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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Osteoonkologie und Knochengesundheit

# Osteoonkologie und Knochengesundheit

- **Versionen 2002–2018:**

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

- **Version 2019:**

Diel / Kolberg-Liedtke

# Bisphosphonate beim metastasierten Mammakarzinom

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- **Hyperkalzämie**
- **Reduktion skelettaler 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**

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
1a	A	++
1a	A	++
5	D	++
5	D	-
5	D	-

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### Metaanalysen and Reviews (metastatic breast cancer)

1. Coleman R, Body JJ, Aapro M, et al. ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014;25 Suppl 3:iii124-37.
2. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
3. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017

### 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

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- Reduktion der Hyperkalzämie
- Reduktion skelettaler Komplikationen
- Reduktion von Knochenschmerzen
- Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen
- Therapie nach ossärer Progression
  - Progression unter Bisphosphonaten
- Bestimmung von Knochenresorptionsmarkern zur Therapiekontrolle
- Alleinige Therapie zur Analgesie bei Knochenschmerzen

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

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### 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.

### Statement: Progression under bisphosphonates


1. Fizazi, K, Lipton, A, Mariette, X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 27:1564-71, 2009

#### Clinical relevance of bone resorption marker

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

#### Bisphosphonates for bone pain control

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



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## Longer-Interval vs Standard Dosing of Zoledronic Acid

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

SRE after 2 yrs:	29.5 % zoledronic acid every 4 weeks
	28.6 % zoledronic acid every 12 weeks
  
- **<sup>2</sup> Optimze-2-trial:** n = 460 with metastatic breast cancer
 

SRE after 1 year <sup>3</sup> :	22.0% zoledronic acid every 4 weeks
	23.2% zoledronic acid every 12 weeks

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

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

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

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

## 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	++
▪ 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	++
▪ Denosumab 120 mg s.c. q12w	4	C	-
▪ Andere Dosierungen oder Schemata, wie z.B. aus den Studien zur adjuvanten Situation oder Osteoporosetherapie	5	D	--

1. Templeton AJ et al. Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS5095)
2. O'Carrigan B, Wong MH, Willson ML et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10:CD003474. doi: 10.1002/14651858.CD003474.pub4.
3. Van Poznak C, Somerfield MR, Barlow WE et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 35(35):3978-3986, 2017
4. Ibrahim MF, 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
5. Amadori D, Aglietta M, Alessi B et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 14(7):663-70, 2013
6. Himmelstein AL, Foster JC, Khatcheressian JL et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 317(1):48-58, 2017
7. Hortobagyi GN, Van Poznak C, Harker WG et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in



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

Ossäre Metastasen Radionuklidtherapie			
	Oxford		
	LoE	GR	AGO
<p>■ Tumorprogression nach Ausschöpfung der Standardtherapie multipler / disseminierter Skelettmetastasen und intolerabler Knochenschmerzen</p> <ul style="list-style-type: none"> <li>■ <sup>186</sup>Rhenium-hydroxyethyliden-diphosphonat</li> <li>■ <sup>153</sup>Samarium</li> <li>■ <sup>89</sup>Strontium</li> <li>■ <sup>223</sup>Radium</li> <li>■ <sup>177</sup>Lu-EDTMP</li> </ul>	1b	B	+
	2b	B	+
	1b	B	+
	1b	B	+
	1b	B	+
	1b	B	+
Cave: Gefahr der Myelosuppression und Panzytopenie			

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## Reviews / Overview

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

## <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  $^{223}\text{Ra}$ -dichloride. J Nucl Med 55(2):268-74, 2015

#### $^{177}\text{Lu}$ (Lutetium)-EDTMP

1. Agarwal KK, Singla S, Arora G, Bal C. ( $^{177}\text{Lu}$ )-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  $^{153}\text{Sm}$ -EDTMP and  $^{177}\text{Lu}$ -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.

# 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. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol 16:1613-24, 1998
5. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl:S165-75
6. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogrammonkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 13.01.2018)

## Knochenmetastasen – Spinales Kompressionssyndrom / Paraplegie


	Oxford		
	LoE	GR	AGO
■ Operation zur Dekompression, Reduktion der Tumormasse und Stabilisierung (< 24 h) sowie Bestrahlung der Wirbelsäule (RT)	2b	C	++
■ Bestrahlung der WS (< 24 h) +/- Steroide	3b	C	++
■ Sofortiger Therapiebeginn	1c	D	++

Patienten in Studien mit unterschiedlichen Tumorentitäten!

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

Clin Oncol 16:1613-24, 1998

8. Regine WF, Tibbs PA, Young A et al. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. Int J Radiat Oncol Biol Phys 2003;57(Suppl.):S125. abstract #3
9. Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 82: 570–594, 2000
10. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine: evaluation and treatment. Clin Orthop 2003;415 Suppl: S 165–175
11. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. Int J Radiat Oncol Biol Phys 46: 1163–1169, 2000
12. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogrammonkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 13.01.2018)



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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)

\*Studienteilnahme empfohlen

1. Ju DG, Yurter A, Gokaslan ZL et al. Diagnosis and surgical management of breast cancer metastatic to the spine. World J Clin Oncol 10;5(3):263-71, 2014
2. Wood TJ, Racano A, Yeung H et al. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol 21(13):4081-9, 2014
3. Ali SM, Harvey HA, Lipton A: Metastatic breast cancer: overview of treatment. Clin Orthop Rel Res 2003;1 (415S) (Suppl): 132–137
4. Fourney DR, Gokaslan ZL: Thoracolumbar spine: surgical treatment of metastatic disease. Curr Opin Orthop 14 (3): 144–152, 2013
5. Fourney DR, Schomer DF, Nader R et al: Percutaneous and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 98 (Suppl): 21–30, 2003
6. Walker MP, Yaszemski MJ, Kim CW et al. Metastatic disease of the spine. Evaluation and treatment. Clin Orthop Rel Res (415S) (Suppl): 165–175, 2003
7. Berenson J1, Pflugmacher R, Jarzem P et al. Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a



multicentre, randomised controlled trial. Lancet Oncol 12(3):225-35, 2011

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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 Schmerz- zunahme mit Dexamethason	1b	B	+
▪ Strahlentherapie mit Hyperthermie	2b	B	+/-
<b>Nur wenige Studien mit Mammakarzinompatientinnen!</b>			

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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
3. Hartsell WF, Scott C, Bruner DW et al. Phase III randomised trial of 8 Gy in 1 fraction vs. 30 Gy in 10 fractions for palliation of painful bone metastases: preliminary results of RTOG 97-14. Int J Radiat Oncol Biol Phys 2003;57(Suppl.):S124. abstract #1
4. McDonald R, Ding K, Brundage M et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol 3(7):953-959, 2017
5. Lutz S, Berk L, Chang E et al. American Society for Radiation Oncology (ASTRO) Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 79(4):965-976, 2011
6. Hoskin PJ, Yarnold JR, Roos DR et al. Second Workshop on Palliative Radiotherapy and Symptom Control: Radiotherapy for bone metastases. Clin Oncol (R Coll Radiol) 13:88-90, 2001
7. McQuay HJ, Collins SL, Carroll D et al. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev

2000;2:CD001793

8. Wu J, Bezjak A, Chow E et al. A consensus development approach to define national research priorities in bone metastases: proceedings from NCIC CTG workshop. Clin Oncol (R Coll Radiol) 15: 496–499, 2003
9. Chow E, Harris K, Fan G et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 25:1423-36, 2007
10. Chow E, Meyer RM, Ding K et al. Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. Lancet Oncol 16(15):1463-72, 2015
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# Knochenmetastasen: Schmerztherapie nach Vorbestrahlung

## Rekurrenter Knochenschmerz in vorbestrahlten Arealen des Skeletts

- Einmalige RT \*
- Fraktionierte RT \*
- Radionuklidtherapie
- MR-gesteuerter hochfokussierter Ultraschall
- Radiofrequenzablation
- Kryoablation

Oxford		
LoE	GR	AGO
3b	C	++
3b	C	++
3b	C	+
1b	B	+
4	C	+
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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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. Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 82:570-594, 2000
4. Haddad P, Wong R, Wilson P et al. Factors influencing the use of single versus multiple fractions of palliative radiotherapy for bone metastases: a 5-year review and comparison to a survey. Int J Radiat Oncol Biol Phys 2003;57(Suppl.):S278. abstract #1029
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6. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm.onkologie.de/Supportive->


Therapie.95.0.html (Zugriff am 18.01.2018)

#### Magnetic resonance-guided focused ultrasound

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

#### Cryoablation / Radiofrequency ablation

1. Dechamps F, Farouil G, Ternes N, Gaudin A, Hakime A, Tselikas L, Teriitehau C, Baudin E, Auperin A, de Baere T. Thermal ablation techniques: a curative treatment of bone metastases in selected patients? Eur Radiol 24(8):1971-80, 2014
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 <b>Nebenwirkungen und Toxizitäten von Bisphosphonaten (BP) und Denosumab (Db)</b>																			
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1D</p> <p>www.ago-online.de FORSCHEN LEHREN HEILEN</p>	<table> <tr> <th></th><th>LoE</th></tr> <tr> <td>▪ Nierenfunktionsstörungen durch i.v. Amino-Bisphosphonat</td><td>1b</td></tr> <tr> <td>▪ Kieferosteonekrose (ONJ) typisch unter i.v. BPs und Denosumab (1,3% / 1,8%)</td><td>1b</td></tr> <tr> <td>▪ Assoziation mit (parallelem) Einsatz von antiangiogenetische Therapien</td><td>3b</td></tr> <tr> <td>▪ Ausgeprägte Fälle mit Hypokalzämie (Dmab &gt; BP)</td><td>1b</td></tr> <tr> <td>▪ Akut-Phase-Reaktion (i.v. Amino-BPs und Denosumab) 10–30 %</td><td>1b</td></tr> <tr> <td>▪ Gastrointestinale Nebenwirkungen (orale BPs) 2–10 %</td><td>1b</td></tr> <tr> <td>▪ Atypische Femurfrakturen (absolutes Risiko: 11/10.0000 Personenjahre mit BP-Einnahme)</td><td>2b</td></tr> <tr> <td>▪ Sehr selten: Uveitis / Scleritis bei Bisphosphonaten</td><td>4</td></tr> </table>		LoE	▪ Nierenfunktionsstörungen durch i.v. Amino-Bisphosphonat	1b	▪ Kieferosteonekrose (ONJ) typisch unter i.v. BPs und Denosumab (1,3% / 1,8%)	1b	▪ Assoziation mit (parallelem) Einsatz von antiangiogenetische Therapien	3b	▪ Ausgeprägte Fälle mit Hypokalzämie (Dmab > BP)	1b	▪ Akut-Phase-Reaktion (i.v. Amino-BPs und Denosumab) 10–30 %	1b	▪ Gastrointestinale Nebenwirkungen (orale BPs) 2–10 %	1b	▪ Atypische Femurfrakturen (absolutes Risiko: 11/10.0000 Personenjahre mit BP-Einnahme)	2b	▪ Sehr selten: Uveitis / Scleritis bei Bisphosphonaten	4
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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

<div>  <b>Häufige Nebenwirkungen unter Behandlung mit Bisphosphonaten / Denosumab</b> </div>						
Drug	Akute Phase Reaktion	Nieren tox.	Obere GI-NW	Diarrhoe	Kiefer- osteo- nekr.	
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.
Pamidronate 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	0	+	+	

Cave Hypocalciämie unter antiresorptiver Therapie bei  
ossären Metastasen !

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## Empfehlungen für die Prävention von Kieferosteonekrosen (ONJ)

Oxford LoE: 4	GR: C	AGO: +
<ul style="list-style-type: none"> <li>■ Unter Bisphosphonat- bzw. Denosumabtherapie Vermeidung elektiver Zahnbehandlungen mit Manipulationen am Kieferknochen. Falls unvermeidbar wird der prophylaktische Einsatz von Antibiotika empfohlen (LoE 2b)</li> <li>■ Zahnsanierung vor einer Bisphosphonat- bzw. Denosumabtherapie, falls möglich (LoE 2b)</li> <li>■ Information der Patientinnen über ONJ-Risiko und Instruieren über Frühsymptome</li> <li>■ Bei hohem ONJ-Risiko, Anwendung oraler Bisphosphonate</li> <li>■ Gute Zahnhygiene, nur mäßiger Alkoholkonsum sowie Nikotinverzicht</li> </ul>		
<p>Unter adjuvanter Bisphosphonattherapie ist das Risiko für Kieferosteonekrosen gering</p>		

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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Therapie.95.0.html (Zugriff am 13.01.2017)



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# Adjuvante osteoprotektive Therapie zur Verbesserung der Prognose

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	Oxford		
	LoE	GR	AGO
▪ <b>Clodronate (oral)</b>			
▪ Postmenopausale Patientinnen	1a	A	+
▪ Prämenopausale Patientinnen	1a	B	+/-
▪ <b>Aminobisphosphonate (iv oder oral)</b>			
▪ Postmenopausale Patientinnen	1a	A	+
▪ Prämenopausale Patientinnen	1a	B	+/-
▪ <b>Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)</b>			
▪ Postmenopausale Patientinnen Stadium II und III	1b	B	-
▪ <b>Denosumab (60 mg s.c. q6m)</b>			
▪ Postmenopausale Patientinnen unter AI-Therapie	1b <sup>a</sup>	B	+/-

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### Clodronate

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### Denosumab

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#### Guidelines

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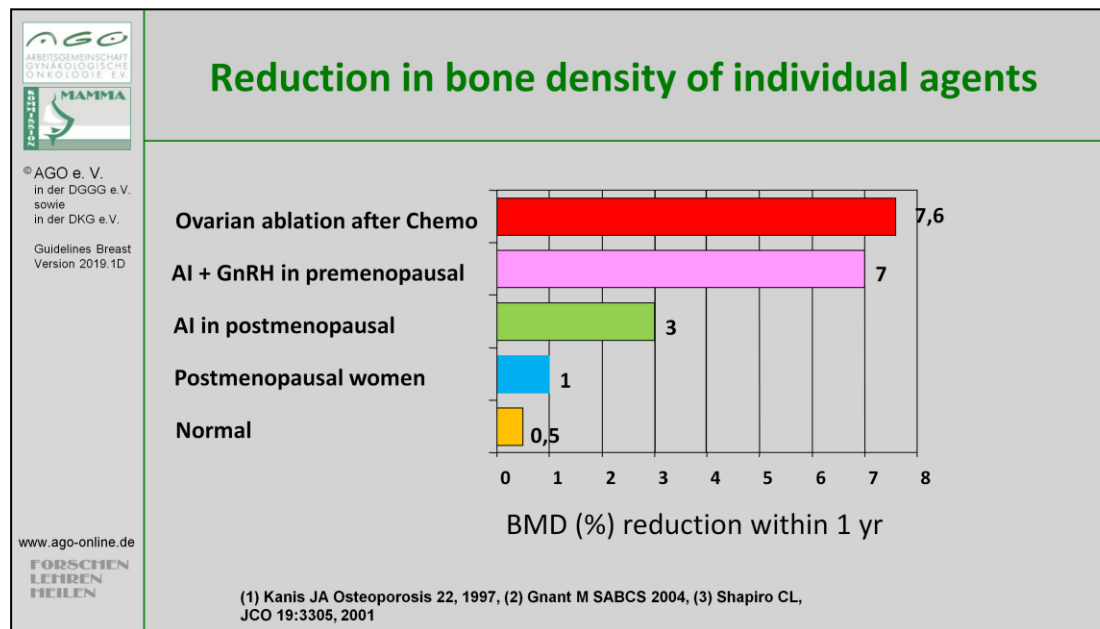
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## Dosierung adjuvanter Bisphosphonate zur Verbesserung des Überlebens

- 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 D 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)

1. Coleman R, Body JJ, Aapro M et al. ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014;25 Suppl 3:iii124-37,
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 3;386(10001):1353-61, 2015
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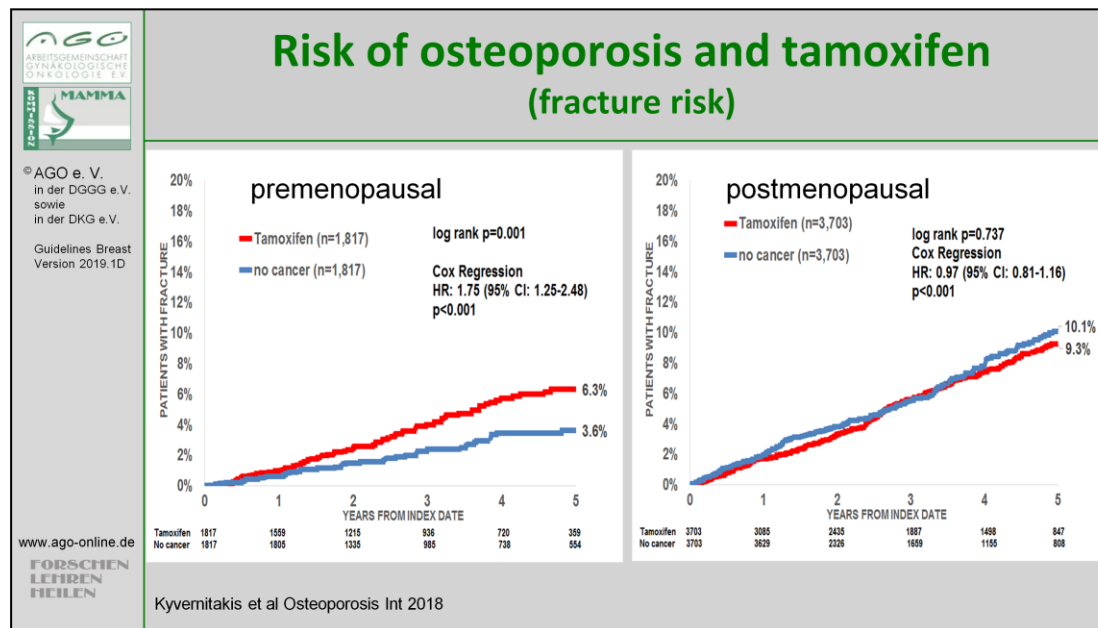


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	Oxford		
	LoE	GR	AGO
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▪ Bisphosphonate			
▪ Therapie	1b	B	++
▪ Prävention	1b	A	+
▪ Denosumab			
▪ Therapie	1b	B	++
▪ Prävention	1b	A	+
▪ HRT	5	D	-
▪ Klinisches Assessment des Osteoporoserisikos vor Therapie	5	D	++
▪ DXA-Scan vor endokriner Therapie und/oder bei vorzeitiger Menopause	5	D	+
▪ Antiresorptive Therapie bei reduzierter Knochendichte	5	D	++
▪ Risikoadaptierte Kontrolle der Knochendichte im Verlauf (DXA-Scan)	5	D	+

1. Coleman R, Body JJ, Aapro M et al. ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014;25 Suppl 3:iii124-37.
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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)\***

	Oxford		
	LoE	GR	AGO
▪ Sportl. / körperl. Aktivität	4	C	++
▪ Vermeidung von Immobilisation	4	C	++
▪ Kalzium (1.000–1.500 mg/d)**	4	C	++
▪ Vit. D3 (800–2.000 U/d oder 20.000 U/w)	4	C	++
▪ Nikotinverzicht, nur mäßiger Alkoholkonsum	2b	B	++
▪ Vermeidung eines BMI < 20 kg/m <sup>2</sup>	3b	C	++
▪ Antiresorptive Therapie nach Beendigung einer Denosumabtherapie	4	C	+/-
▪ Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage)			

\* [http://www.dv-osteologie.org/dvo\\_leitlinien/dvo-leitlinie-2014](http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2014); Überarbeitung 2018 erwartet  
\*\* bei eingeschränkter Aufnahme über die Nahrung (Gabe nur in Verbindung mit Vitamin D3)

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<http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf>
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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 J Bone Miner Res 2017 Nov 4. doi: 10.1002/jbmr.3337. [Epub ahead of print]

Medikamentöse Therapie der Osteoporose			
	Oxford		
	LoE	GR	AGO
■ Alendronat 70 mg po/w*	1b	B	++
■ Denosumab 60 mg sc/6m*	1b	B	++
■ Ibandronat 150 mg po/m*	1b	B	++
■ Ibandronat 3 mg iv/3 m	1b	B	++
■ PTH (1-84) 100 µg sc/d	1b	B	+
■ Raloxifen 60 mg po/d (nur Wirbelsäule)	1b	B	+/-
■ Risedronat 35 mg po/w*	1b	B	++
■ Strontiumranelat 2 g po/d**	1b	B	+
■ Teriparatid (1-34) 20 µg sc/d	1b	B	+
■ Zoledronat 5 mg iv/12 m*	1b	B	++

\* Wurde bei MammaCa-Patientinnen mit Tumorthherapie assoziierter Osteoporose getestet

\*\* Erhöhtes Risiko für Myokardinfarkte; nur bei postmenopausalen Patientinnen mit schwerer Osteoporose und hohem Frakturrisiko

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1. German guidelines for the treatment of osteoporosis by the DVO: <http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf>, in Überarbeitung
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### Raloxifen


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

### Strontium renalate

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

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





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**Aktuell in Überarbeitung**

**TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSE THERAPIE 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  $\geq 2,5$  mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- $\geq 3$  niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

mit freundlicher Genehmigung des DVO-Vorstands, Überarbeitung 2018 erwartet

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