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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](http://www.gbg.de))**

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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%

### Risk factors (see also references slide CNS incidence)

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


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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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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 Jan 23. pii: noaa013. doi: 10.1093/neuonc/noaa013. [Epub ahead of print]

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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## Diagnosis-specific Graded Prognostic Assessment (DS-GPA) Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

	0	0.5	1	1.5	2	Score
<b>Prognostic Factor</b>						
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 DS-GPA:**  
**DS-GPA 0–1.0 = 3.4 months**  
**DS-GPA 1.5–2.0 = 7.7 months**  
**DS-GPA 2.5–3.0 = 15.1 months**  
**DS-GPA 3.5–4.0 = 25.3 months**  
**DS-GPA confirmed as prognostic factor**

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive.

Sperduto PW et al, JCO 2012; Nagtegaal SHJ et al, Radiother Oncol 2019

### 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, 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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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.
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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.



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## WBRT-30-BC – zur Abschätzung des Risikos von Hirnmetastasen

- Based on 170 patients
- WBRT: whole brain radiotherapy alone  
(30 Gy in 30 sessions)

Characteristic	6-month OS rate (%)	Scoring points
<b>Karnofsky performance score</b>		
<70%	8	1
70%	32	3
>70%	72	7
<b>Time between 1.diagnosis of breast cancer and WBRT</b>		
≤33 months	29	3
≥34 months	38	4
<b>Extra-cerebral metastatic disease</b>		
No	53	5
Yes	28	3


Prognostic group	OS at 6 months (%)
6-9 points	8
10-12 points	41
13-15 points	68
16 points	100

Regarding the PPV to identify patients who will live 6 months or longer after WBRT, the WBRT-30-BC (100%) was superior to both DS-GPA (74%) and Rades-Score (68%). Janssen S et al, Radiol Oncol, 2019

Janssen S, Hansen HC, Dziggel L, Schild SE, Rades D. A new instrument for predicting survival of patients with cerebral metastases from breast cancer developed in a homogeneously treated cohort. Radiol Oncol. 2019 May 8;53(2):219-224. doi: 10.2478/raon-2019-0020.

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<b>Alleinige Lokalthherapie: SRS (<math>\leq</math> 4cm) oder FSRT oder Resektion</b>	<b>2b</b>	<b>B</b>	<b>++</b>
<b>Resektion + Bestrahlung des Tumorbetts (ohne WBRT)</b>	<b>1b</b>	<b>B</b>	<b>++</b>
<b>WBRT + Boost (SRS, FSRT) oder Resektion + WBRT</b>	<b>2a</b>	<b>B</b>	<b>+</b>
<b>Alleinige WBRT</b>	<b>2b</b>	<b>B</b>	<b>+</b>
<b>Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand</b>			
<b>Hippocampusschonung</b>	<b>2b</b>	<b>C</b>	<b>+/-</b>
<ul style="list-style-type: none"> <li>▪ SRS/FSRT o. Resektion + WBRT verbessert lokale und Symptomkontrolle, nicht das Überleben. WBRT führt zu größerer neurokognitiver Beeinträchtigung</li> </ul>			

[SRS = stereotactic radiosurgery (einzeitig); FSRT = fractionated stereotactic radiotherapy, WBRT = whole brain radiotherapy]



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## Singuläre / solitäre Hirnmetastase

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2. 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.
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.
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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.
8. 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.
  9. 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.
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  18. de Almeida Bastos DC, Maldaun MVC, Sawaya R, et al.: Histopathological subtypes and survival outcomes in breast cancer patients with brain metastases in the targeted therapy era. *Neuro-Oncology Practice* 5(3), 161–169, 2018

	Oxford		
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Alleinige Lokalthherapie: SRS (≤ 4 cm) oder FSRT	2b	B	++
WBRT + Boost (SRS, FSRT)	2a	B	++
Alleinige WBRT	2b	B	+
Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand			
Hippocampusschonung	2b	C	+/-
<ul style="list-style-type: none"> <li>Die Zahl der stereotaktisch sinnvoll zu bestrahlenden Metastasen ist von Lokalisation, Größe und anderen Faktoren, z.B. Anzahl, Vorbehandlung und Karnovsky Score abhängig</li> <li>WBRT zusätzlich zu SRS/FSRT verbessert die lokale und Symptomkontrolle, nicht aber das Überleben. Gleichzeitig scheint bei zusätzlicher WBRT eine größere neurokognitive Beeinträchtigung aufzutreten</li> <li>Bei einer limitierten Anzahl von Hirnmetastasen Präferenz zur stereotaktischen Bestrahlung</li> </ul>			
[SRS = stereotactic radiosurgery (einzeitig); FSRT = fractionated stereotactic radiotherapy, WBRT = whole brain radiotherapy]			




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	<h2 style="text-align: center;">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>© AGO e. V. in der DGGG e. V. sowie in der DKG e. V.</p> <p>Guidelines Breast Version 2020 1D</p>	<p><b>Study design:</b> Patients with 1-3 brain metastases, each &lt; 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 &gt; 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><b>Conclusion:</b> 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>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<p>* Remark: No hippocampus-sparing was applied</p> <p>Brown A, Asher AL, Ballman K, Farace E, Cerhan J, Anderson K, et al. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839</p>

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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.

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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\*:**

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

\* Falls möglich stereotaktische Strahlentherapie bevorzugt

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## Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

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

\* Symptomadaptiert  
\*\* Falls lokale Therapien (OP, SRS, FSRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangenen Bestrahlung, Vorbelastung und Lokalisation  
[WBRT = whole brain radiotherapy]

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Beibehalten des aktuellen Therapieschemas bei Erstdiagnose zerebraler Metastase und bei extrazerebral stabiler Erkrankungssituation</li> </ul>	2c	C	+
<ul style="list-style-type: none"> <li>Lapatinib + Capecitabin als initiale Behandlung (HER2 pos. Fälle)</li> </ul>	2b	B	+/-
<ul style="list-style-type: none"> <li>Chemotherapie als alleinige Primärbehandlung</li> </ul>	3a	D	-
<ul style="list-style-type: none"> <li>Antikonvulsiva nur bei Anfallssymptomatik</li> </ul>	3a	C	+
<ul style="list-style-type: none"> <li>Glucocorticoide nur wenn Symptome und / oder Verdrängungseffekt (Dexamethason mit größter Evidenz)</li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>Für Pat. mit schlechter Prognose best supportive care, und/ oder palliative Versorgung ohne weitere Therapie als Option</li> </ul>	5	D	+



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<b>Leptomeningeosis carcinomatosa</b>			
<b>Therapie</b>			
	<b>Oxford</b>		
	<b>LoE</b>	<b>GR</b>	<b>AGO</b>
<b>Intrathekale oder intraventrikuläre Therapie</b>			
▪ MTX 10-15 mg 2-3x/ Woche (+/- Folsäure-Rescue)	2b	B	+
▪ Liposomales Cytarabin 50 mg, q 2w*	3b	C	+
▪ Thiohepa	3b	C	+/-
▪ Steroide	4	D	+/-
▪ Trastuzumab (HER2-pos. Fälle)	4	C	+/-
<b>Systemtherapie</b>			
	<b>3b</b>	<b>B</b>	<b>+</b>
<b>Radiotherapie</b>			
▪ 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			
* Bis auf Weiteres nicht erhältlich			



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