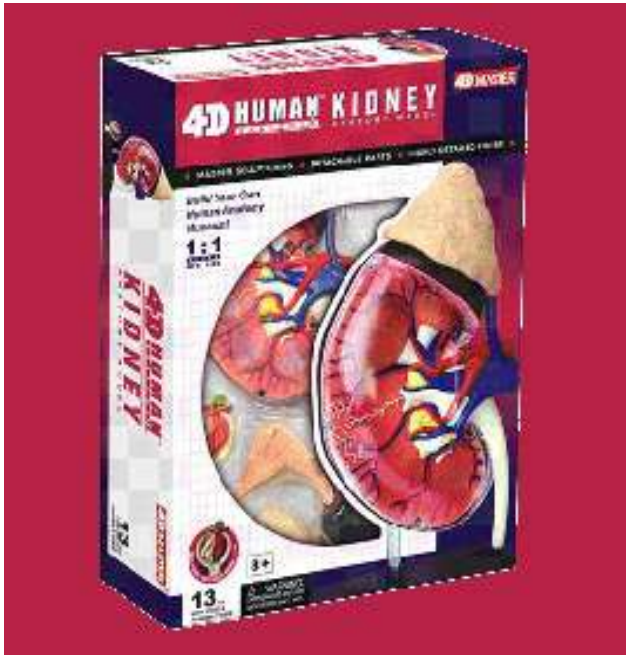
❗

<u>Short FUP</u> (median 13 mo, median OS not reached, no long term data on safety and efficacy)

<u>Several primary cancers types</u> (PC and CRC most frequent)

<u>Lot of N</u> (may bias safety..)

2021: The «Kidney model»



THE LANCET
Oncology

COMMENT | VOLUME 22, ISSUE 12, P1644-1645, DECEMBER 01, 2021

Oligometastatic renal cell carcinoma: radiotherapy as a new standard of care?

Nicolas Magné • Igor Latorzeff

Published: December, 2021 • DOI: https://doi.org/10.1016/S1470-2045(21)00665-3 • Check for updates

Platinum Priority – Kidney Cancer

Editorial by XXX on pp. x–y of this issue

Stereotactic Radiotherapy and Short-course Pembrolizumab for Oligometastatic Renal Cell Carcinoma—The RAPPORT Trial

Shankar Siva [a,b,], Mathias Bressel [a], Simon T. Wood [c,d], Mark G. Shaw [a], Sherene Loi [a,b], Shahneen K. Sandhu [a,b], Ben Tran [a,b], Arun A. Azad [a,b], Jeremy H. Lewin [a], Katharine E. Cuff [c,d], Howard Y. Liu [c,d], Daniel Moon [a,e], Jeremy Goad [a], Lih-Ming Wong [e], Michael LimJoon [a], Jennifer Mooi [a], Sarat Chander [a], Declan G. Murphy [a,b], Nathan Lawrentschuk [a,e], David Pryor [c,f]*

Highlights ASCO GU 2021

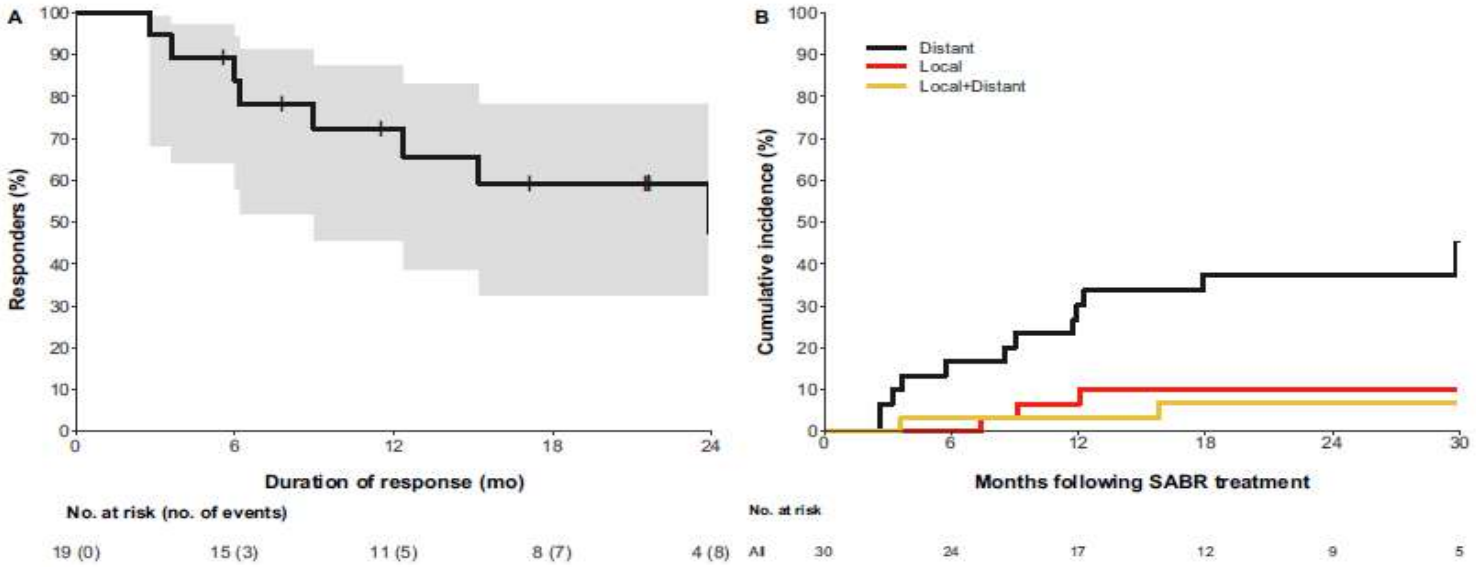


Fig. 4 – (A) Duration of response. (B) Cumulative incidence of failures. SABR = stereotactic ablative body radiotherapy.

- **Median FUP 28 mo**
- **No grade 4/5 AEs reported**

  Four G3 AEs (2 pneumonitis, 1 dyspnea, 1 increased ALT-AST)
- **ORR 63%, DCR 83%**
- **Median PFS: 15.6 mo**
- **1- and 2-yr FFLP: 94% and 92%.**
  1- and 2-yr OS: 90% and 74%
  1- and 2yr PFS: 60% and 45%

Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial

Chad Tang*, Pavlos Msaouel*, Kieko Hara, Haesun Choi, Venus Le, Amishi Y Shah, Jennifer Wang, Eric Jonasch, Seungtaek Choi, Quynh-nhu Nguyen, Prajnan Das, Surendra Prajapati, Zhiqian Yu, Khaja Khan, Steven Powell, Ravi Murthy, Kanishka Sircar, Nizar M Tannir

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

- 30 pts enrolled with < 5 mts lesions
- No more that 1 prev. systemic therapy
- SBRT to all lesions (or HypoRT when not possible)

COPRIMARY ENDPOINTS:

Feasibility of the treatment (< 7 days of delay) ✓

At a median FUP of 17.5 mo, 13 pts underwent PD ✓

1 yr PFS: 64%, median PFS 22.7 mo.

Safety Data

2 G3 (muscle weakness, back pain)

1G4 (Hyperglycaemia)

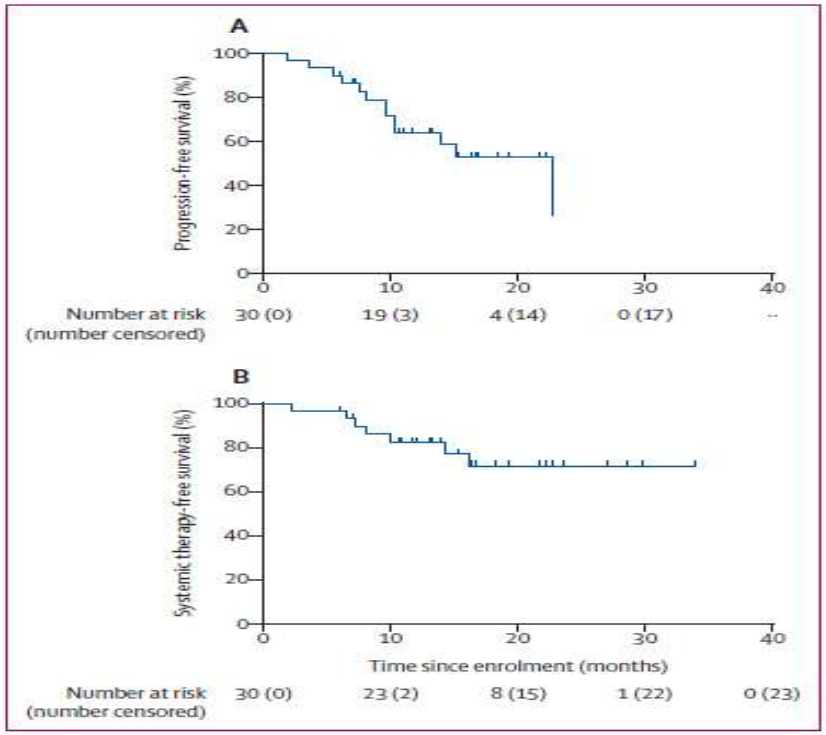


Figure 2: Kaplan-Meier plots of progression-free survival (A) and systemic therapy-free survival (B)

Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study

Patrick Cheung[a], *Samir Patel*[b], *Scott A. North*[c], *Arjun Sahgal*[a], *William Chu*[a], *Hany Soliman*, *Belal Ahmad*[d], *Eric Winquist*[e], *Tamim Niazi*[f], *Francois Patenaude*[g], *Gerald Lim*[h], *Daniel Yick Chin Heng*[i], *Arbind Dubey*[j], *Piotr Czaykowski*[k], *Rebecca K.S. Wong*[l], *Anand Swaminath*[m], *Scott C. Morgan*[n], *Rupi Mangat*[o], *Sareh Keshavarzi*[p], *Georg A. Bjarnason*[q,*]

37 pts, 57 irradiated lesions

Median FUP: 11.8 mo

Median BED: 72 Gy

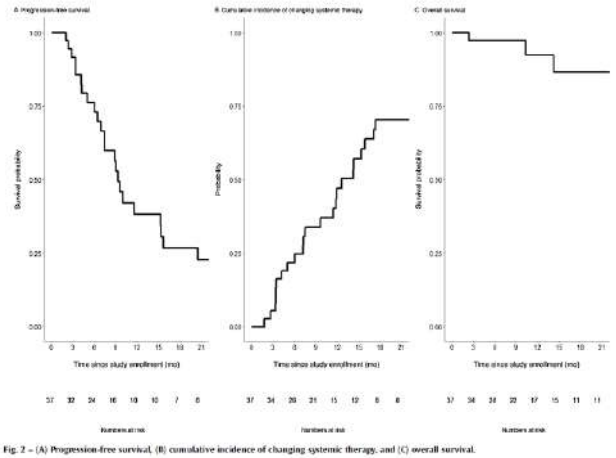


Fig. 2 – (A) Progression-free survival, (B) cumulative incidence of changing systemic therapy, and (C) overall survival.

- ✓ **1-yr LC: 93%**
- ✓ **Median PFS: 9.3 mo**
- ✓ **Median t to NEST: 12.6 mo**
- ✓ **1-yr OS: 92%**
- ✓ **No AEs ≥ G3**

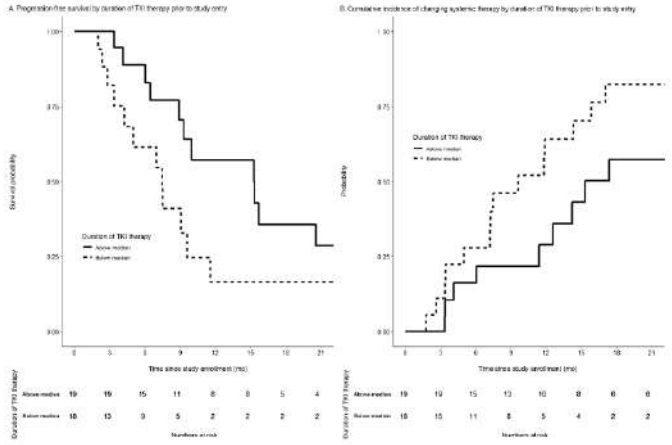


Fig. 3 – (A) Progression-free survival stratified by the duration of TKI therapy prior to study entry (above and below median) and (B) cumulative incidence of changing systemic therapy stratified by the duration of TKI therapy prior to study entry (above and below median).
TKI = tyrosine kinase inhibitor.

Meeting Abstract | 2021 Genitourinary Cancers Symposium

RENAL CELL CANCER

Patterns of progression in patients treated with nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214.

Nizar M. Tannir, Robert J. Motzer, Laurence Albiges, Elizabeth R. Plimack, Saby George, Thomas Powles, ...

Pts w/ RP, n (%)	T only	NT only	NL only	Mixed	Unassigned
NIVO+IPI; all N = 299	71 (23.7)	27 (9.0)	106 (35.5)	71 (23.7)	24 (8.0)
SUN; all N = 289	75 (26.0)	33 (11.4)	74 (25.6)	86 (29.8)	21 (7.3)
NIVO+IPI; post-response N = 71	14 (19.7)	12 (16.9)	36 (50.7)	5 (7.0)	4 (5.6)
SUN; post-response N = 84	31 (36.9)	3 (3.6)	23 (27.4)	22 (26.2)	5 (6.0)

Mixed column includes T+NT, T+NL, NT+NL, and T+NT+NL.

Highlights ASCO GU 2021

Among pts who received NIVO + IPI, 106 of 299 (35.5%) RPs resulted from NL only compared to 74 of 289 (25.6%) of those who were treated with SUTENT, and this differential was more pronounced in patients with an initial confirmed response

most NL-only RPs in initial responders occurred in a **single organ** (94.4% for NIVO + IPI; (87.0%) for SUTENT) with the most common being lymph nodes, for both regimens

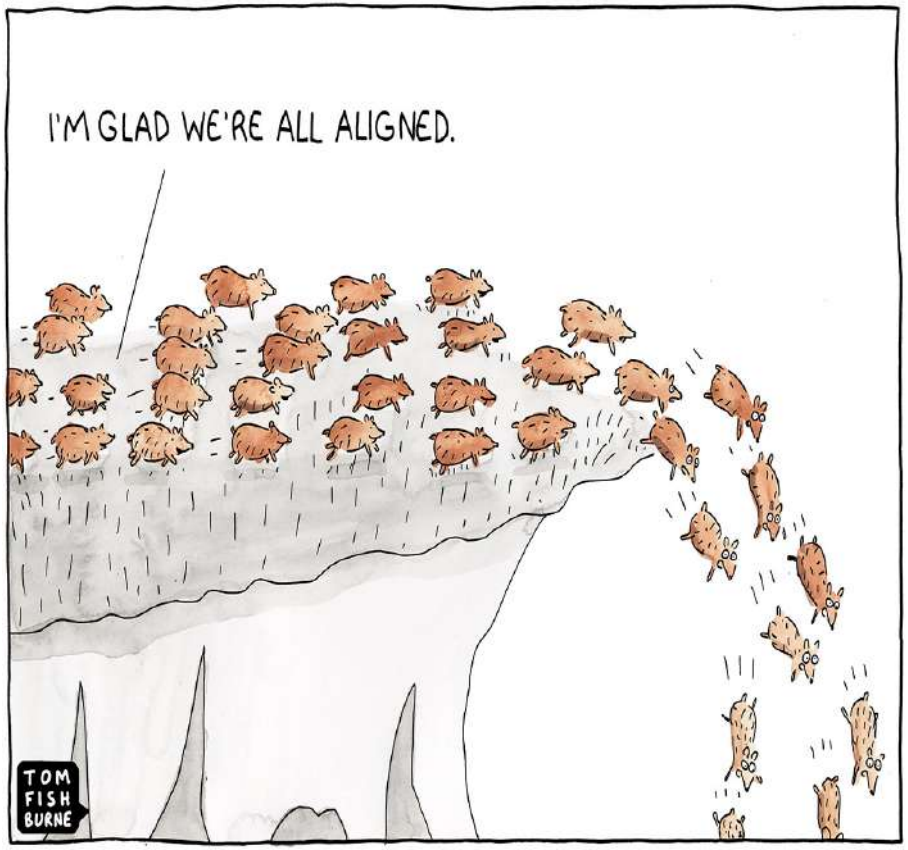
…What's the story, Kidney Glory?!

TABLE 4. Select Ongoing Clinical Trials Investigating Radiotherapy in the Treatment of mRCC

Trial Number (Name)	Phase	No. of Patients	Intervention	Control	Primary Endpoint(s)	Trial Start
NCT02811250 (RSR-1)	I	13	SBRT (8–12 Gy in 4–5 fractions)	NA	Safety	October 2010
NCT01896271	II	26	High-dose IL-2 + SBRT (8–20 Gy in 1–3 fractions)	NA	ORR	October 2013
NCT02019576	II	68	Sunitinib + SBRT to metastatic sites	NA	Locoregional control at 1 year	May 2014
NCT02306954	II	84	High-dose IL-2	High-dose IL-2 and SBRT (2 doses, 20 Gy)	ORR	December2014
NCT02781506	II	7	Nivolumab + SBRT (1–3 fractions)	NA	ORR	June 2016
NCT02599779 (OZM-065)	II	35	Pembrolizumab with SBRT at progression	Pembrolizumab lead-in SBRT given before second course of pembrolizumab	PFS	December 2016
NCT03065179 (RADVAX)	II	29	Ipilimumab + nivolumab + SBRT	NA	Safety	March 2017
NCT03469713 (NIVES)	II	69	Nivolumab + SBRT (30 Gy in 3 fractions)	NA	ORR	July 2017
NCT04299646 (GETUG-StORM-01)	II	114	Systemic treatment (VEGF, mTOR inhibitor, immunotherapy)	Systemic treatment + SBRT	PFS	July 2020
NCT04090710 (CYTOSHRINK)	II	78	Ipilimumab + nivolumab	Ipilimumab + nivolumab and SBRT (30–40 Gy in 5 fractions)	PFS	January 2020

Abbreviations: mRCC, metastatic renal cell carcinoma; SBRT, stereotactic body radiation therapy NA, not available; IL-2, interleukin-2; ORR, overall response rate; PFS, progression-free survival.

SBRT to oligomets…are we all in the same page?



KARL R. POPPER

THE LOGIC OF SCIENTIFIC DISCOVERY

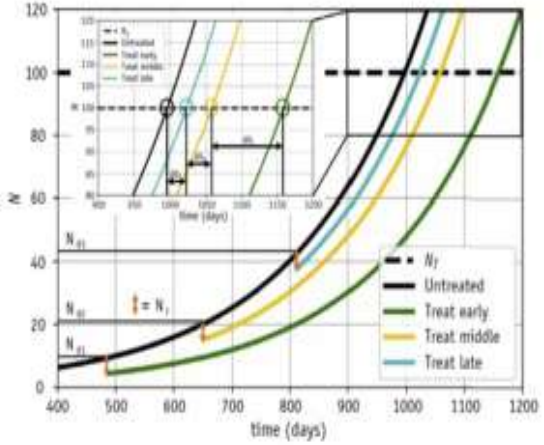
A striking new picture of the aims of science and of the 20th-century revolution in scientific thought

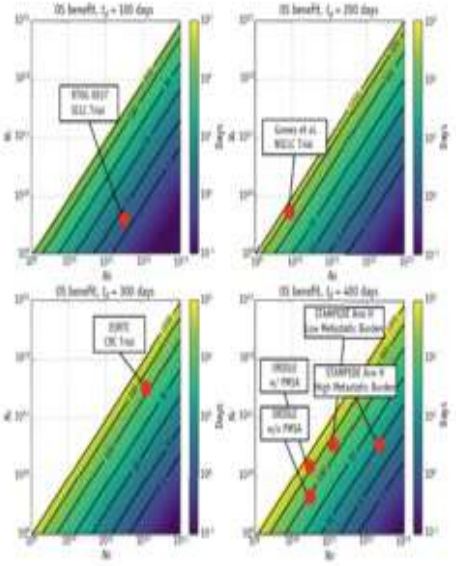
Clinical Investigation

Revisiting a Null Hypothesis: Exploring the Parameters of Oligometastasis Treatment

Jessica A. Scarborough, MS,[*,†] Martin C. Tom, MD,[‡] Michael W. Kattan, PhD,[§] and Jacob G. Scott, MD, DPhil[*,†,‖]

**Translational Hematology and Oncology Research, Cleveland Clinic, Cleveland, Ohio; [†]Systems Biology and Bioinformatics Program, Department of Nutrition, Case Western Reserve School of Medicine, Cleveland, Ohio; [‡]Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida; [§]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio; and [‖]Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio*





Sbrt to oligomets: a user-friendly-guide…

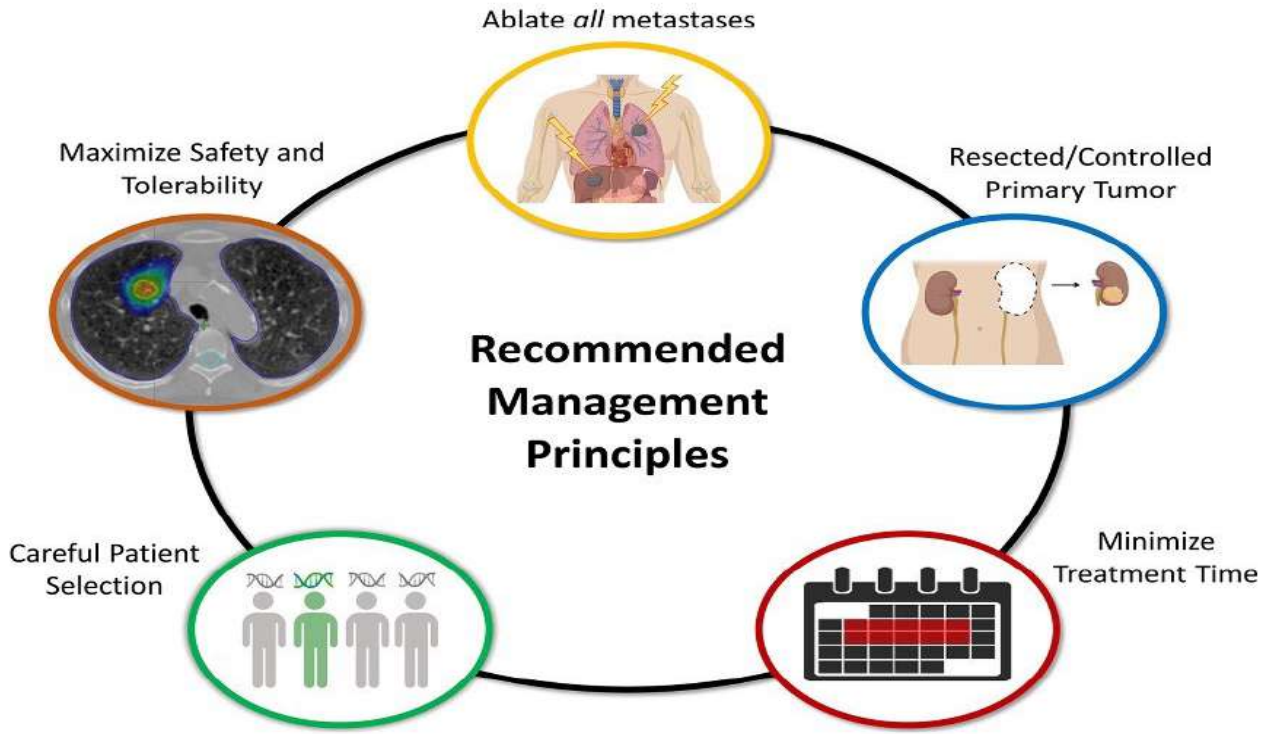


FIGURE 3. Recommended management principles for oligometastatic and oligoprogressive disease: (I) ablate all sites of gross metastatic disease; (II) ensure the primary tumor is resected or controlled; (III) carefully select patients; (IV) maximize safety and tolerability of SABR; (V) minimize treatment time to ensure expedient initiation or resumption of systemic therapy.

Scientific Article

Practical Considerations for the Implementation of a Stereotactic Body Radiation Therapy Program for Oligo-Metastases

Matthew Chan, MD, FRCPC,[a,b] David Palma, MD, PhD, FRCPC,[c] Aisling Barry, MD, FRCPC,[a,b] Andrew Hope, MD, FRCPC,[a,b] Richard Moore, RCSI,[a,b] Melissa O'Neil, MRT(T),[d] Janet Papadakos, MEd, PhD,[e] Devin Schellenberg, MD, FRCPC,[f] Tony Tadic, PhD,[a,g] C. Jillian Tsai, MD, PhD,[h] and Meredith Giuliani, MBBS, MEd, FRCPC[a,b,*]

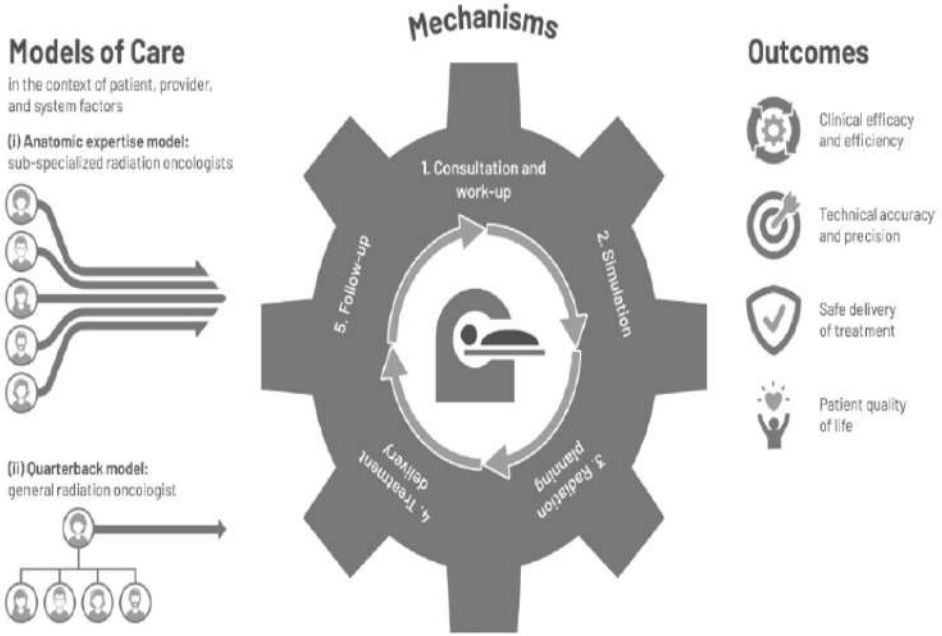


Figure 1 Program theory of operational factors in an oligo-metastasis stereotactic body radiation therapy program. A realist approach was used to evaluate the implementation of oligo-metastasis stereotactic body radiation therapy programs in the setting of diverse and complex health care systems.

Table 1 Summary of recommendations

Context	Mechanism	Outcomes
Anatomic expertise versus quarterback model: Patient • Performance status, mobility • Proximity, personal finances Provider • Oncologist subsite expertise • Departmental workflow (eg, planning team organization, QA) • Technology (eg, immobilization, treatment machine, image guidance) System • Cancer center size • Community versus academic center • Expertise of radiology department • Radiology/interventional capacity (eg, imaging, biopsy, fiducials)	**Consultation and workup** • Single provider arranges staging with minimum necessary tests (eg, imaging, biopsies) • Multidisciplinary tumor board review • Careful attention to previous treatments (eg, including radioisotopes and systemic therapy) • Treat on clinical trial when possible **Simulation** • Scan multiple sites at same session/d • Use minimum effective immobilization when safe (eg, common patient positions/immobilization for multiple sites) • Consider single primary data set for multiple sites if overlapping dose (eg, lower lung and adrenal metastasis) **Radiation planning** • Attention to previous and current overlapping dose, including anatomic deformation of previous dose • Use single isocenter for multiple close targets to reduce treatment time • Careful attention to image registration with possible anatomic expert consultation (eg, liver, spine) • Select dose-fractionation that safely facilitates cumulative doses, using same fraction number for multiple sites where possible • Adherence to strict QA protocols subject to ongoing quality improvement **Treatment delivery** • Minimize fraction number (eg, single fraction for lung), treat multiple sites on same day or interdigitate to reduce overall/daily treatment time • Minimize system errors with team communication, thorough documentation, and standardized nomenclature **Follow-up** • Avoid unnecessary visits (multiple practitioners) and imaging scans • Expert radiology review for suspicious post-SBRT findings	Clinical efficacy and efficiency • Improved LC, PFS, OS • Reduced time from referral to RT completion Technical accuracy and precision • Target receiving planned dose Safe delivery of treatment • Minimizing errors in delivery of planned dose • Minimizing RT-related toxicity Quality of life • Consistency of oncologist • Minimizing immobilization and duration of treatment • Avoiding unnecessary follow-up • Reducing financial toxicity

Local and Systemic therapies integration in the setting of RCTs

Table 3 Recommendations for timing of systemic therapy from selected oligo-metastases clinical trials

Study	Stop pre-SBRT			Restart post-SBRT	Notes
	Targeted molecular therapy	Cytotoxic therapy	Immuno-therapy		
SABR-COMET[8]	4 wk prior	4 wk prior	4 wk prior	2 wk post	Hormonal therapy allowed during RT
SABR-COMET 10[10]	2 wk prior	2 wk prior	2 wk prior	1 wk post	Hormonal therapy allowed during RT Radioenhancers (eg, gemcitabine) discouraged within first month
NRG LU-002[17]	Not specified	Must register within 35 d of completion of prior induction chemotherapy NOS	Not specified	2 wk post	Excluded: prior bevacizumab or other targeted therapy for NSCLC in first line setting
NRG BR-002[18]	2-3 wk prior for 2-4 wk cycles; 1 wk prior for weekly cycles Concurrent palbociclib, everolimus, trastuzumab-emantansine not permitted.	2-3 wk prior for 2-4 wk cycles; 1 wk prior for weekly cycles Concurrent cytotoxic therapy not permitted	Not specified	4 wk post	Concurrent hormone therapy, bone supportive therapy, biologics (eg, trastuzumab, pertuzumab) permitted. Experimental therapeutics require 30-d washout (eg, bevacizumab)
Gomez et al (2019)[6]	TKIs (eg, erlotinib) permitted with standard (≤3 Gy/fraction) and hypofractionation (≥3 Gy/fraction)	Not specified	Not specified	Not specified	Bevacizumab not permitted within 2 wks before SBRT

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer; RT = radiation; SBRT = stereotactic body radiation therapy; TKI = tyrosine-kinase inhibitor.

1) Moving towards the creationg of a **OMD tumor board**

2) General recommendation to **include OMD pts in the setting of RCTs**

Original Investigation

April 22, 2021

Evaluation of Safety of Stereotactic Body Radiotherapy for the Treatment of Patients With Multiple Metastases

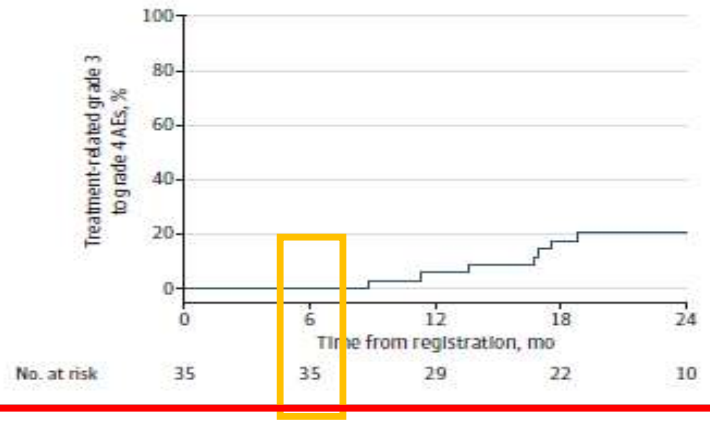
Findings From the NRG-BR001 Phase 1 Trial

Safety requirements for the treatment of 3-4 mets, or 2 in close proximity

- RT plans prioritized to respect CNS dose constraints, than dose distribution and then other OARs tolerance
- Robust QA program (complex benchmark case, validated imaging quality, phantom study)

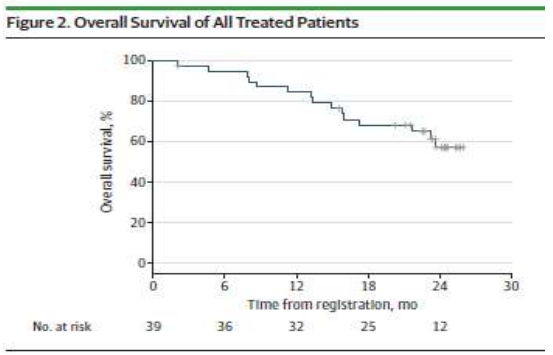
PE: DLT
SE: AEs ≥ G3 in within 180 days of treatment

Figure 1. Time to Treatment-Related Grade 3 to Grade 4 Adverse Events (AEs) Occurring Greater Than 180 Days After the Start of Stereotactic Body Radiation Therapy for All Evaluable Patients



8 G3 Aes most likely related to protocol therapy occur after 6 months……need for extended FUP!

Figure 2. Overall Survival of All Treated Patients



Median OS not reached!

Phase 3 Multi-Center, Prospective, Randomized Trial Comparing Single-Dose 24 Gy Radiation Therapy to a 3-Fraction SBRT Regimen in the Treatment of Oligometastatic Cancer

Michael J. Zelefsky, MD,* Yoshiya Yamada, MD,* Carlo Greco, MD,† Eric Lis, MD,‡ Heiko Schöder, MD,§ Stephanie Lobaugh, MS,‖ Zhigang Zhang, PhD,‖ Steve Braunstein, MD,¶ Mark H. Bilsky, MD,# Simon N. Powell, MD, PhD,* Richard Kolesnick, MD,** and Zvi Fuks, MD*

117 OMD pts, 154 irradiated lesions

Randomization 1:1 (24 Gy vs 9Gyx3)

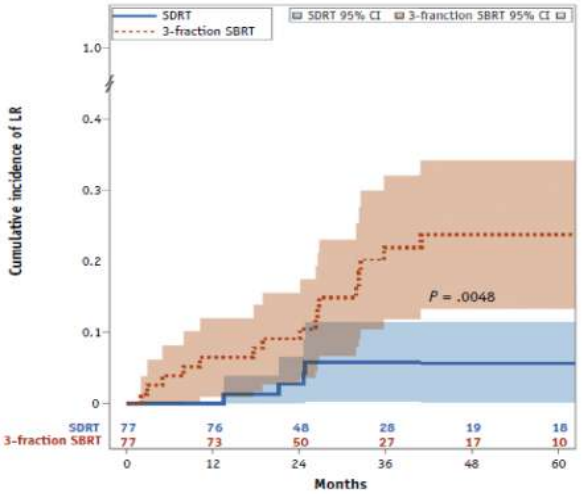


Fig. 1. Cumulative incidence of local recurrence (LR) and progression of disease within the irradiated region, demonstrating superior outcomes of ablative single-dose radiation therapy (SDRT) compared with fractionated stereotactic body radiation therapy (SBRT).

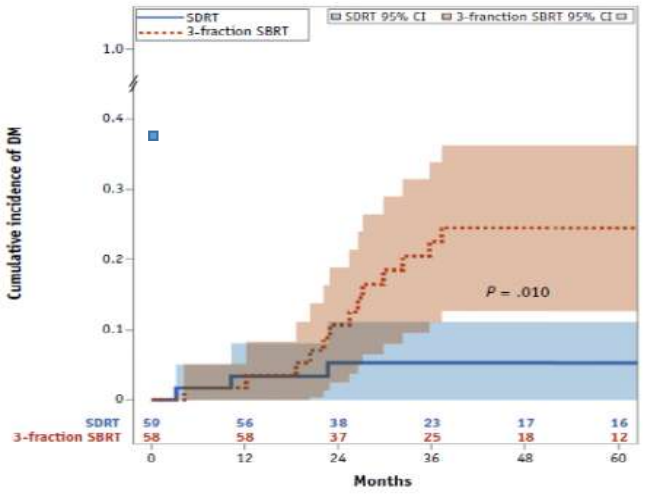


Fig. 2. Cumulative incidence of distant metastases (DM) and progression of disease outside of the irradiated field, showing superior outcomes of ablative single-dose radiation therapy (SDRT) compared with fractionated stereotactic body radiation therapy (SBRT).

Significantly lower cumulative incidence of LR and DM in the Single-Dose group

No differences in terms of ≥G2 events

In Silico Single-Fraction Stereotactic Ablative Radiation Therapy for the Treatment of Thoracic and Abdominal Oligometastatic Disease With Online Adaptive Magnetic Resonance Guidance

Sangjune Lee, MD, MSE, FRCPC,[a,b] Poonam Yadav, PhD, DABR,[a] Albert J. van der Kogel, PhD,[a] John Bayouth, PhD,[a] and Michael F. Bassetti, MD, PhD[a,*]

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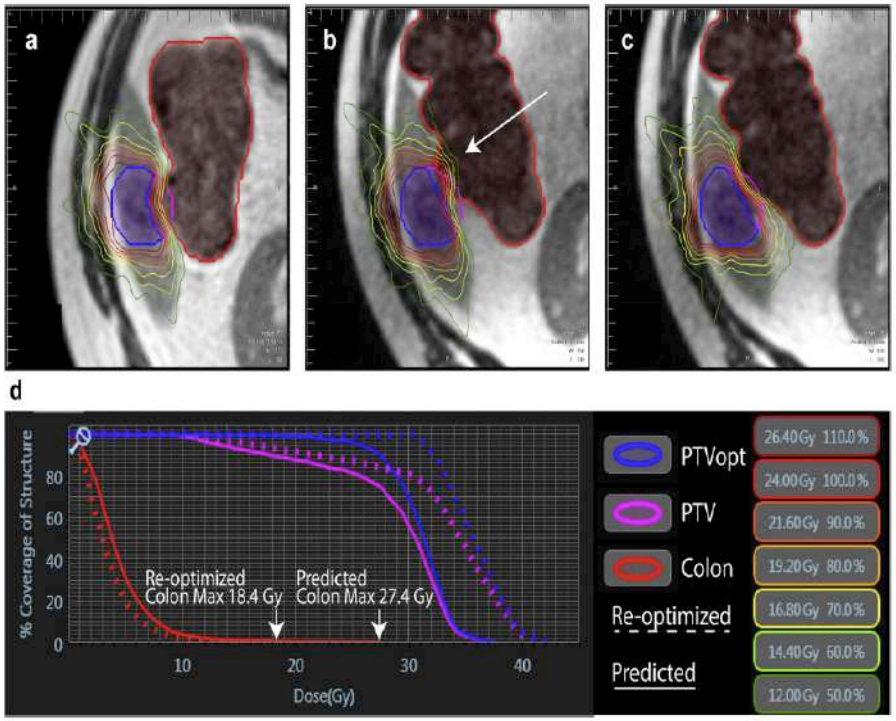
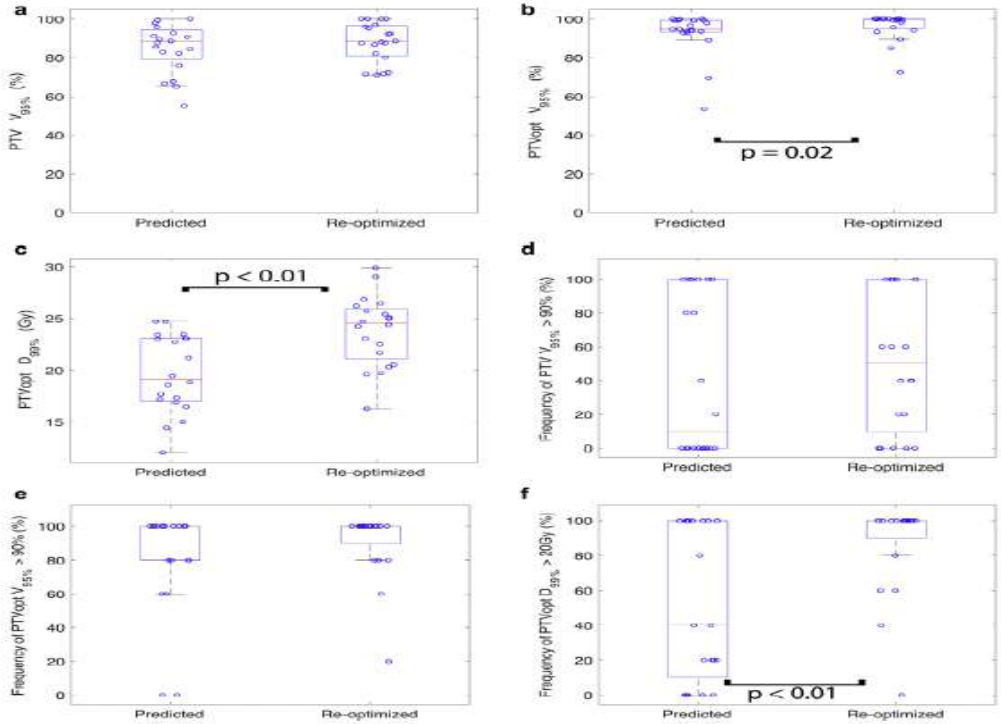




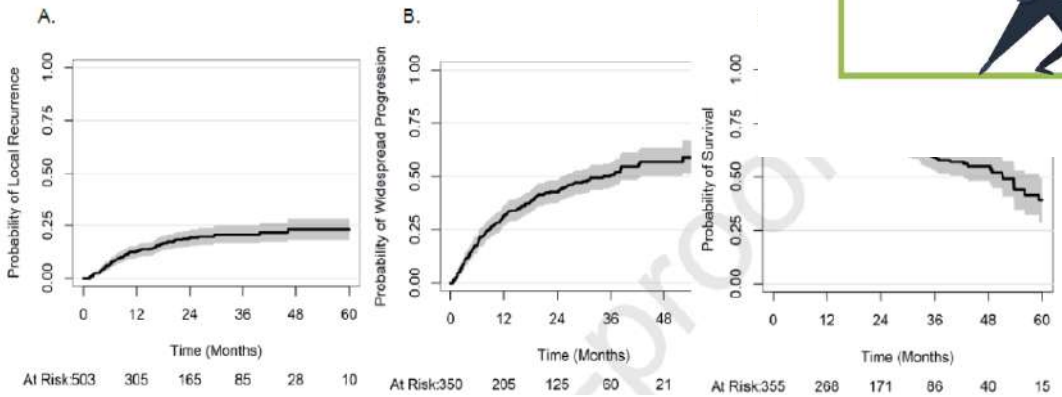
An International Pooled Analysis of SBRT Outcomes to Oligometastatic Spine and Non-Spine Bone Metastases

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], and Kristin J. Redmond[1]

[1]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [3]University of Turin, Turin, Italy, [4]Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH, [5]Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, QLD, Australia

Covariate for All Bone Lesions	Sub-HR (95% CI)	pValue
Radioresistant Histology	2.49 (1.61-3.87)	<0.001
Treatment at initial oligometastatic presentation to SBRT	0.58 (0.34-0.97)	0.038
PTV size ≥median	2.11 (1.28-3.46)	0.0033
PTV Dmin (BED10) ≥median	0.53 (0.33-0.87)	0.011

Figure 1: Plots of cumulative incidence of local recurrence, cumulative incidence of w progression, and overall survival



Covariate for Spine Lesions	Sub-HR (95% CI)	pValue
Radioresistant Histology	2.11 (1.25-3.57)	0.0051
PTV Dmin (BED10) ≥median	0.46 (0.26-0.82)	0.0085
Epidural Disease	1.99 (1.13-3.49)	0.016

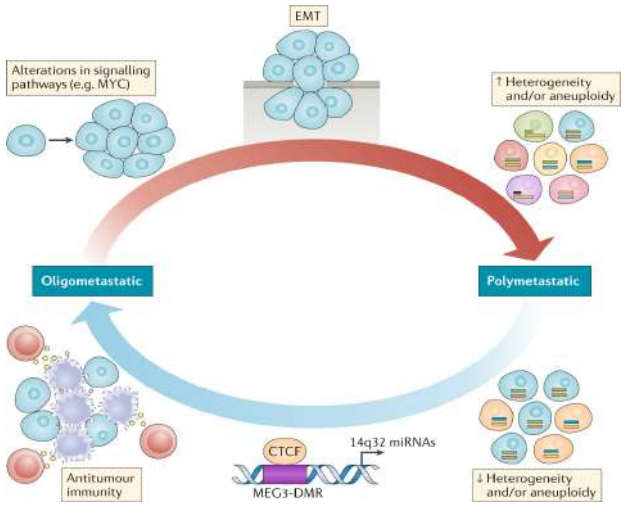
Covariate for Non-Spine Bone Lesions	Sub-HR (95% CI)	pValue
Primary Histology		
Prostate	1	
Renal cell	10.8 (3.21-36.1)	<0.001
NSCLC	6.48 (2.05-20.5)	0.0015
Other	2.60 (0.75-9.0)	0.13
PTV size ≥median	5.02 (1.39-18.2)	0.014

Advances in radioimmunotherapy 3

Integration of radiotherapy and immunotherapy for treatment of oligometastases

Sean P Pitroda, Steven J Chmura, Ralph R Weichselbaum

- Both tumor and host factors can influence biological heterogeneity in the virulence of metastatic disease
- Molecular subtyping of mts has shown the role of immunity (innate and adaptive) in restricting the metastatic dissemination.
- ICIs >> immune reponse, possibly curing metastatic state?
- Adding RT as an immunomodulatory agent



SBRT and IO: a perfect match?

- Systemic response to IO against subclinical and clinical disease are more frequent when disease burden is low
- RT effect on debulking larger disease sites
- Adding IO to address micrometastatic disease , in order to comprehensively treat all clinical disease

OLIGO-AIRO: a national survey on the role of radiation oncologist in the management of OLIGO-metastatic patients on the behalf of AIRO

Rosario Mazzola[1] · Barbara Alicja Jereczek-Fossa[2,3] · Paolo Antognoni[4] · Nadia Di Muzio[5,6] · Luca Nicosia[1] · Andrea Lancia[7] · Ivan Fazio[8] · Silvia Chiesa[9] · Mattia F. Osti[10] · Stefano Pergolizzi[11] · Davide Franceschini[12] · Piercarlo Gentile[13] · Luca Triggiani[14] · Filippo Alongi[1,15]

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]

***Panel:* Characteristics of oligometastatic disease**

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?

(…eagerly awaited!)

	Histology	Treatments		Estimated enrolment	Inclusion criteria	Primary endpoint
		Experimental group	Control group			
NRG-BR002 (NCT02364557)	Breast cancer	Systemic treatment with metastasis-directed treatment (SBRT or surgery or both)	Systemic treatment	402 patients	≤2 metastases (maximum diameter ≤5 cm); controlled primary tumour; ECOG status ≤2	Overall survival
NRG-LU002 (NCT03137771)	NSCLC	Systemic chemotherapy with localised treatment (SBRT to metastases and SBRT or hypofractionated radiotherapy to primary tumour)	Systemic chemotherapy	300 patients	≤3 metastases without progression after first-line systemic treatment; ECOG status ≤2	Overall survival
SABR-COMET 10 (NCT03721341)	Any cancer	SBRT plus standard of care treatment (chemotherapy, immunotherapy, hormones, or observation, at the discretion of the treating oncologist)	Standard of care treatment (chemotherapy, immunotherapy, hormones, or observation, at the discretion of the treating oncologist)	159 patients	4–10 metastases (maximum diameter ≤5 cm); controlled primary tumour; Karnofsky performance status >60; life-expectancy >6 months	Overall survival
CORE (NCT02759783)	Breast, prostate, or NSCLC	Systemic treatment with localised treatment	Systemic treatment with or without palliative radiotherapy	245 patients	≤3 metastases (maximum diameter <5 cm in lung, <6 cm in all other tissues); controlled primary tumour; ECOG status ≤2; life-expectancy >6 months	Progression-free survival

SBRT=stereotactic body radiotherapy. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer.

Table: **Prospective randomised phase 3 trials of localised therapy for oligometastatic disease**

› Oncologist. 2021 Jun;26(6):e1085-e1086. doi: 10.1002/onco.13747. Epub 2021 Apr 9.

Judging a Fish by Its Ability to Climb a Tree? A Call for Novel Endpoints in the Appraisal of Ablative Local Treatments of Oligometastatic Cancer

Mauro Loi [1], Marco Alifano [2], Marta Scorsetti [3 4], Joost J Nuyttens [5], Lorenzo Livi [1]

Trial ID/name	Population and study design	Accrual target	Intervention	Primary endpoints
NCT02364557/BR002	Phase 2/3; women with breast cancer and ≤4 metastases	*n* = 402	SABR or surgery versus standard of care	PFS (Phase 2) and OS (Phase 3)
NCT03862911/SABR-COMET-3	Phase 3; solid tumour patients with ≤ 3 metastases	*n* = 297	SABR versus standard of care (2:1 randomisation)	OS
NCT03721341/SABR-COMET-10	Phase 3; solid tumour patients with 4–10 metastases	*n* = 159	SABR versus standard of care (2:1 randomisation)	OS
NCT03137771/NRG LU002	Phase 2/3; NSCLC patients with ≤3 extracranial metastases with stable disease after first-line chemotherapy	*n* = 300	Maintenance chemotherapy versus SABR or surgery followed by maintenance chemotherapy	PFS (Phase 2) and OS (Phase 3)
NCT02417662/SARON	Phase 3; NSCLC with ≤ 3 metastases	*n* = 340	Platinum-based chemotherapy versus SABR + platinum-based chemotherapy	OS
NCT02893332/SINDAS	Phase 3; EGFR-mutated NSCLC with ≤5 metastases	*n* = 200	SABR + EGFR-inhibitor versus EGFR-inhibitor	PFS
NCT03808662/CURB-Oligoprogression: PROMISE-004	Phase 2; oligometastatic or polymetastatic NSCLC or breast cancer patients with ≤5 sites of metastatic progression	*n* = 160	Early SABR to sites of progression followed by standard of care versus standard of care	PFS
NCT02756793/STOP	Phase 2; NSCLC with ≤ 5 sites of metastatic progression	*n* = 54	SABR with continuation of current systemic therapy versus physician choice (2:1 randomisation)	PFS
NCT03256981/HALT	Phase 2; NSCLC with response to TKI therapy but progression in ≤3 metastatic sites	*n* = 110	SABR with continuation of TKI versus continued TKI alone	PFS
NCT03599765/EXTEND	Phase 2; solid malignancies with ≤ 5 metastatic sites	*n* = 367	MDT (surgery, radiation, or ablation) then standard of care versus standard of care.	PFS
NCT03410043/NORTHSTAR	Phase 2; stage IIIB/IV EGFR mutant NSCLC not amenable to curative intent therapy	*n* = 143	MDT (surgery and/or radiation) to target lesions after induction osimertinib versus osimertinib alone	PFS
NCT03808337/PROMISE-005	Phase 2; NSCLC or breast cancer patients with ≤ 5 metastases	*n* = 141	SABR versus standard of care	PFS

EGFR epidermal growth factor receptor, *TKI* tyrosine kinase inhibitor, *NSCLC* non-small cell lung cancer, *SABR* stereotactic ablative radiotherapy, *OS* overall survival.

«corrected disease-free survival» ?
(time from ALT to PD non amenable of another ALT)

«Time to widespread progression»

«NEST» (next line systemic treatment-free survival)

editorials

Oligometastatic Disease in Context of the Radiation Oncology Alternative Payment Model: Implications for Local Consolidative Therapy

Matthew S. Ning, MD, MPH[1]; David Boyce-Fappiano, MD, MHM[1]; and Nikhil G. Thaker, MD[2]

4-fold increase of SBRT utilization in oligometastatic cancer from 2011 to 2017, and counting..

Practice delivery costs increase with the number of treated sites (more resources for separate dosimetric plans, set-up immobilization, IGRT, treatment delivery).

Historically looking financial models for bundled payments NOT ADEQUATE for the increasing trend of LCT for oligometastatic disease.

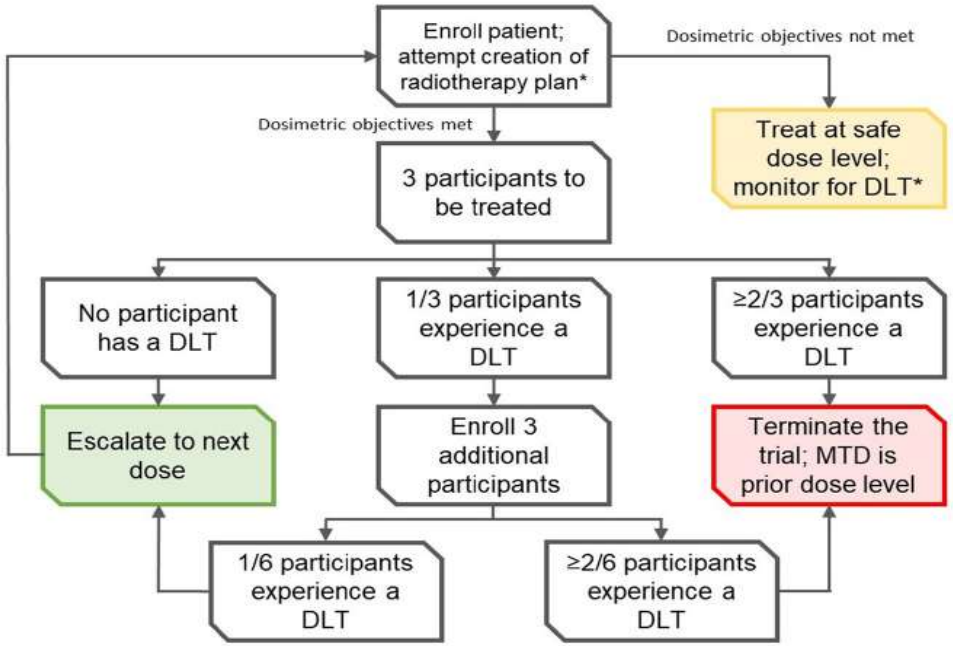
Fail to recognize the complexity associated with multicourse treatment delivery:
undervaluing of the true cost of LCT

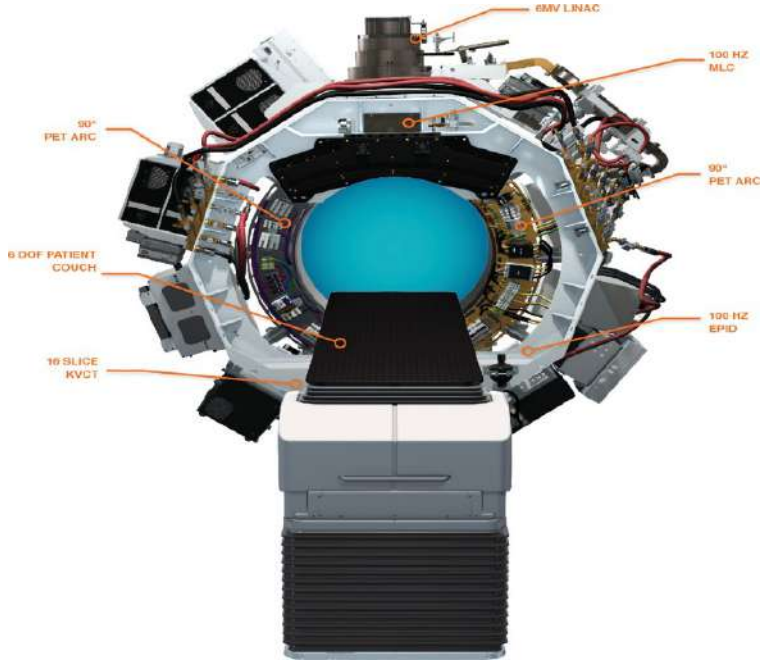
n of disease sites, *n* of RT courses, treatment intent , modalities used: all clinical factors that guide management and drive cost must be taken into consideration

STUDY PROTOCOL

Ablative radiation therapy to restrain everything safely treatable (ARREST): study protocol for a phase I trial treating polymetastatic cancer with stereotactic radiotherapy

Glenn S. Bauman[1*], Mark T. Corkum[1], Hatim Fakir[2], Timothy K. Nguyen[1] and David A. Palma[1]





CONCLUSIONS

- OMD offers a unique therapeutic window to ablate visible sites of disease, thereby reducing tumor burden and preventing progression to polymetastatic state

- We should focus on a formal separation and description of different clinical scenarios of OMD, formal criteria that define OMD, implementing standardized imaging

- In this setting, SBRT may defer the start of systemic therapy, and by doing so preserving patients' QOL from cumulative toxic effects of systemic therapy.

- Evidence is emerging that a radical treatment of OMD pts may yield an extended OS. However, majority of the studies are still retrospective and evaluate pts with singluar mets.
- Need for prospective high quality evidence for SRT use in OMD and ODP in the setting of RCTs

- Integrated evidence is coming from national and internation registry-based study cohorts and Phase II trials. Nomograms may aid in selecting OMD pts most likely to benefit from ablative therapy.

- RCTs are also required to ascertain the optimal sequence of SABR with different systemic therapies.

- Especially synchronous oligometastases, multimodality treatment with integration of local therapies may be advocated and should be ideally discussed in a multidisciplinary tumor board