Brain Metastases

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- 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 brain 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 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. 1 / 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).

- in young: brain metastases occur in 15-15% of patients who die of systemic cancer (50% adults, 6-10% children) - only 1/5 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%

- *of head and neck (e.g. squamous cell carcinoma, esophageal/blasticoma)

- **much more frequent than spinal leptomeningeal or intramedullary metastases

- 20% of cancer deaths.

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

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 (metalloproteinasises, cathepsins)
   - different tumors metastasize preferentially to different organs - cells with similar embryonic origins have similar growth constraints and express similar sets of adhesion molecules, such as vascular addressins expression on endothelial cells (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 angio genesis © (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 (35-50%)
   - small-cell carcinomas (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.
   - 80% lung cancer patients who survive > 2 yrs have 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!
5. Brain (3-10%)
6. GI tract (3-9%)
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.
   - leptomeningeal metastases - from lung and breast cancer, melanoma, hematopoietic tumors.

Propensity to spread to brain

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

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)

References

1. *Leukemia > lymphomas > osteogenic sarcomas > rhadomyosarcomas > Ewing sarcoma*
2. *G2R0-822.7/0.005 are common in adolescents and young adults aged 15-21 years.*
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 tends 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, choriocarcinoma).
- proliferation - variable and often higher than in primary neoplasm

**LOCATION**

- 85% in cerebrum (metastases prefer anatomical arterial “watershed areas” and gray matter–white matter junctions)
- choroid plexus invasion in breast cancer
- choroid plexus invasion in breast cancer

Laryngeal metastasis, determination of survivability:

- occasionally, metastatic CNS tumors seed along walls of ventricles or are located in pituitary gland, choroid plexus, or pre-existing lesion like meningioma.
- cancer-cell trafficking may not be entirely random - factors produced by stromal cells may guide final destination (e.g. retropertioneal and pelvic cancers tend to metastasize to posterior fossa; breast cancer favors pituitary gland).
- 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.
- adenoscarcinomas may contain collections of mucoid material.
- haemorrhage is relatively frequent in metastases of choriocarcinoma, 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)

**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 (glialosis, inflammation and fibril microvascular proliferation).
- small cell carcinomas of lung may show relatively diffuse (“pseudogliomatosus”) 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.B Intracerebral subcortical metastasis of small cell lung carcinoma.
**Leptomeningeal metastasis of non-Hodgkin lymphoma. B Dural metastasis of breast carcinoma.**

Leptomeningeal metastasis of colon carcinoma (A,B). Note the perivascular infiltration of the cerebral cortex (B).

Intraspinal dural metastasis of lung adenocarcinoma (C,D).

Metastasis from lung carcinoma.

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**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.

Brain metastasis clinically presents in time frame related to primary tumor:
- **precocious** (undetected primary);
- **synchronous** (simultaneous primary);
- **metachronous** (anteceodent primary) - most common!

DIAGNOSIS

BLOOD STUDIES

1. CBC
2. Electrolyte panel
3. Coagulation screen
4. Liver function panel
5. Specific markers:
   - CEA, PSA, CA125, CA153, AFP, HCG, LDH.
   - anti-Yo antibody in cerebellar degeneration;
   - anti-Hu antibody in limbic encephalopathy;
   - anti-Ri antibody in opsoclonus and ataxia.

e.g. if no primary malignancy is found but anti-Yo is present in woman, 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 → chest CT; if negative → CT of abdomen-pelvis
5. Mammogram
6. Whole-body FDG PET/CT
7. 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.

IMAGING OF NEURAXIS

Neither methods are useful for differentiating metastasis from primary brain tumors!

**CONTRAST CT**

- many are invisible (isodense) → underestimation.
- some deposits are spontaneously dense (esp. malignant melanoma).

MRI WITH GADOLINIUM

- gold standard

- 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.

- brain and skull mts image review protocol:
  - parenchymal - gadolinium MPGRE, FLAIR (not all mts enhance so FLAIR is even more sensitive, esp. for small mts)
  - calvarial - DWI (bright areas in the skull); vs. bone marrow abnormalities - will be diffuse signal along entire skull

- circumscribed
- mild T1-hypointensity, T2-hyperintensity
• T1-MRI has highest sensitivity! (T2 may miss some lesions!!)
• well-demarcated, approximately spherical lesions.
• may not always produce vasogenic edema.
• hypointense or isointense on T1, bright on T2.
• enhancement is variable: some enhance brightly and solidly (esp. small lesions), others are in ring configuration (esp. large lesions - core of necrosis).

N.B. administration of three times usual dose of gadolinium is more sensitive than standard protocol for detection of brain metastases.¹

• if MRI is normal → repeat with triple-dose gadolinium in 1 month.

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

Leptomeningeal metastasis - 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.

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

A. T2-MRI reveals two isodense masses - one in subependymal region and one near cortex (arrows).
B. Contrast T1-MRI reveals enhancement of two masses seen on T2 as well as third mass in left frontal lobe (arrows).
C. Contrast T1-MRI through pons reveals at least four other enhancing metastatic lesions. Note absence of edema.¹
PET
- The value of fluorodeoxyglucose PET is highly questionable based on the limited sensitivity of FDG PET for brain tumors in comparison to the physiologically high levels of glucose metabolism in healthy brain parenchyma - FDG PET has poor sensitivity (27%) for BM detection.
- Increased expression of amino acid transporters in BM compared with healthy brain tissue renders radiolabeled amino acids suitable for PET imaging based on high tumor-to-background contrast.

**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>Estradiol 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 choriocarcinoma 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).
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.

Brain metastases with symptoms related to mass effect

- **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**: Dexamethasone is the best drug choice (minimal mineralocorticoid effect).

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

**AEDS**

- **seizure prophylaxis** (not necessary if no history of seizure; i.e. anticonvulsants must be administered only to patients at risk for seizure)
- anticonvulsants should be started (routinely) before radiation therapy / surgery.
- incidence of postoperative seizures - 18-24%
- most commonly used drugs are LEVETIRACETAM, PHENYTOIN, CARBAMAZEPINE, VALPROIC ACID.

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

- **Level 3 recommendation**: Prophylactic AEDs are not recommended for patients with brain metastases who did not undergo surgical resection and are otherwise seizure-free.

- **Level 3 recommendation**: Postcraniotomy AED use for seizure-free patients is not recommended.

**ANTICOAGULATION**

Intracranial hemorrhage is frequently observed in patients with brain metastases but therapeutic anticoagulation does not increase the risk of intracranial hemorrhage.
matched, retrospective cohort study of 293 cancer patients with brain metastasis (104 with thymic, 74 melanoma, and 185 controls)

no differences in the cumulative incidence of intracranial hematoma at 1 year in the enoxaparin and control cohorts for measurable (19% vs 21%, Gray test P=0.97, HR 1.02 [90%CI 0.66-1.59]), significant (21% vs 22%, P=0.87), and total (44% vs 37%, P=0.13) intracranial hematomas.

risk of intracranial hemorrhage was fourfold higher (adjusted HR 3.98, 90% CI 2.41-6.57, P<0.001) in metastatic melanoma or renal cell carcinoma (N=66) than lung cancer (N=153), but risk was not influenced by enoxaparin.

EVOLUTION OF MODERN TREATMENT

• historical standard for the treatment of brain metastases was whole brain radiotherapy (WBRT), which was the subject of the initial Radiation Therapy Oncology Group (RTOG) randomized trials.

• Outcomes after WBRT for patients with brain metastases were poor, with median OS of only 3 to 4 for most patients. Survival for all patients varies between 6 months of life expectancy, regardless of the extent of intracranial disease.

• The initial standard for the treatment of brain metastases was whole brain radiotherapy (WBRT), which was the subject of the initial Radiation Therapy Oncology Group (RTOG) randomized trials.

• Outcomes after WBRT for patients with brain metastases were poor, with median OS of only 3 to 4 months for most patients. Survival for all patients varies between 6 months of life expectancy, regardless of the extent of intracranial disease.

SURGERY

- metastasectomy

• Indications for surgical resection in patient with good performance status: a) metastases > 3.5 cm (lesions < 2 cm - SRS + WBRT - less tissue diagnosis is needed) b) life-threatening strategic or located metastases** (steroid-resistant neurological symptoms) despite multiple cerebral metastases (symptomatic lesion is resected for, resecting other lesions → radiotherapy)

- need for tissue diagnosis (even if not met → XRT):

• Contraindications to surgery

1) radiosensitive tumor (e.g. small-cell lung tumor, germ-cell tumor, lymphoma / leukemia / melanoma, myeloma, chordoma, choriocarcinoma)

2) N.B. nonsmall cell lung metastases are mostly radioresistant – may benefit from surgery.

3) life expectancy < 3 months (WBRT indicated)

4) multiple lesions.

5) 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.

• 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 adjunction

* Ongoing generally recommended surgical resection to minimize risk of cavity LR

** N.B. surgery is followed by radiation – either SRS or whole-brain radiation therapy (WBRT).
Survival, median survival, and local control. Level 1 recommendation

CNS Systematic Review and Evidence

- Survive, median survival, and local control. Level 1 recommendation
- Critique: Results
  - 84 patients with single brain metastasis; arms: Patchell et al. (1990); Vecht et al. (1993); Mintz et al. (1996)

Surgery vs. WBRT for WBRT alone for solitary metastases

Surgical resection of a solitary metastasis has survival benefit (but...) - appropriate selection is necessary - surgical morbidity must be low

Three class 1 evidence RTCs:

   - Prospective randomized trial:
     - a) surgical removal followed by radiotherapy (surgical group) – 25 patients
     - b) needle biopsy and radiotherapy (radiation group) – 23 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 = 0.006) in patients with stable extracranial disease.
   - N.B. 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 (63 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 alone arm 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 Karnofsky 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 study group and breast carcinomas in WBRT group.

Radiation therapy always after resection (SRS and/or WBRT) is recommended over surgery. No differences in survival, median survival, and local control.

- Survival, median survival, and local control. Level 1 recommendation
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Radiation therapy always after resection (SRS and/or WBRT) is recommended over surgery. No differences in survival, median survival, and local control.
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 SENSITIZERS**

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

**Level 1 recommendation:** The use of temozolomide 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).

N.B. always aim for hippocampus-sparing WBRT (look for lesions in mesial temporal lobes)

- 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!

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

**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**

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry out all job duties, sexual performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted physically, still able to work, patient not disabled and able to carry out work of light or sedentary nature, e.g. light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Satisfied, and capable of all of above but unable to carry out any work activities, up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Completely disabled: Cannot carry on any work activity. Totally confined to bed or chair</td>
</tr>
<tr>
<td>4</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Adjuvant WBRT vs. observation - retrospective review from Mayo Clinic

- 30 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 resected single metastasis.
- post-operative WBRT reduces recurrence of brain metastases and reduces death from neurological causes:

**OPTIMAL METHODOLOGY**

**CNS Systematic 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 (BED) 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 Systematic 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: Similar cranial irradiation is given to prevent brain metastases (e.g. 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 MESENTHYINE to potentially delay, lessen, or prevent the associated neurocognitive toxicity.

TUMOR HISTOPATHOLOGY OR MOLECULAR STATUS

CNS Systematic 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.

STEREOTACTIC RADIOSURGERY (SRS)

Favorable characteristics of brain metastases for SRS:
1. Radiographically distinct on MR/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)
2. Boost after WBRT for single or multiple brain metastases
3. Recurrent brain metastases after WBRT or surgery
4. Adjuvant to surgery:
   a) after gross total resection (to surgical bed with nice regular margins ± any other < 3 cm lesions) instead of WBRT
   b) residual tumor after resection

Contraindications for Radiosurgery: large volume tumors causing symptomatic mass effect on the brain.

A. Stereotactic radiosurgery (SRS) - another standard of care for limited number of lesions (number is undefined but maybe up to 8)
   - minimum doses to the margin typically range from 14-24 Gy in a single session. provided by 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 (pioneered by Stanford group).
   - Current standard - do not include a brain margin (some centers include 1-2 mm of margin only to compensate for system inaccuracy).
   - patients may receive a single stress dose of corticosteroids at the conclusion of the SRS procedure.
   - for radiosensitive tumors, necrotizing 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 mets.

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 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 2-4 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 overall survival.

B. Fractionated stereotactic radiotherapy (fSRT) - equally effective to radiosurgery.

Dose – depends on tumor size
- if ≤ 2 cm, use 24 Gy (unless close to brainstem or optic structures)

Best results are for tumors < 1 cm in diameter!

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>≤ 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% (78 – 92%)</td>
</tr>
<tr>
<td>14</td>
<td>49% (34 – 65%)</td>
</tr>
</tbody>
</table>

Brain Metastases Onc32 (13)
Postoperative SRS

An early retrospective study from Stanford included 72 patients treated with postoperative SRS between 1999 and 2006, and 46 of these were treated to the resection cavity with an additional margin. An important finding was that cavity local control was significantly higher in patients with less conformal SRS plans. Conformity 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]. In order for the target to be completely encompassed by the prescription isodose line, CI must be ≥1. The arteriole Glioma Resection (AGRI) study found that the CI 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 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 expansion following a single conformally treated patient with a 2-mm expansion compared with the historical control of patients treated without a margin.26 The use of a margin was found to have significantly improved 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 = 0.04), while the 1-yr toxicity rates with and without the margin were 3% and 8%, respectively (P = 0.27). These findings led to the adoption of an expansion (generally 1-2 mm) to the cavity in 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 delineation uncertainty:

- uncertainty of posturgical cavity size (if SRS planning 4-5 weeks postop is done on immediate postop MRI): study from Dartmouth reported that about half of cavities (45.6%) were stable in size, as defined as a change in volume of <2 cm³, but about a quarter (23.3%) shrank by >2 cm³, and about the same proportion (30.2%) enlarged by >2 cm³.

Preoperative 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 administering postoperative SRS post-cavity resection, the theoretical risk of tumor spillage into CSF at the time of surgery (→ leptomeningeal disease (LMD)), investigators began to study the use of preoperative SRS as an alternative paradigm to maximize local control of the resection cavity and minimize Neuroscience treatment associated with WBRT.

Preoperative SRS treats the preoperative intact brain metastasis volume, which is well defined, readily identifiable on imaging, and does not require any margin expansion for target delineation uncertainty, i.e., the target field is the same as the gross tumor volume (GTV) as well as the added margin. Vs. the postoperative PTV, will always include a larger volume of normal brain tissue since the target includes a 1- to 2-mm expansion of the cavity into normal brain → increasing risk of radiation necrosis.

Preoperative SRS is given prior to surgery, with the potential advantage of increased patient compliance given the variable postoperative clinical course for patients, the variable timing of surgery and published studies of preoperative SRS (which included patients treated through 2014 at a single institutional study of 180 patients, of which 66 (36.7%) underwent preop SRS and 114 (63.3%) underwent postop SRS. Patients characteristic were well balanced between groups except for higher rates of performance status score of 0 (62.1% vs 28.9%, P < 0.001) and primary breast cancer (27% vs 5.5%, P < 0.001) for preop SRS. The preop SRS cohort also had lower median PTV (0.2 vs 2 mm³, P < 0.001) and prescribed dose (14.5 vs 18 Gy, P < 0.001) due to the 20% dose reduction, but similar GTV volume (8.3 vs 9.2 mL, P = .85). The median imaging follow-up period was 24.6 mo for alive patients.

- another potential issue with preoperative SRS is the possibility of subtotal resection after SRS

- Postoperative SRS

- One of the potential issues with preoperative SRS is the uncertainty of postsurgical cavity size

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SRS vs. WBRT

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 than their "cutoff 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 also played a role. CNS specialists who 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 5.6 in low-volume vs 4.1 in minimal-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.”

SRS vs. WBRT for Brain Metastases - N07TC - randomized trial conducted at 48 North American centers (194 patients with 1 brain met.; 59% from lungs):
- SRS was as effective as WBRT in terms of overall survival (11.5 vs 11.8 months).
- SRS provided better cognitive outcomes and better quality of life:
  - Median cognitive decline-free survival was 3.2 months for SRS and 2.8 months for WBRT (hazard ratio, 2.05; p < 0.001).
- SRS was better for patients whose cognition was "modest" compared to WBRT.
  - At 3 months following treatment, declines in QOL and physical well-being were significantly worse after SRS than after WBRT.
- WBRT was superior for the local control (WBRT provided higher overall intracranial tumor control than SRS at 6 months (90.0% vs 74.0%) and 12 months (78.6% and 54.7%) and better quality of life (mean QOL change from baseline: -0.0 to -0.3 for WBRT, 0.0 to 0.2 for SRS).

Conclusions:
- There is no significant difference in survival when WBRT-alone receives postop WBRT.
- WBRT and SRS avoid the well-known toxicities of WBRT. Furthermore, due to less time commitment and a quicker recovery after SRS, patients can restart systemic therapies more rapidly. SRS to the surgical cavity after resection of brain metastases should be considered a standard of care.

big tumor going for emergency OR – postop better WBRT (to control tumor spillage).

WBRT ± SRS

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

Level 1 recommendation: In patients with 2 to 3 brain metastases not amenable to surgery, the addition of SRS to WBRT is not recommended to.

WBRT ± SRS for 1-3 metastases ≤ 4 cm (RTOG 9508 trial)


- class I evidence.
- WBRT total 37.5 Gy.

RTOG trial

WBRT + SRS Survival Time

Mean

Survival

Survival

Conclusion:
1) SRS boost following WBRT is better than WBRT alone and should be a standard treatment for a single brain metastasis.
2) SRS boost following WBRT improves performance in all patients with ≤ 3 metastases and should be considered for all patients with 2-3 brain metastases.
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. 70-71% in the WBRT-alone arm; median survival was not statistically different between the two groups (7 months for WBRT alone vs 11 months for WBRT and radiosurgery boost [p = 0.223]). survival difference 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 a single SRS to achieve a significant survival.

newer WBRT delivery techniques using hippocampal avoidance may lessen the SRS advantage regarding neurocognition.

no difference between groups for OS, cavity LR, or distant brain failure in the adjusted analysis.

univariate 1-yr cumulative incidence of cavity LR was 13.9% vs 12.6% (P = 0.33) for preop from SRS.

preop SRS had a significantly lower cumulative incidence of LMC recurrence (P = 0.01) compared with postop SRS, with 1-yr rate of 2.2% vs 8.3% and 2-yr rates of 3.2% vs 16.6%, respectively. Postop SRS retained a significantly higher risk of LMC compared to preop in the adjusted analysis (HR: 4.03, 95% CI: 1.2-13.6, P = 0.02).

similar results were found for radiation necrosis and symptomatic radiation necrosis, with 1- and 2-yr cumulative incidence of symptomatic radiation necrosis of 14.6% vs 1.5% and 16.4% vs 4.9%, respectively (P = 0.01). Postop SRS retained a significantly higher risk of symptomatic radiation necrosis in the adjusted analysis (HR: 8.14, 95% CI: 2.16-30.74, P = 0.02).

composite outcome (cavity LR, symptomatic radiation necrosis, and LMC relapse) as an indicator of overall toxicity and tumor control was also assessed: preop SRS had significantly lower rates of the composite endpoint compared with postop SRS, with rates of 15.9% vs 31.8% and 2-yr rates of 27.9% vs 39.3%, respectively (P = 0.02). Postop SRS retained a significantly higher risk of the composite endpoint in the adjusted analysis (HR: 1.99, 95% CI: 1.16-3.42, P = 0.01).

similar results by the randomized trial – median cognitive decline-free survival was 3.2 months for SRS and 2.8 months for WBRT (hazard ratio, 2.05; p < 0.001). – effect of SRS on cognition is “modest” compared to WBRT. – at 3 months following treatment, declines in QOL and physical well-being were significantly worse after SRS than after WBRT.

mean QOL change from baseline: -0.5 vs -7.0, P = 0.03; mean well-being change from baseline: 0.4 vs -2.2, P = 0.002; at 6 months, physical well-being remained significantly better for SRS patients than for WBRT patients (decline of -3.2 vs -15.1, P = 0.04). – WBRT was superior for the local control (WBRT provided higher overall intracranial tumor control than SRS at 6 months (90.0% vs 74.0%) and 12 months (78.6% and 54.7%) and better quality of life (mean QOL change from baseline: -0.0 to -0.3 for WBRT, 0.0 to 0.2 for SRS).

Similar results were found for radiation necrosis and symptomatic radiation necrosis, with 1- and 2-yr cumulative incidence of symptomatic radiation necrosis of 14.6% vs 1.5% and 16.4% vs 4.9%, respectively (P = 0.01). Postop SRS retained a significantly higher risk of symptomatic radiation necrosis in the adjusted analysis (HR: 8.14, 95% CI: 2.16-30.74, P = 0.02).

conclusions:
- SRS boost following WBRT is better than WBRT alone and should be a standard treatment for a single brain metastasis.
- SRS boost following WBRT improves performance in all patients with ≤ 3 metastases and should be considered for all patients with 2-3 brain metastases.
- 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. 70-71% in the WBRT-alone arm; median survival was not statistically different between the two groups (7 months for WBRT alone vs 11 months for WBRT and radiosurgery boost [p = 0.223]). survival difference dependent on the extent of extracranial disease (p = 0.02).


newer WBRT delivery techniques using hippocampal avoidance may lessen the SRS advantage regarding neurocognition.
• class I evidence.
• WBRT total 30 Gy in 10 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.

<table>
<thead>
<tr>
<th>JSROG trial</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS</td>
<td>8 months</td>
</tr>
<tr>
<td>SRS + WBRT</td>
<td>7.5 months</td>
</tr>
<tr>
<td>Statistical</td>
<td>None</td>
</tr>
</tbody>
</table>

• commencement 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.

Conclusions:
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 prospective randomized study.
• withholding WBRT in favor of SRS alone is associated with improved neurocognition and increased survival, but decreased local and distant control.

Radiotherapy Practice Guideline for Metastatic Brain Tumors (Guideline Report #5-08, original guideline 2006)
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 (esp. 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 + SRS vs SRS + WBRT
• 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.

SRS vs. SURGERY
No prospective trials available.
• both are excellent treatment options for solitary brain metastases.

Laser Intestinal Thermal Therapy (LITT)
has been used to treat recurrent brain metastasis after SRS.

Repeat SRS is another option although local control rate is lower (e.g. tumor control rate was 53.5% by Im Young Kim et al. 2018) than after primary SRS.

LASER (LITT)
• Dr. Daniel – do not use LITT upfront, always do SRS first (vs. recurrent glioma – prefers LITT first and then SRS for LITT failure).
• risk factors for earlier local recurrence after LITT:
  o incompletely ablated lesions
  o recurrent lesions (as opposed to newly-diagnosed lesions)
  o larger lesions (> 6 cc)
  o dural-based lesions
  o no systemic therapy within 3 mos after LITT
• LITT is able to disrupt BBB with peak of permeability in 1-2 wk after LITT, and resolved in 4-6 wk — therapeutic window for systemic therapy!
CHEMOTHERAPY
- depends on systemic disease, tumor type, and stage. Most tumors that metastasize to brain are not chemosensitive1 (most sensitive - small cell lung cancer and seminoma).
  • 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).

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)
See recommendations for specific cancers
Level 1 recommendation: Cytotoxic chemotherapy alone for brain metastases is not recommended as it has not been shown to increase overall survival.
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
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

ROLE OF EXTRACRANIAL DISEASE
Most important factor for decision making – status of extracranial disease!
• 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.

ROLE OF TREATMENT MODALITY
Median 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) (Caiancoss et al. 1980)

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

Relapse rates beyond 2 yr following SRS alone for brain metastases - low in patients who do not suffer intracranial relapse within the first 2 yr and with low volume brain metastases, supporting a practice of less frequent screening beyond 2 yr.

- predictors of intracranial failure beyond 2 yr: 
  - failure before 2 yr (HR = 2.2, 95% CI: 1.2-4.3, P = .01)
  - total tumor volume ≥ 5cc (HR = 2.3, 95% CI: 1.2-4.3, P = .01)

**ROLE OF NUMBER OF METASTASES**

- presence of multiple brain metastases per se is not an indicator of an adverse prognosis compared to a single brain metastasis.

**RPA/RTG Classification**

**Radiation Therapy Oncology Group (RTOG)** classes for predicting outcome in brain metastases (i.e., recursive partition 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</td>
<td>age ≤ 65 yrs</td>
<td>Controlled primary disease, no extracranial metastases</td>
<td>11 (11.5 for single metastasis, 6.0 for multiple metastases)</td>
<td>16.1</td>
</tr>
<tr>
<td>2</td>
<td>age &gt; 65 yrs</td>
<td>Not group 1 or 3</td>
<td>8 (0.1 for single metastasis, 4.1 for multiple metastases)</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>


RPA classification has also been shown to have prognostic value in patients treated surgically.


**Meta-analysis of five randomized RTOG studies (1960 patients) → less subjective, more quantitative, easier to use scale:**

**Points:**
- 0
- 0.5
- 1.0

<table>
<thead>
<tr>
<th>Age</th>
<th>18 to 60</th>
<th>60 to 70</th>
<th>&gt; 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80</td>
<td>&gt; 80</td>
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<tr>
<td>Number of CNS metastases</td>
<td>&gt; 3</td>
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**Diagnosis Specific GPA (Median Survival):**

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<td>3.8</td>
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<tr>
<td>2</td>
<td>3.8</td>
<td>7.9</td>
<td>11.7</td>
<td>14.3</td>
<td>15</td>
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</tbody>
</table>

**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; LG: Lung and Other; LSM: Lung and Small cell; LSIQ: Lung and Squamous cell; OA: Other and Adenocarcinoma; OG: Other and GI; OR: Other and Renal; OSQ: Other and Squamous cell; SM: Skin-Melanoma; OO: Other and Other; PR: Partial Resection; CGTR: Complete/Gross total resection):
Brain Metastases


Specific Metastases

CNS melanoma

- 66-75% melanomas give brain metastasis! (melanocytes are derived from neural crest)
- most often multifocal
- unique tendency to hemorrhage!
- particularly prone to give pial implants.

Neurocutaneous melanosis - congenital giant hairy melanocytic nevi 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.

DIAGNOSIS

- CT – tends to be isodense or hyperdense; 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 region.
TREATMENT & PROGNOSIS

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

- Melanoma that metastasizes to CNS is incurable

1-3 lesions:
- a) surgical removal ± whole brain radiation
- b) radiosurgery ± whole brain radiation

Multiple metastases:
- a) whole brain radiation
- b) chemotherapy:
  - DACABRABINE – FDA approved for melanoma
  - TEMOZOLOMIDE
  - PILMU/MAZ (Yervoy®) – 3-10 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.
  - definitively act antagonistically (by suppressing immune response)

- while BRAF mutations are found in up to 66% of primary malignant melanomas, cerebral metastases harbor BRAF V600E mutations in 42%.
- BRAF inhibitors (BRAFi) VEMURAFENIB and DABRAFENIB are FDA approved for melanomas that express V600E; control rates are better for dabrafenib (31%) compared to vemurafenib (16%), presumably based on the better penetration of BBB due to its smaller size and molecular structure.

- There is insufficient evidence to make recommendations regarding BRAF inhibitors (BRAFi) DABRAFENIB and VEMURAFENIB for brain metastases due to melanoma.

LUNG CANCER

- Treatment is whole brain radiation (even for single symptomatic metastasis)
- Newer trend – chemotheraphy with concurrent SRS – tumor tends to shrink very rapidly; WBRT reserved for failures.
- *e.g. over eloquent cortex; if symptomatic due to global mass effect and tumor is large → surgical debulking before radiation

- CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019). Level 2 recommendation: SRS + chemotherapy is recommended to improve overall survival and progression free survival in lung adenocarcinoma patients.

NON-SMALL CELL

- CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019). Level 1 recommendation: temozolomide is not recommended as a treatment for patients with triple negative breast cancer.

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

BREAST 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.

- Inadequate 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: > >

Please visit website at www.NeurosurgeryResident.net