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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 2003–2018:**
**Bischoff / Diel / Fehm / Friedrich / Gerber /
Huober / Loibl / Lück / Maass / Müller / Nitz /
Jackisch / Jonat / Junkermann / Rody / Schütz /
Stickeler / Witzel**
- **Version 2019:**
Solbach / Witzel
in cooperation with:
Petra Feyer and Dirk Rades (DEGRO)



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CNS Metastases in Breast Cancer – Incidence

- **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 extracerebral sites with improved prognosis**
 - **Increasing use of MRI in 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 (BC)

Risk Factors

■ **Primary Tumor:**

- Negative estrogen receptor status (basal-like cell type / triple-negative)
- High grading, high Ki-67 index
- HER2 and/or EGFR (HER1) overexpression
- Molecular subtype (Luminal B, HER2 positive, triple-negative)

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

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

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Graded Prognostic Assessment (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:
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

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

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.


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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Rades Score* - Worksheet to Estimate Survival from Brain Metastases (BM) by plus chemotherapy Diagnosis


Prognostic Factor	6-months survival rate(%)	Score
age ≤ 60 Jahre ≥ 61 Jahre	43	4
	25	3
Karnofsky-Index < 70 ≥ 70	8	1
	53	5
Extracranial metastases no yes	51	5
	24	2
Interval from first diagnosis to WBRT ≤ 8 months > 8 months	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., STO 2008
Dziggel et al., STO 2013

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2. Rades, D., L. Dziggel, S. Janssen et al. (2016). "A Survival Score for Patients Receiving Stereotactic Radiosurgery Alone for Brain Metastases from Breast Cancer." Anticancer Res 36(3): 1073-1076



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Single / Solitary Brain Metastasis

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (≤ 4 cm) o. FSRT or Resection	2b	B	++
Resection + Irradiation of the tumor bed (without WBRT)	1b	B	++
WBRT + Boost (SRS, FSRT) or Resection + WBRT	2a	B	+
WBRT alone*	2b	B	+
Hippocampal-sparing	2b	C	+/-


- WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms, but has no survival benefit. WBRT impairs neurocognitive function.
- In case of resection of the tumor the tumor bed has to be irradiated (either local RT or boost in case of WBRT). In general there is no advantage of surgical resection over RT.

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

* Patients with reduced general conditions and limited life expectancy

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Oligo-Brain Metastases

	Oxford	
	LoE	GR
Local therapy alone: SRS (≤ 4 cm) or FSRT	2b	B
WBRT + Boost (SRS, FSRT)	2a	B
WBRT alone *	2b	B
Hippocampal-sparing	2b	C

WBRT alone *

Hippocampal-sparing


- Maximal number of metastases treated by SRS depends on localization, size and additional factors
- 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 preferred

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

* Patients with reduced general conditions and limited life expectancy

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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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.
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 Brain Metastases if Stereotactic Radiotherapy is not Indicated

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

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

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

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

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Re-Bestrahlung bei Rezidiv

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Systemic and Symptomatic Therapy of Brain Metastases*			
	Oxford		
	LoE	GR	AGO
■ Continuation of the actual systemic therapy if first diagnosis of brain metastases and stable extracranial disease	2c	C	+
■ Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)	2b	B	+/-
■ Chemotherapy alone as primary treatment	3	D	-
■ Anticonvulsants only if symptoms of seizures	3	C	+
■ Glucocorticoids only when symptoms and / or mass effect	3	C	++

* In addition to local therapy



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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Leptomeningeal Carcinomatosis Local Therapy		
<p>Intrathecal or ventricular therapy</p> <ul style="list-style-type: none"> ▪ MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue) ▪ Liposomal cytarabine 50 mg, q 2w* ▪ Thiothepa ▪ Steroids ▪ Trastuzumab (HER2 pos. disease) <p>Systemic Therapy</p> <p>Radiotherapy</p> <ul style="list-style-type: none"> ▪ Focal (bulky disease) ▪ WBRT ▪ Neuroaxis (disseminated spinal lesions) <p>Due to poor prognosis consider best supportive care, especially in patients with poor performance status</p> <p>* Currently not available</p>	Oxford		
	LoE	GR	AGO
	2b	B	+
	3b	C	+
	3b	C	+/-
	4	D	+/-
	4	C	+/-
	3b	B	+
	4	D	+
	4	D	+
	4	D	+/-

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