Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

CNS Metastases in Breast Cancer
CNS Metastases in Breast Cancer

Versions 2003–2014:
Bischoff / Diel / Friedrich / Gerber / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

Version 2015:
Jackisch / Huober
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 knowledge about treatment of brain metastases from breast cancer since most studies are not breast cancer specific. Therefore, participation in the german registry study is recommended.
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>≤ 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>
</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
### Independent Prognostic Factors in BM

Multivariate analyses of significant factors associated with survival after WBRT

- OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %
- Median survival time by Recursive partitioning analysis (RPA) class in months: Class I: 11.7, class II: 6.2 and class III: 3.0

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>P</th>
<th>HR</th>
<th>(95%-confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURGICAL RES</td>
<td>&lt;0.0001</td>
<td>4.34</td>
<td>2.5</td>
</tr>
<tr>
<td>SINGLE METASTASES</td>
<td>0.14</td>
<td>1.08</td>
<td>0.97</td>
</tr>
<tr>
<td>KPS &gt;= 70</td>
<td>0.55</td>
<td>1.31</td>
<td>0.55</td>
</tr>
<tr>
<td>BRAIN MET SCORE (BS-BM)</td>
<td>0.58</td>
<td>0.63</td>
<td>0.12</td>
</tr>
<tr>
<td>RPA</td>
<td>&lt;0.0001</td>
<td>1.64</td>
<td>1.32</td>
</tr>
<tr>
<td>CONTR PRIM TU</td>
<td>0.66</td>
<td>0.92</td>
<td>0.63</td>
</tr>
<tr>
<td>NO EXCRANIAL MET</td>
<td>&lt;0.0001</td>
<td>2.38</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Viani GA et al. BMC Cancer 2007, 7:53
Brain Metastases (1–3 Lesions)

WBRT + SRS boost or neurosurgery (vs. WBRT)  
Improved local control rate  

SRS (lesions < 3 cm) or neurosurgery +/- WBRT*  

WBRT**  
Stereotactic fractionated RT (SFRT)  

* In individual cases additional WBRT may be omitted. Additional WBRT provides improved local control rate and symptom control but not survival benefit in all patient cohorts. Combined treatment is recommended especially in patients with single brain metastases and good performance status.

** In patients with poor prognosis and / or performance status

SRS = stereotactic radiosurgery  
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 > ~ 3 cm not allowing stereotactic radiosurgery
- Surgically favorable location

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery
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></td>
<td>19%</td>
<td>31% (p=0.040)</td>
</tr>
<tr>
<td>New lesions</td>
<td>23%</td>
<td>42% (p=0.008)</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>48% (p=0.023)</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
Multiple Brain Metastases (>3 Lesions)

- WBRT (add corticosteroids*)
  - Prolonged RT (≥ 1 week)
- Radiochemotherapy
- Chemotherapy alone
- Corticosteroids alone

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

In case of radioresistance / recurrence:

- Chemotherapy alone
- Lapatinib +/- Capecitabine (HER2 pos. disease)
- T-DM1 (HER2 pos. disease)
- Re-radiation (if feasible)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>3a</th>
<th>D</th>
<th>+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>3a</td>
<td>D</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

*Symptom adjusted therapy
Possible Treatment Approach for Brain Metastases (BM) in Breast Cancer*

Single BM
- Controlled extra-CNS disease and KPS ≥ 70
- Extra-CNS disease not controlled or KPS < 70

BM ≤ 3
- Controlled extra-CNS disease and KPS ≥ 70
- Extra-CNS disease not controlled or KPS < 70

BM > 3
- Controlled extra-CNS disease and KPS ≥ 70
- Extra-CNS disease not controlled or KPS < 70

- Controlled extra-CNS disease + KPS ≥ 70

<table>
<thead>
<tr>
<th>BM: brain met.</th>
<th>RS: radiosurgery</th>
<th>SRT: stereotactic radiotherapy</th>
<th>WBRT: whole brain radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: chemotherapy</td>
<td>± adjuvant WBRT</td>
<td>± sequential systemic CT</td>
<td>± surgery ± RS/SRT ± systemic CT</td>
</tr>
<tr>
<td>± adjuvant WBRT ± sequential systemic CT</td>
<td>± systemic CT</td>
<td></td>
<td></td>
</tr>
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</table>

*Adapted from Bertolini F et al. CNS Oncology 2015;4(1):37-46
Systemic and Symptomatic Therapy of Brain Metastases

- Continue anti-HER2-treatment in case of extracranial remission (HER2 pos. disease) 2c C +
- Lapatinib + Capecitabine as initial treatment (HER2 pos. disease) 1b B +/-
- Chemotherapy alone as primary treatment 3 D -
- Routine prophylactic use of anticonvulsants 3 C -
- Glucocorticoids (only when symptoms and / or mass effect) 3 C ++
Leptomeningeal Carcinomatosis

Local Therapy

**Intrathecal or ventricular therapy**

- MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)  
  Oxford / AGO LoE / GR: 2b B ++
- Liposomal cytarabine 50 mg, q 2w  
  Oxford / AGO LoE / GR: 3b C ++
- Thiothepa  
  Oxford / AGO LoE / GR: 3b C +
- Steroids  
  Oxford / AGO LoE / GR: 4 D +/-
- Trastuzumab (HER2 pos. disease)  
  Oxford / AGO LoE / GR: 4 C +/-

**Radiotherapy**

- Focal (bulky disease)  
  Oxford / AGO LoE / GR: 4 D +
- WBRT  
  Oxford / AGO LoE / GR: 4 D +
- Neuroaxis (disseminated spinal lesions)  
  Oxford / AGO LoE / GR: 4 D +/-

Due to bad prognosis consider best supportive care, especially in patients with poor performance status
CNS Metastases in Breast Cancer (2/13)

No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/13)

No further information

References:

**CNS Metastases in Breast Cancer (BC) Risk Factors (4/13)**

*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:*


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 (5/13)

No further information

References:

References for Breast-GPA:


Further References: Prognostic Factors for Survival:

Independent Prognostic Factors in BM (6/13)

No further information

Reference:

Brain Metastases (1-3 lesions) (7/13)

No further information

References:


Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (8/13)

No further information

No references
Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study (9/13)

No further information

Reference:

Multiple Brain Metastases (10/13)

No further information

References:


Re-Radiation


Radiochemotherapy

Possible treatment Approach for Brain Metastases in Breast Cancer (11/13)

No further information

Reference:

Systemic and Symptomatic Therapy of Brain Metastases (12/13)

No further information

References:


Chemotherapy


Anticonvulsants

Steroids

Leptomeningeal Carcinomatosis Local Therapy (13/13)

No further information

References:


**Trastuzumab intrathecal**


**MTX high dose**