Guidelines Breast
Version 2017.1

Osteooncology and Bone Health

Osteooncology and Bone Health

Guidelines Breast
Version 2017.1

- **Versions 2002-2016:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Hanf / Huober / Jackisch / Janni / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon
- **Version 2017:**
  Diel / Liedtke

Bisphosphonates in Metastatic Breast Cancer

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ Hypercalcemia	1a	A	++
➢ Reduction of skeletal events (complications)	1a	A	++
➢ Reduction of bone pain	1a	A	++
➢ Increasing bone pain-free survival	1a	A	++
➢ Treatment beyond osseous progression	5	D	++

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2017.1

Denosumab in Metastatic Breast Cancer

	Oxford / AGO LoE / GR		
➢ **Reduction of hypercalcemia**	1a	A	++
➢ **Reduction of skeletal complications**	1a	A	++
➢ **Reduction of bone pain**	1a	A	++
➢ **Increasing bone pain-free survival**	1b	A	++
➢ **Treatment beyond progression**	5	D	+
➢ **Progression while on bisphosphonates**	4	C	+/-

www.ago-online.de

Further Information

References

CALGB 70604: Longer-Interval vs Standard Dosing of Zoledronic Acid

- 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study

- SRE within 2 yrs: 29.5 % zoledronic acid every 4 weeks
  28.6 % zoledronic acid every 12 weeks

Himelstein et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58.

Bone Modifying Agents for the Therapy of Bone Metastases

Guidelines Breast
Version 2017.1

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

	Oxford / AGO LoE / GR		
➢ Clodronate PO 1600 mg daily	1a	A	++
➢ Clodronate IV 1500 mg q3w / q4w	1a	A	++
➢ Pamidronate IV 90 mg q3w / q4w	1a	A	++
➢ Ibandronate IV 6 mg q3w / q4w	1a	A	++
➢ Ibandronate PO 50 mg daily	1a	A	++
➢ Zoledronate IV 4 mg			
➢ q4w	1a	A	+
➢ q12w	1a	A	++
➢ Denosumab 120 mg s.c. q4w	1a	A	++
➢ Denosumab 120 mg s.c. q12w	4	C	-
➢ Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis	5	D	- -

Skeletal Metastases
Treatment with Radionuclids

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
➢ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisit: hot spots in the bone scintigraphy)**	**1b**	**B**	**+**
➢ **^{186}Rhenium-hydroxyethylidene-diphosphonat**	**2b**	**B**	**+**
➢ **^{153}Samarium**	**1b**	**B**	**+**
➢ **^{89}Strontium**	**1b**	**B**	**+**
➢ **^{223}Radium**	**1b**	**B**	**+**

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2017.1

Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b **GR: C** **AGO: ++**

- **Spinal cord compression**
  - **With progressive neurological symptoms**
  - **With pathological fractures**
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

www.ago-online.de

Further Information

References

Bone Metastases
Acute Spinal Cord Compression / Paraplegia

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ Decompression surgery, reduction of tumor volume, stabilisation surgery (< 24 h) and irradiation of the spine (RT)	2b	C	++
➢ Irradiation of the spine (< 24 h) +/- steroids	3b	C	++
➢ Immediate start of treatment	1c	D	++

Clinical trials have included patients with different tumor entities!

www.ago-online.de

Further Information

References

Surgery for Bone Metastases

Technical Aspects

Spine and limbs

Oxford LoE: 3b **GR: C** **AGO: +**

- **Marrow splints**
- **Plate osteosynthesis**
- **Compound osteosynthesis (replacement by PMMA and osteosynthesis)**
- **Vertebral replacement by titanspacer**
- **Tumor-Endoprothesis**
- **Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor**
- **Kypho-IORT (in studies only)***
- **Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)**

*Study participation recommended

www.ago-online.de

Further Information

References

Metastatic Bone Disease: Radiotherapy (RT)

Bone metastases

	Oxford / AGO LoE / GR		
➢ With fracture risk	1a	B	++
➢ With functional impairment	1a	B	++
➢ With bone pain	1a	B	++
➢ Single dose RT = fractionated RT	2a	B	++
➢ With neuropathic bone pain	1b	B	++
➢ Asymptomatic isolated bone metastases	5	D	+/-
➢ Reduction of radiation induced pain flare by dexamethasone	1b	B	+

Only few studies included breast cancer patients!

Metastatic Bone Disease
Recurrent Bone Pain after RT

	Oxford / AGO LoE / GR		
Recurrent bone pain in pre-irradiated parts of the skeleton			
➢ **Single dose RT***	3b	C	++
➢ **Fractionated RT***	3b	C	+
➢ **Radionuclid therapy**	3b	C	+
➢ **Magnetic resonance-guided focused ultrasound**	1b	B	+
➢ **Radiofrequency ablation**	4	C	+
➢ **Cryoablation**	4	C	+

***Dosing and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.**

www.ago-online.de

Further Information

References

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

	Oxford LoE
➢ **Renal function deterioration due to IV-aminobisphosphonates**	**1b**
➢ **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3 % / 1.8 %)**	**1b**
➢ Association with (simultaneous) anti-angiogenetic therapies	**3b**
➢ **Severe hypocalcemia (Dmab > BPs)**	**1b**
➢ **Acute Phase Reaction (IV Amino-BPs, Db) 10–30 %**	**1b**
➢ **Gastrointestinal side effects (oral BPs) 2–10 %**	**1b**
➢ **Atypical femur fractures** (absolute risk of 11 per 10,000 person years of BP use)	**2b**

www.ago-online.de

Further Information

References

Guidelines Breast
Version 2017.1

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4 **GR: C** **AGO: +**

- **During bisphosphonate or denosumab treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)**
- **Optimize dental status before start of bisphosphonate or denosumab treatment, if feasible (LoE 2b)**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended**

In adjuvant bisphosphonate therapy, ONJ was rare

www.ago-online.de

Further Information

References

Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
Clodronate (oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Aminobisphosphonates (iv or oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Denosumab (60 mg s.c., q6mo)			
Postmenopausal patients	1b[a]	B	+/-

www.ago-online.de

Further Information

References

Guidelines Breast
Version 2017.1

Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
- **Clodronate po 1600 mg/d (Bonefos/ Clodronic acid)**
- **Clodronate po 1040 mg/d (Ostac)**
- **Aminobisphosphonates:**
- **Zoledronate iv 4 mg/6 m (Zometa/ Zoledronic acid)**
- **Ibandronate po 50 mg/d (Bondronat/ Ibandronic acid)**
- **Pamidronate po (orally not available in most countries)**
- **Risedronate po 35 mg/w*(Actonel/ Risedronic acid)**
- **Alendronate po 70 mg/w (Fosamax/ Alendronic acid)**
- **Optimal duration yet to be definded; in adjuvant studies duration of BP treatment varied from 2–5 years**

Aminobisphosphonates include:
Zoledronic acid (65 %), oral ibandronate (24 %), oral pamidronate (8 %), oral risedronate (2 %), oral alendronate (1 %) (data from EBCTCG-metaanalysis)

www.ago-online.de

Further Information

References

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR
Bisphosphonates	
Therapy	1b B ++
Prevention	1b A +
Denosumab	
Therapy	1b B ++
Prevention	1b A +
Hormone replacement therapy	5 D -
DXA-scan at baseline in pts with AI or with premature menopause	5 D +
Repeat DXA-scan based on risk	5 D +

www.ago-online.de

Further Information

References

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Guidelines Breast
Version 2017.1

Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

	Oxford / AGO LoE / GR		
➢ Physical activity	4	C	++
➢ Avoiding immobilisation	4	C	++
➢ Calcium (1000–1500 mg/d)**	4	C	++
➢ Vitamine D3 suppl. (800–2000 U/d)	4	C	++
➢ Cessation of smoking, reduction of alcohol	2b	B	++
➢ Avoiding BMI < 20 mg/m^2	3b	C	++
➢ Drugs approved for the treatment of osteoporosis in adults (see next slide)			

*http://www.dv-osteologie.org/dvo_leitlinien/osteoporose-leitlinie-2014
**if nutritional supply is insufficient, (in combination with Vit D3 only)

www.ago-online.de

Further Information

References

Guidelines Breast
Version 2017.1

Medical Treatment of Osteoporosis

	Oxford / AGO LoE / GR		
➢ Alendronate 70 mg po/w*	1b	B	++
➢ Denosumab 60 mg sc/6m*	1b	B	++
➢ Ibandronate 150 mg po/m*	1b	B	++
➢ Ibandronate 3 mg iv/3m	1b	B	++
➢ Parathyroid hormone (1-84) 100 µg sc/d	1b	B	+
➢ Raloxifene 60 mg po/d (improves spine only)	1b	B	+/-
➢ Risedronate 35 mg po/w*	1b	B	++
➢ Strontium ranelate 2 g po/d **	1b	B	+
➢ Teriparatide (1-34) 20 µg sc/d	1b	B	+
➢ Zoledronate 5 mg iv/12 m*	1b	B	++

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis
**Elevated risk of myocardial infarction. Substance restricted to postmenopausal pats. with severe osteoporosis and high risk of fractures

http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kitteltaschenversion%2015.12.2014.pdf

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.[1]

Lebensalter in Jahren		T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.)				
Frau	**Mann**[2]	**-2,0 bis -2,5**	**-2,5 bis -3,0**	**-3,0 bis -3,5**	**-3,5 bis -4,0**	**< -4,0**
50-60	60-70	Nein	Nein	Nein	Nein	Ja
60-65	70-75	Nein	Nein	Nein	Ja	Ja
65-70	75-80	Nein	Nein	Ja	Ja	Ja
70-75	80-85	Nein	Ja	Ja	Ja	Ja
>75	>85	Ja	Ja	Ja	Ja	Ja

[1] Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).

[2] bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score [3,4], wenn:

- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

Photo Courtesy of the DVO

Osteooncology and Bone Health (2/20)

No further information

No references

Bisphosphonates in Metastatic Breast Cancer (3/20)

No further information

References:

Metaanalysen and Reviews (metastatic breast cancer):

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37.
2. Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. 2005;(2):CD003474.
3. Ross JR, Saunders Y, Edmonds PM et al. Systematic Review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ 2003 ;327 :469-474
4. Hillner BE, Ingle JN, Chlebowski RT. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer, J Clin Oncol 2003; 21:4042-4057.
5. Machado M, Cruz LS, Tannus G, et al.Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: A meta-analysis of randomized clinical trials. Clin Ther 2009;31:962–979.

Results of Phase III trials (metastatic breast cancer):

1. Body JJ, Diel IJ, Lichinitser MR et al. Intravenous Ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003;14:1399-1405.
2. Diel IJ, Body JJ, Lichinitser MR et al. Improved quality of life for long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004;40:1704-1712.
3. Body JJ, Diel IJ, Lichinitser M et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with with metastatic bone disease; results from two randomized, placebo-controlled phase III studies. Br J Cancer 2004; 90:1133-1137.
4. Tripathy D, Lichinitser M, Lazarev A et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. Ann Oncol 2004;15:743-750.

5. Rosen LS, Gordon D, Kaminski M et al. . Long-term efficacy and safety of zoledronic acid compared with pamidonate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer. Cancer 2003; 98:1735-1744.
6. Rosen LS, Gordon DH, Dugan W et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004; 100:36-43

Denosumab in Metastatic Breast Cancer (4/20)

No further information

References:

Denosumab - Therapy of bone metastases and skeletal related complications:

1. Wang X, Yang KH, Wanyan P, Tian JH. Comparison of the efficacy and safety of denosumab versus bisphosphonates in breast cancer and bone metastases treatment: A meta-analysis of randomized controlled trials. Oncol Lett 2014;7(6):1997-2002
2. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A.. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, J Clin Oncol 2010;28:5132-5139
3. Lipton A,Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res 2008;14:6690–6699
4. Lipton A,Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol 2007;*25:*4431–4437.

Statement: Progression under bisphosphonates

1. Fizazi, K, Lipton, A, Mariette, X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 2009; 27:1564.

CALBG 70604: Longer-Interval vs Standard Dosing of Zoledronic Acid (5/20)

No further information

No references

Bone modifying Agents for the Therapy of Bone Metastases (6/20)

No further information

References:

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37
2. Hortobagyi GN et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9500).
3. Addison CL, Pond GR, Zhao H, Mazzarello S, Vandermeer L, Goldstein R, Amir E, Clemons M. Effects of de-escalated bisphosphonate therapy on bone turnover biomarkers in breast cancer patients with bone metastases. Springerplus. 2014 Oct 1;3:577. doi: 10.1186/2193-1801-3-577. eCollection 2014
4. Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, Gao G, Wu L, Sohn W, Jun S: Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 27(10):1564-1571, 2009
5. Templeton AJ et al. Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS5095)
6. Ibrahim MF, Mazzarello S, Shorr R, Vandermeer L, Jacobs C, Hilton J, Hutton B, Clemons M. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. Ann Oncol. 26(11):2205-13, 2015
7. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, Qin R, Go RS, Grubbs SS, O'Connor T, Velasco MR Jr, Weckstein D, O'Mara A, Loprinzi CL, Shapiro CL. Effect of Longer-Interval vs

Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58.

Skeletal Metastasis Treatment with Radionuclids (7/20)

No further information

References:

Reviews / Overview

1. Hoskin PJ: Radioisotopes for metastatic bone pain. Lancet Oncol. 2005 Jun;6(6):353-4
2. Bauman G, Chrrette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radioth Oncol 2005; 75: 258-70
3. Roque M, Martinez MJ, Alonso-Coello P et al (2004) Radioisotopes for metastatic bone pain (Cochrane Review). In: The Cochrane Library, Issue 3. Chichester, UK: John Wiley & Sons, Ltd. (Cochrane Database Syst Rev 2003:CD003347)

^{186}Rhenium (^{186}Re-HEDP)

1. de Klerk JM, van het Schip AD, Zonnenberg BA, van Dijk A, Quirijnen JM, Blijham GH, van Rijk PP. Phase 1 study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. J Nucl Med 1996;37:244-49
2. Han SH, Zonneberg BA, de Klerk JM, Quirijnen JM, van het Schip AD, van Dijk A, Blijham GH, van Rijk PP. 186Re-etidronate in breast cancer patients with metastatic bone pain. J Nucl Med 1999;40:639-42
3. Kolesnikov-Gauthier H, Carpentier P, Depreux P, Vennin P, Caty A, Sulman C. Evaluation of toxicity and efficacy of 186Re-hydroxyethylidene diphosphonate in patients with painful bone metastases of prostate or breast cancer. J Nucl Med 2000;41:1689-94

4. Limouris GS, Shukla SK, Condi-Paphiti A, Gennatas C, Kouvaris I, Vitoratos N, Manetou A, Dardoufas C, Rigas V, Vlahos L. Palliative therapy using rhenium-186-HEDP in painful breast osseous metastases. Anticancer Res 1997;17:1767-72

^{153}Samarium (^{153}Sm-EDTMP)

1. Anderson PM, Wiseman GA, Dispenzieri A, Arndt CA, Hartmann LC, Smithson WA, Mullan BP, Bruland OS. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 2002;20:189-96
2. Serafini AN. Systemic metabolic radiotherapy with samarium-153 EDTMP for the treatment of painful bone metastasis. Q J Nucl Med. 2001;45:91-9

^{89}Strontium (^{89}Sr-Chlorid)

1. Baziotis N, Yakoumakis E, Zissimopoulos A, Geronicola-Trapali X, Malamitsi J, Proukakis C. Strontium-89 chloride in the treatment of bone metastases from breast cancer. Oncology 1998;55:377-81
2. Fuster D, Herranz D, Vidal-Sicart S, Munoz M, Conill C, Mateos JJ, Martin F, Pons F. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun 2000;21:623-26
3. Kasalicky J, Krajska V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. Eur J Nucl Med 1998;25:1362-67
4. Sciuto R, Festa A, Pasqualoni R, Semprebene A, Rea S, Bergomi S, Maini CL. Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. Breast Cancer Res Treat 2001;66:101-19

223Ra-dichloride:

1. Pandit-Taskar N, Larson SM, Carrasquillo JA. Bone-seeking radiopharmaceuticals for treatment of osseous metastases, Part 1: α therapy with 223Ra-dichloride. J Nucl Med 55(2):268-74, 2015

Metastatic Bone Disease of the Spine – Indication for surgery (8/20)

Further information:

References:

1. Wood TJ, Racano A, Yeung H, Farrokhyar F, Ghert M, Deheshi BM. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 2014;21(13):4081-9.
2. Ju DG, Yurter A, Gokaslan ZL, Sciubba DM. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 2014;10;5(3):263-71.
3. Rades D, Veninga T, Stalpers LJ, Schulte R, Hoskin PJ, Poortmans P, Schild SE, Rudat V. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. Int J Radiat Oncol Biol Phys. 2006 Jan 1;64(1):182-8. Epub 2005 Sep 28.
4. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol. 1998;16:1613-24
5. Walker MP, Yaszemski MJ, Kim CW, Talac R, Currier BL. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl:S165-75

Bone Metastases Acute Spinal Cord Compression / Paraplegia (9/20)

Further information:

References:

1. Souchon R, Feyer P, Thomssen C, Fehm T, Diel I, Nitz U, Janni W, Bischoff J, Sauer R. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 2010;5:401-7
2. Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Sauer R. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185:417-424
3. Rades D, Heidenreich E, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2002;53:975-9
4. Rades D, Karstens JH, Hoskin PJ, et al. Escalation of radiation dose beyond 30 Gy in 10 fractions for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2007;67:525-31
5. Rades D, Veninga T, Stalpers LJ, et al. Outcome after radiotherapy alone for metastatic spinal cord compression in patients with oligometastases. J Clin Oncol 2007;25:50-6
6. Regine WF, Tibbs PA, Young A, et al. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. Int J Radiat Oncol Biol Phys 2003:57(Suppl.):S125. abstract #3
7. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol 1998;16:1613-24

8. Regine WF, Tibbs PA, Young A, Payne R, Saris S, Kryscio RJ, Patchell RA. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. Int J Radiat Oncol Biol Phys 2003:57(Suppl.):S125. abstract #3
9. Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 2000; 82: 570–594
10. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl: S 165–175
11. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. Int J Radiat Oncol Biol Phys 2000;46: 1163–1169

Surgery for Bone Metastases Technical Aspects (10/20)

Further information:

References:

1. Ju DG, Yurter A, Gokaslan ZL, Sciubba DM. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 2014;10;5(3):263-71,
2. Wood TJ, Racano A, Yeung H, Farrokhyar F, Ghert M, Deheshi BM. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 2014;21(13):4081-9.
3. Ali SM, Harvey HA, Lipton A: Metastatic breast cancer: overview of treatment. Clin Orthop Rel Res 2003;1 (415S) (Suppl): 132–137
4. Fourney DR, Gokaslan ZL: Thoracolumbar spine: surgical treatment of metastatic disease. Curr Opin Orthop 2003;14 (3): 144–152
5. Fourney DR, Schomer DF, Nader R et al: Percutaneous and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 2003;98 (Suppl): 21–30
6. Walker MP, Yaszemski MJ, Kim CW, Talac R, Currier BL. Metastatic disease of the spine. Evaluation and treatment. Clin Orthop Rel Res 1 2003;(415S) (Suppl): 165–175
7. Berenson J1, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vrionis F; Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12(3):225-35

Metastatic Bone Disease: Radiotherapy (11/20)

Further information:

References:

1. Souchon R, Feyer P, Thomssen C, Fehm T, Diel I, Nitz U, Janni W, Bischoff J, Sauer R. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 2010;5:401-7
2. Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Sauer R. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185:417-424
3. Hartsell WF, Scott C, Bruner DW, Scarantino CW, Ivker R, Roach M, Suh J, Demas W, Movsas B. Phase III randomised trial of 8 Gy in 1 fraction vs. 30 Gy in 10 fractions for palliation of painful bone metastases: preliminary results of RTOG 97-14. Int J Radiat Oncol Biol Phys 2003:57(Suppl.):S124. abstract #1
4. Hoskin PJ, Yarnold JR, Roos DR, Bentzen S. Second Workshop on Palliative Radiotherapy and Symptom Control: Radiotherapy for bone metastases. Clin Oncol (R Coll Radiol) 2001;13:88-90
5. McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev 2000;2:CD001793
6. Hoskin PJ, Yarnold JR, Roos DR, Bentzen S (2001) Second Workshop on Palliative Radiotherapy and Symptom Control: Radiotherapy for bone metastases. Clin Oncol (R Coll Radiol) 13: 88–90
7. Wu J, Bezjak A, Chow E et al (2003) A consensus development approach to define national research priorities in bone metastases: proceedings from NCIC CTG workshop. Clin Oncol (R Coll Radiol) 15: 496–499
8. Chow E, Harris K,Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-36

9. Chow E Meyer RM, Ding K, Nabid A, Chabot P, Wong P, Ahmed S, Kuk J, Dar AR, Mahmud A, Fairchild A, Wilson CF, Wu JS, Dennis K, Brundage M, DeAngelis C, Wong RK. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. Lancet Oncol 16(15):1463-72, 2015

Metastatic Bone Disease Recurrent Bone Pain after RT (12/20)

Further information:

References:

Recurrent bone pain in pre-irradiated parts of the skeleton

1. Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Sauer R. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 2009;185:417-424
2. Souchon R, Feyer P, Thomssen C, Fehm T, Diel I, Nitz U, Janni W, Bischoff J, Sauer R. Clinical recommendations of DEGRO and AGO on preferred standard palliative radiotherapy (RT) of bone and cerebral metastases, metastatic spinal cord compression, and leptomeningeal carcinomatosis in breast cancer. Breast Care 2010;5:401-7
3. Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 2000;82:570-594
4. Haddad P, Wong R, Wilson P, McLean M, Levin W, Bezjak A. Factors influencing the use of single versus multiple fractions of palliative radiotherapy for bone metastases: a 5-year review and comparison to a survey. Int J Radiat Oncol Biol Phys 2003:57(Suppl.):S278. abstract #1029
5. Van der Linden Y, Lok J, Steenland E, Martijn H, Marijnen C, Leer J. Re-irradiation of painful bone metastases: a further analysis of the Dutch Bone Metastasis Study. Int J Radiat Oncol Biol Phys 2003:57(Suppl.):S222. abstract #163

Magnetic resonance-guided focused ultrasound

1. Hurwitz MD, Ghanouni P, Kanaev SV, et al. Magnetic resonance-guided focused ultrasound for patients with painful bone metastases: phase III trial results. J Natl Cancer Inst 2014; 106.

Cryoablation / Radiofrequency ablation

1. Dechamps F, Farouil G, Ternes N, Gaudin A, Hakime A, Tselikas L, Teriitehau C, Baudin E, Auperin A, de Baere T. Thermal ablation techniques: a curative treatment of bone metastases in selected patients? Eur Radiol 24(8):1971-80, 2014
2. Hegg RM, Kurup AN, Schmit GD, Weisbrod AJ, Atwell TD, Olivier KR, Moynihan TJ, Callstrom MR. Cryoablation of sternal metastases for pain palliation and local tumor control. J Vasc Interv Radiol 25(11):1665-70, 2014

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (13/20)

Further information:

References

Bisphosphonates

1. Schilcher, J., V. Koeppen, P. Aspenberg and K. Michaelsson : Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthop 2015;100-107
2. Body JJ. Breast Cancer: Bisphosphonate therapy for metastatic bone disease. Clin Cancer Res. 2006; 12(20 Suppl):6258s-6263s.
3. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer. 2008;98(11):1736-40.
4. Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. Nat Clin Pract Oncol. 2007:4(1):42-55.
5. Tralongo, P, Repetto, L, Di Mari, A, et al. Safety of long-term administration of bisphosphonates in elderly cancer patients. Oncology 2004; 67:112.
6. Chang, JT, Green, L, Beitz, J. Renal failure with the use of zoledronic acid. N Engl J Med 2003;
7. Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S, American Society of Clinical Oncology:American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol. 2003;21(21):4042-57.
8. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, Crinò L, Dirix L, Gnant M, Gralow J, Hadji P, Hortobagyi GN, Jonat W, Lipton A, Monnier A, Paterson AH, Rizzoli R, Saad F, Thürlimann B. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 2008;19(3):420-32.

Denosumab

1. Stopeck AT et al. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, J Clin Oncol 28:5132-5139
2. Taylor KH, Middlefell LS, and Mizen KD, "Osteonecrosis of the Jaws Induced by Anti-RANK Ligand Therapy," Br J Oral Maxillofac Surg, 2010, 48(3):221-3.

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ) (14/20)

Further information

References:

1. Sivolella, S., F. Lumachi, E. Stellini and L. Favero . Denosumab and anti-angiogenetic drug-related osteonecrosis of the jaw: an uncommon but potentially severe disease. Anticancer Res 2013,33(5): 1793-1797
2. Izzotti A, Menini M, Pulliero A, Dini G, Cartiglia C, Pera P, Baldi D. Biphosphonates-associated osteonecrosis of the jaw: the role of gene-environment interaction. J Prev Med Hyg 2013,54(3): 138-145.
3. Fehm T, Felsenberg D, Krimmel M, Solomayer E, Wallwiener D, Hadjii P.Bisphosphonate-associated osteonecrosis of the jaw in breast cancer patients: recommendations for prevention and treatment. Breast. 2009;18(4):213-7.
4. Khan AA, Sándor GK, Dore E, Morrison AD, Alsahli M, Amin F, Peters E, Hanley DA, Chaudry SR, Dempster DW, Glorieux FH, Neville AJ, Talwar RM, Clokie CM, Al Mardini M, Paul T, Khosla S, Josse RG, Sutherland S, Lam DK, Carmichael RP, Blanas N, Kendler D, Petak S, St-Marie LG, Brown J, Evans AW, Rios L, Compston JE; Canadian Association of Oral and Maxillofacial Surgeons. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 2008;35(7):1391-7.
5. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons.American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2007;65(3):369-76.

Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage (15/20)

No further information

References:

Clodronate:

1. Ben-Aharon I, Vidal L, Rizel S, Yerushalmi R, Shpilberg O, Sulkes A, Stemmer SM. Bisphosphonates in the adjuvant setting of breast cancer therapy--effect on survival: a systematic review and meta-analysis. PLoS One. 2013 Aug 26;8(8):e70044. doi: 10.1371/journal.pone.0070044. eCollection 2013. Review.
2. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer: an Overview. Clin Oncol 2013;25:135-45
3. Coleman R, Gnant M, Paterson A et al. Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer. A meta-analysis of individual patients data from randomized trials. SABCS 2013, abstract S4-07
4. Zhu J, Zheng Y, Zhou Z. Oral adjuvant clodronate therapy could improve overall survival in early breast cancer. Results from an updated systematic review and meta-analysis. Eur J Cancer 2013 ;49:2086-92
5. Diel IJ, Solomayer EF, Costa SD, Gollan C, Goerner R, Wallwiener D, Kaufmann M, Bastert G: Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med 1998;339:357-63.
6. Diel IJ, Jaschke A, Solomayer EF, Gollan C, Bastert G, Sohn C, Schuetz F: Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow—a long-term follow-up. Ann Oncol 2008;19: 2007-2011.
7. Powles TJ, McCloskey E, Paterson AH et al. Oral clodronate and reduction in loss of bone mineral density in women with operable breast cancer. J Natl Cancer Inst 1998;90:704-8.

8. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C : Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol. 2004;43(7):650-656;

Adjuvant Aminobisphosphonates

1. Ben-Aharon I, Vidal L, Rizel S, Yerushalmi R, Shpilberg O, Sulkes A, Stemmer SM. Bisphosphonates in the adjuvant setting of breast cancer therapy--effect on survival: a systematic review and meta-analysis. PLoS One. 2013 Aug 26;8(8):e70044. doi: 10.1371/journal.pone.0070044. eCollection 2013. Review.
2. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer: an Overview. Clin Oncol 2013;25:135-45
3. Valachis A, Polyzos NP, Coleman RE et al. Adjuvant therapy with zoledronic acid in patients with breast cancer. A systematic review and meta-analysis. The Oncologist 2013;18:353-61
4. Coleman R, Gnant M, Paterson A et al. Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer. A meta-analysis of individual patients data from randomized trials. SABCS 2013, abstract S4-07
5. Coleman RE, Thorpe HC, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Davies C, Bell R. Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). 33. SABCS 2010, S4-5.
6. Yan T, Yin W, Zhou Q et al. The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials. Eur J Cancer 2012; 48:187-95
7. Brufsky AM, Bosserman LD, Caradonna RR, Haley BB, Jones CM, Moore HC, Jin L, Warsi GM, Ericson SG, Perez EA. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer. 2009;9(2):77-85.

8. Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Neven P, von Minckwitz G, Miller J, Schenk N, Coleman R. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol 2010;21(11):2188-94.
9. Hadji P, Coleman RE, Wilson C, Powles TJ, Clézardin P, Aapro M, Costa L, Body JJ, Markopoulos C, Santini D, Diel I, Di Leo A, Cameron D, Dodwell D, Smith I, Gnant M, Gray R, Harbeck N, Thurlimann B, Untch M, Cortes J, Martin M, Albert US, Conte PF, Ejlertsen B, Bergh J, Kaufmann M, Holen I. Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European Panel. Ann Oncol. 2015 Dec 17. pii: mdv617.
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T, Paterson A, Gnant M, Anderson S, Diel I, Gralow J, von Minckwitz G, Moebus V, Bergh J, Pritchard KI, Bliss J, Cameron D, Evans V, Pan H, Peto R, Bradley R, Gray R. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015

Dosage of Adjuvant Bisphosphonates for Improvement of Survival (16/20)

No further information

References:

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37,
2. Coleman R, Gnant M, Paterson A et al. Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer. A meta-analysis of individual patients data from randomized trials. SABCS 2013, abstract S4-07

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/20)

No further information

References:

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37.
2. German guidelines for the treatment of osteoporosis by the DVO: http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf
3. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, Wette V, Balic M, Haslbauer F, Melbinger E, Bjelic-Radisic V, Artner-Matuschek S, Fitzal F, Marth C, Sevelda P, Mlineritsch B, Steger GG, Manfreda D, Exner R, Egle D, Bergh J, Kainberger F, Talbot S, Warner D, Fesl C, Singer CF; Austrian Breast and Colorectal Cancer Study Group. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 386(9992):433-43, 2015

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (18/20)

No further information

References:

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37.
2. German guidelines for the treatment of osteoporosis by the DVO: http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf
3. Tatsuno I, Terano T, Nakamura M, Suzuki K, Kubota K, Yamaguchi J, Yoshida T, Suzuki S, Tanaka T, Shozu M. Lifestyle and osteoporosis in middle-aged and elderly women: Chiba bone survey. Endocr J. 2013;60(5):643-50
4. Zhu K, Prince RL. Lifestyle and Osteoporosis. Current Osteoporosis Reports 2015,13(1),52-59.

Medical Treatment of Osteoporosis (19/20)

No further information

References:

1. German guidelines for the treatment of osteoporosis by the DVO:
2. http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf
3. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014,25 Suppl 3:iii124-37.
4. http://www.akdae.de/Arzneimittelsicherheit/RHB/Archiv/2013/20130513.pdf

Raloxifen

1. Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int. 2006;17(2):313.

Strontium renalate

1. Kaufman JM, Audran M, Bianchi G, Braga V, Diaz-Curiel M, Francis RM, Goemaere S, Josse R, Palacios S, Ringe JD, Felsenberg D, Boonen S .Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 2013,98(2): 592-601.
2. Reginster, J. Y. Cardiac concerns associated with strontium ranelate. Expert Opin Drug Safe 2014, 13(9): 1209-1213

Guidelines of the DVO (20/20)

No further information

References:

1. German guidelines for the treatment of osteoporosis by the DVO: http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf
2. http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-leitlinie%20Osteoporose%202014%20Kitteltaschenversion%2015.12.2014.pdf