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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

ZNS-Metastasen beim Mammakarzinom



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ZNS-Metastasen beim Mammakarzinom

- **Versionen 2003–2018:**
**Bischoff / Diel / Fehm / Friedrich / Gerber / Huober /
Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat /
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 - **Version 2019:**
Solbach/ Witzel
- unter Mitarbeit von:**
Petra Feyer und Dirk Rades (DEGRO)



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ZNS-Metastasen beim Mammakarzinom – Inzidenz

- **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
- **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)**

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ZNS-Metastasen beim Mammakarzinom – Risikofaktoren

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

ZNS-Metastasen sind häufiger Östrogenrezeptor-neg. und überexprimieren häufiger HER2 und / oder EGFR

Keine Evidenz für Hirnmetastasen-Screening 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.
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Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

1. Arvold, N. D., K. S. Oh, A. Niemierko et al. (2012). "Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype." Breast Cancer Res Treat 136(1): 153-160.
2. 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.
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5. Han CH, Brastianos PK: Genetic characterization of brain metastases in the era of targeted therapy. Frontiers in oncology 2017;7:230.
6. 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.
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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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Graded Prognostic Assessment (GPA)

Arbeitsblatt zur Abschätzung des Mortalitätsrisikos bei Hirnmetastasen (BM)

Prognostic Factor	0	0.5	1	1.5	2	Score
KPS	< 50	60	70–80	90–100	n/a	—
Subtype	Basal	n/a	LumA	HER2	LumB	—
Age, years	> 60	< 60	n/a	n/a	n/a	—
Sum total						—

Median survival by GPA:
GPA 0–1.0 = 3.4 months
GPA 1.5–2.0 = 7.7 months
GPA 2.5–3.0 = 15.1 months
GPA 3.5–4.0 = 25.3 months

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases;
 ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

Sperduto PW, J Clin Oncol 2012, 30:419-425


Breast-GPA

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2. 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
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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.
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Rades Score* – zur Abschätzung des Mortalitätsrisikos bei Hirnmetastasen (BM)

Prognostic Factor	Überleben nach 6 Monaten (%)	Score
Alter ≤ 60 Jahre ≥ 61 Jahre	43	4
	25	3
Karnofsky-Index < 70 ≥ 70	8	1
	53	5
Extrakranielle Metastasen Nein Ja	51	5
	24	2
Intervall von Erstdiagnose bis WBRT ≤ 8 Monate > 8 Monate	32	3
	36	4

Median survival by Rades-Score:
Rades-Score 9–10 = 2 months
Rades-Score 11–13 = 3 months
Rades-Score 14–16 = 5 months
Rades-Score 17–18 = 12 months

* Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed, validated in 350 new patients

Rades et al., ST0 2008
Dziggel et al., ST0 2013

1. Rades D, Dziggel L, Segedin B et al.: A simple survival score for patients with brain metastases from breast cancer. Strahlenther Onkol. 2013;189:664-7.
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Singuläre / solitäre Hirnmetastase

	Oxford		
	LoE	GR	AGO
Alleinige Lokalthherapie: SRS (≤ 4cm) oder FSRT oder Resektion	2b	B	++
Resektion + Bestrahlung des Tumorbetts (ohne WBRT)	1b	B	++
WBRT + Boost (SRS, FSRT) oder Resektion + WBRT	2a	B	+
Alleinige WBRT*	2b	B	+
Hippocampusschonung	2b	C	+/-
<ul style="list-style-type: none"> ▪ SRS/FSRT o. Resektion + WBRT verbessert lokale Kontrolle und Symptomkontrolle, nicht das Überleben. WBRT führt zu größerer neurokognitiver Beeinträchtigung ▪ Bei neurochirurgischer Resektion Nachbestrahlung des Tumorbetts (alleinige lokale RT oder Boost bei WBRT) empfohlen. Resektion ohne Vorteil gegenüber einer Strahlentherapie. Entscheidungsfindung siehe Dia 11 			
SRS = stereotactic radiosurgery (einzeitig)			
FSRT = fractionated stereotactic radiotherapy			
WBRT = whole brain radiotherapy			

* Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand

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- 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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Oligo-Hirnmetastasen

Oxford		
LoE	GR	AGO
2b	B	++
2a	B	++
2b	B	+
2b	C	+/-

Alleinige Lokalthherapie: SRS (≤ 4 cm) oder FSRT

WBRT + Boost (SRS, FSRT)

Alleinige WBRT*

Hippocampusschonung



- Die Zahl der stereotaktisch sinnvoll zu bestrahlenden Metastasen ist von Lokalisation, Größe und anderen Faktoren abhängig
- WBRT zusätzlich zu SRS/FSRT verbessert die lokale Kontrolle und Symptomkontrolle, nicht aber das Überleben. Gleichzeitig scheint bei zusätzlicher WBRT eine größere neurokognitive Beeinträchtigung aufzutreten
- Bei einer limitierten Anzahl von Hirnmetastasen Präferenz zur stereotaktischen Bestrahlung

SRS = stereotactic radiosurgery (einzeitig)
 FSRT = fractionated stereotactic radiotherapy
 WBRT = whole brain radiotherapy


* Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand

1. Brown A, Asher AL, Ballman K et al.: A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839Soon YY1,
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- 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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1. Brown A, Asher AL, Ballman K et al.: A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839.



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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, Soffiotti 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, Costa A, Senkus E et al.: 3rd eso-esmo international consensus guidelines for advanced breast cancer (abc 3). Breast 2017;31:244-259.
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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Guidelines Breast
Version 2019.1D

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FORSCHEN
LEHREN
HEILEN

Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportiv Steroide)	1a	A	++
▪ Hippocampusschonung	2b	C	+/-
▪ Corticosteroide allein*	3a	B	+/-
▪ Chemotherapie allein	3a	D	+/-
▪ Radiochemotherapie zur Kontrolle intrazerebral	3b	C	-
▪ Erneute WBRT bei Rezidiv**	4	C	+/-

SRS = stereotactic radiosurgery (einzeitig)
FSRT = fractionated stereotactic radiotherapy
WBRT = whole brain radiotherapy

* Symptomadapiert
 ** Falls lokale Therapien (OP, SRS, FSRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangenen Bestrahlung, Vorbelastung und Lokalisation

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Radiochemotherapy

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Re-Bestrahlung bei Rezidiv

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	Oxford		
	LoE	GR	AGO
 <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</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2>Systemische und symptomatische Therapie von Hirnmetastasen*</h2>		
■ Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation	2c	C	+
■ Lapatinib + Capecitabin als initiale Behandlung (HER2 pos. Fälle)	2b	B	+/-
■ Chemotherapie als alleinige Primärbehandlung	3	D	-
■ Antikonvulsiva nur bei Anfallssymptomatik	3	C	+
■ Glucocorticoide nur wenn Symptome und / oder Verdrängungseffekt	3	C	++
* zusätzlich zu lokalen Maßnahmen			

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Systemic therapy for patients with brain metastases

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Anticonvulsants

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Steroids

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FORSCHEN
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Leptomeningeosis carcinomatosa

Therapie

Intrathekale oder intraventrikuläre Therapie

- MTX 10-15 mg 2-3x/ Woche (+/- Folsäure-Rescue)
- Liposomales Cytarabin 50 mg, q 2w*
- Thiothepa
- Steroide
- Trastuzumab (HER2-pos. Fälle)

Systemtherapie

Radiotherapie

- Fokal (bei größerem Tumolvolumen)
- WBRT
- Neuroachse (disseminierte spinale Herde)

Aufgrund der schlechten Prognose einer Leptomeningeosis carcinomatosa sollte auch eine rein symptomatische Therapie erwogen werden

* Bis auf Weiteres nicht erhältlich

Oxford		
LoE	GR	AGO
Intrathekale oder intraventrikuläre Therapie		
2b	B	+
3b	C	+
3b	C	+/-
4	D	+/-
4	C	+/-
3b	B	+
Systemtherapie		
4	D	+
4	D	+
4	D	+/-

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Trastuzumab intrathecal

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MTX high dose

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