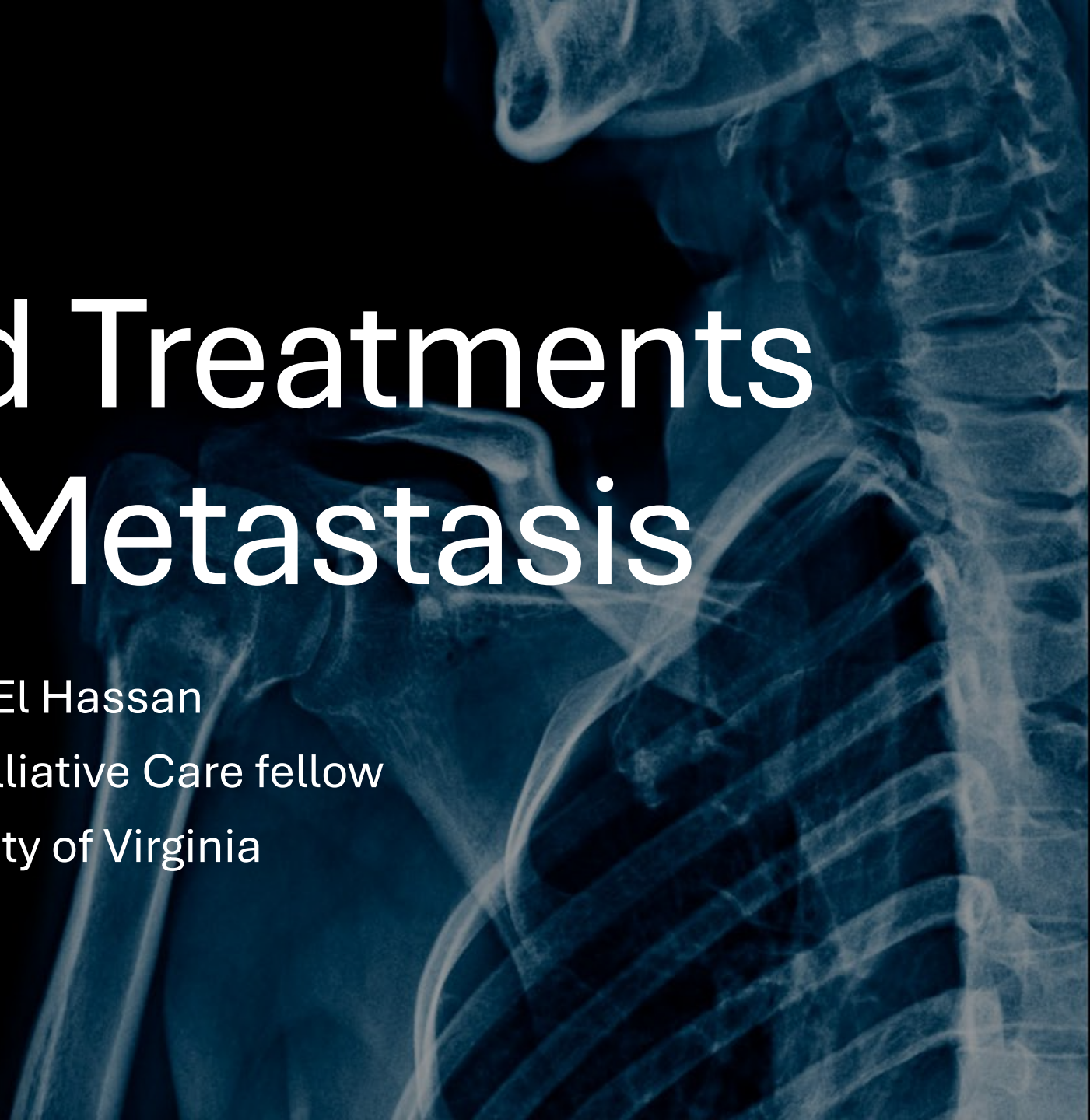
Non-Opioid Treatments for Bone Metastasis



Ziad El Hassan

Hospice & Palliative Care fellow

University of Virginia

Objectives

- Identify the key mechanisms and types of bone metastases (osteolytic, osteoblastic, and mixed) and describe how they contribute to cancer-induced bone pain (CIBP) in palliative care patients.
- Compare non-opioid pharmacological and non-pharmacological treatment options for managing CIBP, including their mechanisms, indications, typical dosing, and main limitations or side effects.
- Evaluate advanced interventional approaches for refractory or complicated bone metastasis pain, including criteria for patient selection and expected outcomes.

- This is the case of a **22-year-old male** with a pertinent past medical history of **metastatic cardiac angiosarcoma**, complicated by malignant pleural effusion and **infiltrative lytic disease involving the left iliac wing, left acetabulum, and right inferior pubic ramus**.

Prior Treatments and Clinical Course

Initial Outpatient Pain Management

- Oral opioids were attempted prior to hospitalization, including **oxycodone** and **hydromorphone**.
- **Long-acting morphine** was subsequently added.
- His final outpatient regimen prior to hospitalization consisted of:
  - Morphine ER 30 mg TID
  - Oxycodone 15 mg every 4 hours PRN
  - Pregabalin (Lyrica) 150 mg BID

Hospitalization – September 2025

- The patient was hospitalized in **September 2025** due to **uncontrolled pain**.
- A **fentanyl PCA** was initiated; however, his opioid requirements continued to escalate, reaching a **total of 6425 mcg**, with an estimated **MEDD of 1285 mg**.

Opioid Rotation and Adjuvant Therapy

- **Methadone 10 mg TID** was initiated, and **duloxetine (Cymbalta)** was added for neuropathic pain.
- The PCA was rotated from fentanyl to **hydromorphone**.
- Despite these changes, the patient continued to require **38 mg of IV hydromorphone via PCA**, with an estimated **MEDD of 660 mg**.
- **Methadone was increased to 15 mg TID**, but hydromorphone requirements continued to rise, with the **total MEDD exceeding 1800 mg**.

Radiation Therapy

- Given persistent uncontrolled pain, **Radiation Oncology** was consulted.
- The patient underwent **15 fractions of palliative external beam radiation therapy (EBRT)**.

- Steroid Therapy
  - **Prednisone** 20 mg daily was initiated for 5 days.
- Further Opioid Escalation
  - **Methadone** was titrated to 20 mg TID and subsequently to **30 mg TID**
  - **Oral hydromorphone** 12 mg every 3 hours PRN was used for breakthrough
- Opioid-Related Complications
  - The patient subsequently developed multiple opioid-related adverse effects,
    - Opioid-induced **myoclonus**
    - **Respiratory depression**, requiring end-tidal CO, monitoring
    - Worsening opioid-induced constipation (OIC)

Interventional Pain Management

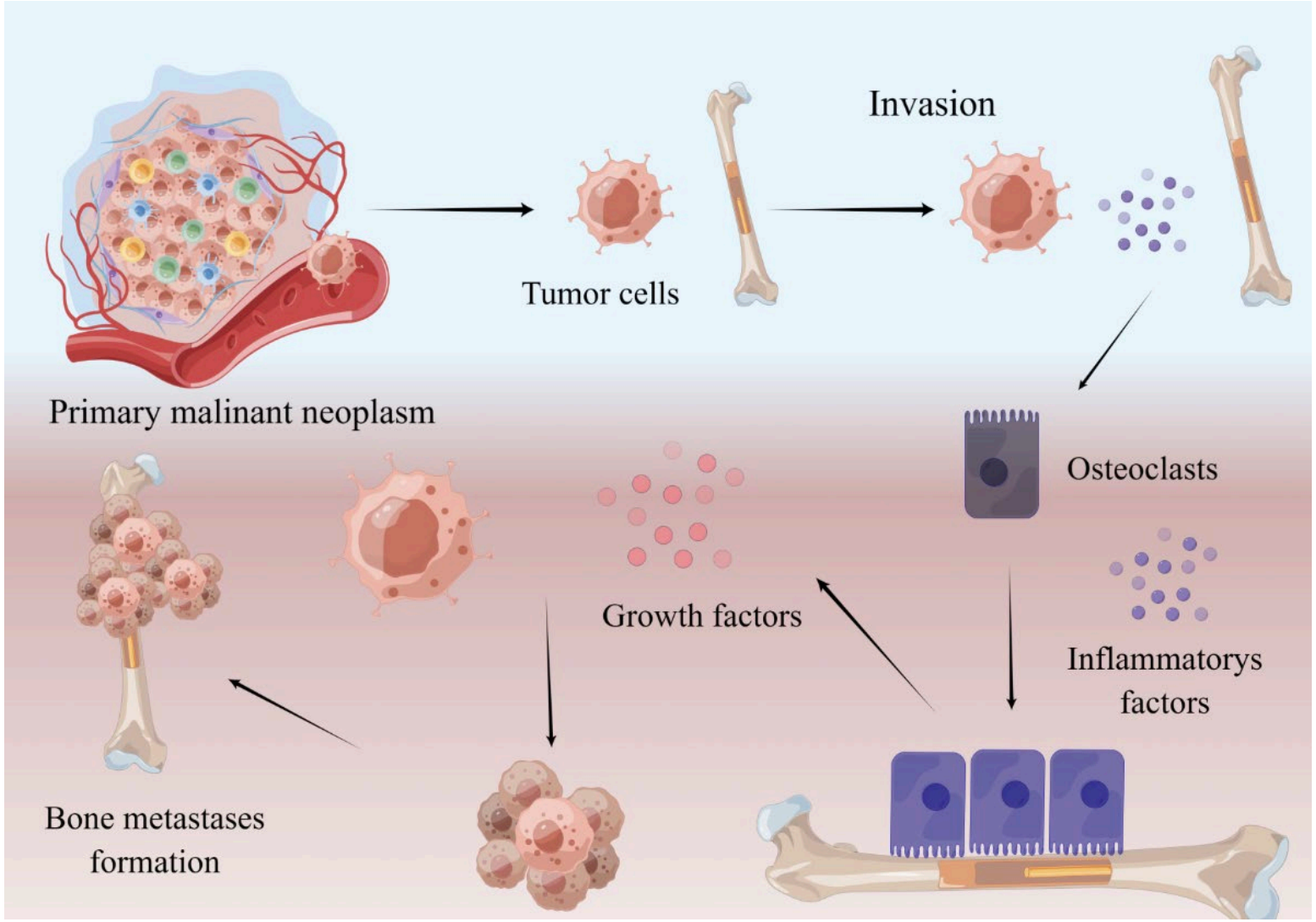
- The **Acute Pain Service (APS)** was consulted for **intrathecal pump (ITP) placement with patient-controlled bolus capability**.
- A **methadone taper** was initiated along with adjustments to breakthrough medications.
- APS gradually titrated the intrathecal pump to:
  - **Hydromorphone 750 mcg/day**
  - **Bupivacaine infusion**
  - **Patient Therapy Manager (PTM): hydromorphone 30 mcg + bupivacaine 0.03 mg per dose**

Introduction

- Skeleton is one of the most common sites of metastasis.
- It profoundly impacts our patients' physical and mental health.
- In recent years, survival times for the cancer patient population have increased, making effective symptom control even more essential to improve and maintain quality of life.

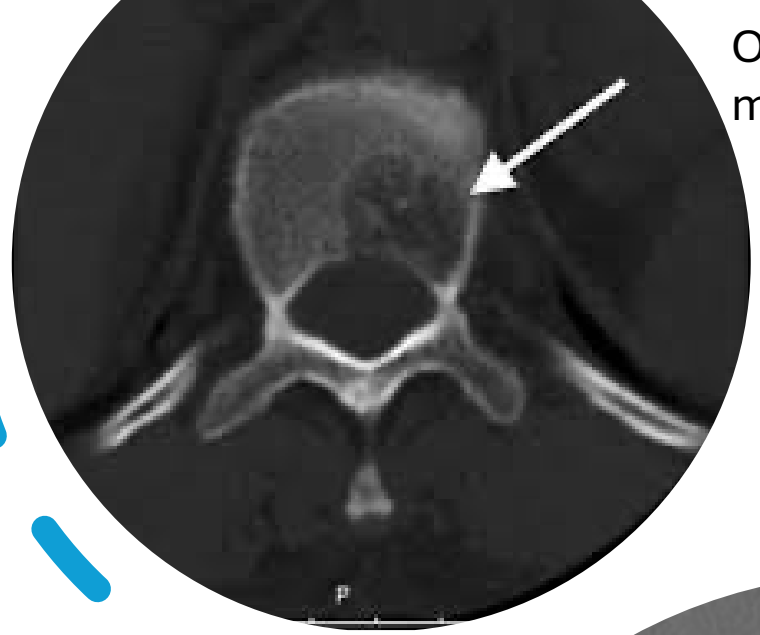
Mechanism of Bone Metastasis

Tumor cells ➔ RANKL, VEGF, TNF-α & other IL are secreted➔ Osteoclast activation➔ Favorable conditions for tumor growth➔ Specific tumors can promote osteoblast activation.

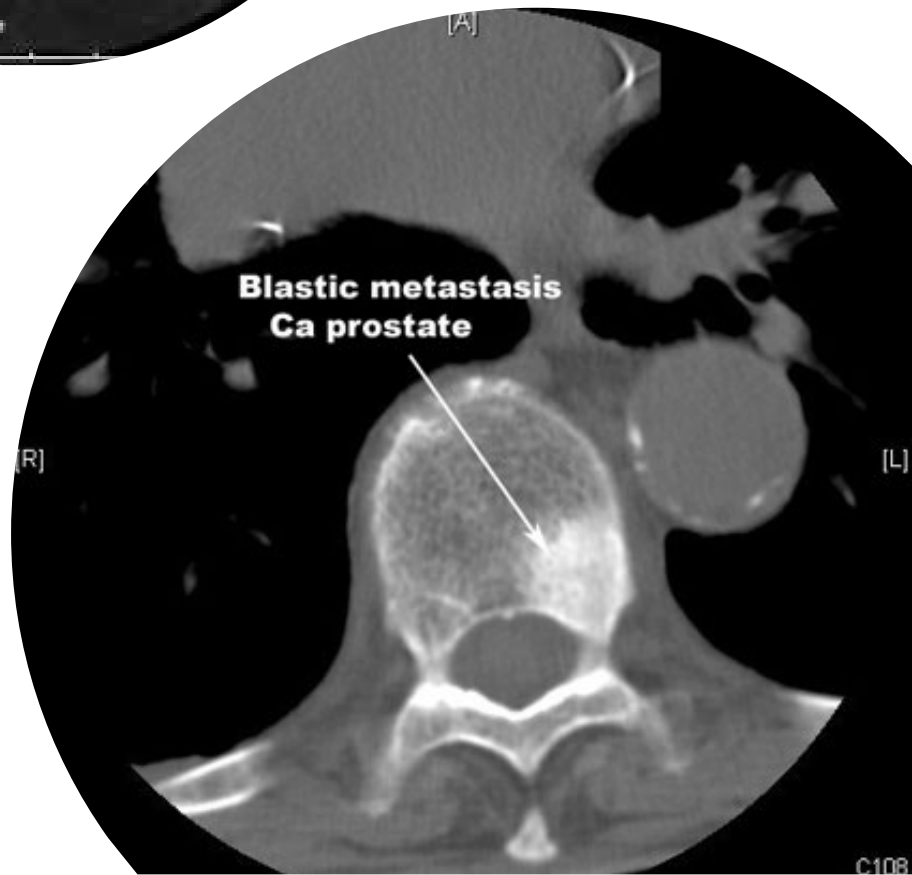


Osteoblastic vs Osteolytic lesions

- Osteoblastic cancers:
  - Prostate CA
  - Carcinoid
  - SCLCA
- Mixed:
  - Breast CA
  - GI malignancies
  - Squamous CA
- Lytic cancers:
  - RCC
  - MM
  - Melanoma
  - Many others

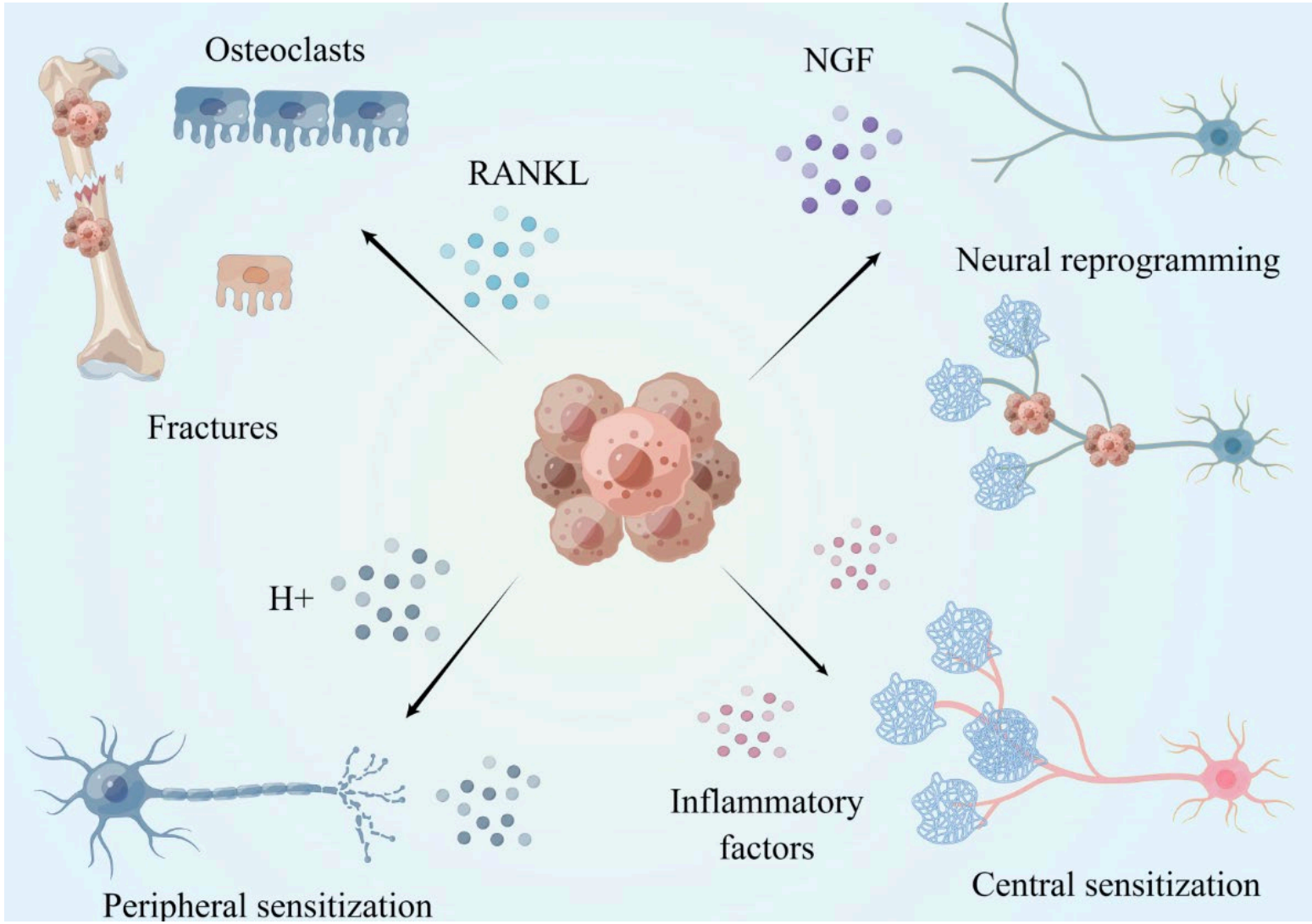


Osteolytic metastasis



Mechanism of CIBP

1. Inflammatory process
2. Ischemic
3. Compressive/Muscular
4. Injurious neuropathological processes



Skeletal Related Events (SRE)

- Morbidities or symptoms associated with metastatic bone:
  1. Pain (most common)
  2. Impending or pathological fractures
  3. Compression of nerve roots and/or spinal cord
  4. Hypercalcemia
- Notably, 1/3 of patients can experience no symptoms.
- Bone pain results in constant baseline pain punctuated by intermittent episodes of severe pain. Hence, the importance of utilizing long and short acting medications if surgical/radiological options were not viable.

Evaluation & Diagnosis

1. Plain X-ray:
   - Good initial test for bone pain. However, it can only detect if mineral loss is more than 25-50%.
2. Tc 99 bone scintigraphy:
   - Relatively cheap as it provides inspection of the whole skeleton.
   - Shows osteoblastic lesions.
   - Pure osteolytic lesions will not be picked up.
3. FDG PET scan:
   - Detects both.
4. CT/MRI:
   - Better spatial resolution. MRI further identifies spinal cord involvement.

Interview of patient, radiograph, CT, and MRI of the lesion

Patient has known metastatic bone disease

Patient has a known cancer but no known bone metastases

Serum tumor marker elevation or presence of multiple skeletal foci by bone scintigraphy or PET/CT

Yes

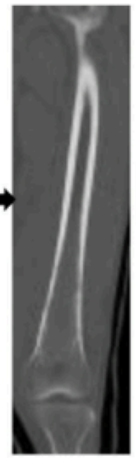
No

Bone destruction or sclerotic +
Periosteal reaction −

Metastatic bone tumor

Patient has no known history of active cancer

Physical examinations
CT of the chest, abdomen, and pelvis
Blood tests
Serum tumor marker: PSA, AFP, CEA, protein electrophoresis, sIL2-R
Urine test: hematuria, Bence Jones protein, urine cytology
Bone scintigraphy or PET/CT



Ill-defined
Bone destruction +
Periosteal reaction +

Osteomyelitis

Biopsy or curettage

Primary lesion remains unclear

Biopsy

Primary lesion identified

Sclerotic rim+
Bone destruction −
Periosteal reaction −

Primary benign bone tumor

Biopsy

Curettage or conservative therapy

Multidisciplinary team discussion

Ill-defined
Sclerotic rim−
Bone destruction +
Periosteal reaction +

Primary malignant bone tumor

Biopsy

Chest CT
Bone scintigraphy
PET/CT

Wide resection ± chemotherapy

Expected survival of <6 weeks

Best supportive care

Expected survival of ≥6 weeks

Treatment

Choice of Treatment

- Depends on the following:
  1. Patient’s general health condition
  2. Extent of the disease
  3. Complications resulting from the disease
  4. Life expectancy

Physical Therapy

- It focuses on pain relief, restoring mobility, and preventing future fractures through gentle strengthening, posture correction, and balance training.

- This can be a good starting point for patients with no or minimal malignant pain, in whom some discomfort may be attributed to pathologic vertebral fractures.

- The patient may also use short-acting opioids prior to these sessions to improve compliance.

Nonopioid Medication Management

- Malignant bone growth recruits immune cells with massive inflammatory cytokines and mediator potentials such PGE2, NGF, TNF-α, and proinflammatory IL.
- NSAIDs are 1st-line therapy for mild-to-moderate CIBP.
- Associated with cardiovascular, nephrological, and gastrointestinal risks.
- Tylenol, while effective for mild pain relief, it lacks the anti-inflammatory properties of NSAIDs.

Anti-Histamine

- Commonly used as a palliative, second-line treatment to alleviate bone pain induced by colony-stimulating factors (G-CSF) like pegfilgrastim (Neulasta). Not necessarily metastatic bone pain.

- Acts by blocking histamine-induced inflammation and swelling in the bone marrow.

- Loratadine (Claritin) 10 mg daily is the most investigated and used antihistamine.

Steroids

- Recommended as an adjuvant analgesic for cancer-related bone pain.
- Mechanism: decreasing tumor-related edema or inhibition of prostaglandin and leukotriene synthesis.
- Agent: dexamethasone is likely the most prescribed corticosteroid for cancer-related bone pain due to its lower mineralocorticoid effect and long half-life, which allows once-daily dosing.
- Dose for cancer-related bone pain: most studies support total daily doses of 2 to 8 mg of oral dexamethasone either given once in the AM or divided over BID dosing.
- Dose for an acute pain crisis from bone pain: in the event of an acute pain crisis unresponsive to parenteral opioids, some experts suggest a loading dose of 8-10 mg x1 followed by 4 to 8 mg BID, with the goal of tapering to the lowest dose that continues to provide adequate analgesia.

Steroids

- Dose for prevention of pain from radiation therapy of bone metastases: a systematic review of several randomized controlled trials found that corticosteroids led to a significant relative risk reduction of 43% in the incidence of pain flares from radiation therapy to bone metastases. Dexamethasone 8 mg oral daily for 5 days is a commonly described dose regimen for this indication.
- Duration of therapy: While the optimal duration is unknown, a corticosteroid taper is usually not necessary if taking 4 mg or less of dexamethasone for less for 3 weeks or less. Therefore, if no benefit is seen within 5-7 days, the corticosteroid likely can be discontinued. If beneficial, the drug should be tapered to the lowest effective dose or, if possible, discontinued to avoid long-term adverse effects.

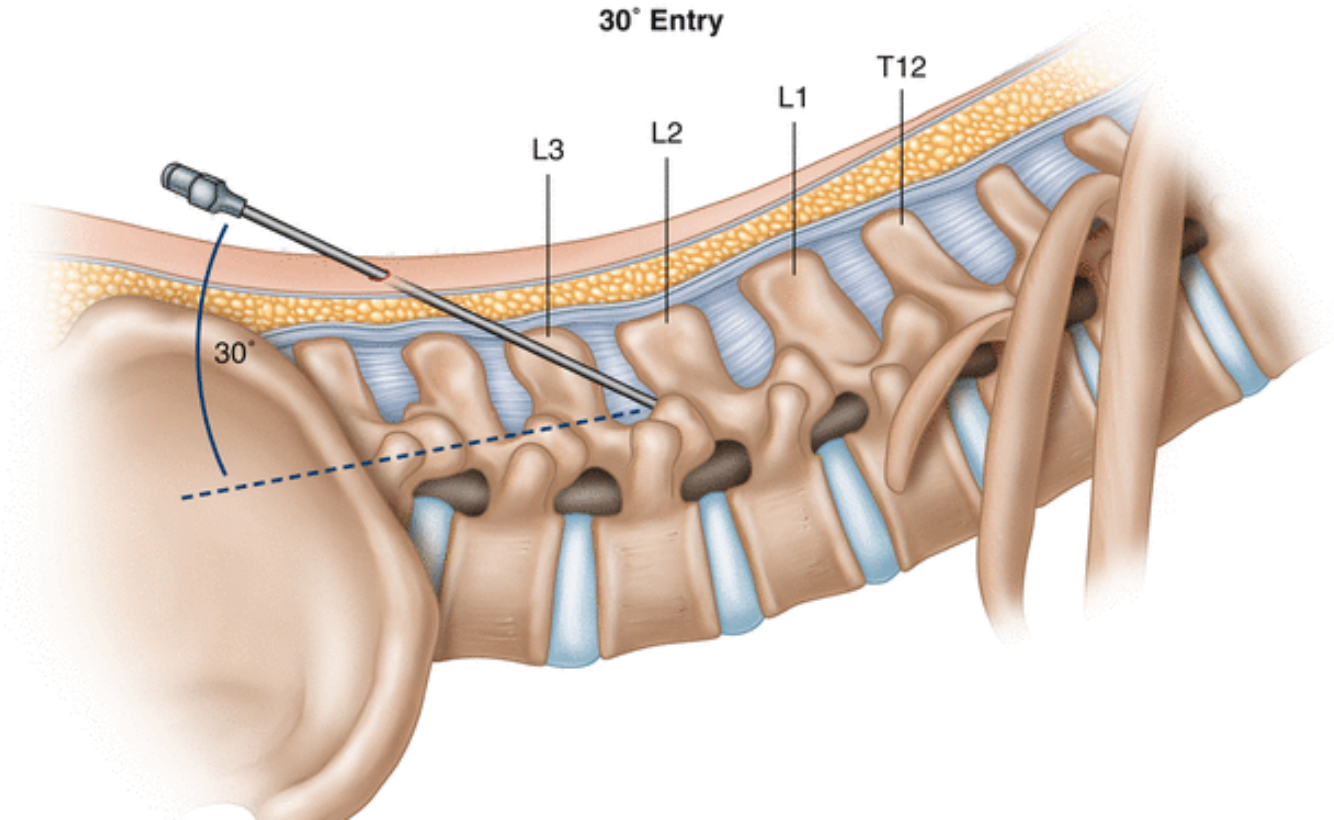
Steroids

- **Side effects** account for discontinuation of steroids in 5% of patients. The risk of side effects correlates with dose and duration of treatment.
  - Early side effects (days): thrush (~30%), edema (20%), dyspepsia, peptic ulcer diseases, symptoms (insomnia, delirium, and anxiety), glucose intolerance.
  - Delayed side effects (weeks to months): adrenal suppression, myopathy leading to proximal muscle weakness in limbs, moon facies/fat redistribution, susceptibility to infection, osteoporosis, skin fragility, impaired wound healing.

Lidocaine patches

- Lidocaine patches are effective, safe, and often used as a localized, non-opioid adjuvant treatment for cancer-related pain, especially for superficial metastatic bone pain with neuropathic pain such as shoulder or rib cage pains.
- **Dosage**: Up to 3 patches can be used simultaneously, typically for up to 18 hours per day, followed by a 6-hour patch-free interval.
- **Side Effects:** Generally well-tolerated, with rare and mild local side effects like skin irritation or rash.
- **Contraindications:** Avoid application on broken skin and in patients with severe hepatic impairment. Weak evidence.

Epidural Intrathecal Opioids



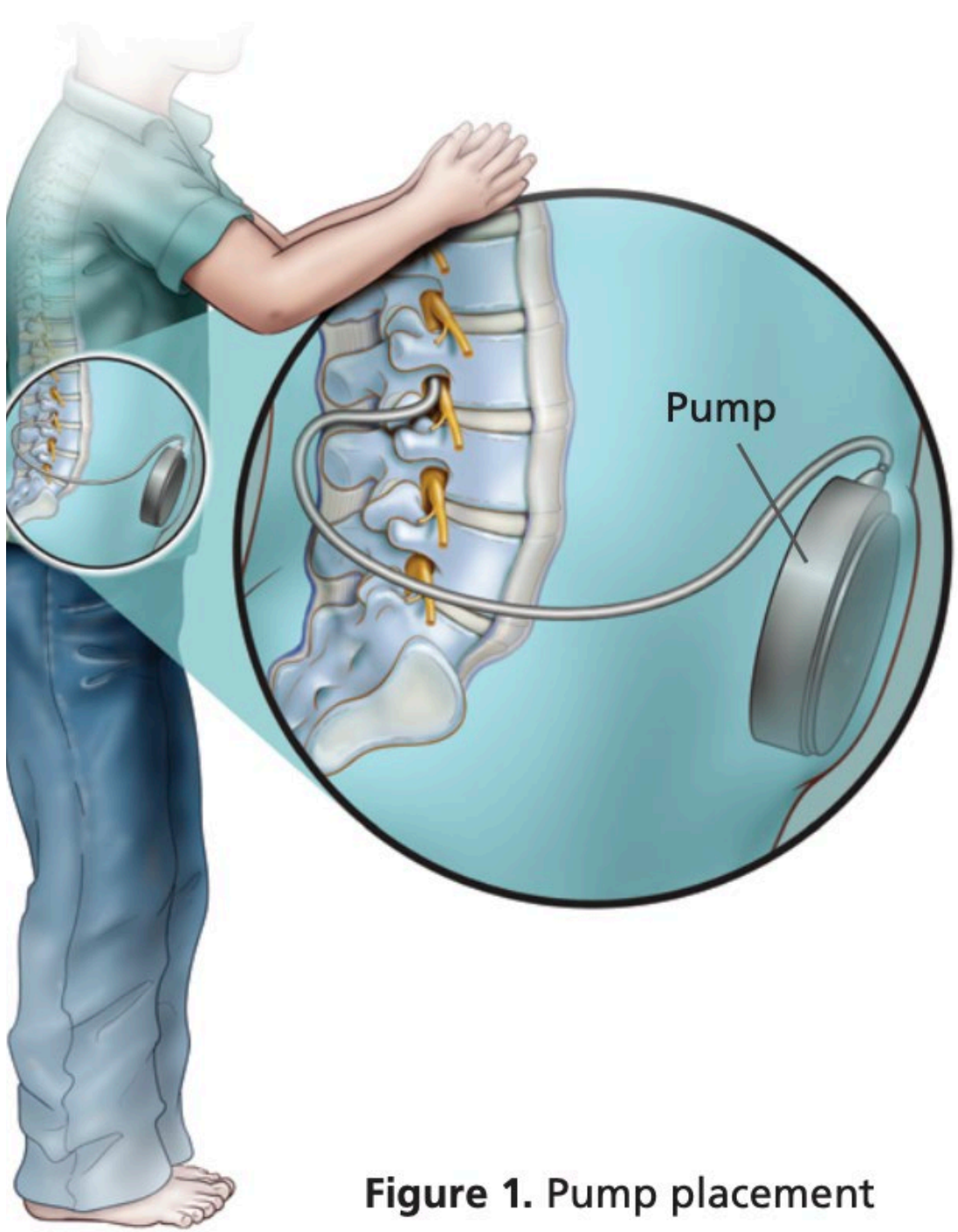


Figure 1. Pump placement

Epidural Intrathecal Opioids

- Epidural or intrathecal (spinal) opioids are advanced interventional options for managing severe, refractory bone metastatic pain in patients with advanced cancer.
- Targeted analgesia at much lower doses than systemic administration. Thus, reduces opioid side effects like sedation, nausea, constipation, and respiratory depression.
- Common requirements:
  1. Inadequate pain relief despite high-dose systemic opioids (MEDD >200).
  2. Dose-limiting side effects from systemic opioids
  3. Life expectancy often >3–6 months
  4. Failure of or intolerance to less invasive options (e.g., bisphosphonates, radiotherapy, nerve blocks)

Surgical Interventions

- Patients with a short life expectancy would not qualify.
- Surgical Resection for patients with a single site of metastasis.
- Tumor resection and reconstruction would be a 1st line for patients unstable spine, spinal cord compression or nerve function injury
- Timely surgical intervention can fully relieve CIBP.
- Scoring systems can utilized to estimate prognosis such Tokuhashi scoring system.
- Steroids can be utilized for a short duration for immediate neurologic relief until surgery.

Tokuhashi Scoring System

General condition (Karnofsky Performance Status)	**Good (KPS 80%-100%)**	**+2**	
	Moderate (KPS 50%-70%)	+1	
	Poor (KPS 10%-40%)	0	
Number of extraspinal bone metastases foci	**0**	**+2**	
	1-2	+1	
	≥3	0	
Number of metastases in the vertebral body	1	+2	
	2	**+1**	
	≥3	0	
Metastases to the major internal organs	**No metastases**	**+2**	
	Removable	+1	
	Unremovable	0	

Primary site of the cancer	**Thyroid, prostate, breast, carcinoid tumor**	**+5**
	Rectum	+4
	Kidney, uterus	+3
	Others	+2
	Liver, gallbladder, unidentified	+1
	Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0

Spinal cord palsy (Frankel Grade)

Frankel Grade:

- Grade A: Complete motor and sensory involvement.
- Grade B: Complete motor involvement, some sensory sparing including sacral sparing.
- Grade C: Functionally useless motor sparing.
- Grade D: Functional motor sparing.
- Grade E: No neurologic involvement.

None (Frankel E)	**+2**
Incomplete (Frankel C, D)	+1
Complete (Frankel A, B)	0

14 points

Revised Tokuhashi Score

≥12 months

Mean Survial

Copy Results

Next Steps

Surgical Interventions

- Spinal separation surgery can be offered for those who cannot tolerate total spine resection.
  - It would decompress the spinal cord as well as create a safe gap for high-dose radiation (SBRT).
- Percutaneous vertebroplasty (PVP) or Percutaneous kyphoplasty (PKP) are offered for compression fractures without spinal involvements.
  - The heat released during the procedure can kill local nerves and effectively relieve the pain associated with thoracolumbar pathologies.
  - Post-operative adjuvant radiotherapy can be also be offered.

Prophylactic Fixation

- Typically considered for long bones (the femur or humerus) when there's a high risk of impending fracture, as opposed to waiting for an actual break to occur.
- Several scoring systems and criteria help determine when surgery is warranted:
  - **Mirels' Criteria**: This is a widely used scoring system based on four factors:
    - Site of lesion (upper limb: 1 point; lower limb: 2; peritrochanteric: 3)
    - Pain (mild: 1; moderate: 2; functional: 3)
    - Lesion type (blastic: 1; mixed: 2; lytic: 3)
    - Size relative to bone diameter (<1/3: 1; 1/3-2/3: 2; >2/3: 3)
- Total scores range from 4 to 12:
  - Score of 8 or higher recommends prophylactic fixation, as it correlates with a fracture risk of about 15-33%.
  - Scores of 7-8 may involve clinical judgment,
  - Scores of ≤7 often suggests non-surgical management like radiation.

Radiation Therapy

- Common Methods:
  1. External beam radiation therapy (EBRT)
  2. Stereotactic body radiotherapy (SBRT)
  3. Wide field/half-body irradiation

Radiotherapy

- Safe and effective in patients who cannot tolerate surgical options.
- Bone ossification occurs within 3-6 weeks.
- 60% experiences significant pain relief!
- Stereotactic body radiotherapy (SBRT) can deliver high-dose radiation to tumors while protecting adjacent normal tissues.
- It is worth noting that radiotherapy may lead to the occurrence of fracture or nerve injury in the spinal cord.

Treatment of spine metastasis ± cord compressio

Treatment	Pros	Cons
Steroid	Immediate neurologic relief	Short duration
External beam radiotherapy	Main-stay treatment Pain relief Neurologic improvement Non-invasive	Protracted course Pain recurrence Neurologic progression Knocks down bone marro
Surgery (Circumferential decompression, Laminectomy)	Rapid neurologic improvement Tissue diagnosis	Invasive Reconstruction is needed Long recovery time Needs radiotherapy
Vertebroplasty	Pain relief Improve spinal stability?	No tumor control Chemical leakage
Radiosurgery	Rapid pain & neurologic relief Spinal cord decompression Non-invasive Convenience Bone marrow sparing	Cannot correct compression fracture or Spine instability

Stereotactic Body Radiation Therapy

- Highly concentrated form of radiation that can irradiate target tissue at high doses without affecting surrounding normal tissue including the spinal cord.
- Increases risk of compression fractures by 14%.
- Meta-analysis showed that it improved pain 65-81% of patients compared to the 58% who underwent EBRT.

Wide Field/Half-Body Irradiation

- Palliative radiation therapy technique used to treat patients with widespread, painful bone metastases from cancers such as prostate, breast, or lung.
- It involves delivering radiation to approximately half of the body in a single large field, typically divided into:
  - Upper hemibody irradiation (UHBI) covering from the head to the mid-thigh.
  - or
  - Lower hemibody irradiation (LHBI) from the mid-thigh to the feet.

Wide Field/Half-Body Irradiation

- HBI is indicated for:
  - Multiple symptomatic bone metastases causing intractable pain, especially when not controlled by opioids or other analgesics.
  - Widespread skeletal involvement where local radiation would be impractical (e.g., >3-5 sites).
  - Patients with good performance status (e.g., ECOG 0-2) and life expectancy >1-3 months, as it requires tolerance for potential acute toxicities.
  - Cases unresponsive to systemic therapies like bisphosphonates, denosumab, or chemotherapy.

Radiofrequency Ablation

- Also known as Osteocool!
- It consists of microwave ablation and low-temperature ablation.
- Studies have shown that it leads to effective pain control in around 64-77% of cases.
- RFA can be performed prior to PVP or PKP to ablate tumor tissue, create a cavity for more controlled and uniform cement placement, and reduce the risk of cement leakage (particularly venous or posterior epidural extravasation).

Radionuclide-Targeted Therapy

- Treats multiple metastatic tumors simultaneously, primarly used to palliate pain osteoblastic lesions.
- Tracers act as calcium transfer agents or bind hydroxyapatite in bone releasing ionizing radiation in areas of osteoblast activity.
- Alpha emission radionuclides such as ^{223}RA, & ^{143}Pr have good clinical value in preclinical and clinical practice.
  - For instance, Radium Dichloride delivers more radiation to the tumor and less radiation to the surrounding. Hence, less toxicity with only 10% suffering from nausea, vomiting and diarrhea.
- Meta-analysis studies have shown significant pain control in metastatic castration-resistant prostate cancer.

Radionuclide-Targeted Therapy

- Beta emission radionuclides such Samarium-153 & Strontium-89 binds to hydroxyapatite to effectively treat painful osteoblastic metastasis.
- Approximately 75% of patients experience pain relief, and up to 25% may become pain-free.
- The primary toxicity is myelosuppression, which is generally temporary.
- Contraindicated in cases of spinal cord compression, a high risk of fracture of the bones of the lower extremities, or pregnancy and lactation.

Bone-Targeted Therapy

- Bisphosphonates:
  - Pyrophosphate analogues
  - Combines hydroxyapatite on the bone surface ➔ prevents osteoclasts. However, osteoblastic lesions can also lead to increased osteolysis and bone turnover.
  - Reduces Hypercalcemia and SREs.
  - Do not any significant effect on acute pain. Pain in relief in a few weeks can reach 50-75% and last for up to 12 months.
  - They are generally excreted by kidneys
  - Poor PO bioavailability due to Calcium binding. Needs to be taken on empty stomach.
  - Delay onset and lower incidence of SREs.

Bone-Targeted Therapy

- Clodronate was inferior to IV Pamidronate in relieving pain after 3 months of treatment.

Summary of Studies Assessing Metastatic Bone Pain with Standard or Low Doses of Bisphosphonates

No. Patients/Primary Cancer	Scheduling	Study	Results	Reference
Clodronate				
144 breast cancer	1,600 mg/day oral for 1 year	Double-blind, placebo-controlled trial	Significantly reduced pain and analgesic use vs. placebo ($P = 0.01$ and 0.02, respectively)	19
55 various neoplasms	1,600 mg/day oral for 1 year	Double-blind, placebo-controlled trial	Decreased pain ($P = 0.03$), no significant difference in analgesic use	21
Pamidronate				
382 breast cancer	90 mg i.v. every 3–4 weeks, for up to 2 years	Double-blind, placebo-controlled trial	Significant difference in pain scores at 9 and 14 months ($P \leq 0.05$)	23
754 breast cancer	90 mg i.v. every 3–4 weeks, for up to 2 years	Double-blind, placebo-controlled trial. (pooled analysis of two trials)	Final bone pain scores were greater than baseline after 2 years ($P = 0.007$) Analgesic use increased more with pamidronate than with placebo	25
51 breast cancer	90 mg i.v. monthly for 4 months	Controlled trial vs. oral clodronate	Pamidronate significantly ($P = 0.05$) improved pain scores compared with clodronate after 3 months ($P < 0.012$) and 4 months	22
392 multiple myeloma	90 mg i.v. every 4 weeks for 9 months	Double-blind, placebo-controlled study	Pain scores decreased from baseline, only significant at 7 months ($P \leq 0.05$)	27
378 prostate cancer	90 mg i.v. every 3 weeks for 27 weeks	Double-blind, placebo-controlled (pooled analysis of two trials)	No significant or sustained effects on pain scores	28

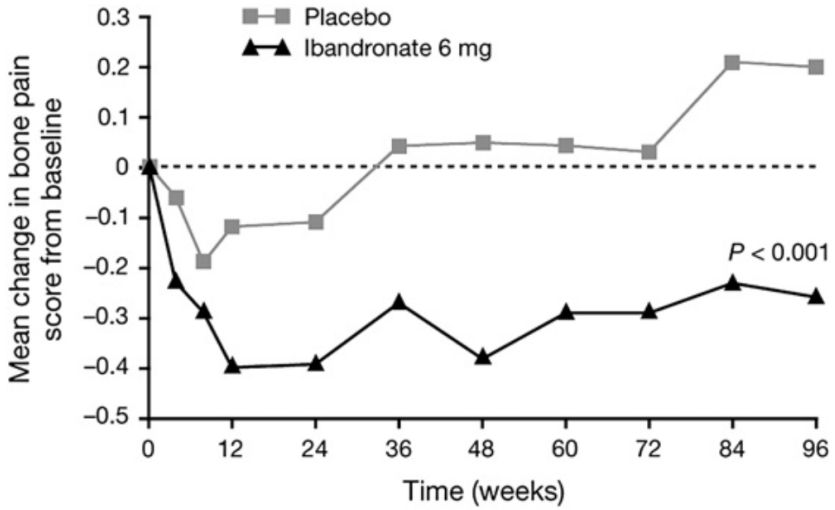
Bone-Targeted Therapy

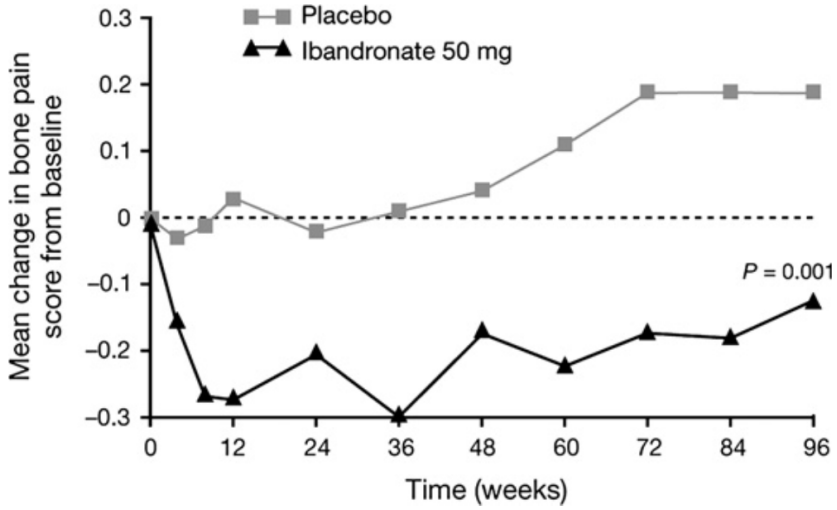
Zoledronic acid				
1,648 multiple myeloma and breast cancer	4 mg i.v. every 3–4 weeks for 13 months	Multicenter double-blind trial vs. pamidronate 90 mg every 3–4 weeks	Bone pain was below baseline for 13 months. Analgesic scores were unchanged	12
773 lung and other solid tumors	4 mg i.v. every 3 weeks for 9 months	Multicenter, double-blind, placebo-controlled trial	Bone pain increased from baseline	30
643 prostate cancer	4 mg i.v. every 3 weeks for 15 months	Double-blind, placebo-controlled trial	Bone pain and analgesic use increased over time	13
227 breast cancer	4 mg i.v. every 4 weeks for 12 months	Randomized, placebo-controlled study	Statistically significant decrease from baseline in mean composite BPI score ($P = 0.0004$). Analgesic scores not different	34
20 prostate cancer	4 mg i.v. every 3 weeks for 6 months	Nonblinded study	Bone pain significantly reduced after 1 ($P = 0.007$) and 3 months ($P = 0.011$)	32
604 various primary cancers	4 mg i.v. every 3–4 weeks	Multicenter, prospective single-arm study	Mean VAS pain scores reduced significantly from baseline until treatment end (36 weeks, $P < 0.0001$). Mean analgesic scores also decreased ($P < 0.0001$)	33
613 multiple myeloma, breast, and prostate cancer	4 mg i.v. every 3–4 weeks	Nonblinded study	Reductions in mean VAS scores from baseline over six study visits. Only statistically significant at visits four and five. Total mean FACT-G quality-of-life score remained constant	37

- Zoledronic acid is the most effective in reducing serum calcium in patient with hypercalcemia and life-threatening complications from osteolytic bone metastases.
- A less intensive schedule (Q12Wks) was reportedly non-inferior for breast CA, prostateCA and MM.

Bone-Targeted Therapy

Ibandronate				
466 breast cancer	6 mg i.v. every 3 weeks	Multicenter, double-blind, placebo-controlled trial	Bone pain remained below baseline for 2 years	41,42
564 breast cancer	50 mg/day oral	Multicenter, double-blind, placebo-controlled trial	Bone pain remained below baseline for 2 years. At endpoint, bone pain scores were reduced significantly from baseline compared to placebo ($P = 0.001$). Analgesic use was significantly reduced ($P = 0.019$)	43,44
99 multiple myeloma for up to 2 years	2 mg i.v. every month placebo-controlled trial	Double-blind study	Bone pain was significantly reduced compared to baseline ($P < 0.047$). No difference in analgesic use	45





Bone-Targeted Therapy

- The main adverse events associated with bisphosphonate therapy are:
  - Acute-phase reactions
  - Gastrointestinal toxicity
  - Renal toxicity
  - Bisphosphonate-induced esophagitis with PO options
  - Osteonecrosis of the jaw

Bone-Targeted Therapy

- Denosumab:
  - Fully human monoclonal antibody
  - Binds and neutralize RANKL with high affinity and specificity to inhibit osteoclast.
  - Dose: 120 mg subcutaneous Q4Wks.
  - Denosumab is superior to Zoledronic acid in delaying onset of SREs but no survival benefit with either.
    - Does not affect kidney function
    - Costly and can cause hypocalcemia and osteonecrosis of jaw
  - Side effects:
    - Hypocalcemia
    - Osteonecrosis of the jaw

Bone-Targeted Therapy

- Denosumab:
  - Vitamin D and Calcium should be given to all patients on it.
  - Development of SRE is not a sign of treatment failure. Do not stop the medication as it can delay 2nd SRE or subsequent complications.
- Ipton et al. performed a randomized controlled trial comparing denosumab and zoledronic acid for their ability to prevent skeletal-related events of bone metastases from various cancers. Denosumab was superior to zoledronic acid in preventing skeletal-related events in patients with bone metastases, regardless of performance status, baseline visceral metastasis presence/absence, bone metastasis number, and urinary N-telopeptide level.
- No difference in serious adverse events except for nephrotoxicity.

Anticonvulsants & Antidepressants

- Neuropathic pain is a important component of CIBP as continuous peripheral stimulation promotes neuroplastic change in the dorsal root ganglion neurons, increasing sensitivity and lowering the pain threshold
- Direct nerve damage can also occur to nerve endings by cancer invasion.
  - Anticonvulsants:
    - Pregabalin is increasingly being used, particularly effective for short/medium term CIBP.
    - Gabapentin has been used but it's efficacy in CIBP treatment has been limited.
  - Antidepressants:
    - Duloxetine
    - Amitriptyline

Complementary & Alternative Medicine

- Traditional Chinese medicine:
  - They are generally well tolerated with light toxicity/side effects.
  - Astragalus a traditional herb, shows promise by inhibiting inflammation, boosting immunity, and protecting nerves, often used in complex formulas with other herbs like aconitum to reduce pain and opioid reliance, targeting mechanisms like bone resorption and nerve sensitization, though large trials are needed.
    - Psoralen, Scutellaria Barbata, Atractylodes Macrocephala, and Corydalis are plants that work with similar mechanisms.
  - Scorpion venom, particularly from Buthus martensii Karsch, and its derivative components are being researched as a traditional Chinese medicine (TCM) approach to alleviate CIBP.
    - BmK AGAP can alleviate bone cancer pain by inhibiting bone destruction and reducing the activation of glial cells (astrocytes and microglia) in the spinal cord, which are responsible for pain transmission

Complementary & Alternative Medicine

- Huachansu is a Chinese medicine derived from dried toad venom, is used as an adjunctive treatment for CIBP.
  - While the exact mechanisms are not fully elucidated, Huachansu is used to alleviate pain and improve the quality of life in cancer patients
- Acupuncture with electrical stimulation has the potential to reduce opioid requirement and their side effects.
  - It activates sympathetic nerve fibers to increase endogenous opioids and inflammatory factors such as β- Endorphin and 5-HT.

Questions?

References

1. Glithero C. **The Challenges of Managing Bone Pain in Cancer**. Ulster Med J. 2020 Jan;89(1):7-10. Epub 2020 Feb 18. PMID: 32218619; PMCID: PMC7027188.
2. Vidhya K, Vandana KD. **Newer Techniques for Bone Pain Palliation in Patients with Skeletal Metastasis**. Clin Oncol. 2024; 9: 2101. ISSN: 2474-1663. Available at: https://www.clinicsinoncology.com/open-access/newer-techniques-for-bone-pain-palliation-in-patients-withnbsp-9773.pdf
3. Jing D, Zhao Q, Zhao Y, Lu X, Feng Y, Zhao B, Zhao X. **Management of pain in patients with bone metastases**. Front Oncol. 2023 Mar 16;13:1156618. doi: 10.3389/fonc.2023.1156618. PMID: 37007073; PMCID: PMC10063159.
4. Nielsen OS. **Palliative treatment of bone metastases**. Acta Oncol. 1996;35 Suppl 5:58-60. doi: 10.3109/02841869609083971. PMID: 9142968.
5. Tsukamoto S, Kido A, Tanaka Y, Facchini G, Peta G, Rossi G, Mavrogenis AF. **Current Overview of Treatment for Metastatic Bone Disease**. Curr Oncol. 2021 Aug 29;28(5):3347-3372. doi: 10.3390/curroncol28050290. PMID: 34590591; PMCID: PMC8482272.
6. Gralow J, Tripathy D. **Managing metastatic bone pain: the role of bisphosphonates**. J Pain Symptom Manage. 2007 Apr;33(4):462-72. doi: 10.1016/j.jpainsymman.2007.01.001. PMID: 17397707.
7. Fabregat C, Almendros S, Navarro-Martin A, Gonzalez J. **Pain Flare-Effect Prophylaxis With Corticosteroids on Bone Radiotherapy Treatment: A Systematic Review**. Pain Pract. 2020 Jan;20(1):101-109. doi: 10.1111/papr.12823. Epub 2019 Sep 15. PMID: 31342618.

Thank you!