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Guidelines Breast
Version 2024.1D

FORSCHEN
LEHREN
HEILEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Osteonkologie und Knochengesundheit



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Osteonkologie und Knochengesundheit

- **Versionen 2002–2023:**

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

- **Version 2024:**

Reimer / Rhiem

		Oxford		
		LoE	GR	AGO
 <p>AGGEMEINSCHAFT GYNAKOLOGISCHE ONKOLOGIE e.V.</p> <p>MAMMA</p> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> ▪ Therapie der Hyperkalzämie ▪ Reduktion skelettaler Ereignisse / Komplikationen ▪ Reduktion von Knochenschmerzen ▪ Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen ▪ Therapie nach ossärer Progression ▪ Bestimmung von Knochenresorptionsmarkern zur Therapiekontrolle ▪ Alleinige Therapie zur Analgesie bei Knochenschmerzen 	<p>1a</p> <p>1a</p> <p>1a</p> <p>1a</p> <p>5</p> <p>5</p> <p>5</p>	<p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>D</p> <p>D</p> <p>D</p>	<p>++</p> <p>++</p> <p>++</p> <p>++</p> <p>++</p> <p>-</p> <p>-</p>

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

	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

Denosumab 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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Ossäre Metastasen Radionuklidtherapie

Oxford		
LoE	GR	AGO
1b	B	+
2b	B	+
1b	B	+
1b	B	+
2b	B	+
2b	C	+
1b	B	+

▪ **Tumorprogression nach Ausschöpfung der Standardtherapie multipler / disseminierter Skelettmetastasen und intolerabler Knochenschmerzen**

- ¹⁸⁶Rhenium-HEDP (hydroxyethyliden-diphosphonat)
- ¹⁵³Samarium-EDTMP
- ⁸⁹Strontium
- ²²³Radium
- ¹⁷⁷Lu-EDTMP
- ¹⁸⁸Rhenium-HEDP

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

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 ²²³Ra-dichloride. *J Nucl Med* 55(2):268-74, 2015
2. Rugo HS, Van Poznak CH, Neven P et al. Radium-223 in women with hormone receptor-positive bone-metastatic breast cancer receiving endocrine therapy: pooled analysis of two international, phase 2, randomized, double-blind, placebo-controlled trials. *Breast Cancer Res Treat* 2023 Dec 20. Doi: 10.1007/s10549-023-07147-z.

¹⁷⁷Lu (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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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: 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. 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.

		Oxford		
		LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	▪ 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 (REaCT-BTA trial)	1b	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
3. Clemons M, Liu M, Stober C, Pond G, et al.; REaCT investigators. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. J Bone Oncol. 2021 Sep 2;30:100388. doi: 10.1016/j.jbo.2021.100388. PMID: 34567960; PMCID: PMC8449269.

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 2021; 29: 2305-2317



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Knochenmetastasen in der Wirbelsäule

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
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* 2021; 88: 402-412



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Knochenmetastasen – Spinales Kompressionssyndrom / Paraplegie

Oxford		
LoE	GR	AGO
2b	C	++
3b	C	++
1c	D	++
2a	C	+

- **Operation zur Dekompression, Reduktion der Tumormasse und Stabilisierung (< 24 h) sowie Bestrahlung der Wirbelsäule**

- **Bestrahlung der Wirbelsäule (< 24 h)**
 - Bestrahlungsregime (1 x 8-10 Gy vs. mehrere Fraktionen) in Abhängigkeit von der Gesamtprognose, Allgemeinzustand und Präferenz der Patientin

- **Sofortiger Therapiebeginn**
- **Steroide (Beginn bei ersten Symptomen)**
 - Dexamethason 16-24 mg/d, dann Reduktion über 2 Wochen

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
6. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31: 1650-1663

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.
3. Alpantaki K, Ioannidis A, Raptis K et al. Surgery for spinal metastatic tumors: Prognostication systems in clinical practice (Review). Mol Clin Oncol. 2020;12(5):399-402, doi: 10.3892/mco.2020.2008

Radiation therapy: Randomized studies:


1. 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, doi: 10.1001/jama.2019.17913.
2. Rades D, Segedin B, Conde-Moreno AJ et al. Radiotherapy With 4 Gy x 5 Versus 3 Gy x 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)
3. Thirion PG, Dunne MT, Kelly PJ et al. Non-inferiority randomised phase 3 trial comparing two radiation schedules (single vs. five fractions) in malignant spinal cord compression. Br J Cancer. 2020;122(9):1315-1323. doi: 10.1038/s41416-020-0768-z
4. Maranzano E, Bellavita R, Rossi R et al. Short-Course Versus Split-Course Radiotherapy in Metastatic Spinal Cord Compression: Results of a Phase III, Randomized, Multicenter Trial. J Clin Oncol. 2005;23(15):3358-65. doi: 10.1200/JCO.2005.08.193.
5. Maranzano E, Trippa F, Casale M et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol. 2009;93(2):174-9, doi: 10.1016/j.radonc.2009.05.012.

Radiation therapy: Non-randomized studies:

1. Rades D, Cacicedo J, Conde-Moreno AJ et al. Precision Radiation Therapy for Metastatic Spinal Cord Compression: Final Results of the PRE-MODE Trial. *Int J Radiat Oncol Biol Phys* 2020;106(4):780-789. doi: 10.1016/j.ijrobp.2019.11.401.
2. Rades D, Conde-Moreno AJ, Cacicedo J et al. 1x8 Gy versus 5x4 Gy for metastatic epidural spinal cord compression: a matched-pair study of three prognostic patient subgroups. *Radiat Oncol* 2018;13(1):21. doi: 10.1186/s13014-018-0968-3.
3. Rades D, Lange M, Veninga T et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2011;79(2):524-30
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, 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

Steroids: Systematic review:

1. Kumar A, Weber MH, Gokaslan Z et al. Metastatic Spinal Cord Compression and Steroid Treatment A Systematic Review. *Clin Spine Surg.* 2017;30(4):156-163. doi: 10.1097/BSD.0000000000000528.



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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)**

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
8. 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

9. Bludau F, Winter L, Welzel G et al. Long-term outcome after combined kyphoplasty and intraoperative radiotherapy (Kypho-IORT) for vertebral tumors. *Radiat Oncol* 2020; 15: 263

		Oxford		
		LoE	GR	AGO
Rekurrenter Knochenschmerz in vorbestrahlten Arealen des Skeletts				
▪	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

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
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. 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
4. Chow E, Meyer RM, Chen BE et al. Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial. J Clin Oncol. 2014;32(34):3867-73. doi: 10.1200/JCO.2014.57.6264.

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
3. De Marini P, Cazzato RL, Auloge P et al. Percutaneous image-guided thermal ablation of bone metastases: a retrospective propensity study comparing the safety profile of radio-frequency ablation and cryo-ablation. Int J Hyperthermia 2020;37(1):1386-1394. doi: 10.1080/02656736.2020.1859628.

Nebenwirkungen und Toxizitäten von Bisphosphonaten (BP) und Denosumab (Dmab)	
	<u>LoE</u>
▪ 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
▪ Erhöhtes Frakturrisiko nach Absetzen von Dmab	3b
▪ 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.
3. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 98(11):1736-40., 2008
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 4(1):42-55, 2007
5. Tralongo, P, Repetto, L, Di Mari, A, et al. Safety of long-term administration of bisphosphonates in elderly cancer patients. Oncology 67:11216, 2004
6. Chang, JT, Green, L, Beitz, J. Renal failure with the use of zoledronic acid. N Engl J Med 349(17):1676-9, 2003
7. Hillner BE, Ingle JN, Chlebowski RT et al. 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 21(21):4042-57, 2003
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
9. Clark EM, Durup D: Inflammatory eye reactions with bisphosphonates and other osteoporosis medications: What are the risks? Ther Adv Musculoskelet Dis 7:11-16, 2015.

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
3. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2020; 31: 1650-1663.
4. Wang R, Rajanayagam S, Ngan J et al. Incidence of post-denosumab rebound hypercalcaemia in bony-metastatic breast cancer. *Calcif Tissue Int* 2022; 111: 391-395.

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*. 2021; 29: 2305-2317.

		Oxford		
		LoE	GR	AGO
Knochenmetastasen				
▪	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	2b	B	+/-
▪	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 (MSCC). *Strahlenther Onkol* 185:417-424, 2009
3. Hartsell WF, Scott CB, Bruner DW et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97(11):798-804. doi: 10.1093/jnci/dji139.
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, Balboni T, Jones J et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol.* 2017;7(1):4-12. doi: 10.1016/j.prro.2016.08.001
6. McQuay HJ, Collins SL, Carroll D et al. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev* 2000;2:CD001793
7. Chow R, Hoskin P, Hollenberg D et al. Efficacy of single fraction conventional radiation therapy for painful uncomplicated bone metastases: a systematic review and meta-analysis. *Ann Palliat Med.* 2017;6(2):125-142. doi: 10.21037/apm.2016.12.04.
8. 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

9. 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
10. 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
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.
12. Gillespie EF, Yang JC, Mathis NJ et al. Prophylactic radiation therapy versus standard of care for patients with high-risk asymptomatic bone metastases: a multicenter, randomized phase II clinical trial. *J Clin Oncol* 2024; 42: 38-46.



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Prophylactic Radiation Therapy versus Standard of Care for Patients with High-Risk Asymptomatic Bone Metastases

A multicenter randomized controlled Phase II clinical trial

- **Cohort:** 78 adult patients (24% breast) with high-risk bone metastases (n = 122), stratified by histology and planned SOC (systemic therapy or observation), randomly assigned in a 1:1 ratio to receive RT to asymptomatic bone metastases or SOC alone
- **Results:** 1 year: RT vs. SOC: SRE in one of 62 bone metastases (1.6%) vs. 14 of 49 bone metastases (29%) ($P < .001$) with significantly fewer patients hospitalized for SRE in the RT arm compared with the SOC arm (0 v 4, $P = .045$); median follow-up of 2.5 years: OS was significantly longer in the RT arm (hazard ratio [HR], 0.49; 95% CI, 0.27 to 0.89; $P = .018$)

1. Gillespie EF, Yang JC, Mathis NJ, et al. Prophylactic Radiation Therapy Versus Standard of Care for Patients With High-Risk Asymptomatic Bone Metastases: A Multicenter, Randomized Phase II Clinical Trial. *J Clin Oncol.* 2024;42(1):38-46. doi:10.1200/JCO.23.00753

 <h2 style="text-align: center; color: green;">Common Side Effects during Treatment with Bisphosphonates / Denosumab</h2>						
Drug	Acute phase-reaction	Kidney Tox.	Upper GI-tract	Diarrhea	ONJ	
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	Aminobisph.
Ibandronate 6 mg i.v.	+	0	0	0	+	Aminobisph.
Zoledronate 4 mg i.v. (q4w oder q12w)	+	+	0	0	+	Aminobisph.
Pamidronate 90 mg i.v.	+	+	0	0	+	Aminobisph.
Zoledronate 4 mg i.v. q6m	+	0	0	0	0	Aminobisph.
Denosumab 120 mg s.c. q4w	+	0	0	+	+	

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Cave: Hypocalcaemia under antiresorptive therapy for osseous metastases!

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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7. Hillner BE, Ingle JN, Chlebowski RT et al. 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 21(21):4042-57, 2003
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Denosumab

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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



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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**
- **Zahnsanierung vor einer Bisphosphonat- bzw. Denosumabtherapie, falls möglich**
- **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 %)**

AGSMO patientenbezogener Laufzettel
<https://www.onkosupport.de/asors/content/e4125/e4405>

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
2. Fehm T, Felsenberg D, Krimmel M et al. Bisphosphonate-associated osteonecrosis of the jaw in breast cancer patients: recommendations for prevention and treatment. Breast 18(4):213-7, 2009
3. Khan AA, Sándor GK, Dore E et al. Canadian Association of Oral and Maxillofacial Surgeons. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 35(7):1391-7, 2008
4. Advisory Task Force on Bisphosphonate-Related Osteonecrosis 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 65(3):369-76, 2007
5. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017
6. 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
7. Yarom N, Shapiro CL, Peterson DE et al Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice

Guideline. J Clin Oncol. 2019; 37(25):2270-2290. doi: 10.1200/JCO.19.01186.

8. S3-Guideline: Antiresorptiva-assoziierte Kiefernekrose (AR-ONJ) AWMF Register Nr 007 – 091, Stand: 02.12.2018 , gültig bis 01.12.2023; https://www.awmf.org/uploads/tx_szleitlinien/007-091l_S3_Antiresorptiva-assoziierte-Kiefernekrosen-AR-ONJ_2018-12.pdf
9. <https://www.onkosupport.de/asors/content/e4125/e4405>

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

* unabhängig vom intrinsischen Subtyp



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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
4. Diel IJ, Jaschke A, Solomayer EF et al. 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 19: 2007-2011, 2008
5. 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 90:704-8, 1998
6. Saarto T, Vehmanen L, Virkkunen P et al. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol 43(7):650-656, 2004
7. 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.

Adjuvant Aminobisphosphonates

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. 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 18:353-61, 2013
4. Coleman RE, Thorpe HC, Cameron D et al. Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). 33. SABCs 2010, S4-5.
5. Brufsky AM, Bosserman LD, Caradonna RR et al. 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 9(2):77-85, 2009
6. Eidtmann H, de Boer R, Bundred N et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol 21(11):2188-94, 2010
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.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 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
9. 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.
10. Friedl TWP, Fehm T, Müller V et al. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Aug 1;7(8):1149-1157. doi: 10.1001/jamaoncol.2021.1854.PMID: 34165508


Denosumab

1. Gnant M, Pfeiler G, Steger GG, Austrian Breast and Colorectal Cancer Study Group. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSC-18): disease-free survival results from a randomised, double-blind,

- placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Mar;20(3):339-351.
2. Gnant M, Frantal S, Pfeiler G et al. Long-term outcomes of adjuvant denosumab in breast cancer: Fracture reduction and survival results from 3,425 patients in the randomised, double-blind, placebo-controlled ABCSG-18 trial. J Clin Oncol 40, 2022 (suppl 16; abstr 507)
 3. Coleman R, Finkelstein DM, Barrios C et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020 21(1):60-72.

Guidelines

1. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017
2. Eisen A, Somerfield MR, Accordino MK, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol 2022; 40: 787-800.



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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 adjuvanter BP-Gabe muss noch definiert werden (in den Studien Dauer der BP: 2 - 5 Jahre)**

* Nutzung NHS Predict Tool zur Effektabschätzung des Einsatzes von Bisphosphonaten auf das Gesamtüberleben, <https://breast.predict.nhs.uk/tool>

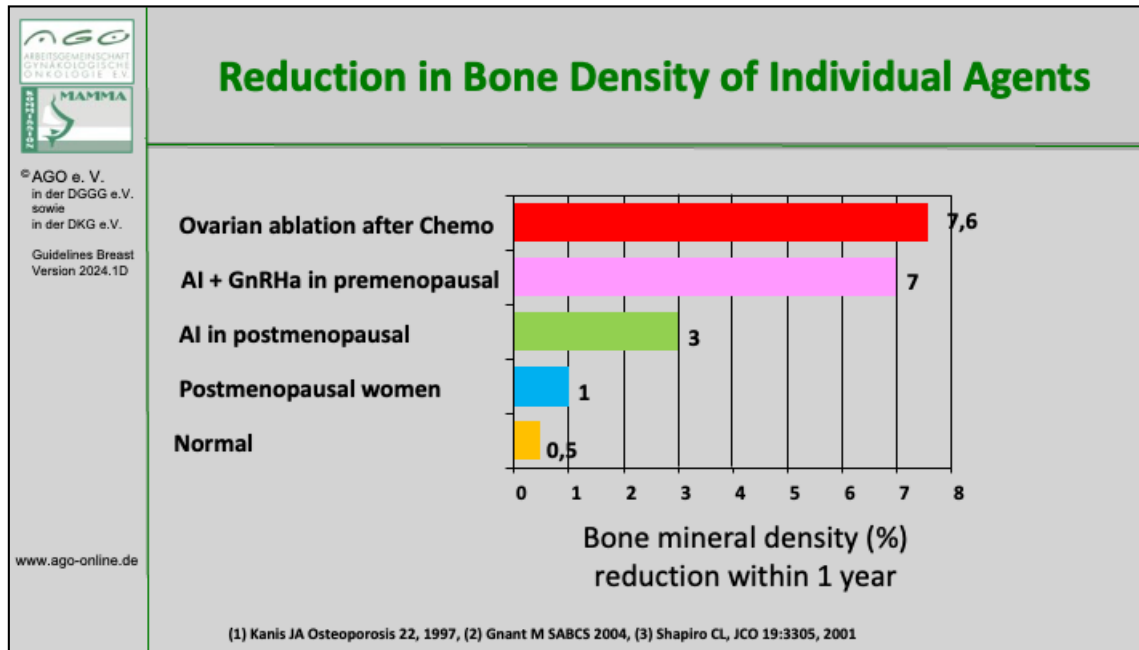
1. Coleman R, Hadji P, Body JJ et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020; 31(12):1650-1663. doi: 10.1016/j.annonc.2020.07.019.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015
3. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35(18):2062-2081, 2017
4. Gralow JR, Barlow WE, Paterson AHG et al. Phase III randomized trial of bisphosphonates as adjuvant therapy in breast cancer: S0307. J Natl Cancer Inst. 2019. pii: djz215. doi: 10.1093/jnci/djz215
5. Friedl TWP, Fehm T, Müller V et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment: a phase 3 randomized clinical trial. JAMA Oncol 2021; 7: 1149-1157.
6. Eisen A, Somerfield MR, Accordino MK, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol 2022; 40: 787-800.

 SUCCESS A trial <i>(Friedl et al., JAMA Oncol 2021; 7: 1149-1157)</i>		
	2 y ZOL (n = 1.447)	5 y ZOL (n = 1.540)
	(4 mg IV every 3 mo for 2 y)	(4 mg IV every 3 mo for 2 y + 4 mg IV every 6 mo for 3 y)
Survival	No differences for DFS, OS, DDFS	
Bone recurrences	n = 28	n = 25
Adverse Events		
Grade III/IV	n = 98 (5.1% of patients)	n = 159 (7.6% of patients)
SRE bone pain	3.7%	8.3%
Arthralgia	3.1%	5.1%
Fractures	n = 3	n = 14
ONJ	n = 5	n = 11

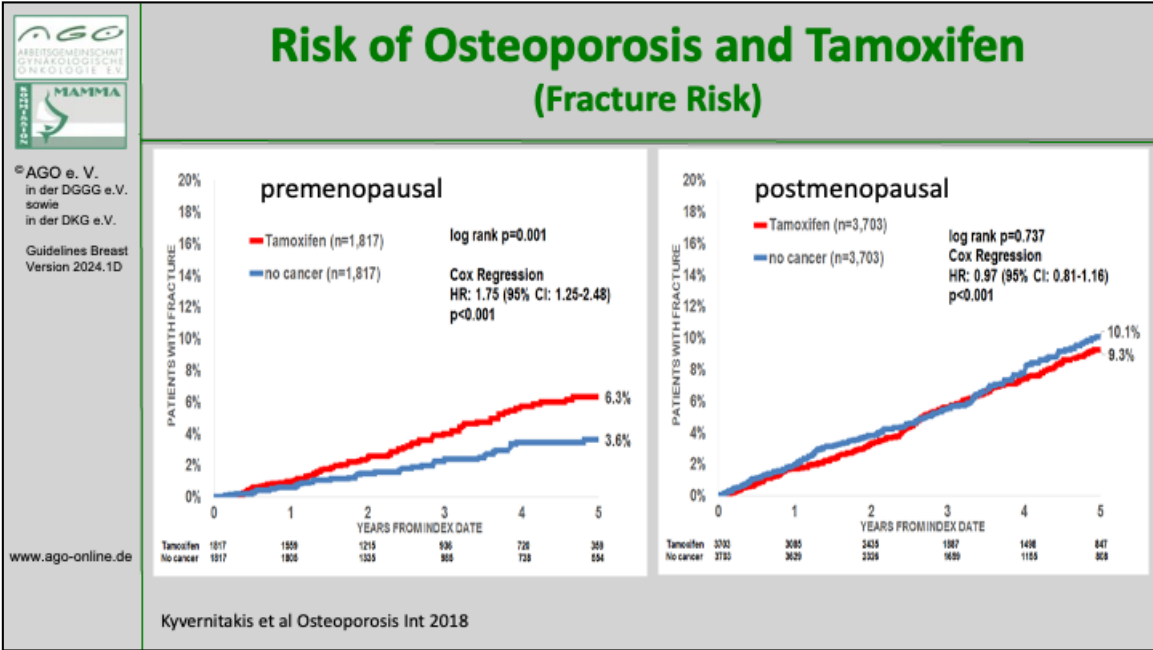
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1. Friedl TWP, Fehm T, Müller V, Lichtenegger W, Blohmer J, Lorenz R, Forstbauer H, Fink V, Bekes I, Huober J, Jückstock J, Schneeweiss A, Tesch H, Mahner S, Brucker SY, Heinrich G, Häberle L, Fasching PA, Beckmann MW, Coleman RE, Janni W, Rack B. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2021 Aug 1;7(8):1149-1157. doi: 10.1001/jamaoncol.2021.1854. PMID: 34165508; PMCID: PMC8227465.



1. Kanis JA, Delmas P, Burckhardt P et al. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1997;7(4):390-406. doi: 10.1007/BF01623782.
2. Shapiro CL, Manola J, Leboff MJ. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol. 2001;19(14):3306-11. doi: 10.1200/JCO.2001.19.14.3306.



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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	▪ Bisphosphonate			
	▪ Therapie	1b	B	++
	▪ Prävention (2–5 J.)	1b	A	+
	▪ nach Absetzen von Denosumab (zeitlich begrenzt für 1-2 Jahre)	3c	C	+
	▪ Denosumab			
	▪ Therapie	1b	B	++
	▪ Prävention (bis max. 3 J.)	1b	A	+/-
	▪ HRT	5	D	-
	▪ Vitamin K2 Substitution	2b	B	-
	▪ Klinisches Assessment des Osteoporoserisikos vor Therapie nach DVO S3-Leitlinie (Stand 09/2023)			++
	▪ Routinemäßige Bestimmung von 25-Hydroxy-Vitamin D-Spiegel	3d	B	+/-
	▪ DXA-Scan vor endokriner Therapie und / oder bei vorzeitiger Menopause	5	D	+
▪ Antiresorptive Therapie entsprechend DVO S3-Leitlinie (Stand 09/2023)			++	
▪ Risikoadaptierte Kontrolle der Knochendichte im Verlauf (DXA-Scan)	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.
2. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und Männern ab dem 50. Lebensjahr: Leitlinie des Dachverbandes der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V. 2023; Langfassung V2.1. AWMF-Register-Nr.: 183/001; <https://dv-osteologie.org/osteoporose-leitlinien>
3. Gnant M, Pfeiler G, Dubsy PC et al. Adjuvant denosumab in breast cancer (ABC SG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 386(9992):433-43, 2015
4. Hadji P, Coleman RE, Wilson C. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol 27(3):379-90, 2016
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
6. Chukir T, Liu Y, Farooki A. Antiresorptive agents' bone-protective and adjuvant effects in postmenopausal women with early breast cancer. Br J Clin Pharmacol. 2019 Jun;85(6):1125-1135.
7. Pineda-Moncusí M, Garcia-Giralt N, Diez-Perez A et al. Increased Fracture Risk in Women Treated With Aromatase Inhibitors

Versus Tamoxifen: Beneficial Effect of Bisphosphonates. *J Bone Miner Res.* 2019 Oct 9. doi: 10.1002/jbmr.3886.


8. Anastasilakis AD, Makras P, Yavropoulou MP. Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review. *J Clin Med* 2021; 10: 152. <https://doi.org/10.3390/jcm10010152>

Vitamin K

1. Rønn, S. H., Harsløf, T., Pedersen, S. B., & Langdahl, B. L. (2016). Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women. *European journal of endocrinology*, 175(6), 541-549. LoE2
2. Su S, He N, Men P, Song C, Zhai S. The efficacy and safety of menatetrenone in the management of osteoporosis: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int.* 2019 Jun;30(6):1175-1186. doi: 10.1007/s00198-019-04853-7. Epub 2019 Feb 7. Erratum in: *Osteoporos Int.* 2021 Oct;32(10):2141-2142. PMID: 30734066.



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Therapie und Prävention des Tumortherapie induzierten Knochenmasseverlusts / Osteoporose

Weitere Empfehlungen (in Analogie zur DVO-Leitlinie, Stand 09/2023)*

	Oxford		
	LoE	GR	AGO
▪ Sportliche / körperliche Aktivität	4	C	++
▪ Vermeidung von Immobilisation	4	C	++
▪ Kalzium (mindestens 1.000 mg/d)**	4	C	++
▪ Vit. D3 (800 I.E./d)	4	C	++
▪ Nikotinverzicht, nur mäßiger Alkoholkonsum	2b	B	++
▪ Vermeidung eines BMI < 20 kg/m ²	3b	C	++
▪ Bisphosphonate nach Beendigung einer Denosumabtherapie (zeitlich begrenzt für 1-2 Jahre)	3c	C	+
▪ Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage)			

* <https://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
3. 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 27(3):379-90, 2016
4. Chapurlat R. Effects and Management of Denosumab Discontinuation. Joint Bone Spine. 2018 Jan 6. pii: S1297-319X(18)30001-0. doi: 10.1016/j.jbspin.2017.12.013
6. Tsourdi E, Langdahl B, Cohen-Solal M et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone 105:11-17, 2017
7. 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
8. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und bei Männern ab dem 50. Lebensjahr. Leitlinie des Dachverbandes der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V. 2023; Langfassung V2.1, AWMF-Register-Nr.: 183/001; <https://dv-osteologie.org/osteoporose-leitlinien>



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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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		LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	▪ Alendronat 70 mg p.o./w*	1b	B	++
	▪ Zoledronat 5 mg i.v./12 m*	1b	B	++
	▪ Ibandronat 150 mg p.o./m*	1b	B	++
	▪ Ibandronat 3 mg i.v./3m	1b	B	++
	▪ Risedronat 35 mg p.o./w*	1b	B	++
	▪ Denosumab 60 mg s.c./6m*	1b	B	++
	▪ Raloxifen 60 mg p.o./d (nur Wirbelsäule)	1b	B	+/-
	▪ Parathormon 100 µg s.c./d	1b	B	+
	▪ Strontiumranelat 2 g p.o./d**	1b	B	+
	▪ Teriparatid 20 µg s.c./d	1b	B	+
▪ Romosozumab 210 mg s.c./m über 12 Monate***	1b	B	+	

* Wurde bei MaCa-Patientinnen mit Tumortherapie assoziierter Osteoporose getestet
 ** Erhöhtes Risiko für Myokardinfarkte; nur bei postmenopausalen Patientinnen mit schwerer Osteoporose und hohem Frakturrisiko
 *** Erhöhtes Risiko für Myokardinfarkte und CVI ; nur bei postmenopausalen Pat. mit schwerer Osteoporose und hohem Frakturrisiko

1. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und bei Männern ab dem 50. Lebensjahr. Leitlinie des Dachverbandes der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaften e.V. 2023; Langfassung V2.1, AWMF-Register-Nr.: 183/001; <https://dv-osteologie.org/osteoporose-leitlinien>
2. 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.
3. 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 2016; 27(3):379-90

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 ranelate

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
2. Reginster, J. Y. Cardiac concerns associated with strontium ranelate. Expert Opin Drug Safe 13(9): 1209-1213, 2014

Romosozumab

1. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017;377:1417-27. <https://doi.org/10.1056/nejmoa1708322>
2. F. Cosman, D.B. Crittenden, J.D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, et al., Romosozumab treatment in postmenopausal women with osteoporosis, *N. Engl. J. Med.* 375 (16) (2016) 1532–1543, <https://doi.org/10.1056/NEJMoa1607948>
3. Geusens P, Feldman R , Oates M et al Romosozumab reduces incidence of new vertebral fractures across severity grades among postmenopausal women with osteoporosis. *Bone* 2022 Jan;154:116209. doi: 10.1016/j.bone.2021.116209



Indication for Osteoporosis Drug Therapy (as of 09/2023)

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DVO Guideline Osteoporosis 2023

Short version including:

- Risk factor table for therapy threshold determination
- Tables for determining therapy thresholds (women, men)

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