Neurocognition in Patients with Brain Metastases

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Treatment Outcomes I

Traditional endpoints of efficacy:

- Physician’s point of view:
  - Primary: OS
  - Secondary: PFS
  - Parameters of disease like MRI, rCBV, PET
  - Karnofsky, Barthel

MRI T2  rCBV  FET PET
Treatment Outcomes II

Secondary/tertiary endpoints of efficacy:

- Patient’s point of view (patient reported outcomes)
- Largely ignored earlier due to dismal outcome
  - Health-related quality of life (HRQOL)
  - Depression
  - Fatigue
  - Neurocognitive functioning
Relevance of Neurocognitive Deficits

- Subtle cognitive impairment: ↓ HRQOL
- Recognizing effects of disease & therapy on neurocognitive outcomes important:
  - formulating treatment modifications
  - formulating strategies for rehabilitation
- maxime functional ability
Neurocognitive Functioning in Patients with Brain Metastases

- Brain mets
- Surgery
- SRS, WBRT
- Chemotherapy
- Corticosteroids
- Epilepsy
- AED’s
- Fatigue and depression
- ... all other intrinsic brain diseases, general diseases, endogeneous and exogeneous intoxications ...
Incidence of Neurocognitive Deficits

▶ Majority significant neurocognitive deficits
  ▣ more common than physical disability

▶ Range: subtle problems with concentration, memory, affect, and personality to severe dementia

▶ Early report (1989): dementia in 11% patients who survived 1 year after WBRT
  ▣ HOWEVER, none of patients treated with conventional schedules and doses developed serious long-term dementia!
Incidence of Neurocognitive Deficits

- Prospective studies in SCLC with PCI: cognitive deficits prior to RT
  - 97% impaired at baseline (Komaki, 1995)
  - 40%–60% at randomization (Arriagada 1995; Gregor, 1997)
- Deficits unrelated to age, gender, previous therapy (Gregor, 1997)
- Treatment and subsequent reduction in brain tumor load may even lead to improved neurocognitive function (Li, 2006)
Cognitive Assessment in Routine Clinical Context Feasible

- Extensive neurocognitive assessments in 55 brain metastases patients ➔
  - Excellent compliance rates prior to (95%), upon completion of (84%), and 1 month after (70%) WBRT (Regine, 2004)

- 100% compliance in single institution study in 30 patients (Herman, 2003)

- Large phase III trial (401 brain mets + WBRT + Motexafin Gadolinium)
  - 90.5% of patients baseline cognitive impairment (Meyers, 2004)
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Neurocognitive Functioning

... all other intrinsic brain diseases, general diseases, endogenous and exogenous intoxications ...
Aims Neurosurgery

- Local control, prolonging survival

- Reduce symptoms
  - improve neurological outcome
  - improve epilepsy control
  - improve cognitive outcome

Balance
- maximum tumor resection
- minimal functional damage
Local Therapy: Neurosurgery (Chargari, 2010)

Surgical resection of single operable metastases indicated in patients with good control of extra cerebral metastatic disease & good prognostic group (KPS, age)

<table>
<thead>
<tr>
<th>Study</th>
<th>Total number of patients/patients with breast cancer</th>
<th>Number of metastases</th>
<th>Focal treatment</th>
<th>Brain relapse (%)*, WBRT alone vs combined treatment</th>
<th>Median overall survival (months), WBRT alone vs combined treatment</th>
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<tbody>
<tr>
<td>Patchell et al. (1990)</td>
<td>48/3 (6.3%)</td>
<td>Single</td>
<td>Surgery</td>
<td>52 vs 20 (P&lt;0.02)</td>
<td>3.5 vs 9.2 (P&lt;0.05)</td>
</tr>
<tr>
<td>Noordijk et al. (1994)</td>
<td>63/12 (19%)</td>
<td>Single</td>
<td>Surgery</td>
<td>NA</td>
<td>6 vs 10 (P&lt;0.05)</td>
</tr>
<tr>
<td>Mintz et al. (1996)</td>
<td>84/8 (11.9%)</td>
<td>Single</td>
<td>Surgery</td>
<td>NA</td>
<td>6.3 vs 5.6 (NS)</td>
</tr>
</tbody>
</table>

WBRT + resection associated with fewer recurrence and better HRQOL when compared to WBRT alone
Two studies also demonstrated survival benefit
Surgery Effects on Cognition

NO data on brain metastases!

- EOR decisive?
- Focal cognitive deficits related to tumor location
- Differentiation difficult
  - Intracranial pressure
  - Corticosteroids
  - AEDs
  - Psychological effects
Impact of Resection on Cognition

- Beneficial because of reduction of tumor mass
- Tumors in right hemisphere less risk
- Mainly (transient) neurological deficits owing to damage of normal surrounding tissue and/or edema
Tumor Location & Mood

► Ventromedial Prefrontal & Parietal Cortex:
  - anxiety
  - irritability
  - fatigue

► Dorsolateral Prefrontal & Somatosensory Cortex:
  - indifference
  - euphoria
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Neurocognitive Functioning
Local Therapy: SRS

- Single metastasis, but resection not possible due to site of metastases or patient’s poor medical condition
- Highly conformational irradiation approaches such as Gamma Knife or Cyber knife radiation
- 3 or fewer brain metastases <4 cm in greatest dimension
- Low toxicity, high local control, cost effective
- 5 – 10% radiation necrosis, depending on follow-up
Local Therapy: WBRT & SRS (Chargari, 2010)

**Table 2** | Randomized phase III trials of focal treatment alone versus focal treatment plus WBRT

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<td>Patchell et al. (1998)</td>
<td>95/9 (9.5%)</td>
<td>Single</td>
<td>Surgery</td>
<td>70 vs 18 ($P&lt;0.001$)</td>
<td>9.8 vs 11 (NS)</td>
</tr>
<tr>
<td>Aoyama et al. (2006)</td>
<td>132/9 (6.9%)</td>
<td>1–4</td>
<td>SRS</td>
<td>76.4 vs 46.8 ($P&lt;0.001$)</td>
<td>8 vs 7.5 (NS)</td>
</tr>
<tr>
<td>Mueller et al. (2009)</td>
<td>359/42 (11.7%)</td>
<td>1–3</td>
<td>SRS or surgery</td>
<td>54 vs 31.4 ($P&lt;0.001$)</td>
<td>10.9 vs 10.9 (NS)</td>
</tr>
</tbody>
</table>
| Chougule et al. (2000) | 73/NA                                                | 1–3                  | Gamma Knife®   | LR: 13 vs 9
New BM: 43 vs 19                                              | 7 vs 5 (NS)                                                                 |

Local Control improved with combined therapy, reduced frequency of intracranial relapse
BUT: Lack of benefit in overall survival
WBRT + SRS results in greater risk of significant decline in neurocognitive function
“Dose-Limiting Toxicity” for the Brain

- Necrosis rates of ~5% starting at 60 Gy
  - 72 Gy with altered fractionation
- Visual damage of ~1-3% starting at >54 Gy
- Endocrine damage starts at ~45 Gy
- Cochlear dysfunction starts at >50 Gy

- Neurocognitive damage
  - Depends on what you measure, when, & age
Determinants of Radiation-Induced Injury

- Fraction size
- Advanced age (>60 years)
- Higher total dose
- Volume of brain irradiated
- Chemotherapy
- Co-morbid vascular risk factors
  - E.g., diabetes mellitus
Effects Radiotherapy on Cognition

Late Delayed Radiation Injury

- 3 months to 3 years (or longer) after RT
- Necrosis subcortical white matter
- Cortical atrophy
- Demyelination
- Vascular changes
Radiation-Induced Injury

Subcortical white matter changes

- Neurobehavioral slowing
- Apathy
- Fine motor control
- Executive functions (mental flexibility)
- Memory (retrieval)

FLAIR MRI, 6 mo after WBRT (30 Gy) for lung metastasis
The hippocampus plays a significant role in RT induced dementia

Doses as low as 2 Gy cause significant toxicity to the hippocampus

Conformal avoidance of the hippocampus may help reduce neurocognitive deficits
Hippocampus Avoidance with IMRT

IMRT with tomotherapy achieves significant dose reduction (hippocampus), while delivering 30 Gy to the rest of the brain.
Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study


**Summary**

Background: Because survival benefits of treatment with radiotherapy are questionable and such treatment can cause substantial damage to the brain, an optimal management strategy for low-grade glioma remains controversial. We aimed to identify the specific effects of radiotherapy on objective and self-reported cognitive function, and on cognitive impairment over time. In patients with low-grade glioma treated with radiotherapy.

Methods: 195 patients with low-grade glioma (WHO grade 2) underwent radiotherapy (50%) or no surgery (50%) with a median follow-up of 195 months. The Rey Auditory Verbal Learning Test was used to assess verbal memory.

Results: Verbal Memory (Rey Auditory Verbal Learning Test) was significantly lower in the radiotherapy group compared to the no surgery group. Additionally, the effects of other medical factors, especially antiepileptic drug use, on cognitive function in glioma patients deserve attention.

Introduction: Among adult cancer patients, patients with gliomas (WHO grade 2–4) have a greater risk of cognitive impairment than healthy controls. Our aims were to determine the specific effects of radiotherapy on cognitive function and to identify other medical factors that may contribute to cognitive impairment.

Luis 2002; 360: 1281–88

**Figure**

Verbal Memory (Rey Auditory Verbal Learning Test) over time for different groups: Controls, No RT, <= 2 Gy, > 2 Gy.
Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up


**Summary**

**Background** Our previous study on cognitive functioning among 195 patients with low-grade glioma (LGG) a mean of 6 years after diagnosis suggested that the tumour itself, rather than the radiotherapy used to treat it, has the most...
Verbal Memory

<table>
<thead>
<tr>
<th>Measure: MEASURE_1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
</tr>
<tr>
<td>MEMVER</td>
</tr>
<tr>
<td>MEMVER * RADIO</td>
</tr>
<tr>
<td>Error(MEMVER)</td>
</tr>
</tbody>
</table>

6 years ↓

12 years ↓

- RT+ (n=34)
- RT- (n=33)
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Chemotherapeutic agents in brain metastasis

- Most large molecules and electrically charged molecules cannot cross the BBB
- Unfavorable characteristics of most anticancer agents, cytotoxics, and molecularly targeted agents
Chemotherapeutic agents

- Systemic anti-cancer therapies for control of primary or extracranial metastatic disease, before or after diagnosis of brain metastases
- Many agents have effects on brain function
- Chemotherapy-related cognitive impairment in 17% – 75% patients
  - subtle neurocognitive deficits more common than dementia
Chemotherapy-Induced Cognitive Dysfunction

- Most commonly affected domains:
  - Attention, learning, and processing speed consistent with disruption of frontal network systems

- Etiology differs according to agents used
Chemotherapy-Induced Cognitive Dysfunction

- Methotrexate and 5FU are particularly neurotoxic
- Cisplatin, etoposide and vincristine:
  - White matter injury (Komaki, 1995)
- Reasons for brain damage
  - Direct injury to the gray and white matter
  - Microvascular injury
  - Secondary insults due to immune-mediated inflammatory responses
Candidate mechanisms

- Blood–Brain Barrier integrity
- DNA damage and telomere shortening
  - e.g., AD, MCI
- Cytokine deregulation
- Individual genetic susceptibility
  - blood–brain barrier transporters
  - DNA repair mechanisms
  - cytokine regulation
  - neuronal repair and plasticity
  - neurotransmission
Conclusions

- Radiotherapy + chemotherapy plays a major role in the management of most brain metastases.
- Newer technologies may allow an improved therapeutic index.
- Except for SRS, unfavorable characteristics of most anticancer agents, cytotoxics, and molecularly targeted agents.
Future Directions

- Increase enrollment in early phase clinical trials to identify active agents for clinical use

- Strategies to avoid long term CNS complication of therapy

- Behavioral tools for anticipating/measuring long-term neurocognitive deficits

- HRQOL assessment of long term effect of systemic and CNS directed therapies
Thank you!
Laboratory/epidemiological research

Discovery of correlation between behavior or exposure and disease

Is the empirical basis for attributing causal effect consistent across diverse populations and study designs? (“validated discovery”)

Redirect research effort elsewhere

Does the envisioned clinical need justify expenditure of resources?

Can a specific lifestyle alteration be identified that would mitigate the risk factor?

yes

no
RT to brain causes white matter damage and particularly affects hippocampal-dependent functions of learning, memory, and spatial information processing.

Medication plus memory training

Imaging, protein, inflammatory and genetic markers of neurocognitive function need further validation.

Animal models are relevant for assessing neurocognitive outcomes

Large scale multimodality study in primary or brain mets or PCI