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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

- **Versions 2003-2023:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Krug / Loibl / Lück / Lüftner / Maass / Müller / Nitz / Park-Simon / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2024:**

  Maass / Witzel

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CNS Metastases in Breast Cancer

- **Breast cancer is the 2nd most common cause of CNS metastases.**
- **In metastatic breast cancer patients:**
  - **Parenchymal CNS metastases: ~ 30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (up to 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).**

Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

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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

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CNS Metastases in Breast Cancer
Tumour biology

- **Primary Tumor:**
  - **Negative hormone receptor 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)**
  - **Inflammatory breast cancer**
- **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 = 10.4%**
- **There is no evidence for a survival benefit of BM-screening in asymptomatic BC-patients.**

Updated Breast-GPA (Graded Prognostic Assessment) Worksheet to Estimate Survival from Brain Metastases (BM)

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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 positive, HER2 positive ECM: extracranial metastases BM: brain metastases

Sperduto PW et al. JCO 2020

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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (< 2-3 cm) oder SRT (>2-4 cm)	1b	B	++
Single / Solitary Metastasis:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed (without WBRT)			
Oligo-Brain Metastases:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed and SRS or SRT of unresected metastases (without WBRT)			
WBRT + Boost (SRS, SRT) or resection + WBRT	2a	B	+
WBRT alone	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing (if prognosis is favourable)**	1b	B	+

*** 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

Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

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- **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

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)

- **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.

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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**

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Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportive steroids[1])	1a	A	++
▪ Hippocampal-sparing radiotherapy[2] (if prognosis is favourable)	1b	B	+
▪ Corticosteroids alone[1]	3a	B	+/-
▪ Systemic therapy alone	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2 breast cancer)[3]	2b	C	+
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence[4]	4	C	+/-

[1]adapted to symptoms; [2]metastases in hippocampus excluded; [3]only if regimens with proven clinical activity in active brain metastases are used; [4]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

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

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Symptomatic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Anticonvulsants only if symptoms of seizures	3a	C	+
▪ Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence)	3a	C	++
▪ For patients with bad prognosis and reduced physical common conditions best supportive care is an option	5	D	+

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Clinical Classification of Brain Metastases

Stable brain metastases (definition: RECIST / RANO):
stabilization after treatment of brain metastases.

Stable brain metastases (definition: DESTINY-BREAST03):
stable brain metastases ≥ 2 weeks after whole brain radiotherapy, asymptomatic, no requirement of corticosteroid or anticonvulsant therapy

Active brain metastases (definition: HER2Climb):
locally pretreated brain metastases with progressive disease or newly diagnosed brain metastases not needing immediate local therapy
or
untreated brain metastases not needing immediate local therapy

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Systemic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Interdisciplinary treatment planning (tumor board)	5	D	++
▪ Systemic therapy alone as primary treatment	3a	D	+/-
▪ For newly diagnosed or progressive asymptomatic brain metastases (only for HER2-positive breast cancer)*	2b	C	+
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease**	2c	C	+

*only if regimens with proven clinical activity in active brain metastases are used
** only in case of adequate local treatment of brain metastases

Systemic Therapy of Brain Metastases: HER2 positive

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

* efficacy demonstrated in active and stable brain metastases based on trial inclusion criteria

** efficacy demonstrated in stable asymptomatic brain metastases based on trial inclusion criteria

Clinical trials including HER2 positive patients with brain metastases

Trial	Phase	N**	Brain metastases	Combination	IC-ORR
HER2Climb[1,2*]	II	291	Stable + active	Tucatinib+Trastuzumab+ Capecitabine	47%
HER2Climb02[3]	III	204	Stable + active	Tucatinib + T-DM1	42%
DESTINY-B03[4]	III	36	Stable	Trastuzumab-Deruxtecan	64%
TUXEDO-1[5]	II	15	Active	Trastuzumab-Deruxtecan	73%
DEBBRAH[6]	II	21	Stable + active	Trastuzumab-Deruxtecan	46.2% (active) 66.7% (all patients)
KAMILLA[7]	III	398	Stable	T-DM1	21%
LANDSCAPE[8]	II	45	Active	Lapatinib + Capecitabin	66%
NALA[9]	III	161	Stable	Neratinib + Capecitabine	23%
TBCRC-022[10]	II	49	Active	Neratinib + Capecitabine	49% (Lapatinib-naive) 33% (prior Lapatinib)
PATRICIA[11]	II	39	Active	Pertuzumab + high dose Trastuzumab	11%
NEfERT-T[12]	II	29	Asymptomatic	Paclitaxel + Neratinib	Not reported; CNS incidence⇩

**reference list*

Adapted from O'Brian B et al. SABCS 2022

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Leptomeningeal Carcinomatosis: Therapy

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	Oxford		
	LoE	GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3 x/ week (+/- folinic acid rescue)	2b	B	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	3a	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis Craniospinal irradiation (disseminated spinal lesions)	2b	B	+/-

Intrathecal administration of Trastuzumab

	Kumthekar PU et al.[1]	**Oberkampf F et al.[2]**
Type of study	Multicenter, Phase Ib/II	Multicenter, Phase Ib/II
N	34	19
Trastuzumab delivery	80 mg intrathecally twice weekly	150 mg intrathecally weekly
CBR	69.2% (PR: 19.2%, SD 50%)	
Median PFS	-	5.9 months
Median OS	8.3 months	7.9 months

[1]Kumthekar PU et al. Neuro Oncol. 2022, [2]Oberkampf F et al. Neuro Oncol. 2022