Bone Health in the Cancer Patient

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Primary Care and Oncology: Practical Lessons Conference

Brea Community Center

May 10, 2018
Why is this an important topic?

Advances in our understanding of tumor biology have led to improved treatment strategies.

As a result:

• Patients are living longer
• Incidence of bone mets is on the rise
• Bone is the 3rd most common organ involved by metastases
• Most common site of distant metastasis from primary breast and prostate cancer
• Increase in bone mets means increase in comorbidities:
  • Pain, decreased mobility, hypercalcemia, spinal cord or nerve root compression
Agenda

• Normal bone physiology
• Pathophysiology of bone metastases
• Incidence/epidemiology of bone mets
• Clinical Consequences of bone mets: Skeletal Related Events (SREs)
• Diagnosis of bone metastases, which imaging modality is best?
• Treatment of symptomatic bone metastases
• Prevention of skeletal related events (SREs)
• Prevention of bone metastases
• Prevention of bone loss in patients on endocrine therapy
• Safety concerns
• Summary
Normal Bone | *Dynamic Tissue*

Normal healthy bones are in a constant state of remodeling

- Preserves skeletal size
- Preserves skeletal shape
- Preserves structural integrity
- Regulates mineral homeostasis

- Osteoblasts, osteoclasts, and osteocytes work together to couple these processes
Normal Bone | The Major Players

- **Osteoclasts**
  - Terminally differentiated myeloid cells
  - Adapted to remove mineralized bone
  - CSF-1 and RANKL critical regulators

- **Osteoblasts**
  - Develop from pluripotent mesenchymal stem cells
  - Runx2 master regulator
  - Roles in bone remodeling:
    - Express osteoclastogenic factors
    - Production of bone matrix proteins
    - Bone mineralization

- **Osteocytes**
  - Terminally differentiated osteoblasts entombed in calcified bone matrix
  - Cocooned in fluid filled cavities
  - Long dendritic processes that interact with other cells

Pathophysiology | Setting Up Shop

Seed and Soil: tumor seeding $\rightarrow$ dormancy $\rightarrow$ metastatic growth

- Primary tumor cells gain access to angiolymphatic vessels
- Tumor cells transported to distant organs via circulatory system
- Most disseminated tumor cells die
- Bone marrow microenvironment...
  - May act as a reservoir for malignant cells
  - HSC niche is a site where tumor cells can remain dormant for years
- Some tumor types have a particular affinity for bone

Pathophysiology | The Microenvironment

Tumor cells produce cytokines and growth factors leading to a vicious cycle

Cytokines and GFs released including PTHRP, prostaglandins, ILs, others

↓

Increased production of RANKL

↓

Activation of osteoclasts

↓

As bone matrix is broken down, bone-derived GFs are released

↓

Increased growth and proliferation of tumor cells

↓

The cycle perpetuates

Ann Oncol. 2014;25(suppl_3):iii124-iii137
Bone Mets | *Incidence and Epidemiology*

*Highest incidence in breast and prostate cancer*

### Metastatic Bone Disease
*Epidemiology - Etiology*

<table>
<thead>
<tr>
<th></th>
<th>Estimated Number of Persons Living with Cancer</th>
<th>Number of New Cases in 2004</th>
<th>Incidence of Bone Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>2,184,125 (24%)</td>
<td>217,440 (16%)</td>
<td>65-75%</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,838,653 (20%)</td>
<td>230,110 (17%)</td>
<td>65-75%</td>
</tr>
<tr>
<td>Bladder</td>
<td>521,945 (6%)</td>
<td>60,240 (4%)</td>
<td>40%</td>
</tr>
<tr>
<td>Lung</td>
<td>388,538 (4%)</td>
<td>173,770 (13%)</td>
<td>30-40%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>273,642 (3%)</td>
<td>23,600 (2%)</td>
<td>60%</td>
</tr>
<tr>
<td>Other</td>
<td>4,013,458 (43%)</td>
<td>705,160 (52%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9,220,361 (100%)</strong></td>
<td><strong>1,368,030 (100%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

2. Coleman, R.E. Cancer Treatment Reviews 2001;27:165-176
Bone Mets | Clinical Consequences

Reduced quality of life, mobility, social function, and increased medical costs

- Pathologic Fracture
- Radiotherapy to Bone
- Surgery to Bone
- Spinal Cord Compression

+ HYPERCALCAEMIA
Bone Mets | Lytic vs. Sclerotic Lesions

- Early detection is critical
  - Accurate staging and optimal treatment
  - Implementing treatments to reduce risk of SREs
    - Surgical fixation
    - Radiotherapy
    - Bisphosphonate/denosumab therapy
- Most common sites of bone mets are axial skeleton
- Lytic lesions
  - Tumor cells release factors that upregulate osteoclast activity
    - PTHR, TNF alpha or beta, IL-1, IL-6
    - Net osteolysis
  - Radiolucent areas in bone
  - Aggressive
  - Myeloma, lung ca, thyroid ca, and renal cell ca
- Sclerotic/blastic lesions
  - Radiopaque areas in bone
  - Slower progression
  - Lymphomas, prostate and breast cancer
  - Tumor cells release factors that upregulate osteoblasts
    - EGF, TGR alpha and beta, insulin-like GFs
    - Net osteosclerosis
- Mixed lesions – combination of both processes
Hybrid imaging combines the strengths of imaging modalities

**Structural Imaging**
- Plain radiographs, CT scan, MRI
- Interrogate lesion structure within bone

**Functional Imaging**
- Nuclear medicine scans
- Quantitatively assesses the function of bone or tumor cells

  - **“Bone seeking” osteotropic radioisotopes**
    - Technetium 99 labelled diphosphonates (bone scans)
    - 18F NaF (PET scans)

  - **“Tumor seeking” oncotropic agents**
    - 18F labelled fluorodeoxyglucose (FDG) – nonspecific
    - Indium 111 pentetreotide (octreoscan) - specific

**Hybrid Imaging**
- PET/CT, PET/MRI
- Shows functional properties of bone metastases with precise structural detail
- PET/MRI showing highest potential for early diagnosis
## Diagnosis | Imaging Techniques

<table>
<thead>
<tr>
<th>Modality</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain radiographs</td>
<td>• Insensitive test for asymptomatic bone mets</td>
</tr>
<tr>
<td></td>
<td>• 50-70% of bone must be destroyed to detect on plain films</td>
</tr>
<tr>
<td>Bone scintigraphy (bone scan)</td>
<td>• Sensitivity 78%, specificity 48%</td>
</tr>
<tr>
<td></td>
<td>• Widespread availability</td>
</tr>
<tr>
<td></td>
<td>• Images the entire skeleton</td>
</tr>
<tr>
<td></td>
<td>• Can detect bone mets up to 18 mos earlier than plain films</td>
</tr>
<tr>
<td></td>
<td>• Nonspecific, false positives, treatment flare</td>
</tr>
<tr>
<td></td>
<td>• Need additional imaging (CT or MRI) for correlation</td>
</tr>
<tr>
<td>CT scan</td>
<td>• Sensitivity 74%, specificity 56%</td>
</tr>
<tr>
<td></td>
<td>• Excellent resolution of cortical and trabecular bone</td>
</tr>
<tr>
<td></td>
<td>• Preferred for evaluating the ribs</td>
</tr>
<tr>
<td></td>
<td>• Reduces burden of imaging for patient</td>
</tr>
<tr>
<td></td>
<td>• Can be used to guide perc biopsy</td>
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## Diagnosis

### Imaging Techniques

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| MRI               | • Sensitivity 95%, specificity 90%  
                     • Excellent soft tissue resolution  
                     • Ideal for assessing spread in/extension from marrow cavity  
                     • Preferred when evaluating for cord compression |
| 18F FDG-PET/CT    | • Sensitivity 98%, specificity 56% (increases to >90% for PET/CT)               |

*NOTE: With PET alone, sensitivity may vary among different histologies; well differentiated and indolent tumors can go undetected*
Treatment | Palliative Radiation

Highly effective for localized bone pain

- Overall RR 85%, w/ complete relief in 50%
- 50% of responders show benefit in 1-2 weeks
- If no improvement after 6 weeks, unlikely
- No difference in outcomes between fractionated and single fraction

- Targeted radiotherapy in certain tumor types
  - Radium chloride (Xofigo) for prostate cancer
    - Minimal systemic effects
    - NEJM 2013; 369:213-223
      - Randomized phase III trial
      - Addition of radium chloride to best supportive care in CRPC pts showed 3.6 month improvement in OS and improvement in QoL
Treatment | Bone Targeted Agents

For relief of widespread bone pain

Bisphosphonates

- Specifically inhibit osteoclasts
- Concentrate in skeleton primarily at active remodeling sites; Limited distribution
- Interrupt “vicious cycle”
  - Inhibiting osteoclast activity
  - Inhibiting differentiation
  - Inhibiting maturation
  - Directly inducing apoptosis

Denosumab

- Fully humanized moab
- Binds to RANKL w/ high affinity
- Inhibits binding of RANKL to RANK
- As a circulating antibody, reaches all sites w/in bone
**Treatment** | *Denosumab Superior*

*Denosumab is superior to zolendronic acid in preventing SREs*

Lipton et al. European Journal of Cancer 53 (2016) 75-81

- Phase III trial
- Breast ca, prostate ca, or other solid tumors
- > or = 1 bone met
- Denosumab was superior to ZA in preventing SREs in patients with bone mets regardless of:
  - ECOG PS
  - number of bone mets
  - presence/absence of visceral mets
- Overall HR 0.74-0.88, p < 0.0001
Denosumab superior to zolendronic acid in preventing SREs

Lipton et al. European Journal of Cancer 53 (2016) 75-81

Risk of first on study SRE

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>396/1120</td>
<td>341/1141</td>
<td>0.79 (0.69-0.92)</td>
<td>0.0020</td>
</tr>
<tr>
<td>≥1</td>
<td>635/1640</td>
<td>547/1631</td>
<td>0.84 (0.74-0.94)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of bone metastases</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial only</td>
<td>260/672</td>
<td>226/706</td>
<td>0.83 (0.69-1.00)</td>
<td>0.0443</td>
</tr>
<tr>
<td>Appendicular only</td>
<td>144/345</td>
<td>134/387</td>
<td>0.78 (0.61-0.99)</td>
<td>0.0428</td>
</tr>
<tr>
<td>Axial and appendicular</td>
<td>340/833</td>
<td>278/804</td>
<td>0.81 (0.65-0.95)</td>
<td>0.0104</td>
</tr>
</tbody>
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<th>P Value</th>
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<tr>
<td>&lt;2</td>
<td>599/1696</td>
<td>520/1889</td>
<td>0.84 (0.74-0.94)</td>
<td>0.0033</td>
</tr>
<tr>
<td>≥2</td>
<td>463/1072</td>
<td>370/1086</td>
<td>0.78 (0.66-0.90)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence or absence of visceral metastasis</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>403/1152</td>
<td>351/1185</td>
<td>0.80 (0.69-0.93)</td>
<td>0.0026</td>
</tr>
<tr>
<td>No</td>
<td>632/1616</td>
<td>539/1590</td>
<td>0.82 (0.73-0.93)</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>uONX level 1</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>HR* (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>≥43.7 mmol/l</td>
<td>474/1222</td>
<td>438/1254</td>
<td>0.86 (0.75-0.98)</td>
<td>0.0225</td>
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<tr>
<td>&lt;43.7 mmol/l</td>
<td>458/1246</td>
<td>357/1229</td>
<td>0.73 (0.64-0.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| Overall      | 1035/2768            | 890/2775      | 0.82 (0.75-0.89) | <0.0001 |

Risk of subsequent SRE

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>RR* (95% CI)</th>
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<tr>
<td>0</td>
<td>612/1120</td>
<td>498/1141</td>
<td>0.76 (0.66-0.88)</td>
<td>0.0002</td>
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<tr>
<td>≥1</td>
<td>949/1640</td>
<td>794/1631</td>
<td>0.83 (0.74-0.92)</td>
<td>0.0007</td>
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<tr>
<td>Appendicular only</td>
<td>205/345</td>
<td>200/387</td>
<td>0.81 (0.65-1.02)</td>
<td>0.0715</td>
</tr>
<tr>
<td>Axial and appendicular</td>
<td>577/833</td>
<td>441/804</td>
<td>0.70 (0.67-0.91)</td>
<td>0.0018</td>
</tr>
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<th>RR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>867/1696</td>
<td>717/1689</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td>≥2</td>
<td>699/1072</td>
<td>577/1086</td>
<td>0.79 (0.69-0.91)</td>
<td>0.0009</td>
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<th>RR* (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Yes</td>
<td>576/1152</td>
<td>483/1185</td>
<td>0.79 (0.69-0.91)</td>
<td>0.0007</td>
</tr>
<tr>
<td>No</td>
<td>990/1616</td>
<td>811/1590</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0003</td>
</tr>
</tbody>
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<th>uONX level 1</th>
<th>Zeolodronic Acid n/N</th>
<th>Denosumab n/N</th>
<th>RR* (95% CI)</th>
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<tbody>
<tr>
<td>≥43.7 mmol/l</td>
<td>755/1222</td>
<td>664/1254</td>
<td>0.83 (0.73-0.94)</td>
<td>0.0035</td>
</tr>
<tr>
<td>&lt;43.7 mmol/l</td>
<td>658/1246</td>
<td>492/1229</td>
<td>0.74 (0.65-0.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| Overall      | 1566/2788            | 1294/2775     | 0.81 (0.74-0.88) | <0.0001 |
Treatment | *Denosumab Safer*

*Denosumab safer than zolendronic acid*

- Denosumab safe in the setting of kidney disease

- Acute phase reactions less frequent with denosumab
  - Musculoskeletal pain, nausea, fatigue, fevers/rigors

- Caveat: Hypercalcemia is more frequent with denosumab than ZA
  - Start pts on supplemental calcium (1000mg/day) and vitamin D3 (1000-2000 IU/day)
  - Monitor calcium levels regularly
Bone Mets | Breast Cancer

Across all tumor types, breast cancer has highest incidence

- 2-4 events/year if no bone targeting treatment

- **Clin Cancer Res 2006; 12:6243s-6249s**
  - Population based cohort study
  - 36,000 newly diagnosed breast ca pts with 9 year follow up
  - Median survival 16 months with bone mets, only 7 months with bone mets + SRE

- **Ann Oncol, 2011, vol. 22 (2546-2555)**
  - Risk factors that increase fracture risk in postmenopausal women with breast cancer
    - Aromatase inhibitor treatment
    - BMD T-score < -2.5
    - Increasing age (>65)
    - Oral corticosteroid use >6 months
    - Low BMI (<20kg/m2)
    - Family hx of hip fracture
Prevention of SREs | *Breast Cancer*

**ASCO Guideline:** *Recommended to start denosumab or ZA in all patients with bone mets, symptomatic or not*

- Early randomized placebo-controlled trials in the late 1990s showed bisphosphonates can reduce SREs by >33% and increase the median time to first SRE by ~50% in breast cancer patients with at least one bone met.

- Subsequent randomized double blind trials have shown that zolendronic acid is superior to pamidronate (Aredia) and ibandronate (Boniva) in reducing risk for SREs.

- 3 identical phase III double blind trials published in 2010 and 2011 showed denosumab was superior to zolendronic acid in delaying the time to first SRE and subsequent SREs.
Improvements in DFS and OS shown in large randomized adjuvant trials in women with early breast cancer

**ABCSG-12 trial**
- Published their final analysis in 2015
- 94.4-month median follow-up of 1803 *premenopausal* patients with early stage breast cancer
- Improved DFS and OS in women treated with zolendronic acid q6 months x3 years
- Absolute risk reductions with zolendronic acid were 3.4% for DFS and 2.2% for OS.
- Treatments were generally well tolerated, with no reports of renal failure or osteonecrosis of the jaw.

**AZURE trial**
- 3360 pts with stage II or III breast cancer, unselected by *menopausal* status or ER status
- Zolendronic acid q3-4 weeks x6 doses, then q3-6 months up to 5 years
- Cohort of patients with established menopause (>5 years since LMP)
- DFS 71% in control group, 78% in pts treated with ZA (HR 0.75, p = 0.02)
Adjuvant bisphosphonates reduce recurrence in bone and improve survival in women postmenopausal when treatment began

EBCTCG meta-analysis published in 2015

– Individual patient meta-analysis in >18,700 women in randomized trials of adjuvant bisphosphonates in early breast cancer
– Among premenopausal women, no reduction in breast cancer recurrence, distant recurrence, or breast cancer mortality
– Among 11,767 postmenopausal women (>5 yrs since LMP), highly significant
  • 14% reduction in recurrence (RR 0.86, 95% CI 0.78-0.94, P=0.002)
  • 18% reduction in distant recurrence (RR 0.82, 95% CI 0.74-0.92 P=0.0003)
  • 18% reduction in breast ca mortality (RR 0.82, 95% CI 0.73-0.93, P=0.002)
– No differences seen in non-breast cancer mortality
– 15% reduction in bone fractures (RR 0.85, 95% CI 0.75–0.97; P=0.02)
Prevention of SREs | Prostate Cancer

**ASCO Guideline:** Recommended to start denosumab or ZA in all patients with CRPC and bone mets, symptomatic or not

  - Zolendronic acid is the only bisphosphonate to demonstrate a significant reduction in SREs in patients with advanced prostate ca.

- Lancet 2011; 377:813-822
  - Placebo controlled double blind trial comparing denosumab to zolendronic acid for the prevention of SREs in men with bone mets from CRPC
  - Denosumab was superior in delaying time to first SRE (17 months compared to 20.7 months), P=0.008
  - Denosumab associated with an 18% risk reduction in total SREs compared to ZA
Prevention of Mets | Prostate Cancer

Denosumab is the only bone targeting agent approved for prevention of bone metastases in CRPC

- Men with CRPC but no evidence of metastases (only rising PSA on ADT)
- Denosumab significantly increased time to first bone met by 4.2 months compared to placebo (HR 0.85, P = 0.028)
- Denosumab delayed time to first symptomatic bone met (HR 0.84, P=0.032)
- No impact on OS
- AEs and serious AEs were similar between groups except for ONJ and hypocalcemia
  - ONJ incidence 1% in year 1, 3% in year 2, and 4% in year 3.
- Targeting the bone microenvironment can prevent bone metastases
Prevention of SREs | ASCO Guidelines

For breast cancer:
  – It is recommended to start denosumab or zolendronic acid in all patients with bone metastases, whether they are symptomatic or not.

For prostate cancer:
  – It is recommended to start denosumab or zolendronic acid in all patients with CRPC and bone metastases, whether they are symptomatic or not.

For other solid tumors:
  – It is recommended to start denosumab or zolendronic acid in selected patients with advanced lung cancer, renal cell carcinoma, and other solid tumors with bone mets if they have a life expectancy >3 months and are considered high risk for SREs.
Prevention | Treatment Induced Bone Loss

ESMO Clinical Practice Guidelines 2014

Patient with cancer receiving chronic endocrine treatment known to accelerate bone loss

- T-score > -2.0
- And no additional risk factors

- Exercise
- Calcium and vitamin D

- Monitor risk and BMD at 1–2 year intervals

Any 2 of the following risk factors:
- Age > 65
- T-score < -1.5
- Smoking (current and history of)
- BMI < 24
- Family history of hip fracture
- Personal history of fragility fracture above age 50
- Oral glucocorticoid use for >6 months

- T-score < -2.0

- Exercise
- Calcium and vitamin D
- Bisphosphonate therapy

- Monitor BMD every 2 years
- Check compliance with oral therapy

Sacred Encounters  Perfect Care  Healthiest Communities
Safety Concerns

*Both bisphosphonates and denosumab are generally well tolerated*

Side effects to be aware of:

- **Hypocalcemia**
  - More frequent and more likely to be symptomatic with denosumab than ZA
  - Patients should be on calcium and vitamin D3 supplements
    - Calcium 1000mg daily
    - Vitamin D3 (cholecalciferol) 1000 units daily
  - Regularly monitor serum calcium levels

- **Acute phase response (musculoskeletal pain, nausea, fatigue, fevers/rigors)**
  - More frequent with ZA than denosumab

- **Renal toxicity**
  - More frequent with ZA than denosumab
Safety Concerns | Osteonecrosis of Jaw

• Manifests as exposed jaw bone
• The exposed bone does not get blood supply and dies
• Symptoms include pain in jaw or tooth, swelling, infection
• More common in pts getting rx for bone mets than osteoporosis
  – (1-2% vs < 0.0001)
• Risk increased with trauma to the jaw, esp invasive dental procedures like tooth extraction or implants
• Other risk factors:
  – Advanced age
  – Smoking
  – Steroid use
  – Diabetes
  – Gum disease
Safety Concerns | Osteonecrosis of Jaw

Treatment of ONJ

- If mild, treat conservatively with rinses, antibiotics and analgesics
- When severe, surgical debridement may be necessary

Prevention of ONJ

- Good oral hygiene and regular dental care
- Complete dental exam prior to starting bisphosphonates or denosumab
- Tell patients to tell their dentist
- If extractions not necessary, prefer less invasive procedures (like root canal)
- If extraction is necessary, delay starting treatment until site has fully healed and patient asymptomatic
Summary

- Bone is a dynamic tissue
- Bone health is threatened by cancer and by treatments for cancer
- Breast cancer and prostate cancer have a tropism for bone
- Treating early is key to preventing and/or delaying SREs
- For patients on bone targeting agents:
  - **Monitor** calcium levels regularly
  - **Instruct** patients to take supplemental Ca and vitamin D3
  - **Inform** about the risk of ONJ in setting of dental extractions or implants
THANK YOU!

Stevie Otis, M.D.

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