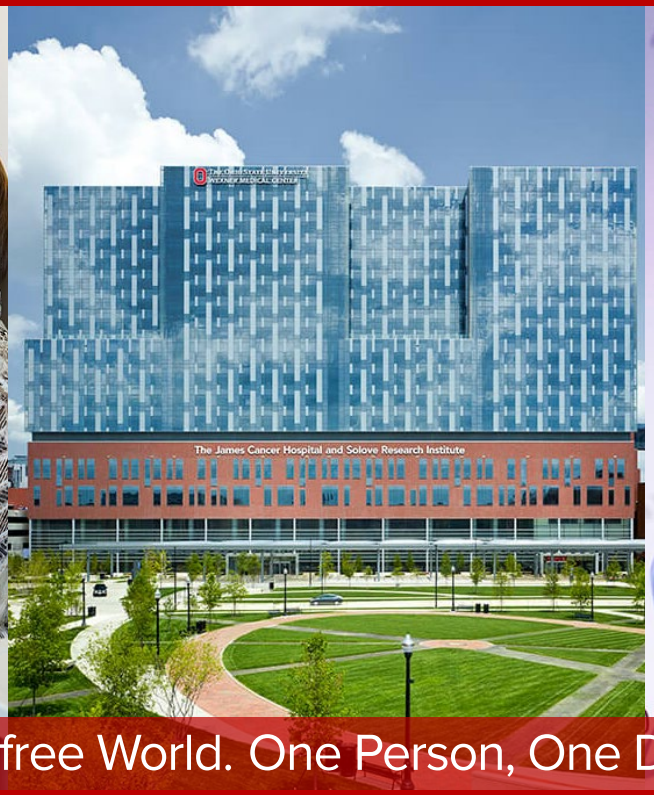

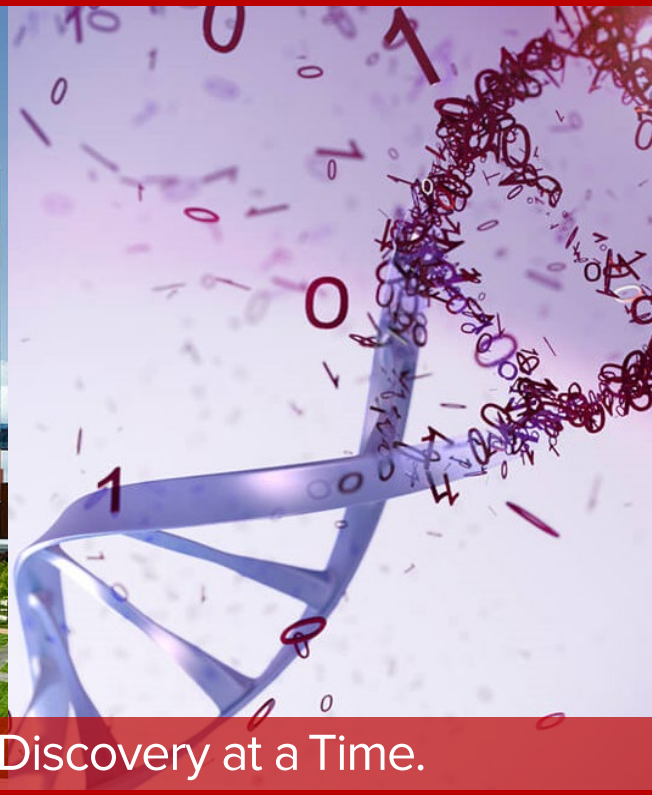

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Spine Oncology: Decision Making and Future Advances

Vikram B Chakravarthy, MD
Jan 9, 2023

Disclosures

- None

Objectives

- Review NOMS and understand how it can be utilized in the decision making of Metastatic Spine Disease
- What is Separation Surgery and how we can improve on existing techniques
- Spine and Peripheral Nerve Oncology Compendium
- Components of an Effective Spine Oncology Program

Patient Evaluation

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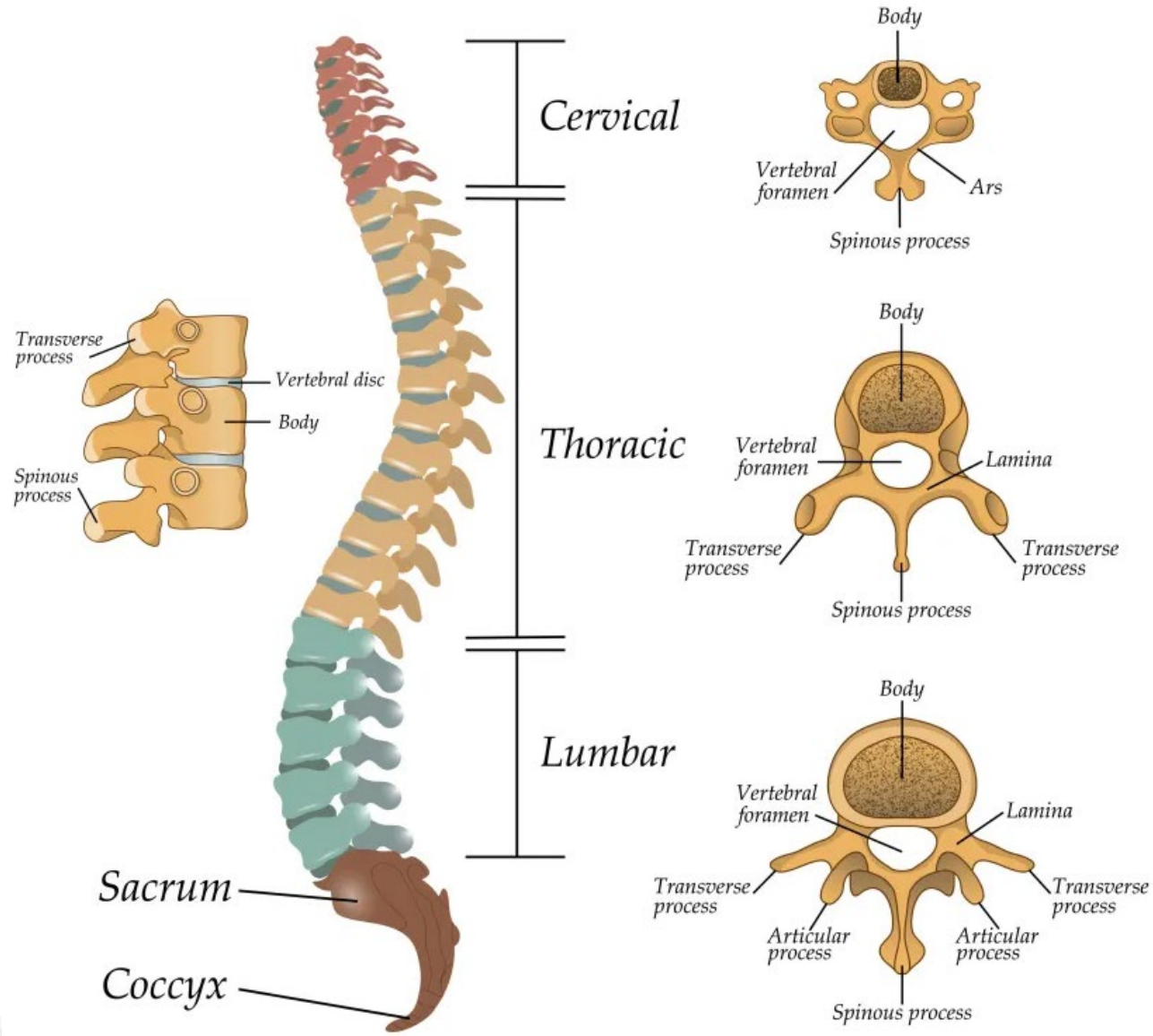
Spine Anatomy



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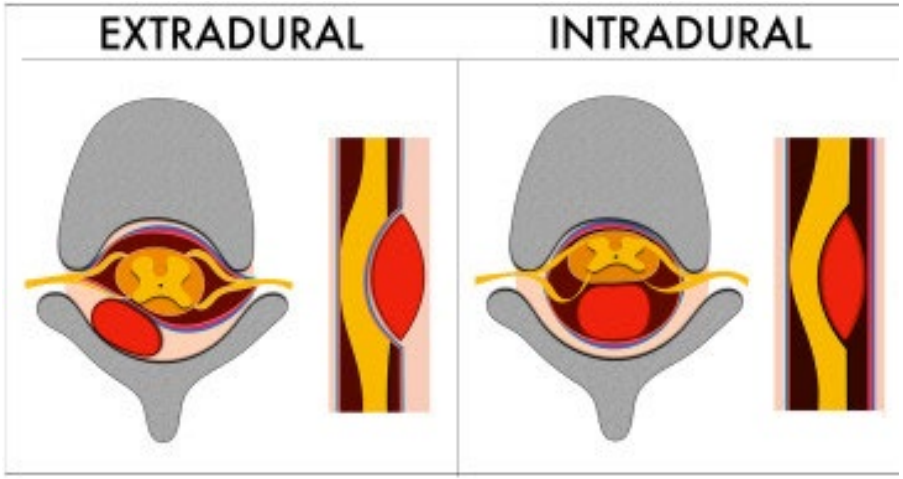
Primary Spinal Column Tumors

- Bone Malignancies
  - Osteoid Osteoma
  - Osteoblastoma
  - Aneurysmal Bone Cyst
  - Giant Cell
  - Chordoma
  - Sarcoma
    - Osteogenic Sarcoma
    - Chondrosarcoma
    - Soft Tissue Sarcomas
- Hematologic Malignancies
  - Plasmacytoma
  - Multiple Myeloma
  - Lymphoma
- Ewing's Sarcoma (PNET)

Classification: Epidural vs. Intradural

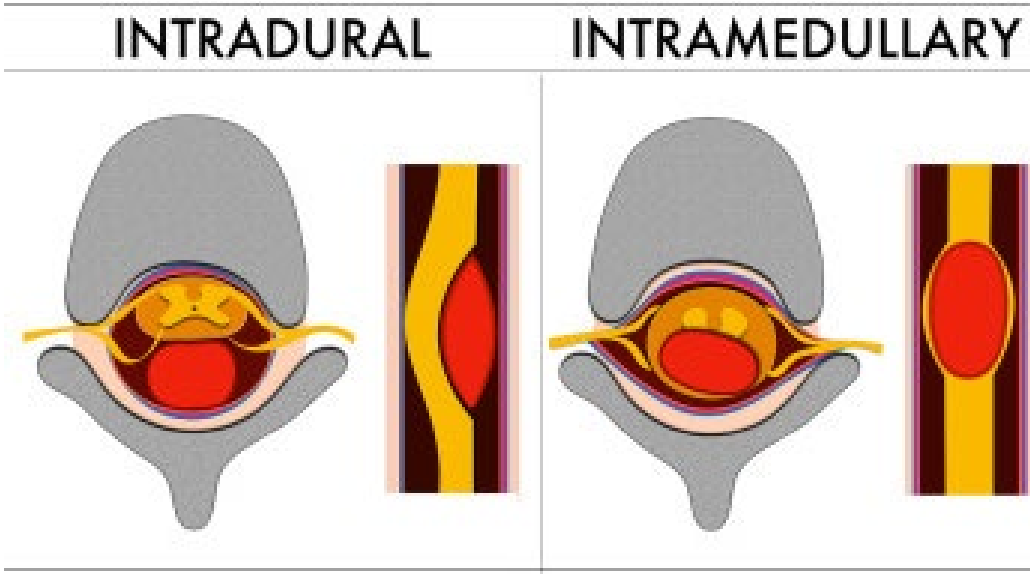
- Epidural
  - Metastatic
    - Breast, Prostate
    - Lung, Colon, Renal Cell, Melanoma, Thyroid
  - Primary: **Benign**
    - Osteoid Osteoma, Osteoblastoma
    - ABC/Giant Cell Tumor
    - Nerve Sheath Tumors: Schwannoma, Neurofibroma, Ganglioneuroma
- Primary: **Malignant**
  - Chordoma
  - Chondrosarcoma



Romano et al. Clinical Imaging 2020

Classification: Intradural

- Intradural (Uncommon, 15%)
  - Intramedullary
    - Astrocytoma
    - Ependymoma
    - Hemangioblastoma
    - Cavernoma
    - Metastasis
    - Lipoma/Epidermoid
  - Extramedullary
    - Meningioma
    - Schwannoma
    - Myxopapillary Ependymoma



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Romano et al. Clinical Imaging 2020

Intradural Extramedullary Tumors

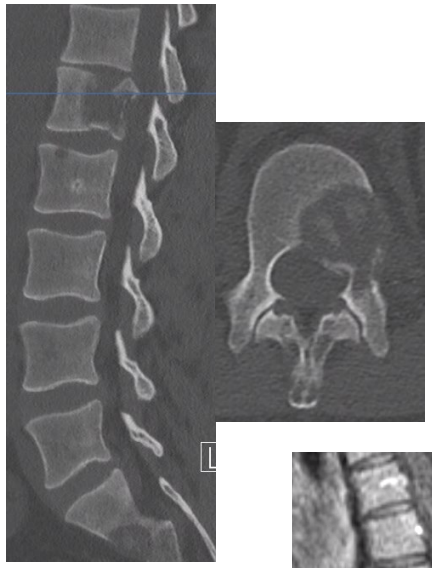
- Schwannoma
- Myxopapillary Ependymoma
- Meningioma
- Paraganglioma

Gross Total Resection: Cure
Exception: Drop Metastases

- Leptomeningeal Tumor → **RT/IT Chemotherapy**

Presentation

- Three predominant Pain Syndromes
  - Biologic
  - Mechanical
  - Myelopathy/Radiculopathy



<u>Significant Treatment Implications</u>

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Presentation: 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

Presentation: Mechanical Pain

- Indicative of bone pathology
- Movement-related pain
- Level dependent
  - CCJ: Flexion, Extension, Rotation
    - Occipital Neuralgia
  - Cervical: Flexion, Extension
  - Thoracic: Extension
    - Recumbency pain
    - Comfortable in kyphosis
  - Lumbar: Mechanical Radiculopathy
    - Axial load pain causing nerve root compression

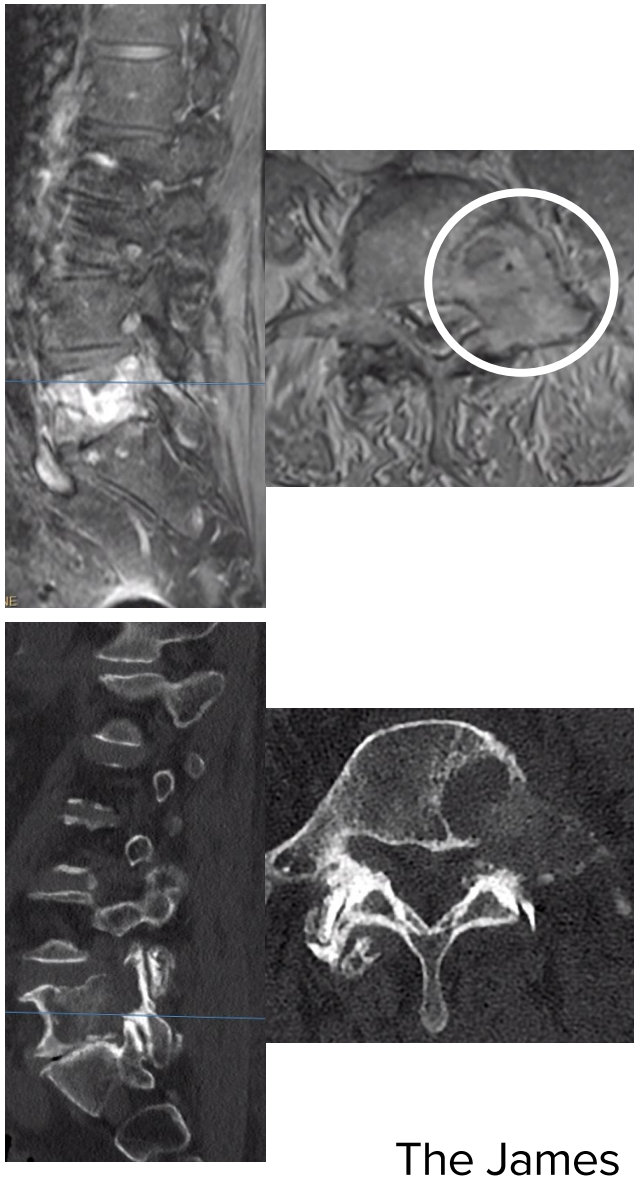
Presentation: Myelopathy

- Indicative of high-grade spinal cord compression
  - Spinothalamic Tract: Loss of Pinprick
  - Corticospinal Tract: Loss of Motor
  - Posterior Column: Loss of Proprioception
  - Autonomic: Bowel or Bladder Dysfunction

Presentation: Radiculopathy

- Indicative of neuroforaminal disease
- Differentiate from the following:
  - Bone lesion
  - Neuropathy
  - Brachial/lumbosacral plexus tumor
  - Leptomeningeal disease

- Treatment: Dependent on tumor histology and degree of epidural disease



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Diagnostic Radiology

- Plain X-rays: Scoliosis
- MRI
  - Screen full neural axis (CTL Spine with contrast)
  - Axial images: evaluate for epidural compression
- CT Myelogram
- CT
  - Evaluate for osseous pathology
- PET Scan/Bone Scan: determine metabolic activity

Metastatic Disease

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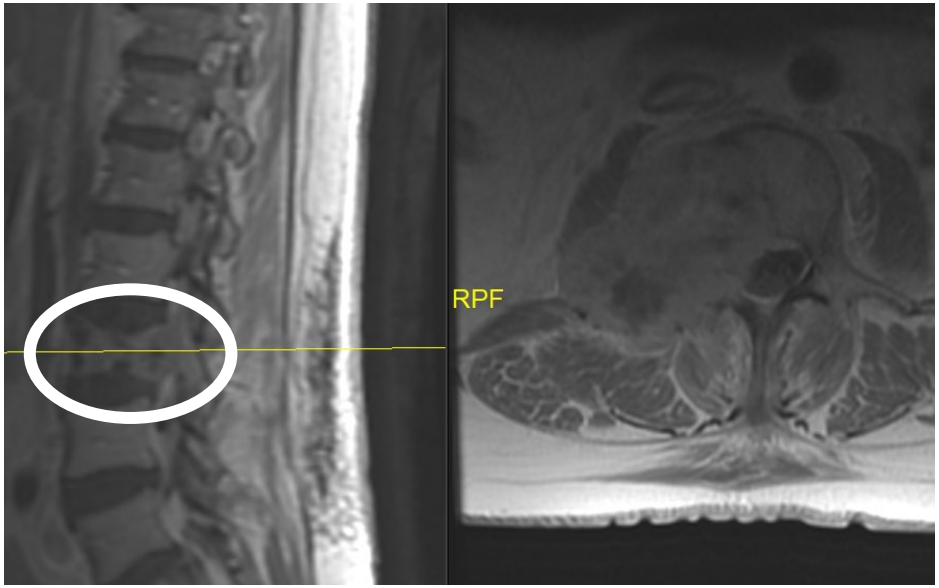
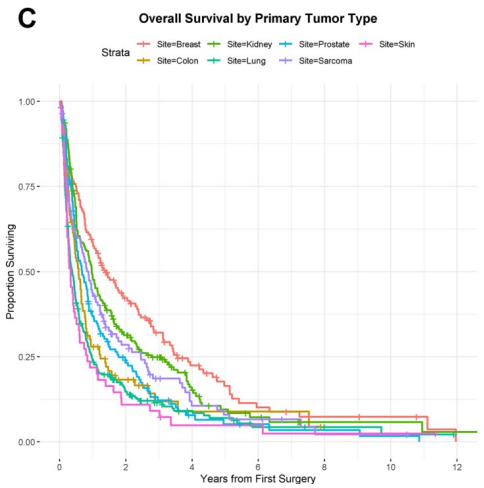
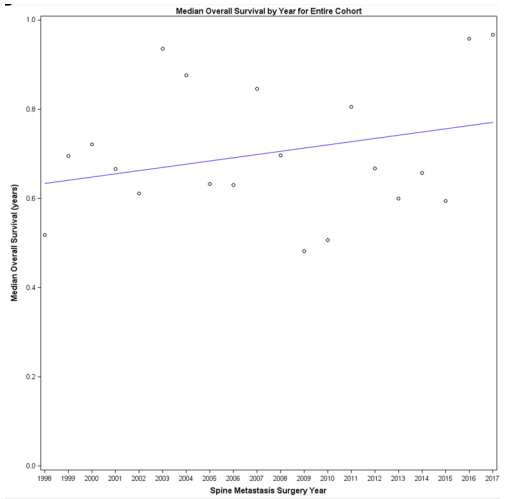
Metastatic Spine Tumors

- 20% of cancer patients develop spine metastases
- Increased incidence of metastatic spine tumors:
  - MR/18FDG-PET imaging have improved detection.
  - Systemic treatments have improved patient survival
    - Different patterns of metastases: Prostate
    - Biologics/Checkpoint inhibitors
      - Visceral > Bone Responses
- Increased Survival

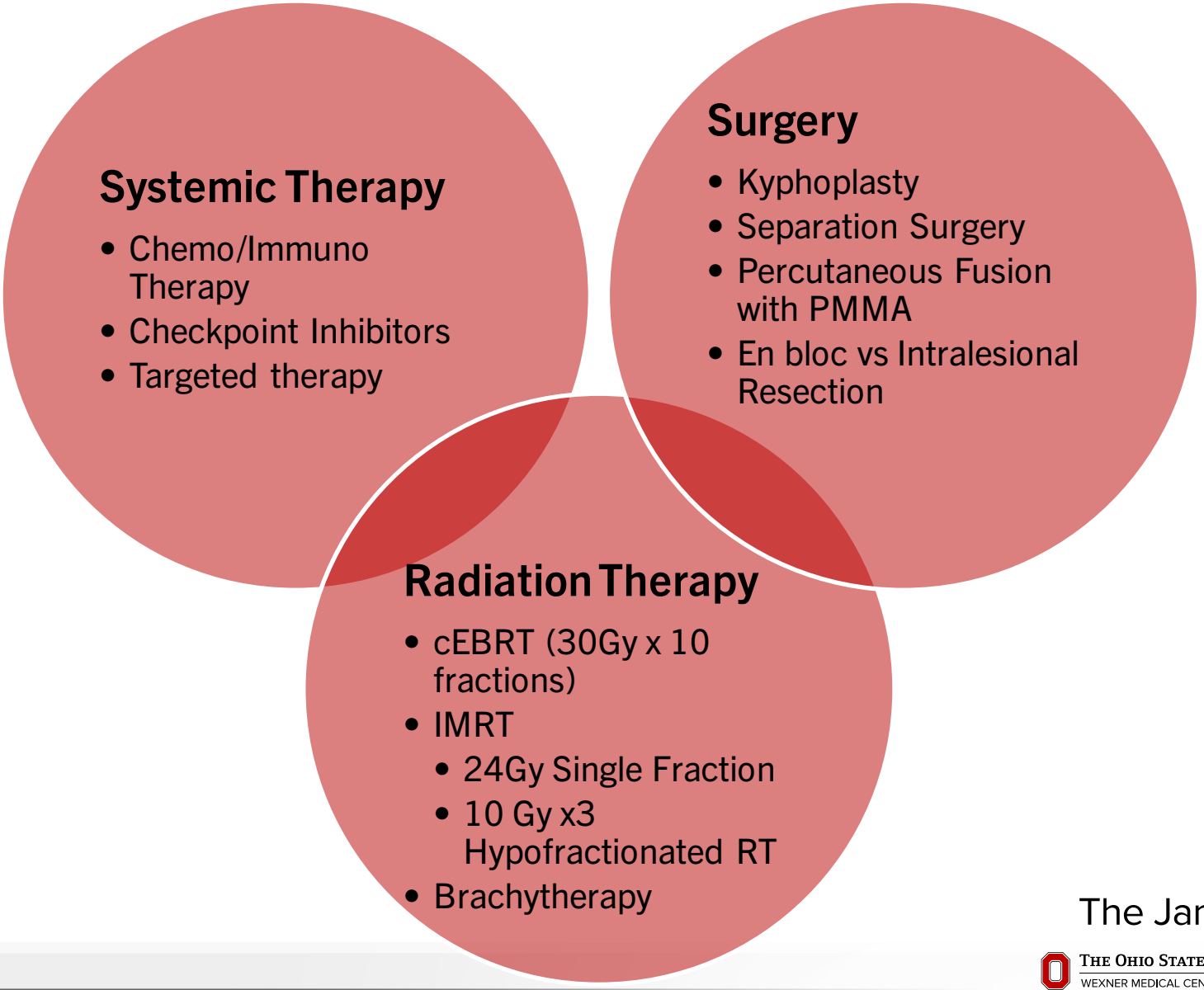






Cobb et al. JNS 1975
Walsh et al. Ann Thorac Surg 1997
Chohan et al. Neurosurgery 2017
Rothrock et al. Neurosurgery 2021

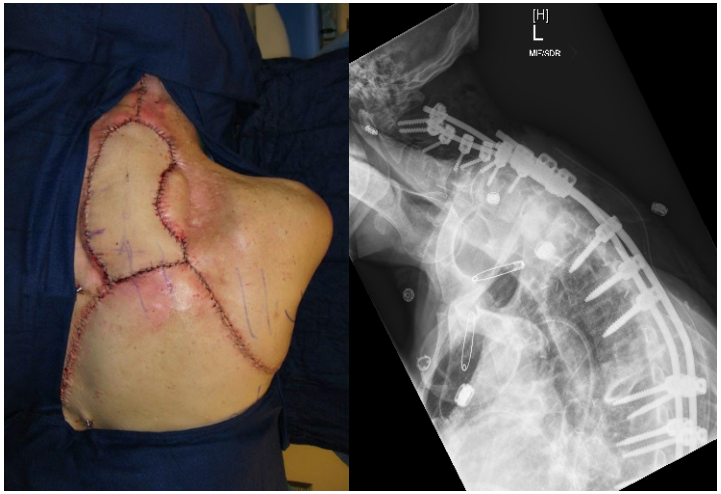
Multi-Disciplinary Approach



Multi-Disciplinary Approach

3 Months postop:
Separation Surgery + SRS

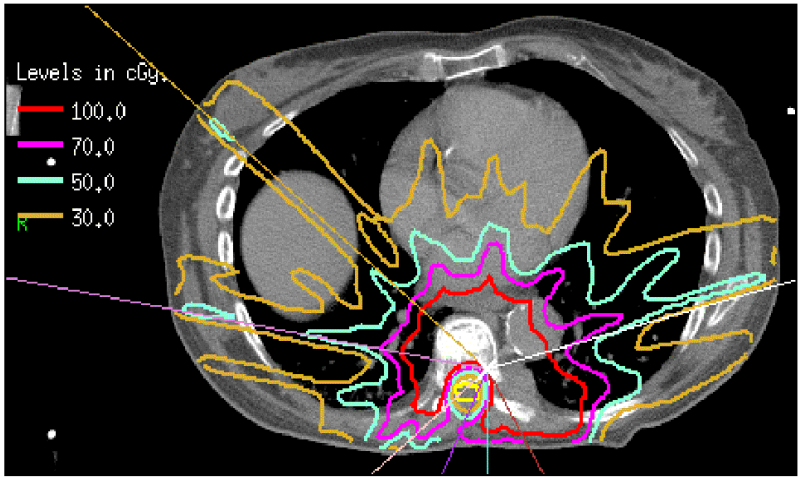
OR



NOMS Decision Framework

- **N**eurologic
- **O**ncologic
- **M**echanical Stability
- **S**ystemic disease

- Systemic Therapy
- Radiation Therapy
- Surgery

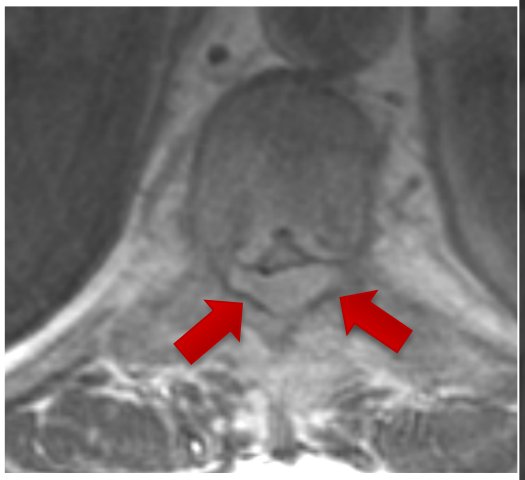


vs.

Bilsky et al. North American Clinics Heme/Onc. 2006
Laufer et.al. Oncologist 2013
Laufer et al. JNS Spine 2019

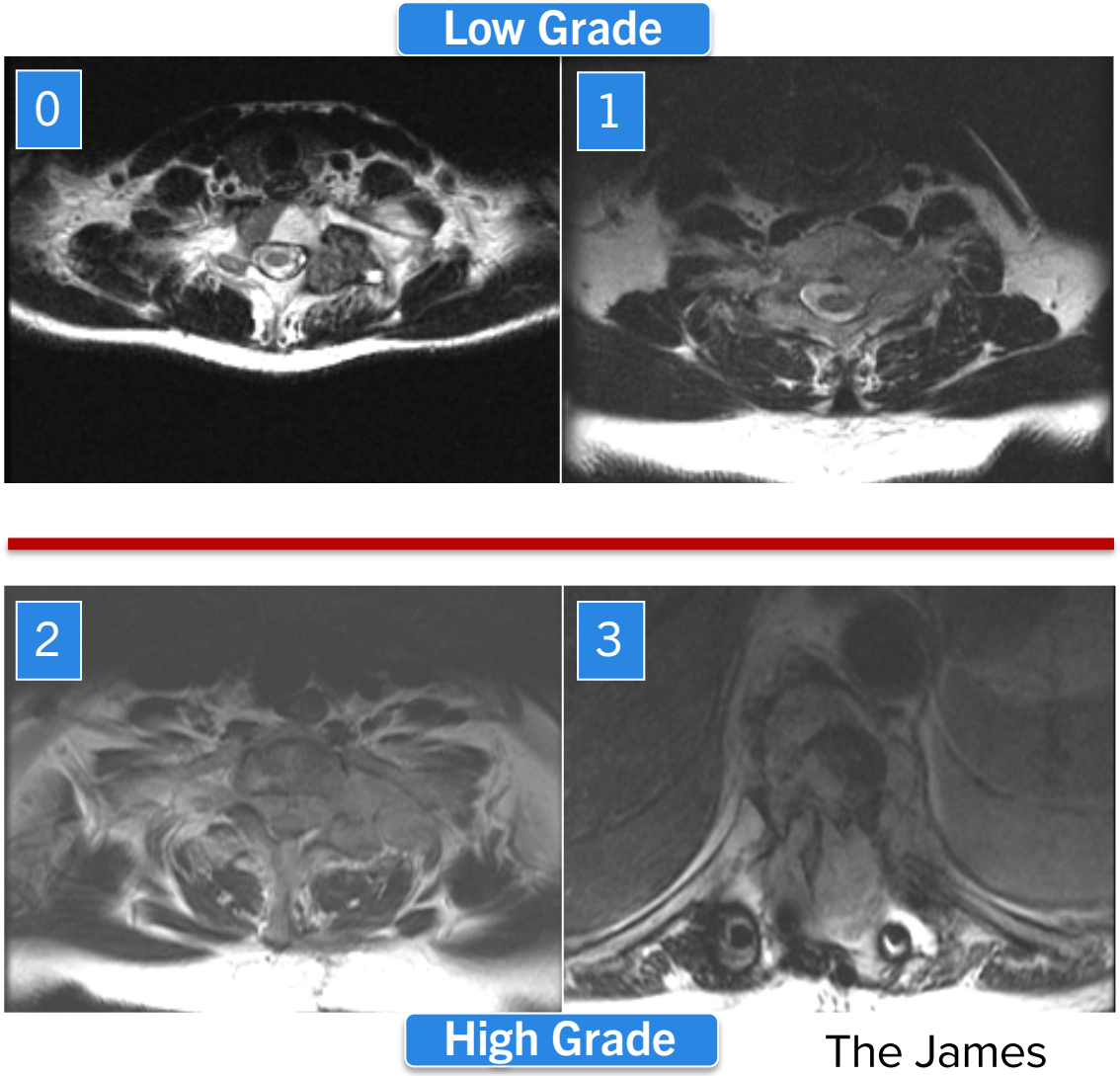
NOMS Decision Framework

- Neurologic
  - Myelopathy/Radiculopathy
  - Degree of ESCC
- Oncologic
  - Radiation Sensitivity
    - cEBRT/SRS
    - Role for Brachytherapy
- Mechanical Instability
  - SINS criteria
    - Kyphoplasty/vertebroplasty
    - Percutaneous Instrumentation
    - Open surgery
- Systemic Disease/Co-morbidities
  - Biologics/Checkpoint inhibitors
  - Survival Nomograms
  - Ablative Radiation



N: Degree of ESCC

- Neurologic
  - Myelopathy
  - Radiculopathy
  - Degree of Epidural Spinal Cord Compression
  - 0: Bone-only disease
  - 1: Epidural extension without cord compression
    - A, B, C
  - 2: SCC with CSF visible around cord
  - 3: SCC, no CSF visible around cord



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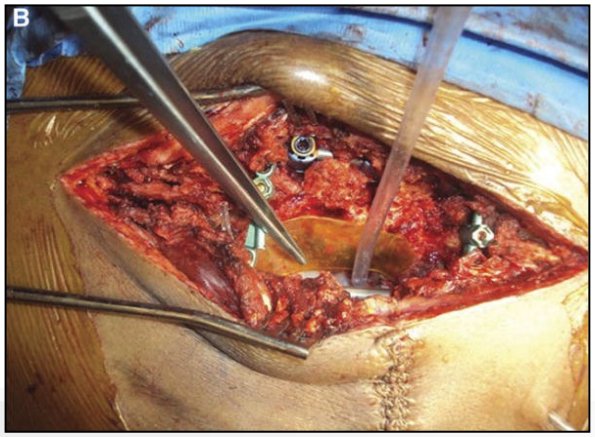
Timing of Treatment: ESCC with Myelopathy

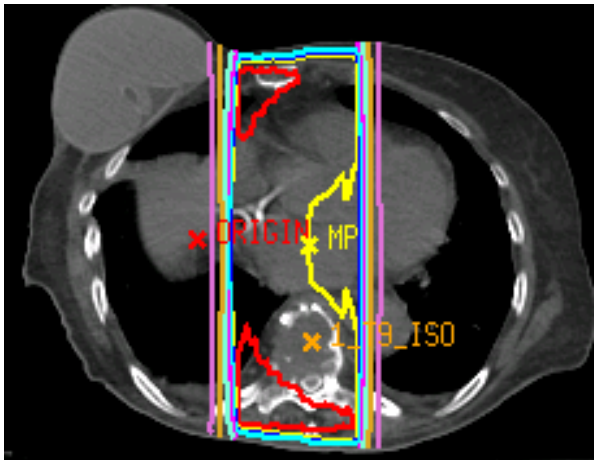
- High-dose steroids
- Subtle myelopathy
  - Decline precipitously
  - Pathophysiology
    - Tumor progression
    - Vascular (rare)
- Goal: Surgery ASAP
  - Systemic/Medical work-up
    - DVT/PE
    - Embolization (RCC)
    - R/O high risk of mortality

NOMS Decision Framework

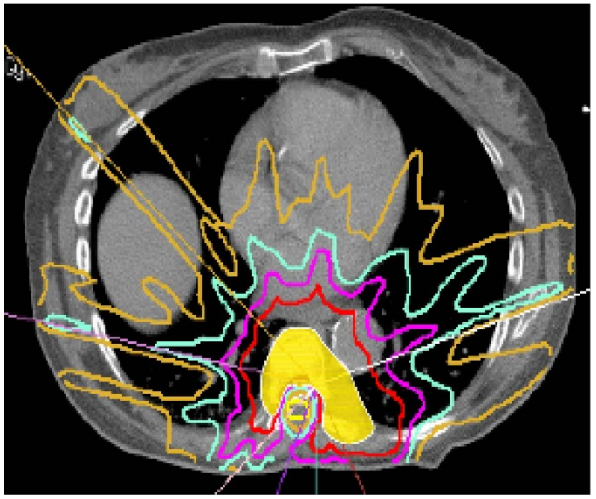
- Neurologic
  - Myelopathy/Radiculopathy
  - Degree of ESCC
- Oncologic
  - Radiation Sensitivity
    - cEBRT
    - SRS
    - Role for Brachytherapy
      - Recurrence/treatment failure



cEBRT

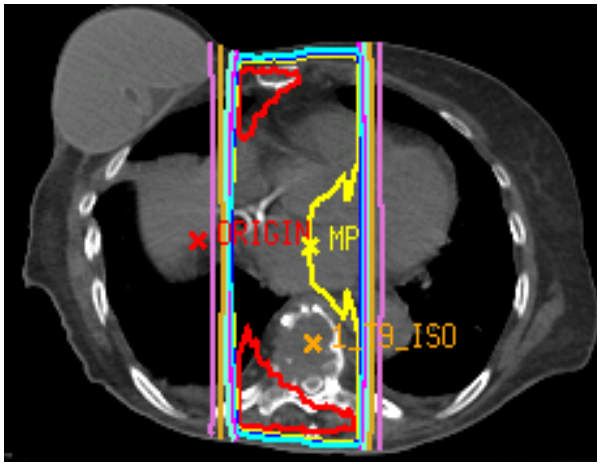


SRS



NOMS: Oncologic (RT)

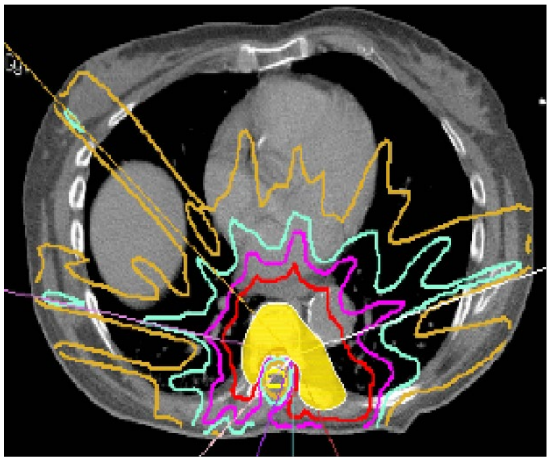
cEBRT



- 4 Field Technique: AP, PA, L Lateral, R Lateral
- Irradiation of large volumes of tissue: skin, soft tissue, bowel
  - Full dose to spinal cord

✓ **More fractions: larger treatment field**

SRS



- High precision
- 3D imaging
- Single Fraction (16-24 Gy) vs Hypofractionation

✓ **Preservation of healthy tissue**

✓ **Cytotoxic tumoral dose**

O: Radiation Sensitivity

	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

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

Gerszten et al. Spine 2009
Maranzano et al. IJROBP 1995
Mizumoto et al. IJROBP 2011

O: Radiation Sensitivity

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

Median Response Duration **11 months**

2y LCR **86%**

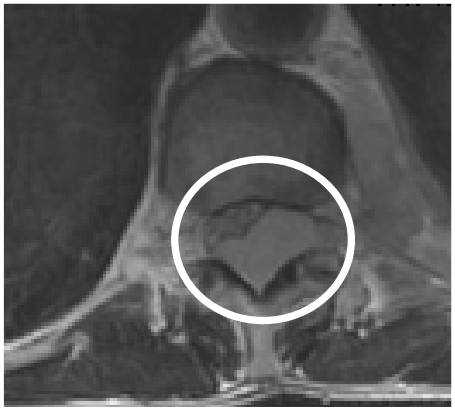
Median Response Duration **3 months**

2y LCR **30%**

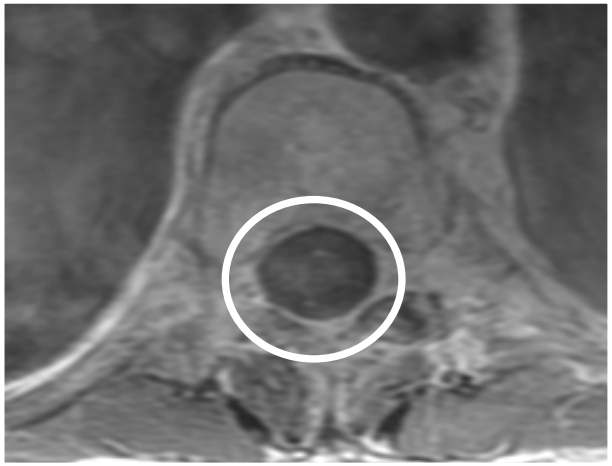
Responses: F-Favorable, I-Intermediate, U-Unfavorable

Gerszten et al. Spine 2009
Maranzano et al. IJROBP 1995
Mizumoto et al. IJROBP 2011

Multiple Myeloma



3 Gy x 10



NOMS Decision Framework

- **Mechanical Instability**
  - **SINS criteria**
    - **Kyphoplasty/vertebroplasty**
    - **Percutaneous instrumentation**
    - **Separation Surgery (Open/MIS)**

SINS
0-6: stable
7-12: potentially unstable
>13: unstable

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	3 2 1 0
Pain	Yes* Non-mechanical pain No	3 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 0
Alignment	Subluxation De novo deformity Normal	4 2 0
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	3 2 1 0
Posterior elements	Bilateral Unilateral None	3 1 0

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Fisher et al. Spine 2010

SINS Case Examples

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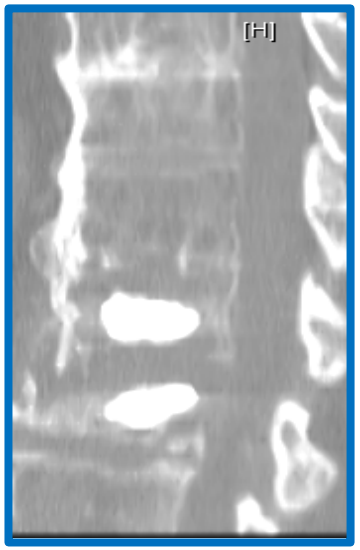
SINS Example: Lumbar

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	3 2 1 0
Pain	Yes* Non-mechanical pain No	3 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 0
Alignment	Subluxation De novo deformity Normal	4 2 0
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	3 2 1 0
Posterior elements	Bilateral Unilateral None	3 1 0

SINS: 10
Potentially Unstable



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CAncer Patient Fracture Evaluation (CAFE) Study

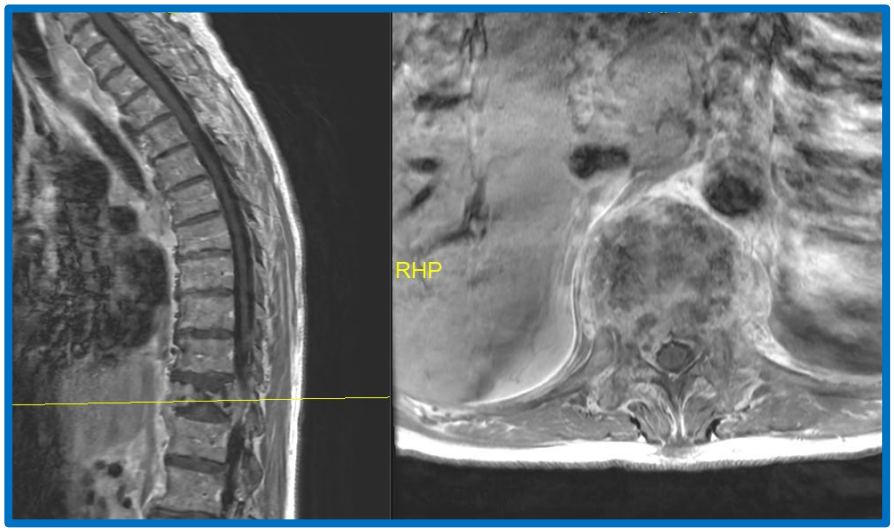
- **134 Patients randomized to kyphoplasty vs. non-surgical management**
  - *Crossover*
  - **73% (38/52) NSM patients that completed the 1-month evaluation eventually crossed over to Kyphoplasty**
  - **55% (21/38) of the patients crossed over within 1 week after their 1-month visit**

- **Outcomes**
  - **Improvements seen at 1-month post-Kyphoplasty were generally maintained through the final 12-month assessment for:**
  - **Back pain 7.3 to 3.5**
  - **Back-specific function**
  - **Quality of life**

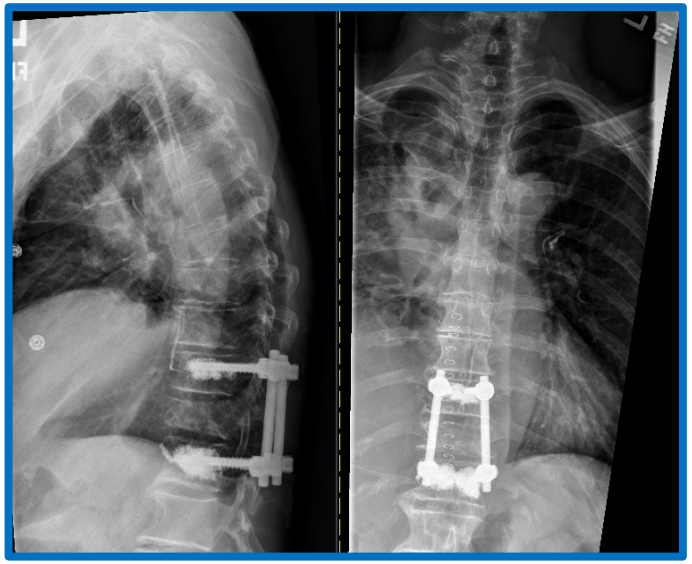
Berenson et al. Lancet Onc 2011

SINS Example: Lumbar

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	(3) 2 1 0
Pain	Yes* Non-mechanical pain No	(3) 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 (0)
Alignment	Subluxation De novo deformity Normal	4 2 (0)
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	(3) 2 1 0
Posterior elements	Bilateral Unilateral None	(3) 1 0



SINS: 15
Unstable



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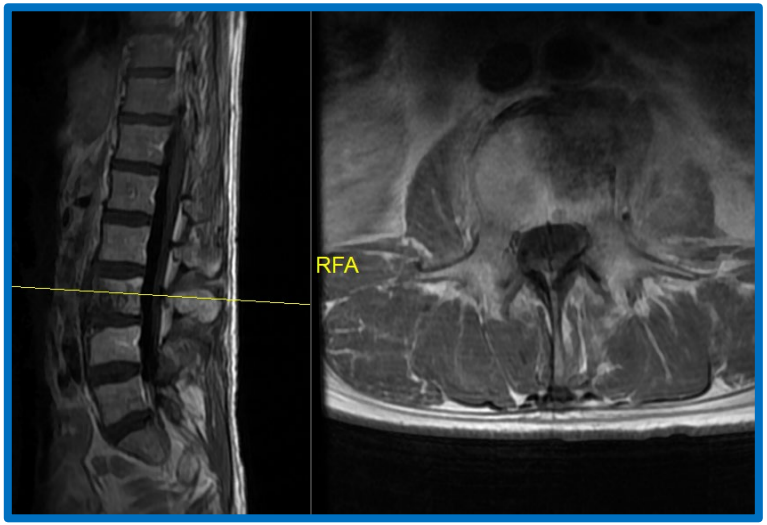
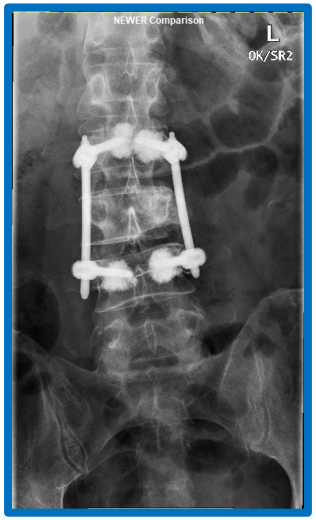
Moussazadeh et al. Spine J 2015
Fisher CG, et.al. Spine 35(22):e 1221-9, 2010

SINS Example: Mechanical Radiculopathy

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	3 2 1 0
Pain	Yes* Non-mechanical pain No	3 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 0
Alignment	Subluxation De novo deformity Normal	4 2 0
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	3 2 1 0
Posterior elements	Bilateral Unilateral None	3 1 0



SINS: 10
Potentially Unstable



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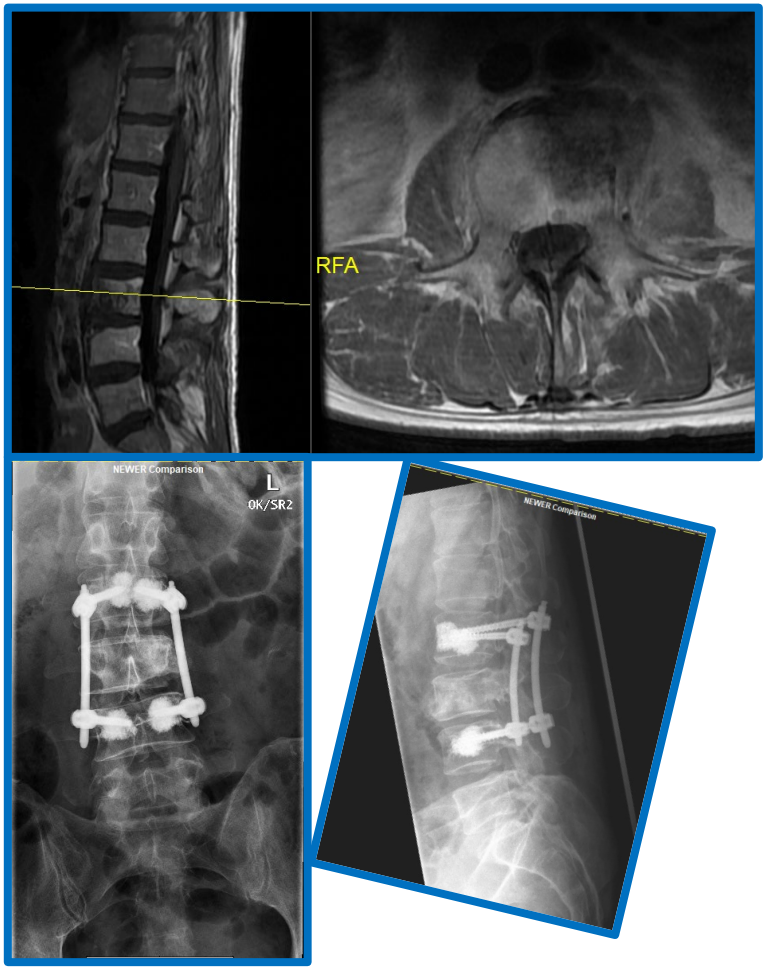
Mechanical Radiculopathy

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	3 2 1 0
Pain	Yes* Non-mechanical pain No	3 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 0
Alignment	Subluxation De novo deformity Normal	4 2 0
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	3 2 1 0
Posterior elements	Bilateral Unilateral None	3 1 0

SINS: 10

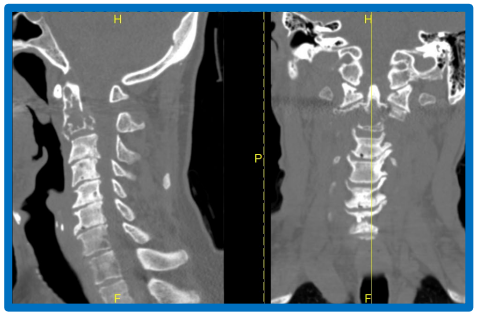


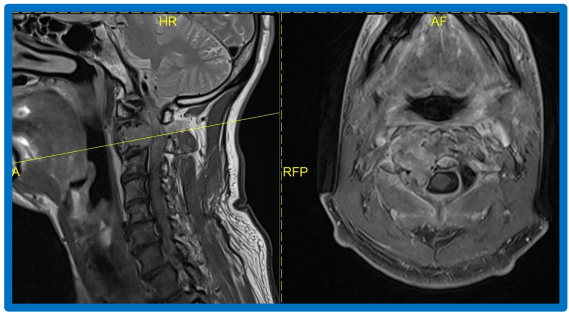
- **55 patients operated for mechanical radiculopathy**
  - **VAS: Preop 8 -> Postop 2**
  - **Pain: 98% improved**
  - **ECOG: 41.5% improved**

Moliterno et al. Spine J 2014

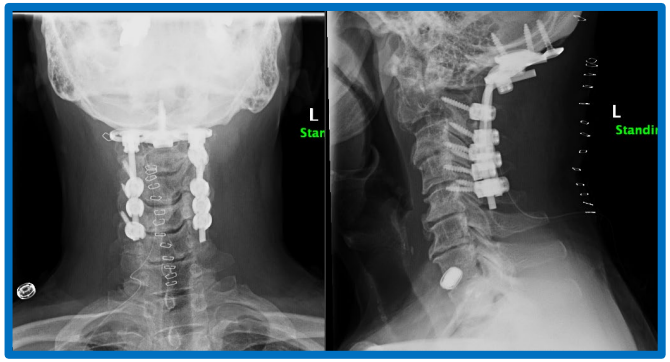
SINS Example: OC

Component	Description	Score
Location	Junctional Mobile (C3-6, L2-4) Semirigid (T3-10) Rigid (S2-5)	3 2 1 0
Pain	Yes* Non-mechanical pain No	3 1 0
Bone Lesion	Lytic Mixed Blastic	2 1 0
Alignment	Subluxation De novo deformity Normal	4 2 0
Vertebral Body	>50% collapse <50% collapse >50% VB involved None of above	3 2 1 0
Posterior elements	Bilateral Unilateral None	3 1 0





SINS: 16 Unstable



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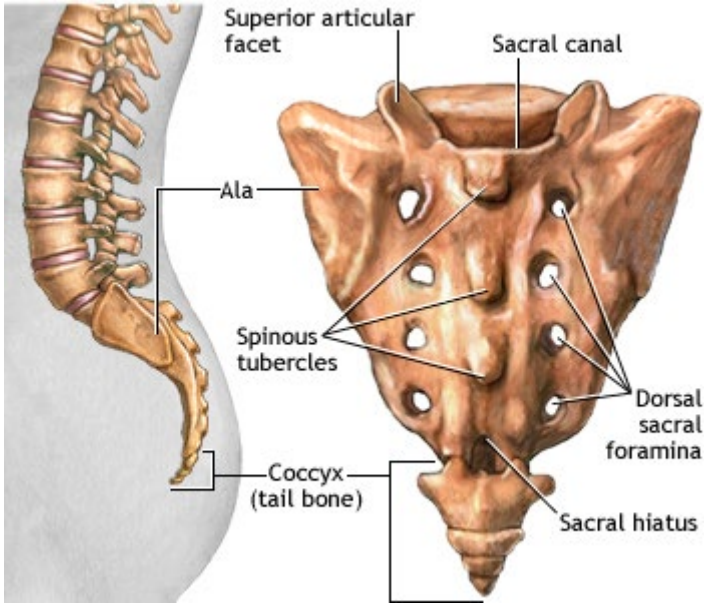
Sacral Metastasis

- Incidence: 1-7%, Rare
- Signify advanced disease
- Sacrum: projects posteriorly and forms the lumbosacral angle
  - Articulation at this angle is subject to shearing forces
- Presentation:
  - Pain
  - Pathologic Fracture
  - Nerve root compression
  - Decreased ambulation
  - Bowel or bladder incontinence



Mika et al. JBJS Reviews 2018
Williams et al. J Ortho Trauma 2016

Sacral Metastases: Sacroplasty

- Often treated with RT given high dose tolerance of cauda equina
- Without instability: Sacroplasty
  - 25 Symptomatic Tumor Associated Sacra Insufficiency Fractures
    - 31 Percutaneous Sacroplasties
    - 80% reduction in VAS @ 6.5 months (8.8 to 4.7)
    - 6/13 with ambulatory impairment required fewer ambulatory aids
    - 18 cases of extravertebral cement with no clinical relevance

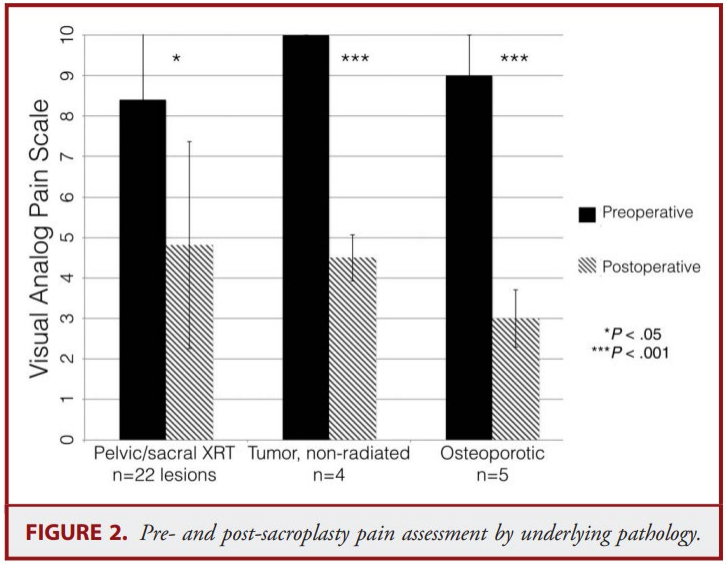
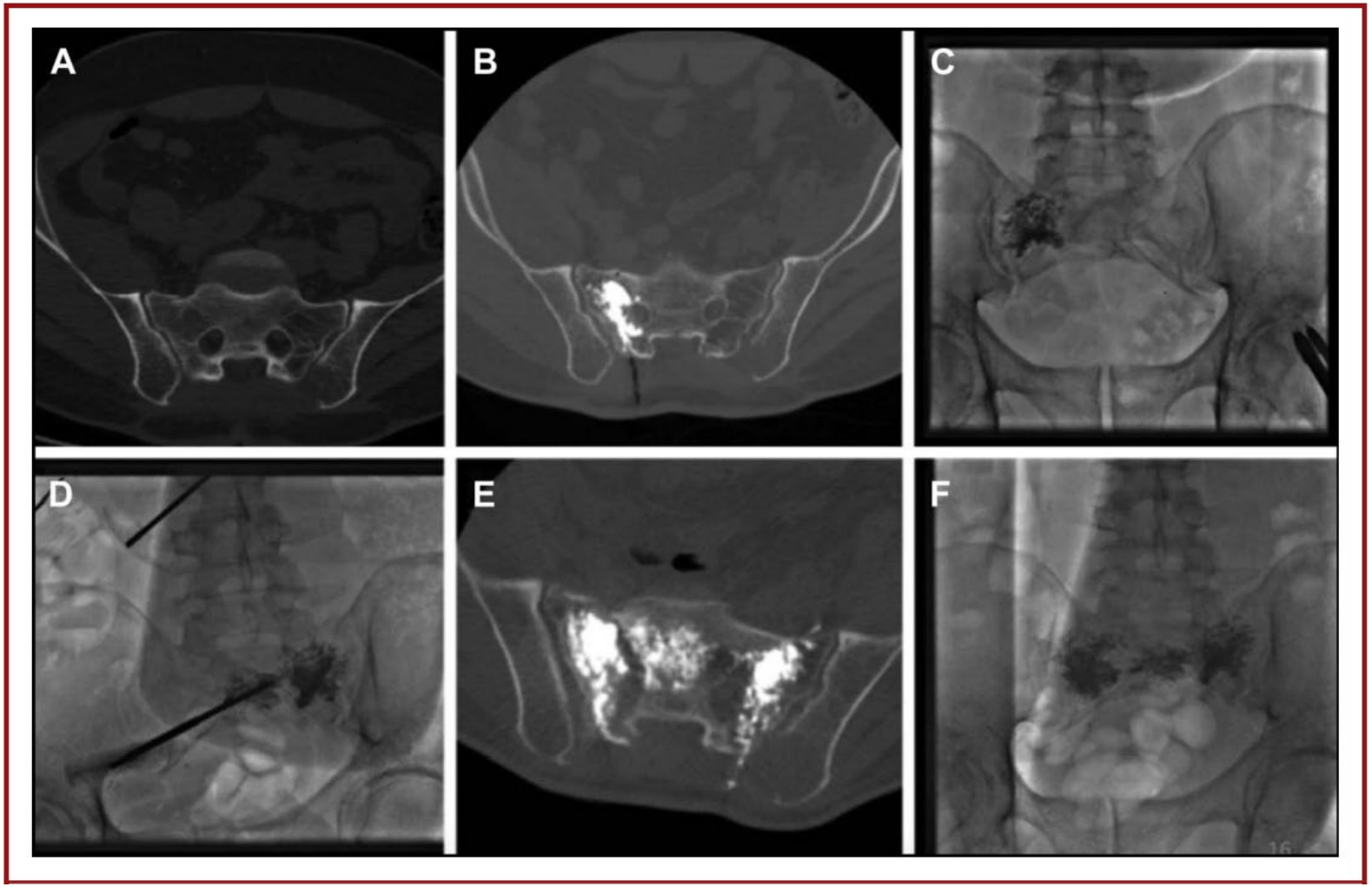


FIGURE 2. *Pre- and post-sacroplasty pain assessment by underlying pathology.*

Moussazadeh et al. Neurosurgery 2015

Sacroplasty



Moussazadeh et al. Neurosurgery 2015

Sacral Metastases: Surgical Options

- Sacral Decompression
- Percutaneous fixation of Sacral insufficiency fracture
- Charest-Morin et al: Surgery + RT (8) vs RT alone (15)
  - Improvements in HRQOL and pain following both treatments

Table 5 Bowel and bladder function per sacral treatment

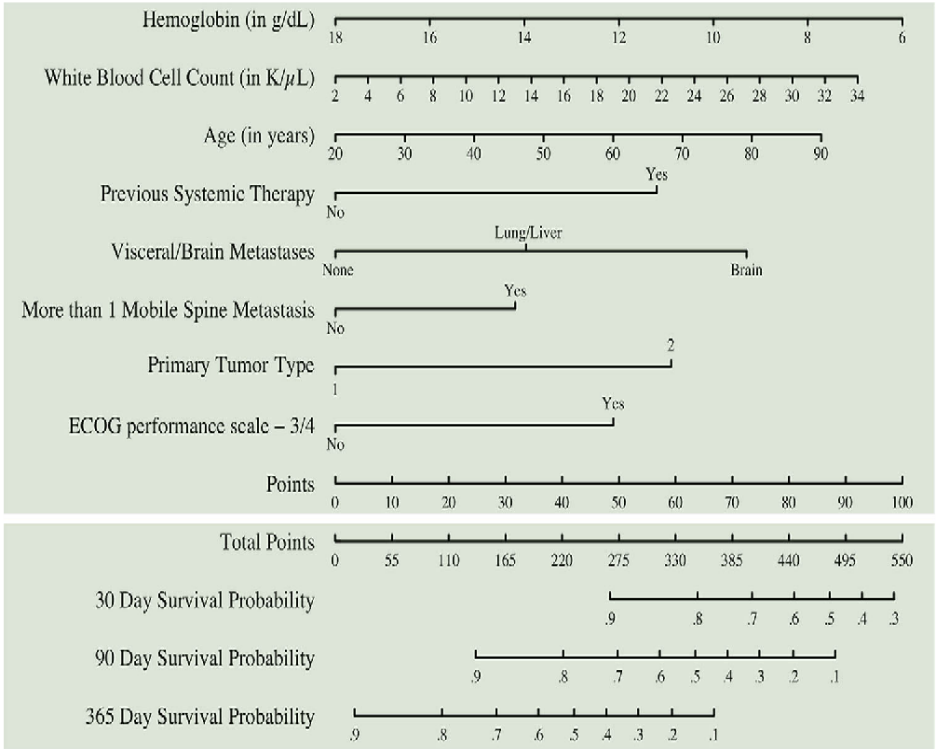
Treatment	Bowel and bladder function	Baseline (%)	6 weeks (%)	3 months (%)	6 months (%)
Surgery (+/– radiotherapy)	n	8	7	4	2
	Normal function	6 (75.0)	7 (100.0)	3 (75.0)	2 (100.0)
	Partial loss	2 (25.0)	0 (0)	1 (25.0)	0 (0)
	Complete	0 (0)	0 (0)	0 (0)	0 (0)
Radiotherapy	n	15	14	12	9
	Normal function	14 (93.3)	14 (100.0)	11 (91.7)	9 (100.0)
	Partial loss	1 (6.7)	0 (0)	1 (8.3)	0 (0)
	Complete	0 (0)	0 (0)	0 (0)	0 (0)
All patients	n	23	21	16	11
	Normal function	20 (87.0)	21 (100.0)	14 (87.5)	11 (100.0)
	Partial loss	3 (13.0)	0 (0)	2 (12.5)	0 (0)
	Complete	0 (0)	0 (0)	0 (0)	0 (0)

Charest-Morin et al. Ann of Translational Medicine 2019

NOMS Decision Framework

- **Systemic Disease/Co-morbidities**
  - **Extent of systemic metastatic tumor burden**
  - **Medical comorbidities**

SORG Nomogram

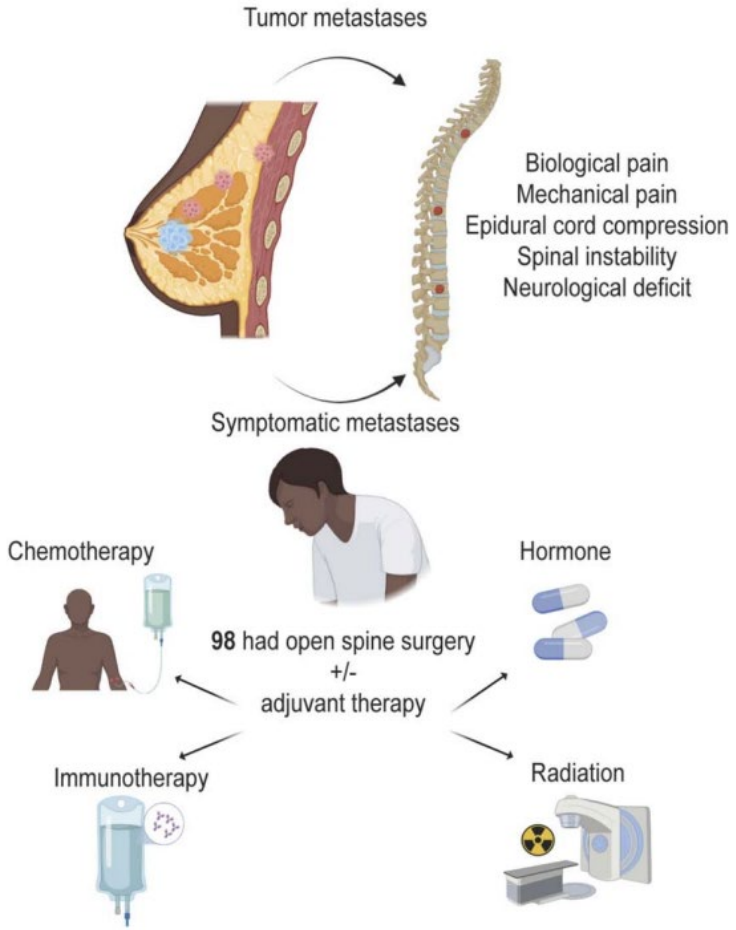


NESMS Score

Parameter		NESMS Points
Modified Bauer Score components	Modified Bauer points	N/A
Primary tumor is NOT lung	1	N/A
Primary tumor is breast or kidney	1	N/A
Solitary skeletal metastasis	1	N/A
No visceral metastasis	1	N/A
Modified Bauer score		
≤2		0
≥3		2
Serum albumin		
<3.5 g/dL		0
≥3.5 g/dL		1
Ambulatory status*		
Non-ambulatory		0
Intact or impaired		1

Pereira et al. JCO 2017
Schoenfeld et al. The Spine Journal 2015

One Step Further…



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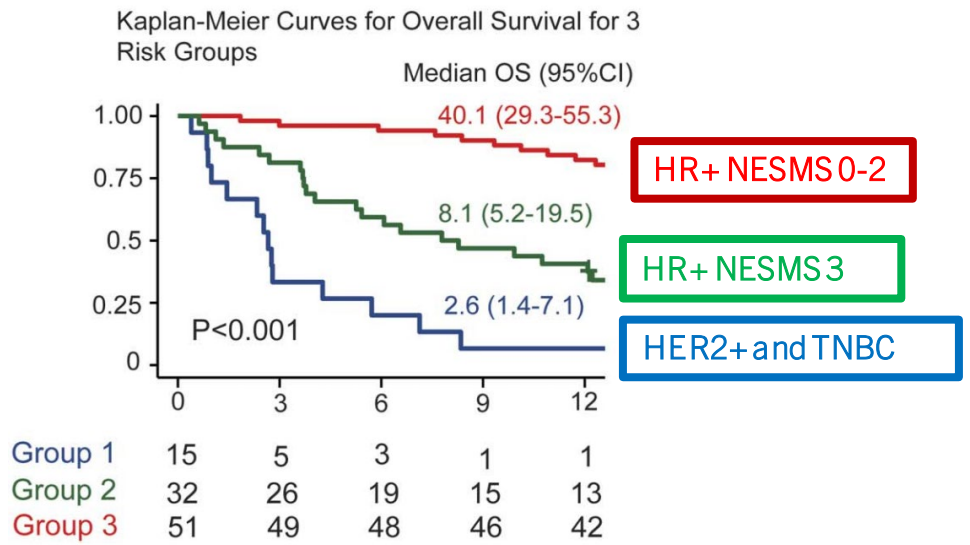

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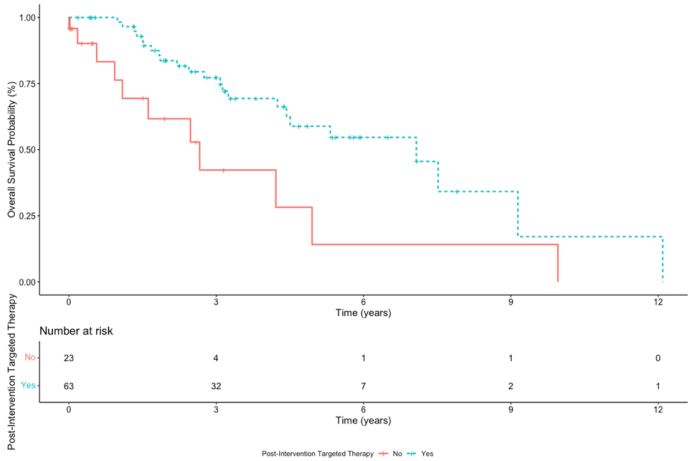
Duvall et al. Neurosurgery 2022

One Step Further…

- 131 Patients: Metastatic Breast Cancer with Spine Metastases
- Underwent Separation Surgery followed by RT (2010-2020)

- **PI3K:** most common gene mutation in patients undergoing surgery
  - Potential indicator of spine metastases

Prevalence of Somatic Gene Alterations		
Mutation	Prevalence	Prevalence of somatic gene alterations in metastatic breast cancer population
PI3K	73 (55.7%)	31 - 45 %
TP53	35 (26.7%)	29 - 37%
ESR1	27 (20.6%)	10 - 17%
FGFR	18 (13.7%)	10%
PTEN	10 (7.6%)	3 - 6%
CDH1	7 (5%)	7 - 9%
GATA	8 (6%)	11 - 15%



Rabah et al. Neurosurgery 2022
Litton et al NEJM 2018
Lawrence et al. Nature 2014

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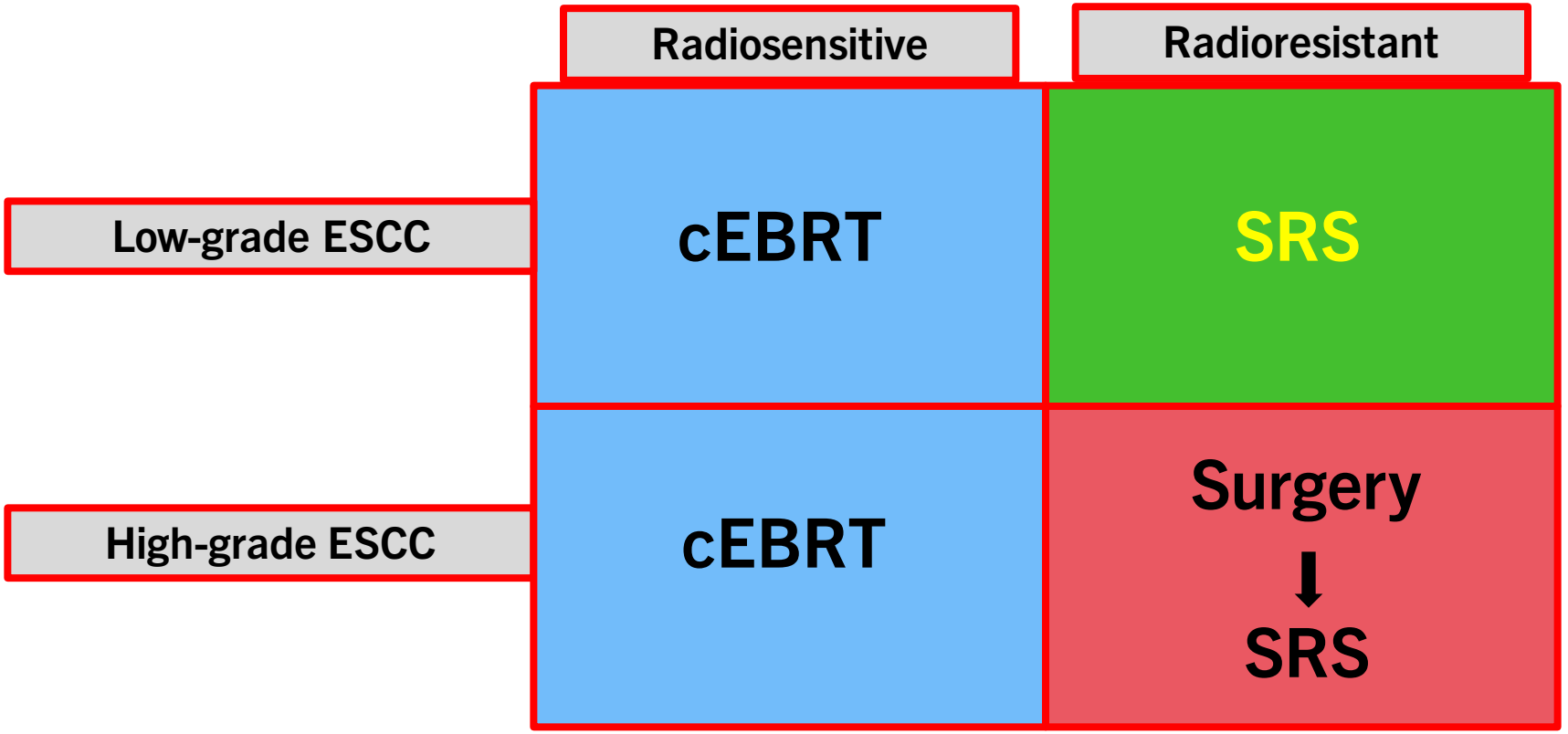
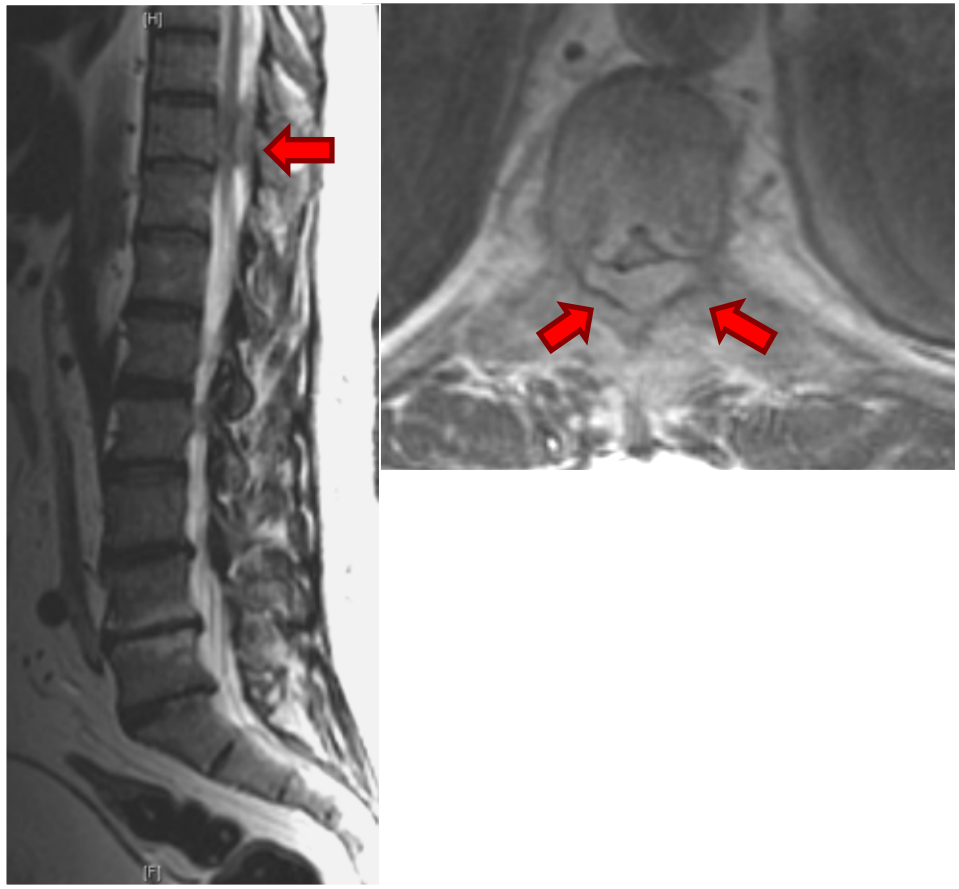
NOMS Simplified



Case Example

- Neurologic
  - Myelopathy: ASIA C
  - Functional Radiculopathy
  - ESCC: 3
- Oncologic
  - Tumor Histology: Lymphoma
  - Radiation or Chemosensitivity: RT-sensitive cEBRT
- Mechanical Stability: Stable
- Systemic Disease and Medical Co-morbidity: NC



High-dose steroids
cEBRT (30 Gy in 10 fractions)

SRS Outcomes and Complications

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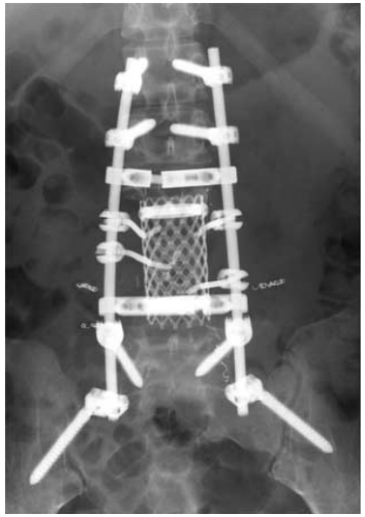
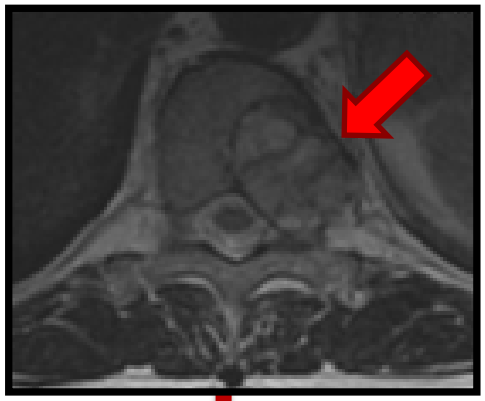
Solitary RCC Metastasis: En bloc vs. SRS

Tomita Score: 4
En bloc resection

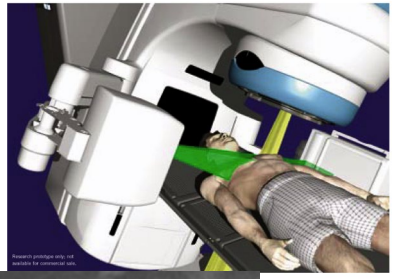


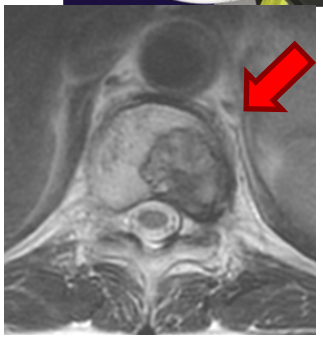
Operative Time 15.5 hours
Mean EBL 5120 mL



T10 Solitary
RCC Metastasis

SRS





Treatment time: 20 minutes
No blood loss; 98% control

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Kawahara et al. Spine 2010
Yamada et al. JNS Focus 2017

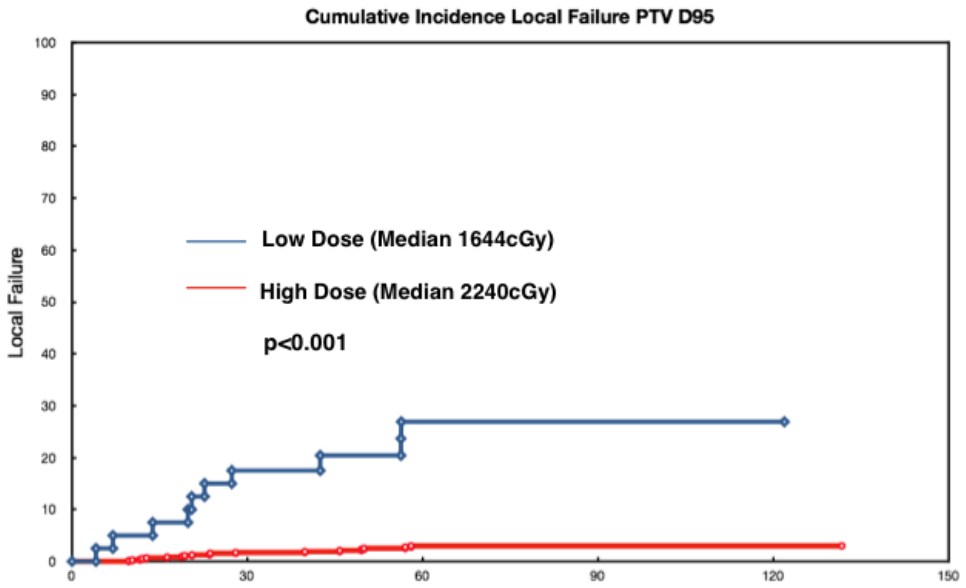
SRS Outcomes: Dose Matters

- –811 tumors
  - –82% Radioresistant
  - –RCC, Sarcoma, Thyroid
- –ESCC 0-1c
- –Median f/u: 26.9 months

- •Prescription Dose: 18-26 Gy SF

- •PTV D95 (Median)
  - –Low Dose: 1644cGy
  - –High dose: 2240 cGy

- •Local Failure: 28 tumors (3.4%)
  - •Significant
    - –Low Dose SRS
  - • Not significant
    - –Histology/Tumor Volume



Incidence of Local Failure			
	Low Dose	High Dose	p-value
12 mos.	5%	0.41%	<0.001
24 mos.	15%	1.6%	<0.001
48 mos.	20%	**2.1%**	<0.001

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Yamada et al. JNS Focus 2017

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SRS Outcomes: Dose Matters

–811 tumors
  –82% Radioresistant
  –RCC, Sarcoma, Thyroid
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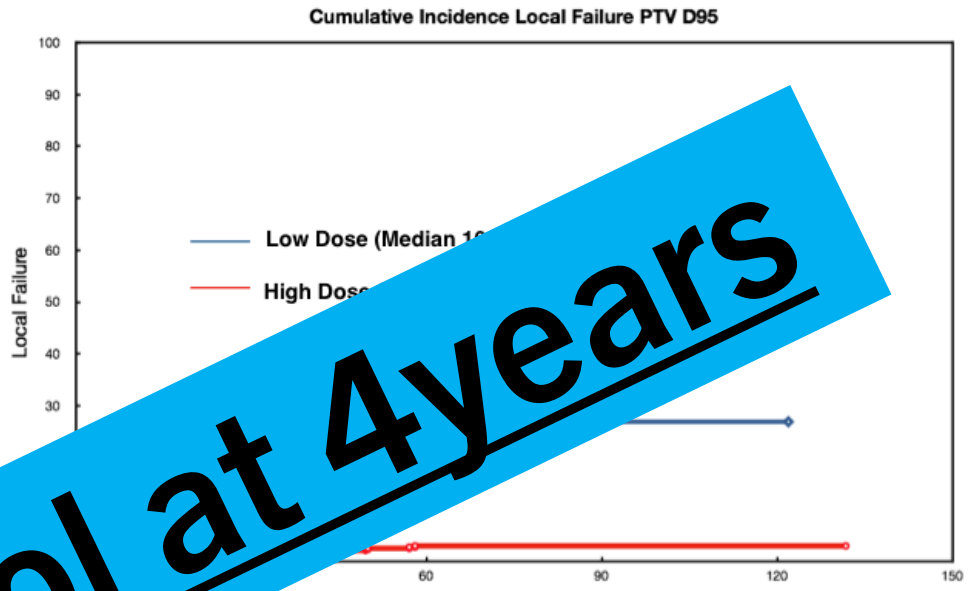

98% Control at 4years

Incidence of Local Failure			
	Low Dose	High Dose	p-value
12 mos.	5%	0.41%	<0.001
24 mos.	15%	1.6%	<0.001
48 mos.	20%	**2.1%**	<0.001

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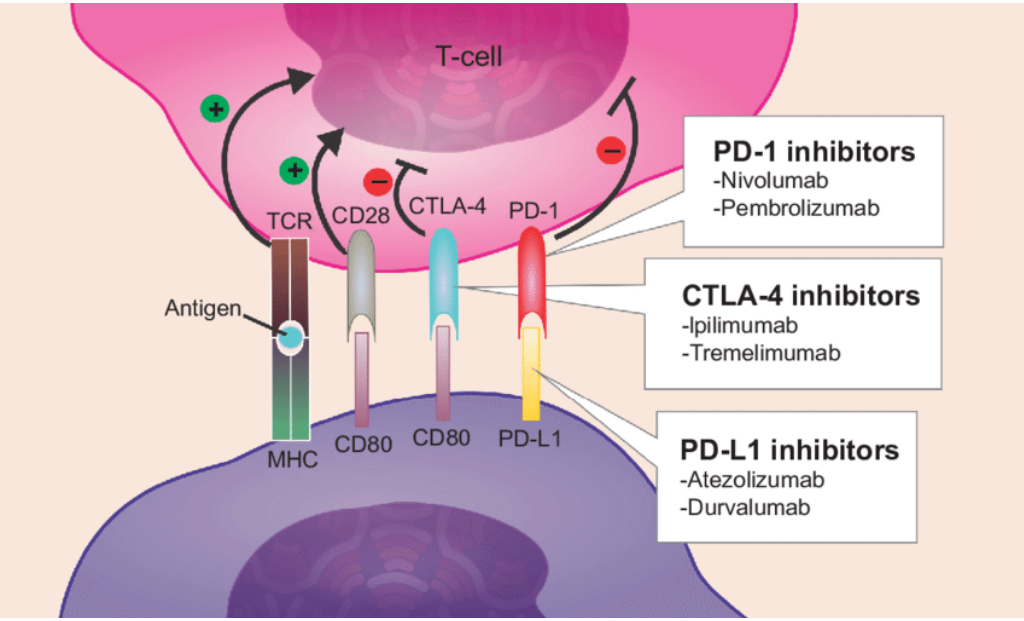
Yamada et al. JNS Focus 2017

Checkpoint Blockade Immunotherapy

- Adding Checkpoint Blockade Immunotherapy to RT
  - Anti-Tumor T-cells can be reprogrammed/activated by the appropriate stimulus
  - Radiosensitizing Immunotherapy: Impact on locoregional control
  - Abscopal Effect: Impact on Systemic or distant control

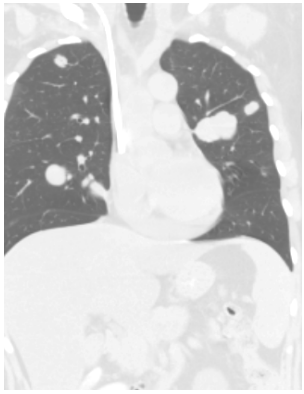


Andrade de Mello et al. OncoTargets and Therapy 2016
Sharabi et al. Lancet Onc 2015

Abscopal Effect

- 1953: **Ab** (Away) and **Scopos** (Target for shooting at)
- Ability of localized radiation to initiate an antitumor response that kills cancer cells distant to the primary target
- Radiation induced activation of immune system
  - Induced release of cytokines and chemokines --> inflammatory tumor microenvironment
- Use of immune checkpoint inhibitors: Ipilimumab, Pembrolizumab

Ipilimumab



SRS

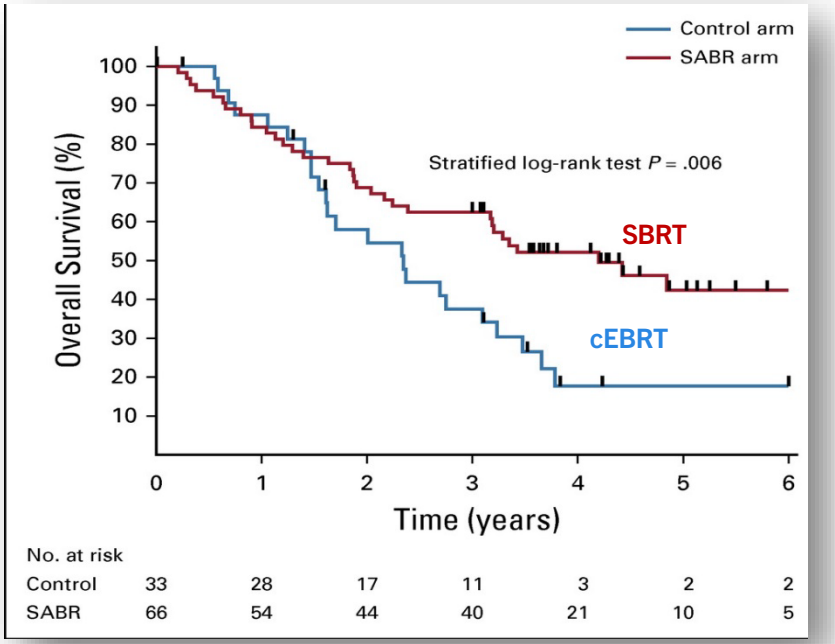
Abscopal Effect

Treatment of Oligometastatic Disease

- **SABR-COMET Trial**
  - Standard of Care vs SABR to 1-5 oligometastases
  - 99 Patients, median follow-up 51 months
  - Improved Median overall survival (50 vs 28 months)
  - Improved 5-year OS (42.3% vs 17.7%)
  - Improved median PFS and 5-year PFS

  ➢ 22-month median OS benefit in patients with a controlled primary tumor and 1-5 oligometastases

Treatment of 1-5 oligometastatic disease matters

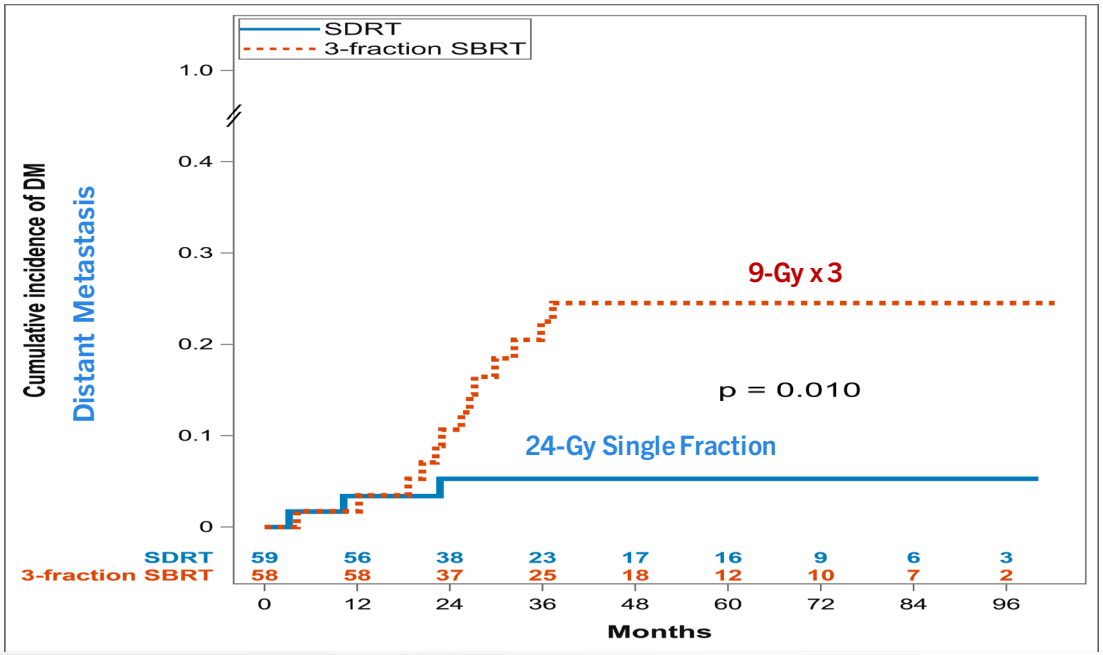


Palma et al. JCO 2020
Zelefsky et al. IJROBP 2021

Treatment of Oligometastatic Disease

Dose Matters

- **PISA Trial**
  - **117 patients**
  - **24 Gy vs 3x9Gy**
  - **24 Gy Single Fraction: improved local control of irradiated oligometastases**
    - **Reduced distant metastases**



Palma et al. JCO 2020
Zelefsky et al. IJROBP 2021

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Treatment of Oligometastatic Disease

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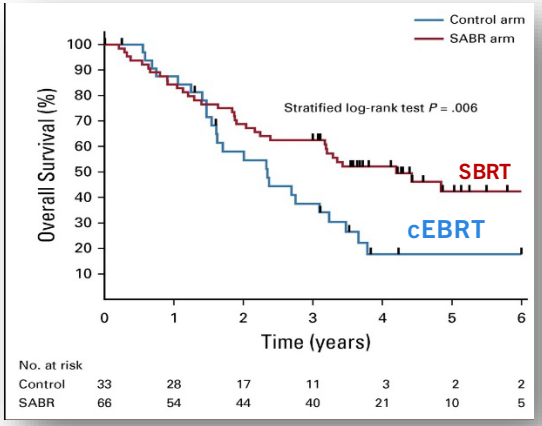
  - 117 pati…
  - 24… …y
  - …ingle Fraction: superior local …ntrol of irradiated oligometastases
    - Reduced metastatic progression

Treatment of 1-5 oligometastatic disease matters

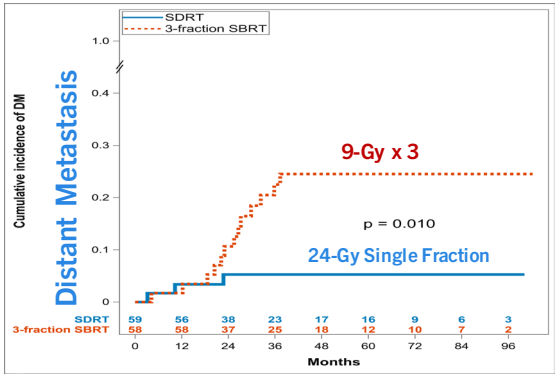
Dose Matters

Oligometastatic Disease

SABR-COMET trial



PISA trial



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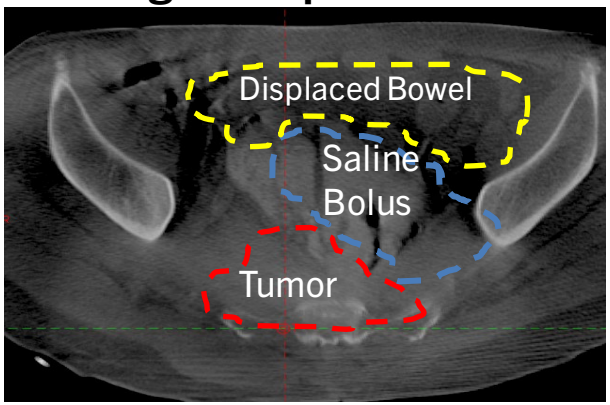
Palma et al. JCO 2020
Zelefsky et al. IJROBP 2021

Organs at Risk: Dose Constraints

Organ Displacement



OAR Toxicity			
OAR	**Dose Constraint**	**Toxicity Grade**	**% Risk**
Skin	Dmax 26 Gy	1-2	5%
Vertebral Body	16-24 Gy 24 Gy	VB Fx Symptomatic	4-40% 7.2%
Esophagus	15 Gy to 2.0 cc 14 Gy to 2.5 cc	≥3	6.8% 0.1%
Kidney	V10 Gy/33% vol.	N/A	0%
Nerve Root/Plexus	24 Gy	≥3	4%
Spinal Cord	Dmax 14 Gy	Myelitis	0.42%

Rose et al. J Clin Oncol 2009
Jawad et al. JNS Spine 2016
Virk et al. JNS Focus 2017
Cox et al. IJROBP 2012
Stubblefield et al. JNS Focus 2017
Sahgal et al. IJROBP 2013
Yamada et al. JNS Focus 2017

SRS Complications

- **Vertebral Compression Fracture**
  - 7.8% (compared to 3% for cEBRT)
  - Risk Factors
    - Pre-existing VCF
    - Lytic tumor type
    - Spinal deformity
  - Risk of VCF decreases as dose per fraction decreased
- **Radiation Myelopathy**
  - 0.4% incidence
  - Late complication, patients may not live long enough to manifest
- **Acute Pain Flare**
- **Esophageal Toxicity**

Huo et al. Surgical Neurology Int 2016

Separation Surgery

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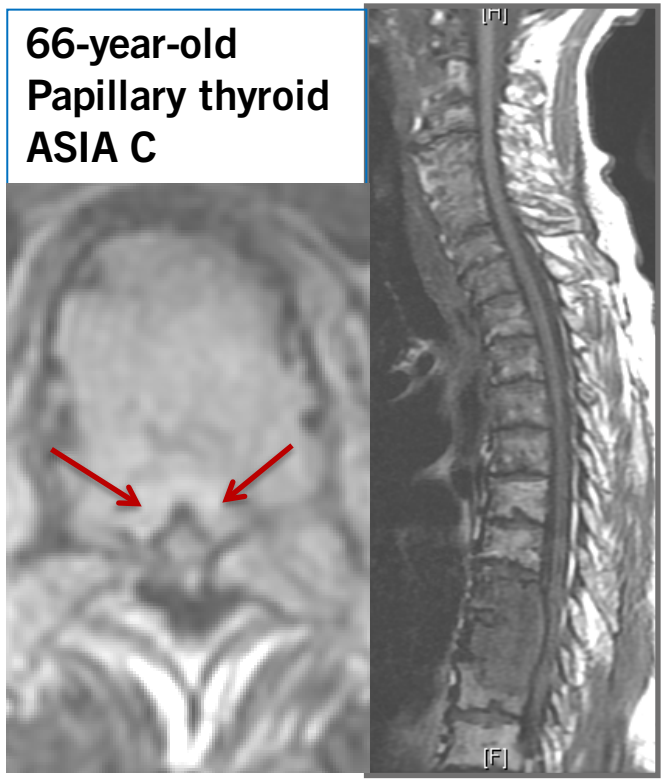
Surgical Goals

- **Palliative**
  - **Preserve Neurologic function**
  - **Local tumor control**
  - **Mechanical stability**
  - **Pain relief**
  - **Improve quality of life**

Separation Surgery + SRS

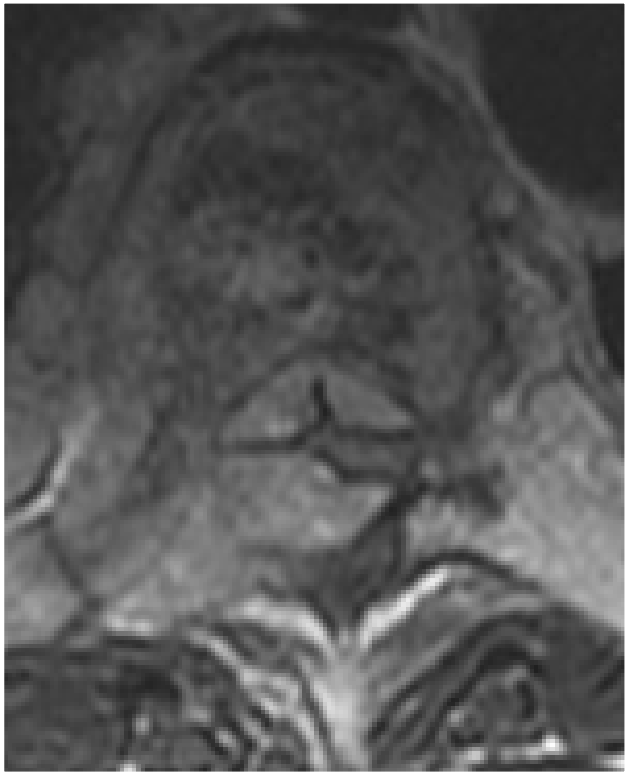
- **Neurologic**
  - Spinal cord decompression
- **Oncologic: Radiation Response**
  - cEBRT: Maximal cytoreduction
    - GTR/en bloc
  - SRS: Reconstitute the thecal sac, target for radiation
    - Separation Surgery
- **Mechanical Stability**
  - Pedicle screw fixation and rods

66-year-old
Papillary thyroid
ASIA C



Surgery for High-Grade ESCC

- Patchell Study
- Prospective randomized trial
- Solid tumors
- HG-ESCC with myelopathy
- Surgery + cEBRT vs. cEBRT alone
- Exclusion criteria
  - RT-sensitive tumors
    - Hematologic Malignancies and GCT
  - Multi-level disease
  - Systemic contraindications to surgery



Patchell et al. Lancet 2005

Surgery for High-Grade ESCC

	Surgery	Radiation	Significance
Overall Ambulation	84% (42/50)	57% (29/51)	**p=.001**
Duration	122 days	13 days	**p=.003**
Recover Ambulation	62% (10/16)	19% (3/16)	**p=.012**
Continence	155 days	17 days	**p=.016**
Narcotics (MSO4)	.4 mg	4-8 mg	**p=.002**
Survival Time	**126 days**	**100 days**	**p=.033**

Bilsky et al. Spine 2009

Surgery + cEBRT, Germany

- 101 patients/106 metastases
- Surgical Approach:
  - Posterolateral: 79%
  - Anterior: 12%
  - Combined Anterior/Posterior: 9%
  - Partial (48%) or Complete Resection (43%): 91%
- Adjuvant Treatment (cEBRT): 100%

- Local Control: 40% @ 6 months
  30% @ 1 year
  4% @ 4 years

- Significant Predictors of Recurrence:
  - Ambulation, Tumor Histology, Completeness of Resection

Klekamp et al. Acta Neurochir (Wien) 1998

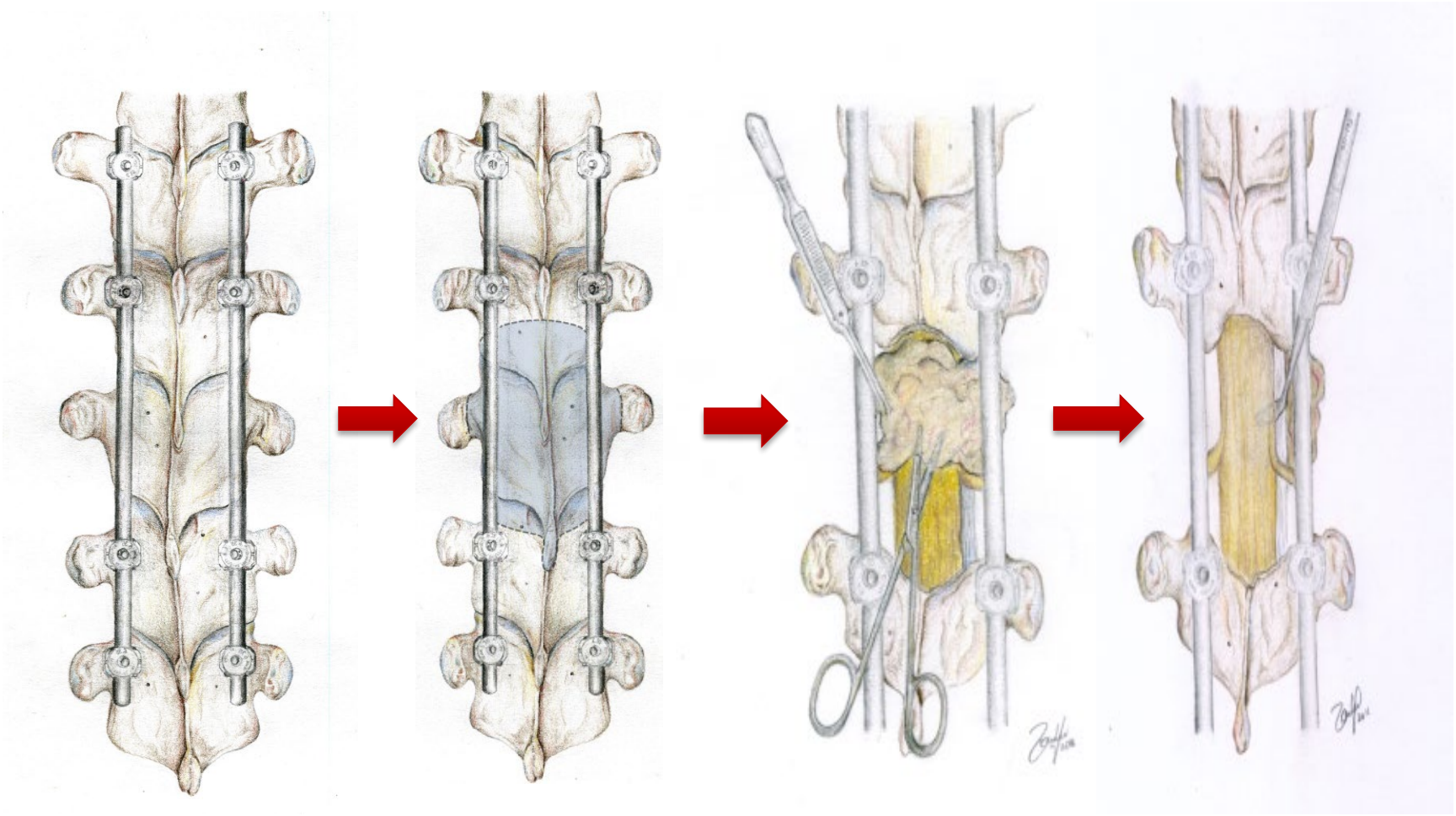
AO Recommendation

- **Clinicians might surgically debulk asymptomatic high grade epidural disease before SBRT to optimize local control**
- **High-grade spinal cord compression due to solid tumor malignancy undergo:**

Surgical decompression and Stabilization followed by RT

(What Kind of Surgery and What Kind of Radiation?)

Separation Surgery



Illustrations by Ran Xu, MD

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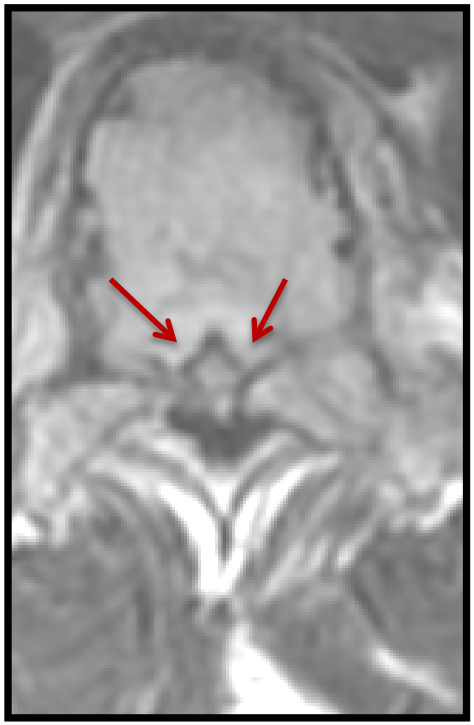
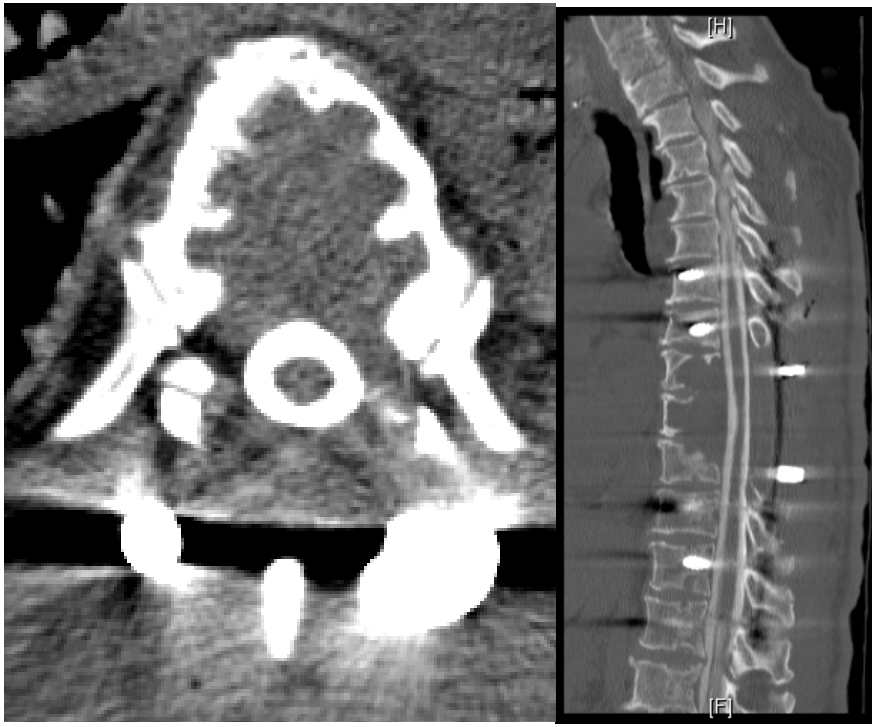
Separation Surgery

MRI: Pre-decompression

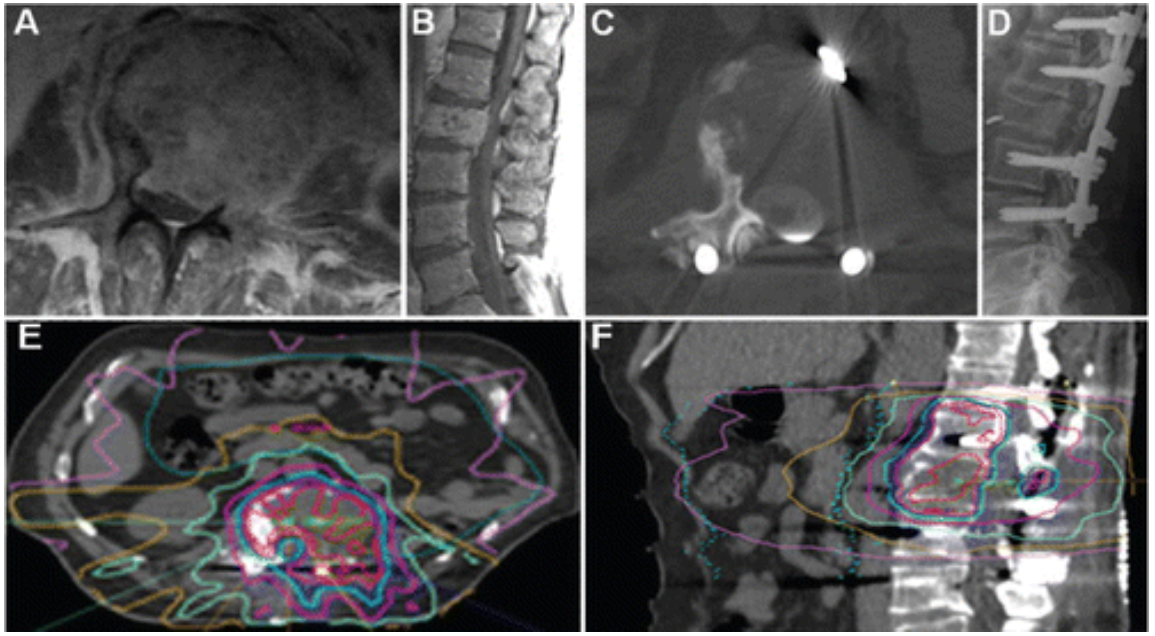


Separation Surgery

CT Myelogram: Post-decompression



Separation Surgery + SRS



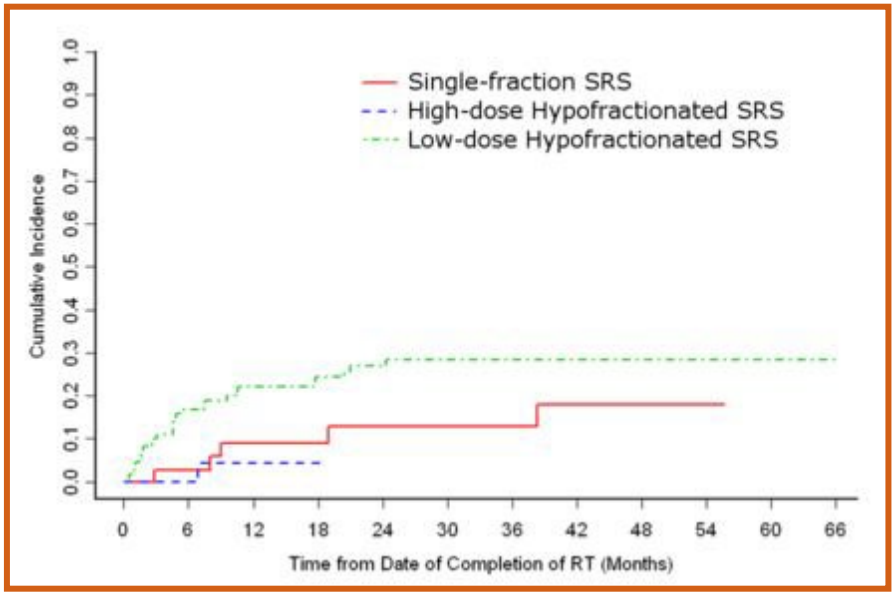
- 186 patients
- 2002-2011
- 7.6 months median f/u
- Tumor Presentation:
  - ESCC 2 or 3: 73%
  - RT-resistant: 77%
  - Failed prior RT: 49%
- SRS strategies:
  - Single Fraction SRS: 24Gy
  - High-Dose Hypofractionated: 8-10Gy x 3
  - Low-Dose Hypofractionated: 6Gy x 5

Laufer et al. JNS Spine 2013

Separation Surgery + SRS

- 1-year overall recurrence
  - Total: 16.4%
    - Single-fraction SRS: 9.0%
    - High-dose hypofractionated: 4.1%*
    - Low-dose hypofractionated: 22.6%
- No neurologic complications
- No association:
  - Radioresistant tumor histologies
  - Previous radiation
  - Epidural extension

84% Local Control



Long Term Survivors

- Retrospective
- 88 patients; survived >2 years after surgery for symptomatic spinal metastases
- Durable tumor control can be achieved in long-term cancer survivors surgically treated for symptomatic spinal metastases with limited complications

- Return to OR: 23%
- Post-Treatment Progression: 10 cases
- 2 asymptomatic broken screws
- 8 cases of asymptomatic progressive kyphotic deformity

Return to OR	
Total cohort	20 (23)
Open surgery	
Early hardware failure	2 (2)
Delayed hardware failure	7 (8)
Tumor recurrence	5 (6)
Wound dehiscence	3 (3)
Epidural hematoma	1 (1)
MIS	
Delayed hardware failure	2 (2)

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Barzilai et al. JNS Spine 2019

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Hybrid Therapy: Patient Reported Outcomes

- PRO's Hybrid Therapy
  - 111 patients
  - Median f/u: 16.7 mos.

- BPI:
  - Worst pain
  - Pain right now
  - Combined BPI:
    - Pain severity
    - Pain interference with daily life
    - Overall pain experience

- MDASI (MD Anderson Symptom Inventory)
  - Spine pain severity
  - General activity
  - Increased nausea

Table 3 Brief Pain Inventory (BPI) and MD Anderson Symptom Inventory (MDASI) individual item results at baseline and 3-month follow-up (primary end point)

		Preoperative Survey				3-Month Postoperative Survey				
Survey	Individual Item	Mean Score	SD	N	%	Mean Score	SD	N	%	Wilcoxon matched pairs test *P* value
BPI	**Worst pain**	6.3	3.1	111	100	4.5	2.8	60	54	**< .0001**
	Least pain	2.7	2.5	111	100	1.6	1.8	61	55	.0072
	Average pain	4.3	2.6	111	100	3.1	2.1	61	55	.004
	Right now pain	3.8	2.9	111	100	2.4	2.2	62	56	**< .0001**
	General activity	5.4	3.8	110	99	3.7	3.2	62	56	.01
	Mood	4.1	3.6	109	98	3.2	2.8	60	54	.02
	Walking ability	4.7	3.6	109	98	3.5	2.9	61	55	.08
	Normal work	5.7	4	109	98	4.2	3.3	62	56	.04
	Relations	2.8	3.4	109	98	2.6	2.9	62	56	.95
	Sleep	4.1	3.6	110	99	3	2.8	60	54	.2
	Enjoyment of life	5.2	3.7	108	97	4	3.2	61	55	.01
	Relief	63.3%	27.7%	100	90	52.7%	32.7%	52	47	.06
MDASI	Pain	6.6	3.2	107	96	5	3.1	63	57	.06
	Fatigue	5.1	3.2	108	97	5.2	3.4	61	55	.56
	Nausea	1.2	2.4	106	95	2.2	2.7	62	56	**.0001**
	Sleep	4.3	3.7	108	97	3.7	3.2	60	54	.68
	Distress	4.3	3.7	105	95	3.2	3.1	61	55	.06
	Shortness of breath	1.7	2.6	108	97	2.1	2.8	62	56	.23
	Memory	1.5	2.3	108	97	2	2.6	62	56	.62
	Appetite	2.5	3	108	97	2.9	3	61	55	.02
	Drowsy	3.1	3.1	108	97	3.2	3	61	55	.13
	Dry mouth	3.1	3.4	108	97	3	3	61	55	.56
	Sadness	3.2	3.5	105	95	2.8	3	61	55	.69
	Vomiting	0.6	1.8	108	97	1	2	60	54	.007
	Numbness	3	3.4	107	96	2.9	3.2	62	56	.49
	Spine pain	4.6	3.8	104	94	2.6	3	60	54	**.0006**
	Limb weakness	3.2	3.6	105	95	3.2	3.2	60	55	.16
	Bowel/Bladder control	0.5	1.6	106	95	0.6	1.6	59	53	.84
	Bowel pattern	2.4	3.3	105	95	2.3	2.9	59	53	.23
	Sexual function	2.1	3.6	98	88	2.8	3.9	57	51	.81
	General activity	5.9	3.7	104	94	4	3.2	61	55	**.0002**
	Mood	4.2	3.4	103	93	3.3	2.8	61	55	.03
	Work	5.8	4	102	92	4.5	3.6	59	53	.04
	Relations	2.8	3.3	102	92	2.8	3	60	55	.97
	Walking	5.1	3.6	95	86	4	3.8	55	50	.18
	Enjoyment of life	5.2	3.7	104	94	4.1	3.5	61	55	.04

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Hybrid Therapy: Renal Cell Carcinoma

92% Local Control

- 90 Patients (median age: 62 years)
  - Median length of stay: 5 days; 87% discharged home
  - Major complication rate: 12%
  - Mean follow-up of 37 months for survivors: only 7 (7.8%)

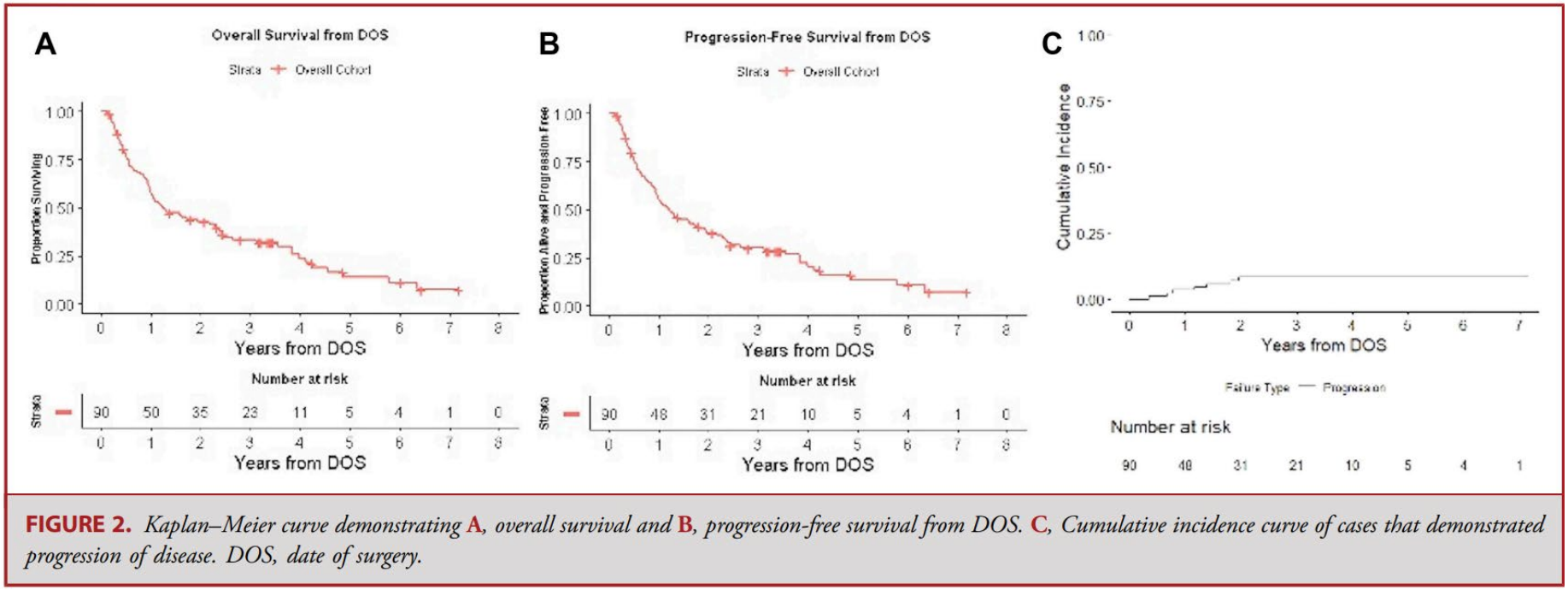

FIGURE 2. *Kaplan–Meier curve demonstrating* **A**, *overall survival and* **B**, *progression-free survival from DOS.* **C**, *Cumulative incidence curve of cases that demonstrated progression of disease. DOS, date of surgery.*

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Hussain et al. Neurosurgery 2022

Hybrid Therapy: Colorectal Carcinoma

87% Local Control @ 2 years

- 50 patients (median age: 55 years)
  -
  -
  -
  -

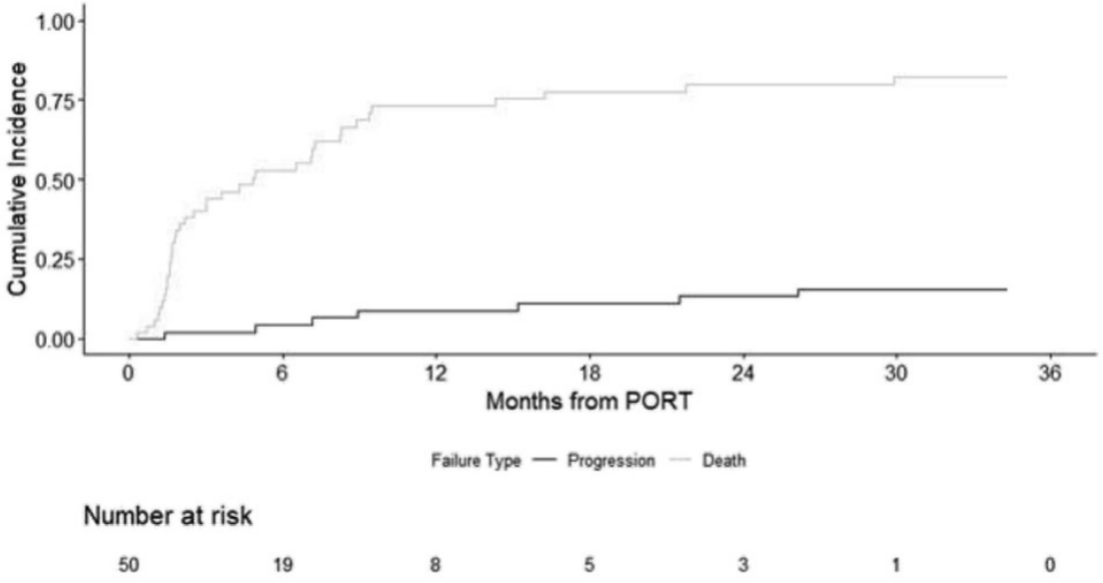

Figure 1. Cumulative incidence of tumor progression and death at time in months from radiotherapy. PORT, postoperative radiotherapy.

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Chakravarthy et al. World Neurosurgery 2022

Hybrid Therapy: Non-Small Cell Lung Cancer

95% Local Control @ 2 years

- 103 patients
  - Overall Survival
  - Progression: 5

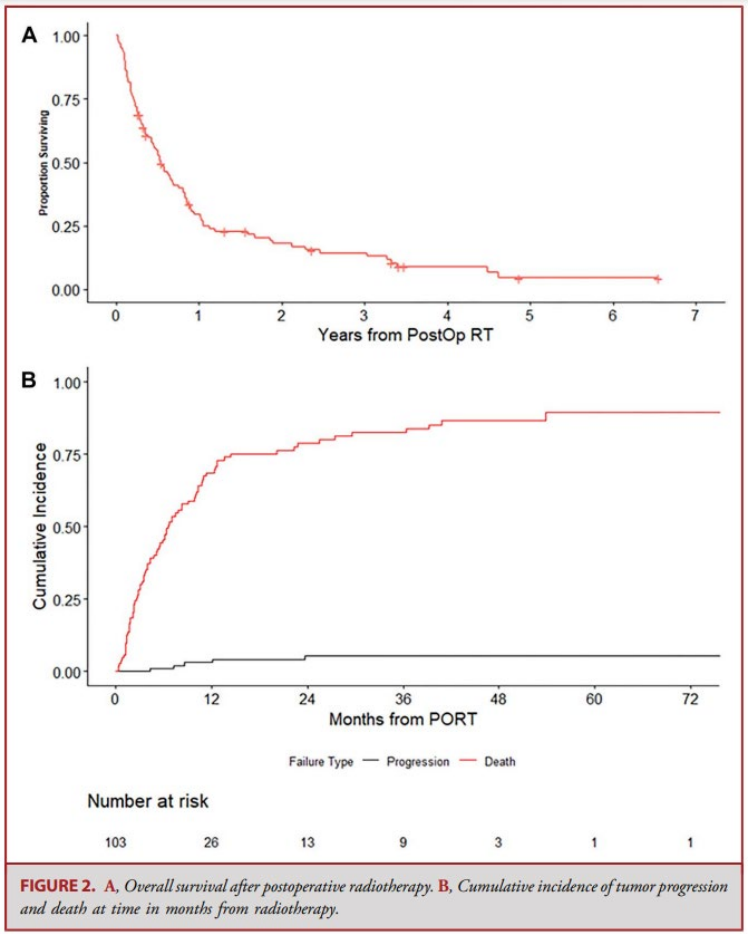

FIGURE 2. A, *Overall survival after postoperative radiotherapy.* B, *Cumulative incidence of tumor progression and death at time in months from radiotherapy.*

Chakravarthy et al. Neurosurgery 2022

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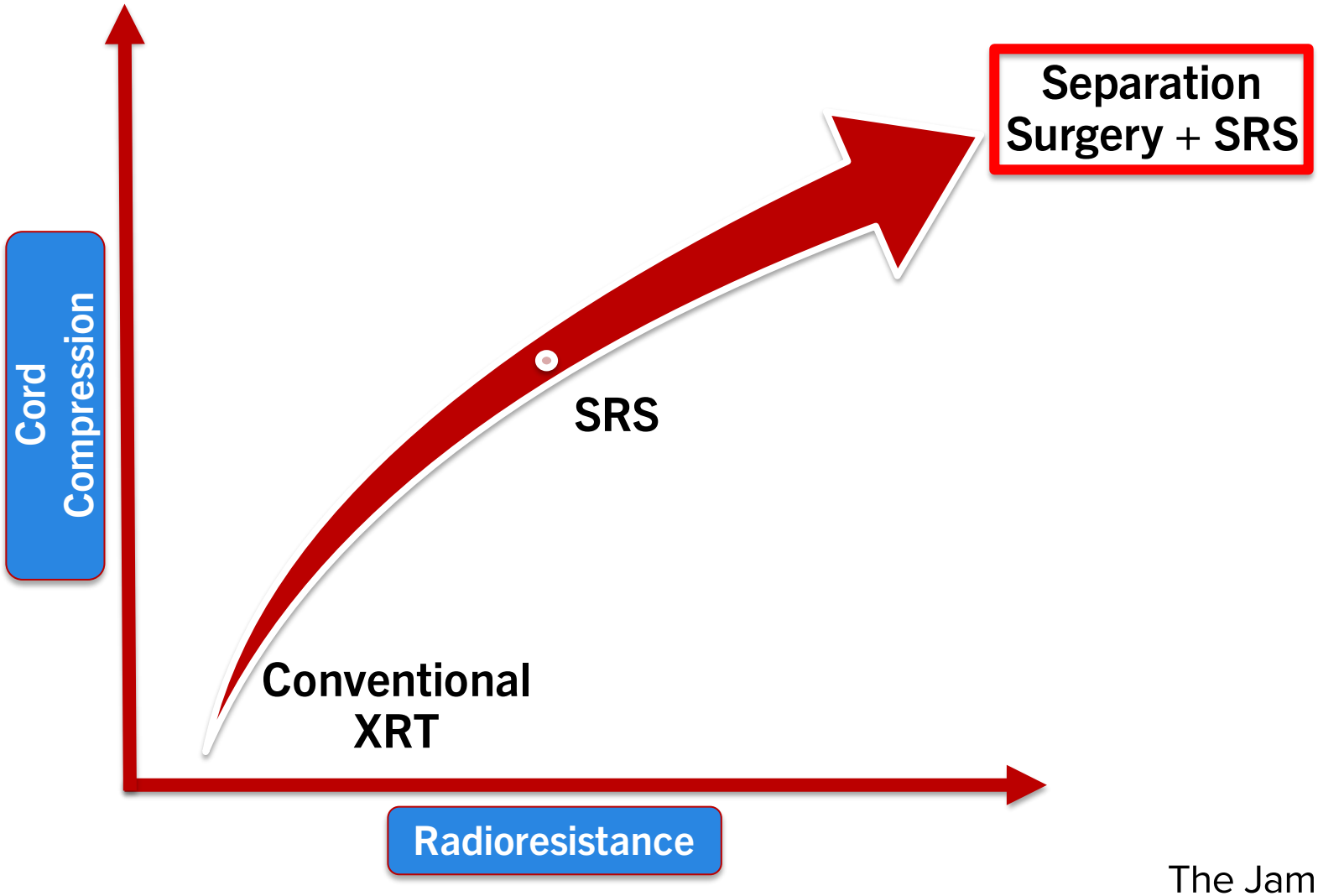
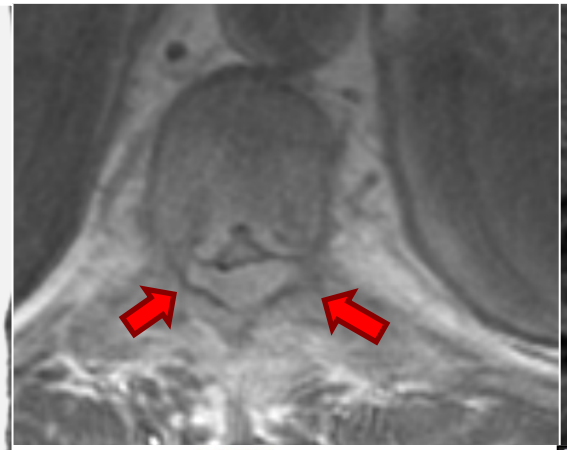
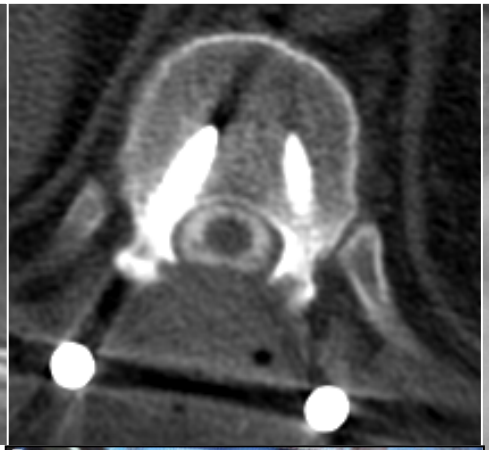
Summary

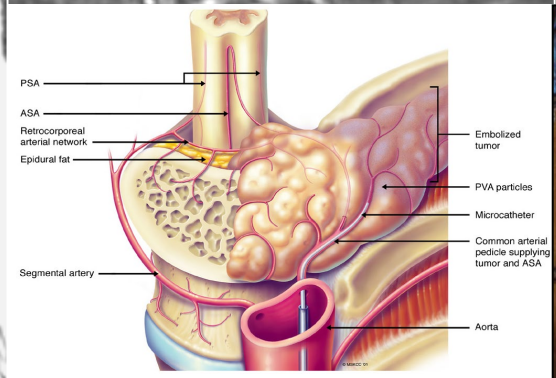

Separation
Surgery + SRS
Cord
Compression
SRS
Conventional
XRT
Radioresistance

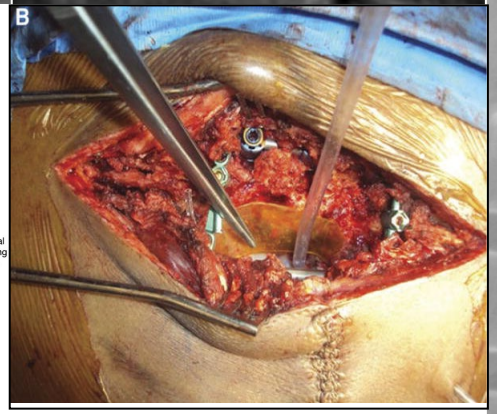
Evolution of Separation Surgery

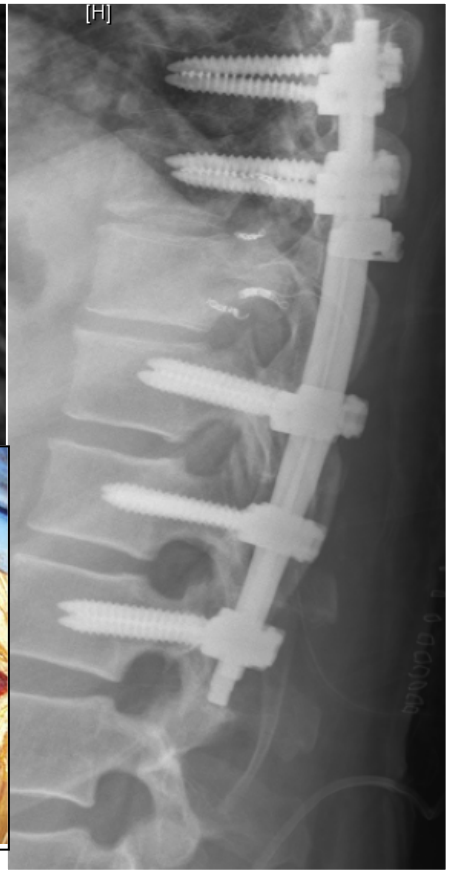
Long Segment Pedicle Screw Fixation











Separation Surgery: Long Constructs

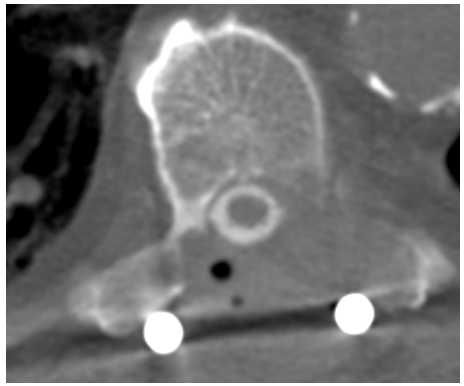
- 318 patients
- Major histologies
  - NSCLC, RCC, Prostate Sarcoma
- Failure Rate: 2.8% (9/318)
  - Rod or Screw Break
  - Screw pull out
  - Symptomatic VB fracture
- Risk Factors
  - Junctional Spine (CT or TL)
  - Post-menopausal females

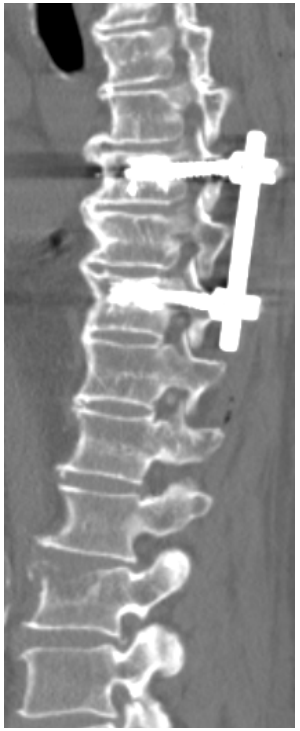
Amankulor et al. Spine 2013

Separation Surgery: Short Constructs

- 44 patients
- Median f/u 11 months
- Levels: Thoracic (43%), Thoracolumbar (11%), Lumbar (45%)
- Major histologies
  - NSCLC, Prostate, Colorectal, Breast
- Failure Rate
  - Requiring Surgery: 2.2% (1/44)

    T3 bilateral pedicle screw fracture
  - Asymptomatic: 6.8%
    - Haloing (4.4%)
    - Progressive Fracture
- PMMA Complications: None





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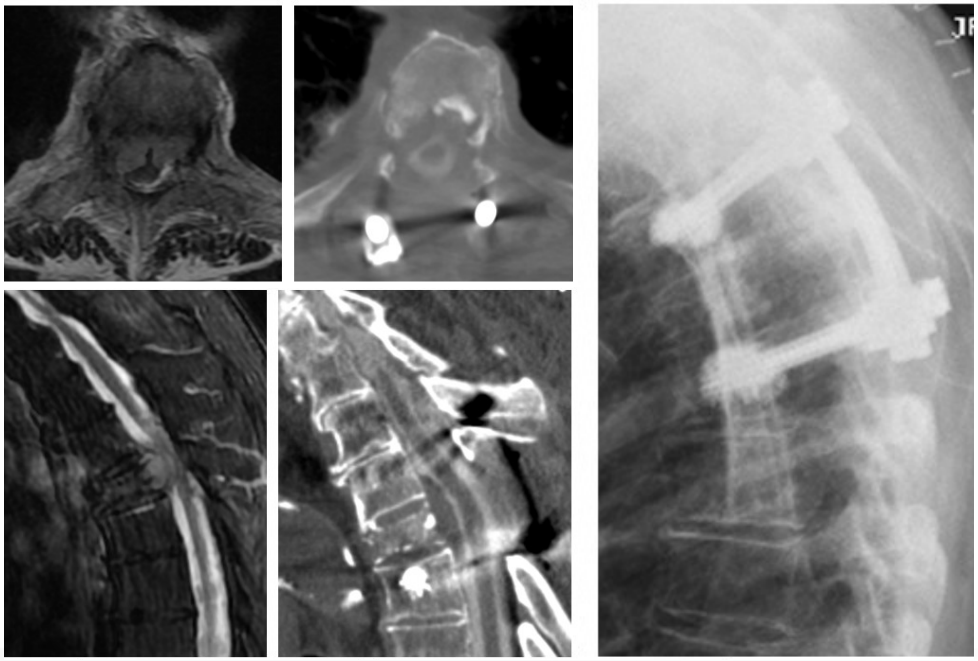
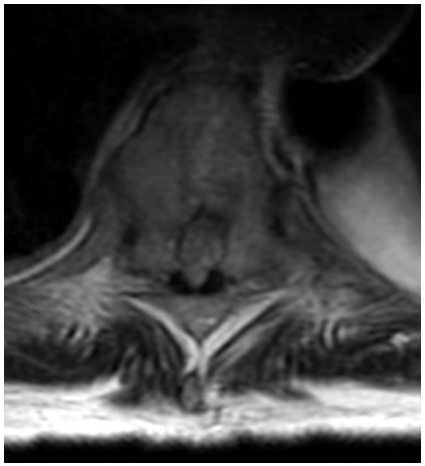
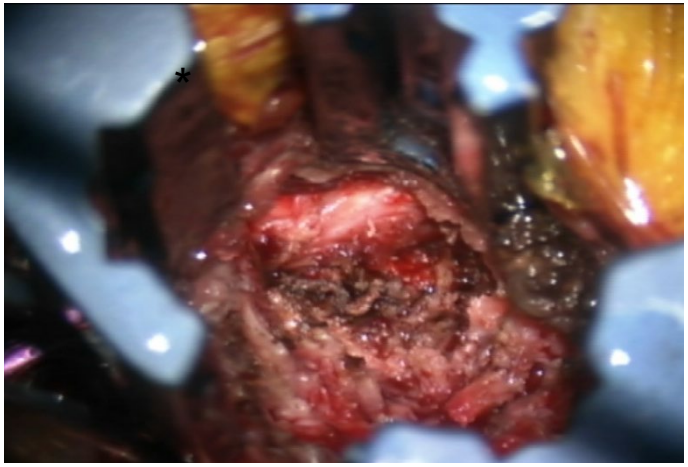
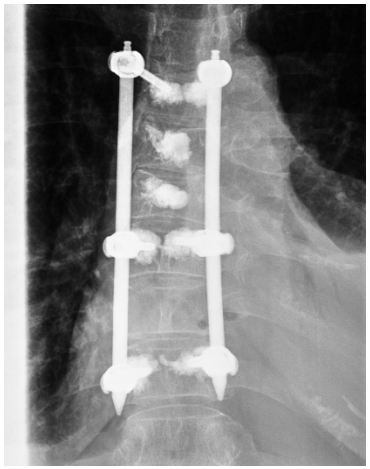
Separation Surgery: MIS Applications

- Percutaneous Pedicle Screw Fixation with Cement Augmentation
- Tubular Access
  - Decompression
  - Facetectomy
  - Transpedicular decompression
- Mini-open Decompression

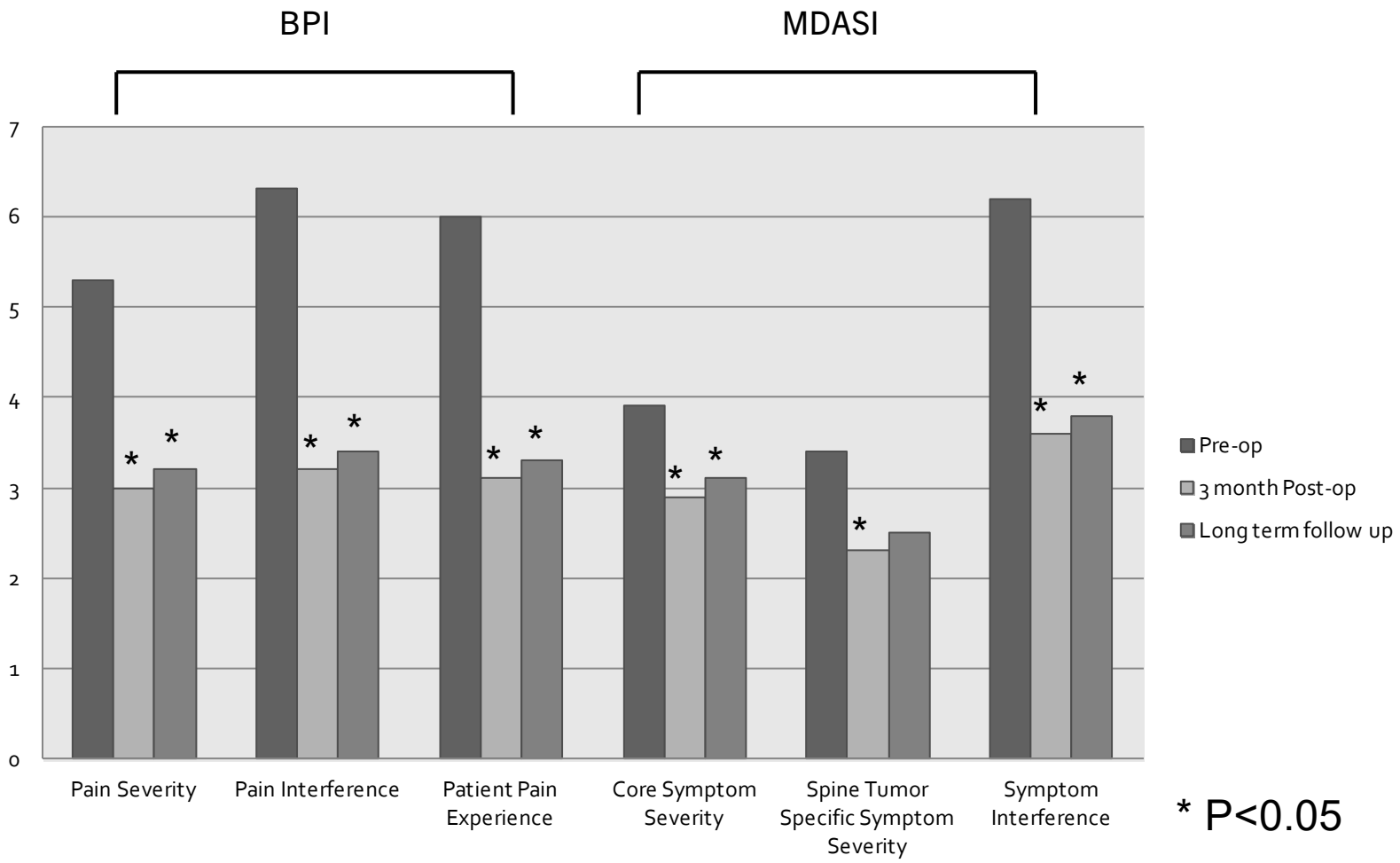


Separation Surgery: MIS Applications

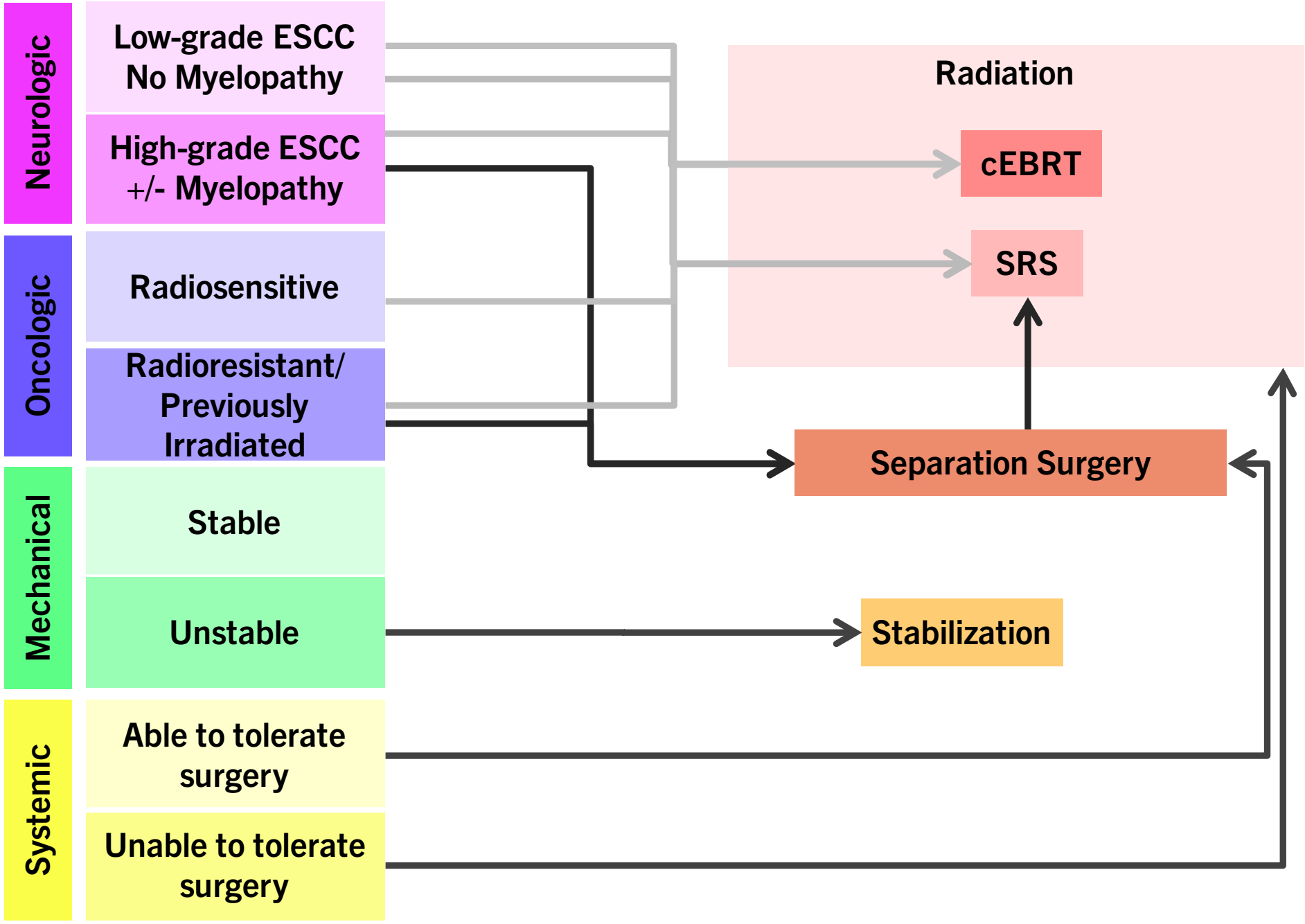




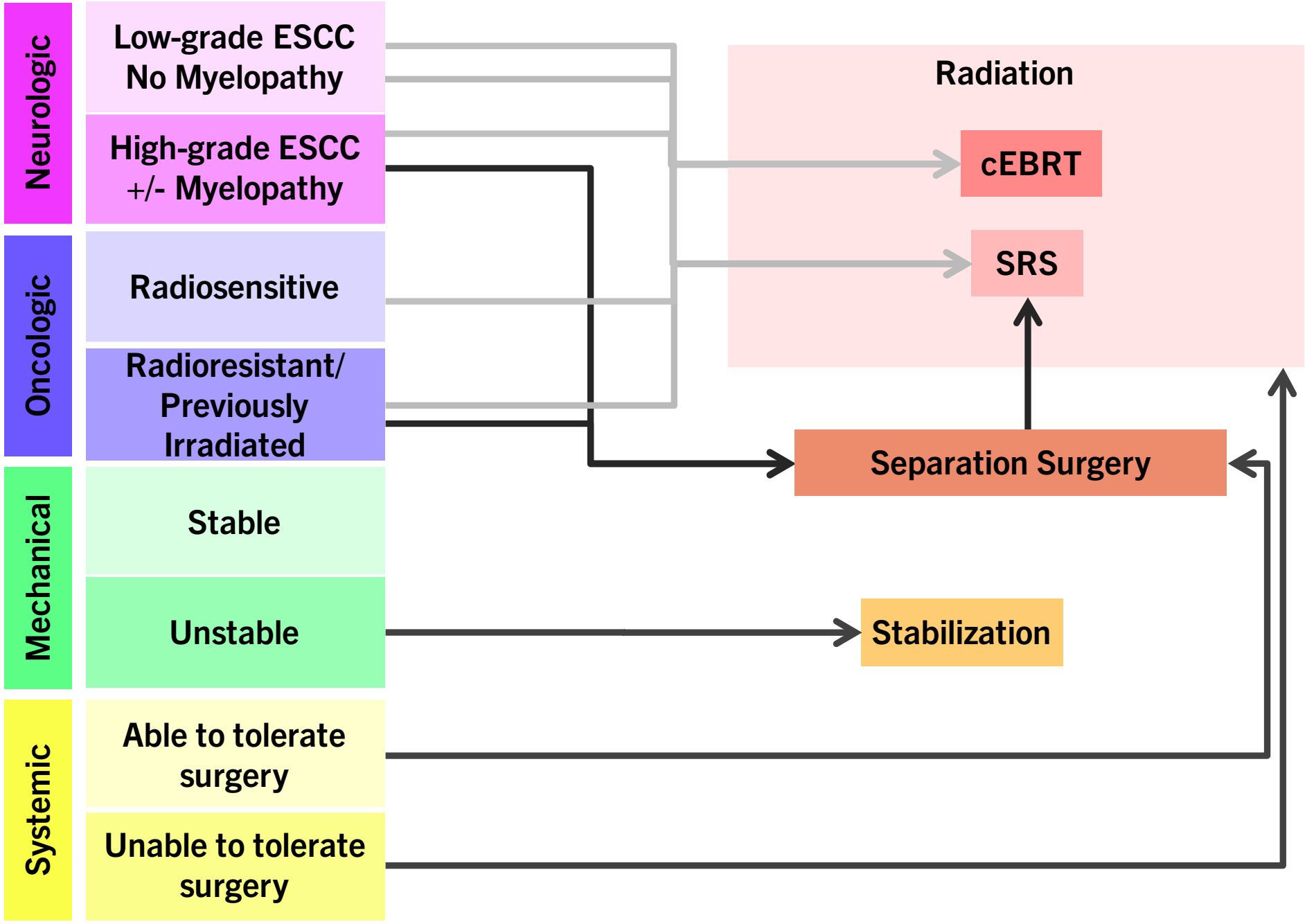



MIS Applications



Barzilai et al. World Neurosurg 2018


Neurologic
Low-grade ESCC
No Myelopathy
High-grade ESCC
+/- Myelopathy
Oncologic
Radiosensitive
Radioresistant/
Previously
Irradiated
Mechanical
Stable
Unstable
Systemic
Able to tolerate
surgery
Unable to tolerate
surgery
Radiation
cEBRT
SRS
Separation Surgery
Stabilization


Neurologic
Low-grade ESCC
No Myelopathy
High-grade ESCC
+/- Myelopathy
Oncologic
Radiosensitive
Radioresistant/
Previously
Irradiated
Mechanical
Stable
Unstable
Systemic
Able to tolerate
surgery
Unable to tolerate
surgery
Radiation
cEBRT
SRS
Separation Surgery
Stabilization

Future Directions

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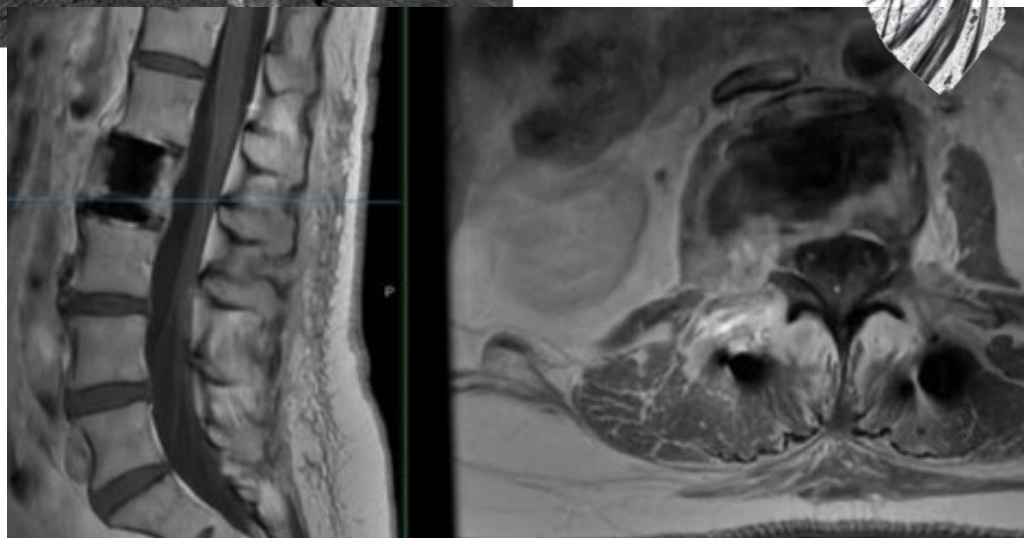
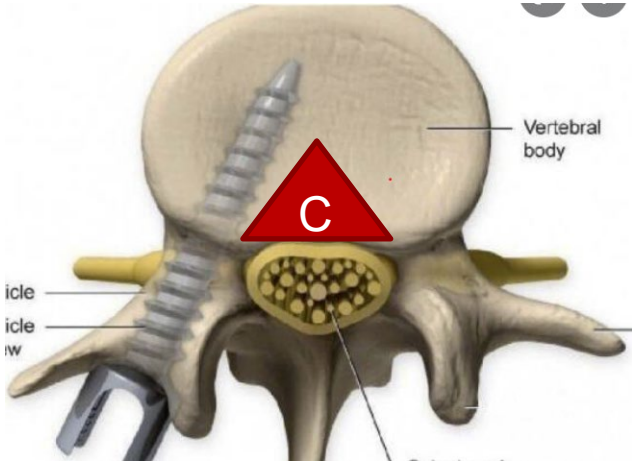
Carbon Fiber/PEEK Instrumentation





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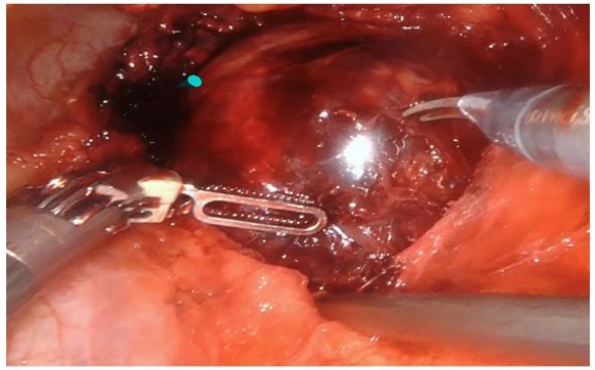
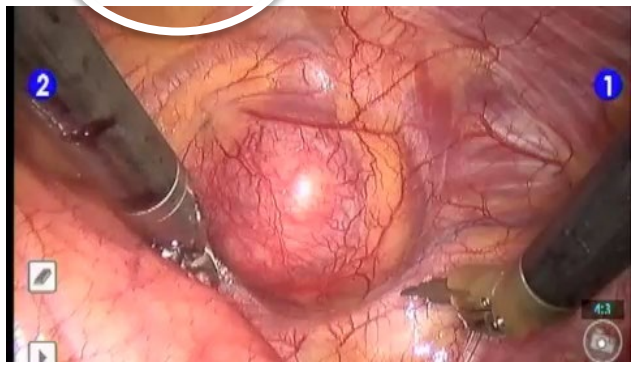
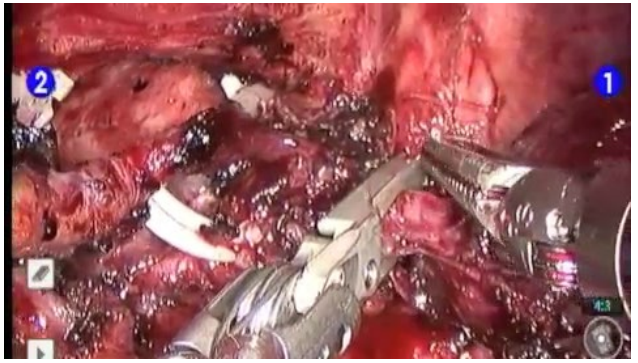
MIS Applications: DaVinci Robot

Presacral

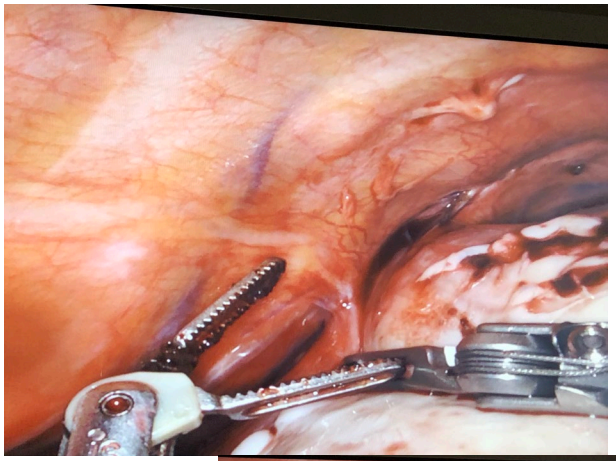


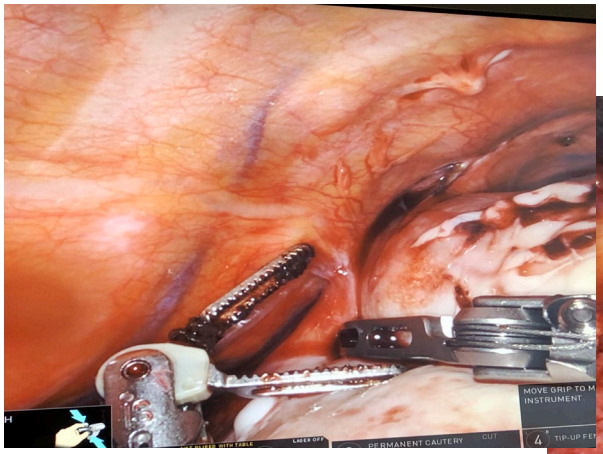
Apical

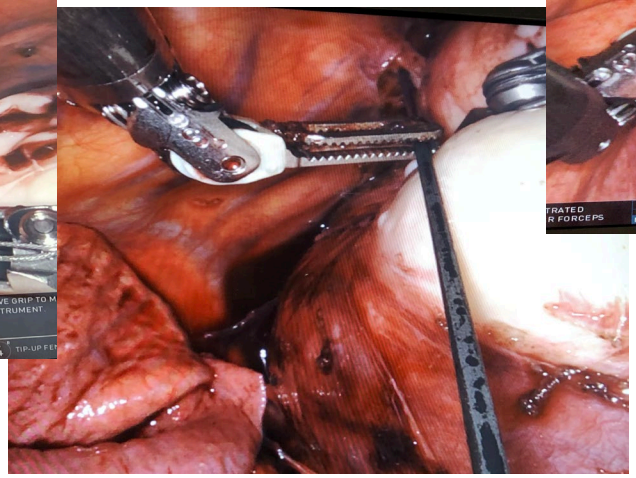




MIS: Da Vinci Robot







Era of Targetable Mutations

Spine

SPINE Volume 41, Number 20S, pp S218–S223

METASTATIC SPINE TUMORS

Molecular Markers and Targeted Therapeutics in Metastatic Tumors of the Spine

Changing the Treatment Paradigms

C. Rory Goodwin, MD, PhD,* Nancy Abu-Bonsrah, BS,* Laurence D. Rhines, MD,†
Jorrit-Jan Verlaan, MD, PhD,‡ Mark H. Bilsky, MD,§ Ilya Laufer, MD,§ Stefano Boriani, MD,¶
Daniel M. Sciubba, MD,* and Chetan Bettegowda, MD, PhD*

The Targeted Therapies Era Beyond the Surgical Point of View: What Spine Surgeons Should Know Before Approaching Spinal Metastases

Fabio Cofano, MD[1], Matteo Monticelli, MD[1], Marco Ajello, MD[1], Francesco Zenga, MD[1], Nicola Marengo, MD[1], Giuseppe Di Perna, MD[1], Roberto Altieri, MD[1], Paola Cassoni, MD[2], Luca Bertero, MD[2], Antonio Melcarne, MD[1], Fulvio Tartara, MD[3], Alessandro Ducati, MD[1], and Diego Garbossa, MD, PhD[1]

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Goodwin et al. Spine 2016
Cofano et al. Cancer Control 2019

Table 1. Lung cancer.

Molecular Feature	Target of Therapies	Drug(s)
EGFR	EGFR TKI	Gefitinib, Erlotinib, Afatinib, Osimertinib
HER 2/HER 4	HER 2/HER 4+	Afatinib
T790M secondary mutation in EGFR		
ALK-EML4 fusion oncogene		
VEGF-A		
PD1		
CheckMate 17		
CheckMate 057		
PD-L1		

Table 2. Breast cancer.

Molecular Feature	Target of Therapies	Drug(s)
Estrogen	Estrogen receptor	Tamoxifen
Aromatase	Aromatase	Letrozole, anastrozole, exemestane
Ovarian estrogens	Luteinizing hormone-releasing hormone analogs	Leuprolide, Goserelin

Table 5. Renal Cell cancer.

Molecular feature	target of therapies	drug(s)
VEGF	TKI, monoclonal antibodies anti VEGF	Sunitinib, Pazopanib, Atixinib, Sorafenib, bevacizumab
CheckMate 214	Ab-antiCheckMate 214	Nivolumab, Ipilimumab, Sunitinib

Abbreviations: TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

Table 6. Thyroid cancer.

Molecular Feature	Target of Therapies	Drug(s)
MAPK pathway	MAPK	Sorafenib, Levantinib, Vandetanib, Cabozantinib

Table 7. Hepatocellular carcinoma.

Molecular Feature	Target of Therapies	Drug(s)
VEGFR-2	VEGFR-2 + cells	Regorafenib, Nivolumab. Cabozantinib, Ramucirumab
MAPK pathway	MAPK	Sorafenib, Lenvatinib

Abbreviations: MAPK, mitogen-activated protein kinase; VEGFR, vascular endothelial growth factor receptor.

Table 8. Colorectal cancer.

Molecular Feature	Target of Therapies	Drug(s)
VEGF pathway	VEGF + cells	Bevacizumab
EGFR pathway	EGFR + cells	Cetuximab, Panitumumab

Abbreviations: EGFR, epithelial growth factor receptor; VEGF, vascular endothelial growth factor.

Table 3. Prostate cance

Molecular Feature	Target c	
Androgen pathways	LHRH li	
Androgen pathways	Enzyme	Ketoconazole;
Androgen pathways	Androgen receptor (AR)	cyproterone acetate, bicalutamide, flutamide, nilutamide, enzalutamide.
Osteoclast proliferation	Receptor activator of nuclear factor kappa-B ligand (RANKL)	Denosumab
Checkpoint inhibitors	CTLA-4, PD1, PD1 ligands PD-L1/PD-L2	Ipilimumab, nivolumab, pembrolizumab, atezolizumab

	cells	
CTLA-4	CTLA-4 + cells	Ipilimumab
PD-1	PD-1 + cells	Nivolumab, Pembrolizumab, Dacarbazine
Tumor cell lysis and immune responses after antigen release and granulocyte-macrophage colony-stimulating factor (GM-CSF).	Immune cells	Talimogen laherparepvec (T-VEC)

Cofano et al. Cancer Control 2019

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Can targeted therapy data be used for prognostication in metastatic spine disease?

- **NSCLC:** A systematic review including 27 studies found that median survival of patients with non-small cell lung cancer being treated with epidermal growth factor receptor (EGFR) inhibitors were improved

- **Melanoma:** Retrospective small cohort of 18 patients found that failing prior immunotherapy treatment was associated with significantly shorter survival following spine surgery

Batista et al. J Clin Neurosci 2016
Shankar et al. Spine 2017

The Impact of Targetable Mutations on Clinical Outcomes of Metastatic Epidural Spinal Cord Compression in Patients with Non-Small Cell Lung Cancer treated with Hybrid Therapy (Surgery followed by Stereotactic Body Radiation Therapy)

Study Population

Retrospective study

103 patients with NSCLC spinal metastases presenting with MESCC

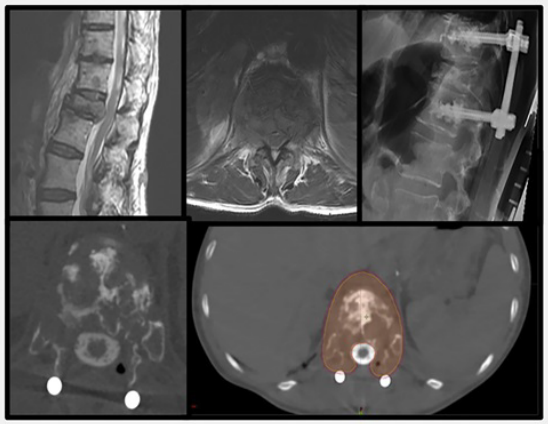
⬇

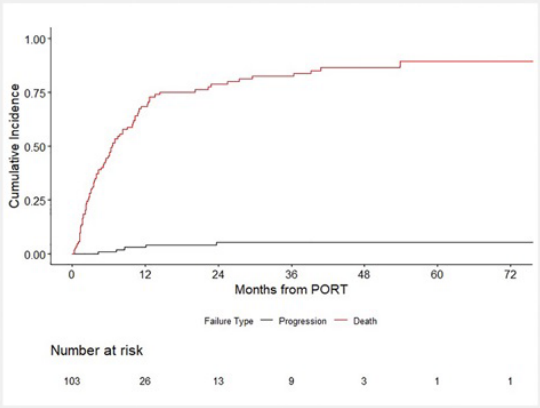
Hybrid Therapy (separation surgery followed by SBRT)

Clinical-Genomic Correlations

Treatment	Tumor mutations
EGFR	EGFR Exon 18/19/20/21
VEGF	TP53
Chemotherapeutic agent(S)	KRAS
Tyrosine Kinase Inhibitor	ALK
PD-1/PDL1 therapy	HER2
	BRAF
	PDL1 expression

Outcomes
Overall survival (OS)
Progression free survival (PFS)
Local tumor control (competing risk setting)





Results

- Hybrid therapy in NSCLC patients presenting with spinal cord compression resulted in 95% local control at 2 years after surgery.

Conclusion

EGFR treatment naïve patients who initiated EGFR targeted therapy **after hybrid therapy** had significantly **longer OS** (HR 0.47, 95% CI 0.23-0.95, *P* = .04) even after adjusting for smoking status.

EGFR-targeted therapy initiated prior to hybrid therapy did not confer a survival benefit.

Patients harboring the EGFR exon 21 mutation portended a 2-fold increase in PFS from date of surgery (HR:0.48, 95%CI:0.24-0.97, *P* = .04).

- Systemic targetable therapy will likely need to be considered in future prognostication models.

Chakravarthy et al

Published by Wolters Kluwer on behalf of the Congress of Neurological Surgeons

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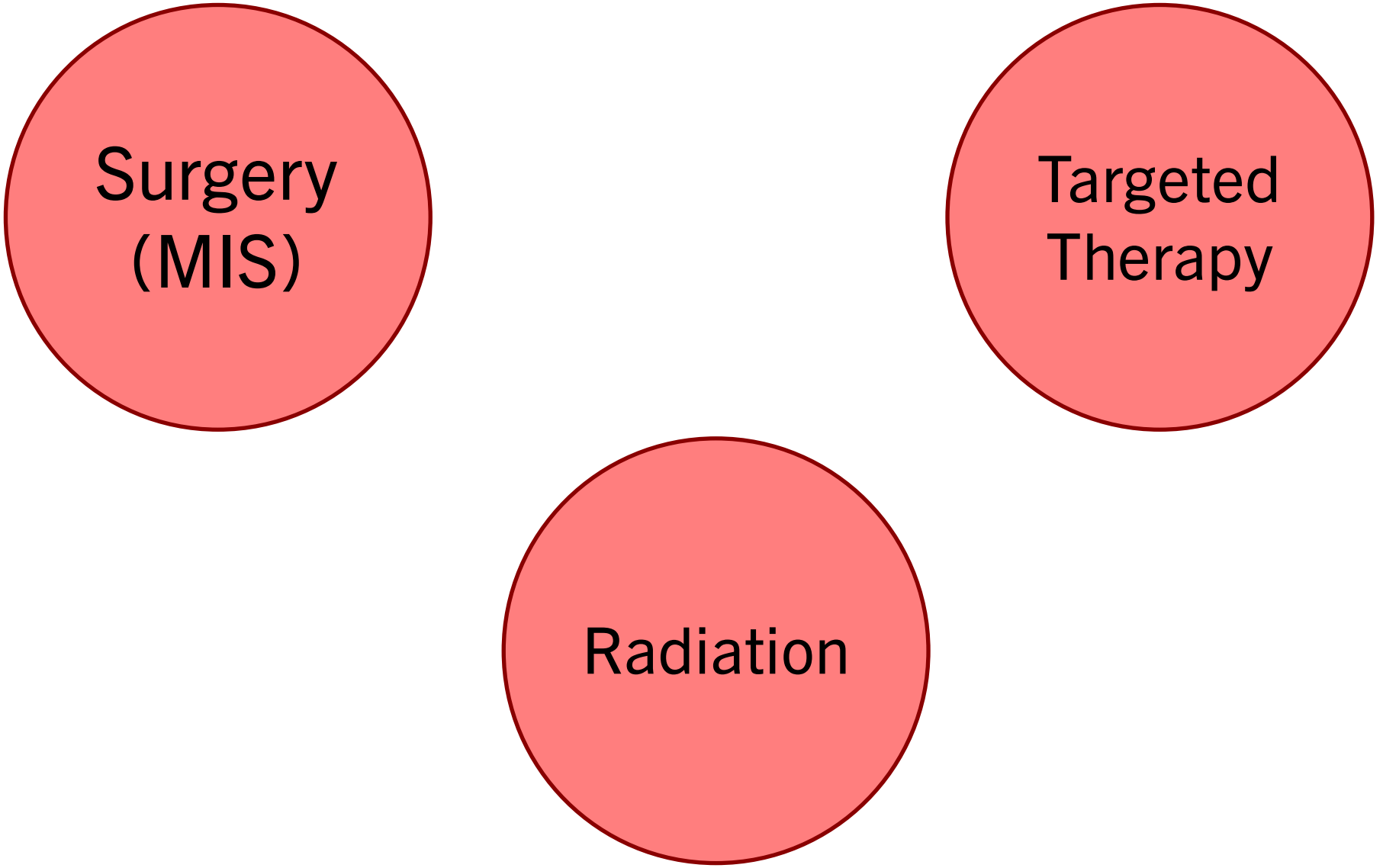
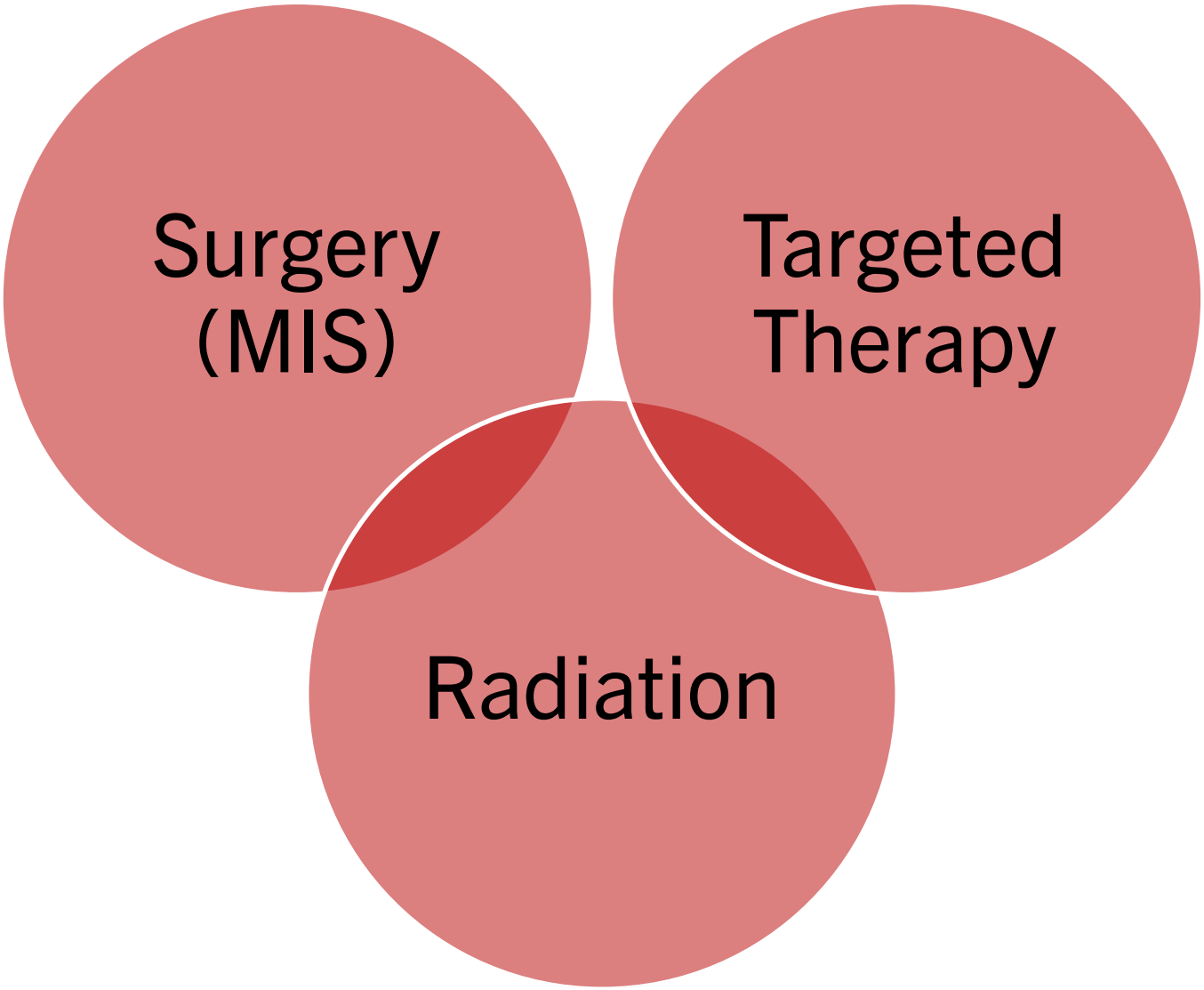

Surgery (MIS)
Targeted Therapy
Radiation



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Final Thoughts

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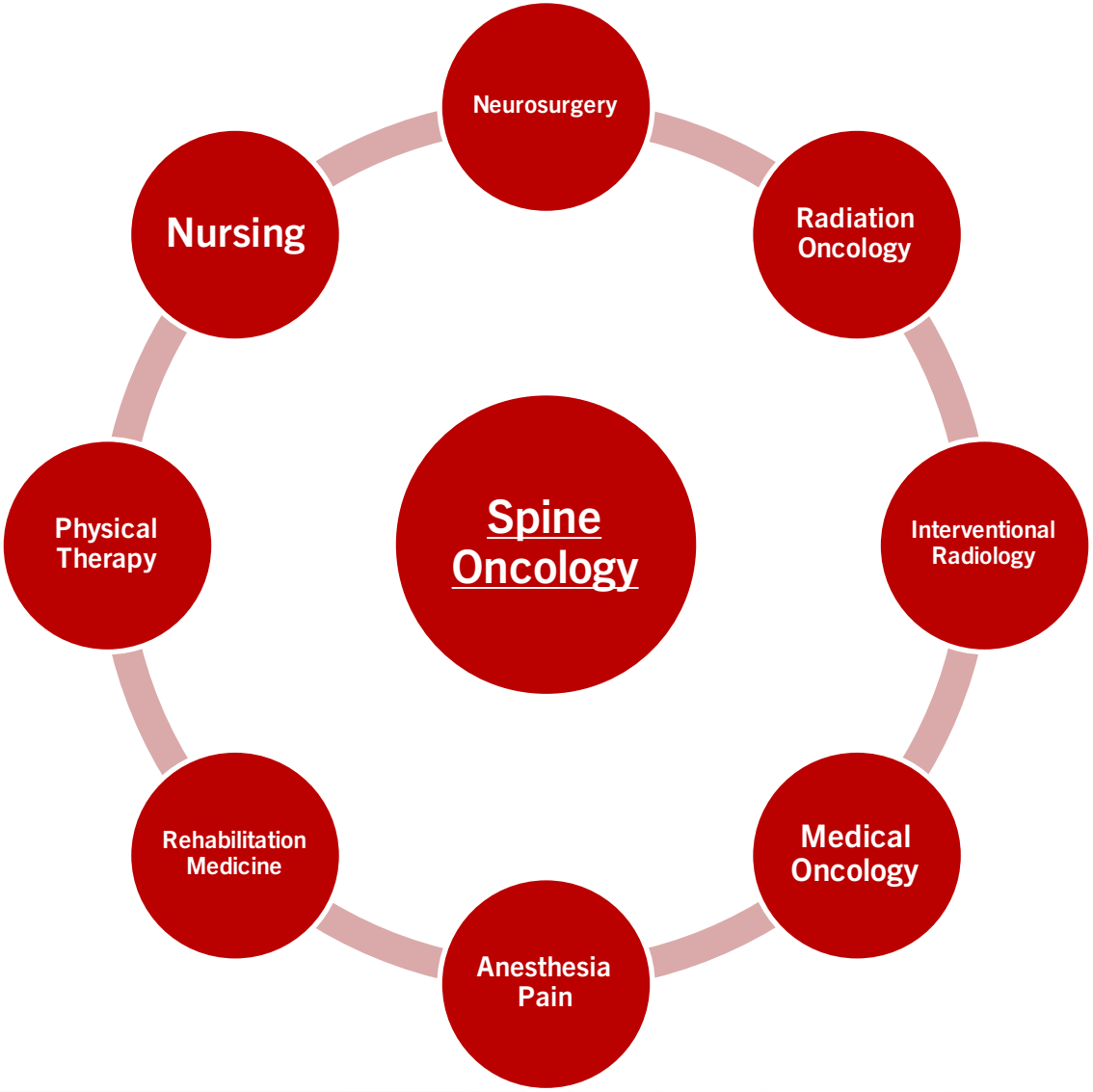
Creating a Cancer-free World.
One Person, One Discovery at a Time.

Multidisciplinary Spine Tumor Program



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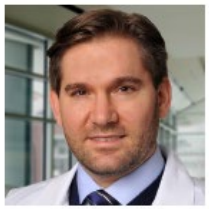

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Thank You

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