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CNS Metastases in Breast Cancer

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- **Versions 2003–2020:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2021:**
  Rody / Huober

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 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)**
- **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**

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

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	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

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**

- **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

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

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 Patients with reduced general condition and limited life expectancy	2b	B	+
Hippocampal-sparing	2b	B	+/-

- **WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms but has no survival benefit. WBRT impairs neurocognitive function.**

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

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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	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing	2b	C	+/-

- 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,

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

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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 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

Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

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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

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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**

*** 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*)	1a	A	++
▪ Hippocampal-sparing radiotherapy	2b	C	+/-
▪ Corticosteroids alone*	3a	B	+/-
▪ Chemotherapy alone	3a	D	+/-
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence**	4	C	+/-

* 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

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

Symptomatic Therapy of Brain Metastases

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	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	+

Systemic Therapy of Brain Metastases

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	Oxford LoE	GR	AGO
▪ Chemotherapy alone as primary treatment	3a	D	-
▪ HER2 pos.			
▪ Tucatinib + Trastuzumab + Capecitabine (after ≥ 2 anti-HER2-therapies)	2b	B	+
▪ T-DM1	2b	B	+/-
▪ Lapatinib + Capecitabine	2b	B	+/-
▪ Neratinib + Capecitabine	2b	B	+/-
▪ Neratinib + Paclitaxel	2b	B	+/-
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease	2c	C	+

CNS-efficacy of systemic anti-HER2 therapy

Study		Study type	Therapy	Efficacy endpoint
HER2Climb[1, 2] Lin[1] et al. Murthy[2] et al	N=612 With brain met n=291	▪ Prospective, randomized (2:1) ▪ Basline brain MRI ▪ BM (n=291) classified as active or stable	**Tuca + T + Cap** (n=198)vs. **Plac + T + Cap** (n=93) **Inclusion:** prior therapy with T-DM1, Per, T	**Tucatinib vs Placeco:** ▪ Median CNS-PFS: 9.9 vs 4.2 mo (HR=0.32, 95% CI 0.22-0.48, p<0.001) ▪ Median OS: 18.1 vs 12.0 mo (HR=0.58, 95 % CI 0.40-0.85, p=0.005) ▪ ORR-IC: 47.3 % (95 % CI 33.7-61.2 %) vs 20.0 % (95% CI 5.7-43.7 %), p=0.03
EMILIA[3] Krop et al	N=991 with brain met n=95	▪ Retrospective, exploratory, not prespecified ▪ Pre study screening (MRI, CT) ▪ study enrollment possibel if CNS-mets were asymptomatic	**T-DM1 versus L + Cap** **Inclusion:** PD after T , Pac No prior T-DM1, L, Cap	**T-DM1 vs L + Cap:** ▪ Median PFS: 5.9 vs. 5.7 mo (HR=1.00; 95% CI 0.54-1.84, p=1.000) ▪ Median time-to symptom-progression: 7.2 vs. 5.5 mo (HR=0.70, 95% CI 0.33-1.48, p=0.338) ▪ Median OS: 26.8 vs. 12.9 mo (HR=0.38, 95% CI 0.18-0.80, p=0.008)
KAMILLA[4] Montemurro et al.	N=2002 N=398 with baseline brain met	▪ Phase IIIb, single arm ▪ Exploratory analysis	**T-DM1** **Inclusion:** Locally advanced/mbc In pts with BM: Prior Anti-HER2-therapy (L,60% T 99%, Per 6%), and cht 99%; prior RT BM 57%) 1line up to > 5line	**T-DM1** • N=126 with measurable BM at baseline • CNS-ORR 21.4 % (95% CI 14.6-29.6) • CBR 42.9 % (95% CI 34.1-52.0) • Median PFS w or w/o BM: 5.5 (95% CI 5.3-5.6)vs. 7.7 mo (95% CI 6.8-8.1) • Median OS w or w/o BM: 18.9 (95% CI 17.1-21.3 vs. 30.0 mo (95% CI 27.6-31.2)
NALA[5] Saura et al	N=621, With brain met N=101	▪ Prospective, randomized (1:1) ▪ enrollment if CNS-mets were stable and asymptomatic ▪ Sec. Endpoint: incidence of CNS intervention	**N +Cap vs L + Cap** **Inclusion**: ≥ 2 anti-HER2 therapies, 33% had prior Tra,Per, T-DM1	**N+Cap vs L+Cap:** Cumulative incidence of CNS intervention : 22.8 % (95% CI 15.5-30.9 %). 29.2 % (95% CI 22.5+36.1 %), p=0.043
NEfERT-T[6] Awada et al.	N= 479	• Exploratory not preplanned subgroup analysis of randomized controlled trial	**N+Pac (n=242) vs T + Pac (n=237)** **Inclusion:** untreated metastatic or recurrent HER2+ BC, L/T as adjuvant/neoadjuvant therapy allowed	**N+Pac vs T + Pac** ▪ Incidence of CNS recurrences: RR 0.48, 95% CI 0.29-0.79, p=0.002 ▪ Time to CNS metastases: HR 0.45, 95% CI 0.26-0.78, p=0.004 ▪ 2 years cumulative CNS incidence: N-Pac 10.1%; T-Pac 20.2%
DESTINY-Breast01[7] Modi et al.	N= 184 With brain met n=24	▪ Prospective, single arm, open label ▪ study enrollment possibel if CNS-mets were stable and asymptomatic (n=24)	**Trastuzumab-Deruxtecan** **Inclusion**: prior therapy with T-DM1, 66% had Per, 100% Tra, 54% other anti-HER2	• **Trastuzumab-Deruxtecan**: • Median CNS-PFS: 18.1 mo (95% CI 6.7-18.1) (all patients 16.4 mo, 95% CI 12.7-n.r.)
Landscape[8] Bachelot et al.	N=45 Untreated brain metastases	Single-arm, phase II	**L + Cap**	**L+Cap** Objective CNS response: 65.9 % (95% CI 50.1-79.5)

(T=Trastuzumab, Tuca=Tucatinib, Plac = Placebo, Cap = Capecitabine, L= Lapatinib, N=Neratinib, Pac =Paclitaxel, Per =Pertuzumab, BM =brain metastases, cht =chemotherapy)

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Leptomeningeal Carcinomatosis: Local Therapy

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	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**