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CNS Metastases in Breast Cancer

CNS Metastases in Breast Cancer

- **Versions 2003-2022:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Loibl / Lück / Lüftner / Maass / Müller / Nitz / Park-Simon / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2023:**
  Fehm / Krug

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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).**

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 = 10 months
Breast-GPA 2.5–3.0 = 13 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR negative, 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 (≤ 4 cm) o. SRT	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

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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

Study design:

Patients with 1-3 brain metastases, each < 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 > 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.*

Conclusion:

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.

* **Remark: No hippocampus-sparing was applied**

Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.

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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

Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer - PATRICIA trial (Phase II) *NCT02536339* -

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N=39 patients with HER2 positive MBC

- with CNS metastases and CNS progression despite prior RT
- stable extracranial disease

Treatment:

Pertuzumab (840 mg loading dose, 420 mg every 3 weeks thereafter)

Trastuzumab (6mg/kg weekly)

Treatment until CNS or systemic progression or unacceptable toxicities

Results:

CNS ORR: 11% with 4 partial remissions

CBR at 4 mths: 68%; CBR at 6 mths: 51%

2 pts with stable disease > 2 years

Conclusion:

High-dose trastuzumab for HER2-positive CNS metastases may warrant further study.

Clinical trials including HER2 positive patients with brain metastases

Trial	Phase	N**	Brain metastases	Combination	IC-ORR
HER2Climb[1*]	II	291	Stable + active	Tucatinib+Trastuzumab+ Capecitabine	47%
DESTINY 03[2]	III	36	Stable	Trastuzumab-Deruxtecan	64%
TUXEDO-1[3]	II	15	Active	Trastuzumab-Deruxtecan	73%
KAMILLA[4]	III	398	Stable	T-DM1	21%
LANDSCAPE[5]	II	45	Active	Lapatinib + Capecitabin	66%
NALA[6]	III	161	Stable	Neratinib + Capecitabine	23%
TBCRC-022[7]	II	49	Active	Neratinib + Capecitabine	49% (Lapatinib-naive) 33% (prior Lapatinib)
PATRICIA[8]	II	39	Active	Pertuzumab + high dose Trastuzumab	11%
NEfERT-T[9]	II	29	Asymptomatic	Paclitaxel + Neratinib	Not reported; CNS incidence⇩

*reference list

Adapted from O'Brian B et al. SABCS 2022

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

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	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