Brain Metastases

Last updated: April 12, 2019

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BRUST CANCER

- tumors that originate outside CNS and spread secondarily to CNS via hematogenous route (metastasis) or by direct invasion from adjacent tissues (not considered metastases in strict sense because they remain in continuity with primary neoplasm).

Metastases from systemic cancer can affect:

a) brain (high blood flow - common site for metastases!)

b) spinal cord

c) peripheral nerves

d) meninges

e) skull

f) vertebrae

EPIDEMIOLOGY

Metastatic tumors are the most common mass lesions in brain (> 50% of total brain tumors but only 6% of pediatric brain tumors)

- metastatic tumors are most common CNS neoplasms. 11/100,000 population / year (probably underestimate due to underdiagnosis and inaccurate reporting)

- 60% patients are 50-70 yrs.

- gender lacks significant independent effect on occurrence of CNS metastasis (male = female).

- age/brain metastases occur in 15-33% of patients who die of systemic cancer (30% adults, 6-10% children) - only 1/3 of these are diagnosed during life

- leptomeningeal metastases 4-15% of solid tumors

- dural metastases in 8-9%

- direct intracranial extension from local primary tumors - rare

- spinal epidural metastases** in 5-10%

- 20% of cancer deaths.

- 15% systemic cancers present with neurologic symptoms! (esp. lung cancers)
ETIOPATHOPHYSIOLOGY

To establish metastatic colony, tumor cells must:
1) grow within primary site
2) escape from primary tumor
3) penetrate* circulatory system (either as single cells or small tumor emboli)
4) survive while circulating
5) arrest in microvasculature of other organ
6) extravasate* into organ parenchyma;
- *most systemic treatments (e.g. chemotherapeutic agents, which may penetrate brain poorly) can transiently weaken BBB - allow systemic disease to be seeded in CNS.
7) efficiently grow and compress (or invade) tissue at secondary site;
- tumor cells modulate expression of fibronectin, collagen, laminin, and change type of integrin receptor on their surface and on surface of surrounding stromal cells -> desegregation of stromal cells -> permissive environment to expand and invade.
8) once in contact with CSF, cells may disseminate ("seed") around CNS
- by producing proteolytic enzymes (metalloproteases, cathepsins)
- different tumors metastasize preferentially to different organs - cells with similar embryologic origins have similar growth constraints and express similar sets of adhesion molecules, such as vascular addressins expression on endothelial cells of e.g. melanoma cells are closely related to CNS cells - melanoma commonly metastasizes to brain.
- tumor cells can survive in environments of low oxygen tension; when tumor increases in volume by >2-3 times, it induces angiogenesis (e.g. angiopoietin 2, vascular endothelial growth factor).

SOURCES IN ADULTS
- mainly hematogenous spread from systemic cancers (only few primary high-grade brain tumors metastasize to other parts of neuraxis)
- Virtually all systemic cancers have capacity for brain metastasis!

1. Lung
- small-cell carcinoma (20% lung cancers) account for 50% brain metastases from lung cancer.
- in patients with newly diagnosed non-small cell lung cancer (NSCLC), 30-50% will develop brain metastases.
- interval between diagnosis of primary lung cancer and brain metastases is ≈ 4 months.
- prophylactic cranial irradiation reduces 2-year cumulative incidence of brain metastases in patients with small-cell carcinoma from 47 to 10%.

2. Breast
- (13-20%) - main source of metastatic disease in women!
- interval between diagnosis of primary breast cancer and brain metastasis is ≈ 3 years.

3. Melanoma
- (9-11%) see below >>

4. GU tract (7-11%) (21% kidney, 46% testes, 5% cervix, 5% ovary)
- prostate carcinoma rarely metastasizes to brain (but frequently to spine)

5. Sarcoma (3-10%)

6. GI tract (3-5%) (3% colon, 2% pancreatic)

7. Head and neck cancer (6%)

8. Neuroblastoma (5%)

9. Lymphoma, mainly non-Hodgkin (1%)

- 10% cases have no identifiable primary source (most often adenocarcinomas or squamous cell carcinomas)
- 11% mass lesions in patients with cancer are not metastases!
- dural metastases - from prostate, breast, lung, hematologic tumors.
- leptomenengial metastases - from lung and breast cancer, melanoma, hematopoietic tumors.

Propensities to spread to brain

Cumulative incidence of brain metastasis with interval after diagnosis of primary tumor:

<table>
<thead>
<tr>
<th>Primary tumor site</th>
<th>≤1 month</th>
<th>1-3 years</th>
<th>&gt;3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>7.8%</td>
<td>14.8%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Renal</td>
<td>1.7%</td>
<td>5.2%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.7%</td>
<td>4.0%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Breast</td>
<td>0.4%</td>
<td>1.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.1%</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

SOURCES IN CHILDREN
- leukemia > lymphomas > osteogenic sarcomas > rhabdomyosarcomas > Ewing sarcoma
- G208-222.7/NT/00/5 are common in adolescents and young adults aged 15-21 years.

PATHOLOGY

- number of tumors:
  - 1 tumor – single tumor (25-50% cases)
  - N.B. up to 50% of patients have only 1 metastasis (but only 50% of those are surgical candidates in terms of extracranial disease)
2-3 tumors – oligometastases
4-8 tumors – diffuse multifocal disease
≥ 9 tumors – malignant disease

- very few are solitary (i.e. only metastasis detected in body).
- melanoma is most likely to be associated with multiple metastases than other tumor types.
- bronchogenic carcinoma tend to outgrow their blood supply and become necrotic, breast carcinoma deposits may also cavitate but are more frequently solid.
- in majority cases edema is substantial (for unclear reasons, some metastases produce almost no edema).
- calcification is unusual in untreated tumors (except for metastases from primary osseous tumors)
- some metastases hemorrhage spontaneously (esp. melanoma, renal cell carcinoma, choroiocarcinoma).
- proliferation - variable and often higher than in primary neoplasm.

LOCATION

- 85% in cerebrum (metastases prefer anatomical arterial “watershed areas” and gray matter-white matter junction)
- adenocarcinomas may contain collections of mucoid material.
- hemorrhage is relatively frequent in metastases of chorio carcinoma, melanoma, renal cell carcinoma.
- melanoma - brown to black colour.
- leptomeningeal metastasis - diffuse opacification of membranes, multiple nodules.
- dural metastases - localized plaques & nodules or diffuse lesions.
- locally extending primary neoplasms in head and neck - significant destruction of skull bones (in some cases, skull is penetrated by relatively subtle perivascular or perineural invasion without major bone destruction)
- metastatic cancers invade brain regions in proportion to both vascularized areas (leptomeninges, ventricles, pituitary gland) receive disproportionately large number of cancers.

MACROSCOPY

- grossly circumscribed and rounded, grey white or tan masses with variable central necrosis and peritumoral edema.
- adenocarcinomas may contain collections of mucoid material.
- haemorrhage is relatively frequent in metastases of chorio carcinoma, melanoma, renal cell carcinoma.
- melanoma - brown to black colour.
- leptomeningeal metastasis - diffuse opacification of membranes, multiple nodules.
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HISTOPATHOLOGY

- diverse as in primary tumors from which they arise.

Parenchymal metastases
- most are histologically relatively well demarcated - expand by growth of groups of tumor cells in Virchow-Robin spaces (rather than by infiltration of single cells in neuropil) → destruction of neuroglial tissue and variety of reactive changes (gliosis, inflammation and florid microvascular proliferation).
- small cell carcinomas of lung may show relatively diffuse (“pseudogliomatous”) infiltration in neuropil
- necrosis may be extensive, leaving recognizable tumor tissue only at periphery of lesion and around blood vessels.

Leptomeningeal metastasis - tumor cells dispersed in subarachnoid and Virchow-Robin spaces and may invade adjacent CNS parenchyma and nerve roots

A.9 Intracerebral subcortical metastasis of small cell lung carcinoma.

B. Extensive spread of small cell lung carcinoma cells along the walls of both lateral ventricles and the third ventricle.

C. Higher magnification of ventricular wall.

D. Diffuse spread of small cell lung carcinoma cells along the walls of both lateral ventricles and the third ventricle.

E. F. Intraventricular/choroid plexus metastasis of lung adenocarcinoma. Note the TTF1 staining of tumor cell nuclei (F).
**IMMUNOHISTOCHEMISTRY**

- similar to original tumors

Immunohistochemical analysis for indication of origin of common metastatic tumors of CNS:

- CDX2, caudal type homeobox transcription factor 2
- GCDFP, gross cystic disease fluid protein
- RCCMa, renal cell carcinoma marker
- TTF, thyroid transcription factor
CLINICAL FEATURES

1. Increased intracranial pressure: headache, altered mental status, nausea

2. Local effect: paresis, ataxia, visual complaints, sensory disturbances.

Headache (42-50%) and seizures* (15-40%) are most common presenting symptoms! *new onset of seizures in patient > 35 years is highly suggestive! (but metastatic tumors are less likely to induce seizures than primary tumors)

10% present acutely with hemorrhage (most of are intramural hemorrhages), seizure, infarct.

10% have behavioral & cognitive dysfunction (35-75%); multiple, varied neurological symptoms: headache, mental alteration, ataxia, cranial nerve dysfunction and radicalpathy.

Brain metastasis clinically presents in time frame related to primary tumor:

- precocious (undetected primary);
- synchronous (simultaneous primary);
- metachronous (ante cedent primary) - most common!

DIAGNOSIS

BLOOD STUDIES

1. CBC
2. Electrolyte panel
3. Coagulation screen
4. Liver function panel

For a patient with anti-Yo antibodies and ataxia, prophylactic total abdominal hysterectomy/bilateral salpingo-oophorectomy is recommended.

SEARCH FOR SYSTEMIC CANCER

1. Stool guaiac
2. Gynecologic / pelvic examination (incl. testicles)
3. Skin and thyroid examination
4. Chest radiography - for any mass lesion in brain, specifically in patients without history of systemic cancer; if negative → CT of abdomen-pelvis; if negative → chest CT
5. Mammogram
6. Bone scan

• if primary tumor is not quickly revealed by careful evaluation, pathologic diagnosis of single brain tumor needs to be disclosed by resection or, if unresectable owing to its position, by biopsy.

N.B. administration of three times usual dose of gadolinium is more sensitive than standard protocol for detection of brain metastases!
- if MRI is normal → repeat with triple-dose gadolinium in 1 month.

**Haemorrhagic metastases, melanomas** - hyperintensity on non-contrast MRI or CT.

**Leptomeningeal metastases** - focal or diffuse leptomeningeal thickening and enhancement (sometimes with dispersed tumor nodules in subarachnoid space); in addition, enhancement and enlargement of cranial nerves and communicating hydrocephalus.

**Dural metastases** - nodular masses or dural thickening along bone structures.

**Metastasis of lung adenocarcinoma (three tumors, one in pineal gland):**

**Adenocarcinoma in right frontal lobe:**

**Miliary brain metastases of breast cancer:**

A) nonenhanced MRI scan appears almost normal.

B) contrast-enhanced MRI shows > 20 separate metastatic lesions with no significant surrounding edema; patient was neurologically normal at time of this scan.

C) T2-MRI reveals two isodense masses - one in subependymal region and one near cortex (arrows).

D) Contrast T1-MRI reveals enhancement of two masses seen on T2 as well as third mass in left frontal lobe (arrows).

E) Contrast T1-MRI through pons reveals at least four other enhancing metastatic lesions. Note absence of edema!
CSF cytological examination in leptomeningeal metastases reveals malignant cells in initial CSF sample in 30%-90% when CSF sampling is repeated in adequate volumes (10 mL).

**BRAIN METASTASES**

MRI shows multiple metastatic tumors: Four metastases on T1-MRI - round and regular; one is irregular and exhibits central necrosis (arrow).

CSF - cytological examination in leptomeningeal metastases reveals malignant cells in initial CSF sample in 30%-90% when CSF sampling is repeated in adequate volumes (10 mL).

Biopsy

Tissue diagnosis should be performed in cases of uncertain etiology!

N.B. always insist on biopsy of extracranial tumor (if known) – brain lesion may be radiosensitive!

- histological evaluation of specimens makes use of antibodies that are tumor / organ specific:

<table>
<thead>
<tr>
<th>Histologic Stain</th>
<th>Tumor Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin</td>
<td>Carcinomas</td>
</tr>
<tr>
<td>Mucicarmine (chromogranin)</td>
<td>Neuroendocrine tumors</td>
</tr>
<tr>
<td>HMB-45</td>
<td>Melanoma</td>
</tr>
<tr>
<td>S-100</td>
<td>Melanoma, sarcoma</td>
</tr>
<tr>
<td>CEA</td>
<td>Adenocarcinomas (colon, stomach, lung, breast, pancreas, uterus, ovary), thyroid medullary carcinoma, squamous carcinoma</td>
</tr>
<tr>
<td>Estrogen and progesterone receptors</td>
<td>Breast and uterus</td>
</tr>
<tr>
<td>Muscle-specific actin</td>
<td>Rhabdomyosarcomas</td>
</tr>
<tr>
<td>Alpha-fetoprotein, human chorionic gonadotropin</td>
<td>GI tumor</td>
</tr>
<tr>
<td>Placental alkaline phosphatase</td>
<td>Germ cell tumors</td>
</tr>
<tr>
<td>Prostatic acid phosphatase or prostate-specific antigen</td>
<td>Prostate carcinomas</td>
</tr>
<tr>
<td>Leukocytic common antigen, immunoglobulins, L26, UCHL 1, Leu-M1, and CD30</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

**TREATMENT**

Radiosurgery Practice Guideline for Metastatic Brain Tumors (Guideline Report #5-08, original guideline 2008).
Brain Lesion Suggestive of Metastasis on MRI

- Known Cancer
  - Not Sure of Brain Met
    - Stereotactic Biopsy or Resection
    - Metastatic Tumor Confirmed
  - Metastatic Work-up
    - No Primary
    - Primary Found

- No Known Cancer
  - Metastatic Work-up
    - No Primary
    - Primary Found
    - Stereotactic Biopsy or Resection
    - Metastatic Tumor Confirmed

1. Discuss roles of SRS, WBRT, Resection and Chemotherapy at different stages in treatment.
2. Assess systemic disease (status of primary and metastases in other organ systems).
3. Address concerns regarding cognitive effects, local and distant tumor control.
4. Help patient choose appropriate management option.
5. Start treatment with patient’s first choice of management.

Radiosurgery Practice Guideline for Metastatic Brain Tumors (Guideline Report #5-08, original guideline 2008)
**MEDICAL MANAGEMENT**

For incidentally discovered brain metastasis without significant mass effect or edema, withholding steroids & antiepileptics is appropriate.

**Steroids**

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Asymptomatic brain metastases without mass effect - insufficient evidence exists to make a recommendation.

**Level 3 recommendation:** Corticosteroids are recommended to provide temporary relief of symptoms related to increased ICP and edema:
- **mild symptoms:** starting dose of 4-8 mg/d of dexamethasone
- **moderate to severe symptoms:** 16 mg/d of dexamethasone

**Level 3 recommendation:** Steroids should be tapered as rapidly as possible but no faster than clinically tolerated.

**Anticoagulation**

Intracranial hemorrhage is frequently observed in patients with brain metastases but therapeutic anticoagulation does not increase the risk of intracranial hemorrhage!
SURGERY

- metastasectomy.

Indications for surgical resection (in patient with good performance status):

- solitary* metastasis > 3 cm (lesions < 2 cm – better SRS unless tissue diagnosis is needed)
- life-threatening strategically located metastasis** (steroid-resistant neurological symptoms; despite other multiple cerebral metastases (symptomatic lesion is resected for remaining lesions → radiotherapy)

* i.e. no other sites of metastasis exist in body
** e.g. cerebellar lesion with ventricular obstruction

Contraindications to surgery:

- radiosensitive tumor (e.g. small-cell lung tumor, germ-cell tumor, lymphoma / leukemia / multiple myeloma, chorocarcinoma)
- N.B. extracranial metastases is important independent predictor of mortality (relative risk 2.3), i.e. most patients succumb to systemic cancer rather than intracranial lesion – may mask benefit of surgery!
- Karnofsky score > 70 (able to function independently)
- life expectancy > 6 months

Requirements (if not met → XRT):

1) lesion in noneloquent area
2) limited number of lesions
3) limited and/or controlled systemic disease

N.B. extracranial metastases is important independent predictor of mortality (relative risk 2.3), i.e. most patients succumb to systemic cancer rather than intracranial lesion – may mask benefit of surgery!

- patients that benefit from surgery most: KPS > 70, younger age, favorable RPA class, and lower Eastern Cooperative Oncology Group score, control of primary tumor, brain metastases diameter < 4 cm, and complete surgical resection.

Contraindications to surgery:

1) radiosensitive tumor (e.g. small-cell lung tumor, germ-cell tumor, lymphoma / leukemia / multiple myeloma, chorocarcinoma)
2) life expectancy < 3 months (WBRT indicated)
3) multiple lesions.
4) leptomeningeal disease.

- metastases are often sharply demarcated from surrounding normal brain - can be removed with minimal damage to functional nervous tissue.
- piecemeal vs. en bloc resection – results the same.
- single brain metastasis:
  - a) undiagnosed primary site → mandatory biopsy for a tissue diagnosis (even in unresectable locations)
  - b) potential extracranial source is identified → biopsy of extracranial lesion before the intracranial disease is addressed.
  - c) primary site unlikely to metastasize to brain (e.g. prostate carcinoma) → biopsy for a tissue diagnosis.

- surgical resection alone has an expected 1 to 2 yr local recurrence (LR) rate of 47-59%, hence adjuvant XRT is generally recommended.
- N.B. surgery is followed by radiation – either SRS or whole-brain radiation therapy (WBRT).

CNS Systemic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumours (2019)

Level 3 recommendation: en bloc tumor resection, as opposed to piecemeal resection, is recommended to decrease the risk of postoperative leptomeningeal disease when resecting single brain metastases.

Level 3 indication: total lesion resection is recommended over subtotal resection in recurrent partitioning analysis class I patients to improve overall survival and prolong time to recurrence.

Level 3 indication: in multiple brain metastases, resection is recommended for lesions inducing symptoms from mass effect that can be reached without inducing new neurological deficit and who have control of their systemic cancer.

- otherwise, WBRT or SRS should both be considered as valid primary therapies.

Recurrent metastases

CNS Systemic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumours (2019)

Level 3 recommendation: surgery is recommended for intracranial recurrence after initial surgery or SRS.

SURGERY + WBRT vs. WBRT alone for solitary metastases:

Surgical resection of a solitary metastasis has survival benefit (but…)

- e.g. appropriate selection is necessary
- surgical morbidity must be low

Three class 1 evidence RTCs:

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>WBRT + WBRT</td>
<td>WBRT</td>
<td>WBRT</td>
</tr>
<tr>
<td></td>
<td>Statistical</td>
<td>Statistical</td>
<td>Statistical</td>
</tr>
<tr>
<td></td>
<td>+ WBRT alone</td>
<td>+ WBRT</td>
<td>+ WBRT</td>
</tr>
<tr>
<td></td>
<td>significance</td>
<td>significance</td>
<td>significance</td>
</tr>
<tr>
<td>Median survival</td>
<td>40 weeks</td>
<td>10 months</td>
<td>50 months</td>
</tr>
<tr>
<td></td>
<td>15 p = 0.01</td>
<td>0.04</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>weeks weeks</td>
<td>months months</td>
<td>months months</td>
</tr>
</tbody>
</table>


Prospective randomized trial:

a) surgical removal followed by radiotheraphy (surgical group) – 25 patients
b) needle biopsy and radiotheraphy (radiation group) – 25 patients
Results:

- recurrence at the site of the original metastasis was less frequent in the surgical group (20% vs. 52%)
- survival was significantly longer in the surgical group (40 vs. 15 weeks)
- surgical group remained functionally independent longer (38 vs. 8 weeks)
- with death from neurological causes used as an endpoint, median survival was greater in the surgery group compared to the WBRT group (62 weeks versus 26 weeks, p < 0.0009).


- excision plus radiotherapy vs. radiotherapy alone - 63 patients with single brain metastasis.
- combined treatment led to a longer survival (p = 0.04) and a longer functionally independent survival [FIS] (p = 0.0016) in patients with stable extracranial disease.
- N.H. patients with progressive extracranial cancer had a median overall survival of 5 months and a FIS of 2.5 months irrespective of given treatment.


- 84 patients with single brain metastasis - arms:
  a) surgery (gross resection = lobectomy) → radiation (30 Gy to the whole brain in 10 fractions over 2 weeks; start no later than 4 weeks after surgery)
  b) radiation alone

Results - the addition of surgery to radiation therapy did not improve the outcome:
1. No difference in survival (6.3 months in R; 5.6 months in S+R)
   - most patients died within the first year
   - risk ratio for mortality in S+R arm compared with R arm alone is 1.55.
2. No differences in 30-day mortality (9.8% in S+R; 7% in R)
3. No differences in morbidity
4. No differences in causes of death
5. No differences in quality of life (mean proportion of days with Kamofsky status > 70%) Critique:
   - 73% of patients in study had extracranial metastases and/or uncontrollable primary disease.
   - distribution of primaries not equal between groups: greater proportion of colorectal carcinomas in surgery group and breast carcinomas in WBRT group.

Radiotherapy

Radiotherapy always after resection (SRS and/or WBRT) - any modality is good for survival benefit but justify use of it!

Combining radiotherapies (WBRT + SRS or SRS + WBRT) improves CNS control but does not improve survival.

Cleveland clinic: SRS → 1-2 days later → surgery
- SRS controls tumor seeding during surgery
- SRS is easier to plan on preop MRI

Stereotactic Radiosurgery in the Management of Limited (1-4) Brain Metastases: Systematic Review and International Stereotactic Radiosurgery Society Practice 2017 Guideline

- there is no detriment to survival by withholding WBRT in the upfront management of brain metastases with SRS.
- while SRS on its own provides a high rate of local control (LC), WBRT may provide further increase in LC.
- WBRT does provide distant brain control with less need for salvage therapy.
- the addition of WBRT does affect neurocognitive function and quality of life more than SRS alone.
- for larger brain metastases, surgical resection should be considered, especially when factoring lower LC with single-sesion radiosurgery.
- there is emerging data showing good LC and/or decreased toxicity with multisession SRS.

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 1 recommendation: Surgery + WBRT is recommended as first-line treatment for single brain metastases with favorable performance status and limited extracranial disease to extend overall survival, median survival, and local controls.

Level 1 recommendation: Surgery + WBRT is superior treatment to WBRT alone for single brain metastases.

Level 3 recommendation: Surgery + SRS is recommended to provide survival benefit.

Level 3 recommendation: Surgery + SRS is recommended as an alternative to SRS alone to benefit overall survival.

Level 3 recommendation: multimodal treatments involving surgery (surgery + WBRT + SRS boost or surgery + WBRT) are recommended as alternatives to WBRT + SRS for providing overall survival and local control benefits.

Radiation Sensitive

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 1 recommendation: The use of temodalolide as a radiation sensitizer is not recommended in the setting of WBRT for breast cancer metastases.

Level 1 recommendation: The use of chloroquine as radiation sensitizer is not recommended in the setting of WBRT.

Whole Brain Radiation Therapy (WBRT)

Current mainstay of palliation * - 30 Gy delivered in 10 fractions over 2 weeks (but all other WBRT regimens give similar outcomes and toxicity).

- indicated for irregular resection cavity, multiple lesions, older patients, low Karnofsky score, life expectancy < 3 months (alternative opinion - patients with widespread systemic metastasis who are unlikely to survive more than few months are best treated with dexamethasone alone).
- risk of neurocognitive decline (vs. SRS):
  - small-cell lung tumor, germ-cell tumors, lymphoma, leukemia, and multiple myeloma are highly susceptible; other types of lung cancer and breast cancers are less sensitive.
  - melanoma, sarcoma and renal-cell carcinoma are not sensitive at all.

*use of WBRT has declined over the past 10 yr as the use of local and systemic therapies has evolved.
Level 3 recommendation: WBRT can be recommended to improve progression-free survival for > 4 brain metastases.

Level 2 recommendation: for patients with good performance (WHO performance status 0 to 2) and < 4 brain metastases – goal is minimizing neurocognitive toxicity, as opposed to maximizing progression-free survival and overall survival.

- WBRT is not recommended (improves intracranial progression-free survival but not overall survival)
- Local therapy (surgery or radiosurgery) without WBRT is recommended.

Level 3 recommendation: for patients with > 4 brain metastases, the addition of WBRT is not recommended unless metastases’ volume (> 7 cc), number (> 15), size, or location does not make them amenable to local therapy (surgical resection or SRS).

WHO / ECOG

ECOG PERFORMANCE STATUS *

Grade ECOG
0 Fully active, able to carry on all pre-illness activities without restrictions
1 Slightly limited in physically strenuous activity, able to carry on all pre-illness activities of daily or ordinary nature, e.g. light housework, office work
2 Sufficiently limited in physically strenuous activity to carry out only light work activities. Up and about more than 50% of waking hours
3 Capable of only light indoor or bedridden activity or stand upright more than 50% of waking hours
4 Completely disabled. Cannot carry on any activity. Totally confined to bed or chair
5 Dead

Adjuvant WBRT vs. observation - retrospective review from Mayo Clinic
- 85 post-surgical patients: 34 received WBRT, 51 were observed
- subsequent brain relapse 21% in WBRT group, 85% in observation group.
- median survival: 21 months in WBRT group vs. 11.5 months in observation group.

Adjuvant WBRT vs. observation for single brain metastases
- surgery vs. surgery + WBRT, class I evidence.
- adults with completely excised single metastasis.
- post-operative WBRT reduces recurrence of brain metastases and reduces death from neurocognitive causes:

<table>
<thead>
<tr>
<th>Surgery alone</th>
<th>Surgery + WBRT</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original recurrence</td>
<td>Rate 46%</td>
<td>10%</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>27 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Overall recurrence</td>
<td>70%</td>
<td>18%</td>
</tr>
<tr>
<td>Median survival</td>
<td>43 weeks</td>
<td>46 weeks</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Neurological 44%</td>
<td>14%</td>
</tr>
<tr>
<td>Systemic</td>
<td>46%</td>
<td>84%</td>
</tr>
<tr>
<td>Length of functional independence</td>
<td>35 weeks</td>
<td>37 weeks</td>
</tr>
</tbody>
</table>

Treatment arms alter the mode but not the time of death - is one cause of death more acceptable by another to patients and their families?
- role of adjuvant WBRT after surgery for solitary lesion, thus, is controversial, growing trend is to postpone WBRT until recurrence and to use fractionated stereotactic radiotherapy with radiosensitizers (e.g. gadolinium texaphyrin, RSR13).

**OPTIMAL METHODOLOGY**

CNS Systemic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 1 recommendation: standard WBRT dose/fractionation schedule (i.e. 30 Gy in 10 fractions or a biological equivalent dose [BED] of 30 Gy (10)) is recommended as altered dose/fractionation schedules do not result in significant differences in median survival or local control.

Level 3 recommendation: Due to concerns regarding neurocognitive effects, higher dose per fraction schedules (such as 20 Gy in 5 fractions) are recommended only for patients with poor performance status or short predicted survival.

**NEUROCOGNITIVE CONSEQUENCES**

CNS Systemic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 2 recommendation: Due to neurocognitive toxicity, local therapy (surgery or SRS) without WBRT is recommended for > 4 brain metastases amenable to local therapy in terms of size and location.

Level 2 recommendation: WBRT doses exceeding 30 Gy given in 10 fractions are not recommended - association of neurocognitive toxicity with increasing total dose and dose per fraction of WBRT.

Level 2 recommendation: if prophylactic cranial irradiation is given to prevent brain metastases (e.g. for small cell lung cancer), the recommended WBRT dose/fractionation regimen is 25 Gy in 10 fractions.

Level 3 recommendation: patients having WBRT should be offered 6 mos of MEMANTINE to potentially delay, lessen, or prevent the associated neurocognitive toxicity.

**TUMOR HISTOPATHOLOGY OR MOLECULAR STATUS**

CNS Systemic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Insufficient evidence to support the choice of any particular dose/fractionation regimen based on histopathology or molecular status.

**STEROTACTIC RADIOTHERAPY (SRS)**

Favorable characteristics of brain metastases for SRS:
1. Radiographically distinct on MRI/CT
2. Pseudosolid shape
3. Displaces normal brain tissue
4. Minimal invasion of normal brain
5. Size at presentation ≤ 3 cm

Indications for Radiosurgery:
1. Newly diagnosed single or multiple brain metastases without significant mass effect – i.e. alternative to surgery (esp. for 2-4 lesions with diameters < 3 cm)

BRAIN METASTASES

Onco32 [12]
Due to target delineation uncertainty, the variable postoperative clinical delineation uncertainty may be prudent.

- minimum doses to the margin typically range from 14–24 Gy in a single session.
- provides excellent local control (80–90%), failure usually occurs outside treatment volume, thus, inclusion of judicious 2–3 mm margin beyond area of postoperative enhancement may be prudent.
- patients may receive a single stress dose of corticosteroids at the conclusion of the SRS procedure.
- for radiosensitive tumors, recognizing single fractions of radiosurgery work better than conventionally fractionated radiotherapy.
- majority of treated brain metastases respond with volume reduction; significant volume reductions (at either 6 or 12 weeks post-SRS) are strongly associated with prolonged local control, less corticosteroid use and stable neurological symptoms.
- very little data are available on repeat SRS for recurrent brain metastases (but, in general, same selection criteria / indications / contraindications are used as for first time diagnosed brain mass).

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 3 recommendations - SRS alone is recommended to improve median overall survival for patients with >4 metastases having a cumulative volume > 7 cc.
- in terms of overall survival, SRS alone is equivalent to surgery + WBRT.
- SRS is an alternative to surgery in solitary metastases when surgery risk is high (and tumor volume and location are acceptable for employment of SRS).
- SRS should be considered for palliative care in the short term if this is consistent with the overall goals of the patient.
- after surgery for solitary brain metastasis, SRS should be used to decrease local recurrence rates.
- for solitary brain metastasis, SRS should be given to decrease the risk of local progression.
- for >4 metastases having a cumulative volume ≤ 7 mL, SRS is recommended for local tumor control, instead of WBRT.
- for >4 metastases having a cumulative volume > 7 mL, SRS alone is recommended to improve median overall survival.

B. Fractionated stereotactic radiotherapy (FSRT) – equally effective to radiosurgery.

Dose – depends on tumor size

If can, use 24 Gy (unless close to brainstem or optic structures)

RTOG 90-05 (Shaw et al., 2000) examined the maximum tolerated dose (MTD) of single session SRS:

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>MTD (Gy, Tumor Margin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0 cm</td>
<td>24*</td>
</tr>
<tr>
<td>2.0 – 3.0 cm</td>
<td>18</td>
</tr>
<tr>
<td>3.1 – 4.0 cm</td>
<td>15</td>
</tr>
</tbody>
</table>

*investigators were afraid to give the higher dose

Cleveland clinic (Mohammadi et al. 2016) examined 1-year local control rates (by margin dose):

<table>
<thead>
<tr>
<th>MTD (Gy, Tumor Margin)</th>
<th>Local control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>85% (76–92%)</td>
</tr>
<tr>
<td>24</td>
<td>49% (30–65%)</td>
</tr>
<tr>
<td>15</td>
<td>45% (23 – 67%)</td>
</tr>
</tbody>
</table>

Postoperative SRS Techniques

The technique for postoperative SRS has evolved over time. An early retrospective study from Stanford included 72 patients treated with postoperative SRS between 1998 and 2006. Most patients were treated to the contoured resection cavity without additional margin. An important finding was that cavity local control was significantly higher in patients with less conformal SRS plans.

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Postoperative SRS: Due to the perceived drawbacks of postoperative SRS, namely the need for cavity margin expansion due to target delineation uncertainty, the variable postoperative clinical course and potential delay in surgery.

A. Stereotactic radiosurgery (SRS) – another standard of care

- limited number of lesions (number is less than 5, but may be up to 5).
- minimum doses to the margin typically range from 14–24 Gy in a single session.
- provides excellent local control (80–90%), failure usually occurs outside treatment volume, thus, inclusion of judicious 2–3 mm margin beyond area of postoperative enhancement may be prudent.
- patients may receive a single stress dose of corticosteroids at the conclusion of the SRS procedure.
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Conformal index (CI) is a measure of the compactness of the high-dose radiation given during SRS relative to the target volume and is calculated as the ratio: [volume of the prescription isodose line/volume of the target]. 25 In order for the target to be completely encompassed by the prescription isodose line, CI needs to be ≥1. The larger the CI, the more volume is being radiated to the prescription dose relative to the volume of the target. The conclusion from this finding was that there was increased risk of marginal miss of the resection cavity in the postoperative SRS setting with more conformal SRS plans compared with less conformal plans as measured by the CI (likely due to difficulty contouring the postoperative cavity), and hence a 2-mm margin expansion on the cavity should be used. The Stanford group started systematically using a 2-mm margin and published a follow-up study comparing outcomes from a prospective group of patients treated with the 2-mm expansion compared with the historical control of patients treated without a margin.26 The use of a margin was found to significantly improve local control without an increase of toxicity. The 1-yr cumulative incidence of cavity LR with and without the margin were 3% and 16%, respectively (P = .04), while the 1-yr toxicity rates with and without the margin were 3% and 8%, respectively (P = .27). These findings led to the adoption of an expansion (generally 1–2 mm) to the cavity as part of standard practice at most institutions in the postoperative SRS setting. The use of these margins does inherently and intentionally increase the volume of normal brain irradiated in order to overcome cavity delineation uncertainty.

Postoperative SRS

Due to the perceived drawbacks of postoperative SRS, namely the need for cavity margin expansion due to target delineation uncertainty, the variable postoperative clinical course and potential delay in surgery.
administering postoperative SRS, and the theoretical risk of tumor spillage into CSF at the time of surgery is a concern. Therefore, an alternative is to maximize local control of the resection cavity and minimize neurocognitive detriment associated with WBRT. Postoperative SRS has several potential advantages compared to postoperative SRS in relation to the time of surgery. The use of preoperative SRS allows a more homogeneous dose to the target volume, reducing the risk of acute toxicity and improving tumor control. Postoperative SRS has been shown to be less effective in achieving local control compared to preoperative SRS, particularly in patients with multiple brain metastases. In addition, preoperative SRS may reduce the risk of postoperative complications, including wound infection or healing difficulties, and there were no perioperative mortality in this study.

Future Directions

Future directions for preoperative SRS include the development of more personalized treatment approaches, taking into account the specific characteristics of individual patients. This may involve the use of advanced imaging techniques to better define the target volume and reduce the risk of underdosing. The need for accurate target delineation and the potential for radiosurgery to achieve local control without the need for CNS pathologic confirmation are areas that require further investigation. The adoption of SRS as a primary treatment modality, particularly in the setting of limited brain metastases, may be further explored.

In conclusion, preoperative SRS is a promising approach for the treatment of patients with brain metastases. Its potential advantages over postoperative SRS include improved local control, reduced radiation necrosis risk, and a lower risk of nonmetastatic disease. Further studies are needed to fully evaluate the role of preoperative SRS in the management of brain metastases.
Among surveyed radiation oncologists (n = 711) who were given hypothetical scenarios, responses for the number of lesions requiring a switch from SRS to WBRT depended on physician characteristics:

- CNS specialists were consistently more likely to treat more metastases with SRS - their "threshold number" for making a switch from SRS to WBRT was significantly higher than that of non-CNS specialists (8.1 vs 5.1 among high-volume providers).
- Patient volume was a factor: as providers treated higher numbers of patients with brain metastases also reported a significantly higher cutoff number compared with those treating a lower volume of patients (8.1 in high-volume providers vs 5.1 in low-volume providers). Dr. Lee (Department of Radiation Oncology at UCLA): "We have evidence to support SRS for 3 brain metastases, but what about 4 or 5? There is no clear evidence either way.”

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**DURATION**

The increasing use of postoperative SRS has only recently been justified with high-quality randomized trials demonstrating benefit in terms of local control and neurocognitive preservation over WBRT. Prospective randomized evidence is needed to determine if preoperative SRS truly has less risk of radiation necrosis and LMD compared to postoperative SRS, as suggested by retrospective studies. To this end, a cooperative group (NRG BN1605) institutional phase II randomized trial is currently in development to address these questions (NRG-BN1605). Patients with 1 to 4 brain metastases, of which 1 requires resection, would be randomized to preoperative vs postoperative single-fraction SRS. This study is designed as a superiority trial with the primary endpoint of LMD relapse, with the hypothesis of significantly less risk of LMD with preoperative than postoperative SRS, with a sample size of 450 patients per arm. Additional work is also being done to determine patterns of LMD recurrence after surgery and SRS (ie, focal vs diffuse and relationship/distance from the cavity), quantity patterns of salvage for postSurgical LMD (ie, focal RT or WBRT), and determine survival and tumor control outcomes after LMD recurrence in this setting.
3) No survival benefit with SRS boost
   - Subgroup analysis: single brain metastasis - mean survival time in the WBRT + SRS group was 6.5 months vs 4.9 months in the WBRT alone group (p = 0.04).
   - similar results by the other trial: local brain control at one year ranged from 82–92% in the SRS boost arm vs 0–71% in the WBRT alone arm; median survival was not statistically different between the two groups (7.5 months for WBRT alone vs. 11 months for WBRT and radiosurgery boost (p = 0.22)); survival was dependent on the extent of extracranial disease (p = 0.02).


SRS + WBRT

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Level 2 recommendation: WBRT can be added to SRS to improve local and distant control keeping in mind the potential for worsened neurocognitive outcomes + unlikely a significant impact on overall survival.

- newer WBRT delivery techniques using hippocampal avoidance may lessen the SRS advantage

SRS ± WBRT for 1-4 metastases ≤ 3 cm (Japanese Radiation Oncology Study Group 99-1 trial)
   - group I evidence.
   - WBRT total 30 Gy in 30 fractions.
   - metastases with a maximum diameter of up to 2 cm were treated with SRS doses of 22–25 Gy and those > 2 cm were treated with 18–20 Gy.
   - SRS dose was reduced by 30% when the treatment was combined with WBRT.

American Society for Radiation Oncology (ASTRO) recommends withholding WBRT in favor of SRS alone for patients with newly diagnosed brain metastases can be treated with radiosurgery boost (p < 0.001) in SRS+WBRT group.

- median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone.

Conclusion:
1) WBRT boost following SRS does not improve survival
2) WBRT boost reduces recurrence of brain metastases
3) patients with newly diagnosed brain metastases can be treated with up-front SRS alone, reserving WBRT for salvage.

SRS ± WBRT for 1-3 metastases
   - class I evidence.
   - patients with single brain metastasis may be treated with up-front SRS alone, reserving WBRT for salvage.

- no recurrence rate at 12 months: 76.4% in the SRS group vs. 46.8% (p = 0.001) in SRS + WBRT group.
- median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone.

Radiosurgery Practice Guideline for Metastatic Brain Tumors (Guideline Report #5-08, original guideline 2008)
   - there is Level I and II-3 evidence that addition of WBRT to SRS for 1–3 newly diagnosed brain metastases does not improve survival compared with SRS alone with WBRT reserved for salvage therapy. There is Level I and II-1 and II-3 evidence: omission of WBRT results in decreased tumor control, both at the site of SRS and also in the remaining untreated brain.

American Society for Radiation Oncology (ASTRO) recommends not routinely add adjuvant WBRT to SRS for limited brain metastases (e.g. from solid tumors) because for most of these patients SRS alone is sufficient and WBRT is associated with diminished cognitive function and worse patient-reported fatigue and quality of life.

SRS vs. WBRT for 1-3 metastases
   - no survival difference: median survivals were 7 (SRS), 5 (SRS + WBRT), and 9 (WBRT) months.
   - local brain control rate: 87% for Gamma Knife® SRS alone, 91% for Gamma Knife® SRS + WBRT.
   - 62% for WBRT only

- in most cases, 2-3 agents are used in combination and in conjunction with whole-brain radiation therapy (WBRT).

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

See recommendations for specific cancers.

- Level I recommendation: cytotoxic chemotherapy alone for brain metastases is not recommended as it has not been shown to increase overall survival.

CHEMOTHERAPY
   - depends on systemic disease, tumor type, and stage.
   - most tumors that metastasize to brain are not chemosensitive (most sensitive - small cell lung cancer and seminomas)
   - development of brain metastases while patients are undergoing systemic chemotherapy indicates that the BBB makes the brain a sanctuary from many chemotherapeutic agents.
   - chemotherapy role is limited to multiple brain metastases or active systemic cancer reasonably likely to respond to chemotherapy.
   - in most cases, 2-3 agents are used in combination and in conjunction with whole-brain radiation therapy (WBRT).

SRS vs. SURGERY
   - No prospective trials available
   - both are excellent treatment options for solitary brain metastases
Level 1 recommendation: chemotherapy following WBRT or SRS for brain metastases is not recommended.

Insufficient evidence to make recommendations regarding vascular endothelial growth factor agents bevacizumab, sunitinib, and sorafenib for solid tumor brain metastases.

EMERGING THERAPIES

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

There is insufficient evidence to make a recommendation regarding the use of high-intensity focused ultrasound (HIFU) or laser interstitial thermal therapy (LITT) or interstitial chemotherapy or brachytherapy or immune therapy.

FOLLOW UP

MRI every 2–3 months for one year, then every 3–4 months (less frequent beyond 2 years if both are present – no relapse before 2 years and tumor total volume < 5 mL)

Univ of Pittsburgh protocol: MRI every 3 mo for the first year of follow-up, every 4 mo for year 2, then every 6 mo thereafter, with limited consensus beyond 4 to 5 yr.

With SRS alone, risk of relapse within 1–2 years is 50-60% (if relapsed within 2 years and volume is > 5 cc, then relapse risk at > 2 years remains 50-60%).

Combining total SRS tumor volume >5 cc and failure during years 0 to 2, the 2 to 4-yr risk of intracranial failure if neither factor was present was 17%; either was 33%; and both was 66%.

PROGNOSIS

Local recurrence rate of brain metastasis is relatively high:
85% after surgery without WBRT.
67% after radiation therapy + stereotactic radiosurgery.

Unknown primary cancer - subgroup with widely divergent prognoses.

Factors associated with improved prognosis:
1. High Karnofsky score (> 70)
2. Age < 60 yrs
3. Number and location of CNS metastases (one brain metastasis - improved quality of life, survival benefit from surgical resection or radiosurgery).
4. Sensitivity of tumor to therapy
5. No systemic disease or systemic disease controlled
6. No systemic metastases within 1 year of diagnosis of primary lesion
7. Female patients

Medium survival:
Surgical resection and WBRT - 36 months
Surgical resection - 22 months
SRS and WBRT - 16 months
SRS - 11 months
WBRT - 6 months
Untreated - 1 month (can be doubled by corticosteroids) (Cairncross et al. 1980)

Nomogram for 6- and 12-month survival and median survival for RTOG brain metastases patients (BA, Breast and Adenocarcinoma; BO, Breast and Other; LA, Lung and Adenocarcinoma; LL, Lung and Large cell; LO, Lung and Other; LS, Lung and Small cell; LSQ, Lung and Squamous cell; OA, Other and Adenocarcinoma; OG, Other and GI; OR, Other and Renal; OSQ, Other and Squamous cell; SMM, Skin-Melanoma; OO, Other and Other; PR, Partial Resection; CGTR, Complete/Gross total resection): Neuro Oncol. 2012 Jul;14(7):910-8. A nomogram for individualized estimation of survival among patients with brain metastasis. Barnholtz-Sloan JS et al.

Most important factor for decision making – status of extracranial disease!

- presence of multiple brain metastases per se is not an indicator of an adverse prognosis compared to a single brain metastasis.
- activity of systemic disease and its propensity to be controlled represent in many studies a significant factor linked to survival.
- in many studies reporting the cause of death, systemic causes of death trump neurological causes of death.
**RPA / RTOG CLASSIFICATION**

Radiation Therapy Oncology Group (RTOG) classes for predicting outcome in brain metastases (i.e. recursive partitioning analysis (RPA) classification on the basis of a retrospective study of 1200 patients treated with whole brain radiotherapy):

<table>
<thead>
<tr>
<th>Class</th>
<th>Karnofsky Score</th>
<th>Systemic Disease</th>
<th>Median Survival (months) with WBRT</th>
<th>Adding SRS boost to WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (age ≤ 65 yrs) ≤ 70</td>
<td>Controlled primary disease, no extracranial metastases</td>
<td>7.0 (13.5 for single metastasis, 6.0 for multiple metastases)</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>2 (age &gt; 65 yrs) ≤ 70</td>
<td>Not group 1 or 3</td>
<td>4.2 (8.1 for single metastasis, 4.1 for multiple metastases)</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>3 &lt; 70</td>
<td></td>
<td></td>
<td>3.7</td>
<td></td>
</tr>
</tbody>
</table>


RPA classification has also been shown to have prognostic value in patients treated surgically. Agboola O et al: Prognostic factors derived from recursive partition analysis (RPA) of radiation therapy oncology group (RTOG) brain metastasis trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiation Oncology Biol Phys 1998; 42: 155 – 159.

**META-ANALYSIS OF FIVE RANDOMIZED RTOG STUDIES** (1960 patients) — less subjective, more quantitative, easier to use scale:

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>50-59</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>KPS &lt; 70</td>
<td>70-80</td>
<td>90-100</td>
<td></td>
</tr>
<tr>
<td>Number of CNS metastases &gt; 3</td>
<td>2-3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Extracranial metastases Present</td>
<td>None</td>
<td></td>
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**TOTAL POINTS**

**MEDIAN SURVIVAL (MOS)**

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<th>5-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>2.6</td>
<td>11</td>
</tr>
<tr>
<td>Solc</td>
<td>5.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Melanoclastoma</td>
<td>4.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Rb-cell</td>
<td>7.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>9.3</td>
<td>16.9</td>
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**DIAGNOSIS SPECIFIC GPA (MEDIAN SURVIVAL):**

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<td></td>
</tr>
<tr>
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**CNS MELANOMA**

- 66-75% melanomas give brain metastasis! (melanocytes are derived from neural crest) Melanoma is tumor type most prone to spread to brain! And does so with multiple brain metastases

- most often multifocal
- unique tendency to hemorrhage!
- particularly prone to give pial implants.

**NEUROTANECOUS MELANOMA** - conglomerant giant hairy melanocytic neri with associated leptomeningeal melanocytosis (involving brain and/or spinal cord); leptomeningeal invasion can cause severe neurological compromise or death!

- PRIMARY INTRACRANIAL MELANOMA can arise from meninges.

---

**SPECIFIC METASTASES**

- CNS MELANOMA: see also p. 3005 >>

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**DIAGNOSIS**


**BRAIN METASTASES**

**Ch32 (18)**
CT – tends to be isodense or hypodense; perilesional edema is usually present. pial implants appear (on contrast CT) as areas of nodular high density or as generalized enhancement along subarachnoid cisterns, fissures, and sulci.

- may appear hyperintense on T1-MRI and hypointense on T2-MRI (due to melanin).
- stereotactic brain biopsy is usually not necessary if primary is known and if imaging is compatible with melanoma.

T2-MRI: at least three foci of signal hypointensity in right hemisphere, largest in right posterior frontal cortex and others deeper in subcortical parietal convexity.

Noncontrast T1-MRI: high signal (melanin or hemorrhage); note extensive surrounding edema:

**TREATMENT & PROGNOSIS**

**Poorly responsive to all treatments** - after melanoma is detected in brain, median survival is 3-4 months!

1-L lesions:
- surgical removal ± whole brain radiation
- radiosurgery ± whole brain radiation

**Multiple metastases:**
- whole brain radiation
- chemotherapy:
  - DACarbazine – FDA approved for melanoma
  - TEMOZOLOMIDE (prolonged myelosuppressive properties)
  - IFILMOMASS (Yervoy®) – 10 mg/kg IV once every 3 weeks → long-term survival similar to patients with advanced melanoma without brain metastases.
  - fully human antibody that blocks CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) → sustained active immune response.
  - stereoid act antagonistically (by suppressing immune response)
  - DABRAFENIB – investigational agent - targets tumors and melanomas that harbor BRAF mutations – reduced size of brain metastases in 9 of 10 patients with advanced melanoma and asymptomatic brain lesions, and led to complete resolution in 4 of these patients.

**Noncontrast T1-MRI:** high signal (melanin or hemorrhage); note extensive surrounding edema:

**Melanoma that metastasizes to CNS is incurable**

**LUNG CANCER**

**SMALL CELL**

Treatment is whole brain radiation (even for single symptomatic* metastasis)

- e.g. over eloquent cortex; if symptomatic due to local mass effect and tumor is large → surgical debulking before radiation

**NON-SMALL CELL**

**BREAST CANCER**

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

There is insufficient evidence to make recommendations regarding **BRAF inhibitors DABRAFENIB and VEMURAFENIB** for brain metastases due to melanoma.

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

**Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)**

There is insufficient evidence to make recommendations regarding **epidermal growth factor receptor inhibitors ERLOTINIB and GEFTINIB** for brain metastasis due to **nonsmall cell lung cancer**.

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)
Level 3 recommendation: WBRT + temozolomide is recommended as a treatment for patients with triple-negative breast cancer.

Level 1 recommendation: afatinib is not recommended for brain metastasis due to breast cancer.

Insufficient evidence to make recommendations regarding HER2 agents TRASTUZUMAB and LAPATINIB for brain metastases due to breast cancer.

BIBLIOGRAPHY for ch. “Neuro-Oncology” — follow this LINK >>