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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

ZNS-Metastasen beim Mammakarzinom



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ZNS-Metastasen beim Mammakarzinom

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ZNS-Metastasen beim Mammakarzinom

- **Das Mammakarzinom ist zweithäufigste Ursache von ZNS-Metastasen.**
- **In Autopsie-Kollektiven:**
 - Parenchymale ZNS-Metastasen: ~ 30–40 %
 - Leptomeningeale ZNS-Metastasen: 5–16 %
- **Stetig steigende Inzidenz (10 % ⇒ 40 %)**
- **Anstieg der Inzidenz verursacht durch:**
 - Effektivere Behandlungsoptionen der extrazerebralen Metastasen
 - Vermehrter Einsatz der MR-Diagnostik
- **Keine Evidenz für Hirnmetastasen-Screening bei asymptomatischen Patientinnen.**
- **Datenlage für Behandlung von ZNS-Metastasen des Mammakarzinoms ist unbefriedigend, da Studien meist nicht Mammakarzinom-spezifisch. Teilnahme an der deutschen Registerstudie zu ZNS-Metastasen Mammakarzinom empfohlen (www.gbg.de).**


1. Berman AT, Thukral AD, Hwang WT et al. Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. Clin Breast Cancer 2013, 13:88-94.
2. Brower, J. V., S. Saha, S. A. Rosenberg et al. (2016). "Management of leptomeningeal metastases: Prognostic factors and associated outcomes." J Clin Neurosci 27: 130-137.
3. Duchnowska R, Jassem J, Goswami CP et al.: Predicting early brain metastases based on clinicopathological factors and gene expression analysis in advanced her2-positive breast cancer patients. J Neurooncol 2015;122:205-216.
4. Duchnowska R, Sperinde J, Chenna A et al.: Quantitative her2 and p95her2 levels in primary breast cancers and matched brain metastases. Neuro Oncol 2015;17:1241-1249.
5. Fidler IJ: The biology of brain metastasis: Challenges for therapy. Cancer journal (Sudbury, Mass) 2015;21:284-293.
6. Gil-Gil MJ, Martinez-Garcia M, Sierra A et al: Breast cancer brain metastases: a review of the literature and a current multidisciplinary management guideline. Clin Transl Oncol 2013
7. Hyun, J. W., I. H. Jeong, A. Joung et al (2016). "Leptomeningeal metastasis: Clinical experience of 519 cases." Eur J Cancer 56: 107-114.
8. Kim, Y.J., J.S. Kim, and I.A. Kim, Molecular subtype predicts incidence and prognosis of brain metastasis from breast cancer in SEER database. J Cancer Res Clin Oncol, 2018. 144(9): p. 1803-1816.
9. Lin NU, Amiri-Kordestani L, Palmieri D et al.: CNS metastases in breast cancer: old challenge, new frontiers. Clin Cancer Res 2013,

19:6404-6418.

10. Le Rhun E, Taillibert S, Chamberlain MC: Neoplastic meningitis due to lung, breast, and melanoma metastases. *Cancer Control* 2017;24:22-32.
11. Mehta MP: Brain metastases: The changing landscape. *Oncology (Williston Park)* 2015;29:257-260.
12. Mustacchi G, Biganzoli L, Pronzato P et al.: Her2-positive metastatic breast cancer: A changing scenario. *Crit Rev Oncol Hematol* 2015;95:78-87.
13. Pahuja S, Puhalla S: Management of breast cancer brain metastases is moving forward, but new options are still needed. *Oncology (Williston Park)* 2014;28:585, 590-582.
14. Quigley MR, Fukui O, Chew B et al.: The shifting landscape of metastatic breast cancer to the CNS. *Neurosurgical review* 2013, 36:377-382.
15. Witzel I, Oliveira-Ferrer L, Pantel K et al.: Breast cancer brain metastases: biology and new clinical perspectives. *Breast Cancer Research*. 2016; 18(1):8.
16. Valiente, M. et al. The evolving landscape of brain metastasis. *Trends Cancer* 2018; 4, 176–196.
17. Kuksis M, Gao Y, Tran W et al.: The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis *Neuro Oncol*. 2021 Jun 1;23(6):894-904.

	Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020				
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D	Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
www.ago-online.de FORSCHEN LEHREN HEILEN	HER2 positive (all)	5971	13% 95% CI: 0.22–0.38	31%	31
	HR- / HER2 positive	2092	13% 95% CI: 0.08–0.20	-	-
	HR+ / HER2 positive	3480	8% 95% CI: 0.05–0.13	-	-
	HR- / HER2 negative	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
	HR+ / HER2 negative	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33
Kuksis M, Gao Y, Tran W et al. Neuro Oncol. 2021 Jun 1;23(6):894-904					

1. Kuksis M, Gao Y, Tran W et al.: The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis Neuro Oncol. 2021 Jun 1;23(6):894-904



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ZNS-Metastasen beim Mammakarzinom – Tumorbilogie

- **Primärtumor:**
 - Negativer Hormonrezeptor-Status (Basalzell-Typ / triple-negativ)
 - Hohes Grading, hohes Ki-67
 - HER2 und / oder EGFR (HER1) Überexpression
 - Molekularer Subtyp (HER2 positiv, triple-negativ, Luminal B)

- **ZNS-Metastasen:**
häufiger Östrogenrezeptor-neg. und HER2 und / oder EGFR positiv

- **Primärtumor und ZNS-Metastasen: Diskordanz des molekularen Subtyp**
 - für ER = 16,7 % und für PR = 25,2 %
 - für HER2 = 10,4 %

- Es gibt keine Evidenz für die Suche nach cerebralen Metastasen bei asymptomatischen Patientinnen

Risk factors (see also references slide CNS incidence)


1. Hess KR, Esteva FJ: Effect of HER2 status on distant recurrence in early stage breast cancer. Breast Cancer Res Treat 2013, 137:449-455.
2. Ishihara M, Mukai H, Nagai S et al.: Retrospective analysis of risk factors for central nervous system metastases in operable breast cancer: effects of biologic subtype and Ki67 overexpression on survival. Oncology 2013, 84:135-140
3. Nie F, Yang J, Wen S et al.: Involvement of epidermal growth factor receptor overexpression in the promotion of breast cancer brain metastasis. Cancer 2012, 118:5198-5209.
4. Pivot X, Manikhas A, Zurawski B et al.: Cerebel (egf111438): A phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2015;33:1564-1573.
5. Soni A, Ren Z, Hameed O et al.: Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol 2015;143:471-478.
6. Shen Q, Sahin AA, Hess KR et al.: Breast cancer with brain metastases: Clinicopathologic features, survival, and paired biomarker analysis. Oncologist 2015;20:466-473.
7. Tomasevic ZI, Rakocevic Z, Tomasevic ZM et al.: Incidence of brain metastases in early stage HER2 3+ breast cancer patients; is there a role for brain CT in asymptomatic patients?, J BUON. 2012 Apr-Jun;17(2):249-53.

Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

1. Kuksis M, Gao Y, Tran W et al.: The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis Neuro Oncol. 2021 Jun 1;23(6):894-904.
2. Arvold, ND, Oh, KS, Niemierko A et al.: Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. Breast Cancer Res Treat 2012 136(1): 153-160.
3. Bachmann C, Grischke EM, Staebler A et al: Receptor change-clinicopathologic analysis of matched pairs of primary and cerebral metastatic breast cancer. J Cancer Res Clin Oncol 2013, 139:1909-1916.
4. Bachmann C, Grischke EM, Fehm T et al.: CNS metastases of breast cancer show discordant immunohistochemical phenotype compared to primary. J Cancer Res Clin Oncol 2013, 139:551-556.
5. Duchnowska R, Dziadziuszko R, Trojanowski T et al.: Conversion of epidermal growth factor receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Res 2012, 14:R119.
6. Han CH, Brastianos PK: Genetic characterization of brain metastases in the era of targeted therapy. Frontiers in oncology 2017;7:230.
7. Hohensee I, Lamszus K, Riethdorf S et al.: Frequent genetic alterations in EGFR- and HER2-driven pathways in breast cancer brain metastases. Am J Pathol 2013, 183:83-95.
8. Kaidar-Person O, Meattini I, Jain P et al.: Discrepancies between biomarkers of primary breast cancer and subsequent brain metastases: An international multicenter study. Breast Cancer Res Treat 2017.
9. Timmer M, Werner JM, Rohn G et al.: Discordance and conversion rates of progesterone-, estrogen-, and her2/neu-receptor status in primary breast cancer and brain metastasis mainly triggered by hormone therapy. Anticancer Res 2017;37:4859-4865.
1. Molekulare Diskordanz Primärtumor – Metastase:Hulsbergen AFC, Claes A, Kavouridis VK, et al. Subtype switching in breast cancer brain metastases: a multicenter analysis. Neuro Oncol. 2020 Aug 17;22(8):1173-1181.
2. Morgan AJ, Giannoudis A, Palmieri C. The genomic landscape of breast cancer brain metastases: a systematic review. Lancet Oncol. 2021 Jan;22(1):e7-e17.

There is no evidence for BM-screening in asymptomatic BC-patients

1. Niwinska A, Tacikowska M, Murawska M: The effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival and cause of death. Int J Radiat Oncol Biol Phys 2010, 77:1134-1139.



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Updated Breast-GPA (Graded Prognostic Assessment) Worksheet to Estimate Survival from Brain Metastases (BM)

Prognostic Factor	0	0.5	1	1.5	Score
KPS	≤ 60	70-80	90-100	n/a	
Subtype	Basal	LumA	n/a	HER2 or LumB	
Age, years	≥ 60	< 60	n/a	n/a	
ECM	present	absent	n/a	n/a	
No of BM	≥ 2	1	n/a	n/a	
					Sum total

Median survival by Breast-GPA:

Breast-GPA 0–1.0 = 6 months

Breast-GPA 1.5–2.0 = 10 months

Breast-GPA 2.5–3.0 = 13 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR negative, HER2 positive. ECM: extracranial metastases BM: brain metastases
Sperduto PW et al, JCO 2020

Breast-GPA

1. Sperduto PW, Kased N, Roberge D et al.: Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012, 30:419-425.
2. Sperduto PW, Mesko S, Li J et al.: Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient. J Clin Oncol. 2020 Nov 10;38(32):3773-3784.
3. Sperduto PW, Mesko S, Li J, et al.: Beyond an updated Graded Prognostic Assessment (Breast GPA): A prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys 2020 107;334-343.
4. Sperduto PW, Kased N, Roberge D et al.: Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. Int J Radiat Oncol Biol Phys 2012, 82:2111-2117
5. Sperduto PW, Shanley R, Luo X et al.: Secondary analysis of rtog 9508, a phase 3 randomized trial of whole-brain radiation therapy versus wbrt plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (gpa). Int J Radiat Oncol Biol Phys 2014;90:526-531.
6. Riecke K, Müller V, Weide R et al.: Predicting Prognosis of Breast Cancer Patients with Brain Metastases in the BMBC Registry-Comparison of Three Different GPA Prognostic Scores. Cancers (Basel). 2021 Feb 17;13(4):844.

Prognostic Factors for Survival

1. Castaneda CA, Flores R, Rojas KY et al.: Prognostic factors for patients with newly diagnosed brain metastasis from breast cancer. *CNS Oncol* 2015;4:137-145.
2. Huttenlocher S, Dziggel L, Hornung D et al.: A new prognostic instrument to predict the probability of developing new cerebral metastases after radiosurgery alone. *Radiation oncology* 2014;9:215.
3. Laakmann, E., K. Riecke, Y. Goy et al.: (2016). "Comparison of nine prognostic scores in patients with brain metastases of breast cancer receiving radiotherapy of the brain." *J Cancer Res Clin Oncol* 142(1): 325-332.
4. Rades D, Huttenlocher S, Hornung D et al.: Do patients with very few brain metastases from breast cancer benefit from whole-brain radiotherapy in addition to radiosurgery? *Radiation oncology* 2014;9:267.
5. Subbiah IM, Lei X, Weinberg JS et al.: Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. *J Clin Oncol* 2015;33:2239-2245.
6. Xu Z, Schlesinger D, Toulmin S et al.: Impact of triple-negative phenotype on prognosis of patients with breast cancer brain metastases. *Int J Radiat Oncol Biol Phys* 2012, 84:612-618.
7. Xu Z, Marko NF, Chao ST et al.: Relationship between HER2 status and prognosis in women with brain metastases from breast cancer. *Int J Radiat Oncol Biol Phys* 2012, 82:e739-747.
8. Nagtegaal SHJ, Claes A, Suijkerbuijk KPM, et al.: Comparing survival predicted by the diagnosis-specific Graded Prognostic Assessment (DS-GPA) to actual survival in patients with 1-10 brain metastases treated with stereotactic radiosurgery. *Radiother Oncol*. 2019 Sep;138:173-179. doi: 10.1016/j.radonc.2019.06.033. Epub 2019 Jul 11.


Singuläre Hirnmetastasen und Oligohirnmetastasen*			
	Oxford		
	LoE	GR	AGO
Alleinige Lokaltherapie: SRS (≤ 4 cm) oder FSRT	1b	B	++
Singuläre Metastase	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts (ohne WBRT)			
Oligometastasen	1b	B	++
OP (wenn indiziert) + Bestrahlung des Tumorbetts und SRS oder FSRT der nicht-resezierten Metastasen (ohne WBRT)			
WBRT + Boost (SRS, FSRT) oder Resektion + WBRT	2a	B	+
Alleinige WBRT	2b	B	+
Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand			
Hippocampuschonung** (bei günstiger Prognose)	1b	B	+

* Oligohirnmetastasierung oder limitierte Metastasierung bezieht sich vor allem auf bis zu 4 Hirnmetastasen, unter bestimmten Voraussetzungen bis zu 10 (Gesamtvolumen < 15 ml)
 ** Ausschlusskriterium: Metastasen in der Hippocampus-Region
 [SRS = stereotactic radiosurgery (einzeitig); FSRT = fractionated stereotactic radiotherapy, WBRT = whole brain radiotherapy]

1. Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.
2. Aoyama H, Shirato H, Tago M et al.: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006 Jun 7;295(21):2483-91.
3. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011, 29:134-141.
4. Kayama T, Sato S, Sakurada K et al: Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. J Clin Oncol. 2018 Jun 20;JCO2018786186. doi: 10.1200/JCO.2018.78.6186.
5. Brown, P.D., et al., Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol, 2017. 18(8): p. 1049-1060.
6. Ling DC, Vargo JA, Wegner RE et al.: Postoperative stereotactic radiosurgery to the resection cavity for large brain metastases: Clinical outcomes, predictors of intracranial failure, and implications for optimal patient selection. Neurosurgery 2015;76:150-156; discussion 156-157; quiz 157.
7. Patchell RA, Tibbs PA, Regine WF et al.: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998 Nov 4;280(17):1485-9

8. Brown PD, Gondi V, Pugh S et al.: Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00. *J Clin Oncol* 2020 Apr 1; 38(10): 1019–1029.
9. Cardoso F, Paluch-Shimon S, Senkus E et al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020 Dec;31(12):1623-1649.
10. Cho E, Rubinstein L, Stevenson P et al.: The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most? *Breast Cancer Res Treat* 2015;149:743-749.
11. Halasz, L. M., H. Uno, M. Hughes et al.: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 2016 122(13): 2091-2100.
12. Liu Y, Alexander BM, Chen YH et al.: Salvage whole brain radiotherapy or stereotactic radiosurgery after initial stereotactic radiosurgery for 1-4 brain metastases. *J Neurooncol* 2015;124:429-437.
13. Miller, J. A., R. Kotecha and J. H. Suh: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 2016; 122(20): 3243-3244
14. Mix, M., R. Elmarzouky, T. O'Connor et al.: Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy. *J Neurosurg* 2016; 125(Suppl 1): 26-30
15. Rades D, Huttenlocher S, Rudat V et al.: Radiosurgery with 20 Gy provides better local control of 1-3 brain metastases from breast cancer than with lower doses. *Anticancer Res* 2015;35:333-336.
16. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol* 2017;19:162-174.
17. Tham IW, Lim KH, Koh WY et al.: Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2014 Mar 1;3:CD009454. doi: 10.1002/14651858.CD009454.pub2.
18. Tsao M, Xu W, Sahgal A: A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* 2012, 118:2486-2493.
19. Yamamoto M, Serizawa T, Shuto T et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15(4):387-95.
20. Ersoy TF, Mokhtari N, Brainman D et al.: Surgical Treatment of Cerebellar Metastases: Survival Benefits, Complications and Timing Issues. *Cancers (Basel)*. 2021 Oct 20;13(21):5263.
21. Andrews DW, Scott CB, Sperduto PW et al.: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004 May 22;363(9422):1665-72.

22. Rodríguez de Dios N, Couñago F, Murcia-Mejía M et al.:Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECF-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
23. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
24. Li J, Ludmir EB, Wang Y et al. Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. Int J Radiat Oncol Biol Phys 2020; 108(3):S21-S22.
25. Hartgerink D, Bruynzeel A, Eekers D et al. A Dutch phase III randomized multicenter trial: whole brain radiotherapy versus stereotactic radiotherapy for 4-10 brain metastases. Neurooncol Adv. 2021;3(1):vdab021.
26. Belderbos JSA, De Ruysscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849.



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Singuläre Hirnmetastasen und Oligohirnmetastasen*


- Lokale Therapieansätze (OP; SRS; FSRT) indiziert in Abhängigkeit von der Lokalisation, Größe, Anzahl, Vorbehandlung, Karnofsky-Performance-Scale, Gesamtprognose.
- Die WBRT zusätzlich zur SRS verbessert die intrakranielle Kontrolle. Sie verlängert nicht die Zeit der funktionellen Unabhängigkeit und verbessert nicht das Gesamtüberleben.
- Die WBRT führt zu größerer neurokognitiver Beeinträchtigung.
- Bei einer limitierten Anzahl* von Hirnmetastasen Präferenz zur stereotaktischen Bestrahlung.
- Postoperative Bestrahlung des Tumorbetts:
 - Singuläre Hirnmetastase (Resektionshöhle < 5 cm): SRS v. WBRT kein Unterschied im OS.
 - Oligometastasen: SRS des Tumorbetts und der nicht-resezierten Metastasen v. WBRT kein Unterschied im OS

* Oligohirnmetastasierung oder limitierte Metastasierung bezieht sich vor allem auf bis zu 4 Hirnmetastasen, unter bestimmten Voraussetzungen bis zu 10 (Gesamtvolumen < 15 ml)
[SRS = stereotactic radiosurgery (einzeitig); FSRT = fractionated stereotactic radiotherapy, WBRT = whole brain radiotherapy]


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2. Aoyama H, Shirato H, Tago M et al.: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006 Jun 7;295(21):2483-91.
3. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011, 29:134-141.
4. Kayama T, Sato S, Sakurada K et al: Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. J Clin Oncol. 2018 Jun 20;JCO2018786186. doi: 10.1200/JCO.2018.78.6186.
5. Brown, P.D., et al., Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol, 2017. 18(8): p. 1049-1060.
6. Ling DC, Vargo JA, Wegner RE et al.: Postoperative stereotactic radiosurgery to the resection cavity for large brain metastases: Clinical outcomes, predictors of intracranial failure, and implications for optimal patient selection. Neurosurgery 2015;76:150-156; discussion 156-157; quiz 157.
7. Patchell RA, Tibbs PA, Regine WF et al.: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998 Nov 4;280(17):1485-9

8. Brown PD, Gondi V, Pugh S et al.: Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00. *J Clin Oncol* 2020 Apr 1; 38(10): 1019–1029.
9. Cardoso F, Paluch-Shimon S, Senkus E et al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020 Dec;31(12):1623-1649.
10. Cho E, Rubinstein L, Stevenson P et al.: The use of stereotactic radiosurgery for brain metastases from breast cancer: Who benefits most? *Breast Cancer Res Treat* 2015;149:743-749.
11. Halasz, L. M., H. Uno, M. Hughes et al.: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 2016 122(13): 2091-2100.
12. Liu Y, Alexander BM, Chen YH et al.: Salvage whole brain radiotherapy or stereotactic radiosurgery after initial stereotactic radiosurgery for 1-4 brain metastases. *J Neurooncol* 2015;124:429-437.
13. Miller, J. A., R. Kotecha and J. H. Suh: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 2016; 122(20): 3243-3244
14. Mix, M., R. Elmarzouky, T. O'Connor et al.: Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy. *J Neurosurg* 2016; 125(Suppl 1): 26-30
15. Rades D, Huttenlocher S, Rudat V et al.: Radiosurgery with 20 Gy provides better local control of 1-3 brain metastases from breast cancer than with lower doses. *Anticancer Res* 2015;35:333-336.
16. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol* 2017;19:162-174.
17. Tham IW, Lim KH, Koh WY et al.: Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2014 Mar 1;3:CD009454. doi: 10.1002/14651858.CD009454.pub2.
18. Tsao M, Xu W, Sahgal A: A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* 2012, 118:2486-2493.
19. Yamamoto M, Serizawa T, Shuto T et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15(4):387-95.
20. Ersoy TF, Mokhtari N, Brainman D et al.: Surgical Treatment of Cerebellar Metastases: Survival Benefits, Complications and Timing Issues. *Cancers (Basel)*. 2021 Oct 20;13(21):5263.
21. Andrews DW, Scott CB, Sperduto PW et al.: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004 May 22;363(9422):1665-72.

22. Rodríguez de Dios N, Couñago F, Murcia-Mejía M et al.:Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECF-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
23. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
24. Li J, Ludmir EB, Wang Y et al. Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial. Int J Radiat Oncol Biol Phys 2020; 108(3):S21-S22.
25. Hartgerink D, Bruynzeel A, Eekers D et al. A Dutch phase III randomized multicenter trial: whole brain radiotherapy versus stereotactic radiotherapy for 4-10 brain metastases. Neurooncol Adv. 2021;3(1):vdab021.
26. Belderbos JSA, De Ruyscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center; color: green;">NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases</h2> <p>Study design: Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.*</p> <p>Conclusion: Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.</p> <p>* Remark: No hippocampus-sparing was applied</p> <p>Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.</p>
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1. Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.



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Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

	2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation after surgical resection or radiosurgery			
	after surgical resection (n = 160)		after radiosurgery (n = 199)	
	WBRT	observation	WBRT	observation
Local recurrence	27%	59% (p < 0.001)	19 %	31% (p = 0.040)
New lesions	23%	42% (p = 0.008)	33 %	48% (p = 0.023)

- Only 12% of the patients had brain metastases from breast cancer.
- Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; p = .89).
- Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.

Kocher M. J Clin Oncol 2011, 29:134-141

1. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29:134-41.



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Mögliche Entscheidungsfaktoren Neurochirurgie vs. Stereotaktische Strahlentherapie

Pro Neurochirurgie:

- Histologische Sicherung nach z. B. langem rezidivfreiem Intervall
- Sofortige Dekompression notwendig, lebensbedrohliche Symptome
- Stereotaktische Radiotherapie (SRS oder FSRT) bei singulärer Metastase aufgrund der Größe nicht möglich

Pro primäre Radiotherapie*:

- Tumorlokalisation nicht geeignet für chirurgische Resektion
- Mehr als eine Läsionen ohne die oben genannten Kriterien

* Falls möglich stereotaktische Strahlentherapie bevorzugt

1. Cardoso F, Paluch-Shimon S, Senkus E et al.: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
2. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.



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Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportiv Steroide*)	1a	A	++
▪ Hippocampuschonung** (bei günstiger Prognose)	1b	B	+
▪ Glukokortikoide allein*	3a	B	+/-
▪ Chemotherapie +/- zielgerichtete Therapie allein	3a	D	+/-
▪ Radiochemotherapie	3b	C	-
▪ Erneute WBRT bei Rezidiv***	4	C	+/-

* Symptomadaptiert
** Ausschlusskriterium: Metastasen in der Hippocampus-Region
*** Falls lokale Therapien (OP, SRS, FSRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangenen Bestrahlung, Vorbelastung und Lokalisation

SRS = stereotactic radiosurgery
FSRT = fractionated stereotactic radiotherapy
WBRT = whole brain radiotherapy

1. Awad R, Fogarty G, Hong A et al.: Hippocampal avoidance with volumetric modulated arc therapy in melanoma brain metastases - the first Australian experience. Radiation oncology 2013;8:62.
2. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013 Jan;14(1):64-71.
3. Caine C, Deshmukh S, Gondi V et al.: Cogstate computerized memory tests in patients with brain metastases: Secondary endpoint results of nrg oncology rtog 0933. J Neurooncol 2015.
4. Cao KI, Lebas N, Gerber S et al.: Phase ii randomized study of whole-brain radiation therapy with or without concurrent temozolomide for brain metastases from breast cancer. Ann Oncol 2015;26:89-94.
5. Geraud, A., H. P. Xu, P. Beuzeboc et al. "Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer." J Neurooncol. 2016
6. Gondi V, Pugh SL, Tome WA et al.: Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (rtog 0933): A phase II multi-institutional trial. J Clin Oncol 2014;32:3810-3816.
7. Krop IE, Lin NU, Blackwell K et al.: Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol. 2015; 26(1):113-9. doi: 10.1093/annonc/mdu486.


8. Stokes TB, Niranjan A, Kano H et al.: White matter changes in breast cancer brain metastases patients who undergo radiosurgery alone compared to whole brain radiation therapy plus radiosurgery. J Neurooncol 2015;121:583-590.
9. Sutherland S et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases-the UK experience. Br J Cancer 2010; 16: 102(6): 995 – 1002.
10. Brown PD, Gondi V, Pugh S et al.:Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC00.J Clin Oncol 2020 Apr 1; 38(10): 1019–1029.
11. Rodríguez de Dios N, Couñago F, Murcia-Mejía M et al.:Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOEC-SEOR Study. J Clin Oncol. 2021 Oct 1;39(28):3118-3127.
12. Belderbos JSA, De Ruysscher DKM, De Jaeger K et al.: Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol. 2021 May;16(5):840-849.

Radiochemotherapy

1. Ammirati M, Cobbs CS, Linskey ME et al.: The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010, 96:85-96.
2. Lassman AB, Abrey LE, Shah GD et al.: Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol 2006, 78:255-260.

Re-Bestrahlung bei Rezidiv

1. Huang, Z., B. Sun, G. Shen et al.: Brain metastasis reirradiation in patients with advanced breast cancer. J Radiat Res 2016. Oct 5. [Epub ahead of print] DOI 10.1093/jrr/rrw087
2. Minniti, G., C. Scaringi, S. Paolin et al.: Repeated stereotactic radiosurgery for patients with progressive brain metastases. J Neurooncol 2016; 126(1): 91-97.
3. Shen, C. J., M. Lim and L. R. Kleinberg (2016). "Controversies in the Therapy of Brain Metastases: Shifting Paradigms in an Era of Effective Systemic Therapy and Longer-Term Survivorship." Curr Treat Options Oncol 2016; 17(9): 46.



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Symptomatische Therapie von Hirnmetastasen

	Oxford		
	LoE	GR	AGO
▪ Antikonvulsiva nur bei Anfallssymptomatik	3a	C	+
▪ Glukokortikoide nur, wenn Symptome und / oder Verdrängungseffekt (Dexamethason mit größter Evidenz)	3a	C	++
▪ Für Pat. mit schlechter Prognose best supportive care, und / oder palliative Versorgung ohne weitere Therapie als Option	5	D	+


Anticonvulsants

1. Lobos-Urbina D, Kittsteiner-Manubens L, Pena J: Is primary prevention with antiepileptic drugs effective in brain tumors or brain metastases? Medwave 2017;17:e6871.
2. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.

Steroids

1. Ryken TC, McDermott M, Robinson PD et al.: The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010, 96:103-114.
2. Soffietti R, Abacioglu U, Baumert B et al.: Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the european association of neuro-oncology (eano). Neuro Oncol 2017;19:162-174.
3. Chang SM, Messersmith H, Ahluwalia M, et al: Anticonvulsant prophylaxis and steroid use in adults with metastatic brain tumors: summary of SNO and ASCO endorsement of the Congress of Neurological Surgeons guidelines. Neuro-Oncology 21(4), 424–427, 2019 | doi:10.1093/neuonc/noz034
4. Nahed BV, Alvarez-Breckenridge C, Brastianos RK et al. . Congress of neurological surgeons systematic review and evidence-based guidelines on the role of surgery in the management of adults with metastatic brain tumors. Neurosurgery. 2019;84(3):E152-E155.

5. Chen CC, Rennert RC, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of prophylactic anticonvulsants in the treatment of adults with metastatic brain tumors. *Neurosurgery*. 2019;84(3):E195-E197



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Klinische Einordnung von Hirnmetastasen

Stabile Hirnmetastase (Definition: RECIST / RANO): Stabilisierung nach vorangehender Behandlung der Hirnmetastase(n)

Stabile Hirnmetastase (Definition analog DESTINY-Breast03-Studie): stabile Hirnmetastasen 2 Wochen nach Ganzhirnbestrahlung, keine Symptome, keine Medikation mit Kortikosteroiden, Antikonvulsiva

Aktive Hirnmetastase (Definition analog HER2Climb-Studie):

lokal vorbehandelt: progrediente oder neue Hirnmetastase(n), bei denen keine sofortige erneute lokale Behandlung indiziert ist
oder
lokal unbehandelte Hirnmetastase(n), für die keine sofortige lokale Behandlung indiziert ist.

1. Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. CNS Oncol. 2019 Mar 1;8(1):CNS28.
2. Le Rhun E, Guckenberger M, Smits M et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332-1347.
3. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, N Engl J Med 2020; 382(7):597-609
4. Hurvitz S., Kim SB, Chung WP et al. :Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03, General Session 3, SABCS 2021

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Systemische Therapie von Hirnmetastasen: Allgemeine Grundsätze

	Oxford		
	LoE	GR	AGO
▪ Interdisziplinäre Behandlungsplanung	5	D	++
▪ Chemotherapie +/- zielgerichtete Therapie als alleinige Primärbehandlung	3a	D	+/-
▪ Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation	2c	C	+

1. Karam I, Hamilton S, Nichol A et al.: Population-based outcomes after brain radiotherapy in patients with brain metastases from breast cancer in the Pre-Trastuzumab and Trastuzumab eras. Radiation oncology 2013, 8:12.
2. Lin NU: Targeted therapies in brain metastases. Current treatment options in neurology 2014, 16:276.
3. Mehta AI, Brufsky AM, Sampson JH: Therapeutic approaches for HER2-positive brain metastases: circumventing the blood-brain barrier. Cancer Treat Rev 2013, 39:261-269.
4. Mounsey LA, Deal AM, Keith KC et al.: Changing natural history of her2-positive breast cancer metastatic to the brain in the era of new targeted therapies. Clin Breast Cancer 2017.
5. Pessina F, Navarria P, Cozzi L et al.: Outcome evaluation of her2 breast cancer patients with limited brain metastasis. Anticancer Res 2017;37:7057-7062.
6. Tarhan MO, Demir L, Somali I et al.: The clinicopathological evaluation of the breast cancer patients with brain metastases: predictors of survival. Clin Exp Metastasis 2013, 30:201-213.
7. Teplinsky E, Esteva FJ: Systemic therapy for her2-positive central nervous system disease: Where we are and where do we go from here? Curr Oncol Rep 2015;17:46.
8. Yuan P, Gao SL: Management of breast cancer brain metastases: Focus on human epidermal growth factor receptor 2-positive breast cancer. Chronic diseases and translational medicine 2017;3:21-32.
9. Zhang Q, Chen J, Yu X et al.: Survival benefit of anti-her2 therapy after whole-brain radiotherapy in her2-positive breast cancer

- patients with brain metastasis. *Breast Cancer* 2016; Sep;23(5):732-9. doi: 10.1007/s12282-015-0631-x. Epub 2015 Aug 13
10. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol.* 2013;14(1):64-71.
 11. Montemurro F, Delaloge S, Barrios CH et al., Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial, *Ann Oncol* 2020; 31:1350-1358
 12. Petrelli et al., The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis, *Eur J Cancer*, 2017;84:141-148
 13. Saura C, Oliveira M, Feng YH et al., Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With 2 HER2-Directed Regimens: Phase III NALA Trial, *J Clin Oncol.* 2020; 38(27):3138-3149
 14. Awada A, Colomer R, Inoue K et al., Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial, *JAMA Oncol.* 2016; 2(12):1557-1564
 15. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, *N Engl J Med* 2020; 382(7):597-609
 16. Bartsch R, Berghoff AS, Vogl U et al.: Activity of t-dm1 in her2-positive breast cancer brain metastases. *Clin Exp Metastasis* 2015;32:729-737.
 17. Cortes, J., V. Dieras, J. Ro et al.: Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol* 2015; 16(16): 1700-1710.
 18. Fabi, A., et al., T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer. *Breast*, 2018. 41: p. 137-143.
 19. Freedman RA, Gelman RS, Melisko ME et al: TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). *Journal of Clinical Oncology* 2017, 35(15_suppl):1005-1005.
 20. Geraud A, Xu HP, Beuzeboc P et al.: Preliminary experience of the concurrent use of radiosurgery and t-dm1 for brain metastases in her2-positive metastatic breast cancer. *J Neurooncol* 2017;131:69-72.
 21. Jacot, W., E. Pons, J. S. Frenel et al.: Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases." *Breast Cancer Res Treat* 2016; 157(2): 307-318.

22. Niwinska, A. Brain metastases as site of first and isolated recurrence of breast cancer: the role of systemic therapy after local treatment. *Clin Exp Metastasis* 2016; 33(7): 677-685
23. Okines A, Irfan T, Khabra K et al.: Development and responses of brain metastases during treatment with trastuzumab emtansine (t-dm1) for her2 positive advanced breast cancer: A single institution experience. *Breast J* 2017.
24. Perez, E. A., A. Awada, J. O'Shaughnessy et al.: Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2015; 16(15): 1556-1568
25. Vici P, Pizzuti L, Michelotti A et al.: A retrospective multicentric observational study of trastuzumab emtansine in her2 positive metastatic breast cancer: A real-world experience. *Oncotarget* 2017.
26. Lin NU, Borges V, Anders C et al., Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial, *J Clin Oncol* 2020, 38:2610-2619.
27. Krop IE, Lin NU, Blackwell K et al., Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA, *Ann Oncol* 2015, 26(1):113-119
28. Modi S, Saura C, Yamashita T et al., Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer, *N Engl J Med.* 2020, 382: 610–621.
29. Hurvitz S., Kim SB, Chung WP et al. :Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03, General Session 3, SABCs 2021

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Systemische Therapie von Hirnmetastasen: HER2 positiv

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabin*	2b	B	+
▪ Trastuzumab-Deruxtecan**	2b	B	+
▪ T-DM1	2b	B	+/-
▪ Lapatinib + Capecitabin	2b	B	+/-
▪ Neratinib + Capecitabin	2b	B	+/-
▪ Neratinib + Paclitaxel	2b	B	+/-

* Wirksamkeit belegt bei aktiven und stabilen Hirnmetastasen

** Wirksamkeit bei stabilen Hirnmetastasen ohne Symptome, keine Medikation mit Kortikosteroiden oder Antikonvulsiva

1. Karam I, Hamilton S, Nichol A et al.: Population-based outcomes after brain radiotherapy in patients with brain metastases from breast cancer in the Pre-Trastuzumab and Trastuzumab eras. Radiation oncology 2013, 8:12.
2. Lin NU: Targeted therapies in brain metastases. Current treatment options in neurology 2014, 16:276.
3. Mehta AI, Brufsky AM, Sampson JH: Therapeutic approaches for HER2-positive brain metastases: circumventing the blood-brain barrier. Cancer Treat Rev 2013, 39:261-269.
4. Mounsey LA, Deal AM, Keith KC et al.: Changing natural history of her2-positive breast cancer metastatic to the brain in the era of new targeted therapies. Clin Breast Cancer 2017.
5. Pessina F, Navarria P, Cozzi L et al.: Outcome evaluation of her2 breast cancer patients with limited brain metastasis. Anticancer Res 2017;37:7057-7062.
6. Tarhan MO, Demir L, Somali I et al.: The clinicopathological evaluation of the breast cancer patients with brain metastases: predictors of survival. Clin Exp Metastasis 2013, 30:201-213.
7. Teplinsky E, Esteva FJ: Systemic therapy for her2-positive central nervous system disease: Where we are and where do we go from here? Curr Oncol Rep 2015;17:46.
8. Yuan P, Gao SL: Management of breast cancer brain metastases: Focus on human epidermal growth factor receptor 2-positive breast cancer. Chronic diseases and translational medicine 2017;3:21-32.
9. Zhang Q, Chen J, Yu X et al.: Survival benefit of anti-her2 therapy after whole-brain radiotherapy in her2-positive breast cancer

- patients with brain metastasis. *Breast Cancer* 2016; Sep;23(5):732-9. doi: 10.1007/s12282-015-0631-x. Epub 2015 Aug 13
10. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol.* 2013;14(1):64-71.
 11. Montemurro F, Delaloge S, Barrios CH et al., Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial, *Ann Oncol* 2020; 31:1350-1358
 12. Petrelli et al., The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis, *Eur J Cancer*, 2017;84:141-148
 13. Saura C, Oliveira M, Feng YH et al., Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With 2 HER2-Directed Regimens: Phase III NALA Trial, *J Clin Oncol.* 2020; 38(27):3138-3149
 14. Awada A, Colomer R, Inoue K et al., Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial, *JAMA Oncol.* 2016; 2(12):1557-1564
 15. Murthy RK, Loi S, Okines A et al., Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer, *N Engl J Med* 2020; 382(7):597-609
 16. Bartsch R, Berghoff AS, Vogl U et al.: Activity of t-dm1 in her2-positive breast cancer brain metastases. *Clin Exp Metastasis* 2015;32:729-737.
 17. Cortes, J., V. Dieras, J. Ro et al.: Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol* 2015; 16(16): 1700-1710.
 18. Fabi, A., et al., T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer. *Breast*, 2018. 41: p. 137-143.
 19. Freedman RA, Gelman RS, Melisko ME et al: TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). *Journal of Clinical Oncology* 2017, 35(15_suppl):1005-1005.
 20. Geraud A, Xu HP, Beuzeboc P et al.: Preliminary experience of the concurrent use of radiosurgery and t-dm1 for brain metastases in her2-positive metastatic breast cancer. *J Neurooncol* 2017;131:69-72.
 21. Jacot, W., E. Pons, J. S. Frenel et al.: Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases." *Breast Cancer Res Treat* 2016; 157(2): 307-318.

22. Niwinska, A. Brain metastases as site of first and isolated recurrence of breast cancer: the role of systemic therapy after local treatment. *Clin Exp Metastasis* 2016; 33(7): 677-685
23. Okines A, Irfan T, Khabra K et al.: Development and responses of brain metastases during treatment with trastuzumab emtansine (t-dm1) for her2 positive advanced breast cancer: A single institution experience. *Breast J* 2017.
24. Perez, E. A., A. Awada, J. O'Shaughnessy et al.: Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2015; 16(15): 1556-1568
25. Vici P, Pizzuti L, Michelotti A et al.: A retrospective multicentric observational study of trastuzumab emtansine in her2 positive metastatic breast cancer: A real-world experience. *Oncotarget* 2017.
26. Lin NU, Borges V, Anders C et al., Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial, *J Clin Oncol* 2020, 38:2610-2619.
27. Krop IE, Lin NU, Blackwell K et al., Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA, *Ann Oncol* 2015, 26(1):113-119
28. Modi S, Saura C, Yamashita T et al., Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer, *N Engl J Med.* 2020, 382: 610–621.
29. Hurvitz S., Kim SB, Chung WP et al. :Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03, General Session 3, SABCs 2021

Leptomeningeosis carcinomatosa Therapie			
	Oxford		
	LoE	GR	AGO
Intrathekale oder intraventriculäre Therapie			
▪ MTX 10-15 mg 2-3 x/Woche (+/- Folsäure-Rescue) (Red. S3-Leitlinie, Satz unten)	2b	B	+/-
▪ Steroide	4	D	+/-
▪ Trastuzumab (HER2-pos. Fälle)	4	C	+/-
Systemtherapie	3b	B	+
Radiotherapie			
▪ Fokal (bei größerem Tumolvolumen)	4	D	+
▪ WBRT	4	D	+
▪ Neuroachse (disseminierte spinale Herde)	4	D	+/-
Aufgrund der schlechten Prognose einer Leptomeningeosis carcinomatosa sollte auch eine rein symptomatische Therapie erwogen werden.			

1. Brower, J. V., S. Saha, S. A. Rosenberg et al.: Management of leptomeningeal metastases: Prognostic factors and associated outcomes. J Clin Neurosci 2016; 27: 130-137.
2. Boogerd W, van den Bent MJ, Koehler PJ et al.: The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. Eur J Cancer 2004;40:2726-2733.
3. Cardoso F, Costa A, Senkus E et al.: 3rd eso-esmo international consensus guidelines for advanced breast cancer (abc 3). Breast 2017;31:244-259.
4. Cole BF, Glantz MJ, Jaeckle KA et al.: Quality-of-life-adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neoplastic meningitis. Cancer 2003, 97:3053-3060.
5. Chamberlain M, Junck L, Brandsma D et al.: Leptomeningeal metastases: A rano proposal for response criteria. Neuro Oncol 2017;19:484-492.
6. Glantz MJ, Jaeckle KA, Chamberlain MC et al.: A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 1999, 5:3394-3402.
7. Grossman SA, Finkelstein DM, Ruckdeschel JC et al.: Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol 1993, 11:561-569.
8. Jaeckle KA, Phuphanich S, Bent MJ et al.: Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release

formulation of cytarabine. Br J Cancer 2001, 84:157-163.

9. Kak M, Nanda R, Ramsdale EE et al.: Treatment of leptomeningeal carcinomatosis: Current challenges and future opportunities. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2015;22:632-637.
10. Kingston, B., et al., Treatment and prognosis of leptomeningeal disease secondary to metastatic breast cancer: A single-centre experience. Breast, 2017. 36: p. 54-59.
11. Le Rhun E, Weller M, Brandsma D et al.: Eano-esmo clinical practice guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. Ann Oncol 2017;28:iv84-iv99.
12. Le Rhun E, Ruda R, Devos P et al.: Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across europe. J Neurooncol 2017;133:419-427.
13. Le Rhun E, Taillibert S, Zairi F et al.: A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. J Neurooncol 2013, 113:83-92.
14. Le Rhun E, Taillibert S, Devos P et al.: Salvage intracerebrospinal fluid thiotepa in breast cancer-related leptomeningeal metastases: a retrospective case series. Anticancer Drugs 2013, 24:1093-1097.
15. Morikawa, A., L. Jordan, R. Rozner et al.: Characteristics and Outcomes of Patients With Breast Cancer With Leptomeningeal Metastasis. Clin Breast Cancer 2016; Jul 25. pii: S1526-8209(16)30177-X. doi: 10.1016/j.clbc.2016.07.002. [Epub ahead of print]
16. Wang EC, Huang AJ, Huang KE et al.: Leptomeningeal failure in patients with breast cancer receiving stereotactic radiosurgery for brain metastases. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2017.

Trastuzumab intrathecal

1. Lu NT, Raizer J, Gabor EP et al.: Intrathecal trastuzumab: Immunotherapy improves the prognosis of leptomeningeal metastases in her-2+ breast cancer patient. Journal for immunotherapy of cancer 2015;3:41.
2. Stemmler HJ, Schmitt M, Harbeck N et al.: Application of intrathecal trastuzumab (Herceptintrade mark) for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer. Oncol Rep 2006, 15:1373-1377.
3. Zagouri F, Sergeantanis TN, Bartsch R et al.: Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 2013, 139:13-22

MTX high dose

1. Lassman AB, Abrey LE, Shah GD et al.: Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol 2006, 78:255-260.