Abstracts

CLIN-NEURO-COGNITIVE

NC-02. ASSESSING NEURO-COGNITVE STATUS IN NEWLY PRESENTING PATIENTS WITH SUPRATENTORIAL INTRACRANIAL TUMOURS.
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INTRODUCTION: Neurocognitive endpoints are increasingly included in clinical trials in neuro-oncological settings (Meyers & Brown, 2006). There is a need to identify short, repeatable measures of cognition that are sensitive to reliably identify this group of patients. METHODS: Newly presenting patients with a radiological diagnosis of an intracranial tumour (n = 118) were assessed, prior to any surgical intervention, on a number of standardised cognitive and other measures as part of a larger study (Scotland et al., 2012). Their performance was compared postoperatively and preoperatively with that of patients with other brain tumours. RESULTS: The intracranial tumour cohort had significantly lower scores than did the spinal surgery and healthy control groups on the majority of the tests. The intracranial tumour cohort had significantly lower scores than did the spinal surgery and healthy control groups on the majority of the tests. Immediate and delayed memory (Auditory Verbal Learning Test, AVLT; p < 0.001); Trail Making Test (20 items); digit-symbol coding (p < 0.001); and verbal fluency (Controlled Oral Word Association Test, COWAT; p = 0.002 and p < 0.001, respectively). There was a moderate-to-large effect size in the participant group for all tests. DISCUSSION/CONCLUSIONS: The AVLT, Trail Making Test Part B, and COWAT are sensitive measures of cognitive impairment in patients with brain tumours and support Meyers & Brown’s (2006) proposal for the inclusion of these tests in clinical trials that have neurocognitive endpoints. The verbal fluency test, in particular, has a number of potential advantages for use in neuro-oncological settings, given that it can be completed by patients with focal motor deficits and is available in alternate forms to reduce practice effects.

NC-03. A STANDARD NEUROLINGUISTIC APPROACH TO AWAKE BRAIN SURGERY
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OBJECTIVES: Intraoperative direct electrical stimulation (DES) is increasingly used in patients who undergo surgery for tumours in eloquent areas. Although a positive impact of DES on postoperative linguistic outcome is generally advocated, the literature is only sparsely documented with information about the linguistic methods applied in awake surgery. Moreover, linguistic testing during DES is generally limited to object naming and counting tasks. No studies exist in which a standardised linguistic protocol was used to reliably identify the critical language areas. The aim of this study is to develop a standardised linguistic test battery for critical language areas in awake surgery. METHODS: Based on a critical review of the available data in the literature, an extensive linguistic test battery will be compiled to investigate linguistic functions in the pre-, intra- and postoperative phases of awake surgery. Phonological, semantic, syntactic and more general linguistic tests will be included. A normative study of the linguistic test battery will be administered to a control group of native Dutch-speaking (Flemish) adults (N = 200) and to a preliminary study group of 10 patients undergoing awake surgery. RESULTS: The data from the control and study groups will be described in terms of variables such as error distribution, age, sex, years of education, and geographical region. Anatomoclinical correlations will be investigated in the study group. Based on the findings of these analyses, the linguistic test battery will be finalised and used in pre-, intra- and postoperative settings to identify eloquent areas. CONCLUSIONS: With the development of a standardised linguistic test battery, a valuable instrument will become available to reliably identify and preserve linguistic functions in patients undergoing awake surgery for tumours in eloquent brain regions. Consequently, the test battery will substantially increase intraoperative comfort and improve cognitive outcome and quality of life. Moreover, the standard linguistic approach will enhance the scientific reliability of the neurosurgical procedure.

NC-04. HIPPOCAMPUS AS A DOSE CONSTRAINT MODEL TO PRESERVE NEUROCognition IN YOUNG PATIENTS WITH LOW-GRaDE BRAIN TUMORS TREATED WITH Focal STEREOTACTIC CONFORMAL RADIOThERAPY: DATA FROM A PROSPECTIVE CLINICAL TRIAL
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INTRODUCTION: The aim of this study was to analyze the effect of radiation dose levels on the hippocampus and other brain structures as a dose-constraint model to preserve neurocognition in young patients with low-grade brain tumors treated prospectively with focal stereotactic conformal radiation therapy (SCRT) in an ongoing clinical trial. METHODS: Between 2003 and 2008, we analyzed 50 patients (median age, 13 years) with low-grade/benign residual progressive brain tumors treated with SCRT in an IRB-approved ongoing clinical trial to a dose of 54 Gy/30 Fr/6 weeks with 2-, 3-, and 5-year follow-up. Prospective neuropsychological assessments were performed at baseline before SCRT and subsequently at 6 months, 2 years, 3 years, and 5 years with an age-appropriate battery of neuropsychological tests. All available patients, including the bilateral hippocampi, were drawn on planning imaging datasets for each patient. There was a moderate-to-large effect size in the participant group for all tests. RESULTS: One-third of patients had a > 10% drop in full-scale IQ (FSIQ) over baseline. Comparison of dosimetric data in patients with a significant drop (> 10%) in IQ with that in patients with a maintained IQ revealed that patients receiving > 42.5 Gy (80% of the prescribed dose) to > 13% of the volume (p = 0.048) and > 27 Gy (50% of the prescribed dose) to > 50% of the volume of the left temporal lobe were the ones who had a significant drop in FSIQ (p = 0.06). The mean hippocampus volume was 2.32 cc. Doses to the hippocampus showed a clear significant correlation with a decline in cognition at 3 and 5 years of IQ assessments. CONCLUSION: Our detailed, prospectively collected clinicodosmetric data show that the left temporal lobe and hippocampus are the most important dose-limiting structures in preventing a decline in neurocognition. This should serve as a suitable model for all high-precision RT techniques to improve therapeutic outcomes.

NC-05. A COMPREHENSIVE EVALUATION OF COGNITION IN NEWLY DIAGNOSED HIGH-GRADE GLIOMA.
Caroline A. Racine, Janeine M. Lupo, Annette Molinaro, Anna Parks, Susan M. Chang, Mitchell S. Berger, and Nicholas Butowksi; University of California, San Francisco, San Francisco, CA

Advancements in brain tumor treatments have increased survival rates, resulting in increased interest in quality of life (QOL) outcomes. Patients and caregivers rate cognition as being strongly associated with QOL, but research about which treatment parameters maximize cognitive function, particularly in high-grade glioma (HGG), is limited. Previous studies have used screening measures (e.g., mini-mental state examination) or limited battery of tests (delayed list recall only) that are more likely to be impaired in select patient groups (e.g., those with left-hemisphere tumors) but lack sensitivity in other patients. Defining a time-limited neuropsychological battery that is sensitive to deficits across a wide range of cognitive domains and tumor locations is a crucial first step in examining the long-term effects of treatment on QOL. To this end, we designed a pilot study to examine the feasibility and sensitivity of a comprehensive 90-minute neuropsychological assessment at baseline (presurgery), 3-4 weeks (postsurgery, postradiation), and 4-6 months (postsurgery, postproadisation), with seven completing all three time-points (63.6%). All raw scores were converted to z-scores using age-appropriate normative data. On average, patients at baseline showed declines in celerity (z = -1.34), delayed list recall (z = -1.66), delayed story recall (z = -1.72), delayed figure recall (z = -1.64), complex figure copy (z = -1.78), naming (z = -1.67), and design fluency (z = -1.59). Some patients performed well on delayed list recall but poorly on other tasks, indicating the value of assessing cognition more broadly. In summary, our results indicate that a comprehensive neuropsychological battery is feasible in many HGG patients and that future research may benefit from including additional neuropsychological tests in order to have...
maximal sensitivity. Preliminary results regarding longitudinal outcomes will also be discussed.

NC-06. EXPLORING LATE EFFECTS OF BRAIN IRRADIATION WITH A DELAYED MATCH TO SAMPLE PARADIGM
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BACKGROUND: Cancer survivors who receive radiotherapy to the head are at risk of developing late-delayed cognitive impairment exhibited as progressive deficits in memory, executive function, and attention. Whether this decline is more severe or rapid in patients of increased age has yet to be determined. METHODS: Young (age 18-45 years) and older (65 years and older) adults with a history of brain irradiation were compared to sex- and age-matched controls with no cancer history. Cancer survivors were at least 6 months post-irradiation. A short battery of neuropsychological tests (protocol CCOP 91105) was administered to compare the delayed match to sample (DMS) task from a preclinical model of whole-brain irradiation to standardized assessment. RESULTS: Presently, we have assessed 17 individuals (3 matched pairs per age group). All cancer survivors (n = 6) were also treated with chemotherapy agents. Older adults had significantly more intrusions during Hopkins Verbal Learning Test (HVLT) recognition (p < 0.01), longer completion times on the Trail Making Test Part B (p < 0.03), and longer peg-board completion times [dominant (p < 0.001) and non-dominant (p < 0.01)] than young adults. Cancer survivors remembered significantly more words than controls at the time of testing (HVLT ≤ 0.04) and less of the visual figure immediately after copying it (p < 0.02) and had a larger difference between forward and backward digit spans (p < 0.02). No significant interaction between age group and cancer history was evident at this time. DMS target responses were slower in older adults (p < 0.03), though no difference in accuracy was seen relative to young adults. No significant difference was seen between cancer survivors and control participants. CONCLUSIONS: Preliminary data indicate that the clinical DMS task is too easy for human participants. A version with abstract figures will make the test more difficult and potentially expose deficits in human participants similar to those seen in the preclinical model.

NC-07. LONG-TERM SURVIVORSHIP IN PRIMARY GLOBLASTOMA: A FOCUS ON NEUROCOGNITION
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Primary glioblastoma (GBM) remains a devastating diagnosis with a median overall survival (OS) of 12-16 months. Improved monitoring and treatment have modestly increased survival in the last 10 years, and long-term survivors (LTS) of primary GBM remain rare. Because of the rarity of primary GBM LTS, little is known about cognitive outcomes in LTS. Therefore, we conducted a prospective analysis of neuropsychological function in GBM LTS. LTS was defined as a primary GBM patient still living 5 years or more from diagnosis. Medical records were reviewed for 157 patients who were accrued, 508 were eligible. Patient and treatment characteristics were well balanced between the treatment arms. Study compliance was similar between the treatment arms, with only 32% of patients completing drug therapy or placebo for the remainder did not complete the study mainly because of death or noncompliance. The median follow-up time for censored patients was 12.4 months. LTS of primary GBM had less frequent patients receiving memantine than in those receiving placebo at 24 weeks (p = 0.059 with only 35% statistical power). The memantine arm had significantly longer time to cognitive decline (p = 0.02). The survival probabilities of stable neuropsychological function at 24 weeks were 30.6% and 19.7% in the memantine and placebo arms, respectively. Linear regression demonstrated less decline in patients receiving memantine at 24 weeks on the HVLT-R DR (p = 0.078), HVLT-R Delayed Recognition (p = 0.027), Clinical Trial Battery composite (p = 0.04), and mini-mental state examination (p = 0.003). CONCLUSIONS: Even though no statistically significant difference was seen in delayed recall, strong trends suggest patients treated with WBRT and memantine had better memory and overall cognitive function at week 24.

NC-08. MEMANTINE FOR THE PREVENTION OF COGNITIVE DYSFUNCTION IN PATIENTS RECEIVING WHOLE-BRAIN RADIOTherapy (WBRT): FIRST REPORT OF RTG 0614, A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL
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INTRODUCTION: Radiotherapy (RT) is effective for patients with brain tumors. However, there are concerns regarding cognitive deterioration after RT. Memantine, an N-methyl-D-aspartate receptor antagonist, is beneficial for vascular dementia and Alzheimer’s disease. Thus, the cognitive effects of memantine in patients receiving whole-brain RT (WBRT) were investigated. METHODS: Patients with brain metastases were stratified by recursive partitioning analysis class and prior surgery. Patients received WBRT (35.7 Gy in 15 fractions) and placebo or memantine (20 mg per day) for 24 weeks. Cognitive testing was performed at baseline and 8, 16, 24, and 52 weeks. The primary endpoint was memory decline at 24 weeks as measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR), and 442 patients were needed in order to detect a difference between the treatment arms with 80% power and an alpha of 0.025. Primary and exploratory regression analysis was performed. RESULTS: Of 543 patients who were accrued, 508 were eligible. Patient and treatment characteristics were well balanced between the treatment arms. Study compliance was similar between the treatment arms, with only 32% of patients completing drug therapy or placebo for the remainder did not complete the study mainly because of death or noncompliance. The median follow-up time for censored patients was 12.4 months. HVLT-R DR decline was less frequent in patients receiving memantine than in those receiving placebo at 24 weeks (p = 0.059 with only 35% statistical power). The memantine arm had significantly longer time to cognitive decline (p = 0.02). The survival probabilities of stable neuropsychological function at 24 weeks were 30.6% and 19.7% in the memantine and placebo arms, respectively. Linear regression demonstrated less decline in patients receiving memantine at 24 weeks on the HVLT-R DR (p = 0.078), HVLT-R Delayed Recognition (p = 0.027), Clinical Trial Battery composite (p = 0.04), and mini-mental state examination (p = 0.003). CONCLUSIONS: Even though no statistically significant difference was seen in delayed recall, strong trends suggest patients treated with WBRT and memantine had better memory and overall cognitive function at week 24.

NC-09. TEST-RETEST RELIABILITY OF PRIMARY MOTOR CORTEX MAPPING: NEURONAVIGATED TRANSCRANIAL MAGNETIC BRAIN STIMULATION (nTMS) VERSUS FUNCTIONAL MRI (fMRI)
Carolin Weiss1, Charlotte Nettekoven2, Volker Neuschmelting1, Andrea Eisenhöfer1, Anne Rehme2, Christoph Greulich3, and Roland Goldbrunner4; 1University of Cologne, Cologne, Germany; 2Max Planck Institute for Neurological Research, Cologne, Germany

Presurgical functional brain mapping is essential for optimized resection planning of eloquently located brain tumors. Functional magnetic resonance imaging (fMRI) is the most well-established method of presurgical motor mapping but was shown to have a rather low test-retest reliability, especially for the face and tongue area. Recently, neuronavigated transcranial magnetic stimulation (nTMS) has attracted increasing attention as an alternative motor mapping method that is applicable for clinical routine. However, little is known about the reliability of nTMS. Thus, we compared the reliability of both motor mapping approaches in a preclinical trial. We examined 10 healthy, right-handed subjects on 3 days (day 0, day 3-5, week 3-5) in nTMS at Xiaima 3.2.2, 110% of resting motor threshold on dominant primary motor cortex, motor evoked potential recordings: abductor pollicis brevis, plantar, mentalis, and tongue muscles) and fMRI (Siemens 3T Trio, motor parietal lobe). The primary endpoint was memory decline at 24 weeks on the HVLT-R DR (p = 0.078), HVLT-R Delayed Recognition (p = 0.027), Clinical Trial Battery composite (p = 0.04), and mini-mental state examination (p = 0.003). CONCLUSIONS: Even though no statistically significant difference was seen in delayed recall, strong trends suggest patients treated with WBRT and memantine had better memory and overall cognitive function at week 24.

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there was no difference in the ED of the CoGs (mean 6.7 mm). Regarding the spatial reliability (ie, overlap volumes and ICC), nTMS was superior for hand and foot mappings but not for perioral and tongue mappings. The cor-
total of the perioral showed the tongue area in both assessments. CoGs were similarly reproducible via fMRI and nTMS. Both methods seem sufficiently reliable for clinical application. In terms of spatial reliability, nTMS seemed to be superior for mapping the primary motor areas of the hand and foot but less accurate for the lips and tongue. Thus, both methods may well complement each other in the clinical routine.

NC-10. MAPPING OF THE PERIORAL REGION BY NEURONAVIGATED TRANSCRANIAL MAGNETIC STIMULATION (nTMS) MENTAL MUSCLE SUPERIOR TO ORBICULARIS ORIS MUSCLE FOR MEP RECORDINGS. A TECHNICAL NOTE. Carolin Weisse1, Volker Neuschmelting1, Andrea Eisenbist1, Charlotte Nettekoven1, Anne Rehme1, Christian Grekés1, and Roland Goldbrunner1, 1University of Cologne, Cologne, Germany; 2Max Planck Institute for Neurological Research, Cologne, Germany

Functional brain mapping is important for optimized decision making and resection planning of eloquently located brain tumors. Navigated transcranial magnetic stimulation (nTMS) is a rather novel and precise technique for primary motor cortex mapping. However, detecting the face and tongue representation via nTMS is often limited by dose-dependent direct stimulation effects of facial and trigeminal nerve fibres. Thus, stimulating at the lowest amplitudes possible should be intended. We compared the most frequently used muscles for mapping of the perioral region to determine test-retest reliability and feasibility. We examined 11 healthy subjects three times within 6 weeks via single-pulse nTMS for simultaneous mapping of the orbicularis oris muscle (OO) and mental muscle (MM). Motor evoked potentials were recorded by surface electromyogram electrodes and latency corre-
lation. Reproducible mapping of the perioral muscles was not feasible in 3 of 11 subjects because of direct stimulation effects. The mean latency was 10-11 ms, independent of pre-innervation (21 investigations without and 21 with pre-innervation; mean latency MM at rest 10.69 ms, MM pre-
contracted 11.03 ms, OO at rest 11.33 ms, OO pre-contracted 10.96 ms). When both muscles were stimulated simultaneously, the RMT was usually lower for the MM (75% of cases); the number of positive stimuli (amplitude >30 uV) was significantly higher using MM (mean/session: MM 380 stimuli vs OO 273 stimuli); and the mean amplitude was higher for MM (455 uV vs OO: 342 uV). Intersession reliability was comparable. Presurgical test-retest reliability and feasibility. We examined 11 healthy subjects three

NC-11. MAGNETIC RESONANCE IMAGING ASSOCIATES WITH DIFFERENCES IN NEUROCOGNITIVE PERFORMANCE FOR CANCER SURVIVORS COMPLAINING OF COGNITIVE DEFICITS FOLLOWING BRAIN TUMOR TREATMENT: A CRATION Ann M. Peiffer, Doug Case, Edward G. Shaw, and Stephen Rapp; Wake Forest School of Medicine, Winston-Salem, NC

BACKGROUND: Following brain irradiation, roughly 50% of cancer survivors develop some higher-order neurocognitive impairment that does not resolve and can decline further into dementia. However, predicting those who will develop cognitive impairment following therapy is not currently possible. Magnetic resonance imaging (MRI) markers from clinical scans may provide candidate biomarkers related to cognitive performance. METHODS: Baseline MRI scans and neurocognitive scores were collected from 198 participants enrolled in CCWFU91105 (NCT#00369785) prior to randomization. Subjects self-reported cognitive difficulties and were at least 6 months post-therapy. At minimum, a T1-weighted MRI pre- and post-gadolinium contrast was requested to confirm stable disease in all participants. Additional scans, including fluid-attenuated inversion recovery (FLAIR), diffusion-weighted, perfusion-weighted, and T2-weighted MRI scans, were available for analysis in subgroups of participants. Significance was assessed using statistical parametric mapping (SPM8) with a family-wise error correction of p < 0.05. RESULTS: Because of the vast variability in scan protocols, complete whole-brain imaging (ie, no scan) was found in 50% of post-contast T1-weighted scans. From these, local gray and white matter volumes were determined. Increased processing speed was associated with increased volume of white matter in the Muratoff bundle (ie, subcal-
losal fasciculus), whereas increased verbal fluency was associated with in-
creased volume of subcortical grey matter and bilateral cerebellum. Subgroup analysis of other modality scans (as available: FLAIR and diffusion-weighted) supported these findings. Perfusion of gray matter did not correlate with neurocognitive function in the sub-group receiving arterial spin labeling scans. CONCLUSION: Neurocognitive performance correlated with performance differences on several neurocognitive tests and indicated a strong association between white matter integrity and maintenance of cognitive function in cancer survivors following brain ir-
radiation. Whether a prospective trial from a pretreatment baseline will find

NC-12. CORRELATION BETWEEN NEUROCOGNITIVE FUNCTION AND TOTAL T2-WEIGHTED MRI SIGNAL. ABNORMALITY IN PATIENTS WITH BRAIN TUMORS

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The correlation between neurocognitive function and T2-weighted mag-
etic resonance imaging (MRI) abnormalities was evaluated in patients un-
dergoing local radiation therapy for primary brain tumors. Abnormal white matter was considered nonprogressive tumor compared with nonprogressive tumor. Fifty patients were ana-
yzed; the median age was 52 years (range: 23-84). Treatment consisted of no radiotherapy (RT, n = 9), RT < 6 months (n = 22), or RT > 6 months (n = 21) with bevacizumab (n = 18) or without bevacizumab (n = 33). Neurocognitive function was determined by perfusion MRI of relative cerebro
tbral blood volume (rCBV) utilizing ferumoxytol iron-oxide nanoparticles. High rCBVs (>1.75) in areas with gadolinium-based contrast agent enhance-
ment was considered active tumor (n = 35), whereas rCBV < 1.75 was con-
sidered nonprogressive tumor (n = 15). The total T2 signal abnormality area was

NC-13. INTEGRATING PHYSIOLOGICAL MR IMAGING WITH ASSESSMENT OF NEUROCOGNITIVE FUNCTION

Janine M. Lupo, Caroline A. Racine, Angela Jakarya, Annette Molinaro, Anna Parks, Susan M. Chang, Sarah J. Nelson, Mitchel S. Berger, and Nicholas Butowksi; University of California, San Francisco, CA

Having an objective means of integrating neurocognitive function into the manage-
ment of high-grade glioma (HGG) is becoming increasingly important as new treatments extend survival and the late effects of therapy become relevant. The current frameworks for understanding neu-
rocognitive changes over time are still limited and would benefit from

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assessment at baseline (presurgery), 3-4 weeks postsurgery (preradiation), and 6 months postradiation were evaluated, with six patients completing imaging and neurocognitive testing at all time points. The imaging exam consisted of anatomical imaging, dynamic susceptibility contrast perfusion-weighted imaging, 55-direction diffusion-tensor imaging, and 3-dimensional stereotactic MRI. Patients also underwent a comprehensive 90-minute neuropsychological battery that was sensitive to deficits across a wide range of cognitive domains and tumor locations within the same week as the MRI exam. All raw neurocognitive scores were converted to age-appropriate z-scores and combined across major domains. At baseline, relative cerebral blood volume in normal-appearing white matter (NAWM) was highly correlated with the Montreal Cognitive Assessment screen ($r = 0.76$, $p = 0.04$), whereas less-permeable vessels were associated with memory loss ($r = 0.68$, $p = 0.03$) and global cognitive impairment ($r = 0.88$, $p = 0.003$). Higher apparent diffusion coefficient values were related to impaired motor function ($r = -0.70$, $p = 0.04$). Imaging parameters within nonenhancing tumor were generally not related to baseline cognitive function. Preliminary longitudinal data showed the largest changes in both neurocognitive function and imaging parameters (especially fractional anisotropy) between baseline and post-surgery, while perfusion parameters were most sensitive to longer-term postradiation cognitive changes.