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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Osteooncology and Bone Health

Osteooncology and Bone Health

- **Versions 2002–2019:**

Bischoff / Böhme / Brunnert / Dall / Diel / Fehm /


Fersis / Friedrich/ Friedrichs / Hanf / Huober /

Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff /

Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2020:**

Solbach / Solomayer



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Bisphosphonates in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ 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	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates used alone for pain control	5	D	-

Metaanalysen and Reviews (metastatic breast cancer)

1. Coleman R, Body JJ, Aapro M, et al. ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014;25 Suppl 3:iii124-37.
2. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
3. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017
4. Tesfamariam Y, Jakob T, Wöckel A et al. Adjuvant bisphosphonates or RANK-ligand inhibitors for patients with breast cancer and bone metastases: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2019;137:1-8.

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 14:1399-1405,2003


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* 40:1704-1712, 2004
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* 90:1133-1137., 2004
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* 15:743-750, 2004
5. Rosen LS, Gordon D, Kaminski M et al. . Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer. *Cancer* 98:1735-1744, 2003
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* 100:36-43, 2004

Clinical relevance of bone resorption marker

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. *J Clin Oncol* 35(35):3978-3986, 2017

Bisphosphonates for bone pain control

1. Van Poznak C, Somerfield MR, Barlow W. et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. *J Clin Oncol* 35(35):3978-3986, 2017



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Denosumab in Metastatic Breast Cancer

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
1a	A	++
1b	A	++
5	D	+
4	C	+/-
5	D	-
5	D	-

- **Reduction of hypercalcemia**
- **Reduction of skeletal complications**
- **Reduction of bone pain**
- **Increasing bone pain-free survival**
- **Treatment beyond progression**
 - Progression while on bisphosphonates
- **Use of bone resorption markers for therapy monitoring**
- **Denosumab alone for pain control**

Denosumab - Therapy of bone metastases and skeletal related complications

1. Stopeck AT, Lipton A, Body JJ 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, 2010
2. 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 14:6690–6699, 2008
3. 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 25:4431–4437, 2007
4. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
5. Tesfamariam Y, Jakob T, Wöckel A et al. Adjuvant bisphosphonates or RANK-ligand inhibitors for patients with breast cancer and bone metastases: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2019;137:1-8.

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 27:1564-71, 2009

Clinical relevance of bone resorption marker

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017

Bisphosphonates for bone pain control

1. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017



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Longer-Interval vs Standard Dosing of Zoledronic Acid

- ¹ **CALGB 70604 trial:** n=1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study

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

- ² **Optimize-2-trial:** n=460 with metastatic breast cancer

SRE after 1 year³: 22.0% zoledronic acid every 4 weeks
 23.2% zoledronic acid every 12 weeks

¹ Himmelstein 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 317(1):48-58. 2017

² Hortobagyi GN et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017

³ Patients eligible for this trial had prior exposure to zoledronate or pamidronate for approx. 1 year or more


1. Himmelstein AL, Foster JC, Khatcheressian JL 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 317(1):48-58, 2017
2. Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017
3. Awan AA, Hutton B, Hilton J et al., De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2019;176(3):507-517.

	Oxford		
	LoE	GR	AGO
▪ 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	--

1. 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)
2. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
3. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017
4. Ibrahim MF, Mazzaello S, Shorr R et al. 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
5. Amadori D, Aglietta M, Alessi B et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 14(7):663-70, 2013
6. Himmelstein AL, Foster JC, Khatcheressian JL 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 317(1):48-58, 2017
7. Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in

Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. *JAMA Oncol* 3(7):906-912, 2017

8. Awan AA, Hutton B, Hilton J et al., De-escalation of bone-modifying agents in patients with bone metastases from breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2019;176(3):507-517.
9. Santini D, Galvano A, Pantano F et al. How do skeletal morbidity rate and special toxicities affect 12-week versus 4-week schedule zoledronic acid efficacy? A systematic review and a meta-analysis of randomized trials. *Crit Rev Oncol Hematol.* 2019;142:68-75.



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Skeletal Metastases

Treatment with Radionuclids

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain 	1b	B	+
<ul style="list-style-type: none"> ■ ¹⁸⁶Rhenium-hydroxyethyliden-diphosphonat 	2b	B	+
<ul style="list-style-type: none"> ■ ¹⁵³Samarium 	1b	B	+
<ul style="list-style-type: none"> ■ ⁸⁹Strontium 	1b	B	+
<ul style="list-style-type: none"> ■ ²²³Radium 	2b	C	+
<ul style="list-style-type: none"> ■ ¹⁷⁷Lu-EDTMP 	2b	C	+
<ul style="list-style-type: none"> ■ ¹⁸⁸Rhenium-HEDP 	1b	B	+

Cave: the potential benefits should be weighed against the risk of myelosuppression with pancytopenia

Reviews / Overview

1. Hoskin PJ: Radioisotopes for metastatic bone pain. Lancet Oncol 6(6):353-4, 2005
2. Bauman G, Chrrette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radioth Oncol 75: 258-70, 2005
3. Roque M, Martinez MJ, Alonso-Coello P et al. 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), 2004

¹⁸⁶Rhenium (¹⁸⁶Re-HEDP)

1. de Klerk JM, van het Schip AD, Zonnenberg BA et al. Phase 1 study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. J Nucl Med 137:244-49, 1996
2. Han SH, Zonneberg BA, de Klerk JM et al. ¹⁸⁶Re-etidronate in breast cancer patients with metastatic bone pain. J Nucl Med 40:639-42, 1999
3. Kolesnikov-Gauthier H, Carpentier P, Depreux P et al. Evaluation of toxicity and efficacy of ¹⁸⁶Re-hydroxyethylidene

diphosphonate in patients with painful bone metastases of prostate or breast cancer. J Nucl Med 41:1689-94, 2004

4. Limouris GS, Shukla SK, Condi-Paphiti A et al. Palliative therapy using rhenium-186-HEDP in painful breast osseous metastases. Anticancer Res 17:1767-72, 1997

¹⁵³Samarium (¹⁵³Sm-EDTMP)

1. Anderson PM, Wiseman GA, Dispenzieri A et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. J Clin Oncol 20:189-96, 2002
2. Serafini AN. Systemic metabolic radiotherapy with samarium-153 EDTMP for the treatment of painful bone metastasis. Q J Nucl Med. 45:91-9, 2001
3. Kolesnikov-Gauthier H, Lemoine N, Tresch-Bruneel E et al. Efficacy and safety of ¹⁵³Sm-EDTMP as treatment of painful bone metastasis: a large single-center study. Support Care Cancer. 2017 Sep 17. doi: 10.1007/s00520-017-3885-3

⁸⁹Strontium (⁸⁹Sr-Chlorid)

1. Baziotis N, Yakoumakis E, Zissimopoulos A et al. Strontium-89 chloride in the treatment of bone metastases from breast cancer. Oncology 55:377-81, 1998
2. Fuster D, Herranz D, Vidal-Sicart S et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun 21:623-26, 2002
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 25:1362-67, 1998
4. Sciuto R, Festa A, Pasqualoni R et al. Metastatic bone pain palliation with ⁸⁹Sr and ¹⁸⁶Re-HEDP in breast cancer patients. Breast Cancer Res Treat 66:101-19, 2001


²²³Ra-dichloride:

1. Pandit-Taskar N, Larson SM, Carrasquillo JA. Bone-seeking radiopharmaceuticals for treatment of osseous metastases, Part 1: α

therapy with ^{223}Ra -dichloride. J Nucl Med 55(2):268-74, 2015

^{177}Lu (Lutetium)-EDTMP

1. Agarwal KK, Singla S, Arora G, Bal C. (^{177}Lu)-EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study. Eur J Nucl Med Mol Imaging. 42(1):79-88,2015
2. Sharma S, Singh B, Koul A et al. Comparative Therapeutic Efficacy of ^{153}Sm -EDTMP and ^{177}Lu -EDTMP for Bone Pain Palliation in Patients with Skeletal Metastases: Patients' Pain Score Analysis and Personalized Dosimetry. Front Med (Lausanne). 2017 May 1;4:46. doi: 0.3389/fmed.2017.00046. eCollection 2017.



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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**

1. Wood TJ, Racano A, Yeung H et al. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 21(13):4081-9, 2014
2. Ju DG, Yurter A, Gokaslan ZL et al. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 10;5(3):263-71, 2014
3. Rades D, Veninga T, Stalpers LJ et al. 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 64(1):182-8, 2006
4. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl:S165-75
5. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.2 – 2019 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.2.pdf
6. Ahangar P, Aziz M, Rosenzweig DH et al. Advances in personalized treatment of metastatic spine disease. Ann Transl Med. 2019;7(10):223. Review.

7. Conti A, Acker G, Kluge A et al., Decision Making in Patients With Metastatic Spine. The Role of Minimally Invasive Treatment Modalities. Front Oncol. 2019;19;9:915.



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Bone Metastases Acute Spinal Cord Compression / Paraplegia


	Oxford		
	LoE	GR	AGO
▪ Decompression surgery, reduction of tumor volume, stabilization 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!

1. Souchon R, Feyer P, Thomssen C et al. 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 5:401-7 , 2010
2. Souchon R, Wenz F, Sedlmayer F et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
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 53:975-9, 2002
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 67:525-31, 2007
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 25:50-6 , 2007
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 16:1613-24, 1998

8. 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
9. Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 82: 570–594, 2000
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 46: 1163–1169, 2000
12. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.2 – 2019 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.2.pdf
13. Hoskin PJ, Hopkins K, Misra V et al. Effect of Single-Fraction vs Multifraction Radiotherapy on Ambulatory Status Among Patients With Spinal Canal Compression From Metastatic Cancer: The SCORAD Randomized Clinical Trial. JAMA. 2019;322(21):2084-2094.



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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-Endoprosthesis
- 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

1. Ju DG, Yurter A, Gokaslan ZL et al. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 10;5(3):263-71, 2014
2. Wood TJ, Racano A, Yeung H et al. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 21(13):4081-9, 2014
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 14 (3): 144–152, 2013
5. Fourney DR, Schomer DF, Nader R et al: Percutaneous and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 98 (Suppl): 21–30, 2003
6. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine. Evaluation and treatment. Clin Orthop Rel Res (415S) (Suppl): 165–175, 2003
7. Berenson J1, Pflugmacher R, Jarzem P et al. 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 12(3):225-35, 2011
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Version 1.2 – 2019 AWMF-Register Nr.: 032/054OL. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.2.pdf



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Metastatic Bone Disease: Radiotherapy (RT)

Oxford		
LoE	GR	AGO
1a	B	++
1a	B	++
1a	B	++
2a	B	++
1b	B	++
5	D	+/-
1b	B	+
2b	B	+/-

Bone metastases

- **With fracture risk**
- **With functional impairment**
- **With bone pain**
- Single dose RT = fractionated RT**
- **With neuropathic bone pain**
- **Asymptomatic isolated bone metastasis**
- **Reduction of radiation induced pain flare by dexamethasone**
- **Radiotherapy in combination with hyperthermia**

Limited studies included breast cancer patients!

1. Souchon R, Feyer P, Thomssen C et al. 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 5:401-7, 2010
2. Souchon R, Wenz F, Sedlmayer F, Budach W et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
3. Hartsell WF, Scott C, Bruner DW et al. 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. McDonald R, Ding K, Brundage M et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol 3(7):953-959, 2017
5. Lutz S, Berk L, Chang E et al. American Society for Radiation Oncology (ASTRO) Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 79(4):965-976, 2011
6. Hoskin PJ, Yarnold JR, Roos DR et al. Second Workshop on Palliative Radiotherapy and Symptom Control: Radiotherapy for bone metastases. Clin Oncol (R Coll Radiol) 13:88-90, 2001
7. McQuay HJ, Collins SL, Carroll D et al. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev

2000;2:CD001793

8. Wu J, Bezjak A, Chow E et al. 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, 2003
9. Chow E, Harris K, Fan G et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 25:1423-36, 2007
10. Chow E, Meyer RM, Ding K et al. 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
11. Chi MS, Yang KL, Chang YC et al. Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial. *Int J Radiat Oncol Biol Phys* 100(1):78-87, 2018
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Metastatic Bone Disease Recurrent Bone Pain after RT			
	Oxford		
	LoE	GR	AGO
Recurrent bone pain in pre-irradiated parts of skeleton			
▪ Single dose RT *	3b	C	++
▪ Fractionated RT *	3b	C	++
▪ Radionuclide therapy	3b	C	+
▪ Magnetic resonance-guided focused ultrasound	1b	B	+
▪ Radiofrequency ablation	4	C	+
▪ Cryoablation	4	C	+

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

Recurrent bone pain in pre-irradiated parts of the skeleton

1. Souchon R, Wenz F, Sedlmayer F et al. DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol 185:417-424, 2009
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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

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Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)																			
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<table> <tr> <th></th><th>LoE</th></tr> <tr> <td>▪ Renal function deterioration due to IV-aminobisphosphonates</td><td>1b</td></tr> <tr> <td>▪ Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3 % / 1.8 %)</td><td>1b</td></tr> <tr> <td>▪ Association with (simultaneous) anti-angiogenic therapies</td><td>3b</td></tr> <tr> <td>▪ Severe hypocalcemia (Dmab > BPs)</td><td>1b</td></tr> <tr> <td>▪ Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30 %</td><td>1b</td></tr> <tr> <td>▪ Gastrointestinal side effects (oral BPs) 2–10 %</td><td>1b</td></tr> <tr> <td>▪ Atypical femur fractures (absolute risk of 11 per 10,000 person years of BP use)</td><td>2b</td></tr> <tr> <td>▪ Extremely rare: Uveitis / Scleritis under BP treatment</td><td>4</td></tr> </table>		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-angiogenic therapies	3b	▪ Severe hypocalcemia (Dmab > BPs)	1b	▪ Acute Phase Reaction (IV Amino-BPs, Dmab) 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	▪ Extremely rare: Uveitis / Scleritis under BP treatment	4
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Bisphosphonates

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- Body JJ. Breast Cancer: Bisphosphonate therapy for metastatic bone disease. Clin Cancer Res. 2006; 12(20 Suppl):6258s-6263s.
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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, 2010
2. Taylor KH, Middlefell LS, and Mizen KD, "Osteonecrosis of the Jaws Induced by Anti-RANK Ligand Therapy," Br J Oral Maxillofac Surg 48(3):221-3, 2010

Frequent side effects under treatment with BPs / Denosumab						
Drug	Acute phase- reaction	Kidney Tox.	Upper GI	Diarrhea	Osteo necrosis of the jaw	
Clodronate 1500 i.v.	0	+	0	0	0	Non-Amino.
Clodronate 1600 p.o.	0	0	+	+	0	Non-Amino.
Ibandronate 50 mg p.o.	0	0	+	0	0	Aminobisp.
Ibandronate 6 mg i.v.	+	0	0	0	+	Aminobisp.
Zoledronate 4 mg i.v.						Aminobisp.
q4w oder q12w	+	+	0	0	+	
Pamidronate 90 mg i.v.	+	+	0	0	+	Aminobisp.
Zoledronate 4 mg i.v. q6m	+	0	0	0	0	Aminobisp.
Denosumab 120 mg sc q4w	0	0	0	+	+	
Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!						

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Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 2a

GR: A

AGO: ++

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab (LoE 2a, recommendation grade A)
- Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)
- 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 (<1%)

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<https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf>

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9. <https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf>

Adjuvant Bone Targeted Therapy for Improvement of Prognosis			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Clodronate (oral) <ul style="list-style-type: none"> ■ Postmenopausal patients ■ Premenopausal patients ■ Aminobisphosphonate (iv or oral) <ul style="list-style-type: none"> ■ Postmenopausal patients ■ Premenopausal patients ■ Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m) <ul style="list-style-type: none"> ■ Postmenopausal patients Stage II and III ■ Denosumab (60 mg s.c. q6m) <ul style="list-style-type: none"> ■ Postmenopausal patients undergoing AI therapy 	1a	A	+
	1a	B	+/-
	1a	A	+
	1a	B	+/-
	1b	B	-
	1b	B	+/-



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Clodronate

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Adjuvant Aminobisphosphonates

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1. Gnant M, Pfeiler G, Steger GG, Austrian Breast and Colorectal Cancer Study Group. Adjuvant denosumab in postmenopausal patients

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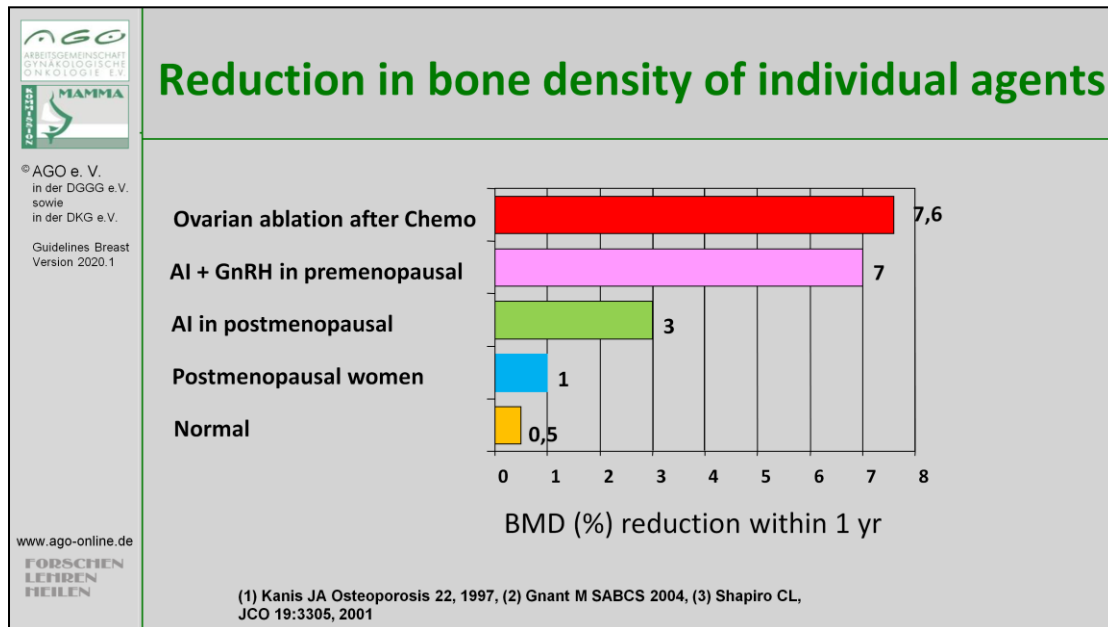
Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
 - Clodronat po 1600 mg/d (Bonefos / Clodronic acid)
 - Clodronat po 1040 mg/d (Ostac / Clodronic acid)

- **Aminobisphosphonates:**
 - Zoledronat iv 4 mg/6 m (Zometa / Zoledronic acid)
 - Ibandronat po 50 mg/d (Bondronat / Ibandronic acid)
 - Pamidronat po (orally not available in most countries)
 - Risedronat po 35 mg/w (Actonel / Risedronic acid)
 - Alendronat po 70 mg/w (Fosamax / Alendronic acid)
 - Optimal duration yet to be defined; 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)

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2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015
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Bisphosphonates

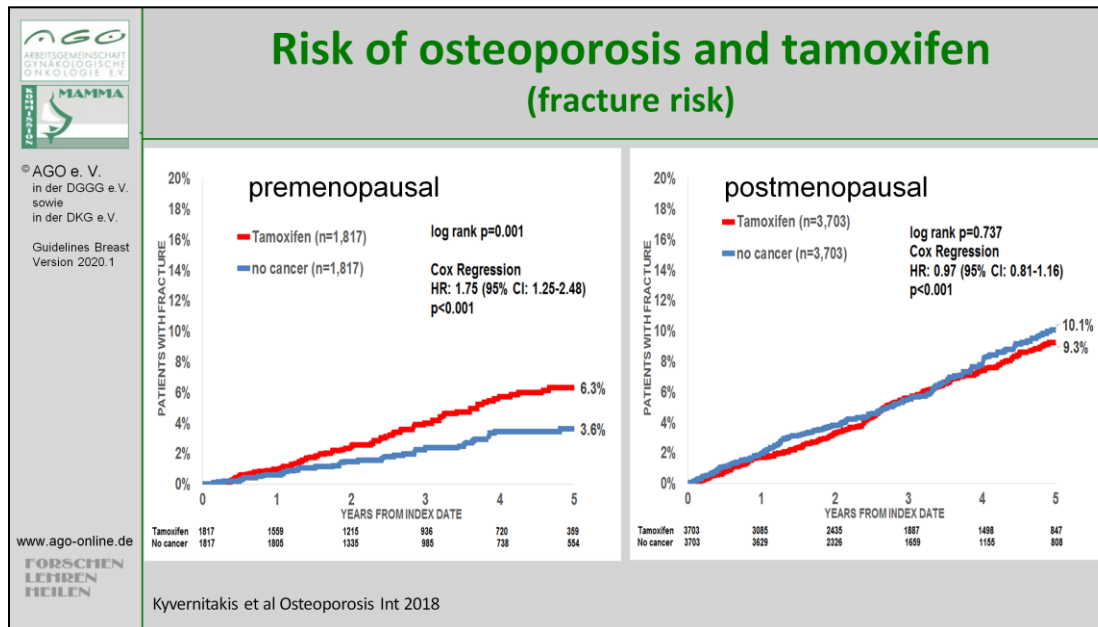
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Denosumab

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Tamoxifen

Stumpf U, Kostev K, Kyvernitakis J et al. Incidence of fractures in young women with breast cancer - a retrospective cohort study. J Bone Oncol. 2019 Jul 26;18:100254. doi: 10.1016/j.jbo.2019.100254.

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Bisphosphonates <ul style="list-style-type: none"> Therapy Prevention (2–5 yrs) after discontinuation of Denosumab (time-limited) Denosumab <ul style="list-style-type: none"> Therapy Prevention (up to max. 3yrs) Hormone replacement therapy Clinical risk assessment for osteoporosis at baseline according to DVO S3 - guidelines DXA-Scan at baseline in pts with endocrine therapy and/or premature menopause Antiresorptive therapy according to according to DVO S3 - guidelines Repeat DXA-scan based on risk 	1b 1b 3c 1b 1b 5 5 5	B A C B A D D D	++ + + ++ + - ++ ++ +




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

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

	Oxford LoE	GR	AGO
■ Physical activity	4	C	++
■ Avoiding immobilisation	4	C	++
■ Calcium (1000–1500 mg/d)**	4	C	++
■ Vitamine D3 suppl. (800–2000 U/d or 20,000 U/w)	4	C	++
■ Stop smoking, reduction of alcohol	2b	B	++
■ Avoiding BMI < 20 mg/m ²	3b	C	++
■ Bisphosphonates after discontinuation of Denosumab (time-limited)	3c	C	+
■ Drugs approved for osteoporosis treatment in adults (see next slide)			

* http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2014; revised version expected in 2018
** if nutritional supply is insufficient, (in combination with Vit D3 only)

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Effect of Denosumab Discontinuation

FREEDOM / FREEDOM Extension Trial

N=1001, ≥ 2 dose of Denosumab or placebo, follow up ≤ 7 months after discontinuation treatment

Vertebral fracture rate per 100 participant year :

- 1.2 during denosumab therapy
- 7.1 after denosumab therapy
- 8.5 placebo

Non vertebral fracture rate per 100 participant year:


2.8 after denosumab vs. 3.8 placebo (n.s.)

Multiple vertebral fracture (% of all vertebral fractures):

60.7% after denosumab therapy vs. 38.7% placebo; p=0.049

Cummings SR et al. J Bone Miner Res 2017

1. Cummings SR, Ferrari S, Eastell R et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res. 2018 Feb;33(2):190-198.



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Medical Treatment of Osteoporosis

	Oxford		
	LoE	GR	AGO
▪ Alendronate 70 mg po/w*	1b	B	++
▪ Denosumab 60 mg sc/6m*	1b	B	++
▪ Ibandronate 150 mg po/m*	1b	B	++
▪ Ibandronat e 3 mg iv/3 m	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	++

* 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 fracture risk.

1. German guidelines for the treatment of osteoporosis by the DVO: AWMF-Register-Nr.: 183/001; https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20Osteoporose%202017_end.pdf
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Raloxifen

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

Strontium renalate

1. Kaufman JM, Audran M, Bianchi G et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 98(2): 592-601, 2013

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https://www.dv-osteologie.org/uploads/Leitlinie%202017/DVO%20Leitlinie_Kitteltaschenversion_16012020.pdf

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSE THERAPIE 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 $\geq 2,5$ 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

1. German guidelines for the treatment of osteoporosis by the DVO: AWMF-Register-Nr.: 183/001; https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20Osteoporose%202017_end.pdf
2. https://www.dv-osteologie.org/uploads/Leitlinie%202017/DVO%20Leitlinie_Kitteltaschenversion_16012020.pdf