

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

## CNS Metastases in Breast Cancer

[www.ago-online.de](http://www.ago-online.de)

FORSCHEN  
LEHREN  
HEILEN

# CNS Metastases in Breast Cancer

- **Versions 2003-2024:**

**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 2025:**

**Budach / Würstlein**

# CNS Metastases in Breast Cancer

©AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

- **Breast cancer is the 2<sup>nd</sup> 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%); optional biopsy**
- **Increasing incidence due to**
  - **More effective treatment of extra-cerebral sites with improved prognosis**
  - **Increasing use of MRI for diagnostic evaluation**
- **No evidence for screening in asymptomatic patients (trials ongoing).**
- **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](http://www.gbg.de)).**

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

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
<b>HER2 positive (all)</b>	5971	13% 95% CI: 0.22–0.38	31%	31
<b>HR- / HER2 positive</b>	2092	13% 95% CI: 0.08–0.20	-	-
<b>HR+ / HER2 positive</b>	3480	8% 95% CI: 0.05–0.13	-	-
<b>HR- / HER2 negative</b>	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
<b>HR+ / HER2 negative</b>	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33

# CNS Metastases in Breast Cancer

## Tumour biology and Risk Factors

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

- **Primary Tumor / risk factors:**
  - **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**
  - **gBRCA mutation**
  - **Age < 40**
  - **Lung metastasis**
  - **Ethnicity**
- **CNS 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)

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

Prognostic Factor	0	0.5	1	1.5	Score
<b>KPS</b>	≤ 60	70-80	90-100	n/a	
<b>Subtype</b>	Basal	LumA	n/a	HER2 or LumB	
<b>Age, years</b>	≥ 60	< 60	n/a	n/a	
<b>ECM</b>	present	absent	n/a	n/a	
<b>No of BM</b>	≥ 2	1	n/a	n/a	
					<b>Sum total</b>

## 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 negative, HER2 positive. ECM: extracranial metastases BM: brain metastases; KPS: Karnofsky Performance Status  
Sperduto PW et al, JCO 2020

# Single / Solitary Brain Metastasis and Oligo-Brain Metastases\*

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

\* Oligometastases refers to ≤ 4 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\*

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

- **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  $\leq 4$  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

© AGO e. V.  
in der DGOG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

## 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, neuro-radiology, and neurosurgery)

- 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.

# Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

## 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

# Management 5 to 10 Brainmetastasis

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

- **WBRT**
- **Hippocampal-sparing radiotherapy<sup>2</sup> (if prognosis is favourable)**
- **SRS or SRT if volume < 15 ml (without WBRT)**
- **surgery + radiotherapy and SRS or SRT of non resectable mets (without WBRT)**
- **Corticosteroids alone<sup>1</sup>**
- **Systemic therapy alone**
  - **For newly diagnosed or progressive asymptomatic brain metastases (only for HER2 breast cancer)<sup>3</sup>**
- **Radiochemotherapy for intracerebral control**

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

<sup>1</sup>adapted to symptoms; <sup>2</sup>metastases in hippocampus excluded; <sup>3</sup>only if regimens with proven clinical activity in active brain metastases are used;

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

# Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated



© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

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

<sup>1</sup>adapted to symptoms; <sup>2</sup>metastases in hippocampus excluded; <sup>3</sup>only if regimens with proven clinical activity in active brain metastases are used; <sup>4</sup> 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

# Symptomatic Therapy of Brain Metastases

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

- **Anticonvulsants only if symptoms of seizures**
- **Glucocorticoids only if symptoms and /  
or mass effect (Dexamethasone with best evidence)**
- **For patients with bad prognosis and reduced physical common  
conditions best supportive care is an option**

Oxford		
LoE	GR	AGO
3a	C	+
3a	C	++
5	D	+

# Clinical Classification of Brain Metastases

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

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

**Stable brain metastases (definition: DESTINY-BREAST03):**  
stable brain metastases  $\geq 2$  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

# Systemic Therapy of Brain Metastases

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

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

© AGO e. V.  
in der DGGG e.V.  
sowie  
in der DKG e.V.

Guidelines Breast  
Version 2025.1E

	Oxford		
	LoE	GR	AGO
▪ <b>Tucatinib + Trastuzumab + Capecitabine*</b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>Trastuzumab-Deruxtecan* <sup>1</sup></b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>T-DM1** <sup>1</sup></b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Lapatinib + Capecitabine**</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Neratinib + Capecitabine**</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Neratinib + Paclitaxel**</b>	<b>2b</b>	<b>B</b>	<b>+/-</b>
▪ <b>High-dose Trastuzumab + Pertuzumab**</b>	<b>2b</b>	<b>C</b>	<b>-</b>

\* 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

<sup>1</sup> elevated risk for radionecrosis in combination stereotactic radiotherapy and

# Leptomeningeal Carcinomatosis: Therapy

Oxford

LoE GR AGO

## Intrathecal or ventricular therapy

- MTX 10-15 mg 2-3 x/week (+/- folinic acid rescue)
- Steroids
- Trastuzumab (HER2 pos. disease)

2b B +/-

4 D +/-

3a C +/-

## Systemic therapy (as for brain metastases)

2b B +

## Best supportive care

## Radiotherapy

- Focal (bulky disease)
- WBRT
- Neuroaxis Craniospinal irradiation (disseminated spinal lesions)

4 D +

4 D +

2b B +/-