Contemporary Treatment of Brain Metastases

Joseph C. T. Chen, MD

The Extent of the Problem

- Incidence of cancer
  - 1 in 5 Americans will die of cancer.
- Incidence of metastatic cancer to brain
  - 170,000 new cases per year in USA
  - 1,900 new cases per year in Scal-KP
- Ten times the number of patients with primary brain tumors.

Primary sites with propensity to metastasize to brain

- Breast
- Lung
- Melanoma
- Renal
- Colon

Pathogenesis of Brain Metastases

Presenting symptoms

- Headache
- Seizures
- Vomiting
- LOC
- Focal deficits

- But: Often found through staging workups
Management issues in Metastatic Disease to Brain

- Diagnosis
- Treatment
- “Holistic approach” versus organ based approach
  - Oncologic Goals
  - QOL goals
- Complication management

Historical Management of Brain Metastases

- Untreated survival
  - Prior to modern imaging techniques
  - Median survival: 1 month
- Corticosteroids
  - Median survival: 3 months
- Radiotherapy
  - Median survival: 6 months
- Surgery
  - For solitary lesion, median survival >12 months
- Radiosurgery
  - For solitary lesion, median survival >12 months

Major Treatment Arms

- Surgery
- Radiotherapy
- WBRT

Definitions

- Adjuvant
  - No residual disease after surgery
- Overall Survival
- Progression Free Survival

WBRT

Table 12. Brain tumor response overall

<table>
<thead>
<tr>
<th>Response</th>
<th>RT</th>
<th>RT + Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>6</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Partial</td>
<td>8</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Stable</td>
<td>11</td>
<td>11 (53%)</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

RT = radiotherapy.
Surgical = microsurgery.

Surgery+WBRT versus WBRT alone

Median Survival improved from 15 to 40 weeks
WBRT+Surgery versus Surgery alone

- Patchell 1998
  - Death due to neurological cause improved when WBRT added.

Surgery+WBRT versus SRS+WBRT

- Two good studies- both retrospective.
  - Schoggl 2000
    - Vienna, GKRS
  - O’Neill 2003
    - Mayo, GKRS
  - Both demonstrate no significant difference in survival.

Patient SL WBRT+SRS

68 yo female with new diagnosis of lung CA synchronous brain metastasis. Presented with hemianopsia

Patient MB - Standalone SRS

68 yo female, breast cancer 1 year prior to presentation Presenting with aphasia

SRS for Eloquent Locations

- RTOG 9508
- SRS+WBRT vs WBRT
- A prospective randomized trial
SRS+WBRT versus SRS alone

- Aoyama *JAMA*, 2006 Jun 7;295(21):2483-91
- Japanese randomized prospective trial with 132 patients randomized

Chang et al 2009

- Superior local control with addition of WBRT to SRS
- Freedom from distant recurrence superior with addition of WBRT
Issues with Chang et al Lancet Oncol

• Stratification to outcome
  ▫ RPA, Number of Mets, Histology
  ▫ NOT cognitive status!
• Lower survival with improved local control?
• Lower survival with improved organ control?
• Cognitive status issues
  ▫ Measurements taken at known time to nadir of neurocognition following WBRT
  ▫ Authors did not correct for AEDs, steroids, sedatives and narcotic pain relievers.

Tumor Bed Radiosurgery
Surgery+SRS

• Mathieu
• Other studies since then
• All have been retrospective

WBRT Local Control with Surgery

• Patchell 1990
• Patchell 1998
• Local control at 12 months of >85%

Tumor bed radiosurgery

• Mathieu 2008 (12m PFS 70%), Prabhu 2012 (12m PFS 78%)
• Both have 12 month control of less than 80%

Practical Issues with Tumor Bed SRS

Does surgery accomplish anything to make definitive treatment easier?

Issues with SRS planning following attempted resection

• 69 yo female with endometrial CA, asymptomatic with cerebellar lesion seen on MRI for unrelated issue.
Issues with SRS planning following attempted resection
• 67 yo male with widespread disease from melanoma presenting with seizure and pneumonia

Pre-Op
Post Op

Issues with SRS planning following attempted resection
• 57 yo male presenting with headaches and dizziness, improved and asymptomatic on steroids

43 yo female with ovarian CA
Presents with malaise

Data Conclusions
• SRS affords control similar to surgery
• In cases with single brain metastases, Surgery+WBRT is superior to WBRT alone. Similarly, WBRT+Surgery is superior to surgery alone.

The role of Chemotherapy
• In past, not seriously considered.
• BBB issues.
  - Drugs not actively transported have been ineffective in past
  ▪ Hydrophilic
  ▪ >500 Da
  ▪ Monoclonal Ab
  ▪ Antisense genetic therapy
  ▪ Viral vectors
  ▪ Stem Cells
• Presently no accepted role for routine use of chemotherapy in management of brain metastases
Bevacizumab (Avastin)

Complication management with SRS
- New neurological deficits
- Radiation necrosis

Imaging evaluation and treatment of radiation necrosis
- Standard contrast-enhanced MRI
- Perfusion MRI
- Spectroscopy
- PET

Treatment of Radiation Necrosis
- Steroids
- Surgery
- Avastin (bevacizumab)
- Time

Patient GM Melanoma

Cost - Thinking in the New Normal
- Rutigliano 1995
  - SRS superior to SR ($40,648 vs. $52,384 per life year)
- Mehta 1997
  - SRS superior to SR ($270 vs. $524 per one life week saved)
- Vuong 2012
  - SRS superior to SR (Cost of 60% of surgery for equivalent life span saved)
Primum no nocere

- The good physician treats the disease; the great physician treats the patient who has the disease – W. Osler