Brain Metastases

Last updated: August 8, 2020

EPIDEMIOLOGY

1. Metastases from systemic cancer can affect (metastasis) or by specific metastases follow treatment.

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- tumors that originate outside CNS and spread secondarily to CNS via hematoogenous 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 underestimated due to underdiagnosis and inaccurate reporting).

- 60% patients are 50-70 yrs.

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

- atypical brain metastases occur in 15-33% of patients who die of systemic cancer (50% 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% (e.g. squamous cell carcinoma, esophageal carcinoma)

- 1. 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 fibrinectin, 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
   - producing proteolytic enzymes (metalloproteinases, 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 (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).

*By producing proteolytic enzymes (metalloproteinases, cathepsins)

 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.
   - 30% 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! (but frequently to spine)

5. Sarcoma (3-10%)

6. GI tract (3-9%) (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.
   ∙ leptomeningeal metastasis - 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 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>7.3%</td>
<td>14.8%</td>
<td>16.3%</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1.7%</td>
<td>5.2%</td>
<td>9.8%</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.7%</td>
<td>4.0%</td>
<td>7.4%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0.4%</td>
<td>1.0%</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.1%</td>
<td>0.6%</td>
<td>1.2%</td>
<td></td>
</tr>
</tbody>
</table>

SOURCES IN CHILDREN

- leukemia > lymphomas > osteogenic sarcomas > rhabdomyosarcomas > Ewing sarcoma
- G2008-C222.7/WHO 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 – clinically 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, 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 junction”)

• astrocytes and astrocytes penetrate into brain, narrow and branch into arterioles
15-18% in cerebellum (esp. colonic, renal, pelvic tumors)
• 3-5% in brainstem
• 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 tissue volume and blood flow - highly 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 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 perivascula or perineural invasion without major bone destruction)

HISTOPATHOLOGY
- diverse as in primary tumors from which they arise.

Parenchymal metastases
- must be 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: B Infratentorial subcortical metastasis of small cell lung carcinoma.

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

F: Higher magnification of ventricular wall.

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

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.

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
- RCCMα, 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 patients > 35 years is highly suggestive! (but metastatic tumors are less likely to induce seizures than primary tumors)

- 10% present acutely with hemorrhage (most are intramural hemorrhages), seizure, infarct.
- Behavioral & cognitive dysfunction (35–75%); miliary metastases can produce progressive confusional state.
- Motor dysfunction (30–60%).
- Hydrocephalus is uncommon (in most cases, CARCINOMATOSIS MENINGITIS is cause).

Brain metastasis clinically presents in time frame related to primary tumor:
- Precocious (undetected primary);
- Synchronous (simultaneous primary);
- Metachronous (anteecedent primary) - most common!

**DIAGNOSIS**

**BLOOD STUDIES**

- CBC
- Electrolyte panel
- Coagulation screen
- Liver function panel
- Specific markers:
  - CEA, PSA, CA125, 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. 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.

**DIAGNOSIS OF NEURAXIS**

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

- Contrast CT - many are invisible (isodense) → underestimation.
- MRI with gadolinium - gold standard

  - Parenchymal - gadolinium MPRAGE, 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.

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

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!
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>GU 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):
**Limited (2-4) Brain Metastases on MRI**

- Confirm limited number of brain metastases with high-resolution, thin slice (2 mm) double dose contrast enhanced MRI.
- Assess systemic disease control and functional status.

**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:** DEKAMETHASONE 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.

**AED**

- 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:** postcranotomy 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!
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 all patients. Surgery is recommended in all patients with brain metastases for whom model-based prognostic models that included factors such as age, extent of metastatic disease, performance status, and number of brain metastases found ranges of expected OS after WBRT of approximately 2 to 4 for the worst prognostic group and up to 7 to 11 mo for the most favorable prognostic group.

In an effort to improve these outcomes, Patchell et al published a landmark randomized trial in 1990 investigating the role of surgical resection in addition to WBRT for patients with a single brain metastasis. This study demonstrated a significant improvement in OS with the addition of surgery prior to WBRT compared to WBRT alone (median OS 40 vs 15 wk, respectively, P < .01). The follow-up study randomized the same patient population with a single brain metastasis to surgery alone or resection followed by WBRT. There was no difference in OS between the randomized arms (median OS 43 vs 48 weeks, respectively, P = .39). However, there were significantly lower rates of local cavity recurrence, distant brain failure, total intracranial failure, and neurological death in the surgery and WBRT arm.

• another major advancement in the treatment of brain metastases was the advent and propagation of stereotactic radiotherapy (SRS). The addition of SRS to WBRT compared with WBRT alone for patients with 1 to 3 brain metastases was found to have a significant improvement in local control and stabilization/improvement of performance status at 6 mo in the phase III RTOG 95-08 trial. The study was negative for the primary endpoint of OS in all patients, but patients with a single brain metastasis were found to have significantly improved OS with SRS boost after WBRT (median OS 6.5 vs 4.9 mo, P = .04). Due to the increasing awareness of the potential negative neurocognitive effects of WBRT and the lack of OS benefit with the addition of WBRT to SRS, several trials investigated SRS alone vs SRS and WBRT for patients with a limited number of brain metastases (defined as up to 3-4, depending on the trial). In terms of tumor control, all trials showed significantly worse local control, distant brain control, and total intracranial control with WBRT alone, but with no detriment in OS with the omission of WBRT. Additionally, the proportion of patients experiencing neurocognitive decline was found to be significantly lower in the SRS alone arms at 3 to 4 mo post-treatment by approximately 25 to 30 absolute percentage points in the 2 trials that used a modern battery of neurocognitive assessments. There were also detrimental impacts on patient quality of life (QOL) associated with receipt of WBRT using validated QOL measures. For these reasons, SRS alone, but with no detriment in OS with the omission of WBRT, has become the preferred initial cranial radiation therapy (RT) treatment for patients with a limited number of brain metastases and good performance status.

SURGERY

-metastasectomy

Indications for surgical resection in good patient status with positive surgery indications:

a) Life expectancy > 6 months

b) Life expectancy > 3 months - Brain lesions > 2 cm - Not SRS feasible (less tissue diagnosis is needed)

c) Life-threatening systemic metastases +/- metastatic neurological symptoms despite other multiple cerebral metastases (symptomatic lesion is resected; for remaining lesions → radiotherapy)

d) *e. no other sites of metastasis exist in body or cerebellar lesion with ventricular obstruction

e) need for tissue diagnosis

Requirements (if not met → XT/R):

1) lesion in eloquent 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!

4) Karnofsky score > 70 (able to function independently)

5) life expectancy > 6 months

• patients that benefit from surgery most: Karnofsky > 70, younger age, favorable RPA class, and lower Eastern Cooperative Oncology Group (ECOG) performance status, 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 / melanoma / myeloma / choriocarcinoma)

N.B. nonsmall cell lung metastases are mostly radiosensitive – may benefit from surgery!

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) unidiagnosed 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 tissue diagnosis

d) surgical resection alone has an expected 1 to 3 yr local recurrence (LR) rate of 47.5%, hence adjuvant

• chemotherapy after surgical resection to minimize risk of cavity LR.

N.B. surgery is followed by radiation – either SRS or whole-brain radiation therapy (WBRT).

CNS Systematic Review and Evidence-Based Guidelines: Treatment of Adults With Metastatic Brain Tumors (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.

EVOLUTION OF MODERN TREATMENT

- matched, retrospective cohort study of 293 cancer patients with brain metastasis (104 with therapeutic metastasectomy and 189 controls)

- no differences in the cumulative incidence of intracranial hemorrhage at 1 year in the metastasectomy and control cohorts for measurable (19% vs 21%, Gray test P=0.97, HR 1.02 (90%CI 0.66-1.50), significant (21% vs 22%, P=0.87), and total (44% vs 37%, P=0.13) intracranial hemorrhages.

- risk of intracranial hemorrhage was fourfold higher (adjusted HR 5.98, 90% CI 2.41-14.57, P<0.001) in melanoma or renal cell carcinoma (N=649) than lung cancer (N=153), but risk was not influenced by metastasectomy.

Brain Metastases Ch132 (10)

- matched retrospective study of 104 patients with brain metastasis (104 with therapeutic metastasectomy and 189 controls)

- no differences in the cumulative incidence of intracranial hemorrhage at 1 year in the metastasectomy and control cohorts for measurable (19% vs 21%, Gray test P=0.97, HR 1.02 (90%CI 0.66-1.50), significant (21% vs 22%, P=0.87), and total (44% vs 37%, P=0.13) intracranial hemorrhages.

- risk of intracranial hemorrhage was fourfold higher (adjusted HR 5.98, 90% CI 2.41-14.57, P<0.001) in melanoma or renal cell carcinoma (N=649) than lung cancer (N=153), but risk was not influenced by metastasectomy.
Survival, median survival, and local control.

- metastases with favorable performance status and limited extracranial disease to extend overall survival.
- Level 1 recommendation

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (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...) – appropriate selection is necessary – surgical morbidity must be low

Three class 1 evidence RTCs:

Study


Treatment

Surgery + WBRT WBBT Statistical significance Surgery + WBRT Statistical significance Surgery + WBRT Statistical significance

Outcome

Median survival

40 weeks to 15 weeks < 0.01 10 months to 6 months < 0.004 5.6 months to 6.3 months


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.


84 patients with single brain metastasis, arms:

- a) surgery (gross resection = lobectomy) → radiation (50 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 radiotherapy did not improve the outcome:

- No difference in survival (63 months in R vs. 5.6 months in S+W)
- most patients died within the first year
- risk ratio for mortality in S+W arm compared with R alone arm is 1:5.5
- No differences in 30-day mortality (9.8% in S+W; 7% in R)
- No differences in morbidity
- No differences in causes of death
- 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 surgery group and breast carcinomas in WBRT group.

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


- 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-session radiosurgery.
- there is emerging data showing good local control and/or decreased toxicity with multisession SRS.

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

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 control.

Brain Tumors (2019)
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

WHO / ECOG

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).

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

– 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!

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 Karnovsky 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.

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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).

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WHOLE-BRAIN RADIATION THERAPY (WBRT)

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WHO / ECOG

ECOG PERFORMANCE STATUS

Grade | ECOG
---|---
0 | Fully active, able to carry on all phases of life's activities without restriction
1 | Restricted physically, unable to carry on all but light work and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2 | Restricted and capable of only limited outdoor work, unable to carry out any activity but able to lead an active indoor life
3 | Confined to bed, able to carry out no activity
4 | Completely disabled, Cannot carry on any activity
5 | Dead

Adjuvant WBRT vs. observation - retrospective review from Mayo Clinic

Smalley SR, HUBB 15:1612-1626, 1997

- 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 neurocognitive causes.

TREATMENT OPTIONS

Level 1 recommendation: standard WBRT dose/fractionation schedule (i.e. 30 Gy in 10 fractions or a biological equivalent dose [BED] of 39 Gy) should be considered as alternate dose/fractionation schedules do not result in significant differences in median survival or local control.

Optimal methodology

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).

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*use of WBRT has declined over the past 10 yr as the use of local and systemic therapies has evolved!
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. 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: WBRT, especially for patients with poor performance status or short predicted survival.

Level 3 recommendation: WBRT is recommended to improve median overall survival for patients with ≥ 4 metastases amenable to local therapy in terms of size and location.

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 similar to MR/CT
2. Pseudospherical 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. Adjutant 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 may be up to 8)

- 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 (pioneered by Stanford group).
- 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 median overall survival for patients with ≤ 4 metastases having a cumulative volume < 17 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.
- for 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% (78 – 92%)</td>
</tr>
<tr>
<td>20</td>
<td>99% (90 – 100%)</td>
</tr>
<tr>
<td>15</td>
<td>45% (24 – 67%)</td>
</tr>
</tbody>
</table>

BRAIN METASTASES
Postoperative SRS

A 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 a 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 prescription isodose line/volume of the target). In order to target the field to be completely encompassed by the prescription isodose line, CI necessarily must 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 study was that the CI was an increased risk factor of the risk of local recurrence in the postoperative SRS setting with more conformal SRS plans compared with less conformal plans as measured by the CI (likely due to difficulty containing 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. The use of a margin was not required to have sufficient coverage of 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 = .86), while the 1-yr toxicity rates with and without the margin were 3% and 9%, 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.

- uncertainty in postcavitary surgical margin (if SRS planning 4-5 weeks postop is done on immediate postop MRI: study found that up to 74% of patients with a gross tumor volume [GTV] > 2 cm² was unstable in size, defined as a change in volume of < 2 cm³, but about a quarter (23.3%) shrunk by > 2 cm³, and about the same proportion (30.2%) enlarged by > 2 cm³).

Properative SRS

Due to the perceived drawbacks of postoperative SRS, namely the need for cavity margin expansion due to the delineation uncertainty and the variable postoperative intact brain metastasis volume, the variability in administering postoperative SRS, and the theoretical risk of tumor spillage into CSF at the time of surgery, (leptomeningeal disease [LMD]), investigators began to use the postoperative SRS as an alternative paradigm for the stabilization of the cavity local control and minimize neurocognitive detriment associated with WBRT.

Postoperative SRS treats the postoperative 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 planning target volume (PTV) is the same as the gross tumor volume (GTV), with no added margin. Vs. the postoperative PTV, will always include a larger volume of normal brain tissue since the target is tumor kill. This effect can be quantified as the oxygen enhancement ratio, which is defined as the ratio of radiation doses during lack of oxygen compared to no lack of oxygen for the same biological effect. Based on this rationale, a 20% dose reduction compared to standard maximum lesion dosimetry SRS dosimetry, as defined by the RTOG 00-10 study, was used for the properative SRS studies.

One of the potential issues with preoperative SRS is the possibility of subdural resection after SRS. The published studies of postoperative SRS (which include patients treated through 2014 at a single institution) did not have any instances of subdural resection and the gross total resection rate was 100%. The current consensus of practice from that institution in the case of subtotal resection would be to observe the residual disease given that it has been treated with a definitive though modestly reduced dose of SRS, reserving salvage local therapy for cases of progression (S. Burri, personal communication, October 27, 2017).

Another issue to note in preoperative SRS is the lack of pathologic confirmation of CNS disease prior to administering SRS, which is not the case in the postoperative setting. The risk of nonneatstastic disease in patients with suspected single brain metastases from trials conducted in the 1980s and 1990s ranged from 1 to 11%. This has led to a more robust availability of data for risk of non-neatstastic disease in patients with multiple brain lesions and/or in the modern era due to the fact that the vast majority of patients are treated with SRS alone without CNS pathologic confirmation. The rate of false-positive imaging results is recognized as comfortably low given the lack of CNS biology requirements on all recent SRS clinical trials and the adoption of SRS alone as the preferred treatment method for patients with a limited number of brain metastases.

SRS and immunotherapy: high dose per fraction RT is associated with increased surface tumor antigen expression. Immunotherapy can be delivered to an intact tumor with intact blood supply and oxygenation. This effect can be quantified as the oxygen enhancement ratio, which is defined as the ratio of radiation doses during lack of oxygen compared to no lack of oxygen for the same biological effect. Based on this rationale, a 20% dose reduction compared to standard maximum lesion dosimetry SRS dosimetry, as defined by the RTOG 00-10 study, was used for the properative SRS studies. One of the potential issues with preoperative SRS is the possibility of subdural resection after SRS. The published studies of postoperative SRS (which include patients treated through 2014 at a single institution) did not have any instances of subdural resection and the gross total resection rate was 100%. The current consensus of practice from that institution in the case of subtotal resection would be to observe the residual disease given that it has been treated with a definitive though modestly reduced dose of SRS, reserving salvage local therapy for cases of progression (S. Burri, personal communication, October 27, 2017).

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Level 2 recommendation

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 depend on physician characteristics:

- CNS specialists were consistently more likely to treat more metastases with SRS - 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 - N107C - randomized trial conducted at 48 North American centers (194 patients with 1-4 brain mets. 94% from using SRS: 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, 2.0; p < 0.0001) – effect of SRS on cognition was "modest” compared to WBRT.
  - o months following treatment, declines in QOL and physical well-being were significantly less pronounced after SRS than after WBRT (mean QOL change from baseline: -1.5 vs -7.0, P = 0.03; mean well-being change from baseline: -4.4 vs -20.2, 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 = 0.046).

- WBRT后 suggested the preferred for the local control (WBRT provided higher overall intracranial tumor control than SRS at 6 months (90.0% vs 74%) 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. Brown (radiation oncologist at the Mayo Clinic in Rochester, MN): “There is no significant difference in survival when a patient receives postoperative SRS or WBRT, and SRS avoids 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 for the surgical cavity after resection of brain metastases should be considered a standard of care.”

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

**WBRT + SRS**

**WSN 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.

**WBRT + SRS for 1-3 metastases ≤ 4 cm (RTOG 9008 trial)**


**Conclusions:**

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 for 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 for 1-4 metastases ≤ 3 cm (Japanese Radiation Oncology Study Group 99-1 trial)
BRAIN METASTASES

- 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.
- 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.

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 was associated with improved neurocognition and increased survival, but decreased local and distant control.

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 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

- Combination of SRS and WBRT for 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. Danisch – 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:
  - incompletely ablated lesions
  - recurrent lesions (as opposed to newly-diagnosed lesions)
  - larger lesions (> 6 cc)
  - dural-based lesions
  - 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 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).

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.
Level I 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
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) (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; LSM, Lung and Small 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):

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**

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

```
<table>
<thead>
<tr>
<th>Class</th>
<th>Karnofsky score</th>
<th>Systemic Disease</th>
<th>Medium Survival (months) with WBRT</th>
<th>Adding SRS boost to WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (age ≤ 65 yrs)</td>
<td>70</td>
<td>Controlled primary disease, no extracranial metastases</td>
<td>2.3 (1.4 for single metastasis, 0.6 for multiple metastases)</td>
<td>9.7</td>
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<tr>
<td>2 (age &gt; 65 yrs)</td>
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<td>Not group 1 or 3</td>
<td>Not applicable</td>
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<tr>
<td>3</td>
<td>70</td>
<td>1</td>
<td>Not applicable</td>
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</tbody>
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<td>Extracranial metastases</td>
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**Meta-analysis of five randomized RTOG studies (1960 patients) – less subjective, more quantitative, easier to use scale:**

```
<table>
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<th>Score</th>
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**Diagnosis Specific GPA (Median Survival):**

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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 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.

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:
- **Dacarbazine** (V600E mutations (marked myelosuppressive properties)
- **Temozolomide** (V600E) – 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.
  - steroids 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 (BRAFis) **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.

**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 (BRAFi) **Dabrafenib** and **Vemurafenib** for brain metastases due to melanoma.

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**LUNG CANCER**

**Small-Cell**

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

Never treat – chemotherapy 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)**

There is insufficient evidence to make recommendations regarding epidermal growth factor receptor inhibitors **cetuximab** and **erlotinib** for brain metastasis due to non-small cell lung 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.

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.

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**BIBLIOGRAPHY**

For ch. “Neuro-Oncology” → follow this LINK >>

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**Viktor’s Notes** for the Neurosurgery Resident
Please visit website at www.NeurosurgeryResident.net