

Patient Selection for advanced and complex techniques

Stereotactic Treatments
Re-Irradiation

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Radiation Oncologist


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Objectives

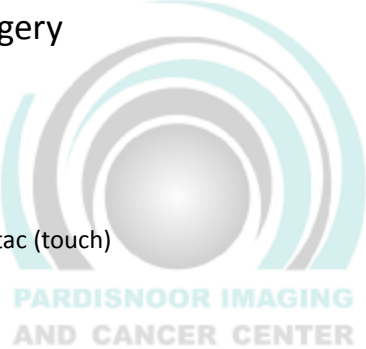
- Hopefully at the end of this session we will be able to have a rough idea on:
 - When to think about SRS or SBRT
 - When to decide to treat a patient who is re-treated
- Quick review on nature and radiobiology of stereotactic treatments
- Indications on SRS and SBRT
 - What evidences say

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SRS – root word!




- Stereotactic Radio-Surgery
 - Stereo: Solid
 - Stare – Strong - سترگ
 - Taxis: Arrangement
 - Ataxia – taxidermy
 - Originated from tag – tac (touch)
 - Tag - Tactile



SRS - history



- 1951; Lars Leksell invented the term
 - Goal which is beautifully achieved was: “a method for a non invasive destruction of intra cranial lesions, inaccessible or unsuitable for open surgery”
 - GK
 - 179 Co sources
- 1974; CT scan



First GK-SRS acoustic neuroma
Localization anatomy based using 2D images
Physics calculation by hand






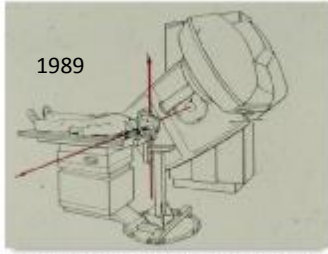
FIGURE 1-1. Lars Leksell and his physicist colleague, Boje Larsson, preparing a patient for SRS with a particle beam accelerator in 1958. (Photo courtesy of L. Dade Lundskod, MD.)



1930
60% Mortality rate of neurosurgery operations


- Advances in CT Scan
- Advances in LINAC based SRS
- Advances in MRI
- Advances in computer systems
- Creation of 3D treatment planning algorithm

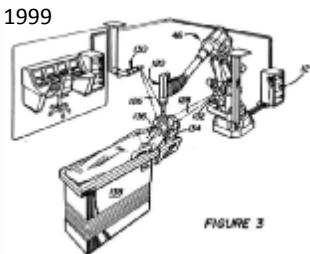





1989

- 2000 Introduction of micro MLC
- 2002 First patient treated on Tomotherapy system





1999



Stereotactic Radiation Treatment

- Highly localized
- High dose per fraction
 - $\geq 6\text{Gy/fr}$ (relatively conservative)
- Small number of fractions
- Potentially ablative
 - Chance of long term response $\sim >80\%$

15/1

18/1


24/1

27/3

30/5

50/5

60/8



A touch on radiobiology of SRS - SBRT

- Very rapid reduction in blood flow over the first 24 hours.
 - Vessels length reduction
- Substantial vascular damage → tumoricidal effect
 - Endothelial damage

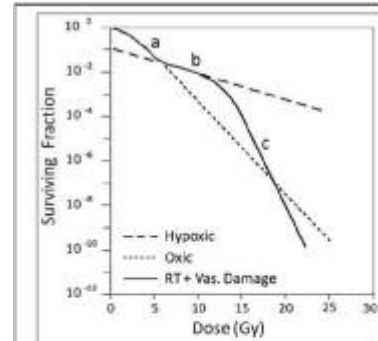
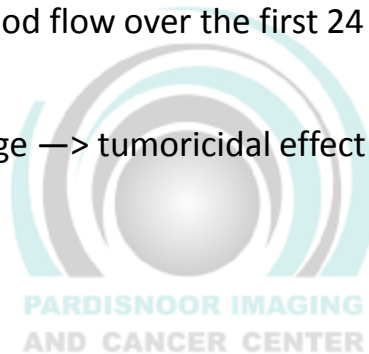


Figure 4
An illustration of how indirect death due to vascular damage could contribute to total clonogenic cell kill in tumors irradiated with large single doses of radiation

The Golden Rule

The normal immune system must operate within a safe window between being too permissive to foreign pathogens and being overly aggressive toward the normal self.

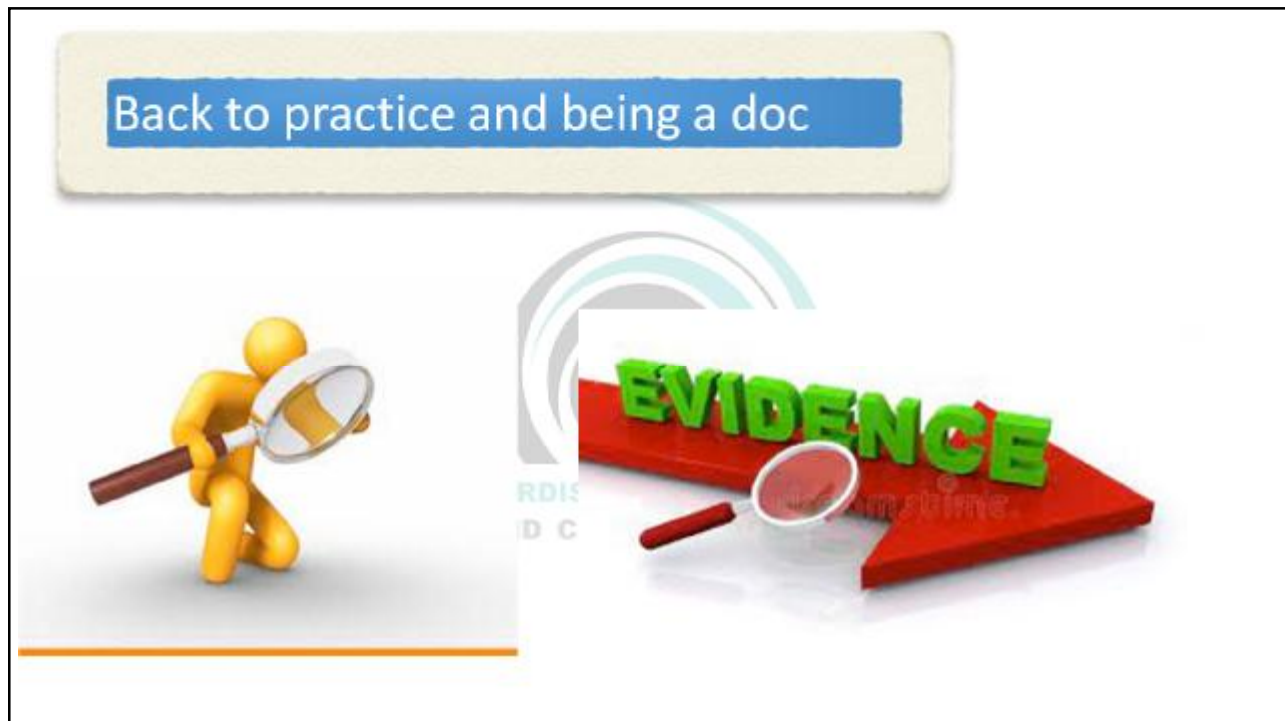
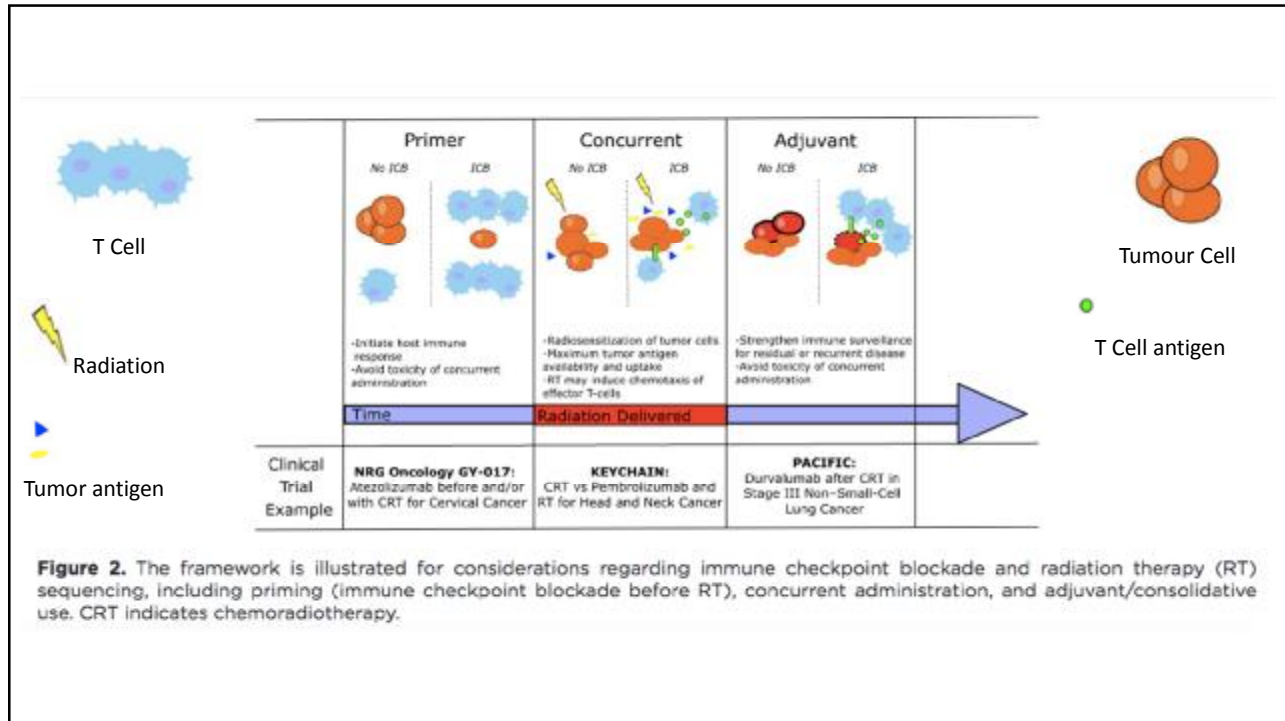
Review Article

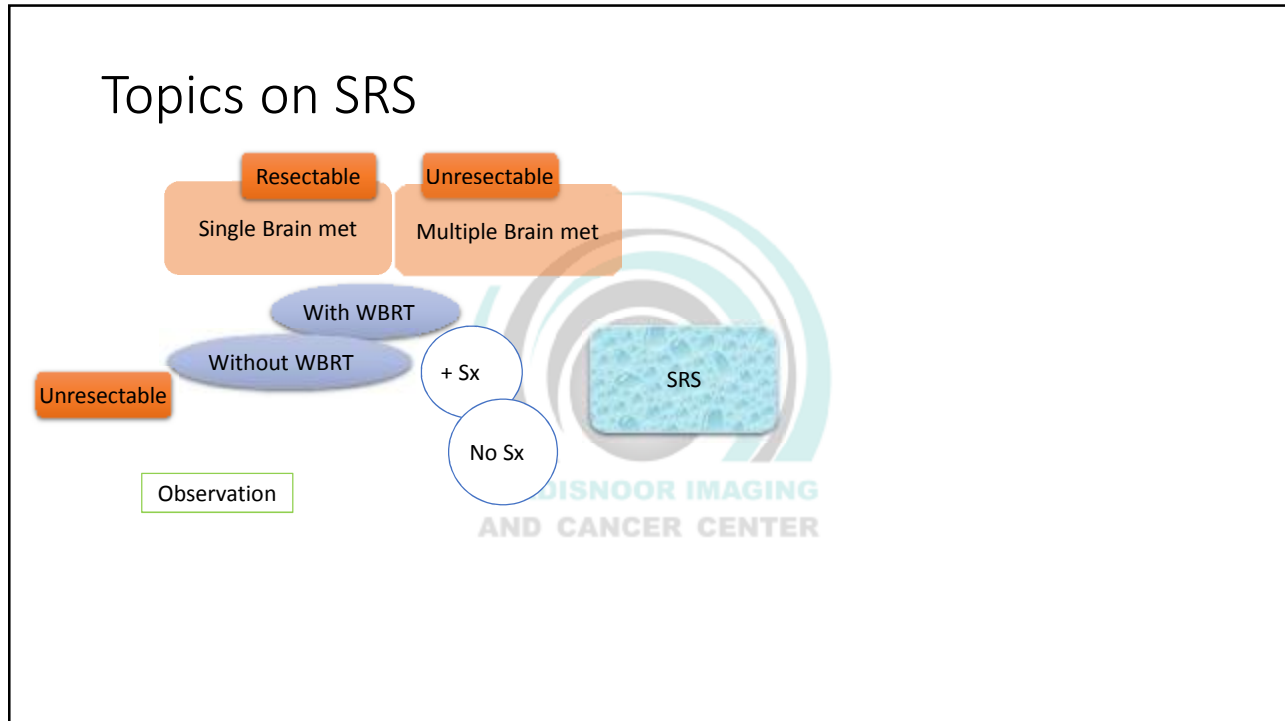
Immunotherapy and Radiation Therapy Sequencing: State of the Data on Timing, Efficacy, and Safety

Casey W. Williamson, MD, MAB¹; Michal V. Sherer, MD²; Dmitry Zamarin, MD, PhD²; Andrew B. Sharabi, MD, PhD¹; Brandon A. Oyer, MD³; Loren K. Mell, MD⁴; and Jyoti S. Mayadevi, MD¹

	Primer	Concurrent	Adjuvant
	<p>NO ICB → ICB</p>	<p>NO ICB → ICB</p>	<p>NO ICB → ICB</p>
	<p>Outside food intake restriction</p> <p>Avoid toxicity of concurrent administration</p>	<p>Reduction of tumor cells</p> <p>Increases tumor antigen availability and uptake</p> <p>RT may induce chemoresistance of effector T cells</p>	<p>Strengthen immune responses for residual or recurrent disease</p> <p>Check function of exhausted administration</p>
	<p>KEYNOTE</p>	<p>KEYNOTE</p>	<p>PACIFIC</p>
Clinical Trial	<p>KEYNOTE-018</p> <p>Atezolizumab before and after with CRT for Cervical Cancer</p>	<p>KEYNOTE-054</p> <p>CRT vs Pembrolizumab and RT for Head and Neck Cancer</p>	<p>PACIFIC</p> <p>Durvalumab (PD-1) in Stage III Non-Small-Cell Lung Cancer</p>
Example			

Figure 2. The framework is illustrated for considerations regarding immune checkpoint blockade and radiation therapy (RT) sequencing, including priming (immune checkpoint blockade before RT), concurrent administration, and adjuvant/consolidative use. CRT indicates chemoradiotherapy.





Surgery +/- RT

Adjuvant WBRT s/p surgery:

- Decreased the rate of intracranial progression
- Reduced the rate of neurological death
- Did not show a survival benefit

	Patchell et al (1990)	Patchell et al (1998)	EORTC 22952
Patients	48 patients with 1 BM and KPS ≥ 70	95 patients with 1 BM and KPS ≥ 70	359 patients with 1-3 BM and WHO PS ≤ 2
Treatment arms	Surgery + WBRT (36/12) Biopsy + WBRT (36/12)	Surgery + WBRT (50/28) Surgery + observation	Surgery + WBRT (30/10) Surgery + observation SRS* + WBRT SRS* + observation
Results	Surgery improved OS (40w vs 15w) and decreased LR (20% vs 52%)	WBRT did not prolong OS (48w vs 43w) WBRT decreased LR (10% vs 46%) and distant failure (18% vs 70%) WBRT had a lower rate of neurologic death (14% vs 44%)	WBRT did not prolong OS (10.7 mo. vs 10.9 mo.) WBRT decreased overall rate of intracranial progression (48% vs 78%) and rate of neurologic death
Significance	Adjuvant WBRT improves OS, LR, and QOL	Adjuvant WBRT after surgery does not improve OS but decreases rate of intracranial progression	Same as Patchell 1998, but validated SRS in this setting

Sx+RT → SOC

Key study: RTOG 9508

WBRT: 37.5 Gy in 15 Fx
SRS: 15-24 Gy per RTOG 9005 protocol

- Randomized to WBRT + observation vs. WBRT + SRS
 - No significant difference in OS (6.5 mo. vs 5.7 mo)
 - SRS improved survival in patients with 1 BM (6.5 mo. vs 4.9 mo.) but not with multiple BM
 - SRS had better LC at 1 year (82% vs 71%) and KPS (43% vs 27%) but did not decrease the rate of neurological death or overall time to progression
 - Established LINAC and GKS as generally equivalent

Take-home point: SRS boost improved LC, KPS, but not OS. Survival benefit noted with single BM.


Multiple brain mets → SRS alone

	JROSG 99-1	Chang et al (2009)	Yamamoto et al (2014)
Patients	132 patients with 1-4 BM and KPS ≥ 70	58 patients with 1-3 BM and KPS ≥ 70	1814 patients total (Group A (2-9 BM): 1254 patients; Group B (≥10 BM): 560 patients)
Treatment arms	SRS (1-2 cm: 22-25 Gy; 2-3 cm: 18-20 Gy) + observation; WBRT (30/10) + SRS*	SRS + observation; SRS + WBRT (30/12); SRS dose per RTOG 9005	All got SRS alone
Results	No significant difference in OS (8.0 mo. vs 7.5 mo. w/ WBRT); WBRT increased LC at 1y (18% vs 7%) and distant control (42% vs 64%); Salvage therapy more frequent after SRS alone (29 v 10)	WBRT more likely to show decline in NCF at 4 mo. (52% vs 24%); WBRT increased LC (100% vs 67%) and distant control (75% vs 45%) at 1y; increased survival in SRS alone (15 mo. vs 6 mo)	No significant difference in OS (5.8 mo. vs 6.9 mo. for group B); Hazard for local recurrence (0.425) and repeat SRS for new lesions (0.732) were significantly lower in group B; no difference in incidence of NCF decline (0.994 HR) or neurological death rates (1.08 vs 0.496 for group B)
Significance	SRS alone is equivalent in survival but overall increased recurrence requires more frequent salvage therapy	WBRT + SRS provides better control but leads to poorer NCF and survival outcomes	Post-SRS outcomes (OS, intracranial relapse, and NCF) were not inferior for patients with ≥10 BM compared to patients with 2-9 BM

Take-home point

- SRS alone vs SRS + WBRT for multiple BM:
 - Has equivalent if not better OS rates
 - Associated with better neurocognitive outcomes
 - Decreased local and distant control requires more frequent salvage therapy
 - Despite an increased need for salvage treatment, SRS is still cost-effective (Hall et al, 2014)

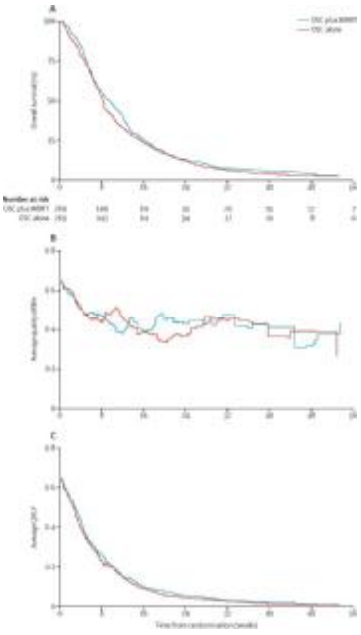
Equivalent survival with better NCF outcomes has made SRS alone a viable therapeutic option despite higher intracranial relapse rates



- Rades et al (2007) performed a retrospective study of 206 patients with 1-2 BM and concluded no difference in OS or LC

Take home point: no randomized trials comparing SRS to surgery alone but appear to have equivalent survival and LC outcomes with the potential for less toxicity with SRS alone

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A non-inferiority trial

Quartz trial

- 538 patients with BM from NSCLC (not suitable for resection or SRS) randomized to WBRT (20/5) + optimal supportive care (OSC), including dexamethasone, vs. OSC alone
 - No significant difference in OS (65 vs. 57 days for OSC), overall QoL, or steroid use
 - Difference for mean quality adjusted life years (QALYs) was only -1.9 days (OSC+WBRT 43.3 vs. OSC 41.4 days)

Significance: first randomized trial to evaluate utility of WBRT to improve either QoL or survival. Further studies needed but results suggests WBRT may not provide a clinically significant benefit in patients who are not candidates for resection or radiosurgery.

The quality-adjusted life year or quality-adjusted life year (QALY) is a **generic measure of disease burden, including both the quality and the quantity of life lived.**

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Topics on SRS

- **Surgery**
 - Rised and uncontrolles ICP
- **SRS**
 - Safe
 - Minimal side effect if done correctly
 - Very effective

Sara's protocol

- Try to keep WBRT as a later resource
- If really mets > 10-11 and the distribution doesn't make you comfortable for SRS


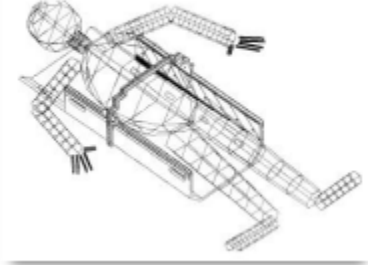
Lars, Dan and Laurent
Leksell



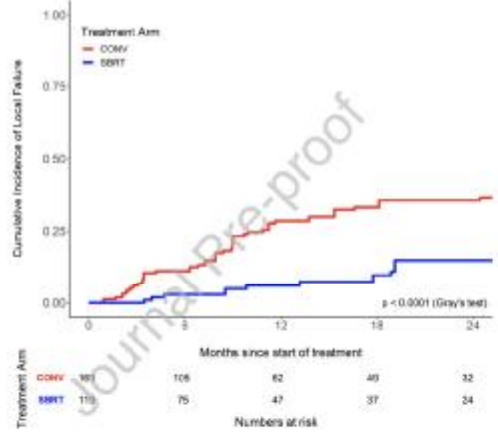
- Matthias Greuter (1564-1638)

SBRT

- **OligoMetastasis**
 - Number of mets
 - Primary histology
 - Progression on systemic disease
 - Systemic disease available or not

1- SBRT Spine



Treatment Arm	CONV	SBRT
Initial	101	110
6 months	106	75
12 months	82	47
18 months	49	37
24 months	32	24

Figure 1. Cumulative incidence of local failure in the SBRT and eEBRT cohort demonstrating statistically significant increase in risk of local failure in the latter

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CLINICAL INVESTIGATION | ARTICLES IN PRESS

Mature Local Control and Reirradiation Rates Comparing Spine Stereotactic Body Radiotherapy to Conventional Palliative External Beam Radiotherapy


K. Liang Zeng, MD • Sten Myrneshaug, MD • Ilery Goldman, MD • Zain A. Hussain, MD • Chia-Lin Tseng, MDCM • Jay Dasky, MD • Mark Ruetten, PhD • Eshetu G. Abenatu, PhD • Christopher D. Witke, MD • Jerome Lapuche, MD • Leonardo da Costa, MD • Pejman Josephir Maralani, MD • Wendy B. Pardisnoor, MD • Arjun Sahgal, MD • [Show less](#)

[Open Access](#) • Published: June 05, 2022 • DOI: <https://doi.org/10.1016/j.ijrobp.2022.05.043>

- ✓ local control (2-yr 14.8% v 35.6%)
- ✓ re-RT (1-yr 2.2% v 15.8%)
- ✓ time to re-RT (median 22.9 v 9.5 mo)

New SOC?

CCTG SC.24/TROG 17.06:
A Randomized Phase II/III Study Comparing 24Gy in 2 Stereotactic Body Radiotherapy (SBRT) Fractions Versus 20Gy in 5 Conventional Palliative Radiotherapy (CRT) Fractions for Patients with Painful Spinal Metastases (NCT02512965)

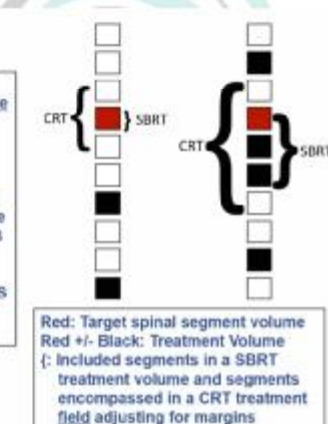


Schema

Spine metastases (Up to 3 contiguous segments) → 1:1 randomization → SBRT: 24 Gy in 2 fractions / CRT: 20 Gy in 5 fractions

Primary endpoint: Complete Pain Response (CR) rate at 3 months

Secondary endpoints:
 -CR at 6 months
 -Radiation Site Specific (RSS) Progression-Free Survival (RSS PFS) at 3 and 6 months
 -QOL
 -Change in the total SINS at 3 and 6 months
 -Overall Survival (OS)



Red: Target spinal segment volume
 Red +/- Black: Treatment Volume
 {}: Included segments in a SBRT treatment volume and segments encompassed in a CRT treatment field adjusting for margins

* Stratification factors: radioresistant (GI, RCC, melanoma, sarcoma) vs. radiosensitive, and presence vs. absence of extra-osseous extension (Mass type)

Adverse Events per CTCAEv4.0


Adverse Event and Worst Reported Grade (2 to 5 only)	CRT (N=115)	SBRT (N=110)
Dysphagia		
2	0/115	1/110 (1%)
3	0/115	1/110 (1%)
Esophagitis¹		
2	0/115	4/110 (4%)
3	2/115 (2%)	0/110
Nausea		
2	2/115 (2%)	1/110 (1%)
3	1/115 (1%)	0/110
Pain¹		
2	4/115 (3%)	2/110 (2%)
3	5/115 (4%)	5/110 (5%)
Fatigue		
3	1/115 (1%)	0/115
Vertebral Compression Fracture		
3	0/115	1/110 (1%)
4	1/115 (1%)	0/110

- Any grade Vertebral Compression Fracture (VCF):
 - 17% CRT $p=0.16$
 - 11% SBRT
- No radiation myelopathy events
- No concerns on central MR image review
- Central RT plan QA review:
 - CRT: 2 major deviations
 - SBRT: 1 major deviation

P2/3 RCT of painful spine mets (≤ 3 levels, SINS ≤ 12)
 -#SBRT (24 Gy/2 fx)
 -RT (20 Gy/5 fx)

↑ pain CR with SBRT at 3 (35% v 14%) & 6 (32% v 16%) mos.

✓ No diff in toxicity




Patient and Treatment Factors Associated with Improved Local Control and Survival in Oligometastatic Bone Disease: Results from a Large Single-Institution Experience Using Stereotactic Body Radiation Therapy

Maria C. Thomas, MD + Yu-Hsi Chen, PhD + Elbot Fibr, BA + Andrew Pangloss, BA + Katherine Juberka, BA + Alexander Spektor, MD, PhD + Tracy A. Balbone, MD, MPH + Mai Anh Huynh, MD, PhD [Show less](#) [Show footnotes](#)

Published: July 12, 2022 + DOI: <https://doi.org/10.1016/j.jrobp.2022.06.096>

- BED10 > 50
- PTV < 150cc for non-spine bone lesions
- Prostate histology
- PS 0-1
- Metachronous




- 2016-2020
- <= 5 mets
- > 18 yrs
- ECOG >0
- Not prostate/breast
- Progression on systemic tx

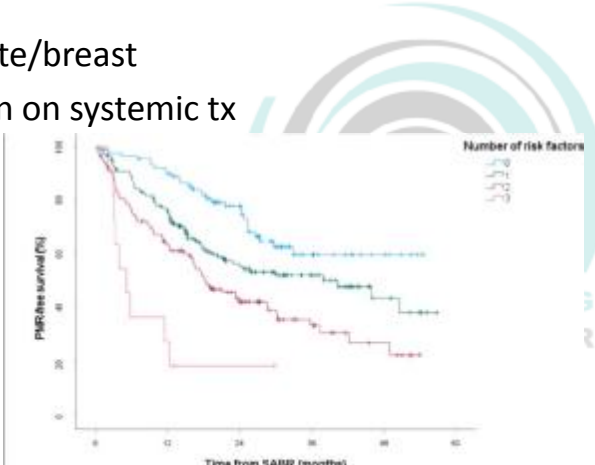
CLINICAL INVESTIGATION | ARTICLES IN PRESS

Predictors of early polymetastatic relapse following stereotactic ablative radiotherapy for up to 5 oligometastases: a secondary analysis of the phase II SABR-5 trial

S Baker, MD PhD + B Mou, MD + W Jang, MD + Q Mathews, PhD + S Tyldesley, MD + RA Olson, MD MSc [Show all authors](#) + [Show footnotes](#)

Published: July 12, 2022 + DOI: <https://doi.org/10.1016/j.jrobp.2022.06.094>

 PlumX Metrics



No. at risk	0	12	24	36	48
0 factors	30	20	11	6	4
1 factor	151	113	67	39	24
2 factors	121	73	34	20	12
3 factors	14	7	4	2	1

The image shows a screenshot of a medical journal article and a clinical trial abstract. The journal article is from the 'International Journal of Radiation Oncology* Biology* Physics', Volume 131, Issue 5, 1 December 2021, Pages 1325-1326. The title is 'Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression – Interim Analysis of the First Randomized Study of Stereotactic Body Radiotherapy in Patients With Oligoprogressive Metastatic Cancers of the Lung and Breast'. The authors listed are C.J. Tsai, J.T. Yang, D.M. Guttman, N. Shaverdian, A.F. Shepherd, J. Eng, D. Geladam, A.J. Xi, A. Namikydouh, A. Iqbal, J.M. Mann, J. Proeshagul, C. Hajj, E.F. Gillespie, S. Suggeman, S. Modi, C. Dang, P. Dziubinski, and S.N. Powell. A red banner below the title states: 'PFS improved after RT for oligoprogression, but effect was driven entirely by NSCLC'. The clinical trial abstract is for 'NRG-BR002: A phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (NCT02364557)'. The authors listed are Steven J. Chmura, Kathryn A. Winter, Hania A Al-Hallaq, Virginia E. Borges, N. T. Jaskowiak, Martha Matuszak, Michael T. Milano, Joseph Kamel Salama, W. A. Woodward, and Julia B. White. A red banner below the title states: 'Addition of RT to standard of care systemic therapy did not improve PFS nor OS'.

My thought process to choose patients for SBRT

- Stable for more than a year on systemic tx
- Young and fit and motivated (me and patient)
- Good performance status
- Real oligomets
 - < 5
 - But I have treated 5-10!!!!
 - ACC, RCC, Sarcoma, when you are stuck in a dead-end

ARTICLES | VOLUME 393, ISSUE 10185, P2051-2058, MAY 18, 2019

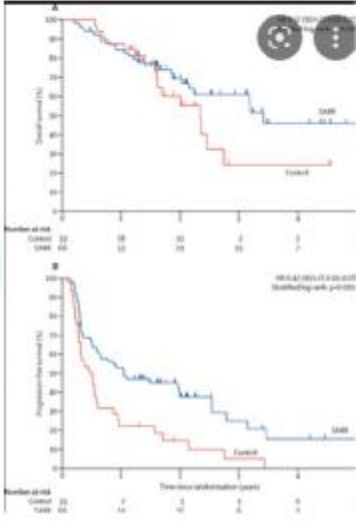
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Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, MD, Robert Olson, MD, Stephen Harrow, PhD, Stewart Gaede, PhD, Alexander V Louie, MD, Cornelis Haasbeek, MD, et al. [Show all authors](#)

Published: April 11, 2019 · DOI: [https://doi.org/10.1016/S0140-6736\(18\)32487-5](https://doi.org/10.1016/S0140-6736(18)32487-5) · [Check for updates](#)

<5 met
99 patients



The figure displays two Kaplan-Meier survival curves comparing Stereotactic Ablative Radiotherapy (SABR) to Standard of Care (SOC) for patients with oligometastatic cancers. The top graph shows Overall Survival (OS) over 24 months, and the bottom graph shows Progression-Free Survival (PFS) over 24 months. In both graphs, the SABR group (blue line) demonstrates significantly better survival outcomes compared to the SOC group (red line). The OS curve shows a clear separation between the groups, with SABR maintaining a higher survival rate throughout the 24-month period. The PFS curve also shows a significant advantage for SABR, with a much slower rate of disease progression compared to SOC. The x-axis for both graphs is 'Time from randomisation (months)' and the y-axis is 'Percentage survival (%)'.

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