Radiotherapy of Brain Metastases and Carcinomatous Meningitis

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16.01.2009
Brain metastases

1 in 4 cancer patients develop brain metastases
In 1/3 - 1/2 of these patients brain metastasis is the direct cause of death

Risk of brain metastasis by tumor type:
- SCLC      up to 80%
- NSCLC     25-30%
- Melanoma  up to 50%
- Breast Ca  20%
- Renal cell Ca 5-10%
- Testicular 8-15%

Tendency:

- Rising incidence in brain metastasis due to increasing life-expectancy for cancer patients
- Modern imaging: earlier detection and intervention and, perhaps, opportunity to control CNS disease
Brain metastases

Signs and symptoms:

Usually insidious start
Sudden onset or acute worsening (often due to hemorrhage into the tumor)

• Elevated intracranial pressure:
  headache (50%), nausea and vomiting, psychomotor retardation
• Focal neurological deficits
• Epileptic seizures (15-20 % )
Brain metastases

**Diagnostics:**
CT, MRI, stereotactic biopsy / excision + histology

Patients with new diagnosis of brain metastasis should be systematically restaged as appropriate for their primary tumor

- **Solitary:** one CNS-lesion, *no* evidence of extracranial metastases
- **Single:** one CNS-lesion *and* extracranial metastases
- **Oligo-** (3 and less)
- **Multiple** (more than 3)

Solitary metastasis: in some cases, an aggressive local therapy is potentially curative
(for example, a case of an adenocarcinoma of the lung: 77.4 months survival after SRS, Pirzkall et al, JCO 1998)
Brain metastases

*Important factors to choose treatment:*
- histology
- Karnofsky index
- age
- number of brain metastases
- volume and localisation of brain metastases
- extension of extracranial disease
- reasonable systemic treatment options, if needed
Brain metastases

**Favorable prognostic factors:**
- Age < 65
- KI $\geq$ 70%
- One lesion
- Feasible surgical approach
- „Beneficiary“ localization of the metastases
- Extracranial disease is controlled
- Meninges are not affected
- CUP
- Long disease free survival
- Neurological symptoms due to local volume (edema) expansion only
### Table 3. Prognostic factors

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain metastases</td>
<td>Alone vs. with other</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>metastases</td>
<td></td>
</tr>
<tr>
<td>KPS*</td>
<td>$\geq 70$ vs. $&lt; 70$</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>$&lt; 65$ vs. $\geq 65$</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>No vs. Yes</td>
<td>0.005</td>
</tr>
<tr>
<td>Histology</td>
<td>Squamous and small cell vs.</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>others</td>
<td></td>
</tr>
<tr>
<td>Primary lesion</td>
<td>Controlled vs. uncontrolled</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Primary site</td>
<td>Breast vs. lung and others</td>
<td>0.001</td>
</tr>
<tr>
<td>Time interval</td>
<td>$&lt; 2$ years vs. $&gt; 2$ years</td>
<td>0.004</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>Single vs. multiple</td>
<td>0.021</td>
</tr>
<tr>
<td>Sentinel lesion side</td>
<td>Left and/or right vs. midline</td>
<td>0.038</td>
</tr>
<tr>
<td>Sentinel location</td>
<td>Frontal, temporal, parietal,</td>
<td></td>
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<tr>
<td></td>
<td>Occipital and basal ganglia</td>
<td></td>
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<tr>
<td></td>
<td>vs. cerebellum and brainstem</td>
<td></td>
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<tr>
<td>Neurologic function</td>
<td>No dysfunction vs. some</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>dysfunction</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>None vs. some</td>
<td>0.003</td>
</tr>
<tr>
<td>Total radiation dose</td>
<td>$\geq 52$ Gy vs. $&lt; 52$ Gy</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Tumor response</td>
<td>Complete or partial</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>response vs. stable or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>progressive</td>
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</tbody>
</table>

**Recursive Tree**

![Recursive Tree](image)

*Fig. 2. Recursive tree.*
### Brain metastases

Prognostic **classes** of patients with brain metastases proposed from RTOG, based on Recursive Partitioning Analysis (**RPA**)

<table>
<thead>
<tr>
<th>Class</th>
<th>Characteristics</th>
<th>Median Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>KPS≥70, primary controlled, age&lt;65 y, metastases to brain only</td>
<td>7.1</td>
</tr>
</tbody>
</table>
| II    | •KPS≥70, primary uncontrolled  
  •KPS≥70, primary controlled, age ≥ 65 y  
  •KPS≥70, primary controlled age<65, metastases to brain and other sites | 4.2 |
| III   | KPS<70 | 2.3 |

*Gaspar L et al, IJROBP 1997*
### Brain metastases

#### Prognosis & therapy

<table>
<thead>
<tr>
<th>Applied therapy</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1-2</td>
</tr>
<tr>
<td>Steroids</td>
<td>2-3</td>
</tr>
<tr>
<td>WBRT+steroids</td>
<td>2-6</td>
</tr>
<tr>
<td>WBRT+chemotherapy</td>
<td>4-8</td>
</tr>
<tr>
<td>Resection+ WBRT</td>
<td>6-&gt;12</td>
</tr>
<tr>
<td>SRS+ WBRT</td>
<td>6-&gt;12</td>
</tr>
</tbody>
</table>

Survival is longer and the quality of life better when brain metastases are treated.
Brain metastases

**Treatment options:**

**Corticosteroids:** ↓perifocal edema → ameliorate many symptoms of brain metastases within some hours  
Significant side effects: myopathy, hyperglycemia, edema, weight gain, avascular necrosis and psychosis  
Dose tapering as soon as possible (with caution during RT, better thereafter).

**Anticonvulsants** (avoid aromatic antiepileptic drugs (PHT, CBZ, VPA) before and during RT). Newer anticonvulsants are preferable: levetiracetam (Keppra), gabapentin (neurontin), lamotrigine(Lamictal) and topiramate (Topamax): Prophylactic anticonvulsants have not been shown to be effective!
Brain metastases

Treatment options:

**Standard:**
Radiotherapy +/- radiosurgery

Neurosurgery +/- radiotherapy

Chemotherapy: in chemosensitive tumors (SCLC, germ-cell tumors, testicular cancer)

**Clinical trials:**
Radiotherapy + chemotherapy (Temozolomid, Talidomid, Teniposid, Gefitinib, Tegafur, CCNU)

Radiotherapy + radiosensitizers
Brain metastases

*Indication for WBRT-only*

- Multiple (> 3-4) metastases
- Oligometastases:
  - Neither surgery nor SRS/SRT are feasible (Tu> 3.5cm or overlapping PTVs)
- Poor performance status (KPS < 60%)
- Age > 70y
- Extensive/active extracranial disease with rare or no reasonable systemic treatment options
- Estimated median survival due to extracranial disease or other comorbidity under 3-6 mts
- SCLC or lymphatic histology
- Breast cancer (under discussion)
Brain metastases  

**WBRT only, technique & fractionation**

2D treatment planning,
6 MV Photons,
2 opposite lateral „helmet“- fields including:
- lamina cribrosa,
- caudal part of temporal lobe,
- skull base;

inferior border: 1 - 2 cm below the foramen magnum
(note: provide sufficient margins in case of pontine metastases)
Brain metastases

**Standard:** conventional fractionation
3 Gy/fx, 30 Gy total dose
In some cases boost 2 x 3 Gy

In case of relatively **good risk** → 2 Gy/fx, 40 Gy total dose
(Or 2,5 Gy/fx up to 35-37,5 Gy total dose)

Poor risk (RPA Stage III) and/or urgent control of neurologic deficits needed → 4 Gy/fx, 20 Gy total dose

No significant differences among various conventional fractionation schemes (30Gy in 10fr, 20gy in 5 fr, 40gy in 20fr)

Larger daily fractions do not appear to prevent recurrence and may increase toxicity (↑risk to die due to brain herniation)

No benefit of altered fractionations as compared to standard (10x 3 Gy /fx, one daily fraction)
Brain metastases

Re-irradiation after WBRT:
- another WBRT is possible (if former good response to irradiation and relapse later than 6 mts after RT)

But:
- necessitate lower dose (1.8 Gy /fx to 19.8-25.2 Gy total dose)
- short-term palliation
- no long-term benefit (2-4 mts median survival)
- high toxicity rates

Therefore:
SRS /SRT or is recommended:
- effective
- good tolerability
- in some cases (even in patients with poor performance status) can yield a survival benefit: median survival of 6-10 mts for SRS is reported and 3.5-12 mts for SRT

If SRS/SRT is not feasible: consider conventional 3D planned RT with 5x5 Gy
Brain metastases

**Surgery + WBRT:**
- KI ≥ 70%,
- controlled primary tumor
- Age <60
- solitary/single metastasis

Surgical resection + WBRT vs WBRT alone:
→ fewer recurrences,
→ better quality of life,
→ longer survival in surgical resection group *Patchell et al, NEJM 1990*

Adjuvant WBRT with 1.8 Gy/fx to a total dose of 50.4 Gy
→ fewer cns recurrences and
→ smaller likelihood to die of neurologic causes
→ no reduction in neurologic death in surgery-only group, even with salvage WBRT. *Patchell et al, JAMA 1998*

Recommended fractionation: 20x 2 Gy, conventional fractionation
Brain metastases  Surgery + WBRT:

Exceptions:
• Surgery is not recommended even for RPA class I patients if singular SCLC-mts, germ-cell tumor, metastatic lymphoma, leukemia, myeloma (surgery only either in case of uncertain histology or emergency) → initial therapy either WBRT or chemotherapy (response rates 56-92% and 30-80% correspondingly)

• Excision can be indicated even in case of more than 3 brain metastases because of emergency due to tumor volume effect

Note: In some exceptional cases after incomplete (R2) excision consider a boost additional to the WBRT 2-3 x3 Gy
Brain metastases

Stereotactic irradiation +/- WBRT

Metastatic tumors: do not infiltrate the brain, have well-circumscribed borders → a good target for highly focused irradiation techniques

Radiosurgery:
• treatment of recurrent metastatic lesion
• a boost to WBRT: better OS with SRS for RPA class I, Andrews et al, Lancet 2004
• a sole therapy

Up to 3-4 brain metastases, < 3 cm, KI ≥ 70%, controlled primary tumor, age < 60 y

<2 cm 22-25 Gy
  2 cm 18-20 Gy

Dose prescription: 80%- isodose surrounding the GTV

If WBRT planned: 30% dose reduction for SRS + 10 x 3 Gy WBRT
Aoyama et al. JAMA, 2006
Brain metastases  

**Stereotactic irradiation +/- WBRT**

Aoyama et al. *JAMA*, 2006

- No significant differences in OS (and death due to neurological relapse) identified
- If WBRT is omitted: more CNS relapses
- Still no agreement whether WBRT after the SRS should be omitted or not

**Proposed approach:**
- SRS only, close follow up (physical examination+ MRI every third month over 2 years), WBRT as salvage
Stereotactic Radiation Therapy:
Salvage-option for brain metastases either unresectable or not amenable for SRS (large lesion close to/in brain stem or mesencephalon)

5x 6 Gy if previous or planned WBRT, otherwise 5x 7Gy
Dose prescription: commonly to a 90% isodose, which encloses the PTV (max. tumor volume MRI&CT +1-2mm)

Limiting factor:
Tolerance of the normal brain tissue, which depends on the dose-volume ratio & brain structure involved:

The volume of normal tissue covered by the 10Gy isodose line is a significant variable for occurrence of radiation-induced tissue changes after single dose irradiation. J.Voges IJROBP 1996

Normal brain volume irradiated with >4 Gy/fx (when totally 5 fractions will be applied) should be kept under 20cc
A.Ernst-Stecken et al, R&O 81, 2006
### Brain metastases

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th>Surgery</th>
<th><strong>Disadvantages</strong></th>
<th><strong>Radiosurgery</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allows histological diagnosis</td>
<td></td>
<td>Minimally invasive</td>
<td></td>
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<tr>
<td>Removes mass effect</td>
<td></td>
<td>No hospitalisation</td>
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<tr>
<td>Improves local control</td>
<td></td>
<td>Cost effective</td>
<td></td>
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<tr>
<td>Treatment of recurrence</td>
<td></td>
<td>Treatment of recurrence</td>
<td></td>
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<tr>
<td>Able to treat large lesions</td>
<td></td>
<td>Treats surgically inaccessible masses</td>
<td></td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Invasive</td>
<td>No histological diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Requires hospitalisation</td>
<td>Limited to small tumors (&lt;15ml)</td>
<td></td>
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<tr>
<td></td>
<td>Limited to 1-3 metastases</td>
<td>Limited to max 4 metastases</td>
<td></td>
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<tr>
<td></td>
<td>Infections</td>
<td>Longer time for resolution of mass effect</td>
<td></td>
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</tbody>
</table>
Carcinomatous meningitis

Definition
Metastatic spread of cancer cells in subarachnoid space:
- solid leptomeningeal metastases,
- diffuse spread of non-adherent cells into the subarachnoid space
- both of these patterns of spread

Malignancies that can lead to carcinomatous meningitis:
- breast ca
- lung ca
- melanoma
- lymphoma und leukemia
- primary brain malignancies (germinoma, medulloblastoma und PNET, ependymoma, seldom- malignant glioma)

Incidence in malignant disease is about 10%

In half of the cases there are additional solid brain metastases present
Most of patients (two thirds) exhibit extracranial spread of primary disease
Carcinomatous meningitis

**Symptoms:**
- Elevated ICP: nausea, vomiting, headache
- Meningeal signs: neck stiffness, pain on straight leg raising
- Brain invasion: focal deficits or diffuse complains (confusion, generalized seizures)
- Cranial nerves palsy (for example, n.abducens affection→ “double vision”)
- Spinal nerve root involvement: neurologic deficits and radicular pain

**Most common complaints:** pain, radicular discomfort, headache, mental status abnormalities and weakness

**Prognosis:** poor
- without treatment **6-8 weeks** (exception- lymphatic malignancy- somewhat better)
- with treatment **2-8 months**

1 year survival is still possible in 5-25% (breast ca, lymphatic malignancy)
Most of the treated patients die due to systemic tumor progression
## Carcinomatous meningitis

<table>
<thead>
<tr>
<th></th>
<th>Median survival, months</th>
</tr>
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<tbody>
<tr>
<td>Without treatment</td>
<td>1.0</td>
</tr>
<tr>
<td>Treatment resistant</td>
<td>2.0</td>
</tr>
</tbody>
</table>

## Histology

<table>
<thead>
<tr>
<th></th>
<th>Median survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>4.0</td>
</tr>
<tr>
<td>NSCLC</td>
<td>6.0</td>
</tr>
<tr>
<td>AIDS-associated Lymphomas</td>
<td>6.0</td>
</tr>
<tr>
<td>Breast Ca</td>
<td>7.5</td>
</tr>
<tr>
<td>Not- AIDS-associated Lymphomas</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Carcinomatous meningitis

- most treatment proposals are not based on prospective randomized trials
- treatment is palliative

**The aim of therapy:**
- prolongation of life expectancy
- relief of pain and neurologic symptoms caused by localized CM

**Treatment choice:** according to prognosis, spread pattern and tumor load in CNS (MRI, CSF)

*Poor:* poor performance status (KI≤60); type of metastases: multiple, in a region of critical vital structures, pronounced neurologic deficits; „bulky“ CNS lesions; massive extracranial spread with rare or no reasonable treatment options left, carcinomatous encephalitis (extensive brain infiltration)

*Good:* good performance status (KI>60); minor neurologic deficits; low extracranial tumor load; several reasonable treatment options left against systemic disease

„Poor“- symptoms palliation only
„Good“- „agressive“ approach
Carcinomatous meningitis

....Therapy choice

2. **Spread pattern according to MRI and craniospinal fluid findings**
   - solid nodal versus diffuse and non-adherent - superficial growth prevails, free cells and cell clumps in CSF

Often combined presentation of nodular/solid and diffuse/non-adherent tumor spread. Thus, combined therapy methods are needed; intrathecal chemotherapy
   +/- RT to sites of obstruction, small RT- volume
   + RT to lesions >1mm
Carcinomatous meningitis

**Treatment options:**

- Corticosteroids (↑ICP, pain/ headache, neurologic deficits)
- Anticonvulsants: only for patients with seizures
- Chemotherapy: intrathekal vs. high dose systemic administration
  - MTX, DepoCyt (liposomales Cytarabine), Thiotepa

Intrathecal chemotherapy: in 70% of patients liquor circulation is obstructed →↑neurotoxicity at one site and less effectiveness at another → small volume RT at the site of obstruction

High dose systemic chemotherapy →↑systemic side effects

- Radiotherapy: alone or in combination with chemotherapy (RT preferably after the chemotherapy administration, never concomitantly)
Carcinomatous meningitis

Investigational chemotherapeutic agents for systemic administration:
• Capecitabine (Xeloda)
• Gefitinib in EGFR pos. NSCLC
• Trastuzumab (Herceptin) systemic/ intrathekal in HER2 pos. breast ca
• Lapatinib for HER2 pos., Herceptin- resistant breast ca

Investigational intrathecal therapies:
• Mafosfamide (pediatric malignancies)
• Etoposide
• Dacarbazine
• Nitrosoureas
• Busulfan
• Trimetrexate
• Melphalane
• Topotecan
• IL-2 (melanoma)
• Rituximab (lymphomas)
Carcinomatous meningitis

*Treatment proposals according to risk group:*

1. **Poor risk**: poor performance status (KPS≤60) and poor prognosis (fast progressive extracranial metastasing with rare or no reasonable treatment options left):

Steroids, analgetics, RT against lesions causing major complaints / deficits

Fractionation: decision on individual basis (symptoms, site and volume of the metastatic lesion): 10x 3 Gy, 4x 5 Gy, 5x 5 Gy...

In exceptional cases of extensive spread of relevant neurologic deficiency: primary craniospinal irradiation: 1.6 Gy/ fx up to 24 Gy total dose followed by a boost on bulky lesions up to 35.2 Gy cumulative dose
Carcinomatous meningitis

2. Good risk 1: good performance status (KI>60) and discreet leptomeningeal spread (few cell clumps in CSF, minor radiologic lesions):

Upfront intrathecal chemotherapy. Small volume RT only in case of obstruction (10x 3 Gy) before or after chemotherapy. After the chemotherapy: only in case of persistent cranial nerve affections: WBRT „helmet“ and C2 inclusive, 2-3 Gy/fx up to 30-36 Gy total dose.

3. Good risk 2: good performance status (KI≥70), age<65 y, controlled extracranial tumor or several reasonable systemic treatment options left. BUT: pronounced leptomeningeal lesions

Initially intrathecal chemotherapy and RT thereafter: WBRT „helmet“, incl. C2 inclusive and bulky sites 2-3 Gy/fx up to 30-36 Gy total dose. In case if chemotherapy is not feasible/inefficient but stable performance status: craniospinal irradiation 1.6 Gy/fx up to 24 Gy total dose, boost to bulky lesions up to 35.2 Gy cumulative dose.
Carcinomatous meningitis

**RT techniques**

1. **WBRT / Intracranial liquor spaces**
   Mainly 2D treatment planning

   „Helmet“: brain, lamina cribrosa, optical nerves up to retina, skull base, cervical vertebrae 1&2.
   2 Gy/fx, 30-36 Gy total dose
   (poor prognosis → 3 Gy/fx, up to 30 Gy total dose)

2. **Focal spinal lesions**:
   Additional vertebra cranial and caudal the last affected level for the safety margins. Whether 2 Gy or 3 Gy/fx → decision on an individual basis
   (prognosis, tumor radiosensitivity, tumor load, treatment volume), up to 30-36 Gy total dose
Carcinomatous meningitis

RT techniques

3. **Total irradiation of the CSF-space**

3D treatment planning
- Positioning: prone, head inclination, ventral gantry rotation 3-5°
- In pediatric patients: supine positioning is possible
- *Helmet*“ (brain, lamina cribrosa, optical nerves up to retina, caudal part of temporal lobe, skull base, cervical vertebrae 3&4) → → S4

![Diagram of simulator film showing patient in the prone position for CNS axis irradiation. d = depth for gap calculation.](image)

*J.Dobbs*  
**Practical treatment planning, 1999**
Carcinomatous meningitis

RT techniques

3. …Total irradiation of the CSF-space
- Adults: vertebral arch roots +1cm
- Pediatric patients: the entire vertebrae
- Middle spinal volume at least up to L1/L2 with steady beam irradiated (field junction under the conus)
- Junction switch: daily or weekly (after 5 fractions)

Entire neuroaxis: 1.6 Gy/fx, 24 Gy total dose, boost up to 35.2 Gy cumulative dose

Other RT-treatment techniques: spinal IMRT, tomotherapy, proton-RT (pediatric patients)