

Systemic & Bone-Targeted Therapies

in Spinal Metastases

Integrating Supportive Care

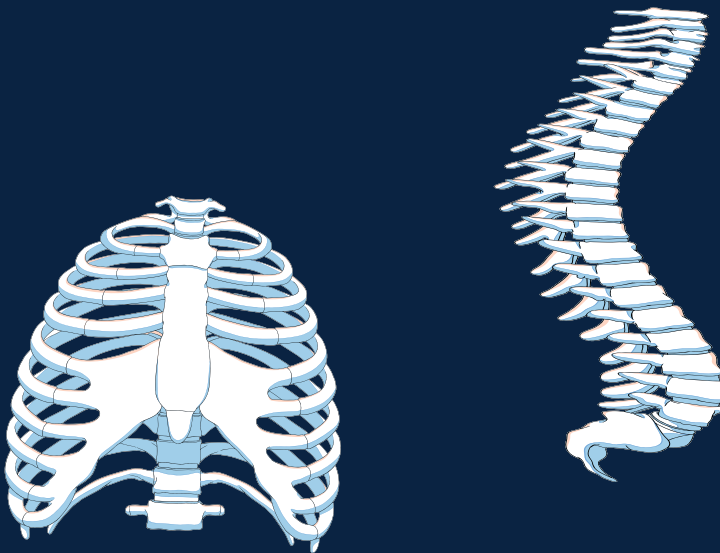
Dr.P. Jovita.M.Martin Daniel

MBBS, MD, DNB, MNAMS, DM., MSc, MRCP (SCE), FRCP

Professor Medical Oncology

Cancer Institute, WIA

Chennai



Learning Objectives

Epidemiology , Impact & Basic Anatomy

Understand the incidence and clinical burden of spinal metastases across primary tumor types

Bone-Targeted Agents

Differentiate bisphosphonates vs. denosumab, indications, dosing, and skeletal-related event prevention

Systemic Oncology

Apply current evidence for chemotherapy, targeted therapy, immunotherapy, and endocrine therapy in spinal metastatic disease

Radiation Integration

Integrate conventional EBRT and SBRT/stereotactic spine radiosurgery within systemic therapy planning

Supportive Care

Implement analgesic strategies, corticosteroid use, rehabilitation, and palliative care principles

Multidisciplinary Approach

Design coordinated care pathways across oncology, spine surgery, radiation, and palliative teams

Section 1: Epidemiology of Spinal Metastases

~40%

of cancer patients
develop bone mets

#1

most common site
of bone metastasis

10–20%

present with
neurologic compromise

3–6 mo

median survival
(without treatment)

Common Primary Tumors Causing Spinal Metastases

73%



Breast

45%



Lung

68%



Prostate

40%



Renal Cell

28%



Thyroid

18%



Melanoma

% with vertebral involvement

Spinal Cord Anatomy & Relevant Compartments

Spinal Column Compartments

Vertebral Body

Anterior column — most common site of metastatic deposit (>85%)

Posterior Elements

Pedicles, laminae, spinous/transverse processes — involvement affects stability

Epidural Space

Between dura and bone — epidural tumor extension causes cord/cauda compression

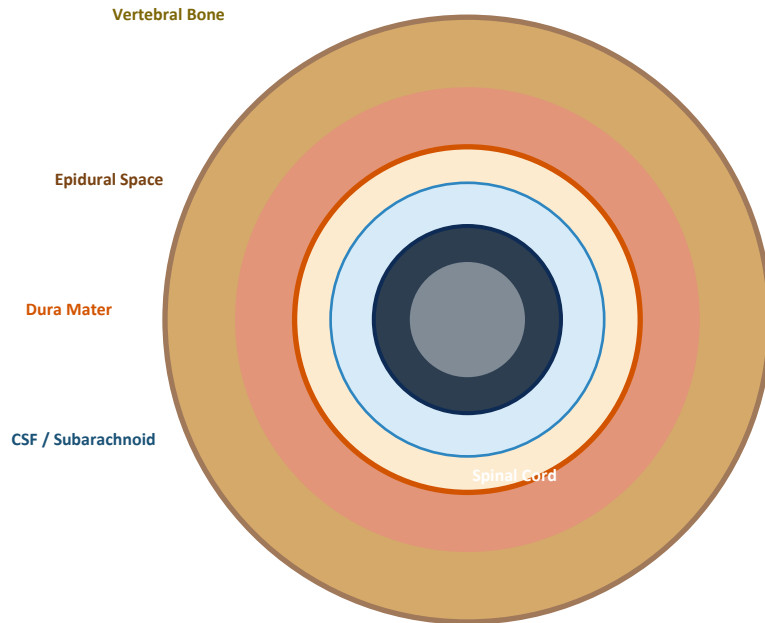
Intradural Extramedullary

Inside dura, outside cord — leptomeningeal/nerve root tumors

Intramedullary

Within cord parenchyma — rare metastases (lung, breast, renal)

Cross-Sectional Anatomy



Clinical Relevance

- Epidural extension → cord/cauda compression → neurological deficit
- Anterior cord syndrome: loss of motor + pain/temp; preserved proprioception
- Vertebral body collapse → kyphotic deformity → mechanical instability
- T4–T9 is a watershed zone — single radicular artery; ischemia risk highest

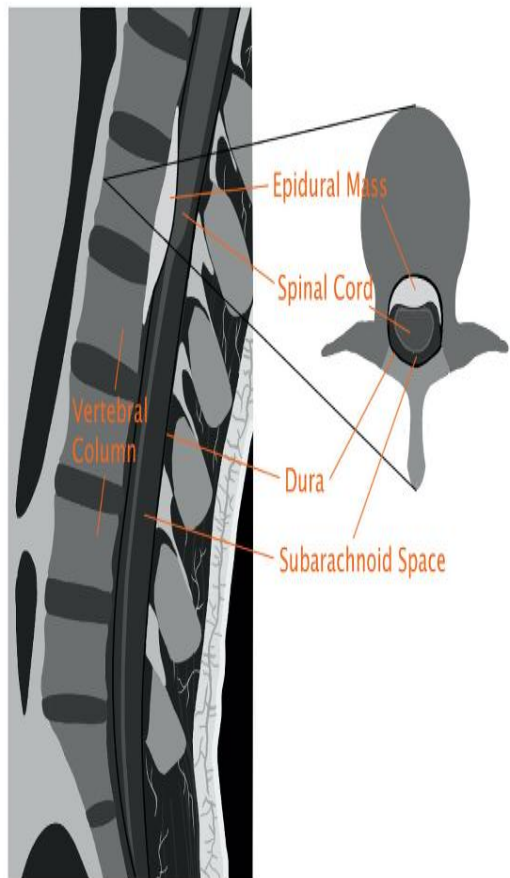
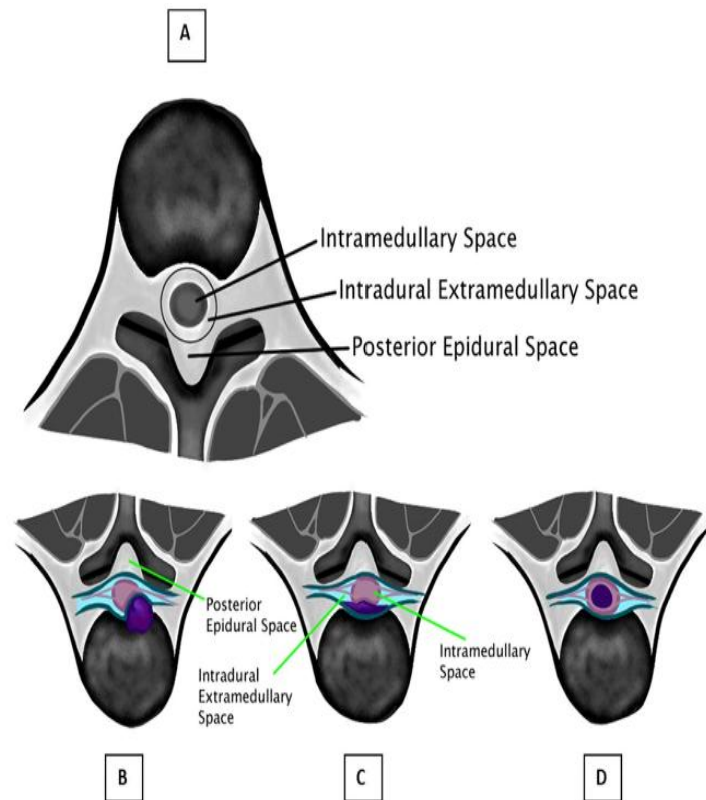


Fig. 2 Sagittal (left) and axial (right) appearances of an epidural mass causing spinal cord compression on T1-weighted post-contrast MRI



1 Axial appearance of the spinal cord showing the different spinal cord compartments (A), and a tumor occupying the extradural space (B), dural-extramedullary space (C), and intramedullary space (D). The tumor in B indents the dura but does not fully occlude the subarachnoid space. In C, the tumor indents the spinal cord and displaces it posteriorly. In D, the tumor is contained completely within the spinal cord, expands its cross-sectional area

SPINAL INSTABILITY NEOPLASMA SCORE (SINS) – GRAPHICAL TABLE

SINS 0-6: "STABILITY" | SINS 7-12: "POSSIBLE INSTABILITY" | SINS 13-18: "INSTABILITY"

Score	4	3	2	1	0
Location		Junctional C0-C2, C7-T2, T11-L1, L5-S1	Mobile spine C3-C6, L2-L4	Semi-rigid T3-T10	Rigid S2-S5
Pain		Yes (relief with recumbency and/or pain with movement/loading of spine)		No (occasional pain but not mechanical)	Pain free lesion
Bone lesion			Lytic	Mixed lytic/blastic	Blastic
Radiographic spinal alignment	Subluxation / translation		De novo deformity Kyphosis/scoliosis		Normal alignment
Vertebral body collapse		>50% collapse	<50% collapse	No collapse, >50% body involved	None
Posterolateral involvement of the spinal elements		Bilateral		Unilateral	None

Illustrated items of the SINS by Wouter Foppen MD PhD, Sander P.J. Mujs MD PhD, Jornt-Jan Verlaan MD PhD, and Charles G. Fisher MD MHC based on the original SINS publication: Fisher CG, et al. Spine 2010; doi: 10.1097/BRS.0b013e3181e16ae2

The SINS score evaluates six key categories:

- 1.Spine Location** – Cervical, thoracic, thoracolumbar, or lumbar regions, as instability risk varies by location.
- 2.Mechanical Pain** – Pain with movement or load-bearing indicates potential instability.
- 3.Bone Lesion Quality** – Lytic, blastic, or mixed lesions affect structural integrity.
- 4.Radiographic Spinal Alignment** – Normal alignment versus subluxation, translation, or deformity.
- 5.Vertebra Body Collapse** – Degree of collapse or tumor involvement in the vertebral body.
- 6.Posterolateral Involvement of Spinal Elements** – Involvement of facets, pedicles, or costovertebral joints

Each category is scored, and the total ranges from **0 to 18**.

Interpretation

- 0–6:** Stable spine; no mechanical instability. Conservative management is usually sufficient
- 7–12:** Indeterminate stability; consultation with a spine surgeon is recommended, especially if mechanical pain is present
- 13–18:** Likely unstable; surgical stabilization is generally indicated for patients fit for surgery

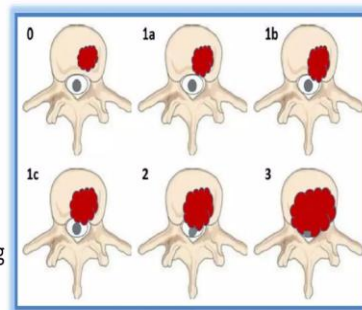
Epidural Spinal Cord Compression (ESCC) — Grading Scale

Grade	Description	Thecal Sac	Cord Status
0	Epidural tumor without displacement of dural sac	Intact	Not compressed
1a	Epidural tumor displaces dural sac — no thecal deformation	Compressed	Not compressed
1b	Epidural tumor deforms thecal sac — cord not abutted	Deformed	Not compressed
1c	Tumor abuts cord — no cord compression on imaging	Deformed	Abutted
2	Cord compressed — CSF still visible around cord	Obliterated	Compressed (CSF visible)
3	Cord compressed — NO CSF visible around cord; cord displaced	Obliterated	Severe compression

💡 **Clinical threshold:** Grade ≥ 2 defines high-grade ESCC — associated with neurological compromise and urgency for intervention. Grade 3 = surgical/SRS emergency.

Grading - Bilsky MSCC grading scale

- **Grade 0 –**
 - Only bony vertebral lesion
- **Grade 1 –**
 - 1a : Grade 0 + Epidural extension
 - 1b : 1a + Thecal sac indentation
 - 1c : 1b + Touching cord
- **Grade 2 –**
 - Grade 1+ SCC without blocking CSF
- **Grade 3 –**
 - Grade 2 + Blockage of CSF flow



Ref : Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the Epidural Spinal Cord Compression Scale. J Neurosurg Spine 2010;13(3):324–328

19

MRI Required
T2 axial at level of max compression
Contrast enhances tumor delineation

Bilsky ESCC Grade — Clinical Decision Framework

Low-Grade ESCC (0 – 1b)

No cord compression on MRI

Thecal sac patent or mildly deformed

Neurologically intact

✓ Primary SRS/SBRT (15–24 Gy × 1–3 fx)

✓ cEBRT for radiosensitive tumors (lymphoma, myeloma, SCLC)

✓ No surgical decompression required

✓ Systemic therapy as indicated

Intermediate ESCC (1c – 2)

Cord abutted or compressed, CSF present

Variable neurological deficits

Multidisciplinary evaluation mandatory

✓ SRS if radioresistant & ESCC ≤ 2

✓ Separation surgery → postop SRS preferred for ESCC 2

✓ cEBRT for radiosensitive histologies

⚠ Steroids: dexamethasone 16 mg loading → 4 mg q6h

High-Grade ESCC (3)

Cord compressed, NO surrounding CSF

Neurological deficit present or imminent

Oncologic emergency — act within 24 h

✓ Surgical decompression (separation surgery)

✓ Postoperative SRS 24–27 Gy in 3 fx, within 4 weeks

✗ SRS alone: unsafe due to cord proximity

✓ High-dose steroids STAT; ICU monitoring if myelopathy



ESCC grade is the single most important determinant of surgical vs. radiation-first strategy. Re-image within 24–48 h if neurological status changes.

SINS Score — Spinal Instability Neoplastic Score

Scoring Parameters

Location

- Junctional (C0–C2, C7–T2, T11–L1, L5–S1): 3 pts
- Mobile (C3–C6, L2–L4): 2 pts
- Semi-rigid (T3–T10): 1 pt
- Rigid (S2–S5): 0 pts

Pain

- Yes — mechanical or positional: 3 pts
- Yes — non-mechanical/incidental: 1 pt
- Pain-free: 0 pts

Bone Lesion Type

- Lytic: 2 pts
- Mixed (lytic/blastic): 1 pt
- Blastic: 0 pts

Spinal Alignment

- Subluxation / Translation present: 4 pts
- De novo deformity (kyphosis/scoliosis): 2 pts
- Normal alignment: 0 pts

Vertebral Body Collapse

- Collapse > 50%: 3 pts
- Collapse < 50%: 2 pts
- No collapse, > 50% body involved: 1 pt
- None of the above: 0 pts

Posterior Element Involvement

- Bilateral: 3 pts
- Unilateral: 1 pt
- None: 0 pts

Interpretation & Management

0 – 6

STABLE

Non-surgical management
Proceed with radiation/systemic therapy
No surgical consultation required

7 – 12

INDETERMINATE

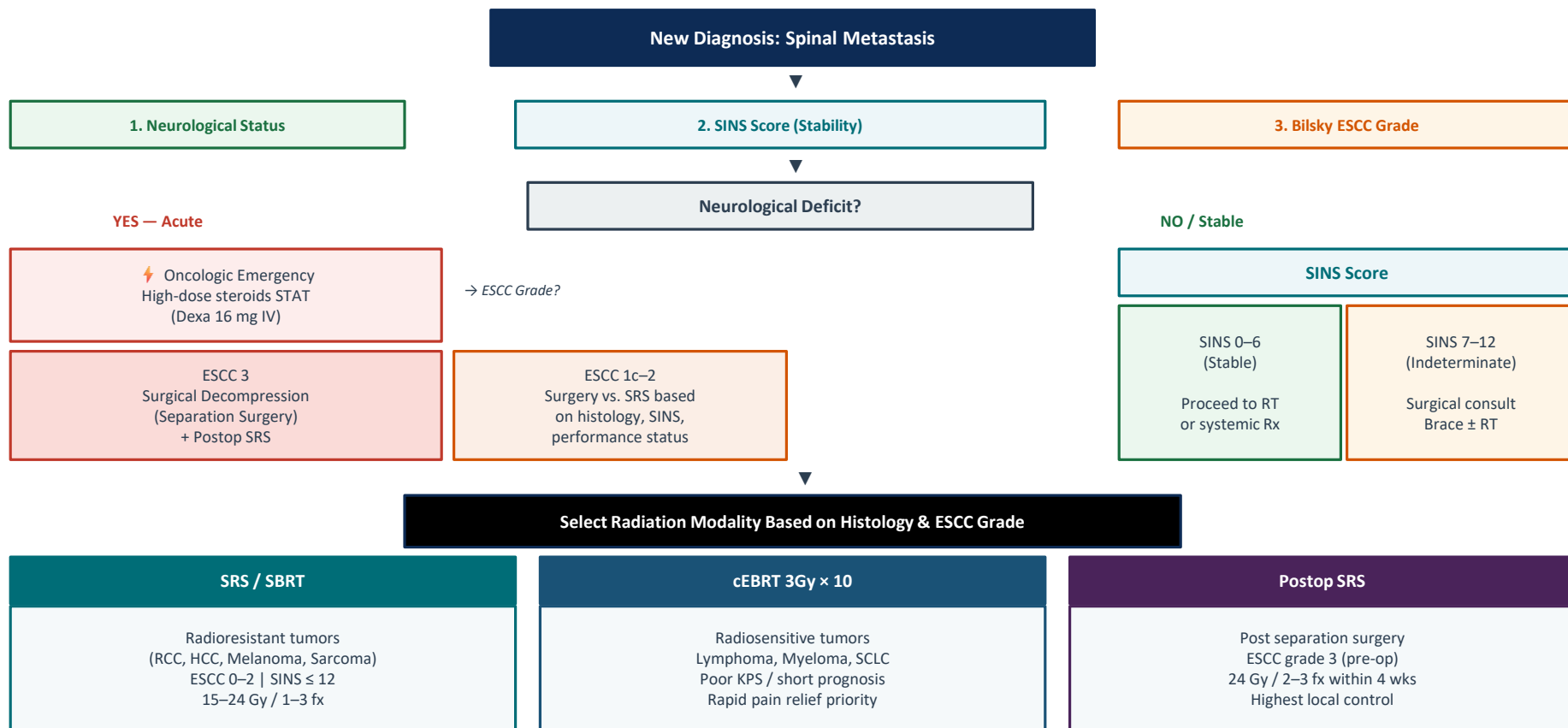
Surgical consultation recommended
Consider bracing/orthosis
MDT discussion before radiation

13 – 18

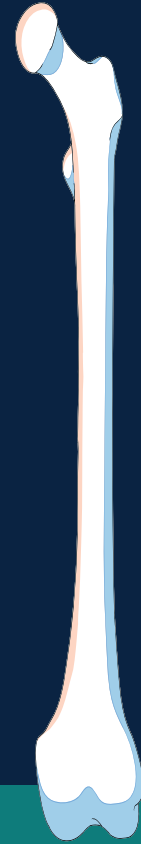
UNSTABLE

Surgical evaluation MANDATORY
Spinal fixation/stabilization before RT
Pre-radiation intervention typically required

Integrated Decision Algorithm — Spinal Metastasis



Section 2: Bone-Targeted Agents



Spinal Metastases: Integrating Supportive Care

Bisphosphonates: Mechanism & Evidence

Mechanism of Action

- Adsorb onto hydroxyapatite crystals at sites of active remodeling
- Inhibit osteoclast-mediated bone resorption (farnesyl pyrophosphate synthase inhibition for N-BPs)
- Reduce osteoclast recruitment, function, and survival
- Indirectly reduce pain via reduction in prostaglandins and cytokines
- Prevent skeletal-related events (SREs): fracture, cord compression, hypercalcemia

Key Bisphosphonate Agents

Zoledronic acid	4 mg IV (15 min)	Monthly → Q3M
Pamidronate	90 mg IV (2 hr)	Monthly
Ibandronate	6 mg IV or 50 mg PO	Monthly
Clodronate	1600 mg/d PO	Daily

Renal monitoring: Zoledronic acid dose-adjust for CrCl < 60 mL/min. Contraindicated if CrCl < 30.

ONJ Prevention:

Dental assessment before initiation. Consider drug holiday for invasive dental procedures.

Denosumab: RANK Ligand Inhibition

RANK/RANKL Pathway

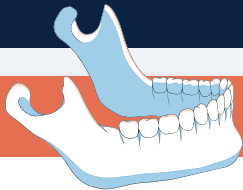
- RANKL expressed by osteoblasts, stromal cells, and tumor cells
- Binds RANK on osteoclast precursors → osteoclastogenesis
- Denosumab (120 mg SC q4w): fully human IgG2 mAb binding RANKL
- Superior to zoledronic acid in delaying first SRE in breast/prostate cancer trials
- No renal dose adjustment required
- Hypocalcemia monitoring: supplement calcium + Vit D

Zoledronic Acid vs. Denosumab

Parameter	ZA	Denosumab
Route	IV	SC
Renal adj.	Required	None
SRE delay (BC)	Reference	Superior
Hypocalcemia	Less	More
ONJ risk	~1–2%	~2%
Rebound effect	None	Yes (on D/C)
Cost	Lower	Higher

Managing Adverse Effects of Bone-Targeted Agents

Osteonecrosis of the Jaw (ONJ)



- Incidence: 0.5–3% with prolonged use
- Risk factors: dental extractions, periodontal disease, corticosteroids, smoking
- Prevention: dental eval, optimize oral hygiene, avoid invasive procedures if possible
- Management: conservative (rinses, antibiotics, debridement); surgery reserved for refractory cases

Renal Toxicity (BPs)

- Zoledronic acid: acute tubular necrosis with rapid IV infusion
- Baseline SCr required; repeat before each dose
- Infuse over ≥ 15 min; avoid if CrCl < 30 mL/min
- Hold therapy for significant renal deterioration

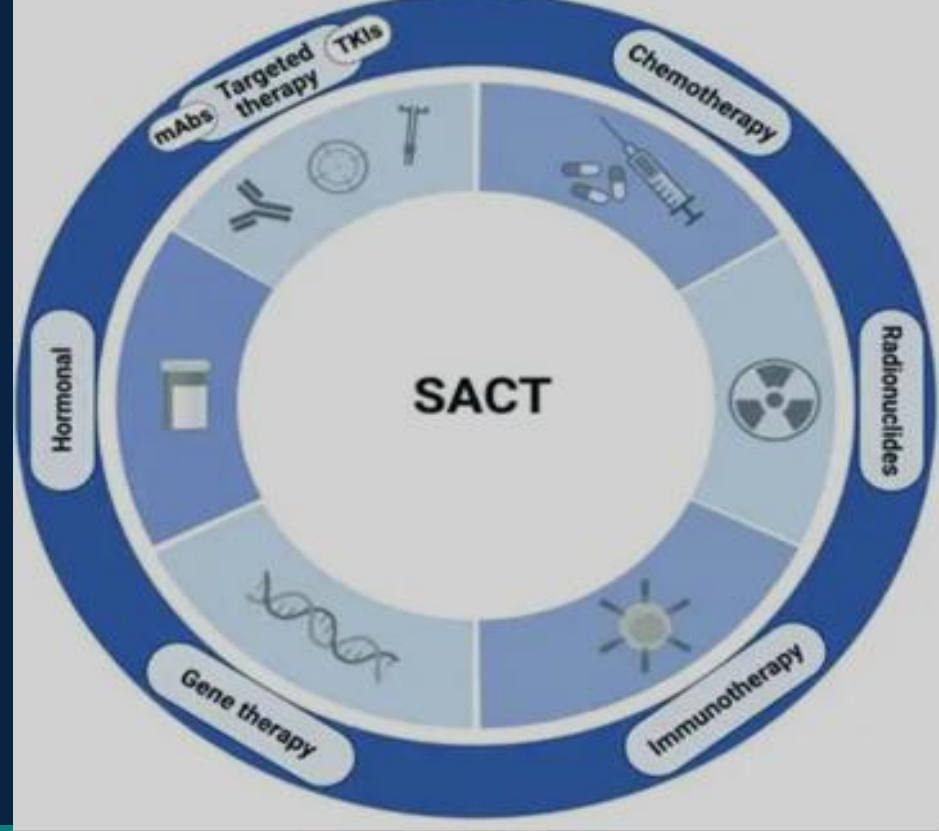
Hypocalcemia

- More common with denosumab (esp. with vitamin D deficiency)
- Supplement: calcium 500 mg BID + vitamin D 400–800 IU daily
- Monitor serum calcium and magnesium
- Correct hypomagnesemia to manage refractory hypocalcemia

Atypical Femur Fractures

- Subtrochanteric or diaphyseal stress fractures
- Risk increases with duration (>3 –5 years)
- Consider drug holiday after 3–5 years in stable disease
- Counsel patients: report thigh/groin pain promptly

Section 3: Systemic Oncologic Therapies



Spinal Metastases: Integrating Supportive Care

Systemic Therapy by Primary Tumor Type

Breast Cancer

- HR+/HER2-: CDK4/6 inhibitor + ET (palbociclib/ribociclib/abemaciclib); fulvestrant; chemotherapy (capecitabine, eribulin)
- HER2+: Trastuzumab-based regimens; T-DM1; tucatinib; pertuzumab
- TNBC: Chemotherapy ± immunotherapy (pembrolizumab); PARP inhibitors (BRCA-mutant); sacituzumab govitecan

Prostate Cancer

- Androgen deprivation therapy (ADT): backbone of mCSPC and mCRPC
- mCSPC: ADT + docetaxel, darolutamide, enzalutamide, or abiraterone
- mCRPC: enzalutamide, abiraterone, cabazitaxel, PARP inhibitors (olaparib, rucaparib for HRR-mut), lutetium-PSMA-617

Lung Cancer

- EGFR-mutant: osimertinib (superior CNS/bone penetration); brain/spine mets respond well
- ALK/ROS1: alectinib, brigatinib, lorlatinib; excellent CNS penetration
- KRAS G12C: sotorasib, adagrasib
- Immunotherapy: pembrolizumab ± chemotherapy; nivolumab/ipilimumab

Renal Cell Carcinoma

- First line: ipilimumab + nivolumab; pembrolizumab + axitinib/lenvatinib; cabozantinib + nivolumab
- VEGFR TKIs (sunitinib, pazopanib, cabozantinib): bone lesion response
- mTOR inhibitors: everolimus, temsirolimus in selected patients

Systemic treatment

Tumor Type	First-Line Treatment	Treatment Efficacy
Hormonal receptor-positive breast cancer	Combination of hormone-therapy and cyclin-dependent kinase 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib)	Median overall survival (OS) is 63.9 months for ribociclib [76]
HER2-positive breast cancer	Combination of taxane-based chemotherapy and dual HER-2 blockade	Median OS is 56.5 months [77]
Castration-sensitive prostate cancer	Androgen deprivation therapy plus hormonal therapy	Median OS > 52 months (median overall survival not yet reached) [78]
Renal cell carcinoma	Combination of a tyrosine-kinase inhibitor (axitinib) and immunotherapy (pembrolizumab) or double immunotherapy (ipilimumab + nivolumab)	Median OS is 45.7 months [79]
Multiple myeloma	Bortezomib (proteasome inhibitor), lenalidomide, and dexamethasone (corticosteroid)	Median OS is 60 months [80]
Testicular germ cell tumors	Platinum-based chemotherapy (e.g., bleomycin + cisplatin + etoposide—good performance status only)	Good-risk disease: 90% cure rate; intermediate-risk disease: 80% cure rate; high-risk disease: 50% cure rate [83]

Targeted Therapy & Immunotherapy: Spine-Specific Considerations

CNS/Bone Penetration

Select TKIs with proven CNS/bone penetration: osimertinib, alectinib, lorlatinib, brigatinib. Assess CSF and bone marrow concentration data when choosing agents in patients with vertebral and epidural disease.

Immunotherapy & Spine RT

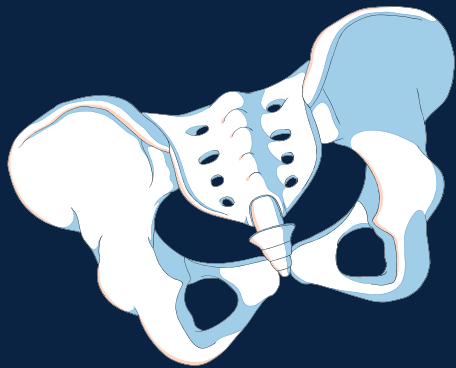
Concurrent SBRT + ICI: emerging synergy (abscopal effect). Timing matters: give ICI before/during RT, not after. Monitor for radiation recall, myelitis, and immune-related adverse events (irAE) in the spine.

Hormone Therapy & Bone

AI-induced bone loss in breast cancer: bone density monitoring (DXA) every 1–2 years. ADT-related osteoporosis in prostate cancer: bisphosphonate or denosumab for T-score < -2.0 or fracture risk (FRAX). Calcium + Vitamin D universal.

Radiopharmaceuticals

Radium-223: α -emitter for mCRPC with symptomatic bone mets (no visceral mets). 6 cycles IV q4w. OS benefit in ALSYMPCA trial. Lutetium PSMA-617: VISION trial; response in bone mets. Emerging: 177Lu-DOTATATE for neuroendocrine tumors with spinal mets.



Section 4: Radiation Therapy Integration

Spinal Metastases: Integrating Supportive Care



Radiation Approaches: EBRT vs. SBRT/SSRS

Conventional EBRT

- Indications: pain palliation, impending/actual cord compression, diffuse spinal disease, poor PS
- Common fractionation: 8 Gy $\times$ 1, 20 Gy $\times$ 5, 30 Gy $\times$ 10
- 8 Gy $\times$ 1 = 20 Gy $\times$ 5 for pain relief (ASTRO guideline-recommended for uncomplicated bone mets)
- Re-irradiation feasible with careful cord dose tracking
- Rapid symptomatic relief (1–2 weeks); systemic agents can be continued

Spine SBRT / SSRS

- Indications: oligometastatic disease, radioresistant histologies (RCC, melanoma, sarcoma), re-irradiation
- Fractionation: 24 Gy $\times$ 1, 27 Gy $\times$ 3, 30–35 Gy $\times$ 5 (SSRS protocols)
- Superior local control vs. EBRT; improved pain response in radioresistant tumors
- Requires careful spinal cord dose constraints (< 14 Gy point max for SSRS)
- Contraindicated: frank cord compression, spinal instability — consider surgical decompression first

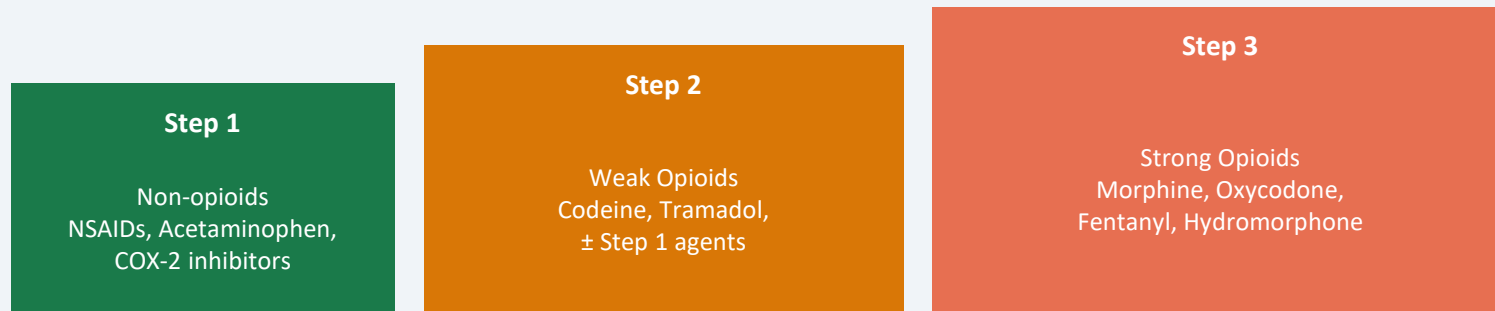


Section 5: Supportive Care Principles

Spinal Metastases: Integrating Supportive Care

Analgesic Strategy in Spinal Metastatic Pain

WHO Analgesic Ladder



Adjuvant Analgesics & Interventional Options

Neuropathic Agents

- Gabapentin 300–1200 mg TID
- Pregabalin 75–300 mg BID
- Duloxetine 30–60 mg daily
- TCAs (amitriptyline): low-dose

Corticosteroids

- Dexamethasone: 4–8 mg q12h
- Rapidly reduces edema around cord
- Wean once oncologic Rx initiated
- Consider prophylactic PPI

Interventional

- Vertebroplasty / kyphoplasty
- Epidural steroid injection
- Celiac/splanchnic block
- Intrathecal pump (refractory pain)

Corticosteroids, Functional Preservation & Rehabilitation

Corticosteroid Use

- Dexamethasone 10–16 mg IV bolus for acute MSCC, then 4 mg q6h
- Evidence for MSCC: high-dose improves motor function and ambulation at 3 months (ASTRO/ESMO)
- Moderate-dose (4 mg q12h) similar efficacy with less toxicity for non-emergent cases
- Monitor: hyperglycemia, GI bleeding (add PPI), infection, psychiatric effects, myopathy
- Taper schedule: begin once definitive RT or surgery initiated; avoid prolonged use

Rehabilitation & Function

- SINS score (Spinal Instability Neoplastic Score): guides surgical vs. non-surgical approach
- ESCC (Epidural Spinal Cord Compression) grading: 0–1c determines RT vs. surgery-first strategy
- Physiotherapy: early mobilization post-RT or post-surgery; minimize deconditioning
- Bracing (TLSO): SINS 7–12 (potentially unstable); prevents deformity during RT
- Occupational therapy: ADL modifications, fall prevention, home safety assessment
- Bowel/bladder management: neurogenic bladder protocol if cord compression present

Surgical Indications: NOMS & SOAPP Decision Frameworks

NOMS Decision Framework

N

Neurologic:

Grade of cord or cauda compression (ESCC scale). High-grade → surgical decompression considered

O

Oncologic:

Radioresponsive (myeloma, lymphoma, seminoma): RT alone.
Radioresistant (RCC, sarcoma): surgery + SBRT

M

Mechanical:

SINS score: stable (0–6) = RT; unstable (13–18) = surgery;
indeterminate (7–12) = spine surgery consult

S

Systemic:

Medical fitness for surgery, performance status, prognosis, life expectancy ≥ 3 months for surgery to benefit

Surgical Approaches

Separation Surgery:

Circumferential decompression creating ≥ 2 mm cord-tumor gap to allow SBRT dose escalation (Patchell trial rationale)

En Bloc Resection:

WBB stage-guided; for primary spine tumors or oligometastatic radioresistant mets with long prognosis

Pedicle Screw Fixation:

Stabilization of unstable/painful segments; can be performed MIS in select cases

Vertebroplasty/Kyphoplasty:

Percutaneous cement augmentation for painful vertebral compression fractures without cord compromise

Post-op RT timing:

SBRT can begin 2–4 weeks post-surgery (allow wound healing); conventional EBRT may start earlier

Section 6: Multidisciplinary Care Integration

Spinal Metastases: Integrating Supportive Care

Multidisciplinary Team: Roles & Integration

Medical Oncologist

Systemic therapy, BTAs, line sequencing

Radiation Oncologist

EBRT, SBRT/SSRS planning, cord dose

**Spinal
Mets
Patient**

Spine Surgeon

NOMS assessment, decompression, stabilization

Pain/Palliative Medicine

Analgesics, QoL, goals of care, ACP

Physio/OT Rehabilitation

Mobilization, bracing, fall prevention

Interventional Radiology

Vertebroplasty, ablation, embolization

Palliative Care, Goals of Care & End-of-Life Planning

Early Palliative Care Integration

- ASCO recommends concurrent palliative care with oncologic therapy
- Temel et al. (NEJM 2010): improved survival + QoL in early palliative care NSCLC
- Address: pain, fatigue, dyspnea, nausea, anxiety, caregiver burden

Goals of Care Conversations

- Prognosis communication using validated tools (PPS, Tokuhashi score, SINS)
- Determine: curative intent vs. life-prolonging vs. comfort-focused
- Align treatment intensity with patient values and functional goals

Advance Care Planning

- POLST/MOLST: document resuscitation and hospitalization preferences
- Advance directives: healthcare proxy designation
- Timely hospice referral: oncologists often refer too late (median < 4 weeks)

Psychosocial & Spiritual Support

- Distress thermometer screening: refer at score ≥ 4
- Social work for financial/logistic barriers to care
- Chaplaincy and spiritual care: often underutilized in oncology

Illustrative Case Integration

Case: 62-year-old woman, HR+/HER2- breast cancer, known vertebral metastases T6 and L3. New back pain, mild bilateral leg weakness, MRI confirms ESCC grade 1b at T6. SINS score 9. Currently on CDK4/6 inhibitor + aromatase inhibitor.

1. Stabilize

Dexamethasone 8 mg q12h IV
Neurologic monitoring q4h
Emergent spine surgery consult

2. Radiate

Spine surgery: SINS 9 → monitoring
SBRT T6: 24 Gy × 1 (radioresistant histology)
Elective EBRT L3 for pain (8 Gy × 1)

3. Systemic

Continue CDK4/6i + AI if stable
Add denosumab 120 mg SC q4w
Calcium + Vitamin D supplementation

4. Supportive

Gabapentin for neuropathic pain
TLSO brace during ambulation
Physio + OT referral; palliative care consult

→ MDT tumor board review within 48 hours; reassess neurologic status, imaging, and treatment goals with patient and family

Key Takeaways

- 1 Spinal metastases require integrated, multidisciplinary management — no single modality suffices.
- 2 Bone-targeted agents (zoledronic acid, denosumab) reduce SREs and should be initiated early; select based on renal function and patient preference.
- 3 Systemic therapy selection must consider tumor histology, biomarkers (HR, HER2, EGFR, ALK, BRCA), and prior treatment history.
- 4 The NOMS framework guides the surgical vs. radiation decision. Separation surgery enables SBRT dose escalation for radioresistant histologies.
- 5 Analgesic management should follow a systematic approach: WHO ladder + adjuvants + interventional options for refractory pain.
- 6 Early concurrent palliative care improves QoL and should be embedded — not deferred — in the care plan from diagnosis of spinal metastases.

Selected References & Guidelines

1. ASCO Clinical Practice Guideline: Bone-Modifying Agents in Metastatic Breast Cancer (2017 update)
2. Loblaw DA et al. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. J Clin Oncol. 2005
3. Bilsky MH et al. The reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine. 2010
4. Fisher CG et al. A novel classification system for spinal instability in neoplastic disease (SINS). Spine. 2010
5. Patchell RA et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer. Lancet. 2005
6. Temel JS et al. Early palliative care for patients with metastatic non–small-cell lung cancer. NEJM. 2010
7. Hoskin P et al. Efficacy of single and multiple fraction radiotherapy for the palliation of painful bone metastases: RTOG 97-14 trial. J Clin Oncol. 2011
8. Fizazi K et al. Radium-223 and Survival in Metastatic Prostate Cancer (ALSYMPCA). NEJM. 2013
9. ESMO Clinical Practice Guidelines: Bone Health in Cancer (2020)
10. Stopeck AT et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer. J Clin Oncol. 2010