Guidelines Breast
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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

- **Versions 2003–2016:**
  Bischoff / Diel / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

- **Version 2017:**
  Fehm / Witzel

  In collaboration with:

  P. Feyer und D. Rades (DEGRO)

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Further Information

References

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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)**

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 positiv, 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

Graded Prognostic Assessment (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:
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

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.

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

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Further Information

References

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

	6-months survival rate(%)	**Score**
Prognostic Factor		
age ≤ 60 years ≥ 61 years	 43 25	 4 3
Karnofsky-Index < 70 ≥ 70	 8 53	 1 5
Extracranial metastases no yes	 51 24	 5 2
Interval from first diagnosis to WBRT ≤ 8 months > 8 months	 32 36	 3 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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Single / Solitary Brain Metastasis

	Oxford/AGO LoE	GR	
Local therapy alone: SRS (≤ 4 cm) o. FSRT o. Resection	**2b**	**B**	**++**
WBRT + Boost (SRS, FSRT) o. Resection + WBRT	**2a**	**B**	**++**
Resection + Irradiation of the tumor bed (without WBRT)	**2b**	**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 impaires neurocognitive function.**
- **In case of resection of the tumor the tumorbed has to be irradiated (either local RT or boost in case of WBRT). In general there is no advantage of surgical resection over RT.**

*** Patients with reduced general conditions and limited life expectancy**

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

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2-3 (2-4) Brain Metastases (Oligo-)

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

* **Patients with reduced general conditions and limited life expectancy**

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

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References

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.

➢**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 (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.

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Further Information

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Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

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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

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References

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Multiple Brain Metastases >3 (4) Lesions

	Oxford / AGO LoE / GR		
➢ WBRT (supportive steroids*)	1a	A	++
➢ SRS/FSRT	4	C	+/-
➢ Hippocampal-sparing radiotherapy	2b	C	+/-
➢ Radiochemotherapy for cerebral disease control	3b	C	-
➢ Chemotherapy alone	3a	D	+/-
➢ Corticosteroids alone*	3a	B	+/-
➢ Re-irradiation if recurrence**	4	C	+/-

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

*** adapted to symptoms**

**** can be discussed depending on the time-intervall from first radiation, prior dose and localization**

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References

Systemic and Symptomatic Therapy of Brain Metastases*

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	Oxford / AGO LoE	GR	
➢ 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)	1b	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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Leptomeningeal Carcinomatosis
Local Therapy

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	Oxford / AGO LoE / GR		
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	+/-
Radiotherapy			
➢ Focal (bulky disease)	4	D	+
➢ WBRT	4	D	+
➢ Neuroaxis (disseminated spinal lesions)	4	D	+/-

Due to bad prognosis consider best supportive care, especially in patients with poor performance status

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CNS Metastases in Breast Cancer (2/14)

No further information

No references

CNS Metastases in Breast Cancer – Incidence (3/14)

No further information

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CNS Metastases in Breast Cancer (BC) Risk Factors (4/14)

Further information:

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an "unmasking" of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

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Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/14)

No further information

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Rades OS-Score (6/14)

No further information

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Single / Solitary Brain Metastases (7/14)

Further information

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was described to be more frequent with the addition of WBRT to SRS. Adjuvant WBRT does not improve overall survival 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.

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Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (11/14)

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Systemic and Symptomatic Therapy of Brain Metastases (13/14)

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In the single-arm phase II trial (Landscape) 45 patients received capecitabine in combination with lapatinib to prolong the time until WBRT. 29 patients had an objective CNS response (65.9%, 95% CI 50.1-79.5); all were partial responses with 49% of patients experiencing a grade 3or4 treatment-related adverse events. Therefore, the landscape trial proves that systemic therapy can prolong the time until local therapy of BM is necessary but no general recommendation for this combination therapy can be made. Several retrospective trials show that T-DM1 is safe in patients with brain metastases In a subcohort of the Kamilla trial 21% of patients after local treatment for BM or asymptomatic brain metastases experienced a complete or partial remission with T-DM1. No newly developed targeted therapy could prove to be superior to other cytotoxic agents in the brain.

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Leptomeningeal Carcinomatosis Local Therapy (14/14)

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