CNS Metastases in Breast Cancer
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- **Versions 2003–2019:**
  Bischoff / Diel / Fehm / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2020:**
  Bauerfeind / Ditsch
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)

8. Kim, Y.J., J.S. Kim, and I.A. Kim, Molecular subtype predicts incidence and prognosis of brain metastasis from breast cancer in SEER


Risk factors (see also references slide CNS incidence)


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


Molekulare Diskordanz Primärtumor – Metastase:

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

### Breast-GPA


### Prognostic Factors for Survival


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>6-month OS rate (%)</th>
<th>Scoring points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky performance score</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>Time between 1st diagnosis of breast cancer and WBRT</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>≤33 months</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>≥34 months</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Extra-cerebral metastatic disease</td>
<td>28</td>
<td>3</td>
</tr>
</tbody>
</table>

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


7. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical


7. Ling DC, Vargo JA, Wegner RE et al.: Postoperative stereotactic radiosurgery to the resection cavity for large brain metastases:

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### Oligo-Brain Metastases

<table>
<thead>
<tr>
<th>Local therapy alone: SRS (≤ 4 cm) or FSRT</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT + Boost (SRS, FSRT)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>WBRT alone</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Patients with reduced general condition and limited life expectancy</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Hippocampal-sparing</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

- 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

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


### Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

<table>
<thead>
<tr>
<th>Factors in favor of neurosurgery:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Histological verification e.g. after a long recurrence-free interval</td>
</tr>
<tr>
<td>- Need for immediate decompression, life-threatening symptoms</td>
</tr>
<tr>
<td>- Tumor size not allowing stereotactic radiotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors in favor of primary radiotherapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tumor location poorly amenable to surgery</td>
</tr>
<tr>
<td>- More than four lesions</td>
</tr>
</tbody>
</table>


Multiple Brain Metastases
if Stereotactic Radiotherapy is not indicated

- WBRT (supportive steroids*)
- Hippocampal-sparing radiotherapy
- Corticosteroids alone*
- Radiochemotherapy for intracerebral control
- WBRT in case of recurrence**

Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>3b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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

* 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

WBRT = whole brain radiotherapy

7. Krop IE, Lin NU, Blackwell K et al.: Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-


Radiochemotherapy


Re-Bestrahlung bei Rezidiv


8. Yuan P, Gao SL: Management of breast cancer brain metastases: Focus on human epidermal growth factor receptor 2-positive...


Systemic therapy for patients with brain metastases


Anticonvulsants

Steroids
# Leptomeningeal Carcinomatosis: Local Therapy

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
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</thead>
<tbody>
<tr>
<td><strong>Intrathecal or ventricular therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)</td>
<td>2b B +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal cytarabine 50 mg, q 2w*</td>
<td>3b C +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiotepa</td>
<td>3b C +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>4 D +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (HER2 pos. disease)</td>
<td>4 C +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td>3b B +</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal (bulky disease)</td>
<td>4 D +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBRT</td>
<td>4 D +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroaxis (disseminated spinal lesions)</td>
<td>4 D +/-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Currently not available

7. Grossman SA, Finkelstein DM, Ruckdeschel JC et al.: Randomized prospective comparison of intraventricular methotrexate and


Trastuzumab intrathecal


2. Stemmler HJ, Schmitt M, Harbeck N et al.: Application of intrathecal trastuzumab (Herceptin trade mark) for treatment of meningeal


**MTX high dose**