Spine Metastasis

2D to SBRT

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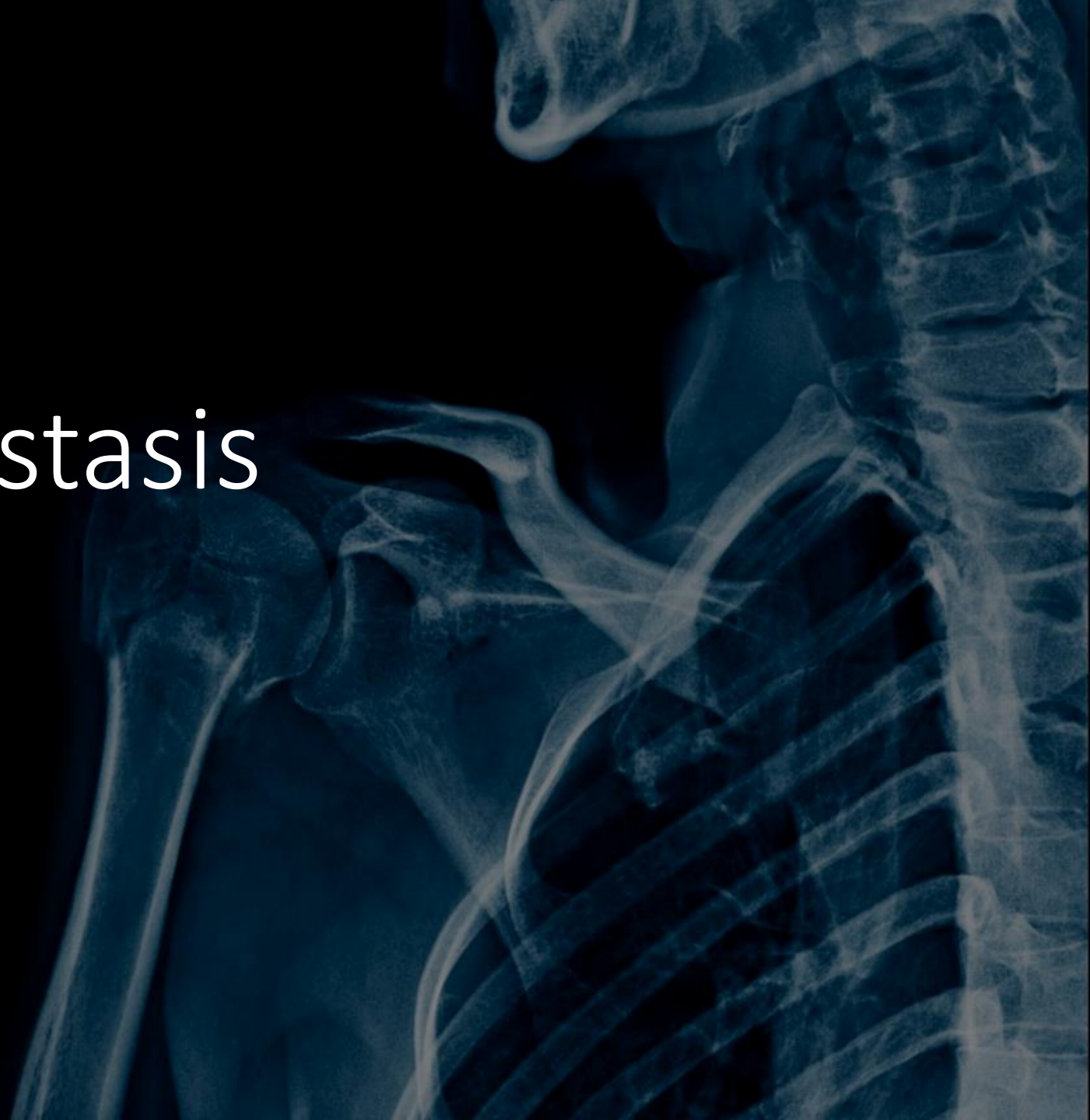


Roadmap

- Introduction
- Bone mets- problem statement and requirement for RT
- Conventional radiation…is it obsolete?
- Where does SBRT fit in……rationale
- Literature review- patient selection
- SBRT process- preplanning/ prerequisite

  Simulation

  contouring

  plan eval

Patterns of recurrence/toxicity

Introduction

Bones are common location for metastases - significant morbidity and mortality.

With the availability of more lines of systemic therapy improving patient survival-desire in select patients to improve durable LC and prevent neurologic compromise.

Introduction

- Bone is third most frequent site of metastasis
- Prostate and breast cancer are responsible for up to 70%) skeletal metastases
- Incidence of bone metastasis by type of tumor,

➢65-75% in Breast Carcinoma

➢65- 75% in Prostate

➢60% in Thyroid

➢30-40% in Lung carcinoma

➢ 40% in bladder

➢ 20-25% in renal cell carcinoma

➢ 14-45% in melanoma.

- Cause morbidity, severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia.
- Most disability is caused by a long bone fracture or epidural extension of tumour into the spine.

Bone metastasis Pain

Inflammatory pain is related to the local release of cytokines and chemical mediators by the tumor cells, periosteal irritation, stimulation of intraosseous nerves.

Mechanical pain is related to the pressure or mass effect of the tumor tissue within the bone, with loss of bone strength thus turn- ing into activity-related pain.

Inhibition of osteoclastic bone reabsorption reduces bone pain.

Use of osteoclast inhibitors, such bisphosphonates and denosumab, reduce bone pain.

Outcome of patients with bone Mets

- The median survival of patients after first bone metastasis by BC is 20 months.
- This is in marked contrast to those with metas- tases of BC in the liver, 3 months
- bone metastases from non-small cell lung cancer, 6 months
- In prostate cancer, men with a good performance status and bone only disease, affecting predominantly the axial skeleton, have a median duration of disease control after androgen blockade of 4years and a median survival of 53 months. This is in marked con- trast to those with visceral disease with a median survival of 30 months and 12 months with visceral disease and poor performance status.27

What are the types of metastatic spinal tumors?

The types of metastatic spinal tumors include:
Extradural:- tumor that forms outside of dura (thin membrane covering the spinal cord), often in bones of spine.
Intradural-extramedullary:-tumor located within the dura, but not in the spinal cord itself. Some 40% of metastatic tumors are of this type.
Intramedullary: A tumour that develops inside the spinal cord.

- Location-
- **Cervical**
- **Thoracic**
- **Lumbar**
- **Sacrum**

Number
Oligometastasis
polymets

Traditional palliative radiation

- Classical treatment approach for symptomatic spine metastases is conventional palliative radiotherapy delivered with two parallel opposed beams with common fractionation regimens
  - 8Gy in 1 fraction
  - 20Gy in 5 fractions
  - 30Gy in 10 fractions.

- Effective in improving symptomatology but poor local control

Technique

- The local-field radiation therapy is considered the conventional treatment of bone metastases.
- Treats the involved bone and yields a pain relief rate of 80-90%
- Several randomized trials have indicated that a single fraction of 8Gy is adequate for pain relief.
- Wide field (half-body, hemibody) radia- tion therapy can be used as primary palliative therapy for wide- spread symptomatic bone metastases or as an adjuvant to local- field radiation to reduce the later expression of occult metastases and to reduce the frequency of re-treatment.

Technique

- It is possible to distinguish: upper wide-field treatments (from skull or C1 to L2-3) - optimal single-dose is 6Gy; mid-body wide-field treatments (from L1 to upper third of the femurs) - optimal single-dose is 8Gy; lower wide-field treatments (from L3-4 to above the knees) - optimal single-dose is 8Gy.
- Wide-field radiation provides pain relief for 64-100% of patients and approximately 50-66% of patients maintain pain relief for the remainder of their lives. The radiation fields must be shaped to reduce exposure of sensitive structures such as lung, gut, kidney and liver.

Goals of stereotactic radiosurgery

- Improve local control over conventional fractionated radiation therapy and to be effective for the treatment of previously irradiated lesions with an acceptable safety profile.
- theoretical advantages as a treatment modality for spinal tumors:

❖ early treat- ment of these lesions before a patient becomes symptomatic

❖ the stability of the spine

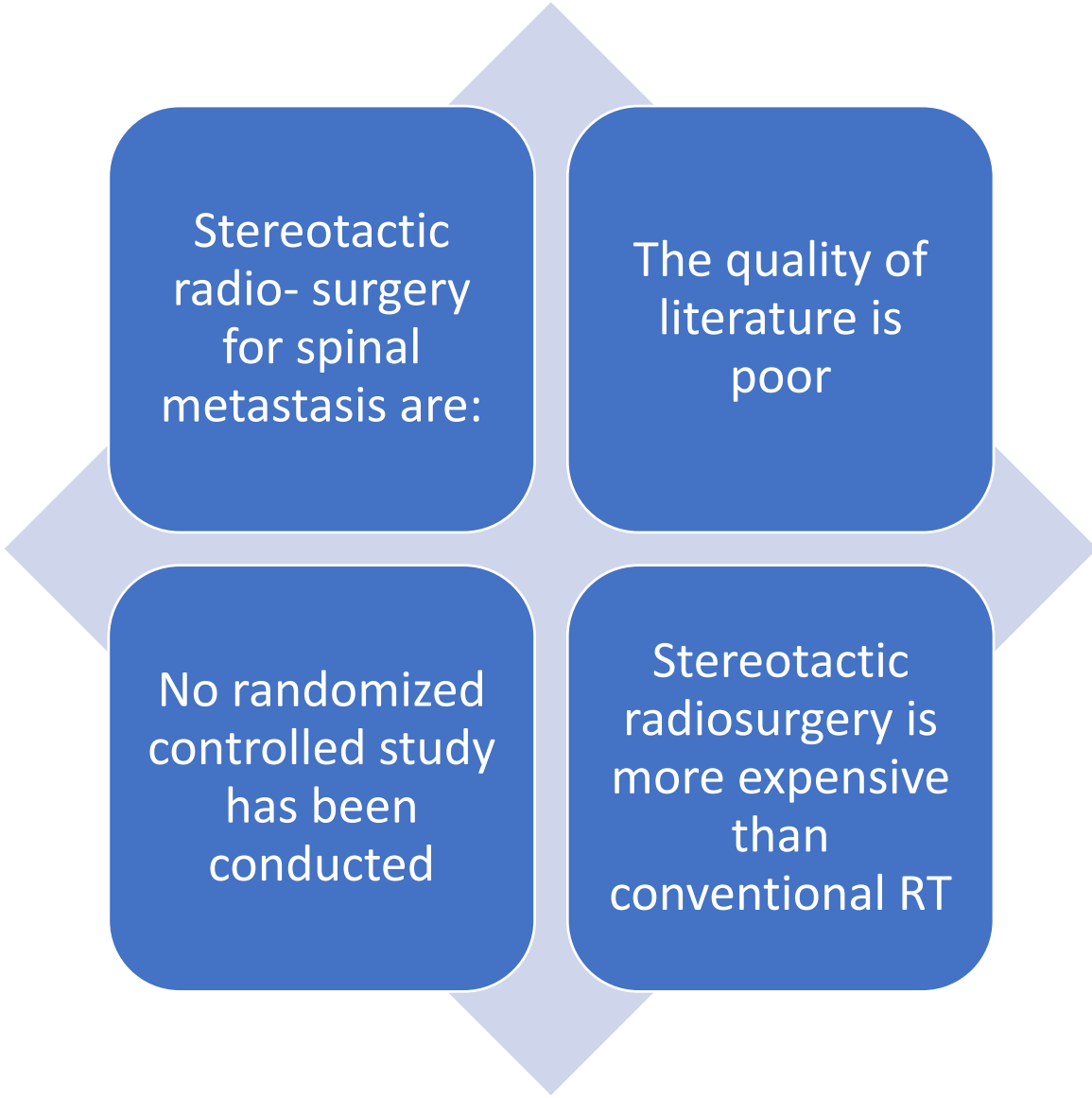
❖ it avoids the need to irradiate large segments of the spinal cord,

❖ the early treatment of spinal lesions may obviate the need for extensive spinal surgery for decompression and fixation in these already debilitated patients and may also avoid the need to irradiate large segments of the spinal column, which is known to have a deleterious effect on bone marrow reserve in these patients.

- The avoidance of open surgery and the preservation of bone-marrow function facilitate continuous chemotherapy in this patient population.
- Other advantage is that treatment can be completed in a single day rather than over the course of several weeks.

But for select people who have a limited number of tumors in the spine, “SBRT is a new standard of care

Limitations



Planning 3DCRT

In vertebral metastases, radiation fields should include

The involved vertebral body

And if necessary the soft tissue tumor),

Plus a vertebral body below and above.

Planning IMRT/VMAT

SBRT where does it fit in?

- Delivery of high biological effective doses (BED) precisely to the spine yields prolonged local control along with pain relief
- In oligometastatic disease, can prolong progression-free survival and potentially delay entry to next line of systemic therapy
- In post-operative setting, neurologic status is maintained through improvements in local control
- For reradiation-it is a method of safely retreating the same or adjacent segments while minimizing dose to critical neurological structures.

Delivery of spine SBRT requires careful patient selection, familiarity with the technique and an understanding of potential toxicities

SBRT vs 3DCRT

- May be preferred over EBRT is in the definitive treatment of patients with symptomatic bone metastases from relatively radioresistant neoplasms (eg, renal cell cancer, melanoma, sarcoma),
- Especially in the setting of vertebral metastases with epidural extension but no high-grade epidural spinal cord compression
- Specific to spine oligometastases. Patients with oligometastatic disease (defined as <5 metastases) showed evidence of better survival compared to those with Poly metastatic disease (>5 metastases)

Epidemiology, Process, and Outcomes of Spine Oncology (EPOSO) study AO Spine multicenter prospective cohort , Barzilai et al

Journey from 2D to 3D & SBRT

Advancements in radiation planning and delivery, mage guidance, robotic patient positioning, and understanding of dose tolerances to critical structures have made spine SBRT possible.

With greater clinical experience, guidelines have been developed to direct safe practice though supporting high-quality Phase 3 randomized data are pending.

Patient Selection

Compared to conventional external beam radiotherapy, spine SBRT is significantly more resource intensive

MDT inclusive of specialized spine surgeons, radiologists & oncologists is essential for careful selection of patients to avoid treatment of those that may not benefit.

A number of schemes have been proposed to assist in identification of patients that benefit most from spine SBRT .

Histology

- Traditionally deemed radioresistant -renal cell carcinoma, melanoma, sarcoma-poor tumor control rates with conventional RT
- Spine SBRT may overcome this radio-resistance.
- In renal cell carcinoma specifically, local control at 1-year has been reported to be >80% (18, 42).

Sensitive histologies, such as hematologic malignancies or small cell lung cancer may warrant upfront systemic therapy or derive similar benefit with conventional radiotherapy.

Prognosis based selection

Patients with spine metastases, represent a heterogenous population

Some may live many years (i.e., a patient with oligometastatic hormone responsive prostate cancer) ---one may consider more aggressive techniques such as SBRT, favouring long term

Others a significantly shorter time interval (i.e., one who has failed second line systemic therapy for widely metastatic pancreatic cancer)--may benefit most from conventional palliative radiotherapy (38), or possibly best supportive care alone.

Systemic Disease and Systemic Treatment Options

Assessment of systemic burden of disease and the availability and response to systemic therapies can influence patients' goals of care.

Widely metastatic disease-urgency to proceed with systemic therapy over focal treatment of minimally symptomatic spinal disease.

Availability of further lines of systemic treatment options - relate to prognosis- preference to conventional techniques in those with high visceral burden of disease with limited further options or prognosis.

Stability and Epidural Spinal Cord Compression

Mechanical spinal instability and presence of high-grade epidural spinal cord compression (ESCC) are independent indications for potential surgical intervention----radiotherapy, either with SBRT or conventional techniques may not be the most appropriate upfront in patients with reasonable prognoses.

Mechanical instability is usually not corrected with radiotherapy alone.

As a method of grading instability, the Spinal Instability Neoplastic Score (a validated assessment tool of spine disease which may warrant surgical intervention

One should identify patients with favorable prognoses who may derive benefit from spine SBRT

- Age
- performance status
- comorbidities
- functional capacity

Patient Selection Tools

Laufer et al. developed a four-point framework in the treatment of spine metastases

Neurologic, Oncologic, Mechanics, and Systemic (NOMS) assessments assist in determining the optimal therapy for patients.

International Spine Oncology Consortium Report - proposes a multidisciplinary algorithm for the management of spine metastases

Prognostic Index for Spine Metastases (PRISM) score

- Accounts for gender, performance status, previous therapy at the intended treatment site, number of organ systems involved, time elapsed between diagnosis and metastasis, and number of spine metastasis.

Groups	OS in months
1(best prognosis)	Not reached
2	24.1
3	13.1
4(Worst Prognosis)	6.5

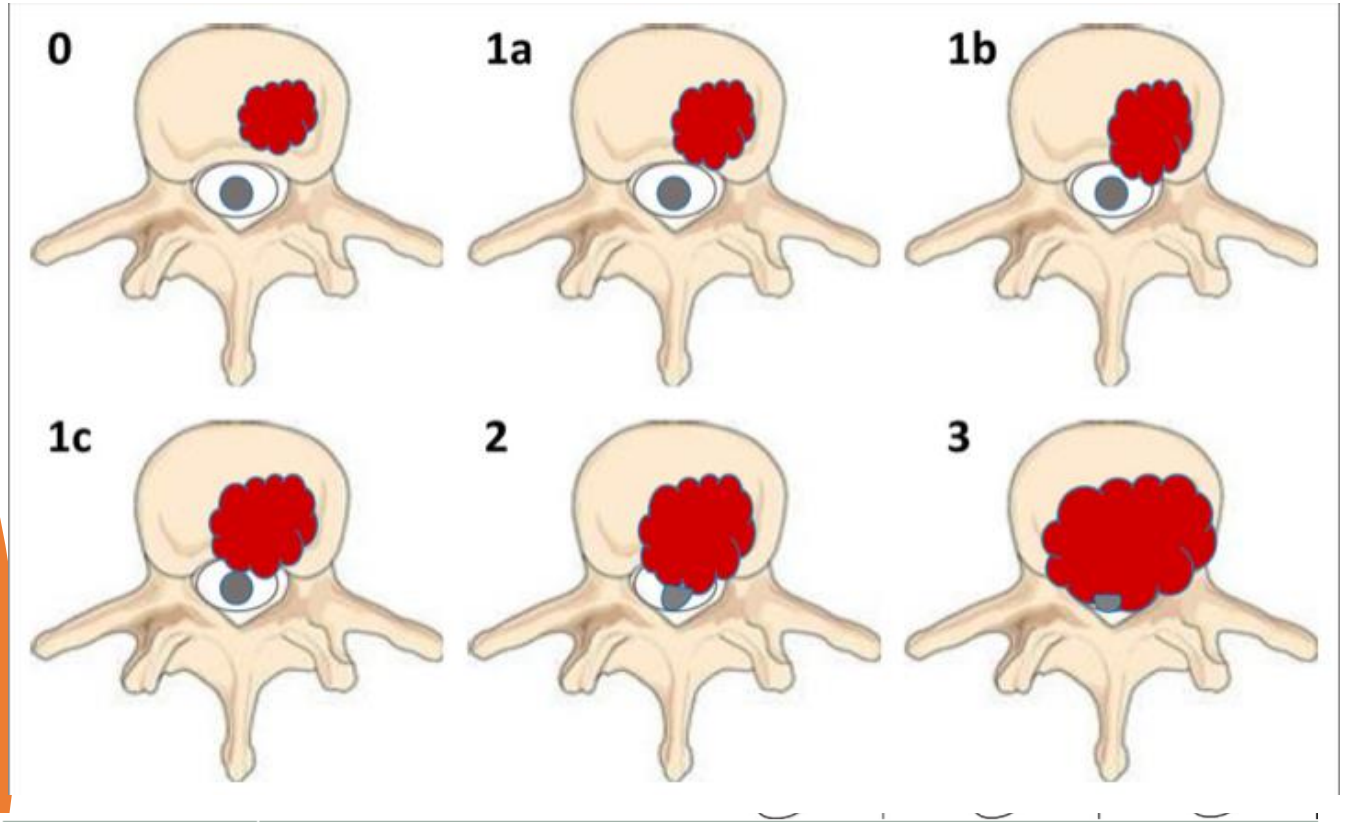
Jensen et al.

Spinal Instability Neoplastic Score (SINS)

Considers location, presence of mechanical pain, type of bony lesion, spinal alignment, vertebral body collapse, and posterolateral involvement and generates a score ranging from 0 to 18,

Parameter	Details	Points
Location	**Junctional** (Occiput-C2, C7-T2, T11-L1, L5-S1) C3-C6, L2-L4 T3-T10 S2-S5	3 2 1 0
Pain	Yes, positional or load-bearing Yes, non-mechanical No,	3 1 0
Bony Lesion Type	Lytic lesion Mixed lytic/blastic Blastic lesion	2 1 0
Radiographic spinal appearance	Subluxation/translation De novo kyphosis/scoliosis/lordosis Normal alignment	4 2 0
Vertebral Body Collapse	>50% collapse <50% collapse No collapse, but >50% of VB involved Absence of above	3 2 1 0
Posterolateral involvement of spinal canal	Facet / Pedicle / costovertebral joint fracture or replacement with tumor Bilateral Unilateral None	 3 1 0
Summation	Stable Potentially stable – Neurosurgical consultation Unstable – Neurosurgical consultation	0-6 7-12 13-18

Bilsky score for grading epidural spinal cord compression



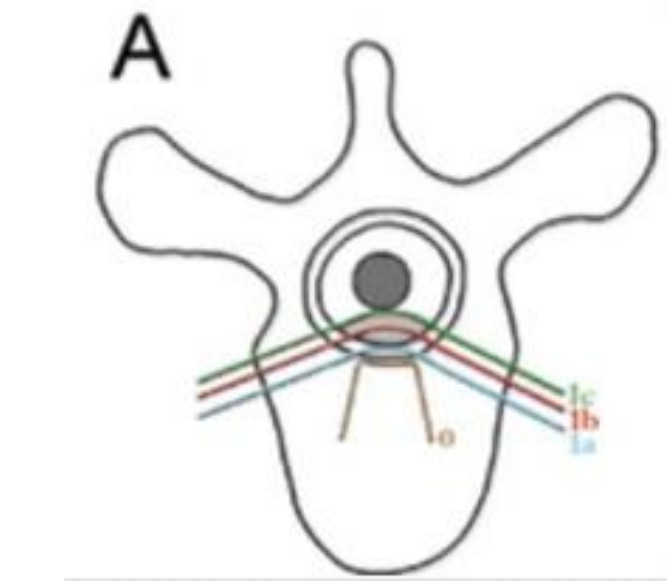
Bilsky Grade	Details
0	Absence of epidural disease
1a	Impingement without deformation of thecal sac
1b	Impingement and deformation of the thecal sac
1c	Deformation of the thecal sac with abutment of the spinal cord
2	Epidural spinal cord compression with visible cerebrospinal fluid (CSF)
3	Epidural spinal cord compression without visible CSF

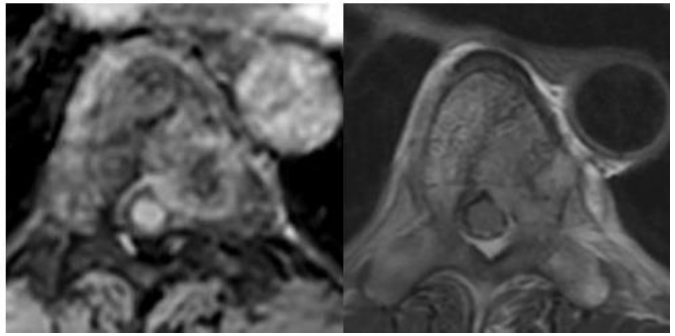
Facilitates communication between health-care providers

Table 1. Approach to Assessment of Suitability for Spine SBRT.

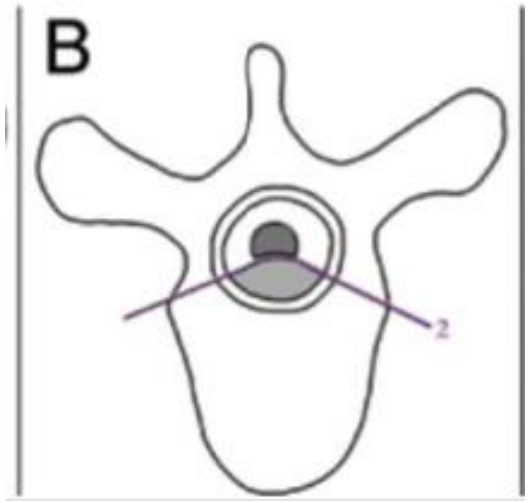
Factors	Suitable	Cautionary	Unsuitable
Patient			
Performance status	ECOG 0-2		ECOG ≥3
Life expectancy	≥3 months		
Pain	Intractable		
Neurologic			Symptomatic cord compression or cauda equina syndrome
Oncologic			
Disease burden	Oligometastatic disease	Widespread, rapidly progressive disease	
Tumor histology	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

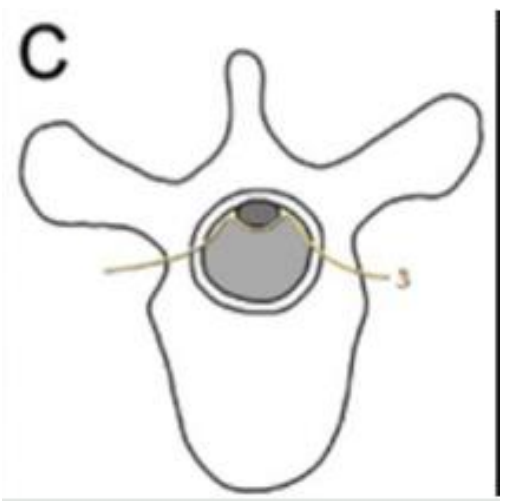
Abbreviations: SBRT, stereotactic body radiotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, epidural spinal cord compression; SINS, Spinal Instability Neoplastic Score; EBRT, external beam radiotherapy; cEBRT, conventional EBRT.





SBRT may be a more appropriate treatment option for those patients with appropriately graded low volume epidural disease.





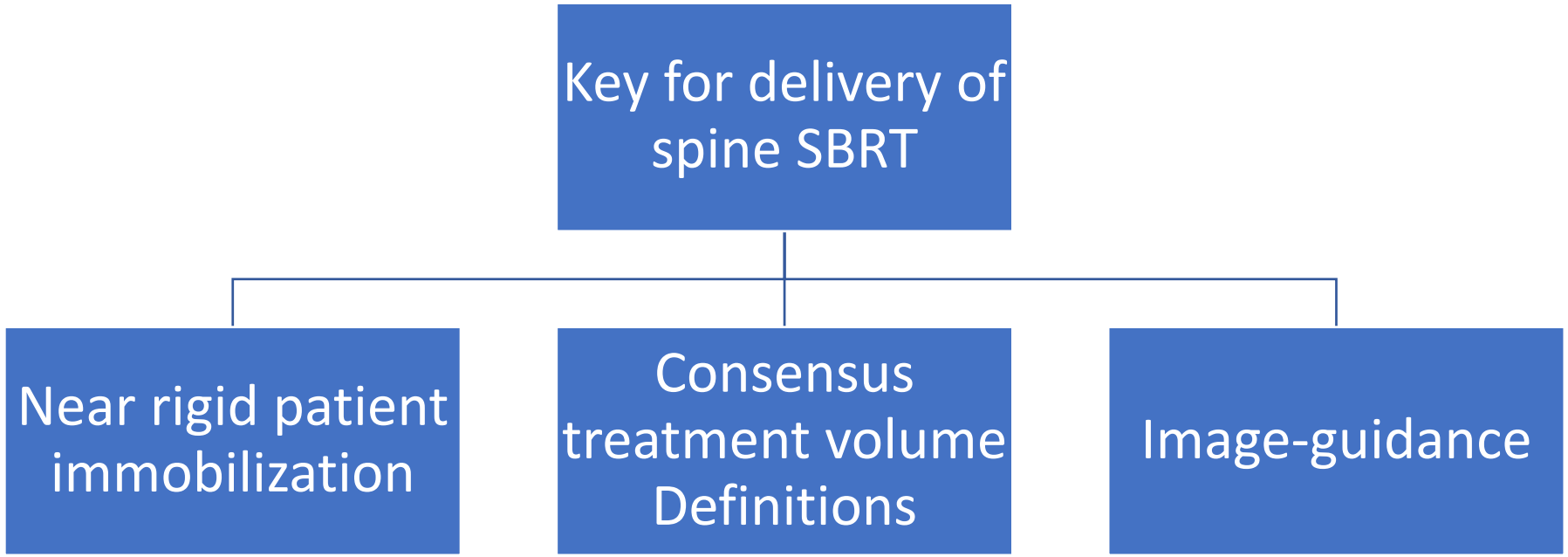
High grade ESCC (Bilsky 2 or 3, and possibly 1c) patients warrant surgical evaluation.

Consideration can be made to separation surgery, in which surgery to establish the epidural space is performed, followed by SBRT

Post-operative SBRT

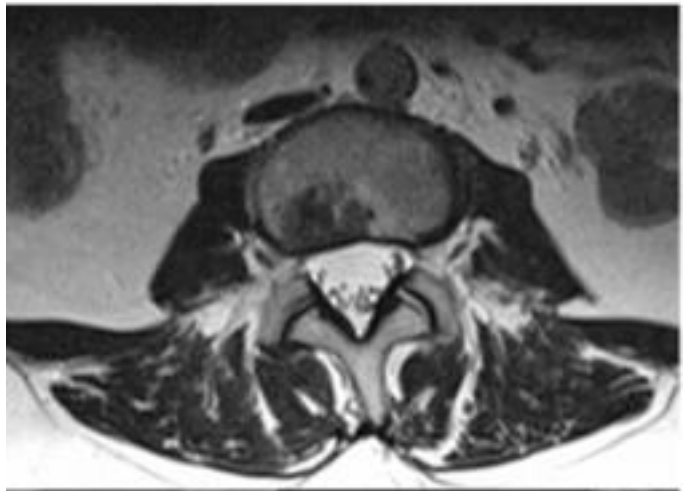
- High grade ESCC and/or mechanical instability often warrants surgical intervention in the appropriate patient population.
- Significant rates of local recurrence (up to 69.3% at 1-year) justifies adjunctive therapies.
- Post-operative RT has traditionally been delivered with conventional techniques - recently SBRT has been explored .
- Post-operative SBRT is well tolerated [no grade 3 or 4 toxicities, 3.8% rate of grade ½ gastrointestinal and genitourinary toxicities, 9% rate of pain flare and vertebral compression fracture (VCF)] with excellent one-year local control between 84 and 88% reported

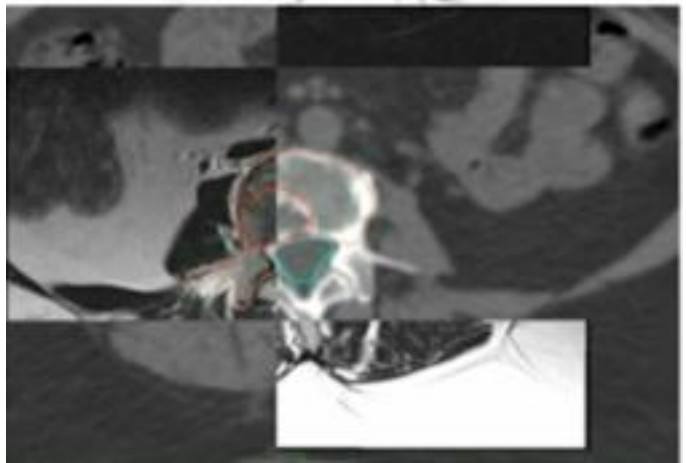
SPINE SBRT TECHNIQUE



SBRT SPINE PLANNING

- MRI essential ideally should be performed in the treatment planning position ,zero gap equal matrix 3 D sequence
- Fusional errors should be minimum- prefer T2 sequence best for identifying epidural extension/ thecal sac/cord epidural
- For decreasing rotational fusion errors fuse MRI spine screen with CT spine





Departmental SOP before implementation

- Standard customized protocol as per available resource
- Use of common language in the team

High Precision RT

Implementing SBRT Spine Program -

- Team Work
- Synchrony
- Training of Staff
- **SOPs**
- **Planning MRI**
- Start with L-Spine as Cauda constraints are easier and less impactful

Simulation*:

- Immobilization using long head and neck thermoplastic mask for lesions above T4
- Utilize dual vacuum system (Body FIX) for LINAC, or vacuum cushion for CyberKnife for lesions T4 or below
- Obtain diagnostic Volumetric MRI for fusion with planning CT scan
- Obtain CT myelogram if metallic hardware hinders visualization of the spinal cord
- Planning CT performed w/o contrast, 1.0 - 1.25mm slices

- * Per institutional preferences and standards

Near rigid patient immobilization is required to allow for inter-fraction reproducibility and minimize planning target volumes, to sculpt dose to intended targets and avoid neurologic toxicities. Many methods of immobilization have been explored which must consider patient comfort during relatively long simulation and treatment times.

The physiologic motion of the spinal cord is <0.5mm in all directions (53), which is relatively insignificant compared to potential gross patient motion.

Our practice is acquisition of a treatment scanning CT scan with patients secured using a BodyFIX device (Elekta AB, Stockholm, Sweden) which has demonstrated reproducibility within 1.2mm and 0.9◦ with 95% confidence (52). Other immobilization devise include custom cradles (25) and stereotactic body frames (54).

- Intra-fraction motion is a further consideration due to potentially long treatment times and patient comfort.
- Using either an evacuated cushion, vacuum body fixation or thermoplastic S-frame mask for lesions treated above T3, Li et al. performed pre-treatment verification cone beam (CBCT) as well as mid-fraction and post-treatment CBCT. The authors found margins required to encompass residual setup errors to be within 2mm with vacuum body fixation and 3mm with the other systems (55). Another study found a 3mm planning margin to be sufficient to account for both intra-fraction and inter-fraction motion, with greatest intra-fraction motion in the x-plane of 0.7mm (95% confidence interval 0.5–1.0mm) (56).
- After acquisition of planning CT scan, axial T1 and T2 weighted volumetric MRI sequences are fused to aid in target and critical neural structure delineation. In those cases where MRI is contraindicated or uninformative, CT myelogram may be an alternative.

Target Delineation

CTV is defined as whole vertebral body +/- pedicles +/- posterior elements

- Exception is tumors located primarily in the posterior elements

Need to include all epidural and paraspinal involvement

Postoperative cases should take into account the pre-operative extent of involvement

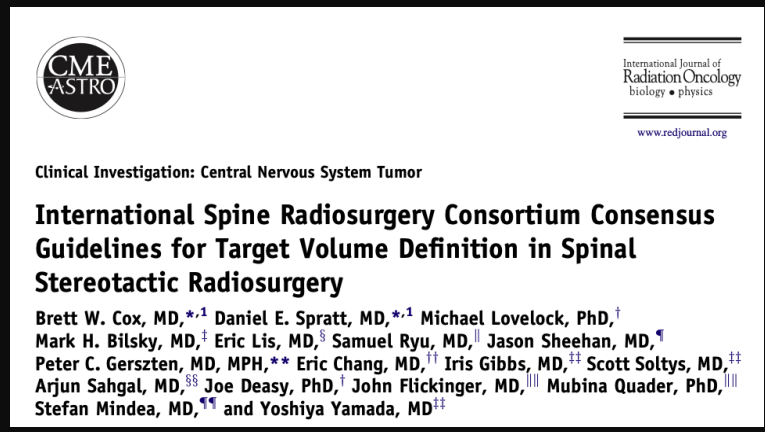
Utilize the consensus contouring guidelines published in IJROBP by Cox et al. (2). and Redmond et al. (6).

- The entire vertebral body, pedicle, transverse process, lamina, or spinous process was included in the CTV if any portion of these regions contained the GTV. Additionally, the next adjacent normal marrow space was typically included in the bony CTV

PTV = CTV + 2-3mm, minus PRV cord

PRV cord is spinal cord as defined on myelogram or MRI +1.5-3mm, can also use thecal sac

- Anatomical Classification-Vertebra divided into 6 sectors:
- 1-Vertebral body
- 2-L pedicle
- 3-L transverse process
- 4-Spinous process
- 5-R transverse process
- 6-R pedicle



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Clinical Investigation: Central Nervous System Tumor

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

Brett W. Cox, MD,[*,1] Daniel E. Spratt, MD,[*,1] 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 Mindea, MD,[¶¶] and Yoshiya Yamada, MD[‡‡]

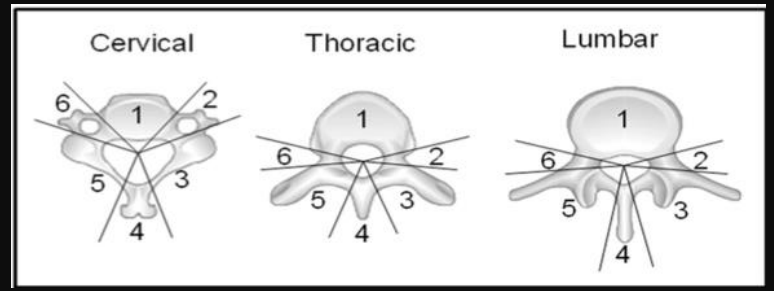


Table 4 Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

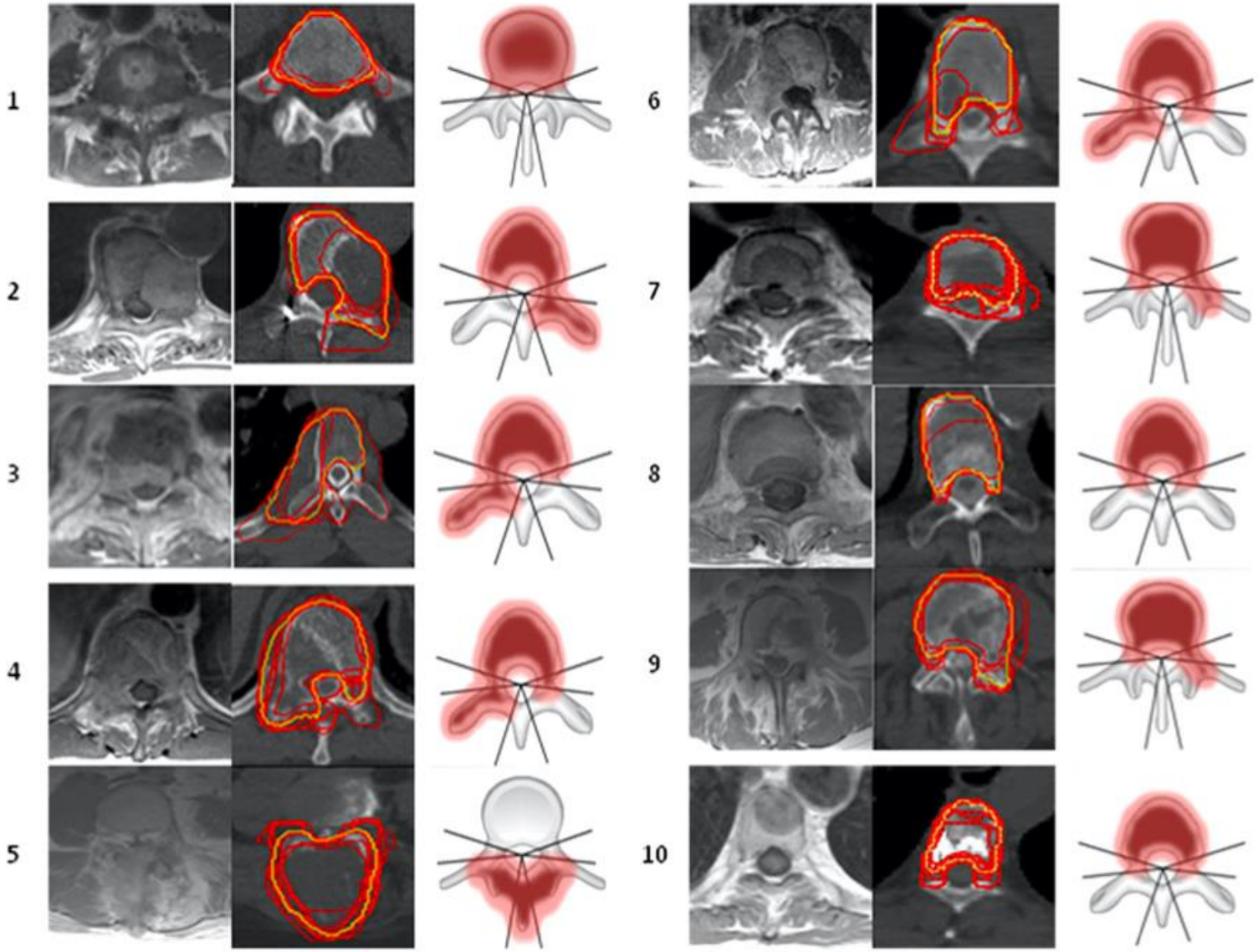
Target volume	Guidelines
GTV	• Contour gross tumor using all available imaging • Include epidural and paraspinal components of tumor
CTV	• Include abnormal marrow signal suspicious for microscopic invasion • Include bony CTV expansion to account for subclinical spread • Should contain GTV • Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression
PTV	• Uniform expansion around CTV • CTV to PTV margin $\leq$3 mm • Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised • Never overlaps with cord • Should contain entire GTV and CTV

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.

Table 3 Guidelines for spinal SRS bony CTV delineation

GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.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2
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10

GTV should utilize all available imaging modalities and include epidural and paraspinal disease extension.

CTV should include areas of potential microscopic extension. In general, if GTV were present within the vertebral body, pedicle, transverse process, lamina, spinous process, the entire region should be included.

As a rule of thumb, the adjacent potential bony region should be included.

For example, GTV involving the vertebral body and right pedicle should correspondingly expand to a CTV encompassing the entire vertebral body, right pedicle, right transverse process and right lamina.

With bone only disease, extraosseous expansion of CTV volumes should not be necessary, specifically into the epidural space or paraspinal soft tissue spaces.

PTV was suggested to be a uniform expansion of ≤3mm, depending on immobilization and image guidance technique

Post op contouring guidelines

Include the entire pre-operative extent of both bony and epidural disease and immediately adjacent bony structures as part of the CTV.

With circumferential epidural disease specifically, a “donut” shaped CTV was applied regardless of the post-operative epidural disease extent. Surgical instrumentation was suggested to be excluded from the CTV.

Post-operative epidural disease extent underestimated treatment volumes and that consideration of pre-operative disease is crucial to prevent subsequent progression*

Redmond et al. consensus contouring guidelines for post-operative spine SBRT

*Chan et al.

Treatment Planning

- 4-8 MV photons, using MLC
- IMRT: 7+ static, coplanar beams
- VMAT: 2-4 rotational arcs
- Common Dose/Fractionation schema:

Dose/Fx	Number of Fx	Total Dose	Notes:
16-24 Gy	1	16-24 Gy	Jabbari et al. 2016 (7) / Sahgal et al. 2008 (8)
10-12 Gy	2	20-24 Gy	Jabbari et al. 2016 / Sahgal et al. 2008
9 Gy	3	27 Gy	Jabbari et al. 2016 / Sahgal et al. 2008
6 Gy	5	30 Gy	Jabbari et al. 2016 / Sahgal et al. 2008

- Dose prescribed to PTV.
  - Goal >/= 80% of PTV, and >/=90% of CTV covered by prescribed IDL
  - Typical coverage: ~ 75% - 85%

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- 4-8 MV photons, using MLC
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  - Typical coverage: ~ 75% - 85%

Consensus Contours

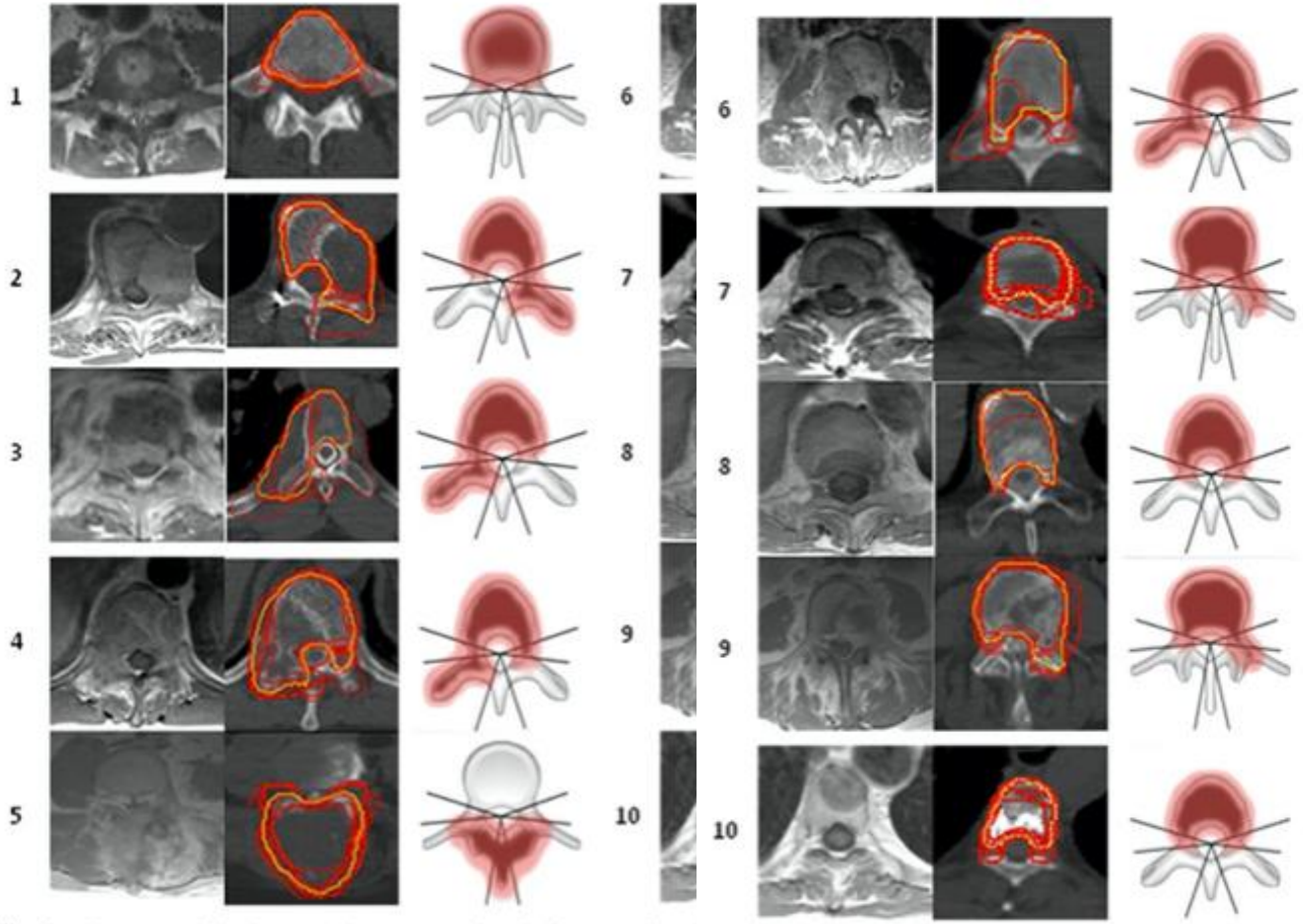


Fig. 2. Consensus clinical target volume contours for spinal stereotactic radiosurgery. Red indicates individual contours and orange indicates consensus contours.

Normal Tissue Tolerances

OAR	Dmax	Volume	Notes
Brachial plexus • 1Fx • 3Fx • 5Fx	• 17.5 Gy / 14 Gy • 24 Gy / 20.4 Gy • 32 Gy / 30 Gy	Max point / <3cc	• RTOG 0631 • RTOG 1021 • RTOG 0813
Cauda Equina • 1Fx • 3Fx • 5Fx	• 16 Gy / 14 Gy • 24 Gy / 20.4 Gy • 32 Gy / 30 Gy	Max point / < 3cc	• RTOG 0631 • *Extrapolated - RTOG 1021* • *Extrapolated - RTOG 0813*
Spinal Cord (no prior RT) • 1Fx • 3Fx • 5Fx	• 12.2 Gy • 20.3 Gy • 25.3 Gy	Max point dose	• Sahgal et al. IJROBP 2013 (9)
Esophagus • 1Fx • 3Fx • 5Fx	• 16 Gy / 11.9 Gy • 25.2 Gy / 17.7 Gy • 105% of PTV prescription / 27.5 Gy	Max point / < 5cc	• RTOG 0631 • RTOG 1021 • RTOG 0813

Cord tolerance – *Prior conventional RT*

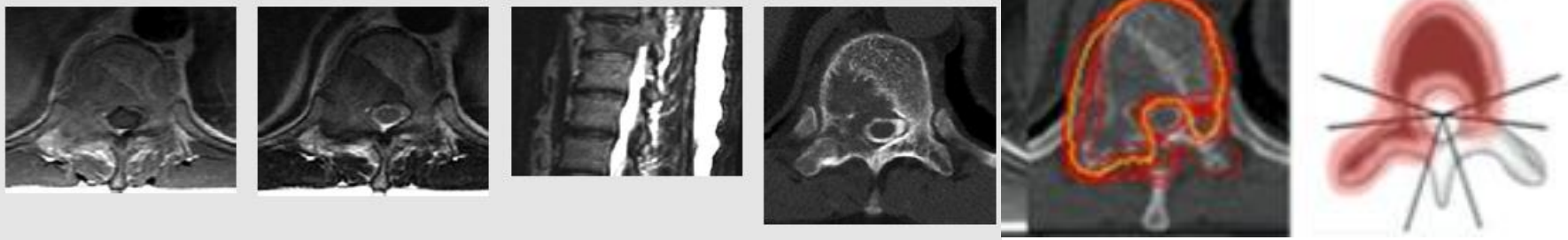
Prior RT	1 Fx SBRT – Max point dose	3 Fx SBRT– Max point dose	5 Fx SBRT– Max point dose
20Gy / 5Fx 30Gy / 10Fx 37.5Gy / 15Fx	9 Gy	14.5 Gy	18 Gy
40Gy / 20 Fx	?	14.5 Gy	18 Gy
50Gy / 25 Fx	?	12.5 Gy	15.5 Gy

Table 4

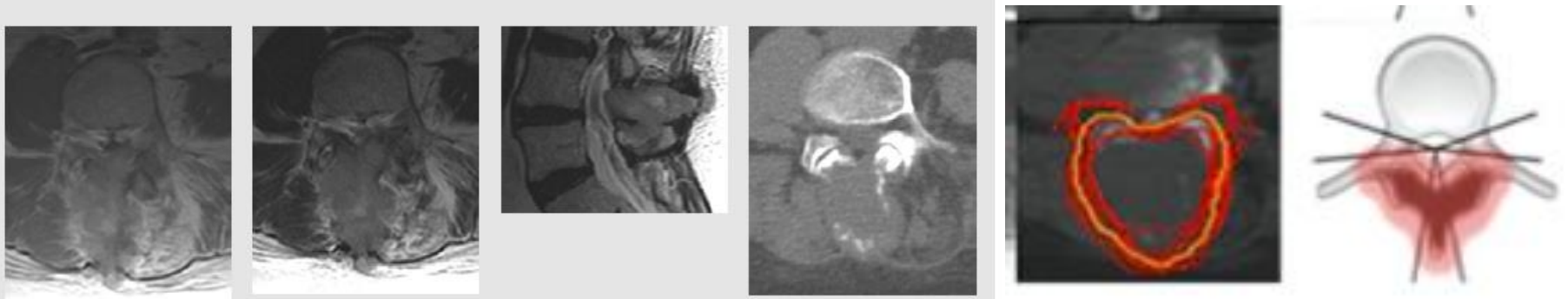
Guidelines for CTV contouring for post-operative SBRT for spine metastases based on pre-operative epidural involvement, and both pre-operative and post-operative bony involvement.

Pre-operative epidural involvement	Pre-operative ISRC bony anatomic involvement	Post-operative ISRC bony CTV recommendation	Post-operative CTV description
Circumferential epidural disease	1–3, 5–6, +/–4	1,2,3,4,5,6	Circumferential treatment including the pre-operative body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process
Anterior epidural involvement in region of central body	1	1	Pre-operative body
Anterior epidural involvement in lateral region of body	1	1,2	Pre-operative body plus ipsilateral pedicle +/– lamina
Epidural involvement anteriorly in the region of the body and unilaterally in the region of pedicle	1,2	1,2,3	Pre-operative body plus ipsilateral pedicle, ipsilateral transverse process and ipsilateral lamina
Epidural involvement anteriorly in the region of the body, unilaterally in the region of pedicle, and posteriorly in the region of the spinous process	1,4,5,6	1,3,4,5,6 +/–2	Pre-operative body plus ipsilateral pedicle, bilateral transverse process, bilateral laminae, and spinous process
Posterior epidural involvement in region of spinous process	4	3,4,5	Pre-operative spinous process, bilateral laminae and bilateral transverse processes
Any of the above plus extensive para-spinal extension	As above	As above	As above plus coverage of the entire pre-operative extent of para-spinal extension

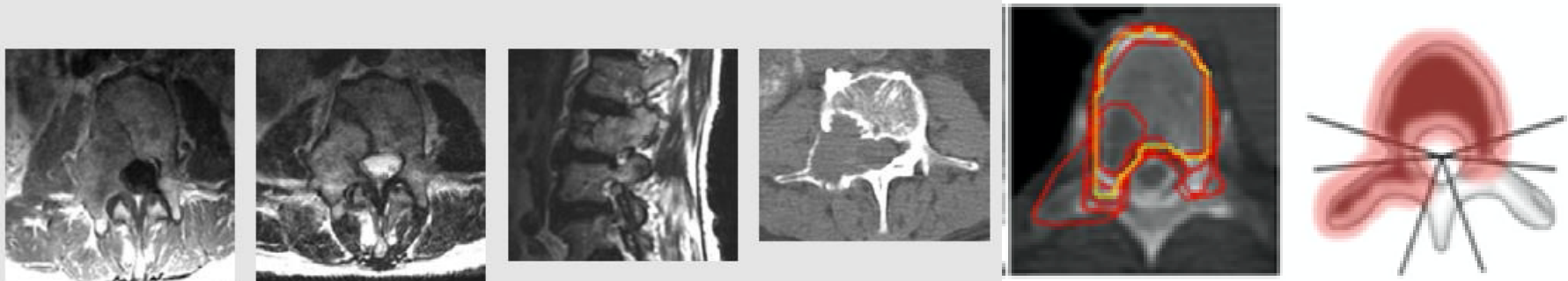
Case 4: T11 lesion involving pedicle and posterior elements, mild ventral and right lateral epidural disease, narrowing of the right T10/11 and T11/12 neural foramina

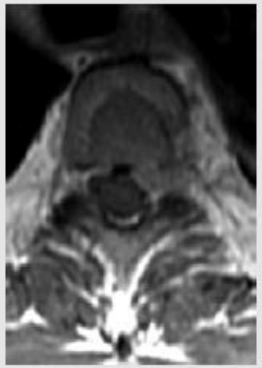
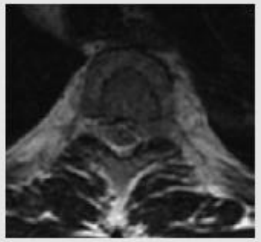
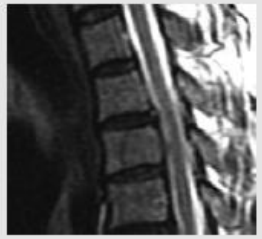
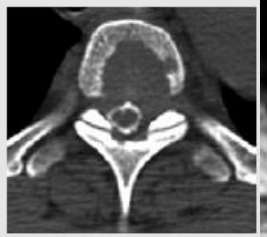
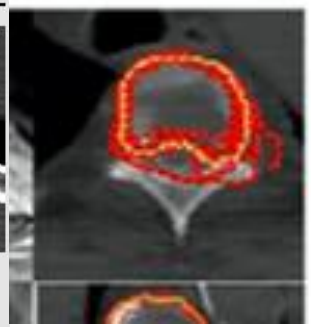
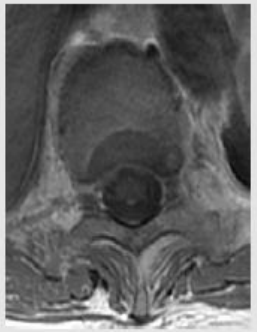
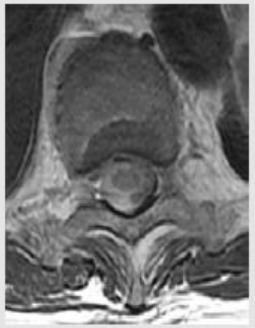
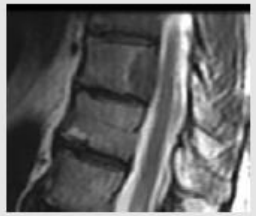
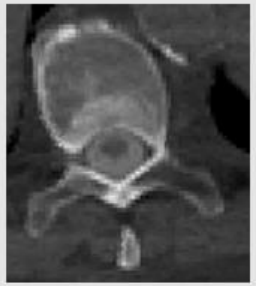
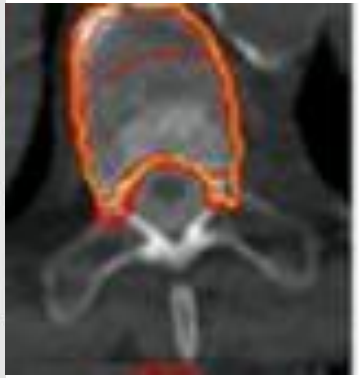


Case 5: L5 lesion centered in the spinous process and extending to the bilateral lamina, bilateral posterior paraspinal musculature, and bilateral dorsal epidural space extension with mild spinal canal compromise

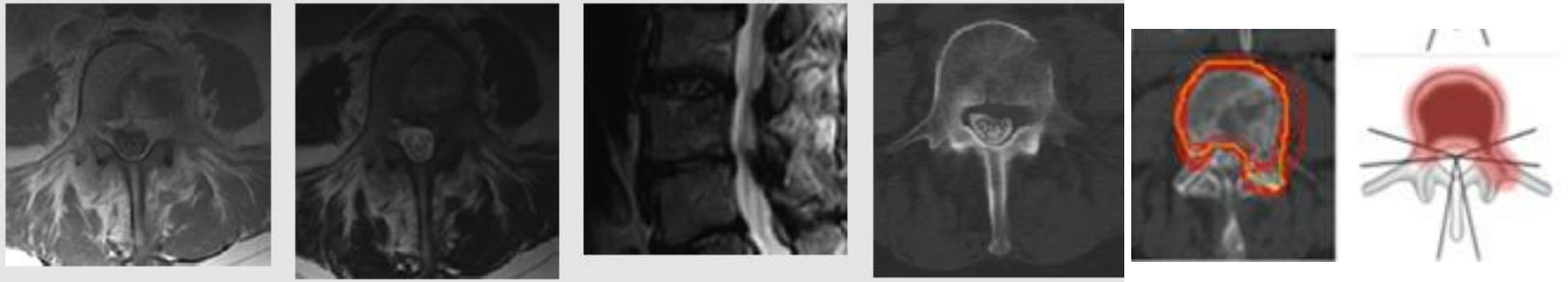


Case 6: L2-3 expansile mass in right-sided VB and right posterior elements with mild right ventral, lateral, and dorsal epidural disease. Involvement of the right L2/3 and L3/4 neural foramina

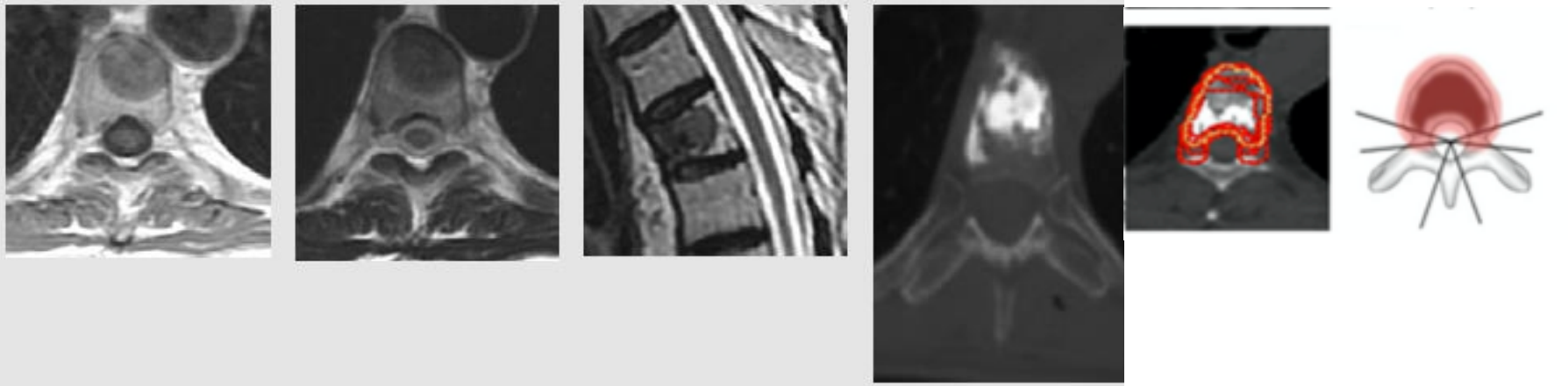


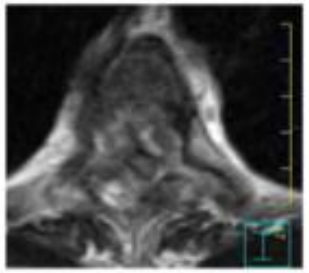
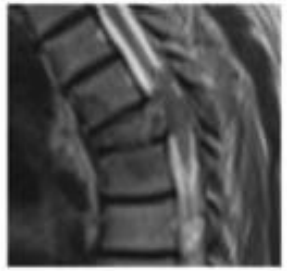
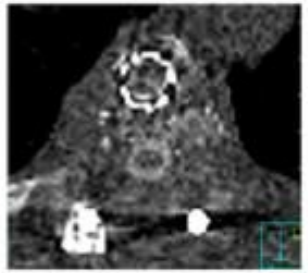
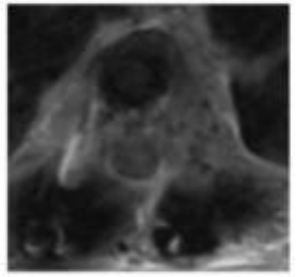
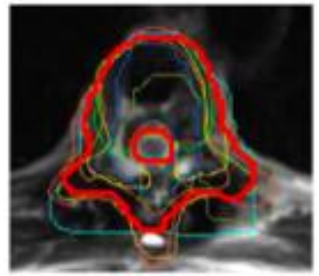
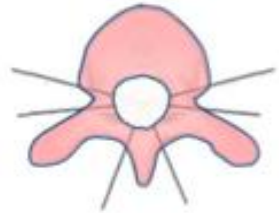
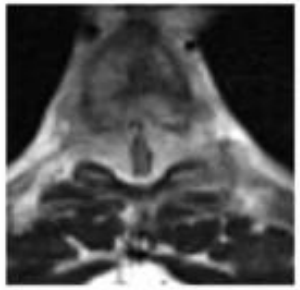
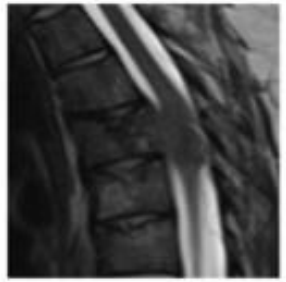
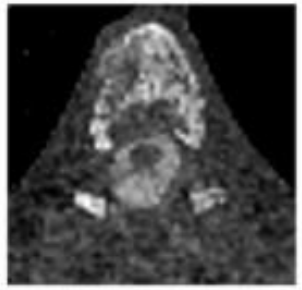
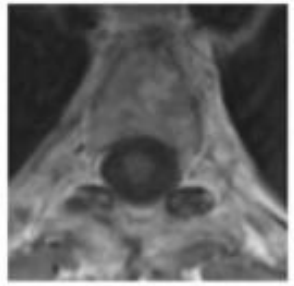
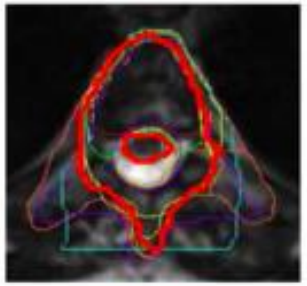
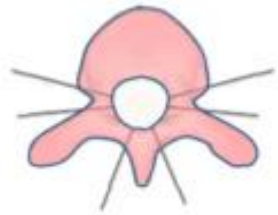
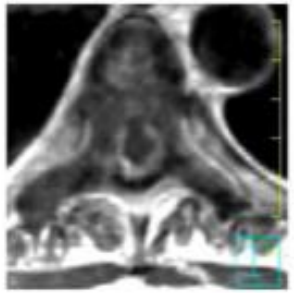
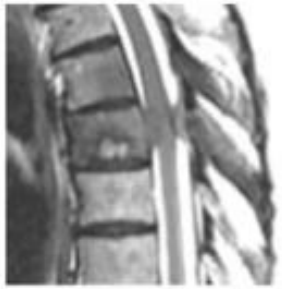
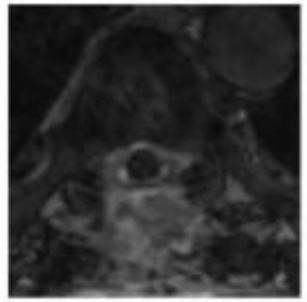
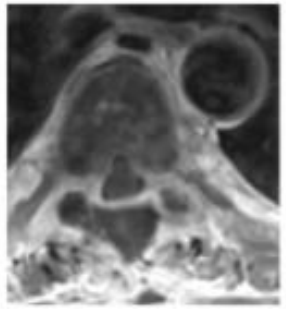
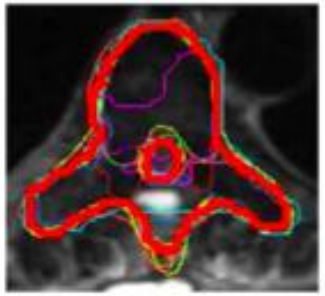
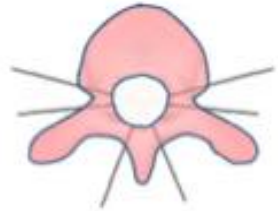
Anatomic description	MRI axial T1 post	MRI axial T2	MRI sagittal	CT		
Case 7: T3 posterior VB lesion extending into the left neural foramen with mild spinal canal compromise and left ventral and lateral epidural extension						
Case 8: T10 lesion in posterior VB						

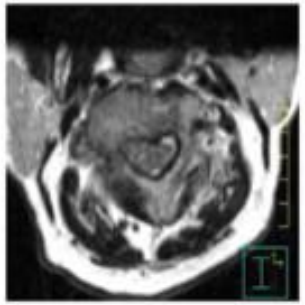
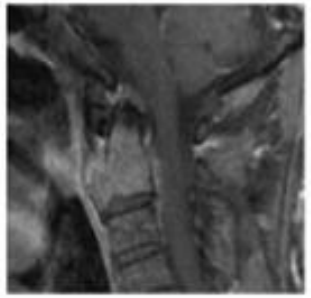
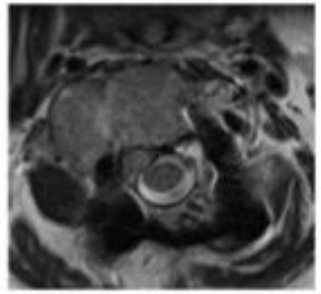
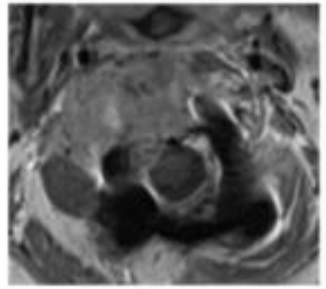
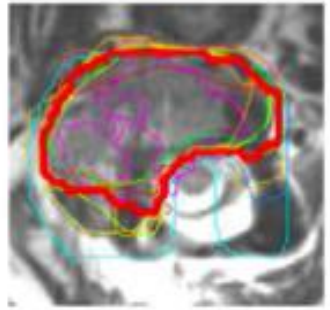
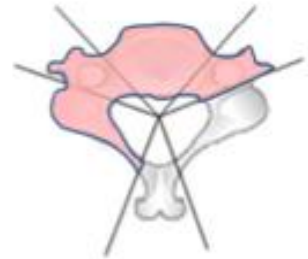
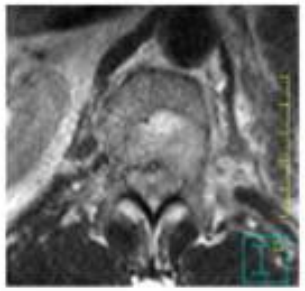
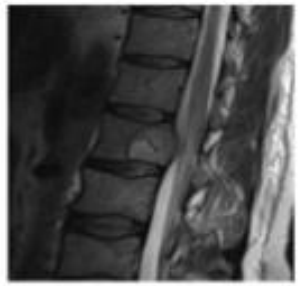
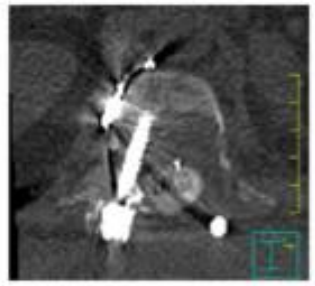
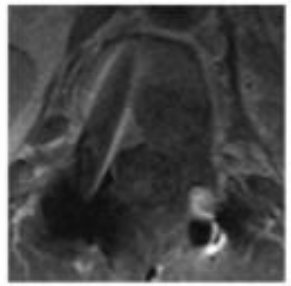
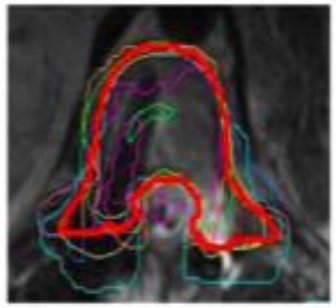
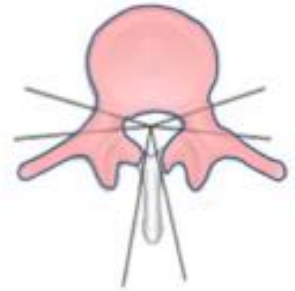
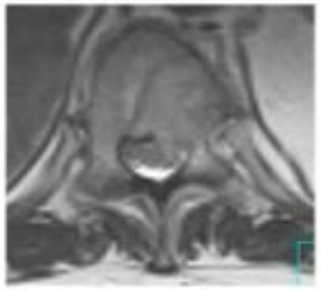
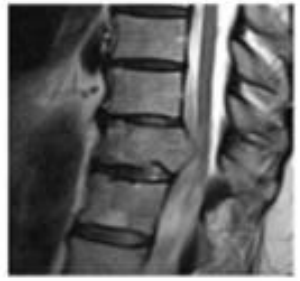
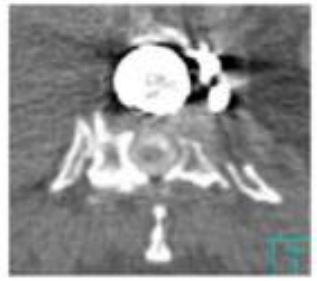
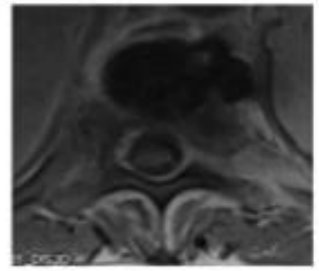
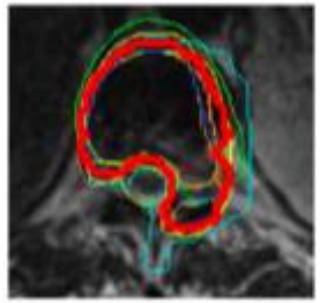
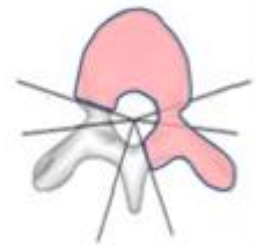
Case 9: L4 diffuse marrow replacement including left pedicle and articular facets, ventral epidural extension, left lateral recess extension, and left L4/5 neural foramen involvement

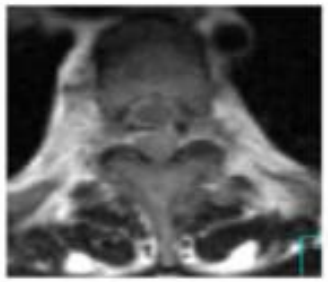
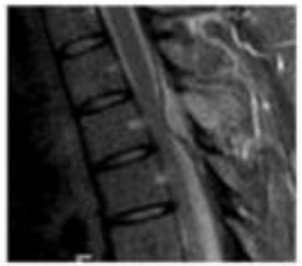
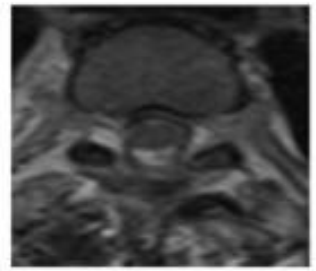
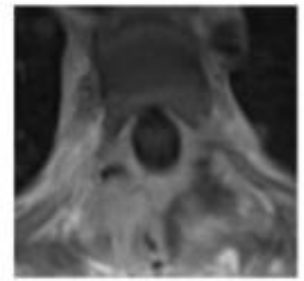
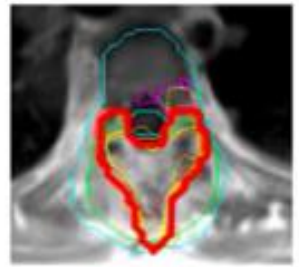
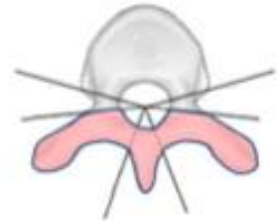
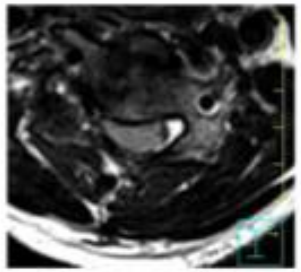
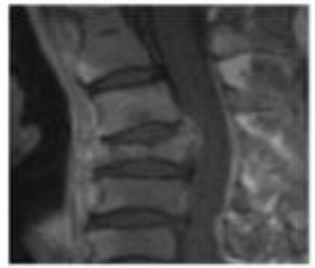
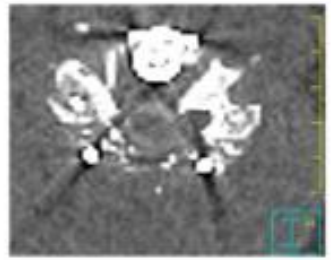
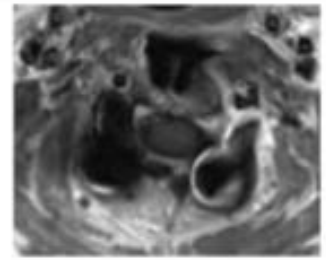
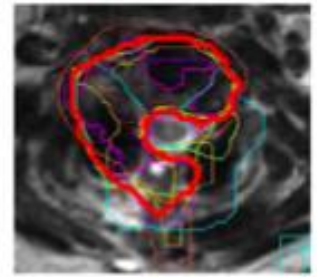
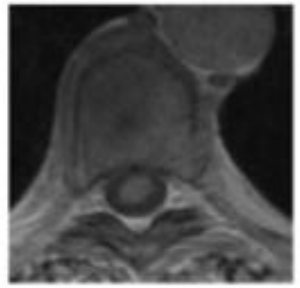
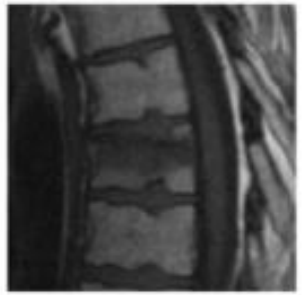
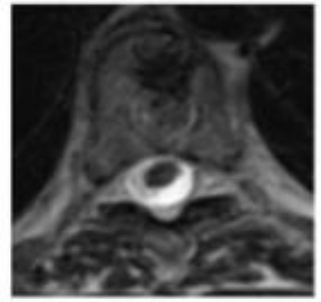
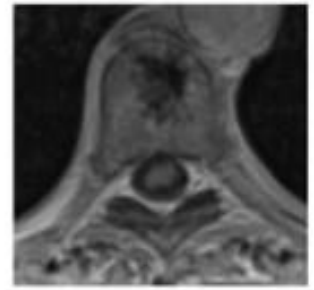
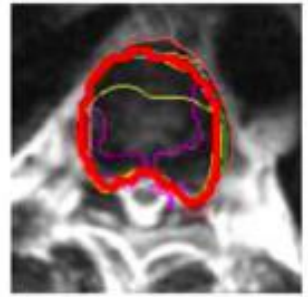
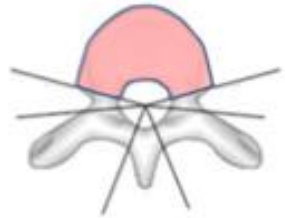


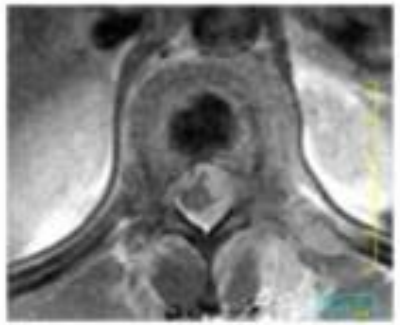
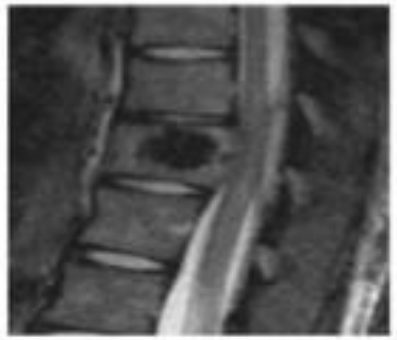
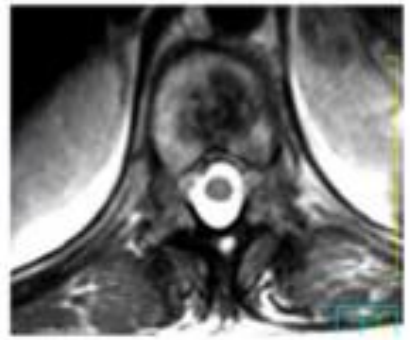
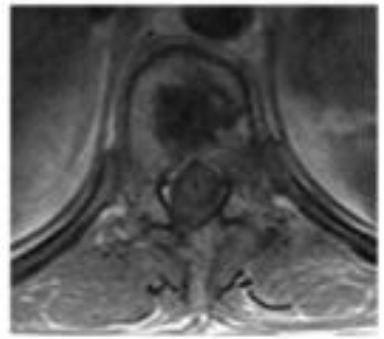
Case 10: T5 lesion with mild superior and inferior endplate infractions resulting in mild loss of VB height. Mild anterior paraspinal extension. Patient underwent T5 kyphoplasty

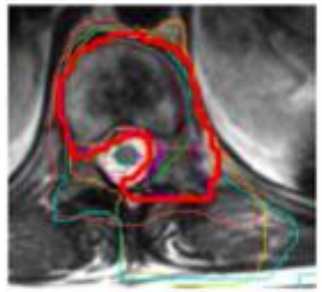
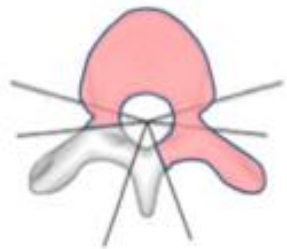


Anatomic description	Pre-operative axial MRI	Pre-operative sagittal MRI	Post-operative axial CT myelogram or T2 MRI	Post-operative axial T1 post MRI	Simulation MRI with individual and consensus CTV contour	Schematic diagram
Case 1: T5 level. Pre-operative circumferential epidural disease with no residual epidural disease post-operatively. Pre-operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process.						
Case 2: T4 level. Pre-operative circumferential epidural disease with focal residual anterior epidural disease post-operatively. Pre-operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process.						
Case 3: T6 level. Pre-operative circumferential epidural disease with residual near circumferential epidural disease post-operatively. Pre-operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, and bilateral laminae.						

Anatomic description	Pre-operative axial MRI	Pre-operative sagittal MRI	Post-operative axial CT myelogram or T2 MRI	Post-operative axial T1 post MRI		
Case 4:C2 level. Pre-operative anterior and right lateral epidural disease status post stabilization and biopsy. Post-operative residual antero-lateral epidural disease. Pre-operative bony involvement includes the body, odontoid, right pedicle, and right transverse process.						
Case 5: L1 level. Pre-operative anterior epidural disease. No residual epidural disease post-operatively. Pre-operative bony involvement includes the body and bilateral pedicles.						
Case 6: T11 level. Pre-operative anterior and left lateral epidural disease. Post-operative residual antero-lateral epidural disease. Pre-operative bony involvement includes the body and left pedicle.						

Anatomic description	Pre-operative axial MRI	Pre-operative sagittal MRI	Post-operative axial CT myelogram or T2 MRI	Post-operative axial T1 post MRI	Simulation MRI with individual and consensus CTV contour	Schematic diagram
Case 7:T3 level. Pre-operative posterior epidural disease. No residual epidural disease post-operatively. Pre-operative bony involvement includes the spinous process, bilateral laminae, and bilateral transverse processes.						
Case 8: C4 level. Pre-operative anterior, right lateral and posterior epidural disease. No residual epidural disease post-operatively. Pre-operative bony involvement includes the body, right pedicle, right transverse process, right lamina, and spinous process.						
Case 9:T9 level. Pre-operative vertebral body fracture without epidural disease status post vertebroplasty. No residual epidural disease post-operatively. Pre-operative bony involvement in the body.						

Anatomic description	Pre-operative axial MRI	Pre-operative sagittal MRI	Post-operative axial CT myelogram or T2 MRI	Post-operative axial T1 post MRI
Case 10: T11 level. Pre-operatively anterior and left lateral epidural disease with extensive paraspinal extension. Post-operative residual antero-lateral epidural disease. Pre-operative bony involvement includes the body, left pedicle, left transverse process, and left lamina.				

Simulation MRI with individual and consensus CTV contour	Schematic diagram
	

Dose Fractionation

Optimal dose fractionation for spine SBRT is unknown.

Common fractionation schemes include 16–24 Gy/1 fraction, 24 Gy/2 fractions, 24–30 Gy/3 fractions, 30 Gy/4 fractions, and 30–40 Gy/5 fractions.

Considerations includes risk of vertebral compression fracture [up to 39% risk with single fractions (60)] and treatment volume, where very large tumors may warrant 4–5 fraction courses.

Single fractions of 15Gy are effective, however, may be related to increased toxicities such as VCF, pain flare and myelopathy, and fractionation may reduce this

Our standard practice is a course of 24–28Gy in 2 fractions or 30Gy in

4 fractions for larger tumors, to maintain an acceptable fracture

risk of 10%.

SBRT Treatment Planning

SBRT treatment planning differs from conventional techniques and

Major difference is allowing hotspots within treatment targets & requirement for sharp drop-offs especially near organs at risk.

CTV and PTV margins are significantly smaller, whilst delivery with non-overlapping and possibly coplaner beams allow for sharp dropoff.

There is an absolute requirement to not violate the thecal sac and spinal cord PRV dose limits for the sake of preventing catastrophic neurologic sequelae It is acceptable for PTV coverage to be compromised.

Task Group 101 of The American
Association of Physicists in Medicine outlines best practices

Dry run & treatment implementation

Once a treatment plan has been generated, assessment of
patient positioning on the treatment unit should be conducted.

Image verification is completed with cone-beam CT after
patient set-up.
A Hexapod robotic couch facilitates set-up correction with
six degrees of freedom.
Subsequent CBCT can then be acquired for assessment of residual setup error, and intrafraction and posttreatment periods to ensure geometric stability.
Other image verification techniques include CT-on-rails and Cyberknife
tracking

OUTCOMES-Response Assessment

RECIST 1.1 are difficult to apply, and tumor specific phenomena exist whereby imaging must be interpreted with caution and with familiarity of expected changes after treatment.

MRI signal changes creating a pseudoprogression phenomenon, as first seen following treatment of brain tumors, can occur after spine SBRT.

Rather than true progression which demonstrates consistent growth over time, the radiographical appearance of pseudoprogression subsequently subsides on serial imaging.

The incidence of pseudoprogression has been reported in the range of 14–37% and risk factors include lytic tumors, earlier volume enlargement, greater GTV to reference non-irradiated vertebral body T2 intensity ratio, and growth confined to 80% of the prescription isodose line

Patterns of recurrence

- Systemic – related to dise
- Local Failure
- Adjacent bone recurrenc
- Epidural Recurrence due t tight dose constraints at c

Patterns of Failure

Two Primary Patterns of Failure

- Adjacent bone recurrence – target delineation
- Epidural Space recurrence d/t tight dose constraints – 'Separation Surgery' + SBRT

- Systemic Progression

SPIne response assessment in Neuro-Oncology (SPINO) guidelines

Method of standardized reporting (70).

Recommendations of imaging response include spine MRI every 2–3 months for the first 12–18 months then every 3–6 months thereafter, interpreted by a radiologist and radiation oncologist jointly treating patients with this technique.

Progression is defined as gross increases in tumor volume, new tumors in epidural space, and neurologic deterioration due to known epidural disease.

Where progression is questionable, serial imaging and consideration of tissue biopsy should be made to rule out pseudoprogression.

Assessment of pain response should be conducted with the Brief Pain Inventory at 3 months posttreatment adopting the consensus guidelines published by theInternational Bone Metastases ConsensusWorking Party (71).

Local Control

Treatment of de-novo metastases with spine SBRT yields favorable local control, in the range of 80–95% in a heterogenous patient population, treated with a number of dose/fractionation regiments ranging from a single 15Gy fraction to 30Gy in 3 fractions .

In a review of nearly 1,400 patients following SBRT, Hall et al. report overall local control of ~90% at 15 months (73).

The largest single institutional experience utilizing 24Gy in 2 fractions as standard for de novo metastases included 279 spinal segments from 145 consecutive patients (10).

Local control at 1- and 2-years was 90.3 and 82.4% with excellent reported safety. There is a relative reduction in 2-year compared to 1-year LC ranging from 66 to 93% (Table 1). This may reflect the heterogenous nature of the mentioned studies, however merits further investigation.

Though control rates at 2-years are still higher than with conventional palliative radiotherapy, in

patients with limited metastatic disease and relatively excellent clinical status, durable LC is the treatment goal and endpoints beyond 1-yearmay be of further interest. In patients who do have local progression at this time point, retreatment with spine SBRT is safe and does offer excellent outcomes, though patients should be discussed in the multidisciplinary setting.

Local Control

Retrospective studies have explored local control with a specific interest in traditionally radioresistant histologies that typically exhibit poor control with conventional external mean radiotherapy.

One-year local control of 83% was reported after treatment of renal cell carcinoma (RCC) spine metastases treated with most common dose of 24Gy in 2 fractions (18).

Ghia et al. also report similar 1-year LC of 82% in RCC, and found that multi-fraction courses yielded inferior outcomes compared to single-fraction (sub-hazard ratio 6.57) which may suggest that BED escalation may be advantageous in radioresistant histologies. The high rates of local control are replicated in patients with sarcoma and melanoma .

Local Control

- In the post-operative setting, inclusion of spine SBRT yields excellent local control, similar to de-novo metastases. Following vertebrectomy or laminectomy, 1-year LC in has been reported to be >80% in multiple studies (47, 77).
- In those where downgrading of epidural disease is surgically possible, local control is further improved (51).
- Considerations and treatment techniques are summarized in a critical review ofpost-operative spine SBRT by Redmond et al.
- Palliation of spine metastases with conventional techniques is limited by cumulative doses tolerated by the spinal cord. Despite high probability of pain response after conventional retreatment (79), local control remains poor which may become problematic for those with favorable prognoses.

Safety Profile

As per systematic review, local control after SBRT in this setting ranged from 66 to 90% at 1-year and improvement in pain scores post treatment ranged from 65 to 81%

Vertebral fracture rate was 12%

treatment related myelopathy- 1.2%.

Hashmi et al. pooled outcomes after retreatment with SBRT in 7 institutions .

The median initial conventional radiotherapy delivered was 30Gy in 10 fractions and 60% were re-treated with a single fraction SBRT. Local control remained excellent at 83%and importantly, there were no cases of radiation myelopathy after treatment of 247 spinal segments.

Pain Response and Quality of Life

- Overall pain response after conventional palliative radiotherapy is ~62% regardless of fractionation schedule, with complete response rates of 24%
- Duration of response can be for months, with retreatment considered after 4 weeks, which may be effective despite initial non-response .
- In spine SBRT, complete pain response ranging between 46 and 92% have been reported

Delivery of higher BED of radiotherapy to the spine may yield improved pain response.

It is unclear the optimal dose fractionation for pain response specifically, and whether this technique offers improvements in pain response compared to conventional radiotherapy.

Recently, Sprave et al. conducted a randomized phase II trial with the endpoint of pain-control, enrolling 55 patients treated with either SBRT (24Gy in a single fraction) vs. 3D conformal radiotherapy to a dose of 30Gy in 10 fractions (84).

The authors assessed response using the parameters as established by the International Bone Consensus Working Party (71).

There was a trend toward improved complete response at 3months (43 vs. 17%, p=0.0568) and at 6 months, rates of complete response were significantly higher in the SBRT group (53 vs. 10%, p = 0.0034). Responses

were also more durable after SBRT. The vertebral compression fracture risk was 8.7% at 3 months and 27.8% at 6 months.

There were no grade ≥ 3 adverse events reported

Randomized phase II/III setting with the ongoing NCIC CTG SC.24 trial comparing conventional palliative radiotherapy to a standardized spine SBRT dose of 24Gy in 2 fractions and RTOG 0631 comparing a single fraction of 16Gy vs. conventional 8Gy in 1 fraction

In a multi-institutional, international analysis of 387 spine segments treated with a median dose of 28Gy in 3 fractions, over 40% of patients with severe pretreatment pain were pain free (definitionally a complete response assuming no increase in analgesic intake) at last follow-up with a median followup duration of 11.5 months

Pain improvement after retreatment with SBRT has similarly reported to be high

- Quality of life is an important endpoint which is frequently assessed in addition to physical symptom outcomes and radiographic disease status.
- Sprave et al. assessed QOL using validated instruments including the EORTC QLQ-BM22, QLQFL13, and QSC-R10 and found that QOL was not worse after SBRT for spine metastases compared to conventional palliative radiotherapy
- This endpoint will also be assessed in the ongoing NCIC CTG.SC24 phase II/III clinical trial.

Predictors of Failure

- Progression after spine SBRT is most common within the epidural space and may reflect the relative underdosing of tumor when intimate with thecal sac, or inherent biological aggressiveness of spine metastases with epidural components
- Al-Omair et al. found that surgical downgrading epidural disease extent resulted in improved local control prior to spine SBRT
- Methods of mitigating this influence on local control include considering escalating the allowable dose to the spinal cord, or interventional surgical techniques to target epidural disease extension.

TOXICITIES

Spine SBRT is generally well-tolerated, and typically a threshold of <5% is accepted as risk of serious adverse events such as myelopathy.

VCF rates have been relatively well-studied after spine SBRT, and a greater understanding of pretreatment assessment and radiotherapy technique has mitigated this risk.

Pain Flare-Defined as a transient increase in pain shortly after commencing

or completing radiotherapy, pain flare is common in approximately a third of patients after conventional palliative radiotherapy (90).

The range of patients developing pain flare after spine SBRT is significant, from 14 to 68%

Dexamethasone has been prospectively evaluated in the prevention of pain flare and reduced its rate from 68 to 19%

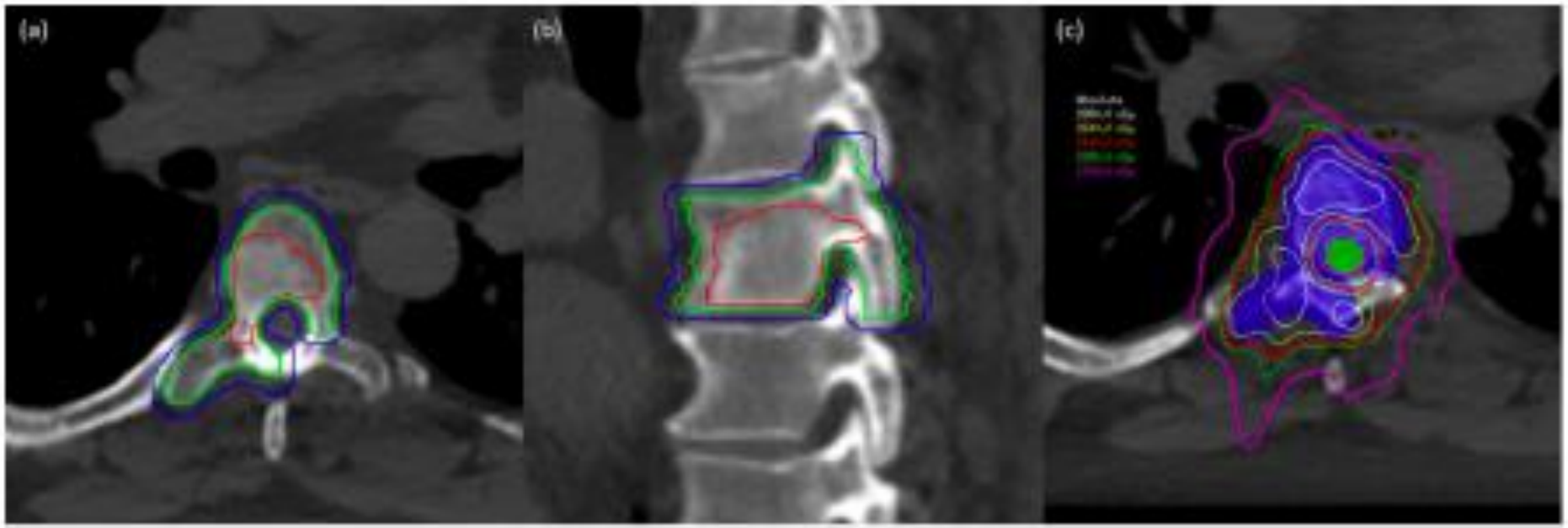


FIGURE 2 | A man with oligometastatic castrate-resistant prostate cancer with painful spine metastases. This man was treated to 24 Gy in 2 fractions. **(a)** Axial planning CT scan demonstrating T6 vertebral level with gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) delineated with red, green, and blue lines, respectively. **(b)** Sagittal planning CT demonstrating T6 vertebral level with GTV, CTV, and PTV in red, green, and blue, respectively. **(c)** Dose distribution at the level of T6 with PTV (colorwash blue) and spinal cord planning organ at risk volume (PRV) in colorwash green. Demonstration of sharp-dose fall-off to respect critical structures while allowing coverage of the target volumes.

Vertebral Compression Fracture

Delivery of a high BEDof radiotherapy generates an intense acute inflammatory effect that is hypothesized to weaken the bony matrix and place patients at risk of VCF (60). The rate of VCF in the range of 11–39% with a crude risk of 13.9% in a review compared to 3% for conventional radiotherapy. Regardless of the mechanism of VCF, both pre-treatment characteristics and treatment related parameters influence the rate of VCF that can result in further pain, and requirement for surgical stabilization. Median time to development of VCF was 2.5 months in a multi-institutional study including 57 fractures .

In retrospective analyses, the aforementioned SINS score includes several elements predictive of VCF including baseline fracture, lytic disease, spine malalignment, >50 vertebral involvement and the overall high SINS score was similarly predictive (60). Lee et al. assessed the capability of SINS in predicting fracture, and found that those in the high SINS group to have a 66.3% risk of fracture at 24 months compared to 21.3% for the low SINS group (99). Further, volume of lytic disease, a refinement of the SINS component, has independently

been demonstrated to predict for SBRT-inducted VCF (100). These data support multidisciplinary assessment of patients with spinal metastases, especially in those with intermediate/high SINS scores who may benefit from surgical or minimally invasive procedures to stabilize the spine prior to radiotherapy.

High dose, single-fraction SBRT has been associated with a higher rate of VCF. Those receiving a single fraction of ≥24Gy, compared to those receiving 20–23Gy and those receiving ≤20Gy had a 39% vs. 23% vs. 11% risk of fracture, respectively.

In support of this, Rose et al. report a fracture rate of 39% after

single doses ranging from 18 to 24Gy (96). Our institution has observed an 8.5% 1-year VCF risk utilizing our standard 24Gy in 2 fraction technique.

- Sprave et al. assessed bone mineral density as a prespecified
- secondary endpoint in their study comparing conventional
- palliative radiotherapy to spine SBRT (101). Both conventional
- radiotherapy and SBRT increased bone mineral density at 3- and
- 6-months with one technique not being statistically significantly
- better. In osteolytic metastases specifically, SBRT increased bone
- density whereas conventional RT did not. These findings support
- the safety of spine SBRT, especially where vertebral body fracture
- is a consideration.

Myelopathy

Radiation myelopathy is a late complication of SBRT and most feared due to potential catastrophic outcomes. A review of nearly 1,400 patients reveal that rates of myelopathy to be

0.4% (73). Point max doses to the spinal cord categorized by number of fractions was reported in a study of nine cases of myelopathy compared to 66 cases without by Sahgal et al. (102).

With two fractions, a point max dose of 12.5, 14.6, 15.7, 16.4, and 17.0Gy yielded an estimated risk of 1, 2, 3, 4, and 5% of myelopathy, respectively. In the reirradiation setting, after conventional external beamradiotherapy, a cumulative thecal sac point maximum dose of 70Gy in equivalent 2Gy per fractions(utilizing an alpha-beta ratio of 2) was suggested as long as

sufficient time had elapsed since initial treatment (≥5 months)

and the point maximum for retreatment should not exceed 25Gy

in equivalent 2Gy fractions (101).

CONCLUSIONS

The recent, first randomized clinical trial demonstrated overall and progression free survival benefits after SBRT to oligometastatic disease which supports prior retrospective

case series (6). The spine is a common site of metastatic bone disease, and as high quality data continue to mature, along with completion of additional randomized clinical trials, it is expected that utility of SBRT to the spine will increase in the future.

Spine SBRT is unique due to the requirement of sharp dose falloff to prevent serious neurologic morbidity. With recent advances in radiotherapy planning, robotic patient

positioning, image guidance and radiotherapy delivery, this has been made possible. Local control is excellent, and pain response is comparable to conventional radiotherapy.

Patient selection is of utmost importance due to this resource intensive technique, and multidisciplinary consultation is warranted.

- Classic palliative radiation is typically delivered with the goal of providing rapid and durable symptom relief, minimizing side effects and minimizing patient and family burden.
- However, in this circumstance an important additional goal of radiotherapy is providing durable local control so as to prevent fracture or spinal cord compression.
- SBRT in particular delivers significantly higher BED, more precisely, and in a shorter time frame.
- However, the treatment goal (i.e., ablation) is different than the goals of traditional palliative radiation therapy.
- Randomized phase II trial from the University of Heidelberg demonstrated that SBRT may confer an advantage over conventionally fractionated radiotherapy with respect to pain control (11)

Introduction

- A phase II study (RTOG 0631) comparing SBRT with single fraction EBRT demonstrated promising results with respect to feasibility and accurate use of SBRT to treat spinal metastases
- Important to consider the impact of radiation on the structural stability of the vertebral body, which has a not insignificant risk of therapy related vertebral fracture (14% in one study)
- To help decide regarding treatment techniques (i.e., conventional fractionation *vs.* SBRT *vs.* surgery) physicians can use validated criteria such as the Spinal Instability Neoplastic Score (SINS) which evaluates spinal stability (46).
- Given the proximity of spine metastases to critical structures such as the spinal cord, clinicians should also consider degrees of epidural extension evaluated by the Bilsky score
- Grade II and III disease may warrant traditional fractionation over SBRT if surgical decompression is not considered as the proximity of the tumor to the spinal cord may not be amenable to high dose per fraction therapy in spite of the rapid dose fall off. Patients with grade I disease on the other hand may be better candidates for SBRT.

- Advanced technologies can otherwise offer advantages in patients who have had prior RT where normal tissue tolerance is at its limit, especially with respect to the spinal cord (i.e., preventing radiation induced myelopathy) (
- SBRT can also be useful in the avoidance of other critical organs such as the bowel.
- Optimal inclusion criteria for spine SBRT are patients with good to excellent performance status, have oligometastatic disease, have no more than 3 spinal levels involved, have no or minimal spinal instability or high grade epidural disease, have a radioresistant tumor histology, and have not had any prior conventional EBRT to the affected level (or at least 5 months from delivery of prior therapy).
- Estimate the prognosis of patients and consider whether the patient will live long enough to deem the treatment cost effective
- . Potential prognostic models for patients with spinal metastases include the Revised Tokuhashi score [2005], Tomita score [2001], and Modified Baur score.

SBRT for re-irradiation

- Chow *et al.* published data that suggested that patients requiring repeat radiation therapy could be reasonably retreated with conventional 8 Gy in 1 fraction (52). No difference between single fraction radiotherapy and multifraction therapy, except in patients with SINS scores >11 with single fraction therapy
- With respect to SBRT re-irradiation, Garg *et al.* have published results evaluating 27–30 Gy in 3–5 fractions after conventional palliative radiotherapy. One year radiographic local control and overall survival in 59 patients were both 76% with acceptable toxicity, most commonly grade 1 or 2 fatigue.
- Two patients experienced mild to moderate lumbar plexopathy without ambulatory dysfunction

- Mahadevan *et al.* also reported their outcomes of SBRT re-irradiation for recurrent epidural spinal metastases. Sixty patients were treated to 24–30 Gy in 3–5 fractions depending on tumor proximity to the spinal cord.
- Median overall survival was 11 months and median progression free survival was 8 months without any significant toxicity aside from fatigue. Ninety-three percent of patients had stable or improved disease and 65% experienced pain relief

- Spratt *et al.* (56) have developed an integrated multidisciplinary algorithm for spinal metastases which can be used as a guide.

TABLE 1 | Outcomes after spine SBRT for *de novo* metastases.

References	Patients/spinal segments (n/n)	Histology	Dose fractionation [dose (Gy)/fractions]	Follow-up duration (median, months)	Local control (time, if available)	Pain response
Tseng et al. (10)	145/279	Mixed	24/2	15	90.3% (1-year) 82.4% (2-years)	NR
Azad et al. (11)	25/25	Mixed	15–25.5/1–5	18	84%	2/3 had pain relief
Anand et al. (12)	52/76	Mixed	24–27/1–3	8.5	94% (1-year) 83% (2-years)	90–94% complete pain relief
Bishop et al. (13)	285/332	Mixed	Median tumor dose 43 Gy (BED, a/b = 10)	19	88% (1-year) 82% (3-years)	NR
Sellin et al. (14)	37/40	RCC	24–30/1–5	49.0	57%	41% report pain improvement
Bate et al. (15)	24/24*	Mixed	16–30/1–5	9.8	96% (1-year)	NR
Sohn et al. (16)	13/13	RCC	38/4 (median)	NR	86% (1-year)	77% overall (23% complete pain response)
Guckenberger et al. (17)	301/387	Mixed	10–60/1–20	11.8	90% (1-year) 84% (2-years)	44% with severe pre-treatment pain, pain free. 56% with mild/moderate pre-treatment pain, pain free.
Thibault et al. (18)	51/51*	RCC	18–30/1–5	12.3	83% (1-year) 66% (2-years)	NR
Garg et al. (19)	47/47	Mixed	16–24/1	17.8	88% (18 months)	18 patients pain-free post-treatment compared to 13 patients pre-treatment
Chang et al. (20)	93/131	Mixed	NR	23.7	89% (1-year)	NR
Gill et al. (21)	14/14*	Mixed	30–35/5	34	80% (1-year) 73% (2-years)	NR
Wang et al. (22)	149/166	Mixed	27–30/3	15.9	81% (1-year) 72% (2-years)	54% pain free at 6-months, compared to 26% at baseline
Staehler et al. (23)	55/105	RCC	19–20/1	33.4	94% (1-year) 90% (2-years)	Median pre-treatment score 5, median post-treatment score 0 1 week after
Sahgal et al. (24)	14/18	Mixed	24/3 (median)	9	72%	NR
Yamada et al. (25)	93/103	Mixed	18–24/1	15	93% (2-years)	NR
Chang et al. (26)	17/22	Mixed	27–30/3–5	NR	68%	Narcotic usage fell from 60% at baseline to 36% at 6 months
Gerszten et al. (27)	8/8*	Breast	15–22.5/1	16	100%	Long-term axial and radicular pain improvement occurred in 96% who were treated primarily for pain
Ryu et al. (28)	49/61	Mixed	10–16/1	NR	96% (9-months)	Overall response 85%

Spinal cord compression

- Timely radiotherapy must be delivered with or without neurosurgery to prevent long term deficits.
- Treatment decisions in this scenario must be informed by the patient's overall clinical trajectory, prognosis, histology, symptoms, and patient preferences.
- Patchell *et al.*, published data suggesting that patients with SCC had superior outcomes in the end points of ability to walk and retention of ability to walk with combination surgery and radiotherapy compared to radiotherapy alone (57). **As such, consultation with Neurosurgery should always be considered in this clinical scenario.**
- When considering prescription dose, longer dose and fractionation schemes were found to have higher local control in one trial.
- Higher BED techniques (such as SBRT) are more likely to control tumors compressing the cord. The latter aspect is a more important consideration in patients with longer life expectancies.

- Henry Ford Hospital and MD Anderson Cancer Center have reported their experience with the use of single fraction SBRT for epidural spinal cord compression with promising results
- SBRT is a very labor-intensive procedure and even with a generalizable class solution, it can take a few days for the planning and quality assurance process to be completed and neurological deterioration can occur during that time
- Potential benefits of SBRT should be weighed against the urgency of the clinical scenario, especially when considering the significantly reduced planning time associated with 2D or 3D conformal therapy.

- If a patient has a relative short life expectancy (<3 months) -strongly consider a short course of radiotherapy as there is no difference in motor function or overall survival.
- Data suggests that short course radiotherapy is as effective as long course therapy in patients with poor prognosis
- To estimate prognosis, clinicians can utilize any one of the number of validated scoring criteria are available

Table 5 Spinal cord compression

Study	Type of study	Sample size	Population	Treatment arm(s)	Dose/fractionation	Modality	Response rate	Tumor control	Survival outcomes	Toxicity	Comments
Ryu et al. [14]	Prospective feasibility study	10	Patients with 1–2 contiguous vertebral metastases with or without SCC	EBRT followed by SRS	25 Gy in 10 fractions EBRT followed by SRS boost 6–8 Gy in 1 fraction	EBRT and SRS	Complete relief in 5/9 patients, remaining 4/9 able to reduce pain medication; time to pain relief 2–4 weeks, 2 patients with 0/5 strength before treatment- 1 with complete motor recovery the other with partial recovery	–	–	No acute toxicity clinically detected during mean follow- up of 6 months	–
Ghia et al. [15]	Prospective Phase I	32	Inoperable patients with MESCC	SRS	18–24 Gy x1 depending on histology	–	–	1-year LC 89%	mOS 25.6 months	No cases of PM with median f/u 17 months	Incremental spinal cord constraint relaxation up to dose maximum of 16 Gy was performed

SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; LC, local control; mOS, median overall survival; SCC, spinal cord compression; MESCC, metastatic epidural spinal cord compression.

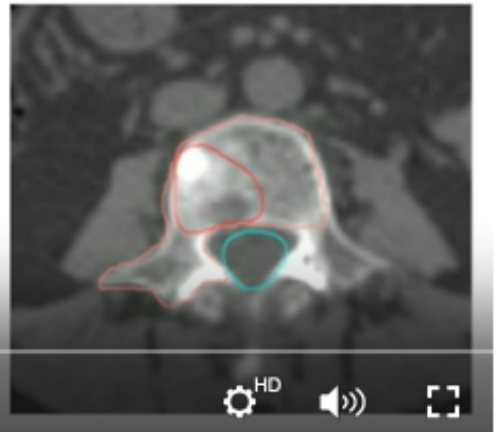
Table 6 Liver metastases

Study	Type of study	Sample size	Population	Treatment arm(s)	Dose/ fractionation	Modality	Response rate	Tumor control	Survival outcomes	Toxicity	Comments
Rusthoven et al. [16]	Prospective multi-institutional Phase II trial	47	Patients with 1–3 hepatic lesions, maximum tumor diameter <6 cm	SBRT	60 Gy in 3 fractions in Phase II arm	SBRT	–	Local progression only in 3 lesions at median of 7.5 months, 95% in-field LC at 1 year; 92% in-field LC at 2 years (100% if maximum diameter <3 cm)	mOS 20.5 months	1 patient with G3 or higher AE	47 patients with 68 lesions, median f/u 16 months, median maximal tumor diameter 2.7 cm
Hong et al. [17]	Prospective Phase II trial	69	Patients with 1–4 liver metastases and Child-Pugh A	Proton SBRT	30–50 Gy equivalent in 5 fractions, median dose 40 GyE	Proton SBRT	–	1- and 3-year LC 71.9% and 61.2%, respectively. Tumors ≥ 6 cm with similar 1-year LC 73.9%.	mOS 16.1 months	No G3–5 toxicity	Median tumor size 2.5 cm, Median f/u 30.1 months, KRAS mutation strongly predicted poor LC

SBRT, stereotactic body radiotherapy; LC, local control; f/u, follow-up.

Spine SBRT

- Efficacy depends on delivering very high doses to target
- Possible due to major evolution in RT delivery techniques
- Spinal cord – critical OAR



Spine SBRT in the Management of Spinal Tumors

The impact of modern technology in radiation therapy has opened up new options that previously were hard to achieve with conventional RT treatments. One such example is the ability to deliver high doses of radiation therapy in a precise manner to a delicate body site such as the spine. Advanced imaging, comprehensive treatment planning as well as high precision treatment delivery techniques are contributing to achieving better clinical outcomes.

Potential Toxicities:

Acute

- Dermatitis
- Esophagitis
- Nausea/vomiting
- Pain flare
- Fatigue

- *Consider premedication with medrol dose-pak or 4mg Dexamethasone*
- *Consider antiemetics if treating near stomach*

Late

- Skin discoloration/fibrosis
- Vertebral compression fracture
  - Higher risk if >20Gy per fraction
  - Peak incidence is 2-3 months after XRT
- Radiation myelopathy
- Radiation plexopathy
- Esophageal stricture / stenosis

Reported accuracy of commercially available SBRT immobilization devices

Site	System	Reported accuracy (mm)
Lung	Elekta body frame	1.8–5
	MI body fix	2.5–3
	Leinbinger body frame	2–4.4
Liver	Elekta body frame	≤4.4
	MI body fix	≤3.2
	Leinbinger body frame	1.8–4.4
Spine	MI body fix	≈1
	Body cast	≈3
	Fiducial marker tracking	2

Therapeutic Ratio

"Had Coutard and Baclesse not pioneered fractionation, radiotherapy probably would have fallen into oblivion due to the morbidities of single shot...
... *(fractionation)* exploit Repopulation, Redistribution, Reoxygenation, Repair and Radiosensitivity"

– Eli Glatstein, 1997

Myelopathy in Re-RT

HyTEC Organ-Specific Paper

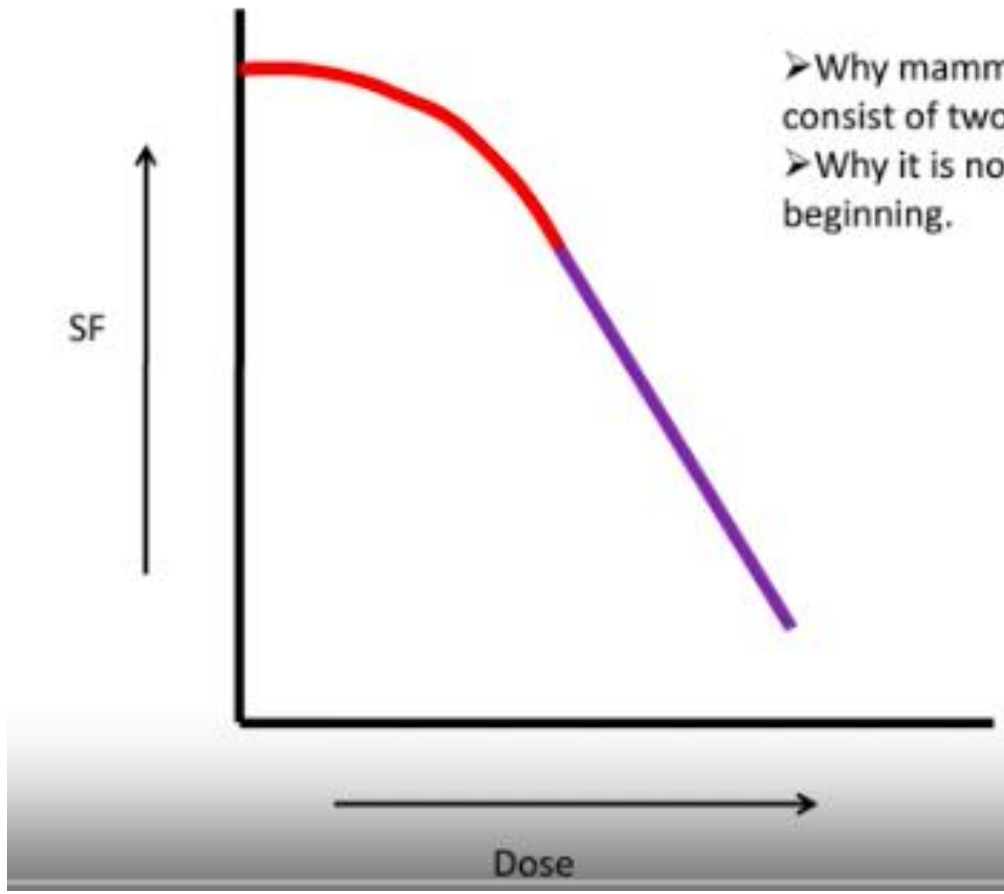
Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Arjun Sahgal, MD,* Joe H. Chang, MBChB, PhD,* Lijun Ma, PhD,† Lawrence B. Marks, MD,‡ Michael T. Milano, MD, PhD,§ Paul Medin, PhD,‖ Andrzej Niemierko, PhD,¶ Scott G. Soltys, MD,# Wolfgang A. Tomé, PhD,** C. Shun Wong, MD,* Ellen Yorke, PhD,†† Jimm Grimm, PhD,‡‡ and Andrew Jackson, PhD‡‡

- **Recomendations-**
- Cumulative EQD2 Dmax 70 Gy
- SBRT EQD2 Dmax 25 Gy
- SBRT EQD2 Dmax to Cumulative EQD2 Dmax ratio 0.5
- alpha/beta = 2
- minimum time interval to Re-RT - 5 months

Sahgal et al, IJROBP 2019

Cell Survival Curve



➢Why mammalian cell survival curve consist of two portion?

➢Why it is not exponential from the very beginning.

- ***Multi Target Model***
- ***Linear Quadratic (LQ) Model***

Vascular End al injury

Abscopal Eff

Dose Constraints – TG 101

Predicted Myelopathy in Spine SBRT

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

- **Thecal Sac**

Sahgal et al, IJROBP 2012

DRY RUN

Treatment Verification
Reproduce Set up
Verify Isocentre
Clinicallly mode up each field
Check beam clearance for collision(especially in NC fileds)
Check for interlock

- MLC interlock? Reinitialized but can not clear means corruption of MLC files - **undeliverable beam**
- Potential MU problem? For example > 1000 for any single field beyond machine capability for non-SRS beams

Treatment Delivery

XVI Imager
Hexa- 6D couch desirable
Imaging protocol selection- better delineation on certain window parameters
Very CBCT – apply shifts
If very long treatment time- then intrafraction CBCCT

SBRT Spine Planning

- Bowel Preparation – to reduce bowel gas artefacts
- Supine, **Vacloc**/Alpha Craddle, **Bodyfix**
- Thermoplastic mask for C-Spine

- **Planning CT**
- 1.25-2.5mm slice thick
- Slice gap = 0
- Additional 5mm whole spine CT

- I/V contrast not needed, except D spine
- Oral contrast duodenum, eso

➢Data Acquisition
➢ Planning
➢Plan Execution

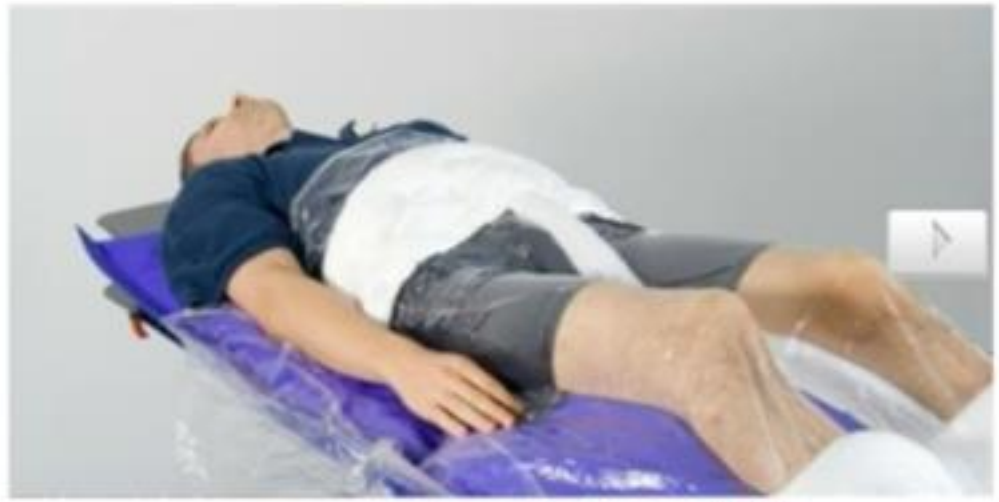


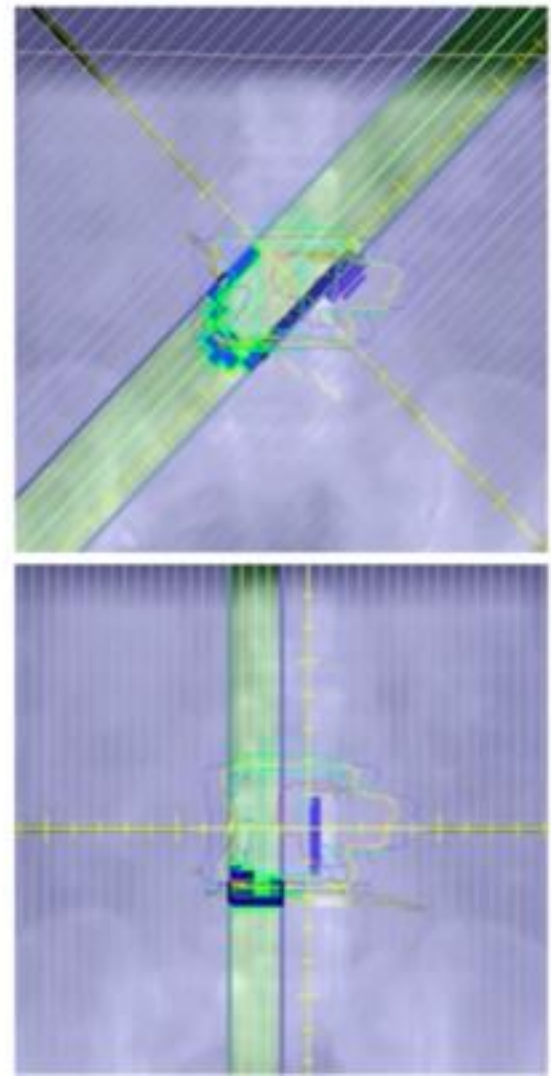
Image Courtesy - Elekta

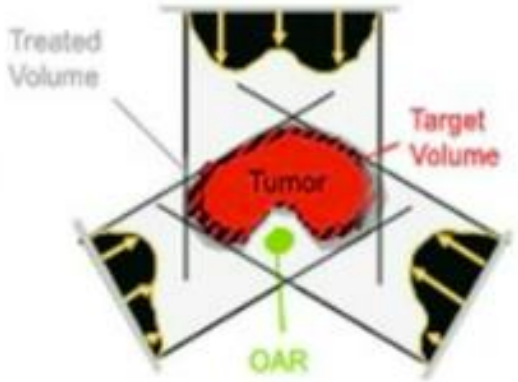
SBRT Planning

- **AAPM TG 101**

- 6 MV, FFF desirable
- Grid size <3mm

- MLC – 5mm vs 2.5mm, Cones
- **Small Field dosimetry**
- Multiple, non-coplanar, **non-isocentric** beams
- VMAT - Arcs – usually 2 coplanar arcs
- Collimator Angle





- Small, highly Precise Target
- Reduced PTV margin
- Lesser number of normal cells irradiated to Px dose
- Lesser dependency on Repair, Repopulation for NTCP

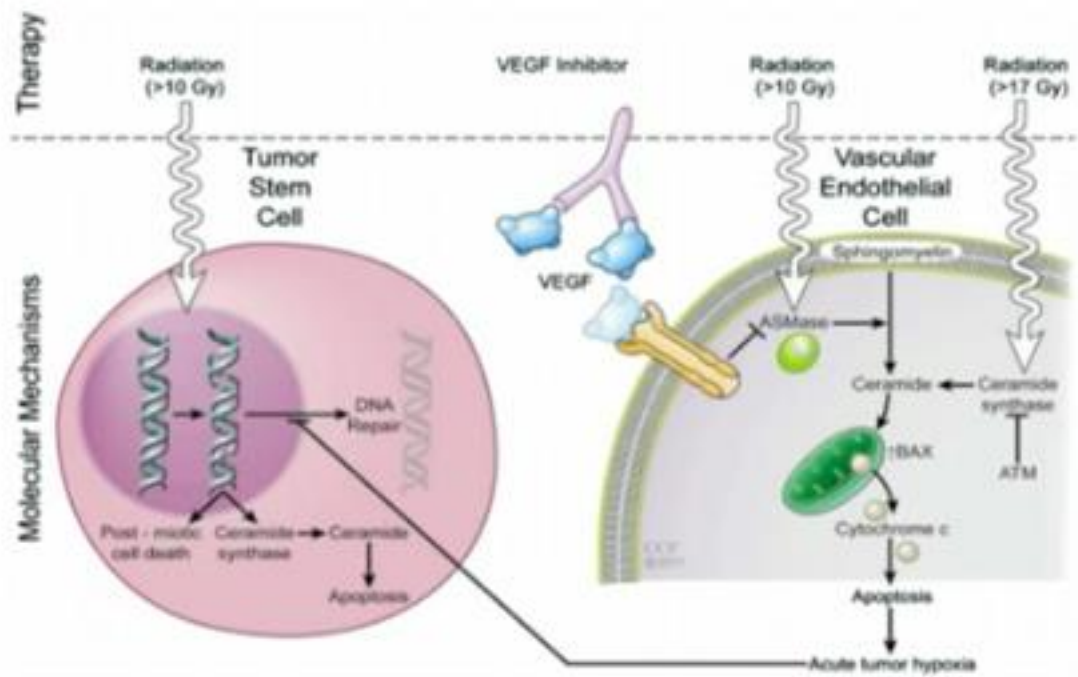
Parameter	SRS/SBRT disadvantage	SRS/SBRT advantage
Repair	Limits the number of cycles of damage and repair that separates the tumor response from normal tissue toxicity	Improved tumor targeting reduces the dose to normal tissues and the need for sparing by fractionation
Reoxygenation	Fewer treatment cycles potentially reduces inter-fraction reoxygenation and thus increases radioresistance	None
Repopulation	None	Much reduces or eliminates tumor repopulation during shorter treatment — specifically relevant to radiation resistant tumor stem cells
Redistribution	Reduced numbers of fractions will affect the cell cycle distribution of remaining viable cells. Though redistribution could favor fractionated RT which provides a higher probability of catching cells in their vulnerable cell cycle states, the clinical significance is unknown	
Radiosensitivity	None	Multi-log cell kill reduces the variability in tumor radiosensitivity primarily observed within the shoulder region of the cell survival curve. Single-[illegible] doses ≥10 Gy may [illegible]

High D/# may counter

Adopted from Vaughan & Rao, 2016

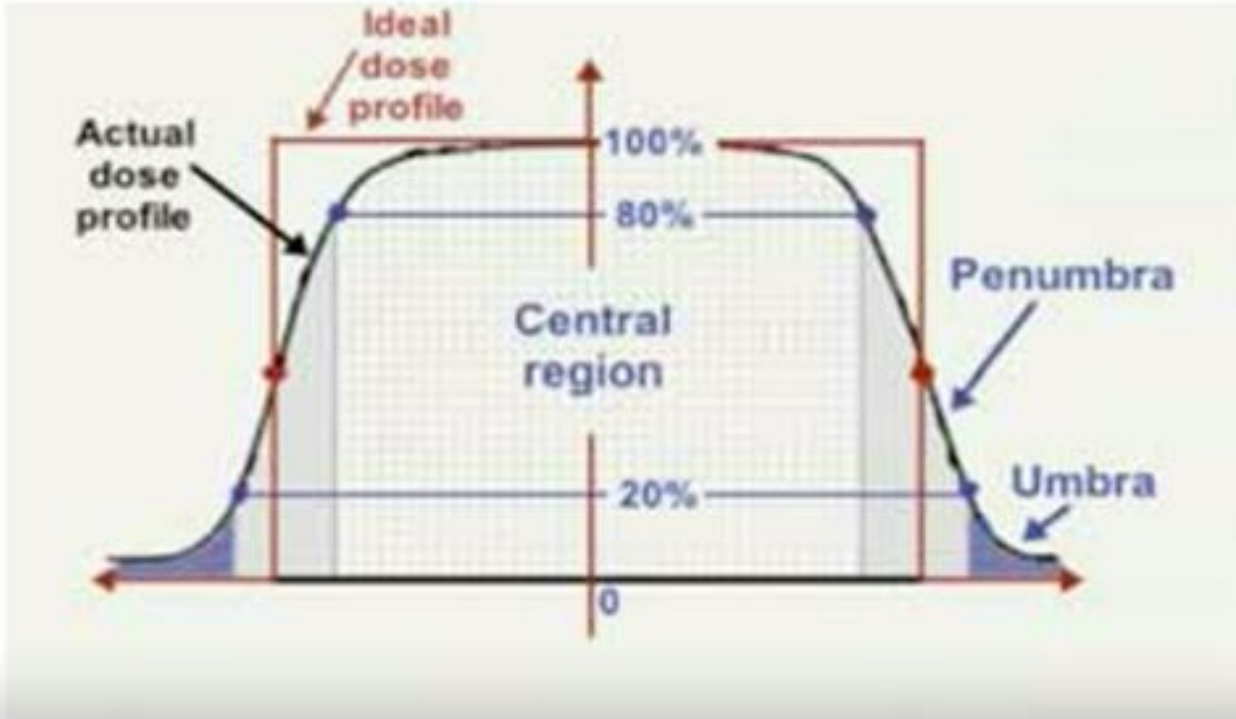
HD

Radiobiology of Radiosurgery



Balagamwala et al, Technol Res Cancer Treat 2012

SBRT Physics



- Beam Profile – LA 6 MV flattened

SBRT Physics

- Prescribe at

  50% IDL for GammaKnife

  80% IDL for Linac Based SRS
- Penumbra

Characteristic	Conventional RT	SRS/SBRT
Prescription dose per fraction	≤3 Gy	≥5 Gy
Number of fractions	≥10	≤5
Dose distribution	Homogeneous (max PTV dose ≈105–110 %)	Heterogeneous (max PTV dose ≈110–200 %)[a]
Dose gradient outside PTV	Shallow slope	Steep slope
Prescription isodose line	≈90–95 %	≈50–95 %[a]
Target definition	Tumor might not have a sharp boundary	Well-delineated target
PTV margin	≈cm	≈mm

Modified from Linda Hong's presentation (Benedict et al. 2010; Hong 2012)

[a]Heterogeneity of SRS/SBRT plans is highly dependent on the treatment technique used. The same applies to the prescription isodose lines

Clinical Outcomes

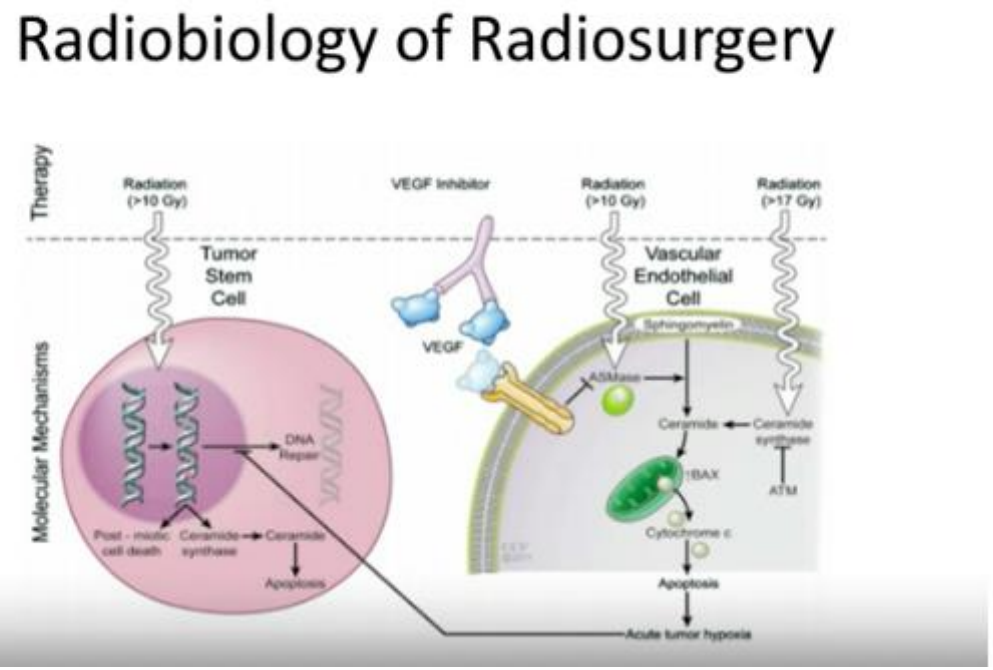
- **Better Pain control**, upto 90% @ > 3 months
- **Complete** pain relief in upto 50% and **Partial** in another 20%
- **Immediate** Pain relief in some - ?Neuronal stunning
- lesser requirement MED (Morphine Equiv Doses) – 30% vs 60%
- **More effective palliation**

- Acceptable VCF (Vertebral Compression #) rates – 5-39%
- Better systemic control – exploratory **i-SBRT**

Conclusions

- 1-3# SBRT is effective, better palliating
- Safe
- Saves time - Delay in Systemic Rx (if indicated), is reduced
- Adequate training, equipment is required but NOT out-of-reach of lesser income countries

- Tumor Board – including Spine Surgeons
- Administrative will, proper costing analysis can help deliver advanced treatment under various Govt schemes



Spine SBRT in the Management of Spinal Tumors

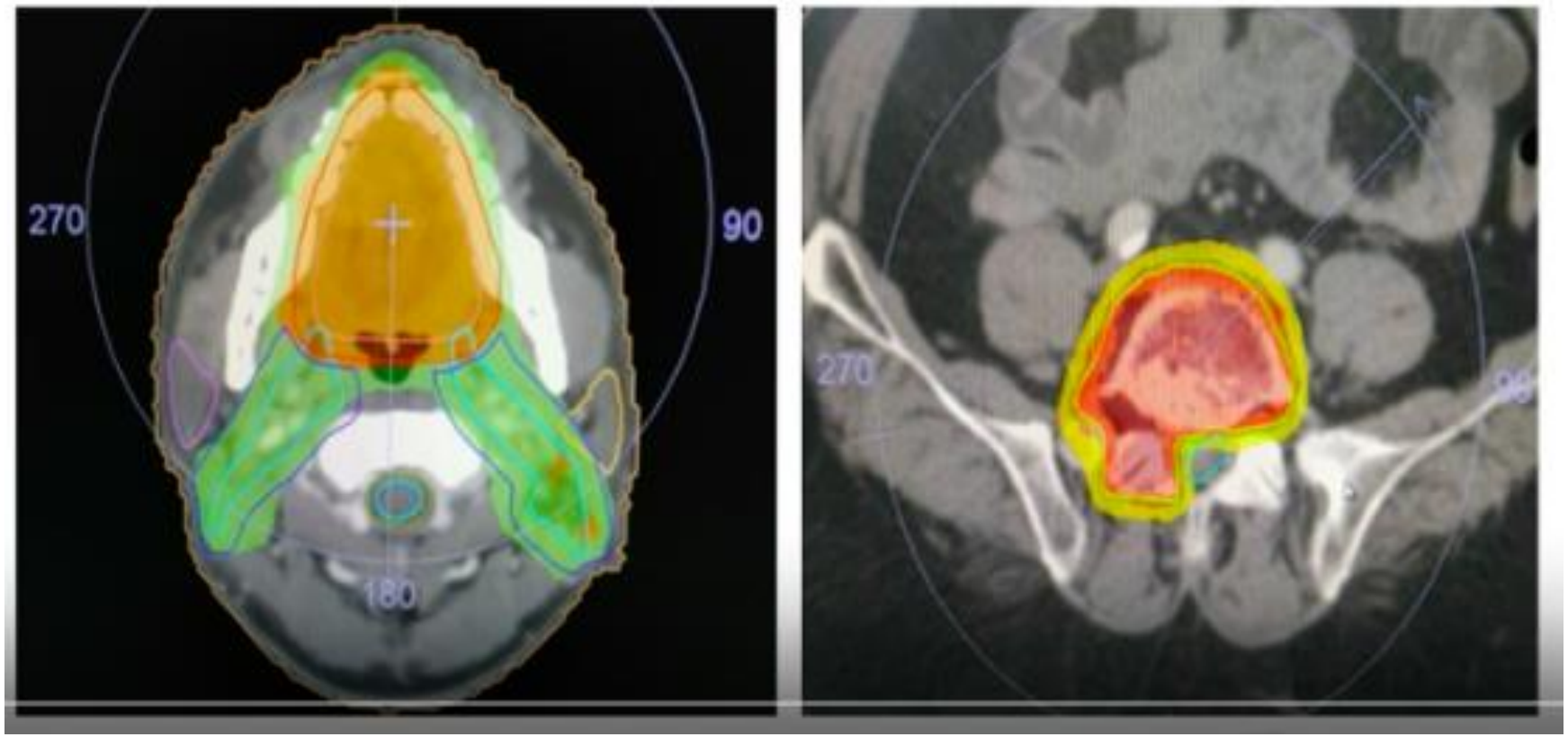
The impact of modern technology in radiation therapy has opened up new options that previously were hard to achieve with conventional RT treatments. One such example is the ability to deliver high doses of radiation therapy in a precise manner to a delicate body site such as the spine. Advanced imaging, comprehensive treatment planning as well as high precision treatment delivery techniques are contributing to achieving better clinical outcomes.

Radiobiology..

- In nutshell, principally,

  a small volume targets can receive higher doses

  adjoining smaller volumes of Normal Tissues can withstand larger doses of Radiation as opposed to large volume targets



Indications

- Vertebral mets
- Meningioma
- Neurofibroma
- Chordoma
- Haemangioblastoma

SBRT Spine criteria

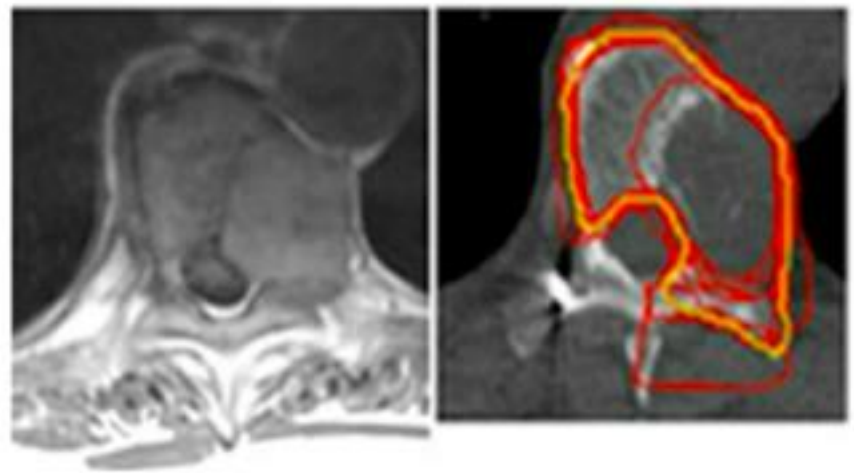
- **Painful Spinal Mets – No Cord Compression**
- Tumor Histology – Breast, Prostate, RCC, Thyroid etc.
- Oligomets @ Presentation
- Oligo-recurrence
- Life expectancy >6 months
- 1-3 lesions in spine
- No/minimal Spine Instability – **SINS 0-6**
- Re-RT to same segment

SINS 7-18 – NSx opinion

SBRT/SRS Target Delineation

- **GTV** – on MRI, CT and PET
  - include STM, if any
- **CTV** – include altered signals on MRI
  - **Involved sectors**
- **PTV** – 1-3mm

  modified @ dural margins
- **Thecal Sac**



- **Dose - >3mm Cord – 16Gy SRS @ 80% IDL (marg 12Gy)**
- **Dose - <3mm Cord – 8Gy x 3# = 24Gy**
  5.8Gy x 5# = 29Gy **- Heterogeneity**

SBRT Spine - Indications

- **Cord Compression** – **No/partial Neurodeficit** (paraparesis) – outcome unlikely to be impacted by protracted SBRT planning
- Limited compression (1–2 segments)
- Assess the Epidural Component – **Bilsky Grade**

  GTV - Cord 1-3mm – **3-5# SBRT upfront** vs

  MISS NSx f/b Postop SBRT

  GTV – Cord <1mm – consider **MISS** NSx f/b Postop SBRT

MISS
Minimally **I**nvasive **S**pine **S**urgery – decompress the Epidural Comp

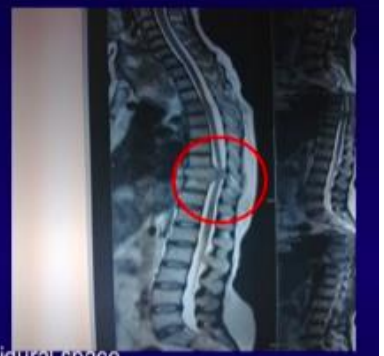
- Cord Compression – **Neuro deficit +**
- <24-48 hrs, improvement with Dexa – NSx opinion
  Can consider **MISS** NSx f/b Postop SBRT
- >48 hrs, No power improvement on Dexa – Pall RT 30Gy/10#

General Principles - Criteria for SBRT

- Inclusion:
  - Spinal or paraspinal metastasis
    - Radioresistant histology
    - Failure of prior EBRT
    - Oligometastatic or bone-only metastatic disease
  - 3 or fewer involved spine segments
  - Stable spinal column
    - Calculate Spinal Instability Neoplastic Score (SINS score)
  - Low grade epidural disease
    - Utilize Bilsky grade
  - Limited extra-spinal systemic disease
  - Life expectancy >3 months
  - KPS > 40-50
- Exclusion:
  - Unstable spine requiring stabilization
  - Previous SBRT to lesion
  - EBRT within 90 days
  - Worsening neurologic deficit
  - Inability to lie flat on table
  - <3-month life expectancy
  - Spinal canal compromise >25%
  - Inability to have MRI
  - Receiving radiosensitizing chemotherapy

Metastatic Spinal Cord Compression

- Most severe complication
- Epidural space is most common
- Incidence 5 %-10%
- Prostate, lung, Breast, Myeloma, NHL
- Site: Thoracic – 60-70%
  Lumbar – 20-25%
  Cervical – 10-15%



Mechanism:

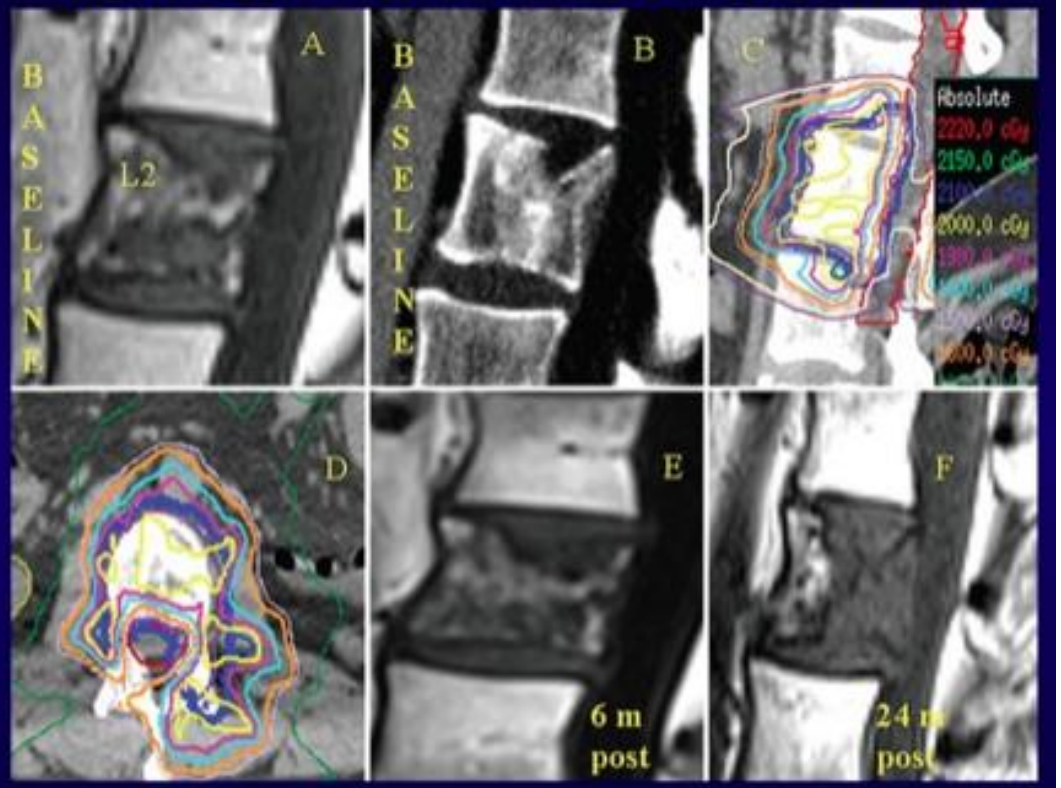
Acute – Compression fracture of spine

Chronic – Extension of metastatic mass from body in to epidural space
Direct infiltration of mass in to the space

Radiosurgery: only few case reports
Higher dose SRS provide rapid tumour regression and reduce spinal cord compressior
Option only if surgery not feasible

Marchetti M et al. Acta Neurochir

Spinal SRS: Vertebral compression fracture



Vertebral compression fracture after high dose SRS is a reality

Spinal SRS: Myelitis

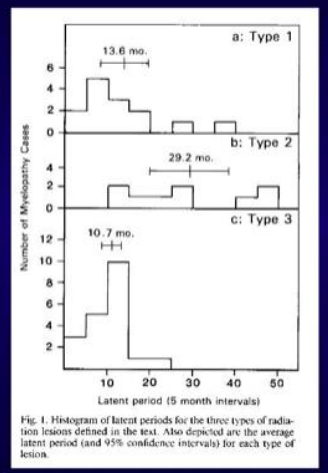


Fig. 1. Histogram of latent periods for the three types of radiation lesions defined in the text. Also depicted are the average latent period (and 95% confidence intervals) for each type of lesion.

Three types
Type 1: White matter changes
Median time: 13.6 mo

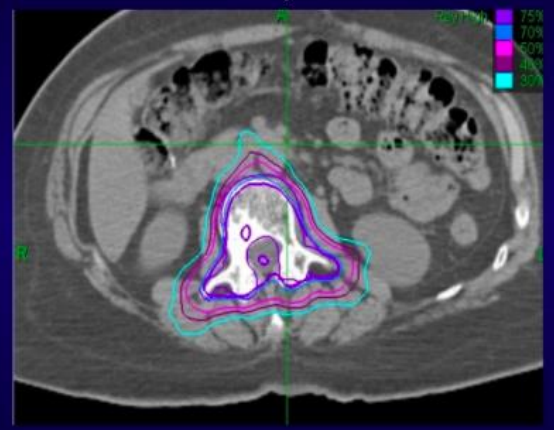
Type 2: Vasacular changes
Median time: 29.2 mo

Type 3: parenchymal & vascular
Median time: 10.7 mo

Need long term follow up for conclusion

Schultheiss et al IJROBP 1987

Bone metastasis: SRS
12Gy/2#



Whole Vertebra (CTV-WV)

Palliative RT dosage schedule in SRS/ fSRS: BED

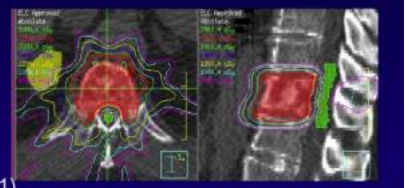
BED values for commonly used CyberKnife™ hypo-fractionated radiosurgery dose schedules

Radiosurgery schedule		BED (Gy)		
Total dose (Gy)	# of fractions	$\alpha/\beta = 2$	$\alpha/\beta = 3$	$\alpha/\beta = 10$
16	1	144	101.3	41.6
18	1	180	126	50.4
20	1	220	153.3	60
20	2	120	86.7	42.8
21	3	94.5	70	38.5
25	5	87.5	66.7	40.3
21	4	76.1	57.8	34.5

BED of 110-140 Gy is delivered with SRS/ fSRS

SRS ONLY to involved verterbra (n=65)

Patient with isolated vertebral bone mets accrued (2001-2007)
Treated with SRS to ONLY involved spine
Dose: 30Gy/5#; 27Gy/3#; 18Gy/1#
RCC: 38%; Thyroid 21%; Sarcoma: 12%
MRI scan done at spine failure / 1 yr



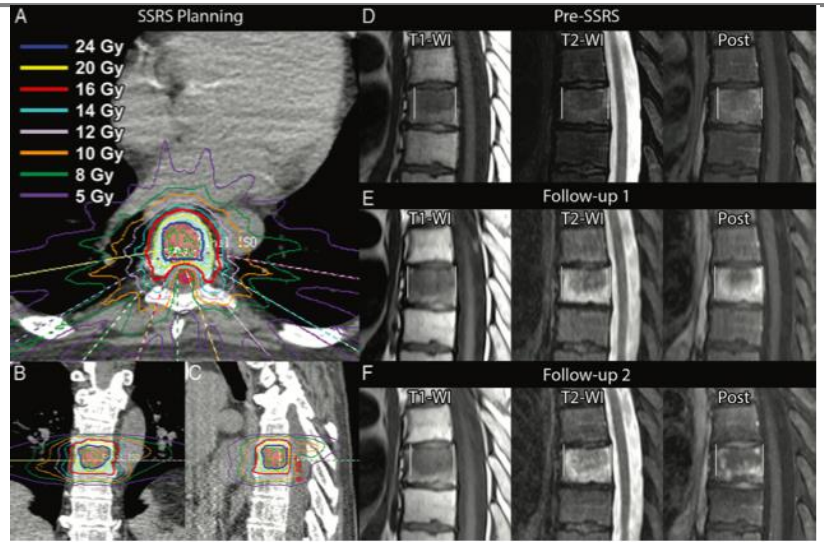
Median FU: 17.9 mo
Overall Survival: 30 mo
Time to Spine failure: 9.7 mo
ONLY 2 pt (3.1%) had only local failure (V+1)

Vertebral level	Isolated vertebral failure; N (%)	With distant vertebral failure n, (%)
V+2	0 (0)	3 (4.6%)
V+1	2 (3.1%)	5 (7.7%)
V-1	0	2 (3%)
V-2	0	3 (4.6%)

ONLY involved vertebral bone RT is enough

IF with IMAGING

Klish DS, et al IJROBP



Palliative RT standard dosage schedule: BED

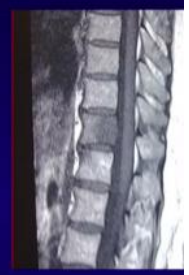
BED Values for commonly used palliative radiotherapy dose schedules

Radiotherapy schedule		BED (Gy)		
Total dose (Gy)	# of fractions	$\alpha/\beta = 2$	$\alpha/\beta = 3$	$\alpha/\beta = 10$
40	20	80	67	48
37.5	15	84	69	44
30	10	75	60	39
20	5	60	47	31
8	1	40	29	14

BED of 70-80 Gy is delivered with Conv RT

Pall RT in bone metastasis

Intention to treat analysis:
Overall response:
SF= 58% (1468 / 2513 pt)
MF= 59% (1466/ 2487 pt)
ODD's ratio= 0.99 (0.95-1.03)



Complete response:
SF= 23% (545/2375 pt)
MF= 24% (558/2351 pt)
ODD's ratio= 0.97 (0.88-1.06)

Increased risk in SF arm:
Pathological #: 3.2% SF Vs 2.8% MF (p=0.75)
Spinal cord compression: 2.8% SF Vs 1.9% MF (p=0.13)

Re-RT rate:
SF= 20% Vs MF 8% (p=0.0001)
Likelihood ratio 2.5

Rationale of SRS study in vertebral mets >16Gy/1#

- Higher overall pain control with higher radiation doses (Ryu 2003; Ryu 2004; Gertzen 2006; Gertzen 2005b).
- Henry Ford Hos exp: SRS dose escalation from 10 Gy to 20 Gy in 2 Gy increments
- Strong trend for increasing pain relief with higher RT doses, dose ≥ 16 Gy (Ryu 2008; Ryu 2007).
- SRS dose ≥ 16 Gy, probability of pain relief > 80%
- University of Pittsburgh Exp: high pain relief dose ≥ 16 Gy (Gerzten 2005; Gertzen 2005b; Gertzen 2006).
- RTOG 0631 Ph III study conducted to evaluate the hypothesis
- Phase III component of this study will use 16 or 18 Gy in 1 fraction.
- Spinal cord constraint is 10 Gy <10% partial spinal cord vol [Ryu 2007].

Conclusions

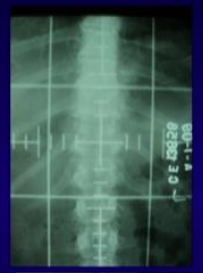
- SRS for solitary & 'Oligo' Vertebral metastasis in a reality. Ph II studies have shown significant benefit with higher dose SRS in terms of pain control, requirement of re-RT
- Ph III studies with 400+ patients with high dose SRS (16Gy), initial results are promising and shows positive outcome
- However, high dose SRS is also associated with high incidence of myelitis & vertebral fracture

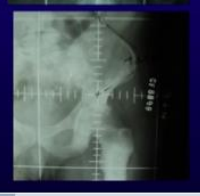
- Spinal metastasis & spinal cord compression, where surgery is morbid SRS reduces the tumour mass and hence compressive symptoms

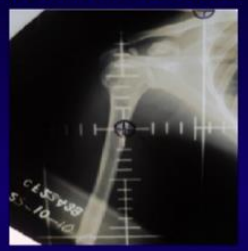
- Primary spinal cord tumours (ependymoma, PXA, Pilocytic astrocytoma): role of SRS is not yet defined and hence should be done only in investigational situation
- Spinal AVMs: SRS is the treatment of choice

- There is no 'head to head' comparative study of different RT delivery machines

Conv RT: Bone metastasis







8Gy/1# OR 30Gy10#
Wide margin
AP/PA field
One vertebra other side in the field

Pain control rate 40-50%

TABLE I. Comparison of typical characteristics of 3D/IMRT radiotherapy and SBRT.

Characteristic	3D/IMRT	SBRT
Dose/fraction	1.8–3 Gy	6–30 Gy
No. of fractions	10–30	1–5
Target definition	CTV/PTV (gross disease+clinical extension): Tumor may not have a sharp boundary.	GTV/CTV/ITV/PTV (well-defined tumors: GTV=CTV)
Margin	Centimeters	Millimeters
Physics/dosimetry monitoring	Indirect	Direct
Required setup accuracy	TG40, TG142	TG40, TG142
Primary imaging modalities used for treatment planning	CT	Multimodality: CT/MR/PET-CT
Redundancy in geometric verification	No	Yes
Maintenance of high spatial targeting accuracy for the entire treatment	Moderately enforced (moderate patient position control and monitoring)	Strictly enforced (sufficient immobilizati and high frequency position monitoring through integrated image guidance)
Need for respiratory motion management	Moderate—Must be at least considered	Highest
Staff training	Highest	Highest+special SBRT training
Technology implementation	Highest	Highest
Radiobiological understanding	Moderately well understood	Poorly understood
Interaction with systemic therapies	Yes	Yes

Safe delivery is of utmost importance due to high fractional dose and small number of fractions

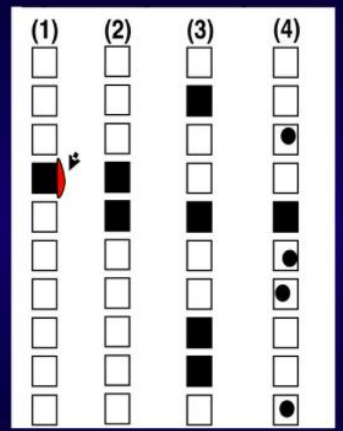
IAEA Trial: Early results

	Response Rate CR+PR @ 4 wk	%	p
4 Gy	66/85	77.64	0.05
8 Gy	80/91	87.91	
	CR	%	p
4 Gy	16/85	18.82	0.005
8 Gy	34/91	37.36	
	Re-RT	%	p
4 Gy	26/85	30.58	0.005
8 Gy	14/91	15.38	

Retreatment time :
4 Gy: Median 4 weeks (4-12 weeks)
8 Gy: Median 12 weeks(4-40 weeks)

Courtesy Dr Nikhil Kalyani

RTOG 0631: Ph III study Eligibility criteria

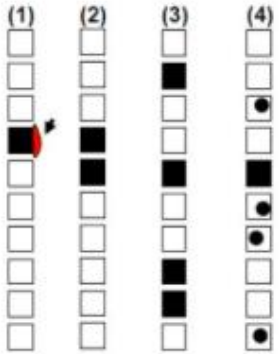


Eligible criteria:
- PS0-1
- Age>18
- NRPS >5

Plan:
Arm 1: 16Gy/1# coverage >90%
Arm 2: 8Gy/1#

End point:
- Pain relief at least 3 points at 3 mo
- QOL: FACT G / Brief pain inventory

PI: Samuel Ryu
Pitsburg Hospital initiated



There can be multiple small metastatic lesions shown in other vertebral bodies as shown in diagram (4) above. The metastatic lesion of each spine should be less than 20% of the vertebral body as opposed to the diffuse vertebral involvement. These small lesions are often seen in the MRI even when bone scan or PET was negative. Most of these lesions are not clinically required to be treated and are therefore not included in the target volume. Only the painful spine (pain score≥ 5) is to be treated .

Pall RT in bone metastasis: RCTs

Author(s) and Country	Year	Treatment Arm	Patient: No. True* Intention-to-Treat	True Randomization: No.	Assessable
Price et al,[18] UK	1986	8 Gy single v 30 Gy/10 fractions	288	288 patients/sites	97
Cole,[19] UK	1989	8 Gy single v 24 Gy/6 fractions	29	29 patients/sites	25
Kagei et al,[20] Japan	1990	8, 10, 12, or 15 Gy single v 20 Gy/4 or 25 Gy/5 or 30 Gy/6 fractions†	27	27 patients/sites	27
Gaze et al,[14] UK	1997	10 Gy single v 22.5 Gy/5 fractions	260 (20 entered twice)*	280 randomizations	240 sites
Foro et al,[16] Spain	1998	8 Gy single v 15 Gy/3 fractions or 30 Gy/10 fractions	75	75 patients/sites	75
Nielsen et al,[21] Denmark and UK	1998	8 Gy single v 20 Gy/5 fractions	241	241 patients/sites	207
Bone Pain Trial Working Party,[15] UK and New Zealand	1999	8 Gy single v 20 Gy/5 fractions	765*	765 patients/sites	681
Koswig and Budach,[22] Germany	1999	8 Gy single v 30 Gy/10 fractions	107	107 patients	107
Steenland et al,[12] The Netherlands	1999	8 Gy single v 24 Gy/6 fractions	1,171	1,171 patients	1,157
Kirkbride et al,[23] Canada	2000 (abstract)	8 Gy single v 20 Gy/5 fractions	398	398 patients	278
Ozsaran et al,[17] Turkey	2001	8 Gy single v 20 Gy/5 fractions or 30 Gy/10 fractions	87	109 fields	109#
Sarkar et al,[5] India	2002	8 Gy single v 30 Gy/10 fractions	73	73 patients	36
Altundag et al,[6] Turkey	2002	5 or 8 Gy single v 30 Gy/10 fractions	54*	60 fields	49
Badzio et al,[7] Poland	2003	8 Gy single v 20 Gy/5 fractions	115	146 sites	126
van der Linden et al,[13] The Netherlands	2004	8 Gy single v 24 Gy/6 fractions	1,157	1,157§ patients	1099
Hartsell et al,[8] US	2005	8 Gy single v 30 Gy/10 fractions	898	898 patients/sites	573
Roos et al,[9] Australia, New Zealand, and UK	2005	8 Gy single v 20 Gy/5 fractions	272	272 patients/sites	234
Kaasa et al,[10] Norway and Sweden	2006	8 Gy single v 30 Gy/10 fractions	376	376 patients/sites	307
Haddad et al,[11] Iran	2006	8 Gy single v 30 Gy/10 fractions	70	70 patients	58

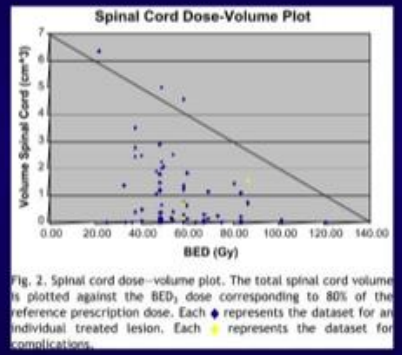


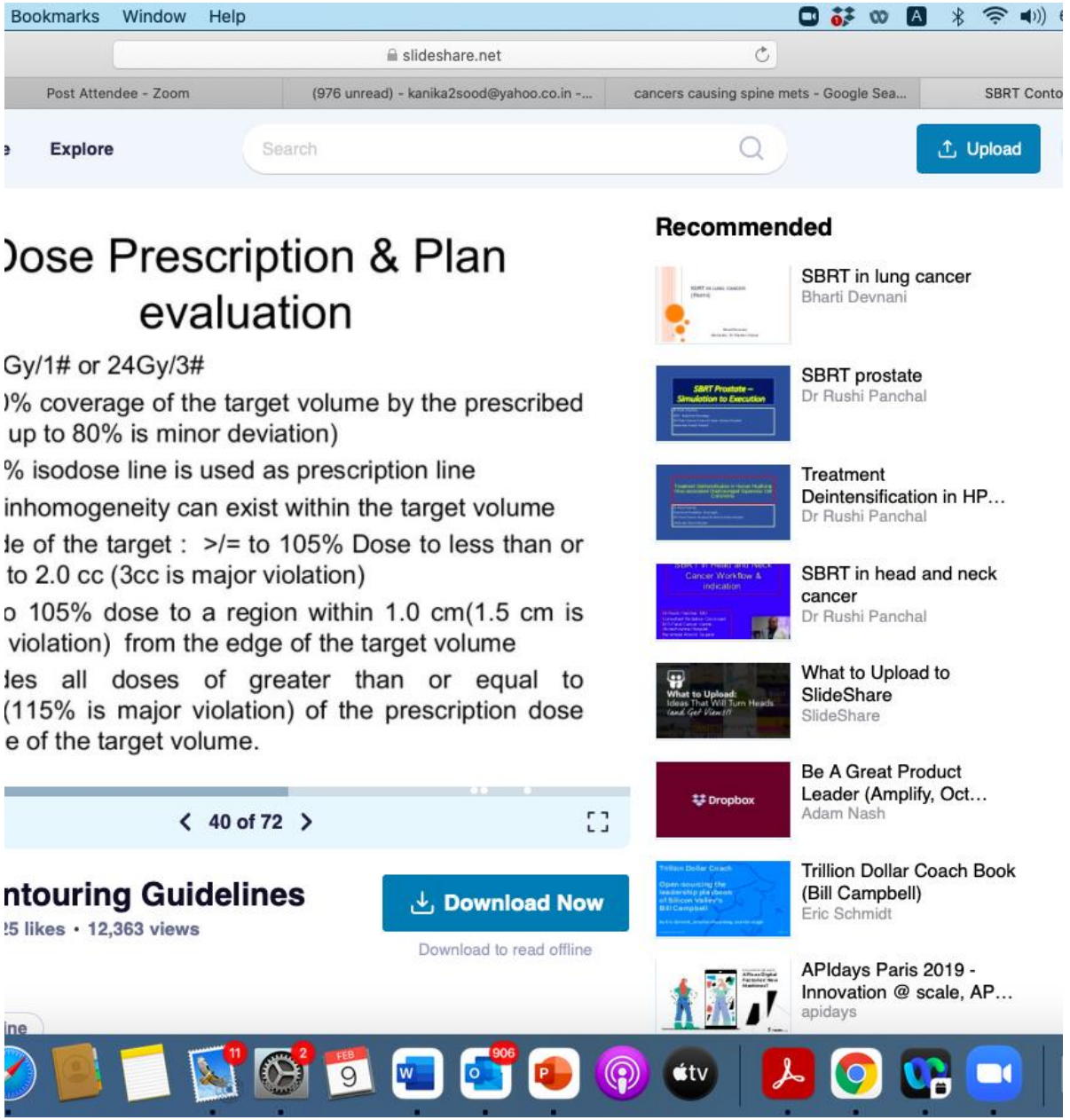
Fig. 2. Spinal cord dose–volume plot. The total spinal cord volume is plotted against the BED_3 dose corresponding to 80% of the reference prescription dose. Each ♦ represents the dataset for an individual treated lesion. Each ▲ represents the dataset for complications.

Study design:
- Standford University experience
- 74 pt with 75% previously treated with RT
- 16Gy/1# to 25Gy/5#

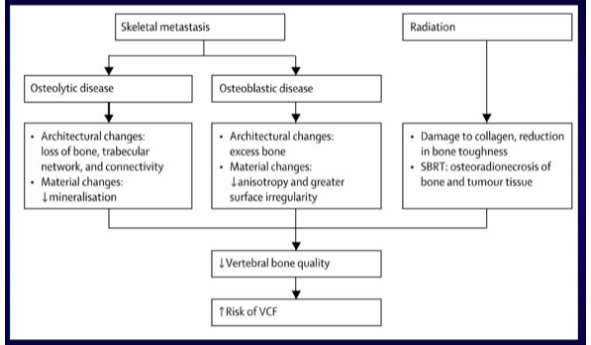
Results:
- Mean FU: 9 months (range 0–33 months)
- At last FU: 36 pts were alive and 38 were dead
- No death was treatment related.
- Symptomatic relief: 84%
- Treatment-related spinal injury: 3 pt.

CyberKnife is a safe SRS option even in previously treated spinal metastasis

Gibbs IC et al Radiat Oncol 2007



Vertebral Compression fracture: Pathophysiology



Success of SRS in spinal mets will depend upon future research on management of VCF & m

Dose constraints: RTOG 0631

Table 1: One Fraction Dose Constraints for Arms 1 and 2

Serial Tissue	Volume	Volume Max (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	Less than or equal to 0.35cc	10 Gy	myelitis
	AND		
Spinal Cord	Less than or equal to 10% of the partial spinal cord	10 Gy	myelitis
	AND		
Spinal Cord	Less than or equal to 0.03cc	14 Gy	myelitis
Cauda Equina	<0.03 cc <5 cc	16 Gy 14 Gy	neuritis
Sacral Plexus	<0.03 cc <5 cc	18 Gy 14.4 Gy	neuropathy
Esophagus*	<0.03 cc <5 cc	16 Gy 11.9 Gy	stenosis/fistula
Ipsilateral Brachial Plexus	<0.03 cc <3 cc	17.5 Gy 14 Gy	neuropathy
Heart/Pericardium	<0.03 cc <15 cc	22 Gy 16 Gy	pericarditis
Great vessels*	<0.03 cc <10 cc	37 Gy 31 Gy	aneurysm
Trachea* and Larynx	<0.03 cc <4 cc	20.2 Gy 10.5 Gy	stenosis/fistula
Skin	<0.03 cc <10 cc	26 Gy 23 Gy	ulceration
Stomach	<0.03 cc <10 cc	16 Gy 11.2 Gy	ulceration/fistula
Duodenum*	<0.03 cc <5 cc	16 Gy 11.2 Gy	ulceration
Jejunum/Ileum*	<0.03 cc <5 cc	15.4 Gy 11.9 Gy	enteritis/obstruction
Colon*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	colitis/fistula
Rectum*	<0.03 cc <20 cc	18.4 Gy 14.3 Gy	proctitis/fistula
Renal hilum/vascular trunk	<2/3 volume	10.6 Gy	malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1000 cc	7.4 Gy	Pneumonitis
Renal cortex (Right & Left)	200 cc	8.4 Gy	Basic renal function

*Avoid circumferential irradiation

RTOG 0631: Ph 2/3 study

Table 1 Patient characteristics (n = 44)

Median age	63 years (range, 25-89)
Gender	
Male	26 (59%)
Female	8 (41%)
Median baseline pain score [a]	7/10
Without pain medication	2 pts (5%)
With pain medication	42 pts (95%)
Zubrod performance status	
0	13 pts (29%)
1	25 pts (57%)
2	6 pts (14%)
No. of spine metastasis	
1	36 pts (82%)
2	8 pts (18%)
Location of index spine metastasis	
C1-C7	4 pts (9%)
T1-T12	21 pts (48%)
L1-L5	19 pts (43%)

pts, patients.
[a] Pain assessed using the Numeric Rating Pain Scale (NRPS).

Table 2 Compliance to quality assurance (primary endpoint)

Image guidance compliance (n = 39)	
Per protocol	35 (90%)
Acceptable variation	2 (5%)
Not evaluable	2 (5%)
Dosimetric evaluation (n = 39)	
Target coverage	
Per protocol	29 (74%)
Variation acceptable	10 (26%)
Deviation unacceptable	0 (0%)
Spinal cord constraint	
Per protocol	39 (100%)
Deviation unacceptable	0 (0%)
Other normal tissue constraints	
Per protocol	29 (74%)
Unacceptable	10 (26%)

74% procedure as per protocol
ONLY 10% unacceptable

OAR Contouring

Normal tissue contouring is required starting at 10 cm above the target volume to 10 cm ~~below the target~~.

Spinal Cord
Two spinal cord contour sets are required for this protocol: the conventional and partial spinal cord volumes. See Section 6.3.1.2 for details.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and muscular layers. The esophagus should be defined starting at least 10 cm above the superior extent of the target volume and continuing on every CT slice to at least 10 cm below the inferior extent of the target volume.

Larynx and Pharynx
The larynx and pharynx will be contoured to the mucosal, submucosa, and cartilages and airway channels associated with these structures.

Trachea and Airway
The trachea and airway adjacent to the spines will be contoured including the mucosal, submucosa and cartilage rings and airway channels.

Lung
Both the right and left lungs should be contoured using pulmonary windows. All inflated and collapsed lung should be contoured; however, paraspinal gross tumor, if any, should not be included in this structure.

Kidney
Both the right and left kidneys should be contoured. Paraspinal gross tumor as defined above should not be included in this structure.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such, it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

IAEA Trial Design: Divided in two groups

Group A (Local Site)	Group B (Hemibody)
Randomization • Arm 1 : 4 Gy / single # • Arm 2 : 8 Gy / single #	**Randomization** • Arm 1: 12 Gy/4# (2 # per day) • Arm 2: 8 Gy / Single #
• 1st reirradiation : after 4 weeks if Mod to Severe pain persists recurrs (**mandatory**) = **8 Gy** • 2nd reirradiation : optional	• Reirradiation: local field after 4 weeks : Optional

Two randomized trials comparing different single fraction schedules

4 Gy Vs 8 Gy
Resp Rate: 44% Vs 69% p=0.001
No diff in CR rates
Reirradiation rate : 20% Vs 9%

Hoskin, P. J Radiother. Oncol 1992.

4Gy Vs 6 Gy Vs 8 Gy
Resp rates: 59%, 73%, 78%
No difference in duration of response, re-RT rate, CR rate.

Jeremic et al : IJROBP 1998.

4 Gy was effective in a large proportion of patients greater acceptance in cases of retreatment, especially in situations when limited tolerance exists

Ph II study: High dose SRS in bone mets (n=120)

Sarcoma with bone metastasis

MF arm: 20-25Gy/5#
SF arm: 24Gy/1#

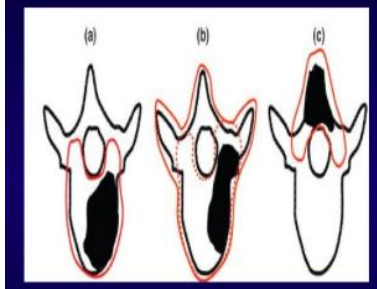
Result:
SF arm: superior LC to MF arm
12-mo LC of 90.8% vs84.1% (P=.007).

Toxicity:
Acute Gr-3 toxicity:1%
Cr Gr-3 toxicity: 4.5%
No Gr>3 toxicities

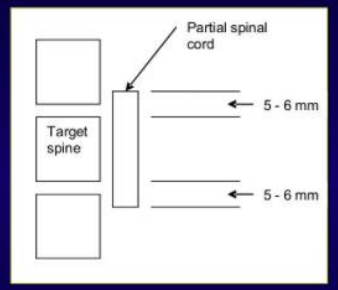
Higher dose SRS: better local control & no increase in toxicity

Folkert et al: IJROBP 2013

RTOG 0631: Contouring



CTV: as per Consensus guideline



Spinal cord partial Vol 10Gy<10% Vol

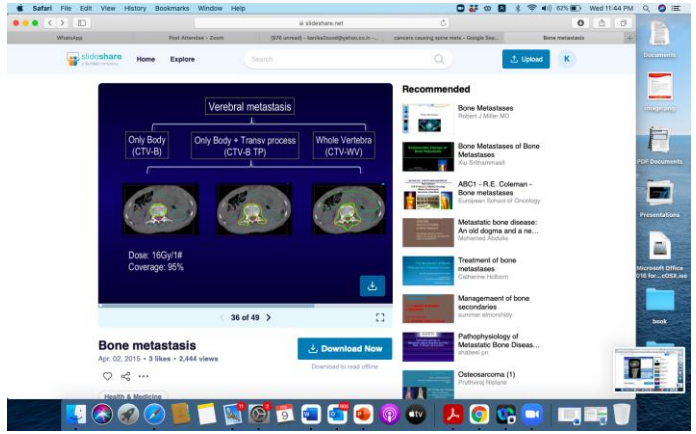
Contraindication

- myeloma or lymphoma
- Non-ambulatory patients
- spinal instability due a compression fracture
- > 50% loss of vertebral body height
- Frank spinal cord compression or displacement or epidural compression within 3 mm of the spinal cord
- Rapid neurologic decline
- Bony retropulsion causing neurologic abnormality
- Prior radiation to Index Spine
- Patients for whom an MRI of the spine is medically contraindicated

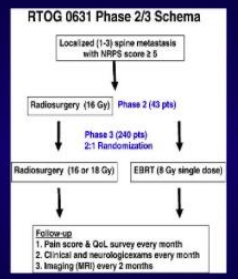
Spinal SRS: Vertebral compression fracture

	Rose et al[35] MSKCC (2009)	Boehling et al[36] MDACC (2012)	Cunha et al[34] UofT (2012)
Number of patients	71 spinal segments in 62 patients	123 spinal segments in 93 patients	167 spinal segments in 90 patients
Median follow-up (months)	13	14·9	7·4
SBRT median or total dose/ fraction	Median 24 Gy (range 18–24)/1	Total 18 Gy/1 (34%), 27 Gy/3 (49%), 30 Gy/5 (17%)	Total 20–24 Gy/1 (19%), 8–18 Gy/1 (3%), 18–24 Gy/2 (25%), 20–27 Gy/3 (35%), 30 Gy/4 (3%), 25–35 Gy/5 (15%)
Tumour characteristics	65% osteolytic, 18% osteosclerotic, 17% mixed	58% osteolytic, 21% osteosclerotic, 21% mixed	48% osteolytic, 26% osteosclerotic, 26% mixed
Tumour location	9% cervical, 66% thoracic, 25% lumbar-sacral	4% cervical, 54% thoracic, 42% lumbar-sacral	18% cervical, 46% thoracic, 36% lumbar-sacral
Incidence of VCF (%)	39%	20%	11%
Time to VCF (months)	Median 25	Median 3	Median 2, mean 3·3, 1-year FFP 87·3%
Salvage interventions (%)	3/27 (11%); 2 surgery, 1 cement augmentation procedure	10/25 (40%), 10 cement augmentation procedures	9/19 (47%); 3 surgery, 6 cement augmentation procedures
Significant predictors of VCF on multivariate proportional hazard analysis	Osteolytic tumour (HR 3·8, 95% CI 1·2–11·4); 41–60% vertebral body involvement (HR 3·9, 95% CI 1·1–14·2)	Age >55 years (HR 5·67, 95% CI 2·13–19·69); pre-SBRT VCF (HR 4·12, 95% CI 1·82–9·21); osteolytic tumour (HR 2·76, 95% CI 1·2–7·1)	Kyphosis/scoliosis (HR 11·1, 95% CI 3·0–41·7); osteolytic tumour (HR 12·2, 95% CI 2·6–58·8); lung histology (HR 4·3, 95% CI 1·2–16); liver histology (HR 34, 95% CI 0·024–192·5), ≥20 Gy dose per fraction (HR 6·82, 95% CI 1·83–25·42)

Vertebral compression fracture: incidence 11-39%



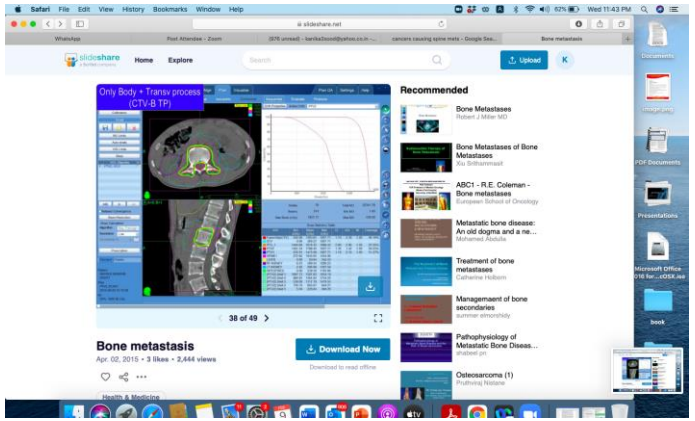
RTOG 0631: Ph 2/3 study



Eligibility criteria:
1-3 spine metastasis with a Numerical Rating Pain Scale (NRPS) score ≥5 received 16 Gy single fraction SRS.

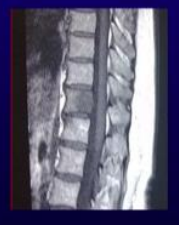
Primary endpoint:
SRS feasibility: IGRT targeting accuracy ≤2 mm

Study design:
Target vol cov >90%,
Spinal cord dose constraints:10 Gy to ≤10% cord vol
Feasibility success rate <70% unacceptable for Ph 3



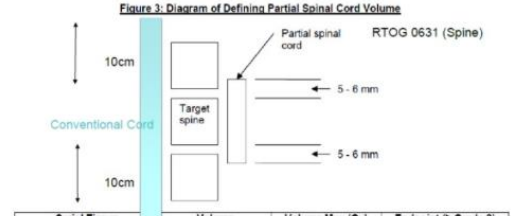
Pall RT in bone metastasis

Systemic review of randomized Pall RT trials: SFs Vs MFs
SFs: 8Gy/1#
MFs: 20Gy/5# OR 30Gy10# OR 40Gy/20#
16 RCTs since 1986
N=>5000
Intention to treat & accessible pt analysis done



Chow E et al JCO 2007

Figure 3: Diagram of Defining Partial Spinal Cord Volume



Serial Tissue	Volume	Volume Max (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	Less than or equal to 0.35cc	10 Gy	myelitis
	AND		
Spinal Cord	Less than or equal to 10% of the partial spinal cord	10 Gy	myelitis
	AND		
Spinal Cord	Less than or equal to 0.03cc	14 Gy	myelitis
Cauda Equina	<0.03 cc <5 cc	16 Gy 14 Gy	Max point dose neuritis

Any spinal cord dose exceeding these constraints is not acceptable and is a major deviation. Radiosurgery is not recommended for any cases that do not meet the spinal cord constraints. Each CT slice within the Radiosurgery plan should be checked to screen any unacceptably high radiation dose to the spinal cord at any particular slice. In this situation, stopping the Radiosurgery or to perform re-planning. Other Critical organs should be analyzed for radiation dose distribution if any of them are transected by any radiation field. Exceeding these limits by more than 2.5% constitutes a minor violation. Exceeding these limits by more than 5% constitutes a major deviation

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