Spine SBRT: A Clinician's Update On Techniques and Outcomes

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August 3, 2017

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ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Disclosures

- **I have no relevant financial or personal relationships/circumstances/conflicts of interest to disclose**

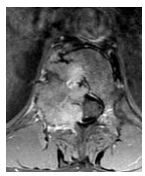
Outline

- **Spinal Metastases**
- **Spine Conventional EBRT**
- **Spine SBRT**
  - Indications/Rationale
  - Technical Considerations
  - Principles of Target Delineation
  - Overview of Outcomes Data
  - Toxicity Avoidance
  - Patterns of Failure
  - Response Assessment

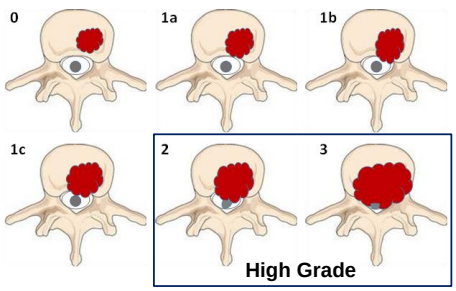
Spinal Metastases

- **Uncomplicated spine metastases**
  - Tumor contained within bone
  - Normal spinal alignment and no fracture
  - Pain that is not positional
  - 5% can progress to MESCC or fracture

- **Complicated spine metastases**
  - Mechanical instability
  - Bulky "Mass" type tumors
  - MESCC
    - Surgical candidates



Bilsky Epidural Spinal Cord Compression (ESCC) Grading Scale



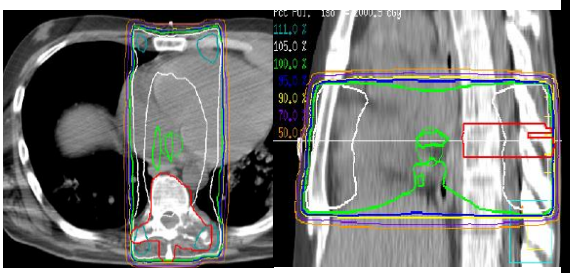
Spinal Instability Neoplastic Score (SINS)

SINS Criterion	Score[a]
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain	
Mechanical	3
Occasional and non-mechanical	1
No pain	0
Bone lesion type	
Lytic	2
Mixed (lytic and blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation	4
Kyphosis/scoliosis	2
Normal alignment	0
Degree of vertebral body collapse or involvement	
>50% collapse	3
<50% collapse	2
No collapse but with >50% body involved	1
None of the above	0
Posterolateral involvement (fracture or replacement by tumor) of spinal elements[b]	
Bilateral	3
Unilateral	1
None	0

[a]Total score: 0 to 6, stability; 7 to 12, indeterminate (possibly impending) instability; 13 to 18, instability.
[b]Facet, pedicle, or costovertebral joint.

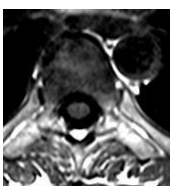
1. Fisher et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976). 2010;35(22):E1221-E1229.
2. Fourney et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol. 2011;29(22):3072-3077.

Conventional EBRT (cEBRT)



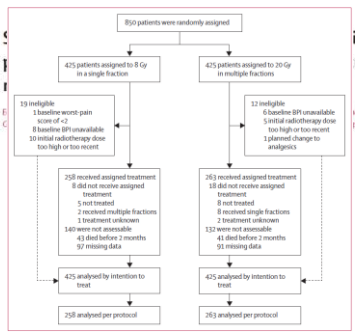
De-novo cEBRT

- **Overall pain response rate ~60%, complete response ~23%[1-2]**
- **Imaging-based LC range from 61-86%, but as low as 46% for mass-type tumors at 1 year[3]**



1. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007;25:1423-1436.
2. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol. 2012;24:112-124.
3. Mizumoto M, Harada H, Asakura H, et al. Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at Shizuoka Cancer Center Hospital. Int J Radiat Oncol Biol Phys. 2011;79:208-213.

cEBRT Re-irradiation: SC.20 multi-center RCT



SC.20 Results

	Intention-to-treat analysis		Per-protocol analysis	
	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N =425)	8 Gy/single fraction (N=258)	20 Gy/multiple fractions (N=263)
Overall response	118 (28%)	135 (32%)	116 (45%)	134 (51%)
Complete response	36 (8%)	30 (7%)	35 (14%)	29 (11%)
Partial response	82 (19%)	105 (25%)	81 (31%)	105 (40%)
Not assessable	162 (38%)	160 (38%)	0	0
Not defined*	92 (22%)	91 (21%)	91 (35%)	91 (35%)
No change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain progression	46 (11%)	32 (8%)	44 (17%)	31 (12%)

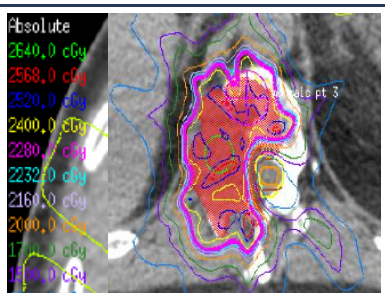
Data are number (%). *Response assessments that could not be classified as complete response, partial response, no change, or pain progression.

Table 2: Response to treatment according to Brief Pain Inventory score and daily oral morphine equivalent at 2 months in the intention-to-treat and per-protocol populations

8Gy/1 non-inferior to 20Gy/5 and less toxic; however, findings not robust in per-protocol analysis, and tradeoffs between efficacy and toxicity must be considered

1. Chow et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol. 2014;15(2):164-171.

Spine SBRT



Technical details for practice of stereotactic body radiotherapy for spinal metastases

Matthew Foote[a], Daniel Letourneau[a], Derek Hyde[b], Eric Masiciotte[a], Raja Ramjeersaad[a], Michael Fehlings[c], Charles Fisher[d], Stephen Lewis[a], Nancy La Macchia[a], Eugene Yu[a], Normand J. Laperriere[a], Arjun Sahgal[a,b,*]

Journal of Clinical Neuroscience

Spine SBRT Indications

Factors	Suitable	Cautionary	Unsuitable
Patient			
Performance status	ECOG 0-2		ECOG ≥3
Life expectancy	≥3 months		
Pain	Intractable		
Neurologic			Symptomatic cord compression or cauda equina syndrome
Oncologic			
Disease burden	Oligometastatic disease	Widespread, rapidly progressive disease	
Tumor histology	Histological proof of malignancy	Radiosensitive (eg, myeloma, lymphoma)	
Systemic therapy	Systemic therapeutic options available or indolent disease course		
Treatment			
Imaging	ESCC (Bilsky) grade 0-1 Up to 3 contiguous or noncontiguous levels	ESCC (Bilsky) grade 2	ESCC (Bilsky) grade 3 or cauda equina compressions >3 contiguous or noncontiguous levels
Spinal stability	SINS 0-6	SINS 7-12	SINS 13-18
Prior radiation	Previous cEBRT to affected level	Previous SBRT to affected level	Previous EBRT to affected level within 90 days or systemic radionuclide within 30 days
Positioning			Inability to tolerate near-rigid body immobilization

Abbreviations: SBRT, stereotactic body radiotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, epidural spinal cord compression; SINS, Spinal Instability Neoplastic Score; EBRT, external beam radiotherapy; cEBRT, conventional EBRT.

Why Spine SBRT?

- **Common doses used in spine SBRT vs. cEBRT**

Total Dose (Gy)	Dose/ Fraction (Gy)	Fractions	Biologic Equivalent Dose (Gy)	Technique
24	24	1	81.6	SBRT
24	12	2	52.8	SBRT
27	9	3	51.3	SBRT
18	10	1	50.4	SBRT
30	6	5	48.0	SBRT
24	8	3	43.2	SBRT
30	3	10	39	EBRT
20	4	5	28	EBRT
8	8	1	14.4	EBRT

- **Represents 2-6x tumor BED as compared to palliative cEBRT**

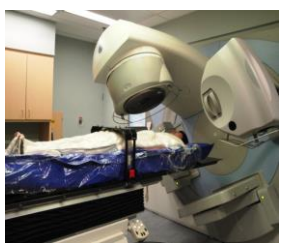
Technical Considerations

How do you do it?

And do it safely?

Technical Considerations at the University of Toronto

- **Near rigid-body immobilization**
  - Ex. BodyFIX
- **Treatment Planning**
  - CT Sim: 1mm slice thickness
  - MRI: volumetric T1/T2 axials for fusion
  - IMRT/VMAT
- **Delivery**
  - 4 mm MLC
  - IGRT
    - CBCT: pre/(intra)/post
    - Correction threshold: 1 mm and 1 degree
  - Rotation Corrections
  - Hexapod robotic couch (6-deg of freedom)

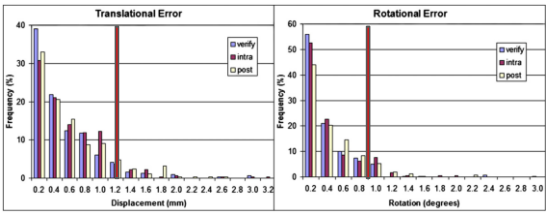


Physics Contribution

Spine Stereotactic Body Radiotherapy Utilizing Cone-Beam CT Image-Guidance With a Robotic Couch: Intrafraction Motion Analysis Accounting for all Six Degrees of Freedom

Derek Hyde, Ph.D.,*† Fiona Lochray, M.R.T.,* Renee Korol, Ph.D.,* Melanie Davidson, Ph.D.,* C. Shun Wong, M.D.,* Lijun Ma, Ph.D.,* and Arjun Sahgal, M.D.*†

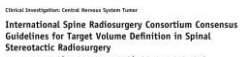
Intra-fractional Motion



Reproducibility of patient positioning during treatment delivery within 1.2mm and 0.9° with 95% confidence

PRV 1.5mm; PTV 2mm

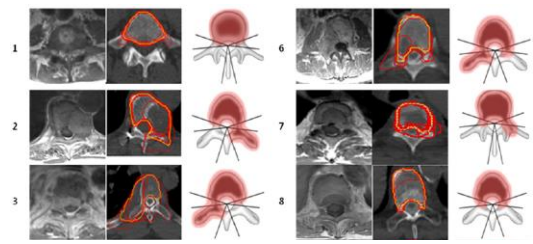
1. Hyde et al. Spine stereotactic body radiotherapy utilizing cone-beam CT image-guidance with a robotic couch: Intrafraction motion analysis accounting for all six degrees of freedom. Int J Radiat Oncol Biol Phys. 2012;82(3):e555–562.


Clinical Investigation: Central Nervous System Tumor

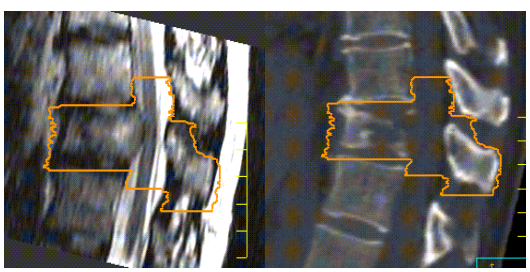
International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

Brett W. Cox, MD,*,† Daniel E. Spratt, MD,*,‡ Michael Lovelock, PhD,‖ Mark H. Bilsky, MD,† Eric Lis, MD,† Samuel Ryu, MD,§ Jason Sheehan, MD,¶ Peter C. Gerszten, MD, MPH,**,†† Eric Chang, MD,‡‡ Iris Gibbs, MD,§§ Scott Soltys, MD,§§ Arjun Sahgal, MD,‡ Joe Deasy, PhD,‖ John Flickinger, MD,§§ Mubina Quader, PhD,‖ Stefan Hinden, MD,†† and Yoshiya Yamada, MD§§

Principles of Target Volume Delineation

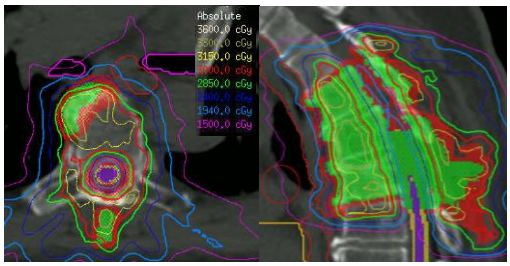


Epidural CTV Cranio-Caudal Extension



5mm CTV cranio-caudally beyond visiable disease within the canal excluding spinal cord

Epidural Disease and Dose Distribution



Multi-Institutional De-Novo SBRT Outcomes

RESEARCH Open Access

Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis

Matthias Guckenberger[1,17], Frederick Mantel[2], Peter C Gerszten[3,17], John C Flickinger[3,17], Arjun Sahgal[4], Daniel Létourneau[5], Inga S Grills[6], Maha Jawad[7], Daniel K Fahim[7], John H Shin[8], Brian Winey[9], Jason Sheehan[10] and Ron Kersh[11]

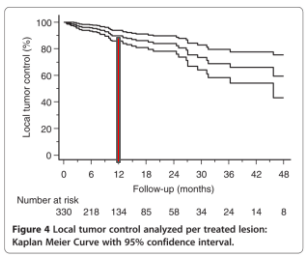


Figure 4 Local tumor control analyzed per treated lesion: Kaplan Meier Curve with 95% confidence interval.

Kaplan Meier

12-month OS: 64.9%

12-month LC: 89.9%

JNS SPINE

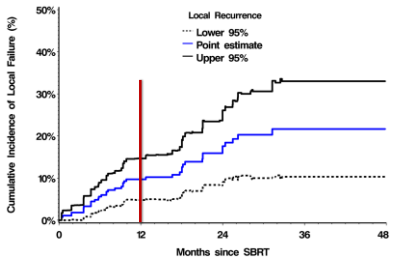
Stereotactic body radiotherapy for de novo spinal metastases: systematic review

International Stereotactic Radiosurgery Society practice guidelines

Zain A. Husain, MD,[1] Arjun Sahgal, MD,[2] Antonio De Salles, MD,[3] Melissa Funaro, MS, MLS,[4] Janis Glover, MLS,[4] Motohiro Hayashi,[5] Masahiro Hiraoka, MD,[6] Marc LaVallee, MD,[7] Lijun Ma, PhD,[8] Roberto Martinez-Alvarez, MD,[9] J. Ian Paddick, MSc,[10] Jean Regis, MD,[11] Ben J. Slotman, MD, PhD,[12] and Samuel Ryu, MD[13]

Authors & Year	Tumors/ Pts Treated (n/n)	Cancer Type	Follow-Up Duration Median (mos)	Local Control Rate (%)	Complete Pain Response (%)	Overall Survival†	Tumor Dose (Gy)/ No. of Fx (range)	BED (α/β = 10) (Gy)
Yamada et al., 2008	103/93	Mixed	15 (all pts)	93 (96/103, crude; 2 yrs)	NR	15 mos (all pts, median)	18–24/1	50.4–81.6 (range)
Sahgal et al., 2009	18/14	Mixed	9	77.8 (14/18, crude)	NR	NR	24/3 (median)	43.2 (median)
Sohn et al., 2014	13/13	RCC	NR	85.7 (1 yr)	23.1	15 mos (median)	38/4 (mean)	74.1 (mean)
Guckenberger et al., 2014	387/301	Mixed	11.8	90 (1 yr), 84 (2 yrs)	58	65% (1 yr), 44% (2 yrs) (median 19.5 mos)	24/3 (median) (10–60/1–20)	43.2 (median) (range 20–78)
Thibault et al., 2014	51/51*	RCC	12.3	84.3 (crude)	NR	64.1% (1 yr)	24/2 (median)	52.8 (median)
Sellin et al., 2015	40/37	RCC	49.0	57	44.4 (with improvement)	16.3 mos (median)	24/1 (median)	81.6 (median)
Bate et al., 2015	24/24*	Mixed	9.8	95.8 (1-yr crude)	NR	NR	22/1 (median) (16–23/1)	70.4 (range 41.6–75.9)
Garg et al., 2012	47*/47	Mixed	NR	87.2 (crude)	NR	NR	18 (GTV), 16 (CTV) (non-RCC); 24 (GTV), 18 (CTV) (RCC)	50.4 (GTV), 41.6 (CTV) (non-RCC); 81.6 (GTV), 50.4 (CTV) (RCC)
Chang et al., 2007	22/17	Mixed	NR	68.1 (7/22 failures)	NR	NR	27–30/3–5	48–51.3 (range)
Chang et al., 2012	131/93	Mixed	23.7	89.2 (1-yr crude)	NR; 89.2 (at 1 yr, "pain control")	19 mos	19.9/1 (mean equivalent)	59.5 (mean)
Gerszten et al., 2005	8/8*	Breast	16	100	NR	NR	12.5–22.5 (mean 19 Gy)	28.13–73.13 (range) (mean 55.1)
Gill et al., 2012	147/14	Mixed	34	85.7	NR	80% (1 yr), 57% (2 yr) (all)	30–35/5	48–59.5 (range)
Ryu et al., 2004	81/49	Mixed	NR (mean 24)	NR	NR (85 complete & partial)	74.3% (1 yr actuarial)	10–18/1	20–41.6 (range)
Staehler et al., 2011	105/55	RCC	33.4	90.4 at 2 yrs	0 (median) on visual analogue scale	17.4 mos (median)	20/1 (median)	60 (median)

Sunnybrook Experience: 24Gy/2



- **LC @ 1 year: 90.3%**
- **LC @ 2 years: 82.4%**

De-novo SBRT Pain Relief Outcomes

Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial

Xin Shelley Wang, Laurence D Rhines, Alman S Shiu, James N Yang, Ugur Selek, Ibrahima Gning, Ping Liu, Pamela K Allen, Syed S Azeem, Paul D Brown, Hadley J Sharp, David C Weksberg, Charles S Cleeland, Eric L Chang

Summary

Background Spinal stereotactic body radiation therapy (SBRT) is increasingly used to manage spinal metastases, yet the technique's effectiveness in controlling the symptom burden of spinal metastases has not been well described. We investigated the clinical benefit of SBRT for managing spinal metastases and reducing cancer-related symptoms.

Methods 149 patients with mechanically stable, non-cord-compressing spinal metastases (166 lesions) were given SBRT in a phase 1–2 study. Patients received a total dose of 27–30 Gy, typically in three fractions. Symptoms were

Lancet Oncol 2012; 13: 395–402
Published Online January 27, 2012
DOI:10.1016/S1470-2045(11)70384-9
See Comment page 328

De-novo SBRT Pain Relief Outcomes

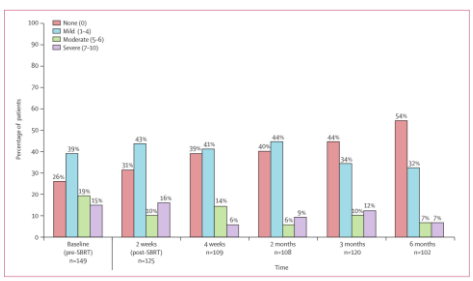
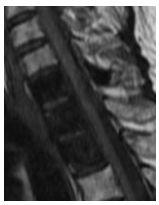


Figure 1: Percentage of patients with no, mild, moderate, or severe pain on the BPI 0–10 scale, before and after SBRT
BPI=Brief Pain Inventory. SBRT=stereotactic body radiotherapy.

Re-irradiation Example Case

- **72M metastatic early castrate resistant prostate ca with multi-level mets to C+T spine treated with conventional RT 20Gy/5 C4-T4**

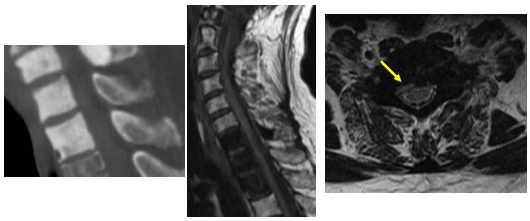
At initial cEBRT



12 months later

Re-irradiation Example Case

- **Right arm paresthesia; Bilsky 1B; SINS 7**
- **ECOG 1**



Prospective Re-irradiation SBRT Outcomes

Prospective Evaluation of Spinal Reirradiation by Using Stereotactic Body Radiation Therapy

The University of Texas MD Anderson Cancer Center Experience

Amit K. Garg, MD[1], Xin-Shelley Wang, MD[1], Almon S. Shiu, PhD[2], Pamela Allen, PhD[2], James Yang, PhD[2], Mary Frances McAleer, MD, PhD[1], Syed Azeem, MD[1], Laurence D. Rhines, MD[1], and Eric L. Chang, MD[1]

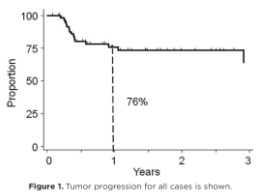


Figure 1. Tumor progression for all cases is shown.

Table 3. Treatment Toxicity

Grade	Neurotoxicity	Hematologic	Gastrointestinal	Other Toxicity (worst grade)
None	44	59	44	22
Grade 1	7	0	6	19
Grade 2	4	0	6	16
Grade 3	2	0	0	0
Grade 4	0	0	0	0

1. Garg AK, Wang X-S, Shiu AS, et al. Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience. Cancer. 2011;117(15):3509-3516.

Multi-Institutional Re-irradiation SBRT Outcomes

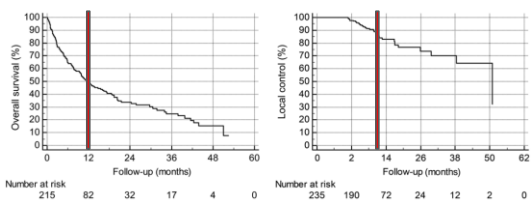
JNS SPINE

CLINICAL ARTICLE
J Neurosurg Spine 25:646–653, 2016

Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis

Ahmed Hashmi, MD,[1] Matthias Guckenberger, MD,[2,3] Ron Kersh, MD,[4] Peter C. Gerszten, MD,[5] Frederick Mantel, MD,[3] Inga S. Grills, MD,[6] John C. Flickinger, MD,[7] John H. Shin, MD,[8] Daniel K. Fahim, MD,[9] Brian Winey, PhD,[10] Kevin Oh, MD,[10] B. C. John Cho, MD, PhD,[11] Daniel Létourneau, PhD,[11] Jason Sheehan, MD, PhD,[12] and Arjun Sahgal, MD[1]

Multi-Institutional Re-irradiation SBRT Outcomes



Kaplan Meier 12-month OS: 64%

12-month LC: 83%

JNS SPINE

Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review

International Stereotactic Radiosurgery Society practice guidelines

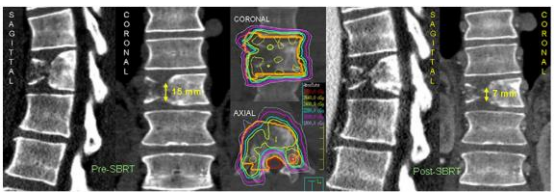
Sten Myrehaug, MD,[1] Arjun Sahgal, MD,[1] Motohiro Hayashi, MD,[2] Marc Levivier, MD,[3] Lijun Ma, PhD,[4] Roberto Martinez, MD,[5] Ian Paddick, MSc,[6] Jean Régis, MD,[7] Samuel Ryu, MD,[8] Ben Slotman, MD, PhD,[9] and Antonio De Salles, MD, PhD[10]

TABLE 4. Spine SBRT reirradiation systematic review: treatment outcomes

Authors & Year	Median FU in Mos (range)	FU Schedule	Definition of Progression	Local Control	Overall Survival	Symptom Assessment Scale	Pain Response
Sahgal et al., 2009	7 (1–48)	Not defined	Radiographic or neurological	1 yr, 82%	Median 21 mos	NR	NR
Choi et al., 2010	7 (4–27)	MRI every 2–3 mos	Radiographic	1 yr, 73%	1 yr, 68%	NR	65% improvement in pain
Garg et al., 2011	17.6 (0.9–67.5)	MRI every 3 mos	Radiographic	1 yr, 76%	Median 22.5 mos, 1 yr, 76%	BPI	Improvement in pain at 6 mos
Damast et al., 2011	12.1 (0.2–63.6)	MRI every 3–4 mos	Radiographic	1 yr all, 66%	Median 13.6 mos	NR	77% improvement in pain
Mahadevan et al., 2011	12 (4–36)	CT 1 mo post, otherwise not defined	Radiographic or neurological	1 yr, 90%	Median 11 mos	NR	79% improvement in pain
Ahmed et al., 2012	8.2	MRI at 2 mos & then every 6 mos ± PET	Radiographic	1 yr, 83%	1 yr, 28%	FACT-G	NR
Chang et al., 2012	17.3	MRI/PET at 3, 6, & 12 mos	Radiographic	1 yr, 81%	Median 11 mos	NR	80.8% control rate at 1 yr
Thibault et al., 2014	12.3 (1.2–55.4)	MRI every 2–3 mos	Radiographic	1 yr, 73%	NR	NR	NR
Thibault et al., 2015[52]	6.8 (0.9–39)	NR	Radiographic	1 yr, 81%	Median 10.0 mos	NR	NR

FACT-G = Functional Assessment of Cancer Therapy–General; FU = follow-up; NR = not reported.

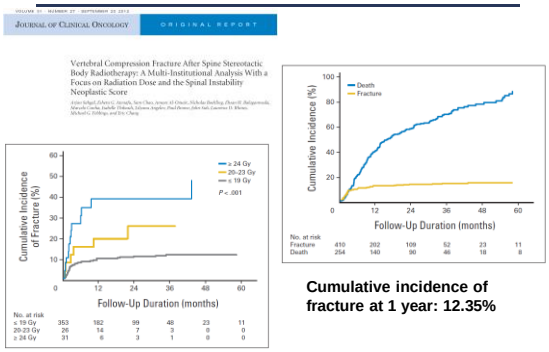
Late Toxicities: VCF Post-SBRT



Baseline VCF **24Gy/1** **Fracture Progression**

1. Cunha MVR, Al-Omair A, Atenafu EG, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): Analysis of predictive factors. Int J Radiat Oncol Biol Phys. 2012;84(3):e343-e349.

Late Toxicities: VCF Post-SBRT



Cumulative incidence of fracture at 1 year: 12.35%

Predictors of VCF

Table 3. Significant Predictors of VCF on Univariate and Multivariate Analysis

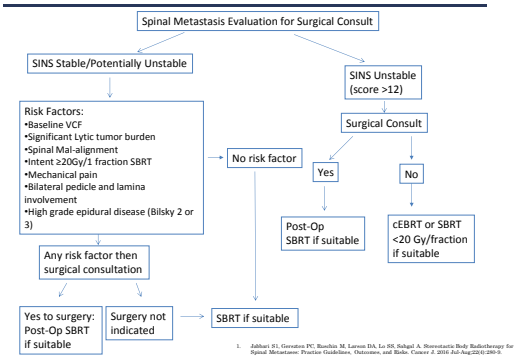
Factor	Univariate *P*	Multivariable Fine and Grey Model *P*	HR	95% CI
Vertebral body collapse	< .001	Global, < .001		
≥ 50% VCF		.0189	6.92	1.38 to 34.77
< 50% VCF		< .001	8.98	4.48 to 18.00
No VCF but > 50% of vertebral body involved		< .001	4.46	2.08 to 9.57
Dose/fraction, Gy	< .001	Global, < .001		
≥ 24		< .001	5.25	2.29 to 12.01
20-23		< .001	4.91	1.96 to 12.28
Alignment	.0027	< .001	2.99	1.57 to 5.70
Bone lesion type	< .001	.0022	3.53	1.58 to 7.93
Paraspinal/epidural extension	.0036	NS		

NOTE. For vertebral body collapse, the reference is no VCF and less than 50% vertebral body involvement; for dose/fraction, the reference is ≤ 19 Gy/fraction; the reference for alignment was normal, and yphosis/scoliosis and subluxation/translation were grouped as only one patient had subluxation; and the reference for bone lesion was grouped according to mixed and osteoblastic tumor versus osteolytic, given that the majority of VCFs occurred in lytic tumors.

Abbreviations: HR, hazard ratio; NS, not significant; VCF, vertebral compression fracture.

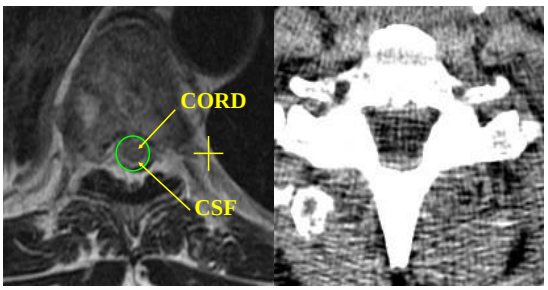
1. Sahgal et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. J Clin Oncol. 2011;31(27):3426-3431.

Prophylactic Surgical Stabilization?

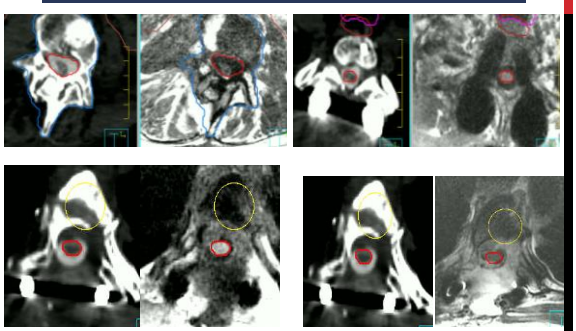


1. Jabbari S1, Gerszten PC, Ruschin M, Larson DA, Lo SS, Sahgal A. Stereotactic Body Radiotherapy for Spinal Metastases: Practice Guidelines, Outcomes, and Risks. Cancer J. 2016 Jul-Aug;22(4):280-9.

Radiation Myelopathy: MR-based Delineation of the Spinal Cord



Radiation Myelopathy: MR-based Delineation of the Spinal Cord

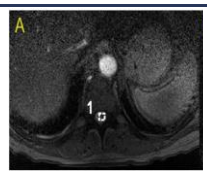


Spinal Cord Motion?

Physics Contribution

Magnetic Resonance Imaging Assessment of Spinal Cord and Cauda Equina Motion in Supine Patients With Spinal Metastases Planned for Spine Stereotactic Body Radiation Therapy

Chia-Lin Tseng, MD,[†] Marshall S. Sussman, PhD,[‡] Eshetu G. Atenafu, MSc, Daniel Letourneau, PhD,[†] Lijun Ma, PhD, Hany Soliman, MD,[†] Isabelle Thibault, MD,[†] B. C. John Cho, MD, PhD, Anna Simeonov, MSc, MRT, Eugene Yu, MD, Michael G. Fehlings, MD, PhD,[§] and Arjun Sahgal, MD[†]



Methods and Materials: We analyzed CNT motion in 65 patients with spinal metastases (11 cervical, 39 thoracic, and 24 lumbar spinal segments) in the supine position using dynamic axial and sagittal magnetic resonance imaging (dMRI, 3T Verio, Siemens) over a 137-second interval. Motion was segregated according to physiologic

Median oscillatory motion 0.16-0.44mm

Median bulk displacements 0.51-0.66mm

Evidence-Based: De-novo SBRT Cord Dose Limits

Clinical Investigation: Central Nervous System Tumor

Probabilities of Radiation Myelopathy Specific to Stereotactic Body Radiation Therapy to Guide Safe Practice

Arjun Sahgal, MD,*[,†] Vivian Weinberg, PhD,[‡] Lijun Ma, PhD,[‡] Eric Chang, MD,[‡] Sam Chao, MD,[‡] Alexander Muacevic, MD,[¶] Alessandra Gorgulho, MD,[**] Scott Soltys, MD,[††] Peter C. Gerszten, MD,[‡‡] Sam Ryu, MD,[§§] Lilyana Angelov, MD,[‖] Iris Gibbs, MD,[††] C. Shun Wong, MD,[‡] and David A. Larson, MD, PhD[‡‡]

Table 5 Predicted Pmax volume absolute doses in Gy for 1 to 5 SBRT that result in 1%-5% probability of radiation myelopathy (RM)

	1 fraction Pmax limit (Gy)	2 fractions Pmax limit (Gy)	3 fractions Pmax limit (Gy)	4 fractions Pmax limit (Gy)	5 fractions Pmax limit (Gy)
1% probability	9.2	12.5	14.8	16.7	18.2
2% probability	10.7	14.6	17.4	19.6	21.5
3% probability	11.5	15.7	18.8	21.2	23.1
4% probability	12.0	16.4	19.6	22.2	24.4
5% probability	12.4	17.0	20.3	23.0	25.3

1. Sahgal A, Weinberg V, Ma L, Chang E, Chao S, Muacevic A, Gorgulho A, Soltys S, Gerszten PC, Ryu S, Angelov L, Gibbs I, Wong CS, Larson DA. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. Int J Radiat Oncol Biol Phys. 2013 Feb 1;85(2):341-7.

Evidence-Based: Re-irradiation SBRT Cord Dose Limits

CLINICAL INVESTIGATION — Central Nervous System Tumor

REIRRADIATION HUMAN SPINAL CORD TOLERANCE FOR STEREOTACTIC BODY RADIOTHERAPY

Arjun Sahgal, M.D.,* Lijun Ma, Ph.D.,† Vivian Weinberg, Ph.D.,† Iris C. Gibbs, M.D.,‡ Sam Chao, M.D.,¶ Uno-Kyu Chang, M.D.,† Maria Werdehausen, M.D.,§* Lilyanna Angelov, M.D.,¶ Eric L. Chang, M.D.,† Moon-Jun Sohn, M.D.,†† Scott G. Soltys, M.D.,‡ Daniel Letourneau, Ph.D.,†† Sam Ryu, M.D.,¶¶ Peter C. Gerszten, M.D.,†† Jack Fowler, Ph.D.,*** C. Shun Wong,††† and David A. Larson.‡

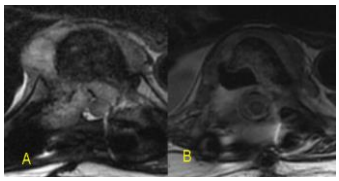
Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
0*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions (30 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions (37.5 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions (42 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions (40 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions (43 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions (50 $Gy_{2/2}$)	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

1. Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2012;82(1):107-116.

Separation Surgery

- **Limited approach where only the epidural component of the tumor is decompressed and stabilization is achieved to facilitate postoperative radiation**
  - Allows high dose SBRT to be delivered while maintaining dose constraints to the spinal cord



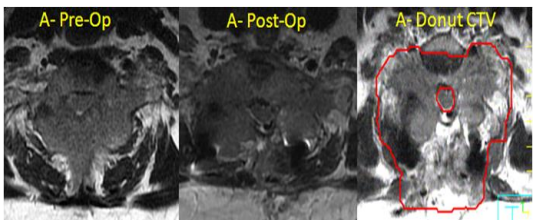
1. Sahgal A, Bilsky M, Chang EL, Ma L, Yamada Y, Rhines LD, Létourneau D, Foote M, Yu E, Larson DA, Fehlings MG. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. J Neurosurg Spine. 2011 Feb;14(2):151-66.

Neuro-Oncology 15(10):1413–1419, 2013.
doi:10.1093/neuonc/not101

NEURO-ONCOLOGY

U of Toronto Experience

Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy



- **LC @ 1 year: 84% OS @ 1 year: 64%**

1. Al-Omair A, Masucci L, Masson-Cote L, Campbell M, Atenafu EG, Parent A, Letourneau D, Yu E, Rampersaud R, Massicotte E, Lewis S, Yee A, Thibault I, Fehlings MG, Sahgal A. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. Neuro Oncol. 2013 Oct;15(10):1413-9.

U of Toronto Post-op SBRT Experience

Preop Bilsky epidural grade	
0	4 (5%)
1a	3 (3.7%)
1b	12 (15%)
1c	13 (16.2%)
2	28 (35%)
3	20 (25%)

Postop Bilsky epidural grade	
0	6 (7.5%)
1a	25 (31.2%)
1b	26 (32.5%)
1c	15 (18.7%)
2	8 (10%)
3	0 (0%)

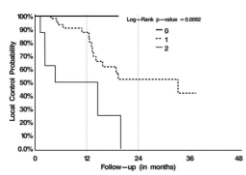


Fig. 3. LC for the entire cohort according to postoperative epidural disease Bilsky grade.

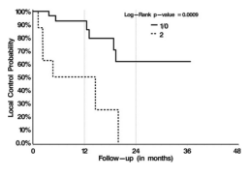


Fig. 4. LC probability for those 48 patients presenting with preoperative Bilsky grade 2 or 3 epidural disease according to their postoperative epidural grade.

1. Al-Omair A, Masucci L, Masson-Cote L, Campbell M, Atenafu EG, Parent A, Letourneau D, Yu E, Rampersaud R, Massicotte E, Lewis S, Yee A, Thibault I, Fehlings MG, Sahgal A. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. Neuro Oncol. 2013 Oct;15(10):1413-9.

MDACC Experience

International Journal of Radiation Oncology Biology Physics
www.redjournal.org

Clinical Investigation

Stereotactic Body Radiation Therapy for Spinal Metastases in the Postoperative Setting: A Secondary Analysis of Mature Phase 1-2 Trials

Randa Tao, MD,* Andrew J. Bishop, MD,* Zachary Brownlee, BS,* Pamela K. Allen, PhD,* Stephen H. Settle, MD, PhD,* Eric L. Chang, MD,* Xin Wang, PhD,* Behrang Amini, MD, PhD,† Nizar M. Tannir, MD,† Claudio Tatsui, MD,† Laurence D. Rhines, MD,† Paul D. Brown, MD,* and Amol J. Ghia, MD*

Preoperative Bilsky grade (n=69)		
0	14	20%
Ia	5	7%
Ib	22	31%
Ic	9	13%
2	17	25%
3	3	4%
Postoperative Bilsky grade (n=69)		
0	57	82%
Ia	6	9%
Ib	6	9%
2-3	0	0

- **66 patients (69 tumors**
- **Fractionation: 16-24Gy/1, 27Gy/3, 30Gy/5**

1. Tao et al. Stereotactic Body Radiation Therapy for Spinal Metastases in the Postoperative Setting: A Secondary Analysis of Mature Phase 1-2 Trials. Int J Radiat Oncol Biol Phys. 2016 Aug 1;95(5):1405-13.

MDACC Post-op SBRT Experience

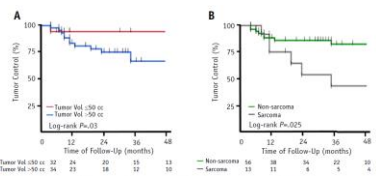
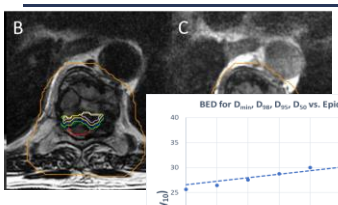


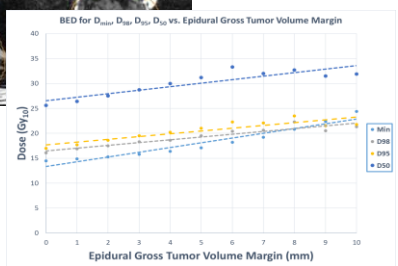
Fig. 1. Kaplan-Meier estimates of the treated tumor control based on (A) tumor volume before surgery and (B) sarcoma status. *Abbreviation:* Vol = volume.

- **LC @ 1 year: 85% OS @ 1 year: 74%**

1. Tao et al. Stereotactic Body Radiation Therapy for Spinal Metastases in the Postoperative Setting: A Secondary Analysis of Mature Phase 1-2 Trials. Int J Radiat Oncol Biol Phys. 2016 Aug 1;95(5):1405-13.

Dosimetric Benefits of Surgical Decompression





- **3.7 – 7.7 Gy_{10} (25.8 – 31.2%) over 6 mm resected margins**
- **0.62 – 1.28 Gy_{10} (4.3 – 5.2%) per mm**

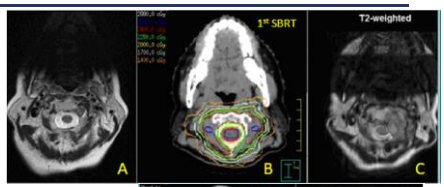
Radiation Myelopathy Summary

- **Radiation myelopathy is a rare event even in the re-irradiation scenario**
- **Evidence based guidelines to guide safe practice applicable to thecal sac or cord + 1.5 mm PRV which represent the safest practice**

Patterns of Failure Post-SBRT

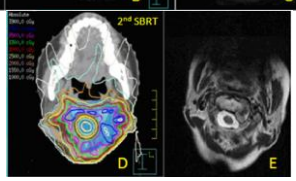
C2 met treated with 24Gy/2

Cord prv: 17Gy



Salvage SBRT delivered with 30Gy/5

Cord prv: 15.5Gy



1. Thibault I, Campbell M, Tseng C-L, et al. Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases. Int J Radiat Oncol Biol Phys. 2015;93(2):353-360.

Re-irradiation SBRT After Initial SBRT

Clinical Investigation

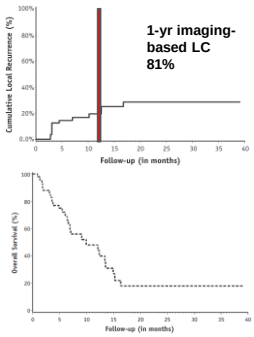
Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases

Isabelle Thibault, MD,* Mikki Campbell, MRT(T),* Chia-Lin Tseng, MD,*,† Eshetu G. Atenafu, MSc,† Daniel Letourneau, PhD,† Eugene Yu, MD,† B.C. John Cho, MD,† Young K. Lee, PhD,* Michael G. Fehlings, MD, PhD,‡ and Arjun Sahgal, MD*,†

Re-irradiation SBRT After Initial SBRT

Table 1 Patient, tumor, and treatment characteristics for the 56 spinal segments treated with a second salvage SBRT course

Characteristic	n = 56 spinal segments
Primary cancer origin	
Renal cell	13 (23.2%)
NSCLC	7 (12.5%)
Thyroid	7 (12.5%)
Prostate	5 (8.9%)
Other	24 (42.9%)
Spinal level	
Cervical	3 (5.4%)
Thoracic	30 (53.6%)
Lumbar	20 (35.7%)
Sacrum	3 (5.4%)
Paraspinal extension	
Yes	47 (83.9%)
No	9 (16.1%)
Bilsky epidural grade	
0	15 (26.8%)
1a	9 (16.1%)
1b	18 (32.1%)
1c	11 (19.6%)
2	3 (5.4%)
3	0 (0%)
CTV shape	
Donut type*	43 (76.8%)
Nondonut	13 (23.2%)
Salvage SBRT total dose/number of fractions	
24-26 Gy/2 fractions	5 (8.9%)
24-30 Gy/3 fractions	8 (14.3%)
20-30 Gy/4 fractions	28 (50.0%)
25-35 Gy/5 fractions	15 (26.8%)



1-yr imaging-based LC 81%

Re-irradiation SBRT After Initial SBRT

Factor	Prior conventional EBRT (n = 24) EBRT	Initial first SBRT course	Salvage second SBRT course	Median total nBED	No prior conventional EBRT (n = 32) Initial first SBRT course	Salvage second SBRT course	Median total nBED
Median prescription absolute total dose in Gy/number of frx with ranges	22.5 (20-30)	24 (20-30)/ 2 (2-5) frx	30 (24-35)/ 4 (2-5) frx	N/A	24 (20-35)/ 2 (1-5) frx	30 (20-35)/ 4 (2-5) frx	N/A
Median prescription total dose nBED (Gy_{10}) and range	23.3 (22.7-32.5)	42.0 (27.8-44.0)	43.8 (31.3-50.0)	111.1	44.0 (33.3-68.0)	43.8 (25.0-49.6)	87.8
Median CTV D90 nBED (Gy_{10}) and range	23.3 (22.7-32.5)	26.8 (16.3-37.7)	29.8 (20.6-47.1)	81.4	32.5 (21.9-49.7)	27.7 (13.6-41.1)	56.5
Median PTV D90 nBED (Gy_{10}) and range	23.3 (22.7-32.5)	25.4 (10.4-35.5)	25.7 (17.7-45.8)	77.0	29.2 (21.3-47.2)	24.3 (11.7-40.6)	52.3
Cord PRV nBED (Gy_2)*							
Median Pmax and range	30.0 (16.9-37.5)	20.8 (12.5-29.9)	21.9 (17.5-26.7)	73.9	31.8 (18.1-40.1)	21.9 (12.4-25.0)	51.3
Median D0.1cc and range	30.0 (16.9-37.5)	17.2 (8.6-21.8)	18.1 (12.4-21.4)	66.8	21.7 (13.2-30.0)	17.7 (8.6-21.7)	40.0
Thecal sac nBED (Gy_2)†							
Median Pmax and range	37.5 (30.0-37.5)	19.7 (14.3-24.7)	24.5 (19.4-32.9)	80.4	33.4 (14.0-67.4)	23.5 (8.8-34.6)	54.6
Median D0.1 cc and range	37.5 (30.0-37.5)	15.3 (11.8-19.4)	20.9 (17.7-25.8)	71.5	25.0 (11.9-60.5)	20.6 (8.4-29.5)	43.6

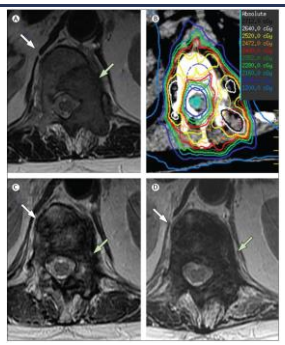
1. Thibault I, Campbell M, Tseng C-L, et al. Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases. Int J Radiat Oncol Biol Phys. 2015;93(2):353-360.

BED= EQD2

Patterns of Failure Post-SBRT Take Home

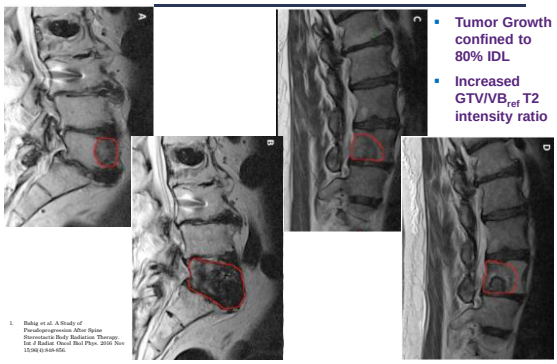
- **Epidural progression is the most common pattern of failure**
  - Relative under-dosing of the epidural space
  - Bad tumor biology
  - Geographic miss
- **Reirradiation spine SBRT, most often with 30 Gy in 4 fractions, for spinal metastases that failed initial SBRT is a feasible and efficacious salvage treatment option**

Challenges of Response Assessment



1. Thibault I, Chang EL, Sheehan J, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Lancet Oncol. 2015;16(16):e595-e603.

Pseudo-progression After Spine SBRT



- **Tumor Growth confined to 80% IDL**
- **Increased GTV/VB_{ref} T2 intensity ratio**

1. Balagamwala EH, Angelov L, Suh JH, et al. A Study of Pseudoprogression After Spine Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):848-856.

Consensus Response Assessment Post-SBRT

Respons… spinal m… assessm…

Isabelle Thibault, Er… Simon S Lo, Alexan… Michael G Fehlings…

Imaging-based local tumour response

- MRI preferred*
- Images should be interpreted by a radiation oncologist and radiologist
- Local control may be defined as the absence of progression within the treated area on serial imaging (two or three consecutive MRI scans 6–8 weeks apart)*
- Local progression may be defined as*
  - Gross unequivocal increase in tumour volume or linear dimension
  - Any new or progressive tumour within the epidural space
  - Neurological deterioration attributable to pre-existing epidural disease with equivocal increased epidural disease dimensions on MRI
- Pseudoprogression and necrosis should be considered, with repeat imaging and biopsy to confirm when in doubt
- RECIST criteria are not optimum to monitor response in spinal metastases treated with SBRT, and consensus criteria for imaging-based tumour response are needed

Pain response

- BPI preferred, with assessment based on worst pain score
- ICPRE should be adopted as standard guidelines for pain response
- Pain response should be assessed at 3 months after SBRT

Imaging follow-up frequency

- Spine MRI every 2–3 months after SBRT for the first 12–18 months, and every 3–6 months thereafter*

Ongoing Studies

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0631

PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

- **Randomizing patients with up to 3 separate sites of spinal metastases to 8 Gy in 1 fraction of cEBRT vs. SBRT to a dose of 16-18 Gy/1**
- **Primary objective:**
  - Pain response rates as measured by the 11-point Numerical Rating Pain Scale (NRPS) at 3 months

Ongoing Studies

CANADIAN CANCER TRIALS GROUP (CCTG)

A RANDOMIZED PHASE II/III STUDY COMPARING STEREOTACTIC BODY RADIOTHERAPY (SBRT) VERSUS CONVENTIONAL PALLIATIVE RADIOTHERAPY (CRT) FOR PATIENTS WITH SPINAL METASTASES

CCTG Protocol Number: **SC.24**

STUDY CHAIR:	Arjun Sahgal
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Canadian SC.24 Schema

Patients with tumours (excluding seminoma, small cell lung cancer and metastases from hematologic malignancies - e.g. lymphoma, myeloma) who have MRI-documented spinal metastases, suitable for receiving radiation therapy, and fulfill the following criteria:

- Pain secondary to spinal metastases requiring treatment
- ≤3 consecutive spinal segments involved by tumour to be included in the target volume

→ RANDOMIZATION →

ARM 1
Standard Conventional Radiotherapy (CRT)**
20 Gy in 5 fractions

ARM 2
Stereotactic Body Radiotherapy (SBRT)***
24 Gy in 2 fractions

Primary Endpoint - Phase III

The primary objective of the phase III study is to assess complete pain response in the treatment area at 3 months post-radiation.

Conclusions

- **Spine SBRT is an emerging field with great promise for patient care**
  - Uniquely suited for selected patients as it allows dose escalation to the tumor while attaining rapid dose falloff to minimize spinal cord doses
  - Good LC and pain response rates in reported series
- **Much work has been done in technique and consistent contouring approach defined**
- **Imaging-based (MRI) outcomes and follow-up now standard: SPINO**
- **Serious toxicities rare although caution must be exercised with respect to cord dose limits and management of VCF risk**
- **Higher level of evidence limited**
  - Randomized trials ongoing to help define practice