Contemporary Management of Brain Metastases

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Definitions

• Primary tumor - original site of cancer
  - Lung, breast, melanoma, renal cell carcinoma, etc.

• Metastasis - tumor cells which have migrated from the original site
  - Brain, bone, other organs (liver metastases with lung primary, etc.)
Overview

- Epidemiology
- Diagnosis
- Imaging
- Radiation: whole brain, stereotactic radiosurgery
- Surgery
- Future treatments

Epidemiology

- Approximately 150-170,000 annually
- Posner and Cherik: 24% of 2375 cancer patients
- Increased age 45-64 but most prevalent over 65
- Presenting symptom of cancer in 15%
- Solitary site of cancer 9%
Incidence is increasing

- Increasing length of survival
- Increasing rate of diagnosis
  - MRI
  - PET scans
  - Protocols
- BBB- blood-brain barrier
  - Relatively immunoprotected environment

Timing of presentation

- **Metachronous 80%**
  - 2+ mos from initial Dx
- **Synchronous**
  - Within 2 mos of Dx
- **Precocious**
  - Diagnosis of brain metastasis before primary tumor

Symptoms

- More dependent on location in brain and growth rate than tumor type
- Headache alone 50%
- Seizures 20%
- Hydrocephalus - blockage of spinal fluid drainage
- Mental status changes (confusion, sleepiness)
- Tumor TIA (mini-stroke) - symptoms which improve
- Asymptomatic 10%
MRI - metastases vs. glioma
(primary brain tumor)

- Multiple
- Well-circumscribed
- Grey-white junction
- Common in posterior fossa

- Single
- Infiltrative
- Cortical
- Uncommon in posterior fossa
Imaging

- Screening
  - Non small cell lung cancer
  - Breast cancer
- Increased sensitivity on triple dose contrast, thin-cut MRI
- Hemorrhagic
  - Melanoma, thyroid, renal, breast, lung
- Possibly CT with contrast, MRI without contrast
  - Less sensitive
Physiologic imaging

- PET scan
  - $^{18}$F-deoxyglucose
  - Increased cellular activity
- SPECT
- Perfusion MRI
- MR spectroscopy (MRS)
FIGURE 2.3. An 81-year-old man with metastatic malignant melanoma. Axial contrast-enhanced 3D magnetization-prepared rapid gradient-echo image (A) shows an enhancing mass in the left frontal lobe with surrounding hypointensity. Axial FDG-PET (B) image reveals a corresponding hypermetabolic focus consistent with malignancy. Coronal FDG-PET (C) demonstrator both the brain mass (arrows) and a second hypermetabolic focus in the gastric antrum (double arrows) that represent unsuspected metastatic disease.

FIGURE 2.5. A 62-year-old woman with metastatic ovarian carcinoma. Axial contrast-enhanced T2WI (A) shows a peripherally enhancing mass lesion in the posterior left frontal lobe, with a punctate central focus of enhancement. Spectroscopy shows the intratumoral region (B) to have elevated Cho and decreased NAA levels, and the peritumoral region (C) to have a normal spectrum. CholG overlay map (D) reveals an abnormally elevated ratio within the tumor (case courtesy of Meng Liu, M.D., New York University Medical Center, New York, NY).
Anticonvulsants

- American Academy of Neurology
- Antiepileptic drugs (AEDs) not needed unless history of seizures
  - Dilantin, phenobarbital
  - Blood levels, interference with other medications
- Peri-operative coverage - one week
- Unclear with newer AEDs - Keppra, Zonegran
Surgical Techniques

- MRI guidance
- Intraoperative MRI
- Intraoperative ultrasound
- Motor strip mapping
- Language mapping
- Awake craniotomy
Patchell 1990

- Randomized study in single brain mets
- 48 patients
- Improvement in median survival for surgery + XRT vs. XRT alone (40w. vs. 15w., p<.01)
- Longer functional independence (38w vs 8w, p<.005)
- Patchell 1998- whole brain radiation after surgery delayed neurologic morbidity and mortality (vs. surgery alone)
- Few randomized surgical trials

Factors favoring excision of a solitary lesion

- Primary disease controlled
- Accessible lesion
- Symptomatic, large (> 4cm), or life-threatening lesion
- Not radiosensitive tumor (not small-cell lung carcinoma)
- Only accessible pathology
- No delay in appropriate treatment from craniotomy
Factors favoring excision of multiple lesions

- Primary disease controlled
- Accessible lesions, less than 4
- Symptomatic, large (> 4cm), or life-threatening lesions
- Not radiosensitive tumor
- Only accessible pathology
- No delay in appropriate treatment from craniotomy

Bindal, Sawaya 1993

- Resection of up to 3 accessible metastases improved survival to the same as those with a single metastasis
- SRS (stereotactic radiosurgery) is a possibility
FIGURE 3.2. A and B, multiple metastatic brain tumors with large dominant lesions. This 45-year-old man presented with headaches and personality change. He had no known primary lesion at the time. He opted to have surgical removal of the largest two lesions for diagnosis and for relief of mass effect. Histology confirmed lung carcinoma. He went on to receive WBRT. He maintained a KPS score of 100 and worked full time for an additional 2 years. He had an overall survival of 27 months from the diagnosis of the brain lesions. This case illustrates some of the issues discussed in the text regarding the use of surgery in multiple brain metastases.

FIGURE 3.3. This 72-year-old man had a remote history of colon cancer. He presented with seizures and mental status change. Brain imaging (A and B) demonstrated a solitary right temporal lesion measuring 1.6 × 2.0 cm, but with significant surrounding edema. His seizures were difficult to control medically. He opted to undergo craniotomy for removal of the lesion, despite the small size. This case illustrates some of the issues discussed in the text regarding the use of surgery versus radiosurgery for patients with a single brain metastasis.
Whole Brain Radiation Therapy (WB XRT)

- 30 Gy in 10 fractions over 2w. vs. 50 Gy in 2 Gy fractions
- Radiosensitive
  - SCLC, germ cell tumors, lymphoma, leukemia, multiple myeloma
- “Radioresistant”
  - Melanoma, renal cell carcinoma, sarcoma
  - Different for radiosurgery

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Complete response (%)</th>
<th>Partial response (%)</th>
</tr>
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<tbody>
<tr>
<td>Small cell lung carcinoma</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Adenocarcinoma (nonbreast)</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All metastases</td>
<td>24</td>
<td>35</td>
</tr>
</tbody>
</table>

XRT Complications

- **Acute < 90d**
  - N/V, alopecia, hearing loss, skin reactions, somnolence
  - Some symptoms reversible
- **Late > 90d**
  - Radiation necrosis, personality changes, memory loss, cognitive deficits, ataxia, incontinence
- **Should be minimal if 30 Gy in 10 fractions or more**
- **Severe complications 5%; total rate higher**
Small cell lung cancer

- 20% of lung cancer
- Oat cell cancer
- Younger, smokers
- Median survival 6-10 mos.
- Mets in 80% of those who survive 2y.
- Radiosensitive- prophylactic WB XRT
- Biopsy of lung lesion important when possible when facing undiagnosed lung mass and brain mass

Stereotactic radiosurgery (SRS)

- Targeted radiation delivery
- Energy sources:
  - gamma knife- Cobalt-60
  - linear accelerator (LINAC)- electron accelerator
  - proton beam
- Cyberknife, Novalis- frameless LINAC
  - Accuracy vs patient comfort
- 18-22 Gy
Surgery vs. Radiosurgery

- Limited data on comparative efficacy
- Need good systemic health for craniotomy
- Mass effect
- Significant edema
- Small, relatively inaccessible lesions
Outcome

- Karnofsky >70 (good neurologic status)
- Age <60
- No systemic metastases
- Controlled primary disease
- >1y. since primary Dx
- Solitary metastasis

Outcome

- No treatment- 1 mo. median survival
- Steroids alone- 2 mos.
- WB XRT 3-6 mos. 50% deaths from intracranial progression
- Surgery, WB XRT 12 mos.
  - Improved for young age, unifocal and accessible disease, good neurologic status
Whole brain radiation vs. radiosurgery boost after surgery

- Whole brain essentially cannot be repeated
- Assumes that primary tumor seeding the brain is a one-time event
- Assumes that survival does not generally last long enough to see side effects of whole brain radiation

**TABLE 5.3. Median survival by primary tumor type**

<table>
<thead>
<tr>
<th>Primary tumor type</th>
<th>No. of patients</th>
<th>Median survival (mo)</th>
<th>No. of patients</th>
<th>Median survival (mo)</th>
<th>No. of patients</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>88</td>
<td>6.9</td>
<td>93</td>
<td>7.1</td>
<td>231</td>
<td>8</td>
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<td>Breast</td>
<td>12</td>
<td>16.6</td>
<td>50</td>
<td>8.6</td>
<td>38</td>
<td>17</td>
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<tr>
<td>Colon</td>
<td>9</td>
<td>3.3</td>
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<tr>
<td>Lung</td>
<td></td>
<td></td>
<td>282</td>
<td>8.7</td>
<td>94</td>
<td>9</td>
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<tr>
<td>NSCLC</td>
<td>40</td>
<td>9.7</td>
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<tr>
<td>SCLC</td>
<td>5</td>
<td>2.8</td>
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<tr>
<td>Renal</td>
<td>49</td>
<td>12.3</td>
<td>62</td>
<td>9.6</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>5.4</td>
<td>82</td>
<td>8.4</td>
<td>39</td>
<td>6</td>
</tr>
</tbody>
</table>

* NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
Surgery + whole brain vs. radiosurgery boost

- Cancer treatment centers disagree
- May recommend whole brain for any patient with one metastasis, even after surgery
  - Risk of complications of whole brain radiation
- May recommend radiosurgery boost after surgery, assuming close follow-up with MRIs
  - Risk of distant recurrence
  - May need radiosurgery, whole brain radiation in future
- Follow closely with MRIs (e.g., every 3 months)

Summary

- Surgical resection of brain metastases should be considered for patients with limited disease in good condition
  - After surgery - whole brain radiation vs. radiosurgery boost
- Radiosurgery - difficult to remove, poor condition for surgery, poor control of overall cancer
- Whole brain radiation 4+ lesions, SCLC
Unanswered questions

• Is the rate of distal failure when avoiding WB XRT significant to the patient?
• Is there a more sensitive method for detecting micro-metastases than MRI?
• Is there a benefit to WB XRT after radiosurgery?
• Is there a benefit with low risks to radiosurgery after whole brain radiation?

Ongoing studies

• European Organisation for Research and Treatment of Cancer (EORTC) 22952-comparison of surgery and radiosurgery +/- XRT
New treatments

- Temodar
  - Alkylating agent which crosses BBB
- Gliadel (BCNU)
  - Chemo wafer placed across the BBB
  - XRT or SRS?
  - Is local vs. distant disease the problem?
- Radiosensitizers
  - Efaproxiral, motexafin gadolinium
- Microwave ablation