Evaluation and Management of Bony Metastatic Disease

Anne N. Normand, MD
Essentia Orthopedics

Hol(e)y bones: what?

Metastatic disease

- 1.7 million new cancer diagnoses expected in 2018 (NCI estimate)
- 50% of patients with cancer will develop metastatic disease
- Metastatic disease is most common “bone tumor”
  - Primary bone malignancies – estimated 3450 new diagnoses in 2017 (ACS, NCI)
Metastatic disease

- 25% of patients with cancer will present with a skeletal lesion
- Skeletal metastases found in autopsy study of 90% of breast cancer patients who died from advanced disease
  - Up to approximately 50% of all patients
  - May be increasing with improved survival

Impact on patients

- Pain
- Instability
- Decreased function
- Loss of independence
- Need for pain medications
  - Side effects

Goals of treatment

- Pain control
- Maintain mobility
- Optimize function
- Skeletal stability
- Prevent fracture
- Functional independence
- Improve quality of life
- Control local tumor
Primary tumor types

- Breast
- Prostate
- Lung
- Renal cell
- Thyroid
- Bladder
- Melanoma
- GI tract

- Multiple myeloma
- Lymphoma

“5 Most Common”

- “BLT with a PickLe”
  - Breast
  - Lung
  - Thyroid
  - Prostate
  - Kidney

Skeletal distribution

- Axial skeleton
  - Most common site for bone metastases
  - Spine - 69%
    - T- and L-spine most often affected, then sacrum
    - Cervical least common
  - Pelvis - 41%
  - Skull
Skeletal distribution

- Appendicular skeleton
  - Femur most common site in extremities
  - Upper extremity involved in 10-15%
    • >90% of lesions in humerus
  - Mets distal to elbow or knee rare

Skeletal distribution

- Acral mets
  - LUNG
  - RENAL
  - 50% of mets distal to elbow and knee secondary to bronchogenic CA

Presentation

- PAIN
  - At rest
  - At night
  - May begin as intermittent pain, then become constant
  - May increase with activity
- Swelling
- Increased warmth
- Erythema
- Bone lesion on imaging studies
- Possible pathologic fracture
  - 7-10% present this way
Radiographs

- Lytic
  - Destruction of bone
- Blastic
  - Increased density of bone
- Mixed
- Aggressive or nonaggressive?
- Extent of disease?

- No tumor produces ONLY one type of appearance - looks can be deceiving

Looks can be deceiving…but here are some general rules

- Breast - lytic, mixed, or sclerotic
- Lung - most are lytic, may be sclerotic
- Prostate - usually sclerotic (beware if lytic - usually very vascular!)
- Renal cell - lytic, expansile
- Thyroid - lytic

Radiographic appearance

[Images of radiographs]
Bone scan

- Other sites of metastatic disease
- Identifies areas of bone turnover
- Shows you where to look

CT scan

- Evaluate cortical integrity
- Allows some assessment of extent of lesion
- Can be useful in planning reconstruction

MRI

- Detailed examination of
  - Marrow detail
  - Extent of bony involvement
  - Soft tissue extension
  - Relationship to surrounding structures, especially if soft tissue mass is present
**PET CT**

- Combines nuclear medicine & anatomic imaging
- Shows metabolic activity in tissue
  - Radiolabeled glucose

---

**Pathologic fracture**

- Occurs through bone whose structural integrity has been weakened by tumor
- Usually occurs with normal activities (ie, physiologic loading) or with minor trauma

---

**Impending fracture**

- Ability to predict risk of fracture imperfect
- Number of factors to consider
  - Patient wishes
  - Underlying disease
  - Comorbidities
  - Structural issues
- Better to treat prior to fracture if possible
- Don’t just treat the x-rays
Impending fracture

• “Classic” criteria
  – Lesion >2.5 cm
  – Lesion occupies >50% of bone diameter
  – Length of lesion is more than twice the bone diameter
  – Lesser trochanter avulsion
  – Lesion in area subjected to high stress
  • Subtrochanteric region of femur, femoral neck


Mirels’ classification

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Upper limb</td>
<td>Lower limb</td>
<td>Peritrochanteric</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Moderate</td>
<td>Functional</td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic</td>
<td>Mixed</td>
<td>Lytic</td>
</tr>
<tr>
<td>Size (Diameter)</td>
<td>&lt;1/3</td>
<td>1/3-2/3</td>
<td>&gt;2/3</td>
</tr>
</tbody>
</table>


Mirels’ classification

• Add score for each of the 4 variables
• Mirels - retrospective study
  – found that a score of 8 equated to a 15% risk of fracture, while a score of 9 indicated a 30% risk

Mirels’ classification

- Treatment recommendations
  - Score ≥ 8: prophylactic fixation
  - Score < 8: non-operative measures, such as radiation therapy

  - These are only recommendations - there are always exceptions!


Patient Scenarios

- Patient with known osseous metastatic disease
- Patient with history of carcinoma, no known metastases, new bone lesion
- Patient over 40 years of age with solitary bone lesion and no history of cancer

Known metastatic disease

- Can usually assume a painful bony lesion represents metastasis from known primary cancer
- Plan treatment
+ cancer history, no known bony mets, new bone lesion

- Must prove that bone disease is related to primary carcinoma
  - Two types of cancer can occur!
  - Rule out sarcoma
- BIOPSY before treatment

No prior cancer, new bone lesion

- Thorough history & physical exam
  - Breast, prostate, thyroid
  - Evaluate area of pain
    - ? Mass, tenderness, instability, strength
  - Weight loss
  - Smoking history
  - Family history

No prior cancer, new bone lesion

- Imaging studies
  - X-rays – entire bone affected by lesion, possibly chest
  - CT scan - chest/abdomen/pelvis, possibly of lesion
  - MRI of lesion
  - Bone scan - ? multiple bone lesions
No prior cancer, new bone lesion

- Laboratory tests
  - CBC w/differential
  - Metabolic profile with ionized calcium
  - SPEP/UPEP
  - LDH, alkaline phosphatase, hepatic panel, coags
  - Urinalysis
  - PSA
  - TSH, parathyroid hormone levels
  - Possible CEA or CA-129 based on clinical suspicion

No prior cancer, new bone lesion

- Full evaluation needed, particularly in adult over age 40
- Broad differential diagnosis
- BIOPSY!!!
Avoid this!

Biopsy

• CT-guided biopsy with core needle
  – Diagnostic accuracy up to 90%
• FNA
  – Usually not for bone lesions
• Open biopsy
  – Failed needle biopsy
  – Certain clinical situations
  – Avoid contamination of tissue planes

Treatment modalities

• Pain management/activity modification
• Bisphosphonates or denosumab
• Chemotherapy
• Hormonal therapy
• Immunotherapy
• Radiation therapy
  – External beam
  – Cyberknife or other radiosurgery
  – Radiopharmaceutical
• Ablation
  – Role not well defined
• Surgery
Bisphosphonates

- Inhibit osteoclast activity
- First shown to reduce pain and skeletal events in multiple myeloma and breast cancer
- Applications for activity many tumor types
- Treatment for hypercalcemia of malignancy

Hypercalcemia

- Complication of bone metastases
- Affect 10-40% of cancer patients
- Most common—Squamous cell cancers, breast, renal, ovarian, multiple myeloma
- Symptoms: anorexia, nausea, vomiting, polydipsia, polyuria, dehydration, constipation, confusion
- “Stones, bones, moans, and psychiatric overtones”

Hypercalcemia

- Treatment
  - Bisphosphonates
  - Hydration
  - +/- diuresis
- Management of underlying disease
Denosumab

- IgG2 monoclonal antibody
- Blocks RANKL which leads to decreased osteoclastic bone resorption
- Shown to reduce skeletal-related events
- Inhibitory effect on tumor cells as well

Medical therapy

- Depends on tumor type
  - Cytotoxic chemotherapy
  - Hormonal manipulation
    - Eg. hormonal castration in prostate cancer, tamoxifen in breast cancer
  - Targeted agents versus specific disease
  - Immunotherapy
- May be used as adjuvant with other approaches such as surgery and radiation
  - Decrease pain, aid with local tumor control
  - Some systemic effects

Radiation therapy

- Effective for many patients
- Certain tumor types are more sensitive to XRT
  - Lung cancer versus renal cell
- Not always sufficient - eg, impending fracture
- Skin considerations
- Need to radiate entire bone
- May also be used as adjuvant therapy after surgical stabilization
Radiation

- Treatment protocols vary widely
- Dose determined by tumor type, extent of disease, type of therapy (adjuvant or sole means of control)
- Length of time for treatment
- Palliative measure versus long-term control
- Generally administered after fixation of impending or true pathologic fracture
Radiation therapy

Radiosurgery

- CyberKnife may prove useful in management of skeletal metastases
- More focused, higher dose radiation to affected area while sparing surrounding tissues
- Selective use
CyberKnife

Radioisotopes

- Localize to bone involved by tumor
- Effective local tumoricidal activity, little "collateral damage"
- Best results in treatment of blastic metastases
  - Prostate, breast
Other approaches

- Ablation
  - RFA – heat
  - cryoablation
- Filling defect with bone cement (PMMA)
  - Vertebroplasty/kyphoplasty
  - Cementoplasty
- Selective usage; data evolving

Principles of surgical fixation

- Always remember the bone itself is abnormal - compromised healing potential
- Cannot treat pathologic fractures like traumatic fractures through normal bone
  - Increased failure rates with "normal" techniques

Principles of surgical fixation

- Span entire bone to “protect” it
- Provide as much “instant stability” as possible
  - No need to wait for healing
- Construct must be durable enough to last the remainder of the patient's life
- Don't take time away - don’t just fix the x-rays!
  - Careful risk/benefit analysis
  - Patient MUST participate in decision-making process
Surgery: Resection

- Applicable in certain situations
- Expendable bones
  - E.g. fibula
- Portions of pelvis

Surgery: Intramedullary nailing

- Closed versus open
- Workhorse
- Allows weight bearing right away
- Spans entire bone

Surgery: Intramedullary nailing

- Femur
  - Antegrade recon nails preferred
  - Stabilize entire bone
  - Lock proximally and distally
- +/- curettage and cementation of metastatic deposit
- Radiation post-op
Surgery: Intramedullary nailing
- Humerus
- Antegrade nails
- Locked proximally
- Able to lock distally if needed

Surgical fixation: Intramedullary fixation
- Flexible intramedullary nails
  - Mostly used in upper extremity lesions
- Especially useful for distal humeral lesions
- Augment with curettage and cementation of lesion
  - Local tumor control

Surgery: Endoprosthesis
- Endoprosthesis - replace bone
- Useful at major joints: hip, knee, shoulder, elbow
- Extensive bone destruction prevents fixation
Surgery: Endoprosthesis

- Functional results usually good - similar to those achieved in patients with primary bone malignancies
- Immediate function
- More extensive surgery
- Long-stemmed components offer protection to entire bone

Prognosis

- Still very difficult to predict remaining lifespan for any given patient
- Some special situations
  - Renal cell CA with solitary bone metastasis
  - Breast CA with bone only disease
  - Prostate CA with small number of metastatic sites, specific sites

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Advanced disease</th>
<th>Median survival (mos)</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>95-100</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Breast</td>
<td>65-75</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Prostate</td>
<td>65-75</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Lung</td>
<td>30-40</td>
<td>&lt;6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Kidney</td>
<td>20-25</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>60</td>
<td>48</td>
<td>40</td>
</tr>
</tbody>
</table>

Metastatic carcinoma of unknown origin

- Up to 30% of patients presenting with metastatic disease
- Successful identification of primary source in 7-50% of patients
  - Lung CA - most common tumor to present this way
- Mean survival - less than 12 months
  - Only 20% survive more than 1 year

Metastatic carcinoma of unknown origin

- Want to identify treatable/curable tumors
  - Caveat: don’t get lost in diagnostic testing that may not help!
- Determine extent of involvement, primary tumor site, confirm diagnosis, evaluate musculoskeletal issues related to metastasis, treat both sites of disease if able
- Protocols exist for systemic management
Metastatic bone disease

- Directions for future research/improvement
  - Predictors of metastatic disease
  - Prevention of metastatic disease
  - Novel, effective therapies
  - Ways to monitor response to treatment
  - Patient factors
  - Improve ability to identify patients at risk and intervene early

Questions?

Thank you!!!!

Sources

Sources


Resources

- American Cancer Society: [www.cancer.org](http://www.cancer.org)
- National Comprehensive Cancer Network: [www.nccn.org](http://www.nccn.org)