CNS Metastases in Breast Cancer
CNS  Metastases in Breast Cancer

- **Versions 2003–2015:**
  Bischoff / Diel / Friedrich / Gerber / Huober / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

- **Version 2016:**
  Loibl / Müller

In collaboration with:

P. Feyer und D. Rades (DEGRO)
Breast cancer is the 2\textsuperscript{nd} most common cause of CNS metastases

At autopsy:

- Parenchymal CNS metastases: $\sim 30$–$40\%$
- Leptomeningeal CNS metastases: $\sim 5$–$16\%$

Increasing incidence (10 $\Rightarrow$ 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

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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
<td>n/a</td>
<td></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
Background OS-Score (Rades et al.)

- Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed.
- This score was based on the four independent prognostic factors that were significantly associated with survival on multivariate analysis: age, performance status, extracranial metastases at the time of WBRT, and interval between tumor diagnosis and WBRT.
- The score for each prognostic factor was determined by dividing the 6-month survival rate (in %) by 10.
- The total score for each patient represented the sum of the scores for each prognostic factor.
- Total scores ranged from 9 to 18 points, and patients were divided into four groups.
WBRT: Survival Score (N=1,085)

<table>
<thead>
<tr>
<th>Score</th>
<th>Überleben nach 6 Monaten (%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0%</td>
<td>1.0</td>
</tr>
<tr>
<td>0.1</td>
<td>10%</td>
<td>4.0</td>
</tr>
<tr>
<td>0.2</td>
<td>20%</td>
<td>3.0</td>
</tr>
<tr>
<td>0.3</td>
<td>30%</td>
<td>5.0</td>
</tr>
<tr>
<td>0.4</td>
<td>40%</td>
<td>4.0</td>
</tr>
<tr>
<td>0.5</td>
<td>50%</td>
<td>5.0</td>
</tr>
<tr>
<td>0.6</td>
<td>60%</td>
<td>4.0</td>
</tr>
<tr>
<td>0.7</td>
<td>70%</td>
<td>5.0</td>
</tr>
<tr>
<td>0.8</td>
<td>80%</td>
<td>4.0</td>
</tr>
<tr>
<td>0.9</td>
<td>90%</td>
<td>5.0</td>
</tr>
<tr>
<td>1.0</td>
<td>100%</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Score is already validated (350 new patients).

Rades et al., STO 2008
Dziggel et al., STO 2013
Single / Sole Brain Metastases

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

• WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.
• 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

Oxford/AGO
LoE / GR

2b B ++
2a B ++
2b B +
2b B +

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 *  

- WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.  
- *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
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 |
|-------------------------------------------------|-------------------------------------------------|
| after surgical resection (n=160)                | after radiosurgery (n=199)                       |
| WBRT    | observation                                   | WBRT    | observation                                   |
| Local recurrence                               | Local recurrence                               |
| 27%     | 59%                                           | 19%     | 31%                                           |
| (p<0.001)                                     | (p=0.040)                                      |
| New lesions                                    | New lesions                                    |
| 23%     | 42%                                           | 33%     | 48%                                           |
| (p=0.008)                                     | (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.

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:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery
- More than two lesions
Multiple Brain Metastases >3 (4) Lesions

- WBRT (supportive steroids*)  
  **Oxford / AGO LoE / GR**: 1a A ++

- Hippocampus-sparing radiotherapy  
  **Oxford / AGO LoE / GR**: 2b C +/-

- Radiochemotherapy for cerebral disease control  
  **Oxford / AGO LoE / GR**: 3b C -

- Chemotherapy alone  
  **Oxford / AGO LoE / GR**: 3a D +/-

- Corticosteroids alone*  
  **Oxford / AGO LoE / GR**: 3a B +/-

*Adapted to symptoms
# Systemic and Symptomatic Therapy of Brain Metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue anti-HER2-treatment</td>
<td>2c C +</td>
</tr>
<tr>
<td>Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Chemotherapy alone as primary treatment</td>
<td>3 D -</td>
</tr>
<tr>
<td>Anticonvulsants only if symptoms of seizures</td>
<td>3 C +</td>
</tr>
<tr>
<td>Glucocorticoids only when symptoms and / or mass effect</td>
<td>3 C ++</td>
</tr>
</tbody>
</table>
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)

Due to bad prognosis consider best supportive care, especially in patients with poor performance status
CNS Metastases in Breast Cancer (2/15)

_No further information_

_No references_
CNS Metastases in Breast Cancer – Incidence (3/15)

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 (5/15)

No further information

References:

References for Breast-GPA:

Further References: Prognostic Factors for Survival:


**Rades OS-Score (6-7/15)**

*No further information*

**Reference:**

Singe / Solitary Brain Metastases (8/15)

No further information

References:


Brain Metastases 2-3 (2-4) lesions (9/15)

No further information

References:

See references Slide 8
NCCTG N0574 (Alliance): (10/15)

No further information

Reference:

EORTC 22952-26001 Study (11/15)

No further information

Reference:

Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (12/15)

No further information

No references
Multiple Brain Metastases (13/15)

No further information

References:


Radiochemotherapy


Systemic and Symptomatic Therapy of Brain Metastases (14/15)

No further information

References:


Chemotherapy

Anticonvulsants


Steroids

Leptomeningeal Carcinomatosis Local Therapy (15/15)

No further information

References:


**Trastuzumab intrathecal**


MTX high dose