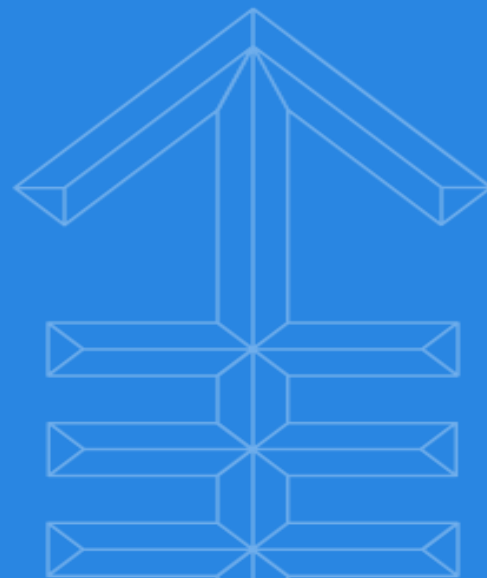




Memorial Sloan Kettering
Cancer Center

The Role of Spine Radiosurgery in the Management of Spine Metastases ACRO 2020

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Disclosures

- The Department of Radiation Oncology at Memorial Sloan Kettering Cancer Center has a research agreement with Varian Medical Systems.
- Dr. Yamada has received speakers honoraria from Varian Medical Systems.
- Institute for Medical Education Speakers honoraria
- BrainLab Speakers Bureau
- Vision RT Speakers Bureau
- University of Wollongong, Consulting Professor



Spine Tumors

- 20% of cancer patients will develop spine metastases.^{1,2}
- Increased number of spine tumors:
 - MR- imaging has improved detection
 - Systemic treatments have improved survival leading to an increased # of metastases
 - Biologics more effective for visceral than bone disease
 - Challenge to understand the impact of biologics on wound healing/RT sensitizers
- Explosion of new technologies and, thus, interest in spine tumors:
 - Surgery
 - Techniques : Separation Surgery/En bloc spondylectomy
 - Instrumentation: Pedicle Screw Fixation (Percutaneous)
 - Newer alloys (Titanium, Cobalt-Chrome, PEEK)
 - Embolization
 - Rotation flaps for wound dehiscence
 - Percutaneous cement augmentation (Vertebroplasty/Kyphoplasty)
 - Radiation
 - Stereotactic Radiosurgery
 - Proton Beam

¹ Cobb, C.A., 3rd, et.al. Indications for nonoperative treatment of spinal cord compression due to breast cancer. J Neurosurg, 47(5): 653, 1975

² Walsh, G.L., et al., Anterior approaches to the thoracic spine in patients with cancer: indications and results. Ann Thorac Surg, 1997. 64(6): p. 1611



- **Three Predominant Pain Syndromes:**
 - **Biologic**
 - **Mechanical**
 - **Radiculopathy**
- **Myelopathy**
- **Significant treatment implications**



- **Biologic pain**
 - Tumor related-pain
 - Predominant pain syndrome (95%)
 - Night or morning pain that resolves over the course of the day
 - Inflammatory mediators
 - Mechanism: Diurnal variation in endogenous steroid secretion
 - Treatment: Steroids/RT



Clinical Presentation

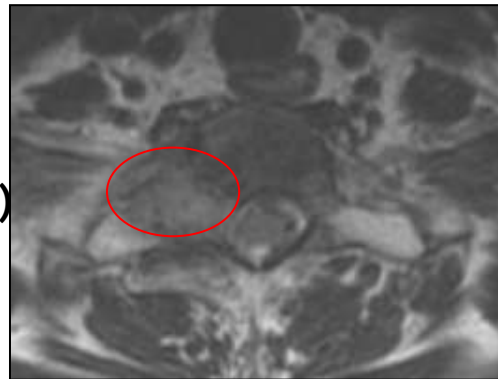
- **Mechanical Pain**
- Indicative of bone pathology
- Movement-related pain
- Level dependent
 - AA: Flexion/extension/rotation
 - SAC: Flexion/extension
 - Thoracic: Extension
 - Lumbar: Mechanical Radiculopathy¹
- Radiographic correlates integrated into SINS
- Treatment: Open surgery/PMMA augmentation
Percutaneous pedicle screws
Radiation/chemotherapy ineffective



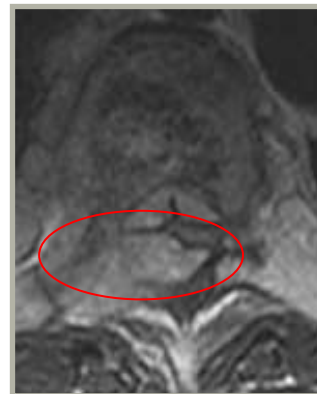
¹Moliterno J, et al. Improvement in pain after lumbar surgery in cancer patients with mechanical radiculopathy. Spine J. 2014, epub ahead of print



- **Radiculopathy**
- Indicative of neuroforaminal disease
- Differentiate from the following:
 - Bone lesion (eg. L3 vs. femur fracture)
 - Neuropathy
 - Brachial/Lumbosacral Plexus Tumor
 - Leptomeningeal Tumor
- Treatment: Dependent on tumor histology and degree of ESCC, often RT in absence of instability

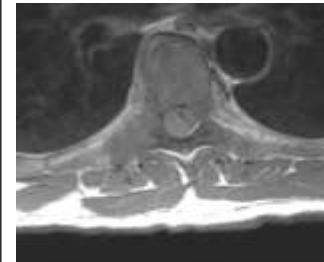


- **Myelopathy:**
 - Indicative of high-grade ESCC
 - Spinothalamic tracts (Pinprick)
 - Corticospinal tracts (Motor)
 - Posterior Columns (Proprioception)
 - Autonomic (Bowel and Bladder)
 - ✓ Neurogenic vs. other (eg. narcotics)
 - ✓ Perineal numbness
 - ✓ Conus medullaris or sacrum
 - ✓ Other spinal levels: Significant degree of paralysis
- Treatment: Dependent on the radiosensitivity of the tumor



Goals of Treatment

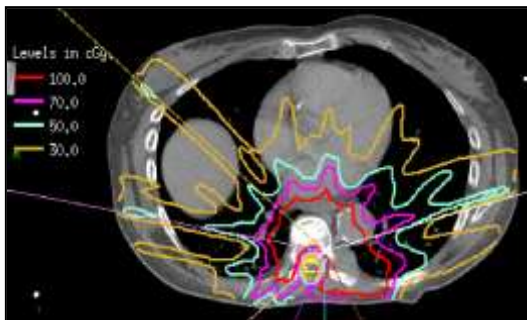
- **Metastasis**
- **Palliation**
 - **Pain Control**
 - **Neurology**
 - **Oncology**
 - **Mechanical Stability**



Treatment Considerations

NOMS^{1,2}

- **N**eurologic
 - **O**ncologic
 - **M**echanical Stability
 - **S**ystemic disease
-
- Systemic Therapy
 - Radiation Therapy
 - Surgery



vs.



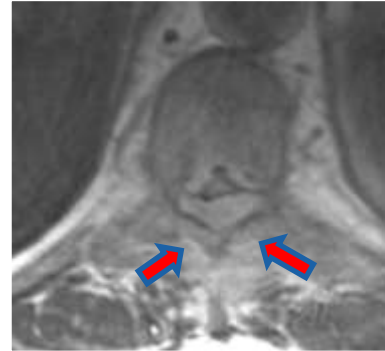
¹Bilsky MH, Smith M. Surgical approach to epidural spinal cord compression. *Hematology/Oncology Clinics of North America.*;20(6):1307-1313;2006.
²Bilsky MH, Azeem S. The NOMS framework for decision making in metastatic cervical spine tumors. *Current Opinions in Orthopedics* 2007;18(3):263-269.



Treatment Considerations

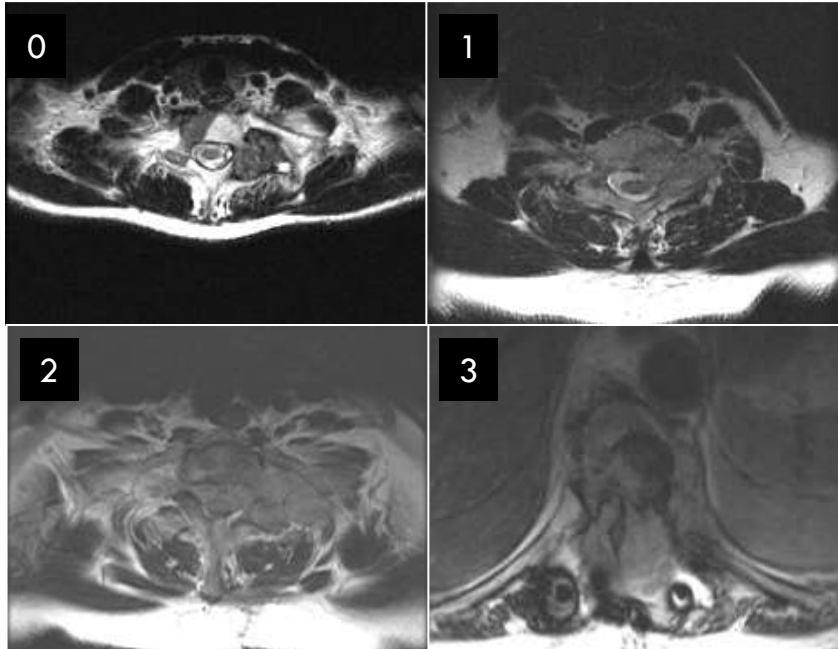
NOMS

- **Neurologic**
 - Myelopathy
 - Functional Radiculopathy
 - Degree of epidural spinal cord compression
- **Oncologic**
 - Tumor Histology
 - Radiation or Chemosensitivity
- **Mechanical Instability**
- **Systemic Disease and Medical Co-morbidity**



N: ESCC

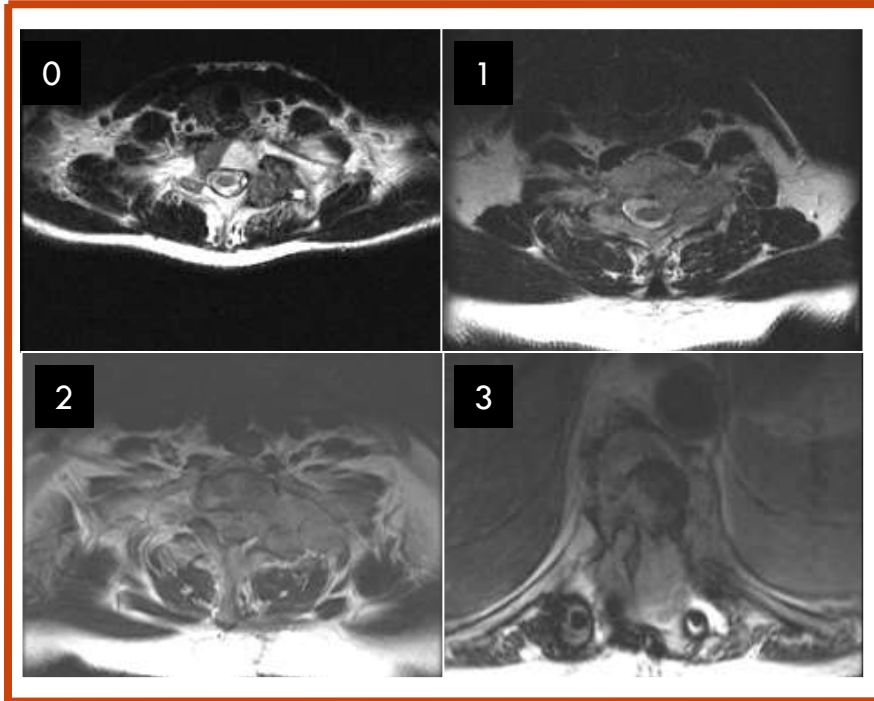
O: Radiation Sensitivity



Radiation Sensitivity	Tumor Histology
Sensitive	Myeloma Lymphoma
Moderately Sensitive	Prostate Breast
Moderately Resistant	Colon NSCLC
Highly Resistant	Thyroid Renal Sarcoma Melanoma

N: ESCC

O: Radiation Sensitivity

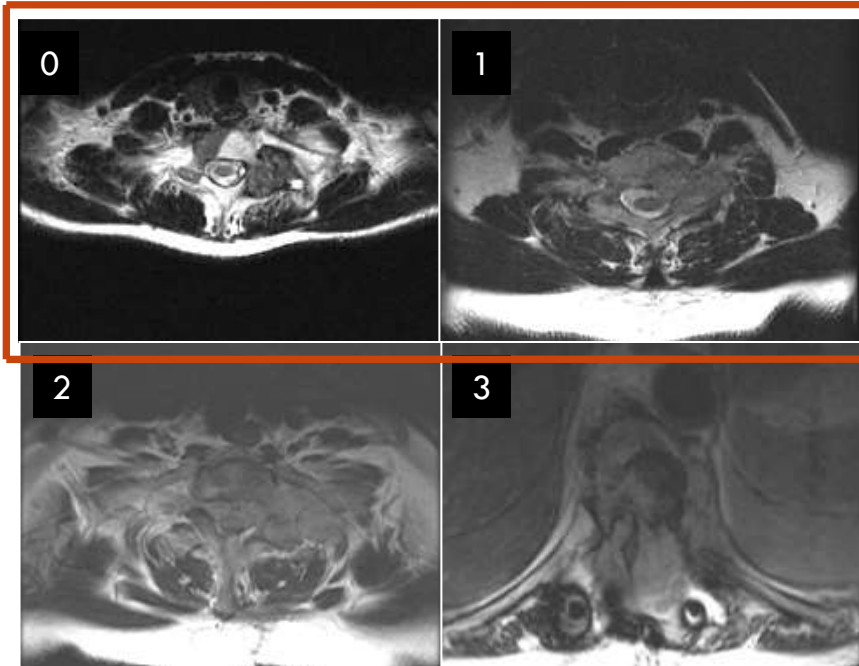


cEBRT (30Gy in 10)

Radiation Sensitivity	Tumor Histology
Sensitive	Myeloma Lymphoma
Moderately Sensitive	Prostate Breast
Moderately Resistant	Colon NSCLC
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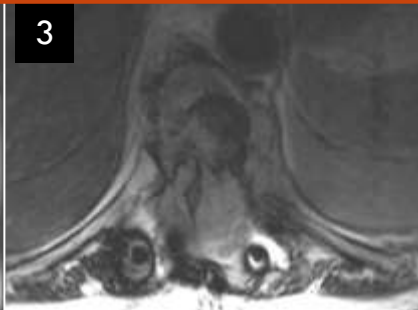
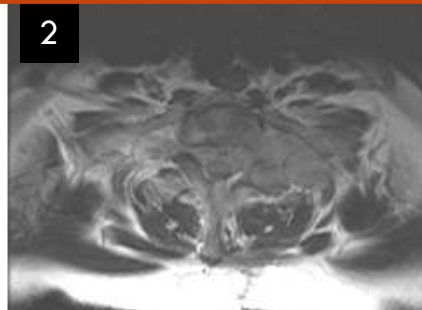
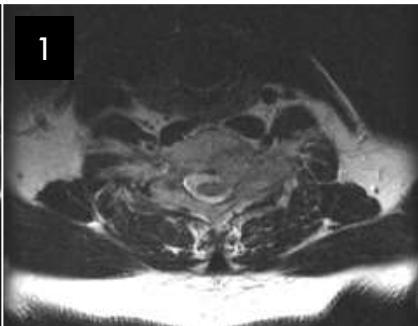
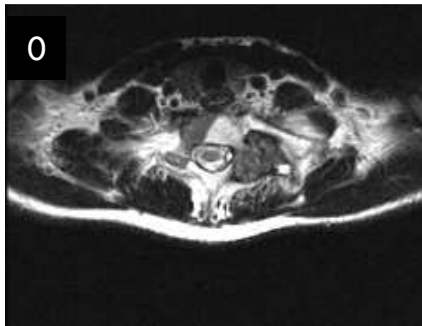
SRS

24Gy or 9Gy x 3



N: ESCC

O: Radiation Sensitivity



Radiation Sensitivity	Tumor Histology
Sensitive	Myeloma Lymphoma
Moderately Sensitive	Prostate Breast
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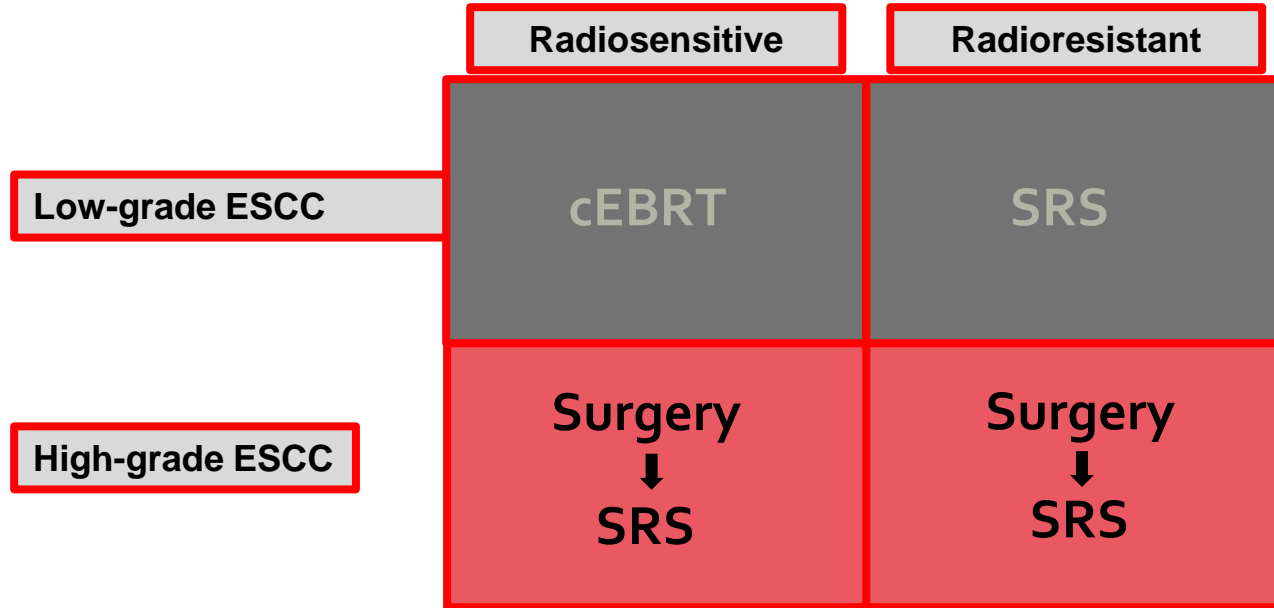
Surgery + SRS

Neurologic and Oncologic Assessment - Not Myelopathic

	Radiosensitive	Radioresistant
Low-grade ESCC	cEBRT	SRS
High-grade ESCC	cEBRT	Surgery ↓ SRS



Neurologic and Oncologic Assessment - Myelopathic



Histologic Classification

Radiosensitivity to cEBRT (30 Gy in 10)

NOMS

	Lymphoma Seminoma Myeloma	Breast	Prostate	Sarcoma	Melanoma	GI	NSCLC	Renal
Gilbert	F	F	U	U	U	U	U	U
Maranzano	F	F	F	U	U	U	U	U
Rades	F	I	I	I	U	I	U	I
Rades	F	F	F	U	U	U	U	U
Katagiri	F	F	F	U	U	U	U	U
Maranzano	F	F	F	U	U	U	U	U
Rades	F	I	I	I	U	I	U	I

Responses: F-Favorable, I-Intermediate, U-Unfavorable

Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: What are the options, indications, and outcomes. Spine 34(22S):S78-92, 2009



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	Radiosensitive			Radioresistant				
	Lymphoma Seminoma Myeloma	Breast	Prostate	Sarcoma	Melanoma	GI	NSCLC	Renal
Gilbert	F	F	U	U	U	U	U	U
Maranzano	F	F	F	U	U	U	U	U
Rades	F	I	I	I	U	I	U	I
Rades	F	F	F	U	U	U	U	U
Katagiri	F	F	F	U	U	U	U	U
Maranzano	F	F	F	U	U	U	U	U
Rades	F	I	I	I	U	I	U	I

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	Radiosensitive			Radioresistant					
	Lymphoma Seminoma Myeloma	Breast	Prostate	Sarcoma	Melanoma	GI	NSCLC	Renal	
Gilbert	F	F	II	U	II	II	II	U	
Maranzano	Median Response Duration 11 months ¹			U	Median Response Duration 3 months ¹			U	
Rades				I				U	I
Rades				U				U	U
Katagiri				U			U	U	
Maranzano	F	2y LCR 86% ²	F	U	2y LCR 30% ²			U	
Rades	F		I	I				U	I

Responses: F-Favorable, I-Intermediate, U-Unfavorable

Conventional RT: Durability of Response

- UK/NZ Bone Mets RCT Trial
- N=761
- 800cGyx1 vs 2000cGy/5 or 3000cGy/10
- 30% available for FU at 12 months
- Nearly 100% increase in relapse at 12 months vs 3 months
- **Acceptable/relevant in the 21st Century?**

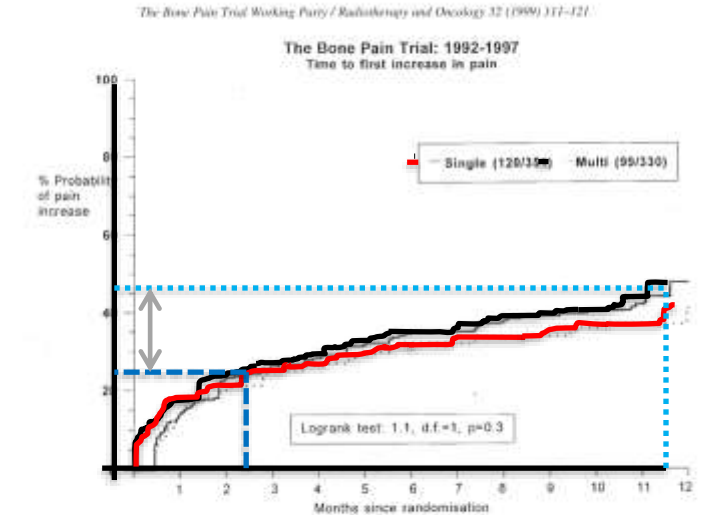
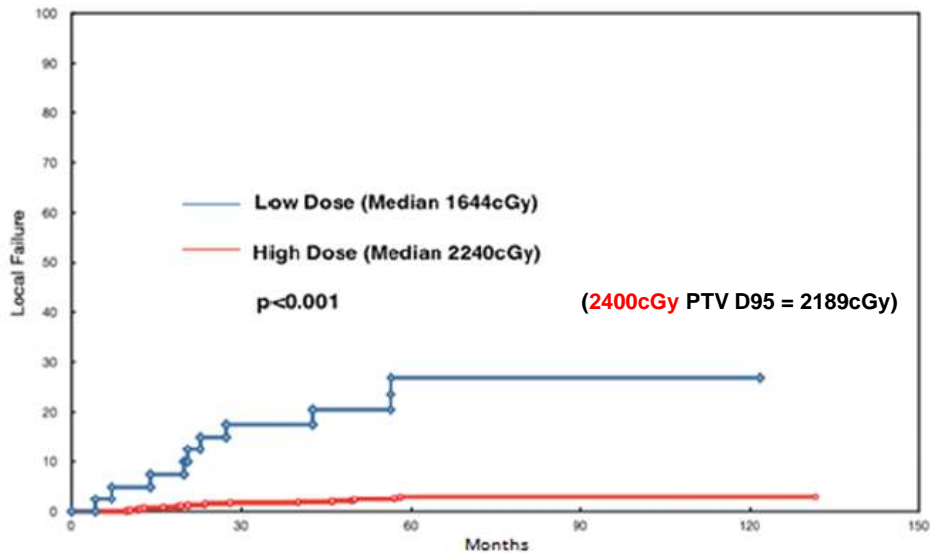


Fig. 5. Time from randomisation to first increase in pain score in 761 patients randomised to single or multiple fraction radiotherapy.

8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol. 1999 Aug;52(2):111-21.



Spine Radiosurgery: PTV Dose Cumulative Incidence of Failure



CIF% (95%CI)	12 months	24 months	36 months	48 months
Overall	0.63% (0.08-1.2%)	2.3% (1.2-3.3%)	2.6% (1.2-3.7%)	3.1% (1.8-4.4%)
PTV D95 Low Dose	5% (0-12%)	15% (3.7-26%)	18% (5.5-30%)	20% (7.4-33%)
PTV D95 High Dose	0.41% (0-0.87%)	1.6% (0.65-2.5%)	1.7% (0.75-2.7%)	2.1% (1-3.2%)

MSKCC Single Fraction UVA N=811

Local Control: Histology/Tumor Size Not Significant

Factor	HR	P-value
PTV Volume (continuous, divided by 100)	1.14	0.25
GTV Volume (continuous, divided by 100)	1.30	0.06
<i>PTV D95 (continuous, Gy)</i>	<i>0.70</i>	<i><0.001</i>
<i>GTV D95 (continuous, Gy)</i>	<i>0.77</i>	<i><0.001</i>
PTV V95 (continuous)	0.96	<0.25
GTV V95 (continuous)	0.97	0.13
<i>Histology (Radiosensitive vs Radioresistant)</i>	<i>1.44</i>	<i>0.40</i>

Yamada et al. Impact of histology and delivered dose on local control of spine metastases treated with stereotactic radiosurgery. Neurosurg Focus, 2017



Radisurgery

Recommendations



A strong recommendation can be made with low-quality evidence that radiosurgery should be considered over conventional fractionated radiotherapy for the treatment of solid tumor spine metastases in the setting of oligometastatic disease and/or radioresistant histology in which no relative contraindications exist.



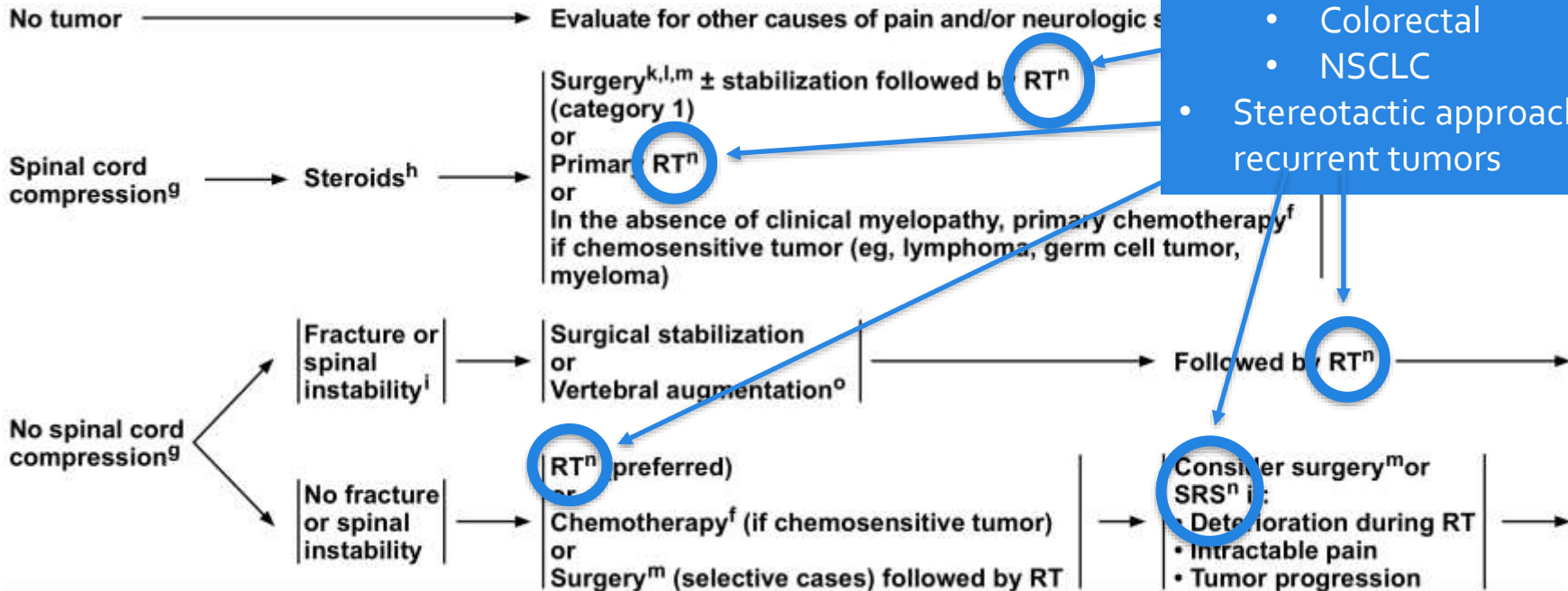
NCCN Guideline: Spine Metastasis



NCCN Guidelines Version 3.2019 Metastatic Spine Tumors

PRESENTATION

TREATMENT



Consider Spine Radiosurgery:

- Oligometastatic disease
- Radioresistant histologies:
 - Renal cell
 - Melanoma
 - Sarcoma
 - Hepatocellular
 - Colorectal
 - NSCLC
- Stereotactic approaches for recurrent tumors

- According to NCCN guidelines, spine stereotactic radiosurgery is appropriate for spinal metastases in which of the following conditions?
 - Radioresistant histologies such as sarcoma and renal cell carcinoma
 - Only for the retreatment of previously irradiated tumors
 - Should not be used in combination with surgery
 - Should not be used in combination with immunotherapy
 - Spine radiosurgery should not be given when epidural disease is present



Radiosurgery is Unique

- Radiosurgery is completely different than conventionally fractionated radiation
 - Radiosurgery is an **ablative** treatment
 - There are unique mechanisms of response
 - **Endovascular effects**
 - **Immunologic effects**
 - The complications of radiosurgery are different than conventionally fractionated radiation
 - Volumes of normal tissue involved are much or tightly controlled
 - Tolerance of high dose to small volumes
 - ***Spine SBRT as salvage for previously irradiated metastases***

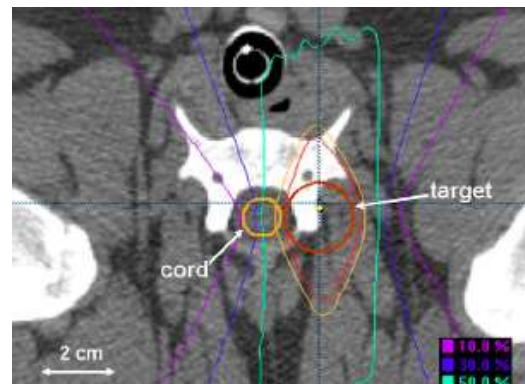


Dose Response in Previously Irradiated Pig Spinal Cord

Medin et al. Int J Radiat Oncol Biol Phys 2010

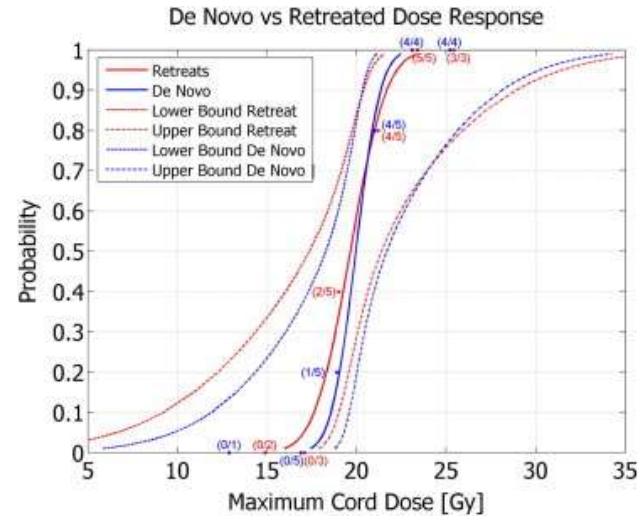
- 23 mature mini pigs received 3000cGy/10
- Single Fraction Spine SRS one year later

Dose	N	Deficit	FU
14 Gy	2	0	40 weeks
16 Gy	3	0	52 weeks
18 Gy	5	2	48-52 weeks
20 Gy	5	4	52 weeks
22 Gy	5	5	20 weeks
24 Gy	3	3	14-19 weeks



Pig Cord Reirradiation Histopathology

- No changes at 14-16 Gy
- 18-20 Gy changes limited to small foci of demyelination
- 22-24 Gy extensive tissue damage including grey matter infarction
- Pigs reirradiated with SRS one year after 3000cGy/10 no different that pigs receiving de novo SRS.



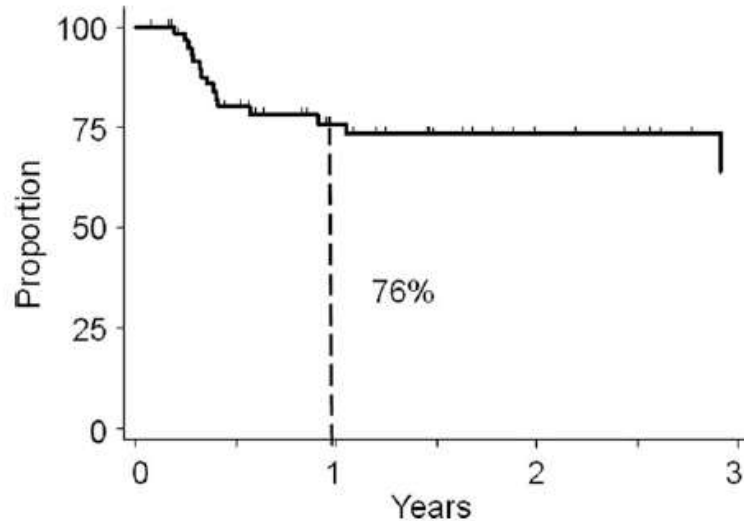
- 96% calculated recovery after 3000cGy/10 after one year.



MD Anderson: Phase II Salvage IGRT

Garg et al, Cancer 2011

- N =63 lesions
- 16 LF
- Median FU 13 months
- Prior XRT < 45 Gy
- Prior XRT > 3months
- 600cGyx5 or 900cGyx3
- Mean cord dose: 10 Gy



Local Control



Salvage with Conventional RT

Rades et al. Cancer 2008; 113(5): 1090-96

- **N = 124** MSCC in previously irradiated spines
- **800cGyx1, 300cGy-400cGyx5, 300cGyx7, 200cGyx10-12, 180cGyx17**
- **Median survival 7 months** after reirradiation
- **52% recurrence within 6 months, 79% recurred within 12 months**
- **67% remained ambulatory at 6 months, 43% remained ambulatory at 12 months.**
- **No cases of myelopathy**



Re-irradiation with SBRT

Study (year)	Tumors treated/patients treated	Tumors treated/patients previously treated with RT (median prior total dose)	Follow-up, months (range)	Local control	Number of local failures post-SBRT	Overall survival	Tumor dose/number of fractions	Pain response (%)	Ref.
Choi <i>et al.</i> (2010)	51/42	51/42 (40 Gy)	Median: 7 (2–47)	87% (6 months) 73% (12 months)	25% (13 out of 51 tumors)	68% (12 months)	Median 20 Gy/2 fx (range: 10–30 Gy/1–5 fx)	65	(18)
Mahadevan <i>et al.</i> (2010)	81/60	81/60 (30 Gy)	Median: 12 (3–39)	93%	7% (4 out of 60 tumors)	Median overall survival: 11 months	25–30 Gy/5 fx (35 tumors)/ 24 Gy/3 fx (46 tumors)	65	(21)
Garg <i>et al.</i> (2011)	63/59	63/59 (30 Gy)	Mean: 17.6 (0.9–67.5)	76% (12 months)	25% (16 out of 63 tumors)	76% at 1 year	27 Gy/3 fx (50/59)/ 30 Gy/5 fx (8/59)/ 20 Gy/5 fx (1/59)		(17)
Damast <i>et al.</i> (2011)	97/94	97/94 (30 Gy)	Median: 12.1 (0.2–63.6)	66% (12 months)	45% in those treated with 20 Gy/5 fx (19 out of 42 tumors) 26% in those treated with 30 Gy/5 fx (14 out of 55 tumors)	52% at 1 year in patients treated with 20 Gy/5 fx 59% at 1 year in patients treated with 30 Gy/5 fx	20 Gy/5 fx (42 tumors) 30 Gy/5 fx (55 tumors)	85 had some pain relief (35/41 patients)	(16)
Sahgal <i>et al.</i> (2009)	60/39	37/25 (36 Gy)	Median: 7 (1–48)	92% (12 months)	8% (3 out of 37 tumors)	45% (24 months)	Median: 24 Gy/3 fx (range: 8–30 Gy/1–5 fx)		(14)
Total	352/294	329/280	Median: 11.14 (0.2–67.5)	260 of 329 tumors treated (79%)	69 of 329 tumors treated (21%)				

fx: Fractions; RT: Radiotherapy; SBRT: Stereotactic body radiotherapy.

Masucci GL. Stereotactic body radiotherapy is an effective treatment in reirradiating spinal metastases: current status and practical considerations for safe practice. *Expert review of anticancer therapy.* 12 2011;11(12):1923-1933.



Spine Reirradiation SBRT Toxicity

Mantel et al Radiat Oncol 2013, 8:7

Author	Patients/Treatments	Dose 1 st RT Course (Median)	Interval (Median months)	Reirradiation TD/Fracions	FU (Months)	Myelopathy
Milker-Zobel 2003	18/19	38Gy	17.7	39.6Gy	12.3	0%
Mahan 2005	8/8	30Gy	N/S	30Gy/15	15.2	0%
Sahgal 2009	25/37	36Gy	11	24Gy/3	7	0%
Choi 2010	42/51	40Gy	19	20Gy/2	7	N=1 G4
Sterzing 2010	36/36	17.5	34.8/11	46.5	7.5	0%
Damast 2010	95/97	30Gy	N/S	20-30Gy/5	12.1	0%
Garg 2011	59/63	30Gy	20	27-30Gy/3-5	13	N=2 G3 peripheral n
Mahadevan 2011	60/81	30Gy	20	24-30/3-5	12	N=3 radicular pain N =1 LE weakness
Chang 2012	49/54	39Gy	25	27Gy/3	17.3	0%

- Concerning reirradiation of recurrent spine metastases:
 - SBRT is the only safe way to repeat radiation therapy to a spine segment that has been previously irradiated
 - There is no role for the use of single fraction SBRT for reirradiation of recurrent spine disease.
 - The presence of surgical hardware near the spinal canal is a contraindication for reirradiation
 - Salvage SBRT for previously irradiated recurrent spine tumors can provide local in control in greater than 75% of cases
 - Patients who cannot undergo MRI imaging should not be offered spine SBRT



NO Mechanical InstabilityS

- **Recognition of instability as an indication for surgery or percutaneous cement augmentation prior to RT**
- **Spine Oncology Study Group (SOSG) created a scoring system Spine Instability Neoplastic Score or SINS¹**
 - Integrates systematic literature review with expert opinion
 - Reliable: High inter and intra-rater reliability²
 - Valid: Substantial agreement between SINS score and expert opinion²

¹Fisher CG, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine. 2010;35(22):E1221-9.

²Fourney DR, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol 2011;29(22):3072-71



Spine Instability Neoplastic Score (SINS)

SINS Component	Description	Score
Location	Junctional (Occ-C2, C7-T2, T11-L1, L5-S)	3
	Mobile (C3-6, L2-4)	2
	Semirigid (T3-10)	1
	Rigid (S2-5)	0
Pain	Yes*	3
	Occasional non-mechanical pain	1
	No	0
Bone Lesion	Lytic	2
	Mixed	1
	Blastic	0
Alignment	Subluxation / translation	4
	De novo deformity	2
	Normal	0
Vertebral Body	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0

Tallied Score from 6 components

Stable	Potential y Unstable	Unstabl e
0-6	7-12	13-18

Fisher CG, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine 35(22):E1221-9, 2010



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	De novo deformity	2
	Normal	0
Vertebral Body	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0

Tallied Score from 6 components

Stable	Potential y Unstable	Unstabl e
0-6	7-12	13-18

Fisher CG, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine 35(22):E1221-9, 2010



Spine Instability Neoplastic Score (SINS)

SINS Component	Description	Score
Location	Junctional (Occ-C2, C7-T2, T11-L1, L5-S)	3
	Mobile (C3-6, L2-4)	2
	Semirigid (T3-10)	1
	Rigid (S2-5)	0
Pain	Yes*	3
	Occasional non-mechanical pain	1
	No	0
Bone Lesion	Lytic	2
	Mixed	1
	Blastic	0
Alignment	Subluxation / translation	4
	De novo deformity	2
	Normal	0
Vertebral Body	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
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Vertebral Body	>50% collapse	3
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	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0

Tallied Score from 6 components

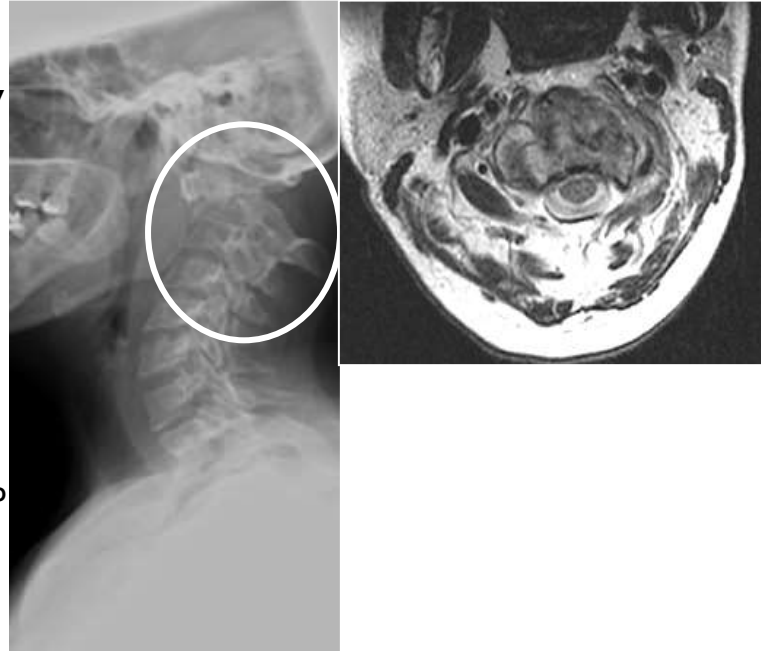
Stable	Potential y Unstable	Unstabl e
0-6	7-12	13-18

Fisher CG, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine 35(22):E1221-9, 2010



Case Example

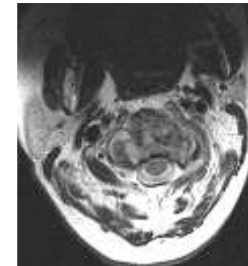
- 45 y.o. female with hormone-refractory breast carcinoma
- Presents with progressive neck pain on flexion, extension and lateral rotation
- Neurologically intact except severe right occipital neuralgia
- Imaging:
 - Plain X-rays: C1-C2 fracture subluxation 5 mm anterior translation/45 degree angulation
 - MR: Lytic bone destruction



SINS Component	Description	Score
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	De novo deformity	2
	Normal	0
Vertebral Body	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0



SINS=17
Unstable



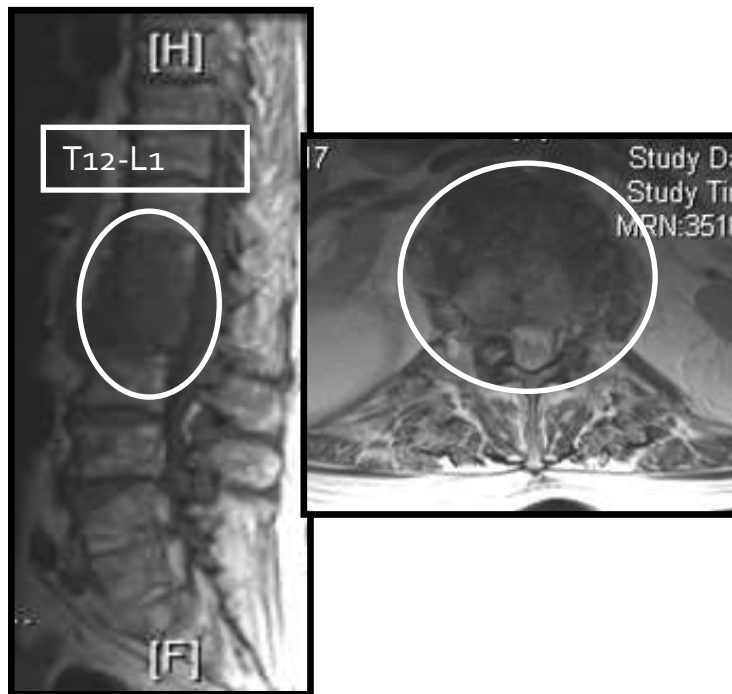
Spine SBRT alone is not indicated in which of the following?

- A patient who has never received radiation
- A patient who has a mechanically unstable spine
- A patient who is claustrophobic
- A patient who has a platelet count less than 75,000
- A patient who has an allergy to iodinated intravenous CT contrast



Case example

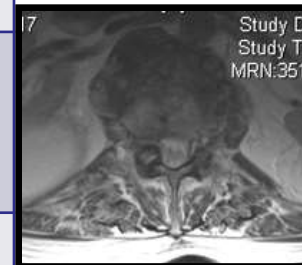
- 85 year old, hx of CASHD,
- 8 weeks of progressive worsening mechanical back pain (10/10)
- MRI scan
- Metastatic w/u negative
- Emergency admission for biopsy
- Multiple myeloma
- Revlimid



SINS Component	Description	Score
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	Semirigid (T3-10)	1
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Alignment	Subluxation / translation	4
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	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0



SINS=10
Potentially
Unstable



Percutaneous Cement Augmentation



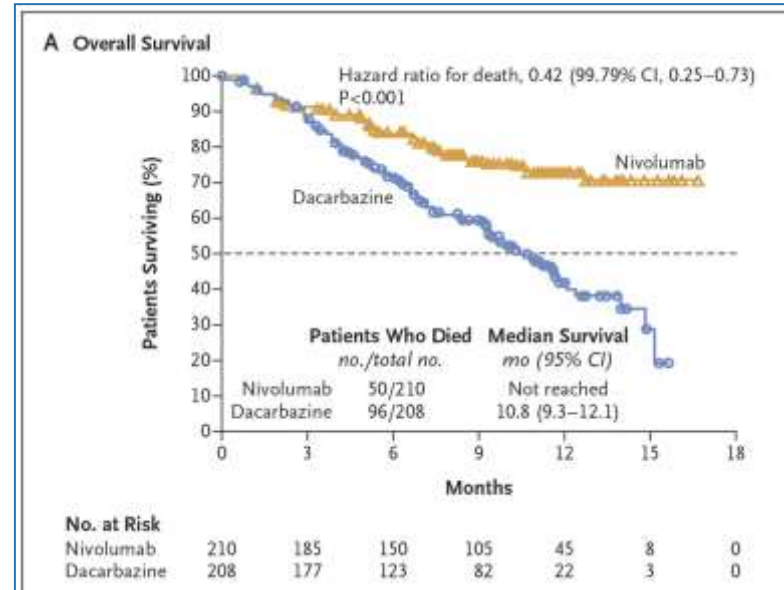
- Patient can tolerate proposed procedure
- In conjunction with Oncologist and Internist
- EOD
 - ❖ PET, or CT CAP +/- bone scan
 - ❖ MRI complete neuraxis
 - ❖ Biopsy for confirmation
- Medical
 - ❖ Cardiac, Pulmonary Function Tests, Dopplers



Improving Survival with Stage IV Disease

- Improved survival with stage IV disease
- Increasing incidence of metastases
 - Spine
- Demand for *durable* tx that matches or exceeds survival
- Limiting toxicity is important-*QOL*
- **Solution: IGRT/SBRT**

Survival End Points: Nivolumab vs. DTIC



NOM Systemic Disease

Undifferentiated Sarcoma
18cm paraspinal tumor
ASIA C
IVC clot extending to R
atrium

N: High-grade ESCC
O: RT-resistant
M: No instability
S: Risk of surgical mortality
prohibitively high

