14:40-15:10
Nutritional Approach and Medications for Bone Health

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Dr Aapro is/was a consultant for
Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of
Amgen, Bayer Schering, Biocon, Cephalon, Chugai, DRL, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Novartis, Ono Pharmaceuticals, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

No responsibility accepted for involuntary errors or omissions. The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others.
Bone health in the elderly cancer patient: a SIOG Position Paper

J.J. Body, E. Terpos, B. Tombal, P. Hadji, A. Arif, A. Young, M. Aapro, R. Coleman

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Reference: YCTR V 1560

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The menu

• Why osteoporosis?
• A unifying topic: bone health
• To conclude
The menu

• YOU please tell me why osteoporosis?

• A unifying topic: bone health

• To conclude
Osteoporosis in Cancer Patients

- Bone density decreases with age
- AI treatment and ADT are associated with an increased risk of osteoporosis. Tamoxifen is somewhat “protective” (in postmenopausal women)
- Treatment induced bone loss can be managed with additional medication such as vitamin D and calcium supplements, weight bearing exercise and bisphosphonates/denosumab
- AI induced decrease in bone density reverses after treatment termination

RE Coleman et al. Breast Cancer Res Treat. 2010
The menu

- Why osteoporosis?

- A unifying topic: bone health

- To conclude
About Anna and Boris

Anna is 72 years old and was diagnosed with a pT1c (18 mm) pN1(1/13)M0 ductal invasive G1 ER100 PgR100 Ki67 5% breast cancer. She had conservative surgery and will receive radiation. In addition she will have an AI. But the BMD shows a T score of -2.0 at both hips ( -2.5 or lower is osteoporosis ). She is on Ca, Vit D and exercises regularly.

Would you suggest a BMA? ( do not mind local restrictions )
Would you suggest denosumab or a bisphosphonate?
About Anna and Boris

Anna’s husband Boris is also 72 years old and was diagnosed with a prostate cancer for which, after radiation therapy, a 3 year androgen deprivation therapy has been suggested.

Do you believe he is at risk of bone fracture? Would you suggest a BMA? Would you suggest denosumab or a bisphosphonate?
Limitations:

- Literature rather than individual patient data meta-analysis
- Reports of trials with different durations of follow-up
- Information on the potentially confounding baseline host factors (e.g., obesity, hypertension, diabetes, and family history of events of interest) or the use of concurrent medications was not reported
Change in Bone Mineral Density in the first 12 months of therapy with various cancer treatments*

AI: aromatase inhibitors; CIOF: chemotherapy-induced ovarian failure


*TAM ONLY PROTECTIVE IN POSTMENOPAUSAL WOMEN
ZO-FAST (N = 1,065):
ZOL ↑ BMD During AI Therapy—60-Month Results

<table>
<thead>
<tr>
<th>Duration</th>
<th>Immediate ZOL</th>
<th>Delayed ZOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mo</td>
<td>360 (Δ 5.8%)</td>
<td>369</td>
</tr>
<tr>
<td>24 mo</td>
<td>339 (Δ 8.1%)</td>
<td>343</td>
</tr>
<tr>
<td>36 mo</td>
<td>313 (Δ 8.6%)</td>
<td>311</td>
</tr>
<tr>
<td>48 mo</td>
<td>290 (Δ 8.9%)</td>
<td>294</td>
</tr>
<tr>
<td>60 mo</td>
<td>264 (Δ 9.7%)</td>
<td>264</td>
</tr>
</tbody>
</table>

P < .0001 for each

Abbreviations: BMD, bone mineral density; LS, lumbar spine; ZOL, zoledronic acid.

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

Summary
Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).
Adjuvant bisphosphonates reduce the rate of bone metastasis and improve breast cancer survival in post-menopausal patients.

EBCTCG Lancet 2015
Do you think this difference is big enough to justify consideration of adjuvant BPs in routine?
Adjuvant AIs reduce the rate relapse and improve breast cancer survival in post-menopausal patients compared to tamoxifen.

EBCTCG Lancet 2015
Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel

P. Hadji\textsuperscript{1,}\textdagger, R. E. Coleman\textsuperscript{2*},\textdagger, C. Wilson\textsuperscript{2}, T. J. Powles\textsuperscript{3}, P. Clézardin\textsuperscript{4}, M. Aapro\textsuperscript{5}, L. Costa\textsuperscript{6}, J.-J. Body\textsuperscript{7}, C. Markopoulous\textsuperscript{8}, D. Santini\textsuperscript{9}, I. Diel\textsuperscript{10}, A. Di Leo\textsuperscript{11}, D. Cameron\textsuperscript{12}, D. Dodwell\textsuperscript{13}, I. Smith\textsuperscript{14}, M. Gnant\textsuperscript{15}, R. Gray\textsuperscript{16}, N. Harbeck\textsuperscript{17}, B. Thurlimann\textsuperscript{18}, M. Untch\textsuperscript{19}, J. Cortes\textsuperscript{20}, M. Martin\textsuperscript{21}, U.-S. Albert\textsuperscript{1}, P.-F. Conte\textsuperscript{22}, B. Ejlersen\textsuperscript{23,24}, J. Bergh\textsuperscript{25}, M. Kaufmann\textsuperscript{26} & I. Holen\textsuperscript{2}
The Impact of Adjuvant Denosumab on Disease-Free Survival
Results from 3,425 Postmenopausal Patients of the ABCSG-18 Trial

Michael Gnant
Professor of Surgery, Medical University of Vienna
Austrian Breast & Colorectal Cancer Study Group
ABCSD-18 Results of the DFS ITT Analysis

<table>
<thead>
<tr>
<th>Number of Events / Patients</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>203 / 1,709</td>
<td>0.816 (0.66 - 1.00)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>167 / 1,711</td>
<td></td>
</tr>
</tbody>
</table>

Disease-free survival, %

Patients at risk

Placebo: 1709 1663 1626 1578 1443 1289 1086 958 779 693 534 454 289 241 115 73
Denosumab: 1711 1676 1623 1584 1424 1296 1102 984 779 714 548 479 300 252 115 66

stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density

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The menu

- Why osteoporosis?

A unifying topic: bone health

To conclude
Androgen deprivation therapy: Side effects

- Bone loss with increased risk of fracture\(^1,2\)
- Baseline bone density
- Prevent risk of osteoporosis

- Increased risk of diabetes\(^3\)
- Increased risk of fatal cardiac events\(^4\)–\(^6\)

Caution in patients with:
- History of stroke
- Chronic heart failure
- Myocardial infarction

CTIBL is more rapid than naturally occurring bone loss

Bone loss induced by ADT for prostate cancer is rapid and clinically significant

**Denosumab in men receiving ADT for prostate cancer**

**Cumulative incidence of new vertebral fracture**

- **Placebo (n = 673)**
- **SC Denosumab (n = 679)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Subject Incidence</th>
<th>Percentage of Subjects</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>13</td>
<td>1.9%</td>
<td>0.15</td>
<td>.004</td>
</tr>
<tr>
<td>24</td>
<td>22</td>
<td>3.3%</td>
<td>0.31</td>
<td>.004</td>
</tr>
<tr>
<td>36</td>
<td>26</td>
<td>3.9%</td>
<td>0.38</td>
<td>.006</td>
</tr>
</tbody>
</table>

**RR = relative risk.**

ESMO clinical practice guideline: Bone health in cancer patients

• Clinicians treating cancer patients need to be aware of:
  • Treatments to reduce skeletal morbidity in metastatic disease
  • Strategies to minimise cancer treatment-induced skeletal damage

• ESMO guidelines “provide a framework for maintaining bone health in patients with cancer”
Prevention of bone loss in patients with treatments known to increase the risk of fractures

- Baseline fracture risk factor assessment
  - e.g. age >65 years, smoking, oral corticosteroid use >6 months, low BMI (<20), family history of hip-fracture, personal history of fragility fracture after age 50

- Bone mineral density (BMD) measurement

- Lifestyle changes
  - Take more weight-bearing exercise
  - Stop smoking
  - Reduce alcohol consumption

- Dietary measures and supplements
  - Adequate calcium (1000 mg/day) intake
  - Supplementary vitamin D (to total intake of 1000–2000 units/day)

- In selected cases – bone directed anti-resorptive therapy to manage low BMD or rapid bone loss

# Regulatory approval for anti-resorptive agents in cancer patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention of skeletal-related events</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. every 3–4 weeks</td>
<td>All solid tumours and multiple myeloma</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. every 4 weeks</td>
<td>All solid tumours</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3–4 weeks</td>
<td>Breast cancer and multiple myeloma</td>
</tr>
<tr>
<td>Clodronate 1600 mg p.o. daily</td>
<td>Osteolytic lesions*</td>
</tr>
<tr>
<td>Ibandronate 50 mg p.o. daily</td>
<td>Breast cancer*</td>
</tr>
<tr>
<td>Ibandronate 6 mg i.v. monthly</td>
<td>Breast cancer*</td>
</tr>
<tr>
<td><strong>Prevention of breast cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. monthly x 6, then 3–6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Clodronate 1600 mg daily</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of prostate cancer metastases</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. monthly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prevention of treatment-induced bone loss</strong></td>
<td></td>
</tr>
<tr>
<td>Denosumab 60 mg s.c. 6 monthly</td>
<td>Prostate and breast cancer</td>
</tr>
<tr>
<td>Zoledronic acid 4 mg i.v. 6 monthly</td>
<td>None</td>
</tr>
<tr>
<td>Alendronate 70 mg p.o. weekly</td>
<td>None</td>
</tr>
<tr>
<td>Risedronate 35 mg p.o. weekly</td>
<td>None</td>
</tr>
<tr>
<td>Ibandronate 150 mg p.o. monthly</td>
<td>None</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v. every 3 months</td>
<td>None</td>
</tr>
</tbody>
</table>

*European approval only (not US)

i.v. – intravenous; s.c. subcutaneous; p.o. per oral

Treatment recommendations

- Bisphosphonates and denosumab prevent bone loss associated with ovarian suppression/aromatase inhibitors in early breast cancer and androgen deprivation therapy in prostate cancer

Prevention of treatment-induced bone loss

ESMO - Recommended Algorithm for managing Bone Health during Breast Cancer Treatment

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

Any 2 of the following RF:
- Age >65 years
- T-score < -1.5
- Smoking (current or history)
- BMI < 20
- Family history of hip fracture
- Personal history of fragility fracture >50 years
- Oral glucocorticoid use for > 6 months

T-score > -2.0 and no additional risk factors
- Exercise
- Calcium and vitamin D
- Monitor risk and BMD at 1–2 year intervals

T-score < -2.0
- Exercise
- Calcium and vitamin D
- Bisphosphonate therapy (zoledronic acid, alendronate, risedronate, ibandronate) and Denosumab*
- Monitor BMD every 2 years
- Check compliance with oral therapy

*in view of ABCSG-18 data

Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial


Summary

**Background** Adjuvant endocrine therapy compromises bone health in patients with breast cancer, causing osteopenia, osteoporosis, and fractures. Antiresorptive treatments such as bisphosphonates prevent and counteract these side-effects. In this trial, we aimed to investigate the effects of the anti-RANK ligand antibody denosumab in postmenopausal, aromatase inhibitor-treated patients with early-stage hormone receptor-positive breast cancer.
Primary End Point Results

<table>
<thead>
<tr>
<th>Number of Fractures / Patients</th>
<th>Hazard ratio vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>176 / 1,709</td>
<td>0.50 (0.39 - 0.65)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>92 / 1,711</td>
<td></td>
</tr>
</tbody>
</table>

Risk of fracture, %

Time since randomization, months

Patients at risk
Placebo 1709 1660 1470 1265 1069 921 785 637 513 384 275 185 112
Denosumab 1711 1665 1488 1297 1118 965 823 688 549 432 305 221

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About Anna and Boris

Anna is 72 years old and was diagnosed with a pT1c (18 mm) pN1(1/13)M0 ductal invasive G1 ER100 PgR100 Ki67 5% breast cancer. She had conservative surgery and will receive radiation. In addition she will have an AI. But the BMD shows a T score of -2.0 at both hips ( -2.5 or lower is osteoporosis ). She is on Ca, Vit D and exercises regularly.

Would you suggest a BMA?
Would you suggest denosumab or a bisphosphonate?
Anna’s husband Boris is also 72 years old and was diagnosed with a prostate cancer for which, after radiation therapy, a 3 year androgen deprivation therapy has been suggested.

Do you believe he is at risk of bone fracture? Would you suggest a BMA? Would you suggest denosumab or a bisphosphonate?
Anna and Boris are now 78 years old. They are off therapy, still on calcium, vitamin D and they exercise regularly. Anna’s BMD is T-1.7 as she was on BPs for 5 years and Boris refused the test and treatment.
ADJUVANT SETTING

ADVANCED DISEASE
Bone metastases can have debilitating consequences\(^1\)

**Disease**
- Bone metastases

**SREs**
- Fracture
- Radiation to bone
- Spinal cord compression
- Hypercalcemia
- Surgery to bone (incl. cementoplasty)

**Consequences**
- Loss of autonomy
- Significant morbidity
- Reduced quality of life\(^2\)
- Bone pain
- Increased healthcare costs and resources

**Ultimate consequence**
- Decreased survival

---

clinical practice guidelines

Management of cancer pain: ESMO Clinical Practice Guidelines†

C. I. Ripamonti¹, D. Santini², E. Maranzano³, M. Berti⁴ & F. Roila⁵, on behalf of the ESMO Guidelines Working Group*

¹Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale Tumori, Milan, Italy; ²Oncologia Medica, Università Campus Bio-Medico, Rome, Italy; ³Department of Oncology, Radiation Oncology Centre, S. Maria Hospital, Terri, Italy; ⁴Anaesthesiology Intensive Care and Pain Therapy, University Hospital Parma, Parma, Italy; ⁵Department of Medical Oncology, S. Maria Hospital, Terri, Italy
Long-term relief of metastatic bone pain

Mean BPI change from baseline

- IV Zoledronic acid
- Placebo
- IV Ibandronate
- Placebo

*P < .05 versus baseline.

Denosumab is also effective in pain control

- **Time to pain worsening (≥ 2-point increase)**

  ![Graph showing pain worsening with Denosumab and Zoledronic Acid.](Image)

  - **Proportion of Subjects Without a ≥ 2-Point Increase**
  - **Study Week**
  - **Subjects at Risk**
    - **Zoledronic Acid**: 2440, 1303, 914, 692
    - **Denosumab**: 2476, 1391, 955, 719

  - **HR** 0.92 (95% CI: 0.86–0.99)
  - **P = 0.026**

  - **KM Estimate of Median Days**:
    - **Denosumab**: 181
    - **Zoledronic Acid**: 169

  - Pain worsening was delayed with denosumab compared with zoledronic acid

*223 ZA patients and 219 denosumab patients reported baseline worst pain scores of 9 and 10 and were thus ineligible to reach a 2-point increase.

When to start Bone Targeted Therapy

- It takes some months before the benefit is evident as bone lesions need time to heal

- Thus guidelines indicate: start immediately after diagnosis of bone metastases

- BUT use clinical judgment: if the patient’s life expectancy is very short, it might not be useful

Aapro et al Annals of Oncology 2008
Denosumab efficacy results across pivotal studies in patients with bone metastases*

Breast Cancer (n=2046)¹

Prostate Cancer (n=1901)²

Other Solid Tumors or Multiple Myeloma (n=1776)³

*All data come from the primary analysis phase of these studies

Similar overall disease-progression and survival

**Overall Disease Progression**

- **Proportion of Subjects without Disease Progression**
  - **Study Month**: 0 6 12 18 24 30
  - **Proportion**: 1.0 0.8 0.6 0.4 0.2
  - **HR**: 1.02 (95% CI: 0.95, 1.08)
  - **P**: 0.63

**Overall Survival**

- **Proportion of Subjects Survived**
  - **Study Month**: 0 6 12 18 24 30
  - **Proportion**: 1.0 0.8 0.6 0.4 0.2
  - **HR**: 0.99 (95% CI: 0.91, 1.07)
  - **P**: 0.71

**KM Estimate of Median Months**

- **Zoledronic Acid**: 8.8
- **Denosumab**: 8.6
- **Zoledronic Acid**: 22.3
- **Denosumab**: 22.5

Adverse events in the presence of denosumab or zoledronic acid: ONJ and others

<table>
<thead>
<tr>
<th>Patient incidence, n (%)</th>
<th>Zoledronic Acid (n=2836)</th>
<th>Denosumab (n=2841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (AEs)</td>
<td>2745 (96.8)</td>
<td>2734 (96.2)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>895 (31.6)</td>
<td>876 (30.8)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>859 (30.3)</td>
<td>771 (27.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>766 (27.0)</td>
<td>769 (27.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>747 (26.3)</td>
<td>718 (25.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>694 (24.5)</td>
<td>656 (23.1)</td>
</tr>
<tr>
<td>CTCAE Grade 3, 4 or 5 AEs</td>
<td>2009 (70.8)</td>
<td>2000 (70.4)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1620 (57.1)</td>
<td>1599 (56.3)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>280 (9.9)</td>
<td>270 (9.5)</td>
</tr>
<tr>
<td>Infectious AEs</td>
<td>1218 (42.9)</td>
<td>1233 (43.4)</td>
</tr>
<tr>
<td>Infectious serious AEs</td>
<td>309 (10.9)</td>
<td>329 (11.6)</td>
</tr>
<tr>
<td><strong>Acute phase reactions (first 3 days)</strong></td>
<td>572 (20.2)</td>
<td>246 (8.7)</td>
</tr>
<tr>
<td>Renal AEs*</td>
<td>335 (11.8)</td>
<td>262 (9.2)</td>
</tr>
<tr>
<td>Cumulative rate of ONJ</td>
<td>37 (1.3)</td>
<td>52 (1.8)</td>
</tr>
<tr>
<td>Year 1</td>
<td>15 (0.5)</td>
<td>22 (0.8)</td>
</tr>
<tr>
<td>Year 2</td>
<td>28 (1.0)</td>
<td>51 (1.8)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>141 (5.0)</td>
<td>273 (9.6)</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>18 (0.6)</td>
<td>28 (1.0)</td>
</tr>
</tbody>
</table>

*Includes increased blood creatinine, renal failure, acute renal failure, proteinuria, renal impairment, oliguria, increased blood urea, hypercreatininemia, decreased urine output, anuria, decreased creatinine renal clearance, azotemia, chronic renal failure, abnormal renal function test and abnormal blood creatinine. ONJ; osteonecrosis of the jaw.

WHAT DOSE OF BPs TO USE in M1 BrCA

PLEASE NOTICE THAT RECENT STUDIES INDICATE THAT MONTHLY ZOLEDRONIC ACID MAY NOT BE NEEDED FOR LONG-TERM CONTROL OF SREs

HOWEVER EXPERT CONSENSUS SUGGESTS MONTHLY FOR 3-6 MONTHS before 3 monthly

Amadori Lancet 2014; Hortobagyi ASCO 2014; Himelstein ASCO 2015
<table>
<thead>
<tr>
<th>Event</th>
<th>Q Month N = 911</th>
<th>Q 3 Months N = 911</th>
<th>HR (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ZA dose (median)</td>
<td>56 mg</td>
<td>24 mg</td>
<td>— (&lt; 0.01)</td>
</tr>
<tr>
<td>Dose delays</td>
<td>62%</td>
<td>37%</td>
<td>— (&lt; 0.01)</td>
</tr>
<tr>
<td>Any SRE</td>
<td>260</td>
<td>253</td>
<td>1.05 (0.60)</td>
</tr>
<tr>
<td>Any SRE – breast pts (N = 820)</td>
<td>113</td>
<td>119</td>
<td>0.90 (0.43)</td>
</tr>
<tr>
<td>Any SRE – prostate pts (N = 660)</td>
<td>107</td>
<td>101</td>
<td>1.15 (0.31)</td>
</tr>
<tr>
<td>Any SRE – myeloma pts (N = 265)</td>
<td>35</td>
<td>30</td>
<td>1.30 (0.29)</td>
</tr>
<tr>
<td>Bone RT</td>
<td>185</td>
<td>163</td>
<td>1.16 (0.18)</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>62</td>
<td>79</td>
<td>0.78 (0.13)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>23</td>
<td>30</td>
<td>0.75 (0.30)</td>
</tr>
<tr>
<td>Bone surgery</td>
<td>22</td>
<td>42</td>
<td>0.51 (0.01)</td>
</tr>
<tr>
<td>Jaw osteonecrosis</td>
<td>18</td>
<td>9</td>
<td>— (0.08)</td>
</tr>
<tr>
<td>Grade 2-4 creatinine increase</td>
<td>11</td>
<td>5</td>
<td>— (0.46)</td>
</tr>
</tbody>
</table>
NOT IN GUIDELINES:
FIRST YOU EVALUATE
THE FRACTURE RISK…

HOW?
EVALUATION FRACTURE RISK

Mirels score

The Mirels system classifies the risk of pathologic fracture based on scoring four variables on a scale of 1-3: location of lesion, radiographic appearance, size, and pain. An overall score is calculated, and a recommendation for or against prophylactic fixation is made.

<table>
<thead>
<tr>
<th>Location</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity</td>
<td>1</td>
<td>Lower extremity</td>
<td>Intertrochanteric</td>
</tr>
<tr>
<td>Radiographic appearance</td>
<td>Blastic</td>
<td>Mixed</td>
<td>Lytic</td>
</tr>
<tr>
<td>Size$^a$</td>
<td>&lt; 1/3</td>
<td>1/3 - 2/3</td>
<td>&gt;2/3</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Moderate</td>
<td>Functional$^b$</td>
</tr>
</tbody>
</table>

$^a$ Size is determined as a fraction of the cortical thickness.
$^b$ Functional pain is defined as severe pain or pain aggravated by limb function.
<table>
<thead>
<tr>
<th>Score</th>
<th>Fracture Risk</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥9</td>
<td>33%-100%</td>
<td>Prophylactic fixation is recommended</td>
</tr>
<tr>
<td>=8</td>
<td>15%</td>
<td>Clinical judgment should be used</td>
</tr>
<tr>
<td>≤7</td>
<td>&lt;4%</td>
<td>Observation and radiation therapy can be used</td>
</tr>
</tbody>
</table>

As an example, the lytic, intertrochanteric lesion shown above takes up >2/3 of the cortical thickness, getting an overall score of 9 in the absence of any clinical information about the degree of pain.

**References**

Spinal Instability Neoplastic Score: An Analysis of Reliability and Validity From the Spine Oncology Study Group

<table>
<thead>
<tr>
<th>SINS Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)</td>
<td>3</td>
</tr>
<tr>
<td>Mobile spine (C3-C6, L2-L4)</td>
<td>2</td>
</tr>
<tr>
<td>Semirigid (T3-T10)</td>
<td>1</td>
</tr>
<tr>
<td>Rigid (S2-S5)</td>
<td>0</td>
</tr>
<tr>
<td>Pain*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Occasional pain but not mechanical</td>
<td>1</td>
</tr>
<tr>
<td>Pain-free lesion</td>
<td>0</td>
</tr>
<tr>
<td>Bone lesion</td>
<td></td>
</tr>
<tr>
<td>Lytic</td>
<td>2</td>
</tr>
<tr>
<td>Mixed (lytic/blastic)</td>
<td>1</td>
</tr>
<tr>
<td>Blastic</td>
<td>0</td>
</tr>
<tr>
<td>Radiographic spinal alignment</td>
<td></td>
</tr>
<tr>
<td>Subluxation/translation present</td>
<td>4</td>
</tr>
<tr>
<td>De novo deformity (kyphosis/scoliosis)</td>
<td>2</td>
</tr>
<tr>
<td>Normal alignment</td>
<td>0</td>
</tr>
<tr>
<td>Vertebral body collapse</td>
<td></td>
</tr>
<tr>
<td>&gt; 50% collapse</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 50% collapse</td>
<td>2</td>
</tr>
<tr>
<td>No collapse with &gt; 50% body involved</td>
<td>1</td>
</tr>
<tr>
<td>None of the above</td>
<td>0</td>
</tr>
<tr>
<td>Posterolateral involvement of spinal elements†</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>3</td>
</tr>
<tr>
<td>Unilateral</td>
<td>1</td>
</tr>
<tr>
<td>None of the above</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Data adapted.14

Abbreviation: SINS, Spinal Instability Neoplastic Score.

*Pain improvement with recumbency and/or pain with movement/loading of spine.

†Facet, pedicle, or costovertebral joint fracture or replacement with tumor.
SINS score
(Spinal Instability Neoplastic Score)

Evaluation of fracture risk:

- Score 0-6: stable
- Score 7-12: moderate risk
- Score 13-18: unstable

Fourney et al JCO 2011
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