Current Approaches to Metastatic Bone Disease
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Scope of the problem

- 1,437,180 new cases of cancer in USA annually
- 60% of these breast, prostate, lung or kidney primary
- 50% - 70% of all cancer patients develop bone metastases during course of their disease
- 80% of patients with prostate, breast, lung kidney and thyroid
- 10% develop pathologic fracture
Breast

- 50-75% develop bone metastases
- Mixed lesions
- Median survival with bone mets - 2007 - 32 months 2007
- 2013 - 55.5 months
- 5 year survival 20% - trending up 22%
- 63% of cost of caring for metastatic breast cancer due to skeletal disease

UC San Diego Medical Center
Prostate

- 90% incidence of bone mets in patients who die from prostate cancer
- Commonly mixed
  Median survival 40 months
- 5 year survival 25%
Lung

- 50% incidence of bone metastases
- Typically lytic
- Prognosis with bone metastases generally poor, with median survival 6 months
Renal

- 50% incidence of bone metastases - lytic
- High incidence of hardware failure and local recurrence with intralesional procedure
- In RARE circumstances excision of solitary bone metastasis may have curative intent
Bone metastases not a preterminal event

- Patients with bone mets from prostate ca - median survival 40 months and 5 year survival 25%
- Patients with bone mets from breast ca - median survival now 32 months and 5 year survival over 20%
- Patients with liver mets from breast ca - median survival 3 months
Modes of Presentation

- Skeletal pain
- Hypercalcemia
- Pathological fracture
- Spinal cord compression
Etiology of pain in skeletal metastases

- Inflammatory (COX-2)
- Neuropathic
- Tumorigenic (endothelin-1)
  - All these usually constant pain, regardless of activity
- Mechanical
  - Often worse with activity, but may be at rest
Investigation of patients with suspected metastatic bone disease (known ca)

- Serum Ca, Mg, Phos, Albumin, ALP
- Plain radiograph of affected region
- Total body bone scan/bone survey/PET
- CT for pelvic/acetabular lesions
- MRI for spine or assessment of soft tissue masses
- If considering surgery, should have c-spine x-rays
4 TENETS OF MANAGEMENT

1) Relieve pain
2) Preserve/Restore Function
3) Maintenance of patient independence
4) Control disease progression

When to NOT operate: when these goals are attainable without OR
Overall Health of Patient

- Assess visceral and metabolic health
- Consider prior treatment and effect of prior therapy
- Assess longevity
Non-surgical Therapy

- Hormones
- Radiation
- Chemotherapy
- Bisphophonates
- Novel Therapies
Radiotherapy

- Very effective in breast and prostate cancer
- Extremely effective in hematological cancer
- Less effective in renal cell ca
- One dose (8Gy) vs. 5 doses (20Gy)
Role of Post-op Radiation after ORIF of Pathologic Fractures

Functional status 1 or 2 (normal use +/- pain)

- 53% S+RT vs 11.5% SA

Second orthopaedic procedures

- 2.9% S+RT vs 15% SA

Overall survival

- median 12.4 mos S+RT vs 3.3 mos SA

Multivariate analysis

- only RT associated with function (p=0.04)
Take home messages

- Anybody with metastatic bone disease needs radiation
- If the lesion is at risk of pathologic fracture in the lower extremity, operate first, irradiate after
- Otherwise, irradiate first and operate later if necessary
Hormones

- Prostate and Breast cancer
- Effective at various stages of disease
- Effective prior to chemotherapy
Chemotherapy

- Extremely effective in lymphoma, myeloma
- Very effective in breast & prostate
- Effective in small cell ca
- Ineffective in squamous lung or renal cell
Bisphosphonates

- Effective in myeloma, breast, prostate
- Effective in hypercalcemia
Bisphosphonates: Mechanisms of Action

- Inhibition of osteoclast maturation, recruitment, and function
- Reduced production of cytokines (e.g., IL-6)
- Direct anti-tumor activity (static and lytic)
- Inhibition of tumor cell dissemination, invasion, and adhesion to bone matrix
- Antiangiogenic effects
- May be synergistic with chemotherapy
- Additive effect with radiation
Bisphosphonates: Breast Carcinoma

Hortobagyi et al, NEJM 1996

median 7.0 months

median 13.1 months
Reduction in New Metastases in Breast Cancer with Adjuvants Clodronate Tx

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clodronate</th>
<th>Control</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Distant Mets</td>
<td>21</td>
<td>42</td>
<td>&lt;0.001</td>
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<tr>
<td>Bone Mets</td>
<td>12</td>
<td>25</td>
<td>0.003</td>
</tr>
<tr>
<td>Visceral Mets</td>
<td>13</td>
<td>27</td>
<td>0.003</td>
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<tr>
<td>Deaths</td>
<td>2</td>
<td>22</td>
<td>0.001</td>
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Diel et al, NEJM 1998
Bisphosphonates cont’d

- ASCO Recommendation

- For patients with plain radiographic evidence of bone destruction, 90 mg IV pamidronate over 2h, q monthly

- Zometa—also monthly but in 15 minutes - more $

- Denusimab - better?? - mAb against RANK-L
  

- Bone destruction on other imaging is reasonable evidence to commence Rx

- Likely all patients with metastatic bone disease, regardless of primary, should commence therapy
Novel Therapies

- Metastases likely arise due to receptor ligand interaction in bone - targeted therapies
- RANK - RANK l interaction
- Expression of certain integrin subtypes (αvβ3) in breast cancer cells lead to 20-fold increase in bone metastases anti-integrin trials are ongoing
- Anti-angiogenic factors in renal cell ca
- Stimulation of COX-2 production in breast cancer cells enhances bone metastases
Pain in Bone Metastases

- Important to discern pattern and therefore likely cause of pain
- Mechanical pain - stabilization
- Tumorigenic or inflammatory pain - radiation/chemo or removal of tumor
Predicting Pathologic Fracture Risk

Indications for Prophylactic Fixation:

- > 2.5 cm
- >50% cortical destruction
- pain unresponsive to radiation
- pathologic lesser trochanter fracture

Bertin, JBJS 1984, 66A:770
Harrington, JBJS 1981, 63A:653
### Predicting Impending Pathologic Fractures: Mirels Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Site</td>
<td>UE</td>
<td>LE</td>
<td>prox femur</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 (dia)</td>
<td>&lt;1/3</td>
<td>1/3-2/3</td>
<td>&gt;2/3</td>
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Predicting Impending Pathologic Fractures: Mirels Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>Fracture Risk</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>7</td>
<td>4%</td>
<td>Radiate</td>
</tr>
<tr>
<td>8</td>
<td>15%</td>
<td>?</td>
</tr>
<tr>
<td>9</td>
<td>33%</td>
<td>Operate</td>
</tr>
<tr>
<td>10</td>
<td>72%</td>
<td>Operate</td>
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`score > size > pain > lesion > site`
Prophylactic fixation improves outcomes

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<thead>
<tr>
<th></th>
<th>Prophylactic</th>
<th>Completed Fracture</th>
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<tbody>
<tr>
<td>Blood Loss</td>
<td>438cc</td>
<td>636cc</td>
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<tr>
<td>Length of Stay</td>
<td>7d</td>
<td>11d</td>
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<tr>
<td>% discharge home</td>
<td>79%</td>
<td>56%</td>
</tr>
<tr>
<td>% ambulatory</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>35%</td>
<td>25%</td>
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<tr>
<td>2 year survival</td>
<td>19%</td>
<td>10%</td>
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Metastatic Bone Disease
Orthopaedic Considerations

- Assume the Fracture Will NEVER Heal
- Plan for Immediate Unrestricted Activities
- 1 Operation Per Bone
- Cement

- If Secure Fixation is Not Possible, RESECT and RECONSTRUCT

- Ask yourself - if I fix this fracture, will I allow the patient to get up and walk on it - if not, consider replacement
Femoral Neck Lesions

- Is there any point in fixing prior to fracture?
- If the lesion is painful, should you do a fixation operation?
Inter-trochanteric Zone

- High risk of fracture—especially if lesser is off
- Generally disease spreads into head
- Fixation device with cement for early disease
- Usually arthroplasty
Subtrochanteric

- Major risk for fracture
- Most important to recognize lesion prior to fracture
- If no fracture, can stabilize with recon nail if neck not involved
Always use a recon nail...
Subtrochanteric

- Extension to femoral neck
- Can replace with standard hip implant
- If lesion extends down femur use a long stem
Beware of metastatic renal cell carcinoma

- Significantly higher likelihood of hardware failure
- Should consider curettage, cement after embolization
- Alternative - replacement
Impending fractures

Unlike in femur, impending fractures in humerus can be treated with radiation and sling/brace.

Reserve surgical management for symptomatic lesions refractory to radiation/chemo.
Pathologic fractures

Treatment controversial

In undisplaced fractures through lesions responsive to radiation (lymphoma, myeloma, breast) functional bracing can occasionally be associated with successful healing

Majority require surgical management
Proximal & distal fractures

- Can usually be managed by prosthetic replacement
- Retention of humeral head with tuberosities associated with better function
Diaphyseal fractures
- Nail vs. plate
Remember - not every pathologic fracture in someone over 50 is from metastatic disease! Biopsy if unclear prior to nailing.
The Dilemma

Because of better treatment of metastatic disease, patients are living longer, and therefore are likely to present with more advanced skeletal disease and pathologic fractures.

Longer survival also means that implant choice has to account for the expected function and life expectancy.

These patients should be treated aggressively to provide maximal quality of life for their entire lifespan.
Future Directions

• Better understanding of the bone-tumor interface biology and the specific drivers that allow homing of tumor and metastasis to bone

• 3D reconstructive software to predict fractures

• Human diseases xenografts are key to advancing our understanding of disease in niche specific environments

• First successful human prostate cancer metastatic to bone model