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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Osteoonkologie und Knochengesundheit



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# Osteoonkologie und Knochengesundheit

## ■ Versionen 2002–2021:

**Banys-Paluchowski / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm  
/ Fersis / Friedrich / Friedrichs / Hanf / Huober / Jackisch / Janni /  
Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl /  
Schütz / Seegenschmiedt / Solbach / Solomayer / Souchon**

## ■ Version 2022:

**Reimer / Solomayer**

Bisphosphonate beim metastasierten Mammakarzinom			
	Oxford		
	LoE	GR	AGO
▪ Therapie der Hyperkalzämie	1a	A	++
▪ Reduktion skelettaler Ereignisse / Komplikationen	1a	A	++
▪ Reduktion von Knochenschmerzen	1a	A	++
▪ Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen	1a	A	++
▪ Therapie nach ossärer Progression	5	D	++
▪ Bestimmung von Knochenresorptionsmarkern zur Therapiekontrolle	5	D	-
▪ Alleinige Therapie zur Analgesie bei Knochenschmerzen	5	D	-

#### Meta-analyses and Reviews (metastatic breast cancer)

1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
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

Denosumab beim metastasierten Mammakarzinom			
	Oxford		
	LoE	GR	AGO
▪ Therapie der Hyperkalzämie	1a	A	++
▪ Reduktion skelettaler Ereignisse / Komplikationen	1a	A	++
▪ Reduktion von Knochenschmerzen	1a	A	++
▪ Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen	1b	A	++
▪ Therapie nach ossärer Progression	5	D	+
▪ Progression unter Bisphosphonaten	4	C	+/-
▪ Bestimmung von Knochenresorptionsmarkern zur Therapiekontrolle	5	D	-
▪ Alleinige Therapie zur Analgesie bei Knochenschmerzen	5	D	-

#### 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.

#### 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
2. Mjelstad A, Zakariasson G, Valachis A et al. Optimizing antiresorptive treatment in patients with bone metastases: time to


initiation, switching strategies, and treatment duration. Support Care Cancer. 2019;27(10):3859-3867. doi: 10.1007/s00520-019-04676-6.

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 Bone-Targeted Agents

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

SRE after 2 years:	29.5% zoledronic acid every 4 weeks
	28.6% zoledronic acid every 12 weeks
  
- **OPTIMIZE-2 trial:** n = 416 women with metastatic breast cancer, prior exposure to zoledronate or pamidronate for approx. 1 year or more
 

SRE after 1 year:	22.0% zoledronic acid every 4 weeks
	23.2% zoledronic acid every 12 weeks
  
- **REaCT-BTA trial:** n = 263 metastatic cancer (160 breast, 103 prostate)  
 Denosumab (n = 148), zoledronate (n = 63) or pamidronate (n = 52) q4w vs. q12w  
 Primary endpoint (non-inferiority of q12w vs. q4w in HRQoL) reached  
 Cumulative SSE after 1 year:    7.6% bone-targeted agent every 4 weeks  
    16.6% bone-targeted agent every 12 weeks (p = 0.27)

### Randomized trials – Zoledronic acid:

1. CALGB 70604: 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. OPTIMIZE-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. 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

### Randomized trials – Other bone-targeted agents

1. REaCT-BTA: Clemons M, Ong M, Stober C et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer 2021; 142: 132-140
2. Amir E, Freedman O, Carlsson L et al. Randomized Feasibility Study of De-escalated (Every 12 wk) Versus Standard (Every 3 to 4 wk) Intravenous Pamidronate in Women With Low-risk Bone Metastases From Breast Cancer. Am J Clin Oncol 2013; 36: 436-442

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 Onc 2007; 25 (28): 4431-4437

Non-randomized studies:

1. Addison CL, Bouganim N, Hilton J et al. A phase II, multicentre trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events. Breast Cancer Res Treat 2014; 144: 615-624

Systematic reviews:

1. 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.



Bisphosphonate und Denosumab für die Therapie von Knochenmetastasen			
	Oxford		
	LoE	GR	AGO
▪ Clodronat p.o. 1600 mg täglich	1a	A	++
▪ Clodronat i.v. 1500 mg q3w / q4w	1a	A	++
▪ Pamidronat i.v. 90 mg			
▪ q3w / q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Ibandronat i.v. 6 mg q3w / q4w	1a	A	++
▪ Ibandronat p.o. 50 mg täglich	1a	A	++
▪ Zoledronat i.v. 4 mg			
▪ q4w	1a	A	+
▪ q12w	1a	A	++
▪ Denosumab 120 mg s.c.			
▪ q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Andere Dosierungen oder Schemata, wie z. B. aus den Studien zur adjuvanten Situation oder Osteoporosetherapie	5	D	--
▪ Geplanter sequentieller Einsatz von verschiedenen Substanzen	2b	B	+/-

#### Reviews / Guidelines:

1. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
2. 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
3. Ibrahim MF, Mazzarello 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
4. 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.
5. Shapiro CL, Moriarty JP, Dusetzina S et al. Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). J Clin Oncol. 2017; 35(35):3949-3955.

#### Zoledronic acid:

1. Himelstein 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. 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
4. 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.

#### Pamidronate:

1. Amir E, Freedman O, Carlsson L et al. Randomized Feasibility Study of De-escalated (Every 12 wk) Versus Standard (Every 3 to 4 wk) Intravenous Pamidronate in Women With Low-risk Bone Metastases From Breast Cancer. Am J Clin Oncol 2013; 36: 436-442
2. Addison CL, Bouganim N, Hilton J et al. A phase II, multicentre trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events. Breast Cancer Res Treat 2014; 144: 615-624

#### Denosumab & bisphosphonates:

1. Clemons M, Ong M, Stober C et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer 2021; 142: 132-140
2. 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 Onc 2007; 25 (28): 4431-4437

#### Denosumab:

1. Templeton AJ, Stalder L, Bernhard J 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)

#### Sequential therapy with different BTAs:

1. Srivastava A, Noguera-Gonzales GM, Geng Y et al. Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. *Support Care Cancer*. 2020. doi: 10.1007/s00520-020-05882-3.



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## Ossäre Metastasen Radionuklidtherapie

	Oxford		
	LoE	GR	AGO
■ <b>Tumorprogression nach Ausschöpfung der Standardtherapie multipler / disseminierter Skelettmetastasen und intolerabler Knochenschmerzen</b>	<b>1b</b>	<b>B</b>	<b>+</b>
■ <sup>186</sup> Rhenium-HEDP (hydroxyethyliden-diphosphonat)	2b	B	+
■ <sup>153</sup> Samarium-EDTMP	1b	B	+
■ <sup>89</sup> Strontium	1b	B	+
■ <sup>223</sup> Radium	2b	C	+
■ <sup>177</sup> Lu-EDTMP	2b	C	+
■ <sup>188</sup> Rhenium-HEDP	1b	B	+

**Cave: die potentiellen Vorteile sollten gegenüber der Gefahr der Myelosuppression und Panzytopenie abgewogen werden**

### Reviews / Overview

1. Hoskin PJ: Radioisotopes for metastatic bone pain. Lancet Oncol 6(6):353-4, 2005
2. Bauman G, Chrette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radioth Oncol 75: 258-70, 2005
3. Roque i Figuls M, Martinez-Zapata MJ, Scott-Brown M et al. Radioisotopes for metastatic bone pain (Cochrane Review). In: The Cochrane Library 2011, Issue 7. John Wiley & Sons, Ltd. Art. No.: CD003347. DOI: 10.1002/14651858.CD003347.pub2

### <sup>186</sup>Rhenium (<sup>186</sup>Re-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. <sup>186</sup>Re-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 <sup>186</sup>Re-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

#### <sup>153</sup>Samarium (<sup>153</sup>Sm-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 <sup>153</sup>Sm-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

#### <sup>89</sup>Strontium (<sup>89</sup>Sr-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 <sup>89</sup>Sr and <sup>186</sup>Re-HEDP in breast cancer patients. Breast Cancer Res Treat 66:101-19, 2001

#### <sup>223</sup>Ra-dichloride:

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

#### <sup>177</sup>Lu (Lutetium)-EDTMP

1. Agarwal KK, Singla S, Arora G, Bal C. (<sup>177</sup>)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 <sup>153</sup>Sm-EDTMP and <sup>177</sup>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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## Knochenmetastasen in der Wirbelsäule

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### Operationsindikatoren

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

- **Spinales Kompressionssyndrom**
  - Mit progredienter neurologischer Symptomatik
  - Mit pathologischen Frakturen
- **Instabilität der Wirbelkörper**
- **Läsionen in vorbestrahlten Teilen der Wirbelsäule**

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 1.3 – 2020 AWMF-Register Nr.: 032/054OL. [https://www.leitlinienprogramm-onkologie.de/fileadmin/user\\_upload/Downloads/Leitlinien/Supportivtherapie/LL\\_Supportiv\\_Langversion\\_1.3.pdf](https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.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.

8. Schoenfeld AJ, Le HV, Marjoua Y et al. Assessing the utility of a clinical prediction score regarding 30-day morbidity and mortality following metastatic spinal surgery: the New England Spinal Metastasis Score (NESMS). *Spine J.* 2016;16(4):482-90, doi: 10.1016/j.spinee.2015.09.043
9. Rothrock RJ, Barzilai O, Reiner AS et al. Survival Trends After Surgery for Spinal Metastatic Tumors: 20-Year Cancer Center Experience. *Neurosurgery* 2020;nyaa380, doi: 10.1093/neuros/nyaa380.



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## Knochenmetastasen – Spinales Kompressionssyndrom / Paraplegie

	Oxford		
	LoE	GR	AGO
▪ <b>Operation zur Dekompression, Reduktion der Tumormasse und Stabilisierung (&lt; 24 h) sowie Bestrahlung der Wirbelsäule</b>	2b	C	++
▪ <b>Bestrahlung der Wirbelsäule (&lt; 24 h)</b>	3b	C	++
▪ Bestrahlungsregime (1 x 8-10 Gy vs. mehrere Fraktionen) in Abhängigkeit von der Gesamtprognose, Allgemeinzustand und Präferenz der Patientin			
▪ <b>Sofortiger Therapiebeginn</b>	1c	D	++
▪ <b>Steroide (Beginn bei ersten Symptomen)</b>	2a	C	+

**In klinischen Studien wurden Patienten mit unterschiedlichen Tumorentitäten eingeschlossen!**

### Recommendations and Clinical Practice Guidelines:

1. Loblaw DA, Mitera G, Ford M et al. A 2011 Updated Systematic Review and Clinical Practice Guideline for the Management of Malignant Extradural Spinal Cord Compression. Int J Radiat Oncol Biol Phys. 2012;84(2):312-7. doi: 10.1016/j.ijrobp.2012.01.014.
2. 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
3. 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
4. Groenen KHJ, van der Linden YM, Brouwer T et al. The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management. Cancer Treat Rev 2018;69:29-38. doi: 10.1016/j.ctrv.2018.05.013.
5. Guideline Program Oncology (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive care of oncological patients – Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. [https://www.leitlinienprogramm-onkologie.de/fileadmin/user\\_upload/Downloads/Leitlinien/Supportivtherapie/LL\\_Supportiv\\_Langversion\\_1.3.pdf](https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf)

### Reviews:



1. Loblaw A, George KJ, Misra V. Surgical and Radiotherapeutic Management of Malignant Extradural Spinal Cord Compression. Clin Oncol (R Coll Radiol) 2020;32(11):745-752. doi: 10.1016/j.clon.2020.07.022.

#### Operative therapy:

1. Patchell RA, Tibbs PA, Regine WF et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005 Aug 20-26;366(9486):643-8, doi: 10.1016/S0140-6736(05)66954-1.
2. Yang XG, Lun DX, Hu YC et al. Prognostic effect of factors involved in revised Tokuhashi score system for patients with spinal metastases: a systematic review and Meta-analysis. BMC Cancer 2018;18(1):1248. doi: 10.1186/s12885-018-5139-2.
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#### Radiation therapy: Randomized studies:


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## Knochenmetastasen: Operationstechniken

**Wirbelsäule und Extremitäten**

Oxford LoE: 3b
GR: C
AGO: +

- **Marknagelung**
- **Plattenosteosynthesen**
- **Verbundosteosynthesen (Osteosynthese und Einbringen von PMMA)**
- **Wirbelkörperersatz durch Titanspacer**
- **Tumorendoprothesen**
- **Vertebroplastie / Kyphoplastie +/- Thermoablation des Tumors**
- **Kypho-IORT\* (nur in Studien)**
- **Resektion einzelner Knochenmetastasen in der oligometastatischen Situation (Sternum, Rippen, Wirbelkörper)**

\* Studententeilnahme empfohlen

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Version 1.3 – 2020 AWMF-Register Nr.: 032/054OL. [https://www.leitlinienprogramm-onkologie.de/fileadmin/user\\_upload/Downloads/Leitlinien/Supportivtherapie/LL\\_Supportiv\\_Langversion\\_1.3.pdf](https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf)

Knochenmetastasen: Strahlentherapie			
	Oxford		
	LoE	GR	AGO
<b>Knochenmetastasen</b>			
▪ Mit Frakturrisiko	1a	B	++
▪ Mit Funktionseinschränkung	1a	B	++
▪ Mit Schmerzen	1a	B	++
einmalige RT = fraktionierte RT	2a	B	++
▪ Mit neuropathischem Schmerz	1b	B	++
▪ Asymptomatische isolierte Metastasen	5	D	+/-
▪ Reduktion der Strahlentherapie induzierten Schmerzzunahme mit Dexamethason	1b	B	+
▪ Strahlentherapie mit Hyperthermie	2b	B	+/-
Nur wenige Studien mit Mammakarzinompatientinnen!			

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 (MSSC). Strahlenther Onkol 185:417-424, 2009
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for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. *Lancet Oncol* 16(15):1463-72, 2015

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11. Pin Y, Paix A, Le Fevre C et al. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. *Crit Rev Oncol Hematol*. 2018;123:132-137. doi: 10.1016/j.critrevonc.2018.01.006.

Knochenmetastasen: Schmerztherapie nach Vorbestrahlung			
	Oxford		
	LoE	GR	AGO
<b>Rekurrenter Knochenschmerz in vorbestrahlten Arealen des Skeletts</b>			
▪ Einmalige RT *	3b	C	++
▪ Fraktionierte RT *	3b	C	++
▪ Radionuklidtherapie	2b	B	+
▪ MR-gesteuerter hochfokussierter Ultraschall	1b	B	+
▪ Radiofrequenzablation	4	C	+
▪ Kryoablation	4	C	+
* Dosis und Fraktionierung hängt von der Lokalisation, vom Intervall zur letzten Strahlentherapie sowie von Dosis und Fraktionierung der ersten Strahlentherapie ab.			

#### Recurrent bone pain in pre-irradiated parts of the skeleton

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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

1. Dechamps F, Farouil G, Ternes N et al.: 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 et al.: Cryoablation of sternal metastases for pain palliation and local tumor control. J Vasc Interv Radiol 25(11):1665-70, 2014
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Nebenwirkungen und Toxizitäten von Bisphosphonaten (BP) und Denosumab (Dmab)	
	LoE
▪ Nierenfunktionsstörungen durch i.v. Amino-BP	1b
▪ Kieferosteonekrose (ONJ) typisch unter i.v. BPs und Dmab (1,4–2,8 % / 1,3–3,2 %)	1b
▪ Assoziation mit (parallelem) Einsatz von antiangiogenetischen Therapien	3b
▪ Ausgeprägte Fälle mit Hypokalzämie (Dmab > BP)	1b
▪ Akut-Phase-Reaktion (i.v. Amino-BPs und Dmab) 10–30 %	1b
▪ Gastrointestinale Nebenwirkungen (orale BPs) 2–10 %	1b
▪ Atypische Femurfrakturen (absolutes Risiko: 11/10.000 Personenjahre mit BP-Einnahme)	2b
▪ Sehr selten: Uveitis / Scleritis bei Behandlung mit BPs	4

### Bisphosphonates


1. Schilcher, J., V. Koeppen, P. Aspenberg et al. Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthop 100-107, 2015
2. Body JJ. Breast Cancer: Bisphosphonate therapy for metastatic bone disease. Clin Cancer Res. 2006; 12(20 Suppl):6258s-6263s.
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8. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 19(3):420-32, 2008
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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
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### Sequential therapy

1. Srivastava et al., Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. Support Care Cancer. 2020 Nov 15. doi: 10.1007/s00520-020-05882-3. Online ahead of print.

 <b>Häufige Nebenwirkungen unter Behandlung mit Bisphosphonaten / Denosumab</b>						
Drug	Akut- Phase- Reaktion	Nieren tox.	Obere GI-NW	Diarrhoe	ONJ	
Clodronat 1500 i.v.	0	+	0	0	0	Non-Amino.
Clodronat 1600 p.o.	0	0	+	+	0	Non-Amino.
Ibandronat 50 mg p.o.	0	0	+	0	0	Aminobisph.
Ibandronat 6 mg i.v.	+	0	0	0	+	Aminobisph.
Zoledronat 4 mg i.v. (q4w oder q12w)	+	+	0	0	+	Aminobisph.
Pamidronat 90 mg i.v.	+	+	0	0	+	Aminobisph.
Zoledronat 4 mg i.v. q6m	+	0	0	0	0	Aminobisph.
Denosumab 120 mg sc q4w	+	0	0	+	+	

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**Cave: Hypokalzämie unter antiresorptiver Therapie bei ossären Metastasen!**

### Bisphosphonates

1. Schilcher, J., V. Koeppen, P. Aspenberg et al. Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthop 100-107, 2015
2. 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
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## Empfehlungen für die Prävention von Kieferosteonekrosen (ONJ)

Oxford LoE: 2a
GR: A
AGO: ++

- Unter Bisphosphonat- bzw. Denosumabtherapie Vermeidung elektiver Zahnbehandlungen mit Manipulationen am Kieferknochen. Falls unvermeidbar wird der prophylaktische Einsatz von Antibiotika empfohlen (LoE 2a, Empfehlungsgrad A)
- Zahnsanierung vor einer Bisphosphonat- bzw. Denosumabtherapie, falls möglich (LoE 2a, Empfehlungsgrad A)
- Information der Patientinnen über ONJ-Risiko und Instruieren über Frühsymptome
- Bei hohem ONJ-Risiko Anwendung oraler Bisphosphonate
- Gute Zahnhygiene, nur mäßiger Alkoholkonsum sowie Nikotinverzicht
- Unter adjuvanter Bisphosphonattherapie ist das Risiko für ONJ gering (< 1 %)

ASORS Evaluation

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

1. Izzotti A, Menini M, Pulliero A et al. Bisphosphonates-associated osteonecrosis of the jaw: the role of gene-environment interaction. J Prev Med Hyg 54(3): 138-145, 2013
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9. <https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf>

Adjuvante osteoprotektive Therapie zur Verbesserung der Prognose			
	Oxford		
	LoE	GR	AGO
<b>Clodronate (oral)</b> <ul style="list-style-type: none"> <li>Postmenopausale Patientinnen</li> <li>Prämenopausale Patientinnen</li> </ul>	1a	A	+
	1a	B	+/-
<b>Aminobisphosphonate (i.v. oder oral)</b> <ul style="list-style-type: none"> <li>Postmenopausale Patientinnen</li> <li>Prämenopausale Patientinnen</li> </ul>	1a	A	+
	1a	B	+/-
<b>Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)</b> <ul style="list-style-type: none"> <li>Postmenopausale Patientinnen Stadium II und III</li> </ul>	1b	B	-
<b>Denosumab (60 mg s.c. q6m)</b> <ul style="list-style-type: none"> <li>Postmenopausale Patientinnen unter AI-Therapie</li> </ul>	1b	B	+/-

### Clodronate

1. Ben-Aharon I, Vidal L, Rizel S et al. 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 25:135-45, 2013
3. 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 49:2086-92, 2013
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### Adjuvant Aminobisphosphonates

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7. Hadji P, Coleman RE, Wilson C et al. Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European Panel. Ann Oncol. 2015 Dec 17. pii: mdv617.
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### Denosumab

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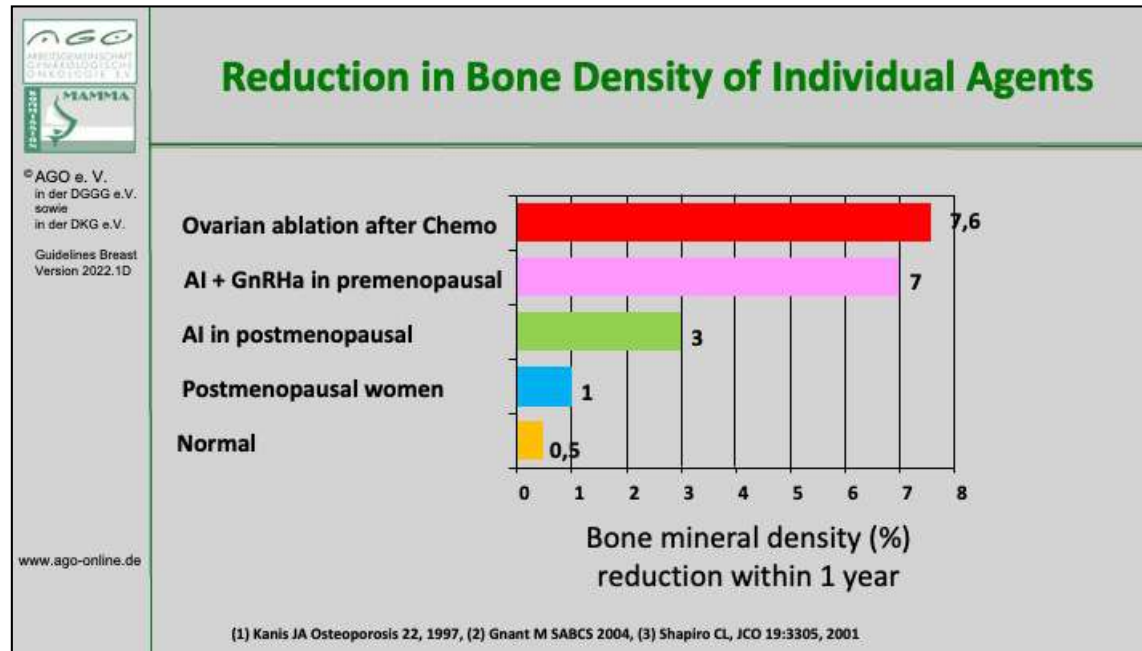
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## Dosierung adjuvanter Bisphosphonate zur Verbesserung des Überlebens

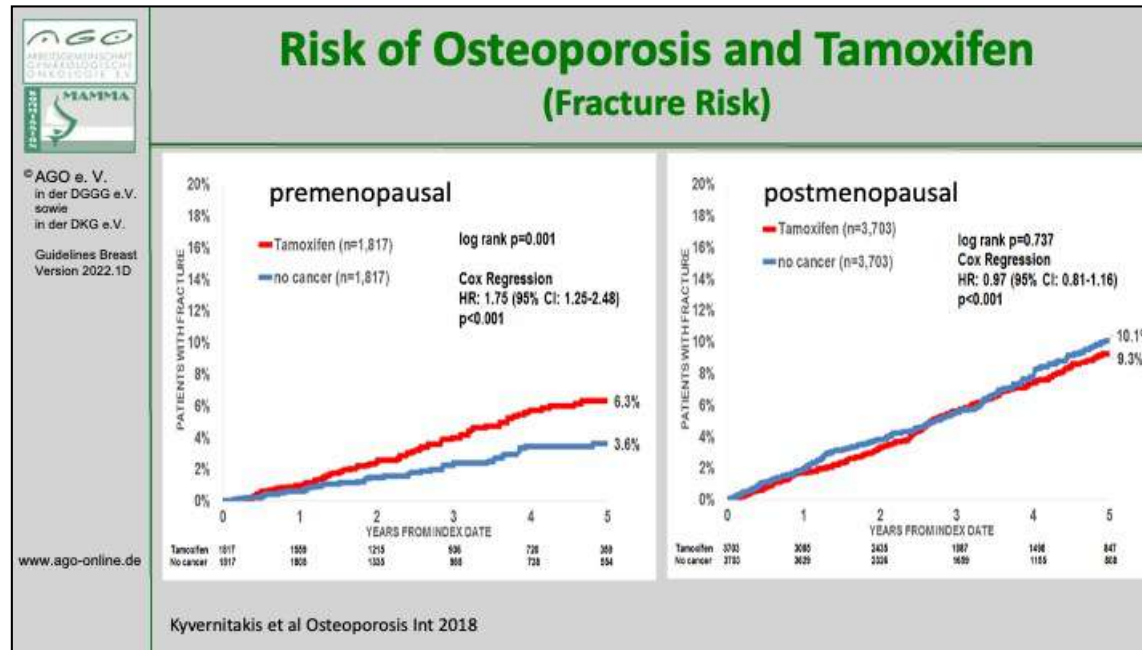
- **Nicht-Aminobisphosphonate:**
  - Clodronat p.o. 1600 mg/d (Bonefos / Clodronsäure)
  - Clodronat p.o. 1040 mg/d (Ostac)
- **Aminobisphosphonate:**
  - Zoledronat i.v. 4 mg/6 m (Zometa / Zoledronsäure)
  - Ibandronat p.o. 50 mg/d (Bondronat / Ibandronsäure)
  - Pamidronat p.o. (in oraler Form in Deutschland nicht verfügbar)
  - Risedronat p.o. 35 mg/w (Actonel / Risedronsäure)
  - Alendronat p.o. 70 mg/w (Fosamax / Alendronsäure)
  - Optimale Dauer der adjuvanten BP-Gabe muss noch definiert werden (in den Studien Dauer der BP: 2–5 Jahre)

**Zu den Aminobisphosphonaten gehören:**  
 Zoledronsäure (65 %), orales Ibandronat (24 %), orales Pamidronat (8 %),  
 orales Risedronat (2 %), orales Alendronat (1 %) (Daten aus der EBCTCG-Metaanalyse)

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Therapie und Prävention des Tumorthherapie induzierten Knochenmasseverlusts / Osteoporose			
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	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Bisphosphonate</b> <ul style="list-style-type: none"> <li>▪ Therapie</li> <li>▪ Prävention (2–5 J.)</li> <li>▪ nach Absetzen von Denosumab (zeitlich begrenzt für 1-2 Jahre)</li> </ul> </li> <li>■ <b>Denosumab</b> <ul style="list-style-type: none"> <li>▪ Therapie</li> <li>▪ Prävention (bis max. 3 J.)</li> </ul> </li> <li>■ <b>HRT</b></li> <li>■ <b>Klinisches Assessment des Osteoporoserisikos vor Therapie nach DVO S3-Leitlinie</b></li> <li>■ <b>DXA-Scan vor endokriner Therapie und / oder bei vorzeitiger Menopause</b></li> <li>■ <b>Antiresorptive Therapie entsprechend DVO S3-Leitlinie</b></li> <li>■ <b>Risikoadaptierte Kontrolle der Knochendichte im Verlauf (DXA-Scan)</b></li> </ul>	1b	B	++
	1b	A	+
	3c	C	+
	1b	B	++
	1b	A	+/-
	5	D	-
			++
	5	D	+
			++
	5	D	+

1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
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## Therapie und Prävention des Tumorthherapie induzierten Knochenmasseverlusts / Osteoporose

**Weitere Empfehlungen (in Analogie zur DVO-Leitlinie zur Prophylaxe, Diagnostik und Therapie der Osteoporose)\***


- Sportl. / körperl. Aktivität
- Vermeidung von Immobilisation
- Kalzium (1.000–1.500 mg/d)\*\*
- Vit. D3 (800–2.000 U/d oder 20.000 U/w)
- Nikotinverzicht, nur mäßiger Alkoholkonsum
- Vermeidung eines BMI < 20 kg/m<sup>2</sup>
- Bisphosphonate nach Beendigung einer Denosumabtherapie (zeitlich begrenzt für 1-2 Jahre)
- Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage)

Oxford		
LoE	GR	AGO
4	C	++
4	C	++
4	C	++
4	C	++
2b	B	++
3b	C	++
3c	C	+

\* <http://www.dv-osteologie.org/osteoporose-leitlinien>

\*\* bei eingeschränkter Aufnahme über die Nahrung (Gabe nur in Verbindung mit Vitamin D3)

1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019
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## Effect of Denosumab Discontinuation

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### 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

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Medikamentöse Therapie der Osteoporose			
	Oxford		
	LoE	GR	AGO
▪ Alendronat 70 mg p.o./w*	1b	B	++
▪ Denosumab 60 mg s.c./6m*	1b	B	++
▪ Ibandronat 150 mg p.o./m*	1b	B	++
▪ Ibandronat 3 mg i.v./3 m	1b	B	++
▪ Parathormon (1-84) 100 µg s.c./d	1b	B	+
▪ Raloxifen 60 mg p.o./d (nur Wirbelsäule)	1b	B	+/-
▪ Risedronat 35 mg p.o./w*	1b	B	++
▪ Strontiumranelat 2 g p.o./d**	1b	B	+
▪ Teriparatid (1-34) 20 µg s.c./d	1b	B	+
▪ Zoledronat 5 mg i.v./12 m*	1b	B	++

\* Wurde bei MaCa-Patientinnen mit Tumorthherapie assoziierter Osteoporose getestet  
 \*\* Erhöhtes Risiko für Myokardinfarkte; nur bei postmenopausalen Patientinnen mit schwerer Osteoporose und hohem Frakturrisiko


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](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 AA Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int 17(2):313, 2006

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**TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROTHERAPIE NACH RISIKOPROFIL** in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.<sup>1</sup>

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 <sup>2</sup>	-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

<sup>1</sup> Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).  
<sup>2</sup> bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

**Therapieindikation auch schon bei um 1,0 höherem T-Score<sup>3,4</sup>, 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)

**mit freundlicher Genehmigung des DVO-Vorstands**

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](https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20Osteoporose%202017_end.pdf)
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