Neurocognitive Testing in Multicenter Clinical Trials

Jeffrey S. Wefel, Ph.D.
MD Anderson Cancer Center

Common Concerns

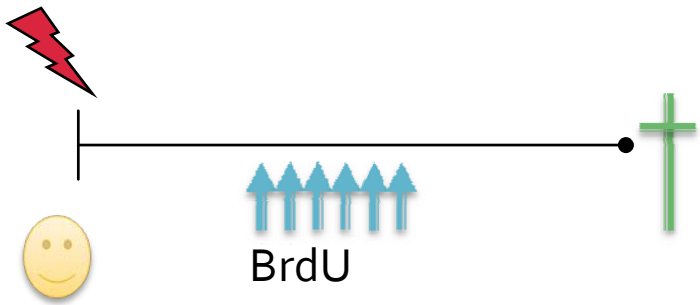
- "The prospect of being diagnosed with brain metastases, especially in HER2+ metastatic breast disease, is terrifying, as it heralds a compromised and dependent life as a result of fatigue-inducing and memory-scrambling whole brain radiation and personality altering steroid treatments." (Wadasadawala et al., J Can Res Ther, 2007)
- "....various systemic therapies have failed to improve the dismal outcome. In the absence of effective therapies, whole-brain radiotherapy has become the mainstay of treatment for brain metastases. Yet, whole-brain radiation can leave patients with persistent fatigue, permanent hair loss, profound memory problems and other serious cognitive-deficit side effects that may worsen with time, raising serious quality-of-life issues as patients are able to live longer."
- "Areas for future research include the need for an understanding of site-specific metastasis, effective anticancer strategies for sanctuary sites, assays to detect drug accumulation in sanctuary sites, prevention of CNS metastasis, improving the therapeutic ratio of systemic and CNS-directed therapies, behavioral tools for anticipating/measuring long-term neurocognitive defects, and quality of life assessment of the long-term effect of systemic and CNS-directed therapies." (Arragon-Ching&Zujewski, CCR, 2007)

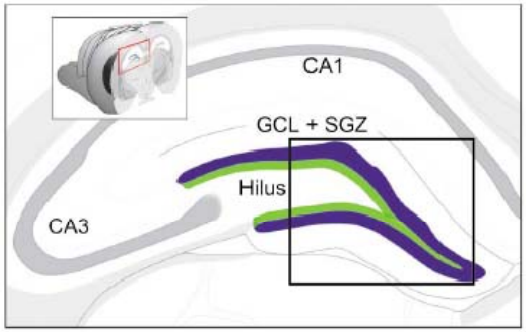
Why should we study cognition?

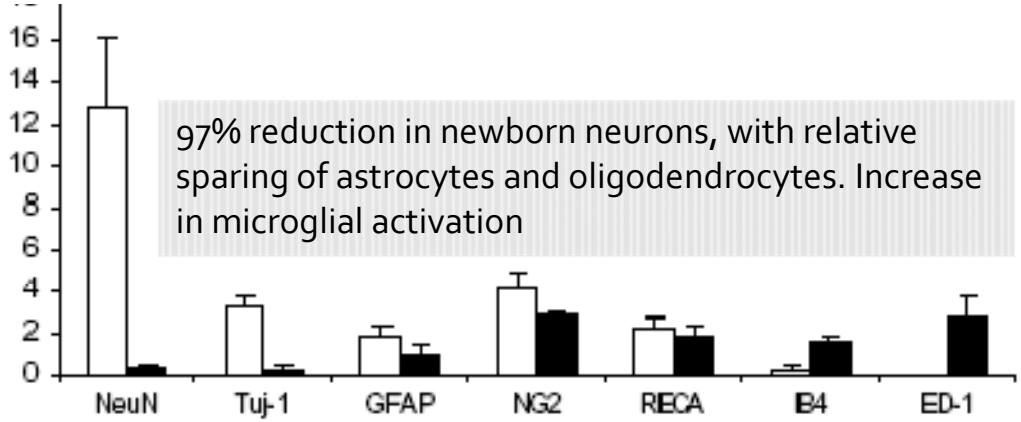
- Survival
  - Well accepted, easy to measure … but, difficult to achieve and requires large sample sizes
  - Non-CNS deaths are common, problematic outcome for studies of CNS disease and treatment
- Cognitive Function
  - Relevant for patients
    - Critical for occupational and scholastic success, familial and social well being, independence and QOL
  - Patients with brain mets are cognitively impaired at time of diagnosis
  - Cognitive function is related to survival, and, decline is associated with tumor progression
  - Cognitive decline may also be a toxicity of treatment
  - Evaluate survival outcomes in the context of patient clinical status (net clinical benefit)
    - What are the NC problems prior to treatment. Do different treatment regimens: improve NCF due to better tumor control, slow expected decline associated with disease, have more or less short and long term neurotoxicity? Are these outcomes the same for all brain met patients?

Why should we study cognition?

Mechanisms of Neurocognitive Dysfunction







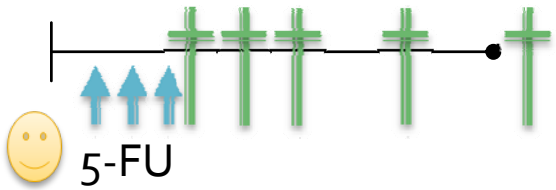
97% reduction in newborn neurons, with relative sparing of astrocytes and oligodendrocytes. Increase in microglial activation

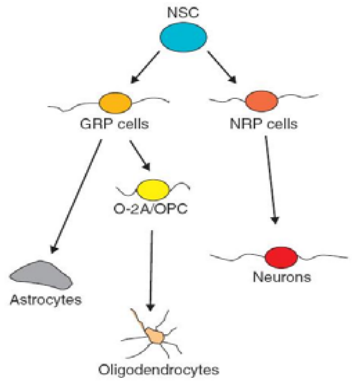
RT: ↑apoptosis,↓cell proliferation,↓ neuronal differentiation in hippo. Microglialinflamm→ cytokines→ inhospitable microenvironment to make new neurons (NPC will not differentiate into neurons)

Monje et al., 2002

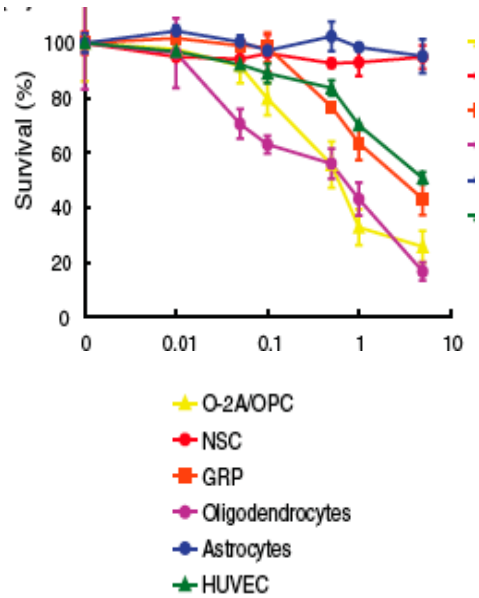
Why should we study cognition?

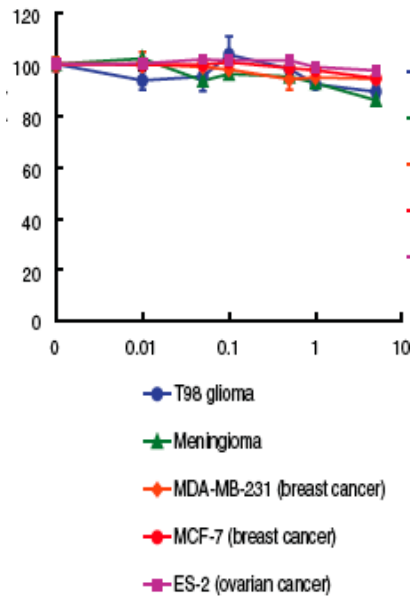
Mechanisms of Neurocognitive Dysfunction

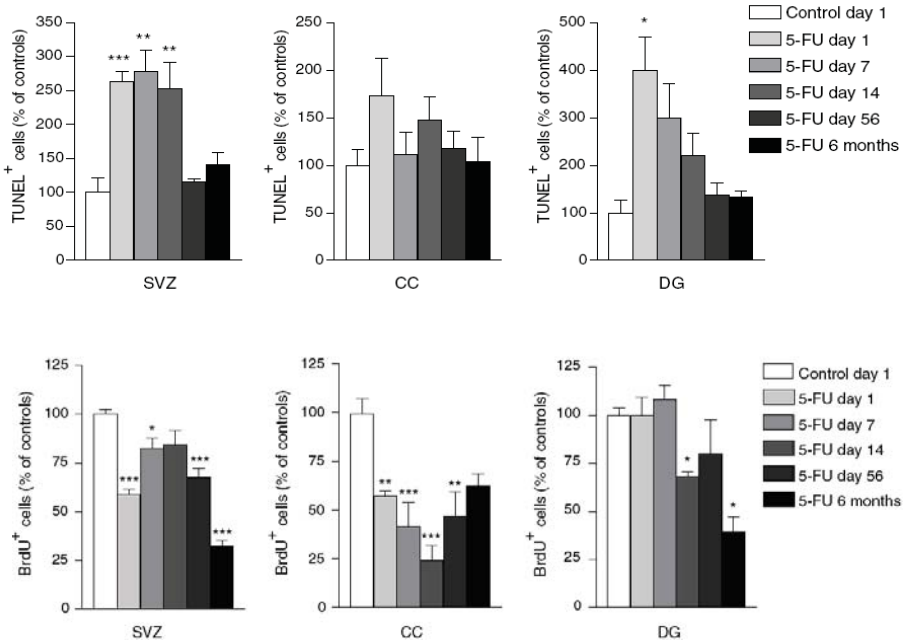




Marked and prolonged increase of cell death in the 5-FU treatment group→toxicity to nondividingoligodendrocytes and lineage-committed progenitgor cells (neural and O-2A). Suppressed proliferation with delayed effects - not associated with inflammation/vascular damage



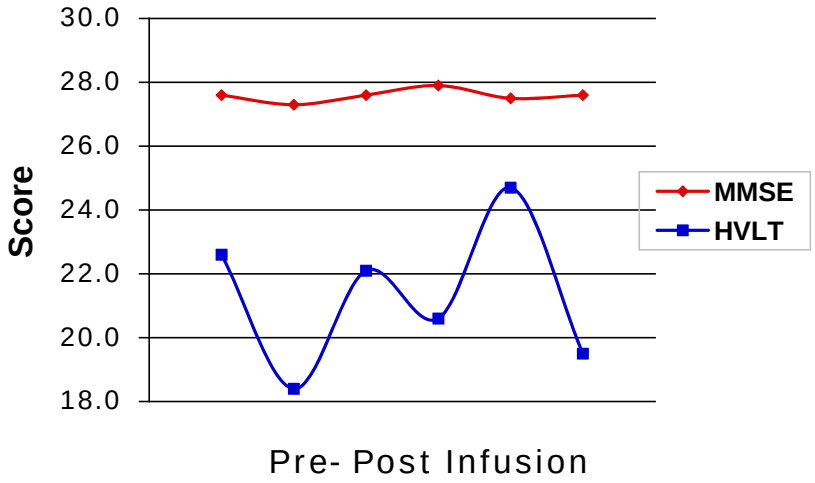




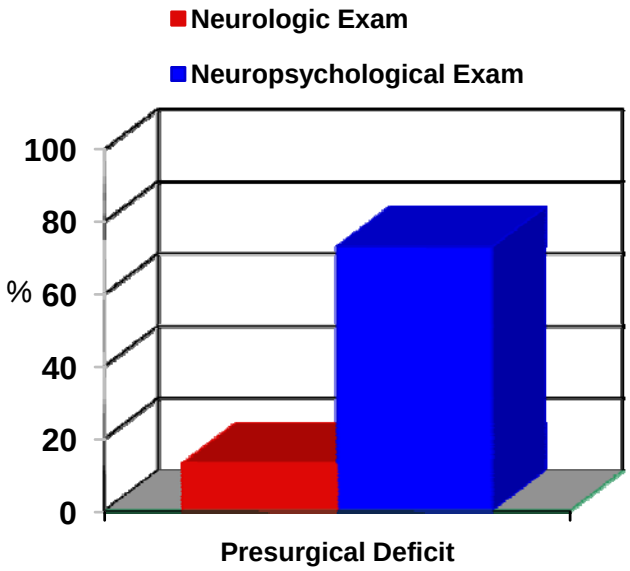
Han et al., 2008

Why not use MMSE, Neuro Exam or PRO?

- MMSE
  - Recognized as an inadequate tool



- Neurologic Exam
  - Insular region gliomas



- PRO of Cognitive Function
  - Subjective, Response shift
  - Not correlated with cognitive testing
  - Insight and accurate recall required

How do we study cognition (in clinical trials)?

- What are cognitive tests
  - They are *not* subjective patient reported outcomes (PRO)
  - The are objective, standardized performance based tests of neurologic function
    - Quantitative outcomes
    - Published population normative data
    - Demonstrated reliability and validity related evidence
- Characteristics of a clinical trial battery
  - Psychometrically sound measures (i.e., known reliability and validity)
  - Objective and standardized = unbiased, multi-institutional equivalence
  - Brief (25 minutes)
  - Repeatable (alternate forms to reduce practice effects)
  - Most patients are able to complete testing (limited ceiling and floor effects)
  - Can be administered by a trained nurse/CRA/healthcare provider

How do we study cognition (in clinical trials)?

- Study Neuropsychologist
  - Assist with study design (including follow up interval, analysis, interpretation)
  - Copyright and Permission to Use
    - "In accordance with the Standards for Educational and Psychological Testing and PAR's competency-based qualification guidelines, many tests and materials sold by PAR are available only to those professionals who are appropriately trained to administer, score, and interpret psychological tests."
    - CRFs
  - Train study site test administrators (about 1 hour)
    - Test administration procedure document
    - Web based training video: demonstrates test administration, common patient errors and standardized methods of examiner correction
    - Post test
    - Practice test administration
    - Teleconference/email re: errors and/or additional training
    - Certification documentation and communication with coordinating site (CTSU, RTOG, etc)
    - Centralized scoring and QA throughout the trial

Clinical Trial Test Battery

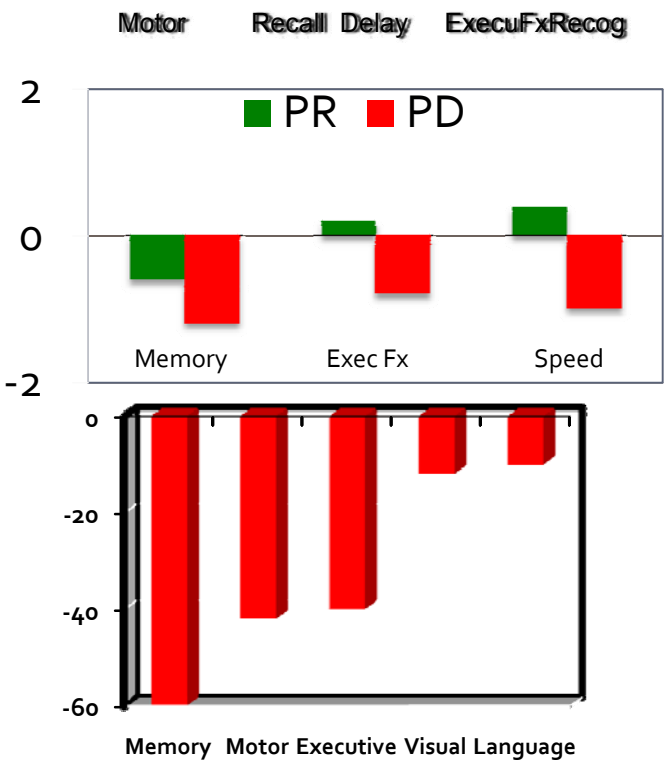
- Memory (Hopkins Verbal Learning Test- Revised)
  - Ability to learn and recall new information
  - Outcome variable: Number of words recalled
- Psychomotor Processing Speed (Trail Making Test Part A)
  - Rate at which we can interpret & process incoming stimuli and generate a behavioral response
  - Outcome variable: Time in seconds
- Executive Function (Trail Making Test Part B, Controlled Oral Word Association)
  - Ability to plan, monitor and adapt our behavior to changing contingencies, divided attention
  - Outcome variable: Time in seconds and Number of words produced

Trials Measuring Cognitive Function

- Mets
  - ID00-377: SRS+/- WBRT in patients with 1-3 brain mets
  - NS97-199 : Surgery vsradiosurgery for single brain met
  - RTOG 0214: A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced NSCLC
  - PCYC : Motexafingadolineum trials
  - ECOG and ACOSOG
- Primary BT
  - RTOG 0424, RTOG 0525, RTOG 0825, RTOG 0834, NCCTG N0577, Genentech, AngioChem …
- Symptom intervention trials:
  - RTOG 0614: A randomized, phase III, double blind, placebo-controlled trial of memantine for prevention of cognitive dysfunction in patients receiving whole brain radiotherapy
  - Molecular correlative endpoints to "personalize therapy"
- FEASIBILITY HAS BEEN DEMONSTRATED
  - ≈1000 test administrators have been trained in numerous cooperative group and sponsored trials
  - Good patient compliance (87-98% at baseline, 77-87% at 6 months)
  - Infrastructure to assist in implementing/disseminating neurocognitive tests
  - Multidisciplinary collaborations (new faces: neuropsychologists)
  - Investigator buy in/support

Examples of what we have learned

- Brain met patients (90%) are symptomatic at baseline (z<-1.5)
  - NCF is correlated with lesion volume
  - NCF correlated with functional independence, QOL
  - NCF occurs before decline in independence & QOL (net lead time: 56-153 days)
- Tumor growth correlatesw/ cognitive decline
  - 4 months after WBRT±MGd
- Cognitive change may occur in absence of radiographic change



Meyers et al., JCO, 2004; Li et al., IJROBP, 2008; MDACC

Summary

- In brain mets, NCF
  - Predicts survival
  - Highly associated with progression of brain met
  - Decline in NCF occurs in advance of decline in independence and QOL
  - Can demonstrate differential treatment toxicity
  - Minimally, can be used to contextualize any potential survival benefit
  - Primary endpoint in trials targeting symptom prevention or symptom palliation (NC decline)
- Requires the use of objective, standardized performance based measures (not PROs)
- *Feasible*: The demonstrated success in cooperative group and sponsored trials, in brain mets, and non-CNS malignancies, speaks to the feasibility of incorporating neurocognitive testing into clinical trial designs
- Composite outcomes (survival and cognitive function) should be developed