Brain Metastases: Management

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Increasing incidence of cerebral metastases

Factors responsible

1. Increased survival of cancer patients
2. Enhanced ability to diagnose CNS tumors due to improved imaging
3. Most chemotherapeutic agents do not cross the blood brain barrier (BBB)
4. Some chemotherapeutic agents may transiently weaken the BBB which facilitates seeding
• **Most common**: lung, breast
• Melanoma, renal cell carcinoma, and choriocarcinoma: **high propensity to metastasize to the brain**
• **Intracranial hemorrhage**: Melanoma, renal cell carcinoma, choriocarcinoma, and thyroid carcinomas
• GI cancers: **mucoid components or fluid-filled cysts**.
• Most common route of spread: **HEMATOGENOUS**

• Internal carotid or vertebrobasilar arteries or from the Bateson venous plexus along the spinal cord.

• Metastatic cells preferentially localize at:
  - the **gray-white junction**
  - **vascular “border zones”** between two major vascular supplies: decreasing caliber of the blood vessels in these areas limiting further progression of the cells
METASTASES OF PRIMARY CNS TUMORS
Spread via CSF pathways

More commonly seen with:
1. High grade gliomas (10-25%)
2. PNETs, especially Medulloblastoma
3. Ependymoma (11%)
4. Choroid plexus tumors
5. Pineal region tumors
   - Germ cell tumors
   - Pineocytoma and pineoblastoma
6. Rarely
   - Oligodendrogliomas (1%)
   - Hemangioblastomas
   - Primary CNS melanoma
METASTASES OF PRIMARY CNS TUMORS

Extraneural spread

Although less common, it commonly occurs with the following:

1. **Medulloblastoma** (cerebellar PNET): *Most common primary responsible for extraneural spread*. May spread to lung, bone marrow, lymph nodes, abdomen
2. Meningioma: rarely goes to heart or lungs
3. Malignant astrocytomas rarely metastasize systemically
4. Ependymomas
5. Pineoblastomas
6. Meningeal sarcomas
7. Choroid plexus tumors
8. **Tumors that spread through CSF pathways may spread via a CSF shunt** (e.g. to peritoneum via a VP shunt or hematogenously with a VA shunt)
• CNS metastases most often involved the brain parenchyma, leptomeninges, and spinal epidural space.

• Distribution: reflects the blood flow, with approximately 80% in cerebrum, 15% in cerebellum, and 5% in brainstem (Autopsy series of Posner and Chernik. Adv Neurol. 1978 Intracranial metastases from systemic cancer).

• Leptomeninges: hematologic malignancies—acute leukemias and lymphomas.
Clinical Features

- Depends on the area of metastasis.

  Forsyth PA, Posner JB. Headaches in patients with brain tumors: A study of 111 patients. Neurology 1993;43:1678–1683. There are no specific features of headache that predict the presence of a brain metastasis; in fact, the “classic” headache features thought to correspond to brain tumors (severe headache, worse in the morning, associated with nausea and vomiting) were found in only in 9 of 111 patients (8 percent) with brain tumors.
LEPTOMENINGEAL METASTASIS

The leptomeninges may be the site of metastases from primary CNS malignancies (34%) extra-cranial hematological (11%) solid (46%) malignancies.

Solid tumors include adenocarcinomas from breast, lung (small cell type), stomach, and malignant melanoma.

Observed as curvilinear or nodular pial enhancement along the basal cisterns or sulci in 35%.
LEPTOMENINGEAL METASTASES

• Hydrocephalus in 13%.
• Cranial nerve deposits in 11%.
• Any new cranial nerve palsy in a patient with known cancer warrants evaluation for leptomeningeal disease.
• Up to 60 percent of patients with leptomeningeal carcinomatosis will have radicular nerve symptoms (distal weakness, neuropathic back pain) related to involvement of the nerve roots. This high frequency may be due to the tendency of tumor cells to settle at the dependent portion of the neuraxis, often along the cauda equina and sacral nerve roots.
# CSF findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening Pressure</td>
<td>60–550 MM H₂O</td>
</tr>
<tr>
<td>Protein</td>
<td>24–2400 mg/100ml</td>
</tr>
<tr>
<td>Cell Count</td>
<td>0–1800 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic &amp; mononuclear predominance</td>
</tr>
<tr>
<td>Glucose</td>
<td>0–225 mg/100ml</td>
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<tr>
<td>Positive Cytology</td>
<td>Positive 45–90% of cases</td>
</tr>
<tr>
<td></td>
<td>Commonly requires 2–3 samples</td>
</tr>
</tbody>
</table>
DURAL METASTASES

- Commonly caused by systemic breast carcinoma, pulmonary adenocarcinoma, squamous cell carcinoma, and renal cell carcinomas.

- More prone to recurrent disease (>41%).

- Overall survival is similar to that of patients with parenchymal disease.

- Chronic subdural hematomas in cancer patients may be masking dural metastases.
IMAGING STRATEGY

• CT retains a limited but important role as an initial diagnostic tool to exclude neurosurgical emergencies.

• A contrast-enhanced MRI study with volumetric 3D sequences and diffusion data should be performed.

• Spectroscopic and pMRI should be performed to help differentiate metastases from other tumor and tumor-mimicking lesions.

• Both sMRI and pMRI can also be used to guide stereotactic biopsy to the most proliferative area of the tumor.
MANAGEMENT OPTIONS

• Surgery: craniotomy and resection
• Radiotherapy: WBRT
• Radiosurgery: SRS
• Chemotherapy
### RPA Classes

**TABLE 4.2. Recursive partitioning analysis classes for brain metastases**

<table>
<thead>
<tr>
<th></th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS score</td>
<td>≥70</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Primary disease status</td>
<td>Controlled systemic disease</td>
<td>Uncontrolled systemic disease</td>
<td>Any systemic disease</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>&lt;65</td>
<td>≥65</td>
<td>Any</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>None</td>
<td>Present</td>
<td>Any</td>
</tr>
<tr>
<td>AUTHOR AND YEAR</td>
<td>NATURE OF STUDY</td>
<td>NAME OF METASTASES / PATIENT</td>
<td>RANDOMIZATION SCHEME</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Patchell 1990</td>
<td>Effect of resection added to WBRT</td>
<td>1 (solitary)</td>
<td>WBRT+ biopsy WBRT+ resection</td>
</tr>
<tr>
<td>Vecht 1993</td>
<td>Effect of resection added to WBRT</td>
<td>1 (solitary)</td>
<td>WBRT+ biopsy WBRT+ resection</td>
</tr>
<tr>
<td>Patchell 1998</td>
<td>Effect of WBRT after resection</td>
<td>1 (solitary)</td>
<td>Resection + observation Resection + WBRT</td>
</tr>
<tr>
<td>Andrews 2004</td>
<td>Effect of SRS boost after WBRT</td>
<td>&lt;3</td>
<td>WBRT alone WBRT+ SRS boost</td>
</tr>
<tr>
<td>Mehta 2003</td>
<td>Effect of motexafin gadolinium with WBRT</td>
<td>Multiple</td>
<td>WBRT alone WBRT+ motexafin gadolinium</td>
</tr>
<tr>
<td>Suh 2006</td>
<td>Effect of efaproxiral with WBRT</td>
<td>Multiple</td>
<td>WBRT alone WBRT+ efaproxiral</td>
</tr>
<tr>
<td>Aoyama 2006</td>
<td>Effect of omitting WBRT after SRS</td>
<td>&lt;4</td>
<td>SRS + observation SRS + WBRT</td>
</tr>
<tr>
<td>Muacevic 2008</td>
<td>Effect of SRS alone vs resection + WBRT</td>
<td>1 (solitary)</td>
<td>SRS + observation Resection + WBRT</td>
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</table>
• Patchell '90  48 pts (10% breast primary)
  • Surgery alone vs Surgery ->WBRT
• functional independence  8 vs 38 weeks
• Recurrence  18% vs 70%
• Survival  15 vs 40 weeks

• Noordijk '94  63 pts (19% breast primary)
  • Surgery alone vs Surgery ->WBRT
• Survival  18 vs 36 weeks
• Benefit of combined therapy seen only in pts with stable or absent extracranial disease

• Mintz '96
  • Surgery alone vs Surgery ->WBRT
• Survival  no difference
Surgery : Patient selection

- Radiology-number/size/location
- Histology
- Clinical status
Tumor number

• Single mets-most appropriate surgical candidates: *Vecht 1993/Patchell 1990*

• Multiple mets: *Bindal et al* concluded- resecting multiple mets is as effective as resecting single as along as all lesions are resected.
Tumor size

- >3 cm - surgery
- <5 mm / deep seated - SRS
- 1-3 cm : no RCT so far hence other factors should be used to decide like : potential for surgical morbidity/extent of systemic disease/medical comorbidities
Tumor location

• Deep seated tumor/tumors within eloquent areas are not good surgical candidates
Histology

- SCLC, lymphoma, germ cell tumors - radio/chemo sensitive - best treated with fractionated radiation/chemotherapy
- Melanoma/ RCC/ sarcomas - radioresistent, hence surgery
Clinical status

• The most significant determinant of ultimate outcome: status of systemic disease = activity and extent of primary tumor and systemic mets (noncerebral)

• Patchell /Mintz

• Good response to steroids = good response to surgery

Survival
- RPA Class 1
- Higher KPS score
- Controlled systemic disease
- Younger age
- Lower tumor number

Primary tumor type
- Breast (versus others)
- Melanoma (versus others)
SURGICAL RESECTION SHOULD BE CONSIDERED SERIOUSLY IN PTS WITH SINGLE METASTASES AND STABLE OR ABSENT EXTRACRANIAL DISEASE

Factors
Single tumor
Surgical accessibility
Good tumor localization/identification
Young age
KPS score ≥ 70
RPA Class 1
Control of extracranial disease
Confirmation of tissue histology
Need for immediate tumor debulking
Large tumor size (≥3 cm)
Undiagnosed primary tumor
Long disease-free interval
Absence of leptomeningeal involvement
Surgery In Recurrent Metastases

- Shown to improve survival and quality of life in patients with recurrent disease.
  

- Surgical debulking and intraoperative histological confirmation
Surgical technique

- Round, well demarcated from surrounding edematous brain with a gliotic pseudocapsule
- Superficial lesion - transcortical
- Deep seated - transsulcal
WHOLE-BRAIN RADIATION THERAPY (WBRT)

• Treatment of choice for metastases that impinge on eloquent areas, or are too large, numerous, or disseminated for surgery or RS.

• Response rates after WBRT vary, (complete or partial responses 60% ) .

• Vecht 1993: Effect of resection added to WBRT : WBRT+ biopsy vs. WBRT+ resection: Resection produced longer survival time and reduced tumor recurrence

• Patchell 1998: Effect of WBRT after resection: Resection + observation vs. Resection + WBRT-WBRT reduced tumor recurrence
# RPA Classes

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*TABLE 4.2. Recursive partitioning analysis classes for brain metastases*
• The Radiation Therapy Oncology Group (RTOG) has attempted to determine the optimal dose fractionation schedules for patients with brain metastasis in various randomized trials.

• All these trials have failed to show any benefit in survival for different doses and fractionation schedules of treatment.

• 20-40 Gy delivered over 1-4 weeks
Complications of WBRT

- Acute effects: fatigue, reversible hair loss, scalp erythema, hyperpigmentation
- Somnolence syndrome (esp in children): fatigue, irritability, anorexia
- Long term: necrosis, personality and memory changes (both short- and longterm memory), and neurocognitive deficits.
Radio surgery: deliver a high dose of radiation to a target volume, destroying all cells within the target boundaries.

Advantages
- No risk of hemorrhage/infection
- No tumor seeding
- Less hospital stay

Disadvantages
- Exacerbation of peritumoral edema
- Long term steroid use
- Radiation necrosis
- Auchter-SRS + WBRT produces better outcome than SURGERY+WBRT for single brain mets
- Bindal-SURGERY better than SRS in survival, recurrence and local morbidity
- Muacevic-SRS is as effective as surgery+WBRT in controlling local tumor, but may require ADJUVANT WBRT to curb distant recurrences
➤ **Single metastases**
  • Median Survival after brain diagnosis 15-18 months
  • Median Survival after SRS 7-13 months

➤ **Retrospective analysis (SRS vs Surgery) (15% breast primary)**
Conflicting results for single metastases

➤ **RTOG 95-08 ’02 333 pts (1-3 metastases)**
  • SRS + WBRT vs WBRT alone
  • Survival no difference
  • Improvement KPS 43% vs 27% (p=0.03)
  • Local tumor control (1 yr) 82% vs 71% (p=0.01)
• In most cases, it seems reasonable to limit SRS to patients with 1 to 3 brain metastases (small, deep seated tumors) and who have controlled extracranial disease and adequate performance status.
Prognostic factors for tumor control

Smaller tumor size
Lower tumor number
Longer time to brain metastases
Adjunct WBRT
Supratentorial location (versus infratentorial)
New lesion (versus recurrent)
Surgery or Radio surgery

- The tumor location and size and the presence of edema are important considerations.

- Tumors that are large, in a favorable location for resection, and are associated with mass effect should be surgically resected.

- Surgery should also be considered for patients with an unknown primary lesion or at the time of a possible first metastasis from a known primary lesion because of the need for tissue diagnosis.

- Small tumors (<3 cm) should be treated with RS if they are unresectable.

- Small tumors that are resectable and are associated with minimal edema can be treated with either surgery or RS.
CHEMOTHERAPY

• Chemosensitive tumors: SCLC, breast, germ cell tumors, lymphomas
• Germ cell tumors like choriocarcinoma and germinoma: standard therapy
• Phase 3 study of teniposide in SCLC: CHEMO VS. WBRT+CHEMO: better results in WBRT COHORT
TREATMENT GUIDELINES

- Always start with **STEROIDS**

- For patients with a resectable new solitary metastasis or a symptomatic metastasis with mass effect: **Sx followed by WBRT**

- Active systemic disease and poor prognosis: **PALLIATIVE CARE**

- RPA Class 3: **PALLIATIVE CARE**

- Deep seated /small sized tumors: **RS**

- Multiple mets: **WBRT/RS**

- RS should be considered when surgery is contraindicated.
- >3 cm with abundant surrounding edema: **Sx + WBRT**
- 1-3 cm without abundant edema: **RS can be tried**

- The most significant determinant of ultimate outcome: **status of systemic disease**
- Still additional trials are needed to establish clear guide lines.
THANKYOU