CNS Metastases in Breast Cancer
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- **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
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).

19:6404-6418.

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

**Risk factors (see also references slide CNS incidence)**

8. Warren LEG, Niman SM, Remolano MC et al. Incidence, characteristics, and management of central nervous system metastases in

**Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR**


There is no evidence for BM-screening in asymptomatic BC-patients

Breast-GPA


**Prognostic Factors for Survival**


Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

- 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


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

Multiple Brain Metastases

If Stereotactic Radiotherapy is not indicated

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

\(^1\)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, SRT) is not indicated and / or possible

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Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases
6. Bachelot T, Romieu G, Campone M et al.: Lapatinib plus capecitabine in patients with previously untreated brain metastases from


Radiochemotherapy

Re-Bestrahlung bei Rezidiv
Symptomatic Therapy of Brain Metastases

- 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

Anticonvulsants

Steroids
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

4. Hurvitz S., Kim SB, Chung WP et al. :Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03, General Session 3, SABCS 2021
## Systemic Therapy of Brain Metastases

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

*only if regimens with proven clinical activity in active brain metastases are used

** only in case of adequate local treatment of brain metastases


### Systemic treatment alone for pts with newly diagnosed or progressive asymptomatic brain metastases


Systemic Therapy of Brain Metastases: HER2 positive

Tucatinib + Trastuzumab + Capecitabine:

**Trastuzumab-Deruxtecan:**

3. Yamanaka T, Niikura N, Nomura H et al.: Trastuzumab deruxtecan for the treatment of patients with HER2-positive breast cancer with brain and/or leptomeningeal metastases: A multicenter retrospective study (ROSET-BM study) SABCS 2022;PD7-01

**T-DM1:**

Lapatinib + Capecitabin:
2. Petrelli et al., The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis, Eur J Cancer, 2017;84:141-148

Neratinib + Capecitabin:

Neratinib + Paclitaxel:

Trastuzumab + Pertuzumab:
### Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer

**PATRICIA trial (Phase II) NCT02536339**

<table>
<thead>
<tr>
<th>N=39 patients with HER2 positive MBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>with CNS metastases and CNS progression despite prior RT</td>
</tr>
<tr>
<td>stable extracranial disease</td>
</tr>
</tbody>
</table>

**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.

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Clinical trials including HER2 positive patients with brain metastases

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N**</th>
<th>Brain metastases</th>
<th>Combination</th>
<th>IC-ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2CLIMB1*</td>
<td>II</td>
<td>291</td>
<td>Stable + active</td>
<td>Tucatinib+Trastuzumab+Capecitabine</td>
<td>47%</td>
</tr>
<tr>
<td>DESTINY 032</td>
<td>III</td>
<td>36</td>
<td>Stable</td>
<td>Trastuzumab-Deruxtecan</td>
<td>64%</td>
</tr>
<tr>
<td>TUXEDO-13</td>
<td>II</td>
<td>15</td>
<td>Active</td>
<td>Trastuzumab-Deruxtecan</td>
<td>73%</td>
</tr>
<tr>
<td>KAMILLA4</td>
<td>III</td>
<td>398</td>
<td>Stable</td>
<td>T-DM1</td>
<td>21%</td>
</tr>
<tr>
<td>LANDSCAPE5</td>
<td>II</td>
<td>45</td>
<td>Active</td>
<td>Lapatinib + Capecitabine</td>
<td>66%</td>
</tr>
<tr>
<td>NALA5</td>
<td>III</td>
<td>161</td>
<td>Stable</td>
<td>Trastuzumab + Capecitabine</td>
<td>23%</td>
</tr>
<tr>
<td>TBCRC-0227</td>
<td>II</td>
<td>49</td>
<td>Active</td>
<td>Neratinib + Capecitabine</td>
<td>49% (Lapatinib-naive) 33% (prior Lapatinib)</td>
</tr>
<tr>
<td>PATRICIA6</td>
<td>II</td>
<td>39</td>
<td>Active</td>
<td>Pertuzumab + high dose</td>
<td>11%</td>
</tr>
<tr>
<td>NEFERT-T9</td>
<td>II</td>
<td>29</td>
<td>Asymptomatic</td>
<td>Paclitaxel + Neratinib</td>
<td>Not reported; CNS incidence 0</td>
</tr>
</tbody>
</table>

*reference list Adapted from O’Brien B et al. SABCS 2022


Cancer Previously Treated With 2 HER2-Directed Regimens: Phase III NALA Trial, J Clin Oncol. 2020; 38(27):3138-3149


Review:

Methotrexat:

<table>
<thead>
<tr>
<th>Intrathecal or ventricular therapy</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• MTX 10–15 mg 2–3 x/week (+/- folinic acid rescue)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>• Steroids</td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>• Trastuzumab (HER2 pos. disease)</td>
<td>3a</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic therapy</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b B +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Focal (bulky disease)</td>
<td>4</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>• WBRT</td>
<td>4</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>• Neuroaxis Craniospinal irradiation (disseminated spinal lesions)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
MTX high dose

Trastuzumab intrathecal.

Radiotherapy (Craniospinal irradiation):