CNS Metastases in Breast Cancer
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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)
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

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
<td>LumA</td>
<td>HER2</td>
<td>LumB</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>6-months survival rate(%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60 years</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>≥ 61 years</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td><strong>Karnofsky-Index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>≥ 70</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td><strong>Extracranial metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td>yes</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td><strong>Interval from first diagnosis to WBRT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 8 months</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 8 months</td>
<td>36</td>
<td>4</td>
</tr>
</tbody>
</table>

**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
Single / Solitary Brain Metastasis

Local therapy alone: SRS (≤ 4 cm) o. FSRT o. Resection
WBRT + Boost (SRS, FSRT) o. Resection + WBRT
Resection + Irradiation of the tumor bed (without WBRT)
WBRT alone*
Hippocampal-sparing

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

Local therapy alone: SRS (≤ 4 cm) or FSRT

WBRT + Boost (SRS, FSRT)

WBRT alone *

Hippocampal-sparing

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

* Patients with reduced general conditions and limited life expectancy

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

Oxford/AGO
LoE / GR

2b B ++
2a B ++
2b B +
2b C +/-
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.

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

2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation

<table>
<thead>
<tr>
<th></th>
<th>after surgical resection (n=160)</th>
<th>after radiosurgery (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBRT</td>
<td>observation</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>27%</td>
<td>59% (p&lt;0.001)</td>
</tr>
<tr>
<td>New lesions</td>
<td>23%</td>
<td>42% (p=0.008)</td>
</tr>
</tbody>
</table>

- 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
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
Multiple Brain Metastases >3 (4) Lesions

- WBRT (supportive steroids*)
- SRS/FSRT
- Hippocampal-sparing radiotherapy
- Radiochemotherapy for cerebral disease control
- Chemotherapy alone
- Corticosteroids alone*
- Re-irradiation if recurrence**

*adapted to symptoms

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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Level</th>
<th>LoE</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT (supportive steroids*)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>SRS/FSRT</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Hippocampal-sparing radiotherapy</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Radiochemotherapy for cerebral disease control</td>
<td>3b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>3a</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Corticosteroids alone*</td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Re-irradiation if recurrence**</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

SRS = stereotactic radiosurgery
FSRT = fractionated stereotactic radiotherapy
WBRT = whole brain radiotherapy
Systemic and Symptomatic Therapy of Brain Metastases*

- Continuation of the actual systemic therapy if first diagnosis of brain metastases and stable extracranial disease
- Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)
- Chemotherapy alone as primary treatment
- Anticonvulsants only if symptoms of seizures
- Glucocorticoids only when symptoms and / or mass effect

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>2c</th>
<th>C</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>B</td>
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<td>3</td>
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<tr>
<td>3</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>

* In addition to local therapy
Leptomeningeal Carcinomatosis
Local Therapy

**Intrathecal or ventricular therapy**

- MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)
- Liposomal cytarabine 50 mg, q 2w
- Thiothepa
- Steroids
- Trastuzumab (HER2 pos. disease)

**Radiotherapy**

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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Notes</th>
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<tbody>
<tr>
<td>MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Liposomal cytarabine 50 mg, q 2w</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Thiothepa</td>
<td>3b</td>
<td>C</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>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<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 (disseminated spinal lesions)</td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Due to bad prognosis consider best supportive care, especially in patients with poor performance status
CNS Metastases in Breast Cancer (2/14)

No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/14)

No further information

References:

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).

References:

References risk factors (see also references slide CNS incidence):


References

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


References: 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 (5/14)

No further information

References:

References for Breast-GPA:


Further References: Prognostic Factors for Survival:


Rades OS-Score (6/14)

No further information

Reference:


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.

References:


Brain Metastases 2-3 (2-4) lesions (8/14)

No further information

References:

See references Slide 7
No further information

Reference:

**Reference:**

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

No further information

No references
Multiple Brain Metastases (12/14)

No further information

References:


Radiochemotherapy


Re-Bestrahlung bei Rezidiv


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

Further information:

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 3 or 4 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.

References:


Chemotherapy


**Anticonvulsants**


**Steroids**

Leptomeningeal Carcinomatosis Local Therapy (14/14)

No further information

References:

Trastuzumab intrathecal


MTX high dose