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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

ZNS-Metastasen beim Mammakarzinom



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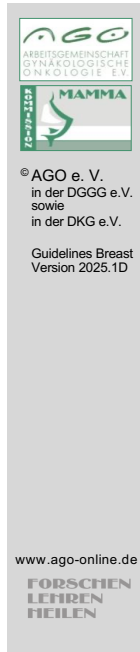
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ZNS-Metastasen beim Mammakarzinom

- **Versionen 2003-2024:**
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- **Version 2025:**
Budach / Würstlein

ZNS-Metastasen beim Mammakarzinom



- **Das Mammakarzinom ist zweithäufigste Ursache von ZNS-Metastasen.**
- **In Kollektiven von Patientinnen mit metastasiertem Mammakarzinom:**
 - Parenchymale ZNS-Metastasen: ~ 30-40 %
 - Leptomeningeale ZNS-Metastasen: 5-16 %
- **Steigende Inzidenz (bis zu 40 %); Biopsie zur Differentialdiagnose empfohlen**
- **Anstieg der Inzidenz verursacht durch:**
 - Effektivere Behandlungsoptionen der extrazerebralen Metastasen
 - Vermehrter Einsatz der MR-Diagnostik
- **Keine Evidenz für Hirnmetastasen-Screening bei asymptomatischen Patientinnen (laufende Studien).**
- **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. 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.
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Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
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

ZNS-Metastasen beim Mammakarzinom – Tumorbiologie und Risikofaktoren

- **Primärtumor / Risikofaktoren**
 - **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)**
 - **Inflammatorisches Mammakarzinom**
 - ***gBRCA* Mutation**
 - **Alter < 40**
 - **Lungenmetastasierung**
 - **Ethnizität**
- **ZNS-Metastasen:**
häufiger Östrogenrezeptor-neg. und HER2 und / oder EGFR positiv
- **Primärtumor und ZNS-Metastasen: Diskordanz des molekularen Subtyps**
 - für ER = 16,7 % und für PR = 25,2 %
 - für HER2 = 10,4 %
- **Es gibt keine Evidenz für einen Überlebensvorteil durch die Suche nach cerebralen Metastasen bei asymptomatischen Patientinnen**

Risk factors (see also references slide CNS incidence)

1. 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.
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Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

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Molekulare Diskordanz Primärtumor – Metastase:

1. 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.
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There is no evidence for BM-screening in asymptomatic BC-patients

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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 = 13 months

Breast-GPA 2.5-3.0 = 24 months

Breast-GPA 3.5-4.0 = 36 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, KPS: Karnofsky Performance Status

Sperduto PW et al, JCO 2020

Breast-GPA

1. 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.
2. 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.
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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. 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:.
5. 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.
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Singuläre Hirnmetastasen und Oligohirnmetastasen*

	Oxford		
	LoE	GR	AGO
Alleinige Lokalthherapie: SRS (< 2-3 cm) oder SRT (> 2-4 cm)	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 SRT der nicht-resezierten Metastasen (ohne WBRT)			
WBRT + Boost (SRS, SRT) oder Resektion + WBRT	2a	B	+/-
Alleinige WBRT	2b	B	+/-
Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand			
Hippocampusschonung**	1b	B	+

* Oligohirnmetastasierung bis zu 4 Hirnmetastasen

** Ausschlusskriterium: Metastasen in der Hippocampus-Region

SRS = stereotactic radiosurgery (einzeitig); SRT = stereotactic radiotherapy (fraktioniert), WBRT = whole brain radiotherapy

1. 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.
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5. 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.
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9. 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.
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11. Kocher M, Soffiatti 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.
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13. 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.
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15. 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
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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

- Local therapy (surgery, SRS, SRT) depends on localization, size, number of metastases, previous therapy, Karnofsky-Performance-Scale, prognosis.
- WBRT in addition to SRS/SRT improves intracranial control, but does not improve duration of functional independence and overall survival.
- WBRT impairs neurocognitive function.
- In case of limited* number of brain metastases, SRS / SRT are preferred.
- Postoperative radiotherapy:

Single/solitary brain metastasis (resection cavity < 5 cm): SRS v. WBRT no difference in overall survival.

Oligo-brain metastases: SRS of surgical cavity and SRS of unresected metastases v. WBRT no difference in overall survival.

* Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases

** Metastases in Hippocampus excluded

SRS = stereotactic radiosurgery (single session), SRT = stereotactic RT (fractionated); WBRT = whole brain radiotherapy

1. 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
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Radiation necrosis (RN) after stereotactic radiotherapy

Incidence and imaging characteristics

- RN should be considered in case of suspected progression of previously irradiated brain metastases as differential diagnosis
- Increase in contrast enhancement on MRI/CT, edema present, typically appearing 6-18 months after RT, progressive course without adequate treatment, correlation with radiotherapy plan is essential
- Additional imaging (i.e. FET-PET,CT/MRI perfusion) may be considered.
- Incidence 5-10% after SRS/SRT, approx. half of the patients are symptomatic

Risk factors

- Increasing diameter of treated metastases, previous irradiation (whole-brain radiotherapy or previous stereotactic radiotherapy to the same lesion), SRS for metastases > 3 cm (prefer SRT), association with concurrent systemic treatment equivocal

Management (in close coordination with treating radiation oncologist, neuro-radiology, and neurosurgery)

- Follow-up with MRI is warranted in asymptomatic cases with uncritical size and location
- In symptomatic patients and/or critical size/location, interdisciplinary management is essential. Options include dexamethasone, bevacizumab (off label), and surgery.

Adapted from Bernhardt et al. Strahlenther Onkol 2022. 198: 971-883.

1. Bernhardt D, König L, Grosu A, et al.: Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guideline for central nervous system radiation necrosis part 1: classification and a multistep approach for diagnosis. Strahlenther Onkol. 2022 Oct;198(10):873-883. doi: 10.1007/s00066-022-01994-3. Epub 2022 Aug 29. PMID: 36038669; PMCID: PMC9515024.
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Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
- Need for immediate decompression, life-threatening symptoms
- Tumor size not allowing stereotactic radiotherapy

Factors in favor of primary radiotherapy*:

- Tumor location poorly amenable to surgery
- More than four lesions
- Comparable local control for SRS/SRT vs. surgery + postoperative RT

* stereotactic radiotherapy should be preferred if possible

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.
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Management bei 5-10 Hirnmetastasen

	Oxford		
	LoE	Gr	AGO
▪ WBRT	1a	A	++
▪ Hippocampusschonung² (bei günstiger Prognose)	1b	B	+
▪ SRS oder SRT sofern Gesamtvolumen < 15 ml (ohne WBRT)	2b	B	+
▪ OP (großer Herde) + Bestrahlung des Tumorbetts und SRS oder SRT der nicht-resezierten Metastasen (ohne WBRT)	3a	C	+
▪ Glukokortikoide allein¹	3a	B	+/-
▪ Systemtherapie als alleinige Primärbehandlung	3a	D	+/-
• bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv) ³	2b	C	+
▪ Radiochemotherapie	3b	C	-

¹ Symptomadaptiert; ²Ausschlusskriterium: Metastasen in der Hippocampus-Region; ³vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen.

SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy (fractionated); WBRT= whole brain radiotherapy

1. 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.
2. 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.
3. 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
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7. Stokes TB, Niranjana 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.

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Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases

1. 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.
2. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329.
3. 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
4. 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.
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7. 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
8. Werter IM, Rimmelzwaal S, Burchell GL, et al. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 ;14(22):5612. doi: 10.3390/cancers14225612. PMID: 36428705; PMCID: PMC9688214.

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

Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford		
	LoE	GR	AGO
▪ WBRT	1a	A	++
▪ Hippocampuschonung² (bei günstiger Prognose)	1b	B	+
▪ Glukokortikoide allein¹	3a	B	+/-
▪ Systemtherapie als alleinige Primärbehandlung	3a	D	+/-
• bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv) ³	2b	C	+
▪ Radiochemotherapie	3b	C	-
▪ Erneute WBRT bei Rezidiv⁴	4	C	+/-

¹Symptomadaptiert; ²Ausschlusskriterium: Metastasen in der Hippocampus-Region; ³vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen; ⁴Falls lokale Therapien (OP, SRS, SRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangenen Bestrahlung, Vorbelastung und Lokalisation

SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy (fractionated); WBRT = whole brain radiotherapy

1. 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.
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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.

Symptomatische Therapie von Hirnmetastasen

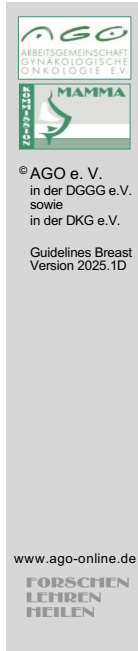
	Oxford		
	LoE	GR	AGO
▪ Antikonvulsiva nur bei Anfallssymptomatik	3a	C	+
▪ Glukokortikoide nur, wenn Symptome und / oder Verdrängungseffekt (Dexamethason mit größter Evidenz)	3a	C	++
▪ Für Pat. mit schlechter Prognose best supportive care, und / oder palliative Versorgung ohne weitere Therapie als Option	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. Soffiatti 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. 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
2. 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
3. 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.
4. Soffiatti 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.



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 SA, Hegg R, Chung WP et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023 Jan 14;401(10371):105-117.
5. Hurvitz SA. A Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients (pts) With HER2-Positive (HER2+) Metastatic Breast Cancer (mBC) With Brain Metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. ESMO 2023

Systemische Therapie von Hirnmetastasen: Allgemeine Grundsätze

	Oxford		
	LoE	GR	AGO
▪ Interdisziplinäre Behandlungsplanung (Tumorboard)	5	D	++
▪ Systemtherapie als alleinige Primärbehandlung	3a	D	+/-
▪ bei asymptomatischen Hirnmetastasen oder asymptomatischem zerebralen Progress (gilt nur bei HER2 positiv)*	2b	C	+
▪ Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation**	2c	C	+

* vorausgesetzt: Schema mit nachgewiesener Aktivität bei aktiven Hirnmetastasen

** vorausgesetzt: Adäquate lokale Therapie der Hirnmetastasen

- 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. doi: 10.1016/j.annonc.2020.09.010. Epub 2020 Sep 23. PMID: 32979513; PMCID: PMC7510449.
- 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.
- Ramakrishna N, Anders CK, Lin NU et al. Management of Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases: ASCO Guideline Update. J Clin Oncol. 2022;40(23):2636-2655. doi: 10.1200/JCO.22.00520.
- Vogelbaum MA, Brown PD, Messersmith H, et al.. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol. 2022 Feb 10;40(5):492-516. doi: 10.1200/JCO.21.02314. Epub 2021 Dec 21. Erratum in: J Clin Oncol. 2022 Apr 20;40(12):1392. PMID: 34932393.
- Borm K et al :DEGRO guideline for personalized radiotherapy of brain metastases and leptomeningeal carcinomatosis in patients with breast cancer. Strahlenther Onkol. 2024 Mar 15;200(4):259–275

Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases

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4. Hurvitz SA, Loi S, O`Shaughnessy et al. HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer. *SABCS 2023*, GS01-10
5. 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.
6. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. *JAMA Oncol*. 2022;;e225610. doi: 10.1001/jamaoncol.2022.5610. Epub ahead of print. PMID: 36454580; PMCID: PMC9716438.
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Systemische Therapie bei Hirnmetastasen: HER2 positiv

	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabin*	1b	B	+
▪ Trastuzumab-Deruxtecan ¹ *	1b	B	+
▪ T-DM1 ^{1**}	2b	B	+/-
▪ Lapatinib + Capecitabin**	2b	B	+/-
▪ Neratinib + Capecitabin**	2b	B	+/-
▪ Neratinib + Paclitaxel**	2b	B	+/-
▪ High-dose Trastuzumab + Pertuzumab**	2b	C	-

* Wirksamkeit bei aktiven und stabilen Hirnmetastasen basierend auf Studieneinschlusskriterien vorhanden

**Wirksamkeit bei stabilen Hirnmetastasen basierend auf Studieneinschlusskriterien vorhanden

¹ Hinweis auf erhöhtes Risiko für Radionekrosen im Falle einer Radiochirurgie / stereotaktischen RT in Kombination mit ADCs

Tucatinib + Trastuzumab + Capecitabin:

1. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329.
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5. Werter IM, Rimmelzwaal S, Burchell GL, et al. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 ;14(22):5612.
6. Yu J et al. Tyrosine kinase inhibitors in HER2-positive breast cancer brain metastases: A systematic review and meta-analysis. Cancer Medicine. 2023;12:15090–15100.

Trastuzumab-Deruxtecan:

1. Bartsch R, Berghoff AS, Furtner J et al. Final outcome analysis from the phase II TUXEDO-1 trial of Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain metastases: *Neur Oncol*. 2024 Dec 5; 26 (12) 2305-2315
2. Cortés J, Kim SB, Chung WP, Im SA et al; DESTINY-Breast03 Trial Investigators. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med*. 2022;386(12):1143-1154.
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5. Werter IM, Rimmelzwaal S, Burchell GL, de Gruijl TD, Konings IR, van der Vliet HJ, Menke-van der Houven van Oordt CW. Systemic Therapy for Patients with HER2-Positive Breast Cancer and Brain Metastases: A Systematic Review and Meta-Analysis. *Cancers (Basel)*. 2022;14(22):5612. doi: 10.3390/cancers14225612. PMID: 36428705; PMCID: PMC9688214.
6. Yamanaka T, Niikura N, Nomura H et al.: Trastuzumab deruxtecan for the treatment of patients with HER2-positive breast cancer with brain and/or leptomeningeal metastases: A multicenter retrospective study (ROSET-BM study) *SABCS 2022*;PD7-01
7. Michelon I et al: Trastuzumab deruxtecan in human epidermal growth factor receptor 2-positive breast cancer brain metastases: a systematic review and meta-analysis. *ESMO open*, 2024, doi.org/10.1016/j.esmoop.2024.102233
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9. Harbeck N et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nature Medicine* | Volume 30 | December 2024 | 3717–3727
10. Bartsch R, Preusser M. Trastuzumab deruxtecan: Defining a novel systemic treatment standard for HER2 positive breast cancer brain metastasis? *Neuro Oncol* 2024 Dec 5; 26 (12): 2157-2148

T-DM1:

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Leptomeningeosis carcinomatosa Therapie

	Oxford		
	LoE	GR	AGO
Intrathekale oder intraventrikuläre Therapie			
▪ MTX 10-15 mg 2-3 x/Woche (+/- Folsäure-Rescue)	2b	B	+/-
▪ Steroide	4	D	+/-
▪ Trastuzumab (HER2-pos.)	3a	C	+/-
Systemtherapie (wie bei cerebraler Metastasierung)	2b	B	+
Best supportive care			
Radiotherapie			
▪ Fokal (bei größerem Tumolvolumen)	4	D	+
▪ WBRT	4	D	+
▪ Neuroachse (disseminierte spinale Herde)	2b	B	+/-

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