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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

CNS Metastases in Breast Cancer

CNS Metastases in Breast Cancer

- **Versions 2003–2019:**
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CNS Metastases in Breast Cancer

- **Breast cancer is the 2nd most common cause of CNS metastases**
- **At autopsy:**
 - Parenchymal CNS metastases: ~ 30–40%
 - Leptomeningeal CNS metastases: ~ 5–16%
- **Increasing incidence (10 % ⇔ 40 %)**
- **Increasing incidence due to**
 - More effective treatment of extra-cerebral sites with improved prognosis
 - Increasing use of MRI for diagnostic evaluation
- **Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de)**

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CNS Metastases in Breast Cancer

Tumour biology

- **Primary Tumor:**
 - Negative hormonereceptor status (basal-like cell type / triple-negative)
 - High grade, high Ki-67 index
 - HER2 and/or EGFR (HER1) overexpression
 - Molecular subtype (Luminal B, HER2 positive, triple-negative)
- **Brain metastases are more likely estrogen receptor negative and overexpress HER2 and/or EGFR**
- **Discordance of molecular subtype between primary tumor and brain metastases: for ER= 16,7%, for PR = 25,2% and Her2 neu = 10,4%**
- **There is no evidence for BM-screening in asymptomatic BC-patients**

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


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Molekulare Diskordanz Primärtumor – Metastase:

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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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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
Prognostic Factor						
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:

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.
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Prognostic Factors for Survival

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

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


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%).

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

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

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.


	<h1>Single / Solitary Brain Metastasis</h1>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p>	Local therapy alone: SRS (≤ 4 cm) o. FSRT or resection		
Resection + irradiation of the tumor bed (without WBRT)			
WBRT + Boost (SRS, FSRT) or resection + WBRT			
WBRT alone Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing			
<ul style="list-style-type: none"> WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms, but has no survival benefit. WBRT impairs neurocognitive function. 			
<p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>			
<p>SRS = stereotactic radiosurgery (single session), FSRT = fractionated stereotactic RT; WBRT = whole brain radiotherapy,</p>			

Oxford		
LoE	GR	AGO
2b	B	++
1b	B	++
2a	B	+
2b	B	+
2b	C	+/-


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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-Brain Metastases

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (≤ 4 cm) or FSRT	2b	B	++
WBRT + Boost (SRS, FSRT)	2a	B	++
WBRT alone			
Patients with reduced general condition and limited life expectancy	2b	B	+
Hippocampal-sparing	2b	C	+/-
<ul style="list-style-type: none"> Maximal number of metastases treated by SRS depends on localization, size, and additional factors e.g. number of metastases, pre-treatment, Karnofsky.Index WBRT in addition to SRS/FSRT improves local control and symptoms, but has no survival benefit. Additional WBRT seems to impair neurocognitive function In case of limited number of brain metastases, SRS/FSRT are preferred 			

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


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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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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

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.
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Multiple Brain Metastases

if Stereotactic Radiotherapy is not indicated

- **WBRT (supportive steroids*)**
- **Hippocampal-sparing radiotherapy**
- **Corticosteroids alone***
- **Radiochemotherapy for intracerebral control**
- **WBRT in case of recurrence****

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

* adapted to symptoms
** can be discussed depending on time-interval from first radiation, prior dose, and localization if local therapy (surgery, SRS, FSRT) is not indicated and / or possible
WBRT = whole brain radiotherapy

	Oxford		
	LoE	GR	AGO
1a	A	++	
2b	C	+/-	
3a	B	+/-	
3b	C	-	
4	C	+/-	

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	Oxford		
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<div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de FORSCHEN LEHREN HEILEN</p> </div>	<h2>Systemic and Symptomatic Therapy of Brain Metastases*</h2>		
<ul style="list-style-type: none"> Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease Lapatinib + Capecitabine as initial treatment (HER2 pos. disease) Chemotherapy alone as primary treatment Anticonvulsants only if symptoms of seizures Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence) For patients with bad prognosis and reduced physical common conditions best supportive care is an option 	<p>2c</p> <p>2b</p> <p>3a</p> <p>3a</p> <p>3a</p> <p>5</p>	<p>C</p> <p>B</p> <p>D</p> <p>C</p> <p>C</p> <p>D</p>	<p>+</p> <p>+/-</p> <p>-</p> <p>+</p> <p>++</p> <p>+</p>

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Leptomeningeal Carcinomatosis: Local Therapy		
	Oxford		
	LoE	GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)	2b	B	+
▪ Liposomal cytarabine 50 mg, q 2w*	3b	C	+
▪ Thiothepa	3b	C	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	4	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis (disseminated spinal lesions)	4	D	+/-
Due to poor prognosis, consider best supportive care, especially in patients with poor performance status			
* Currently not available			

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